Gold Nanotubes from Organic Scaffolds for Biomedical Applications

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Abstract. Nanoparticles are the cutting edge of the rapidly developing field of nanotechnology, which enables visualization and manipulation of matter down to the atomic level. Their unique size to volume ratio, shape and thermal stability make these materials superior, and rapidly usable in various bio-medical applications. This brief review summarize the recent advances in the field of applied nanomaterials with an emphasis in designing nanoscale devices with pre-defined structure, and their potential applications in the field of biology and medicine.

Introduction

The term 'Nanotechnology' [1] refers to technological developments on the nanometer scale, usually 0.1-100 nm, and was coined by Taniguchi in 1974 [2] to describe the precision manufacture of materials with nanometer tolerances. In 1980s the term was reinvented and its definition expanded by K. Eric Drexler [3]. Since then this field has rapidly evolved. It is primarily benefiting from the development of instrumentation by the physical community, which enables visualization and manipulation of matter down to the atomic level [4, 5], and become readily applicable to variety of fields from electronics to biology and/or medicine including drug and gene delivery [6, 7], tissue engineering [8, 9], MRI contrast agent [10], detection of proteins [11], separation and purification of biological molecules and cells [12] and bio detection of pathogens [13].

Self-assembly and self-organization processes are the thread that connects the processing of chemical reactions to the convolution and materialization of a dynamic system. Artificial self-assembly derives its principles from nature and its processes, and uses this understanding to design nanoscale devices with pre-defined function. However, complex forms of organized matter cannot be synthesized bond-by-bond. Rather, a new type of synthesis based on non-covalent forces is necessary to generate functional entities from the bottom up. The conceptualization of an organized state of matter requires in-depth understanding not only of chemical reactivity but also of the non-covalent forces necessary to translate chemical information into functional superstructures. This review briefly overview the recent development in the field of nano sized superstructures with a prospective application in opto-electronics to biology and medicine.

Tubular nano objectives

Self-assembled tubular nano objects constitute important components of nanomaterials, and are of interest due to their numerous possible applications. They appealed because of their curved features that differentiate between inner and outer surfaces as well as boundaries. Due to the characteristic curved geometry, they can be used for self assembly into more complex architectures [14]. There are several possible ways to design open- ended hollow tubular structures, such as a) helical molecules, to form hollow and folded structures, b) rod like molecules, to form molecular bundles, c) macro-cycles, to form continuous tubes, and d) sector or wedge-shaped molecules, to form continuous cylinders.

A two dimensional sheet- like starting material can be used either as rolled or sealed at opposing edges to produce a tube- shaped structure. Such processes have been noted in formation of carbon nanotubes from graphite [15, 16]. Linear precursors can form tubular structures by coiling into hollow, helical conformations. This motif is illustrated by β- helical structures formed by the natural antibiotic gramicidin A [17]. Assembly of stave or rod-like subunits into barrel or bundle-shaped frame works can also form hollow structures. This design includes trans membrane pores, which is formed by β- barrel proteins such as α- hemolysin [18], and ion channel [19]. Tubular arrays can be prepared from stacking of disc or sector- shaped subunits. Self-assembly of the tobacco mosaic virus (TMV) coat protein is perhaps the best-known biological instance of this structure [20].

Carbon Nanotubes

The Carbon nanotubes are widely recognized as the most essential nanomaterial, compiling an impressive list of superlatives since their discovery in 1991 [15]. They are recognized as the ultimate carbon fiber with the highest strength of any material [21, 22], the highest thermal conductivity [23], and they have been shown to possess outstanding field emission properties [24]. They can also function as the active semiconductor in nano scale devices [25]. Nevertheless, it seems fair to say that the real opportunities for carbon nanotube chemistry still lie in the future. There is probably no other material with so much potential, but which offers so many challenges in the preparation [26], agglomeration, dispersion, purification from catalyst residues, carbon nanoparticles, and amorphous carbon, their separation according to length, diameter, solubility and chirality into semi conducting and metallic nanotubes [27], and finally to the in-depth understanding and control of their formation and chemistry. All of these challenges lie before us, and impure carbon nanotubes still cost more than gold. More research and development works are needed to resolve these issues.

Tubular molecular assembly

There is interest in synthetic organic nanotubes, which are manifest from a consideration of biological systems. Due to these reasons, many researchers have focused on the construction of simpler synthetic tubes for a number of different applications. For example, hollow tubular structures act as conduits of chemical information in the form of trans membrane ion channels [28]. They provide closed reaction chambers, and change their conductivity upon exposure to a suitable analyte, which was illustrated by protein- folding chaperonins [29] and protein degradation enzymes [30], sensory materials for water, organic vapors or in artificial nose devices [31]. In the course of evolution, nature has developed a multitude of biomacromolecules modified to deal with complicated tasks such as information storage, support of tissue, transport, and performance of localized chemical transformations. Although large number of researchers in the fields of chemistry and physics have been pursuing the same goals using synthetic systems, nucleic acids and proteins still outclass man made materials. This has made an increasing number of scientists over the past decades turn their eye to nature to design and synthesize increasingly precise nano scopic structures using synthetic polymeric materials potentially useful for target biomedical applications [32].

It was first proposed by Urry in 1971 and then independently by Ramachandran and Chandrasekhar that β- helical conformations are common in linear peptides composed of alternating D- and L- α- amino acids (D, L- peptides) due to the conformational requirements for β-sheet hydrogen bonding [33, 34]. The β- helices are peptide super secondary structural motifs in which backbone folds into a helical conformation stabilized by β-sheet-type hydrogen bonding. β- helices can exist in either right or left-handed conformations depending on peptide length, residue composition, and prevailing chirality [34]. In all such structures, amino acid side chains radiate outward, leaving an unoccluded central pore running the length of the helix axis. The average radius of the β-helix pore depends upon the helix periodicity, or number of residues per turn, with larger periodicities giving rise to larger pores. In principle, helix periodicity can be controlled by varying the backbone hydrogen- bonding register. β- helices are potentially attractive scaffolds for preparation of tubular structures with tailored internal dimension and can be potentially use as biological semiconductors [35].

Desantis and co-workers recognized that peptides comprised of an even number of alternating D- and L- amino acids displaying conformationally equivalent β- type dihedral angles, which would form closed rings capable of stacking through backbone- backbone hydrogen bonding [36]. The resulting hollow cylindrical structures are conceptually related to the β- helical conformations adopted by linear D, L- peptides [37]. In 1993, Khazanovich and coworkers first demonstrated the formation of hollow tubular structures by the stacking of cyclic D, L-peptide rings [38]. One advantage of cyclic D, L-peptide nanotubes with respect to their β- helical counterparts is the possibility of rigorously controlling the internal diameter of the nanotube by simply varying the size of the peptide ring [39].

Conformation of ordered organic nano structures
The study of conformationally ordered structures from synthetic chain molecules is an important problem with an ultimate aim to mimic the properties and functions of natural biopolymers [40]. Well-defined conformations of non-biological conformationally ordered structure have been achieved by a variety of strategies including intramolecular hydrogen bonding, donor-acceptor complexation, metal coordination interactions, and solvophovic interactions.

Hydrogen Bonding Interaction. According to Gellman [41], the term "foldamer" describes any polymer with a strong tendency to adopt a specific compact conformation. The foldamers can be designed by the identification of new backbones with well-defined structural preferences. It is thus further described as oligomers of modest length that in solution display such a specific conformational preference in solution. Gellman used poly (α- amino acid)s to make α- helices with the 3_{10} helical structures, which has been extrapolated to the design of other helical structures based on oligomers of β- peptides [41], and functionalized with number of metallic nanoparticles [42]. Gellman also showed that formation of a specific protein helix is associated with a particular type of backbone hydrogen bonding. However, the nearest neighbour interactions involve five or seven membered hydrogen bonded rings, which do not allow optimal hydrogen bond geometries. They also demonstrated that cyclic monomer in the backbone have particular preference for the formation of helical structure [43].

Seebach and coworkers have developed hetero- hexa-β-peptides, which form helical structures in water as well as in organic solvents [44]. They demonstrated that the conformational restrictions in the backbone imposed by the use of cyclic monomers were not a prerequisite for the formation of these helical structures. Gellman's group later showed the incorporation of cyclic β- amino acids in the sequence do have a positive effect on the stabilization of the helix, and potentially be useful in functionalization with various nanoparticles [45]. Lehn's group has published a similar approach using oligoisophthalamides. They were folded into helical aggregates through the formation of hydrogen bonds. In this work, cyanuric acid is used as a template, and oligomer folds into a helix, forming hydrogen bonds to the guest molecule such as metals and composites [46]. The aggregated helices generate fibers, which in turn cluster to form bundles of lengths up to several micrometers.

A templating agent is not required for the folding of oligo (pyridinecarboxamide)s. These molecules fold the formation of intramolecular hydrogen bonds into double helices. Upon heating, these double helices dissociate into single- helical strands [47]. Hamilton and coworkers have also constructed oligoanthranilamides from anthranillic acid and pyridine 2, 6 dicarboxylic acid moieties. They utilize hydrogen bonds between nearest and neighbour groups to rigidify their structure, and maintain a helical conformation [48].

Attractive Electron Donor Acceptor (AEDA) Interaction. Lokey and Iverson have employed attractive electron donor- acceptor (AEDA) interactions between di-alkoxynaphthalene and naphthalenetetraacarboxylic diimide unit respectively. These structures take advantage of the stacking propensities of the aromatic electron donor- acceptor interactions of covalently linked

subunits. The stack structures were termed "aedamers", were believed to adopt a "pleated secondary structure" in aqueous solution [49]. Solubility of the aedamers can be controlled by using different amino acids as the linkers between the donor and acceptor units. Nguyen and Iverson used hydrophilic (Aspartic acid) and hydrophobic (Leucine) residues one after another as linkers between the aromatic units provide amphiphilic stacks, which aggregated in aqueous media [50]. Aedamers have also been shown to have potential applications in the area of molecular sensors [51]. The aedamer was synthesized with a hope of mimicking the leucine zipper motif found in peptide systems. This was attempted by creating an oligomer that would have one side lined by a hydrophobic unit (Leucine) and the other side by a hydrophilic unit (Aspartic acid). These oligomers intramolecularly folds in solution and undergoes an increase in intermolecular aggregation. Furthermore, it was found that upon heating above 80 °C, the aqueous solution of aedamer undergo an irreversible conformational change. At room temperature, aedamer solutions are red wine color due to the acceptor- donor interactions. Upon heating, the aedamers begin to unfold and expose the hydrophobic backbones to solution leading to colorless, presumably tangled aggregate. The author compared the behavior of these aedamers with helix collagen. It was proposed that the color change (red wine to colorless) could therefore be used as a temperature sensor indicating when a threshold temperature has been reached.

Metal Coordination Interaction. Metal ion complexation has been used to direct the helical folding of many oligomeric compounds. The resulting complexes are known as helicates. The metal complexes used are generally labile. This property allows rapid and reversible formation of coordinate bonds. Oligopyridines have been thoroughly investigated for their ability to adopt helical conformations upon metal coordination [52]. The same oligomers may adopt different helical conformations depending on the metal ion. Arana's group [53] studied sexipyridines (spy) for their ability to adopt helical conformations upon metal coordination. Alkanethiol side chains on oligomers promote solubility of the longer chains. Investigations on spy strands and their di- and trinuclear helical complexes were investigated with the goal of forming different metal coordination spheres both synthetically and electrochemically.

Solvophobic Interaction. The folding of oligo (m-phenyleneethynylene)s into helical stacks driven by solvophobic effects was reported by Moore and coworkers [54]. The molecules exhibit a large degree of conformational flexibility due to the fact that rotation is possible around the ethylene linkers, which allows switching between the transoid and cisoid states. The latter easily form helical conformation. In these systems, the helical preference is controlled by several different factors. These include the meta connectivity of repeat units. It allows the oligomer to fold back upon itself, and the use of polar side chains and a nonpolar backbone. Hecht and coworkers [55] developed a conceptually new approach to generate organic nanotubes. A linear polymer chain forms a helically folded conformation by solvophobic interactions followed by intramolecular crosslinking to yield rigid organic nanotubes with an inner hole. This method allows for control over the nanotube's dimension as well as the location of the inner and outer surface functionalities. These functionalized nano objects are potentially interesting building blocks for the construction of new materials and devices. In addition, it was postulated that when oligomers of sufficient length are dissolved into a polar solvent, a helical conformation would result. This conformation maximizes the favorable interactions between the polar solvent and polar side chain, which capitalize aromatic- aromatic folding interactions, and reduces the unfavorable contacts between the hydrocarbon backbone and the polar solvent. Additional support for the formation of the helix was provided by binding of metal ions with nitrile functionality incorporated in the central cavity of the tubular structure [56].

Helical structural confirmation by intramolecular cross-linking. Some researchers have used intramolecular cross-linking to lock the helical structures and bind metal ions with appropriate functionality. It is not always necessary to lock the conformation, and to bind metal ions because many systems form stable helical conformations by self-assembly. Cross-linking might be needed if

the nanostructure is susceptible to damage during subsequent modifications and/or applications. Zimmerman and coworkers [57], and Hecht and coworkers [55] have prepared organic nanotubes that can be cross-linked following self-assembly, which could potentially bind metal ions to form a core-shell helical structure.

Gold nanoparticle

Nanostructured materials are of intense interest, and considerable effort has been devoted to design and controlled fabrication of nanostructured materials with functional properties as nano-biomaterial [58]. These nanostructured materials generally composed of inorganic and oligo/polymeric materials. The interest in nanoscale materials stems from the fact that their properties such as optical, electrical, mechanical, chemical are a function of their size, composition, and structural order. These provide additional degrees of freedom in preparing materials with desired properties, and allow combinations of properties not attainable with conventional materials. Therefore, effective strategies are necessary to build tailored nano-materials reliably and predictably in order to meet the ever- increasing structural and compositional complexity demands placed on materials synthesis and performance by Nano technology. Self-assembled nano structured materials represent attractive building blocks from which to create ordered and complex materials.

Nanoparticles of metallic, semi conducting, and magnetic materials have generated research interest lately because of their potential uses in opto electronics, catalysis, chemical and biological sensing, and drug delivery etc. Over the last decade there have been immense efforts to fabricate core shell materials with tailored structural, optical, and surface properties [59, 60]. Investigations have largely been spurred by the applicability of such materials in modern materials science, and by their technological importance. The creation of core-shell colloidal structures is also of interest from a fundamental and academic viewpoint, especially in the areas of colloid and interface science [61]. They can be utilized as model systems to investigate factors governing colloidal interactions and stabilization [62], and to gain valuable information on the properties of concentrated dispersions [63]. This typically involves tailoring the surface properties of particles, often accomplished by coating or encapsulating them within a shell of a preferred material. Core -shell particles often exhibit improved physical and chemical properties over their single- component counterparts, and hence are potentially useful in a broader range of applications. Therefore, methods to "engineer" such materials with controlled precision have long been sought [59, 60].

In recent years, the nanoparticles particularly metal nanoparticles receive expanded attention in biomedical research [64]. Among the metallic particles, the study of colloidal gold particles stands out in particular [65] due to their unique properties [66, 67]. Gold nanoparticles are used in a variety of medical applications such as diagnosis and therapeutics based on their optical and electronic properties, particularly their strong surface plasmon resonance (SPR) absorption in aqueous media around 520 nm. The strong SPR is due to the high electronic polarizability of small particles, which yield a very high extinction coefficient. The resonance frequency is dependent on the size, shape, material properties, surrounding medium and the state of aggregation of the nanoparticles [68]. The SPR absorption and other unique properties resulting from their small size can be exploited in a range of applications in bio-imaging, chemical and biological sensing [69], optical filters [70], and single electron transistors [71].

Halas and coworkers [72] developed a procedure to make a gold nano-shell on a silica core, and Jung's group [69] used a silica surface with tin to seed gold nucleation, and make gold nano-shells on silica. However, another approach that has drawn great interest recently is the metallic nano rod [73] or metal nano-shell [74, 75]. Metal nano-shells are composite nanoparticles consisting of a dielectric core coated with a thin metal shell. The plasmon resonance of a metal nano-shell may be shifted throughout the visible and near infrared by varying the ratio of the core to the shell thickness [74, 75]. The properties of these particles can be distinctly different from those of individual

nanoparticles. They can possess unique size and length dependent optical and electronic properties, thereby making them of promise in technological applications such as photonic materials, surface enhanced Raman scattering, chemical and biological sensing.

When gold nano particles are used to cover the surface, the surface coverage is typically around 30% [76] in one step growth process. This surface coverage can be increased to be close to that of a close packed monolayer, if surface modified metal nano materials are used [77]. Although, the above strategy leads to uniform metal shell coating, they do not yield a dense packing of nano particles on the larger spheres. However, such surface coatings can prevent further growth of the deposited nanoparticles through, for example, electro-less plating. The ability to control the morphology and structure of the coatings through electro-less platings is particularly interesting in applications that require custom-made optical properties [78]. The surface coverage can be significantly increased by exploiting the adsorption behavior of charged ligand-gold nanoparticles into preassembled polyelectrolyte (PE) alternate layers on colloid structures [79]. It was also shown that these Au_{NP}/PE coated particles could be assembled into ordered arrays, which display tunable optical properties [80] depending on the gold nanoparticles loading, and potentially useful in drug delivery applications [67, 81].

One explicit side of the nanostructured materials is still unexplored, and not many published data is available with the core shell morphology of the nanotube. It is well known that the plasmon resonance absorption frequency is dependent on the size, shape, and material properties of the nanoparticles [68]. Hecht and coworkers studied poly (m- phenyleneethynylene), and they showed that poly (m- phenyleneethylene) is given the helical conformation by solvophobic interaction in polar solvent. Their high degree of uniformity makes them relatively easy to self –assemble into a uniform helical structure, and used as a core template to structure core-shell gold nanotube [55].

In summary, gold nano-shells can be prepared in many different ways, and they have many applications, which depend on the size, shape and materials of the shell. So far in our limited understanding, the tube type nano-shell is not yet explored. Furthermore, the development of new methods to prepare nanoparticles with tailored properties such as electrical, optical, electrochemical, magnetic, surface, etc. will be central to the exploitation of nanostructured tube. So, it would be worthwhile to prepare gold nano tubes and characterize them for their potential applications.

Conclusion

The controlled synthesis of discrete nanostructures is still an exciting challenge that remains the corner stone of the bottom-up approach. Over last decade, a large number of reports have been published, describing different ways of synthesizing and confirming the structure of nanotubes as mentioned above. There are a number of possible applications of synthetic nanotubes ranging from opto-electronics to medicine. As of today, the majority of nanoparticles used in medicinal applications mainly focus drug delivery to cure/treat various health problems. Due to that reason, many researchers have focused on the construction of simpler synthetic tubes for application as sensory materials for water, organic vapors, and explosives either by fluorescence quenching or in artificial nose devices, which change their conductivity upon exposure to a suitable analyte. Moreover, these synthetic tubes could use as tailored molecular reaction vessels, molecular sieves, or nanoscale fluidic transport systems, novel cytotoxic and controlled- release drug- delivery agents and material science applications including bio-mineralization and site isolation of chromophores or template for the construction of new materials.

Acknowledgements

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