

Biomedical Applications of Nitrogen Doped Graphene: A Review

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Abstract

Graphene has been focusing of research due to its extraordinary properties. The discovery of graphene opens up new dimension in the field of materials research and nanotechnology. The various characteristics of graphene have a wide range of applications. from health to aerospace. Many methods can be used to synthesize graphene. Graphene and graphene-based materials have applications in different fields due to unusual electrical, mechanical and thermal properties of these materials. Doping of nitrogen is found to enhance various properties of graphene and have wide range of applications. In this review, an overview of the effect of nitrogen doping in graphene is discussed. Synthesis of nitrogen doped graphene, effect of nitrogen doping on the structure of graphene and different applications of nitrogen doped graphene, are briefly explained. Due to biocompatibility, nitrogen doped graphene has wide range of applications in biomedical science.

Introduction

Carbon and its compounds are the backbone of life on the planet earth. A lot of research has been carried out on materials based on carbon such as graphene, carbon nanotubes, active carbon and carbon nanofibers. Graphene is a mono layer of graphite, tightly bound in a hexagonal honeycomb lattice. In 2004, It was extracted from thin layers of graphite using Scotch tape isolated by physicists Andre Geim and his team [1]. The discovery of graphene is considered as one of the most perfect successes in the field of science and technology [2]. When the layers of graphene are kept on top of each other with an interplanar spacing of 0.335 nm, graphite is formed. The layers of graphene in graphite are held together by van der Waals forces [3]. It is the

thinnest compound known till date. It is one atom thick, the lightest material known and even stronger than steel, the best conductor of heat at room temperature and also the best conductor of electricity [4]. Graphene is an eco-friendly because carbon is the chemical basis for all known life on earth. Due to these extra ordinary thermal, mechanical, and electrical properties, graphene has been explored in high-frequency electronics, bio, chemical and magnetic sensors, ultra-wide bandwidth photodetectors, and energy storage and generation [5-10].

Graphene is a wonder material due to its extraordinary properties. It is harder than diamond but more elastic than rubber; It is tougher than steel yet lighter than aluminum. Graphene is the strongest known material[1]. Its high electron mobility is about 100 times faster than silicon; it conducts heat better than diamond; its electrical conductivity is better than copper; it is optically transparent but it is so dense that it is impermeable to gases – not even helium can pass through it; it absorbs very less amount of reflecting light. These amazing properties make graphene suitable for a largerange of applications in the fields of electronics, optics, sensors, and biodevices[11].

Graphene oxide is a single sheet of graphite oxide and exhibits good performance. It can be attained by exfoliation of graphite oxide. The easily changeable functional groups of graphene oxide facilitate the variation on the surface and make it an excellent material as composites with many materials.

The properties of graphene completely depend on the number of graphene's layers and the defects present in these layers[2].Doping is the most possible method for controlling the semiconducting properties of a semiconductor. The band structure of graphene is highly dependent on the nature of dopant atom. Graphene has zero band gap as its Fermi level lies on the top of its valence band and touches the conduction band. The doping in graphene modifies its electronic structure as the Fermi level shifts either in valence or conduction band that depend on the electronic structure of dopants[12].

Doping of heteroatom such as nitrogen, boron, oxygen, sulfur and phosphorous into carbon lattice could alter the electron system of graphene leading to enhance the properties of doped graphene[12]. Atomic radius and electronegativity of nitrogen are 0.70 Å and 3.04 respectively whereas that of carbon are 0.77 Å and 2.55 respectively. Due to comparable atomic size as that

of carbon, nitrogen (N) is considered as the excellent dopant in graphene. Nitrogen doping can influence Fermi level of graphene [13].

Carbon-based nanomaterials such as carbon dots, graphene oxide nanoparticles, and graphene quantum dots have good biocompatibility and photostability. Nitrogen doping can change the spin density and charge distribution of neighboring carbons [14]. Nitrogen doped graphene is a promising candidate for electrocatalytic reactions such as the oxygen reduction reaction (ORR) [15]. The electrical properties of graphene could be modifying by electron rich nitrogen doping, making the N doped graphene as a potential candidate for sensors and electronics [16]. N doped graphene is highly active in modifying its band gap to attain new properties for device applications [17]. N in graphene quantum dots (GQDs) lattice can severely modify the chemical and electronic properties due to formation of more active sites which can lead to extraordinary behavior which could be broadly useful in various fields [18]. Doping of a graphene layer strongly depends on quantity and the type of dopants created in the honeycomb lattice [19].

In this review, an overview of the effect of nitrogen doping in graphene is discussed. In this review, synthesis of N doped graphene, effect of nitrogen doping on the structure of graphene and different applications of nitrogen doped graphene, are briefly explained. Nitrogen doped graphene has wide range of applications in biomedical science.

Structure of graphene

A single-layer graphene is defined as a single two-dimensional hexagonal sheet of carbon atoms. Bi-layer and few-layer graphene has 2 and 3 to 10 layers of such two-dimensional sheets, respectively. Graphene has a hybridized sp^2 bonding. It has three in-plane σ bonds/atom and π orbitals perpendicular to the plane. The strong σ bonds work as the firm backbone of the hexagonal structure whereas the out of plane π bonds control interaction between different graphene layers.

2 D sheet of graphene can be set to make 3D graphite, set rolling to make 1D nanotubes, and enfolded to make 0D fullerenes [3].

Ground state electronic configuration of carbon is $1s^2 2s^2 2p_x^1 2p_y^1 2p_z^0$ as shown in Figure. 1. In carbon, electrons in the valence shell can form three kinds of hybridization sp , sp^1 and sp^2 . When carbon atoms share sp^2 electrons with their three neighboring carbon atoms, a layer of honeycomb network of planar structure is formed known as monolayer graphene [2]. The tightly packed carbon atoms and sp^2 orbital hybridization give stability to graphene. The grouping of

orbitals s , p_x , and p_y form the σ -bond and p_z electron make the π -bond. These π -bonds hybridize together to form the π -bands which are responsible for enhanced electronic behavior of graphene. In single layer graphene, carbon atoms bond with surrounding carbon atoms with sp^2 hybridization forming a benzene ring in which each atom donates an unpaired electron [3]. The unit cell of a graphene crystal contains two carbon atoms, and the unit-cell vectors a_1 and a_2 have lattice constant of $2.46 \text{ \AA}$ as shown in Fig.1. The distance of the C-C bond is around 0.142 nm [20].

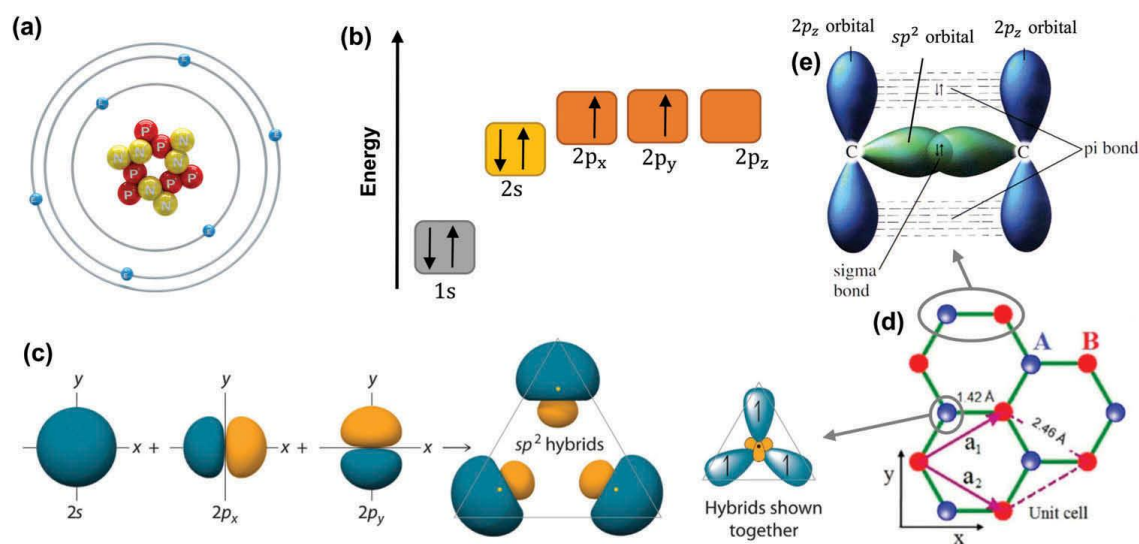


Figure 1.(a) Atomic structure of a carbon atom. (b) Energy levels of outer electrons in carbon atoms. (c) The formation of sp^2 hybrids. (d) The crystal lattice of graphene, where A and B are carbon atoms belonging to different sub-lattices, a_1 and a_2 are unit-cell vectors. (e) Sigma bond and pi bond formed by sp^2 hybridization: Reprinted from ref [20].

Graphene is regarded as a unit structure of CNT, graphite and fullerene. In other words, graphene is composed of a closely packed single layer of carbon atoms, forming a 2D honeycomb lattice plane as shown in Fig. 2. The thickness of graphene layer is only 0.35 nm .

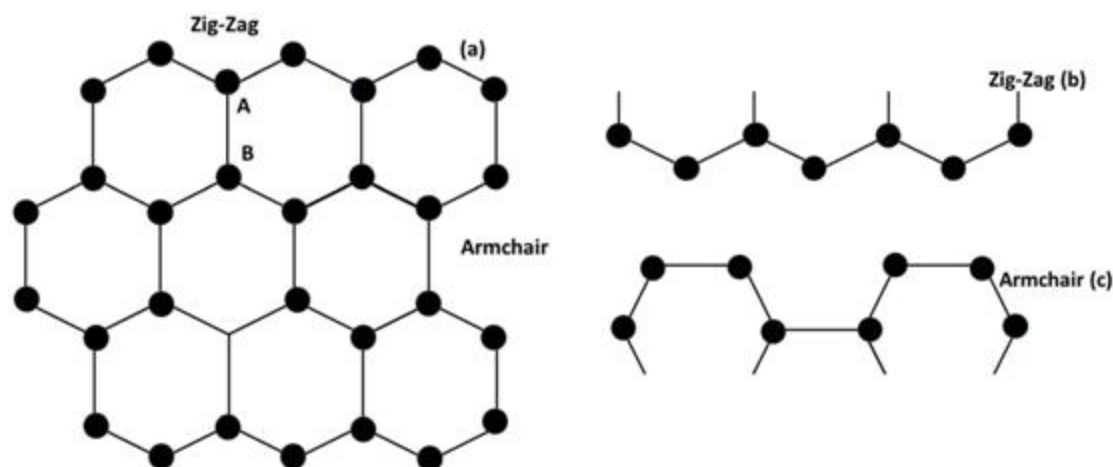


Figure. 2(a) Graphene structure, (b) zig-zag type- and (c) armchair types of graphene: Reprinted from ref [21]

Graphene can be group into zigzag and armchair which depends on different carbon chains as shown in Fig. 2. The zigzag edge graphene nanoribbon typically behaves like a metal whereas a nanoribbon with an armchair edge behaves like either a metal or a semiconductor [21].

Synthesis of graphene and N-doped graphene

Since graphene was first isolated Scotch tape method. The main concern in graphene synthesis is to produce samples with large carrier mobility and less density of defects. Many methods have been developed to produce graphene. Mechanical exfoliation produces high-quality, high-mobility graphene flakes but due to high time consumption, large scale production is not possible using mechanical exfoliation. The graphene sheets are prepared by mechanical exfoliation of highly oriented pyrolytic graphite. This method, known as scotch-tape method, is still widely used in many laboratories to obtain perfectly structured graphene layer. However, this method is not suitable for mass production of graphene [22]. The other method for producing defect-free graphene is the mild exfoliation of graphite [23].

Graphene has also been prepared by thermal decomposition of SiC wafer under ultrahigh vacuum conditions [24]. For the high mass-production of graphene, chemical vapor deposition (CVD) has been used. In this method, the furnace is cooled down from around 1000 °C to room temperature at very low pressure in the presence of a catalyst [25]. The chemical or thermal reduction of graphite oxide is another mass-production method of synthesizing graphene [26].

Nitrogen-doped single layer graphene can be synthesized using CVD method from pyridine along with a small amount of methane [27]. High-temperature heat treatment can be used to produce nitrogen doped graphene using solid carbon source and nitrogen source. [28, 29] In gas annealing method, the solid carbon source and nitrogen source gas is heated above 500°C for some hours in a tube furnace. [30] Nitrogen doped GQDs were synthesized from carbon nano-onions using laser ablation in liquid. This method offered fast production times. [31] N₂ Nitrogen plasma method is widely used to synthesize nitrogen doped graphene. In this method, there is a carbon source on the substrate which is exposed to nitrogen plasma. This method is easy and cheaper than other chemical methods because of applicability at room temperature [32]. Eco-friendly hydrothermal reaction could be used to prepare nitrogen doped graphene sheets were prepared using Ammonium carbonate and an aqueous dispersion of graphene oxide [33]. Dry and high energy wet ball milling methods could be used to synthesize nitrogen doped graphene. In dry ball milling, the dry carbon material like graphite powder is mixed with under N₂ or NH₃ gas filled environment [34] whereas in high energy wet ball milling graphene oxide (GO) and melamine powders is dispersed in the water as a starting material [35].

Structure of nitrogen doped graphene

Nitrogen is considered as the most appropriate dopant in graphene as it is next to carbon in the periodic table and the bond length of N–C is comparable to the bond length of C–C bond leading to small distortion of the graphene lattice [13].

In Nitrogen doping in Graphene leads to formation of configurations such as nitrogen graphitic-N, pyridinic-N, pyrrolic-N, nitrilic-N and oxidized-N as shown in Figure 3. These configurations depend on the mechanism of bonding of nitrogen with carbon atoms thereby changing the local charge distribution and density of states that can affect the catalytic, electronic and sensing properties. [36].

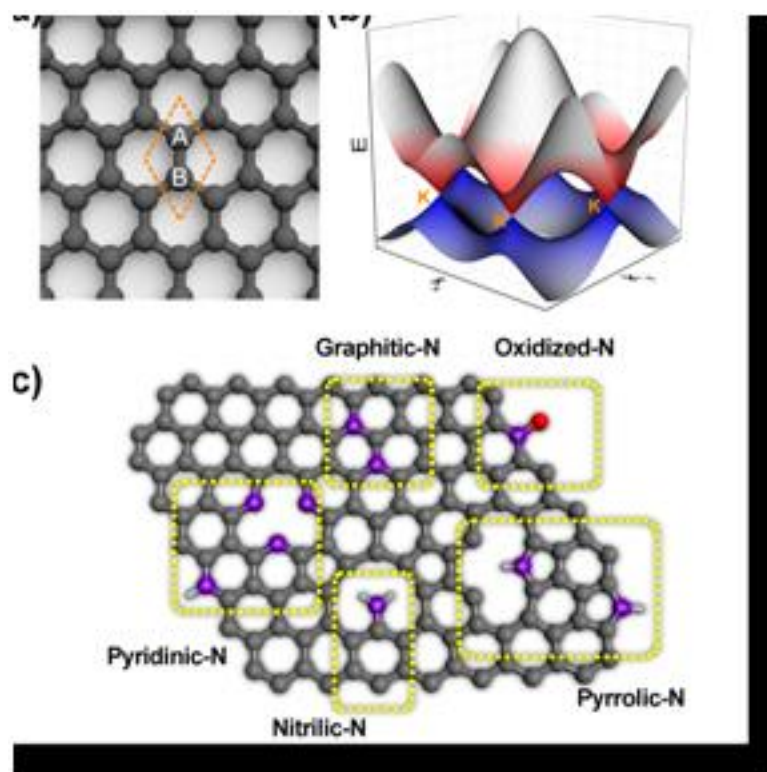


Figure 3. (a) Atomic structure and (b) electronic band structure of pristine graphene and (c) Common nitrogen dopant configurations in graphene: Reprinted from ref [36]

The oxygen reduction reaction (ORR) determines the general performance of fuel cells and has slow kinetics [15]. Mainly materials such as platinum and its alloys are used at the cathode but due to high price and shortage of these metals can be used in limited applications. Nitrogen doping in graphene can efficiently change the spin density and charge distribution of neighboring carbon atoms resulting oxygen reduction reaction. Hence, low-cost carbon nanotubes and nitrogen-doped graphene (NG) can be used as cathode [37].

There are five types of representative models for nitrogen doping in graphene namely quaternary (NQ), pyrrolic (N5), pyridinic (N6, N6nH), and three-pyridinic (3N6) as shown in Fig.4. [38].

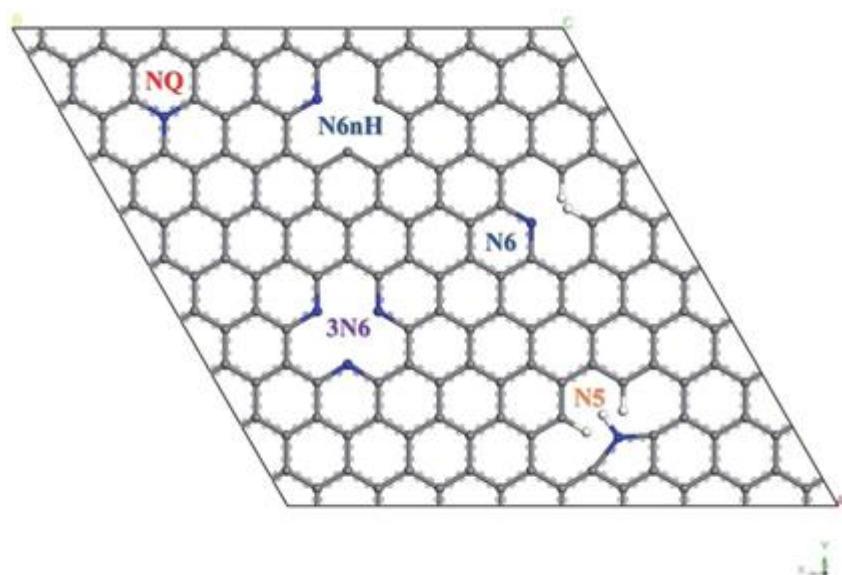


Figure 4.:Five models of nitrogen doped graphene: Reprinted from ref [38]

The free energy diagram and formation energies of each step are shown in Fig.5. It can be observed that step of oxygen adsorption is uphill for all models which decides the performance of ORR. It has been observed that N6 shows the lowest overall reaction free energy at U0. Therefore, using DFT calculations it can be concluded that N6 is the best candidate for ORR [38].

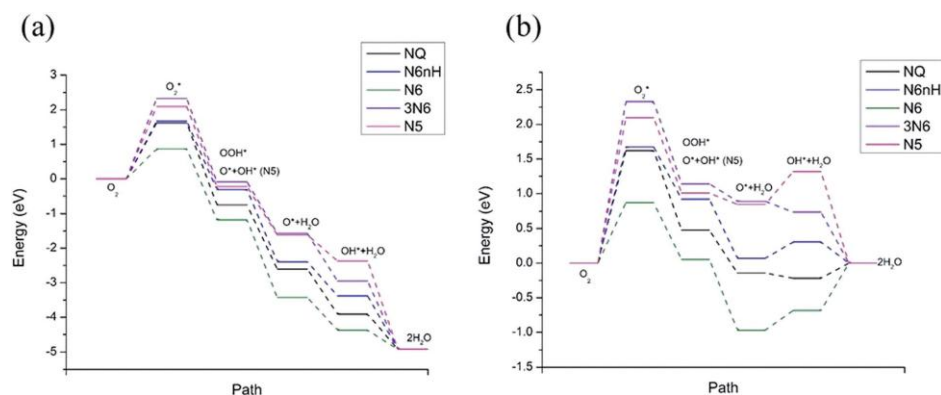


Figure. 5: Free energy diagrams at (a) $U_0 = 0$ V (vs. NHE) and (b) at $U_{eq} = 1.23$ V:Reprinted from ref [38]

Nitrogen doping in graphene found to improve the electronic structure of the graphene by increasing the charge carrier density and modifying the quantum capacitance due to which

interfacial capacitance increases. Quantum capacitance is found to increase with increasing nitrogen doping. Dopants can lead to change the density of states which give rise to enhance quantum capacitance [39]. The models of graphitic, pyridinic and pyrrolic N-doped graphene for different concentrations is given in Fig.6.

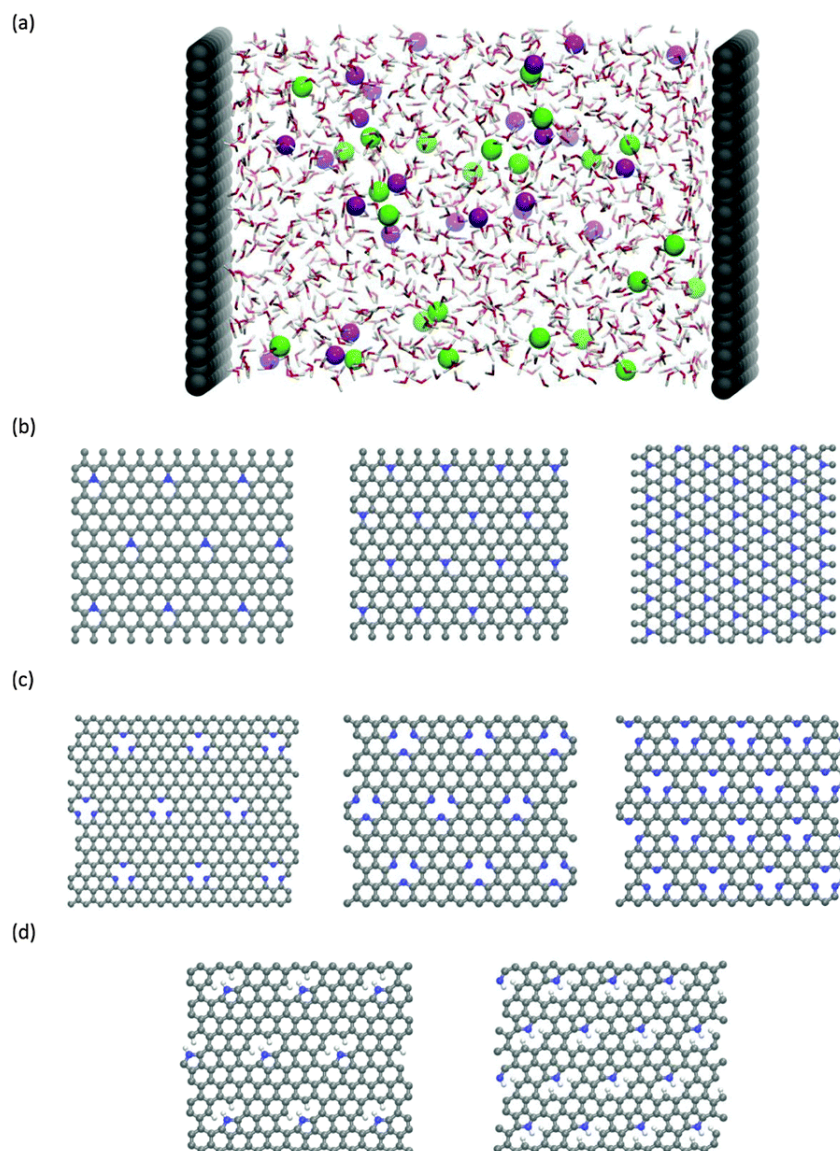


Figure. 6(a) Picture of the MD simulation system; (b) graphitic N-doped graphene sheets having a doping percentage of 3.1%, 5.5% and 12.5% from left to right; (c) pyridinic N-doped graphene having a doping percentage of 6.1%, 9.7% and 17.6% from left to right; (d) pyrrolic N-doped graphene with a doping percentage of 3.2% and 5.9% from left to right. The concentration percentage is defined by the atom ratio from the number of atoms

in the system (C and N). For instance, the N concentration is N atoms/(N atoms + C atoms). Grey, blue, purple, green, red and white balls denote the carbon, nitrogen, Na⁺, Cl, oxygen and hydrogen atoms, respectively:Reprinted from ref [40]

MD simulation and DFT are employed to determine the EDL capacitance and quantum capacitance in graphitic, pyridinic and pyrrolic N-doped graphene for different concentrations [40].The quantum capacitance and density of states of pristine, graphitic, pyridinic and pyrrolic N-doped graphene are plotted in Fig. 7.

It has been observed that in pyridinic and graphitic configurations quantum capacitance increases in large amount while pyrrolic configuration shows a “V”-shaped curve alike the pristine graphene. In the pyrrolic nitrogen doping configuration, due to formation of the N-H bond, the nitrogen atom give an additional electron to the P_zorbital but the associated C vacancy resulting into the loss of one electron in the delocalized p bond so the number of electrons does not change. Therefore, quantum capacitance and density of states plots of pyrrolic-N-doped graphene is similar to pristine graphene.

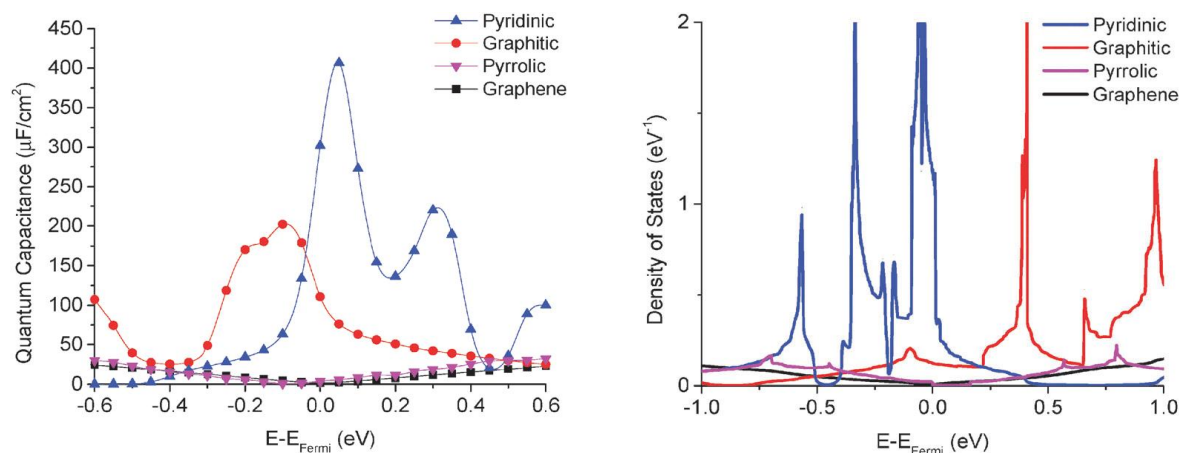


Figure. 7Quantum capacitances of graphitic, pyridinic, and pyrrolic N-doped graphene and pristine graphene, with a mole fraction of nitrogen at 3.1%, 9.7%, and 3.2%, respectively:Reprinted from ref [40]

In Graphitic nitrogen doping configuration, an electron is donated resulting one more electron to the delocalized p bond as compared to carbon atom. Therefore, the “Dirac Point” shifts to a higher energy position resulting to an increase in the Fermi level and the quantum capacitance increases [40]. In pyridinic nitrogen doping, even after no change in the number of electrons on the P_z orbital of nitrogen, a carbon vacancy is created giving rise to lose one electron and the system behave like a p-doping semiconductor. Hence the “Dirac Point” moves down and the density of states near the Fermi level rises significantly resulting an increase in quantum capacitance [39].

Scanning tunneling microscopy (STM), Transmission electron microscopy (TEM), X-ray diffraction (XRD), Raman spectroscopy, X-ray photoelectron spectroscopy (XPS) characterization, X-ray absorption of near-edge structure (XANES) N_2 adsorption/desorption isotherm, energy dispersive spectrum (EDX), selected area electron diffraction (SAED) is widely used to characterize nitrogen doped graphene.

Application of nitrogen doped graphene

The N-graphene have enhanced properties as compared to the pristine graphene as a large number of the structural defects and new sites were induced during the process of nitrogen doping. The different electro negativity of nitrogen and carbon in the N-graphene caused into many applications in different fields.

Nitrogen-doped graphene nanosheets synthesized by chemical-intercalation/thermal-exfoliation of graphite is used as a conductive filler for a polymer resin adhesive and improve performance of a silver-filled electrically conductive adhesive [41].

The effects of the different nitrogen functionalities on the drug delivery performance of the nitrogen doped Graphene quantum dots (N-GQDs) were studied by MD simulations and DFT calculations. Results indicated that the center N-GQDs had shown better results in drug delivery than the pristine GQDs [42]. Photoluminescent (PL) results showed that N-GQDs synthesized by hydrothermal route might be a possible bioimaging agent for in vitro imaging [43]. N-GQDs could be used as fluorescence probes for the detection of Fe^{3+} ions with high sensitivity. Due to enhanced optical properties, exceptional solubility, low cytotoxicity and low cost, these particles have applications in the field of optoelectronics and bioimaging [44, 45].

Expensive platinum group materials are found to be the best cathodic oxygen reduction reaction (ORR) catalyst[46].The cathodic oxygen reduction reaction (ORR) is important reaction in fuel cells. It has been investigated that N doped graphene are considered as a perfect candidate for ORR. [15]N doped graphene is considered to be hopeful, cheap material used in energy storage applications and have potential be used as a supercapacitor due to high electron mobility and high surface area[47].

Ni or co atoms implanted on N doped graphene were fabricated and used to modify the separators of Li–S batteriesfor outstanding rate performance and cycling stability [48,49].

Brilliant blue (BB) is a kind of artificialcolor which has been widely used in food additive. It has been investigated that disproportionate addition of brilliant blue will affect the quality and safety of food products. N-GQDs method was used successfully to analyze brilliant blue in wine samples [50].

N -GQD have potential to be used asan efficient two-photon fluorescent probe for cellular and deep tissue imaging. Because of large imaging depth of N-GQD, these particles have applications to monitor the biological activity of deep tissues and detecting disease of living biosystems [51].Nitrogen doped graphene could be used to fabricate an electrochemical DNA due to its high electron transfer efficiency and large surface area for probe, these biosensorsshowedvery high sensitivity, good selectivity, and repeatability [52]. Nitrogen doped graphene have outstanding electrical properties and a large surface area for enzyme loading and biocatalytic reactions and is a promising candidate for electrochemical biosensors or biofuel cells [53].N doped Graphene quantum dots are used as a sensor to detect Staphylococcus aureus and E. coli bacteria[54].Nanocomposite of N -GQD showed a high sensitivity for cholesterol detection [55].

Conclusion

Graphene is considered as a wonder material having a wide range of applications from health to aerospace.Many methods can be used to synthesize graphene. Graphene and graphene-based materials have applications in different fields due to unusual electrical, mechanical and thermal properties of these materials. Doping of nitrogen is found to enhance various properties of graphene and have wide range of applications. In this review, various method to synthesize

nitrogen doped graphene, effect of nitrogen doping on the structure of graphene and different applications of nitrogen doped graphene, are briefly explained.

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