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RESEARCH ARTICLE

MOLECULAR DYNAMICS SIMULATION STUDIES ON THE INTERACTION OF TYPE I COLLAGEN TELOPEPTIDES WITH CYCLODEXTRINS

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ABSTRACT

Molecular Dynamics (MD) simulations is computational methods of studying physical movements of molecules, atoms in Nitrogen body. Montecarlo method of simulating the molecules are more common and widely used for bio-molecules on other hand it is numerical methods of predicting the realistic motion of the atoms in biological system. In this current study ,collagen the commercial important peptides were chosen for the molecular modeling studies in Insilco analysis. The complex form of N and C telopeptides of α-I collagen (I) and α-II collagen (I) with α and β cyclodextrin(CD) and water molecules were studied using simulation program available in discovery studio 2.01v. Finally it was observed that (α(I)-C - α CD) and (α(I)-C - β CD) has the maximum value for the total energy, electrostatic energy and Van der Waals energy. This also may be due to the presence of more amino acid residues when compared with other peptide fragments.

INTRODUCTION

Molecular Dynamics (MD) simulations is computational methods of studying physical movements of molecules, atoms in Nitrogen body. During this virtual study, the atoms and molecules were allowed to interact for a period and the motion of the biological body was studied using trajectory. A theoretical method gains more importance in recent years, molecular Dynamics (MD) simulations to study structure-function relationship in peptides and proteins. Ultimate goal of molecular Dynamics (MD) simulations of peptide or proteins is to understand the biological function and to sample the conformational space. Montecarlo method of simulating the molecules are more common and widely used for bio-molecules on other hand it is numerical methods of predicting the realistic motion of the atoms in biological system. there are different types of constraints that involved in simulation of system such as Micro canonical ensemble (NVE), Canonical ensemble (NVT) and Isothermal–isobaric (NPT) ensemble, based on the system the appropriate constraints was chosen and simulation was performed.

There are lots of filed were collagen plays a vital role .As a commercial product, collagen can be part of natural, stabilized tissue that is used in devices such as bioprosthetic heart valve, etc. It can also be fabricated as a reconstituted, purified product from animal sources for e.g. as in wound dressings. Both types of uses have distinct properties that offer special advantages to the final product. One of the frequent challenges in the design of collagen implants is to modify collagen chemically in a way that the rate of its degradation at the implantation site is either accelerated or slowed down to a desired level. Collagen types I, II, III and V are the primary types that constitute the essential part of collagen in bone, cartilage, tendon, skin and muscle. While each collagen type is more or less unique, all collagen molecules share a triple helical structure, and the presence of 4-hydroxyproline provides a distinctive marker for these molecules (Palsson and Bhatia, 2004; Farach Carson *et al.*, 2007). These collagen molecules pack together to form long thin fibrils of similar structure (Wyckoff *et al.*, 1935; Clark *et al.*, 1935). It has been shown that the assembly of type I collagen from rat tail tendon is a multistep process which is temperature dependant (Hayashi and Nagai, 1974). The exact sequence of the assembly is not known, but the removal of nonhelical ends of the molecule alters the kinetics suggesting that there may be a rate limiting conformational change dependant on the non-helical ends (Hayashi and Nagai, 1973). Studies concerning the events of collagen fibril formation have stressed the role of the extra helical extensions of the collagen molecule in the process (Prockop and Hulmes, 1994). The present study is directed towards the enhancement of the stability of collagen by incorporating cyclodextrins as an additive. Sugars and polyols have been widely used by biochemists to protect the native structure of proteins and the enzyme activity from thermal denaturation or inactivation. The attempt to use a blend of collagen- cyclodextrin mixture is sure to have an effect on the denaturing property of collagen.

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Investigation and simulation of the hierarchical structure of collagen offers new ideas in the design and fabrication of new functional materials with a new stabilizing agent. We already modeled Telopeptide of α-I collagen (I) and α-II collagen (I) have been modeled using Modeller9V7 in our previous studies we docked with cyclodextrins. In a current study we mainly focused on molecular dynamics behavior of Collagen α -I (I), N-Telopeptide and C-Telopeptide complex with α and β Cyclodextrins. Simultaneously we processed with Collagen α -II (I) N-Telopeptide and C-Telopeptide complex with α and β Cyclodextrins.

Sequence details of telopepides were obtained from SWISSPROT database. Collagen α -I (I) of human with N-terminal telopeptide and C-terminal telopeptide sequence is "QLSYGYDEKSTGGISVP" and "SAGFD FSFLPQPPQE KAHDGGRYYRA". On the same way Collagen α -II(I) of human with N-terminal telopeptide and C-terminal telopeptide sequence is "QYDGKGUGLGP" and RGDK GEPGEKGPRGL respectively.

MATERIALS AND METHODS

Calculate energy

The Calculate Energy protocol allows you to evaluate the potential energy of a specified structure. You can also use several methods to estimate the entropy of the system. The Calculate Energy protocol can be used to confirm that a given system does not exhibit serious distortion from typical equilibrium molecular geometries or possess substantial atomic overlap. Alternatively, the Calculate Energy protocol can be used to compare the relative stability of different configurations of the same structure; or as a prelude to lengthy simulations to confirm the availability of appropriate force field parameters.

Energy minimization

All dynamics simulations begin with an initial structure that may be derived from experimental data or from theoretical model buildings. Energy minimization is performed on structures prior to dynamics to relax the conformation and remove steric overlap that produces bad contacts. In the absence of an experimental structure, a minimized ideal geometry can be used as a starting point. Each of the minimization methods available in CHARMm, together with implementation considerations such as Adopted Basis-set Newton-Raphson (ABNR),Steepest Descent, Conjugate Gradient (CONJ) (Flectcher and Reeves, 1964), Powell (POWE) (Powell, 1977) and Smart Minimizer. All these minimization methods are available through acclerys discovery studio 2.01v also, the Minimization protocol minimizes the energy of a structure through geometry optimization (Haile, 1992; Brooks, 1985; Powell, 1969; Press *et al.*, 1987).

Solvation

The Solvation protocol allows you to create an explicitly solvated system using CHARMm. Water molecules and optionally counterions can be added to a molecule. Water molecules may be added in several methods with a variety of boundary conditions, including a sphere or a box. With periodic boundary conditions, either a cubic, orthorhombic, or a truncated octahedron cell shape can be selected(Allen and Tildesley,1987). In addition, it prepares the special constraints to allow simulation of these waters, either explicit periodic boundary or spherical harmonics constraints. An explicit solvation model might be employed when examining the effect of aqueous solvation on the range of interactions possible for a ligand with its binding site using a molecular dynamics simulation. Typically, the solvated model generated by this protocol is used as input for other simulation protocols, such as the Standard Dynamics Cascade protocol.

Molecular dynamics

One of the most important computational techniques in CHARMm is molecular dynamics simulation. In CHARMm, molecular dynamics simulations are performed using a classical mechanics approach in which Newton's equations of motion are integrated for all atoms in the system. Molecular dynamics can be used to generate a realistic model of a structure's motion, perform conformational searching, produce a time series analysis of structural and energetic properties, explore energy decay, and analyze solvent effects. The method used in CHARMm to constrain these motions is the SHAKE algorithm (Straatsma *et al.*, 1986). SHAKE is available in the Equilibration, Heating, Minimization, and Production protocols, as well as the Standard Dynamics Cascade. The SHAKE option can be applied to all covalent bonds involving hydrogen atoms. A two-fold increase in the time step (to 0.002 ps) (Brown and Clark, 1991; Berendsen *et al.*, 1984)

RESULTS AND DISCUSSION

Initially, docking was performed using Auto dock and each docked complex of Collagen α -I (I), N-Telopeptide and C-Telopeptide with α and β Cyclodextrins and Collagen α -II (I) N-Telopeptide and C-Telopeptide complex with α and β Cyclodextrins were converted into PDB for and analyzed using Discovery Studio for simulation studies. Simulation Studies were carried out for each complex using Discovery Studio. For this process, energy has calculated and entropy estimates using the program called calculate energy under simulation package in discovery studio (Table 1). Here entropy of the system has been estimated based on rotation, translation, and vibrational components. Before that the molecule has been typed with a CHARMm force field. Then energy minimization has been performed for each complex, which updated the coordinates of the complex and energy properties were added using the program called minimization under simulation package in Discovery Studio. An initial minimization stage, typically using the robust steepest descent (SD) algorithm to resolve any initial poor contacts within the system without creating large distortions in the overall structure. Then each complex has been solvated by adding water molecules. Solvent molecules were added as sphere and harmonic restraints applied for the simulation of the solvent (Fig 1). This has been done using the program under simulation package in Discovery Studio. Again, the energy of the complex in the presence of solvent molecules was minimized. This second minimization

stage typically used the Adopted Basis Newton-Raphson (ABNR) method. Table 2 details about the energy of the telopeptides after two stage of minimization.

Then dynamics simulation studies have performed for each docked complex by adjusting the temperature of a molecule from 277K-313 K using the program called dynamics by heating under simulation package in discovery studio. Then molecular dynamics simulation heating stage was employed to

Table 1. Initial energy of each Telopeptide and cyclodextrine(CD) complex

Telopeptide	Potential Energy(Kcal/mol)	VanderWaals Energy (Kcal/mol)	Electrostatic Energy (Kcal/mol)	RMS Gradient (Kcal/(mol*angstrom)
α(I)C with α-CD	0.16938E+14	0.18938E+14	-0.10229 E+04	0.19638E+14
α(I)C with β-CD	0.16938E+14	0.16938E+14	-0.10712E+04	0.19455E+14
α(I)N with α-CD	14650.59694	14643.02652	-378.94461	6192.68806
α(I)N with β-CD	2410.40178	2433.53041	-458.58758	607.84150
α(II)C with α-CD	4782.64093	4677.51080	-316.64877	2254.25168
α(II)C with β-CD	2031.69926	1950.83439	-393.89107	698.75601
α(II)N with α-CD	503.85878	437.76117	-300.86721	91.49338
α(II)N with β-CD	457.44603	335.60660	-299.63165	56.42133

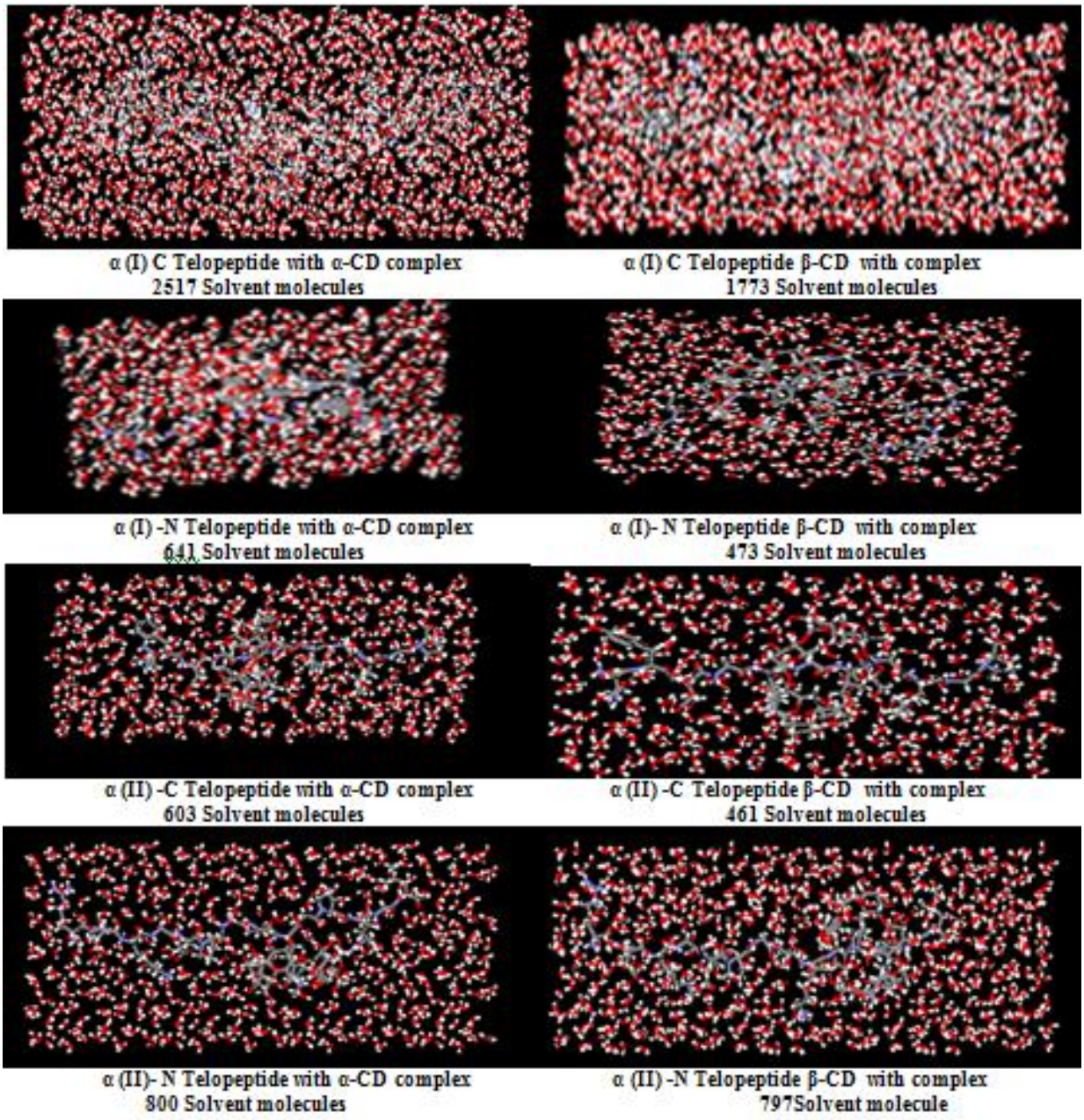

Fig. 1. Water molecules added to Collagen telopeptides complex with CD

Table 2. Energy value after two stage of minimization

Telopeptide	Initial Potential Energy (Kcal/mol)	Potential Energy (Kcal/mol)	Van der Waals Energy(Kcal/mol)	Electrostatic Energy (Kcal/mol)	Initial RMS gradient (Kcal/(mol*angstrom)	Final RMS gradient tKcal/(mol*angstrom)
α(I)C with α-CD	0.217E+17	-137513.5	2686.5	-91091.3568	0.431E+16	2.75
α(I)C with β-CD	15609756706	-97405.61	1548.3	-59674.3	5734216041	2.434
α(I)N with α-CD	0.390E+13	-35480.35	553.47	-1925326	0.10628E+13	3.00188
α(I)N with β-CD	401258.70	-26358.33	461.95	-12698.54	28527.27	2.930
α(II)C with α-CD	33197.9	-32296.46	630.39	-16957.171	4207.69	3.074
α(II)C with β-CD	5849123255.4	-24919.230	281.41	-12133.54	32567800256	2.83
α(II)N with α-CD	6268.965	-43936.830	484.27	-24535.68	476.45	2.67
α(II)N with β-CD	9403542.3	-42670.82	717.4	-24290.35	3399966.90	3.10

Table 3. Final energy parameters of telopeptides after dynamics production

Telopeptide	Initial Potential Energy (Kcal/mol)	Potential Energy (Kcal/mol)	Van der Waals Energy (Kcal/mol)	Electro static Energy (Kcal/mol)	Initial RMS gradient (Kcal/(mol*angstrom)	Final RMS gradient (Kcal/(mol*angstrom)	Electro static Energy (Kcal/mol)
α(I)C with α-CD	-142432.5	-134060.9	-142906.9	8845.99	342.80	2139.27	-96352.13
α(I)C with β-CD	-99806.17	-93496.90	-100059.5	6562.65	341.55	1292.12	-62624.93
α(I)N with α-CD	-36314.11	-34048.65	-36413.73	2365.07	345.7	399.6	-20203.61
α(I)N with β-CD	-27017.45	-25238.72	-27083.46	1844.74	314.5	300.9	-13703.82
α(II)C with α-CD	-33631.00	-31624.66	-33732.10	2107.44	338.76	417.5	-18010.58
α(II)C with β-CD	-25840.59	-24220.76	-25988.38	1767.62	352.5	148.2	-12895.71
α(II)N with α-CD	-45432.65	-42803.54	-45622.49	2818.94	344.64	397.1	-25772.81
α(II)N with β-CD	-43893.58	-41284.19	-44123.86	2839.67	345.66	579.01	-25548.2

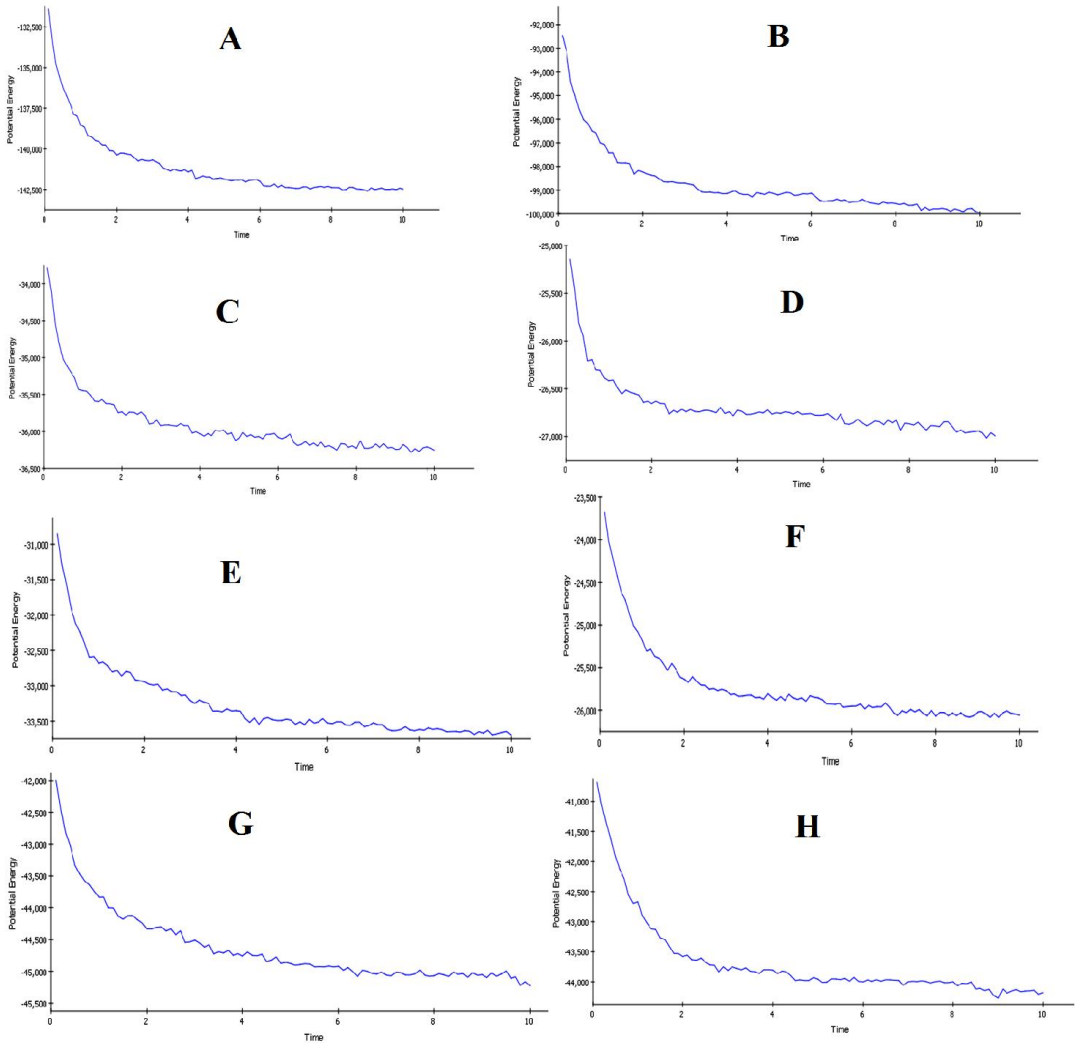

Fig 2. Potential energy of the telopeptide complex with cyclodextrin (CD) and water molecules

add thermal energy to the system to reach a target temperature. A standard molecular dynamics simulation stage is then employed to equilibrate the system at a target temperature. The purpose of the equilibration stage is to ensure that the energy in the system is distributed appropriately among all degrees of freedom. This allows the system to achieve thermal equilibration at the target temperature. Finally production of dynamics was carried out to calculate the final energy parameters of the complex telopeptides with cyclodextrin (CD) and water molecules (Table 3). The above graph (Fig. 2) shows the potential time of the telopeptides with respective to time, A: It shows that the potential energy drops from a value of -131,000 to a minimum value of -142,500 for the system α(I)-C - α CD. B: It shows that the potential energy drops from a value of -92,500 to a minimum value of -100,000 for the system α (I)-C - β CD. C: It shows that the potential energy drops from a value of -33600 to a minimum value of -36,100 for the system α (I)-N - α CD. D: It shows that the potential energy drops from a value of -25,200 to a minimum value of -26,700 for the system α (I)-N - β CD. E: It shows that the potential energy drops from a value of -39,800 to a minimum value of -33,700 for the system α (II)-C - α CD. F: It shows that the potential energy drops from a value of -26,000 to a minimum value of -23,600 for the system α (II)-C - β CD. G: It shows that the potential energy drops from a value of -42,000 to a minimum value of -45,000 for the system α (II)-N - α CD. H: It shows that the potential energy drops from a value of -39,500 to a minimum value of -44,100 for the system α (II)-N - β CD.

Conclusion

It is seen that the initial and final potential energy for the system, comprising the α (I) chain has the maximum value when compared with the interaction of the different peptide fragments with that of α cyclodextrins (α(I)-C - α CD). This may be due to the reason that the number of amino acids in the peptide fragment is higher than other telopeptides. The temperature at which this minimum potential energy is derived is 342.8 degree Kelvin. Analyzing the interactions of the peptide fragments with β cyclodextrins, it is observed that the initial and final potential energy of the system α (I)-C - β CD is the maximum. Here again, the number of amino acids is larger in number and hence may be the higher value. The system (α(I)-C - α CD) has the maximum value for the total energy, electrostatic energy and Van der Waals energy. This also may be due to the presence of more amino acid residues when compared with other peptide fragments.

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