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Diphenylalanine peptide nanotube: charge transport, band gap and its relevance to potential biomedical applications

N. Santhanamoorthi,[1†] P. Kolandaivel,[1] L. Adler-Abramovich,[2] E. Gazit[2], S. Filipek,[3] Sowmya Viswanathan,[4] Anthony Strzelczyk,[5] V. Renugopalakrishnan[5,6*]

[1]*Department of Physics, Bharathiar University, Coimbatore 641046, India*
[2]*Department of Molecular Microbiology and Biotechnology, Tel Aviv University, Tel Aviv, Israel*
[3]*Faculty of Chemistry, University of Warsaw, 02-093 Warsaw, Poland*
[4]*Wellesley Hospital/ Partners Healthcare System, Newton, MA 02462, USA*
[5]*Children's Hospital, Harvard Medical School, Boston, MA 02115, USA*
[6]*Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115 USA*

[*]Corresponding author. Tel: (+1) 6173738914; E-mail: v.renugopalakrishnan@neu.edu
[†]Present Address: Department of Chemistry, University of Minnesota, MN 55455, USA

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ABSTRACT

Peptide nanotubes (PNT) are emerging alternates frontier to carbon nanotubes (CNT). PNT's can be engineered by solid phase synthesis with desired properties. Chemically PNT's are reactive in sharp contrast to CNT's and hence require less site specific functionalization for nanotechnology applications. In this paper we are reporting the electronic coupling between the Phe-Phe dipeptide which is calculated using the density functional theory method. The calculations are performed for linear and cyclic structures of diphenylalanine peptide. The calculated electronic coupling is sensitive to the peptide electronic structure and shows a significant dependence for conformations. The band gaps obtained for PNT are compared with Boron Nitride and CNT. Peptide nanotubes (PNT) exhibit no cytotoxicity and hence offer tantalizing prospects in biomedical applications for example in drug delivery.

Keywords: Phe-Phe dipeptide; charge transfer; band gap; peptide nanotube; boron nitride nanotube.

N. Santhanamoorthi is working as a Post Doctoral Research Associate in the Department of Chemistry, University of Minnesota, USA. He received his Ph.D. in Physics from the Bharathiar University, Coimbatore, India. During his Ph.D. program he was awarded Senior Research Fellowship by CSIR, India. Also, he obtained DST-DFG international fellowship and worked in Technical University of Munich, Munich, Germany for about six months.

P. Kolandaivel is the Director of School of Physical Sciences, Bharathiar University, Coimbatore, India. His current research interests are focused on the atomic and molecular properties of diverse biomolecules like proteins, nucleic acids etc., clusters, nanoscale materials and various others by applying the concepts of quantum mechanics. He has authored more than 100 publications in well-reputed journals having impact factor of about two with an overall citations around 400. He has contributed a Chapter "Quantum Chemistry of Bonding and Interactions" in the book entitled "Chemical Reactivity Theory- A Density Functional View" (2009), CRC Press, Taylor and Francis, USA. He has worked as visiting scientist/visiting professor at various universities abroad like Department of Chemistry, Universidade de Santiago de Compostela, Santiago, Spain; Department of Chemistry, Sophia University, Tokyo, Japan (twice); Department of Molecular Bio-Physics, German Cancer Research Institute, Heidelberg, Germany; Emerson Center for Scientific Computation, University of Emory, Atlanta, USA; and Center for Computational Chemistry, University of Bristol, Bristol, UK and Institute of Physical Chemistry, Technical University of München, München, Germany.

Sowmya Viswanathan is working as an associate professor at the dept. of Internal Medicine, Newton Wellesley Hospital, Newton, Massachusetts. She also holds the following positions: Session Chair on Biosensors, International Symposium on Material Sciences and Regenerative Medicine, November 2010, Taipei, Taiwan; Organizing Committee, Energy : Today & Tomorrow, Asian Institute of Technology, Bangkok, Thailand, Oct. 17-19, 2010; Associate Professor, Dept. of Internal Medicine, University of Massachusetts Memorial Medical Center, Worcester, Massachusetts ; Primary Care Physician, Medical Associates of Greater Boston; Health care professional with medical degree and 14 years of vast clinical experience combined with diverse leadership experience including Medical Director of Outpatient division of SOAR Clinical Research Program at UMass, Medical Director of Health Care and Rehab facility, Medical Director of Home Health Care ,Executive leadership

position at UMass Medical Center as Physician Quality Officer for Ambulatory Medicine, International Consultant for a major medical device company, Medical Consultant for a Biopharmaceutical company & Staff attending Physician including teaching, preceptor positions. Also holding an Executive member position in the House of Delegates of Massachusetts Medical Society and therefore involved in key policy making decisions for the state of Massachusetts. Proven ability to initiate collaborative efforts with various organizations, set the tone to help execute the organisation's vision and also promote teamwork within the parent organization. Most recent endeavor being an Expert Consultant in the Obama-Biden Transition Healthcare Team. Research areas: Biosensors; Single Platform Integrated Microsized Cholesterol, Triglycerides, Glucose, Hb A1c sensor; Implantable Bio Fuel Cell for Medical Devices.

V. Renugopalakrishnan, American Biophysicist , "Renu" and his group in Bionanoscience at Children's Hospital - Harvard focus on the interface between protein engineering and nanotechnology. He has been on Harvard faculty since 1984, starting from Assistant Professor to a Professor. In recent years his laboratory has been targeting proteins as intelligent and innovative biomaterials in solar cells, fuel cells, very high density data storage, bio fuel cells, and tagged on to CNT for directed drug delivery, sensors. He teaches and is guiding MD PhD program at Walter Bradford Cannon Society, First Year MD Students, "New Pathway in Medical Education" as a part of Harvard-MIT Health Sciences program and is currently spearheading a campus-wide effort in bio inspired devices. He is funded by NSF, US Air Force, NIH. He was Wallace H Coulter Chair and Professor at the University of Florida, Miami. He had been a visiting Professor in Denmark and India. He obtained his B.Sc. from the Madras University, entered graduate school in the Dept. of Chemistry, Columbia University, New York, NY and Rockefeller University, New York, NY and had worked with Prof Harold C Urey, Nobel Chemistry Laureate, Prof. Barbara Low and obtained his Ph.D. in Biophysical Sciences from State University of New York, Buffalo, NY. He is the author of more than 250 publications, 2 monographs – 1991, 2006, 1 Graduate Level Textbook in Bionanoscience (under development), and member of academies. He serves on 6 Editorial Boards of Journals. His scientific lineage traces its origin to Prof G N Ramachandran, FRS, Biochemistry to Nobel Laureate Prof Stanford Moore, Rockefeller University, New York, NY ; experimental studies of protein structural biology to Prof Dan Wesley Urry, Univ of Minneapolis, Minnesota ; Prof Melvin J Glimcher, Harvard to mineralization of connective tissue macromolecules, to Prof. Richard Collins Lord, MIT on Raman Spectroscopy of Proteins. With Sowmya, he is spearheading Bioengineering efforts at Harvard Medical School.

Introduction

Carbon nanotubes (CNT) since their discovery by Iijima [**1**] have emerged as a versatile material in nanotechnological applications. When proteins are coupled with carbon nanotubes (CNT), (Strzelczyk et al. from Harvard laboratories, US Patent Disclosure) [**2**], the full functional potential of proteins are realized to a much greater extent than protein-based biosensors since CNT's facilitate the charge transfer processvery efficiently. The nano-dimensions of carbon nanotubes and their electronic properties make them an ideal candidate for anchoring the proteins for biochemical sensing [**3**]. Lab-on-a-chip device based on amperometric sensing technology based on carbon nanotube covalent linked to glucose oxidase, cholesterol oxidase and esterase, bovine pancreatic lipase, fructosyl valine amino oxidase that will measure cholesterol, triglycerides, glucose and Hb A1C from a single drop of blood in an integrated single platform, (Sowmya Viswanathan and V. Renugopalakrishnan, to be submitted), in biofuel cell (J. Dudzik, et al., to be submitted). Leveraging full potential of CNT require their *a priori* functionalization to interface with biological macromolecules through chemical methods. PNT and protein nanotubes offer an alternate to CNT since they are chemically more reactive and do not require functionalization [**4, 5**]. Peptides can be produced by solid phase synthesis and modified with greater ease by peptide engineering. In this report, we are comparing the band gap of diphenylalanine PNT with CNT in our continuing exploration of PNT in nanotechnological applications [**6, 7**].

The study of charge transfer (CT) mediated by protein molecules is one of the most fundamental processes in chemistry and biology. There are many experimental [**8**] and theoretical [**9, 10**] reports of intramolecular long-range CT in proteins and peptides that explain how protein molecules control CT process. Hence, CT in these biological systems [**11-16**], have therefore been the interesting subject of intensive experimental and theoretical studies and have been investigated in detail in recent several decades, but still much remain to be learned about the structural features of the amino acid residues that could behave as charge (hole or electron) mediators. Earlier studies suggest that CT in proteins or peptides strongly depend on its conformation [**17-21**]. In this letter, we describe the study of CT in diphenylalanine peptide (Phe-Phe), based on the fragment orbital method, which examines the role of conformational change on the magnitude of charge transfer parameters. We show that considerable changes in the magnitude of electronic coupling between the molecular orbitals corresponding to hole (or electron) transfer may arise with geometric changes.

The Phe-Phe peptide is of a special interest due to its ability to form ordered nano-assemblies of unique physical, chemical and mechanical properties [**22-25**]. Other aromatic dipeptide can also self-assemble into ordered structures such as tubes, spheres, plate and hydrogels [**26-30**]. Moreover, Phe-Phe nanotubes based electrochemical biosensors had shown a large increase in their sensitivity upon the modification of the electrode surfaces with a forest-like nanotube arrays [**31-33**]. While the mechanism of increased measured electrode current of the electrochemical sensors is not fully understood, mechanism of charge transfer may have a significant role in this process.

Computational methodology

The charge transport through peptide bond of Phe-Phe peptide is described by the Tight-binding Hamiltonian method [**19-21, 34, 35**]. The Hamiltonian is given by:

$$H = \sum_{i=1}^{n} \varepsilon_i(\theta(t)) a_i^{+} a_i + \sum_{\substack{i,j \\ i \neq j}}^{n} J_{ij}(\theta(t)) a_i^{+} a_j \qquad \text{----- (1)}$$

In the above equation, a_i^{+} and a_i are the creation and annihilation operators of a charge at the *i*th amino acid subgroup in the dipeptide, $\varepsilon_i = \langle \varphi_i | H | \varphi_i \rangle$ is the site-energy of the charge and $J_{i,j} = \langle \varphi_i | H | \varphi_j \rangle$ is the charge transfer integral between highest occupied molecular

orbitals (HOMOs) or lowest unoccupied molecular orbitals (LUMOs) of subgroups *i* and *j*. In equation 1 both ε_i and J_{ij} depend on inter- and intra-molecular degrees of freedom, collectively denoted as $\theta(t)$.

These parameters were computed for linear and cyclic structures of Phe-Phe peptide using fragment orbital approach as implemented in Amsterdam Density Functional (ADF) theory program [**36**]. The present system consists of two phenylalanine amide subgroups which have been represented in terms of two individual fragments**.** The molecular orbitals generated through single point energy calculation for each fragment have been used as a basis set in further single point energy calculation for full dipeptide. That is, the molecular orbitals of a dipeptide are expressed as a linear combination of the molecular orbitals of the individual phenylalanine amide subgroup, φ_i. The final output of the ADF calculation will provide the overlap matrix, *S*, the eigenvector matrix, *C*, and the eigenvalue matrix, *E*. Then the site-energy, $\langle \varphi_i | h_{KS} | \varphi_i \rangle$ and charge transfer integral, $\langle \varphi_i | h_{KS} | \varphi_j \rangle$ are calculated using the relation $hKS = SCEC^{-1}$. The generalized effective charge transfer integral can be defined in terms of the charge transfer integral (*J*), spatial overlap integral (*S*) and site-energy (ε) as [**19-21, 37**].

$$J_{eff} = J - \frac{S(\varepsilon_1 + \varepsilon_2)}{2}. \quad \text{-----(2)}$$

In the present study, all DFT calculations were performed with an atomic basis set of Slater-type orbitals (STOs) of triple-ξ quality including one set of polarization functions on each atom (TZP basis set in ADF) [**36**]. The Generalized Gradient Approximation (GGA) type, Becke's exchange functional [**38**] is used in DFT calculation together with the correlation part of Perdew **[39]**, denoted as BP. This proceeds from the Local Density Approximation (LDA) for the exchange and correlation functional based on the parameterization of the electron gas data given by Vosko, Wilk and Nusair (VWN)[**40**]. Further, the band gap energies of the Phe-Phe peptide have been calculated from the frontier molecular orbitals. The HOMO–LUMO energy difference represents the energy band gap that provides the basis for electrical conduction.

Further, the fragment containing five Phe-Phe dipeptides in oligomeric assembly was taken from the NMR structure of Alzheimer's amyloid-β42 (Aβ42) fibrils (Protein Data Bank code 2BEG) [**41**]. The narrow β-sheets of Phe-Phe were prepared by removal of other amino acids (17-18 and 21-42) from the Aβ42 structure. Resulting structures were multiplicated, assembled to form ionic interactions with adjacent β-sheets and optimized in YASARA program version 10.2 [**42**] using Yasara2 forcefield (modification of AMBER99 forcefield).

Experimental

Preparation of initial peptides solutions

The peptides H-Phe-Phe-OH and Cyclo-Phe-Phe were purchased from Bachem. Fresh stock solutions were prepared by dissolving lyophilized form of the H-Phe-Phe-OH peptides in 1,1,1,3,3,3-hexafluoro-2-propanol, HFP (Sigma-Aldrich, USA) at a concentration of 100 mg/ml. The cyclo-Phe-Phe peptide was dissolved in HFP to a concentration of 25 mg/ml and was sonicated until a clear solution appeared. The peptide stock solutions were diluted to a final concentration of 2 mg/ml in ddH_2O.

Scanning electron microscopy (SEM)

The peptide solutions were placed on a glass cover slip, allowed to dry at room temperature, and coated with gold. Scanning electron microscopy images were made using a JSM JEOL 6300 SEM operating at 5 kV.

Results and discussion

The Scanning electron microscopy images of the linear and cyclic Phe-Phe dipeptide nanotubes are shown in **Fig 1**. The Phe-Phe linear peptide self-assemble in solution to form elongated discrete ordered nanotubes structures, the length of these tubes is a few microns long (**Fig. 1a**). Moreover, Phe-Phe cyclic peptide also self assembles into elongated ordered structures (**Fig. 1b**)

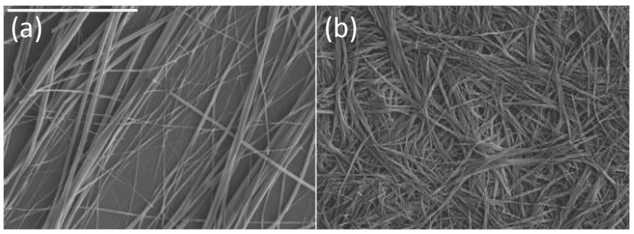

Fig. 1. Scanning electron microscopy images of the peptide nanotubes (a) Phe-Phe linear peptide nanotubes, and (b) Phe-Phe cyclic peptide nanotubes.

The linear and cyclic structures of Phe-Phe peptide have been optimized using the density functional theory of Becke's three parameter exact exchange functional combined with gradient corrected correlation functional of Lee Yang and Parr (B3LYP) with 6-31G* basis set using Gaussian 03W package [**43**]. The calculated harmonic vibrational frequencies using same level of theory indicate that both the optimized structures of Phe-Phe peptide are at stationary point without any imaginary frequencies. The optimized linear and cyclic structures of Phe-Phe peptide are shown in **Fig. 2**. The charge transfer parameters such as electronic coupling (also called as charge transfer integral), spatial overlap integral and site energy (energy of the charge when it is localized at particular phenylalanine subgroup) for both hole and electron transport between the fragments of Phe-Phe peptide have been calculated based on the fragment orbital method and are provided in **Table 1**. The effective charge transfer integral have been calculated for hole and electron transport using the eq. 2 and are summarized in **Table 1**. From the table, it is clearly infer that, electronic coupling between highest occupied molecular orbitals of Phe-Phe peptide is maximum (1.102 eV) in the cyclic structure. It seems that the cyclic structure is more favorable for the hole transport. Whereas, the coupling between lowest unoccupied molecular orbitals of Phe-Phe peptide is maximum (0.278 eV) in the linear

structure compare to the cyclic structure, which indicates that the electron transport is efficient in the linear structure. The present DFT results indicates that the cyclic structure of Phe-Phe peptide is favorable for hole transport and linear structure is favorable for electron transport.

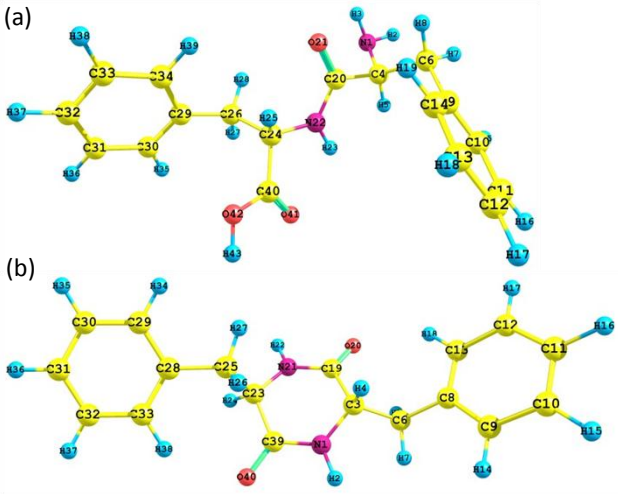

Fig. 2. The optimized (a) Linear and (b) cyclic structures of Phe-Phe dipeptide.

Table 1. The calculated values of charge transfer integral (J in eV), spatial overlap integral (S in eV), site energies (ε_1, ε_2 in eV) and effective charge transfer integral (J_{eff} in eV) for linear and cyclic structures of diphenylalanine peptide.

Parameters	HOLE		ELECTRON	
	Linear	Cyclic	Linear	Cyclic
J	0.266	-1.838	0.336	0.167
S	-8.148×10^{-3}	8.096×10^{-2}	-2.099×10^{-2}	-3.290×10^{-3}
ε_1	-6.317	-8.433	-2.764	-2.826
ε_2	-13.991	-9.734	-2.754	-2.861
J_{eff}	0.183	1.102	0.278	0.158

The site-energies which are calculated as the diagonal matrix elements of the Kohn-Sham Hamiltonian for the linear and cyclic structures of the Phe-Phe dipeptide and are given in **Table 1**. Even though the same amino acids (phenylalanine) are used in the present study, the calculated site energy values are not identical with each other. This energy difference act as a barrier for both hole and electron transport. The difference between the site energies for hole transport in Phe-Phe cyclic structure is only in the order of 1eV and the effective charge transfer integral is maximum. For electron transport, the linear structure has the minimum site energy difference, (0.01eV) and large electronic coupling values compare to cyclic. That is the positive charge (Hole) will migrate easily in the cyclic structure of Phe-Phe peptide where as in the linear structure electron transport in much efficient.

The energy band gap values are calculated as the difference between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for both the linear and cyclic forms of Phe-Phe peptide and are presented in **Table 2**. The calculated band gap values show that, the linear structure has less band gap values compare to the cyclic structure. Our previous calculation [**5**] also predicts that the linear structure has minimum band gap values. The present band gap values of Phe-Phe peptide are nearer to the band gap values of CNT with BN nanotubes.

Table 2. The calculated values of HOMO (in hartrees), LUMO (in hartrees) and band gap (in eV) for linear and cyclic structures of diphenylalanine peptide.

System	HOMO	LUMO	Band gap (Eg)	CNT[a] Band gap	BN[b] Band gap
Phe-Phe linear	0.23604	0.03034	5.59	4.0	5.5-6.2
Phe-Phe cyclic	0.24031	0.00447	6.41		

[a]Ref. [**36**], [b]Ref. [**37, 38**]

The literature shows that the CNT with BN tubes has uniform band gap values of 4 eV in all diameters [**44**]. Therefore we can tune the band gap values of peptides by means of changing the conformation. The calculated bandgap values of peptide nanotubes are compared with the energy gaps of the inorganic nanotubes such as CNT, BN and BCN, shows that peptides nanotubes to be one of the most challenging and promising field in bioelectronic applications. Blase et al. [**45**] theoretically calculated the bandgap of 5.5 eV for the BN nanotubes of diameter of 1 nm and predicted that it is especially independent on tube size or helicity. Recently, Yu et al. [**46**] report PL analysis over a large number of BN nanotubes with diameters from 2.5 to 100 nm by using a vacuum ultraviolet (VUV) synchrotron radiation source with variable energies up to 6.2 eV. It is well known that the smaller diameter CNTs are metallic while the larger diameter CNT's are semi conducting in nature with BN tubes that show uniform band gap of 4 eV for an entire range of diameters [**44**]. Electron-energy loss spectroscopy (EELS) has found a large range of energy bandgaps from 5.3 to 5.8 eV from different nanotubes in different sizes [**47**]. The calculated band gaps of peptide nanotubes are comparatively equal to the conventional inorganic nanotubes which emphasize that the use of these transparent biomaterials in the field of nanoelectronic devices and other materials science applications.

Molecular modeling

The long and curved β-sheet of Aβ42 contains Phe-Phe motif which is assumed to enhance its oligomerization and to form fibrils. In the NMR structure of Aβ42 [**41**] the hydrophobic amino acids are disposed on both sides of β-sheet and there is also an internal ionic interaction between Asp23 and Lys28 from adjacent β-threads. Very similar arrangement was proposed for oligomeric state of Phe-Phe dipeptides. The dipepdides are connected by hydrogen bonds formed by peptide groups (so they form narrow β-sheet) and additionally by π-π interactions of their phenyl rings (**Fig. 3a**). Such narrow β-sheets are attracted to each other via ionic interactions between charged N- and C-termini of dipeptides (**Fig. 3b**). Eventually, they can form tubular construct by linking many of such substructures (**Fig. 3c**). For formation of cylinder of 30 nm in diameter it is required about 110 dipeptides in the circular arrangement.

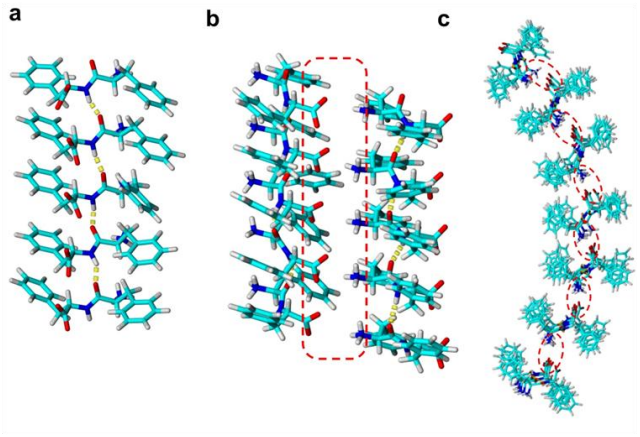

Fig. 3. Model of interactions between Phe-Phe dipeptides. a) Row of dipeptides linked by hydrogen bonds of peptide bonds (narrow β-sheet) and π-π interactions of phenyl rings. The structure is identical to that found in Alzheimer's amyloid-β fibrils (containing Phe-Phe motif) resolved by NMR methods (PDB code 2BEG). b) Proposed ionic interactions between adjacent β-sheets of dipeptides. Marked area denotes ionic interactions. c) Fragment of tubular arrangement of β-sheets of dipeptides of roughly 30 nm in diameter (not in scale). Marked areas denote ionic interactions. Top view.

Conclusion

In this paper we have studied the charge migration through the peptide bond in diphenylalanine peptide based on fragment orbital approach. The calculations were performed for linear and cyclic structures of diphenylalanine peptide. The positive charge (Hole) will migrate easily in the cyclic structure of Phe-Phe peptide where as in the linear structure electron transport in much efficient. The results show that the migration of charge is conformational dependent. The molecular dynamics calculations show that, the higher phe-phe oligomeric structure can form the cylinder structure in the diameter of 30 nm which is in agreement with the experimental study. The calculated band gaps of peptide nanotubes are comparatively equal to the conventional inorganic nanotubes which emphasize that the use of these transparent biomaterials in the field of nanoelectronic devices and other materials science, especially biomedical, applications. Peptide nanotubes which self-assemble into unique nanostructures driven by intermolecular forces are chemically reactive building blocks offer a new world of nanotubes which have unexplored applications in drug delivery, solar cell, fuel cells and sensors. Peptide nanotubes do not pose environmental threats or cytotoxicity like its inorganic counterparts.

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