UNIT V: ADVANCED CONCEPTS/TOPICS IN CHEMISTRY

Characteristics of molecular motors:

Molecular motors are biological molecular machines that are the essential agents of movement in living organisms. A motor is a device that consumes energy in one form and converts it into motion or mechanical work. Ex. Many protein- based molecular motors make use of the chemical free energy released by the hydrolysis of ATP in order to perform mechanical work. This type of motors is superior to man- made motors in terms of efficiency of energy.

Some important examples of naturally occurring molecular motors are:

I. *Cytoskeletal motors:* Myosines are responsible for muscle contraction, intercellular cargo transport and producing cellular tension.
Kenesin is another kind of motor which moves cargo inside ces away from nucleus
Dynein: produce the axonemal beating of cilia & flagella

II *Polymerisation motors:* Actin: Polymerisation generates energy used for propulsion in presence of ATP

Microtubules: Polymerisation in presence of GTP

Dynamin: is responsible for the separation of clathrin buds from plasma membrane by using GTP

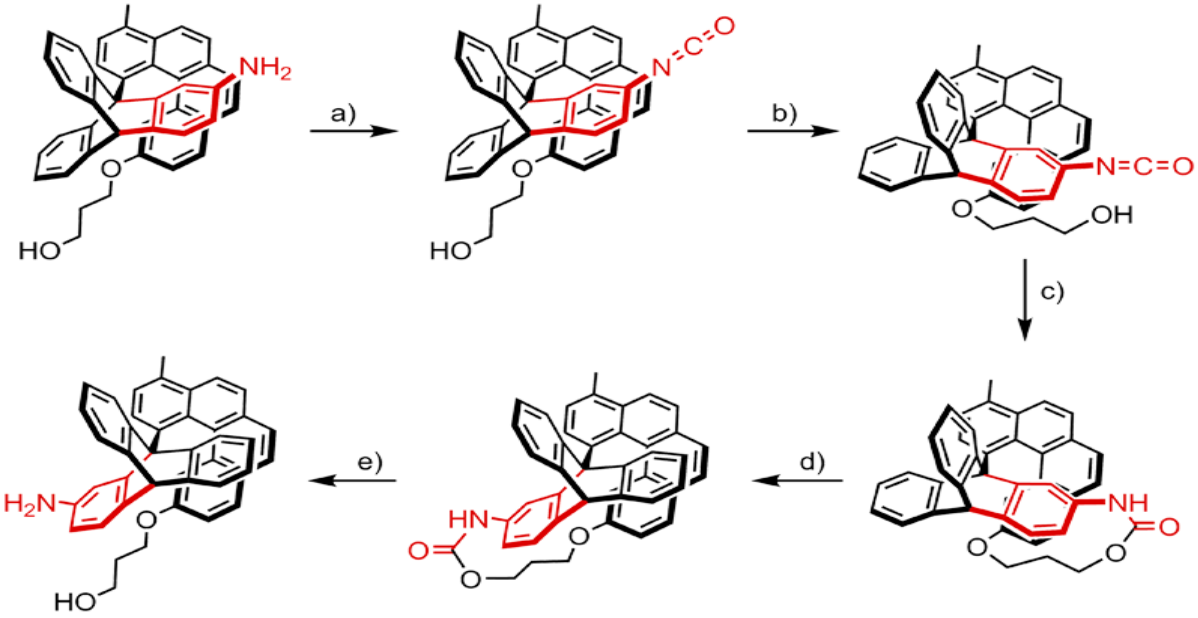
III. *Rotary motors*: F_0F_1-ATP synthase: Is a family of protein which convert the chemical energy in ATP to the electrochemical energy of a proton gradient across a membrane.
ATP synthesis in mitochondria and chloroplasts and pumping of protons across the vascular membrane. The pumping protons across the membrane is driven by rotary motors.

IV. *Nucleic acid motors*: RNA polymerase which transcribe RNA from a DNA template
DNA polymerase turns single-stranded DNA into double stranded DNA. Helicases separates double strands of nucleic acids prior to transcription or replication by using ATP.

V. *Enzymatic motors:* Urease, aldolase, Hexokinase etc.,

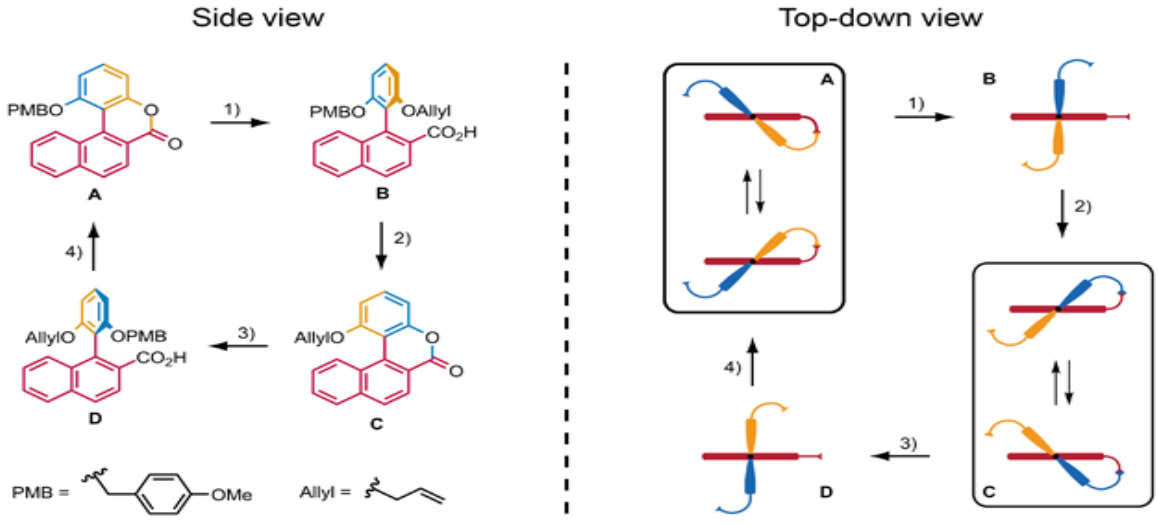
VI. *Synthetic molecular motors:* Synthetic molecular motors are capable of producing continuous directional rotation under an energy input. Many chemist pursuing synthetic motors, the basic requirement for a synthetic motor are repetitive 360^0motion, the consumption of energy and unidirectional rotation. These are classified into two major groups.
1. Chemically driven rotary molecular motors
2. Light-driven rotary molecular motors

Chemically driven rotary molecular motors: An example of a prototype for a synthetic chemically driven rotary molecular motor was reported by KELLY, system is made up from a three bladed triptycene and a Helicene capable of performing a unidirectional 120^0rotation of triptycene moiety in five steps



The prototype of a chemically driven rotary molecular motor

The second example is the work carried out by feringa and co-workers who was awarded noble prize, in 2016 carried out 360^0 full rotation of a molecular motor in four stages as shown below.



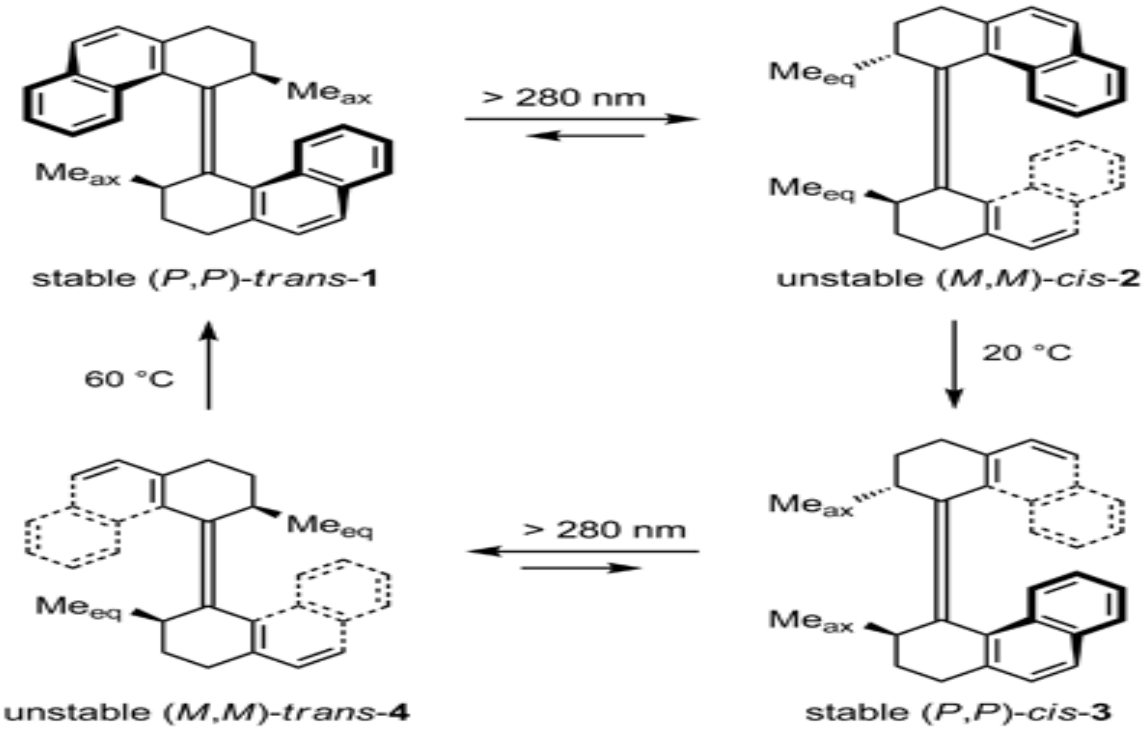
The chemically driven rotary molecular motor

Light-driven rotary molecular motors:

In 1999 the laboratory of Prof. Dr. Ben L. Feringa at the University of Groningen, The Netherlands, reported the creation of a unidirectional

molecular rotor.[9] Their 360° molecular motor system consists of a bis-helicene connected by an alkene double bond displaying axial chirality and having two stereo enters. One cycle of unidirectional rotation takes 4 reaction steps. The first step is a low temperature endothermic photo isomerization of the trans (P,P) isomer 1 to the cis (M,M) 2 where P stands for the right-handed helix and M for the left-handed helix. In this process, the two axial methyl groups are converted into two less satirically favourable equatorial methyl groups. By increasing the temperature to 20 °C these methyl groups convert back exothermally to the (P,P) cis axial groups (3) in a helix inversion. Because the axial isomer is more stable than the equatorial isomer, reverse rotation is blocked. A second photo isomerization converts (P,P) cis 3 into (M,M) trans 4, again with accompanying formation of satirically unfavourable equatorial methyl groups. A thermal isomerization process at 60 °C closes the 360° cycle back to the axial positions.

Scientists and engineers have learnt from the selectivity, specificity, precision and accuracy of biological processes and the ensembles so formed on a cellular and sub-cellular level and strive to apply these concepts in the laboratory to create molecular devices and machines. Natural machines such as ATP-ase, DNA-polymerase, rhodopsin, ribosomes etc. are all complex and fascinating examples of natures approach to nano-scaled machines. The synthesis and assembly of molecular building blocks capable of functioning in a controlled way and in a wholly synthetic sense is an achievable goal and, to this end, prototypical machines that demonstrate specific tasks or design features are being reported in ever increasing amounts. In fact, a simple web of science search identifies over 450 papers with the term ‘molecular machine’ in its title over the past decade.



Rotary cycle of the light-driven rotary molecular motor

To generalize the design principles of a molecular level machine, the following criteria have been identified as important features: 1) what energy input is required to make the machine perform work, 2) what is the type and level of movement performed by its components, 3) how will the machine's function be detected and monitored during operation, 4) does the system have a plausible repeat operation and can this establish a recurring process, 5) what is the timescale for a complete cycle of operation, and 6) what level and type of function is to be performed by the machine .

A major hurdle to overcome is the long reaction time for complete rotation in these systems, which does not compare to rotation speeds displayed by motor proteins in biological systems. In the fastest system to date, with a fluorene lower half, the half-life of the thermal helix inversion is 0.005 seconds. This compound is synthesized using the Barton-Kellogg reaction. In this molecule the slowest step in its rotation, the thermally induced helix-inversion, is believed to proceed much more quickly because the larger tert-butyl group makes the unstable isomer even less stable than when the methyl group is used. This is because the unstable isomer is more destabilized than the transition state that leads to helix-inversion. The different behaviour of the two molecules is illustrated by the fact that the half-life time for the compound with a methyl group instead of a tert-butyl group is 3.2 minutes.

The Feringa principle has been incorporated into a prototype Nano car. The car synthesized has a helicene-derived engine with an oligo (phenylene ethynylene) chassis and four carborane wheels and is expected to be able to move on a solid surface with scanning tunnelling microscopy monitoring, although so far this has not been observed. The motor does not perform with fullerene wheels because they quench the photochemistry of the motor moiety. Feringa motors have also been shown to remain operable when chemically attached to solid surfaces. The ability of certain Feringa systems to act as an asymmetric catalyst has also been demonstrated.

Synthetic/ Artificial molecular machines: The artificial molecular machines are simple and small when compared to natural molecular machines. The first artificial molecular machines

Synthesised by sir, J.F. Stoddart, is a molecular shuttle and rotaxane molecule, where a ring is mechanically inter-locked into an axe with two bulky stoppers. Hence rotaxanes are mechanically interlocked molecular architectures, provided with direct molecular motion.

I. *Molecular motors*: Molecular motors are the molecules that are capable of rotary motion around a single or double bond. Single bond motors as seen in the previous topic are fuelled by chemical reactions where as double bond motors are fuelled by light. The rotation speed of the motor can be tuned by careful molecular design e.g. bis-heicane.
II. *Molecular propeller*: II. A molecular propeller is a molecule that can propel fluids when rotated, due to its special shapes that is designed in analogy to microscopic propeller. It has several molecular scale blades attached to a pitch angle around the circumference of a nano scale shaft.

For example muscle gyroscope-a p-phenylene rotor

III. *Molecular switch*: A molecular switch is a molecule that can be reversible shifted between two or more stable states in response to the environmental stimuli, such as change in pH, light, temperature, electric current, microenvironment or in presence of ions and other ligands currently synthetic molecular switches have important applications in molecule computers or responsive drug delivery systems. Ex. Azobenzenes, stilbeneses.

IV. *Molecular shuttle*: A molecule capable of shutting molecules or ions from one location to another. A common molecular shuttle is a rotaxane where the macro cycle can move between two sites or stations along the dumbbell back bone.

Biologically molecular machines:

Some biological machines are motor proteins, such as myosin which is responsible for muscle contraction-kinesin moves cargo inside cells away from the nucleus along microtubules and dynein other biological machines are responsible for energy production. For example ATP synthase harness energy from proton gradients across membranes to drive turbine-lite motion used to synthesise ATP, which is the energy currency of the cell, still machines like DNA polymerase are responsible for gene expression for replicating DNA, RNA polymerase are responsible for production of MRNA, These machines that have been artificially constructed.

Applications of Biologically machines:

- They could be used to identify and destroy cancer cells.
- Molecular technology deals with the molecular assemblers, biological machines which results Nano robots introduced into the body to repair or detect damages and infections.
- The molecular motor myosin is responsible for generating the force for muscle contraction
- Kinesin is a molecular machine which moves along microtubules which carries membrane enclosed organelles away from the neuronal cell body..
- The cardiac muscle myosin and actin are the molecular machines responsible for the contraction of heat muscles.
- Molecular motors convert chemical and electrical energy to mechanical work and operate close to the level of thermal energy.
- Biological motors pay crucial role in a large number of cellular functions like muscle contraction, vascular transport in the cytoplasm, segregation of chromosomes during mitosis and meiosis

2. Interlocked Molecules – Catenanes

Mechanically-interlocked molecules have attracted considerable attention as the basis of molecular devices and nanoscale machines long after the first reported syntheses of these chemical curiosities in the mid 1960's . Catenanes (from

the Latin catena meaning chain) are the most common of this class and are defined by their interlocking molecular rings (Figure 1a). Rotaxanes (rota meaning wheel, axis meaning axle) are another common form (Figure 1b). With respect to nomenclature, the number (represented as n) is enclosed in square brackets, [n] and describes the number of molecular parts involved in mechanical bonding. For example, a [2]catenane denotes two interlocking rings, a [4]catenane denotes four interlocking rings.

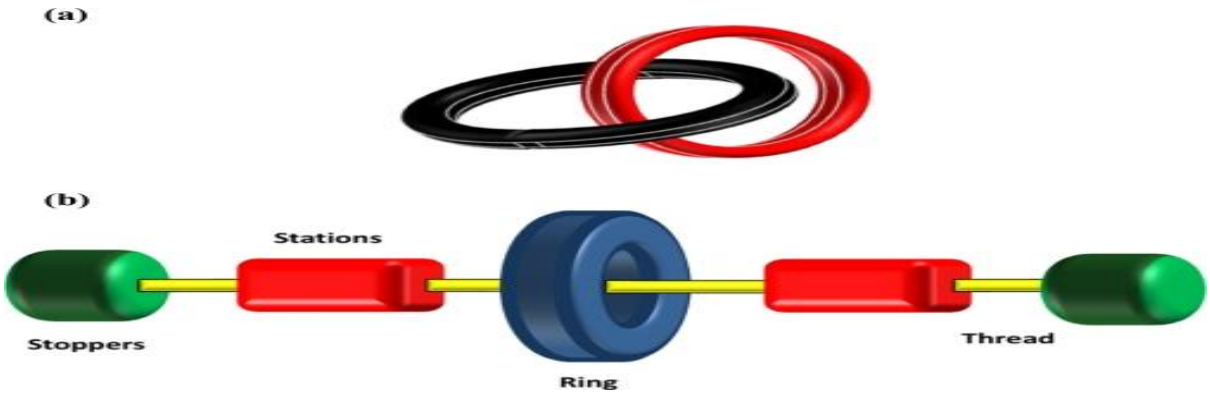
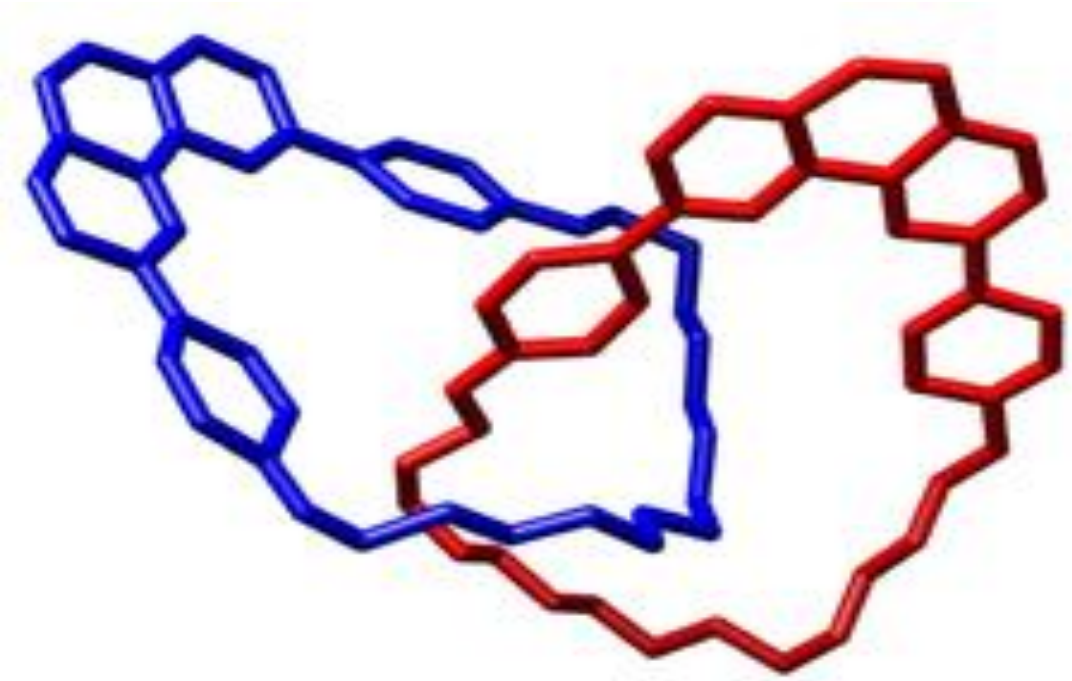


Figure 1: Schematic representation of two different types of interlocked molecules that have shown potential as molecular level machinery components. (a) Interlocked ring structures referred to as catenanes and (b) interlocked ring and thread terminated by bulky stoppers are termed rotaxanes.

The molecular dynamics of each component with respect to the other can be controlled and has been shown to be the basis of simple molecular devices. Recent developments in synthetic paradigms (template-direction etc) has allowed for the preparation of a variety of catenanes and more complex structures, such as trefoil knots in high yield. The preparation of interlocked molecules involves two integral steps: (i) the molecular recognition and arrangement of the non-interlocked components in a threaded fashion – so-called self-assembly, and (ii) covalent bond forming reactions post molecular recognition, which mechanically-interlocks the two components. The syntheses of interlocking molecules were once deemed a great synthetic challenge, with often more than 20 multiple-step syntheses being employed using the covalent approach and ultimately leading to a statistical result with yields of less than one percent. Synthetic strategies based on various non-covalent templates have been proposed by several research groups, leading to efficient preparative procedures with yields typically above 50%. Synthetic template-directed strategies are based on non-covalent interactions, such as hydrogen bonding, donor-acceptor interactions and metal complexation, which are used to assemble a pre-organized macrocyclic component and a linear component in a threading process, which after a bond-forming reaction, affords the interlocked molecules . In addition, knotted interlocked molecules have also been prepared from single-stranded DNA amongst other molecules . Of the non-covalent templates described in the literature, the most promising synthetic strategy are those utilizing transition metal templates or complementary π-electron-rich and π-electron-deficient recognition sites.



Crystal structure of a catenane reported by Sauvage and coworkers.

The metal ion template strategy was first developed by Sauvage and co-workers using copper(I) ions and phenanthroline ligands . The shape and mutually orthogonal arrangement of the disubstituted phenanthroline ligands would encapsulate the tetrahedral copper(I) metal ion, generating the necessary cross-over point for catenane formation giving a pseudo-tetrahedral complex (Figure 2(i)). With the introduction of hydroxyl groups on the phenyl substituents of the phenanthroline ligand, the half-rings could undergo a Williamson ether macrocyclization reaction, as seen in Figure 2(ii). This synthesis provided a simplistic and efficient means for preparing catenanes but also rotaxanes and to a smaller extent knotted molecules . By changing the oxidation state of the metal, or by competing ligation, the metal ion could be removed to give the free catenane. Sauvage's phenanthroline catenane undergoes a co-conformational change, which involves the circumrotation of both the macrocycles through the cavity of each other upon demetallation, leading to a conformation in which the phenanthroline ligands to be positioned away from each other (Figure 2(iii)). This is an example of a chemically controllable catenane.

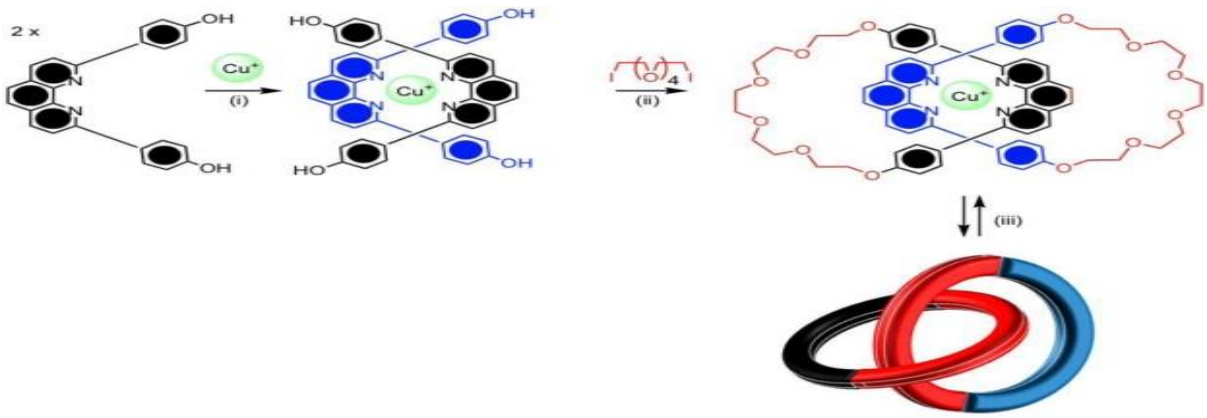


Figure 2 :Sauvage's copper(I) template synthesis of an interlocked catenane in two sequential steps: (i) coordination of the disubstituted phenanthroline ligand to the metal; (ii) mechanical interlocking by a covalent bond forming reaction; (iii) Demetallation leads to a specific conformational change.

In addition, the co-conformational motion can also be controlled electrochemically by reversible oxidation/reduction reactions of the metal centre and judicial choice of the ligands. For example, while copper(I) prefers a four-coordinate environment, copper (II) prefers a five-coordinate environment leading to ligands capable of stabilizing this ion upon oxidation. The example shown in Figure 3 is a model for a molecular switch based on a [2]catenane . This model demonstrated in earlier work by Sauvage uses one of the macrocyclic rings to contain two discrete binding sites on opposing sides of the ring– terpyridyl (terpy) and diphenylphenanthroline (dpp). The second macrocyclic ring contains only a single dpp binding unit. Upon changing the oxidation state of the copper(I) to copper(II), the dpp/terpy conformation is adopted to favor the five-coordinate copper(II) preference. These manipulations have lead to the formation of molecular switches and muscles .

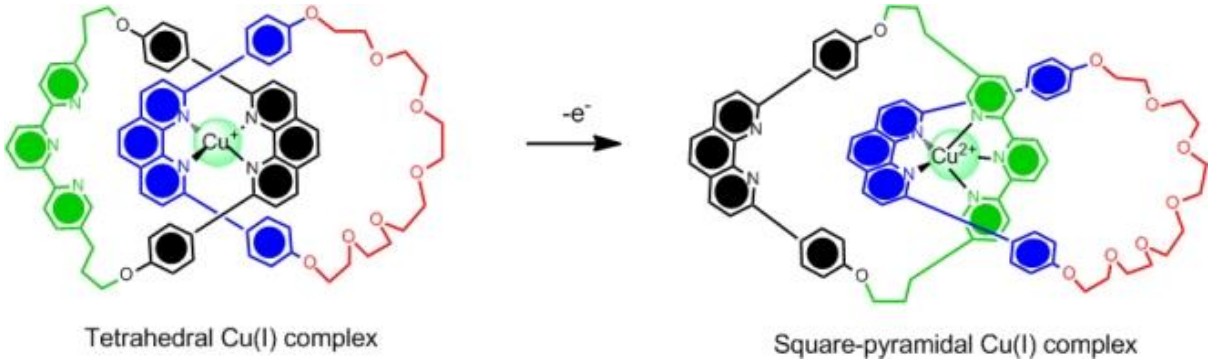


Figure 3 : A model for a catenane-based molecular switch that is redox-switchable by control of the copper oxidation state .

3. Interlocked Molecules – Rotaxanes

Rotaxanes differ from catenanes in that they are composed of both ring (cyclic) and axle (acyclic) components. A [2]rotaxane is formed when a thread, dumbbell or axle component is mechanically interlocked with a ring component. If the axle component is stoppered at both ends with bulky functional groups to prevent disassociation of the ring component at ambient temperature (Figure 1b), the system is called a rotaxane. If there are no stoppers or the stoppers are not of sufficient size to preclude dissociation at ambient temperature, the molecular assembly is called a [2]pseudorotaxane. A [3]rotaxane is typically formed when two rings are threaded onto an axle component, though two axles and one ring also satisfy the definition. There are three common methods to prepare rotaxanes, namely capping, clipping and slipping but a more recent improvement via a template effect has improved yields over what was previously achieved by statistical synthesis. The worth of

rotaxanes as a molecular form of abacus or transport agent and their capacity to shuttle (molecular motion) and switch (molecular logic) has seen research in the area flourish over the past decade and much effort has been dedicated to advancing synthetic methodologies for enhanced functions .

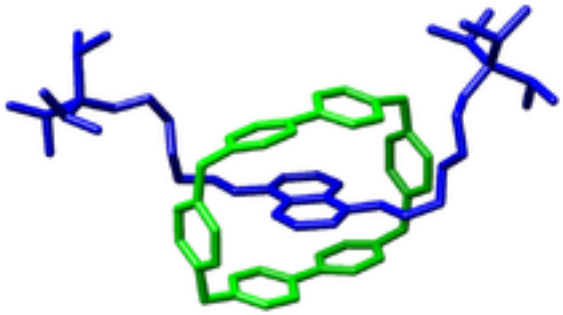


Fig:Structure of a rotaxane that has a cyclobis(paraquat-p-phenylene) macrocycle.

The use of rotaxanes as a prototype for a class of molecular machines has arisen as a result of their ability to undergo translational isomerisation between two or more structures (Figure 4). This isomerisation is a result of the translational molecular motion of the macrocyclic ring along the acyclic component. The equilibration and dynamic behavior back and forth along the acyclic component is also known as shuttling in the same way a bus or tram may move between two stations at an airport. This shuttling can take place up to 40,000 times per second. Molecular recognition sites are built into both components to produce thermodynamic sinks resulting in points along the linear component where the two or more components predominantly reside through a bias. Again, an electronic complementarity between the components is vital for both synthesis and function. This complementarity often means that rotaxanes are often highly colored species.

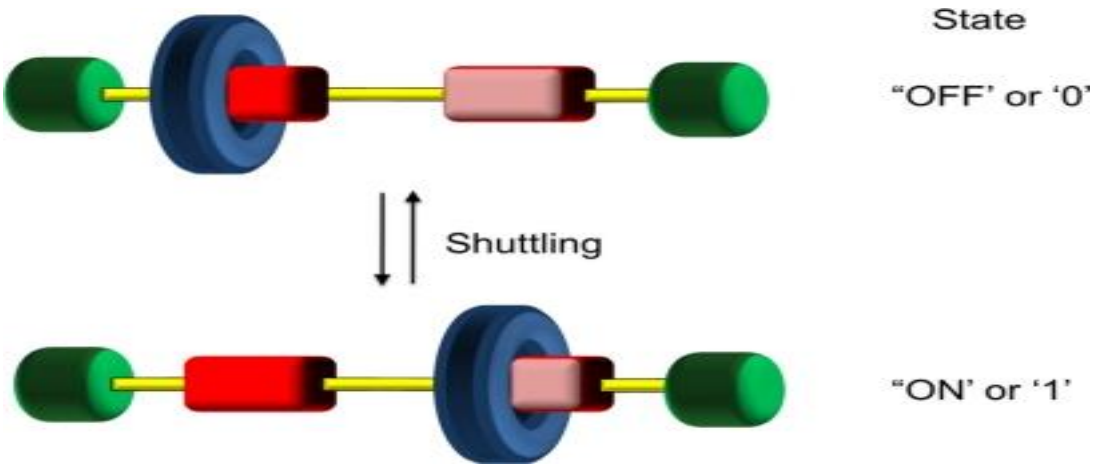


Figure 4 :Rotaxanes are able to 'shuttle' between two different states indicating switching (ON/OFF) or binary processes (0/1). Shuttling is a form of translational isomerism. The challenge is controlling this motion.

Metal complexing sites, quite often of different denticity (i.e., bidentate and tridentate) have been a popular choice for “stations” on axle components, with molecular shuttling driven by electrochemical stimulation. Sauvage and co-workers have since shown stations of the same denticity may also be incorporated into the axle structure and function as a [2]rotaxane via electrochemical means . In this example, the axle binding sites include a highly shielding phenanthroline ligand and a non sterically hindering bipyridine chelate while the complementarity to afford copper complexation is provided by a bisquinoline unit in the macrocylic ring (Figure 5). Although the preparation involves a multi-step synthesis, the electrochemical-induced shuttling between the two stations is a fast, clean process and shows promise for multi-state machine developments in the future.

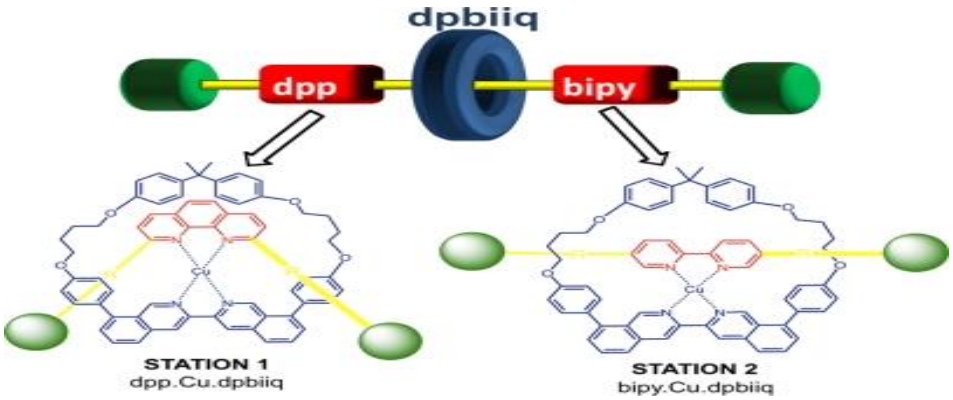
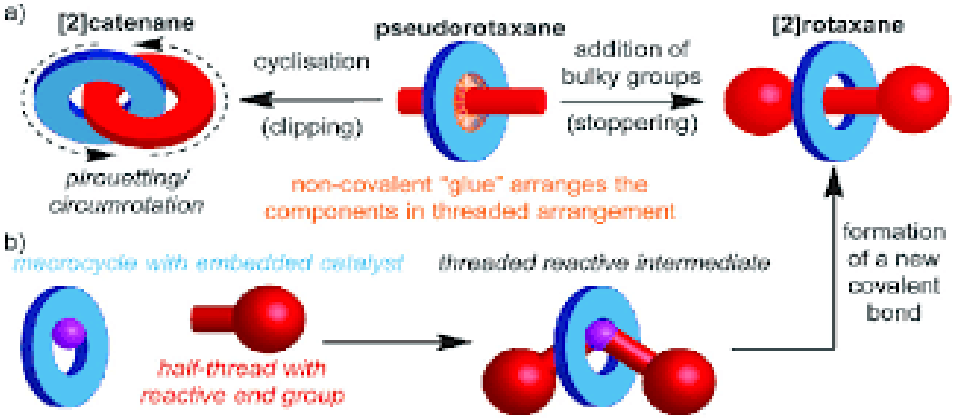


Figure 5: Copper-complexing [2]rotaxane comprising two different bidentate stations [43]. The diphenylbiisoquinoline ligand (dpbiiq) site in the macrocyclic ring structure is complementary to either the diphenylphenanthroline (dpp) or bipyridine (bipy) sites along the threading molecule and shuttling is possible upon electrochemically-driven complexation events with copper.



Capping

Rotaxane synthesis: can be carried out via a "capping," "clipping, "slipping" or "active template" mechanism. Synthesis via the capping method relies strongly upon a thermodynamically driven template effect; that is, the "thread" is held within the "macrocycle" by non-covalent interactions, for example rotaxinations with cyclodextrin macrocycles involve exploitation of the hydrophobic effect. This dynamic complex or

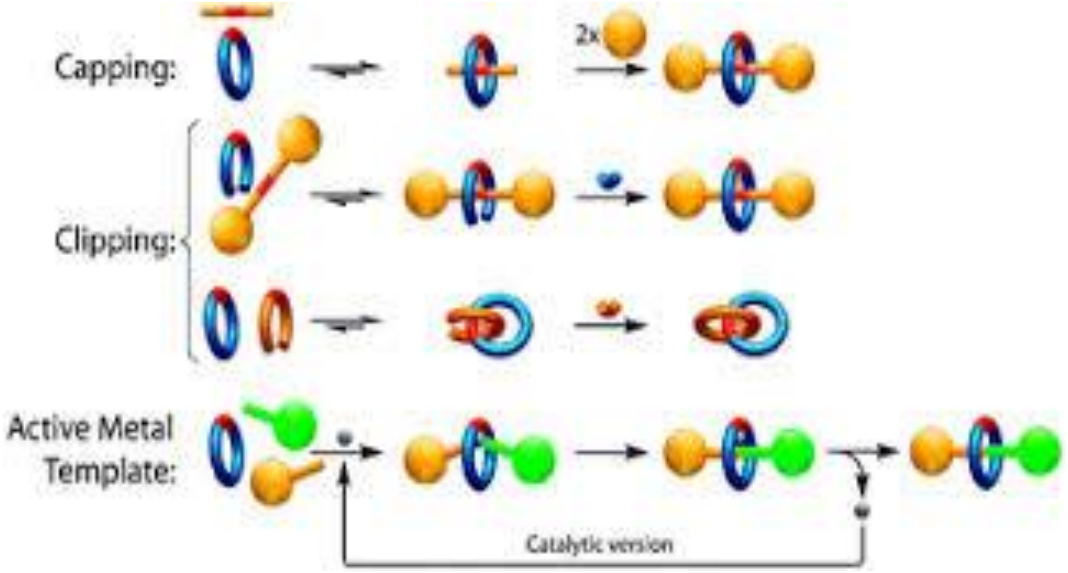
pseudorotaxane is then converted to the rotaxane by reacting the ends of the threaded guest with large groups, preventing disassociation.

Clipping

The clipping method is similar to the capping reaction except that in this case the dumbbell shaped molecule is complete and is bound to a partial macrocycle. The partial macrocycle then undergoes a ring closing reaction around the dumbbell-shaped molecule, forming the rotaxane.

Slipping

The method of slipping is one which exploits the thermodynamic stability of the rotaxane. If the end groups of the dumbbell are an appropriate size it will be able to reversibly thread through the macrocycle at higher temperatures. By cooling the dynamic complex, it becomes kinetically trapped as a rotaxane at the lower temperature.



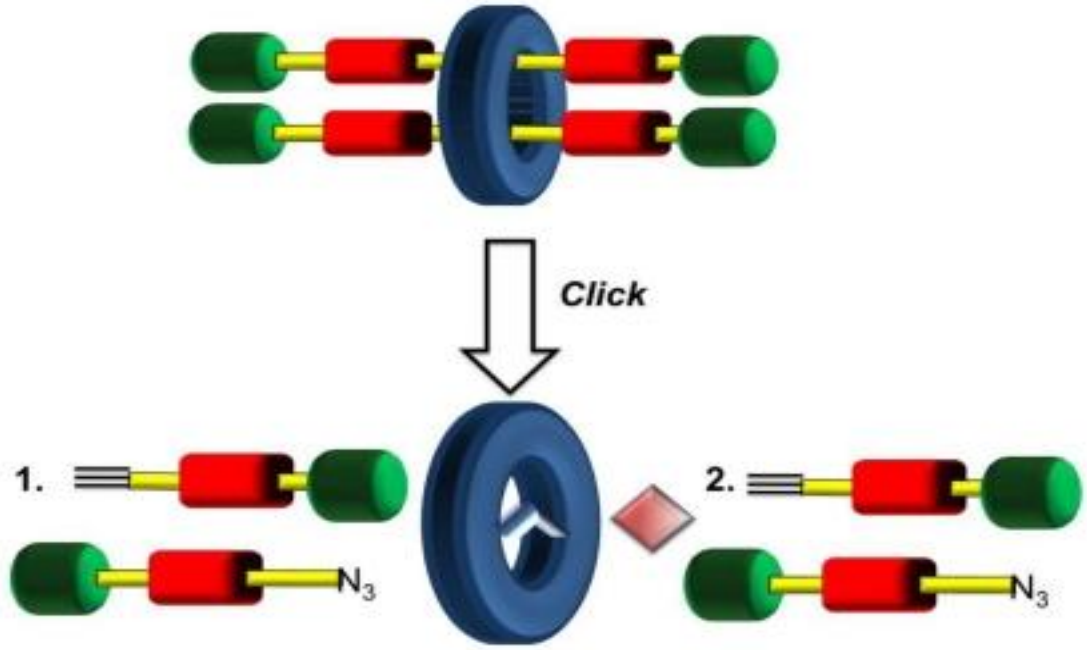


Figure 9: Template-assisted, one pot synthesis of a [3]rotaxane. Two, successive covalent bonds are formed (via the CuAAC click reaction) assisted by ligation to the ring yielding an interlocked structure consisting of two threaded components .

4. Molecular switch

A molecular switch is a molecule that can be reversibly shifted between two or more stable states. The molecules may be shifted between the states in response to environmental stimuli, such as changes in pH, light, temperature, an electric current, microenvironment, or in the presence of ions and other ligands. In some cases, a combination of stimuli is required. The oldest forms of synthetic molecular switches are pH indicators, which display distinct colours as a function of pH. Currently synthetic molecular switches are of interest in the field of nanotechnology for application in molecular computers or responsive drug delivery systems. Molecular switches are also important in biology because many biological functions are based on it, for instance allosteric regulation and vision. They are also one of the simplest examples of molecular machines.

Acido-chromic molecular switches

The capacity of some compounds to change in function of the pH was known since te sixteenth century. This effect was even known before the discovery of the acidity/basicity concept. Those are found in a wide range of plants like roses, cornflowers, primroses and violets. Robert Boyle was the first person to describe this effect, employing plant juices (in the forms of solution and impregnated paper. The most common use of these compounds is the pH indicators, which are molecules with acid/basic properties and whereas the different forms present different colours. When an acid or a base is added, the equilibrium between the two forms will be displaced.

For examples: Phenolphthalein is a weak acid and its unionised molecules are colourless. On ionisation it gives pink colour due to ph^-ions which are pink in colour. Hence phenolphthalein gives pink colour in alkaline medium and colourless in acidic medium and pH range is 8.0-9.6

$$HPh\ (colourless) \leftrightarrow H^+ + ph^-(pale\ pink)$$

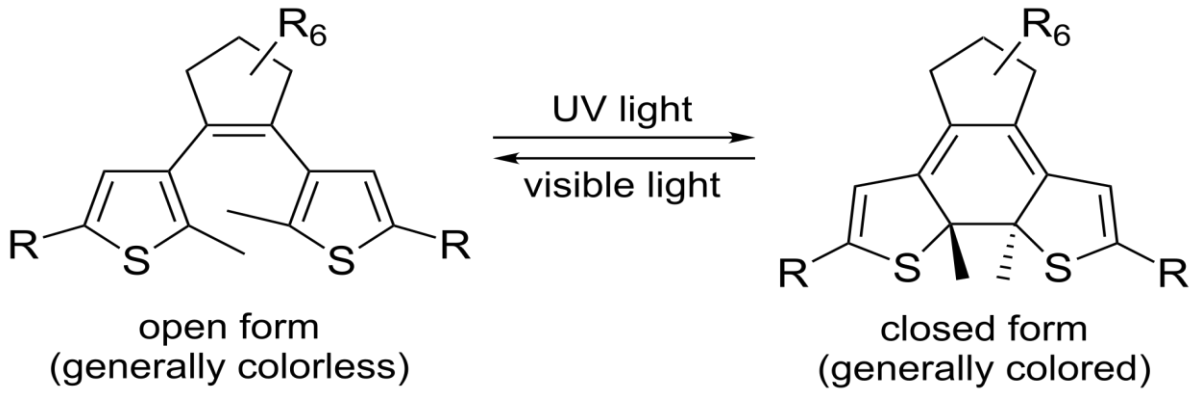
Methyl orange is a weak base. It changes colour in the P^H range 3.1-4.5 from yellow to red in basic medium to acidic medium respectively.

$$Me\ (Yellow) + H_2O \leftrightarrow MeH^+\ (Red) + OH^-$$

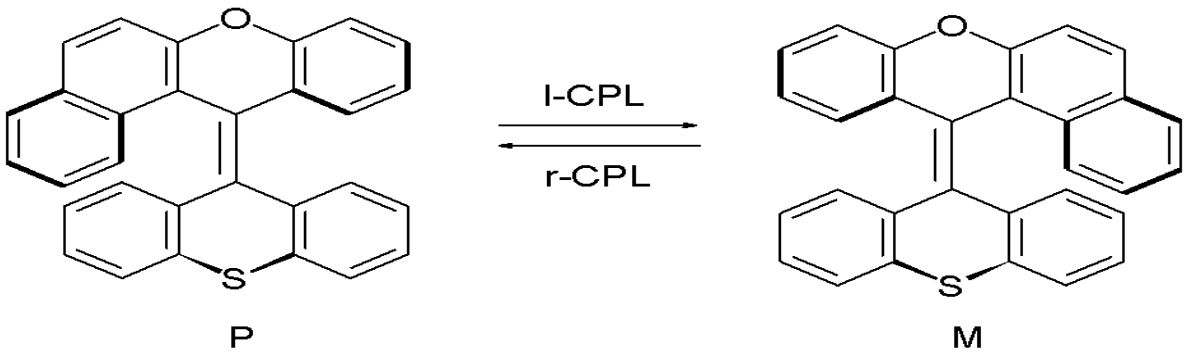
Mostly these molecular switches are used to detect equivalent point in titrations

Photochromic molecular switches

A widely studied class are photochromic compounds which are able to switch between electronic configurations when irradiated by light of a specific wavelength. Each state has a specific absorption maximum which can then be read out by UV-VIS spectroscopy. Members of this class include azobenzenes, diarylethenes, dithienylethenes, fulgides, stilbenes, spiropyrans and phenoxynaphthacene quinones.



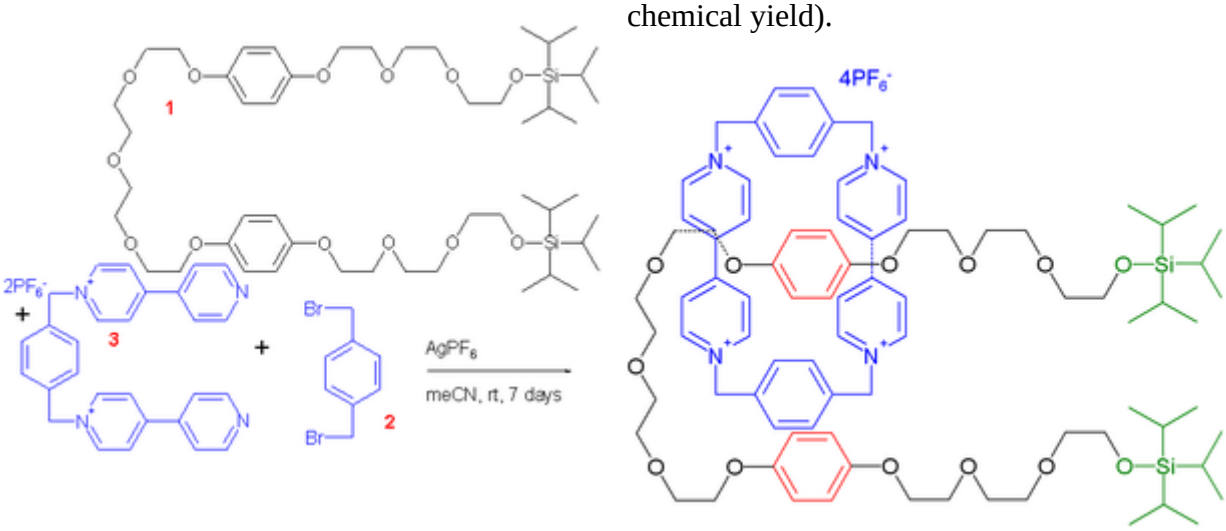
Chiroptical molecular switches are a specific subgroup with photochemical switching taking place between an enantiomeric pairs. In these compounds the readout is by circular dichroism rather than by ordinary spectroscopy. Hindered alkenes such as the one depicted below change their helicity (see: planar chirality) as response to irradiation with right or left-handed circularly polarized light



Chiroptical molecular switches that show directional motion are considered synthetic molecular motors:

Acid-base controlled Molecular shuttle:

A molecular shuttle in supramolecular chemistry is a special type of molecular machine capable of shuttling molecules or ions from one location to another. This field is of relevance to nanotechnology in its quest for nanoscale electronic components and also to biology where many biochemical functions are based on molecular shuttles. Academic interest also exists for synthetic molecular shuttles, the first prototype reported in 1991 based on a rotaxane. This device is based on a molecular thread composed of an ethyleneglycol chain interrupted by two arene groups acting as so-called stations. The terminal units (or stoppers) on this wire are bulky triisopropylsilyl groups. The bead is a tetracationic cyclophane based on two bipyridine groups and two para-phenylene groups. The bead is locked to one of the stations by pi-pi interactions but since the activation energy for migration from one station to the other station is only 13 kcal/mol (54 kJ/mol) the bead shuttles between them. The stoppers prevent the bead from slipping from the thread. Chemical synthesis of this device is based on molecular self-assembly from a preformed thread and two bead fragments (32% chemical yield).



molecularshuttlecomponents Molecularshuttle

Molecular elevators:

The advent of molecular elevators is a landmark of synthesized molecular machines, which was firstly reported by Stoddart's group in 2004. Molecular elevators are a class of rotaxanes which express the up-and-down motion of their platform component interlocked with a rig-like component. As shown in Fig, the triply interlocked rotaxane $24H_3^{3+}$ is made up of a multivalent platform of rings containing three crown ether macro cycles and the trifurcated rig-like component possesses dibenzylammonium and $BIPY^{2+}$ recognition sites. The movement of the elevator depends on the protonation and deprotonation of the dibenzylammonium ions with acid and base. It has been estimated from a thermodynamic analysis that the elevator movement from the upper to

lower level could generate a force of up to 200 pN. When investigating how the rig and platform components move with respect to each other, they found that the translational motions of each ring operate in a stepwise manner, rather than by a concerted motion of the entire platform, owing to the conformational flexibility of the rig. This well-defined mechanical movement also reveal that the multivalent compounds can be harnessed to perform nontrivial mechanical movements.

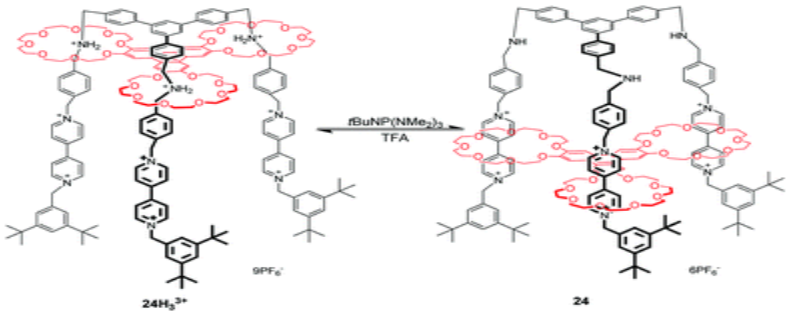
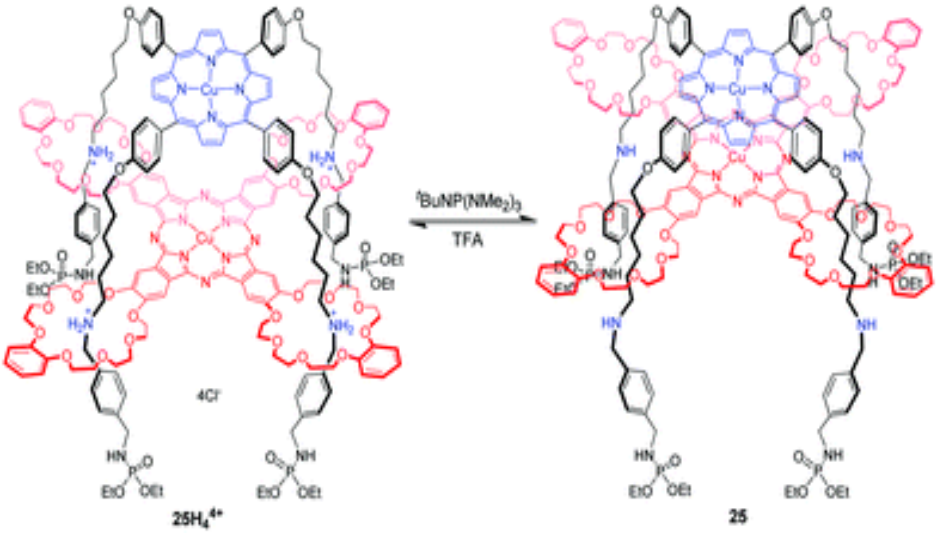


Fig. Stoddart's molecular elevator.

Another example of a molecular elevator was introduced by Tanaka in the form of four-fold rotaxane $25H_4^{4+,}$ in which the Cu(ii) porphyrin rig with four alkyl ammonium chains is mechanically linked to crown ethers of a Cu(ii) phthalocyanine tetramacrocycle by a facial stacking (Fig). The spin–spin interactions between the Cu^{2+} centres are sensitively influenced by their distance and relative spatial configuration. This expectation was confirmed by electron paramagnetic resonance (EPR) spectroscopy, which revealed that the spin-exchange interactions occur only in compressed 25 and not in $25H_4^{4+}$. By acid–base stimuli, the switchable spin–spin communication between mechanically interlocked metal complexes was well demonstrated. This concept would encourage us to prepare the supramolecular architectures with switchable functions related to nanomagnetism, conductivity, and photonic properties.



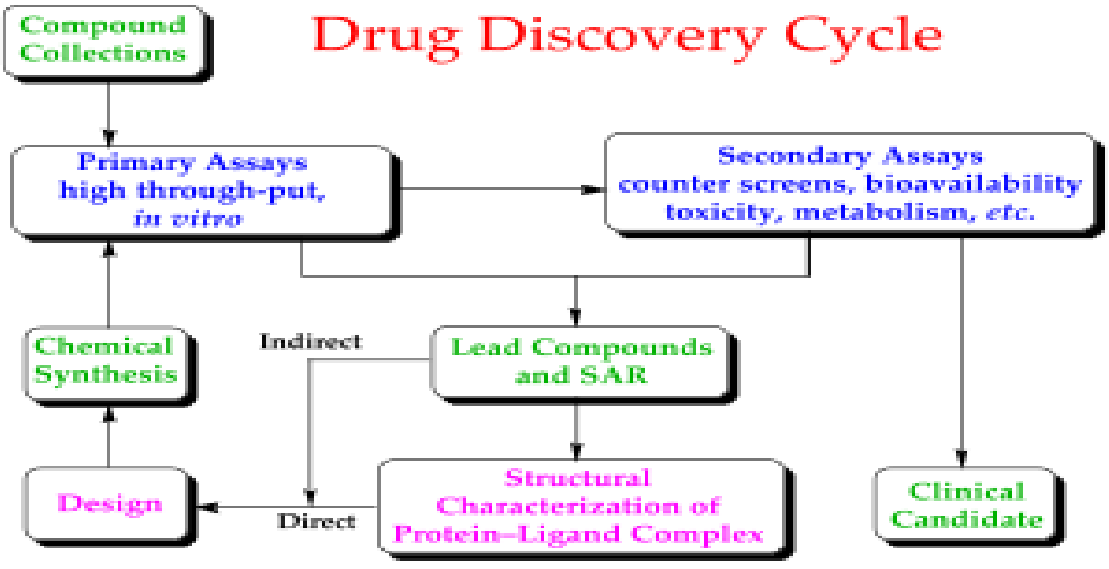
Tanaka's molecular elevator.

Docking (molecular):

In the field of molecular modelling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions. The associations between biologically relevant molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g., agonism vs antagonism). Therefore, docking is useful for predicting both the strength and type of signal produced.

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes.

Drug design:



Drug design, often referred to as rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bimolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques. This type of modeling is sometimes referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the bio molecular target is known as structure-based drug design. In addition to small molecules, biopharmaceuticals including peptides and especially therapeutic antibodies are an

increasingly important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also been developed.

The phrase "drug design" is to some extent a misnomer. A more accurate term is ligand design (i.e., design of a molecule that will bind tightly to its target). Although design techniques for prediction of binding affinity are reasonably successful, there are many other properties, such as bioavailability, metabolic half-life, side effects, etc., that first must be optimized before a ligand can become a safe and efficacious drug. These other characteristics are often difficult to predict with rational design techniques. Nevertheless, due to high attrition rates, especially during clinical phases of drug development, more attention is being focused early in the drug design process on selecting candidate drugs whose physicochemical properties are predicted to result in fewer complications during development and hence more likely to lead to an approved, marketed drug. Furthermore, in vitro experiments complemented with computation methods are increasingly used in early drug discovery to select compounds with more favourable ADME (absorption, distribution, metabolism, and excretion) and toxicological profiles.