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Supramolecular chemistry: An overview

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ABSTRACT

The present review emphasize on the current status of non covalent organic reactions and its importance in the field of synthetic chemistry. Also possible implications of it in drug synthesis. It refers to the area of chemistry beyond the molecules and focuses on the chemical systems made up of a discrete number of assembled molecular subunits or components.

Key words: Non covalent interactions, Organic synthesis, supramolecular chemistry.

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INTRODUCTION

The nature of noncovalent interactions, focusing our interest on hydrogen bonding and π-π interactions, which should play an important role in the stabilization of the alkene within our catalyst. Some examples of importance of these interactions, when cinchona derivatives are used as asymmetric catalyst in various organic reactions, will also be described. [1]

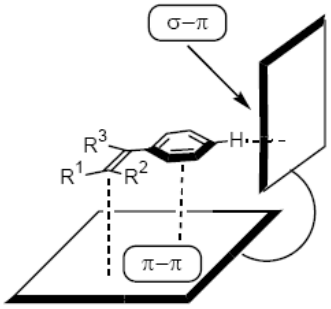

Figure II.1

Van der Waals interactions

Atoms and molecules can interact together leading to the formation of a molecule, by covalent interactions, or a molecular cluster, by noncovalent interactions. A covalent bond is formed when partially occupied orbital of the interacting atoms overlap and a pair of electrons are shared by these atoms.[1] Covalent bonds are shorter than 2 Å. Noncovalent interactions act at distances of several angstroms, thus overlap is unnecessary. Noncovalent interactions originated from interactions between a permanent dipole and an induce dipole or from an instantaneous time variable multiple and an induced multiple. hydrogen bonding, π-π interactions, cation-π interactions, etc…Non covalent interactions are weak interactions. Represented below are collected several "normal "values (in KJ/ mol) of some of the most important interactions: In general, the energy of interaction between two molecules can be represented as:

$$E_{total} = E_{electrostatic} + E_{induction} + E_{dispersion} + E_{repulsion}$$

The electrostatic, induction and dispersion energy terms are basically attractive. The repulsive term (E repulsion) prevents the subsystems from approaching too closely. The energy of interaction of two molecules in solution includes association of the two Molecules and displacement of solvent. [2] In a polar solvent, the dominant electrostatic interaction will originate from the association energy. All these factors have to be taken into account in any noncovalent interaction.

Ex: Cinchona alkaloid

Important noncovalent interactions have been implicated in cinchona alkaloid catalyzed Processes. Some representative examples, where cinchona derivatives were used for chiral discrimination, are given below. Two main interactions can be observed in these examples: H bond between the hydroxyl moiety at 9 position of the cinchona alkaloid derivative and an oxygen atom of the reagent or/ and π-π interactions between the flat Quinoline ring or the aromatic linker group and the aromatic ring present in the substrate. One of the most important studies on these interactions came from the asymmetric dihydroxylation of alkenes catalyzed by OsO4. The highly enantioselective osmylation of olefins was rationalized on the basis of π-π interactions of the alkene with the ligand. [3]

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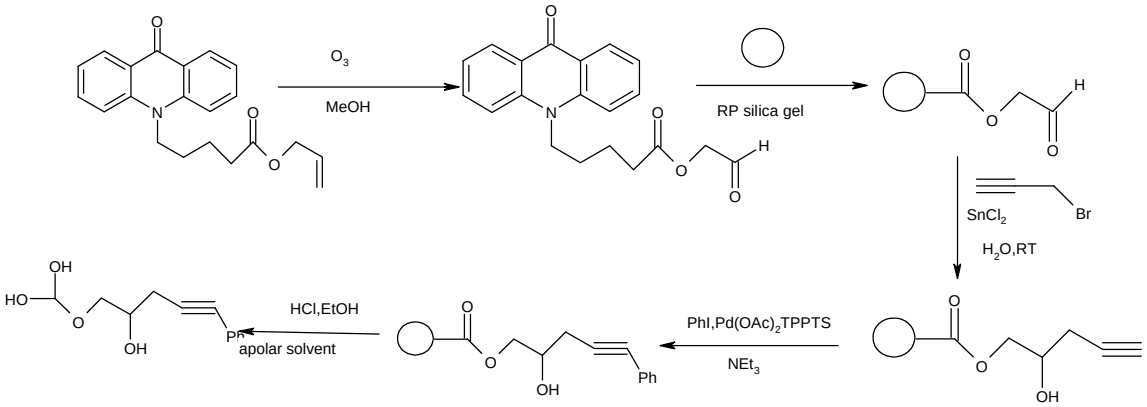
Noncovalent solid-phase organic synthesis [4]

NC-SPOS is a form of Solid-phase synthesis where by the organic substrate is bonded to the solid phase not by a covalent bond but by other chemical interactions. This bond may consist of an induced dipole interaction between a hydrophobic matrix and a hydrophobic anchor. As long as the reaction medium is hydrophilic (polar) in nature the anchor will remain on the solid phase. Switching to a nonpolar solvent releases the organic substrate containing the anchor.In one experimental setup the hydrophobic matrix is RP silica gel (C_{18}) and the anchor is acridone. Acridone is N-alkylated and the terminal alkene group is converted into an aldehyde by ozonolysis. This compound is bonded to RP silica gel and this system is subjected to a tandem sequence of organic reactions. The first reaction is a Barbier reaction with propargylic bromide in water (green chemistry) and the second reaction is a Sonogashira coupling. Substrates may vary in these sequences and in this way a chemical library of new compounds can be realized.



Supramolecular chemistry

It refers to the area of chemistry beyond the molecules and focuses on the chemical systems made up of a discrete number of assembled molecular subunits or components. The forces responsible for the spatial organization may vary from weak (intermolecular forces, electrostatic or hydrogen bonding) to strong (covalent bonding), provided that the degree of electronic coupling between the molecular component remains small with respect to relevant energy parameters of the component [5,6] While traditional chemistry focuses on the covalent bond, supramolecular chemistry examines the weaker and reversible noncovalent interactions between molecules. These forces include hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, pi-pi interactions and electrostatic effects. Important concepts that have been demonstrated by supramolecular chemistry include molecular self-assembly, folding, molecular recognition, host-guest chemistry, mechanically-interlocked molecular architectures, and dynamic covalent chemistry.[7] The study of non-covalent interactions is crucial to understanding many biological processes from cell structure to vision that rely on these forces for structure and function. Biological systems are often the inspiration for supramolecular research.

History

The existence of intermolecular forces was first postulated by Johannes Diderik van der Waals in 1873. However, it is with Nobel laureate Hermann Emil Fischer that supramolecular chemistry has its philosophical roots. In 1890, Fischer suggested that enzyme-substrate interactions take the form of a "lock and key", pre-empting the concepts of molecular recognition and host-guest chemistry. In the early twentieth century noncovalent bonds were understood in gradually more detail, with the hydrogen bond being described by Latimer and Rodebush in 1920.The use of these principles led to an increasing understanding of protein structure and other biological processes. For instance, the important breakthrough that allowed the elucidation of the double helical structure of DNA occurred when it was realized that there are two separate strands of nucleotides connected through hydrogen bonds. The use of noncovalent bonds is essential to replication because they allow the strands to be separated and used to template new double stranded DNA. Concomitantly, chemists began to recognize and study synthetic structures based on noncovalent interactions, such as micelles and microemulsions.Eventually, chemists

were able to take these concepts and apply them to synthetic systems. The breakthrough came in the 1960s with the synthesis of the crown ethers by Charles J. Pedersen. Following this work, other researchers such as Donald J. Cram, Jean-Marie Lehn and Fritz Vogtle became active in synthesizing shape- and ion-selective receptors, and throughout the 1980s research in the area gathered a rapid pace with concepts such as mechanically-interlocked molecular architectures emerging.The importance of supramolecular chemistry was established by the 1987 Nobel Prize for Chemistry which was awarded to Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen in recognition of their work in this area.[8] The development of selective "host-guest" complexes in particular, in which a host molecule recognizes and selectively binds a certain guest, was cited as an important contribution.In the 1990s, supramolecular chemistry became even more sophisticated, with researchers such as James Fraser Stoddart developing molecular machinery and highly complex self-assembled structures, and Itamar Willner developing sensors and methods of electronic and biological interfacing. During this period, electrochemical and photochemical motifs became integrated into supramolecular systems in order to increase functionality, research into synthetic self-replicating system began, and work on molecular information processing devices began. The emerging science of nanotechnology also had a strong influence on the subject, with building blocks such as fullerenes, nanoparticles, and dendrimers becoming involved in synthetic systems.

Control of supramolecular chemistry

Thermodynamics

Supramolecular chemistry deals with subtle interactions, and consequently control over the processes involved can require great precision. In particular, noncovalent bonds have low energies and often no activation energy for formation. As demonstrated by the Arrhenius equation, this means that, unlike in covalent bond-forming chemistry, the rate of bond formation is not increased at higher temperatures. In fact, chemical equilibrium equations show that the low bond energy results in a shift towards the breaking of supramolecular complexes at higher temperatures.However, low temperatures can also be problematic to supramolecular processes. Supramolecular chemistry can require molecules to distort into thermodynamically disfavored conformations (e.g. during the "slipping" synthesis of rotaxanes), and may include some covalent chemistry that goes along with the supramolecular. In addition, the dynamic nature of supramolecular chemistry is utilized in many systems (e.g. molecular mechanics), and cooling the system would slow these processes.Thus, thermodynamics is an important tool to design, control, and study supramolecular chemistry. Perhaps the most striking example is that of warm-blooded biological systems, which cease to operate entirely outside a very narrow temperature range.

Environment

The molecular environment around a supramolecular system is also of prime importance to its operation and stability. Many solvents have strong hydrogen bonding, electrostatic, and charge-transfer capabilities, and are therefore able to become involved in complex equilibria with the system, even breaking complexes completely. For this reason, the choice of solvent can be critical.

Concepts in supramolecular chemistry

Molecular self-assembly

Molecular self-assembly is the construction of systems without guidance or management from an outside source (other than to provide a suitable environment). The molecules are directed to assemble through noncovalent interactions. Self-assembly may be subdivided into intermolecular self-assembly (to form a supramolecular assembly), and intramolecular self-assembly (or folding as demonstrated by foldamers and

polypeptides). Molecular self-assembly also allows the construction of larger structures such as micelles, membranes, vesicles, liquid crystals, and is important to crystal engineering [9].

Molecular recognition and complexation

Molecular recognition is the specific binding of a guest molecule to a complementary host molecule to form a host-guest complex. Often, the definition of which species is the "host" and which is the "guest" is arbitrary. The molecules are able to identify each other using noncovalent interactions. Key applications of this field are the construction of molecular sensors and catalysis [10-12].

Template-directed synthesis

Molecular recognition and self-assembly may be used with reactive species in order to pre-organize a system for a chemical reaction (to form one or more covalent bonds). It may be considered a special case of supramolecular catalysis. Noncovalent bonds between the reactants and a "template" hold the reactive sites of the reactants close together, facilitating the desired chemistry. This technique is particularly useful for situations where the desired reaction conformation is thermodynamically or kinetically unlikely, such as in the preparation of large macrocycles. This pre-organization also serves purposes such as minimizing side reactions, lowering the activation energy of the reaction, and producing desired stereochemistry. After the reaction has taken place, the template may remain in place, be forcibly removed, or may be "automatically" decomplexed on account of the different recognition properties of the reaction product. The template may be as simple as a single metal ion or may be extremely complex.

Mechanically-interlocked molecular architectures

Mechanically-interlocked molecular architectures consist of molecules that are linked only as a consequence of their topology. Some noncovalent interactions may exist between the different components (often those that were utilized in the construction of the system), but covalent bonds do not. Supramolecular chemistry, and template-directed synthesis in particular, is key to the efficient synthesis of the compounds. Examples of mechanically-interlocked molecular architectures include catenanes, rotaxanes, molecular knots, and molecular Borromean rings [13].

Biomimetics

Many synthetic supramolecular systems are designed to copy functions of biological systems. These biomimetic architectures can be used to learn about both the biological model and the synthetic implementation. Examples include photoelectrochemical systems, catalytic systems, protein design and self-replication [14].

Imprinting

Molecular imprinting describes a process by which a host is constructed from small molecules using a suitable molecular species as a template. After construction, the template is removed leaving only the host. The template for host construction may be subtly different from the guest that the finished host bind. In its simplest form, imprinting utilizes only steric interactions, but more complex systems also incorporate hydrogen bonding and other interactions to improve binding strength and specificity [15].

Building blocks of supramolecular chemistry

Supramolecular systems are rarely designed from first principles. Rather, chemists have a range of well-studied structural and functional building blocks that they are able to use to build up larger functional architectures. Many of these exist as whole families of similar units, from which the analog with the exact desired properties can be chosen.

Synthetic recognition motifs

The pi-pi charge-transfer interactions of bipyridinium with dioxyarenes or diaminoarenes have been used extensively for the construction of mechanically interlocked systems and in crystal engineering. The use of crown ether binding with metal or ammonium cations is ubiquitous in supramolecular chemistry.The complexation of porphyrins or phthalocyanines around metal ions gives access to catalytic, photochemical and electrochemical properties as well as complexation. These units are used a great deal by nature.

Macrocycles

Macrocycles are very useful in supramolecular chemistry, as they provide whole cavities that can completely surround guest molecules and may be chemically modified to fine-tune their properties.Cyclodextrins, calixarenes, cucurbiturils and crown ethers are readily synthesized in large quantities, and are therefore convenient for use in supramolecular systems. More complex cyclophanes, and cryptands can be synthesized to provide more taliored recognition properties.

Structural units

Many supramolecular systems require their components to have suitable spacing and conformations relative to each other, and therefore easily-employed structural units are required.Commonly used spacers and connecting groups include polyether chains, biphenyls and triphenyls, and simple alkyl chains. The chemistry for creating and connecting these units is very well understood. nanoparticles, nanorods, fullerenes and dendrimers offer nanometer-sized structure and encapsulation units.Surfaces can be used as scaffolds for the construction of complex systems and also for interfacing electrochemical systems with electrodes. Regular surfaces can be used for the construction of self-assembled monolayers and multilayers.

Photo-/electro-chemically active units

Porphyrins, and phthalocyanines have highly tunable photochemical and electrochemical activity as well as the potential for forming complexes.Photochromic and photoisomerizable groups have the ability to change their shapes and properties (including binding properties) upon exposure to light. TTF and quinones have more than one stable oxidation state, and therefore can be switched with redox chemistry or electrochemistry. Other units such as benzidine derivatives, viologens groups and fullerenes, have also been utilized in supramolecular electrochemical devices.

Biologically-derived units

The extremely strong complexation between avidin and biotin is instrumental in blood clotting, and has been used as the recognition motif to construct synthetic systems.The binding of enzymes with their cofactors has been used as a route to produce modified enzymes, electrically contacted enzymes, and even photoswitchable enzymes. DNA has been used both as a structural and as a functional unit in synthetic supramolecular systems.

Applications [16]

Materials technology

Supramolecular chemistry and molecular self-assembly processes in particular have been applied to the development of new materials. Large structures can be readily accessed using bottom-up synthesis as they are composed of small molecules requiring fewer steps to synthesize. Thus most of the bottom-up approaches to nanotechnology are based on supramolecular chemistry.

Catalysis

A major application of supramolecular chemistry is the design and understanding of catalysts and catalysis. Noncovalent interactions are extremely important in catalysis, binding reactants into conformations suitable for reaction and lowering the transition state energy of reaction. Template-directed synthesis is a special case of supramolecular catalysis. Encapsulation systems such as micelles and dendrimers are also used in catalysis to create microenvironments suitable for reactions (or steps in reactions) to progress that is not possible to use on a macroscopic scale.

Medicine

Supramolecular chemistry is also important to the development of new pharmaceutical therapies by understanding the interactions at a drug binding site. The area of drug delivery has also made critical advances as a result of supramolecular chemistry providing encapsulation and targeted release mechanisms. In addition, supramolecular systems have been designed to disrupt protein-protein interactions that are important to cellular function.

Data storage and processing

Supramolecular chemistry has been used to demonstrate computation functions on a molecular scale. In many cases, photonic or chemical signals have been used in these components, but electrical interfacing of these units has also been shown by supramolecular signal transduction devices. Data storage has been accomplished by the use of molecular switches with photochromic and photoisomerizable units, by electrochromic and redox-switchable units, and even by molecular motion. Synthetic molecular logic gates have been demonstrated on a conceptual level. Even full-scale computations have been achieved by semi-synthetic DNA computers.

Green chemistry

Research in supramolecular chemistry also has application in green chemistry where reactions have been developed which proceed in the solid state directed by non-covalent bonding. Such procedures are highly desirable since they reduce the need for solvents during the production of chemicals.

Other devices and functions

Supramolecular chemistry is often pursued to develop new functions that cannot appear from a single molecule. These functions also include magnetic properties, light responsiveness, self-healing polymers, molecular sensors, etc. Supramolecular research has been applied to develop high-tech sensors, processes to treat radioactive waste, and contrast agents for CAT scans.

In synthetic chemistry

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Covalent and non-covalent functionalization and solubilization of double-walled carbon nanotubes in non polar and aqueous media [17]

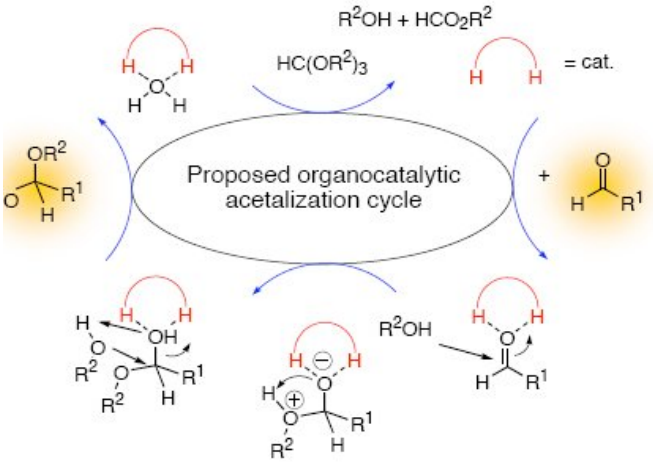
Double-walled carbon nanotubes (DWNTs) have been functionalized by both covalent and non-covalent means. Covalent functionalization has been carried out by attaching an aliphatic amide function to DWNTs which enable solubilization in non-polar solvents. Solubilization in non-polar solvents has also been accomplished by non-covalent functionalization by using 1-pyrenebutanoicacid succinimidyl ester (PYBS). Non-covalent functionalization of DWNTs has been carried out by using polyethylene glycol (PEG) and polyoxyethylene(40)nonylphenyl ether (IGPAL), both of which enable solubilization in aqueous media. These functionalized DWNTs have been characterized by transmission electron microscopy, IR and Raman spectroscopy.

Noncovalent Organocatalysis [18]

Organocatalysis combines the concepts of molecular recognition and Supramolecular chemistry with enzyme-like catalytic concepts; this branch of research may therefore be coined with the notion of "the hunt for the smallest enzyme."Noting that about half of all enzymes do not carry a metal center it is obvious that this approach has long been underappreciated. Although organocatalysis as such is a new field, it is already possible to catalyze many types of organic reactions with small, welldesigned organic molecules. This circumvents the use of often toxic metals, and the preparation of the catalysts is much easier as it relies on the well-developed synthetic arsenal for tailor-making organic structures. While many approaches rely on covalent attachment of the catalyst (e.g, proline catalysis), we focus entirely on non-covalently bound catalysts; he talk will emphasize the notion of noncovalent bonding that is in line with Pauling's aradigms of enzyme activity. In our group we have developed hydrogen-bonding thioureabased atalysts that are effective in catalyzing Diels-Alder reactions, acid-free cetalizations, epoxide openings and other reactions. Many other groups have not picked this catalytic principle and apply it to a manifold of fascinating reactions.

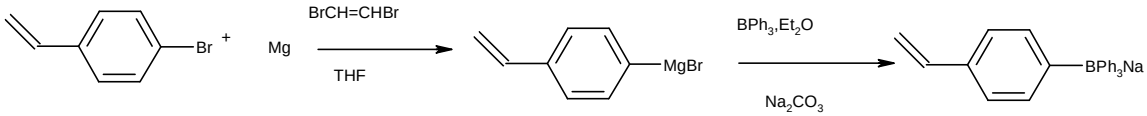
Phase-transfer catalysis (PTC) [18]

It is a special case of organocatalysis that has been around for several decades; PTC has enormous industrial applications. Our aim was to develop completely novel PTC reactions, for instance, metal-free PTC radical reactions for the direct halogenation of unactivated hydrocarbons.5 This shows the power of the organocatalytic approach as some of these reactions are not even feasible (e.g, iodination) with their organometallic counterparts.



Disperse Amphiphilic Submicron Particles as Non-Covalent Supports for Cationic Homogeneous Catalysts [19]

A simple method for the effective immobilization of homogeneous catalysts on polystyrene colloids via non-covalent binding is demonstrated. Stable latices with sufficiently high loading of accessible borate anions are prepared via emulsion polymerization. Incorporation of cationic rhodium complexes, supported via their borate counter-anion is efficient, and these supported homogeneous catalysts maintain constant catalytic activity for C¼C hydrogenation during several recycles, with very low metal leaching.



The Role of Noncovalent Interactions in Electrocatalysis: Trends in Fuel Cell Reactions on Pt in Alkaline Solutions [20]

Classical models of metal electrode-electrolyte interfaces have generally focused on either covalent interactions between adsorbates and the corresponding solid surfacesor on long-range electrolyte/metal electrostatic interactions. We demonstrate that these traditional models for describing the catalytic activity of the electrochemical interfaces are not sufficient, and to understand electrocatalytic trends in the oxygen reduction reaction (ORR), the hydrogen oxidation reaction (HOR), and the oxidation of methanol on Pt surfaces in alkaline electrolytes, noncovalent interactions, such as hydrogen bonding, cation-water, and cation-OHads bonding, must also be taken into consideration.

Pressure and temperature as tools for investigating the role of individual non-covalent interactions in enzymatic reactions Sulfolobus solfataricus carboxypeptidase as a model enzyme [21]

Sulfolobus solfataricus carboxypeptidase, (CPSso), is a heat- and pressure-resistant zinc-metalloprotease. Thanks to its properties, it is an ideal tool for investigating the role of non-covalent interactions in substrate binding. It has broad substrate specificity as it can cleave any N-blocked amino acid (except for N-blocked proline). Its catalytic and kinetic mechanisms are well understood, and the hydrolytic reaction is easily detectable spectrophotometrically. Here, we report investigations on the pressure- and temperature-dependence of the kinetic parameters (turnover number and Michaelis constant) of CPSso using several benzoyl- and 3-(2-furyl)acryloyl-amino acids as substrates. This approach enabled us to study these parameters in terms of individual rate constants and establish that the release of the free amino acid is the rate-limiting step, making it possible to dissect the individual non-covalent interactions participating in substrate binding. In keeping with molecular docking experiments performed on the 3D model of CPSso available to date, our results show that both hydrophobic and energetic interactions (i.e, stacking and van der Waals) are mainly involved, but their contribution varies strongly, probably due to changes in the conformational state of the enzyme.

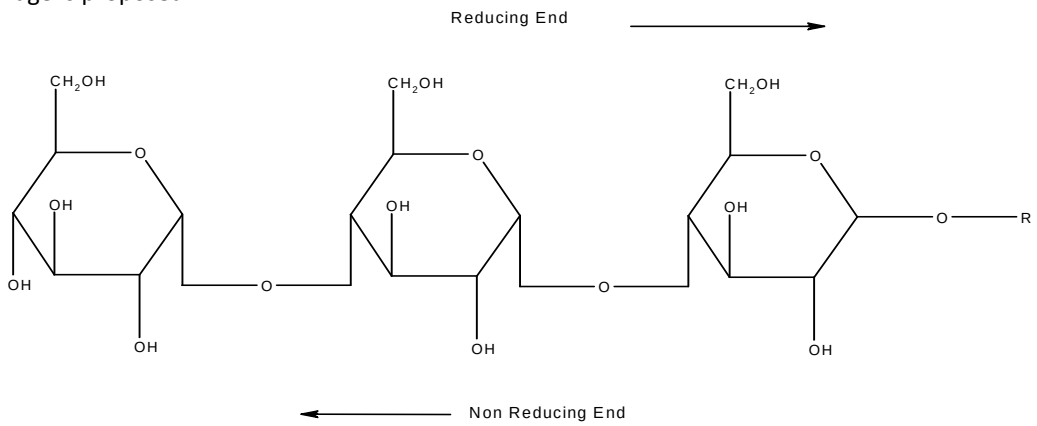
Noncovalent Interactions of Drugs with Immune Receptors May Mediate Drug-induced Hypersensitivity Reactions [22]

Drug-induced hypersensitivity reactions are instructive examples of immune reactions against low molecular weight compounds. Classically, such reactions have been explained by the hapten concept, according to which the small antigen covalently modifi es an endogenous protein; recent studies show strong associations of several HLA olecules with hypersensitivity. In recent years, however, evidence has become stronger that not all drugs need to bind covalently to the major histocompatibility complex (MHC)-peptideN complex in order to trigger

an immune response. Rather, some drugs may bind reversibly to the MHC or possibly to the T-cell receptor (TCR), eliciting immune reactions akin to the pharmacological activation of other receptors. While the exact mechanism is still a matter of debate, noncovalent drug presentation clearly leads to the activation of drugspecific T cells. In some patients with hypersensitivity, such a response may occur within hours of even the fi rst exposure to the drug. Thus, the reaction to the drug may not be the result of a classical, primary response but rather be mediated by existing, preactivated T cells that display cross-reactivity for the drug and have additional peptide) specifi city as well. In this way, certain drugs may circumvent the checkpoints for immune activation imposed by the classical antigen processing and presentation mechanisms, which may help to explain the idiosyncratic nature of many drug hypersensitivity reactions.

Using Non-Covalent Complexes to Direct the Fragmentation of Glycosidic Bonds in the Gas Phase [23]

An investigation of the gas phase chemistry of proton bound oligosaccharide (S)–ligand (L) non-covalent complexes, [S _ H _ L]_ has been carried out using electrospray ionization (ESI) and tandem mass spectrometry in a quadrupole ion trap. When subjected to collision-induced dissociation (CID), these [S _ H _ L]_ complexes undergo a range of reactions that can be broadly classified into three main types: (1) Simple dissociation into the individual monomers;(2) cleavage of the oligosaccharide to form B-type sequence ions; (3) cleavage of the ligand species. The second type of reaction is particularly interesting as it can produce a “ladder series” of [Bx _ L]_ ions via ligand induced oligosaccharide bond cleavage. This novel gas phase reaction greatly simplifies the sequencing of oligosaccharides. Both the oligosaccharide and ligand were found to influence the type of reaction pathway observed, with the “ladder series” of [Bx _ L]_ ions being favored for permethylated oligosaccharides and for bifunctional ligands. Cytosine is a particularly good ligand at facilitating the formation of [Bx _ L]_ ions.Analogies with condensed phase chemistry of sugars is made and a potential mechanism for ligand induced oligosaccharide bond cleavage is proposed.



Preparation of new bis(oxazoline) ligand bearing non-covalent interaction sites and an application in the ighly asymmetric Diels–Alder reaction [24]

Interligand interactions around metal center are important for demonstrating selectivity and specificity in catalysis of transition metal complexes. In order to achieve high selectivity and efficiency for asymmetric reactions, ternary complexes consisting of metal–ligand–substrate have been designed.

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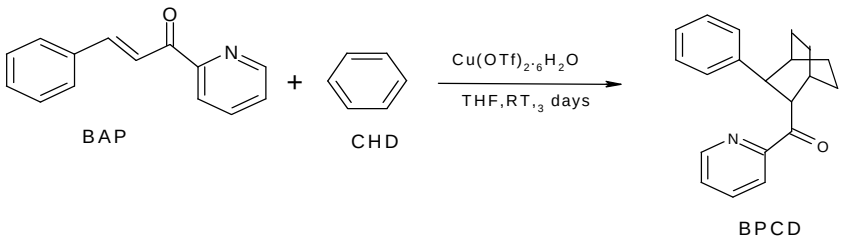

Scheme: Asymmetric Diels Alder Reaction

CONCLUSION

The present review provides an idea about the recent methods of synthesis of pharmaceutical agents and drugs like Porphyrine, Pyridinium derivatives etc. It has been proved to be powerful tool for the synthesis of various biologically active chiral compounds.It also modifies the drug interactions within the body.

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