

Review

Functionalization of Carbon Nanomaterials for Biomedical Applications

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Abstract: Over the past decade, carbon nanostructures (CNSs) have been widely used in a variety of biomedical applications. Examples are the use of CNSs for drug and protein delivery or in tools to locally dispense nucleic acids to fight tumor affections. CNSs were successfully utilized in diagnostics and in noninvasive and highly sensitive imaging devices thanks to their optical properties in the near infrared region. However, biomedical applications require a complete biocompatibility to avoid adverse reactions of the immune system and CNSs potentials for biodegradability. Water is one of the main constituents of the living matter. Unfortunately, one of the disadvantages of CNSs is their poor solubility. Surface functionalization of CNSs is commonly utilized as an efficient solution to both tune the surface wettability of CNSs and impart biocompatible properties. Grafting functional groups onto the CNSs surface consists in bonding the desired chemical species on the carbon nanoparticles via wet or dry processes leading to the formation of a stable interaction. This latter may be of different nature as the van Der Waals, the electrostatic or the covalent, the π - π interaction, the hydrogen bond etc. depending on the process and on the functional molecule at play. Grafting is utilized for multiple purposes including bonding mimetic agents such as polyethylene glycol, drug/protein adsorption, attaching nanostructures to increase the CNSs opacity to selected wavelengths or provide magnetic properties. This makes the CNSs a very versatile tool for a broad selection of applications as medicinal biochips, new high-performance platforms for magnetic resonance (MR), photothermal therapy, molecular imaging, tissue engineering, and neuroscience. The scope of this work is to highlight up-to-date using of the functionalized carbon materials such as graphene, carbon fibers, carbon nanotubes, fullerene and nanodiamonds in biomedical applications.

Keywords: carbon nanostructures; chemical processing; functionalization; biocompatibility; biomedicine

1. Introduction

Difficulties in overcoming the limited control over biophysical and biochemical characteristics in traditional biomaterials have hampered their use in biomedical applications. This pushed the research of novel materials showing multiple properties that allow advanced functionalities. In this respect, carbon nanostructures (CNSs) thanks to the multiple uncommon properties, have had an impressive impact on scientific research with important technological implications. Carbon is one of the prototypal elements showing an organization in different allotropic forms (as sketched in Figure 1): from the zero-dimension fullerenes [1] and carbon quantum dots [2,3], to the one dimensional carbon nanotubes (CNTs) [4], to the two-dimensional graphene atomic sheet [5], to the 3D bulk graphite or diamond crystals where atoms are pure sp^2 or sp^3 hybrids organized in the hexagonal or cubic lattice, respectively [6].

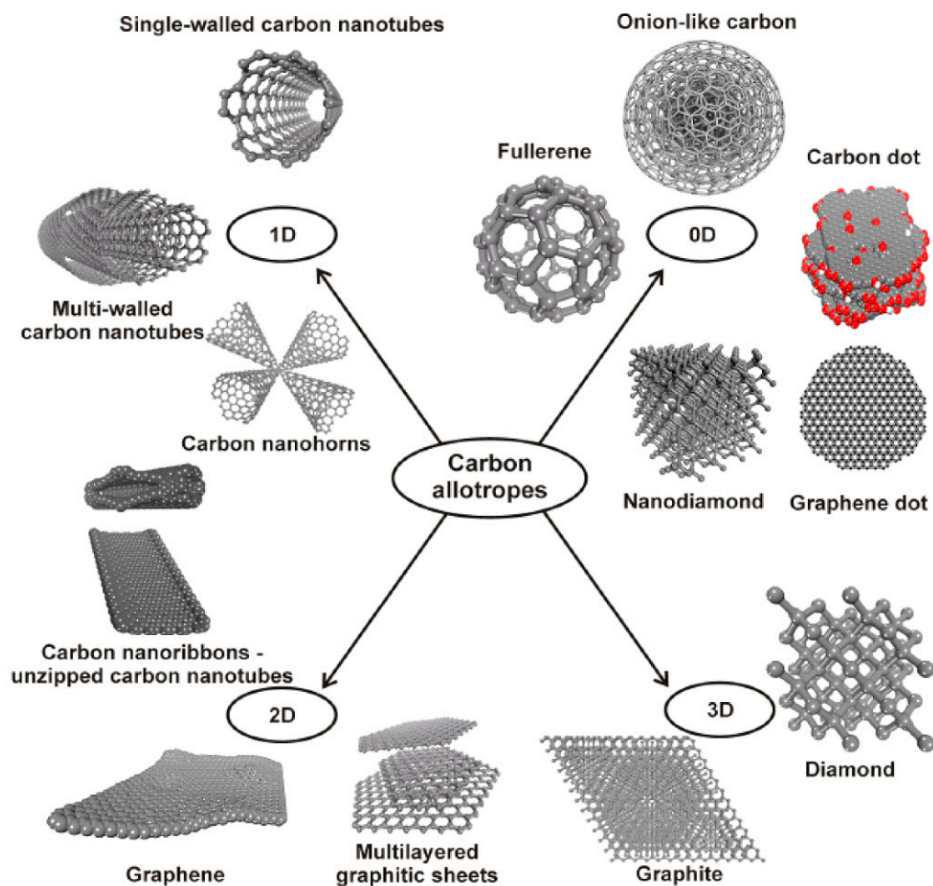


Figure 1. The different forms of the carbon allotropes (Reprinted with permission from [7]).

The interesting electrical, chemical, and mechanical properties of these objects, have led to a number of different types of applications. Concerning biology and biomedicine, the big potential of carbon nanomaterials is the possibility to tune the CNS dimensions, the capability to functionalize the surface, and the high chemical stability coupled to the optical and biomimetic properties. As an example, CNTs and fullerenes soon after their discovery have been studied for biosensing, drug delivery, and bioimaging [8,9]. Recently they experienced a revival for their application in the regenerative medicine [10], cancer therapy, and theranostic applications [11].

Figure 2 summarizes the possible applications of CNSs in biomedicine. The possibility to easily functionalizing the CNS surface is coupled with their unique optical properties such as intrinsic fluorescence, high photostability and the possibility to tune their emission, which are open important perspectives for their use in the imaging and diagnosis of cells and tissues. The possibility of modifying the CNS surface with oxygen or nitrogen based functional groups, enhances their properties and broadens the ensemble of applications facilitating the interaction with the hosting entity (cell, tissue, human body).

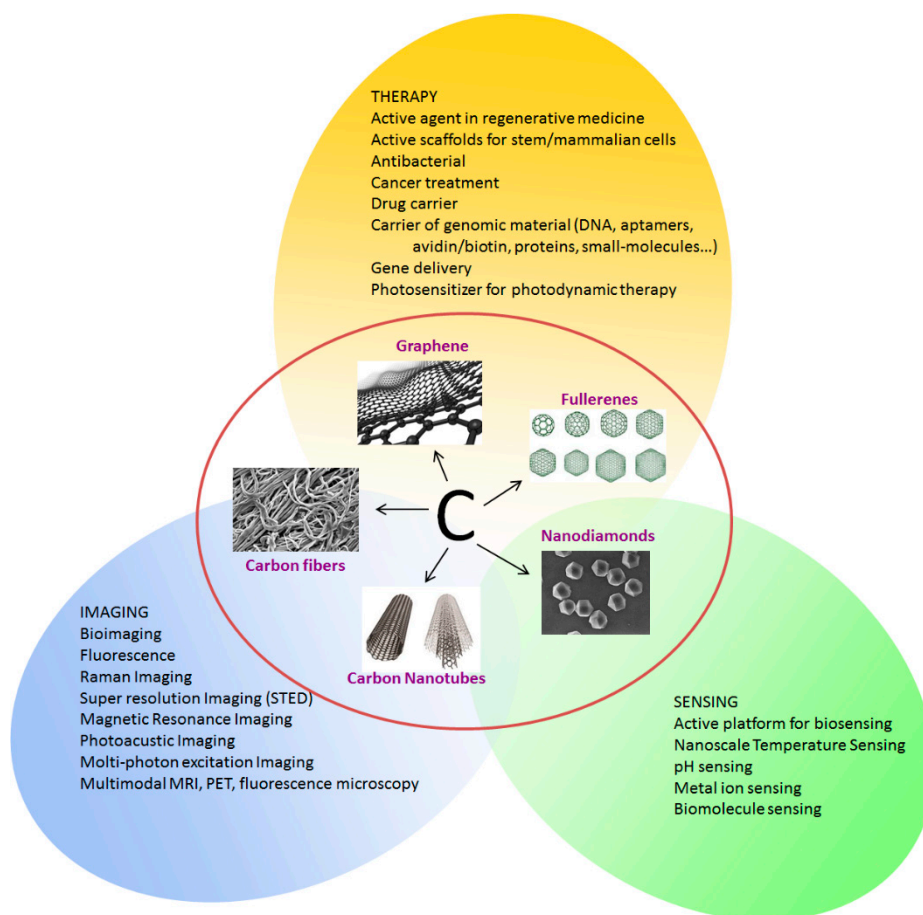


Figure 2. Carbon nanostructures and their applications in biomedicine.

The high surface area, and good mechanical and electrical properties render the CNSs as optimal platforms for theranostic applications. However, in dealing with therapies, stability in aqueous suspensions have become one of the major issues for their practical utilization in biomedicine [12,13]. This problem is generally overcome by activating the CNS surface using covalent approaches, such as oxidation, ozonolysis, plasma treatments, and dehydronation [13]. Coming to the applications in biomedicine, some studies have pointed out the anti-inflammatory properties of treated CNSs [14] although mechanisms behind this behavior has still not fully understood. More defined is the role of CNSs in fighting cancer diseases [15] as fluorescent markers for tumor tissue detection [16–18], sensors for early cancer detection [19–21], drug carriers [22,23], cancer phototherapy [24] and theranostics in general [25,26]. Recently, CNSs have been used to directly influence the biological activities of living matter. As an example, CNSs can stimulate the production of reactive oxygen species (ROS) when internalized in cancer cells, interfering with their biological functions. Graphene and fullerenes are proposed as potential candidates for cancer therapy thanks to their ability to activate molecular oxygen to ROS upon light irradiation [27,28]. CNSs and ROS production are also utilized to control microbial proliferation [29]. ROS at high concentrations causes a series of mitochondrial damages including DNA mutations, change in the membrane permeability, change of the respiratory functions, affects the Ca^{2+} homeostasis, and the mitochondrial defense systems [30]. These adverse effects easily induce cell death by apoptosis. Regarding therapy, CNS are widely utilized for drug delivery, thanks to the possibility of functionalizing their surface to enhance the targeting functions and to impart mimetic properties toward the immune system or cross biological barriers [31]. CNSs have been successfully applied in the delivery of diverse active principles such as small molecules, peptides, proteins, or nucleic acids [32], significantly increase the solubility of poorly soluble drugs, reducing cytotoxicity toward normal tissues, and improving therapeutic efficacy [32]. Considering applications in biomedicine, the CNS

optical properties are utilized in several modalities. They are utilized in one-photon and two-photon imaging, photoacoustic imaging, Raman and near-infrared imaging and their fluorescence properties have been deeply investigated for sensing applications in cell labelling and diagnosis [33–40].

Functionalization is a necessary unavoidable step to make CNSs a multifunctional, multimodal, high-performancetool for biomedicine. Modification of the surface chemical properties of CNSs, by grafting selected functional groups and proceed with a surface engineering with multi-step processing is used to lower toxicity, enhance water solubility, and add various specific functions [41–43]. This review aims at illustrating the state-of-the-art methods of carbon functionalization and their characterization, providing an overview of recent applications of CNSs in biomedicine. Also discuss the concerns regarding the degree of biocompatibility and potential toxicity of CNS illustrating the possible solutions.

2. Graphene

Graphene is composed of single-layer carbon atoms which are packed into a two-dimensional planar structure with a honeycomb lattice. Carbon atoms in graphene are sp^2 hybridized and connected with three neighboring carbon atoms via σ bonds, while π bonds are formed with an additional unhybridized p_z -orbital perpendicular to the planar structure [44]. The in-planar σ bond in graphene has a length about 1.42 Å, even shorter than the sp^3 bond distance of 1.54 Å in diamond, which gives graphene great mechanical strength, with a breaking strength of 42 N m⁻¹ and Young's modulus of 1.0 TPa [45]. The conjugated out-of-planar π bond network allows electron dislocation, providing graphene with high charge mobility (200,000 cm² V⁻¹ s⁻¹ in suspended graphene [46]) and good electrical conductivity (6300 S cm⁻¹ of graphene film [46]). Graphene is also highly thermal conductive and a thermal conductivity of about 5000 Wm K⁻¹ was measured on single layer graphene [47]. Thanks to its single-atom thickness and 2D structure, graphene has an exceptional high theoretical specific surface area of 2630 m² g⁻¹ [48] and superior optical transparency of 97.7% to white light [49].

In addition to this set of unique chemical and physical properties, graphene also has derivatives, graphene oxide (GO) and reduced graphene oxide (rGO), which increase its functionalization capability and broaden its applications. GO can be considered as the oxidized form of graphene and there are abundant oxygen-containing function groups on their honeycomb structure, while rGO is the product of GO after a reduction process that partially restores the graphene structure whilst leaving some oxygen functionalities and defects. Graphene and its derivatives have been making essential changes in the field of energy technology [49], electronics, photonics [50] and catalysis [51] since the successfully isolation of single graphene layers from graphite using scotch tape method in 2004 [5]. The biomedical application is an emerging frontier to graphene and its derivatives. According to their attributes, graphene has been investigated as potential material in biosensors, drug delivery, bioimaging, and tissue engineering.

Accurate sensing and detection of biomolecules are crucial since biomolecules play critical roles in all life processes. Biosensors are designed and built for this purpose. Generally, biosensors are constructed from two structural parts: a receptor and a transducer. The former is usually a bioactive molecule which recognizes one or a group of analytes through a specific interaction with analytes, while the latter transfers the chemical information from the recognition event to a readable signal [52]. The unique properties of graphene make it an outstanding material for biosensors. Its high surface-to-volume ratio facilitates the attachments of molecules or particles to enhance a biosensor's sensitivity. The quick electron mobility, high and surface-dependent electrical conductivity provide the device a low Johnson and 1/f noises [53]. The easy functionalization can be used to further enhance the response current. Furthermore, its strong mechanical properties give biosensor stability and flexibility, for example, biosensors based on graphene nanowalls for lactate measurement remained highly uniform in response after 250 bending process and 100 twisting process [54]. Biosensors built from graphene based material has been developed for detection of H₂O₂ [55], glucose [56], dopamine [57], DNA [58–60], and RNA [61,62]. We will take glucose as an example to discuss graphene application in biosensors.

One of the most important biosensors is for the detection of glucose because it plays very important role in the diagnosis and therapy of diabetes. In recent years, great effort has been devoted to the third-generation glucose sensor, which can overcome the sensing dependence on dissolved oxygen in the first-generation sensors and the need of mediators in the second-generation sensors [63]. Same as the former two generations, glucose oxidase (GOx) with a flavin adenine dinucleotide (FAD) as cofactor is used to react with glucose in biological samples, with glucose oxidized by GOx into gluconic acid while GOx(FAD) reduced into GOx(FADH₂). Then GOx is directly recycled at the electrode surface by electrochemical oxidation of GOx(FADH₂) through a two electron process. Graphene materials have been widely used to make the direct electron transfer (DET) possible. For example, Kang et al. fabricated GOx-graphene-chitosan film on a glassy carbon electrode. A much higher GOx loading was obtained as compared with a glassy carbon surface (GCE), and DET was observed by studying the electrochemical behavior of GOx. The sensor exhibited a wide linearity range from 0.08 to 12 mM glucose with a detection limit of 0.02 mM and a sensitivity of 37.93 $\mu\text{A mM}^{-1} \text{cm}^{-2}$ [64]. Although many graphene-containing glucose sensors were claimed to promote DET, there is a doubt about this process since they were tested in ambient conditions, where oxygen can act as a natural mediator of oxidase. The test in a N₂-saturated solution of GOx adsorbed on electrochemically-reduced GO on GCE showed that GOx with enzyme activity could not directly transfer electrons to the electrode since FAD is deeply embedded within a protective protein shell and there is a long distance between the active GOx and the electrode surface [65]. Therefore, it is still a challenge to obtain DET for third generation glucose sensors. The incoming fourth generation non-enzymatic glucose sensor is possibly one solution, which uses the principle of electrocatalytic oxidation of glucose on metal nanoparticle surfaces, as depicted in Figure 3. Graphene-based material can be used to anchor the metal nanoparticles. Pd/GO [66], Pt/GO [67], Cu/graphene [68], gold nanosheets/graphene fiber [69], and Co-Ni/N-doped graphene [70] have been investigated as materials for glucose sensors.

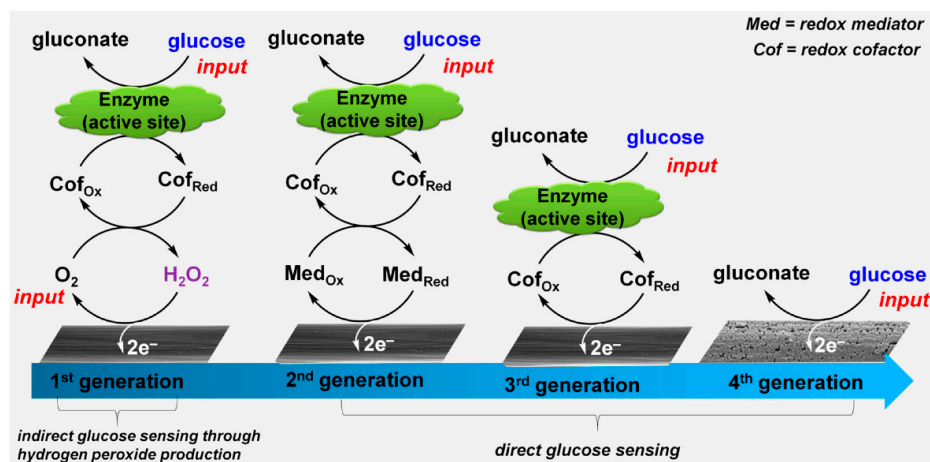


Figure 3. Sensor development for glucose detection. Reprinted with permission from [63].

Graphene and its derivatives are also interesting materials for drug delivery because the two sides of graphene-based material are accessible to load drug molecules. The feasibility for further functionalization can provide pathways to obtain stable dispersion in physiological buffers and improve their biocompatibility. The loading of drug can be through π - π stacking interaction, hydrogen bonding, or hydrophobic interactions [71], while the drug release can be accomplished due to the pH difference of the tumor microenvironment, the cellular redox environment, the specific biomolecules, or external physical stimuli, e.g., light, magnetic field, temperature [72].

The pioneer work using graphene based material for drug delivery was done by Dai's group in 2008 [73]. They adsorbed SN38, a FDA approved prodrug for colon cancer treatment, onto polyethylene glycol (PEG)-functionalized GO. They observed that the loading amount of SN38 increased to 0.1 g on 1 g PEG-GO from no loading on pure PEG polymer. The SN38-PEG-GO was water soluble

and stable in phosphate buffer saline and mouse serum and showed enhanced cell killing ability compared with a water-soluble drug CPT-11. This pioneer study has stimulated the reach on the delivery of various drugs, e.g., doxorubicin hydrochloride (DOX) [74–78], chlorin e6 (Ce6) [79,80], camptothecin (CPT) [81,82], methotrexate (MTX) [83–85], and ibuprofen [86]. As the most effective drug for cancer treatment, DOX is widely investigated. For example, GO was successfully functionalized using chitosan and dextran by a layer-by-layer self-assembly technique. DOX was loaded into the nanocomposite via π - π stacking and electrostatic attraction. The functionalization not only improved the dispersion the DOX-loaded GO nanosheets in physiological conditions, but also decreased the non-specific protein adsorption of GO nanosheets. The nanocomposites were able to be untaken by MCF-7 cells and DOX loaded counterpart had a strong cytotoxicity to cancer cells [87]. When DOX was loaded onto chitosan modified Ag-GO hybrid particles, an antibacterial activity was added in addition to anti-cancer performance [88]. To increase cancer treatment efficiency, it is necessary to develop a delivery carrier which can bond with multiple drugs simultaneously. By grafting GO with poly(*N*-isopropylacrylamide) via covalent interaction, the functionalized GO proved to be an efficient carrier for both hydrophilic DOX and hydrophobic indomethacin (IMC). The release of both of the loaded drugs can be triggered by a pH change of the microenvironment [89]. Two anticancer drugs, quercetin and gefitinib, were also reported to be successfully loaded on and released from polyvinylpyrrolidone (PVP) modified GO, exhibiting higher cytotoxicity to PA-1 ovarian cancer cells in comparison to the individual drugs loaded onto a GO polymer composite [90].

Another important field of graphene biomedical application is bioimaging. Bioimaging enable us to understand biological process happening in the living cells, tissues and organs using an imaging probe. The versatile surface functionalization coupled with high surface area, good biocompatibility and unique optical properties of graphene-based materials make them good materials for improving the currently used imaging probes for exploring new probes. Currently, there are several main imaging techniques, that is, fluorescence imaging, Raman imaging, magnetic resonance imaging etc. [91]. Electron paramagnetic resonance imaging (EPRI) is a relatively new and developing technique for imaging, in which radicals are used as imaging agents. Carbon blacks was also reported as an EPRI medium for localized measurements of tissue oxygenation [92]. Recently, graphene nanoribbons have shown to be promising material for oxygen detection using the EPRI technique [93]. However, here, we will focus mainly on the mostly used techniques.

For fluorescence imaging, Sun et al. prepared single-layer GO sheets down to less than 10 nm, covalently grafted with PEG and used as a probe for imaging. Since the prepared GO and PEG-GO showed photoluminescence in the IR and NIR regions, NIR photoluminescence was selectively detected on positive Raji B-cell surface after PEG-GO was conjugated with a B-cell specific antibody Rituxan (anti-CD20) and incubated with B-cells and T-cells [94]. To explore the possibility of in vivo imaging, fluorescent dyes co-conjugated onto GO to enhance the fluorescent signal. Cy7, a common NIR fluorescent dye is used to label PEG-nanographene sheets. In vivo fluorescence imaging revealed high tumor uptake in several xenograft tumor mouse models. Coupled with strong optical absorbance of the nanographene sheet in the NIR region, this material proved to be an excellent in vivo imaging probe as well as photothermal therapy agent [95]. However, due to the potential risk of photobleaching of the fluorescent dyes, upconversion nanoparticles have been used to anchor on graphene-based material to obtain fluorescent imaging. GO quantum dots functionalized with $\text{NaYF}_4:\text{Yb}^{3+}$, Er^{3+} upconversion nanoparticles and hypocrellin A (a commonly used chemotherapy drug and a photo-sensitizer) were taken up by tumor cells and improved upconversion signal properties. The HeLa cells can be detected and imaged when treated with 5 g mL^{-1} of the functionalized GO quantum dots [96].

Raman mapping is also a powerful tool for bioimaging since both graphene and GO show unique Raman signals. However, since the Raman signals from graphene-based material are weak, Au nanoparticles are usually decorated on the graphene surface to enhance the intensity of the Raman signal through surface enhanced Raman scattering (SERS). By the decoration of GO and rGO, Raman imaging for HeLa 229 and HepG2 hepatocarcinoma cells was realized, respectively [97,98]. In another

study, Au nanoparticles were wrapped by graphene oxide and this material showed enhanced Raman signal compared with GO only. HeLa cells were clearly imaged after a treatment with Au@GO nanoparticles for 24 h [99].

Magnetic resonance imaging (MRI) is a widely used technique for medical diagnosis in hospitals and clinics. In order to obtain good diagnosis quality, contrast agents are usually used to increase the contrast between the examined part and normal parts. Gd^{3+} chelates are the most used T_1 contrast agents to get brighter images, but they suffer from the release of free Gd^{3+} ions which are very toxic because they block calcium channels since they have similar ionic size as Ca^{2+} . A new T_1 contrast agent based on water dispersible Gd_2O_3 /GO nanocomposites was synthesized by Wang et al. using a facile solvent evaporation method. Gd_2O_3 /GO exhibited better biocompatibility and higher relaxivity value than the typical commercial MRI T_1 contrast agent Gd-DTPA [100]. Iron containing magnetic nanomaterials, e.g., Fe_3O_4 , and $CoFeO_4$, are important components of the T_2 contrast agent, through which much darker images can be obtained. However, these nanomaterials tend to aggregate and precipitate in practical application. This problem was solved by using Fe_3O_4 functionalized graphene oxide as report by Zhou et al. [101]. The prepared Fe_3O_4 -GO hybrid demonstrated good hydrophilicity, less cytotoxicity, high NRI enhancement with the relaxivity of $493 \text{ mM}^{-1} \text{ s}^{-1}$ as well as an MRI contrast effect of BxPC-3 cells [101].

Last but not the least, is graphene's biological application to tissue engineering. Tissue engineering is an interdisciplinary field that involves the knowledge of bioengineering, the life sciences, and the clinical sciences towards solving the critical medical problems of tissue loss and organ failure [102]. Graphene-based material has attracted great attention for application in tissue engineering due to their strong mechanical strength, excellent electrical conductivity, and versatile surface modification properties. Their applications in cardiac, neural, bone, cartilage, skeletal, and skin/adipose tissue engineering and regeneration have been investigated [103]. For example, Kim et al. prepared graphene-incorporated chitosan substrata and studied their effects on the adhesion and differentiation of human mesenchymal stem cells. Their results showed that the adhesion and differentiation of human mesenchymal stem cells were greatly enhanced due to the asymmetrical nanotopology environment of the RGO-chitosan substrata and the enhancement of cell-substrate interaction and cell-cell contacts [104].

2.1. Synthesis

The interactions between biomolecules and graphene-based material depend greatly on the properties of graphene-based materials, e.g., layer number, lateral dimension, chemical residual, surface charge and surface functional groups, while synthesis methods of graphene-based materials have led to large difference in their properties. There have several synthesis methods developed for graphene synthesis along with the intense study on their applications. These synthesis methods can be generally divided into two categories: the bottom-up approach and the top-down approach.

2.1.1. Bottom-Up Synthesis

The bottom-up synthesis approach builds graphene from atom levels and it includes three main synthesis methods: epitaxial growth on silicon carbide (SiC), the chemical vapor deposition method (CVD) and plasma-enhanced chemical vapor deposition (PECVD). Epitaxial graphene growth on SiC uses the thermal decomposition of SiC at high temperature under vacuum or in inert gas. Since carbon has neglectable vapor pressure compared to silicon, graphene layers are formed on the SiC surface after silicon sublimation. This method was firstly reported in 1965 by Badani. In this study, SiC crystals were annealed in vacuum in an induction furnace up to 2280°C for an hour and the development of a graphite lattice was found on SiC crystals [105]. Later research by Van Bommel et al. suggested that a monolayer of graphene had already formed at temperatures as low as 800°C under ultra-high vacuum. They also observed that graphite layers were formed on both the C-face and Si-face of the SiC crystals. The C-face generated a polycrystalline graphite layer, while Si-face

generated a monocrystalline graphite layer [106]. However, this method suffered from low quality graphene with varied thickness of small graphene grains due to the surface morphology change of SiC from high temperature annealing under vacuum. To slow down the sublimation rate, annealing SiC in an argon atmosphere [107] or in an external Si flux [108], or depositing a nickel [109] or cobalt [110] layer on SiC, were proved effective in controlling the resulted graphene quality. Epitaxial graphene growth on SiC is a promising method to produce graphene on semi-insulating material which can then be directly used as electronic materials without transferring, but for biomedical application, it may hinder its application because in most cases graphene transfers are required.

One of the most studied methods for producing high quality, large area graphene is the CVD method. During the CVD process, a precursor gas containing hydrocarbon molecules is charged into the reactor, in which hydrocarbon molecules are catalytically decomposed into carbon radicals and arranged into a graphene structure on the catalytic layer of the substrate. Methane is the most used precursor for graphene production using the CVD method, but there are also plenty of other gas precursors used, e.g., acetylene [111], ethylene [112], propene [113], or liquid precursors like methanol [114], ethanol [115], propanol [114], hexane [116], benzene [117], or even solid precursors like poly(methyl methacrylate) (PMMA) [118], and amorphous carbon [119]. The catalysts investigated include nickel (Ni) [120], copper (Cu) [120], Rhodium (Rh) [121], cobalt (Co) [122] or alloys [123–125]. The catalyst layer was proved not only to lower the activation energy for precursor decomposition, but also led to different graphene formation mechanisms. Graphene growth on Ni is a carbon segregation and precipitation process since Ni has a high carbon solubility at elevated temperatures. During the cooling down process, carbon solubility in Ni decreases and carbon atoms diffuse out from the Ni-C solid solution and precipitate on the Ni surface to form graphene films. However, Cu has much lower carbon solubility than Ni and there is only a small amount of carbon dissolved in Cu, thus the carbon source of graphene growth on Cu is directly from precursor decomposition. Furthermore, graphene growth on Cu is a self-limiting process, which is preferable to form single layer graphene than Ni [120,126]. The properties of the obtained graphene, e.g., layer number, crystal size and layer number, are affected by several factors such as precursors, assistant gases, catalyst layer, and temperature.

PECVD has been developed to synthesize graphene at a much lower temperature than CVD with a shorter deposition time. This method can overcome the evaporation problem of catalyst layer at high temperature. For example, Malesevich prepared free standing 4–6-layer graphene at a temperature of 700 °C using a microwave PECVD method. However, one problem of the PECVD method is the generation of plenty of defects in the graphene structure due to the interaction of high energetic particles with the growing surface [127].

2.1.2. Top-Down Synthesis

The top-down synthesis separates graphene sheets from high-quality graphite which contains stacked multi-layer graphene using a mechanical or chemical approach. It includes the mechanical exfoliation method, the chemical exfoliation method and the GO reduction method.

The mechanical exfoliation method is the first documented method to successfully separate graphene from graphite. It used scotch adhesive tape to break the van de Waals force between layers of graphite by a repeated sticking and lifting process [5]. This method can produce high quality graphene, but suffers from the problem of scalability which hinders its commercialization. Ultrasonic force is also used to produce graphene in solvents, e.g., *N*-methylpyrrolidone (NMP), utilizing the strong interactions between solvents and graphene [128]. Another kind of force used is the shear force in the ball-milling process. The ball-milling can be processed in both wet [129] and dry form [130]. It is a problem to separate graphene for both the ultrasonic and ball-milling methods since some un-exfoliated graphite is mixed with graphene sheets. The ball-milling method also has shortcomings of the formation of amorphous carbon and defect generation on the produced graphene.

One versatile method for the large-scale synthesis of graphene, to be exact rGO, is the reduction of GO. This method generally includes two steps: GO production and GO reduction to rGO. To generate

GO, the Hummers method is usually used to oxidize graphite. In the oxidation process, graphite reacts with sodium nitrate, concentrated sulfuric acid, and potassium permanganate, which introduces oxygen-containing functional groups onto graphite sheets [131]. The graphene oxide layer can be separated by ultrasonic treatment in polar solvent, especially in water, due to the enlarged layer spacing as the functional groups are introduced. As already discussed, GO itself can be used for biomedical applications because of their easy functionalization as a result of the presence of functional groups. It can, as well, restore its graphene structure through electrochemical reduction [132], thermal reduction [133], chemical reduction [134] or hydro/solvothermal method [135,136]. Chemical reduction is widely used for GO reduction and a variety of reductants have been studied. There are several reductants which are effective for GO reduction to rGO, e.g., hydrazine [137], sodium borohydride [138], hydrohalic acid [139], and ascorbic acid [140]. For biomedical applications, chemical residues from reductants will affect rGO performance and its biocompatibility since most of them are toxic. Recently, green reductants such as plant extracts, sugars, microorganisms, and amino acids have been exploited to remove this barrier [134]. For example, baker's yeast containing nicotinamide adenine dinucleotide phosphate (NADPH) has been used as a reducing agent and functionalizing agent. The amine functional group of NADPH can easily couple with the epoxy functionalities of GO and forms stable water dispersion of yeast-rGO [141]. These effects aimed at preparing biocompatible rGO through chemical reduction.

2.2. Functionalized Graphene-Based Materials

For biomedical applications, the surface functionalization of graphene-based material is essential. Firstly, surface functionalization with PEG [142] or dextran [143], was reported to largely decrease the toxicity and improve the biocompatibility of graphene. Secondly, a good dispersion of graphene-based materials is critical. However, graphene and rGO with low oxygen content are hydrophobic in polar solvents and they tend to aggregate in aqueous solution. Even water-soluble GO, which is rich with oxygen-containing functional groups, is liable to aggregate in physiological buffers with salts due to a charge-screening effect [144,145]. More importantly, the surface functionalization brings functional centers important for biological applications, for example, the Au nanoparticle for Raman imaging.

Up to date, surface functionalization of graphene and its derivatives can be processed via two strategies: non-covalent binding and covalent binding. As shown in Figure 4, noncovalent functionalization can proceed through the adsorption of biomolecules via the van der Waals force, π - π interactions, while covalent functionalization can be performed by grafting biomolecules using chemical reactions between biomolecules and oxygen-containing functional groups of GO or dipolar cycloaddition reaction on graphene.

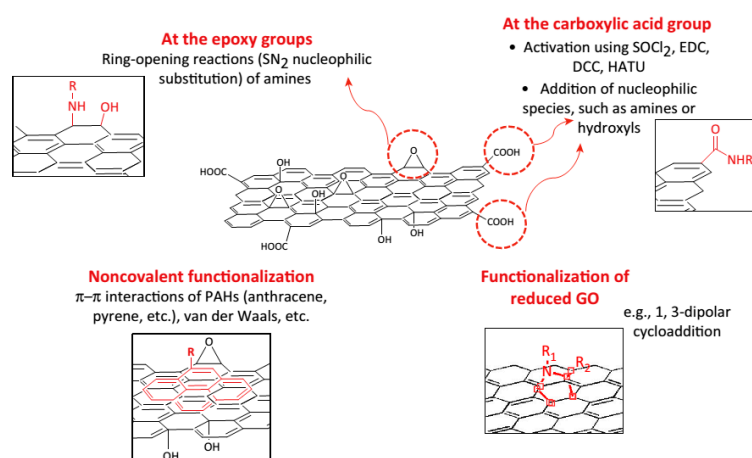


Figure 4. Different approaches for the surface functionalization of graphene-based materials. Reprinted with permission from [146].

2.2.1. Non-Covalent Functionalized Graphene-Based Materials

We will firstly discuss the non-covalent functionalization of graphene-based materials with surfactants, polymers, or biomolecules. The forces involved for non-covalent functionalization include hydrophobic interactions, π - π stacking, or electrostatic binding.

The hydrophobic nature of graphene and rGO can be used to adsorb the aliphatic parts of surfactants through hydrophobic interactions. This process makes the polar parts of surfactants interact with the surrounding environment, enhancing the stability of the surfactant-functionalized graphene or rGO in polar solvents, especially in aqueous solution. Assali et al. [147] functionalized graphene sheets with three different surfactants, cetrimide, sodium dodecyl sulfate, and tween 80, in 1% w/v surfactant solution with 30 min sonication. After functionalization with surfactants, the graphene sheets became totally dispersed and all three dispersions kept good stability for more than three months without the formation of any precipitate. In other studies, rGO functionalized with tween 20 [148] and Pluronic F127 [149] were prepared by adding the surfactant during the GO reduction with hydrazine hydrate. After reduction, both functionalized rGO materials formed a stable homogeneous black solution.

Electrostatic interactions are also effective in functionalizing graphene-based material. Since GO sheets are negatively charged, a positively charged molecule can therefore bind to the GO surface via electrostatic force. Feng et al. prepared GO-polyethyleneimine (PEI) complexes by simply mixing PEI solution with GO solution, followed by separation and washing after 10 min sonication and overnight stirring. The obtained GO-PEI complexes are positively charged and negatively charged DNA was also loaded on it by electrostatic interactions [150]. Fang et al. prepared chitosan-mediated graphene suspensions by simply adding the GO suspension to the solution of chitosan under stirring. Since GO is negatively charged and chitosan is positively charged, when GO was added to the solution of chitosan, every GO sheet was immediately wrapped by large amounts of chitosan molecules through electrostatic attractions. Then, the GO sheets were isolated as individual ones and a uniform dispersion formed. The system is pH responsive and has potential for biomedicine application [151].

Thanks to the conjugated out-of-planar π bond network of graphene-based materials, molecules containing aromatic rings can attach to the surface of graphene-based materials by π - π interactions. Husale et al. [152] observed that ssDNA bound only to the graphene and not to the SiO₂ substrate, confirming that the binding energy is mainly due to the π - π stacking interaction. This phenomenon was reported to be used to design DNA sensors [153]. The π - π interaction is widely investigated as a force to load aromatic rings containing drugs on graphene-based materials for drug delivery. Anti-cancer drugs DOX, and quercetin together with gefitinib were successfully loaded and delivered with PEG-GO and PVP-GO, respectively [90,154].

2.2.2. Covalent Functionalized Graphene-Based Materials

As we discussed above, GO bears carboxyl, epoxy, and hydroxyl groups on its surface, which provide reactive sites for biomolecule covalent functionalization. The functionalization can be through the amidation reaction of the carboxylic acid group of GO with amine groups in polymers. In 2008, Dai's group prepared PEG functionalized nano-graphene oxide (nGO) for the delivery of an insoluble cancer drug. The functionalization of nGO was performed in three steps. Firstly, nGO was synthesized using a modified Hummer's method. Then the obtained nGO was carboxylic acid modified using 3M NaOH solution or chloroacetic acid in NaOH solution. Then six-armed PEG-amine stars were conjugated to the carboxylic acid group on nGO via a carbodiimide catalyzed amide formation [73,94]. This material showed superior stability in biological solution. This PEGylation method has been widely used to functionalize graphene-based material for varieties of biomedical applications [81,83,155,156].

During the functionalization process, if PEG-diamine is used instead of PEG-amine, the functionalized GO has an amine functional group on the surface for further functionalization. For example, as shown in Figure 5, gold nanorods (Au NRs) coated with rGO-PEG (rGO-PEG-Au) were synthesized for the selective killing of uropathogenic E. coli UTI89 which is associated with urinary tract infection. The first step for rGO-PEG-NH₂ synthesis followed the sample procedure from Dai's group

but replacing PEG-NH₂ with NH₂-PEG-NH₂ (Figure 5A). In the second step, cetyltrimethylammonium bromide (CTAB) protected Au NRs were prepared using a seed-mediated procedure and pegylated with PEG-dicarboxylic to get HOOC-PEG-Au NRs. Then the reaction between rGO-PEG-NH₂ and HOOC-PEG-Au NRs formed the final product (Figure 5B). This product was proven to be a powerful photothermal agent for the effective killing of the target bacteria with a 99% killing efficiency [157]. The carbodiimide catalyst during the amidation reaction forms an unstable reactive O-acylisourea ester which also reacts water. To improve the stability of the intermediate and promote the creation of the amide type linkage, another co-catalyst, e.g., N-hydroxysuccinimide (NHS), is usually added during the functionalization of GO with polymers. As demonstrated in Figure 6, a graphene-chitosan composite was formed by an unstable O-acylisourea ester and a semi-stable amine-reactive NHS-ester which reacted with amine on chitosan. Based on this composite, mechanically robust graphene oxide fibers were formed using a wet spinning approach [158]. Poly(ethyleneimine) was also successfully covalently functionalized on poly(acrylic acid) modified GO after activating the carboxylic acid group using EDC/NHS. In vitro cell studies revealed that GO-PEI composites promoted proliferation and focal adhesions in hMSCs with potential use as tissue scaffolds [159].

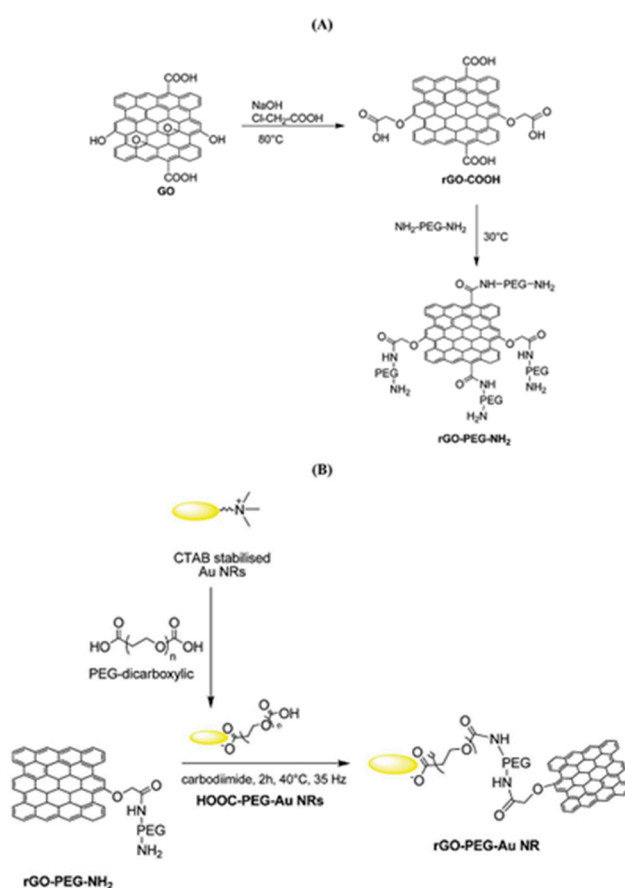


Figure 5. (A) Formation of PEG-modified reduced graphene oxide (rGO-PEG-NH₂) and (B) rGO-PEG-Au NRs coated through the covalent linking of rGO-PEG-NH₂. Reprinted with permission from [157].

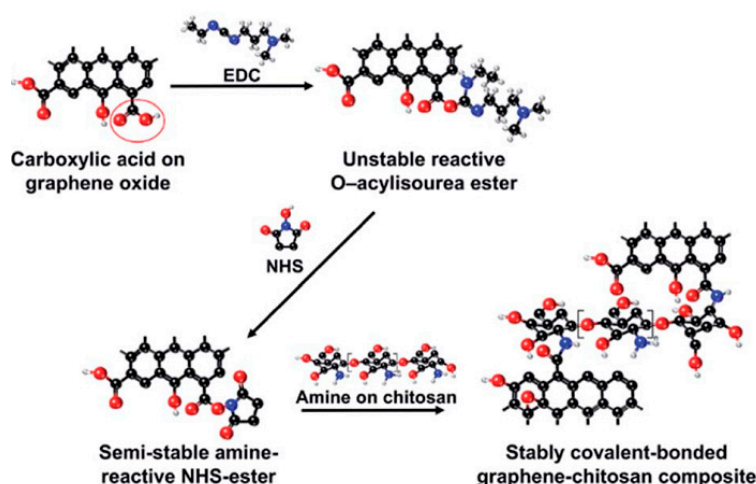


Figure 6. Reaction pathways of EDC and NHS intermediated functionalization of GO with chitosan. Reprinted with permission from [158].

Esterification is another reaction which is frequently used to functionalize GO. Monica Veca et al. prepared PVA functionalized few-layer graphene material through the carbodiimide-activated esterification reaction in DMSO between the carboxylic acid moiety on the nanosheets and hydroxyl groups on PVA. After functionalization with PVA, a stable solution was formed in DMSO and hot water [160]. Salavagione et al. firstly converted the carboxylic acid groups of GO into acryl chlorides using SOCl_2 in DMF. Then the acryl chloride-derivative graphite was reacted with PVA in DMSO to obtain PVA-functionalized GO. The obtained composite is soluble in DMSO and water with the aid of heat [161]. PVC-modified GO was also synthesized by same group [162].

Besides the reaction with the carboxylic groups of GO, it is found that the epoxy group can also be used for the functionalization of GO with polymers. Shan et al. [163] prepared poly-L-lysine (PLL) covalently functionalized graphene through the reaction of epoxy groups on GO and amino groups on PLL in the presence of KOH, followed by reduction by NaBH_4 solution. PLL-functionalized graphene is water soluble and biocompatible and has the potential to be a promising material for biomedical applications.

For graphene and rGO which have no or less oxygen-containing functional groups, free radical addition and 1,3-dipolar cycloaddition are good choices for covalent functionalization. A good example of free radical addition is the diazotization reaction. This reaction proceeds as following: generation of the diazonium salt from the amino reagent using a nitrite species, single electron transfer between the diazonium salt and the graphene material, radical addition, formation of the phenol and adsorption of phenol onto the graphene sheet [41,164]. Wei et al. functionalized rGO with p-aminobenzoic acid, which formed the diazonium ions through diazotization with a wet chemical method. After loading with PEI and FA, it was proven to be a good carrier for DOX to arrest cancer cells [165]. 1,3-dipolar cycloaddition method was applied by Prato et al. using azomethine ylide to modify few-layer graphene. The obtained functionalized material can be further modified for use in the biomedical field [166].

2.2.3. Nanoparticle Functionalized Graphene-Based Materials

A large number of inorganic nanostructures such as Au [97,98,167], Ag [168], Pd [66], Pt [67,169], Cu [68], Fe_3O_4 [101,170], Gd_2O_3 [100], and NaYF_4 -based upconversion nanocrystals [96] have been anchored on graphene-based materials for a variety of biomedical applications. Au NRs/GO core-shell nanocomposites was loaded with DOX for a combined chemo- and photothermal targeted treatment of cancer cells [171]. In certain cases, the integration of Au into graphene nanosheets to efficiently improve the sensitivity and detection limit, as demonstrated by Shan et al.'s study on Au/rGO functionalized with DOX for glucose detection [172]. Au and Ag decorated graphene-based materials were also used

for Raman imaging [145]. Li et al. prepared folic acid- $\text{Fe}_3\text{O}_4@\text{nGO-DOX}$ using nGO encapsulated Fe_3O_4 , which is very effective for simultaneous tumor MRI imaging and target therapy [173].

Utilizing upconversion nanocrystals is a promising method for NIR light-mediated bioimaging and photothermal and photodynamic therapy. Gulzar et al. [131,174] covalently functionalized nGO with core-shell structured upconversion nanoparticles in the steps as shown in Figure 7. Oleic acid stabilized $\text{NaGdF}_4:\text{Yb}^{3+}, \text{Er}^{3+}$ was firstly synthesized followed by the formation of a $\text{NaGdF}_4:\text{Nd}^{3+}, \text{Yb}^{3+}$ shell around it. The surface of the core-shell structure was then amino-modified via a phase transfer process using 2-aminoethyl dihydrogen phosphate (AEP). GO was made using a modified Hummer's method and PEGylated using the EDC intermediated synthesis method. Carbodiimide cross linking reaction between the amino group of amino-modified core-shell upconversion nanoparticles and the carboxyl group of NGO-PEG was employed for the covalent grafting of the upconversion core-shell structure. After loading with Ce_6 , cytotoxicity assays revealed decent biocompatibility and minor toxicity. This multifunctional cancer therapy platform has achieved superior therapeutic efficacy for in vitro and in vivo cancer therapy.

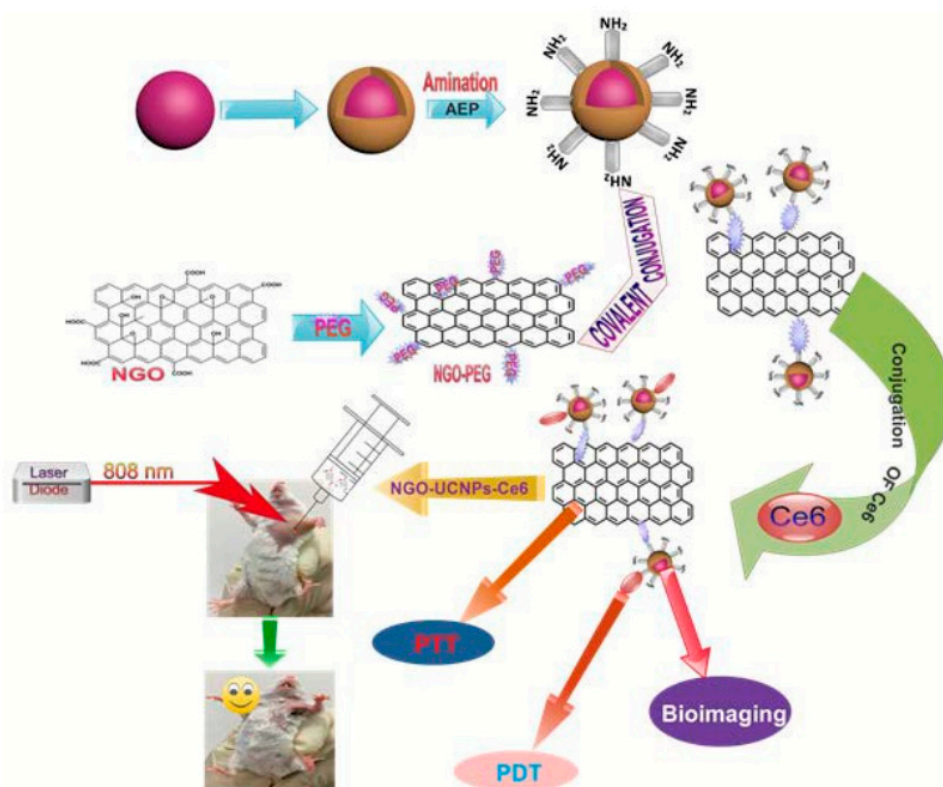


Figure 7. Covalent functionalization of nGO with core-shell upconversion nanoparticles. Reprinted with permission from [174].

3. Carbon Nanotubes

Carbon Nanotubes (CNTs) are one kind of carbon allotrope which has a seamless hollow cylindrical shape. Like carbons in graphene, carbon atoms in CNTs are also bonded with three neighboring carbon atoms in a sp^2 configuration forming the hexagonal units. Conceptually, CNTs are considered as rolled-up graphene sheets in certain directions. The rolling up of single-layer graphene and multi-layer graphene form single-wall CNTs (SWCNTs) and multi-wall CNTs (MWCNTs), respectively. Therefore, CNTs and graphene share many of the interesting properties. For example, SWCNTs have strong mechanical strength, with a Young's modulus value range from 320 to 1470 GPa and breaking forces ranging from 13 to 52 GPa [175]. The electrical conductivity of the CNTs along the axis of a single CNT was reported to be as high as $2 \times 10^7 \text{ S m}^{-1}$ [176], while for MWCNTs the electrical conductivity is

about 2×10^5 S/m [177]. The thermal conductivity of individual SWCNT was reported to be $3500 \text{ W m}^{-1} \text{ K}^{-1}$ [178], above that of bulk graphite (about $2000 \text{ W m}^{-1} \text{ K}^{-1}$), for individual MWCNT the value is about $3000 \text{ W m}^{-1} \text{ K}^{-1}$ [179]. SWCNTs have a high theoretical surface area of $1315 \text{ m}^2 \text{ g}^{-1}$ [180], although only about half that of graphene; however, the experimental values depend greatly on the quality of the SWCNTs and the highest value reported is $1587 \text{ m}^2 \text{ g}^{-1}$ [181]. The one-dimensional tubular morphology of CNTs also bring them unique properties. CNTs have super high length-to-diameter aspect ratio with a diameter of 0.4–2.5 nm and a length of 20–1000 nm for SWCNTs, and a diameter of 1.4–100 nm and a length of 1–500 μm for MWCNTs, respectively [182]. Individual CNT can be either metallic or semiconducting depending on the orientation of the lattice with respect to the tube axis, which is called chirality [183]. The tubular shape provides CNTs with a certain internal volume which can be applied to house specific functionalities. Furthermore, the curvature of CNTs makes CNTs generally much easier than pristine graphene for chemical functionalization.

Since the report of MWCNTs in 1991 by Iijima's group [4] and the reports of SWCNTs in 1993 by the same group [184] and Bethune's group [185], scientific research has boomed afterwards for the methodology development of CNT synthesis and exploration of their potential application in various fields because of their unique physicochemical properties. Their applications include but are not limited to electronics [186], energy [187], environment [188], atomic force microscopes [189] and nanomedicine [190]. Biomedical applications are one of the most important fields for CNTs. We will discuss below how CNTs work as materials for biosensors, drug delivery, bioimaging and tissue engineering.

Because of their high aspect ratio, high mechanical strength, and high electron transfer rates, CNTs have been considered as excellent material for biosensors. As we discussed in the graphene section, biosensors include two components, an acceptor and a transducer. When analytes contact the sensor, the reaction between analytes and acceptor generate an electrochemical or photo signal which is then transferred to the processing part to accomplish the sensing aim. With a tubular structure and superior electrical conductivity, CNTs are expected to be versatile material to enhance the direct electron transfer so as to increase the sensitivity of the sensor. Zhang et al. reported the use of functionalized SWCNTs as electrical connectors between the enzyme acceptor, GOx, and the Au electrodes for the glucose detector. A clear dependence of the electrical communication on the length of the CNTs was observed. The sensor with a 25 nm CNT revealed an approximate 1.5-fold current signal as compared with the electrode with 50 nm CNT. The author assumed that the electrical communication controlled by the length of CNTs might be due to the wall defect sites which act as local barriers to charge transport [191]. Recently, Rernglit et al. soaked GOx into porous CNT film on a Pt disk electrode and trapped it beneath a topcoat of electrodeposition paint. The resulting sensors produced a glucose signal that was linear up to 40 mM, with a 50 μM detection limit. This glucose sensor proved to have a signal stability over 100 h of continuous operation [192]. Enzyme-based biosensors with CNTs were also designed for the detection of various other analytes, e.g., tyrosinase on polypyrrole-SWCNTs for dopamine detection [193], glutamate dehydrogenase-nicotinamide adenine dinucleotide on chitosan-MWCNTs for glutamate sensing [194], D-fructose dehydrogenase on 3,4-dihydroxybenzaldehyde on CNTs for fructose determination [195], anti-NS1 antibodies on CNTs electrode for virus NS1 protein detection [196], and DNA probes on MWCNTs modified glass carbon electrode for miRNA sensing [197]. Recently, the research on CNT application in biosensors transited to non-enzyme based sensors. For example, a glucose biosensor was constructed using NiCoO₂ nanosheets on CNTs. This sensor displayed good performance for glucose with a response sensitivity of $1424.41 \mu\text{A mM}^{-1}$, and a low detection limit of $1.14 \mu\text{M}$ [198]. A dendrimer-encapsulated Pt nanoparticle-CNT composite-based electrochemical biosensor was fabricated for the detection of hydrogen peroxide, ascorbic acid, and acetaminophen in the concentration ranges of 10 μM –10 mM, 50 μM –8 mM and 20 μM –1 mM, respectively, with rapid current response and good reproducibility [199].

CNTs have been considered an excellent potential vehicle for drug delivery since their discovery. Their high surface area and internal volume determines the high loading of drugs not only by the outer

wall surface but also the internal cavity. Their 1D needle-like morphology facilitate CNT penetration through the cell membranes of targeted cells and the CNTs have already proven to have the capability to smartly deliver to desired sites after appropriate functionalization [200]. In 2007, Dai and coworkers reported the preparation of water-soluble phospholipid (PL)-PEG modified SWCNTs and loaded the DOX drug on them. An extremely high drug loading of about 50–60 w.t% was obtained, which is remarkably higher than the about 8–10 wt.% for conventional liposomes. The SWCNT-DOX complex remained stable in normal physiological environments and released fast in acidic tumor cells [201]. In their later research, paclitaxel (PTX), a widely used cancer chemotherapy drug was conjugated onto PEGylated SWCNTs and obtained a water-soluble SWCNT-PTX conjugate. A 10-fold higher PTX uptake by SWCNT and prolonged blood circulation were observed. Thus, it had a higher efficacy in suppressing tumor growth than clinical Taxol in a murine 4T1 breast cancer model. Furthermore, this SWCNT-PTX caused no obvious toxic effects to normal organs [202]. Recently, Karthika et al. used TiO_2 -Au coated MWCNTs to deliver DOX. A drug loading capacity of 0.45 mg mL^{-1} was achieved. The delivered drug showed great efficiency in treating A549 and MCF7 cancer cells, with a releasing capacity of about 91% for 10 h [203]. Other drugs were also reported as delivered using SWCNTs or MWCNTs as carriers, for example, gemcitabine on FA-MWCNTs for breast cancer cells [204], daunorubicin on aptamer-SWCNTs for leukemia T-cells [205], 10-hydroxycamptothecin (HCPT) on diaminotriethylene glycol-MWCNTs for H22 tumor cells [206], curcumin on polysaccharides-SWCNTs for human lung adenocarcinoma cells [207], lobaplatin on PEG-CNTs for liver cancer cells [208], and formononetin on hydroxypropyl-cyclodextrin modified SWCNTs for MCF-7 cells and Hela cells [209].

Bioimaging is another important application for CNTs. In 2002, the observation of band-gap fluorescence from individual semiconducting SWCNTs in sodium dodecyl sulfate (SDS) opened the possibility to of using band-gap fluorescence for bioimaging [210]. There are several advantages to the use of band gap fluorescence of CNTs for bioimaging. First of all, in the NIR emission band of semiconducting CNTs, cells, tissues, and other biological molecules show much less autofluorescence and thus minimize the background signals. Furthermore, NIR light can penetrate the biological tissues, ensuring the non-invasive imaging of cells under skin. Dai and coworkers reported the development of antibody functionalized SWCNTs as NIR fluorescent labels for probing cell surface receptors with high specificity and high sensitivity. The authors prepared highly water soluble and biologically inert phospholipid (PL)-PEG modified SWCNTs. Then Rituxan and Herceptin antibodies were conjugated onto the functionalized SWCNTs for the recognition of CD20 cell surface and HER2/new receptors, respectively. By detecting the intrinsic NIR photoluminescence of semiconducting SWCNTs, the authors observed the selective binding of SWCNTs-antibody conjugates to cell surface receptors [211]. Later on, they studied the *in vivo* NIR photoluminescence imaging in live mice. Firstly, PL-PEG modified SWCNTs solution was prepared by exchange with sodium cholate with PL-PEG. The exchange SWCNTs demonstrated the ability to achieve a high image contrast at a relatively low dose (17 mg L^{-1}) for whole-mouse imaging [212]. Recently, Hirata used NIR fluorescence imaging to monitor the SWCNTs locally implanted in mice. SWCNTs were implanted between the periosteum and parietal bone of mice. Fluorescence was observed in the cranial region, not in other organs, demonstrating that the implanted MWCNTs remain at the site of implantation and did not accumulate in detectable quantities in other organs [213]. Interestingly, visible photoluminescence was also observed on functionalized SWCNTs and MWCNTs due to the trapping of excitation energy by the defect sites in the CNT structure [214]. The defects-and-functionalization dependent photoluminescence has also been used for bioimaging. For example, Lin et al. created fluorescent quantum defects in SWCNTs using NaClO and UV irradiation. With injection of only about 100 ng of the prepared SWCNTs in mice, high contrast images displayed clearly vascular and lymphatic structures under 980 nm excitation [215]. Raman is also a commonly used imaging technique and CNTs have been reported in this application. DNA wrapped SWCNTs have been used for Raman scattering and fluorescence spectra and they showed continued emission and staining and spectra changes upon uptake [216]. Surface-enhanced Raman scattering (SERS) has recently applied to enhance the Raman signal for bioimaging; for example,

Au functionalized with DNA on SWCNTs for Hela cell imaging [217]. The last imaging technique we will mention here is MRI imaging, in which CNTs have been used as a carrier for contrast agents to improve the imaging quality, e.g., Fe₃O₄/MWCNTs [218], Gd-DTPA/SWCNT [219].

With respect to tissue engineering, CNTs have been reported to replace conventional materials because of their strong mechanical strength and excellent electrical conductivity. CNTs were reported as fillers to reinforce polymeric biomaterials for the strengthening of their structural integrity and to achieve better biomechanical properties. A 77% higher elastic modulus and 60% increase in mechanical stress were obtained with 5% MWCNT addition to chitosan films in comparison with pure chitosan films. It was also found that cell viability and proliferation succeeded after MWCNT reinforcing, and at the same time, no toxic effects were detected [220]. To fully utilize the mechanical and electrical properties of CNTs, CNT based scaffolds were built for tissue engineering. Rajesh et al. developed a CNT-alginate-hydroxyapatite tricomponent composite scaffold used for bone tissue engineering. In vivo studies showed that the composite scaffold showed good cell proliferation, cell differentiation, and cell attachment, which proved to be a promising candidate for bone tissue engineering [220]. Functionalized CNTs was also studied for nerve tissue engineering. Polypyrrole on chitosan-polyurethane with functionalized MWCNTs were reported to accelerate the regrowth, proliferation and migration of Schwann cells and the differentiation of rat pheochromocytoma cells [221].

3.1. Synthesis

A large number of methods have been developed CNT synthesis. Hereafter, we will briefly introduce the most used synthesis methods—the arc discharge method, laser ablation method and the chemical vapor deposition method.

The arc discharge method is a well established method for CNT synthesis. In the synthesis process, helium gas is filled into the reaction chamber, where two electrodes are separated in a distance of 1–2 mm. The anode is usually made of high purity graphite and metal catalyst, while the cathode is made of high purity graphite. Once an arc current is triggered between the anode and cathode, graphite and metal catalyst in anode evaporates and condenses onto the cathode surface or reactor inner wall to form CNTs and other impurities. Products from the arc discharge method usually contain both SWCNTs and MWCNTs. The reactor atmosphere, pressure, and arc current are important parameters for the process to control the yield and quality of CNTs [222].

Laser ablation is an important method for CNT synthesis, with a more controlled manner than the arc discharge method. The synthesis process proceeds in a quartz tube heated in a tubular furnace. Inside the quartz tube, a target made of high-purity graphite with small amount of metallic catalyst is used as a carbon source. A scanning laser beam is focused onto the target at a high temperature under an inert gas flow, which causes the evaporation of the carbon and metallic catalyst. The re-condensation of the carbon and catalyst vapor on a cooled collector along the downstream flow forms CNTs with impurities [223]. This process is cost consumable since it uses high energy power to vaporize the target, but this process has a high yield and produces primarily SWCNTs.

CVD is a widely used method for low temperature, low-cost bulk production of CNTs. The CVD process proceeds in a flow furnace. The carbon source is usually hydrocarbons such as methane, acetylene, ethane, ethylene or alcohols. The metallic catalyst, e.g., Ni, Co, Fe, can be used in a very fine powder or coated onto a substrate. When the reaction gas passes through the flow furnace at a high temperature about 1000 °C, hydrocarbon molecules decomposed into active carbon species on the catalyst surface and diffuse into the metal nanoparticles. When the carbon atoms are saturated in the metal nanoparticles, carbon precipitates out and forms tubular carbon solids with a sp² structure. The characteristics of CNTs by the CVD method are dependent on the operation pressure, temperature, hydrocarbon concentration, the nature of the support and the time of the reaction [224]. To lower the reaction temperature for the CVD method, plasma-enhanced CVD (PECVD) has been developed [225].

3.2. Functionalized CNTs

With their unique properties, CNTs are expected to be versatile materials for biomedical application. However, there is one problem that hinders their practical application. Due to the hydrophobic nature of the walls of CNTs, the freshly prepared CNTs tend to aggregate into bundles via the van der Waals force. Therefore, it is difficult to separate single CNTs and make stable biocompatible solutions in most solvents, especially not possible in water. Surface functionalization has provided efficient solutions to solve this problem. Furthermore, surface functionalization could also provide efficient intracellular uptake and increase the possibility of the attachment of different functional groups onto the surface of CNTs for biomedical applications [226]. CNTs functionalization can be generally divided into two groups: noncovalent functionalization, and covalent functionalization.

3.2.1. Noncovalent Functionalization

Noncovalent functionalization is the process of adsorption or wrapping of surfactants, polymers or biopolymers onto the surface of CNTs. The noncovalent functionalization processes offer several advantages. Firstly, they are usually quick and it is not difficult to achieve effective de-bundling of CNTs and get good dispersion in water. Secondly, they are expected to bring less disturbance to the sp^2 structure of CNTs and subsequently preserve, to most extent, their mechanical and electrical properties. Furthermore, most surfactants are easy to obtain and have already been used in pharmaceutical products [227]. In principle, the nonpolar part will adsorb on the CNT surface with the polar end sticking out to contact with the solvent used. Moore et al. tested a series of anionic, cationic and nonionic surfactants for their ability to suspend individual SWCNTs. For the ionic surfactants, sodium dodecylbenzene sulfonate (SDBS) showed the best result. For the nonionic systems, surfactant with higher molecular weight suspend more SWCNTs [228]. Ciofani et al. found that pretreatment with stirring at 70 °C followed by a sonication procedure doubled the MWCNTs concentrations, reaching $160 \mu\text{g mL}^{-1}$ in 0.1% pluronic solution [229]. Good dispersion was also obtained with surfactants of sodium dodecyl sulfate [230], sodium dodecylbenzene sulfonate [231], Igepal [232], and more.

Polymers, especially conjugated polymers, are extensively used to wrap CNTs as a result of π - π stacking and van der Waals interactions between the conjugated polymer chains containing aromatic rings and the surface of CNTs [233]. For example, Petrov investigated pyrene containing polymer for the dispersion of CNTs. They synthesized copolymer, poly(MMA-co-PyMMP), with methyl methacrylate (MMA) and (1-pyrene)methyl-2-propenoate (PyMMP) by atom transfer radical polymerization. The copolymer was wrapped around MWCNTs by mixing copolymer and CNTs with a certain weight ratio. After functionalization, MWCNTs formed stable dispersion in THF, chloroform and toluene [234]. Non-covalent functionalization and dispersion were also achieved through polymer wrapping using sulfonated polyaniline [235], poly-L-lysine [236], Zn-porphyrin polymer [237], and oligothiophene-terminated poly(ethylene glycol) [238].

For biomedical applications, the functionalization with biomolecules is preferred. DNA-assisted dispersion and separation of carbon nanotubes were discovered by Zheng et al. [239]. Bundled CNTs were successfully separated into individual CNTs under sonication with the addition of single-stranded DNA (ssDNA). Theoretical calculation revealed that, as shown in Figure 8, ssDNA wrapped the CNT with the bases stack into nanotubes, while leaving the sugar-phosphate backbone exposed, which makes the functionalized CNT easy to solvate. Their later study showed that the ssDNA wrapping of CNTs is sequence dependent. When the n value of a sequence $d(\text{GT})_n$ is between 10 to 45, the electrostatics between the ssDNA and CNT are suitable for the CNTs to be separated by anion exchange chromatography [240]. Sanz et al. optimized DNA binding to CNTs by a non-covalent method and developed a bilayer functionalization method that utilized RNA-wrapping to solubilize the nanotubes and a cationic polymer as a bridge between the RNA-nanotube and the DNA. Their method showed important potential for gene delivery [241]. Taeger et al.'s study revealed that protein, such as hydrophobin, can work in the same role as ssDNA to successfully disperse CNTs and it can suspend CNTs as efficiently as ssDNA [242].

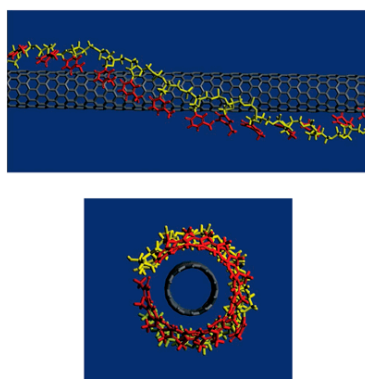


Figure 8. Theoretical calculation results showing ssDNA converted CNTs are water soluble. Reprinted with permission from [239].

3.2.2. Covalent Functionalization

Covalent functionalization is widely used to disperse CNTs, to improve CNT biocompatibility and to bring biomedical functionality to CNTs. The covalent functionalization process involves several chemical reactions, through which covalent chemical bonds are formed between CNTs and the entities for functionalization. They can be divided into two categories: (i) oxidation and end/defect functionalization, and (ii) side wall covalent functionalization.

The main purpose of the oxidation of CNTs is to purify the CNTs. This process cuts tubes into short pieces and removes impurities inside CNTs, such as amorphous carbon and metallic catalysts. At the same time, it opens the tube ends of CNTs and brings in tube-end oxygen functional groups, such as carboxylic acid, ketone, alcohol, and ester groups. Meanwhile the oxidation process generates defects on the tube wall, for example holes with oxygenated functional groups [70,243].

The widely used method for CNT oxidation is solution oxidation in acid solution using HNO_3 [244], $\text{HNO}_3/\text{H}_2\text{SO}_4$ [245], and $\text{KMnO}_4/\text{H}_2\text{SO}_4$ [246].

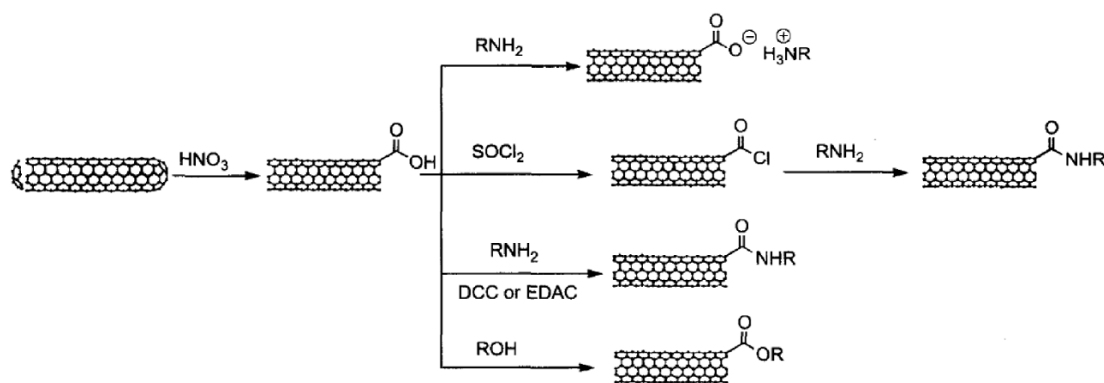


Figure 9. Different chemical reactions for end functionalization of CNTs. Reprinted with permission from [247].

The total acidic sites in oxidation purified SWCNTs are about 1–3% determined by acid-base titration [248]. These acidic sites play important roles in the further functionalization of CNTs, as shown in Figure 9. Further modification can be accomplished through four reaction pathways. The first reaction with the carboxylic group on end (or defects), as shown in Figure 9, is through simple acid-based reaction forming CNT-carboxylate zwitterion. Octadecylamine (ODA) has been reported to solubilize CNTs using the CNT-carboxylate zwitterion formation reaction [249,250]. The second reaction is the amidation reaction which is widely used to graft RNH_2 on to CNTs as well as graphene through the formation of $-\text{CO}-\text{NH}-$ bonding. During this reaction, the carboxylic group needs to be activated by

the formation of acyl chlorides by reacting with thionyl chloride, or through the formation of unstable and sub-stable intermediates by reacting with EDC/NHS, as we have discussed in the graphene section. These reactions have been extensively used for further functionalization with PEG-NH₂ to improve biocompatibility and to provide sites for biomedical functionalities [251–254]. Another functionalization pathway of CNT end and defects is through the esterification reaction between the surface carboxylic group on CNTs with ROH. One example is the grafting of poly(hexamethylene carbonate-co-caprolactone)diol, a biodegradable polyol, onto MWCNTs [255].

Side wall covalent functionalization of CNTs usually involves the breaking of sp² bonding networks to form sp³ binding on CNT walls. Therefore, it generally requires harsh reaction conditions and leads to extreme changes in the properties of the CNTs. The chemical reaction for this purpose includes: carbene addition, fluorination, arylation, 1,3 dipolar cycloaddition, nitrene addition, radical addition, nucleophilic addition, hydrogenation, and grafting polymerization. Carbene addition was reported to have been carried out firstly by Chen et al. using dichlorocarbene, which was produced from phenyl(bromodichloromethyl)mercury. The author's Raman results proved the addition of dichlorocarbon to the wall of the SWCNTs [256,257]. The fluorination functionalization of CNTs is by direct reaction with fluorine at about 400 °C, thanks to the high reactivity, oxidizing properties, and highest electronegativity of fluorine. The fluorination method is very useful since it provides an opportunity to introduce the alkyl group by replacing the fluorine atom using a Grignard agent or organolithium [258]. Covalent functionalization of CNTs via an arylation reaction involves the reaction of CNTs with aniline or its derivative in DMF. This reaction can proceed with a radical initiator. A dipolar reaction mechanism was proposed for this reaction. The functionalized CNTs dispersed well in acetonitrile, toluene and water and the dispersion was stable for more than one month [259]. The covalent functionalization of CNTs based on a 1,3-dipolar cycloaddition of azomethine ylides, generated by the condensation of an α -amino and an aldehyde, was reported by Georgakilas et al. The modified nanotubes are remarkable soluble in most organic solvents and even in water [260]. This is a versatile functionalization method and it has been reported to prepare functionalized CNTs for biomedical applications. For example, Samori et al. functionalized oxidized CNTs with amine moieties through the 1,3-dipolar cycloaddition of azomethine ylides. The introduced amine moieties were used as a cleavable linker to conjugate the anticancer drug methotrexate. The hybrid conjugate showed enhanced anticancer activities to human breast cancer cells [261]. The various functionalization pathways are summarized in Figure 10.

Nitrene addition is another cycloaddition reaction which is used for CNTs covalent functionalization to add a variety of different groups such as alkyl chains, aromatic groups, dendrimers and more. Holzinger et al. used oxycarbonyl nitrenes to react with SWCNTs in 1,2-dichlorobenzene under a nitrogen atmosphere. After thermally induced N₂ extrusion, nitrene addition resulted in the formation of alkoxycarbonylaziridino-SWCNTs. Such functionalization increased the solubility of SWCNTs in organic solvents [262]. Recently, interesting research on nitrene cycloaddition reported the preservation of π -conjugation in covalently functionalized CNTs. In CNT side wall functionalization, some sp² carbons is changed into sp³ carbons which break the π -conjugation of the sp² network. The quenching of the fluorescence of CNTs has been observed after exposure to different reactants [263]. The authors developed a [2+1] cycloaddition reaction based on electron-poor aromatic nitrene, monoazidodichloro-triazine. The electron-poor aromatic nitrene conjugated onto SWCNTs through [2+1] cycloaddition to form an intermediate adduct with high strain. Then the ring of intermediate adducts opened the ring to re-hybrid to fully conjugated hetero-bridged nanotubes (Figure 11) [91].

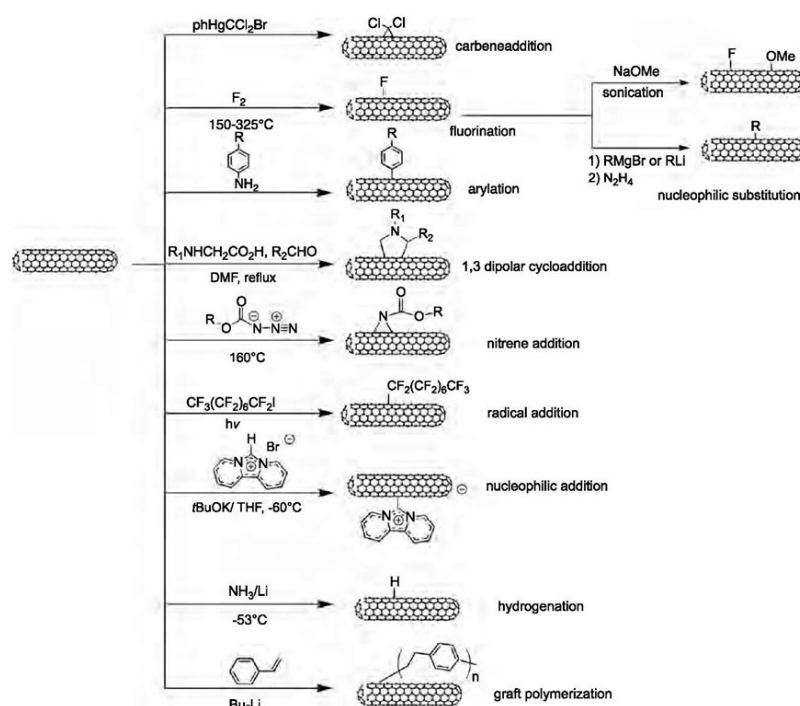


Figure 10. Different chemical reactions for side wall covalent functionalization of CNTs. Reprinted with permission from [247].

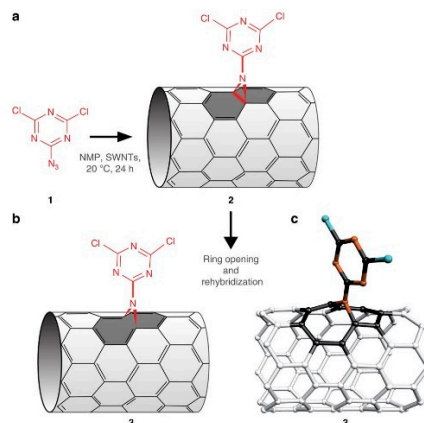


Figure 11. Synthesis of functionalized CNTs which preserve π conjugation. Reprinted with permission from [264].

The radical functionalization of CNTs was reported with the use of perfluorinated alkyl iodides under UV light to generate radicals which functionalized SWCNTs. The products showed enhanced dispersion in CHCl_3 [265]. In another study, photolysis of perfluoroazooctane was performed to modify the sidewall of SWCNTs based on radical reactions [266]. A simple approach to covalently functionalize CNTs is through diazonium salts ($\text{R-N}_2^+\text{X}^-$). In the reaction, the reactive species are radicals, which forms through electron transfer between CNTs and the aryl diazonium salts. This reaction can proceed in organic or water media, or through electrochemical ways [267].

Nucleophilic addition is another method for side wall modification. Holzinger et al. used nucleophilic carbene, dipyridyl imidazolidine to react with electrophilic π systems to give zwitterionic adducts. In the addition reaction, one negative charge per carbene is transferred to the tube surface, thus offering a further parameter for modifying tube properties [268]. Other covalent functionalization

methods for side walls include hydrogenation using carbanion complexes of lithium in liquid ammonia [269] and graft polymerization of styrene monomer using butyllithium as an initiator [270].

4. NanoDiamonds and Diamond Films

As with conventional diamond crystals, nanodiamonds (NDs) are, also pure sp^3 hybrids with the only difference being that the crystal size now is in the nanometer range.

In diamond, the sp^3 hybridization leads to a tetrahedral symmetry in which carbon atoms are bonded through strong covalent bonds. This perfect symmetric arrangement of the four electron orbitals explains why diamond possesses a density higher than that of graphite (3.514 g per cubic cm). Thanks to the tetrahedral structure, diamond also shows an unpaired resistance to compression, and hardness which is the highest with respect to all other substances on both the Vickers and Mohs scales. It is also the reason for the diamond's extraordinary strength. There are no precise measurements of diamond tensile strength. Theoretical estimations have been calculated to be between 90 and 225 GPa, depending on the crystal orientation. These properties have been known from antiquity and were utilized to scratch other materials. Diamond is an insulating crystal classified as wide-bandgap material. Its remarkable resistivity from 10^{11} to $10^{18} \Omega\cdot m$, results from the high stability of the electronic structure and makes it the material of choice for high powered devices. On the contrary, diamond shows a very prominent phonon mobility leading to the best heat conductivity, 3320 W/(m·K) at RT, up to five times the amount of that of copper. High stability/strength of molecular bonds, the absence of reactive sites and free electron pairs make diamond chemically very inert even in contact with strong acids. Diamond can react with the oxygen of an air atmosphere at a temperature of $\sim 700^\circ C$ [271], leading to decomposition in CO, CO₂. Finally, diamond has a high refracting index varying from 2.465 in the violet to 2.409 in the red. This generates the prismatic colors of gemstones. Diamond absorption depends mainly on the defects contained in the crystal. There are several different extrinsic defects in diamond such as nitrogen, boron, phosphorous, hydrogen, nickel, cobalt, silicon, germanium and sulphur. Among them, nitrogen is the more common color center of diamond leading to a variety of defects called A-, B-, C- N₂, N₃ centers. In the visible, their characteristic absorption transitions fall at 575, 527, 478, 465, 452, 435, and 423 nm [272–274]. Concentration of nitrogen defects is used to classify diamond in type Ia with about 95% of all natural diamonds where the nitrogen impurities are $\sim 0.3\%$ (3000 ppm). Type Ib diamonds, which are about 0.1% of all natural diamonds, the nitrogen impurities are up to 0.05% (500 ppm). About 1–2% of all natural diamonds are type IIa. They are almost or entirely impurity free, and this explains why they are colourless and possesses the highest thermal conductivity. Finally, type IIb diamonds constitute $\sim 0.1\%$ of all natural diamonds, making them very rare and precious. They have the lowest level of nitrogen impurities but contain significant boron impurities.

The advent of HPHT and CVD technologies, with the possibility of synthesizing diamonds at reasonable costs, have fostered the use of diamond based technologies with outcomes in a variety of ordinary commercial products. Diamond lenses for optical applications for high-power high-energy radiations or harsh environments is an example [275,276]. Diamond with its outstanding thermal conductivity coupled with the high isolating power [277] makes it desirable in high power electrical devices [278,279]. Diamond hardness [280] and the capability to efficiently dissipate heat [281] is exploited in diamond coatings for processing hard materials [282] and for surgical blades [283]. Diamond in form of nanoparticles replays the properties of bulk diamonds in terms of biocompatibility and mechanical, optical, thermal, and electrical properties. These nanostructures are utilized in a variety of applications such as energy storage, catalysis, electroanalysis, tribology and lubrication, chromatography, and mass spectrometry [284].

Although NDs are widely utilized in industry, applications of diamond in biology and medicine has only started to appear a decade ago. It has been demonstrated that NDs do not influence cell metabolic activity, cell differentiation, growth and proliferation [285,286]. The NDs special biocompatibility and safety can be coupled to the rich chemistry provided by the diamond surface [287] which

enables the grafting of a wide variety of molecules [288,289]. This renders diamond an extraordinary platform useful for different kinds of applications [284,290] spanning from quantum sensing [291,292], to fluorescent probes and tracking [293,294], bioimaging [295,296], drug delivery [297,298] and nano-biomedicine [299,300].

Lattice defects impart photoluminescent properties to NDs which can be used as biolabels or as biomarkers in lifesciences. Among the defects the nitrogen vacancy can be optically interrogated in high sensitivity magnetometry experiments and in quantum detection of temperature gradients in living cells [301,302]. For example, the optically detected magnetic resonance (ODMR) of negatively charged nitrogen vacancy centres in diamond has applications in temperature mapping, and the measurement of magnetic fields in single cells. However, color centers of NDs, in particular nitrogen and silicon vacancies, are of great interest also for imaging applications because they possess a strong absorption at 560 nm while they emit at ~ 700 nm. They are very stable under irradiation which makes them attractive for long-term, three-dimensional imaging and tracking in live cells [303,304]. The intense emission from NDs is currently utilized in super resolution stimulated emission depletion microscopy (STEM) and correlative scanning electron and confocal microscopy. An example is shown in Figure 12.

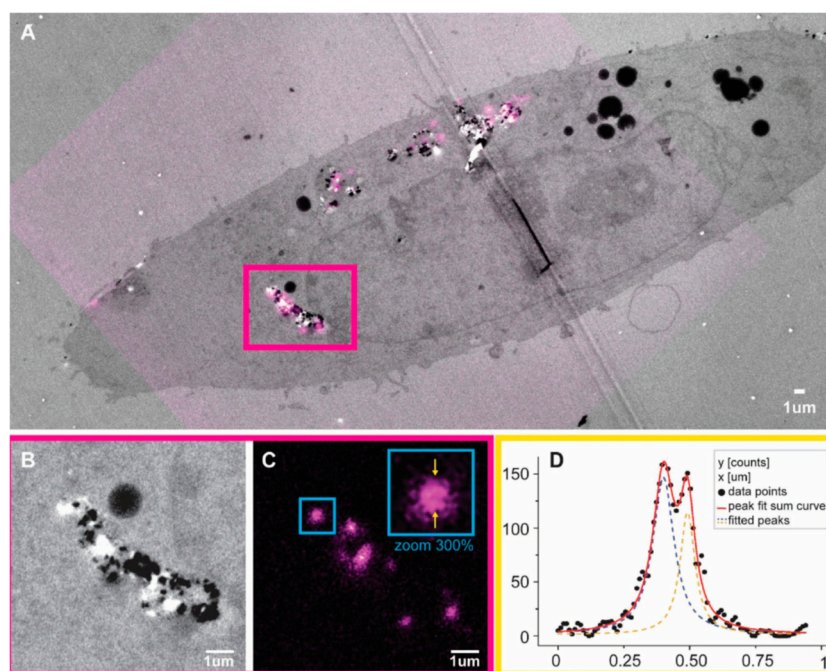


Figure 12. Stimulated emission depletion microscopy (STED-TEM) correlative imaging of intracellular FNDs in TEM sections. (A) A correlation result on a single cell is shown, with TEM in gray and fluorescence signal from FNDs in magenta. (B,C) A zoomed section of the correlation result is shown for TEM and STED, respectively. (C) It is shown that it is possible to use the STED depletion to improve resolution with FNDs. The visual estimation is confirmed in a line profile measurement over a FND cluster, highlighted in (C). (D) The line profile values, and a two-peak Lorentzian fit of the data: the two distinct peaks are ≈ 90 nm apart. Reproduced with permission from [305].

Apart from fluorescent labelling, another possibility is to attach antibodies to the ND surface to target specific structures of the cells. As an example, in [306] the authors functionalized NDs with a bifunctional peptide enabling cell penetration and recognition of the amyloid- β aggregates, which are markers for the Alzheimer's disease. Diamond also opens perspectives for the detection of multiple parameters. Raman spectra of diamond and cells peak in rather different energy regions namely 1332 cm^{-1} and $2800\text{--}3200\text{ cm}^{-1}$. This was exploited to visualize how lysozyme interacts with bacteria [307]. Diamond nanoparticles are utilized in drug delivery where the possibility of

modifying the surface with a wide selection of functional groups allows both the bonding of antibodies and electrostatic drug fixation. This enables the ability to carry a large variety of therapeutics and environment-dependent release [308]. This coupled with the high biocompatibility and the possibility of performing imaging and sensing, opens the way to theranostics [295,299,303,309]. In the era of genomics, different types of nanoparticles were studied as nanocarriers for gene delivery. NDs are also attractive because their ample surface functionalization possibilities helping cell penetration and localized gene release [310]. In [311] authors were able to functionalize DNDs with two silanes enabling the generation of DND conjugates with fluorescein isothiocyanate (FITC) dyes and single-stranded DNA oligomers. Among the therapeutic use of ND, it has been demonstrated that NDs are useful in radiotherapy. When cancer cells are infiltrated with hydrogenated NDs, irradiation is more efficient [312], also in tissue normally resistant to radiotherapy. Authors attribute this effect to increased reactivity towards oxygen groups and to electron emission from irradiated NDs. Diamond and nanodiamond are superior platforms for tissue scaffolds, bone regeneration, and in surgical implants [313]. Thanks to the superior hardness and Young's modulus NDs are beneficial in enhancing the mechanical and chemical properties of polymeric scaffolds [314]. In the following, we present a survey of the current research regarding the synthesis, and physicochemical properties of the NDs in relation to their surface functionalization, with the potential applications in biomedicine.

4.1. Synthesis

The name “nanodiamond” is used to indicate crystals which can be distinguished on the basis of their size. In particular, the NDs are considered as nanocrystalline when the crystal size is <100 nm or ultrananocrystalline if <10 nm [315]. NDs can also be classified considering the synthesis process: detonation NDs (DNDs) [284,316], chemical vapor deposited NDs (CVD-NDs) [317,318], pulsed laser ablation NDs (PLA-NDs) [319,320] and high pressure high temperature NDs (HPHT-NDs) [321] followed by grinding [322]. Examples of the NDs produced using these techniques are shown in Figure 13. Other less common techniques are production of NDs by electron [323] or ion [324] irradiation of graphite or carbon onions [325]. DNDs were firstly produced in USSR about 50 years ago using detonation processes [326]. DNDs are produced by an explosion of an explosive mixture made of trinitrotoluene (TNT) and cyclotrimethylenetrinitramine (RDX) in a closed chamber. The high temperature and pressure reached in the chamber led to the formation of a suspension of diamond crystals with a typical average size of about 5 nm [284]. The production method leads to the formation of a graphitic layer on the surface and a certain amount of impurities and structural defects [327]. Although the small dimensions lead to a high surface to volume ratio, they make impracticable any manipulation if well defined defects are needed, as quantum sensing requires. Much higher quality is obtained using CVD to produce diamonds. In a typical CVD process, a mixture of hydrogen and methane is utilized for diamond film growth [318]. While methane or other hydrocarbon precursors are utilized to provide the carbon atoms, hydrogen is utilized to saturate the dangling bonds on the diamond surface. In addition hydrogen can help cleave the neutral hydrocarbon molecules with the generation of radicals such as CH_2 . These radicals can react with the diamond surface and form amorphous graphite or sp^3 diamond like structures [318]. The presence of hydrogen helps form pure diamond crystals since it etches the graphitic phase [315]. In this way it is possible to synthesize polycrystalline ultranano-, nano-, and micro-crystalline diamond films where the grain boundaries are composed by sp^2 -bonded amorphous carbon atoms. Nanocrystalline diamond films display a typical surface roughness in the range of 30–50 nm. PECVD is a good method to prepare specifically fluorescing diamond film using a relatively low temperature [328]. However, CVD processes have been optimized for the production of single-crystalline possessing electronic grade quality with defect densities of less than 10^2 cm^{-2} and atomically smooth surfaces.

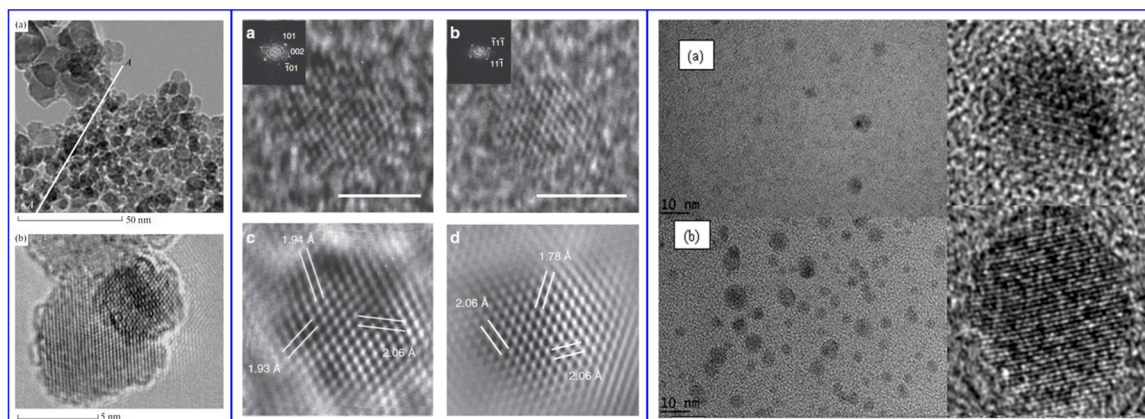


Figure 13. Panel 1: (a) low resolution TEM image of detonation ND powder; (b) high resolution TEM scan along the AA direction shown in (a) ND nanocrystals with their lattice orientation (Reprinted with permission from [329]); Panel 2: high-resolution TEM of two nanodiamonds nanodiamonds produced by a microplasma in ethanol vapors imaged along the (010) (a) and (110) (b) zone axes. Inverse FFT images (c,d) confirm that the particles are lonsdaleite (a,c) and n-diamond (b,d), respectively. Scale bars, 2 nm (reprinted with permission from [330]). Panel 3: high resolution TEM of nanodiamonds grown by pulsed laser ablation in liquid media (PLAL) with different laser energy: (a) 135 μJ for 3 h; (b) 1 h 180 μJ . (adapted with permission from [331]).

Pulsed laser deposition (PLD) is an alternative method to produce films possessing complex stoichiometry. PLD is performed under vacuum and uses high power femtosecond lasers to locally vaporize a target and is followed by the deposition of the vaporized species on a substrate. An evolution of PLD is the laser ablation in liquid media (PLAL). In this case a laser with power exceeding the 10^8 W/cm^2 causes a violent ejection of material from the target. The presence of a liquid environment confines the expansion leading to a significant increase of the pressure. This effect has been exploited to synthesize materials which, as in the case of diamond, require high pressure and high temperatures [320]. In particular, the shocks generated by the pressure waves and temperature quenching due to the liquid create favorable conditions for nanodiamond formation. Using PLAL in water, NDs of 25–250 nm can be produced in agreement with growth kinetics models [332,333]. In addition, the PLAL is able to remove the graphitic amorphous phase even if purification of the NDs is still required. A high pressure high temperature method is utilized to synthesize high quality type Ib, IIa and IIb diamond single crystals that are important in quantum sensing, which is out of the scope of this review. Finally, electron or ion irradiation of graphite or carbon onions has also been proven to induce nanodiamond formation. The transformation of the graphite to diamond requires overcoming the kinetic barrier between the two phases. This occurs only at extreme pressures and high temperatures. These conditions may be obtained by irradiating carbon onions with an electron beam. In these conditions, carbon onions undergo heavy self-compression leading to the nucleation of diamond crystals in their cores [325,334]. This process can be extended to convert graphite to diamond using high-temperature electron irradiation even without the application of pressure [335]. However, irradiation based methods cannot be used to produce large amounts of material and the interest in these synthesis procedure is essentially for base research.

4.2. Functionalized NanoDiamond

The utilization of NDs for biomedicine needs the particulate be suspended in a stable colloidal dispersion. However, NDs easily undergo agglomeration which renders them useless as fluorescent probes, or drug delivery carriers, and in other applications. This is related to the ζ potential which reflects the surface charge on these nanoparticles. Generally a colloidal suspension is considered stable when the ζ potential is lower than -30 mV or higher than 30 mV . The ζ potential strongly depends on the ND surface treatment and on the pH of the dispersing liquid. At $\text{pH} = 7$, vacuum annealed NDs show a $\zeta \sim -30 \text{ mV}$ due to the presence of surface oxidation [336]. The use of strong acids to

remove the graphitic shell covering the diamond core, induces strong surface oxidation thus reducing the value of ζ and increasing the colloidal suspension stability [337]. The behavior of the NDs in a colloidal suspension depends on both the characteristics of the liquid environment and on the ND surface properties. It is then important to establish exact protocols for surface homogenization to obtain reproducible and uniform surface chemistry. Some synthesis techniques give the possibility of defining the diamond surface termination. As an example, in CVD processes generally the surface is H terminated. Differently, the DNDs possess rather variable surface chemistry composed by hydroxyl, carbonyl, ether and carboxyl functional groups in different proportions requiring homogenization. Due to the production process, DNDs are covered by a graphitic shell which must be removed. The process utilized to this scope determines the nature of the chemical groups on surface and thus the value of the ζ potential [337,338]. Purification of DNDs is made using highly oxidizing agents such as strong acids, singlet oxygen in NaOH, strong ozone, and air treated in the presence of a catalyst [338]. These processes also lead to a more reproducible surface composition. DND carboxylation is obtained in strong acids as mixtures of $\text{H}_2\text{SO}_4/\text{HNO}_3$, or with $\text{H}_2\text{SO}_4/\text{HNO}_3/\text{H}_2\text{O}_2$ which are both effective methods to remove non-diamond carbon and terminate the surface with $-(\text{COOH})$ [339]. Another possibility is DND treatment in supercritical water [340]. Surface carboxylation may also be obtained in vapor phases in air at a temperature ranging between 350 and 450 °C [341] or in ozone at 150–200 °C [342]. Other chemical processes are applied to obtain hydroxyl homogenization. Depending on the initial surface composition of the NDs, oxidative, reductive or mechanical techniques are selected. In the case of DNDs where a graphitic shell is present, an efficient hydroxylation is performed in a mixture of FeSO_4 and H_2O_2 (Fenton). The reagents readily attack the non-diamond impurities producing OH radicals which will terminate the ND surface [343]. Another possible route is the use of borane which can reduce carbonyl groups of DNDs apart from lactones and esters [344]. Finally hydroxylation of the DND surface may also be obtained via mechanical methods such as milling and ultrasounds in water which induce radical reactions leading to the $-(\text{OH})$ termination [345]. Another possibility is to surface terminate the diamond surface with hydrogen. This may be accomplished in a hydrogen atmosphere at 900 °C [346]. However, this method can be applied only to films due to the etching properties of H. For diamond nanoparticles hydrogen plasma at low temperatures is performed [347].

Generally, the use of nanodiamonds in biomedicine requires functionalization with biological molecules to gain mimetic properties or the stable attachment of enzymes, proteins, and peptides for biosensing, targeting. One of the most viable approaches for grafting is the formation of extremely robust covalent bonds also leading to biointerface stability at relatively high temperatures. The proverbial stability and inertness of diamond has been considered for a long time as an obstacle to the surface functionalization. However, during the last 15 years a broad list of different processes have been developed to modify the diamond surface. The electrochemical reduction of aryldiazonium salts proposed by Kuo long time ago [348] offers a useful method to derivatize diamond [349] and nanodiamond surfaces [350]. During the functionalization process, the aryldiazonium cations draw electrons away from a reaction center while rather stable N_2 molecules are released as sketched in the Figure 14. These two elements concur to facilitate the reduction of the aryldiazonium salts. Essentially the process proceeds with a charge transfer from the diamond to the dinitrogen groups of the salt ion inducing a release of a N_2 molecule. Then the aryldiazonium cations are reduced and organic molecules bond to the diamond surface [345].

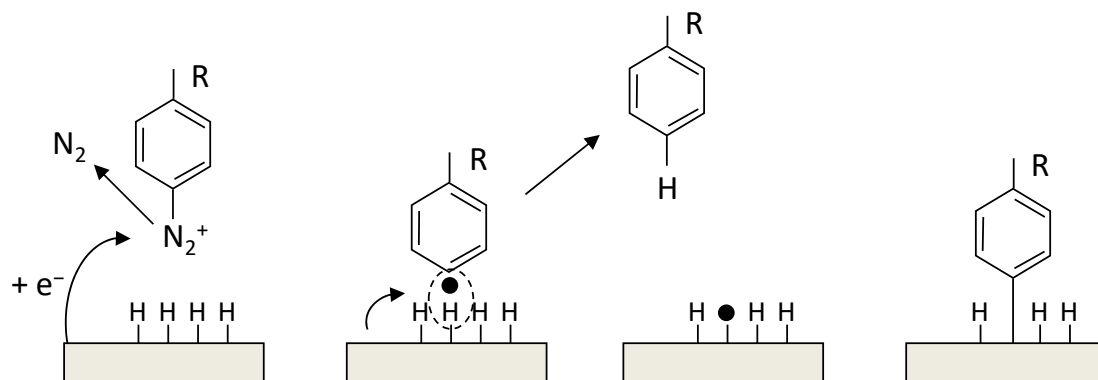


Figure 14. Electrochemical reduction of aryl diazonium salts and linking of organic molecules via stable covalent bonds.

The popularity of this functionalization stems from the simplicity of the reaction requiring only hydrogen terminated diamond surfaces it provides a wide range of functional groups. However, a precise control over the density of the grafted molecules is difficult and the electrochemical reduction easily leads to the formation of multilayers. This problem was solved using an alternative organic molecule which was self assembled in a monolayer on a nanocrystalline diamond film [351]. In this work, authors dissolved dissolved 4-nitro-1,1-biphenyl-4-diazonium tetrafluoroborate in acetonitrile and stirred for 72 h.

The reaction scheme is sketched in Figure 15.

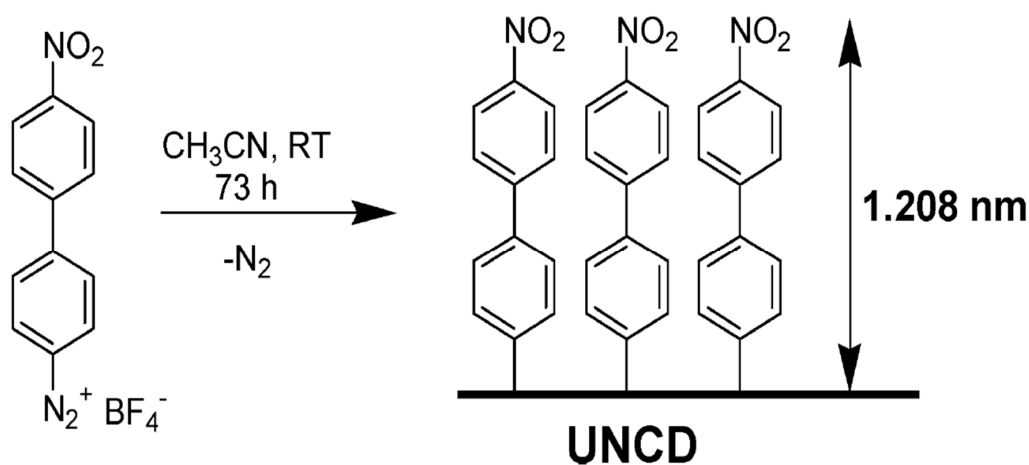


Figure 15. Reaction scheme of the 4-nitro-1,1-biphenyl-4-diazonium tetrafluoroborate molecule with UNCD to form a self assembled monolayer with estimated thickness of 1.208 nm (reprinted with permission from [351]).

Grafting of chlorine-based, amine or carboxyl groups on hydrogen terminated diamond surfaces may be performed using photochemical processes. Originally, UV radiation from a low pressure mercury lamp was used to initiate the reaction between liquid solutions of fluorinated alkene and alkanes organic molecules and the immersed diamond surfaces [352]. Similar reactions can be obtained using non fluorinated compounds. In the proposed mechanism, UV light induces the photoemission of an electron from the H-terminated diamond due to its negative electron affinity. This leaves highly reactive sites on the diamond surface that then induce a nucleophilic attack by the double bond moieties of the organic molecules. The chemical process is shown in Figure 16. The possibility of selecting the desired alkane molecule termination renders this process very useful for further bonding of biological molecules such as DNA oligonucleotides. Initially the w-unsaturated amine of 10-aminodec-1-ene

molecules was protected with the trifluoroacetamide functional groups. UV irradiation of these molecules in presence of a H-diamond substrate leads to the activation of the diamond surface and attachment of the 10-aminodec-1-ene molecules. Deprotection of the amine renders these groups available for interactions with DNA oligomers.

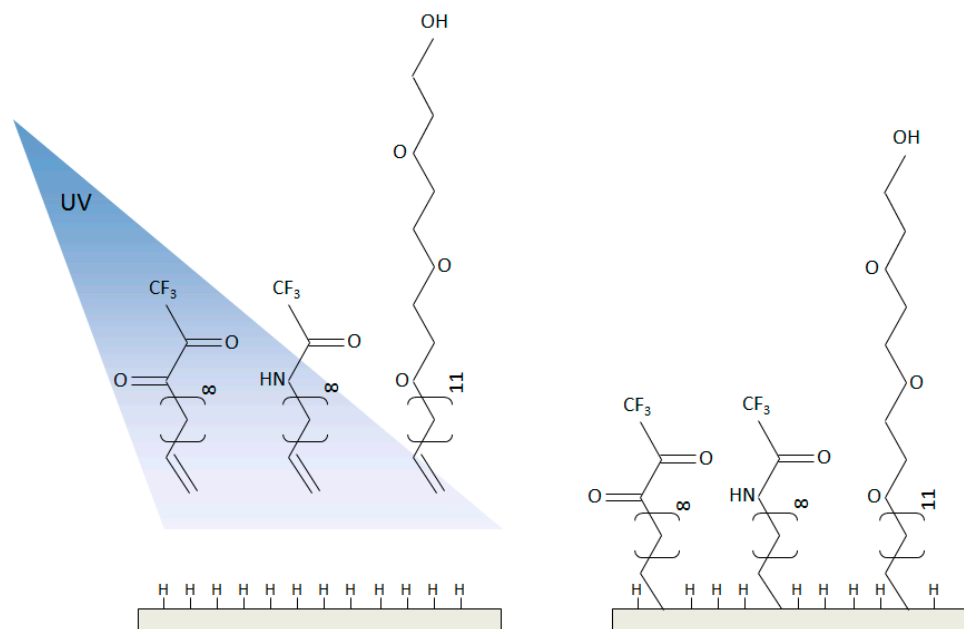


Figure 16. UV- photografting of alkene molecules on H-terminated diamond surfaces.

Photochemical functionalization may also be performed using oxygen terminated diamond surfaces. The oxidation process leads to the presence of oxygen moieties as hydroxyl ($-OH$), ketone ($C=O$), and ether ($C-O-C$) groups [353]. The authors showed that when heating oxidized diamond surfaces at $\sim 200^\circ C$, they are able to selectively bond 1-octadecene molecules via covalent $C-O-C$ bonds. The chemical process is sketched in Figure 17.

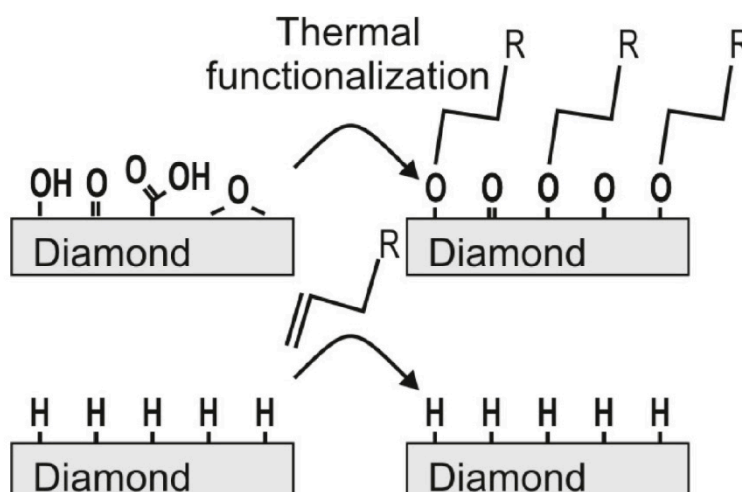


Figure 17. The thermal functionalization scheme on oxygenated and hydrogenated diamond surfaces. Reproduced with permission from [353].

Specific attention requires the amination of the diamond surfaces since this termination is one of the most commonly used to attach biological molecules. Methylamine can react with chlorinated diamond surfaces leading to surface amination [354]. After, it was demonstrated that amination can

also be performed on more common hydrogenated diamond surfaces under UV irradiation [355]. Diamond films were introduced in a chamber in a pure nitrogen atmosphere. Applying irradiation as a 253.7 nm wavelength, the authors were able to induce an amine functionalization. 21-mer probe DNA oligonucleotides were then bonded to the diamond amines and a solution-gate FET sensor was fabricated. The stability of the whole functionalization was made by controlling the shift of the gate potential in successive hybridization/denaturation cycles [355]. Another possibility is to use a cold NH_3 plasma treatment of hydrogenated diamond substrate which is able to induce terminal amino groups [356].

DND functionalization requires the process be performed in a solution. In [357] aminated DNDs were produced by linking ethylenediamine to purified carboxylated nanocrystals to obtain covalently bonded epoxycomposites. In another work [358], bead assisted sonic disintegration was utilized to deagglomerate DNDs. Deagglomerated nanocrystals were then treated with mineral acids at high temperatures to induce surface oxidation. Then the chemistry of the diamond surface can be modified with a variety of reagents. For example, we used the reaction with various trialkoxy silanes such as 3-aminopropyl silanes with methoxy and ethoxy groups leading to the grafting of these silanes onto the diamond surface, as shown in Figure 18.

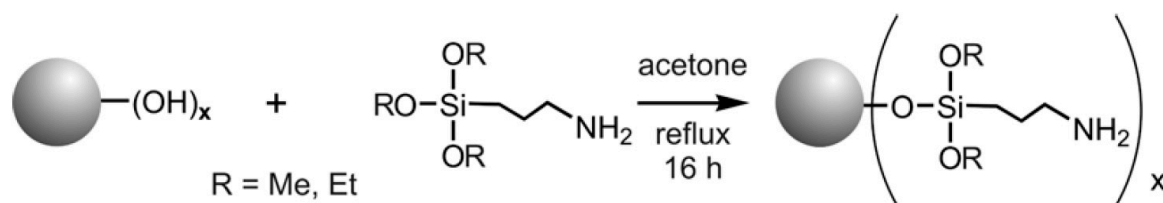


Figure 18. Grafting of trialkoxy silanes homogenized DNDs (reprinted with permission from [358]).

In [359], a very clean surface amination is performed using a one-step process consisting of UV irradiation of the diamond surface in an ammonia atmosphere. XPS analysis confirmed that only amino-groups were grafted on the diamond surfaces. This not only allows further surface engineering with a wide class of biological molecules, but also preserves the surface conductivity which is needed for sensing applications.

5. Carbon Fibers

Carbon fibers (CFs) are fibrous carbon materials that have a graphitic structure with strong crystallite covalent bonds that are highly anisotropic. Carbon fibers are polycrystalline materials containing at least 92% of carbon atoms. These fibers are characterized by a two-dimensional long-range order of carbon atoms arranged in planar hexagonal networks forming stacks in the third dimension without any regularity. As a consequence, they show outstanding mechanical properties along the axis direction but poor mechanical properties in the transverse direction due to the weak van der Waals forces between the layers typical of graphite [360]. Carbon fibers display rather different mechanical properties: tensile strengths from 5.65 to 1.5 GPa and specific modulus from 407 to 106 GPa [360] which may exceed the strength and modulus of steel, 2.39 and 26.6 GPa, respectively [361]. Different types of thermal and stretching treatments can be applied to improve the CF orientation thus increasing the Yang modulus [361]. However, because they are more expensive when compared with other competitors such as glass fibers or plastic fibers, they are used in high performance specialized materials. Typical applications are those requiring lightness and high mechanical properties, particularly in the aerospace and aircraft industries [362]. Besides mechanical properties, CFs display also chemical stability and good electrical, thermal, optical, and structural properties so they are applied in various fields including civil engineering, military, and competition sports [363]. In addition CFs after unloading, have a complete elastic recovery which makes them resistant to fatigue [364]. In industry, CF are added to other materials such as plastic, ceramic, and metals to make composites with superior strength and

high specific modulus, low density, low thermal expansion, heat resistance and improved chemical stability [365].

Since the 1970s, CF have been investigated for use in biomedicine. The reason for this are the mechanical properties and chemical inertness which provide obvious benefits of using CFs as biomaterials. These characteristics are the prerequisite for biocompatibility and long-term in vivo stability. In addition, the CFs can be manufactured in various shapes, can be easily combined with conventional biomaterials, and display high radiolucency [365]. Since CFs have a local structure similar to graphite, they are good electrical conductors with resistivity in the range from $9.5 \cdot 10^{-6}$ to $18 \cdot 10^{-6} \Omega\text{m}$. They can be utilized in voltammetric recognition of biological molecules [366], to make electrodes for neural recording [367,368], or the stimulation of cardiomyocytes [369]. Concerning regeneration medicine, CFs are mainly utilized to fabricate scaffolds for tissue repair. In this respect, CFs are utilized to fabricate scaffolds to enhance tissue regeneration in both soft [370] and hard tissues [371]. Cartilage tissues are a complex environment because, differently from other tissues, they are not self-healing and are rather difficult to regenerate [372]. Nowadays, the majority of the scaffolds produced for cartilage repair fail because of insufficient mechanical strength and structural resilience [370]. In [373], additive 3D printing is utilized to sinter polyamide/CF composite in a computer designed complex structures. Human mesenchymal stem cells were cultivated to improve the scaffold performances in terms of promoting cell adhesion, proliferation, and viability. Images of stained cultured cells on these scaffolds showed a good degree of spreading, demonstrating that CFs promoted the colonization and viability of cells and the chondrogenic differentiation of mesenchymal stem cells. CFs are also utilized in orthoplasty. As an example, composite scaffolds were produced mixing cellulose-hydroxyapatite and functionalized CF to enhance flexural and compressive properties. Results showed that those scaffolds are capable of generating favorable biological properties, allowing preosteoblast cells to proliferate and differentiate [374]. Hip joint sockets and knee joint liners are already produced and applied to patients. A recent work summarized the outcomes of studies evaluating CFR-PEEK as an articulating surface in orthopedic implants [375]. This investigation showed that CF-PEEK based composites utilized for hip replacements, pins, plates, tibial nails, cups, stems, and spinal cages, possess significant mechanical benefits under a number of tests and higher durability and corrosion resistance while maintaining good biocompatibility. CFs are mixed with other polymers such as ultra high molecular weight polyethylene, epoxy resins, and polyamide, displaying good compatibility with the surrounding bones, and rigid fixation while improving the mechanical properties of these polymers [365]. The corrosion resistance and the exceptional strength of CFs are also utilized in regenerative medicine. The variety of surface chemistries and functionalities that can be grafted on the CF surface induce specific bioactivities in relation to their location; for example, improving the adhesion and proliferation of osteoblasts on CF based scaffolds [376]. Another interesting application regards muscles where local electrical stimuli enhance cell proliferation, differentiation, and tissue regeneration, favoring myoblast differentiation into myocytes [377]. CFs functionalized with carbon nanotubes showed remarkable high metabolic activity of myocytes. In addition, the possibility of fabricating fiber oriented scaffolds might be beneficial for a more efficient cell differentiation and higher myotube formation [378]. Poly(lactic-co-glycolic) acid/CF composites were used to generate a carbon nanofiber reinforced patch. The presence of CF induces a high protein adsorption increasing cardiomyocytes proliferation and growth [379], and an understanding of their functions [380]. Results showed that CF-based scaffolds have great potential in becoming the primary treatment in the case of end-stage heart failures [379].

CFs were also found to stimulate wound healing [381]. In the 1980s, carbon fibers were used in clinics to make an active scaffold, inducing tendon regeneration or ligament repair [382,383]. Unfortunately, the weak forces between graphitic planes induced shear stresses, causing formation of debris. Finally, CF-reinforced composite materials were successfully utilized for bone repair. In addition to the improvement of the mechanical properties, CFs added other characteristics such flexibility and improved osseointegration [365].

5.1. Synthesis of Carbon Fibers

First attempts to synthesize carbon fibers date back to 1879 with experiments by Edison to fabricate carbon filaments suitable for the electric lamp. He dissolved cellulosic materials and then extruded the solution in a spin bath to obtain the cellulose in form of fibers. Subsequent carbonization at high temperature in the absence of air led to the formation of weak filaments which were then reinforced by cracking a layer of pyrolytic carbon onto the surface. Nowadays the synthesis of CFs is made starting from three different precursors: polyacrylonitrile (PAN), rayon (regenerated cellulosic fibers), and petroleum pitch. An example is reported in Figure 19.

The original synthesis process of CFs from PAN fibers was firstly carried out by R.C. Houtz who heated a PAN fiber for 4–16 h in air at 200 °C [384]. During heating, the PAN fibers underwent a dehydrogenation reaction with the formation of heterocyclic fused rings. In more recent PAN processing, the synthesis proceeds with the polymerization of PAN and the production of fibers by spinning, then fibers are oxidized and carbonized. Finally, surface treatment is performed to allow better coupling with other materials. Production of CFs using PAN holds the main part of the CF market because PAN fibers allow a faster pyrolysis, PAN chains can be aligned, PAN fibers can be stretched up to 800% further improving the chain alignment, PAN decomposes before melting and provides a high amount of product when pyrolyzed at 1000 °C [385]. CFs produced from PAN are commonly utilized as reinforcement to produce high performance composites for applications in sporting goods, aerospace, and automotive industry [386]. To improve the CF performances, more aligned chains in PAN should be obtained. One possibility is to add comonomers to PAN to form a copolymer [387]. This is made by mixing methacrylate and itaconic comonomers. The first reduces the glass transition temperature while the second acts as an initiator for the formation of the ladder polymers. The final result is an improvement of the 2% to 5% of chain alignment in the final product.

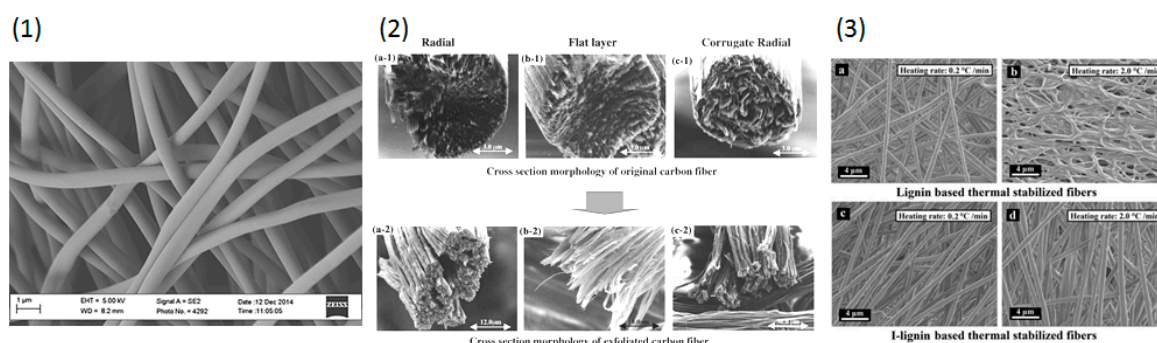


Figure 19. SEM images of carbon fibers (CFs) synthesized from different precursors: (1) SEM image of polyacrylonitrile (PAN) nanofibers after carbonization at 850 °C (reprinted with permission from [388]); (2) Morphological changes of pitch carbon fibers having different textures before exfoliation top after exfoliation bottom; from left: radial, flat layer, and corrugate radial, (reprinted with permission from [389]); (3) SEM images of the stabilized lignin fibers at the heating rates of (a) 0.2 °C min⁻¹ and (b) 2.0 °C min⁻¹, and iodine stabilized lignin fibers at the heating rates of (c) 0.2 °C min⁻¹ and (d) 2.0 °C min⁻¹ (reprinted with permission from [390]).

Another commercially available CF was produced from rayon in the sixties, achieved strength of 2.76 GPa and a modulus of 345 GPa. Let us remember that pure graphite is characterized by a strength of 100 GPa and a modulus of ~1 TPa [385]. Rayon is a promising precursor for CF production since cellulosic precursors have high thermal conductivity, high purity, mechanical flexibility, and low cost. In addition, it forms strong carbon fibers with pyrolysis. The process of producing the precursor for the CF is rather complex and regards the cellulose purification and production of rayon filaments. These are produced by wet spinning from capillaries in an acid spin bath which induces cross linking of cellulose molecules and coagulation in rayon filaments. Slowing down the cellulose regeneration and stretching processes leads to greater crystalline domains within the fiber inducing higher rayon tenacity.

Similar to PAN-based fibres, rayon fibers are thermally stabilized in inert atmosphere where the cellulose fibers undergo a decomposition in a range of temperatures between 200 and 380 °C. The mass loss with emission of volatiles in form of CO, CO₂ explains why the carbon yield is only between 10% and 30%. Therefore, the selection of suitable stabilizer materials is essential for increasing the carbon yield and properties of the final products [391]. The final step regards the carbonization of rayon fibers into graphite-like layers through repolymerization. The conversion occurs in a temperature range between 300 up to 900 °C where semiordered carbonaceous structures are formed in inert atmosphere. Graphitization of the material at 900–3000 °C takes place and high-modulus fibers are produced with the formation of an enhanced order of graphene stacks [391].

An alternative method to synthesize carbon fibers developed in the 1970s is based on pitch [392]. The pitch can be derived from petroleum or coal but the first is preferred because coal-derived pitch is a more rough material requiring refining. Differently from PAN and rayon, the pitch is composed by low molecular weight components with minor thermal stability. Based on the optical properties, pitch precursors are classified as isotropic and anisotropic. The isotropic pitches are used to produce general purpose carbon fibers which are non-graphitic and have poorer properties. Anisotropic mesophase pitch produces high performance CFs containing a large amount of graphitic domains. Pitch mesophases can be produced either by the thermal polymerization of petroleum- or coal-pitches. Also, the fabrication of CFs from pitch consists of spinning, stabilization, and carbonization. In the melt spinning [393], the precursor is melted, extruded through capillaries to form the fibers which are drawn while they are cooling. The stabilization of the pitch fibers is made via oxidation in air. To keep the fiber structure orientated, oxidation must be performed at a temperature below the fiber softening point (~250–350 °C) for a duration ranging from 30 min to several h. The ketone, carbonyl, and carboxyl groups on the oxidized fiber surface induce strong hydrogen bonding between the adjacent molecules facilitating the three-dimensional cross-linking. Finally, the carbonization and graphitization of stabilized precursor fibers are performed initially at 700–900 °C to avoid formation of defects due to the excessive release of volatiles. Then carbonization is carried out at 1500–1800 °C. It has been shown that increasing the carbonization temperature, it is possible to increase the preferred alignment of the crystalline domains [394] and then graphitization may be performed up to 3000 °C.

5.2. Functionalization of Carbon Fibers

Among all the reinforcing fibers, CFs offer the highest specific modulus and highest specific strength. Thanks to their impressive mechanical properties, CFs are widely used as reinforcement of composite materials. Composites based on CFs are suited to applications where low weight, strength and outstanding fatigue characteristics such as stiffness are essential requirements. CFs can also be selected for their resistance to high temperature, the chemical inertness, the electrical and thermal conductivity and low linear coefficient of thermal expansion [395].

CFs are widely applied in aerospace, nuclear, and general engineering, in transportation, and all sectors requiring components with superior resistance to fatigue and degeneration (bearings, gears, cams, fan blades, etc.). However, emerging are also applications in biomedicine where novel materials display the capability to interface with a complex environment where corrosion resistance and tunable mechanical properties are desirable. One of the most important sector of CF application is the fiber/polymer composites where the polymeric materials are polyether ether ketone or epoxy resins polyurethane. They are utilized in prosthetic in hip joint, in spinal fixation, in bone fracture fixation. The advantage of using the CF/PEEK composite is that they have specific modulus similar to bone thereby avoiding interface disruption with risk of bone loss [396]. CFs have shown good biocompatibility by both in vivo and in vitro experiments [397]. CF/carbon composites, scaffolds made of CF find application in regenerative medicine, drug delivery, nerve stimulation ([367,370,397,398]; see Figure 20).

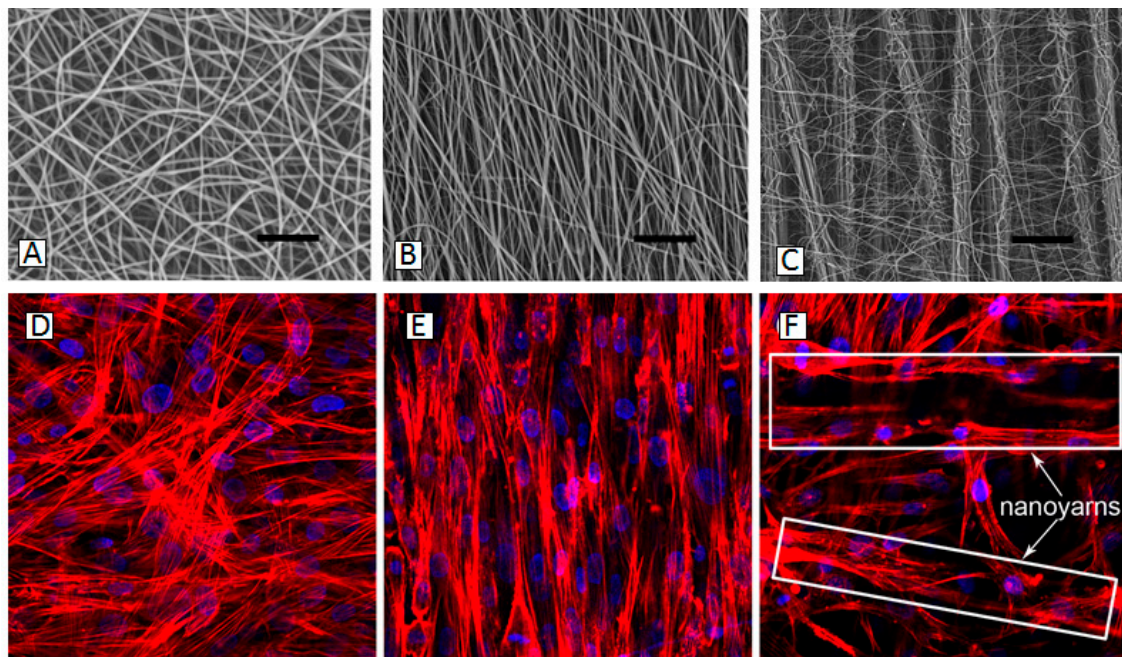


Figure 20. SEM images of electrospun SF/P(LLA-CL): (A) random nanofibrous scaffold; aligned nanofibrous scaffold (B), and (C) nanofibrous reinforced scaffold with yarns twisted by aligned nanofibers (scale bars: 20 μm for (A,B); 100 μm for (C)). Confocal microscopy fluorescence images show the actin filaments (red) and nuclei (blue) of MSCs on the random nanofibrous scaffold (A), aligned nanofibrous scaffold (B) and nanofibrous reinforced scaffold (C) after 7-day culture. Magnifications of all images are 400x. Adapted with permission from [399].

In all these cases, the surface termination, which drives the interaction with the composite material and the living matter, is important. Regarding CFs, the carbonization process at high temperature generates a chemically inert graphitic surface which may be important for biocompatibility. However, this hinders the interaction with other matrix materials and likely behaves as a defect, degrading the overall mechanical properties. Generally, when CFs are utilized without any kind of surface treatment, the poor adhesion with the surrounding material leads to low interlaminar shear strength [400]. The surface treatments can be classified in two gross categories: (i) treatments using physical means thereby enhancing the surface roughness, the surface area, the number of micro-pores or surface pits leading thus increasing the contact points with the external matrix; (ii) the second type of treatments involves chemical reactions with grafting of reactive functional groups promoting good chemical bonding with the surrounding material and, thanks to the presence of polar groups, renders the CF surface wettable. Different kinds of functional groups can be grafted, increasing the interaction strength with the external matrix [401].

In the majority of the cases, CF are coupled to biomaterials such as polymers or metals to form composites. The main purpose of using CF based bio-composites is to improve the mechanical properties of the material or maintaining the same strength while reducing the weight.

A kind of surface treatment consists of surface oxidation which is carried out in a gas-phase, a liquid-phase or chemically and via catalytic processes [402]. The non-oxidative treatments consist of depositing active forms of carbon, plasma polymerization, and grafting of polymers onto the fiber surface [403]. The majority of surface treatments lead simultaneously to both the changes. However, it is important to consider that methods inducing surface etching have positive effects due to the reasons in (i) and (ii), and on the other side, induce a deterioration of the fiber strength thus adversely affecting the whole mechanical properties of the composite.

Let us turn our attention to CF functionalization and, in particular, to CF oxidation. One common method to perform CF oxidation is to utilize strong acids such as nitric acid [404], a mixture of nitric

and sulphuric acids [405], or hydrochloric acid [406]. The treatment efficacy depends on the acid concentration, the temperature and process duration. The acid treatment leads to the formation of carboxylic acid, ester, lactone, phenol, and quinone structure moieties and the density of polar groups, leading to a surface acid character which increases linearly with process duration. This conclusion is confirmed by other works where the density of polar groups increased as a function of the process severity, bringing an overall enhancement of the surface energy. However, as already observed, acid treatment caused a surface etching with an increase of surface roughness and surface area but a loss in mechanical properties. In [407], authors performed a chemical and thermal attack using nitric, and sulphuric acids, hydrogen peroxide, or thermal treatment at increasing temperatures in atmosphere from 380 to 520 °C, or in nitrogen atmosphere from 500 to 600 °C. Results show that oxidation induces the formation of hydroxyl, carbonyl, carboxyl functional groups due to the chemical attack or the interaction of oxygen with the CF carbon atoms. Increasing the duration of the chemical treatment induces an increase of CF mass loss up to 2.5% for 120 min of processing. The mass loss is more pronounced when thermal treatment is applied. In this case, the temperature growing leads to a faster reaction kinetic of O with the CF carbon atoms. In particular, the thermal attack starts at temperatures around 400 °C and becomes massive at temperatures ~500–550 °C with a CF mass loss up to 70% in the case of treatments in air while it was 11% for treatments in nitrogen. It is confirmed that there is a linear growth of surface energy with the duration of the processes for both the chemical and thermal treatments [407]. In [406], the authors compared the efficiency of chemical and plasma treatments to oxidize the CF surface.

Nitric acid was utilized for chemical treatment while oxygen and argon precursors were used in two distinct plasma processes. Authors found that the nitric acid led to more pronounced changes of the CF surface, introducing a larger number of functional groups and augmenting the roughness. The oxygen plasma caused CF etching, removing carbon atoms with the generation of CO and CO₂ molecules. Finally, the argon plasma treatment surprisingly eliminated fiber defects, reducing the size of critical faults, thereby increasing the CF tensile strength.

Plasma treatments may induce diverse surface changes: (i) removal of surface contaminations providing a better interaction of the fibers with the external matrix; (ii) enhanced fiber/matrix interaction due to increased surface roughness; (iii) increase of surface polarity/surface energy with better surface wettability; and (iv) grafting of desired functional groups depending on the plasma precursor used. In [408], an atmospheric oxygen plasma resulted in the formation of COOH, –C–OH and =C=O groups on the fiber surface, improving the adhesion of CF to epoxy composites, thus enhancing the overall mechanical properties. Similar results were obtained by other authors [409] who observed an increase of the interlaminar shear strength with an increase in the duration of the plasma treatment.

We dedicate a short note to the radiation induced surface modifications of CF. Surface roughening as well as grafting of chemical groups were observed in CF exposed to high-energy gamma-irradiation, UV or laser irradiation. It was found that gamma radiation is able to promote the reaction of CFs suspended in water with the oxygen dissolved in the solution [410]. In another work, similar reactions were induced by UV radiation in atmosphere, thanks to the ozone generated by the UV photons [411].

In general, oxidation treatments are desirable to induce a better coupling of CFs with the matrix of the polymeric or metallic or ceramic materials to produce materials with superior mechanical properties.

6. Fullerenes

Among the other allotropic forms, carbon atoms can arrange in cage-like stable structures. In 1970, this idea was substantiated by theoretical calculations on a C₆₀ structure, describing a superaromatic π -systems and predicting its stability from Hückel calculations [412]. However only in 1985 was the first experimental evidence of fullerenes realized, using a mass spectrometer with spectra dominated by a peak at m/z 720 corresponding to C₆₀ while a second peak at m/z 820 was assigned to C₇₀. Spherical cages of carbon atoms can be obtained alternating hexagons and pentagons. In the case of the more common C₆₀ structure, the bonding situation does not differ from that of the graphite single sheet,

the only difference is the different angle at pentagon corners which force the σ -bonds is out of its usual angle of 120° , leading to surface curvature. Combining pentagons and hexagons, it is possible to generate fullerene structures with a “magic” number of carbon atoms $n = 60, 70, 72, 76, 78, 84, \dots$. Cages with a smaller number of carbon atoms also exist. The smallest possible fullerene is C_{20} , with a dodecahedral structure. Possible structures are C_{2n} molecules with $n = 12, 13, 14, \dots$ where the number of fullerenes grows with increasing n . Interestingly, there are no C_{22} fullerenes. The presence of pentagons forbid bond resonance thereby making C_{60} a non superaromatic structure with poor electron delocalization.

The stable fullerene structures constitute a family of molecules possessing unique properties. They are very strong, fullerenes can sustain pressure as high as 3000 atm. and return to their original shape without being damaged [413]. They possess tensile strength about 20 times higher than that of high-performing steel alloys but a density which is half that of aluminum.

Macroscopic amounts of fullerenes were produced in 1990 by the evaporation and recondensation of graphite [414]. This promoted the use of fullerenes in base and applied research. For example, delocalization of charges makes C_{60} an electron deficient system, reacting easily with electron rich species. This offers the possibility of stabilizing electron donor molecules. This property can be exploited in a donor-acceptor system where fullerenes promote charge separation and reduce the recombination, as for example photovoltaics [415], photochemistry [416], photobiology [417,418], and medicine [419]. Referring to this last sector, nanomedicine is based on the development of new nanosized multifunctional platforms [420]. However, fullerenes display a very poor solubility in aqueous solvents leading to aggregation. This makes these structures in their original form, an unattractive candidate in biological applications as already observed long time ago [421,422]. Functionalization of the fullerene surface may solve the problem, generating fullerenes with excellent solubility in both aqueous and organic solvents [423,424]. Platforms based on functionalized fullerenes are currently utilized as scavengers of reactive oxygen (ROS) and nitrogen species (RNS) produced by normal and abnormal cell metabolisms. Free radicals can induce oxidative stress damaging cells, leading to aging tissue abnormalities, and disease processes [425]. They are detrimental for biological molecules such as proteins, lipids, and DNA. As a whole, free ROS and RNS can induce different biological responses related to different degrees of disorders including neurodegenerative/neuropsychiatric and cardiovascular diseases [425], atherosclerosis and cancer [426]. As an electron deficient system where double bonds can react with free radicals, fullerenes are exceptional free radical interceptor, protecting cells from dysfunctions [427]. However, despite of the free radical scavenging properties, fullerenes can also promote the generation of ROS. The mechanism is shown in Figure 21.

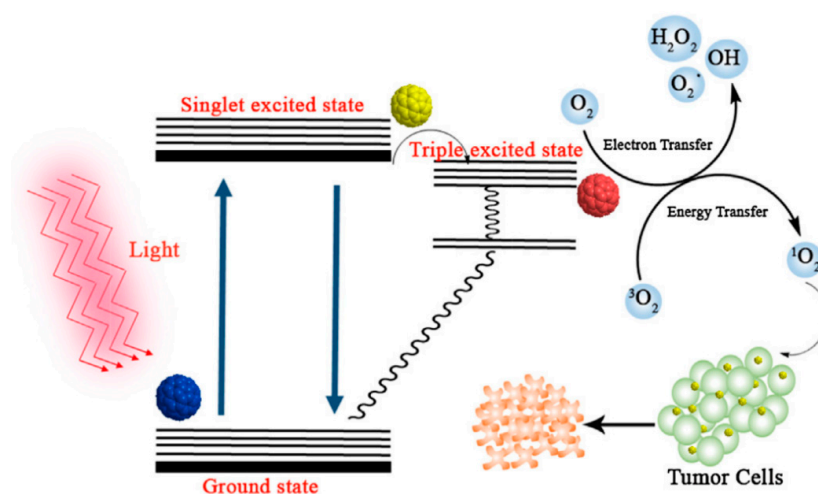


Figure 21. Fullerene mediated generation of ROS and principle of the photodynamic therapy. Reproduced with permission from [428].

Essentially C₆₀ is irradiated with visible light and excited from a S₀ ground state to a singlet excited state S₁. A fast decay follows in a more stable triplet T₁ state which can react with oxygen dissolved in water, producing ¹O₂ ROS. If ¹O₂ ROS is produced inside tumor tissues, it can lead to cell necrosis and death. Fullerenes can be utilized also as carriers for bioactive elements such as drugs, proteins, and genomic material into the cell compartments [429]. Compared to other carriers, fullerenes show the possibility of carrying different payloads, thanks to their biocompatibility which can overcome resistance mechanisms, making the cancer treatment more effective [430]. Fullerenes are also useful to sense biomolecules, enzymes, antibodies or receptors, DNA, or sense the presence of microorganisms, when they are coupled to a transducer [431]. Essentially, fullerene deposited on an electrode can amplify the charge transfer induced by biochemical reactions occurring between an analyte and a target site [432]. When atomic nitrogen is encapsulated in fullerenes [433], because of the narrow EPR lines of nitrogen, it has the potential of being EPRI sensors for imaging. Other therapeutic use of fullerenes are as treatment for osteoporosis. It has been demonstrated that fullerenes conjugated with C(60)(OH)(16)AMBP. Crystal growth studies indicate that C(60)(OH)(16)AMBP reduces hydroxyapatite mineralization by 50% [434]. Crystal growth inhibition technology is highly desired because bone-vectored substances generally target bone areas undergoing formation and resorption processes. Fullerenes also display antimicrobial activity and promising bactericidal activity was observed on *Bacillus subtilis*, *Candida albicans*, and *Escherichia coli* colonies and immunodeficiency virus-reverse transcriptase inhibition was also proved [29,435]. The suppressing activity of fullerenes is ascribed to the generation of ROS under illumination. The fullerene absorbing properties of reactive oxygen/nitrogen species generated by the overexcitation of glutamic acid receptors can be exploited to protect from neurodegenerative diseases like Alzheimer's and Parkinson's diseases [436]. The unpaired antioxidant activity of fullerenes is used to reduce the apoptosis in cortical neurons and to block the receptors of glutamic acid which are accompanied by anti-amyloid action [437]. The same antioxidant activity of fullerenes is exploited in cosmetics to decrease inflammatory lesions and to protect against ultraviolet absorption leading to oxidative cell stress and aging [438].

6.1. Synthesis of Fullerenes

The synthesis of fullerenes is made via pyrolysis of polycyclic aromatic hydrocarbon as naphthalene, corannulene, or higher polycyclic compounds. The molecules are treated at about 1000 °C in an inert atmosphere (usually argon). In these conditions, a decomposition of the molecules occurs with cleavage of the hydrogen bonds and mainly C₆₀ and C₇₀ are produced. Gas pressure is the most important parameter affecting the C₇₀/C₆₀ ratio, with a larger C₇₀ fraction with increasing pressure.

A second method to synthesize fullerenes is an arc discharge produced between two graphite electrodes. When high voltage is applied to two approaching electrodes, an arc develops. The discharge induces vaporization of the graphite with the formation of a plasma. Fullerene are synthesized by condensation of the graphite plasma in particles which deposit on the reactor walls. The process yield is about 15% with C₆₀ constituting about 80% of the fullerene material. Interestingly, small electrodes are normally utilized because vaporized molecules are sensitive to the UV radiation emitted by the arc discharge. Too intense a discharge causes too intense a UV emission, exciting the molecules in a reactive triplet state. These molecules readily interact with formed fullerenes, generating open shell structures and causing a drop in the fullerene yield. A similar synthesis process is the use of high density currents flowing graphite electrodes. If the contact point between the two electrodes is very small, the temperature rises up to 2500–3000 °C, thus vaporizing the graphite. The molecules then precipitate on the cool reactor walls or on a cool finger in the proximity. As for the arc discharge, this process also has to be carried out in inert atmosphere to avoid graphite burning. The process yield may be up to 15% and, after purification, mainly C₆₀ is obtained (C₇₀/C₆₀ = 0.02:0.18).

6.2. Functionalization of Fullerenes

As already pointed out, one of the major problems hindering the utilization of fullerenes for biological applications is its insolubility in water and low solubility in many organic solvents [439]. However, this problem can be successfully solved by functionalizing the fullerene surface. The presence of double bonds in the fullerene chemical structure opens a large variety of possibilities to modify the surface chemistry [440]. Among others, addition reactions are commonly utilized to graft the desired functional groups [441]. Fullerene functionalization is made using two different routes: (i) use of solubilizing agent complexation to partially mask fullerene surface, and (ii) covalent functionalization of the fullerene surface [442,443]. With biomedical applications in mind, we will focus on four different routes utilized to render fullerenes hydrophilic.

The first two reactions regard surface hydroxylation and amination. The presence of these functional groups add a certain polarity to the fullerene thus rendering this molecule reasonably soluble in water. However, there is not a precise control over the density of functional groups grafted on the surface. This constitutes the major disadvantage for their use in the pharmaceutical industry, where reproducibility of each chemical reaction and precise chemical composition is required.

In the second kind of reactions, the tendency of C_{60} to behave as a reactive 2π component in cycloaddition is exploited [444]. This route is very popular and utilized to introduce a large number of complex molecules in a one-pot reaction.

As for other graphite-like systems (graphene, carbon nanotubes ...), the introduction of oxygen based functional groups can be made using strong acids at high temperatures [445]. The reaction leads to the polyhydroxylated of fullerenes. An alternative and frequent method is the use of a basic solution. A very fast reaction is obtained adding a suspension of C_{60} in benzene to an excess NaOH in water. The reaction is carried out in the presence of a small amount of tetrabutylammonium hydroxide acting as a catalyzer [446]. These reactions bring to the formation of an indefinite number of addends. However, despite the lack of control, these reactions are widely utilized to render fullerenes hydro-soluble.

Regarding the amination of C_{60} , in [447], the authors mixed C_{60} in a series of neat aliphatic primary amines (n-propylamine, t-butylamine and dodecylamine) for 16 to 24 h. In other reactions, smaller primary and secondary amine chains (methylamine, diethylamine) reacted with C_{60} and C_{70} fullerenes. The reaction mechanism for the amination of C_{60} with addition at the [6,6] bond is represented in Figure 22.

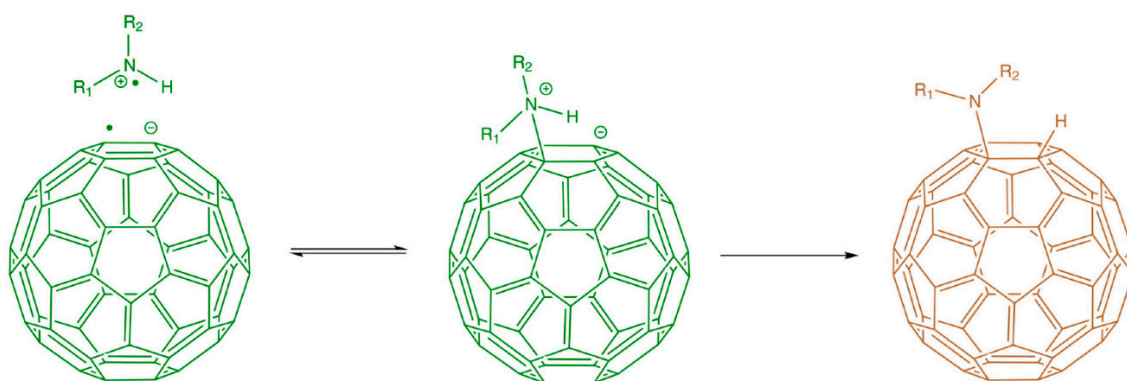


Figure 22. Amination mechanism of C_{60} . The first step is single-electron transfer (a fast process) to produce the C_{60} anion radical which has a characteristic green colour. Radical recombination gives a zwitterion which can be stabilised by proton transfer to give the final product (a slow process giving a brown solution). Reproduced with permission from [448].

Let us turn the attention to the second group of reactions. The 1,3-dipolar cycloaddition of an azomethine ylide to a C_{60} molecule produces a stable pyrrolidinofullerene complex. The reaction scheme is represented in Figure 23. The ylide (ylide is correct) is a reactive intermediate product obtained by the reaction of an α -amino acid with an aldehyde or ketone with subsequent decarboxylation [444]. The resulting compound is a C_{60} with a pyrrolidine ring attached across the [6,6] bond. This reaction is very appealing since it is possible to attach different functionalities since, as it appears in Figure 23, the R1, R2, and R3 groups can be tailored to the desired needs.

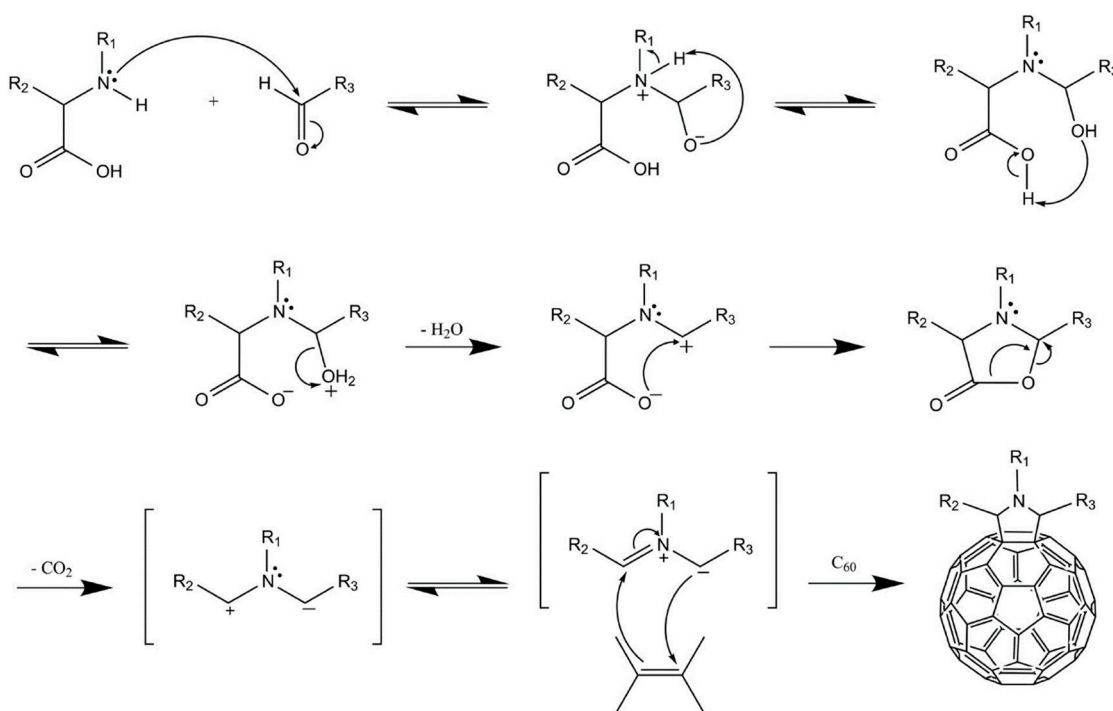


Figure 23. Initial attack of the aldehyde/ketone's polar carbonyl group by the nitrogen lone pair of the amino acid leads to the expulsion of water. Subsequent decarboxylation with loss of CO_2 gives the reactive ylide intermediate. Reproduced with permission from [448].

Differently from the previous amination and hydroxylation processes, this reaction leads to a controlled density of functional groups by fixing the reagent stoichiometry and the reaction time. Because of the symmetry of the fullerene molecules, there are identical [6,6] bonds available for coordination, giving origin to regioisomerism and a lack of control on the adduct position [449]. This could have some implications in biomedicine since regioisomerism may determine the pharmacokinetics and dynamics [450].

An alternative to this process is the cyclopropanation which consists of the bonding of an α -halo ester/ketone to the cage under strongly basic conditions, resulting in a methanofullerene [451]. The reaction scheme is reported in Figure 24 where the strong basic environment causes the deprotonation of the malonate and a nucleophilic attack at the [6,6] position of the fullerene. As for the previous reaction, also in this case, different groups R1 and R2 of the bromomalonate may be selected for specific purposes. The popularity of this reaction stems from the possibility to easily modify the original reaction to produce halogenated intermediates.

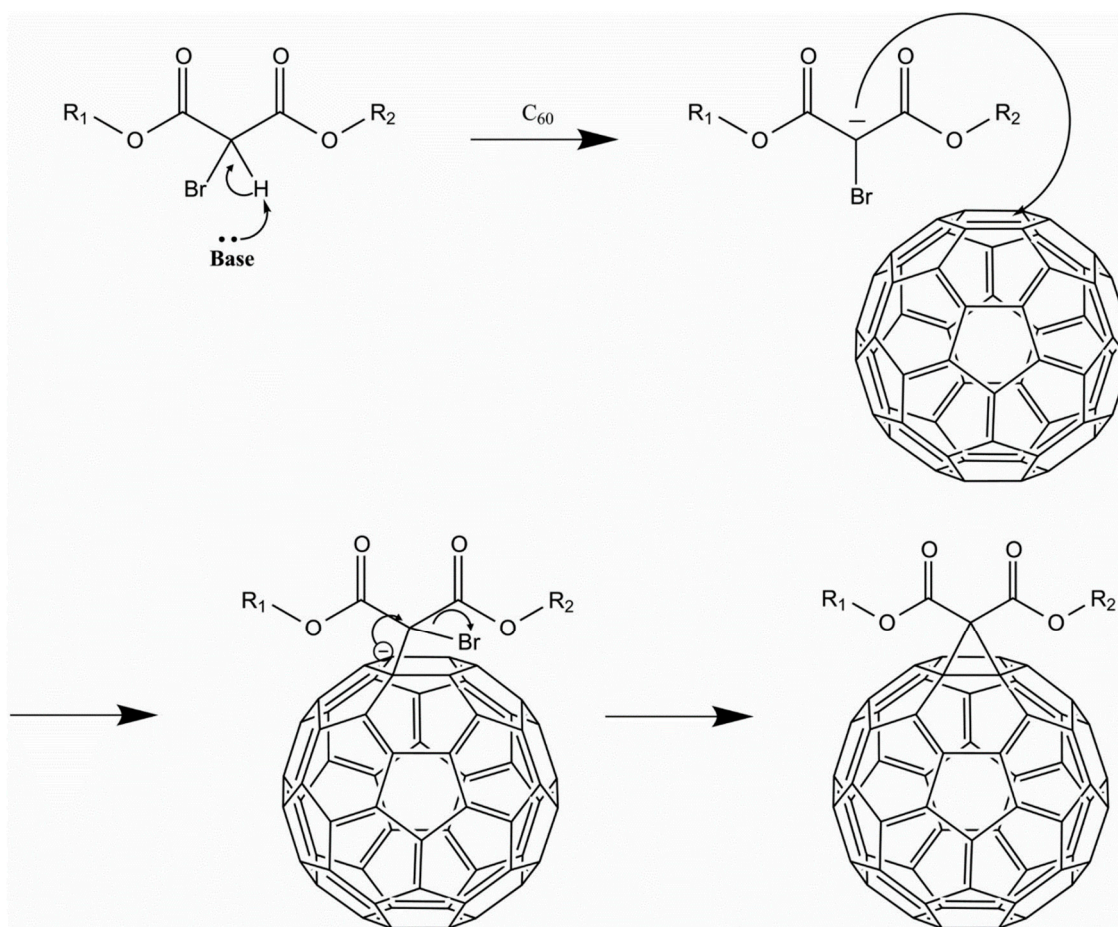


Figure 24. Bingel reaction mechanism. Deprotonation by the strong base gives the nucleophilic malonate anion which then attacks the [6,6] bond. Bromine is then expelled as cyclisation is completed.

An example is given in [452] where C_{60} hexakis-adducts were produced with a cyclopropanation reaction. The presence of a high number of polar groups of these hexakis-adducts make them particularly soluble, which is important for biomedical applications.

The aforementioned four processes are successfully utilized to produce a vast class of products such as the dendro [60] fullerene [453] in which the dendrimers masking the hydrophobic character of fullerenes induce the highest solubility of the product. Pyrrolidine biscalboxylic acid derivatization of C_{60} allows subsequent PEGylation or reaction with the peptide sequence, GABA-GLGVRGA [454].

Metallo fullerenes are another functionalization process where one or more metal atoms are inserted in the fullerene cage. This imparts different reactivities to and properties useful for biomedical applications [455]. Examples are the $Gd@C_{60}$ @ IS CORRECT complex utilized as a contrasting agent for MRI imaging.

Sugars are important components for the biological activity of mammalian cells [456], for their interactions with proteins. There are a series of possible reactions which can be utilized to coordinate sugars with fullerenes. Sugars are firstly bonded to fullerenes via diazoniums [457], azide reactions [458], penta addition [459], cyclopropanation [460], and the Diels-Alder reaction [461]. It is important to observe that in these hybrids, the intrinsic properties of sugar molecules and C_{60} can be preserved despite the mutual interaction thanks to the high flexibility in molecular design which can be utilized to synthesize multifunctional glycofullerenes acting as fluorescent drug carriers and with sensing functions. As an example, fullerenes are ideal electron collectors which can be released to a transducer. They can be located closer to an enzyme active site to detect its catalytic activity [462]. This idea was

utilized in a sensor measuring glucose levels via the oxidation of glucose to gluconic acid catalyzed by the glucose oxidase enzyme/C₆₀ complex [463].

7. Conclusions

Carbon nanomaterials, have been used as multifunctional potent platforms for a number of different biological and biomedical applications. These nanomaterials have been utilized as drug and gene delivery carriers, as fluorescent biolabelling probes, as active elements in photoacoustics, in Raman multiphoton and NIR imaging, as contrasting agents, as electron transfer units in biosensors, as constituents of scaffolds for tissue engineering, and therapeutic principles. The contributions of these carbon nanostructures to the diverse applications derive from their unique physico-chemical properties. Among others, we quote their biocompatibility and the varied routes of surface derivatization. The flexibility offered by these carbon nanomaterials will likely determine a continue utilization of these nanostructures in an ever expanding number of biological applications. Still, a deeper comprehension of the physics behind the behavior of these fascinating objects is need as well as technical and conceptual challenges to be addressed for a better and more efficient application in biomedicine.

Further work should be focused on the following points with respect to their biomedical application. The first and most important aspect is a systematic investigation of their toxicity to the human body, especially in the long-term. Although there has already been some research work carried out to investigate the toxicity of carbon nanomaterials, some controversial conclusions were obtained. The long-term effects of carbon nanomaterials are less reported since these investigations are time-consuming. Secondly, more work on a more precisely controlled synthesis method is still needed for some of these carbon nanomaterials. Usually, materials from different synthesis methods show very different properties and, thus, different biomedical properties. For example, graphene with a single or a few layers is usually required for biomedical applications, which need a more controlled route for their synthesis. With more threats to human health from cancers, medicines based on carbon nanomaterials for cancer treatment has become a hot research area. Carbon materials with versatile functionalization capability provides the possibility of having multifunctional drugs in just one dose. Considering the long period needed for the discovery of a new drug, more effort and more government support is needed to promote their development in this area.

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