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Molecular Interactions in Natural and Synthetic Self-Assembly Systems

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1. Introduction

Tailoring nature is a continuous rediscovered paradigm of scientific community despite of the so called 'independence of the artificial creations' of the new age of technology. The last century discoveries in terms of chemistry science achievements could be easily projected into a design of a perfect elliptic model in continuing creation related to report to nature: an imaginary circle which never close to its natural model, even those new circles became asymptotic smaller and smaller to the imaginary point of model.

Reverences are need to Nature for its ability of using very limited (few) materials to build all variety of forms of lives. Natural materials are self-generated, hierarchical organized, multifunctional, nonlinear, composite, adaptive, self-repairing and biodegradable.

The effort made by chemistry science community during the last century in development of new technologies and materials is enormous, if we are counting the total number of scientific publications only for the last 25 years, but the integration of the new developed theoretical concepts and theories into the body of classical chemistry science is not always keeping the rhythm, and became difficult to find a classical concept and a unitary theory able to explain the new achievements of research results.

Molecular principles of new discovered bio-inspired or bio-hybrid materials and technologies are the new goals of science and our research goes deeply into its creative base: molecules, atoms and sub-atoms world.

Biomimetics or bioinspiration are concepts which have a big dependence of the specialization and discipline: electronic community is using these principles in learning the way biological systems are processing information; biomedical engineers consider the principle as a means of engineering tissues which are natural materials; material scientists view the concept as the only tools available in learning to synthesize materials under ambient conditions and with less impact on environment.

2. Silafins and deoxyuridine, the smart molecules which act as transcriptors in bio-silicas

Marine organisms, including sponges and diatoms, can produce solid silica structures with organized nanoscale morphologies, at ambient and neutral pH using a templated enzymatic mechanism initiated and conducted by a peptide class of substances – silicateins.

Naturally occurring, biomolecular machinery provides excellent platforms to assemble inorganic nanoparticles and two major players are DNA and proteins. The molecular recognition or specific interaction also exists between proteins and DNA, such as transcriptional factors and operator segments of DNA (Mock et al., 2008). The information in living systems is received, stored and transmitted by means of the specific interactions of biomolecules. The accuracy and precision of such interactions can be proved by any creature on the earth.

The ability of using the direct available elementary silicon from see water for building cell walls composed of amorphous, hydrated silicon dioxide (silica) embedded with a specific small organic molecules (Field et al., 1998; Nelson et al., 1995) is the main function of these organisms. The silica-based patterns of nano-sized pores and other cell wall structures of diatoms are so detailed and precisely replicated in more than 105 to 106 species with distinguish taxonomies. Silica patterning in diatoms has been hypothesized to depend on both self-assembly transcription processes and controlled silica polymerization (Brzezinski & Nelson, 1996) by cytoskeletal interactions (Leynaert et al., 2001).

The ability of diatoms to manipulate silicon at the nanoscale exceeds that of human nanotechnology, making the genetic and biochemical underpinnings of biosilicification of great interest in material science.

Marine sponges and diatoms produce silica made skeletons consisting of individualized elements (spicules) of lengths ranging from micrometers to centimeters, which can subsequently fuse or interlock one another. They differ from a skeletal point of view in the number of symmetry axes of their megascleres (ex. monaxons and tetraxons in demosponges and monaxons and triaxons in hexactinellids). The high diversity of spicule shapes and sizes in both fossil and living sponges has been repeatedly reported (Cha et al., 1999; Croce et al., 2004; Field et al., 1998; Fuhrmann et al., 2004; Krasko et al., 2004).

The process of biosilicification in diatoms begins with the active transport of dissolved silicic acid from the aqueous environment into the cell. This is mediated by silicon transporters, or SITS, whose expression and activity also show tight regulation during the cell cycle (Kröger et al., 1996, 1997). Intracellular concentrations of dissolved silicon exceed the solubility of silicic acid (Kröger et al., 2002), suggesting ***the presence of an organic silicon complex*** that may maintain silicon in solution and shepherd it to the silicon deposition vesicle (SDV).

The secretion of spicules in Demospongiae occurs in intracellularly specialized cells, the sclerocytes, where silica is deposited around an ***organic filament*** (Kröger et al., 2002; Schröder et al., 2006). It should be noted at this point that silica is not only deposited in spicules, but also as ribbons in the nucleus (Schröder et al., 2008). The latter observation is interesting insofar as siliceous spikes show a variable size and shape suggesting that silica in those structures is subjected to a high turnover. If the formation of siliceous spicules is inhibited the sponge body collapses (Sumper & Kröger, 2004a). The synthesis of spicules is a rapid process; in *Ephydatia fluviatilis* a 100 mm long megasclere is formed within 40 h (Sumper, 2004b).

Inhibition studies revealed that skeletogenesis of siliceous spicules is enzyme-mediated (Shimizu et al., 1998; Sumper &Lehmann, 2006) process. The siliceous spicules contain a definite axial filament and their synthesis is genetically controlled (Pouget et al., 2007). Experimental evidence suggested that deposition of silica particles induces biological

reactions, most of them similar with that of collagen fibrillogenesis (Poulsen et al., 2003). A major step towards elucidating the formation of siliceous spicules at the molecular level was the finding that the formerly termed `axial organic filament' of siliceous spicules is in reality an enzyme, silicatein, which mediates the apposition of amorphous silica and hence the formation of spicules (Patwardhan et al., 2005; Perry & Keeling-Tucker, 2000). These studies have been performed with the demosponge *T. aurantia*. In contrast to the formation of collagen fibrils disconnected from the synthesis of spicules, those collagen polypeptides which are formed in connection with the silicification are produced in sclerocytes and exopinacocytes (Sumper, 2004b). The sclerocytes secrete the axial filaments, while the exopinacocytes secrete the collagen-like spongin, which functions as an organic sheath around the spicules (Krasko et al., 2000; Menzel et al., 2003).

Long-chain polyamines and phosphoproteins known as silaffins are the only diatom molecules thus far shown to have a direct impact on silica precipitation *in vitro*, with the resulting pore sizes of the formed structures determined by relative proportions of polyamines and silaffins (Cha et al., 1999; Croce et al., 2004; Field et al., 1998; Fuhrmann et al., 2004; Leynart et al., 2001). Diatom transporters have been sequenced and characterized and have been shown to interact directly with silicon to actively transport silicic acid against a large concentration gradient, although the mechanism for intracellular storage of soluble silicic acid is not known (Kröger et al., 1996; 1997).

The elegant work performed by the group of Morse clarified that the axial filaments around which silica is deposited are composed of the enzyme silicatein (Morse, 1999). In that study the silicatein cDNA was isolated from the sponge *S. domuncula* and was found to be closely related to the *T. aurantia* silicatein. As reported earlier (Sumper & Kröger, 2004a) silicatein is closely related to the enzyme cathepsin L. The phylogenetic analysis of the two sponge silicateins shows that they branched off from a common ancestor with the cathepsin L molecules prior to the appearance of sponges. This finding could imply that animals which evolved earlier than sponges already contained silicatein. As silicatein has not been identified in other metazoan phyla it has to be concluded that this gene has been lost during the evolution from sponges to the invertebrate and vertebrate phyla.

Recently it has been shown that the recombinant silicatein catalyzes the reaction of tetraethoxysilane to silica and silicone (Boyd, 2007). The data presented indicate that together with the induction of the gene expression for the axial filament/silicatein which leads to the initial process of spicule formation, the collagen gene is expressed in parallel and in a second cell (Shimizu et al., 1998). Based on inhibition studies it could be demonstrated that the formation of siliceous spicules can occur in the absence of the synthesis of such collagen polypeptides which form the perispicular spongin sheath (Sumper & Lehmann, 2006). This finding suggests that the expression of collagen is not directly connected with the formation of the siliceous spicules.

Silicateins are unique enzymes of sponges (phylum Porifera) that template and catalyze the polymerization of nanoscale silicate to siliceous skeletal elements. These multifunctional spicules are often elaborately shaped, with complex symmetries and together with a protein silintaphin-1, seem to guide silica deposition and subsequent spicular morphogenesis.

There are some incipient studies, both in biochemistry and synthetic chemistry assisted by different *in vivo* or *in situ* characterization techniques dealing with the mechanism revealed.

The results indicate that silicatein-α-mediated biosilicification depends on the concomitant presence of silicatein-α and silintaphin-1. Accordingly, silintaphin-1 might not only enhance the enzymatic activity of silicatein-α, but also accelerate the nonenzymatic polycondensation of the silica product before releasing the fully synthesized biosiliceous polymer (Kröger et al., 1996; 1997; 2002).

Little is known about the course and the control of spicule development, in either marine and freshwater sponges, besides electron microscopic studies, light microscopic investigations using sandwich cultures have been performed to study the spicule. The formation of spicules starts in sclerocytes within a specific vesicle. After the production of an axial organic filament, silicon is deposited around it, and the whole process of forming a spicule (190 µm in length and 6 to 8 µm in diameter) is completed after 40 h, at 21° C. The main actor in templating this mechanism seems to be deoxyuridine, a nucleoside type compound.

Recent works of Prof. Christopher F. van der Walle (Fairhead et al., 2008) show that silicatein α exists into its predominantly β- sheet structure. This conformational structure is produced in a soluble form with mixed α-helix/β-sheet structure akin to its cathepsin L homologue. Conformational transition studies found that β- sheet intermediate structure for silicatein α in marine sponge spicules represents a stable structural intermediate for silica formation process in spicules (Fig. 1).

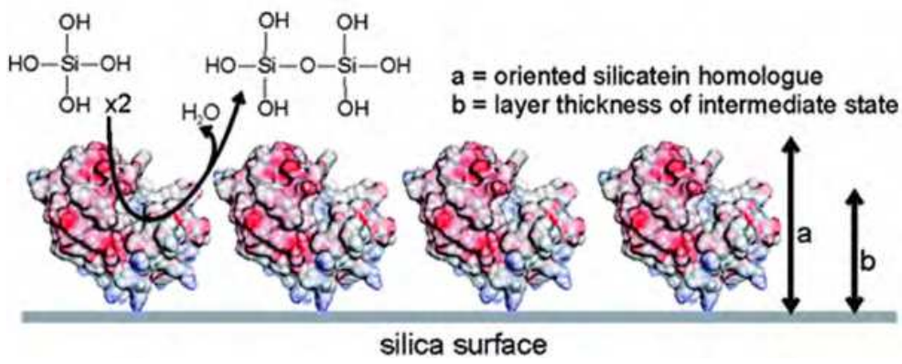


Fig. 1. Illustration of intermediate structure for silicatein α in marine sponge spicules

Very recently (Li et al., 2011) a new nucleoside derivative has been identified and characterized, named 3-acetyl-5-methyl-2′-deoxyuridine (**1**), along with two known compounds 3,5-dimethyl-2′-deoxyuridine (**2**) and 3-methyl-2′-deoxyuridine (**3**), isolated from the cultures of *Streptomyces microflavus*. This strain was an associated actinomycete isolated from the marine sponge *Hymeniacidon perlevis* collected from the coast of Dalian (China).

Sequence analysis of silicatein α showed that the protein was very similar to the human hydrolase, cathepsin L. It was later proven by site directed mutagenesis that silicatein α is a serine hydrolase (Cha et al., 1999; Shimizu et al., 1998). The active site of silicatein α consists of a hydrogen bond that is formed between a histidine and a serine residue. It is proposed that this hydrogen bond between the hydroxyl group of the serine and the imidazole group of the histidine increases the nucleophilicity of the serine residue and thus allows it to catalyze the hydrolysis of silica precursors (Figure 2). Hydrolysis of silica in proximity of the

proteins leads to the proteins themselves acting as templates for the condensation of silica. The silicification process of this marine sponge serves as an excellent model for biomimetic inorganic materials due to its relatively simple idealized reaction mechanism and mild reaction conditions.

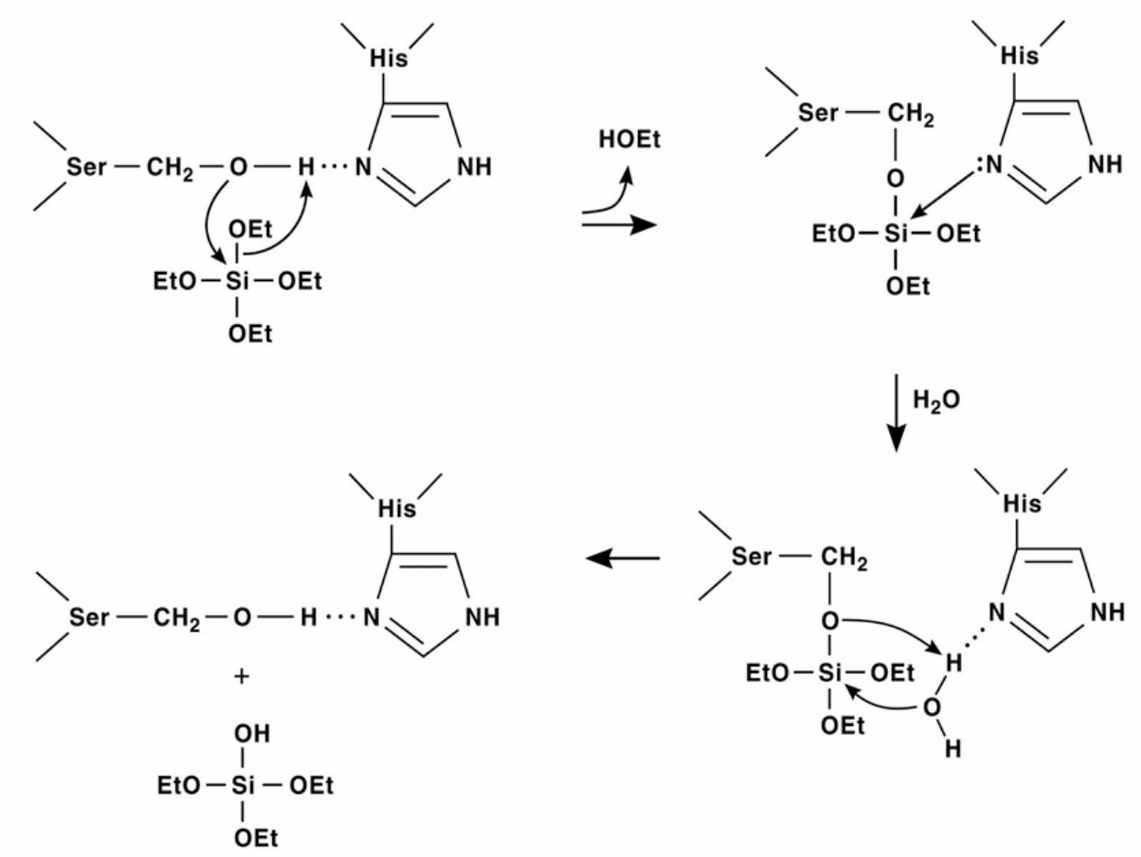


Fig. 2. Proposed hydrolysis reaction of TEOS in the active site of silicatein α (Zhou et al., 1999)

Moreover, the studies using biocatalytical active recombinant silicatein showed that silica formation in sponges is an enzymatic process (Krasko et al., 2000; Schröder et al., 2006). Furthermore, recent studies confirmed the mechanism of self-assembly of silicatein monomers to oligomers and long protein filaments (Croce et al., 2004; Croce et al., 2007; Murr & Morse, 2005;). The results from SAXS examination indicated that the axial filament is formed from a very high degree of organization (hexagonal) of the protein units (Croce et al., 2004; 2007). Müller and coworkers found that silicatein is present not only in the axial filament but also on the surface of the spicules (Müller et al., 2006), supporting the view that growth of spicules occurs through apposition of lamellar silica layer with a distance of 0.2-0.5 µm from each other (Müller et al., 2005).

Using milder extraction conditions (a slightly acidic, aqueous ammonium fluoride solution), native silaffins (termed natSil) have been isolated from *C. fusiformis.* (Kröger et al., 2002).

A complex approach in systematizing this theoretical information will have a significant added value in understanding and developing bio-inspired or bio-similar synthesis. Tailoring nature is the target of this century, so called smart molecules acting as real transcriptors in bio-silica synthesis.

The biomimetic silicatein systems that have been investigated so far have all been able to produce silica at higher rates than reactions without both the nucleophilic and the hydrogen bond donating groups; however, they have not been able to approach the hydrolytic activity of silicatein. It is clear that any biomimetic silicatein system needs to have a structure that can template the condensation, both a nucleophilic and cationic group need to be within hydrogen bonding distance of one another, and they need to have many more active sites per volume to have any chance at replicating the synthesis ability of the native protein. Such a system that could meet all of these requirements is based on peptide amphiphile micelles.

These biomimetic and bioinspired systems could be considered in the same manner as theoretical steps in explaining the mechanisms involved in real biological organisms and as simplified models in new approaches of modern synthetic chemistry. Using concepts and definitions from genetic molecular transcription mechanism we translated those principles to synthetic chemistry as follows:

1. the existence of a "template" unit for initiation of construction process which is not only a complementary building bloc but also having energetic and conformational complementarily as those involved into RNA complementary copy of DNA molecules;
2. decoding of structural information during hole synthesis process which allows the ordered silica network formation, by specific steric effects and similar enzymatic control;
3. the existence of a surface specific intermediary complex stabilized at the silica surface with minimum of kinetic energy involved;
4. the involvement of a hydrogen bonding and electrostatic effects.

During the silica synthesis process in diatoms have been already identified the deposition of silica around an organic filament into sclerocytes cells, those organic filaments partial identified as a complex of proteins. Using the identified proteins, especially cathepsin L. many successfully studies have been conducted in biomimetic silica synthesis as already presented.

Numerous approaches attempt to mimic and derivatize biomineralization processes, including poriferan biosilicification, in order to develop novel biomedical and biotechnological applications (Field et al., 1998). In conducting such studies it was imperative to identify silicatein-binding proteins required for pattern formation. Wiens et al. (2009) described the discovery of silintaphin-1, a unique protein that directs the assembly of silicatein filaments by forming a silicatein-binding scaffold/backbone. They shown that silintaphin-1 also interacts with silicatein that had been immobilized on functionalized g-Fe_2O_3 nanoparticles, thus directing the formation of a composite with distinct rod-like morphology. The resulting hybrid biomaterial combines the unique properties of magnetic iron oxide nanoparticles, a silica-polymerizing enzyme, and a cross-linking protein.

3. Comparison between structural and electronic effects induced by different classes of transcriptors in nano-silica

The silica-anabolic and silica-catabolic enzymes, silicatein and silicase are of extreme interest for a variety of applications in nanobiotechnology. Silica-based materials are widely used in industry and medicine. Therefore, the mechanism(s) underlying biosilica formation in the organisms are of high interest for the design, in particular on the nano-scale, of novel biosilicas to be used in nano(bio)technology.

The study of structural and electronic effects induced by different classes of transcriptors in nano-silica bio-inspired materials is the aim of this chapter, the theoretical aspects being sustained by a complex experimental survey.

Among biogenic minerals, silica appears rather singular. Whereas widespread carbonate and phosphate salts are crystalline iono-covalent solids whose precipitation is dictated by solubility equilibria, silica is an amorphous metal oxide formed by more complex inorganic polymerization processes. Biogenic silica has mainly been studied with regard to the diversity of the species that achieve this biomineralization process and at the level of diversity in the morphology of silica structures (Nelson et al., 1995). It is only recently that chemists turned their attention to the formation process.

Approaches that make use of current biological knowledge to investigate new chemical systems are certainly of great interest. Silica patterning in diatoms appears to rely on proteins that are able to catalyze silicate polymerization and to act as templating agents through self-assembly process, therefore synthetic models that exhibit both properties have been designed.

Cha *et al.* (2000) have synthesised a series of block copolypeptides of cysteinelysine that have the ability to mimic silicatein (a protein found in the silica spicules of the sponge *Tethya aurantia*). The synthesized block copolymers provide the first example of polymers which can hydrolyse and condense an inorganic phase (tetraethoxysilane) and also provide a template in the process. They were able to produce hard mesoporous silica spheres and assemblies of columnar amorphous silica. The same authors determined the specific conditions under which the columnar structures were stabilized and also elucidated the mechanisms involved in hydrolysis and condensation of the inorganic phase. The studies have attracted attention since the inorganic phase was produced from tetraethoxysilane under ambient conditions at a neutral pH.

The interaction of proteins with solid surfaces is not only a fundamental phenomenon but is also key to several important and novel applications. In nanotechnology, protein–surface interactions are pivotal for the assembly of interfacial protein constructs, such as sensors, activators and other functional components at the biological/electronic junction. Because of the great relevance of the protein–surface interaction phenomenon, much effort has been done into the development of protein adsorption experiments and models. The ultimate goals of such studies would be to measure, predict and understand the protein conformation, surface coverage, superstructure and kinetic details of the protein–surface interactions.

Sarikaya et al. (2003) have recently reviewed such molecular biomimetics, including a summary of 28 short peptide sequences that have been found to bind to solid surfaces ranging from platinum to zeolites and gallium arsenide.

Related ideas are explored in a recent review of the design of nanostructured biological materials through self-assembly (Zhang et al., 2002). In another study, biotinylated peptide linkers were attached to a surface *via* streptavidin to bind fibronectin in an oriented manner (Klueh et al., 2003). Such a material is then hoped to solicit a desired biological response (i.e. tissue integration). Perhaps the most exciting application is optical switching and modulation behavior based on proteins affixed to a substrate (Ormos et al., 2002).

There are different models proposed for explaining the protein transcription interactions under silica synthesis. Colloidal-scale models represent the protein as a particle and can accurately predict adsorption kinetics and isotherms. These colloidal-scale models include explicit Brownian dynamics type models (Oberholzer & Lenhoff, 1999; Oberholzer et al., 1997), random sequential adsorption models (Adamczyk et al., 2002; 1990; 1994; Adamczyk & Weronski, 1997), scaled particle theory (Brusatori & Van Tassel, 1999; Van Tassel et al., 1998), slab models (Stahlberg & Jonsson, 1996) and molecular theoretic approaches (Fang & Szleifer, 2001; Satulovsky et al., 2000; Szleifer, 1997). Most of these approaches treat the electrostatics and van der Waals interactions between the colloidal 'particle' and the surface, and thus can capture dependencies on surface charge, protein dipole moment, protein size or solution ionic strength.

Several researchers are exploring detailed atomic representations of proteins. The earliest studies to use protein crystal structures to simulate the adsorption process assumed a completely rigid protein and calculated screened coulomb and Lennard–Jones interactions over all protein rotations and distances (Lu & Park, 1990; Noinville et al., 1995). In rigid atomistic models with electrostatic treatments it was found that a net positively charged protein (lysozyme) could adsorb on a positively charged surface, due to the nonuniformity of the charge distribution on the protein. The orientations of an adsorbed antibody on a surface using a united residue model, whereby each amino acid is represented by a group with averaged electrostatic and van der Waals interactions. Molecular dynamics (MD) was used to simulate 5 ns of multipeptides interacting with gold. Also, MD-based simulations were used to find minimal energy orientations and unfolding trajectories of albumin subunits on graphite.

Latour & Rini, (2002) determined the free energy of individual peptides (in the context of a protein) interacting with a self-assembly monolayer (SAM) surface as a function of distance. These parameterizations could be used in protein–surface energy calculations.

The results clearly support the view that

- the presence of a minimal number of the hydrogen-binding sites is indispensable for transcription of the self-assembled structure into silica network,
- the helicity of silica can be accurately transcribed from that of the template, and
- this method will be applicable for the efficient transcription of self-assembled superstructures into inorganic materials.

Therefore, a variety of superstructural silica materials such as double-helical, twisted-ribbon, single fiber and lotus-like structures are created by a template method with the aid of the hydrogen-bonding interaction of the oligomeric silica species in the binary gel systems. The amino group of added *p*-aminophenyl aldopyranosides in gel fiber acted as

the efficient driving force to produce novel structures of the silica nanotubes. The present system could be useful for transcription of various self-assembled superstructures into silica materials which are eventually applicable to catalysts, memory storage, ceramic filters, etc.

The building of complex structures is promoted by specific links due to the three-dimensional conformations of macromolecules, showing topological variability and diversity. Efficient recognition procedures occur in biology that imply stereospecific structures at the nanometer scale (antibodies, enzymes and so on). In fact, natural materials are highly integrated systems having found a compromise between different properties or functions (such as mechanics, density, permeability, colour and hydrophobia, and so on), often being controlled by a versatile system of sensor arrays. In many biosystems such a high level of integration associates three aspects: miniaturization, with the role to accommodate a maximum of elementary functions in a small volume, hybridization between inorganic and organic components optimizing complementary possibilities and functions and hierarchy.

Synthetic pathways currently investigated concern

- transcription, using pre-organized or self-assembled molecular or supramolecular moulds of an organic (possibly biological) or inorganic nature, used as templates to construct the material by nanocasting and nanolithographic processes;
- synergetic assembly, co-assembling molecular precursors and molecular moulds *in situ*;
- morphosynthesis, using chemical transformations in confined geometries (microemulsions, micelles and vesicles) to produce complex structures, and
- integrative synthesis which combines all the previous methods to produce materials having complex morphologies.

Self-assembling structures will be used to denote complex nano- or micro-structures such as protein aggregates, protein with lipid membranes, and certain intracellular organelles such as vesicles that form spontaneously from the constituent molecules in solution and that are thermodynamically stable. This does not apply to all structures, especially more complex aggregates, cells and organs. Such structures do not normally self-assemble spontaneously in solution, but are assembled step-by-step by energy requiring mechanisms of the cell or organ. Their maintenance also usually requires a continuous input of energy.

By using similar principles of self-assembly, it is now easy to reach to artificially construct 'biomimetic' structures in the laboratory.

Non-specific forces are those that arise between many different types of atoms, molecules, molecular groups or surfaces, and that can usually be described in terms of a generic interaction potential or force-function.

Specific interactions arise when a unique combination of physical forces or bonds between two macromolecules act together cooperatively in space to give rise to a (usually) strong but non-covalent bond. Because such specific interactions typically arise from a synergy of multiple geometric, steric, ionic and directional bonds they are also referred to as 'complementary', 'lock-and-key', 'ligand and receptor (LR)' and 'recognition' interactions.

4. Electronic enhanced effects in biomaterials

This section will identify all important mechanisms involved in bio-similar materials called "electron induced effects" as a part of complex understanding path in transferring key information from biology to smart materials.

Different classes of metallo-proteins in important life mechanism are presented, especially highlighting the spectacular and "strange" combinations which are not easy accepted by scientists, but having a huge potential in complex understanding of nature inspired solutions.

Vanadium is a biologically relevant metal, employed by a variety of organisms: it is in the active centre of two groups of enzymes, such as vanadate-dependent haloperoxidases and vanadium-nitrogenases. In addition, vanadium is accumulated by certain life forms such as sea squirts (*Ascidiaceae*) and *Amanita* mushrooms, e.g. the fly agaric. More generally, vanadium appears to be involved in the regulation of phosphate-metabolising enzymes also in plants and animals; the insulin-mimetic potential of many vanadium compounds (i.e. their anti-diabetic effect) is related to this action.

Such an example is **Vanabins** (also known as **vanadium-associated proteins** or **vanadium chromagen**), a specific group of vandium-binding metalloproteins found in some ascidians and tunicates (sea squirts). Vanabin proteins seem to be involved in collecting and accumulating this metal ion. At present there is no conclusive understanding of why these organisms collect vanadium, and it remains a biological mystery. It has been assumed that vanabins are used for oxigen transport like iron-based hemoglobin or cooper-based hemocyanin. From this point to a complex comparison of special relationship of this metal ion with oxygen at the level of bio- or other important chemical mechanisms, we are interested in presenting the electronic effects induced by a metallic center on the specific interest areas: biology, drugs, new material synthesis.

Vanabins are a unique protein family of vanadium-binding proteins with nine disulfide bonds. Possible binding sites for VO^{2+} in Vanabin2 from a vanadium-rich ascidian *Ascidia sydneiensis samea* have been detected by nuclear magnetic resonance study, but the metal selectivity and metal-binding ability of each site was not examined in detail.

Vanadium accumulated in the ascidians is reduced to the +3 oxidation state *via* the +4 oxidation state and stored in vacuoles of vanadocytes (Michibata et al., 2002). From the vanadocytes of a vanadium-rich ascidian, *Ascidia sydneiensis samea*, were isolated some vanadium binding proteins, designated as Vanabin. Recently, five types of Vanabins have been identified, Vanabin1, Vanabin2, Vanabin3, Vanabin4 and VanabinP that are likely to be involved in vanadium accumulation processes as so-called metallochaperone. Multi-dimensional NMR experiments have revealed the first 3D structure of Vanabin2 in an aqueous solution which shows novel bow-shaped conformation, with four α-helices connected by nine disulfide bonds (Hamada et al., 2005). There are no structural homologues reported so far. The 15N HSQC perturbation experiments of Vanabin2 indicated that vanadyl cations, which are exclusively localized on the same face of the molecule, are coordinated by amine nitrogens derived from amino acid residues such as lysines, arginines, and histidines, as suggested by the EPR results (Fukui et al., 2003).

Under physiological conditions, vanadium ions are limited to the +3, +4 and +5 oxidation states. When vanadate ions (V^{V}) in the seawater are accumulated in the ascidians they are firstly reduced to (V^{IV}) in vanadocytes and then stored in the vacuoles where (V^{IV}) is finally reduced to the +3 oxidation state.

Vanabin2 is selectively bound to V(IV), Fe(III), and Cu(II) ions under acidic conditions. In contrast, Co(II), Ni(II), and Zn(II) ions were bound at pH 6.5 but not at pH 4.5. Changes in pH had no detectable effect on the secondary structure of Vanabin2 under acidic conditions, as determined by circular dichroism spectroscopy, and little variation in the dissociation constant for V(IV) ions was observed in the pH range 4.5-7.5, suggesting that the binding state of the ligands is not affected by acidification. These results suggest that the reason for metal ion dissociation upon acidification is attributable not to a change in secondary structure but, rather, is caused by protonation of the amino acid ligands that complex with V(IV) ions.

Numerous *in vitro* and *in vivo* studies have shown that vanadium has insulin-like effects in liver, skeletal muscle, and adipose tissue (Fukui et al., 2003; Hamada et al., 2005; Michibata et al., 2002). Vanadium at relatively high concentrations *in vitro* and *in vivo* inhibits phosphotyrosine phosphatases (PTPs), thus enhancing insulin receptor phosphorylation and tyrosine kinase (IRTK) activity. However, some studies have demonstrated that vanadium can stimulate glucose uptake independently of any change in IRTK activity, suggesting that there are additional mechanisms for its insulin-mimetic effects. In liver, vanadium compounds have been reported to inhibit lipogenesis and gluconeogenesis and to stimulate glycolysis and glycogen synthesis. In skeletal muscle, vanadium augments glucose uptake, primarily by stimulating glycogen formation. Free oxygen radicals seem to be the key factors acting in a still unclear certain pathologic mechanisms as those presented with relation to vanadium. Vanadium compounds are relatively well known both as free oxygen radicals generators in some inorganic and bio-reaction mechanisms and as complex activators or inhibitors of many enzymes involved in carbohydrate or lipid metabolic pathways.

Special fluorescent properties of some encapsulated vegetal active substances, induced by vanadium sub-oxide species effect, used as co-activators have been considered as first step in evaluation of biocompatibility and biomimetic degree of some nano-materials using these effects induced by vanadium species in bio-systems. The key point for the design of new hybrids encapsulated materials is to extend the accessibility of the inner interfaces for including a new pre-designed vanadium complex able to remain bonded at the surface in the active bio-mimetic conditions and to transfer its electronic effect to the active reaction center. The nature of the interface or the nature of the links and interactions that the organic and inorganic components exchange has been used to design these hybrids.

5. Silica nanotubes – Fabrication and uses

Inorganic materials of nanometric size gained an increased interest for biomedical and biotechnological applications for drug/gene carriers, disease diagnosis and cancer therapy. Although organic structured materials as liposomes, dendrimers and biodegradable

polymers are still playing a key role in nanomedicine, especially due to safety reasons, recent findings regarding the relation between the surface functionalization of inorganic nanomaterials (*e.g.* carbon nanotubes) and biocompatibility (Sayes et al., 2006) have inclined the balance in favor of the later. Other advantages of inorganic nanomaterials are represented by availability due to facile synthetic pathways and the possibility to control shape and size. Inorganic nanomaterials present interesting optical, electrical and physical properties that may help to solve the problem of physical barriers of the cell and therefore to extend the biomedical applications. Finally, their variety of shapes, mesoporous nanoparticles, hollow spheres, nanotubes, offers the possibility to accommodate a large amount of drug/genes inside the pores or cavities that facilitate the control release providing a ”gate” whose opening may be triggered by physical or chemical stimuli. Encapsulation of biological material or drugs into inorganic nanoparticles or nanotubes provide an isolation from the environment and prevent hydrolytic degradation or aggregation (Son et al., 2007) and has the potential to enhance drug availability, reduce its toxicity and enable precision of drug targeting. Drug - delivery to desired physiologic targets is influenced by many anatomic features as the blood brain barrier, branching pathways of the pulmonary system, the tight epithelial junctions of the skin, etc. (Hughes, 2005). Optimum dimensions for the carriers (inorganic or organic) are established: for example the greatest efficacy for delivery into pulmonary system is achieved for particle diameters ~100nm (Courrier et al., 2002). Particles around 50-100 nm in size provide a greater uptake efficacy for gastrointestinal absorption (Desai, 1996a) and transcutaneous permeation (Hussain et al., 2001).

Silica based nanostructured materials were successfully involved as nanocontainers in drug-release applications due to their biologically stable shell surfaces which are slightly hydrophilic. The blood plasma proteins called opsonins absorb onto the particles with hydrophobic surfaces acting as binding enhancer for the process of phagocytosis and the entire system is cleared by the immune system.

Spherical silica nanoparticles with ordered pore structure, MCM type, were synthesized using microemulsion method or by template sol-gel technique using a large variety of structure directing agents, from the common cetyltrimethylamoniumbromide (CTAB) to more complex systems, nonionic surfactants and amphiphilic polymers (Bagshaw et al., 1995; Beck et al., 1992a; Botterhuis et al., 2006; Kresge et al., 1998; Vallet-Regi et al., 2001; Zhao et al., 1998). Although they represent the large majority of silica based mesoporous materials involved in biomedical and biotechnological applications they present limited options in terms of surface modification especially when multifunctionality is required.

Therefore, in the last years, silica nanotubes, with their hollow core structure, ultralarge specific surface areas, very narrow inner pores and catalytic surface properties were considered as attractive alternatives for some applications which require multifunctionality because they present two surfaces with hydroxyl groups (inner and outer) easy to tailor with different functional groups using commercial silane derivatives. By changing the nature of the interior of the nanotube or the outer surface, specific biomolecules for host-guest reactions may be attached onto the surface and the interiors can be loaded with hydrophobic drugs. Multifunctionality may be also achieved by loading and/or coating with superparamagnetic particles and fluorescent molecules necessary for different imaging techniques used in diagnosis.

5.1 Preparation of silica nanotubes by sol-gel polycondensation mediated by organogelators

Templating methods based on fibrous organogels (or hydrogels) represent versatile chemical strategies to prepare nanofibrous materials exhibiting a large variety of morphologies (such as tubes, fibers, rods, ribbons, belts and helices). From the first reports of Shinkai group (Van Bommel et al., 2003a; Jung & Shinkai, 2004b; Jung et al., 2001c; Jung et al., 2000d; Tamaru et al., 2002e) the strategy was successfully employed and the reported experimental data are summarized and discussed in excellent reviews (Jung et al., 2010; Yang et al., 2011; Llusar & Sanchez, 2008).

Low molecular mass organic molecules capable of forming thermoreversible physical (supramolecular) gels at very low concentrations (ca. 10^{-3} mol dm^{-3}, typically lower than 2% w/w) in a wide variety of organic solvents have attracted in the last twenty years considerable interest, an impressive and steadily growing number of gelator molecules are synthesized and characterized in the literature (Banerjee et al., 2009; Sangeetha & Maitra, 2005; Terech et al., 1997; Weiss & Terech, 2006). An organogelator is capable of self-organizing into finely dispersed anisotropic aggregates (nanofibers) by noncovalent interactions such as hydrogen bonding, van der Waals, π-π -stacking, electrostatic and charge-transfer interactions. Noncovalent crosslinks among the nanofibers and/or mechanical entanglements create a three-dimensional network which includes the solvent and so gelation occurs. Upon gelation, the organized self-assembly of these molecules results in the formation of highly anisotropic 3-D structures, mostly in the shape of fibers, but also as ribbons, platelets, tubular structures, or cylinders. The network is commonly destroyed by heating but is reformed on cooling thus rendering the system thermoreversible.

A classification of the existing organogelators could be made according to several different criteria (Llusar & Sanchez, 2008):

a. *chemical nature* – main structural scaffold – cholesterol-, amide-, urea-, amino-acid-, peptide-, cyclohexane-, sugar- based organogelators.
b. *level of complexity of their structure* - organogelators with one, two or more heteroatoms, two-component and hybrid.
c. *type of supramolecular forces involved in their self-assembly into fibrous networks* - H-bonding, van der Waals, hydrophobic/solvophobic, aromatic or π-π stacking, electrostatic/ ionic, charge transfer coordinating bonding, or usually a combination of some of them.
d. *fibrous morphologies of their **S**elf-**A**ssembled **Fi**brous **N**etworks (SAFINs)*- fibrous, twisted or helical, ribbonlike, hollow fibers or tubular, lamelar, vesicular, etc.
e. *structural element or motif enabling an efficient transcription for template synthesis* - covalently or noncovalently attached positive charges, H-donating groups, coordinating or binding groups, etc.
f. *properties and applications* - polymerizable, liquid-crystalline or birrefringent, luminescent or fluorescent organogels, photoresponsive, metal-sensitive, etc.

A typical transcription procedure consists in catalyzed hydrolysis of a silica precursor - tetraethyl orthosilicate (TEOS) or other reactive silane derivative in an organogel formed

by the structure-directing agent and the reaction solvent. The hydrolysis of TEOS followed by the polycondensation of silicate around the gel fibril leads to a silica gel which is dried. The subsequent removal of the organic materials by washing with a suitable organic solvent or calcination yields porous silica. An efficient transcription of the gel fiber structure onto silica requires an effective interaction between the organogel fibers and silica precursor. Thus for sol-gel polycondensation in acidic conditions, when anionic silicate species are present in the system, organogelator should be either with cationic structure or doped with an appropriate amount of cationic analogue (Jung et al., 2000a; Jung et al., 2000b). Under basic conditions the H-bonding groups present on the gel fibrils can interact with the silica precursor and promote good transcription. In some cases the solvent used in the sol-gel polycondensation plaies an important role in the transcription process because the interactions gel fiber-silica precursor may be affected by silica-solvent and gelator-solvent interactions. The use of a long chain phosphonium salt as template in a protic solvent (ethanol) yielded only plate-like silica due to solvent ability to form H-bonds with silicate species, decreasing the strength of the silicate-template electrostatic interactions. The use of an aprotic solvent (benzene) yielded fibrous silica (Huang & Weiss, 2006).

The template synthesis of inorganic nanostructured materials through organogelator approach involves three main synthesis pathways:

a. *in-situ coassembly (IC)* – formation (upon cooling) of an organogel in the appropriate organic solvent and in the presence of the silicate oligomers (and controlled amounts of water and catalysts when necessary), which upon condensation gives rise to an inorganic siloxane-based gel consisting of organogel fibrils coated with partially condensed inorganic species. The organogel is removed either by washing or thermal procedures.

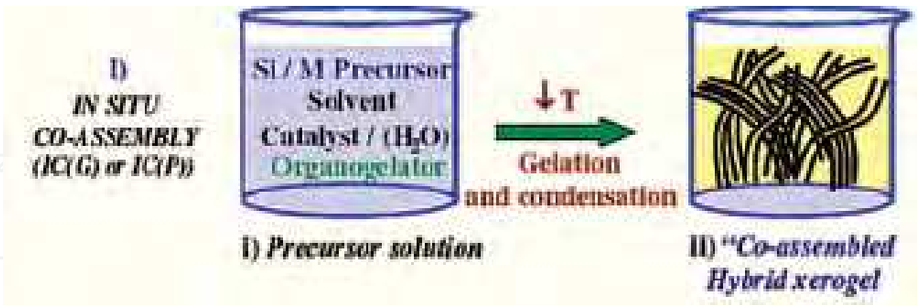


Fig. 3. Strategy for template synthesis of nanotubes mediated by organogelators *in-situ cossembly*. [Reprinted with permission from (Llusar & Sanchez, 2008), Copyright 2008, American Chemical Society]

b. *two-step simple post-transcription (PT)* – the preformed organic xerogel is subsequently impregnated or subjected to postdiffusion of solution of precursor together with water and catalyst in an appropriate solvent.

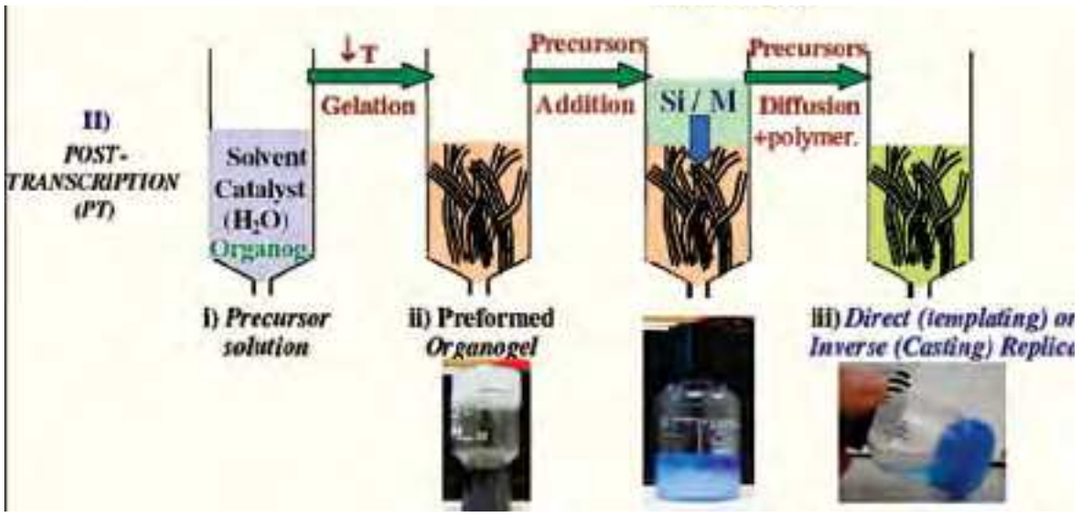
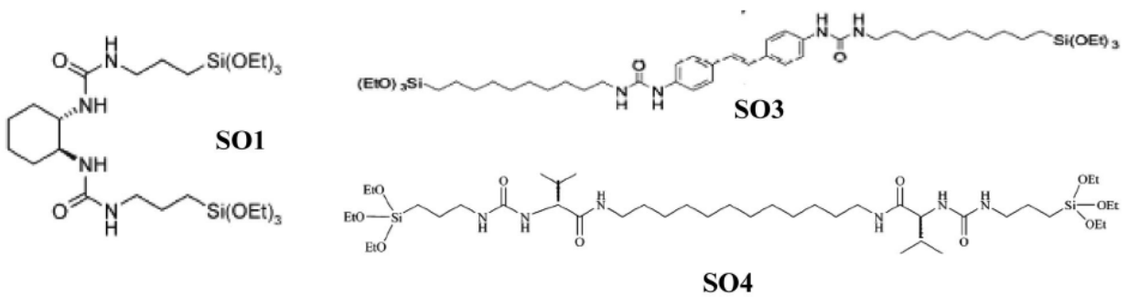


Fig. 4. Strategy for template synthesis of nanotubes mediated by organogelators post-transcription. [Reprinted with permission from (Llusar & Sanchez, 2008), Copyright 2008, American Chemical Society]

c. *self-assembly* (**SA**) process - hybrid **(**organic–inorganic) organogelators, in which the precursors of the inorganic species are already bonded to the organogelator molecules through covalent or coordinative bonds for example sylilated hybrid organogels.



For any strategy involved, the morphology of the resulted nanostructured materials depends upon a variety of factors: the type and concentration of the organogelator, the nature of the solvent, pH value, the use of certain additives, aging time and thermal treatment. In this way variety of silica nanotubes may be produced, such as single walled, double walled, helical, lotus and mesoporous structures.

Single-walled silica nanotubes

The first report on the fabrication of silica tubular structures using an organogelator as template was made by Shinkai group (Ono et al., 1998) involving two cholesterol based organogelators without and with cationic charges in acidic conditions.

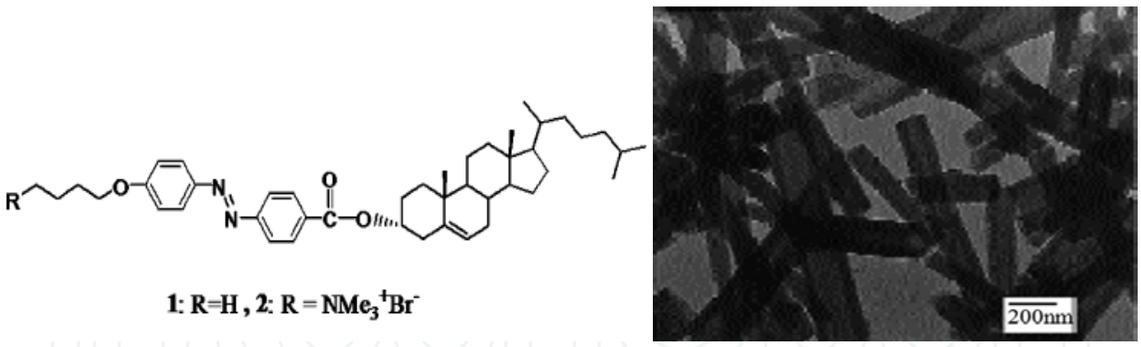


Fig. 5. TEM micrograph of the tubular silica obtained from organogel **2. [**Reproduced from (Ono et al., 1998) by permission of The Royal Society of Chemistry]

Analizing the morphology of the obtained materials using SEM and TEM microscopy, fibrous material with open cavities at tube edges of inner diameter 10-200 nm yielded for the charged template, while the neutral organogelator yielded only granular silica. This is the exemple of how the structure of the template and hence the interaction with silica precursor may influence the competition between the condensation of silica species in the bulk liquid (solution mechanism) and that onto the surface of organogel fibrils (surface mechanism) leading to silica tubes.

Lotus shape silica nanotube

A series of α- and β- glucose derived organogelators with benzene rings substituted with amino or nitro groups were synthesized and used as neutral templates for sol-gel polycondensation of TEOS in the presence of benzylamine as catalyst (Jung et al., 2000). The presence of the amino grup provides the necessary H-binding site that favors the transcription in neutral conditions.

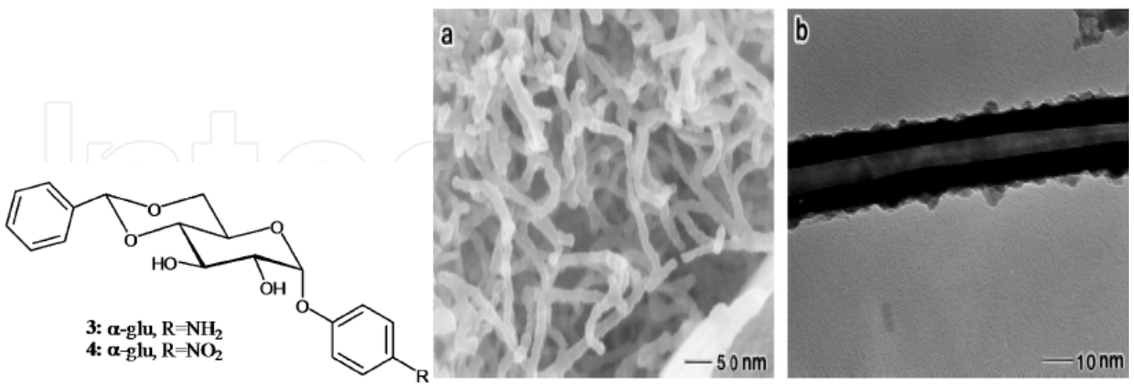


Fig. 6. SEM (a) and TEM (b) micrograph obtained from ethanol organogel **3** after calcinations. [Reproduced from (Jung et al., 2000) by permission of The Royal Society of Chemistry]

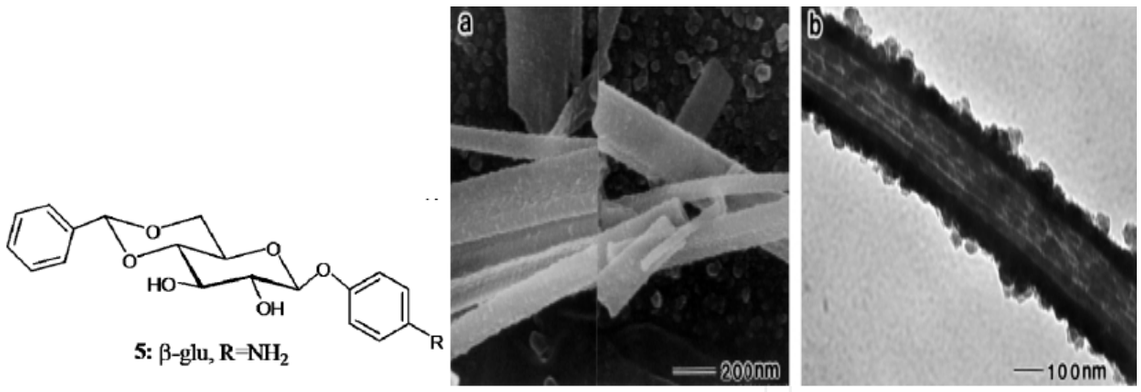


Fig. 7. SEM (a) and TEM (b) micrograph obtained from ethanol organogel **5** after calcinations. [Reproduced from (Jung et al., 2000) by permission of The Royal Society of Chemistry]

For all the amino substituted templates silica nanotubes were obtained: in the case of gelator **3** a tubular structure with a 20–30 nm outer diameter and 350–700 nm in length, and lotus shaped nanotubes of 50–100 nm inner diameters and 150–200 nm outer diameters composed of micro-tubes with diameters of 5–10 nm similar to the lotus root.

Double helical nanotubes

The importance of an appropriate amount of H-bonding sites on an organogelator fibril to achieve a good transcription is illustrated by the results reported by Jung et al. (2002) who associated a sugar-based gelator, **6** and an aminophenyl glucopyranoside **7**. The additional H-bonding sites provided by the amino-groups as well as π-π stacking of phenyl moieties suggested that the self-assembled superstructure in the gel obtained from de mixture of **6**+**7** was oriented into a more explicit chiral packing (Jung et al., 2002). That influenced the morphology of the xerogel obtained from 1:1 mixture in H_2O/MetOH, (10:1 v/v), as compare with that generated from pure gelator in the same mixture of solvents. Additional non-covalent bonds brought by the association of **6** and **7** transformed the 3-D network of bundles (20–500 nm) of partially twisted helical (left-handed) ribbons 20–100 nm width and ca. 315 nm pitch (Jung et al., 2001) observed for the xerogel of **6** into well defined several micrometer long double helical fibers with diameters of 3-25 nm and dimensions comparable to those of double-helical DNA and RNA structures (Jung et al., 2002).

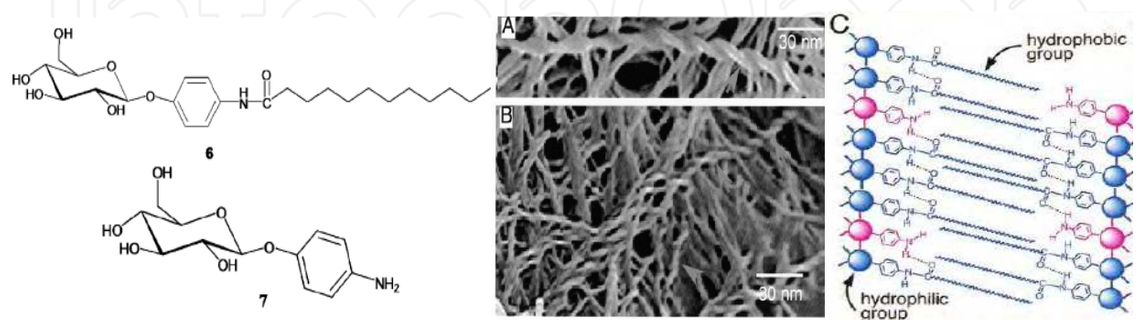
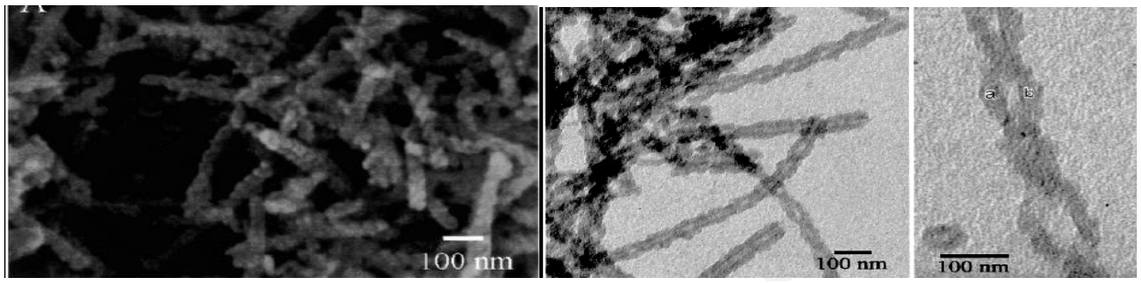


Fig. 8. (A and B) FE-SEM images of the xerogel prepared from the mixed gel of **6** and **7** (1:1 w/w) in H_2O/MetOH (10:1 v/v). (C) A possible self-assembling model in the bilayered chiral fiber from the mixed gel of **6** and **7.** [Reprinted with permission from (Jung et al., 2002), Copyright 2002, American Chemical Society]

Sol–gel polymerization of TEOS in a H_2O/MetOH (10 : 1 v/v) gel of **6** + 7 as a template produced a well defined double-helical nanotube with a diameter of 50-80 nm and a pitch of 50-60 nm as shown by SEM and TEM micrographs.



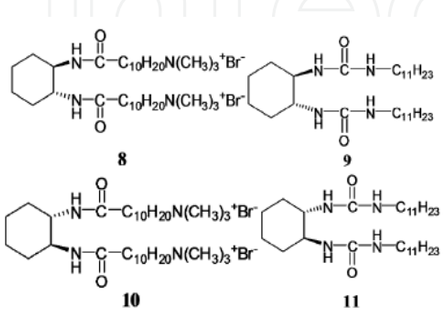
A B C

Fig. 9. (A) FE-SEM and (B and C) TEM images of the double-helical silica nanotube obtained from the mixed gel of **6** and **7** (1:1 w/w) after calcinations. [Reprinted with permission from (Jung et al., 2002), Copyright 2002, American Chemical Society]

The success of the transcription of the double-helical structure of the gel fibrils of **6** and **7** into silica nanotube structure may be explained by H-bonding between the amine moieties and negatively charged oligomeric silica particles. Transcription experiments with the mixture of compounds in different ratios revealed that for lower concentrations of the amino derivative **7** ([**7**/**6**+**7**]<0.2) only conventional granular silica was obtained, supporting the idea of a minimal number of H-binding sites indispensable for the template to achieve transcription.

Right-handed and left-handed single chiral silica nanotubes

Association of chiral neutral and cationic gelators derived from cyclohexanediamine **8-11** were used to fabricate right and left-handed chiralities in silica nanotubes (Jung et al., 2000) using electrostatic interactions. Cationic charge in organogelator is considered as indispensable in the polycondensation of TEOS but the ability to form gels was diminished by the positive charge. As in the case of H-binding sites there is a minimal ratio between charged and neutral gelators that ensures transcription of chirality. Thus, mixtures of urea based, neutral (*1R, 2R*)-**9** and amide-based cationic (*1R, 2R*)-**8** with molar ratios [8/8+9]=20-80% yielded right-handed helical silica structure with outer diameter of 90-120nm. The left-handed helical silica was fabricated with (*1S, 2S*)-enantiomers of gelators **10** and **11.**



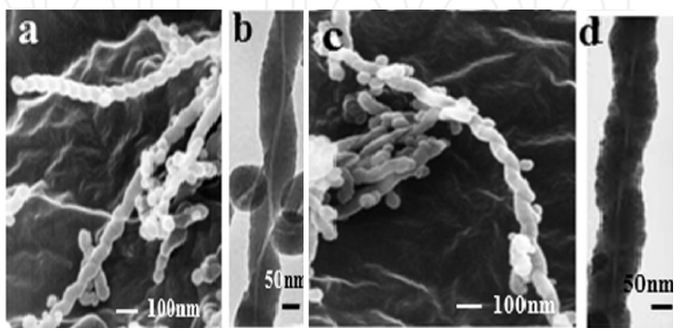
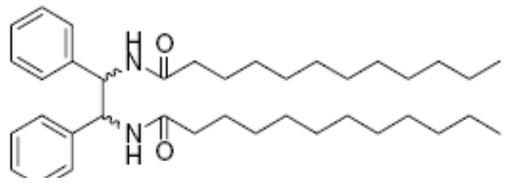


Fig. 10. (a and c) SEM and (b and d) TEM images of (a and b) the right-handed and (c and d) the left-handed helical silica nanotubes from organogels (a and b) **8+9** and (c and d) **10+11**. [Reprinted from (Jung et al., 2000) with permission from John Wiley and sons].

In a recent paper Hyun et al., (2009) suggested that each of the participants in the association has a distinct role in the transcription process: the neutral gelator **12** determines de shape of the organogel fibril and by consequence the shape of the silica nanotube, whilst the cationic amphiphile, **13** influences the polycondensation of TEOS after covering the surface of the organogel fibril formed by the neutral gelator (Hyun et al., 2009). For a better understanding of the mechanism for the transfer of helix and chirality to silica nanotubes Kim et al. (2011) performed crossover experiments: the neutral gelator (*1S, 2S*)-**12** was constant and the cationic amphiphiles varied from (*1S, 2S*)-**13**, (*1R, 2R*)-**13** and (±)-**13**.



*(1S, 2S)***- 12,** *(1R, 2R)*-**12,** and (±)-**12**

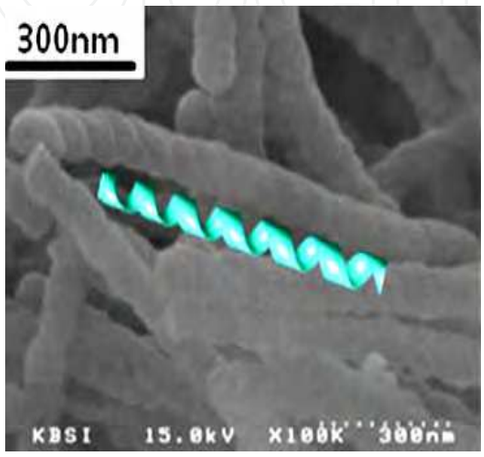
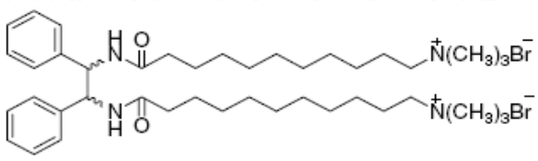


Fig. 11. SEM image of left-handed helical silica nanotubes obtained from the 1:1 mass mixture of (*1S,2S*)-**12** and (1S,2S)-**13**
[Reprinted with permission Editor-in-chief from (Kim et al., 2011)]



(1S, 2S)**- 13,** (1R, 2R)-**13,** and (±)-**13**

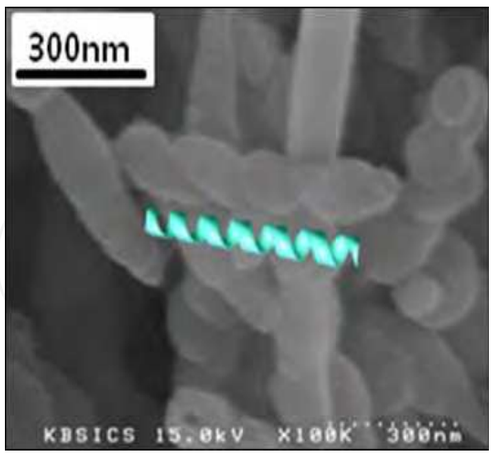


Fig. 12. SEM image of right-handed helical silica nanotubes obtained from the 1:1 mixture of (*1S,2S*)-**12** and (*1R,2R*)-**13**
[Reprinted with permission Editor-in-chief from (Kim et al., 2011)]

In all the experiments silica nanotubes with right-handed helical structure was obtained. Similarly when the neutral gelator (*1R, 2R*)-**12** was associated with enantiomers of cationic amphiphile **13** the resulting silica nanotubes were of a left-handed helical structure. Racemic

mixture of neutral gelator **12** associated with any of the stereoisomers of **13** yielded only non-helical silica tubes.

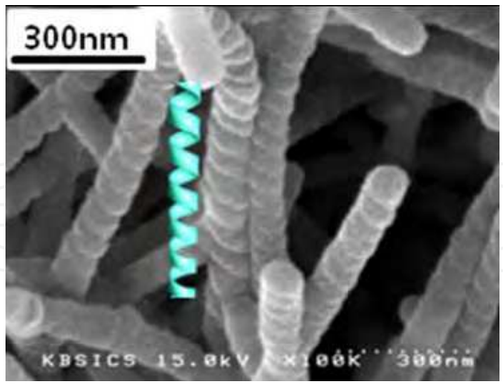


Fig. 13. SEM image of left-handed helical silica nanotubes obtained from the 1 : 1 mass mixture of (*1R,2R*)-**12** and (*1R,2R*)-**13**

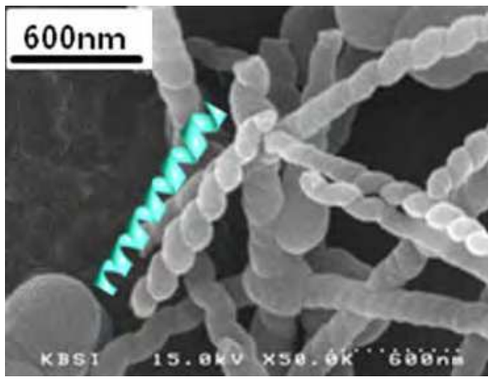


Fig. 14. SEM image of right-handed helical silica nanotubes obtained from the 1 : 1 mass mixture of (*1R,2R*)-**12** and (*1S,2S*)-**13**

The higher purity and yield of helical silica nanotubes obtained by association of diphenylethylenediamine derivatives **12** and **13** as compared with 1,2-cyclohexanediamine derivatives **8-11** may be explained by the existence of an effective π-π stacking interaction between the two phenyl groups essential to the self assembly process in the first case. As proved by the crossover experiments the association of neutral gelator and cationic amphiphile is essential for the hadedness of helical silica nanotubes which is controlled by the stereochemistry of the neutral gelator.

Double-walled silica nanotube

For certain amphiphiles with a polar head and a suitable chiral hydrophobic group self-assembly leads to aggregates with tubular structure generated by a helical ribbon. For exemple 30-crown-10-appended cholesterol gelator, **14** reported by Jung et al., (2001; 2003) with multiple binding sites (for acidic proton and cation, respectively) and two cholesterol skeletons which insure the necessary chirality of the aggregation, forms a tubular structure in the gel system probably generated by a helical ribbon as presented in the TEM image in figure 15.

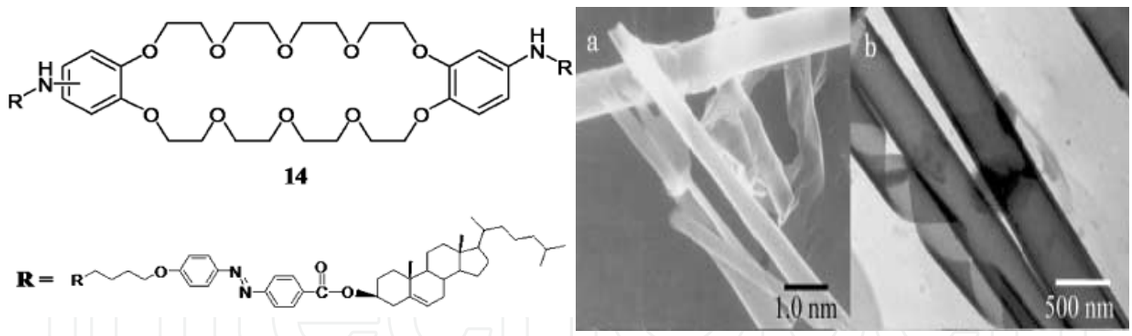


Fig. 15. SEM (a) and TEM (b) pictures of the xerogel **14** prepared from acetic acid. [Reprinted from (Jung et al., 2003) with permission from John Wiley and sons].

Sol-gel polycondensation of TEOS mediated by **14** in the presence of acetic acid yielded, after calcinations a right-handed helical ribbon structure 450-1500 nm width (Fig. 16) and a constant outside diameter of ~ 560 nm. A double layer structure was also observed with an interlayer distance of 8-9 nm (Fig. 16, c) which could be explained by the absorption of TEOS or oligomeric silica particles on both sides/surfaces of the organogelator tubules. Thus, after calcination, smaller cavities with layers of 8-9 nm were generated by the wall of the tubules formed by organogelator whereas the inner cavities with almost constant diameter were created the growth of the helical ribbon.

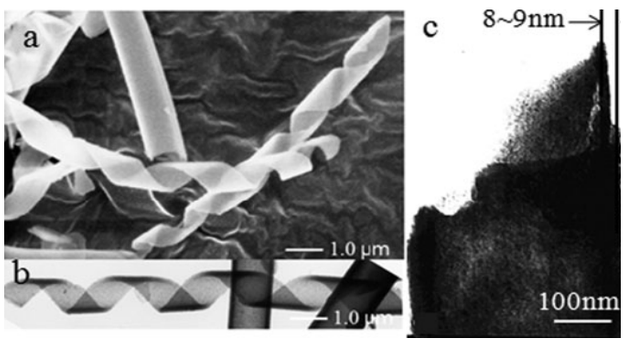


Fig. 16. (a) SEM and (b and c) TEM images of the double-walled silica nanotubes obtained from organogel 14. [Reprinted with Permission from (Jung et al., 2001), Copyright 2001, American Chemical Society]

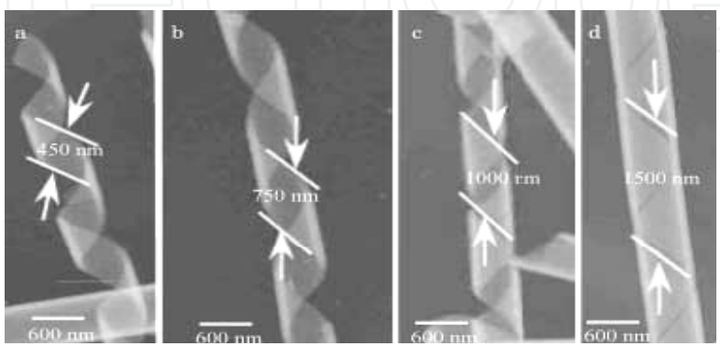


Fig. 17. TEM pictures (a, b, c, and d) of the silica obtained from the **14**- acetic acid gel after calcinations. [Reprinted from (Jung et al., 2003) with permission from John Wiley and sons]

Such materials, with helical higher-order morphology obtained by transcription of chiral assemblies created by weak intermolecular forces, are very useful as chiral catalysts (Sato et al., 2003).

Mesoporous-type helical silica nanofibers

Mesoporous – type helical silica nanofibers were fabricated by Hanabusa et al. using an amino-acid based chiral cationic hydrogelator **15** (Yang et al**.**, 2006). Sol-gel transcription performed in acidic conditions under a shear flow yielded a material consisting of 300 nm in diameter bundles of ultrafine right-handed helical silica nanofibers with 50nm diameters (Fig. 18 a). TEM analysis revealed that the nanofibers present mesoporous pores of 2nm (Fig. 18 b).

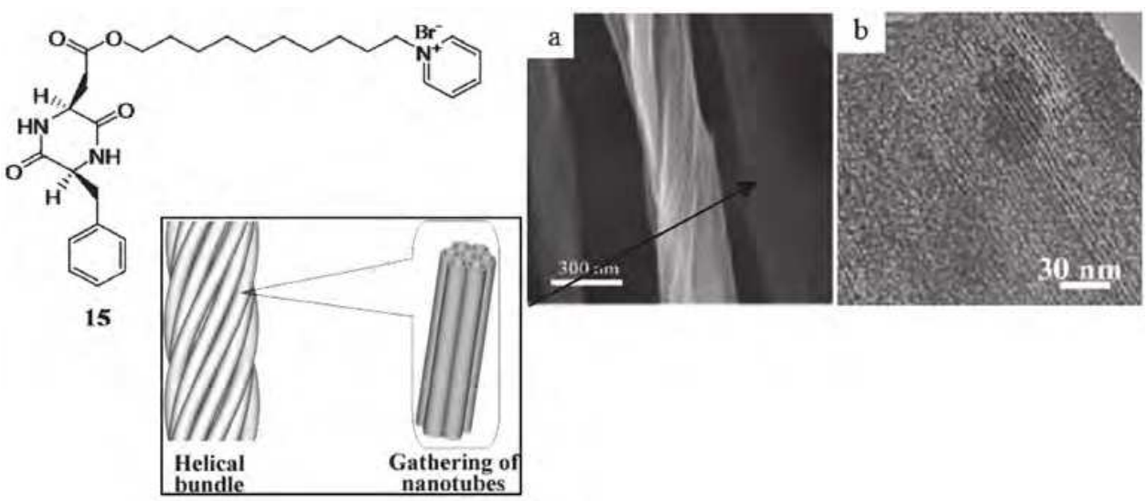


Fig. 18. (a) SEM and (b) TEM images of the right-handed helical silica nanotube with mesopores obtained from hydrogel 15. [Reprinted with Permission from (Yang et al., 2006), Copyright 2006, American Chemical Society]

Such hierarchical structure for the mesoporous silica nanofibers results from a particular formation mechanism: self- assembly of the chiral gelator **15** produces helical single strand gel fibrils on which the silica oligomers are absorbed and the sol-gel polycondensation of silica precursor begins on the surface. This process is parallel with the association of single strand gel-fibrils into multiple strand fibrils which are gathered in helical bundles. Alignment of the formed helical nanofibers is achieved under shearing, Fig. 19.

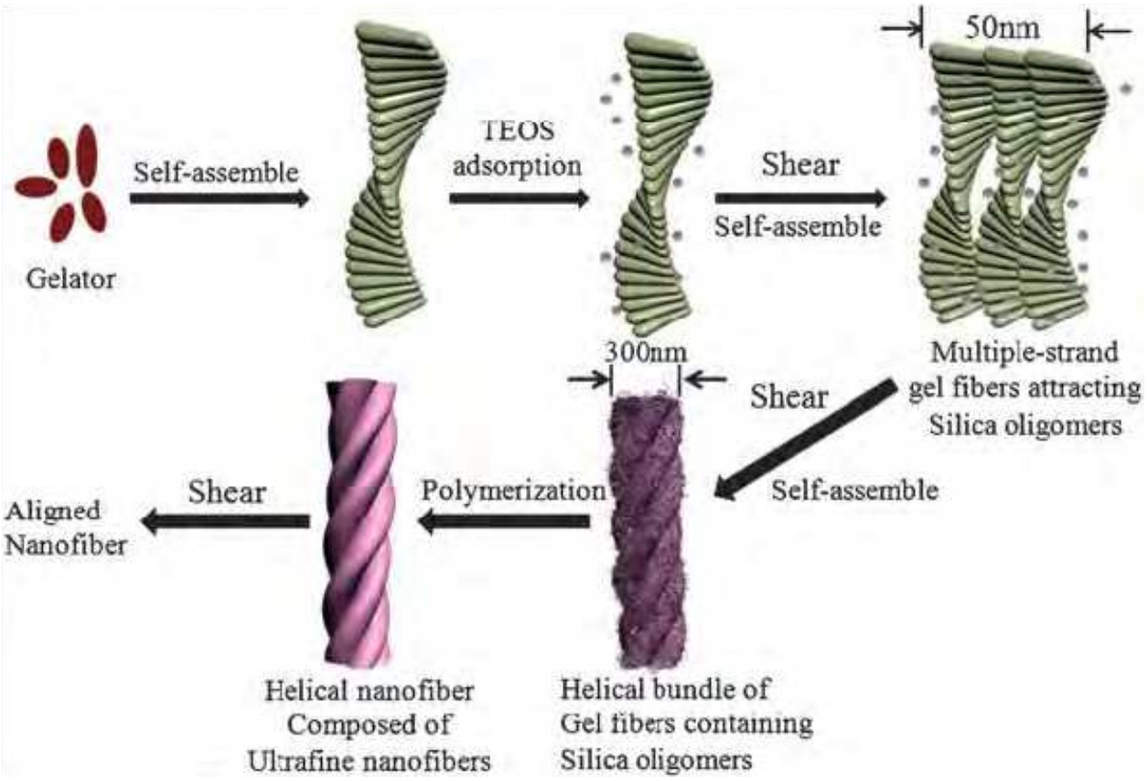


Fig. 19. Schematic representation of formation of mesoporous righthanded helical nanofibers and alignment. [Reproduced from (Jung et al., 2010) by permission of The Royal Society of Chemistry]

Mesoporous silica nanotubes

Hierarchiral silica nanotubes with radially oriented mesoporous channels perpendicular to the central axis of the tube were synthesized by sol-gel polycondensation of TEOS in the presence of the self-assembly anionic surfactant, partially neutralized carboxylate C14-L-AlaS, **16**, a co-structure directing agent, TMAPS (N-trimethoxysilylpropyl- N,N,N-trimethyl ammonium choride and acid catalysis at different molar ratios, C14-L-AlaS:TMAPS: TEOS: HCl: H_2O¼1:x:7:y:1780, (x= 0.1–0.5 ; y =0.3–0.6) (Yu et al., 2008).

SEM and TEM images (Fig. 20) for the calcined silica nanotubes revealed that tube diameter decreased with the degree of neutralization of surfactant **16** and silica tube wall thickness increased both with de degree of neutralization of **16** and the TMAPS/ surfactant molar ratio.

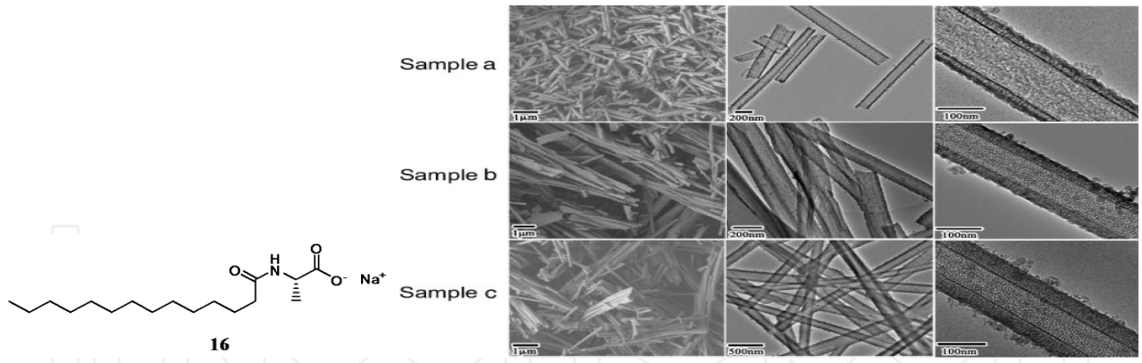


Fig. 20. SEM and (L-TEM and H-TEM images of the calcined mesoporous silica nanotubes synthesized with different degrees of neutralization of **16** (a and b) TMAPS/ surfactant molar ratio (b and c). [Reprinted from (Yu et al., 2008) with permission from John Wiley and sons]

The chiral surfactant has a helical supramolecular aggregation forming tubules with lamellar structured wall composed of several spring-like coiled bilayer structures (Fig. 21 a - c). On addition, TMAPS and TEOS can penetrate into both sides of the tubular cylinder assembly and create by re-assembly the mesoporous structure (Fig. 21 d, e).

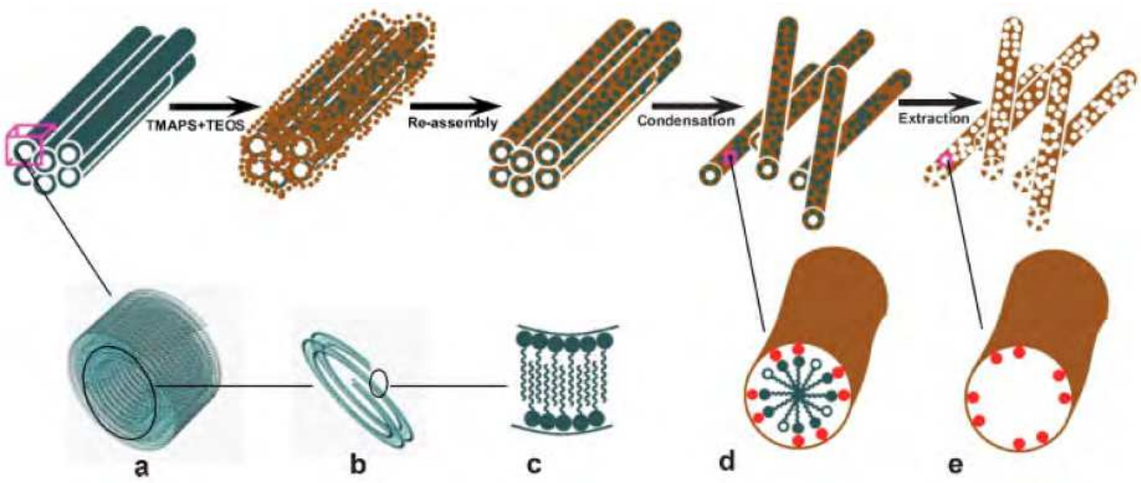


Fig. 21. Schematic illustration of the mesoporous silica nanotube formation process. [Reprinted from (Yu et al., 2008) with permission from John Wiley and sons]

5.2 Preparation of silica nanotubes using inorganic templates

Preparation of silica nanotubes using inorganic templates is based on two main classes of inorganic materials, porous inorganic membranes and inorganic materials, for example carbon nanotubes. Although the first method has limited versatility, especially for the synthesis of chiral materials, it provides the easiest way to control nanotube size and shape because benefits from the use of fabricated inorganic membrane templates with uniform in size cylindrical pores. The inorganic template synthesis of silica nanotubes was developed by Martin group (Hillebrenner et al., 2006; Kang et al., 2005; Martin, 1996; Mitchell et al., 2002) using porous alumina membranes and a sol-gel coating technique. Porous alumina

templates can be prepared by electrochemical anodization on aluminum plate, procedure established by Masuda and Fukuda (1995) and developed lately (Lee et al., 2006) with pore dimension ranging from five to a few hundred nanometers and length from tens of nanometer to hundred of nanometers depending on the anodization time, potential, electrolyte, etc. A (Fig. 22).

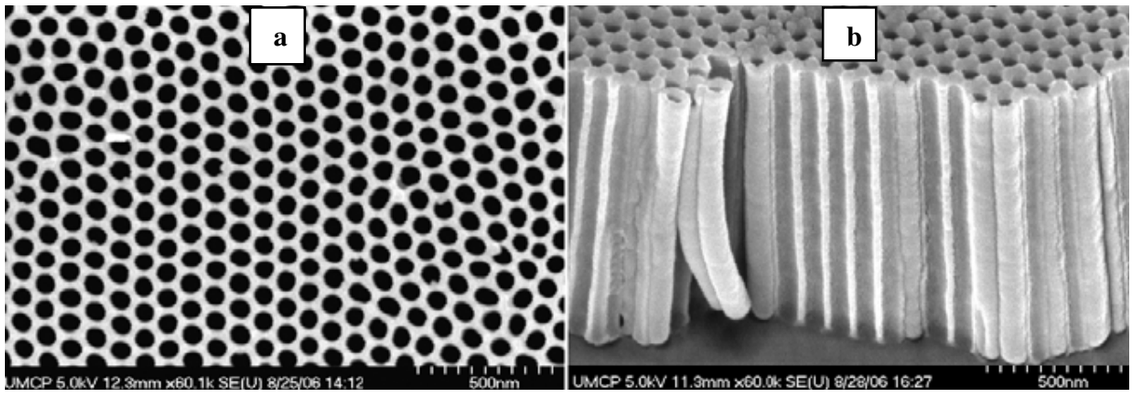


Fig. 22. Field emission scanning electron micrographs (FESEM) of home-made alumina template (60-nm diameter); (a) Top-viewed image and (b) cross-sectional viewed image [Reprinted from (Lee et al., 2006), Copyright 2007, with permission from Elsevier]

A typical template synthesis of silica nanotube using porous alumina membrane is presented in Fig. 23: in the first step thin layers of silica are formed by sol-gel chemistry onto the cylindrical walls of nanopores of the membrane, and then the top layers on both sides are removed by mechanical polishing. The alumina template is selectively dissolved in 25% phosphoric acid to liberate single silica nanotubes (free-standing nanotubes) which are collected by filtration. Thus, depending on the technical characteristics of the membrane as pore diameter and length and the extend of the sol-gel process tubules, test tubes or fibers may be obtained.

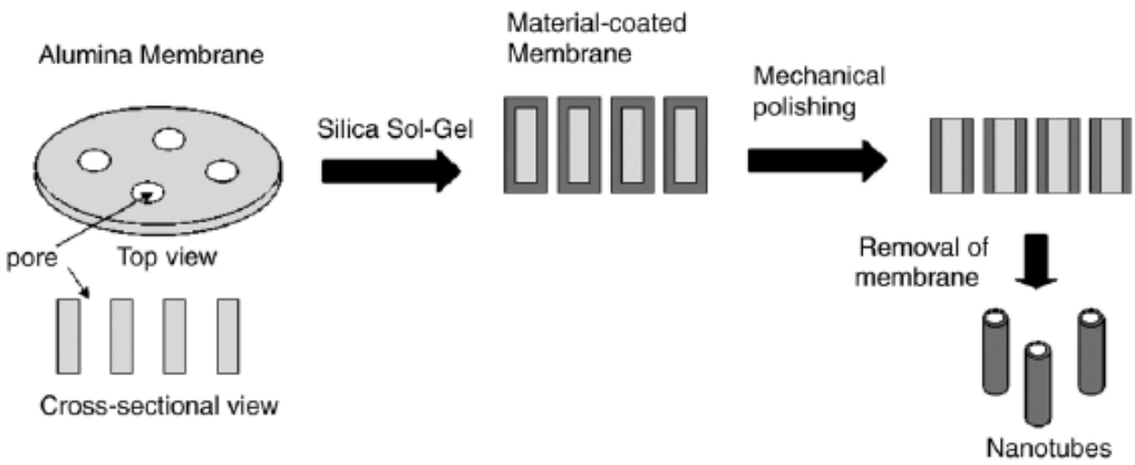


Fig. 23. Schematic illustration of template synthesis using a porous alumina membrane. [Reprinted from (Son et al., 2007), Copyright 2006, with permission from Elsevier]

Another advantage of the inorganic template synthesis of silica nanotubes is the possibility to apply, after the generation of nanotubes in the pores of the alumina template, an useful surface modification method called *diferential functionalization* of the inner and outer surfaces (Mitchell et al., 2002; Son et al., 2006; 2007) using silane chemistry (Fig. 24). The functionalization of the inner surface of the nanotube is performed selectively while still embedded within the pores of the membrane using different silane derivatives. The outer surface of the nanotube, in contact to the pore wall of the template is masked and protected. After dissolution of the template, the free outer surface is modified by a second functionalization.

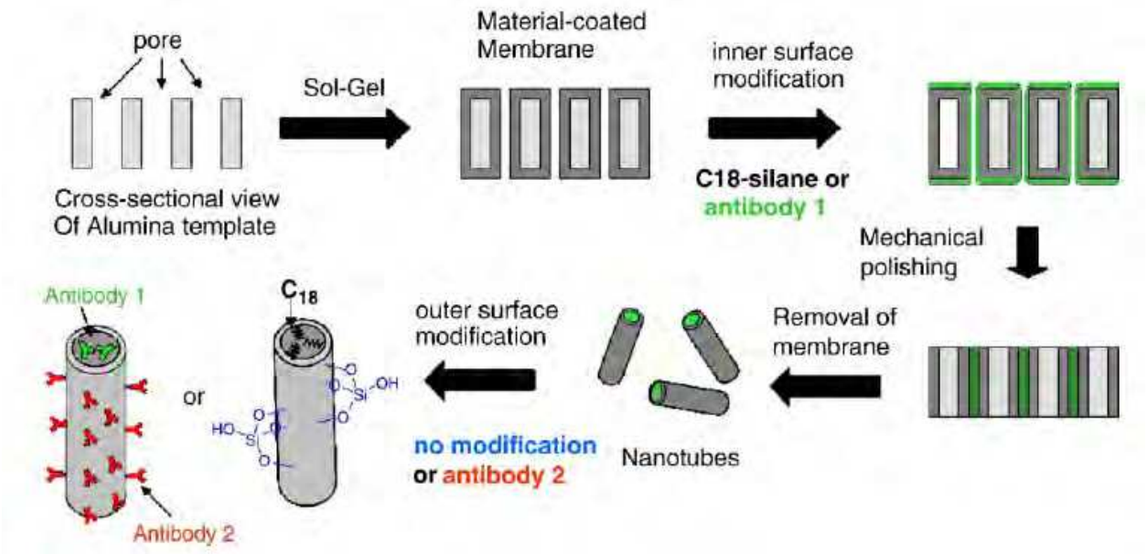


Fig. 24. Schematic of differential functionalization procedure for nanotubes obtained by inorganic template synthesis. [Reprinted from (Son et al., 2007), Copyright 2006, with permission from Elsevier]

Differentially functionalized nanotubes were used as smart nanophase extractors to remove molecules from solution: a hydrophilic outer surface and a hydrophobic inner cavity may be used for extracting lypophilic molecules from aqueous solution (Mitchell et al., 2002). A refinement of the method may lead to molecule-specific nanotubes when the surfaces are modified with enzymes, antibodies, etc. using an intermediate modification of the surfaces with aldehyde silane and attachment of the protein by reaction with free amino groups *via* Schiff base chemistry.

Magnetic silica nanotubes

Magnetic nanoparticles proved to be useful tools in drug-delivery systems, biosensors, different separation processes, enzyme encapsulation and contrast enhancement in magnetic resonance imaging (MRI). Differential functionalization of the spherical particles encounters technical difficulties because of a limited amount of reactive groups and the competition between the two reagents used to introduce different functionalities. This is why magnetic silica nanotubes can be an attractive alternative because they have all the previously described advantages of silica nanotubes-facile synthesis, differential functionalization of outer surfaces

with environment friendly and/or probe molecules to identify specific targets, a geometry that allows a high degree of loading with high amounts of the desired chemical or biological species inside – and the specific applications of magnetic particles for example as targeting drug delivery with MRI capability or magnetic field assisted chemical and biochemical separations (Son et al., 2005). Magnetic silica nanotubes have been synthesized by layer-by-layer deposition methods of preformed magnetite colloidal particles or molecular precursor onto the inner surface of pre-prepared silica nanotubes embedded in a porous alumina template. Another possibility is to perform "surface-sol-gel"(SSG) methods which involves a repeat of two-step deposition cycles, in which the absorption of molecular precursor and the hydrolysis (in the case of oxide film growth) are separated by a post-absorption wash (Kovtyukhova et al., 2003). In SSG procedure, in order to achieve high reproducibility and homogeneity, TEOS is replaced with silicon tetrachloride because its reaction with active hydroxyl groups from the alumina template or silica surface is fast and quasi stoichiometric. The SSG method is composed of multiple cycles of $SiCl_4$ treatment and hydrolysis process, each cycle adding ~1nm of silica on the surface. The layer of magnetite particles was generated after several cycles of silica deposition by dip-coating with a 4:1 mixture solution of 1M $FeCl_3$ and 2M $FeCl_2$, followed by treatment with aqueous ammonia (Son et al., 2006). Magnetic silica nanotubes were prepared by classical sol-gel procedure by polycondensation of TEOS mediated by a cholesterol-based gelato pre-impregnated with nickel acetate. After thermal treatment a reducing agent was used to mineralize Ni nanocrystals on the silica nanotube (Bae et al., 2008).

5.3 The use of silica nanotubes for biological applications

Facile synthetic pathways, the ability to control size and shape, including chirality and the possibility to functionalize the inner and outer surfaces of silica nanotubes in order to specifically accommodate different molecules and finally multifunctionality given by association with magnetic particles or fluorescent molecules enables us to affirm that silica nanotubes play an important and increasing role in biological sciences as drug delivery, imaging and screening, targeting and cell recognition, etc. Several recent examples of contributions made by silica nanotubes in biological sciences are presented in the following sections.

Recognition of protein containing cysteine groups

Magnetic silica nanotubes containing Ni were functionalized with mercaptopropyl-triethoxysilane in order to dope the surface with gold nanoparticles (Fig. 25) which specifically recognized proteins with cysteine groups (Bae et al., 2008).

The biomolecular recognition of Au-doped magnetic silica nanotubes (**Au-MSNT**) was verified by binding of glutathione S-transferase (GST) a protein containing cysteine groups and examination of selective binding of protein on the surface by an immunofluorescence method: anti–GST antibodies could bind specifically to GST on the surface of **Au-MSNT** and can be visualized by confocal microscopy after subsequent binding of fluorescent secondary antibodies (Fig. 26 A). The specificity of the interaction between **Au-MSNT** and cysteine was demonstrated by repeating the experiment with ubiquitin, a protein lacking cysteine from which no fluorescence was observed due to the impossibility to bind to the functionalized nanotubes (Fig. 26 B).

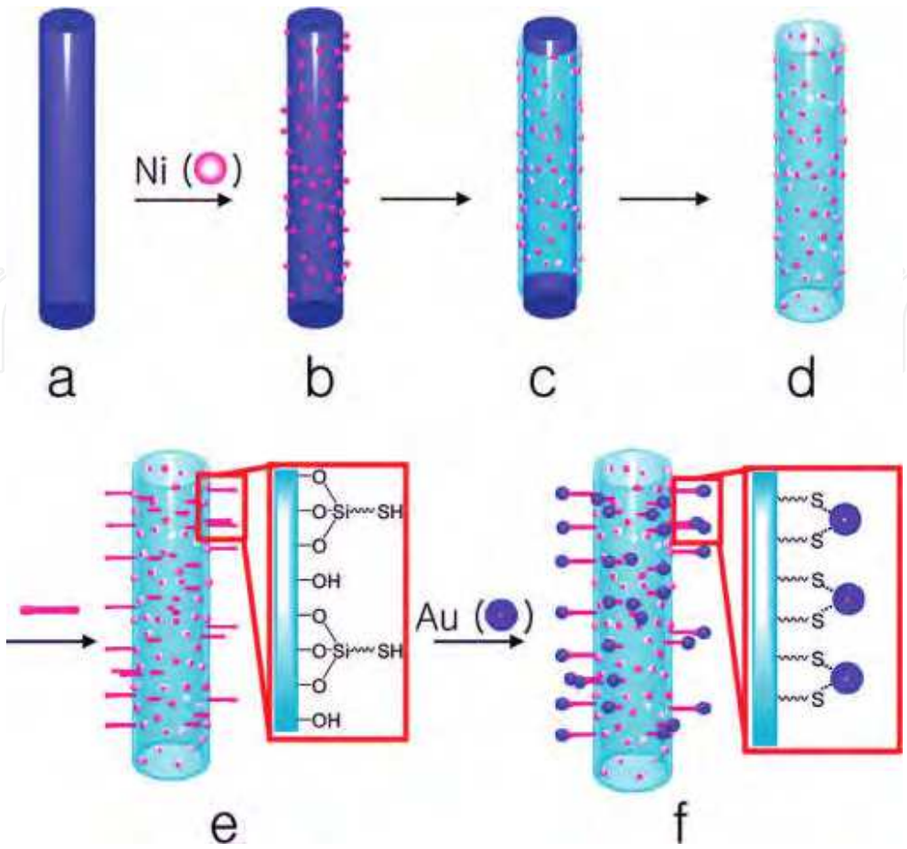


Fig. 25. Overall schemes for the synthesis of the gold-doped silica nanotube obtained from sol-gel transcription. [Reprinted with Permission from (Bae et al., 2008), Copyright 2008, American Chemical Society]

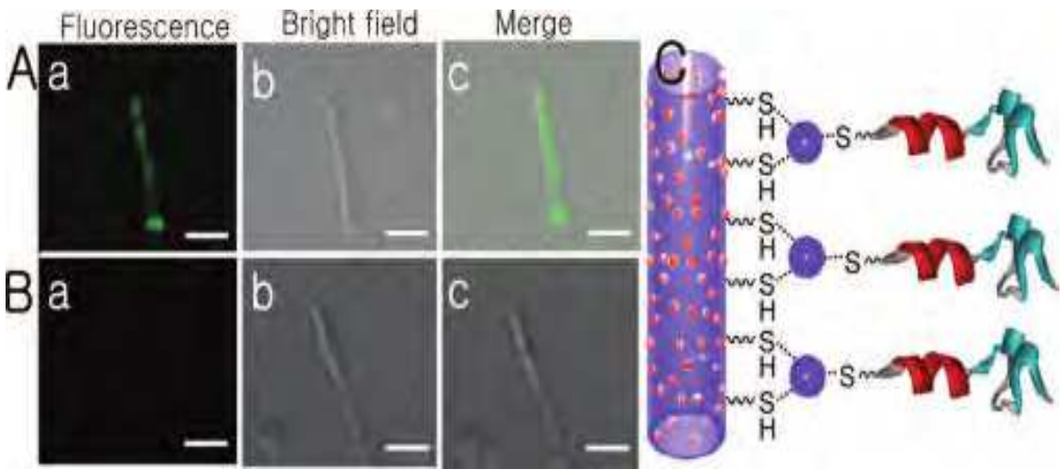


Fig. 26. Confocal images of **Au-MSNT** with (A) GST by treatment of anti-GST antibody and (B) ubiquitin by treatment of antiubiquitin antibody: (a) fluorescence, (b) bright field, and (c) merge images. (C). Illustration for binding mode of **Au-MSNT** with GST protein. Scale bar: 2 μm. [Reprinted with Permission from (Bae et al., 2008), Copyright 2008, American Chemical Society]

Specificity of Au-MSNT for cysteine may be exploited for a biosensor to detect cysteine containing proteins.

Separation of oligonucleotides

Detection of a specific messenger RNA biomolecule can serve as an indicator of the expression of its corresponding protein and as a diagnostic method for some diseases. This can be achieved, for example by specific recognition of an oligoadenosine tail by a solid support bearing covalently attached oligodeoxythymidine through the formation of specific A-T base pairs. A simple and accurate method to separate oligoadenosine derivatives was developed using nucleic acids functionalized silica nanotubes. Sol-gel template synthesis of helical silica nanotubes previously described (Jung et al., 2000) was followed by protection of outer surface with chloropropylsilane and after template removal the inner surface was functionalized with a thymidine derivative as a receptor for adenosine derivatives (Kim et al., 2010). The thymidine-immobilized silica nanotubes (**T-SNTs**) exhibited a well-defined tubular structure with 20 nm of inner diameter and 100 nm of outer diameter (Fig. 27 a, and b), which showed slight aggregation as the result of outer-surface modified by the attachment of chloropropyl silane.

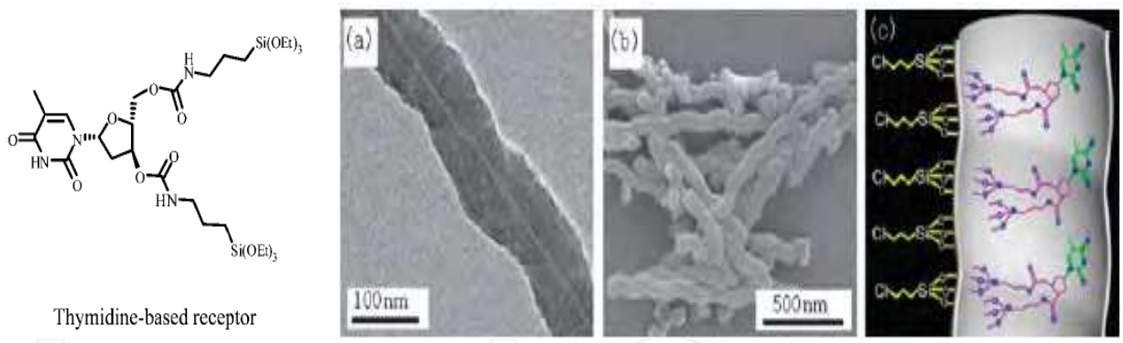


Fig. 27. (a) TEM and (b) SEM images of T-SNTs. (c) Representation of immobilization of thymidine receptor inside SNTs by covalent bonds. [Reproduced from (Kim et al., 2010) by permission of The Royal Society of Chemistry]

Adsorption capacities of **T-SNTs** for nucleic acids and oligonucleotides and specificity for oligoadenosine derivatives were tested on guest molecules containing adenosine and guanosine moieties. Fluorescence spectra of oligoadenosine derivative and oligoguanosine derivative, before and after addition of **T-SNTs**, combined with HPLC analyses demonstrated selectivity for adenosine derivatives (>95%) through the efficient formation of complementary hydrogen bonds in A-T pairs. The presence of the selectively bonded oligoadenosine derivative on **T-SNTs** was demonstrated by a strong fluorescence of the nanotubes isolated after separation (Fig. 28).

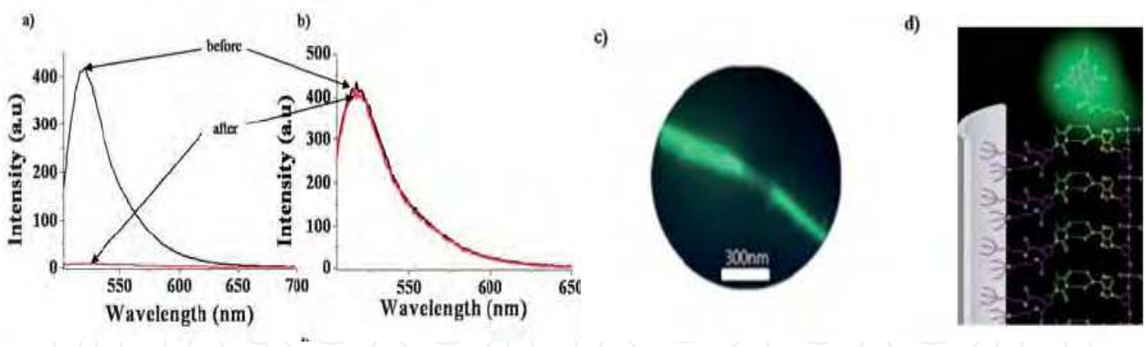


Fig. 28. (a) Fluorescence spectra of oligoadenosine and (b) oligoguanosine (λ = 519 nm) before and after addition of T-SNTs at 37 °C. (c) Fluorescence microscopic image of T-SNTs in the presence of oligoadenosine (λ = 519 nm). d) Representation for binding mode of T-SNTs with 24 by complementary hydrogen bonds between A-T base pairs. [Reproduced from (Kim et al., 2010) by permission of The Royal Society of Chemistry]

Bioseparation of a racemic mixture

Antibody-functionalized nanotubes obtained by differential functionalization were used to separate racemic mixtures. Thus inner and outer surfaces of silica nanotubes obtained with a porous alumina membrane template were functionalized with an aldehyde silane attached before or after they were liberated from the template. The RS selective Fab fragments of the antibody produced against the drug 4-[3-(4-fluorophenyl)-2-hydroxy-1-[1,2,4]-triazol-1-yl-propyl]-benzonitrile (**FTB**) were attached to the nanotubes *via* Schiff base chemistry of aldehyde moieties with free amino groups of the antibody. Racemic mixtures of **FTB** were incubated with Fab-functionalized nanotubes and the efficiency of the chiral separation (selective drug removal) was measured by chiral HPLC (Fig. 29). The efficiency of the

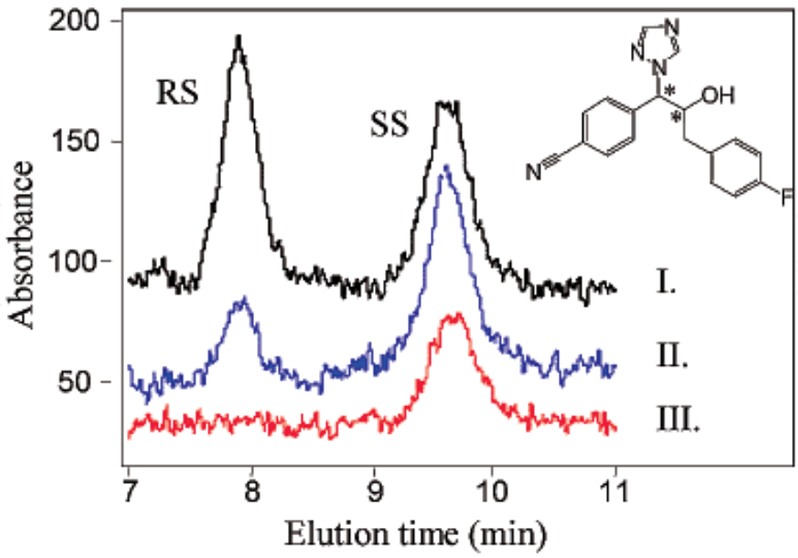


Fig. 29. Chiral HPLC chromatograms for racemic mixtures of FTB before (I) and after (II, III) extraction with 18 mg/mL of 200-nm Fab-containing nanotubes. [Reprinted with Permission from (Mitchell et al., 2002), Copyright 2002, American Chemical Society]

selective extraction of RS enantiomer of **FTB** with Fab-functionalized silica nanotubes depends on the initial concentration of the racemic mixture: 75% for 20μM (II) and 100% for 10μM (III). Non-functionalized nanotubes did not extract measurable quantities of each **FTB** enantiomer from 20μM solution.

Bioseparations by using magnetic silica nanotubes

The ability of functionalized magnetic silica nanotubes (**MNT**) to accommodate targets in the inner void was exploited in magnetic-field-assisted bioseparations by preparing materials with inner surface bonded human immunoglobulins (human-**IgG**) or Bovine Serum Albumin (BSA) using glutardialdehyde as a coupling agent (Son et al., 2005). The human **IgG-MNT** and the **BSA-MST** were tested in separation of a mixture of fluorescein-labeled anti-bovine IgG (green color) and Cy3-labelled antihuman IgG (red). After magnetic separation, the solution changed from the original pink to greenish blue only when **IgG-MNTs** were added, while the solution with **BSA-MNT** remained in its original pink color. This means that red Cy3-labeled anti-human IgG was separated specifically from the solution by human IgG-MNTs. Fluorescence spectra showed that 84% of Cy3-labeled anti-human IgG was separated by human **IgG-MNT** but only 9% by **BSA-MNT**.

Magnetic properties of **IgG-MNT** facilitate and enhance the biointeraction between the outer surface of a functionalized **MNT** and a specific target surface when a magnetic field is applied. Thus, a **MNT** with fluorescein isothiocyanate (**FITC**)-modified inner surface and Rabbit **IgG**-modified outer surface were incubated with the anti-rabbit IgG-modified glass slide for 10 min with and without magnetic field from the bottom of the glass slide (Son et

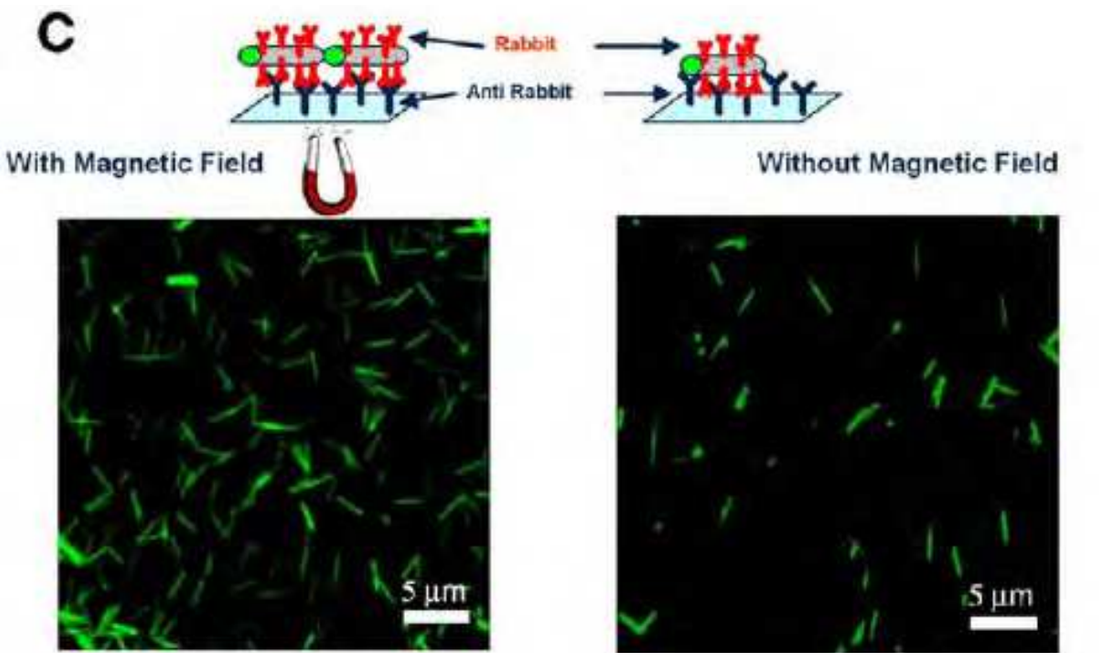


Fig. 30. Fluorescence microscope image of bound FITC-**MNT**- Rabbit **IgG** (60 nm diameter, 3 μm) after incubation with anti-rabbit IgG modified glass with and without magnetic field from the glass substrate. [Reprinted with Permission from (Son et al., 2005) Copyright 2005, American Chemical Society]

al., 2005). The efficiency of antigen–antibody interactions and the influence of magnetic field were investigated by fluorescence microscopy, revealing that binding was enhanced by 4.2 fold when the magnetic field was applied (Fig. 30). Magnetic-field assisted bio-interaction may improve significantly the drug-delivery efficiency when the carrier is a **MNT** loaded with drug inside and having probe molecules such as an antibody, on the outer surface.

Gene delivery

Green and red fluorescent silica nanotubes prepared by layer-by-layer deposition of fluorescent CdSe/ZnS core-shell semiconductor nanocrystals (of ~4nm and ~8nm diameters, respectively) onto the inner surface of pre-prepared silica nanotubes embedded in a porous alumina template (Chen et al., 2005). The inner surfaces were then functionalized with 3-(aminopropyl) trimethoxysilane (APTMS) ligands to facilitate the subsequent loading of negatively charged DNA by electrostatic interactions. The fluorescent nanotubes were loaded with plasmid DNA –carrying the GFP gene labeled with green DNA-stain SYTO-11 in order to monitor DNA localization. Monkey-kidney COS-7 cell were treated with the DNA loaded fluorescent nanotubes and confocal microscopy of the incubated samples showed that nanotubes entered in 60-70% of the cells and they are located mostly in the cytoplasm. Cytotoxicity of DNA loaded fluorescent nanotubes was investigated as well as the protection provided by the silica tube wall from environmental damage. The results indicate that the GFP gene can be loaded into silica nanotubes and successfully delivered to cells.

Immobilization of enzyme catalysts

Hollow silica nanotubes have been utilized as matrices for immobilization of enzymes in order to improve their catalytic efficiency. Glucose-oxidase (GOD) was loaded both to the inner and outer surfaces of silica nanotubes *via* the aldehyde silane route. Dispersed in a solution containing 90 nM glucose, the enzyme activity was monitored by standard dianisidine-based assay and a GOD activity of 0.5 ± 0.2 units/mg of nanotubes was obtained [88]. When the enzyme doped-nanotubes were filtered from the solution, all GOD activity ceased, an indication that immobilization *via* Schiff base chemistry is efficient, no protein leached from the support. Another example is immobilization of Penicillin G acylase (PGA) porous hollow silica nanotubes synthesized *via* a sol–gel route using nano-sized needle-like $CaCO_3$ inorganic templates (Xiao et al., 2006). PGA uptake onto the silica nanotubes was 97.20% and with an adsorption equilibrium time of the enzyme on suport of ca. 120 min, which is far faster than those previously reported supports such as pure silica SBA-15, MCM-41 and poly(vinylacetate-co-divinylbenzene) due to pore size and uniquely large entrances at two ends of the nanotubes.

One can be concluded that the template synthesis of silica nanotubes using organic and inorganic templates presents important advantages as the possibility to control lengths, diameters and wall thickness by adjusting the reaction parameters, obtaining of specific tubular nanostructures as multilayered, chiral or helical, multifunctionality by embedding magnetic particles or fluorescent molecules.

Moreover, functionalization of inner and outer surfaces improved molecular interactions with species of biological interest.

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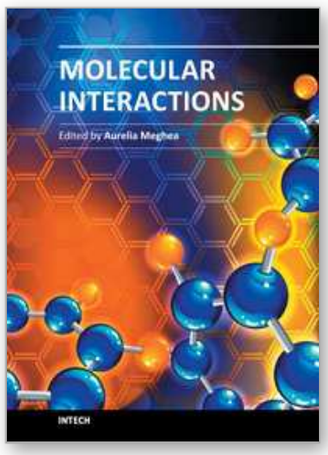

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In a classical approach materials science is mainly dealing with interatomic interactions within molecules, without paying much interest on weak intermolecular interactions. However, the variety of structures actually is the result of weak ordering because of noncovalent interactions. Indeed, for self-assembly to be possible in soft materials, it is evident that forces between molecules must be much weaker than covalent bonds between the atoms of a molecule. The weak intermolecular interactions responsible for molecular ordering in soft materials include hydrogen bonds, coordination bonds in ligands and complexes, ionic and dipolar interactions, van der Waals forces, and hydrophobic interactions. Recent evolutions in nanosciences and nanotechnologies provide strong arguments to support the opportunity and importance of the topics approached in this book, the fundamental and applicative aspects related to molecular interactions being of large interest in both research and innovative environments. We expect this book to have a strong impact at various education and research training levels, for young and experienced researchers from both academia and industry.

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