CHAPTER II

This chapter mainly discuss about the preview of previous literature based on inclusion complex and graphene based supramolecular materials. Further this chapter explores the theory of investigations that are carried out during experiments. Also, the chapter briefs about different type of supramolecular interactions. Finally, the chapter discuss about the future prospect of the present work that can be extended afterwards.

2. LITERATURE REVIEW:

Recently, supramolecular chemistry as well as nanochemistry has gained a lot of interest to the researchers and scientists. That's why both the subjects are being taught in undergraduate and postgraduate degree courses throughout the world. Although, both the fields are highly subjective and also belongs to different areas as supramolecular chemistry deals with non-covalent bond whereas nanochemistry deals with molecular structures having length of 1-100 nm [1,2]. But chemists have found its way to combine both this emerging fields and synthesize different functional nano-supramolecular structures as well as nanocomposites with dimensions on the nanometre scale [4-6]. In the next two sections, we will discuss about literature review on previous works based on host guest chemistry as well as graphene based nanocomposites.

2.1 Host-guest chemistry:

The origin of "molecular recognition" was evolved when Emil Fischer proposed the "lock and key" principle in 1894. According to this concept, an enzyme recognizes and interacts with a substrate such that the binding must be selective similar to lock and a key system [7]. This molecular recognition is one of the core concepts in supramolecular chemistry that consist of selecting binding of substrate also known as guest by a receptor called host molecules [8,9]. In recent times, supramolecular chemistry has become innovative, involving novel concepts and ideas as well as specific experimental techniques and its applicability in different biological and industrial field [10,11]. Let us look at a few examples that have been carried out by different researchers all over the world:

In 1967, Pedersen was accidentally synthesize dibenzo[18]crown-6 which leads to win the Nobel Prize and accelerate the research in host-guest (or inclusion) chemistry [12]. It has been observed that crown ether showed molecular recognition to different guest molecules such as neutral organic molecules, their ions, as well as metal ions.

In 1950s, Friedrich Cramer extensively worked on physical (cavity size) and chemical (reactivity) properties, the structure and chemistry of cyclodextrins (CDs) [13]. He for the first time reported that cyclodextrins are a truncated cone than a cylinder in nature. He showed that CDs could play as a catalyst in chemical reactions through a key–lock interaction similar to that of an enzyme–substrate complex [14].

Cyclodextrins can also be used as a reactant in preparing active polymers products due to its potential applicability such as diagnosis and treatment of cancer, biodegradable capsules, food, drug delivery, and so on [15]. For rapid, flow-through water treatment, Alsbaiee et al. successfully prepared a high-surface-area, mesoporous β-CD polymer, which could rapidly sequester many organic MPs with adsorption rate constants that were 15 to 200 times greater than those of activated carbons and nonporous β-CD adsorbent materials [16].

Cyclodextrins could also be used for the fabrication of novel supramolecular hydrogels for biomedical applications [17]. Supramolecular hydrogels based on CD/homopolymer have been extensively studied where in most of the cases poly ethelyne glycol (PEG), a classic homopolymer chain used. Harada et al. studied the effect of the molecular weight of PEG on the formation of α-CD/PEG complexes. It was observed that the complexes could be formed only when the molecular weight of PEG was greater than 300 [18].

These host molecules are also used for the encapsulation of different drug molecules [19]. W. Su et al. developed a tetrandrine-hydroxypropyl-β-cyclodextrin inclusion complex (TET-HP-β-CD) through inhalation administration and evaluated its therapeutic efficacy for the treatment of pulmonary fibrosis [20].

β-cyclodextrin based covalent organic frameworks (COF) are of high demand for chiral separation. Wang et al. have developed β-CD COF via the condensation

reaction of heptakis(6-amino-6-deoxy)-β-CD and terephthalaldehyde at room temperature through photopolymerization method able to show great potential for chromatographic separation of chiral drugs [21].

2.2 Graphene based nanocomposites:

Material science has always played a vital role in the evolution of technology and provisions for humans and the emergence of the field of nanoscience has made huge changes in the materials applications [22]. Experimental outcome suggest that graphene or graphene based materials have outstanding physical and chemical properties such as led to its application in different industrial and analytical purposes [23].

Graphene oxide based nanocomposites could be used as an efficient and recyclable nano-catalyst for straightforward synthesis of different heterocyclic molecules. Saeed Bahadorikhalili et al. have developed a Cu@βCD-PEG-mesoGO nanocatalyst for one pot synthesis of 2-arylbenzimidazoles and 1,2,3-triazoles using 'click' reaction [24].

Reduced graphene oxide nanosheet is an excellent nanomaterial for photothermal therapy [25]. Cheon et al. developed doxorubicin (DOX)-loaded bovine serum albumin (BSA)-functionalized rGO (DOX-BSA-rGO) nanosheets which could be a powerful tool for chemo-photothermal therapy applications [26].

Graphene-based functional nanocomposite is environment friendly, reusable, and applicable for advanced water purification. Sinha et al. have developed functional nanocomposites G-Fe_2O_3-γ-CD for selective separation of microcystin-LR from contaminated water [27]. Choi et al. have synthesized porous SBA-15/rGO-CD composite scaffold for bisphenol A (BPA) separation from contaminated wastewater [28].

Graphene oxide based nanocomposites are known as an effective recyclable carbo-catalyst for the synthesis of different organic molecules. Emami et al. have synthesized and characterized graphene oxide–polyaniline lignosulfonate (GO-PANI-LS) nanocomposites in synthesizing polysubstituted pyridines [30].

2.3 Theory of investigation:

2.3.1 Stoichiometry:

The stoichiometry (i.e. the ratio of host to guest) of host-guest complexes can be determined through a Job's plot also known as continuous variation method using UV-vis, fluorescence spectral or either NMR titration methods [31]. Experiment is carried out with a series of solutions made up with varying ratios of host and guest from 0:1 through 0.5:0.5 to 1:0 such that the total concentration of host and guest is constant. A plot of relative absorbance at the wavelength of the peak associated with the complex (ΔA) against mole fraction (r) allows us to calculate its stoichiometry. If the Job's plot reaches a maximum at 0.33, the complex has a 1:2 stoichiometry, if the maximum is reached at 0.5, the stoichiometry will be 1:1 and if the peak stands at 0.66, the stoichiometry will be 2:1 (Figure 1).

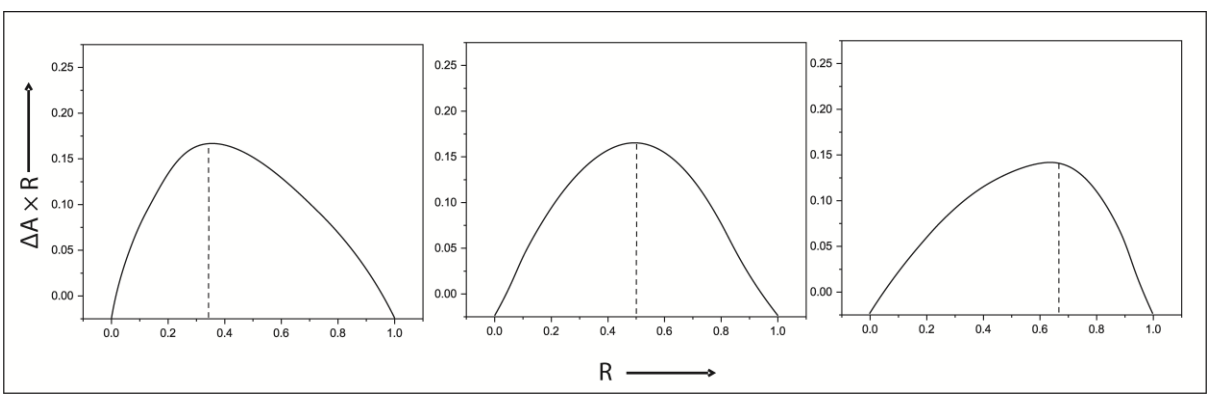

Figure 1: Typical Job's plot depicting the peak position which indicate the stoichiometric ratio between host and guest molecules

2.3.2 Binding constant:

The binding constant also termed as association constant is basically the mathematical expression of degree of association [32]. It is an equilibrium process and the binding of a guest by a host species, or the interaction of two or more species by non-covalent bonds. The binding constant is calculated by Eq. (3 or 4), using the equilibrium concentrations of the species such as host [H], guest [G] and the resulting complex [H.G]. The final value, K_a, has units of $mol.dm^{-3}$ or M^{-1}. These values can range from near zero to very large and for cyclodextrin based supramolecular system, it is generally found to be from 10 to 10^4 M^{-1}. Binding constant helps to quantify the stability of a host–guest inclusion complex in solution

for a given system. It can be calculated from experimental data e.g, titrations monitored by NMR, UV–vis or fluorescence spectroscopy in solution phase which provide information about the position of the equilibrium as shown below (eqn. 1);

$$K_a = \frac{[Host.Guest]}{[Host][Guest]} \text{..... (1)}$$

However, if host–guest complexation process involves encapsulation of more than one guest molecules, then, the overall binding constant are described by summation of each stepwise binding constants, and an overall binding constant for the final complex which is termed beta (β). The general formula of the overall binding constant for n number of guest is shown in eqn. 2;

$$\beta = \frac{[H.G_n]}{[H].[G]^n} \text{..... (2)}$$

Where, H stands for host molecules and G stands for guest moieties. n is the number of guest molecules involved in the inclusion phenomena.

Association constant can be determined using UV-vis titration by Benesi-Hildebrand equation for 1:1 stoichiometry as shown below (eqn. 3):

$$\frac{1}{[A - A_o]} = \frac{1}{K_a[G]_o \Delta\varepsilon} \times \frac{1}{[H]_o} + \frac{1}{\Delta\varepsilon} \text{... ... ... (3)}$$

Where ΔA= [A-A$_o$] stands for difference in absorbance, Δε stands for change in molar extinction coefficient, K$_a$ is the association constant, [H]$_o$ and [G]$_o$ represents initial concentration of host and guest respectively.

For Fluorescence studies, the equation becomes eqn. (4)

$$\frac{1}{F_O - F} = \frac{1}{(F_O - F_{max}) \times K_a \times [CD]^n} + \frac{1}{F_O - F_{max}} \text{..... (4)}$$

Where, Where, F and F$_o$ denote the fluorescence intensity of guest on adding host and pure guest respectively. F$_{max}$ is the saturation fluorescence intensity. K$_a$ is the association constant obtained by dividing intercept by slope. n is the binding stoichiometry between guest and host.

2.3.3 Thermodynamic stability and different thermodynamic parameters:

The thermodynamic parameters of the analyzed inclusion processes, enthalpy change (ΔH°) and entropy change (ΔS°) and Gibbs free energy change (ΔG°) can be obtained by means of the classical van't Hoff equation (eqn. 5 & 6) [33]:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad \ldots\ldots\ldots (5)$$

$$\Delta G^\circ = -RT\ln K_a \quad \ldots\ldots\ldots (6)$$

From association constant value (K_a), all other thermodynamic parameters such as the standard change in Gibbs free energy, ΔG°, enthalpy change ΔH°, and entropy change ΔS° can be easily calculated. Although, K_a value is necessary to calculate the binding affinity between host and guest, the other thermodynamic functions may provide valuable insight into the mechanisms driving the formation of the complexes.

2.3.4 Host-guest inclusion complex in spectroscopic and spectrometric methods:

Infrared (IR) as well as nuclear magnetic resonance (NMR) is very much conventional techniques to confirm the supramolecular formation. It is well known that IR spectroscopy is generally used to identify the functional groups that are present in a molecule. Usually, both the guest and host moiety has its characteristic shape, size and intensity of the absorption peak of different functional group [34]. When, an inclusion complex is formed, there will be broadening, widening, disappearance or change in intensity of the peaks due to complexation. During supramolecular complex formation, a strong hydrogen bond can also be identified with FTIR spectroscopy [35].

Similarly, ^{1}H-NMR spectroscopy is also used to obtain the information of hydrogen and carbon environments after inclusion. When, inclusion complex is formed, there will be line broadening or chemical shift displacement of host and guest molecules [36]. The change in chemical shifts are easily observable for protons located at the inner surface (H-3 and H-5) of the cyclodextrins, when guest molecules are inserted but the chemical shifts of protons (H-1, H-2 & H-4) remain unchanged as located at the outer surface of the Cyclodextrin. Therefore, from NMR

data, change in chemical shifts appeared due to inclusion complex gives information on structural details [37].

With the help of mass spectrometry, it is possible to find the molecular mass of supramolecular assemblies [38]. In supramolecular chemistry, soft ionization technique is one of the used methods to detect weakly associated assemblies and their fragments.

2.3.5 Thermal analysis:

Thermal analysis techniques are one of the most prominent techniques to characterize different type of supramolecular materials and provide us information about thermal stability of the product as they undergo physicochemical changes when subject to heating. It can be of different types such as thermogravimetric (TG), differential thermal analysis (DTA), and differential scanning calorimetry (DSC).

In case of DSC analytical method, pure drug, cyclodextrins and its derivatives and its Inclusion complexes are analyzed as recognition tool. According to the theory, if guest molecules are encapsulated into the cyclodextrin host cavities, their physical characteristics such as melting point, boiling point should be shifted to a different temperature or may get disappeared [39]. Therefore, when guest molecule is treated, a sharp characteristic endothermic melting peak at a definite temperature will be observed. However, β-CD and HP-β-CD will show a single characteristics endothermic peak at about 88^0C and 60^0C which is due to the release of water from the β-CD and HP-β-CD respectively [40]. But, when the guest molecules formed inclusion complex with cyclodextrin, the endothermic peaks will be shifted to a different temperature region. This Phenomena give a strong evidence that inclusion complex has been formed.

2.3.6 Theoretical calculations:

Now-a-days, computational approaches have been extensively used at the atomic level to understand the structural and thermodynamic features involved in the processes of molecular recognition and supramolecular organization. Molecular modelling technique is one of the widely used methods in host-guest chemistry as well as in pharmacology and drug design. In computational chemistry, molecular mechanics (MM), molecular dynamics (MD) are very reliable and inexpensive tool

for conformational analysis. However, dynamical processes of the inclusion complexes can be achieved with the help of molecular dynamics simulations and it is carried out in gas phase as well as in solution phases with time bound upto nano second (ns). Computational methods are extensively used in biological science to identify the active site of various proteins. It gives us an idea about binding free energies through molecular docking with proteins or synthetic macrocyclic hosts, effective interactions as it can be hydrophobic or van der Waals force between host and guest.

2.4 Type of supramolecular interactions:

It is actually the non-covalent interactions that hold supramolecular species together strongly. Non-covalent interactions are considerably weaker than covalent interactions, which can range between 150 kJ.mol^{-1} to 450 kJ.mol^{-1} for single bonds. Non-covalent bonds range from 2 kJ.mol^{-1} for dispersion interactions to 300 kJ.mol^{-1} for 'ion-ion' interactions. It should be noted that when a stable supramolecular complex forms, it is not due to a single non-covalent interaction rather combination of forces. Therefore, it is very much important to design supramolecular components so that balance of all these forces can be manipulated to enhance the overall binding affinity between host and guest. The non-covalent interactions can be of different types of attractions as well as repulsions which are summarised in Figure 2 and will be described in more detail as follows.

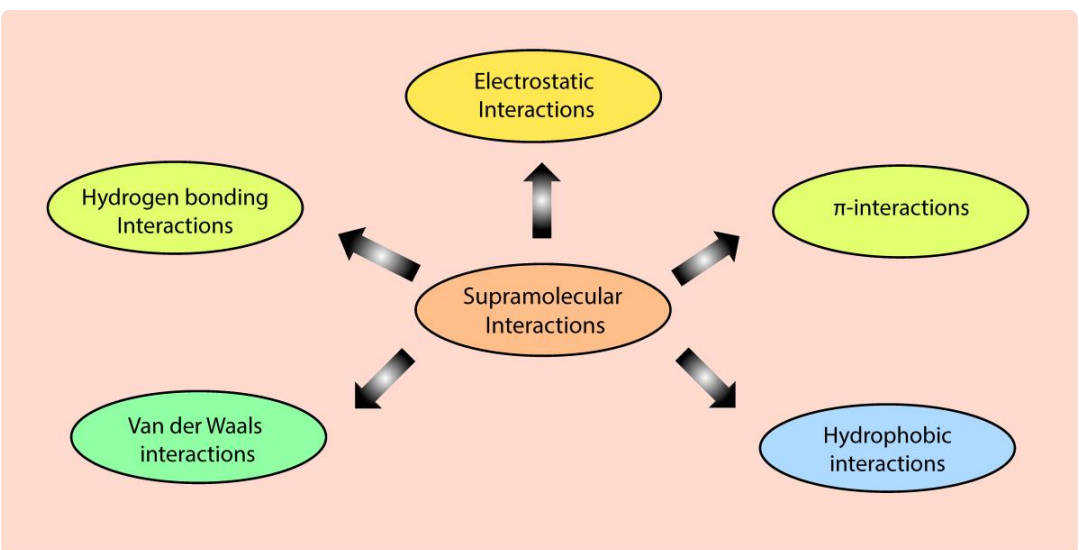

Figure 2: Different types of non-covalent interactions in supramolecular chemistry

2.4.1 Ionic and dipolar interactions:

Ionic and dipolar interactions can be split into three categories: (i) ion–ion interactions, (ii) ion–dipole interactions, and (iii) dipole–dipole interactions, which are based on the Coulombic attraction between opposite charges. The strongest of these interactions is the ion–ion, which is comparable with covalent interactions. Ion–ion interactions are non-directional in nature, so that the interaction can occur through any orientation.

However, ion–dipole and dipole–dipole interactions are orientation-dependant and to obtain the optimal direction two moieties should be present in aligned nature. The strength of these directional interactions is directly dependent upon the species involved (Figure 3a). Ion–dipole interactions are stronger than dipole–dipole interactions (50–500 and 5–25 kJ mol^{-1}, respectively) as ions have a higher charge density than dipoles. Out of these three interactions, dipole–dipole interactions are the weakest directional interaction which helps in bringing species into alignment.

2.4.2 Hydrogen bonding:

The hydrogen bonding interaction is one of the most important non-covalent interactions in making supramolecular construct (Figure 3b). It can also be termed as a special kind of dipole–dipole interaction as when a hydrogen atom covalently attached with an electron rich atom thereby behaving as an electropositive centre due to polarization and forms a hydrogen bond with nearby electron rich atoms. Therefore, hydrogen bonding interactions mainly consist of hydrogen bond donors and acceptors (e.g. amino acids, carbohydrates and nucleobases). Hydrogen bond donors are groups having a hydrogen atom attached to an electronegative atom (such as nitrogen or oxygen), cause a change in dipole where the hydrogen atom carry a small positive charge. Hydrogen bond acceptors carry an electron-withdrawing atom which can interact the positively charge hydrogen atom, e.g, carbonyl moieties.

The strength of hydrogen bonds can vary depending on the system. It depends on the type and nature of the electronegative atom to which the hydrogen atom is attached. Typically, the strengths of this interaction range from 4 to 120

kJ.mol^{-1}, with the vast majority being under 60 kJ.mol^{-1} and scales of hydrogen bond acidity and basicity have been developed.

2.4.3 π-π stacking interactions:

The non covalent interactions between the aromatic moieties are often known as π-π stacking interaction, it also recognised as the interaction between aromatic rings having π orbitals (Figure 3c). The persistence of π-π stacking interactions can be observed by X-RAY crystal diffraction which is a direct and superior one. It has been observed that π-π stacking interaction also includes quadrupole interactions among delocalised π– elections. Aromaticity is the essential condition for π-π stacking interaction to occur but in some cases exception also observed. In short, π-π stacking interaction take place in two aromatic molecules having similar structure and election distribution as well as in election rich and election deficient molecules. It is an important point to note that the polarity of the solvent plays an important role in these two systems. This type of interactions are very important to structure and function of various biological molecules like proteins, cofactors, substrates etc. π-π stacking interactions have significant role in DNA sequencing, for the synthesis of molecular receptors, for the formation of supramolecules, fabrication of sensors, fluorescent and electrogenerated chemiluminescent sensors, for controlled drug release, fabrication of bio sensor as well as chemo sensor.

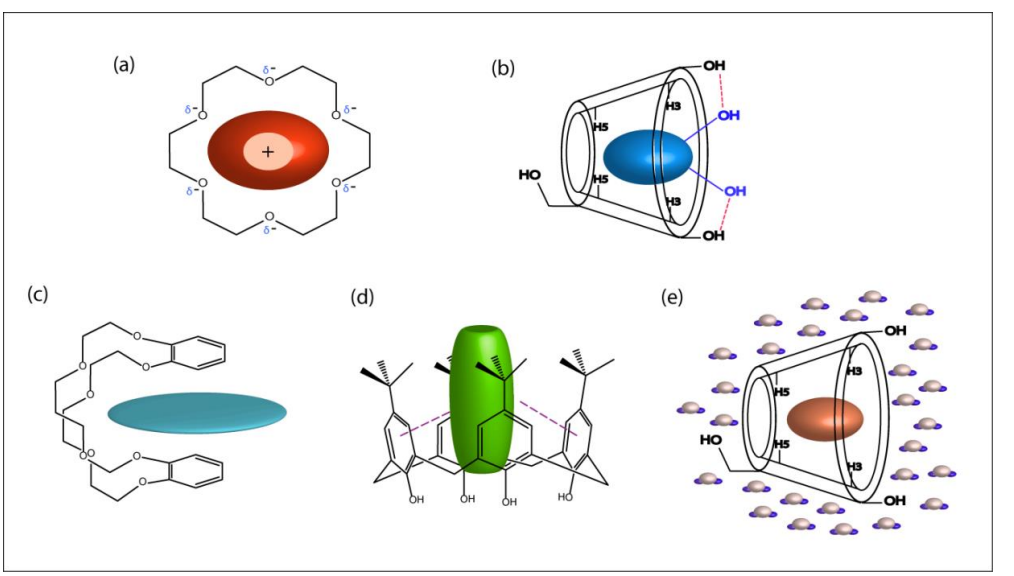

Figure 3 : Schematic representation of different types of interactions (a) ion-dipole interaction (b) hydrogen bonding interaction (c) π-π stacking interaction (d) van der Waals interaction (e) hydrophobic interaction

2.4.4 van der Waals interactions:

Van der Waals interactions emerge when two molecules with strong electron density come in close proximity cause a weak electrostatic attraction force (figure 3d). It can also be sub-divided into two parts such as one is London interaction and the other is exchange and repulsion interaction. The strength of these interactions is dependent on the polarizability of the molecule; the more polarisable the species, then the greater the strength of the interaction. The potential energy of the London interaction decreases rapidly as the distance between the molecules increases. These interactions are non-directional and do not feature highly in supramolecular design. However, van der Waals interactions are important in the formation of inclusion compounds, in which small organic molecules are incorporated into a crystalline lattice, or where small organic molecules have been encapsulated into permanent molecular cavities. The inclusion of toluene within the molecular cavity of the p-tert-butylphenol-based macrocycle, p-tert-butylcalix[4]arene.

2.4.5 Hydrophobic effect:

Hydrophobic effects arise from the exclusion of polar groups such as water or weakly solvated molecules. Hydrophobic interactions play an important role in supramolecular chemistry, when cyclophanes and cyclodextrins are taken into consideration in water (Figure 3e). Hydrophobic effects can be sub divided into two energetic components, namely an enthalpic hydrophobic effect and an entropic hydrophobic effect. Enthalpic hydrophobic interactions occur when a guest replaces the water within a cavity and get stabilized. This occurs quite readily as host cavities are often hydrophobic in nature, inner cavity water does not interact strongly with the host and is therefore of high energy. When the water molecules are replaced by a guest, the energy becomes lowered by the interaction of the former water guest with the bulk solvent present outside the cavity. The entropic hydrophobic effect arises when water molecules that were previously ordered within the cavity becomes disordered when it leaves which increase the entropy resulting in a lowering of Gibbs free energy and thus favour of the process.

2.5 Summary:

Supramolecular chemistry has gained a lot of interest to synthetic chemist because of their practical applicability in different fields. Therefore, its structural characterization needs to be explained in well developed manner. The basic concept and different theories of investigation has been described in this chapter. The main forces responsible for supramolecular complexes are predominantly reversibly non-covalent in nature (hydrogen bonding, electrostatic, van der Waals force, π–π stacking, hydrophoblic effects, etc). The tools used to understand and interpret supramolecular behaviour are also common with many used in molecular biology. In the subsequent chapters, we will discuss about supramolecular construct based on our practical experiments and obtained results.