Chapter-1

Introduction: Supramolecular Chemistry, Host-Guest Interactions and Applications (History, Methods and Common Techniques)
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1.1 Introduction

Supramolecular chemistry\(^1\) is a phenomenal dynamic field of study that describes various topics with roots in traditional organic, inorganic and physical chemistry, as well as in biochemistry. After Pedersen study of cyclic polyether and named them "crown ethers" due to their crown-like shape\(^2\) the supramolecular chemistry became one of the most sought after area of study in chemistry. Lehn\(^3\), studied the formation of compounds/complexes formed by the association of two or more chemical species held together by weak intermolecular forces, like ion-dipole, hydrogen bonding, hydrophobic interactions etc. and he also termed them as supermolecules, this was probably the stepping stone to modern supramolecular chemistry. Lehn during his research found that molecular chemistry involves covalent bonds that govern the structures, properties, and transformations of molecular species but supramolecular chemistry is the domain of chemistry beyond that of molecules that focuses on the chemical systems made up of a discrete number of assembled molecular subunits or components involving non-covalent intermolecular interactions. Its development fills up the needs of resources of molecular chemistry that combined with the formation of non-covalent interactions between host and guest molecules so as to design supramolecular entities. The resulting supramolecular compounds so formed have found applications as catalysts, storage materials, receptors to recognize substrates, DNA replications, fluorogenic chemo-sensors\(^4,5\) etc.

The modern study of supramolecular chemistry is a distinct field arising out of Pedersen’s studies of crown ethers, Cram’s studies of carcerands and spherands,\(^6\) and Lehn’s studies of carcerands. In modern chemistry researchers\(^7\) have studied thiacalixarenes and calixarenes as fluorescent sensor. Supramolecular chemistry can be constructed efficiently by the interactions of organic ligands and metal ions using non-covalent interactions. The atoms bonded by covalent bonds results in a molecule or ligand and the non-covalent interaction of metal atom or ion with these ligand leads to designing of a supramolecule. It may be assumed that the origin of supramolecular metal-organic frameworks is based on the Werner’s studies on coordination compounds\(^8\).

Supramolecular chemistry is quite different from classical molecular chemistry which mainly deals with combinations of atoms that lead to the formation of molecule;
molecule-molecule or molecule-atom combination resulting in macromolecule whereas in supramolecular chemistry, the macromolecule or substituted molecules formed by classical chemistry combine with atom, ion or molecule through weak non covalent interactions which lead to their formation. In modern chemistry, development of receptors or chemo-sensors for the recognition and detection of anions or cations has become an important area of research.

- **Language of supramolecular chemistry**

  The component of supramolecular chemistry has been named as receptor and substrate. Receptor is denoted by ρ (rho) and substrate is denoted by σ (sigma). Receptor is a molecule or entity that provides a cavity for guest and substrate is small component which occupies the cavities by binding through non covalent interactions and act as a guest molecular species. Selective binding of a specific substrate σ to specific receptor ρ resulting in a supramolecule (σ-ρ) involves a recognition process.

  
  ![substrate + receptor → supramolecule]

  

1.2 **Supramolecular compounds**

  Based on cavities or binding sites in host molecules, these are classified into two types as depicted in Figure 1.1

- **Cavitates**

  These are the host molecules with intramolecular cavities and host-guest aggregate is called cavitaté. Formation of cavitates takes place in solution as well as in solid state. Cavitate is a class of supramolecules in which one or more guest molecules are completely encapsulated within the cavity of host molecule possessing intramolecular cavities. These are stable in solid as well as solution state. The main concept of binding of hosts and guests is non-covalent interaction between them. The non-covalent interactions between host and guest molecules are specific in nature.

- **Clathrates**

  Clathrates are class of supramolecules in which included compounds is associated without ordinary chemical union forming a complete enclosure of one set of molecule.
and are generally formed in solid state. These are compounds with extra-molecular cavities. For example cyclotrimeratrylene host (CTV) interacts with acetone involving Van der Waals interactions or gets stabilized due to crystal packing.

Figure 1.1 Representation of clathrates and cavitates with extra-molecular and π intra-molecular binding sites.

1.3 Non-covalent interactions in supramolecular chemistry

The basis of non-covalent interactions depends on the soft and reversible interactions as (hydrogen bonding) that exist between two strands of DNA double helix\(^\text{13}\). Emil Fischer in 1894 gave lock and key model to explain enzyme action and provided the basis of molecular recognition\(^\text{14}\). This lock and key model became a model for recognition of metal cations by receptors and thus non-covalent interactions generally form the basis of biochemical processes. The 2013 Nobel Prize in medicine was awarded for the work on non-covalent interactions as precise control system for the transport and delivery of cellular cargo (machinery regulating vesicle traffic, a major transport system in our cell). The prize was shared by James E. Rothman, Randy W. Schekman and Thomas C. Sudhof\(^\text{15}\).

The main non-covalent interactions are ion-ion interactions, ion-dipole interactions, dipole-dipole interactions, \(\pi\)-M\(^{\alpha^+}\) (pi-cation) interactions, \(\pi\)-\(\pi\) (pi-pi) interactions, hydrogen bonding, Van der Waals forces and coulombic forces\(^\text{16}\). Intermolecular and intramolecular interactions involving aromatic rings are also widely encountered during
the study of non-covalent interactions\textsuperscript{17}. These weak interactions are responsible for a large degree of supramolecule flexibility and enable conformational changes, which are due to specific functioning, like spontaneous self-organization, molecular recognition, transport, regulation, catalysis etc\textsuperscript{18,19}.

In addition to these examples, there are many examples of non-covalent interactions of different types invented in modern chemistry including macromolecular system to simple combined substituted molecules\textsuperscript{20}. These non-covalent interactions system in covalently bonded molecules for guest atom or ion is the base for development of specific receptor or sensor. A molecule that shows selectivity for a specific atom or ion among a series \textit{via} these non-covalent interactions can lead to development of supramolecular system, the molecule is known as a receptor/host/sensor for that specific atom or ion.

\section*{1.4 Design and synthesis of receptors}

Receptors are organic molecules held by covalent bonds and are capable to selectively bind ionic or molecular substrates via intermolecular non-covalent interactions\textsuperscript{21}. It is interesting to design and synthesize novel receptor host molecules\textsuperscript{22,23} because of their increasing important roles in supramolecular chemistry. The study of receptor as large molecules follows two strands that have alternately diverged and intertwined over the subject's history. The first strand explores the natural macromolecules of biology, including proteins, polysaccharides and nucleic acids. The second is concerned with synthetic macromolecules or simple substituted molecules, the invention of which in the early twentieth century launched industries based on plastics such as nylon, polyethylene and Perspex\textsuperscript{24}.

\textbf{Principles of receptor design}

The principle of receptor design and recognition process of a substrate i.e both the design of receptor and energetic aspects are central part of the host - guest system also it should comply with lock and key model\textsuperscript{25}. The following are the principles of receptor design:

\textbf{Information storage and read out}

A receptor should have a capacity to store the information and then read out. The information stored and read out process may involve energy and information changes in form of signals.
Complementarity

Complementarity is necessary approximation and property of a receptor. It competes in two forms a) shape and size i.e. cavity b) chemical complementarity.

a) Shape and size of receptor should be with a suitable cavity for substrate so that cavity may complement substrate. If a molecule or organic ligand does not follow complementarity with substrate then recognition will not be possible.

b) Chemical complementarity should be feasible between the binding groups and lining the interior of the cavity.

Reorganization and pre-organization

Reorganization and pre-organization, both processes are quite essential feature for designing a receptor for substrate. Reorganization of substrate is the change in the geometry of the receptor when a guest molecule or ion approaches the receptor; this may include change in the stereo and energy of the receptor while pre-organization of the receptor is change in geometry before approaching of the substrate to the receptor. There are two modes of receptor behavior

a) Lock and key mode; this mode is totally based on the rigid nature of both substrate and receptor and rigid host reorganize to conformational flexibility of the molecular constituents form the receptor-substrate (host-guest) complex. This type of mode of attraction between receptor and substrate is expected to be very efficient in recognition.

b) Flexibility of receptor; in most biological recognition systems, the extent of degree of flexibility is more than rigidity in the receptor. The approach of the substrate results change in conformation and an organization of the binding site around it with high entropy price.

- Topology

The term topology refers to the consequences of treating molecules as completely flexible objects that helps to describe the molecules. This parameter may apply to receptor, substrate or receptor–substrate complex as individual molecule or species. This also describes concave and convergent (endo-supramolecular chemistry) and divergent (exo-supramolecular chemistry) cases of receptor.
1.5 Self assembly

Self assembly\(^{27}\) is a broader term it concern with the spontaneous association of few or many components results in a discrete oligomer extended polymolecular supramolecule. Hence molecular self-assembly is the process by which molecules adopt a defined arrangement without external influences or external factors. Self assembly can be classified into two types; inter-molecular self-assemblies\(^{28}\) and intra-molecular self assemblies\(^{29}\). In inter-molecular self assembly different types of molecules form extended supramolecules and in intra-molecular self assembly same types of molecules form extended supramolecules. Commonly, the term molecular self assembly is used for intermolecular self assembly, while the intra-molecular self assembly is more commonly called folding. The best example of known inter-molecular self assembling structure in biological systems is naturally occurring DNA, which exists in a double helical form.

1.6 Synthesis of macromolecules and other substituted organic host receptors

After the study of crown ethers by Pedersen the synthesis of macromolecules in cyclic form became the agile area of research. The existence of the calixarenes was introduced by the Petrolite Corporation, synthesized from para-substituted phenols and formaldehyde\(^{30}\). Dr. John Munch also reported some calixarenes which were synthesized by refluxing a mixture of a para-substituted phenol, formaldehyde in presence of small amount of aqueous base in a hydrocarbon solvent such as xylene\(^{31}\).

Preceding this, the condensation of \(p\)-tert-butylphenol with formaldehyde to form cyclic oligomers was investigated as host molecules. The product of this condensation was named calixarenes due to its shape. The synthesis of calixarenes was grouped under the heading of “one-step” procedures however, only a few \(p\)-alkyl-substituted phenols resulted in formation of pure product in reasonable yield\(^ {32}\).

In recent years a number of host molecules\(^{33}\) for ions have been synthesized by many researchers. A simple structured host molecule with an amide-type anion binding site specific for rhenium(I) was developed by Alistair J. Leesas et. al.\(^{34}\) Doo Ok Jang et. al reported a simple class of host molecules specific for anions. L. Fabbrizzi et. al.
invented simple molecules as a class of host molecules\textsuperscript{35}. Masahiro Irie et. al. developed non-cyclic host molecules selective for alkali metal cations\textsuperscript{36}.

Organic ligands self-organize or assemble to provide a host cavity for atoms or ions. These host molecules can be synthesized from the combination of different species with electron donor species in their structure\textsuperscript{37}. A report by Beer and Gale demonstrate that self-assembly of suitably substituted ligands with either Ru(II) or Pt(II) metal ions results in the formation of complexes that are excellent anion receptors\textsuperscript{38}.

1.7 Receptors classification on synthesis or structure base

Receptors based on their structural flexibility are classified as, linear, monopodal, bipodal (two-armed or tweezers-like), multi-armed and macrocyclic receptors. General representations of receptors are shown in Figure 1.2. These are widely applicable in recognition of ions or molecules and can easily bind metal ions or molecules with good to excellent selectivity and specificity. The chain away from the head group easily binds ions or molecules with non-covalent bond of attractions. The receptor arms are responsible for the binding selectivity. Generally supramolecular receptor system in different modes can be explained as depicted in Figure 1.2 that gives an idea about the different shaped receptors with their binding modes.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{receptor_diagram.png}
\caption{General representations of receptors on structure base\textsuperscript{39}.}
\end{figure}
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a) Simple substituted linear/podand/clefts

These are receptors which have a self-organized structure like a cleft or with specific electron rich binding sites. Most of the simple substituted linear receptors follow the charge transfer mechanism for binding with metal ions. The electronic clouds of electron rich elements create environment for binding guest metal ions. Simple substituted receptors are with some advantages that simple substituted molecules are easy to synthesize than macro-cyclic molecules. Some researchers invented a class of these types of receptors with selective binding sites for metal cations. Conza and Wennemers studied a series of urea-based anion receptors. Sophie R. Beeren and Jeremy K. M. discovered a new series of linear hydrazone based receptors specific for dihydrogen phosphate ions. Figure 1.3 represents podand and monopodal receptors that are specific for recognition of alkali metal ions.

Sophie R. Beeren and Jeremy K. M. discovered a new series of linear hydrazone based receptors specific for dihydrogen phosphate ions. Figure 1.3 represents podand and monopodal receptors that are specific for recognition of alkali metal ions.

![Figure 1.3 Simple podand(a) and monopodal(b), receptors for alkali metal ions.](image)

b) Tweezers

In chemistry, tweezers are molecules with self organized two-armed shapes in such a way that they can easily wrap a guest molecule or ion in between their covalent bonded chains. Tweezers-like receptor molecules have proved their potential for molecular or ionic recognition in different fields of chemistry. The nature of interacting forces between receptor and substrate is very helpful for the rational prediction of the structure of a receptor agonist or antagonist is one of the most interesting tasks in supramolecular chemistry. In Figure 1.4 (a), dipodal/tweezer receptor synthesized by condensation of iso-phthalaldehyde and p-toluenesulfonyl hydrazide was found to be selective for Cu$^{2+}$ recognition in CH$_3$CN; Figure 1.4(b) tweezer-like receptor molecules are efficient in their potential for molecular recognition. These are good receptors for small peptides
molecules. Armes of these types’ receptors easily bind the small peptide molecules and wrap them with strong affinity.

![Image](image1.png)

**Figure 1.4** Metal specific (a) and peptide specific (b) two-armed molecular receptors.

c) Three-armed or multi-armed receptors

Three armed receptor is organic molecule where three covalently bonded arms containing binding sites for a guest molecule bonded to one head group by covalent bonds. The arms of receptors are rich with electron denser groups or atoms and can wrap substrate ion or molecule in between them. Multi-armed receptors have many advantages over monopodal or bipodal receptors as they provide better chelating properties and are able to wrap the guest molecules or ions in their arms. The multi-armed artificial receptors (Figure 1.5) have been used in several important applications like recognition of toxic and metal ionic species.

![Image](image2.png)

**Figure 1.5** Three armed molecular receptors.
d) **Macrocyclic or macromolecular receptors**

This is class of receptors possess closed rings or synthetic polymers\(^{52}\) containing intra-molecular or extra-molecular binding sites for guest metal ions or other substrates. A diverse range of different macromolecules have been synthesized specific for metal ions or other molecules. The interaction of macromolecular receptors with small molecules or metal ions has been studied by many researchers and observed their applicability in many biological processes such as the toxic effect of certain chemicals, regulatory mechanisms, pharmacological action of drugs etc. The use of non covalent interactions has led to the designing of compounds directed towards a specific target (metal ion or substrates)\(^{53}\).

![Crown ether and calixarenes](image)

**Figure 1.6** Crown ether and calixarenes a class of macrocyclic receptors.

As macromolecules are large in size and can have different type of shapes, the most common being chains or cyclic. The cyclic macromolecules include calixarenes, thiacalixarenes, azocalixarenes, oxacalixarenes, crownethers, cryptands, dendriomers etc. Calixarenes are macrocycle or cyclic oligomer based on hydroxyl alkylation
product of phenol and aldehydes. Pedersen prepared more than sixty crown ethers which show interesting physical and chemical properties\(^5^4\). Crown ethers and calixarenes are good host for guest atom or ions due to presence of different binding sites as shown in Figure 1.6. The presence of hydrophobic sites may be good binding site for non polar organic substrates while the hydrophilic sites are good binding sites for metal ions or polar substrates.

### 1.8 General techniques of host-guest binding and binding constant

The binding of receptor with guest metal ions can be analyzed by UV-visible, fluorescence, NMR and mass spectroscopic techniques. These techniques allow determination of binding constant or association affinity. Binding constant or binding affinity is a specific numerical value assigned to the host-guest species that denotes stability of the host-guest system\(^5^5\). Binding constant is also some time referred as stability constant or protonation constant\(^5^6\). Binding constant is quantification of supramolecular host-guest complexation that can be mathematically determined by the data observed from various spectroscopic titrations experimentally\(^5^7\). The common techniques for determination of host-guest interactions are;

#### a) NMR measurement

One of informative technique in many situations is \(^1^H\) NMR titration\(^5^8\). Other nucleus of NMR (\(^{1^3}\)C, \(^{1^9}\)F etc.) are also used to determine the stoichiometry of supramolecular complexes. NMR measurements\(^5^9\) are measured at different host-guest concentrations. The technique is very effective because it describes change in chemical shifts due to change in local environment of the host when it binds with guest. Change in chemical shifts suggests the change in symmetry that informs about the binding mode of host with guest. As a result of which it become easy to recognize binding site and thus the proposed structure of complex may be explained on basis of results obtained.

With modern NMR instruments, it is easy to obtained good quality spectra even with sub-millimolar concentrations. Figure 1.7 represents the \(^1^H\) NMR titration of a tri-armed-pyrene-linked molecular receptor with Hg\(^{2+}\) ion.
Figure 1.7 $^1$H NMR titration spectra of a tri-armed-pyrene-linked molecular receptor (2.23 × 10$^{-2}$M) with Hg$^{2+}$ (0–2 equiv) as their nitrate salt in DMSO-d$_6$.

b) UV-visible spectroscopy

Another common and simple method for supramolecular titration experiment is UV-visible spectroscopy$^{60}$. In which with the addition of guest to host there is a shift in absorption maxima and change in absorption density is monitored. This change in absorption density and absorption maxima directly give information of binding of host and guest. This method is very useful at small sub-micro molar concentration$^{61}$ and data is efficient for the determination of association constants. The concentrations taken for UV-visible titration must lie within the region where the absorption band(s) of interest in both the host and its complex are within the limits of the Beer-Lamberts Law ($A=bc\varepsilon$, with A<1). Usually the host cation added to the guest supramolecule does not have any absorption in the region of absorption of host. When complexation between host and guest occurs there is a notable change in the UV-visible spectra or a significant change in the molar absorptivity ($\varepsilon$). All the methods NMR titration, titration by UV-visible spectroscopy and others are affected by change in temperature and concentration. Hence during all supramolecular titration there is need to control temperature, concentration and also impurities present. Figure 1.8 represents UV-visible titration with addition of selective ion hence changes in absorption spectra are observed.
c) Fluorescence spectroscopy

This is a sensitive technique and effective at very low concentrations of both host and guest. It makes routine measurements in the sub-micro molar, even nanomolar (nM) range possible and hence, fluorescence spectroscopy is ideal for the determination of very large association constants. In fact, fluorescence titration must be carried out at relatively low concentration at a particular excitation wavelength. With addition of any one to other i.e., guest to host or host to guest changes in fluorescence spectra are observed. The enhancement or quenching in fluorescence or shifts in fluorescence spectra are clues for host-guest binding. The observed fluorescence at low concentration of a species X can usually be described by equation 1.1

\[
F = I_0 \varepsilon b [X] = k_X [X]
\]  \hspace{1cm} (1.1)

Figure 1.9 represents the fluorescence titration of Hg\textsuperscript{2+} ions with thiacalixphenyl[4]arene tetra-N-(3-propyl) phthalimide (TPTN3PPh) and the information or data can be used to calculate stoichiometry of the complex and association constant using Job’s plot, Benesi Hildebrand plot and Stern–Volmer relation plot etc\textsuperscript{63}. 

Figure 1.8 Change in the UV-visible spectra of host\textsuperscript{62} (20 µM) upon addition of 7.5 equivalent of Cu\textsuperscript{2+} in THF.
Figure 1.9 The changes in the fluorescence spectra upon addition of various amounts of Hg$^{2+}$ ions to thiacalixphenyl[4]arene tetra-N-(3-propyl) phthalimide (TPTN3PPh) in 5% H$_2$O-THF.

d) **Mass spectroscopy**

The mass spectrometry for the study of host-guest complexation and molecular recognition involving either synthetic hosts or biological hosts is the modern area of spectroscopy. The binding selectivities and stoichiometry of complex formed may be examined by using electrospray ionization to transfer non-covalent complexes from solution to the gas phase for analysis.

- **Gas phase study of host-guest chemistry**

The early 1990s gas phase study for molecular recognition was carried out by mass spectrometry, in which the formation, reactions, and dissociation of host-guest complexes were studied in a gas-phase environment. It includes the allowing access to the intrinsic properties of the host–guest complexes because of the absence of solvent effects. Mass spectroscopic technique is highly specific and selective for the host–guest interactions. Most of the early studies involved simple synthetic hosts e.g. crown ethers and their derivatives, calixarenes and derivatives macrocycles, cryptands, acyclic polyethers, such as glymes, and simple guests such as alkali metal ions or ammonium ions.

In Figure 1.10, crown ether and K$^+$ metal ions interaction can easily understood by their mass spectra. The interaction of 15-crown-5 with K$^+$ ion gives mass spectra value and
the mass spectra of 12-crown-4 + K⁺ + 15-crown-5 shows mass peak. Also it is clear from the mass spectra that K⁺ ions show great binding property with 15-crown-5.

Figure 1.10 Collisional activated dissociation mass spectrum of the (12-crown-4+ K⁺ +15-crown-5) complex formed by ESI and analyzed by using a Finnigan LCQ-Duo mass spectrometer.

- **ESI-MS in solution equilibria system**

Electrospray ionization mass spectrometry (ESI-MS) gives the mass spectra directly from solution samples, thus analyzing all the equilibrium species in their starting environment. ESI mass spectroscopy is able to minimize fragmentation, leaving mostly the unaltered species existing in the solution. Mass to charge ratio can easily suggest the stoichiometry of these species. High-resolution mass spectra, MS-ESI spectra and/or the analysis of the isotopic pattern of the peaks gives much better results for complexes and ligands/receptors. Figure 1.11 represents the ESI-MS spectra of Cu²⁺ and 8-hydroxyquinoline (L) in the presence of acetic acid.

Figure 1.11 ESI-MS spectra of Cu²⁺ and 8-hydroxyquinoline (L) in the presence of acetic acid.
1.9 Binding constant and stoichiometry

There are some common methods described for the determination of stoichiometry and binding constant using the information from UV-visible, fluorescence, NMR, mass spectroscopic techniques/titrations. These are described as

a) Method of continuous variations

The method of continuous variations, also called Job’s method, is used to determine the stoichiometry of a metal–ligand complex. To perform the method of continuous variation (Job’s plot), stock solutions of receptor (host) and metal salts (guest) of same concentrations are prepared. Keeping over all concentration constant with addition of varying amount of the host or guest the spectra are recorded. The stoichiometry of host - guest is determined from graph plotted at a complexation wavelength. If \((n_M)_i\) and \((n_L)_i\) are respectively, the moles of metal guest and ligand host in solution \(i\), then equation 1.2 gives the total number of moles.

\[
n_{\text{total}} = (n_M)_i + (n_L)_i \tag{1.2}
\]

The relative amount of ligand and metal in each solution is expressed (equation 1.3 and equation 1.4) as the mole fraction of ligand, \((X_L)_i\), and the mole fraction of metal, \((X_M)_i\).

\[
(X_L)_i = (n_L)_i/n_{\text{total}} \tag{1.3}
\]

\[
(X_M)_i = 1 - (n_L)_i/n_{\text{total}} = (n_M)_i/n_{\text{total}} \tag{1.4}
\]

On monitoring the complexation reaction at a wavelength where the metal–ligand complex absorbs only, the graph of absorbance versus the mole fraction is used to determine stoichiometry of complex. Using equation 1.5, mole fraction of ligand at the intersection determines the value of \(y\) for the metal–ligand complex \(ML_y\).

\[
y = (n_L/n_M) = (X_L/X_M) = (X_L/1 - X_M) \tag{1.5}
\]

In addition to UV-visible spectroscopy other properties may be used for determination of stoichiometry of complexation; any property that correlates linearly with the concentration of metal-ligand (ML) suffices, including kinetics, conductivity, permittivity, NMR spectroscopy, calorimetry, circular dichroism, circularly polarized
luminescence, gravimetric titration, reflexivity, and melting point depression. MacCarthy studied job plot and described the shape of curve provides information about the complexation ratio (Figure 1.12). The position of the maximum at $X_M=0.5$, identified by inspection in the simplest analysis that suggests 1:1 stoichiometry of an $M_m L_n$ complex ($m=n$). The type of complexation may be tetramer, hexamer etc. in all these stoichiometry $m:n$ can be easily explained by the job plot (Figure 1.12a and 1.12b).

![Figure 1.12](image)

**Figure 1.12** (a) Job’s plot showing the statistical variant of the tetramer-based ensemble. (b) Job’s plot showing a statistical ensemble of hexamers in which all forms of complexation stoichiometry can be observed [n=6].

In the plot (Figure 1.12) the graph is able to explain different stoichiometry of complex formed between host-guest species. As the plot between relative integration and mole fraction is plotted and in case of hexamer if maximum height of the graph is in between the mole fraction range; 0-0.2 then the ML stoichiometry will be of 1:5 (hexamer) or 1:3 (tetramer), 0.2-0.4 stoichiometry ratio of ML will be 2:4 or 1:2, 0.4-0.6 stoichiometry ratio of ML will be 3:3 or 1:1, 0.6-0.8 stoichiometry ratio of ML will be 4:2 or 2:1 and 0.8-1.0 stoichiometry ratio of ML will be 5:1 or 3:1.

**b) Mole ratio method**

Mole ratio method is very effective in determining the stoichiometry of complexes formations. In mole-ratio method the amount of one reactant, usually the moles of metal, is held constant, while the amount of the other reactant is varied. It is necessary
that moles of any one metal or ligand (receptor) be kept constant and the absorbance is noticed at that wavelength or may be more than one specific wavelength, where the changes occur due to complexation and where the metal–ligand complex absorbs. The illustrations below in Figure 1.13 show typical results: the mole-ratio plot for the formation of a 1:1, 1:2 and 1:3 (L/M or M/L) complex formations.

![Figure 1.13 Mole ratio plot for stoichiometry determination.](image)

c) **Benesi-Hildebrand method**

The Benesi–Hildebrand method (BH method) is a mathematical approach used in chemistry for the determination of the association constant and stoichiometry of the non-covalent interaction in complexation. This method has been typically applied to reaction equilibria that form one-to-one complexes, such as non-covalent interactions and host–guest molecular complexation. The association constants have been calculated by the spectroscopic titration curve using Benesi-Hildebrand method employing following equations 1.6 for 1:1 stoichiometry.

$$\frac{1}{(A - A_o)} = \frac{1}{(A - A_f)} + \frac{1}{K} (A - A_f) [X] \quad (1.6)$$

Where, $K$ is the association constant, $A$ is absorbance of free receptor, $A_o$ is the observed absorbance of complex and $A_f$ is the absorbance at saturation. $[X]$ is the concentration of ions. Receptor when titrated by gradual addition of metal ion (X), gives the spectrum (UV-visible, fluorescence, NMR) that could be used to draw a plot...
between $1/\Delta A/\Delta \delta/\Delta I$ (absorbance/chemical shift/intensity) vs. $1/[X]$ using above Benesi–Hildebrand equation. Linearity observed (Figure 1.14) in the Benesi Hildebrand plot indicates the formation of a 1:1 complex.

![Figure 1.14](image)

**Figure 1.14** (a) Benesi-Hildebrand plot for determination of stability constant of host-guest interaction with varying concentration of host. (b) Benesi- Hildebrand plot for determination of stability constant of host-guest interaction ions with varying concentration of guest.

### 1.10 Supramolecular receptors: Tunable properties towards useful applications

There is currently intense research in the supramolecular chemistry, which merge the basic experimental sciences towards *vivo* applications. Supramolecular receptors coupled with toxic metal ion can become useful toxicant remover\(^7^6\). Substrate selective receptors with their low cost and non-toxicity are highly applicable as catalysts\(^7^7\), semiconductors materials, switchable systems for data storage and sensors or bioactive compounds\(^7^8\).

As supramolecular chemistry studies the complex species of host-guest interactions formed from molecular components with simpler structures. These interactions are very specific and respond with a specific metal ion among varies metal ions. Hence supramolecules are widely applicable in design and construction of ion selective sensors\(^7^9\).
Due to their superior geometric shapes and cavities, supramolecules can be good host for accommodation of drug molecule. Controlled release of anticancer drugs by calixarenes and other supramolecules might be applicable in targeted chemotherapy\textsuperscript{80}.

The applications of supramolecular synthesis and metal specific receptors towards the generation of metal-organic and organic materials are a multidisciplinary approach that can afford receptors in \textit{vivo} applications. These extraordinary features of supramolecular chemistry have encouraged us to carry out the present research work in this field.
References


15. See the Nobel Prize in Physiology or Medicine **2013**, at [http://www.nobelprize.org](http://www.nobelprize.org)


43. The image are downloaded from http://www.factgasm.com and https://www.containerstore.com, and then edited.


