Supramolecular Chemistry

From Molecule to Molecular Machines

Vandana Bhalla

Supramolecular chemistry as defined by Lehn 'chemistry beyond the molecule' focuses on the development of functional complex architectures through non-covalent interactions. The year 2017, marked the fiftieth anniversary of the serendipitous discovery of crown ethers. Since then, the field is growing, and due to the efforts of various researchers now it is possible to have some control over the arrangement of things on a small scale. In this review article, the concept of supramolecular chemistry, cooperativity responsible for interactions, techniques for determination of thermodynamic parameters of cooperativity, and the contribution of supramolecular chemistry to nanotechnology is described.

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Keywords

Non-covalent interactions, self-assembly, molecular motors, cooperativity, fluorescent chemosensors.

Introduction

Supramolecular chemistry has been defined by phrases such as 'chemistry beyond the molecule', 'chemistry of molecular assemblies and of the intermolecular bond', and 'non-molecular chemistry'. The main objective of supramolecular chemistry is to design and develop novel functional systems by joining multiple chemical components through non-covalent interactions. The year 2017, marked the fiftieth anniversary of publication of first paper in the field of supramolecular chemistry and the thirtieth anniversary of the first Nobel Prize awarded in this field. The Nobel Prize awarded to Jean-Marie Lehn, Donald J Cram, and Charles J Pedersen in 1987, established supramolecular chemistry as a discipline which is now being explored in various areas such as drug development, sensors, catalysis, nanoscience, molecular devices etc. Over the last few decades, the discipline of supramolecular chemistry has emerged as a multidisciplinary domain providing

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opportunities to researchers working in different areas such as chemical science, biological science, physical science, material science and so on.

On the whole, supramolecular chemistry focuses on two overlapping areas, 'supramolecules' and 'molecular assemblies'. A supramolecule is a well-defined discrete system generated through interactions between a molecule (receptor or host) having convergent binding sites such as donor atoms, sites for formation of hydrogen bonds and sizable cavity, and another molecule (analyte or guest) having divergent binding sites such as hydrogen bond acceptor atoms (*Figure* 1). The receptor can be a macromolecule or aggregates and the analyte may be ions (cations and anions) or molecules. For designing a receptor molecule, knowledge of several interactions such as structural/functional information, energetics of the binding event, complementarity of molecular shapes etc., is needed at molecular level. Receptor-analyte affinity is nature inspired and at the heart of many biological processes such as enzyme-substrate, antibody-antigen interactions. On the other hand, well-defined molecular assemblies are generated by spontaneous self-assembly of multiple components under the given set of conditions. The guiding force for the self-assembling process originates from molecular binding events. In the nutshell, for the generation of ordered molecular assemblies, operation is supramolecular but approach is molecular. Recently, self-assembly process has been utilized for generation of functional nanoarchitectures of different shapes and morphologies [1]. This is one of the fastest-growing fields, and over the past decade, supramolecular chemistry has contributed significantly towards the development of nanotechnology. At the interface of these two disciplines – supramolecular chemistry and nanotechnology – lies the domain of nanochemistry.

Historical Background

The famous phrase of Louis Pasteur, "chance favors the prepared mind", reflects the curiosity of Charles J Pederson's prepared

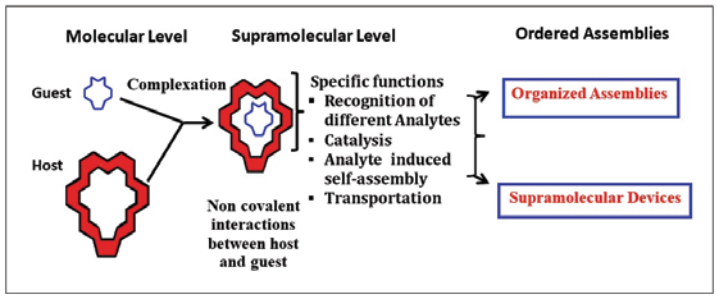

Figure 1. From molecules to structured assemblies [1].

mind [2] when it came to isolating a tiny amount of crystalline by-product from the 'unattractive goo' of an experiment which had gone wrong. Pederson examined the product and the structure of dibenzo-18-crown-6 was determined (*Figure* 2A). Interestingly, in presence of methanol solution of any alkali metal salt, the compound was soluble in methanol. Later studies suggested that the solubility of the compound was due to the presence of metal ion in the 'hole' of the molecule. This unprecedented conclusion marked the emergence of supramolecular chemistry. Furthermore, the unexpected high affinity of the molecule towards K^+ ions added new knowledge about molecular recognition. The publication of this work energized the scientific community and this field grew exponentially. Later in 1987, Charles J Pederson, Donald J Cram [3], and Jean-Marie Lehn [4] were awarded the Nobel Prize in Chemistry for the 'development and use of molecules with structure-specific interactions of high selectivity' (*Figures* 2B and 2C). The discovery of crown ethers, cryptands, and spherands had tremendous impact on the research investigations in the field of inorganic chemistry, organic chemistry, physical organic chemistry, analytical chemistry, and biological chemistry. This field grew due to the increasing number of contributions of different investigators. After the serendipitous discovery of the first 'supramolecule', the second Nobel Prize in the field of supramolecular chemistry was awarded in December 2016, to Sir J Fraser Stoddart, Jean-Pierre Sauvage, and Bernard Feringa[1] for their contributions to the field of molecular machines.

[1] N Jayaraman, 2016 Nobel Prize in Chemistry: Conferring Molecular Machines as Engines of Creativity, *Resonance*, Vol.22, No.9, pp. 835–845, 2017.

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Supramolecular Interactions and Cooperativity in Supramolecular Complexes

The whole range of non-covalent interactions such as coulombic interactions, hydrogen bonding, charge transfer complexes, van der Waals forces, and hydrophobic effect strongly affect the structure and properties of supramolecular systems. Non-covalent interactions are much weaker in comparison to covalent interactions (*Table* 1). However, the small stabilization gained by one weak interaction when added to all small stabilizations from the other interactions leads to the generation of a stable architec-

Box 1. Organic Chemistry vs. Supramolecular Chemistry

A dream target of nature inspired synthesis is to prepare 'smart' functional molecules which are so designed that they themselves are 'able to generate correct architectures'. Despite the excellent contribution of modern organic chemistry towards the development of highly complex materials, the synthetic routes are multistep and tedious. On the other hand, the principles of supramolecular chemistry can be applied to prepare well-defined large and complex architectures in a few steps. Furthermore, most of the organic reactions are kinetically controlled and irreversible. Due to irreversible reaction conditions, there is no possibility of correction of any 'mistake' during the product formation. Moreover, the final product may not be the most stable product. For preparing designed molecules, it is important to understand the mechanism of organic reactions. Interestingly, the key point of supramolecular chemistry is doing the synthesis under thermodynamically controlled conditions rather than kinetically controlled conditions. Due to thermodynamic control, all the steps are reversible and the final product is the most stable product. The interactions and the newly formed bonds are weak. Thus, they can break and reform till most stable structure is achieved. If any 'misconnection' is there, it can be self-corrected as shown in *Figure* A [5]. Self-corrected product is stable while least stable product is formed by misconnection.

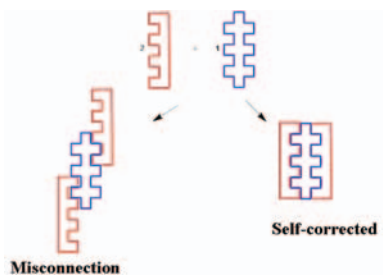

Figure A. The left panel shows the misconnection and the right shows the self-corrected molecule.

Interaction	Strength (kJ mol^{-1})
Covalent Bond	200–400
Ion-Ion	100–360
Ion-Dipole	50–200
Dipole-Dipole	5–50
Hydrogen Bonding	4–120
Cation-π	5–80
π–π	0–50
van der Waals	< 5 (variable depending on surface area)
Hydrophobic	Related to solvent-solvent interaction energy

Table 1. Supramolecular interaction classified under various categories.

ture or stable host-guest complex. The formation of a complex via supramolecular interactions is fast, facile and more stable as compared to that prepared by using principles of organic chemistry (see *Box* 1). Multivalent binding has added advantages of high binding strength, reversibility of binding process, and due to the organization of binding sites in the space, geometry of supramolecular complex can be controlled. Moreover, multivalency effect ensures the formation of discrete supramolecular systems rather than oligomers. Thus, the interactions between a receptor (host) and analyte (guest) strongly depends on multiple binding. On the other hand, in case of self-assembled polymeric supramolecular systems cooperative interactions between multiple chemical components are needed. Due to these cooperative interactions (non-covalent in supramolecular systems) or cooperativity, the free energy change (ΔG) is either decreased or increased over the subsequent interaction steps in a reaction as compared to the first step. If the free energy change is decreased it is called positive cooperativity while an increase in the free energy change suggests negative cooperativity. The positive cooperativity of multiple binding sites present on the host molecule to bind a guest molecule in a way is chelate effect. Very interestingly, many supramolecular architectures are very stable than what would be expected from the presence of chelate/positive cooperativity alone. In general, in discrete supramolecular systems,

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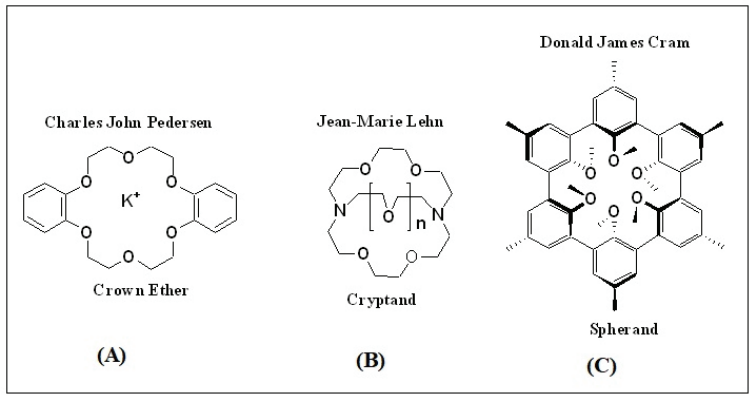

Figure 2. Structures of receptors prepared by Pedersen, Lehn, and Cram.

three different types of cooperativities [6] can occur as shown in *Figure* 3.

1. ***Intermolecular Cooperativity*****:** This type of cooperativity occurs in the systems generated through interaction of a monovalent guest and a multivalent host (*Figure* 3A). A good example of this type of cooperativity is the binding of oxygen molecules and $\alpha_2\beta_2$ heterotetrameric hemoglobin. The binding of first molecule of oxygen brings conformational changes into the structure of protein which increases the binding strength of the receptor (heterotetrameric hemoglobin) with next molecules of oxygen.

2. ***Intramolecular/Chelate Cooperativity*****:** This type of cooperativity occurs only in case of multivalent receptors and multivalent guests (*Figure* 3B). For such type of cooperativity, topology (positioning) of binding sites, and hence spacer length is very important. This type of cooperativity is supplemented by intermolecular cooperativity.

3. ***Interannular Cooperativity*****:** This type of cooperativity is shown in *Figure* 3C where binding of a bivalent guest with a tetravalent receptor preorganize the other binding sites present on the receptor in such a way that the next binding with the guest is increased or decreased. Actually, interannular cooperativity superimposes with intermolecular and intramolecular cooperativity.

Experimental Techniques to Determine Thermodynamic Parameters of Cooperativity

The selection of correct experimental techniques to determine various thermodynamic parameters such as ΔG to determine cooperativity or binding strength is very important. The selection of technique is based on the selection of physical property of the receptor that fits the concentration range which brings maximum change in the equilibria under examination. The most commonly used experimental techniques for the determination of binding strength between receptor and guest (supramolecular titration) are as follows:

1. ***NMR Titration Method*****:** This is one of the most popular methods for supramolecular titration studies. It is very much suitable for providing the information about the small structural changes generated in the receptor in the presence of guest. However, this technique is not suitable for systems having high association constants ($K > 10^5\ M^{-1}$). This is also not a preferred method for the intramolecular chelate systems because the interactions involved in these systems lie in slow exchange region.

2. ***Absorption and Emission Spectroscopic Techniques*****:** The absorption studies (UV-vis studies titration studies) provide limited information about structural changes involved during the binding event, however, the absorption experiments are more useful for thermodynamic analysis. The UV-vis spectroscopy is advantageous because of the operational simplicity of the instrument, high equilibrium constants, and with a suitable chromophore, the studies can be carried out at micromolar concentrations. Similarly, fluorescence spectroscopy is another powerful technique for the investigation of cooperative interactions due to its high sensitivity, operational simplicity, and low background interferences.

3. ***Isothermal Titration Calorimetry (ITC) Method*****:** ITC is a more convenient method to determine binding/association stoichiometry (n), binding/association constant (K), Gibbs free binding/association energy, binding/ association enthalpy and binding/association entropy. ITC is a direct technique to measure heat

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Signaling Binding Events with Fluorescent Chemosensors

The important binding events of supramolecular chemistry can be conveniently signaled through light signals emitted by tailormade molecular devices.

Fluorescence spectroscopy is an active tool in various fields of modern science and medicine, including clinical diagnostics, biotechnology, molecular biology and biochemistry, materials science, and analytical and environmental chemistry. Especially for sensing and visualization of analytes, fluorescence spectroscopy offers significant advantages over other measurement methods, such as microelectrodes, NMR, atomic absorption spectroscopy, and spectrophotometry due to its operational simplicity, detection limit down to single molecules, 'on-off' switchability, high resolution and visualization, and the possibility of human-molecule communication. The important binding events of supramolecular chemistry can be conveniently signaled through light signals emitted by tailormade molecular devices. Fluorescence based molecular devices are important because their emission can be switched between two distinguishable states in presence of external stimuli. In addition, fluorescence is a useful spectroscopy in which the fluorescence signals may be monitored as excitation and emission spectra, intensities, intensity ratios, lifetimes, and even as anisotropy. There are several approaches for designing fluorescence-based materials. Most commonly used approach is depicted in *Figure* 4. Sousa, Czarnik, and de Silva are pioneer workers in this field. They reported a variety of fluorescent chemosensors prepared by connecting fluorophore with the crown-based receptor units. They demonstrated that crown/azacrown when linked to fluorophore showed quenching of the molecular emission due to photoinduced electron transfer (PET) from lone pair of the benzylic heteroatoms of the receptor unit [7]. Interestingly, emission of such systems can be revived by the binding of receptor unit with a guest/analyte through chelation enhanced emission enhancement phenomenon (CHEF) as shown in *Figure* 5 [8]. In-

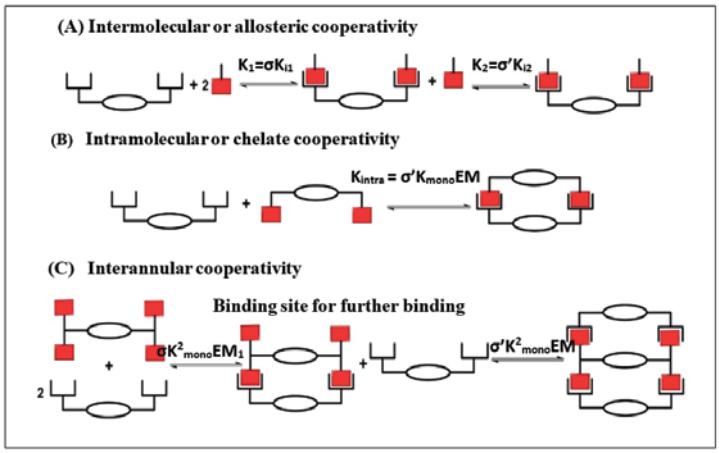

Figure 3. The three types of cooperativity in discrete supramolecular complexes.

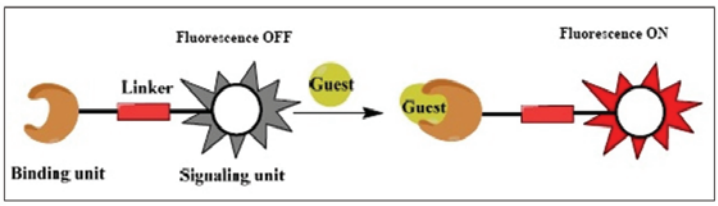

Figure 4. Design of fluorescent chemosensor.

terestingly, highly dilute solutions are required to measure photophysical parameters, such as exciton lifetime, decay rate, and fluorescence efficiency, where the fluorescent molecules are considered as isolated species. This field is still growing and efforts are in progress to develop a new fluorescent chemosensors which can show sensory response in aqueous media (see *Box* 2).

Supramolecular Chemistry and Nanotechnology

Over the last few decades, tremendous progress has been made in the field of 'molecular machines'. These molecular machines are capable of showing controlled repetitive motion and function at the nanoscale. Thus, such materials have great potential in the field of nanotechnology. A molecular machine is actually a system in which a stimulus triggers the motion of one chemical component relative to another, and most importantly some work is done. The key focus in this field is to control directional motion, and thus a variety of molecular walker and rotax-

ane/catenane based systems have been developed.

Molecular Walkers: Molecular walkers have been developed to show directional transport at molecular level. The molecule should

Box 2. Signaling Binding Events with Fluorescent Chemosensors in Aqueous Media

Development of chemosensors which show high emission in aqueous media is very important. However, in most of the cases, fluorescence is quenched or weakened due to exciton coupling, excimer formations, and excitation energy migration to the impurity traps. In 2001 Tang *et al*., reported the term 'aggregation-induced emission (AIE)' materials for such kind of molecules [9]. Unlike other fluorophores showing quenching effect, these molecules show no emission in organic solvent. Amazingly, upon raising the water content, the molecules aggregate and show strong fluorescence. This feature is attributed to the availability of easily rotatable phenyl rings attached to the central core through C-C bond, also called 'rotors'. In solution phase, these rotors are in rotating mode around their vertical axis due to which the energy of approaching photon is dissipated with a non-radiative pathway. Hence, less energy is absorbed by the molecule due to which the molecule is non-luminescent in solution state. But when a bad solvent is added to the solution, the molecule gets aggregated due to poor solubility on the molecular level, and rotation of the rotors is restricted due to the close packing in aggregated state which blocks the non-radiative pathways. This results in the release of excitation energy with radiative pathways to raise the luminescence of the molecule as in *Figure* B.

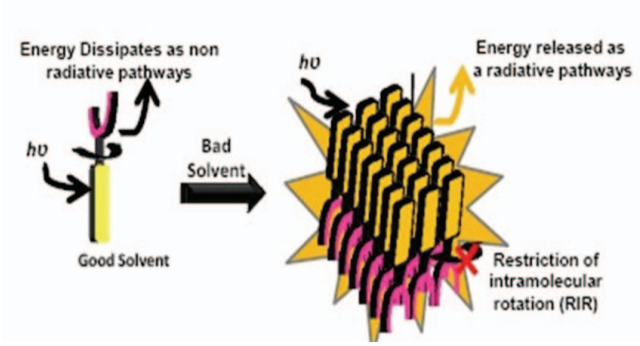

Figure B. Fluorescence turned on due to restricted intramolecular rotation by aggregation formation.

Most of the reported AIE sensors are based on design of molecules which are freely soluble in aqueous/organic media. These molecules undergoes coordination driven aggregation in the presence of analytes. As a result, restriction in intramolecular rotation and hence enhancement in fluorescence emission intensity was observed. The AIE strategy offers advantages such as high selectivity, sensitivity, facile fabrication, ready functionalization, excellent stability, high signal-to-noise ratio, low background interference as well as the simplicity of the fluorescence technique.

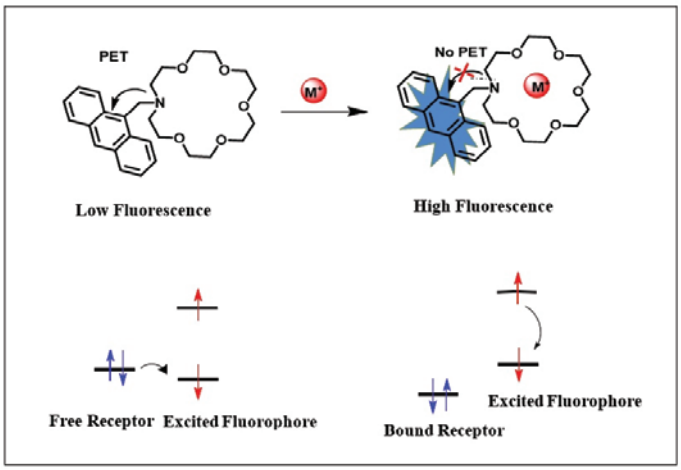

Figure 5. Photoinduced electron transfer phenomenon.

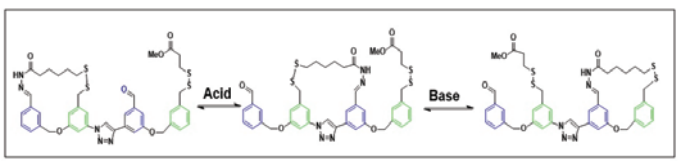

Figure 6. Operation of the first small-molecule walker system by Leigh. Changes in the pH induce the migration of the walker unit from one end of the track to the other by a 'passing-leg' mechanism.

fulfill essential requirements such as processivity (there should be minimum one contact point of molecule with the track during the whole operation) and directionality (molecule walker should move towards one end). Moreover, molecular walker must show autonomous, progressive and repetitive operation. Leigh's group developed the first small molecule-based molecular walker in 2001 [10]. This walker worked on 'passing leg' mechanism. The walker has two feet – disulphide foot and hydrazine foot. Both the 'feet' bind reversibly with the track through covalent bonds and are highly sensitive to pH. Under basic conditions, disulphide foot becomes labile; however hydrazine foot remains covalently attached to the track. On the other hand, under acidic conditions, hydrazine foot becomes labile, and disulphide foot remains covalently attached as shown in *Figure* 6.

Rotaxane Based Molecular Machine: Rotaxanes [11] consist of axels threaded through one or two rings (*Figure* 7). Since rotaxane based systems have interlocked components. The exchange of these components with bulk is practically impossible without

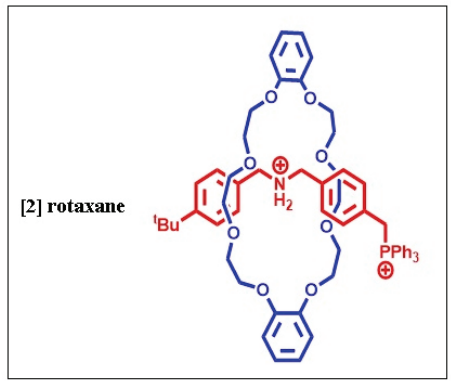

Figure 7. Rotaxane based derivative consists of one (or more) axles threaded through one (or more) rings. Bulky groups at each end of the axle prevents the ring from dethreading.

the cleavage of covalent bonds, and motion of the system is restricted in certain directions. Further, the movement of a component is controlled by intercomponent interactions. The first rotaxane based 'molecular shuttle' was reported by Nobel Laureate Stoddart.

Catenane Based Rotary Motors: Catenanes [11] are composed of interlocked components as shown in *Figure* 8. The research group of Nobel Laureate Sauvage demonstrated the degree of control over the rotary motion of different components of catenanes.

Applications

Development of molecular walkers, rotaxane based machines, and catenane based rotors demonstrate the potential of synthetic chemistry to develop functional materials. These materials exhibit motion on meso/macro state which can be controlled at the molecular level. A variety of molecular machines have already been designed and synthesized, and new approaches have been developed to gain control over the motion of these machines. Efforts are in progress to convert this motion into useful work. These artificial machines will be utilized for the preparation of new materials and energy storage systems, and as predicted by Nobel Laureate Stoddart, "the artificial motors prepared in lab will compete with natural machines in a few decades".

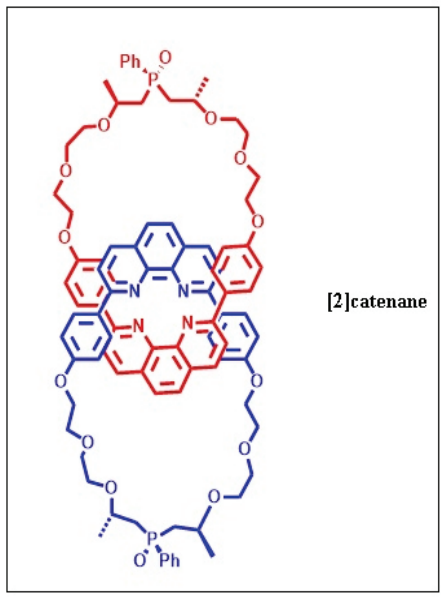

Figure 8. Catenane derivative consists of two (or more) macrocycles threaded through each other.

Conclusion

The key feature of supramolecular chemistry is its ability to reorganize and exchange molecules till the correct combination of building blocks is selected from a collection of different molecular components for the development of thermodynamically and kinetically favored supramolecular entity. Now, the biggest question is to where supramolecular chemistry is heading to? The answer to this query is very simply provided by Prof Lehn. Supramolecular chemistry is significantly contributing towards the growth of molecular chemistry, and hence a new type of adaptive chemistry is evolving. This chemistry aims at allowing reorganization and selection in self-organisation to attain adaptation at the molecular as well as supramolecular level.

Suggested Reading

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