Chapter 1

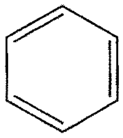
Introduction

1. INTRODUCTION

Life and chemistry can be considered synonyms of each other. Nature is the primary source for all chemicals. Nature is a designer and producer of numerous most complicated molecules by using some of the highly complex processes. But all these things happen in a smooth and spontaneous manner, which has resulted in the very existence of the life. The chemistry practiced by mankind has evolved along with its evolution from a primitive man living in caves to the modern man living among the latest facilitiates. Chemistry was being practiced by man without labeling it as chemistry. Organic chemistry was identified as the chemistry of life and as a separate branch lately. All organic compounds were believed to be produced by living things. Inorganic chemistry was supposed not to be taking place in living organisms. Now again, the boundaries between different branches of chemistry are diminishing. Both organic and inorganic substances take part in the bioprocesses. Numerous organic compounds have been prepared in laboratories outside a living system. But after all they are prepared by living beings. So life and chemistry are synonyms virtually.

1.1. Aromatic Compounds

The compounds with carbon-carbon double bonds are more reactive than the saturated organic compounds. It has long been known that some compounds even with carbon-carbon double bonds present in them were more stable. They were used widely and their characteristics were understood well. They were christened as aromatic compounds because of their typical smell. The concept of aromaticity got clearer with understanding of the structure and resonance in benzene and benzenoid compounds. The concept was possible to be extrapolated to **nonbenzenoid** aromatic compounds[1] (see below) with the help of the Hűckel's rule, which concludes that cyclic compounds with (4n+2) delocalised electrons show aromatic character. The existence of cyclic structure and planarity are requirements in addition to satisfying of the Hűckel's theorem. The aromatic compounds can be identified by their different characteristics including their NMR chemical shifts. Of course all these characteristics are due to the ability of an aromatic compound to sustain an induced ring current. The aromatic compounds are stabilized and the energy of stabilization is called resonance energy. The value of resonance energy is definite and different for each aromatic compound. The value of resonance energy for benzene **1** is 36 K.cal./ mole (152 KJ/mole).



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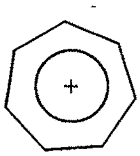

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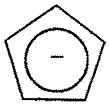

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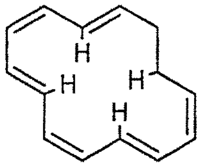
There are other cyclic hydrocarbons in which benzene ring is absent as part of their structure and still show aromaticity. These compounds are known as **nonbenzenoid** aromatic compounds. Thus nonbenzenoid aromatic compounds have a ring system with either more or less number of carbons forming the cycle. Cycloheptatriene cation **2** and cyclopentadinyl anion **3** have seven and five carbons respectively forming the ring but have six delocalised electrons giving aromatic character to these compounds. The aromatic hydrocarbons with more than six delocalised electrons and still having aromatic character are known as annulenes e.g. [14]annulene **4** and [18]annulene **5**.



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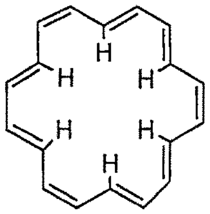

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In the 19th century, coal was the major source of organic compounds and aromatic compounds such as benzene, toluene, phenol, pyridine, aniline, thiophene were obtained from coal. Six member rings made of carbon when fused together form sheets of carbon which can get stacked over one another known as graphite. These graphite sheets under appropriate conditions and with the help of electric energy can be converted to the recently recognized new form of carbon in form of closed spherical cages, collectively known as fullerenes. The prime member of this family, which is formed in major quantity, is made of sixty carbons and is named as "Buckminsterfullerene" **6** after Buckminster Fuller, an architect, mathematician and inventor from the United States of America. He designed the geodesic dome using Euler's theorem according to which twelve pentagons are required to close the network of hexagons. [60]Fullerene **6** is roundest of round edgeless highly symmetrical molecule containing I_h symmetry.

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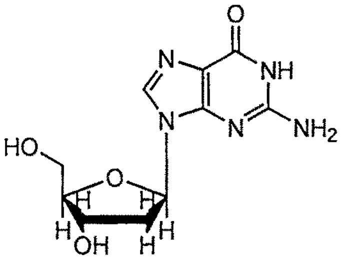
Aromatic compounds in which there is presence of one or more atoms other than carbon forming a ring are called **heterocyclic aromatic compounds.**[2] In six member rings where nitrogen is heteroatom, the unshared pair of nitrogen is not a part of the aromatic sextet while when oxygen or sulphur is the heteroatom, forming the same size ring, it needs to be in its ionic form. In five membered aromatic heterocyclic compounds having N, S, O as the heteroatom lone pair on these elements contribute two electrons in resonance while other four comes from unhybridised p orbitals of the carbon forming two π bonds. Chemistry of these compounds is closely related to benzenoid aromatic compound but form a separate class. There are several five and six membered heterocyclic ring systems containing two or more heteroatoms within the ring. These polyhetero ring systems are present in many natural products. Purin contains four nitrogens with both six membered ring and a five membered ring fused together. One of the lone pairs on the nitrogens present in the five membered ring contributes towards the aromaticity of the compound making it an aromatic system with 10 delocalised π electrons resembling naphthalene. Many of the heterocyclic nitrogen bases present in nucleic acids are purine derivatives such as adenine **7**, and guanine **8** which consequently contribute in the structure of DNA and RNA. Adenosine triphosphate also contains purine in form of adenine.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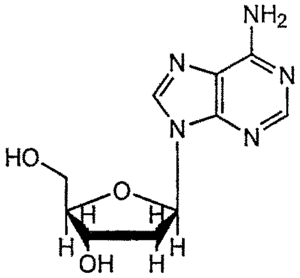
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The formation of complex molecules from simple molecules is facilitated by number of favorable conditions when molecules and ions interact with each other. Molecules and ions interact under the influence of a number of secondary forces, the forces other than covalent or ionic bonding. The formation of nucleic acids from purine and other heteroaromatic compounds via adenine, guanine and other pyrimidine bases takes place with the help of such secondary interactions. Proteins, genes and enzymes are further built up and they control the synthesis of all kinds of biomolecules.

1.2 Secondary Forces

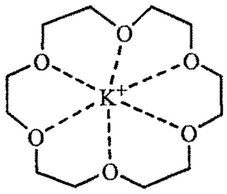
As mentioned above, there are a number of secondary forces acting in nature. All the bioprocesses are based on and helped by these interactions and thus they are extremely important. Most of these interactions are understood well up to now and the major of them are listed below,

1. Ion-dipole interactions
2. Dipole-dipole interaction
3. Hydrogen bonding
4. π–π Stacking
5. Cation–π interactions
6. Van der Waals forces

Hydrophilic and hydrophobic forces[3] are not important in bioprocesses only but are also important in laboratory reactions. Aromatic and heteroaromatic compounds are capable of having one or more of the above forces acting on them.

1.2.1 Ion-dipole interactions

The solvolysis of ionic compounds in polar solvents is one of the simplest examples of this kind. In fact this kind of ion-dipole interaction is present in both solid state and in solution. The same force is in action when crown ether **9** binds with an alkali metal ion. Positive charge on the cation attracts the oxygen lone pairs making it soluble.



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Co-ordinate bonds are also electrostatic in nature. They may have significant covalent character.

1.2.2 Dipole-dipole interaction

The presence of different functional groups in an organic molecule generates dipole moment in the molecule. Polarization of electrons also takes place due to electronegativity difference between two directly attached atoms and the polarizable electron. Each molecule acts as a dipole and alignment of one dipole with another due to attractive interactions takes place **Figure 1**. This helps in a definite arrangement of the molecules in solid state as well as in solution where these interactions are relatively weak.

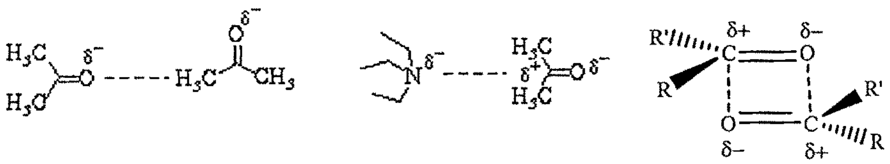
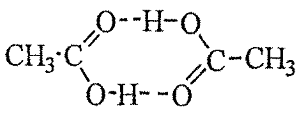


Figure 1

1.2.3 Hydrogen bonding

When a hydrogen atom is attached to an electronegative atom or an electron withdrawing group imbalance of the bonding electrons take place between hydrogen and the atom or group generating a dipole. Alignment of this dipole as described above takes place resulting in higher stabilisation. As hydrogen is always involved in this interaction, it is known as hydrogen bonding e.g. in a carboxylic dimmer **10**. Hydrogen bonding is relatively strong and highly directional. Hydrogen bonding is extremely important not only in arrangement of molecules in solid, liquid and gaseous state and in solution but



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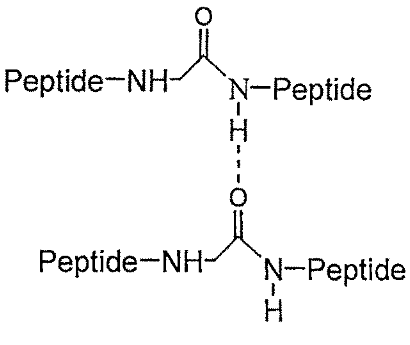

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also in the synthesis of biomolecules and laboratory synthesis. Hydrogen bonding as illustrated in **11,** gives overall shape to many proteins. Role of hydrogen bonding in the double helix structure of DNA **(Figure 2)** is a well-known example. Hydrogen bonds depend on many factors and exist in different lengths, strengths and geometries.[4]

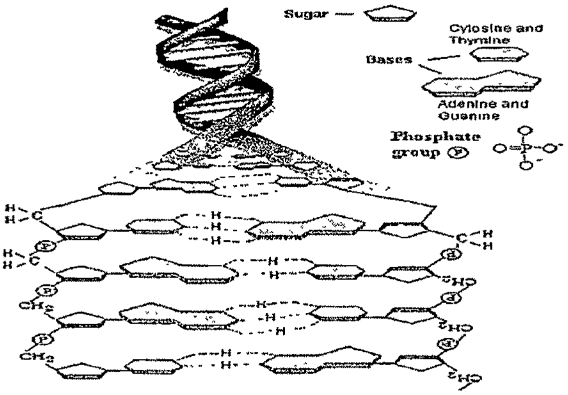
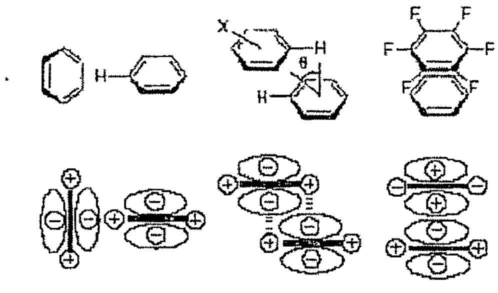


Figure 2

1.2.4 π –π Stacking

π- π Stacking interactions are weaker but important in aromatic compounds. The presence of planarity and delocalised electron cloud in aromatic compounds make π- π stacking interaction possible. The interaction may take place edge-to-edge or face to face

(Figure 3). π- π Stacking interactions are stronger when there are electron rich and electron deficient aromatic molecules involved. Formation of charge-transfer complexes is a result of this type of interaction. It is also present in the double helical structure of DNA. Attractive as well as repulsive forces generated due to π- π stacking interactions determine relative orientation of the molecules.[5] Formation of layers in graphite also results from this interaction.

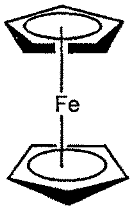


(a) (b) (c)

Figure 3

1.2.5 Cation –π Interactions

Cation-π interactions take place between a metal ion and the electron-rich aromatic compound resulting in interesting molecules like ferrocene **12**. After understanding the structure of ferrocene, many such compounds have been reported.[6]



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1.2.6 Van der Waals forces

Attractive forces between neutral species are referred to as van der Waals forces. Van der Waals' interactions are very weak electrostatic interactions. They are generated due to the polarization of an electron cloud by an adjacent nucleus and are nondirectional. They are not much useful in design of host molecules for selective complexation. Van der Waals forces are the only forces of attraction possible for non-polar molecules like alkanes. In many organic crystalline compounds, van der Waals' forces predominate and due to which their crystals are soft and low melting.

1.3 Molecular Recognition

As stated earlier, the intermolecular and intramolecular forces play a vital role in biological processes. It has been an inherent curiosity and also a need of mankind to understand the processes occurring in nature and apply them for their betterment. In other words, it is the base of development of science. With continuous efforts, it has been possible to understand some of the complex biological processes but there are still a number of mysteries to be resolved. In nature, all the processes are well-organised and highly specific due to which the creation of existing animal and plant species have become possible. All the enzymatic processes are highly substrate specific due to combination of the forces described above along with the other factors. This substrate specificity was compared with lock and key by Emil-Fischer.[7] This substrate specific action of the biomolecules has been termed as "***Molecular recognition***". Thus recognition at molecular level is a fundamental characteristic of biological phenomenon, which plays a critical role in most biological functions, such as enzymatic processes, antigen-antibody interactions, transportation and replication of genetic information. Later on, this phenomenon was extended to molecules synthesised in the laboratory where an organic molecule is capable of holding another molecule or ion with the help of one or more interactive forces. With understanding of these binding processes through weaker secondary forces, it was possible to design and synthesize the molecules, which can bind with other molecules. The conscious efforts progressed later in this direction resulting in development of new branch of chemistry known as "***Supramolecular chemistry***"

1.4 Supramolecular Chemistry

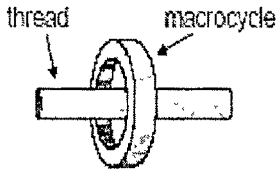
Supramolecular chemistry was termed so because molecular chemistry was limited to the chemistry of molecules with stronger bonding forces like covalent bonds. The chemistry beyond the molecules that result from association of two or more chemical species by intermolecular forces was introduced as "Supramolecular chemistry"

Earlier to this, Powell explained[8] the inclusion compounds formed by enclosing of small molecules in cavities formed by larger molecules using the term '***Clathrates***". Molecular recognition is a part of supramolecular chemistry with highly specific interactions arising out of the geometry of the molecule and non-covalent forces working to bind with other molecule. Such highly specific interactions have led to some useful supramolecular functions. The designing of new biologically active compounds and therapeutics is carried out with the consideration of all these factors, which earlier was based on random preparation and testing of new molecules.

1.5 Host-guest Chemistry

Supramolecular chemistry is also known as "***Host-guest chemistry***". Normally host molecules are designed and synthesized in laboratory with structural features having possibility of non-covalent interactions with molecules having complimentary stereochemical and functional features in them called guest molecules. Supramolecular chemistry serves the basic purpose of mimicking and understanding of biological processes. Investigation of molecular recognition using model compounds is useful in understanding of biochemical functions at molecular level.

It is fascinating for a chemist to carry out enzyme like substrate specific binding with the designed molecules. The chemistry has been then extended to number of fields for various applications. The principle of supramolecular interactions has been applied to new class of compounds known as pseudorotaxanes, rotaxanes, catananes, and cavitands[9] as illustrated in **13, 14 and 15.** Nomenclature of these compounds is based on their



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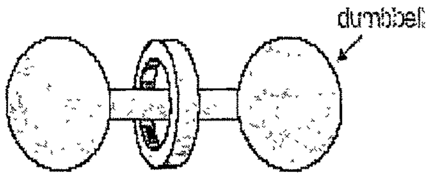

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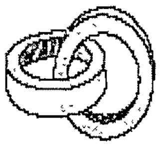

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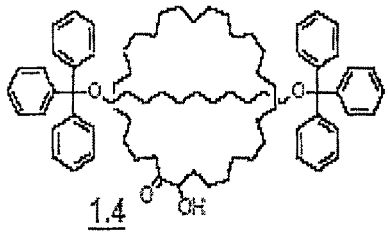

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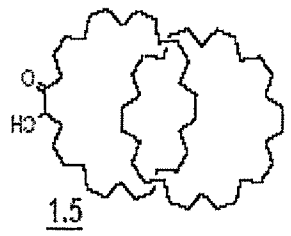

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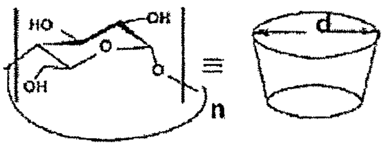
structure and shape. The concept also has been applied to organic synthesis using templates and in synthesis of nano-materials as well as polymeric materials with specific structural features. Numerous self-assembling systems have been prepared or discovered following understanding of supramolecular interactions. Self-assembly is defined as spontaneous self-organisation of molecules into thermodynamically stable, non-covalently joined assemblies.[10] The concept has been widely used in medicinal chemistry for preparation of molecules, which can interact with bio-molecules and yield the desired results.

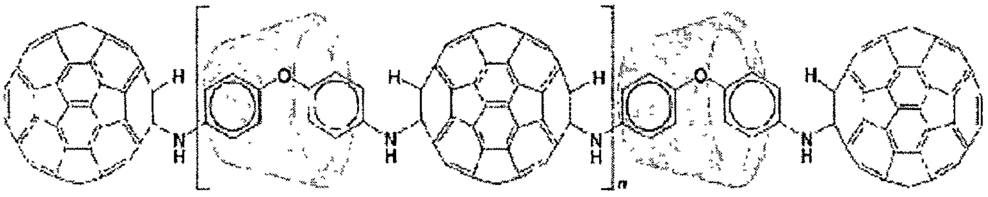
Cyclodextrins (CDs) **16** are natural cage compounds, which can bind with variety of molecules. They are naturally occurring cyclic oligosaccharides composed of 6, 7, 8, α -1, 4- linked D-glucopyranose subunits and are called α-, β-, γ- CD's respectively.



n =	5	6	7
d(Å)=	5.7	8.5	9.5
	α-CD	β-CD	γ-CD

16

They form inclusion compounds. CDs have been used to carry out reactions in their hydrophobic cavities. They have been also employed for making hydrophobic material water-soluble. It has been possible to make polyfullerene **17** water-soluble using CD supramolecular technology.[11]



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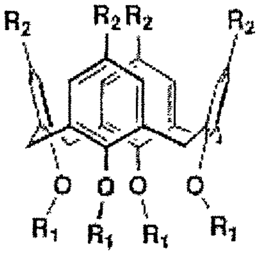
Calixarenes **18** are synthetic molecules having a cavity in their structure. They are basket-shaped, metacyclophanes obtained by *p*-substituted phenols with formaldehyde. They also give different cavity size depending on the units involved in cyclisation. They also have been used for encapsulation of various guest molecules. [12]



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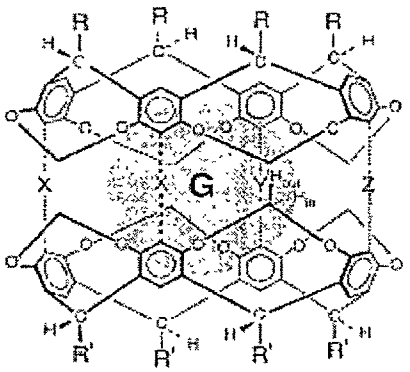
These molecules with a cavity are capable of accommodating appropriate molecules themselves. Coupling of two such molecules can lead to the compounds with close structure known as carceplaxes e.g. **19**. A guest molecular ion can be entrapped in the cage of the molecules during the synthesis. The guest molecule acts as a template in the formation of carceplaxes.



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The use of ions or organic molecules is not limited to the synthesis of carceplaxes but also apply to the synthesis of many other supramolecular assemblies. Templates are distinguished from reagents as they affect the macroscopic geometry of the molecules but do not change the basic chemical reaction. A template aids the construction of complex molecular structure either as a temporary scaffolding agent or sometimes by appearing as a guest in the product. A template organises the molecule or atoms with respect to one or more geometric loci in order to achieve a particular linking of atoms. There can be thermodynamic or kinetic templates.

Binding of metal ions with host molecules may involve chelate effect in addition to supramolecular interactions. The host molecule may have donor atoms in its cyclic structure or in acyclic podand like structure or it may be a rigid cyclic molecule such as a corand or a cryptand. The stabilization by the chelate is highly dependant on the chelate ring size. Many cyclic supramolecular host guest complexes are more stable than would be expected from the chelate effect. Such compounds are stabilized additionally by the macrocyclic effect. Macrocyclic effect is generated due to organization of binding sites in space **(Figure 4)**.

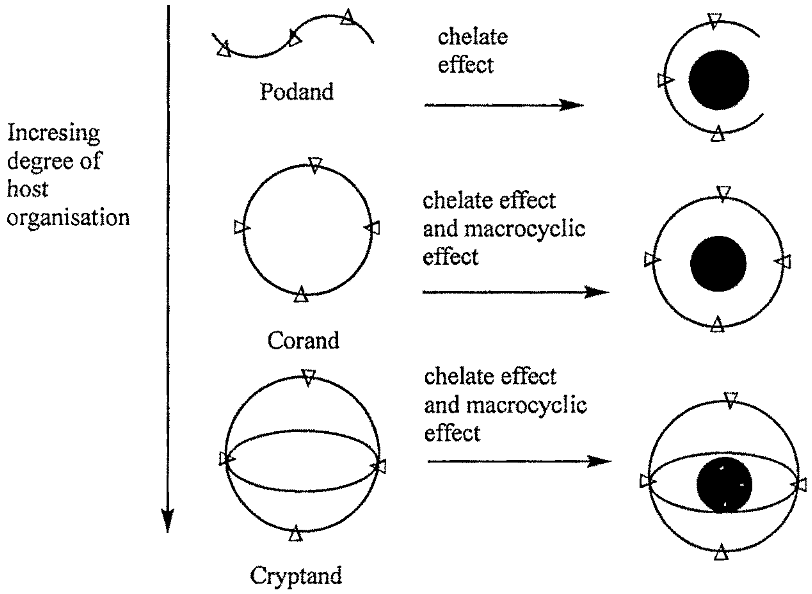


Figure 4

An extent of supramolecular interaction can be measured by using various methods. The host can bind with different guests with different binding energies. Measurement of binding constant is useful for comparison of strength of binding.[13]

$$\text{Host} + \text{Guest} \rightleftharpoons \begin{pmatrix} \text{Host.Guest} \\ \text{complex} \end{pmatrix}$$

$$\text{Binding constant} \quad K = \frac{[\text{Host .Guest}]}{[\text{Host}] \times [\text{Guest}]}$$

$$\text{Selectivity} = \frac{K_{\text{Guest1}}}{K_{\text{Guest2}}}$$

Haemoglobin selectively binds with oxygen in the presence of other gases. Carbon monoxide binds with haemoglobin more strongly and irreversibly. This selectivity can be achieved intelligently manipulating the concepts of preorganisation, complementarity and lock and key analogy with a detailed knowledge of host-guest complexation.

In kinetic selectivity the host binds with a guest faster to form a complex rather than binding with another guest to give a more stable complex. Many biochemical enzymes are kinetically selective. It is much more difficult to achieve time-resolved selectivity in artificial systems.

The thermodynamic stability of a host-guest complex in a given solvent is measured as binding constant K. It depends on the solvent used when the guest is a metal ion M^{n+},

$$M^{n+} + H \xrightleftharpoons{\text{solvent}} [MH]^{n+}$$

For a given solvent,

$$K = \frac{[MH]^{n+}}{[M]^{n+}+[H]}$$

A large binding constant means a more stable complex. Binding constants for crown ethers and alkali metal cations in water are smaller ($10\text{-}10^2$) compared to in methanol (up to 10^6).

1.6 Measurement of Binding Constant

It should be possible to measure a binding constant by using experimental techniques, which can give information about concentration of a complex with changing concentration of the guest molecule.

1.6.1 Potentiometric titration

Potentiometric titration can be used when the host is susceptible to protonation. The protonation constant may be determined by using pH electrodes. The presence of guest molecules will change the shape of the titration curves. By comparing results, stability can be measured.

1.6.2 NMR titration

The binding constant may be measured using NMR at a particular concentration and temperature by simple integration. If complexed and uncomplexed guests can be observed by NMR and the chemical shifts sensitive to complexation, the average between chemical shift of free and bound species are calculated. In a typical NMR titration, small aliquots of the guest is added to a solution of the host of known concentration in a deuterated solvent and NMR spectrum is monitored as a function of guest concentration or host-guest ratio. The changes in chemical shift are noted as a function of the influence by complexation. The location of the most affected signal gives information about the regioselectivity of binding. The shape of the titration curve gives quantitative information about the binding constant. Computer programs are useful for comparing and calculating binding constants.

1.6.3 Fluorescence titration

In case of either of the host or guest or the host-guest complex being fluorescent, fluorescence titration is useful for finding out the extent of complexation. For a 1:1 complexation of a fluorescent guest G with host H, the stability constant can be calculated as follows:

$$K_{11} = \frac{[HG]}{[H][G]}$$

and fluoroscent intensity,

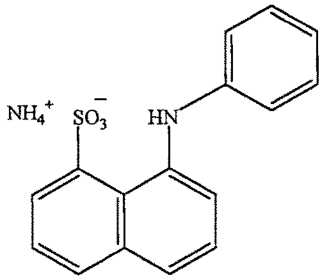
$$F = k_G[G] + k_{11}[HG]$$

$$k = \text{proportionality constant}$$

Ratio of fluorescence in presence of the host and in its absence is used to find out the stability constant for the system because when either the guest or the host-guest is non-fluorescent, the equation is simplified to,

$$\frac{F}{F_0} = 1 + K_{11}[H]$$

8-Anilino-1-naphthalene sulfonic acid ammonium salt **20** is one such commonly used fluorescent guest to probe the complexation ability of a host using fluorescence titration.



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1.6.4 Calorimetric titration

In mixing of host and guest, heat changes are measured during calorimetric titration as a function of changing concentration. The heat changes are related to thermodynamic parameters of complexation.

1.6.5 Partition coefficient

When there is a metal ion as a guest, the distribution coefficient K between aqueous and organic phase may be used to determine the selectivity of the given macrocyclic host at different concentrations when the host is water insoluble.

1.7 Applications

Out of a number of applications supramolecular chemistry is having, its bio-oriented applications have remained the most important of all. Biological systems have provided much of inspiration for the development of supramolecular chemistry. Synthetic supramolecular systems have been designed to mimic the structure or function of biological processes. Such abiotic molecules are termed as models. By using these models[14] and mimicking biological processes[15] in the laboratory, scientists are able to understand many of the properties of real biological processes with the help of relatively simple artificial systems. In biological systems, receptor–substrate binding, a reversible process is extremely selective and of great importance. The selectivity, which is present in enzymes, requires kinetic selectivity and works all along the pathway of the reaction. Only few mechanisms involving enzymes have been definitely established. The achievement of this kind of selectivity is extremely difficult and very little progress has been made in truly functional enzyme models.

Cyclodextrins as mentioned earlier are the cavity containing compounds and are naturally occurring host molecules. They form inclusion complexes with small molecules. Cyclodextrins and modified cyclodextrins are known to catalyse numerous varieties of biochemical and non-biochemical transformations. It is possible to obtain selectivity as cyclodextrins block the reactive position of the aromatic guest molecule inside the cavity and enhance rate of reaction at the unblocked position **(Figure 5)**. One of the examples of their catalytic activity is hydrolysis of aryl or phosphate esters known as esterase mimic activity.

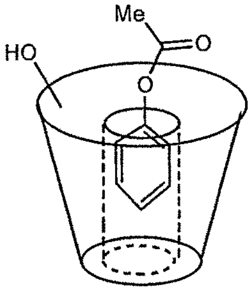
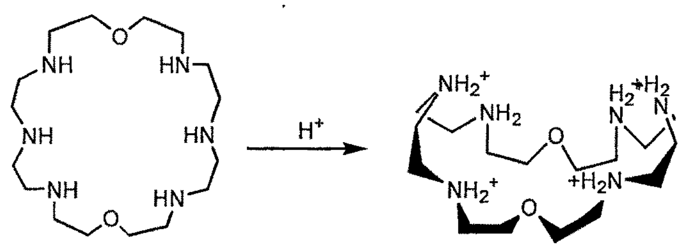


Figure 5

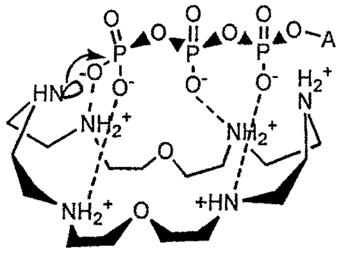
The cyclic aliphatic polyethers containing four or more oxygen having crown like appearance generating due to folding in a particular fashion are known as crown ethers. They have unique ability to form stable complexes with metal ions and primary alkyl ammonium cations.[16-18] Latter-on a number of modified crown ethers have been prepared with cyclic aliphatic, aromatic, heterocyclic and chiral moieties fused or attached with crown-ether framework.[16] Chiral crown ethers such as with binaphthyl unit incorporated are reported to bind selectively with one antipode of amino acid derivatives.[17]

When oxygens are replaced with nitrogens, the heteromacrocyclic structures are named as azacrown ethers. There are crown ethers with both nitrogen and oxygen present in their structure. All these macrocyclic compounds with one or more softer donor atoms incorporated with one macrocyclic ring are collectively called corands. Similar bicyclic and tricyclic systems fall into the class called cryptands. Crown ethers can complex preferentially certain metal ions according to the respective ionic radii. Crown ethers help in understanding selective ion transport across cell membranes.

Lehn has demonstrated an ATPase model using corand[24]N_6O_2, **21** which when protonated adopts a cleft like conformation **22**. The multiply charged macrocycle binds strongly with ATP (compared to ADP) having four negative charge and accelerates the rate of its hydrolysis about 100 times **(Figure 6)**.[18]



21 **22**



-5H⁺ ATP

Figure 6

Similarly, aza tricyclic crown ethers also fold on protonation and bind with anions such as chlorides and azides showing flexibility and organizing according to the demand of the guest.[19] Crown ethers, aza-crown ethers and cryptands with these crown ether features have been attached and combined with a variety of structural subunits having different functional groups, heterocyclic rings, [20] chiral components, [21] porphyrins[22] etc. Two or more crown ethers connected through different kind of spacers and having chelating ability in themselves or closed cage like structures have been prepared by connecting them with two or more spacers providing multiple binding sites.[23] Crown ethers have also been incorporated in polymeric chains[23] like styrene-divinyl benzene co-polymer.[24]

With continuously improving understanding of biological processes by solving of the complex structures of biomolecules and by better understanding of the biochemical processes, it has been possible to improve upon our knowledge of mechanism of the way therapeutic agents act in a physiological system. The availability of advanced computational programmes designed on the basis of the above-mentioned knowledge has made it possible to find out these supramolecular interactions very quickly with clearer visualisation of the active sites of the interacting biomolecule. Improvements in the presently used drugs are being attempted and design of new biologically active molecules has been successful. Thus the concepts in new drug design and drug discovery have totally been changed with emergence of supramolecular chemistry as a separate discipline in chemistry.

1.8 Synthesis of New Classes of Designed Molecules

Supramolecular chemistry has opened up a new front in synthetic organic chemistry with synthesis of molecules having unique structures and shapes. Cram prepared cavitand and spherands named on the basis of their structures and binding abilities.[25] Then Stodart prepared rotaxanes **13**, which have one cyclic structure bound with an open-chain compound or catananes **14** in which two or more rings linked together similar to links in a chain.[26] Calixerenes **17**, caceplexes **18** and carcerands are the molecules with cavity or enforced cavity in their structures and all are synthesized using secondary forces. Synthesis of supramolecules is helped by some ions or small molecules that place the reactants in required arrangement and facilitate bond formation. This effect is known as templation.

1.8.1 Templates

The molecules, which help this orientation in synthesis, are called **'Templates'**. A template is defined as a molecule or an ion, which organises assembly or atom with one or more geometric loci in order to achieve particular linking of the atoms.[27] Templates are extensively used in synthesis of carceplexes, crown ethers and rotaxanes etc.[28] Supramolecules with closed structure have been used as reaction vessels[29] generating selectivity and accelerating the reaction.[30,31] When the resulting supramolecular assembly is a cage formed by coupling of two cavitands or any other way, a template or a guest molecule is most likely to be entrapped in the cage e.g. 18 during their synthesis. Entrapping of a guest or one or more solvent molecules (cf. Chapter-3) may also take place during the crystallization process. There are numerous examples of this type of encapsulation in literature out of which recent examples of carceplexes, carcerands, [29b] and cucurbituril[32] are noteworthy. It is possible to decomplex the host by changing the condition if desired.[30] It is possible to protect the guest from outer phase reactant by stepwise shell closure. [33]

1.8.2 Self-assemblies

Self-assembly is one of the most important results of supramolecular interactions. The spontaneous assembly of molecules into structured, stable, non-covalently joined aggregates is the simple definition of self-assemblies.[34] The assemblies are stable due to thermodynamic stability. Self-assembled systems have different properties from the subunits. A template may help in the formation of directed self-assembly. Self-assemblies are observed in biological systems for example in tobacco mosaic virus (TMV), proteins, enzymes etc. There are some excellent reviews on self-assembling systems.[35] Gibb and Gibb have described the methods for estimating the efficiency of self assemblies and given some hints for drawing assembly trees.[35] Self-assembly of molecules form cavities of nano sizes and can accommodate several guest molecules within the cavity.[36] Formation of rotaxanes and catanene is nothing but the result of self-assembly.[40(a)] Cyclic peptides generating alternating arrangement of D and L amino acids can self assemble into mice increasing permeability of bacterial membranes and resulting in collapse of drug resistance of bacteria.[37]

Another most important application of a supramolecule with chiral binding sites is selective recognition of one of the antipodes from racemates. They can be used for streoselective transport.[38] This streoselectivity is at work in enzymatic reactions. The cause of the reactivity of only one of the enantiomers active as a drug is enantioselective binding of the drug molecule with biomolecules. Supramolecules with chiral binding sites can give chiral complexes, which can be used for enantioselective organic reactions.

Recent developments in preparation and applications of imprinted polymers have established them as a research area. Imprinted polymers can be prepared by using a variety of templates, which live behind their effect in imprinted polymers making them useful for particular applications. Imprinted polymers are artificial molecular recognition materials with unlimited scope in organic synthesis and in chiral catalysis.[39] General scheme for molecularly imprinted polymer (MIP) construction is shown in **Figure 7.**

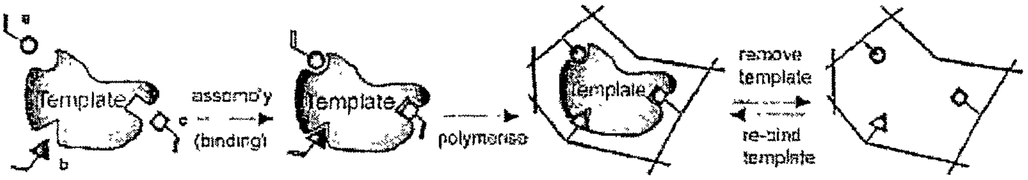


Figure 7

The principle of biological organization in formation of large structures from smaller subunits has been applied in synthesis of self-assembling dendrimers. This results in the chemical synthesis of the compound with nanometer dimensions. Hydrogen bonding plays an important role in self-assembly of dendrimer with polar functionalities.[40] Thus supramolecular chemistry is applicable to synthesis of nano particles of well-defined structure and size, which make the resulting nano material more useful.

1.9 The Present Research Work

The project started with the initial idea of undertaking the study of chemistry of aromatic compounds and leading to polyaromatic compounds with interesting structural features and applications. The chemistry of aromatic compounds and polyaromatic compounds was being revisited with the new perspective to give polyaromatic hydrocarbons and their derivatives with a typical stereo geometric arrangement, which is a part of fullerene structure.[41] This interest led to the synthesis of seco-sumanene on the way to sumanene[42] and other advanced fragments containing fullerene sub-structure.[43] The synthesis of advanced fragments requires high vacuum, high temperature tube furnace and high resolution NMR instrument readily available as the products are obtained as complicated mixtures with unexpected fusion of aromatic rings.[47(a)] After the initial experiments, the focus was diverted to the synthesis of aromatic compounds with a variety of substituents leading to curved geometry, having the functional groups with supramolecular binding abilities and to the synthesis of compounds with closed cage structures. Our synthetic endeavours have been presented in this thesis in the form of the following chapters.

Chapter-1: Introduction

It forms the current introduction chapter, which has dealt with general introduction on the subject of this thesis. We have discussed various supramolecular forces influencing biological systems and subsequently developing artificial systems with the importance of aromatic compounds in supramolecular interactions. The influence of the secondary forces in the development of current trends in chemistry and material science has been projected in this chapter. Supramolecular chemistry, which is the base of the work present in this thesis, has found a number of important applications in current science. Major applications have been briefly presented here.

Chapter- 2 From colour to cavity: Application of tri-phenyl methane dye

A readily available tri-phenyl methane dye has been applied to prepare compounds with structures containing three or more aromatic rings not in a single plane and geometry which would provide the opportunity for the aromatic rings to bind with guest molecules. Introduction of a variety of substituents provides the scope for further modification, which may result in new macromolecules. Introduction of hydrophobic chains result in dipolar compounds, which can form aggregates structures.

Chapter-3 Designing Functionalised Polyaromatic systems for well-controlled Macromolecular synthesis

C_3 Symmetric compounds have generated a special interest in recent years. Synthesis of C_3- symmetric compounds has been carried out starting from aromatic central ring with three-fold coupling reactions with various phenolic aldehydes. The synthesis was favoured by the template effect from Cs^+ ions. A detailed account of the experiments leading to the advanced C_3 symmetric compounds, which can be used as intermediates or building blocks for a variety of supramolecular structures has been presented here.

Chapter 4: C_3- symmetric molecules with Asymmetric recognizing centers Molecules with chiral recognizing centres have got some important applications and uses. They can be applied for preparation of chiral complexes, which can act as chiral catalysts in organic synthesis. These molecules are useful for preparation of imprinted polymers, which can be used for carrying out strereospecific reactions. The supramolecules with chiral centers also recognise and bind with specific enantiomers and act as chiral host molecules. In this chapter we have reported the C_3 symmetric molecules with chiral auxillaries retaining their C_3 symmetric character. Optically pure substrates have been used to react with C_3- symmetric trialdehydes prepared in the earlier chapter. The synthesis and characterization have been discussed.

Chapter 5: Synthesis of an Oval-shaped spherical azacryptand

Cage like supramolecules have greater ability to bind with the guest molecules with selectivity and they have their own symmetrical structural features. Our attempts to prepare a closed supramolecular assembly using rosolic acid have not been with success. There are a few reports on application of tris(2-aminoethyl)amine (TREN) in synthesis of cryptands with nitrogens. We have applied a similar strategy for the preparation of a new cryptand with greater number of binding sites, which can also form hydrogen bond with guests. We report here the synthesis of a new cryptand using TREN having C_3 symmetry.

1.10 REFERENCES

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1. Snyder J.P.; *Non-benzanoid Aromatics* 2 vol: Academic press: New York 1969-1971. Bergmann.

2. Kirby, A.J. *Angew.Chem.Int.Ed. Engl.* 1994, **33**, 551.

3. (a) Yoon, S.S.; Still, W.C. *J. Am. Chem. Soc.* 1993, **115**, 823 (b) Newcomb, L.F.; Haque, T.S.; Gellman, S.H. *J. Am. Chem. Soc.* 1995, **117**, 6509 (c) Tanford, C. *The Hydrophobic Effect* 2nd ed., Wiley, New York, 1980 (d) Ben-Naim, A. *HydrophobicInteractions*, Plenum Press, New York, 1980 (e) Lemieux, R.U. *Acc. Chem Res.* 1996, 373 (f) Wallimann, P.; Marti, T.; Fu¨rer, A.; Diederich, F. *Chem. Rev.* 1997, **97**, 1567

4. (a) Conn, M.M.; Deslongchamps, G.; Mendoza, J.; Rebek, J. Jr. *J. Am. Chem. Soc.* 1993, **115**, 3548 (b) Saenger, W.; Jeffrey, G. A. *Hydrogen Bonding in Biological Structures*, Springer, Berlin, 1994 (c) Jeffrey, G. A. *An Introduction of Hydrogen Bonding*. Oxford University Press, New York, 1997.

5. (a) Dougherty, D. A. *Science* 1996, **271**, 163 (b) Ma, J.C.; Dougherty, D.A. *Chem. Rev.* 1997, **97**, 1303 (c) Ngola, S.M.; Dougherty, D.A. *J. Org. Chem.* 1998, **63**, 4566 (d) Ngoly, S.M.; Kearney, P.C.; Mecozzi, S.; Russell, K.; Dougherty, D.A. *J. Am. Chem. Soc.* 1999, **121**, 1192.

---

6. (a) Hunter, C.A. *Chem. Soc. Rev.* 1994, 101 (b) Mondasini- Denti, T.Z.; Van Gunsteren, W.F.; Diederich F. *J. Am. Chem. Soc.* 1996, **118,** 6044 (c) Hunter, C.A.; Sanders, J.K.M. *J. Am. Chem. Soc.* 1990, **112**, 5525.

7. Behr, J.P. " The Lock-and-key Principle. The state of the Art –100 years on". J. Wiley & Sons: Chichester 1994.

8. Powell, H.M. *J. Chem. Soc.* 1973,61.

9. Philp, D.;Stoddart, J.E. *Angew.Chem.Int.Ed. Engl.*1996, **35**, 1154.

10 Whitesides G.M., Mathias J.P., Seto C.T., *Science*, 1991, **254**, 1312.

11. Samal, S.; Choi B.; Geckeler, K. *Chem. Commun.*, 2000, 1373.

12. Makha, M.; Hardie M. J.; Raston C. L. *Chem. Commun.*, 2002, 1446.

13. Conners, K.A. *Binding Con*stants, John Wiley & Sons: Chichester 1987.

14 Atwood JL, Davies JED, MacNicol DD, Vo¨gtle F, Suslick KS.*Comprehensive Supramolecular Chemistry*. Elsevier: Oxford, 1996.

15. Kirby, A.J. *Angew.Chem.Int.Ed. Engl.* 1994, **33**, 551.

16. Bradshaw, J.S.; Stott, P.E. *Tetrahedron* 1980, **36**, 461.

17. Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* 1978, **8**, 11.

Hosseini, M. W. *Supramolecular catalysis of phosphoryl Anion Transfer Processes', in supramolecular chemistry of anions*, Bianchi, A., K. Bowman-James and E. Garcia-Espana (eds.), Wiley-VCH: Chichester, 1997, 421.

---

19. Kintzinger, J.P.; Lehn, J.M.; Kauffmann, E.; Dye, J.L.; Popov, A.I. *J. Am. Chem. Soc.* 1983, **105**, 7549.

20. Newkome, G.R.; Sauer, J.D.; Broker, J.M.; Hager, D.C. *Chem. Rev.* 1977,77,513.

21. Timko, J. M.; Helgesom, R. C.; Cram, D. J. *J. Am. Chem. Soc.*1978, **100**, 4569.

22. Hamilton, A.D.; Lehn, J. M.; Sessler, J.L. *J. Am. Chem. Soc.* 1986, **108**,5158.

23. Kakuchi, T.; Sasaki, H.;Yokota, K. *Makromole. Chem.* 1988, **189**,1279.

24. Warshavsky, A.; Kalir, R.;Deshe, A.; Berkowitz, H.; Pachornik, A. *J. Am. Chem. Soc.* 1979, **101**, 4249.

25. (a) Cram, D.J. *Science* 1983, **219**,1177 (b) Cram, D.J. *Angew.Chem.Int.Ed. Engl.* 1983, **25**, 1039.

26. (a) Chill, S. *Catanenes, Rotaxanes and konts* Academic Press. 1971 (b) Wasserman, E. *J. Am. Chem. Soc.* 1960, **82**, 4433 (c) Zhou, Q.; Swager, T. M. *J. Am. Chem. Soc.* 1995, **117**, 12593.

27. Busch,D.H. *J. Inclusion Phenom. Mol. Recognit. Chem.* 1992, **12**, 389.

28. (a) Champman, R.G.; Sharman J.C. *Tetrahedron* 1997, **53**,15911. (b) Champman, R.G.; Sharman J.C. *J. Am. Chem. Soc.* 1998, **63**,4103.

29. Jasel, A.; Sharman J. C. *Chem.Rev.* 1999, **99**, 931.

30. Warmuth, R. *Chem. Commun.* 1998,59.

31. Kanj, J.; Rebek, J. Jr. *Nature* 1997, **386**, 50.

---

32. Lee, J.W.; Samal, S.; Selvapalam, N.; Kim,H.J.; Kim, K. *Acc. Chem. Res.* 2003, **36, 621.**

33. Kurbstani, S. K.; Helgeson, R.C.; Cram, D.J. *J. Am. Chem. Soc.*1995, **117**, 1659.

34. Whitesides G.M., Mathias J.P., Seto C.T., *Science*, 1991, **254**, 1312.

35. Gibb, C.L.D.; Gibb, B. C. *J. Supramol.Chem.1* 2001, 39.

36. MacGillivary, L.R.; Holman, K.T.; Atwood, J.L. *J. Supramol.Chem.1* 2001,125.

37. Fernandaz-Lopez, S.; Kim, H.S.; Choi, E.; C. Delgado, M.; Granja, J. R.; Khasanov, A. ; Kraehenbuehl, K.; Long,G. Weinberger, D. A.; Wilcoxen K. M.; Ghadiri, M. R.*Nature* 2001, **412**, 452.

38. Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* 1978, **11**, 8.

39. Alexander, C; Davidson, L.; Hayes, W. *Tetrahedron* 2003,**59**, 2025.

40. Zimermann, S.C.; Zang, F.; Reichert, E.C.; Kolotuchin, S.V. *Science* 1996,**271**,1095.

41. (a) Shah, S.R. 'Fullerenes', Inter University Consortiam (b) Shah, S.R.; Mehta, G. *Aromatics to Polyaromatics: A new perspective,* IVth National Organic Symposium Trust (NORST), Deharadun (March 1994).

42. Mehta, G.; Shah, S. R.; Ravikumar, K. *J. Chem. Soc. Chem. Commun.* 1993,1006.

43. (a) Mehta, G.; Panda, G.; Shah, S. R.; Kunwar, A.C. *J. Chem. Soc. Perkin. Trans. 1* 1997, 2269 (b) Scott, L.T. *Pure Appl.Chem.*1996, **68**, 291. (c) Rabideau, P.W.;

Sygula, A. *Acc. Chem. Res.* 1996, **29**, 235. (d) Mehta, G.; Panda, G. *Tetrahedron Letters* 1997, **38**, 2145 (e) Mehta, G.; Panda, G. *Chem. Commun.* 1997, 2081.