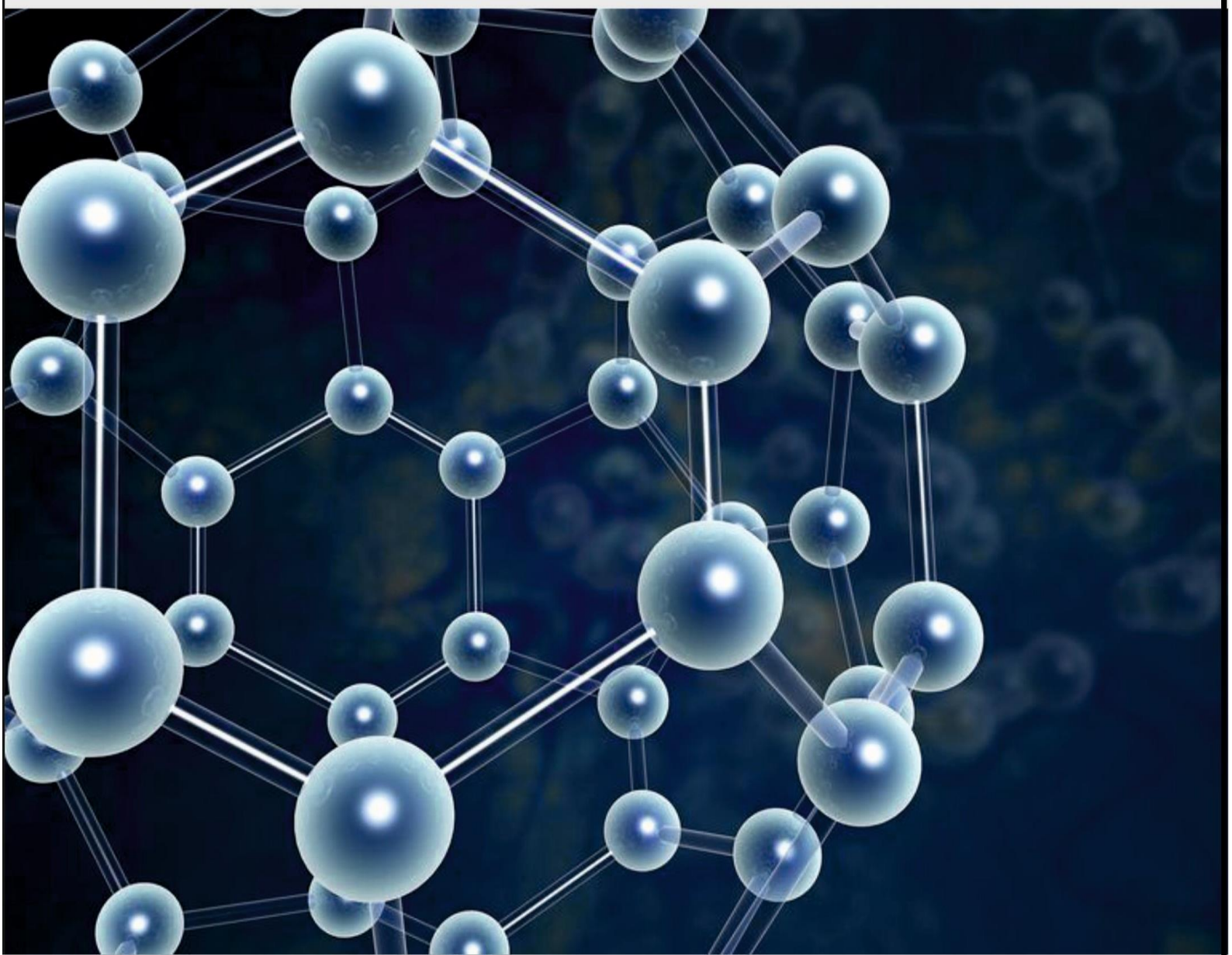
Advanced Organic Chemistry Applications

Editor
Dr. M. R. Jayapal



ADVANCED ORGANIC CHEMISTRY APPLICATIONS

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PREFACE

The manner of Organic Chemistry has changed somewhat since my days as a student in the early 2005s. Most notably, organic chemistry books offer more and better descriptions of topics in related fields such as Biochemistry and Materials Science, the internet allows one to search for information about specific topics, and computer software is readily available for modelling chemical structures and reactions. The overall level of sophistication has also risen for the presentation of traditional themes such as stereochemistry, bonding, reaction mechanisms, spectroscopy, and synthesis.

In spite of these changes, however, the mastery of Organic Chemistry as a course of study still requires a sound knowledge of the principles of molecular structure and chemical reactivity, which are topics introduced in most General Chemistry courses. With such a back-ground, a student studying organic chemistry begins to focus on a more limited set of atomic building blocks, particularly of carbon and its elemental neighbours. And while the study of a smaller portion of the periodic table might be expected to be easily manageable, understanding organic chemistry can still seem overwhelming because of the diverse way s that this handful of elements can combine and interact. To learn organic chemistry, one must grasp the recurring patterns that correlate the presented facts.

Toward that end, this textbook organizes and discusses applications of the patterns of chemical reactivity—which constitutes the majority of the subject matter—by combining information about the structures of functional groups (the reactive portions of a molecule) with the reaction mechanisms (pathways of chemical reactions) that these functional groups undergo. This approach differs from the one presented in many other texts, which describe every type of reaction that can occur for a given functional group; each approach has its advantages and disadvantages.

The one I have utilized here evolved from my objective to integrate discussions about biochemical processes with the types of reactions that are carried out in chemistry laboratories. With the use of two points of reference—structures and mechanisms—the similarities that associate biochemical and synthetic reactions can be appreciated more easily.

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1. An Introduction of Polarography

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1.1 Introduction:

On February 10, 1922, Professor Jaroslav Heyrovsky carried out his pioneering experiment with a dropping mercury electrode from which polarography gradually evolved. Since then, polarography became a mature analytical method capable to adjust ever increasing demands on the sensitivity and selectivity and we believe that up to now mercury electrodes are among the best sensors for electroanalytical measurements[1,5]. Limits of determination gradually decreased from 10^{-5} M in the case of classical polarography[2], through 10^{-7} M for differential pulse polarography[3] to 10^{-11} M for adsorptive stripping voltammetry[4].

Development of mercury electrodes which proceeded from classical dropping mercury electrode[6] through mercury streaming electrode[7], hanging mercury drop electrode[8], static mercury drops electrode[9], mercury film electrode[10], mercury amalgam electrodes[11], mercury microelectrodes, chemically modified mercury electrodes[12], controlled growth mercury electrodes[13] and contractible mercury drop electrodes[14]. This process initiated by Professor Heyrovsky resulted in commercially available reliable mercury electrodes suitable for Nano molar and sub Nano molar concentrations. Further progress in this field can be documented by the above mentioned articles of Novotny and Kowalski and by papers of Gutz on versatile automatic mercury drop electrode[15-16].

Development of measuring techniques that proceeded from classical DC polarography[2], Through oscillopolarography[17], Kalousek's switcher[18], AC polarography[19], Tast polarography[20], Normal pulse polarography[21], Differential pulse polarography[22], Voltammetry[23], Cyclic voltammetry[24], Anodic stripping voltammetry[25], Adsorptive stripping voltammetry[26], Convolution techniques[27-28] and Elimination methods[29-30]. Development of preconcentration techniques on the surface of mercury electrodes enabling a substantial increase of sensitivity which proceeded from anodic stripping voltammetry and cathodic stripping voltammetry to adsorptive stripping voltammetry. The role of Professor Heyrovsky in the development of these methods cannot be underestimated. According to Zuman[31] the main contribution of Professor Heyrovsky consists in:

- Recognition of the importance of potential and its control;
- Recognition of analytical opportunities offered by measuring the limiting currents;
- The introduction of dropping mercury electrode as an invaluable tool of modern electroanalytical chemistry.

1.2 Principle of Technique:

Polarography is based on the unique characteristics of the current-voltage curves obtained with dropping mercury electrode, which was first introduced by Kucera[32] for electro capillary studies. In 1934 Ilkovic[33] derived an equation for the resulting constant. It deals with the measurement and interpretation of current-voltage curves when solution of electroactive substances is electrolyzed in a cell in which one electrode is polarisable i.e. mercury falling gravitationally drop wise from fine bore of capillary glass tube, while the other electrode remains non polarisable (saturated calomel electrode). Since the curves are graphical presentation of the dropping mercury electrodes, the apparatus is called 'polarograph' the curves as polarograms and technique is named as polarography. Thus, it is one of the most essential key to chemical analysis. The flow of current in the electrical circuit is observed only when the voltage is applied to electrodes changes at constant rate, raises the potential of a depolarizer present in the solution 10^{-5} moles/liter range. The current increases with the increasing negative potential of the electrode and during this time the concentration of the depolarizer on the surface of electrode decreases. When this concentration decreases to zero, current reaches to a constant value depending on the rate of depolarizer transport to the surface of electrode. In these conditions we have the maximum current which is often called limiting current.

Advantages of Dropping Mercury Electrode:

There are several advantages of the dropping mercury electrode.

- Each drop falling from the electrode exactly duplicates the behavior of the one that preceded it. This is because successive drops are born into solution of identical time, grow at a same rate and reach at the maximum size. Consequently, the currents are accurately reproducible from one drop to next.
- Solid products cannot accumulate on the electrode surface, changing its properties as it is possible with solid electrode.
- It is much less sensitive to mechanical disturbance than stationary electrode.
- High over potential of reduction of hydrogen ion or water on a mercury surface makes it to investigate processes that can occur only under strongly reducing conditions.

1.3 Applications of Polarography:

Polarography can be extensively applied in the field of inorganic analysis[34], organic chemistry[35], pharmacy[36], metallurgy, geology and archaeology[37], polymer chemistry[38], colloids and surface active substances[39], food chemistry[40], petroleum and fuel analysis[41], Trace analysis[42], rare earth analysis complex studies[43], trace determination of drugs[44-48], quantitative and qualitative analysis of organic compounds including drugs[49-54].

1.3.1 Analysis of Organic Compounds by Polarography:

Polarography has contributed significantly to the understanding of processes involved in the electrolysis of organic compounds. In organic chemistry, polarography can be used in the determination of equilibrium and rate constants, in studies of reaction mechanism, in the search of optimal conditions for some preparative reactions, in studies and comparisons of reactivity's of organic compounds and in correlations of structure with polarographic data.

From polarographic curves, identification of electrolysis with other methods may be used for elucidation of organic electrode process. Many organic functional groups undergo reduction or oxidation at dropping electrode and thus led themselves to polarographic determination. In general, the reactions of organic compounds at the dropping electrode are slower and are often more complex than those of inorganic ions; nevertheless, polarographic investigations can be useful for structure determination and for qualitative and quantitative analysis.

Reactions of organic substances at the dropping electrode usually involve hydrogen ions; a typical reaction can be represented by the equation.

$$R + nH^+ + ne^\ominus \rightleftharpoons RH_n$$

Where RH_n is the reduced form of the reducible compound R. As hydrogen ions (supplied from the solution) are involved in the reaction, the supporting electrolyte must be well buffered. Change in the pH of the supporting electrolyte may even lead to the formation of different reaction products. Thus, in slightly alkaline solution, benzaldehyde is reduced at -1.4 volts with formation of benzyl alcohol, but in acid solution (pH < 2), reduction takes place at –1.0 volts with formation of hydrobenzoin:

$$2C_6H_5CHO + 2H^+ + 2e^\ominus \rightleftharpoons C_6H_5CH(OH)CH(OH)C_6H_5$$

Some organic compounds can be investigated in aqueous solution. It is frequently necessary to add an organic solvent to improve the solubility. Suitable water miscible solvents include ethanol, methanol, ethane-1,2-diol, dioxane, acetonitrile and acetic acid. In some cases, a purely organic solvent must be used and anhydrous materials such as acetic acid, formamide and diethylamine have been employed. Suitable supporting electrolytes in these solvents include lithium perchlorate and tetra-alkyl ammonium salts R_4NX (R = ethyl or butyl; X = iodide or perchlorate).

The following functional groups can be expected to react at the dropping electrode.

C=C (When conjugated with another double bond or an aromatic ring), C□C (when conjugated with an aromatic ring), C–X (X = halogen), C=O (aldehydes, ketones, quinones), dicarboxylic acids in which the carboxyl groups are conjugated with each other, Peroxides, epoxides, C=N, Nitro, nitroso, azo groups, heterocycles with two or more nitrogen atoms in the ring, C=S, S–S and S–H (mercaptans give an anodic wave).

1.3.2 Polar Graphic Study of Metal Complexes:

The chemistry of metal complexes is undergoing a period of a rapid development and engaging the attention of many researchers. Its progress has received an added impetus due to its several applications in chemical, industrial, agricultural, biological and technological fields. Metals that are essential for plant growth and animal nutrition have been found to form complexes with materials present in organisms. Metal-chelate formation also plays significant role in the functioning of enzymes and processes like moderate dyeing in the textile industry and the tanning process as in the leather industry. Their applications in inorganic analysis are of many folds and include detection, determination, purification and solvent extraction through complex formation. Complex forming reagents are extensively applied masking agents in various titrimetric, spectrophotometric, polarographic, chromatographic and electrophoresis methods.

Historically, credit to study inorganic complexes by polarography goes to the pioneering work of Stackelberg, Frey-hold[55] and Lingane[56]. The classical method of analysis was thoroughly discussed by Kolthoff and Lingane[57] in the monograph on polarography and related electrochemical techniques which resulted in remarkable progress and is now extensively used in the study of complexes in solutions. Some of the general developments are presented and discussed by Irving[58], Koryta[59], Westwood and Crow[60-62] in their publications. Excellent reviews have also been published by Vlcek[63-64] on relation between electrochemical reactivity and structure of inert complexes. A beautiful review has also been written by Tamamushi and Sato[65]. The contribution of Lingane, Deford and Hume[66], Ringbom and Erikson[67-68], Kacena and Matousek[69] Schwarzenbach[70-71], Buck[72], Butler[73], Macovsch[74] and Crow are there for study of metal complexes. Schapp and MacMasters[75] have extended Deford and Hume's treatment for study of mixed ligand complexes in solution.

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2. Organic Reactions

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Abstract:

The chemistry of carbon compounds is now referred to as organic chemistry. When the majority of the substances identified in this discipline of chemistry came from living organisms, the word " organic" was first used to characterize it.

The greatest component of chemistry is organic chemistry, which also ranks among the most popular disciplines in terms of both its factual base and its audience size. There are currently more than a million known organic compounds, and thousands more are constantly being found in nature or created in laboratories.[1]

Chemical processes involving organic molecules are known as organic reactions. Functional groups have a strong relationship with several of these reactions. Analysis of features including bond strength, steric hindrance, and the electron affinities of important atoms are all carefully considered in the general theory of these processes.

Covalent bonds found in organic compounds change most frequently during organic processes. These modifications could include bond cleavage, electric bond displacement, energy modifications associated with covalent bond formation, etc. We must.[2]

Keywords:

Covalent bond, steric hindrance, electron affinities, bond strength, energy modifications.

2.1 Types of Organic reactions:

A. Substitution reactions
B. Addition reactions
C. Elimination reactions
D. Rearrangement reactions

2.1.1 Substitution Reactions:

In a substitution reaction, an atom or group of atoms from a molecule are exchanged out for new ones while maintaining the molecule's original structural integrity. Free radical, nucleophilic, and electrophilic substitution reactions are those in which free radicals, nucleophiles, and electrophiles serve as reactive intermediates.[3]

A. Free Radical Substitution Reactions: For instance, methyl chloride is created when methane combines with chlorine in the presence of sunlight by replacing one hydrogen atom with a chlorine atom in a free radical substitution reaction. This reaction is known as a free radical substitution reaction because it uses free radicals as intermediates.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$$

This reaction involves the following steps:

- Cl-Cl $\longrightarrow$ Cl +. Cl
- CH_3 – Cl +. Cl $\longrightarrow$ $^{\cdot}CH_3$ + HCl
- $^{\cdot}CH_3$ + Cl- Cl $\longrightarrow$ H_3C – Cl +. Cl

This reaction may proceed further to replace remaining hydrogen atoms by chlorine to form CH_2Cl_2, $CHCl_3$ and CCl_4 by similar mechanisms.

B. Nucleophilic Substitution Reactions: A nucleophilic substitution process is one in which methyl chloride and aqueous potassium hydroxide react to produce methyl alcohol.

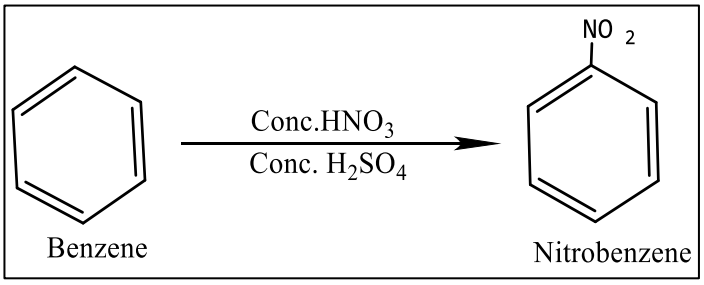
$$CH_3\text{- Cl} + KOH \longrightarrow CH_3OH + KCl$$

In this reaction replacement of Cl by a nucleophile (: OH^-) take place. Substitution reactions of alkyl halide involve nucleophilic substitution reactions.

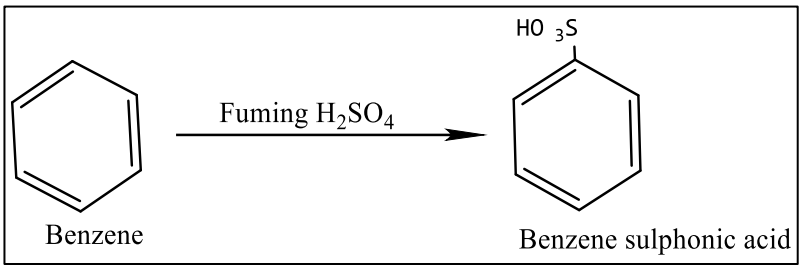
C. Electrophilic Substitution Reactions: Electrophilic substitution reactions include aromatic substitution processes like nitration, sulphonation, Friedel craft reactions, etc. These reactions involve replacement of nuclear hydrogen by an electrophile (Ex- NO_2, R^+ etc)[4]

Example: -

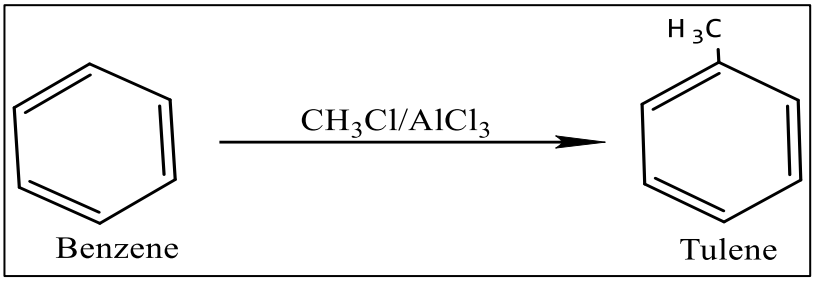
- Nitration



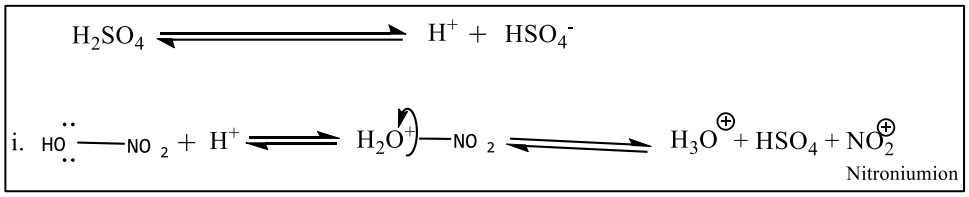
- Sulphonation

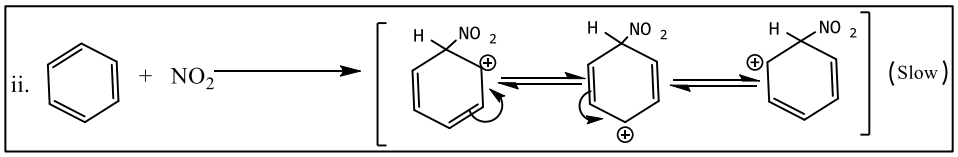


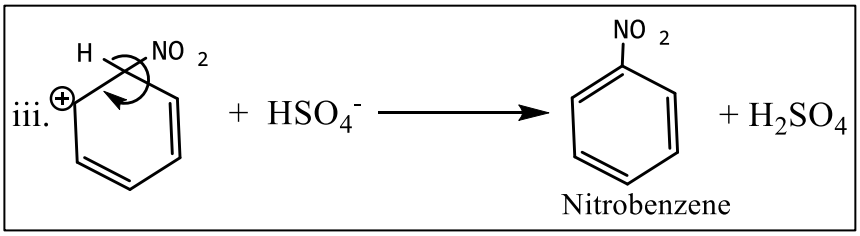
- Friedel craft reaction



- **Mechanism of Nitration:**

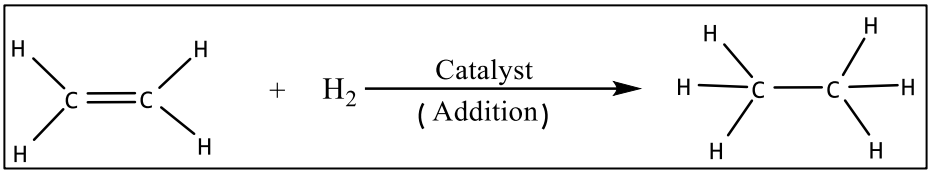






2.1.2 Addition Reactions:

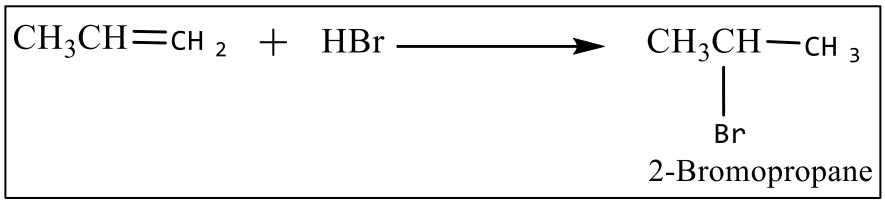
The chemical molecules with double or triple bonds that cause these reactions (unsaturated compounds). These substances easily incorporate hydrogen, haloacids, halogens, etc. into the end product while altering the molecule's shape. For example,



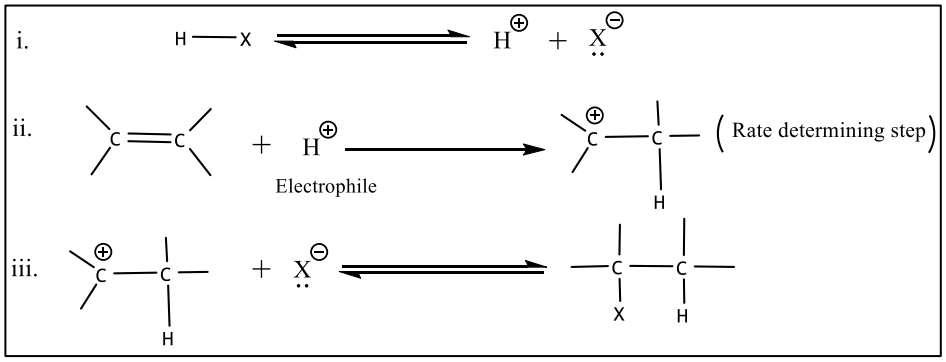
In these reactions, one pi bond, which is weaker than an alpha bond, breaks to produce two new sigma bonds, one on each carbon, which satisfy the valency criteria in the end product.

These reactions are of three types:

A. Electrophilic Additions: These reactions are known as electrophilic addition reactions because they are started by the addition of an electrophile during the rate-determining step. For example,



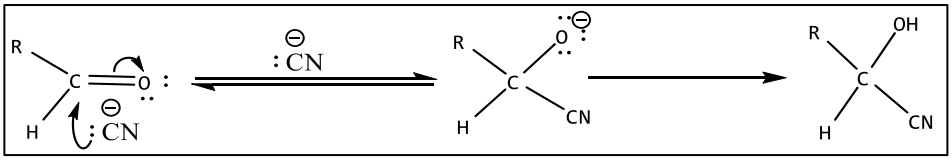
B. Mechanism: It is an electrophilic addition reaction, initiated by the electrophile (H^+) released from the HX. This reaction involves the following steps:



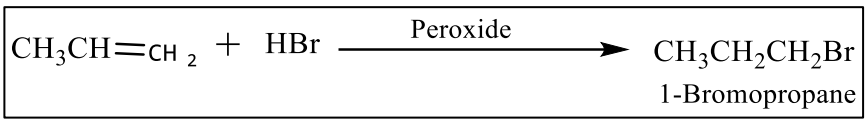
The rate determining step is step (ii) leading to the formation of a **carbocation.**

C. Nucleophilic Additions: Simple aldehydes and ketones' carbon-oxygen double bonds give rise to addition reactions that are typically nucleophilic in nature.

For example, addition of HCN to aldehydes

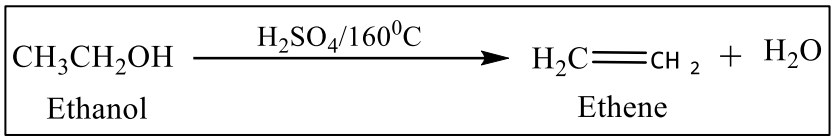


A. Free radical additions: - Free radical mechanism controls the addition reaction of HBr to unsymmetric alkenes (like propene) in the presence of peroxides to produce an anti-Markownikoffs product. Free radical addition reaction is the name given to this process.

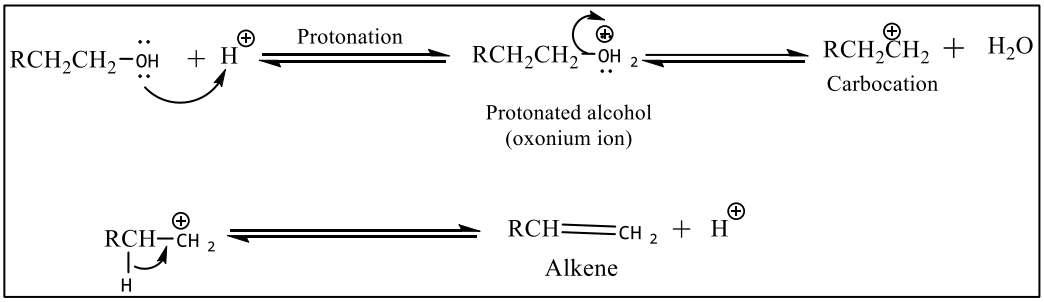


2.1.3 Elimination Reactions:

This reaction is the opposite of the addition reaction. A reactant molecule loses atoms or groups during an elimination process. These reactions result in compounds with many bonds.[5] For example,



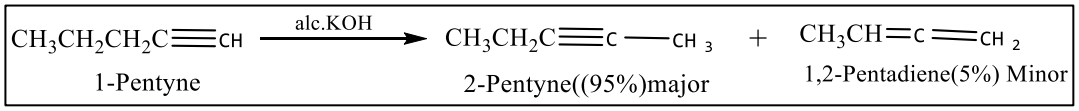
A. Mechanism: It involves protonation of alcoholic group followed by elimination of water and deprotonation.



2.1.4 Rearrangement Reactions:

An atom or a group of atoms may move from one area of a molecule to another area of the same molecule during a rearrangement reaction. Triple bond migration may also be involved.[6]

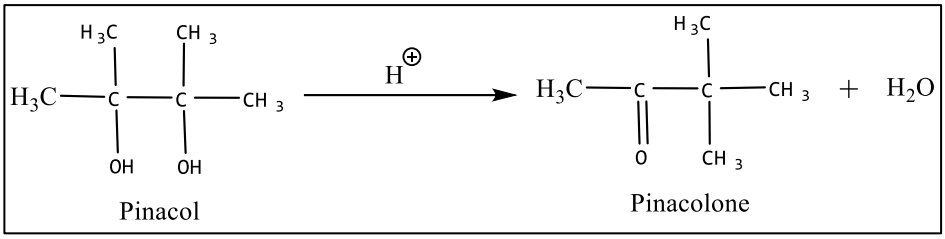
For example, 1-pentylene with alcoholic KOH tend to rearrange with migration or triple bond to form 2-pentylene as major product:



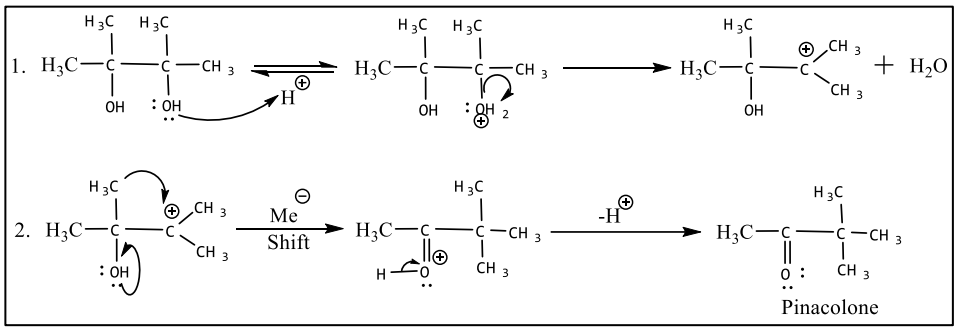
Some of examples of Rearrangement reactions,

A. Pinacol Pinacolone Rearrangement: It involves the dehydration of substituted vicinal diols (pinacols) under acid catalysis, followed by rearranging the carbon skeleton to produce ketones.[7]

For example,



Mechanism:

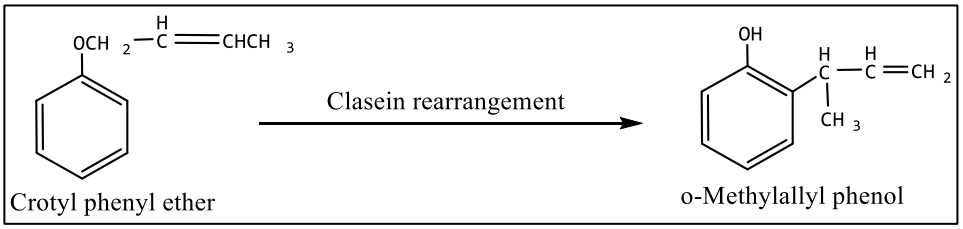


Step 1 involves protonation of that -OH group, which on elimination of water molecule gives most stable carbocation.

Step 2, carbocation undergoes a 1,2-methyl shit to the electron deficient carbon to generate protonated ketone.

B. Claisen Rearrangement: O-allyl ether of phenol undergoes a rearrangement to become o-allylphenol at a temperature of about 200^0C in the absence of any catalyst. The Claisen rearrangement of phenolic allyl ethers is the name of this thermal process.[8]

For Example,



2.2 References:

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3. Emerging Trends in Microwave Chemistry Assisted Extraction of Phytochemicals

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Learning Outcomes:

At the end of this chapter the reader will be able to understand:

- Introduction
- Microwave Chemistry: Principle, Benefits and Applications
- Microwave Assisted Extraction: Principle, Methodology, Advantages and Applications
- Microwave Aided Extraction Technology in Herbal Drug Research
- Microwave Assisted Extraction of Phytochemicals
- Studies using Microwave Assisted Extraction of Phytochemicals
- Conclusion

Abstract:

Plants are considered as natural factories for construction of wide range of phytochemicals. A large number of secondary metabolites like alkaloids, glycosides, tannins, phenolic compounds, resins and flavonoids are manufactured by plants. Developments in natural chemistry research led investigators to documentation and separation of diverse bioactive chemicals. These phytochemicals are widely used as therapeutic agents in treatment and management of various acute and chronic disorders and diseases. The superiority of active herbal preparation is considerably contributed by extraction techniques. Extraction is crucial and first most important step in the development of phytochemicals. Conventional extraction techniques reported to possess few limitations and disadvantages. The principles of microwave chemistry are useful in order to overcome few of the limitations of conventional extraction techniques. Hence in the Microwave assisted extraction has been introduced. This is an effective and new tool with numerous benefits as compared to the old-style approaches of extraction. The important benefits of microwave assisted extraction

are in terms of reduction in cost, time of extraction, amount of solvent used, and energy consumptions. This chapter give brief overview on basic approach, principle and applications of microwave chemistry. This chapters also emphasizes on the microwave assisted extraction techniques and its applications towards the development of phytochemicals.

3.1 Introduction:

The Microwave region is lie in the electromagnetic range between the radio waves and infrared waves. They have wavelengths between 0.01 and 1 meter, and functions in a frequency array between 0.3 and 30 Ghz. Usually a frequency of 2.45 Ghz is utilized for laboratory activities like to conduct the chemical reactions as this waves proper penetration depth which are suitable for the laboratory reactions. Beyond 30 Ghz wavelength frequency, the microwave frequency overlaps with the radio frequency.

Generally, the microwave electromagnetic range is distributed into two categories namely sub-bands including the lower microwave frequency called as L band and the higher frequency known as W band. L band microwave frequency is mainly used for the purpose of communication and W band frequencies are used for the analytical techniques such as spectroscopic characterization. Microwave chemistry is the branch of chemical science which involves the study and utilization microwave radiation to chemical synthesis.

Microwaves action as high frequency electric fields and mainly causes the heating of any material. It generates the mobile electric charges, such as polar molecules in a solvent or accompanying ions in a solid. Thus the microwaves are widely used in various industries including pharmaceutical, biotechnology, chemicals, petroleum and polymer industries.

The Microwave-assisted reactions are fast, clean, and economic and eco-friendly. The principles and approaches of microwave chemistry have been widely used in the natural products chemistry research as well to extract and isolate diverse chemical entities from natural sources like plants and minerals.

3.2 Microwave Chemistry:

In the year 1946, the technology of Microwave technology was originated and discovered. It was started with research performed by Dr. Percy Le Baron Spencer. He was performing laboratory examinations for a new vacuum tube known as magnetron. Magnetron is a device that produces an electromagnetic radiation.

During this experiment, accidentally he discovered that a candy bar in his pocket liquefied on exposure to radiations of microwave. In the year 1947, Dr. Spencer established the idea and recognized that microwaves might be used as a technique of heating.

Then, he intended the first microwave oven for domestic practice. Subsequently, in future years the expansion of microwave radiation and its applications were studied. Table 3.1 provides the information about development and evolution of Microwave chemistry.

Table 3.1: Development and Evolution of Microwave Chemistry

Sr. No.	EVOLUTION	YEAR
1	Discovery of Microwave radiation as heating method	1946
2	Introduction of first commercial domestic micro oven	1947
3	Development of first laboratory useful micro oven instrument	1978
4	Generation of microwave radiations to dry organic materials	1980-1982
5	Utilization of microwave radiation for analysis of chemicals	1983-1985
6	Publication of research papers related to applications of microwave radiation in synthesis of chemicals	1986
7	Emergence and development of Microwave Chemistry as a field of study due to its useful applications in chemical synthesis	1990
8	Development of first high pressure vessel for conducting full digestion of oxides, oils and pharmaceutical samples.	1990
9	Synthesis of chemicals based on microwave radiations using batch system reactor and single mode cavity system	1992-1996
10	Publication of book titled Microwave Enhanced Chemistry-Fundamentals, Sample Preparations, and Applications	1997
11	Introduction of first commercial microwave synthesizer to carry out the chemical preparation.	2000
12	Conduct of various research using microwave chemistry and its applications, commercialization, industrial utility, publication of research papers.	2022

3.2.1 Principle of Microwave Chemistry:

Microwave chemistry is the branch of chemistry that deals with study and applications of microwave radiations to conduct chemical reactions or chemical synthesis and chemical analysis. The approach of Microwave-assisted synthesis works on the basis of aligning dipoles of the substance in an external field via the excitation fashioned by electromagnetic radiations of microwave and is generally performed in mixture with an identified synthesis scheme.

This technique is moderately beneficial as the synthesis development can be modified to produce product with many advantages. The procedure of alignment or orientation of substance by the external electrical field may result in the creation of internal heat which is accountable for a decrease in processing time and energy requisite. It is particularly due to the heating consistency of microwaves. The reaction time can be fairly condensed by accepting microwave-assisted preparations.

A. Benefits of Microwave Chemistry:

Microwave chemistry has many benefits as mentioned below:

- Microwave radiation are extremely effective and used as heating source in chemical synthesis.
- Microwave chemistry is helpful in emerging the cleaner synthetic routes and procedures.
- Microwave chemistry helps to enhance the rate of chemical reactions and improve the percentage yield of product.
- Microwave chemistry helps to achieve the better reproducibility of reactions.
- It helps to deliver efficient and uniform heating to the chemical reactions.
- It also helps to provide the selective heating in a chemical synthesis schemes.

B. Applications of Microwave Chemistry:

The concept and approaches of microwave chemistry is widely used and applicable in various industries. The wide range of applications of microwave chemistry and related techniques are useful in various fields. Figure 3.1: Shows The Applications of Microwave Chemistry in Various Areas.

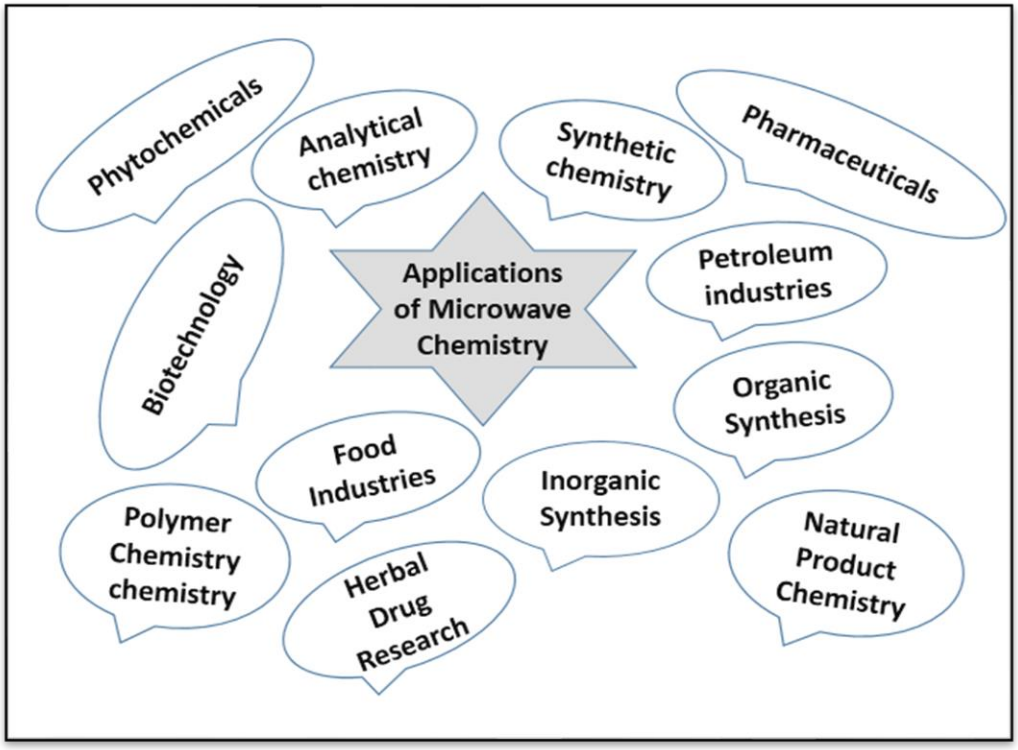


Figure 3.1: Applications of Microwave Chemistry in Various Fields

a. General Applications: The concept of microwave chemistry is widely used in various industries like biotechnology, pharmaceuticals, petroleum, plastics, chemicals and food industries. Various general applications of microwave chemistry are listed as below:

- The microwave chemistry is useful in the field of analytical and synthetic chemistry
- It has wide range of applications in natural products chemistry research.
- Microwave heating is extensively used for ashing in the petroleum and fuels, plastics, pharmaceuticals and food industries.
- Microwave digestion systems are used in analytical laboratories for sample decomposition and preparation.
- Microwave radiation used in trace and ultra-trace metals analysis.
- Microwave extraction is widely used in herbal drug research.
- Microwave assisted extraction systems are used to conduct routine solvent extractions of soils, sediments, sludge, polymers and plastics, pulp and paper, biological tissues, textiles and food samples.
- Microwave assisted moisture analysis has been widely used in the food and beverage, chemical, environmental, organic and pharmaceutical industries.
- Microwave moisture analysis is specifically applied at product development stages such as process and quality control, testing of raw materials, intermediate and finished products.

b. Applications in Chemical Synthesis: The application of microwave radiation are widely useful in the synthesis of large number of chemical moieties. It is widely used in the organic and inorganic synthesis in laboratories. The Microwave-enhanced preparations help the scientist to perform his work faster, get higher yields, and enhance the purity of product. Apart from this due to the advanced instrumentation and innovative research in Microwave chemistry, it has been observed that the yield of product is been scaled up from mg to kg. The techniques of microwave chemistry play valuable role in the organic and inorganic synthesis and few of the important applications are listed as below:

- **Applications in Organic Synthesis:** Organic synthesis can be defined as the synthesis of a preferred organic molecule by using precursors. The Microwave assisted organic preparation is one of the novel research area in the organic preparations as it gives better results with many advantages over the conventional routes and hence Microwave organic preparations are found to exert great role in the synthetic laboratories. The important applications of microwave synthesis in organic synthesis are highlighted as below:

- The Microwave assisted organic preparations are widely used in the pharmaceuticals companies, mainly in order to develop the molecules in the optimization of lead stage in the drug development.
- Literature reported that the scientist has been successfully used the approach of microwave synthesis in conduct of large number of named chemical reactions. Few of these reactions conducted using microwave techniques are listed below:

    - Condensation reactions
    - Cyclisation reactions

- Cycloaddition reaction
- Dehydration
- Diels Alder reaction
- Epoxidation
- Esterification

- Heck reaction
- Hydrogenation of [beta]-lactams
- Hydrolysis
- Mannich reaction
- Protection and deprotection of functional groups
- Reduction reactions
- Suzuki reaction

- **Applications in Inorganic synthesis:** Inorganic preparations can be defined as the preparation of a preferred inorganic compound from suitable precursors. The Microwave assisted inorganic compound synthesis is one of the innovative research region in the inorganic preparations as it gives better results with many advantages over the conventional routes and hence Microwave inorganic preparations are found to exert great role in the synthetic laboratories. The important applications of microwave synthesis in the field of inorganic synthesis are highlighted as below:

- The Microwave assisted inorganic preparations are extensively used in the pharmaceuticals companies, mainly in order to develop the inorganic molecules.
- Microwave chemistry is widely used in the preparation of organometallic derivatives.
- Microwave chemistry is also used in the synthesis of coordination compounds.
- It is used in the synthesis of intercalation molecules.
- It is also used in the preparation of ceramic products.

c. Applications in Polymer Chemistry: Polymer chemistry is one of the important field in the chemistry and it is mainly used in the preparation of Polymer products.

- The concept and approaches of microwave chemistry is widely used in the development of polymers and related products.
- The approaches of microwave techniques are also widely used in order to conduct the polymerization reaction.

3.3 Microwave Assisted Extraction:

The microwave assisted extraction is a model and newest green approach to an analytical method in which microwave radiation frequency is used for the extraction of chemical compounds or isolates particularly from plant materials. This technique utilized to extract the samples or chemical compounds from biological matrices for the purpose of its further analysis. Microwave assisted extraction is a procedure of utilizing the microwave energy to heat liquids in connection with a sample in order to distinct the chemical from the matrix into the liquid. Earlier microwave ovens are utilized for the digestion of samples for metal

analysis. All microwave ovens (Home or the laboratory used) are usually operate at 2.45 GHz frequency. The microwave region found to exists at frequencies of wavelengths from 0.3mm to 1m or 100 GHz to 300 MHz.

Principle of Microwave Assisted Extraction: The basic principles of the microwave assisted extraction method are different from traditional methods of extraction like solid-liquid or simple extraction techniques. As we know the electromagnetic radiations are known to cause the cell structure and this leads to the extraction. When the microwave radiation is passed through the matrix or plant materials, it causes the molecular communication with the wave. Thus the microwave radiation is converted into heat energy that supports the mass transfer from plant cell or material into the solvents. By using this principles, the phytochemicals can be extracted from plant materials by using microwave radiation. The traditional solvent extraction techniques from plant materials trust on the appropriate assortment of solvents and the use of thermal energy and agitation to recover the mass transfer and increase the solubility of the anticipated agent. Hence new system of microwave assisted extraction helps to condense the extraction time, less solvent ingesting, decrease the contamination and superior attention for thermolabile chemicals have added consideration.

Methodology: In order to perform the microwave assisted extraction two methods are utilized using different devices mainly:

- Open Microwave Assisted Extraction System/Atmospheric Microwave Assisted Extraction System
- Closed Microwave Assisted Extraction System/Pressurized Microwave Assisted Extraction System

a. **Open Microwave Assisted Extraction System/Atmospheric Microwave Assisted Extraction System:** In case this method the sample is situated in an open vessel to which a suitable organic liquid is placed. The microwave radiation produced from the magnetron is focused by the waveguide onto the sample/liquid, thus producing the liquid to boil. The hot liquid is then arising into interaction with a water cooled reflux condenser. This effects the liquid to condense and reappearance to the vessel. This procedure is recurrent for a little period of time so allowing compounds of interest to be come out from the sample material into the liquid.
b. **Closed Microwave Assisted Extraction System/Pressurized Microwave Assisted Extraction System:** In this case, the microwave radiations enter into the oven, and are detached by a mode stirrer. The mode stirrer permits an even delivery of microwaves within the oven. In this approach the sample and liquid are situated within the closed container which is typically prepared of microwave transparent resources such as polymers and their derivatives.

3.3.1 Advantages of Microwave Aided Extraction:

A prospective substitute to old-style solid liquid extraction method is the microwave assisted method. Microwave assisted techniques has good number of compensations over the traditional extraction and few of them are listed as below:

- Microwave assisted extraction technique helps to extract multiple samples for at a time.
- Microwave supported extraction method requires small quantity of liquid for extraction.
- Microwave aided extraction technique carries the extraction in very short period of time.
- Microwave assisted extraction gives the Improved yield.
- This technique gives improved accuracy in the results.
- This approach is suitable for the thermolabile chemical extraction.
- It requires remarkably less extraction period and the time of extraction usually extending from few seconds to few minutes.
- It requires very less amount of liquid in extraction and amount is a few milliliters.
- It shows also the better precision due to the automation of the apparatus.
- It is useful to extract heavy metals and pesticide deposit present in very minute units.
- It shows the improved mass transfer mechanism due to the agitation of sample vessels.

3.3.2 Applications of Microwave Supported Extraction Techniques:

The wide range applications of microwave aided extraction technology are listed as below:

- The microwave assisted technique is useful in order to extract large number of phytochemicals from the plant materials.
- It is widely used technique in the extraction of sample in herbal drug industries.
- It has showed the utilization in extraction of sample or analyte from the biological matrix in the bioanaytical laboratories in the clinical research.
- In the analytical research and development department of pharmaceutical industries this approach is extensively used.
- This approach is used in order to extract the secondary bioactive chemicals from the plant materials including alkaloids, glycosides, tannins, polyphenols, flavonoids, terpenes, lignans and phenolic derivatives.
- The closed vessel microwave method is used for the extraction of terpenes from plant material.
- The extraction of imidazolinone herbicides and sulphonylurea herbicides has been carried out and reported in the literatures.
- It has been also used in the extraction of fungicides like hexaconzole from weathered soil.
- The extraction of additives polypropylene and polyethylene has been achieved in the polymer chemistry and related research.
- It has been widely used in the food industries in the preparation of vitamins in foodstuffs.
- It can be used for determination of various metals and metallic compounds like Zn, Pb, and Cu from soils.
- Microwave aided extraction is a consistent source of extraction of phytoconstituents.
- It also can be used for the extraction of essential oils from plant sources.
- This technique also used in the analysis of heavy metals and other pollutants present in the different type soils.
- Microwave supported extraction is used in the synthesis and preparation of pharmaceuticals samples in the pharmaceutical industries.

3.4 Microwave Aided Extraction Technology in Herbal Drug Research:

Herbal medicines are also known as phytomedicines and they have been widely used by human culture. The plants are considered as natural factories for manufacture of numerous phytochemicals or plant compounds. A large quantity of secondary metabolites like alkaloids, glycosides, tannins, phenolic derivatives and flavonoids are manufactured by plants.

They act as a great source in the development of modern medicines. The advancements in natural chemistry sciences directed researchers to documentation and isolation of diverse bioactive phytocompounds. The one of the most important step in the development of herbal medicines include the extraction of plant samples. Based on the basis of physical nature and chemical properties of phytochemicals, several approaches are in procedure to gain the crude extract. Few of the conventionally used extraction techniques in herbal drug industries are listed as below:

- Infusion
- Digestion
- Decoction
- Percolation
- Maceration
- Soxhlet Extraction etc.

The above mentioned extraction techniques are used for the extraction of plant chemicals from plant material but at the same time they are also associated with some limitations and disadvantages like:

- Extraction time is more
- Solvent consumption is more
- Soxhlet extraction method is not suitable because in the method the targeted compound may undergoes the decomposition due to usage of high temperature.
- The traditional extraction technique carries the extraction in more time.
- The traditional extraction technique may give the less yield.
- This technique gives less accuracy in the results.
- This approach is not suitable for the thermolabile chemical extraction.
- It requires remarkably more extraction period and the time of extraction usually extending more than hours.
- It requires more amount of liquid in extraction.
- It shows also the less precision due to the non-automation in the extraction apparatus.
- Many time it is not useful to extract heavy metals and pesticide deposit present in very minute units.
- It shows the less mass transfer mechanism due to the poor agitation of sample vessels.

In order to overcome one or other limitations of the conventional methods the approach of microwave assisted tool has emerged due to its wide range of advantages as discussed earlier in this chapter.

A. Emerging Trends in Microwave Aided Extraction: A Competent and Modern Approach for Pharmaceuticals and Botanicals:

The microwave aided extraction is attentive and targeted technique of extraction of plant chemicals and can be effortlessly joined with other analytical devices like chromatographic techniques. Its treatment is additional made easier due to the automation of the apparatus. This approach is new and widely used in order to develop the modern medicines and pharmaceuticals from the various botanicals. There are many recent advancements and emerging trends in the development of microwave assisted solid extraction techniques from natural matrices. Some recent trends and applications are discussed in this chapter under below headings:

- Development of marker compounds
- Assessment of plant productivity
- Extraction of plant chemicals for drug development and its commercial applications.

a. Development of Markers: The microwave driven extraction tool is also reported for the development of marker compounds from the plant materials. Literature reported various methods and compound which are extracted and isolated using this approach and successfully used for marker based standardization of phytomedicines and related products**.** Few of the marker compounds extracted using microwave techniques are listed as below:

- Vitexin
- Isovitexin

b. Assessment of Plant Productivity: The microwave driven extraction offers the opportunity for performing the multiple extractions which is suitable for the fast screening of an abundant set of samples to assess the efficiency of organisms. For example, in order to compare amount of coumarin and related compounds like melilotic acid, and o-coumaric acid, the microwave assisted technique can be used also it can be used to analyze the productivity of *Melilotus officinalis* plant.

c. Extraction of plant chemicals for drug development and its commercial applications: The plant compounds isolated from the medicinal plants are widely used in the management and treatment of various diseases and disorders. The plant secondary metabolites include alkaloids, flavonoids, tannins, terpenes, polyphenols and many other functional derivatives. The microwave assisted extraction tool has been reported in the literatures in order to extract these plant secondary chemicals with better extraction and activity reports. Few of the examples of such microwave assisted extracted chemicals are discussed as below:

- **Extraction of Alkaloids:** The alkaloids are a famous class of secondary metabolites characterized by the presence of basic nitrogen. These class of compounds are widely used as therapeutic agent in very small amount. Over the years, many active alkaloids have been extracted microwave irradiation tools. Few important examples of execrated alkaloids by this tool are listed as below:

- Extraction and isolation of ephedrine, cocaine, and ergot alkaloids has been reported by using microwave extraction tool.
- An efficient microwave supported extraction protocol as a drug discovery process has been reported for the extraction and isolation of bioactive alkaloids like neferine, dauricine, liensinine, isoliensinine, nuciferine from *Lotus plumule* plant.
- The simultaneous microwave assisted extraction protocol have been developed for the collection of cocaine, cocaethylene, benzoylecgonine, morphine, 6-monoacethylmorphine, and codeine from human urine, hair, and vitreous humor samples.
- The microwave aided aqueous two phase extraction protocol has been reported for the rapid and simultaneous extraction and separation of alkaloids like oxymatrine, Matrine, 5α-hydroxysophocarpine, sophocarpine, oxysophocarpine, cytisine, N-methylcytisine, sophoranol, and sophoridine etc. from the plant *Radix Sophorae tonkinensis*.
- Recently literatures have reported the microwave supported extraction protocol for multicomponent analysis and the extraction of Berberine and polyphenol chemicals from various plant species of *Berberis*.
- Microwave extraction tool also has been used for the extraction of cocaine and benzoylecgonine from the leaves of *Erythroxylum coca.*

- **Extraction of Stilbene-based Polyphenolic Chemicals:** The Stilbene-based polyphenolic chemicals have been widely used as antibacterial, anti-inflammatory, hypolipidemic, cardiovascular, anti-diabetic, anti-ulcer, hepatoprotective, and anticancer agents. The few examples of useful Stilbene-based Polyphenolic Chemicals extracted by using microwave radiations includes: *trans*-resveratrol (3, 5, 4′-trihydroxystilbene), pterostilbene, viniferin, and other polyphenolic-stilbene derivatives etc.
- **Extraction of Terpenoids:** The Terpenes and isoprenoids, in general, expanded much consideration for their many biological functions like hormones, aliphatic tissue anchors, upholding tissue structure, biotic roles like defense compounds, insect or animal attractants, and wide medicinal uses such as flavors, fragrances, and drugs etc. Few examples of terpenes and related derivatives which are extracted using microwave techniques are listed as below:
    - Artemisinin from *Artemisia annua*
    - Paclitaxel from *Taxus baccata L.*

3.5 Microwave Assisted Extraction of Phytochemicals:

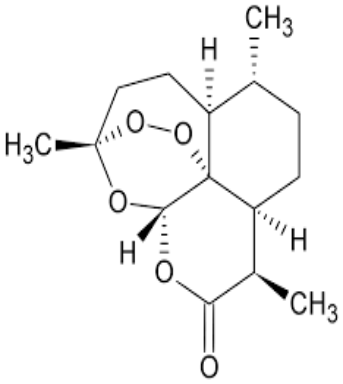
The extraction includes separating dissolvable chemical from non-dissolvable material using suitable liquids. There are two groups of extraction techniques reported for phytochemicals collection namely the traditional and modern extraction techniques. The list of traditional extraction methods includes the Soxhlet, soaking, maceration, digestion, decoction etc. These traditional extraction tools are associated with some limitations. In order to overcome the limitations of older extraction techniques few modern extraction techniques are evolved which includes turbo-fast blending, sonication, ultrasonic aided, subcritical, supercritical, enzyme assisted, pressure assisted, and microwave assisted techniques. Out of all these listed modern methods of extraction, the microwave supported

extraction has established the highest responsiveness due to its condensed consumption of liquid, less operation time, good reproducibility, improved recovery, upright selectivity, and condensed sample manipulation. In recent years, the microwave assisted extraction is usually used in gaining the chemicals of bio origin from plant materials. This has significantly improved the total attention in expansion and growth of research areas in plant chemistry research. It is a green expertise that is operational for taking out the plant compounds from plant sources. The microwave supported extraction has been employed in several ways to extract bioactive compounds from different plant samples. The isolates from these plant materials are being used in nutraceuticals and pharmaceutical uses. The microwave irradiation is mostly used to resolve some of the drawbacks associated with traditional methods. Table 3.2 presents some of the previous studies and the list of phytochemicals extracted from plants using microwave aided technology. The chemical structure of selected phytochemicals extracted using approach of microwave chemistry are given in Karnataka, India.

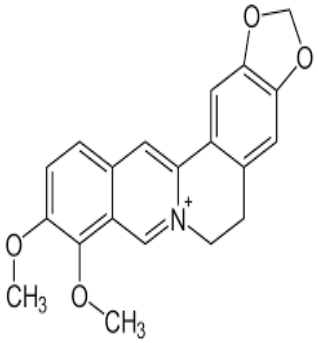
Table 3.2: List of Phytochemicals Extracted by Microwave Chemistry Approach

Sr. No.	Phytochemicals	Source of Plant
1	Artemisinin	*Artemisia annua* L.
2	Berberine	*Berberis aristata*
3	Coumarin	*Melilotus officinalis*
4	Caffeine	Green tea leaves
5	Carvone	*Carum carvi* L.
6	Carvone	*Mentha crispa* L.
7	Curcumin	Turmeric plant
8	Eugenol	*Ocimum basilicum* L.
9	Glycyrrhizic acid	Licorice roots
10	Isorhamnetin-3-O-rutinoside	Sea buckthorn
11	Limonene	*Carum carvi* L.
12	Limonene	*Mentha crispa* L.
13	Linalool	*Ocimum basilicum* L.
14	Monoterpenes	*Lavandula angustifolia* Mill.
15	Oxygenated monoterpenes	*Lavandula angustifolia* Mill.
16	Pectin	Grape fruis

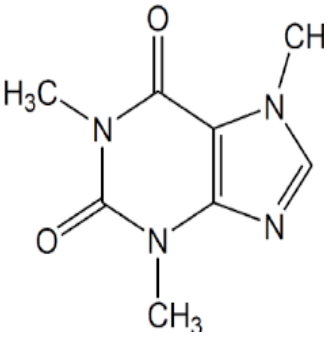
Sr. No.	Phytochemicals	Source of Plant
17	Phenolics chemicals	*Cinnamomum zeylanicum*
18	Polyphenols	Green tea leaves
19	Quercetin	Cranberry
20	Quercetin 3-O-Glucoside	Sea buckthorn
21	Sesquiterpenes	*Lavandula angustifolia* Mill.
22	Silybinin	*Silybum marianum* (L.)
23	Triterpene saponins	*Xanthoceras sorbifolia* Bunge.
24	5,8-Dihydroxycoumarin	Sweet grass leaves
25	5-Hydroxy-8-O-β-D-glucopyranosyl-benzopyranone	Sweet grass leaves



Artemisinin



Berberine



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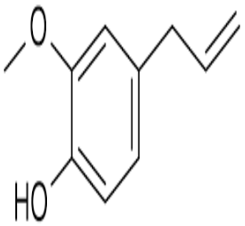

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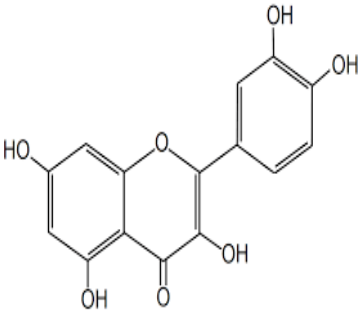

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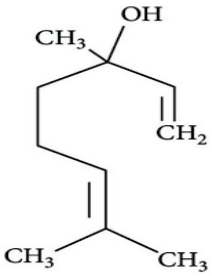

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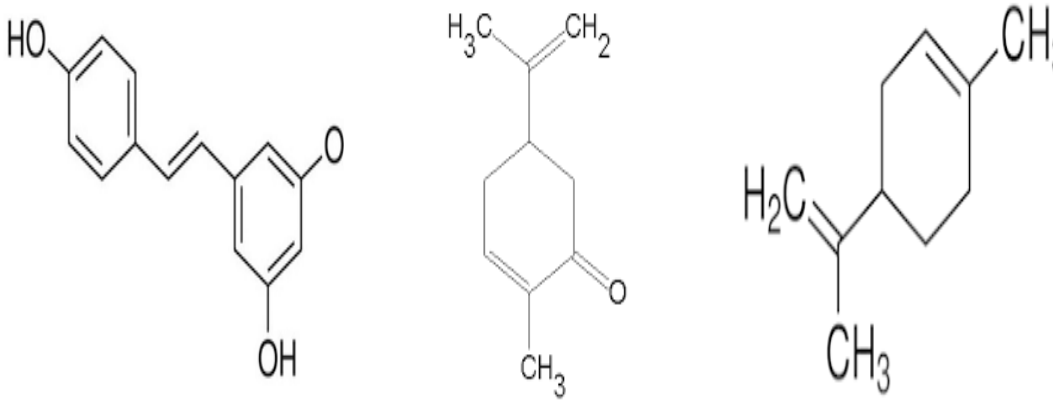

Resveratrol **Carvone** **Limonene**

Figure 3.2: Structures of Phytochemicals Extracted by Microwave Chemistry Approach

3.6 Studies Using Microwave Assisted Extraction of Phytochemicals:

a. **Microwave Aided Extraction of Plant Chemicals from Ficus racemosa:** This research was conducted and published in the literature to optimize the microwave aided extraction procedure for the pulling out of plant chemicals from fruits of Ficus racemosa, which is measured as an underutilized and extreme basis of numerous polyphenols. The extreme phytochemical characteristics were found in the optimized conditions using 30 second of time 3.5 of pH, and 360.55 W microwave power using microwave oven. The research work further identified and quantified the presence of ascorbic acid, catechin, gallic acid, tannic acid, and quercetin. The research showed that F. racemosa can be positively applied for the extraction of phytochemicals by microwave supported extraction technique, which can be further used in food and pharmaceutical productions.
b. **Microwave Aided Extraction of Plant Chemicals from *Nonea pulmonarioides:*** In this research investigation the microwave supported extraction tool was selected to isolate the secondary plant chemicals from *Nonea pulmonarioides*. They suggested that the microwave chemistry approach in extraction is an efficient method. In this study of *N. pulmonarioides*, extracted using microwave extraction technique they found that the faster extraction was obtained in 5 minutes of time with an more yield than the maceration extraction technique. The phytochemical screening specified the existence of several classes of plant secondary compounds.

3.7 Conclusion:

The microwave assisted extraction technique has quickly grown during the latest periods as a technique for the extraction of secondary plant compounds which are of pharmaceutical and nutraceuticals attention. This is a model and innovative approach utilized for the extraction of phytochemicals due to several advantages like less extraction time, decrease in the solvent consumption, more precision and accuracy in results, better yield, and

multiple sample extraction etc. This technique has proven to be operative in all features, including inexpensive and practical, compared to old-style extraction practices. Microwave supported technology showed the effective role in the extraction of plant secondary chemicals including alkaloids, flavonoids, terpenes, polyphenols, Coumarin derivatives, and saponins etc. The advanced instrumentation leads to better extraction and it has helped to develop the modern medicines for management of various diseases and disorders. Hence microwave assisted extraction technique is considered to be an emerging trend and one of the model approach in the field of natural products chemistry research especially it has gained more attention and scope in the phyto chemistry and drug development research.

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4. Application of Synthesized Ion Exchanger Tin (IV) Vanadomolybdate

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Abstract:

The distribution coefficient of Tin (IV) vanadomolybdateion exchanger for various metal ions revealed that the exchanger is selective for Ni2+ and Cu2+ ions, by the help of KD values. Binary separation of some important metal ion pairs was achieved. The ion exchanger may also be employed in the removal of transition metal ions from their aqueous solution. The effective separation of Ca2+and Mg2+ ions from hard water and the removal of colour metal ions were also achieved.

Keywords:

Distribution coefficient, Binary separation, Water softening, Removal of transition metal ions.

4.1 Introduction:

Ion exchange[1,2] is the process in which ions are exchanged between a solution and an insoluble solid. Ion exchange serves as one of the most important analytical technique for the separation of charged species from a solution that would ordinarily be very difficult and time consuming. Ion exchange process may be done with the help of an ion exchanger, interchange of ions of the same charge by other ions[3]. The earliest systematic studies of ion exchange were described with base exchange in minerals present in the soil[4].Ion exchanger may be natural or synthetic. Most natural ion exchangers like zeolites are crystalline materials having cation exchange properties. First synthetic industrial ion exchanger was reported in 1905[5]. In recent years' various zeolites with completely regular crystal structure have been synthesized and these products are exact counterparts of the natural materials. The examples of such kind of material include zeolite 4A[6] and zeolite A[7]. Now a day's synthetic inorganic ion exchangers have drawn the attention since they are less sensitive to higher temperature and to different chemicals and are also selective to certain ions. Further it was shown that three component ion exchangers show a better IEC than the two component ion exchangers. Tin (IV) based ion exchangers have been studied in detail previously by Varshney et al[8]. Various two component ion exchangers based on tin (IV) were reported in the literature[9-14]. Similarly, some examples of three component ion exchangers reported are stannic (IV)silicomolybdate[15], stannic(IV)arsenosilicate[16], stannic(IV)iodophosphate[17], stannic(IV)molybdophosphate[18], stannic(IV)phospho-tungstate[19] and stannic(IV)arsenophosphate[20]. Trace element can be removed from water by a range of physicochemical method such as membrane filtration, precipitation and ion exchange[21].

The present work is concerned with the application of Tin (IV) vanadomolybdate ion exchanger the synthesized ion exchanger finds several applications in analytical chemistry. Ion exchanger process is applied in several cases for separation of Ions that interfere in many analytical procedures may be removed. Some important application of ion exchanger is binary separation of metal ions, water softening and removal of colour metal ions.

4.2 Requirements:

A. Glasswares: Burette converted into column, Funnel, Glasss wool, Burette stand, Chemical balance, Oven, Mangnetic stirrer, Pipette, Beaker, Glass rod, Test tube with Test tube stand. All glass ware that is used throughout the experimental work was Borosil mark.

B. Reagents and Chemicals: Sodium hydroxide, Lead nitrate, Bismuth nitrate and EDTA were Qualigens product. All the acid that is Perchloric acid Hydrochloric acid, Nitric acid were also Qualigens product. Chemicals such as Zinc acetate, Cobalt acetate, Copper acetate, Nickel acetate, Ammonium chloride were also used in the experimental work.

4.3 Experimental:

A. Distribution Behavior:

In order to examine the affinity of tin (IV) vanadomolybdate towards various metal ions, distribution coefficient (k_d) values for ten metal ions were determined by batch process[22-28]. In this process ten equal portions 0.50g each of the exchanger were treated separately with 25ml of 0.1M aqueous metal salt solutions. The mixtures were then kept for twenty-four hours at room temperature and subsequently determination of metal ions was done by titrating the solutions against the standard solution of EDTA (Complexometric Titration)[23] with the help of appropriate indicators. The k_d values as given in Table 4.1 were calculated according to the formula-

$$K_d = \frac{I - F}{F} \times \frac{V}{W}$$

Where, I – Initial volume of the EDTA solution used

F – Final volume of the EDTA solution used

V – Volume of the metal ion solution taken

W – Weight of the exchanger

Table 4.1: Distribution Coefficient for Different Metal Ions with TVM

Sr. No.	Metal ions	Form	K_d(ml/g)
1	Ca^{2+}	Carbonate	2.54
2	Mg^{2+}	Acetate	6.11
3	Zn^{2+}	Acetate	5.33
4	Cu^{2+}	Acetate	12.25
5	Mn^{2+}	Acetate	0.40
6	Co^{2+}	Acetate	0.20
7	Ni^{2+}	Ammonium sulphate	23.67
8	Pb^{2+}	Nitrate	5.09
9	Bi^{3+}	Nitrate	10.73
10	Cd^{2+}	Chloride	6.36

4.4 Separations Achieved:

The values of separation factor for different metal ion pairs obtained for the exchanger were greater than three and the values are obtained by using following formula.

$$\alpha_B^A = \frac{K_d\ Value\ of\ A}{K_d\ Value\ of\ B}$$

Where

α_B^A is separation factor

A. Binary Separation:

The ion exchanger Tin (IV) vanadomolybdatewas also employed for binary separations of Ni-Pb, Zn-Co, Ni-Co, Ni-Mn, Ni-Mg, Cu-Co Combination as indicated by the value of separation factors for these metalions pairs. In binary separations. 0.50g of the exchanger in H^+ form was packed in glass columns. The column was washed with demineralized water and then metal ion mixtures were poured in column separately. The absorbed metal ions were eluted with appropriate eluents one by one. The flow rate of the effluent was maintained at 1ml/min through the elution process. The effluents were collected separately in different conical flasks and metal ions concentration were determined (Complexometric Titration) against disodium EDTA salt solution using suitable indicators[24-28]. The results are summarized in Table 4.2.

Table 4.2: Binary Separation Achieved with The Help of Tin(IV)Vanadomolybdate

Sr. No.	Metal ion pairs	Amount loaded(μg)	Amount found(μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
1	Ni^{2+}	8217	8158	99.21	- 0.79	50ml	0.1M $HClO_4$
	Pb^{2+}	2279	2279	100	0.00	40ml	0.1M HNO_3
2	Zn^{2+}	1831	1766	96.45	- 3.55	40ml	0.2M $HClO_4$
	Co^{2+}	707.16	650.23	91.94	- 8.05	60ml	1.0M NH_4NO_3
3	Ni^{2+}	8217	8334	101.42	+1.42	40ml	0.001M HNO_3
	Co^{2+}	707.16	707.16	100	0.00	60ml	0.1M HNO_3 +0.5M NH_4OH
4	Ni^{2+}	8217	8275	100.71	+ 0.71	50ml	1.0M NH_4Cl + 0.1MHCl
	Mn^{2+}	1540	1428	92.72	- 7.27	30ml	

Sr. No.	Metal ion pairs	Amount loaded(μg)	Amount found(μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
							0.1M HCl
5	Ni^{2+}	8217	8099	98.56	- 1.44	80ml	1.0M HNO_3
	Mg^{2+}	1944	1871	96.24	- 3.76	70ml	0.4M NH_4NO_3
6	Cu^{2+}	2923	2796	95.65	- 4.35	50ml	0.2M HNO_3
	Co^{2+}	707.16	707	99.84	- 0.27	60ml	0.2M $HClO_4$

B. Water Softening:

Hardness causing $Ca^{2+}$and Mg^{2+}were also removed with help of Tin (IV) vanadomolybdate. Column operation was used for the removal of metal ions. The hardness of the water sample was determined by complex metric titration method, in which Eriochrome Black-T was used as an indicator. In water softening, definite volume of hard water sample was passed at rate of 10 drops per minutes through the column maintained the bed of ion exchanger in column. This process is repeated for three times. Hardness causing calcium and magnesium loaded in the column were eluents using 1M HNO_3 and 0.01M $HClO_4$ as eluents respectively. The elution rate was maintained at 5 drops per minute. The eluted Ca^{2+} and Mg^{2+} amount was determined by quantitatively with appropriate indicators. The results are shown in Table 4.3.

Table 4.3. Removal of Ca^{2+} and Mg^{2+} With the Help of TVM

Sr. No.	Metal ions	Amount loaded(μg)	Amount found (μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
1	Ca^{2+}	240.5	218	90.65	-9.35	50ml	1.0M HNO_3
2	Mg^{2+}	1775	1750	98.59	-1.41	50ml	0.01M $HClO_4$

C. Removel of Transition Metal Ions:

Application of the exchanger in removing the metal ions from different water samples was done using by Column method. The determination of Co^{2+}, $Ni^{2+}$and $Cu^{2+}$was done ascertain the amount of these ions in their aqueous solutions. The method of determination was done on the basis of two types. In qualitative determination, different definite volumes of the three solutions were loaded on the ion exchanger packed in three different columns.

The flow rate of ten drops per minutes was maintained the solution were passed three times through the exchanger. The effluents of the three columns were collected in three different containers. The presence of the metal ions in all the containers was confirmed by performing qualitative analysis as given in Table 4.4. All the qualitative test was found to be negative.

Table 4.4: Qualitative Tests for Transition Metal Ions for TVM

Sr. No	Metal ion	Colour of the salt solution before passing through exchanger	Colour of the salt solution after passing through exchanger	Detection of metal ion in the effluent
1	Ni(II)	Green	Colorless	a) Effluent NaOH Solution- No Precipitate Ni(II) absent b) Effluent Ammonia- No Precipitate Ni(II) absent
2	Co(II)	Pink	Colorless	Effluent + Sodium hydroxide Solution-No Precipitate Co(II) absent
3	Cu(II)	Blue	Colorless	a) Effluent NaOH Solution- No Precipitate Cu(II) absent b) Effluent Ammonia- No Precipitate Cu(II) absent

For quantitative determination of metal ions, suitable eluents were passed through all the columns containing loaded exchanger.

After elution process the amount of metal ions was determined by complex metric titration using suitable indicators. The results are shown in Table 4.5.

Table 4.5. Removal of Transition Metal Ions with The Help of TVM

Sr. No.	Metal ion	Amount loaded (μg)	Amount found (μg)	% of Metal ion eluted	% Error
1	Co^{2+}	707.16	665.45	94.10	-5.89
2	Ni^{2+}	8217	8092	98.48	-1.52

Sr. No.	Metal ion	Amount loaded (µg)	Amount found (µg)	% of Metal ion eluted	% Error
3	Cu^{2+}	2923	2798	95.72	-4.27

4.5 Result and Discussion:

The study of the values obtained for distribution coefficient revealed that the material shows high selectivity for Ni^{2+} and Cu^{2+} for which the k_d values were 23.67ml/g and 12.25ml/g respectively. The distribution coefficient for the metal ions (Table 1) follows the sequence-

$Ni^{2+} > Cu^{2+} > Bi^{3+} > Cd^{2+} > Mg^{2+} > Zn^{2+} > Pb^{2+} > Ca^{2+} > Mn^{2+} > Co^{2+}$

In binary Separation of different combinations were quite successful through ion exchanger. The exchanger removed different metal ions to different extent such as 650.23µg Co^{2+} was removed out of 707.16µg Co^{2+} while 8334µg Ni^{2+} was removed out of 8217µg Ni^{2+}. The removal is seen from 91.94% to 101.42%. In Ni –Pb separation, the difference between loaded amount and amount found show that lead is 100% eluted with 0% error and nickel is eluted to 99.21% with -0.79% error. The recovery ranges of nickel is present in all combination from 95-100% and the results are summarized in Table 2.

The synthesized ion exchanger Tin(IV)vanadomolybdate can removed Ca^{2+} and Mg^{2+} from hard water and it may helpful in water softening. The results for these ion exchanger implies that Mg^{2+} can be removed from hard water up to 98.59% and removed of Ca^{2+} is 90.65% and the results are shown in Table 3.

The role of the ion exchanger is found to be useful in decontamination of the chemicals. Detection of the metal ions are (qualitative analysis) made it possible decide the determination process. The results are shown in Table 4. Quantitative determination of metal ions in a sample helped in knowing the amount of metal ion present which in turn was helpful to decide the exchange process. The observation table clearly indicates that Tin (IV) vanadomolybdate was found to be able to decontaminate cobalt 94.10%, Nickel 98.48% and 95.72% Copper respectively. The results are shown in Table 5.

4.6 Conclusion:

In the present work the analytical applications are performed for Tin (IV) vanadomolybdate. The ion exchanger possesses selectivity for trace metals such as, Ni^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}, Co^{2+}. The ion exchanger is also employed for the binary separation of heavy metals present in aqueous media and also used as in water softening.

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5. Biomaterials: Review and Applications

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Abstract:

Since it has been around for almost 50 years, the science of developing biomaterials is not a recent one. The study of biomaterials is known as biomaterial science. It is a contentious field of study that has expanded consistently and dramatically throughout the duration of its existence, with various companies investing sizeable sums of money in the development of new products. Biomaterial science encompasses tissue engineering as well as biology, chemistry, and materials science.

Keywords:

Biomaterials, Review

5.1 Introduction:

A substance that has been altered for usage in a medical environment is essentially a biomaterial. When applied to a more interactive application, such as hydroxyapatite-coated hip implants (such as the Furlong Hip, manufactured by Joint Replacement Instrumentation Ltd. in Sheffield), biomaterials can be either benign or bioactive. One such instance is Sheffield, where such implants can endure up to twenty years. Additionally, biomaterials are regularly utilized in medical procedures, dentistry, and drug delivery.

Although it has been challenging to define the term "biomaterial," more commonly " working definitions that are recognized include: A biomaterial is any material, natural or man-made, that comprises whole or part of a living structure or biomedical device that performs, augments, or replaces a natural function."

A. Applications:

- Joint replacements
- Blood vessel prostheses
- Bone cement
- Bone plates
- Bone cement
- Artificial ligaments and tendons
- Dental implants for tooth fixation
- Contact lenses
- Cochlear implants

Here are the 2 examples.

first intraocular lens

Basic components: Silicone and PMMA (acrylic).


Combining long-term biocompatibility with optical performance is difficult.

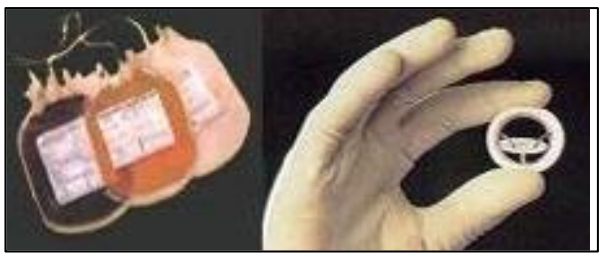



B. Artificial Hip Joints:

Stainless steel, titanium and its alloys, and UHMWPE are the basic materials. Prevention of wear and loosening over long durations (10–15 years) is a challenge.

C. Substitute Heart Valves:

D. Indian Chitra Heart Valve:



E. Vascular Grafts:

Dacron, Teflon, and polyurethane are the basic materials.

Maintenance of mechanical integrity and long-term blood compatibility are obstacles (avoidance of blood clotting).

The proximal load transfers for the human complete hip system shown below is provided by a titanium, dual tapered stem design, significantly lowering possibility of the calcar resorption and proximal hypertrophy Not a fool! System offers a straight stem design and an anatomic fit. Polyethylene serves the function of cartilage in this application. Biomet Corporation is the cited to learn more about hip replacement and the situations under which it is performed, visit the Medline Plus website (many great illustrations).

5.2 Some Commonly Used Biomaterials 2:

a. Silicone rubber
b. Dacron
c. Cellulose
d. Poly (methyl methacrylate)
e. Polyurethanes
f. Hydrogels

g. Stainless steel
h. titanium
i. Alumina
j. Hydroxyapatite
k. Collagen (reprocessed)

Applications:

- Catheters, tubing
- Vascular grafts
- Dialysis membrane
- Intraocular lenses, bone cement
- catheters, Pacemaker leads
- Opthalmological devices, Drug delivery
- Orthopedic devices, stents
- Orthopedic & Dental devices
- Orthopedic & Dental devices
- Orthopedic & Dental devices
- Ophthalmologic applications, wound dressings

A. Protein-Surface Interactions in Biomaterials:

The underlying cause of medical device biocompatibility—or lack thereof—is protein–surface interactions. Proteins quickly adsorb onto the surface of a solid substance that comes into contact with a fluid containing soluble proteins, like a catheter, stent, hip joint replacement, or tissue engineering substrate (such as blood, interstitial fluid, cell culture media). Within seconds to minutes, this saturation happens. Because of this, living cells actually make touch with the molecular structure of a biomaterial when they approach its surface. Living cells are larger than proteins and move more slowly adsorbed protein layer rather than the surface of the material itself. Of course, cells cannot "see" the layer of adsorbed proteins; instead, they probe their environment using membrane-bound receptors that can bind to specific bioactive features that the adsorbed proteins provide.

Following their binding, these receptor-protein interactions are then conveyed through the cell membrane via a number of carefully regulated molecular mechanisms in such a way as to excite particular intracellular activities that ultimately define the response of a cell. As a result, how bioactive locations differ offered by the protein layer that is absorbed is the most essential factor in determining cellular response.

The number, kind, and packing arrangement of proteins that are adsorbed as well as it is possible to control their packing, conformation, and direction on the biomaterial's surface. The emphasis will be on showcasing a few among the most fascinating relatively recent techniques that have been developed and applied to increase our comprehension of the sub molecular principles underpinning how surface chemistry impacts the orientation, conformation, and organisation of adsorbed proteins.

If we want to move past moving from the mostly trial-and-error-based surface design of the present to a future where surfaces are purposefully created to directly regulate adsorbed protein bioactivity, and hence govern cellular response, we must continue to develop our understanding of these processes. Though conceptually straightforward, the vast variety has been made possible—and continues to be made possible—by the complex structural features of soluble proteins found in physiological fluids. —a very difficult subject.

B. Computer Simulation of Protein Adsorption to a Material Surface in Aqueous Solution: Biomaterials Modeling of a Ternary System.

Because biomaterials frequently come into touch with the body or body fluids, crucial aspects like biocompatibility and bio reactivity are controlled by interfacial processes, particularly protein adsorption. A mechanistic understanding of the interactions the development of biotechnology tools like DNA/protein micro arrays and micro fluidic systems will also require the improvement of the interface between biological macromolecules and material surfaces. As a result, the atomistic characterization of structure function correlations at the interface between biological macromolecules and materials surfaces will be crucial for the development of a wide range of bioengineering and biotechnology applications in the future.

They used typical computer modelling software to simulate protein adsorption to a material surface in water. Bovine pancreatic trypsin inhibitor was used to model a multi-component system in which a hydrated protein was present (BPTI), comes into contact with a MgO surface in pure water, molecular dynamics and local minimization were used. In water and in living things, soluble proteins are known to bind to charged substance surfaces. In three distinct initial protein orientations, the simulations demonstrate the binding of BPTI with binding energies of 242, 350, and 241 kcal/mol to MgO in water. Our research shows that in this watery environment, there is hardly any interaction between the atoms of the protein and those of the surface. The solvation layer facilitates important surface binding mechanisms in the interphase (double-layer) area. Although this fact is often not explicitly taken into consideration in the protein adsorption literature, it is anticipated on the basis of traditional electrochemical theory.

C. Carbohydrate derived protein resistant biomaterial:

The Side-chain polyethers obtained from carbohydrates can be made using monomers made from naturally occurring carbohydrates to condensation polymerize. These substances are biodegradable, resistant to proteins, and allow for functionalization in places other than the chain ends. To accomplish desired protein resistance, biodegradability, and/or functionalization, the compounds of the present invention may be formed, at least in part, into various devices, apparatus, and manufactured goods.

D. Hard Tissue: Biomaterial Interactions:

Because bone and cartilage are prone to damage, biomaterials—artificial and modified natural materials—have been effectively employed for many years to replace and/or regenerate these tissues. Science has lately developed the idea of tissue engineering, which

combines the use of biomaterial-based scaffolding, cultured cells, systemic and/or local hormones/mediators, and, more recently, genetic modulators, to try to restore damaged tissues. Since many years ago, musculoskeletal illnesses and disorders have been treated extensively with tissue engineering products, which are essentially biomaterials of various shapes and forms. Currently, materials for replacing bone, cartilage, and joints include ceramics made of hydroxyapatite (HA), calcium phosphate, and polymers like polymethyl methacrylate, as well as metals like titanium, cobalt-chrome, and steel in pure and/or alloy form.

E. Modeling and Simulation of Biomaterials:

Simulation and modelling are being used more and more in materials research. The authors of this paper cover modelling and simulation applications in the emerging subject of biomaterials. The authors don't cover biochemical or biological applications in order to somewhat condense the subject; instead, they concentrate on the structure and characteristics of biomaterials. an explanation of how molecules and groupings of molecules can be studied using atomistic level simulation. After that, we concentrate on simulations of structure and behaviour at the mesoscale, followed by a brief discussion of continuum scale methods.

F. Nano Biomaterials:

Enzymes have been included in detergent recipes for a very long time to help combat particularly difficult filth. Chemical engineer Jonathan Dordick of Troy, New York's Rensselaer Polytechnic Institute is advancing the fight against dirt by employing nanotechnology to create a self-cleaning plastic in which the enzyme molecules are a fundamental component of the substance. The enzymes in the plastic attack bacteria and other pathogens when they come into touch with it, preventing them from adhering to its surface.

G. Bioengineering of Improved Biomaterials Coatings for Extracorporeal Circulation Requires Extended Observation of Blood Biomaterial Interaction under Flow.

Cardiopulmonary bypass systems are frequently hindered by the thrombus development and also infection after prolonged use. The CPB circuitry's insufficient hem compatibility is one cause of several of these issues. In biomaterials science, creating true long-term hem compatibility of biomaterial surfaces is largely unexplored territory. For instance, the bulk of studies evaluating the interactions between blood and biomaterials under flow using the well-known Chandler loop model have only been described for a maximum of two hours.

Two commercial CPB tubings with hem compatible coatings were thoroughly compared in this study with one uncoated control. Examining human whole blood from four separate donors while it was flowing for five hours, analyzing luminal surfaces with scanning electron microscopy, and timing the formation of thrombin were all part of the study. The research showed that the tubing's hem compatibility varied. Furthermore, it seemed that one could only tell one biomaterial covering from another after several hours of blood contact.

Platelet counting, myeloperoxidase quantification, and scanning electron microscopy were the most efficient methods. It is believed that these findings are relevant to the bioengineering of extracorporeal devices that are intended to work for lengthy periods of time in contact with blood.

H. Protein-Based Vascular Tissue Engineering Advances:

Vascular tissue engineering is driven by improved blood artery replacements are clinically necessary, especially for small-diameter applications. Although the blood vessel's form and function are well known, because it is a complicated tissue, it has been difficult to create engineered tissues that are suitable for widespread clinical application. This article discusses vascular tissue engineering techniques that use proteins as the primary matrix or "scaffold" material to create fully biological blood vessel substitutes.

This review specifically discusses the following four vascular tissue engineering methods: Protein hydrogels with cells, crosslinked decellularized natural tissues, self-assembled scaffolds, and protein scaffolds are the first four types of materials. These approaches' benefits and limitations are highlighted together with recent developments in each of these field.

I. Biomaterials: where we have been and where we are going:

The field of biomaterials has had sustained expansion with the steady introduction of fresh concepts and fruitful branches since its founding just over 50 years ago. This assessment outlines our progress to date, the current state of the art, and potential future developments. Here, they highlighted some of the most recent developments in biomaterials with the goal of regulating biological reactions and ultimately promoting healing. Biologically inspired materials that mimic natural processes, the creation of sophisticated three-dimensional (3D) architectures to provide clearly defined patterns for diagnostics, the synthesis of synthetic materials with regulated qualities for medication and cell carriers, and precision immobilization of signalling groups on surfaces are all included in this new generation of biomaterials.

J. Biomaterials for Blood Contacting Applications:

Biomaterials should be taken into account for applications involving blood contact while also considering blood-biomaterial interactions, blood response parameters, and evaluation techniques.

When analyzing blood-biomaterial interactions, factors such protein adsorption, platelet responses, intrinsic coagulation, fibrinolytic activity, erythrocytes, leukocytes, and complement activation can be taken into consideration. Blood response to a biomaterial in a therapeutic environment is influenced by the biomaterial's structure, the presence of an antithrombotic agent, the patient's condition as indicated by the disease and pharmacological therapy, and the particulars of the application. Ex vivo and in vitro procedures are important for biomaterial development, and there are choices for clinical, in vivo, ex vivo, and in vitro evaluation of biomaterials.

K. Biomaterials in Canada: The first four decades:

The 1960s saw the start of Canadian biomaterials research. Significant advancements in a wide range of fields, over the past 40 years, a variety of biomaterials have been developed, including dental, orthopedic, cardiovascular, neurological, and ophthalmic materials. Canadians have also been involved in the tissue engineering derivative industry. The federal and provincial governments provide the majority of the funding for the biomaterials laboratories that are now present at universities and other research institutions from coast to coast. Initiated in 1971, the Canadian Biomaterials Society has contributed significantly to the growth of the industry. In 1996, the Society hosted the Fifth World Biomaterials Congress in Toronto. An overview of Canadian researchers' work during the previous four decades is provided. The scientific field of biomaterials and tissue engineering is deemed to be mature and robust in Canada and is predicted to remain so in the future.

L. Future directions in biomaterials:

The field of medicine has greatly benefited from biomaterials. However, there are still several difficulties. This essay examines three pertinent topics with significant medical issues. First, drug delivery systems; important factors to take into account are interactions between pharmaceuticals and polymers, drug transformation, drug diffusion characteristics, and, if polymer degradation occurs, the products of polymer degradation through polymer matrices. New tailored polymers are also being developed for specialized applications including vaccination and pulsatile release. Second, how cells interact with polymers, including what happens to inert polymers, how to use polymers as templates for tissue regeneration, and how to investigate polymers that make cell transplantation easier. The third category is orthopedic biomaterials, which includes fundamental research on the behaviour of chondrocytes, osteocytes, and connective tissue-free interfaces as well as applied research using computer-aided design of biomaterials and the production of orthopedic biomaterial.

M. Smart Biomaterials Design for Tissue Engineering and Regenerative Medicine:

Tissue engineering (TE), a significant approach in regenerative medicine, has been an active area of scientific research for almost three decades. However, due in part to the small number of biomaterials that have been given human use approval, the clinical application of TE technology has been somewhat constrained.

Even though a lot of great biomaterials have been created recently, their implementation into clinical practice has been delayed. Since biodegradable polymers were initially licensed for use in humans over 30 years ago, many researchers still utilize them today.

N. Systematic Effects of Biomaterials:

The tissue reaction at the implant site is typically the main focus of analyzing the host's reaction to implanted biomaterials. Similar to how looking at battles out of their historical context can lead to incorrect judgements, this can also.

A larger perspective reveals a number of potential and actual systemic consequences of a bacteriological, immunological, metabolic, and carcinogenic character. The absence of epidemiological data makes it difficult to identify these impacts in patients.

O. Biomaterials and Biomedical Devices:

The variables crucial to the integration of biomaterials and technology into tissue are covered in this review. Surface modification approaches and surface-sensitive analytical techniques are mentioned. The effectiveness or biocompatibility of specific biomaterials and devices are assessed using in vitro procedures. There is discussion of current and future directions in dialysis, artificial organs, plasma and cytapheresis, artificial blood or bone substitutes, orthopaedic prostheses, dental materials, neural prostheses, and cardiovascular materials.

P. Biomaterials for Healthcare:

Animal-derived islets were encased in a device with a membrane composed of polycarbonate and a support. The encapsulation chamber was given an extracellular matrix to prevent the islets from congregating. By interconnecting 20 devices, it was possible to implant up to 20 000 pancreatic islets, as needed for testing on a mini-pig in a plate-type support. After up to 92 days following implantation, the biocompatibility of sterile macro devices was examined in normal mini-pigs. Despite the generation of fibrosis, the peripheral immune system did not significantly change or show any signs of an inflammatory response.

Q. Optimization Studies on the Features of an Activated Charcoal supported Unease System:

The enzymatic hydrolysis of urea has been made possible by the successful adsorption of urease onto activated charcoal derived from petroleum. The enzyme support system has been plasma polymerized to coat hexamethyl disiloxane, resulting in a biocompatible surface. Electronic Chemical analysis using spectroscopy and scanning electron microscopy methods were used to evaluate the effectiveness of the resultant coat. Studies on the urease's adsorption, activity, and stability on the support have been made in an effort to improve the properties of the urease supported by charcoal and increase its accessibility for usage in clinical applications.

R. Bioactive Specific Biomaterials: Present and Future:

In order to interact specifically with living systems, bioactive biomaterials are replaced with specific chemical functional groups carried by the macromolecular chain and made of synthetic or artificial polymers.

These polymers, which can be soluble or insoluble, are made from dextran and polystyrene. When these modified polymers come into contact with circulating blood, they have low thrombogenicity because they may be endowed with anticoagulant heparin-like characteristics. It has been specifically designed for other functional polymers to interact with immune system elements.

Other polymers can influence cell development and biological activity or only biological activity when in contact with cells, without necessarily changing all of the features of the cells. From the aforementioned ideas, it is conceivable to show that the biological features of these polymers correlate with a statistically random chemical group distribution along the macromolecular backbone.

S. Macromolecular Engineering of Fluorinated Polymers and Hybrid Composites for Dental Resoration Application:

Investigated were novel polymeric materials that shrink less during polymerization and have low surface energy. New fluorinated ring-opening monomers were synthesised in order to produce the requisite polymers and composite resins. Different polymeric and co-polymeric systems' properties, including reactivity, chemical composition, thermal behaviour, and surface features, were thoroughly investigated. Even at comparatively low fluorinated chain side group concentrations, the ordering of the fluorinated groups caused the polymers to form liquid crystalline mesophases. Surface studies showed the existence of uniform, well-ordered surfaces with low surface tension due to the fluorine enrichment of the air-polymer interface. Fluorinated ring-opening monomers and crosslinkers were used to create dental composite resins. The function of the components in the resin formulations was evaluated in terms of bacterial adhesion, surface topography and composition, and mechanical properties. Without appreciably changing the mechanical properties, the introduction of fluorinated groups resulted in a significant decrease in volume shrinkage. There was a suggested relationship topography, surface energy, and fluorine surface segregation.

T. Toward A Suture Less Vasovasostomy: Use of Biomaterials and Surgical Sealants in A Rodent Vasovasostomy Model:

Vasectomy reversal has become a routine treatment with an annual reversal rate of 3% to 8% and 500,000 to 800,000 vasectomies performed. The gold standard for surgical vas reconstruction is still a two-layer microsurgical vasovasostomy. The process is time-consuming and technically difficult. They discovered how biomaterials and surgical sealants might cut down on the amount of sutures needed, improve the water tightness of anastomoses, and shorten operating times.

5.3 Conclusion:

A substance that has been altered for usage in a medical environment is essentially a biomaterial. Biomaterials may be bioactive or serve a benign purpose, such as in the construction of a heart valve such as hydroxyapatite-coated hip implants, which last up to twenty years and are used for more interactive purposes.

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6. Supramolecular Chemistry, Types of Supramolecular Systems and Its Applications

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6.1 Supramolecular Chemistry:

Supramolecular chemistry, also known as "chemistry beyond the molecule", is a fast-expanding discipline concerned with the chemical interactions of molecules. Recent years have seen a substantial increase in interest in this topic as a result of the possibility of developing novel materials and systems with distinct functions. In this chapter, we will discuss the fundamental concepts of supramolecular chemistry, recent trends and advancements in the field, and potential future applications. Supramolecular chemistry is fundamentally concerned with the interactions between molecules that take place via non-covalent interactions [1], such as hydrogen bonding, metal coordination, hydrophobic interactions, etc., [2]. Through their interactions, molecules can create intricate structures known as supramolecular assemblies, which can exhibit their unique properties. And behavior is different from those of the individual molecules.

One of the main goals of supramolecular chemistry is to design and synthesize molecules that can self-assemble into well-defined structures. These structures can have a wide range of functions, such as the ability to store and release energy, conduct electricity, or act as catalysts. [3] Supramolecular chemistry has several important applications in various fields such as medicine, materials science, nanotechnology, etc.

In medicine, supramolecular systems can be used for targeted drug delivery, as the self-assembling nature of these systems allows for specific targeting of diseased cells. In materials science, supramolecular systems can be used to create new materials with improved mechanical and thermal properties. In nanotechnology, supramolecular systems can be used to create nanoscale devices with a range of applications. [4]

In recent days, supramolecular chemistry is focused on the development of new materials and devices with improved properties and also the development of new synthetic methods and characterization of supramolecular systems. In addition, the development of new theories and models can easily understand their behaviour in the application of these systems in real-world problems, due to the numerous applications and the potential for further discovery, supramolecular chemistry remains a rapidly growing and exciting field.

6.2 Mechanically Interlocked Molecules (Mims):

Mechanically interlocked molecules (MIMs) are a class of supramolecular compounds that are held together by non-covalent interactions, such as hydrogen bonding, electrostatic interactions, and van der Waals forces [5]. There are several different types of MIMs, each with its own unique properties and potential applications. Some of the most well-known types of MIMs are discussed in this chapter.

A. Rotaxanes:

Rotaxanes are a class of molecular structures that consist of a macrocycle, or large ring, that surrounds a smaller and linear component called an axle. The axle is able to move within the macrocycle but it is prevented from completely escaping from the macrocycle due to the presence of one or more stoppers, like bulky groups, that are attached to the axle. This unique mechanical bond between the macrocycle and the axle makes rotaxanes an attractive subject for research in the field of supramolecular chemistry. The structure of rotaxanes resembles A dumbbell-shaped molecule with a ring trapped between its two ends.

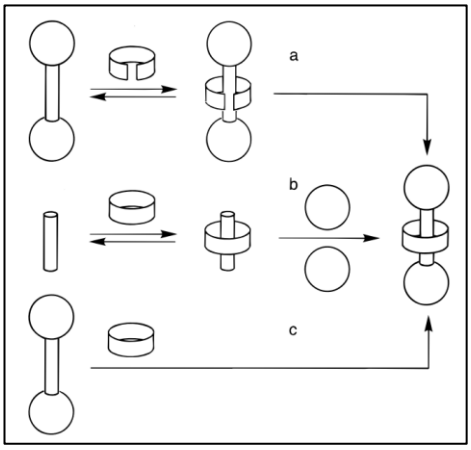

Figure 6.1: Three different approaches to the construction of rotaxanes: (a) "clipping"; (b) "threading"; (c) "slippage" [5].

Rotaxanes have been shown to have potential applications such as drug delivery [6], chemical and biological sensors [7], and data storage [8] due to their ability to undergo dynamic changes in conformation and responsive behavior to external triggers. Furthermore, rotaxanes also have the potential for use in molecular machines and devices as their mechanical bond allows for rotational motion and/or translation of the axle [9].

B. Catenanes:

Catenanes are a class of molecular structures in which two or more interlocked macrocycles are connected in a "chain" formation. They are similar to rotaxanes, but with multiple macrocycles linked together. Catenanes are named based on the number of interlocked rings, e.g. a [2] catenane consists of two interlocked rings (Figure 6.2). The "ane" ending of the term is a reference to alkanes, and catenanes are typically considered to be organic compounds, although they may not always consist of hydrocarbon groups. In situations where the interlocked ring system can act as a ligand for a metal centre, the terms [n] catenand and [n] catenate may also be used, in analogy with the terms cryptand and cryptate. The term "catenand" refers to the free ligand that forms a catenate complex in the presence of metal ions [10].

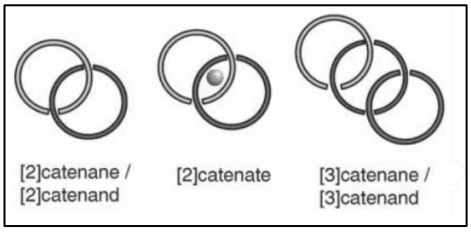

Figure 6.2: Nomenclature and schematic representation of Catenanes [10].

The synthesis of catenanes can be challenging, but various methods have been developed, including template-directed synthesis, mechanically interlocked synthesis, and chemical synthesis [11]. Catenanes have potential applications in fields such as molecular electronics, drug delivery, and as molecular machines. Their unique properties, including their ability to perform mechanical movements in response to external inputs, can be utilized for switching and sensing purposes. They have also been explored as molecular shuttles, molecular switches, and artificial muscles [12].

C. Clathrates:

Clathrates are a class of molecular structures in which a host molecule encapsulates or "traps" a guest molecule inside a cage-like structure. The host molecule forms the walls of the cage, and the guest molecule is held inside by non-covalent interactions such as hydrogen bonding or van der Waals forces.

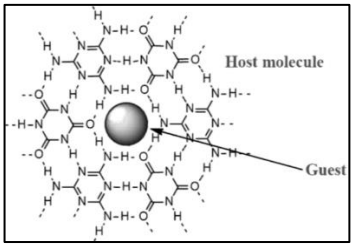

Figure 6.3: Schematic representation of Clathrates

Clathrates have been found in various forms of matter such as gases, liquids, and solids. In the field of chemistry, clathrate hydrates are known for their ability to trap gases such as methane and carbon dioxide, making them of interest for natural gas storage and carbon capture [13]. They also have potential applications in various fields such as drug delivery, catalysis [14], storage of gases like natural gas, hydrogen, and others in solid form, treatment of wastewater and concentration of organic mixtures, as well as separations and storage of gas mixtures. Clathrates are a topic of ongoing research, and the full potential of these structures is yet to be fully understood and harnessed. Further research is needed to develop new synthetic methods and to better understand the properties of these complex structures.

D. Cavitands:

Cavitands are a class of molecular structures that are characterized by a "cavity" or a hollow interior space. These cavities are formed by the arrangement of atoms or chemical groups in a specific way, and they can be either hydrophobic or hydrophilic in nature, which has potential applications in various fields like molecular sensors [15], catalysis, drug delivery, and separation science. In separation and purification, cavitands can be used to sort and isolate specific molecules, such as proteins and enzymes, based on their size and shape. They have also been explored as scaffolds for the formation of supramolecular assemblies, and in the field of host-guest chemistry as receptors for specific molecules [16].

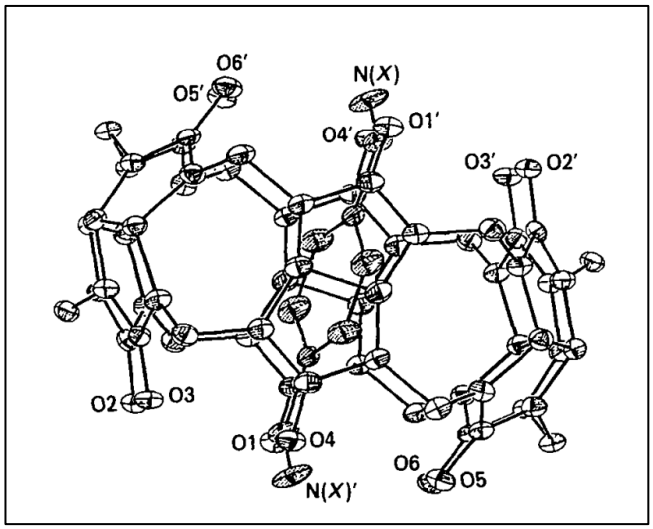

Figure 6.4: A cavitand (cucurbituril) bound with a guest p-xylylenediammonium [16].

F. Cryptands:

Cryptands are a class of molecular structures that have found significant application in the field of supramolecular chemistry. They are characterized by a "crypt" or a hollow cavity that can selectively bind or "capture" specific guest molecules within it. The structure of cryptands is composed of a macrocyclic ring with a number of binding sites that can interact

with specific guest molecules via non-covalent interactions viz., hydrogen bonding or electrostatic interactions. In supramolecular chemistry, cryptands have been used to form various types of assemblies, including host-guest complexes, supramolecular polymers, and supramolecular gels. They have also been explored as receptors for specific molecules, such as small ions or metal ions [17].

Cryptands have numerous applications in a variety of fields such as chemistry, biochemistry, materials science, etc. Their ability to selectively bind specific guest molecules makes them attractive for use in chemical separations, and the formation of supramolecular assemblies can be used to create new materials with specific properties. These molecules are valued for their high selectivity and specificity in recognizing cations, anions, neutral molecules, and even isotopes. They play a crucial role in ion transportation studies and are used as stationary phases in column chromatography for separating cations, anions, and isotopes. In addition, they are utilized in the study of redox systems, photo physical properties, non-linear optics, amphiphiles, sol-gel materials doping, and as structural directing agents in synthesis [18].

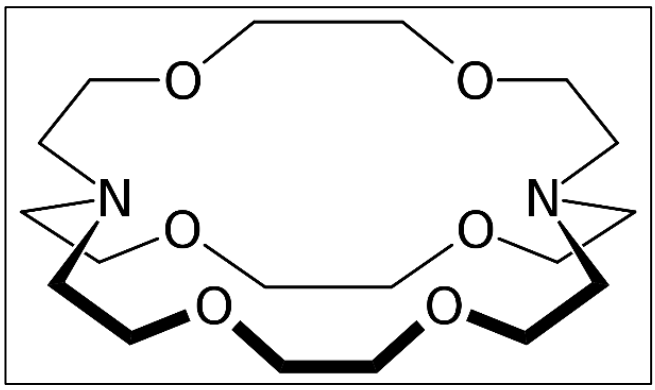

Figure 6.5: Structure of [2.2.2] Cryptand

6.3 Molecular Self-Assembly:

Molecular self-assembly is a fundamental concept in supramolecular chemistry that refers to the process by which individual molecules come together to form ordered structures without any external inputs. This process is driven by non-covalent interactions such as hydrogen bonding, electrostatic interactions, and van der Waals forces. Self-assembly has been used to create a wide range of structures including, but not limited to, vesicles, fibers, gels, and even more complex supramolecular systems [19]. The ability to manipulate and control the self-assembly process is of great interest in supramolecular chemistry, as it allows the creation of new materials with specific properties [20]. Self-assembly can be directed by various strategies such as the use of pre-designed templates or by controlling the chemical composition and stoichiometry of the system. The utilization of self-assembling peptides, small molecules, and lipids is also gaining recognition as a flexible approach to creating new materials with specific characteristics [21]. Molecular self-assembly is an active area of research in supramolecular chemistry and has potential applications in fields such as materials science, nanotechnology, biotechnology, etc.

A. Micelles:

Micelles are a form of supramolecular structures that are composed of a core of hydrophobic units surrounded by a shell of hydrophilic groups. They form spontaneously in water-based solutions and are stabilized by non-covalent interactions such as hydrogen bonding and van der Waals forces. Micelles are of great interest in supramolecular chemistry due to their ability to encapsulate hydrophobic molecules and act as a carrier for drugs and other hydrophobic molecules, allowing for targeted drug delivery and improved bioavailability [22].

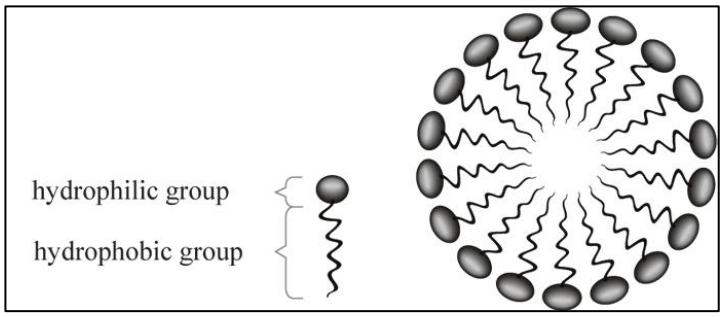

Figure 6.6: Schematic Structure of Micelle

Micelles have a wide range of applications due to their unique properties. Including, drug delivery, biomedical imaging, environmental remediation, cosmetics, etc [23].

B. Lipids:

Lipids are a class of biomolecules that play an important role in supramolecular chemistry. They are composed of a hydrophobic tail and a hydrophilic head, which allows them to spontaneously form structures such as vesicles, bilayers, and micelles in aqueous environments. These structures, known as lipid assemblies, have unique properties that make them of great interest in various fields, including cosmetic and food industries, and in nanotechnology [24]. Lipid assemblies have been used as a model for cell membranes and have been explored as a carrier for drugs and other hydrophobic molecules in targeted drug delivery [25].

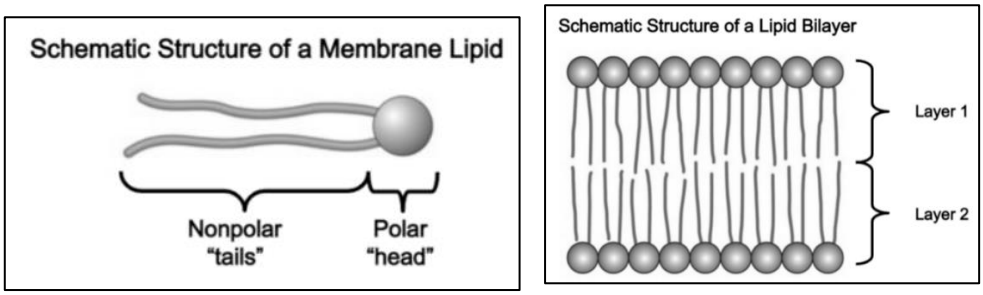

Figure 6.7: Schematic Structure of Lipids

Lipid assemblies have also been explored as a scaffold for the formation of supramolecular assemblies, and as a tool to understand the principles of self-assembly.

C. Liposomes:

Liposomes are a type of supramolecular structure that is composed of a phospholipid bilayer enclosing an aqueous compartment [26]. They are stabilized by non-covalent interactions such as hydrogen bonding and van der Waals forces. Liposomes have been used as a carrier for drugs, allowing for targeted drug delivery and improved bioavailability. Additionally, they have been explored as a means of gene therapy and as a tool for delivering drugs to specific cells or tissues [27].

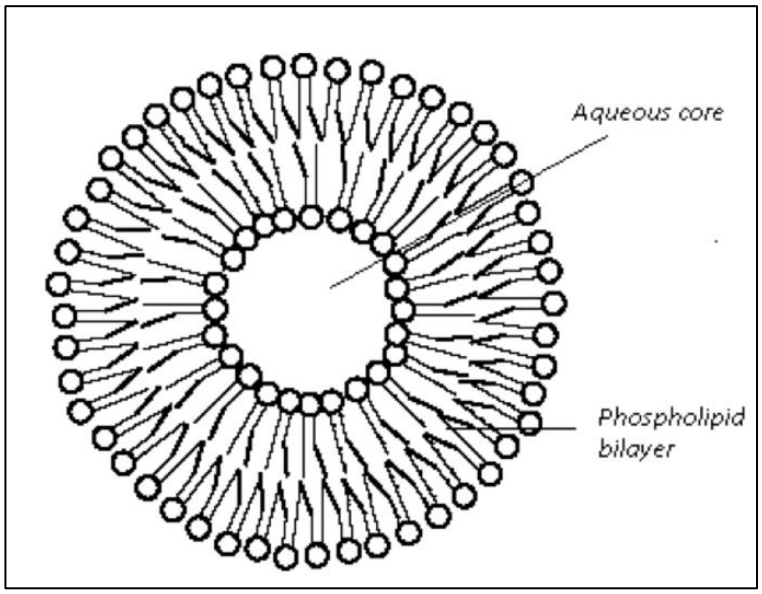

Figure 6.8: Schematic Representation of A Liposome

Liposomes have been used to create new materials with specific properties, such as liposome-based membranes for separation and filtration. Liposomes have also been found to be useful in the field of 'sensing', as they are able to encapsulate and detect specific molecules [28]. In addition, it is also useful in various fields like healthcare, cosmetics, medical imaging techniques, and the agricultural industry.

6.4 Molecular Recognition (Host-Guest Chemistry):

Molecular recognition is the specific interaction between more than two molecules via non-covalent interactions such as hydrogen bonding, metal coordination, hydrophobic forces, Van der Waals forces, pi-pi interactions, electrostatic, and electromagnetic effects. The molecule that receives an incoming entity is referred to as a host molecule, while the incoming entity itself is known as a guest molecule. The main concept of molecular recognition is lock and key. In this model, the host molecule makes interaction with a guest molecule or ion.

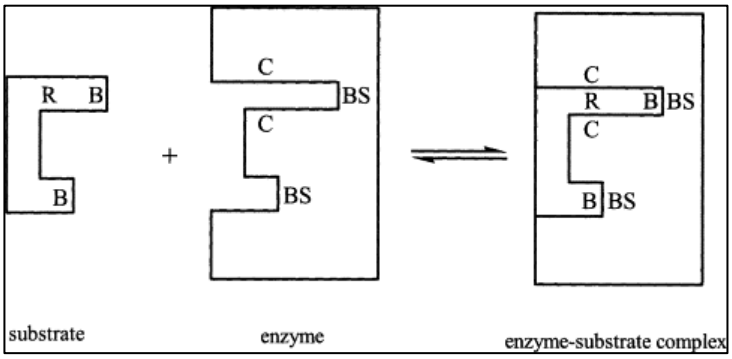

Figure 6.9: Lock and Key Model

Host + Guest= Host Guest Complex; Host = Enzyme; Guest = Substrate

In this complex, the host molecule is bigger in size and also has hollow nature than the guest molecule. Such kinds of interactions are mainly known as the bio-recognition process. Eg., enzyme–inhibitor, antigen-antibody, and DNA- protein interaction.

A. Crown ether:

Crown ethers are the first class of artificial host cyclic compounds which consist of ring groups containing ether (R-O-R). The most common crown ethers are oligomers and ethylene oxide. E.g.; 18-crown-6

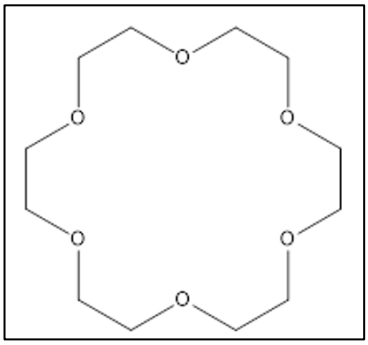

Figure 6.10: Structure Of 18-Crown-6

In the crown ether, the number used in the first is referred to as the number of atoms in the system and the last one says the number of oxygen atoms present in that system. Crown ethers are strongly bound to form complexes with metal ions based on the size of the atom. Crown ethers are soluble in nonpolar solvents because of their hydrophobic character which is mainly useful in phase transfer catalysis [29].

The modification of crown ethers, based on their number of the atom to giving various crown ethers by attaching some functional groups to the edges of the crown ethers, which enrich them with some interesting properties and made them ideal candidates for the fabrication of supramolecular polymers [30].

B. Cyclodextrin:

Cyclodextrin is a naturally occurring cyclic host molecule, which is a family of oligosaccharides of a macrocyclic ring of the glucose subunits joined by 1,4 glycidic bonds constituted by 6-8 glucopyranoside units. Which is prepared by the treatment of starch materials with enzymes. The CD has the molecular recognition capacity, and also enhanced their properties through chemical modification by introducing the –OH groups on the exterior rims. β-CD derivatives are widely used as greener textile auxiliaries for potential applications in the textile industry [31]. E.g.; β cyclodextrin

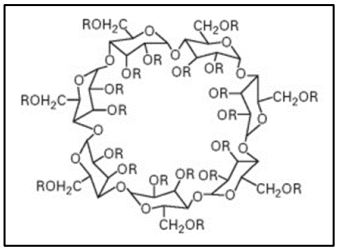

Figure 6.11: Structure Of B Cyclodextrin.

Cyclodextrin sponges are a microporous newly cross-linked 3D network of cyclodextrin that was designed as novel delivery for the lipophilic or hydrophilic active agents. Cyclodextrin's hydrophobic outer cavity and hydrophilic inner cavity enable their ability of novel delivery. Cyclodextrin possesses various applications like they are versatile absorbent for volatile organic compounds abatement [32].

C. Polyamine:

Replacing an oxygen atom in the crown ethers by nitrogen atom-induced cyclic hosts are called macrocyclic polyamines, many synthetic polyamines feature NCH_2CH_2N linkages which contain more than two amino groups most of the alkyl polyamines are natural and some of them are synthesized by the laboratory. Several synthetic polyamines are used in the chemical industry and the research laboratory. They are mainly used as additives to motor oil and as co-reactants (cold hardeners) with epoxy resins. E.g.; Cyclen

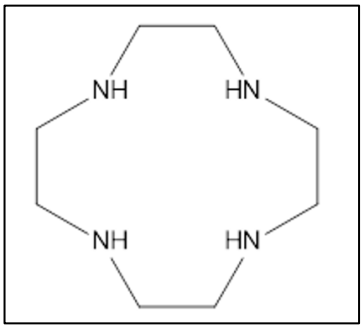

Figure 6.12: Structure Of Cyclen

Polyamines are possible therapeutic agents in biological disorders such as cancer and parasite diseases. They also act as ion–exchange blockers or vectors in gene delivery.

D. Calixarene:

Calixarenes are made from phenol units, which are attached by methylene bridges known as calixarene, and can have different cavity sizes. Each of these has conformation isomers, and the phenolic hydroxyl group is constantly modified. This type of character possesses to made calixarene derivatives with various structural modifications.

This isomeric host has different selectivity in metal ion inclusion in the upper cavity and the lower cavity. The number of phenol inclusion in the calixarene alters the guest molecule size appropriate for effective inclusion.

Calixarenes has attention in the treatment of cancer, it is mainly useful in delivery systems because of its biocompatibility and non-cytotoxicity [33]. And also used in the field of host-guest chemistry and sensing of metal ions.

E. Cyclophane:

Cyclophanes are three-dimensional cyclic hosts made from the linking of aromatic rings between aliphatic units. Cyclophanes are classified as follows, [n] orthocyclophane,[n] metacyclophane,[n] paracyclophane.

The aromatic ring in the cyclophane system is maybe either heterocyclic or carbocyclic. Cyclophane core unit is in many biologically active molecules and is also used in pharmaceutical catalysis [34]. Figure; [6.12**]** paracyclophane

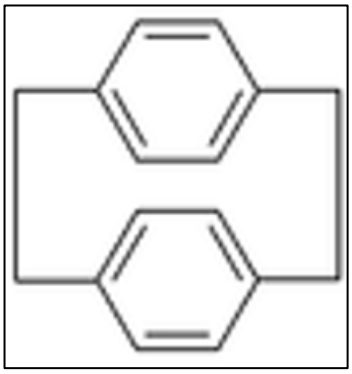

Figure 6.13: Structure of Paracyclophane

The small cyclophanes are the model for the fundamental studies of strain and aromaticity. The short bridges in cyclophanes give free rotations of the ring, and this takes place to thermodynamically disfavoured rotation to each other. This is not in open-chain molecules. This cyclic core was twisted because of the strain on the whole system. This kind of strain only acquires natural cyclophanes, not artificial ones [35].

6.5 Molecular Tree:

A. Dendrimers:

Dendrimers are tree-like macromolecules, which consist of core, branching, and surface units. It is in nanometres to tens of nanometers in size, which is larger than a typically closed molecule (diameter,0.7nm) and smaller than a microsphere(diamatere0.1-10μm). In dendrimers, if we increase the branching units, which will increase the dendrimer generation from zeroth to first, second, and so on.

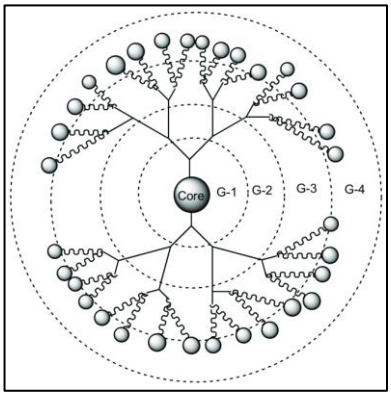

Figure 6.14: Schematic Representation of A Dendrimer Structure [36].

Dendrimers have been widely studied for their potential applications in drug delivery [63], where they can be utilized to transport therapeutic agents directly to diseased cells or tissues. In addition, they have been investigated for their use as imaging agents for diagnosing diseases, as well as in tissue engineering and regenerative medicine, where they can be utilized to deliver growth factors to promote tissue regeneration. Dendrimers have also shown promise as carriers for gene therapy, where they can be used to deliver genes to specific cells, thereby modifying their functions. These and other applications highlight the versatility and potential of dendrimers in the fields of medicine and biology [37].

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7. Recent Updates on Methyl Fluorosulfonyl Difluoroacetate Mediated Synthesis of Trifluoromethylated Molecules

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Abstract:

Organofluorine compounds have been widely used in pharmaceutical and agrochemical field. Triflurorомethylated compounds particularly show extensive applications in field of life sciences and material sciences. The trifluoromethyl group is used in biologically important molecules due to its enhanced anti-oxidant ability, improved metabolic stability and increased lipophilicity of the compound. MFSI, which was first reported by Chen and Wu in 1989 is used as an efficient, safe, resistant to moisture absorption and economical reagent for trifluoromethylation in synthesizing variety of trifluoromethyl containing heterocycles having great significance in drugs and many bioactive molecules. Contrary to its widespread applications, this reagent has not been exploited much and thus a comprehensive review of MFSI mediated trifluoromethylations is reported here, which we believe will provide further exposure to the chemists about this underutilized reagent.

Keywords:

7.1 Introduction:

In current years, a huge variety of applications[1-5] have been steadily developed in the sphere of organofluorine chemistry. Amongst the fluorinated compounds, trifluoromethyl-substituted molecules have created significant interest. The trifluoromethyl group is most attractive moiety and mostly used in pharmaceutical[6-8]and agrochemical industries.[9-13]

There are many CF_3 containing drugs available in market [14-21] (Figure 7.1). It is used in biological applications because of its high electron withdrawing ability, increased anti-oxidant ability, enhanced metabolic stability and increased lipophilicity of the target molecule.[22-25] The trifluoromethyl group can promote the drug efficacy by enhancing electrostatic interactions with targets, elevate cellular permeability and amplify the power towards oxidative metabolism of drug.[5,26,27]

Trifluoromethyl group is also widely used in dye industries in which trifluoromethylation of chromophore prevents from fading when exposed to light.[28,29] Trifluoromethylated polymers have upgraded chemical and thermal stability, better solubility and improved mechanical properties.[30] It has applications in developing batteries and cells.[31-33]

Ritter et al[34] proposed that if more complex trifluoromethylated compound is needed it is easier to start with simple molecule containing trifluoromethyl moiety and then build structure around it. Nagib et al[35] proposed the direct trifluoromethylation of arenes and heteroarenes by C-H activation through photo redox catalysis.

There are various reagents, which are used for trifluoromethylation. Rupert−Prakash reagent, CF_3SiMe_3 (trifluoromethyl) trimethylsilane is used for trifluoromethylation of heteroarenes and highly electron deficient arenes.[36] For trifluoromethylation of arenes and heteroarenes, trifluoromethanesulfonyl chloride (CF_3SO_2Cl) is also used[35].

Moreover, $PhSOCF_3$ and $PhSO_2CF_3$ are used as a source of trifluoromethyl anions.[37-39] Alkynyl triflones[40,41], Togni's reagent[42] and many more reagents (Sulfides[43,44], Sulfoximines[45], Sulfonium Salts[46], Sulfinate Salts, Sulfonyl Halides[47-49]) were evolved for the trifluoromethylation in different substrates.[50]

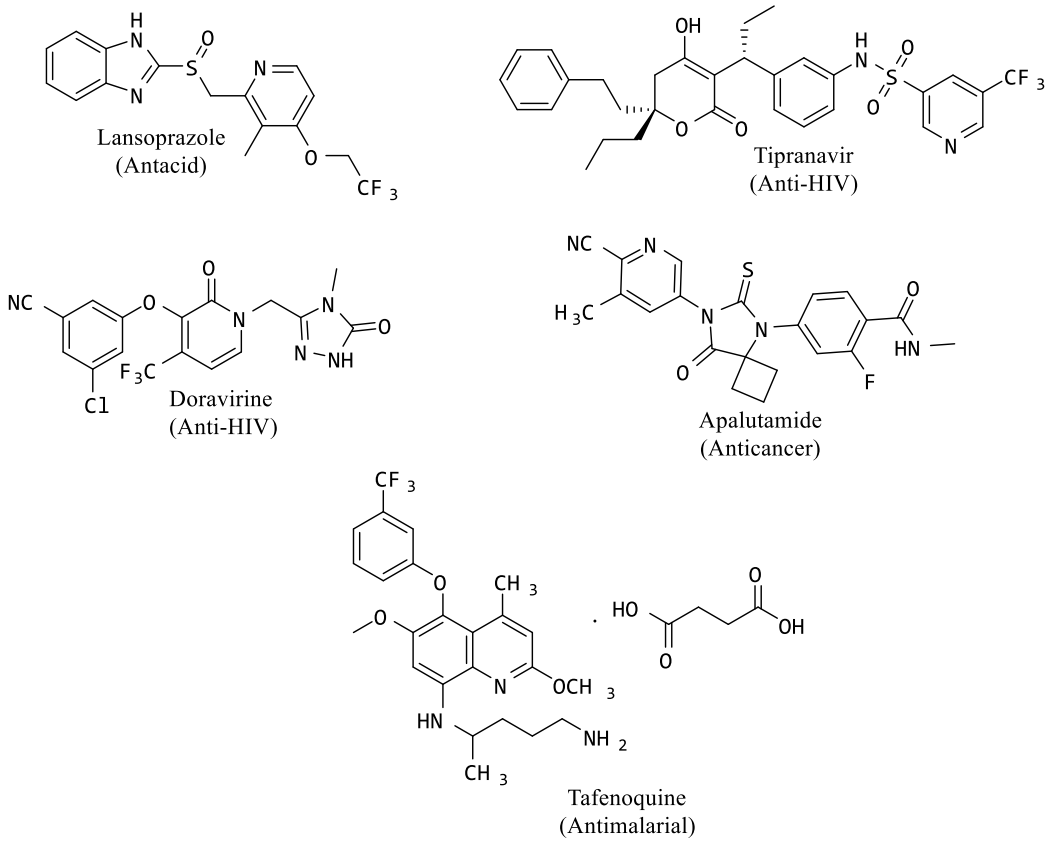


Figure 7.1: CF_3 Containing Drugs

In this chapter, we particularly emphasize on economical and widely used methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSDA or MFSI), reagent. We have focused here on summarizing the literature reports involving the synthetic transformations brought about by MFSI in the last one decade.

7.2 Discovery of trifluoromethylating reagent: Methyl fluorosulfonyldifluoroacetate (MFSI):

Methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSI) reagent also known as Chen's reagent and was first reported by Chen and Wu in 1989[51] as a trifluoromethylating reagent. It has CAS No. 680-15-9 and b.p. 116–118°C.

It is comparatively economical, safe and convenient to use and resistant to moisture absorption.[52] A number of methods have been developed for the trifluoromethylation of different substrates.[53-56] MFSI is used for the synthesis of a wide variety of trifluoromethyl containing heterocycles that is of greater significance in synthesizing drugs and making many bioactive molecules. MFSI is commercially to be held and purchased from the chemical industries but it can also be prepared within the laboratories by using diverse techniques. For example, MFSI can be synthesised *via* reacting 3,3,4,4-tetrafluoro[1,2]oxathiethane-2,2-dioxide with sodium methoxide[57], in two steps from difluoro(fluorosulfonyl)acetic acid[58] or by the addition of methanol to trimethylsilyl fluorosulfonyldifluoroacetate.[59] Finally, the reaction of tetrafluoroethylene with sulfur trioxide gives a useful cyclic compound tetrafluoroethylene β-sulfone.[60,61] Successive reaction with methanol affords MFSI in 85% yield.[62]

MFSI displays the nucleophilic trifluoromethylation reaction and used for trifluoromethylation of aryl halides, alkyl halides and alkenyl halides for diverse copper mediated reactions. Chen and Wu showed the order of reactivity of halide to be RI>RBr>RCl where the bromo derivatives being more useful and the chloro derivatives is quite slow. Presence of CuI is crucial for the success of reaction. KI can also be used as an alternative of CuI.[9]

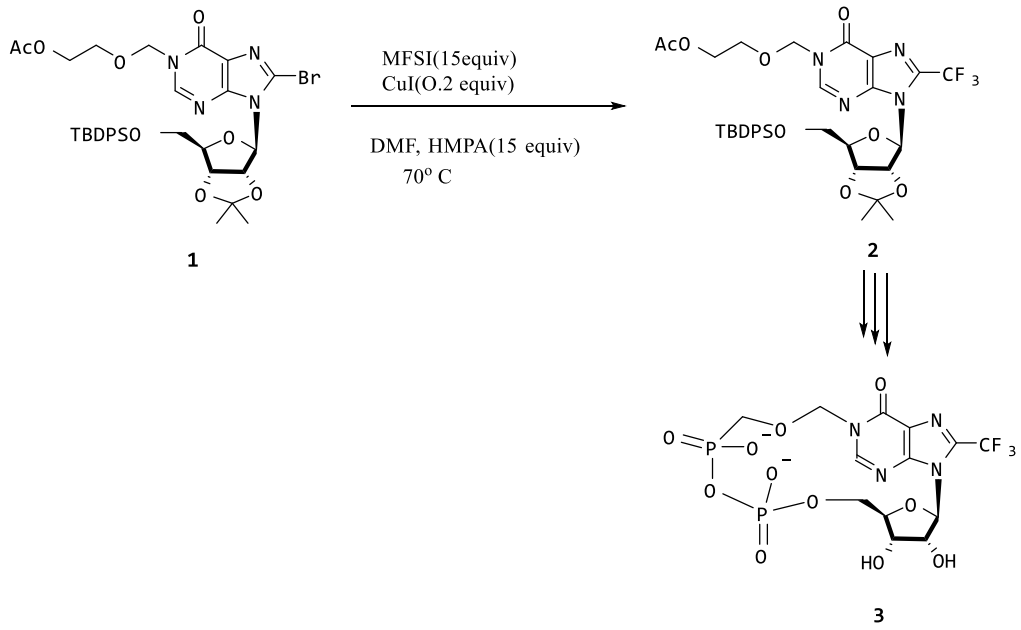
Scope of Methyl Fluorosulfonyldifluoroacetate in Trifluoromethylation reactions

MFSI has been reported in various organic transformations from last so many years and a summary of those reports is being summarised here starting from the year 2010. The triazolylpyridine system are not found in nature in free form but its trifluoromethylated derivatives shows many biological properties like insecticides, antibacterial activity[63], anti-proliferative activity against tumour[64], more cell permeability[65] and many more biological activity[66-70]. Dong et al[71] reported the synthesis of 8- CF_3-cIDPRE **3** (N1 - [(5"-O-Phosphorylethoxy) methyl] -5'-O-phosphoryl -8 - tri-fluoromethylinosine 5", 5"-Cyclic pyrophosphates.

8-CF_3-cIDPRE is agonist and mimics the cADPR (cyclic adenosine 5'-diphosphoribose). 8-CF_3-cIDPRE penetrate the plasma membrane and releases Ca^{2+} which is required in variety of cellular process. Fluorine has strong electron withdrawing property and ability to form hydrogen bonding, it shows metabolic stability and membrane permeability. In this, there is introduction of trifluoromethyl group at 8- position of purine nucleoside, which is important intermediate for synthesis of 8- CF_3-cIDPRE **3**.

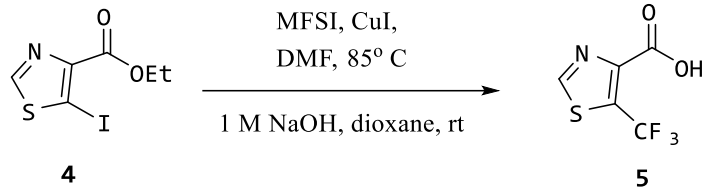
Huang et al[72] also reported the synthesis of trifluoromethylated analogues of cADPR using MFSI. In this, MFSI is used for trifluoromethylation of bromo derivative *viz N*1-[(5``-

Acetoxyethoxy) methyl]-5`- O-TBDPS-2`,3`-O-isopropylidene-8-bromoinosine **1** in the presence of CuI in DMF, HMPA and reaction was stirred for 12hrs at 70° C to form *N*1-[(5``-Acetoxyethoxy) methyl]-5`-O-TBDPS-2`,3`-O-isopropylidene-8-trifluoromethyl inosine **2,** which is an important intermediate and further undergo reaction for synthesis of 8-CF_3-cIDPRE **3** (Scheme 7.1).



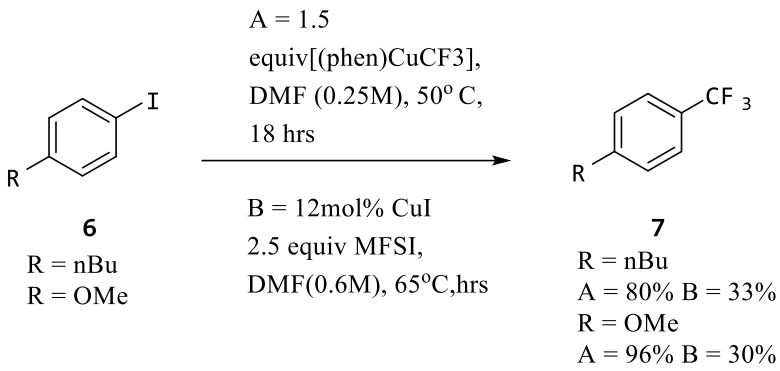
Scheme 7.1: Trifluoromethylation of cyclic adenosine diphosphate ribose.

Hodgetss and his coworker[73] reported that MFSI is used to introduce trifluoromethyl group in thiazole ring **4** to obtain trifluoromethylated product **5**, which is a bioactive molecule. (Scheme 7.2)



Scheme 7.2: Trifluoromethylation of thiazole ring

Boechat et al[74] reported the synthesis of trifluoromethylated derivatives of 1*H*-1,2,4-triazol-3-yl benzenesulfonamide to develop new antimalarial lead compounds with 50%-62% yield. Morimoto et al[75] reported the use of MFSI in copper iodide mediated reactions for the trifluoromethylation of aryl iodides **6** and bromides. The yields of trifluoromethylarene products **7**, which was determined by ^{19}F NMR analysis using 4-$CF_3OC_6H_4OMe$ as internal standard, were much higher (above 80%) under the reaction conditions with 1.5 equiv phen-ligated 1 than with catalytic CuI and 2.5 equiv. $FSO_2CF_2CO_2Me$. (Scheme 7.3).

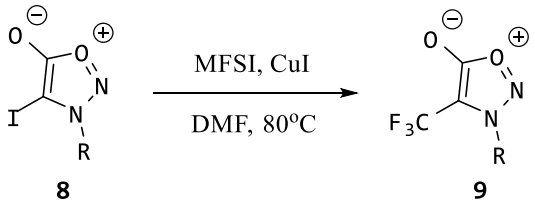


Schemes 7.3: Trifluoromethylation of aryl iodides

Foster et al[76] designed more efficient policy for trifluoromethylation of pyrazoles using MFSI. He reported the trifluoromethylation of 4-iodosyndones **8** to synthesize bioactive 5-trifluoromethylpyrazoles **9** with good yield in the presence of MFSI, CuI and DMF, which was further used as an intermediate to synthesize herbicide fluazolate.

He suggested that when the reaction was accomplished with 4-iodo-*N*-phenylsyndone, the yield of trifluoromethylated product is 79%. When electron-donating substituent like p-methoxyphenyl group is present, the obtained yield is similar (80%).

When the reaction was executed with electron- withdrawing like p-nitro phenyl group, the time taken for trifluoromethylation was increased with comparatively low yield (55%). Non-aromatic group on nitrogen were also accepted under same reaction conditions. (Scheme 7.4).



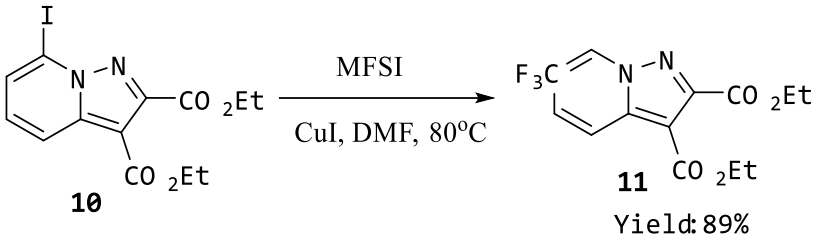
R= Ph

R= Me, Bn, Ph, 4-OMeC_6H_4, 4-$NO_2C_6H_4$

Scheme 7.4: Trifluoromethylation of 4-iodosyndones.

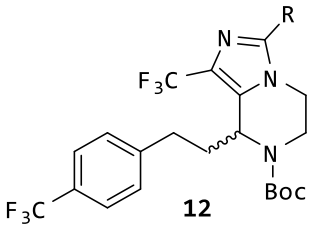
Chong and Bullock[77,79] synthesized 7-Trifluoromethylpyrazolo[1,5-*a*]-pyridinedicarboxylate **11** which is an important intermediate for a potential drug candidate.

MFSI reacted with iodide derivative of pyrazolo[1,5-*a*] pyridine dicarboxylates **10** in the presence of CuI in DMF at 80° C to give trifluoromethylated pyrazolopyridinecarboxylate **11** with 89% yield. (Scheme 7.5)



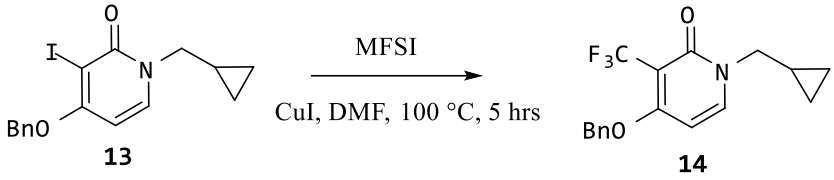
Scheme 7.5: Trifluoromethylation of iodo derivative of pyrazolopyridine dicarboxylates

Sifferlen[79] et al has been reported the incorporation of trifluoromethyl moiety using MFSI in synthesis of bioactive intermediate **12** which was further used in synthesis of 5,6,7,8-tetrahydroimidazo[1,5-*a*] pyrazines which is an orexin receptor antagonist.



Cid et al[80] discovered a novel bioactive derivative of phenylpiperidine substituted pyridones which act as an allosteric modulator of glutamate receptor.

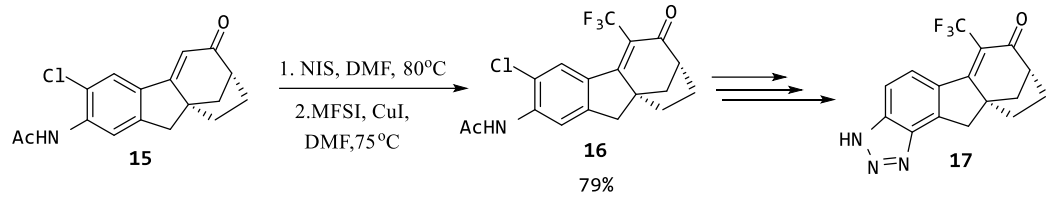
MFSI used for trifluoromethylation of 3-iodopyridones i.e., 4-Benzyloxy-1-cyclopropylmethyl-3-iodo-1*H*-pyridin-2-one **13** to synthesize 3-trifluoromethylpyridone i.e., 4-Benzylox-1-cyclopropylmethyl-3-trifluoromethyl-1*H*-pyridin-2-one **14** which is a key intermediate to form the bioactive molecules. (Scheme 6).



Scheme 6. Trifluoromethylation of 3-iodopyridones

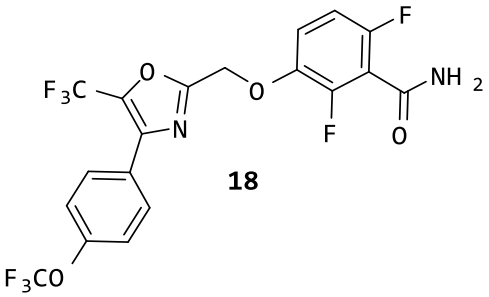
Madess et al[81] discovered derivatives of tetrahydrofluoroene which act as beta agonist for estrogen receptors used in therapy of postmenopausal women for treating the symptoms related with decreased oestrogen level.

Compound **15** undergo iodination followed by trifluoromethylation using MFSI, CuI in DMF to synthesize the compound **16** with high yield which on further transformation give desirable bioactive molecule i.e., tetrahydrofluoroene **17** (Schemes 7.7)

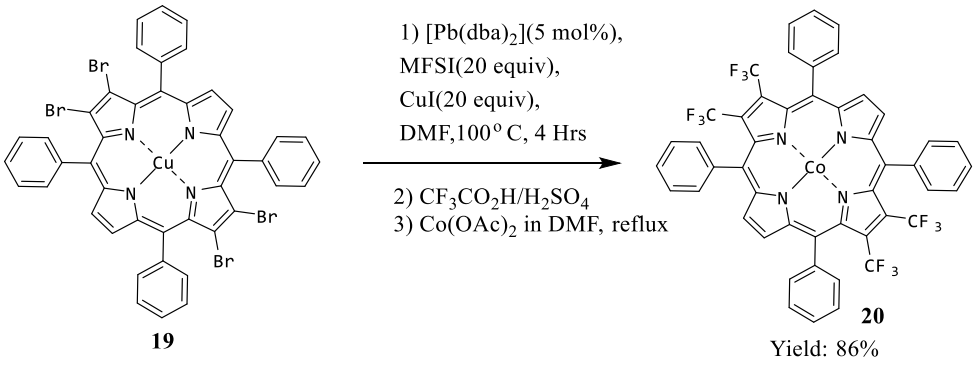


Schemes 7.7: Trifluoromethylation of intermediate in the synthesis of tetrahydrofluoroene

Stokes and coworkers[82] suggested the synthesis of bioactive intermediate **18** by the trifluoromethylation of its oxazolyl iodide intermediate using MFSI.



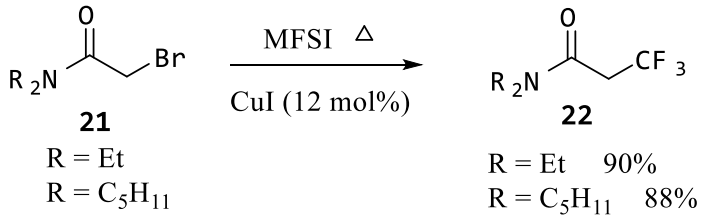
Zhao et al[83] reported that cobalt (II) β-tetrakis- (trifluoromethyl)-meso-tetraphenylporphyrin ($CoTPP(CF_3)_4$) exhibited excellent catalytic selectivity as well as conversion of benzylamines to imines through oxidative coupling with the product yield of 52–89% . He prepared $[Co\{TPP(CF_3)_4\}]$ **19** by the trifluoromethylation of $[Cu(TPPBr_4)]$ **20** in good yield using MFSI and subsequent insertion of Co^{II}. (Schemes 8)



Schemes 7.8: Synthesis of $[Co\{TPP(CF_3)_4\}]$

Zhang et al [84] reported the wide use of MFSI for various copper mediated reactions in a review published in 2014. MFSI was used for trifluoromethylation of aryl halides, alkyl halides and alkenyl halides and trifluoromethylthiolation of aryl halides. Alonso et al [85] reported in their review that MFSI was used as trifluoromethylation of various substrate in presence of CuI.

(a) trifluoromethylation of bromomethyl amide **21** to synthesize parallel trifluoromethyl derivatives **22** with excellent yield. (Schemes 7.9)

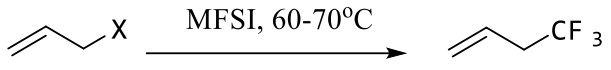


21
R = Et
R = C_5H_{11}

22
R = Et 90%
R = C_5H_{11} 88%

Schemes 7.9: Trifluoromethylation of bromomethyl amide

(b) trifluoromethylation of allyl halide **23** to give trifluoromethylated derivative **24** in high yield. (Schemes 7.10)

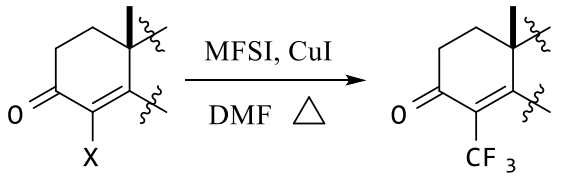


23
X = Br, I

24
Yield :68-70%

Schemes 7.10: Trifluoromethylation of allyl halide

(c) trifluoromethylation of iodo- steroidal molecule **25** to give trifluoromethyl steroids **26** with good yield. Trifluoromethylated flavonoid and antitumor trifluoromethylated flavonoid derivatives were also prepared using this methodology[86] (Schemes 11).



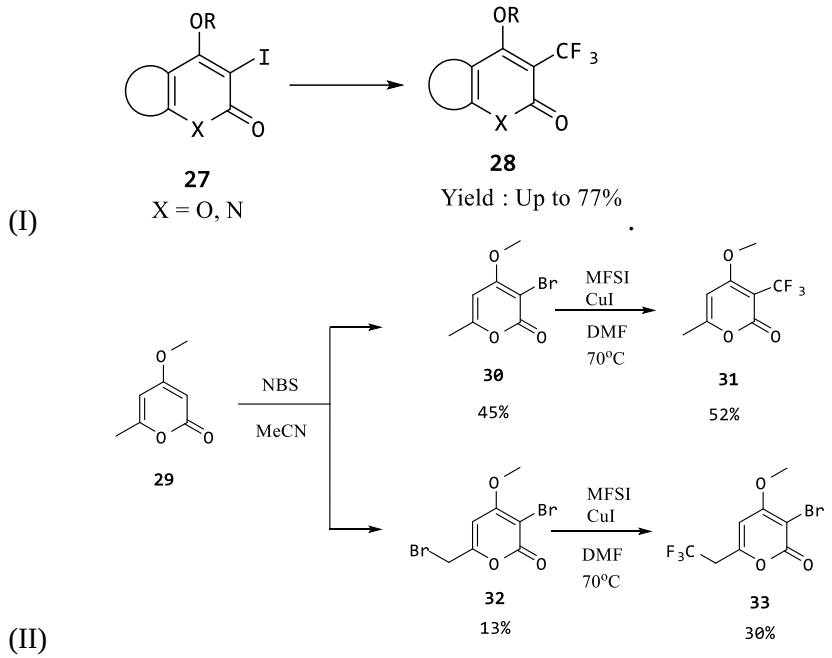
25
X = Br, I

26
Yield : 70-91%

Schemes 7.11: Trifluoromethylation of iodo-steroids

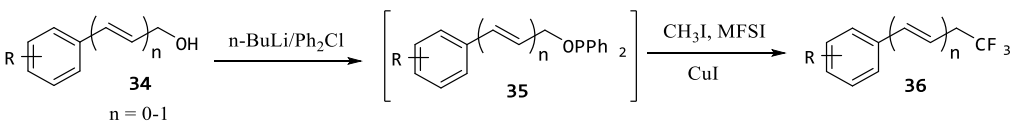
Clarke et al[87] developed the trifuoromethylated series of 4-alkoxy -2-pyrones, pyridones and quinolone using MFSI. These compounds have special biological properties.

They reported that when 1.2 equivalents of MFSI with 1.2 equivalents of copper iodide in DMF were used, good yields were obtained. As shown in scheme 7.12 (I), trifluoromethylation of iodinated starting material **27** gave **28**.

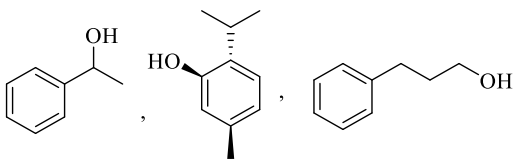


Scheme 7.12: Trifluoromethylation of pyrones, pyridones and quinolones

whereas mono **30** and di brominated **32** products were obtained by the bromination of 4-methoxy -6-methyl -2- pyrones **29**. The bromo derivative further underwent trifluoromethylation to yield product **31** and **33**. [Scheme 7.12(II)]. Li et al[88] suggested an efficient method for the trifluoromethylation of benzyl alcohol or allyl alcohol **34** to obtain various trifluoromethylated compound **36**. Derivatives of **35** were formed by reacting compound **34** (benzyl or allyl alcohol) with *n*-BuLi, Ph_2Cl. Intermediate **35** undergo trifluoromethylation in the presence of methyl iodide and MFSI in the presence of copper iodide when stirred at 80° for 15 hrs to obtain compound **36**. A variety of compounds were prepared from this method. (Scheme 7.13). Electronic density of alcohols affects the yield of reactions. Electron-donating groups such as methoxy and methyl group gave good yield whereas halide-substituted alcohols gave the moderate yield and low yields were observed with secondary alcohols because of steric hindrance.



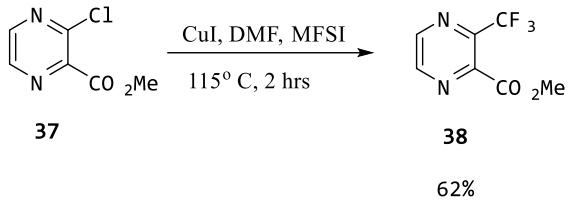
R= p-CF_3, -OMe, p-Me, p-Br, o-Cl, p-Cl,



n= 0,1

Scheme 7.13: Trifluoromethylation of benzyl alcohol or allyl alcohol

Oda et al[89] suggested the application of MFSI for the trifluoromethylation of methyl 3-chloropyrazine-2-carboxylate **37** in the presence of CuI in DMF, toluene and converted into methyl 3-(trifluoromethyl) pyrazine-2-carboxylate **38** which is a key intermediate to synthesize pyraziflumid and many other derivatives. Pyraziflumid shows excellent fungicidal activity partiparticularly against gray mold, Brown rust and powdery mildew. (Scheme 7.14). Sharma et al[90] described the successful nucleophilic trifluoromethylation of differently substituted α-iodinated oxoketene dithioacetals **39** *via* using MFSI in presence of CuI and DMF which provided α-trifuoromethylated oxoketene dithioacetals **40** with good to outstanding yield. Those synthons were further utilized for the synthesis of biologically important diversely substituted trifluoromethylated pyrazoles. (Scheme 7.15).

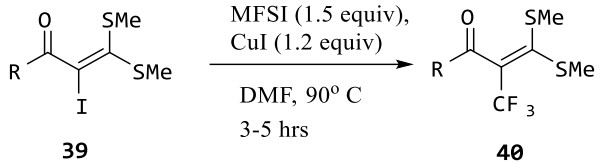


37 **38**

62%

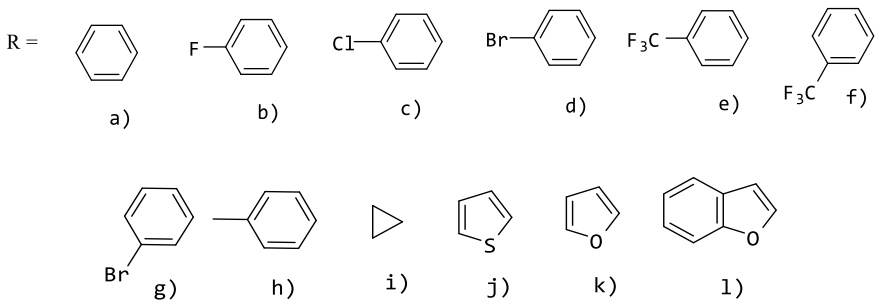
Scheme 7.14. Trifluoromethylation of methyl 3-chloropyrazine-2-carboxylate

Electron withdrawing group present at the *m*- and *p*- position in the α-iodinated oxoketene dithioacetals (b-g) contributed good yield of α-trifuoromethylated oxoketene dithioacetals. Though, electron releasing group in substrarte with *p*-CH_3 gave decent yield. On the other hand, with *o*-CH_3 in α-iodo oxoketene dithioacetals at -*o* or -*p* positions were confirmed unproductive due to incapability towards nucleophilic substitution. High yield was obtained with cyclopropyl substituted substrate. Heteroaromatic substituted α-iodo oxoketene dithioacetals (j – l) produced good to excellent yield.



39 **40**

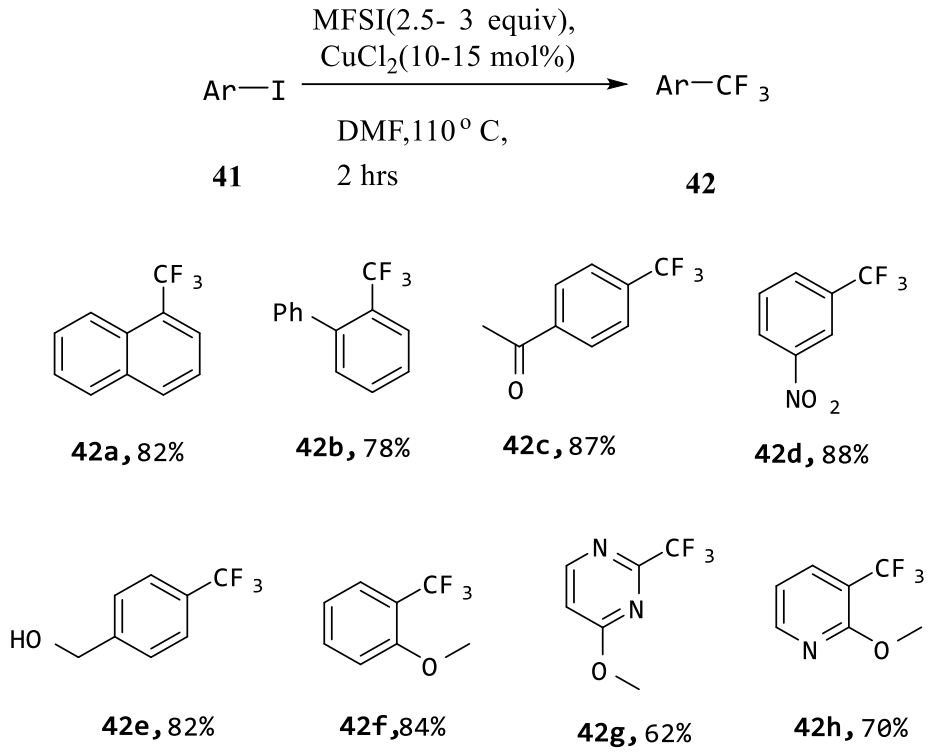
80% - 93%



Scheme 7.15: Trifluoromethylation α - iodinated oxoketene dithioacetals

Zhao and coworkers[91] proposed the nucleophilic trifluoromethylation of various aryl and heteroaryl iodides **4** using MFSI, and carried in the presence of $CuCl_2$ with excellent yield. In their review, they started with the trifluoromethylation of 1- iodonapthalene.

After the successful trifluoromethylation of iodonapthalene, they further synthesized a number of structurally diverse trifluoromethylated (hetero) aryl derivatives **42(a-h)** in the presence of $CuCl_2$ as catalyst at 110°C when stirred for 2 hrs. Effect of others salts of Cu on the yield, were also studied. (Scheme 7.16)

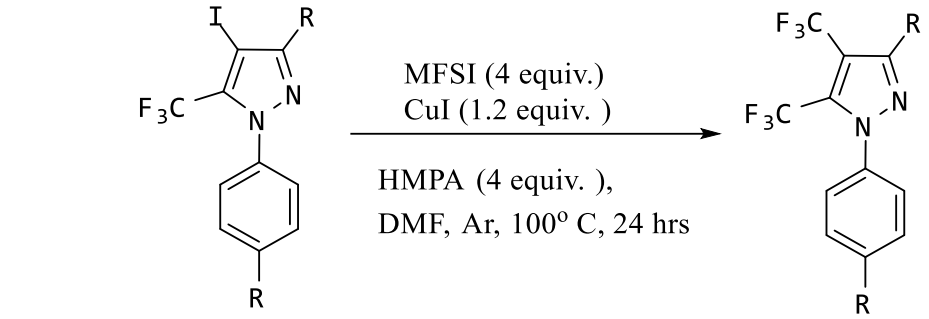


Scheme 7.16: Trifluoromethylation of aryl and heteroaryl iodides

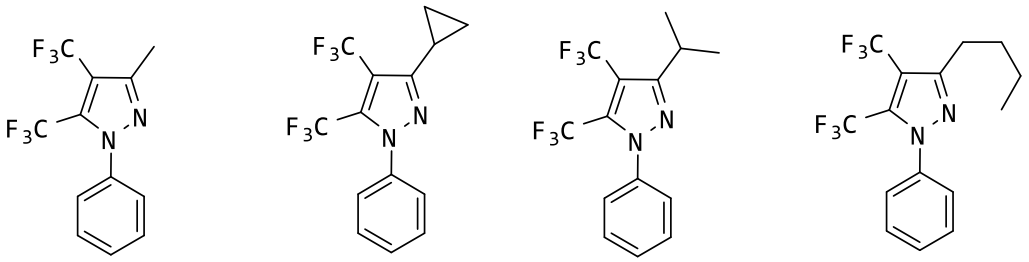
Junges et al[92] reported the trifluoromethylation of 1-aryl-3-alkyl(aryl)-5-trifluoromethyl-4-iodo-1*H*-pyrazoles **43** in CuI, MFSI and HMPA under anhydrous DMF for 24 hrs at 80°C to obtained a chain of 1-aryl-3-alkyl(aryl)-4,5-bis(trifluoromethyl)-1*H*-pyrazoles **44(a-h)** in good yield which showcased the insecticidal property. (Scheme 7.17).

Recently Xie and Hu[93] posted an article on huge application of MFSI in area of organic chemistry wherein they mentioned about the discovery, applications and reactions of Chen's reagent.

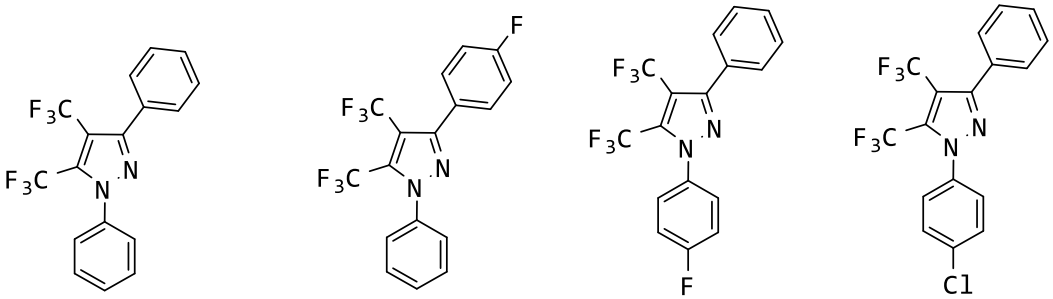
MFSI used normally to acquired trifluoro methylated and difluoro alkylated compounds. Over a decade, a substantial amount of research has been performed to use MFSI as a difluorocarbene precursor and radical difluoro alkylating agent in presence of visible light.



43 **44 (a-h)**



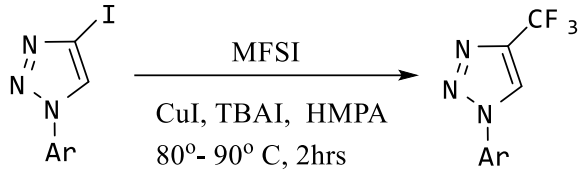
44a, 55% **44b,** 75% **44c** 58% **44d**



44e, 56 % **44f,** 79% **44g,** 77% **44h,** 71%

Scheme 7.17: Trifluoromethylation of 1-aryl-3-alkyl(aryl)-5-trifluoromethyl-4-iodo-1*H*-pyrazoles

Panja et al[94-98] reported the common method for trifluoromethylation of 1-aryl-4-iodo-1*H*-1, 2, 3-triazole **45** which were carried out in TBAI (Tetrabutylammonium iodide), CuI and MFSI, stirred at 80-90°C for 2 hrs. to obtain 1-aryl-4-(trifluoromethyl)-1*H*-1, 2, 3- triazole **46** in moderate yield. (Scheme 7.18). The reaction was not dependent on the electron density of substituent in aryl ring and it was chemoselective when carried out with bromo and chloro derivatives. Consequently, this is a useful method for synthesis of many 1-aryl-4-trifluoromethyltriazoles[99-101] from the respective iodo-precursor. TBAI act as useful reagent as it is solubilizing the Cu and make it available for the reaction.



45 **46**

Ar = 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Cl-C_6H_{44}-F-C_6H_4, 4-CH_3-C_6H_4, C_6H_5, 3,5-$(CF_3)_2$-C_6H_3
4-$COCH_3$-C_6H_4, 4-$CO_2CH_2CH_3$-C_6H_4, 4-CN-C_6H_4, 4-OCF_3-C_6H_4

Scheme 7.18: Trifluoromethylation of 1- aryl 4-iodo-1, 2, 3-triazoles

7. 3 Conclusion:

Since MFSI was discovered in 1989 as a trifluoromethlating reagent, it has found wide application for the trifluoromethylation of aromatic, herteroaromatic and alkenic compounds. A huge number of CF_3 containing biologically important and structurally diverse molecules have been synthesized by using this excellent reagent. Instead, it shows significant advantages over other trifluoromethlating reagent like CF_3CO_2Na and Ruppert Prakash reagent ($TMSCF_3$). Ruppert Prakash reagent is widely used as a trifluromethlating reagent but it is very expensive. MFSI reagent is commercially available, pretty cheaper and persuadable for trifluoromethylation of halogenated compounds. Scientists are doing more research on this reagent in organic synthesis. However, it has been somewhat underutilised by chemical community. We demand for extra attention to this crucial reagent. This reagent will continue to find more uses in the field of life sciences and material science.

7.4 References:

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List of Abbreviations:

CF_3 - Trifluoromethyl

CF_3SiMe_3 - Ruppert-Prakash reagent

CF_3SO_2Cl - Trifluoromethane sulfonyl

$PhSOCF_3$ - Trifluoromethyl sulfoxide

$PhSO_2CF_3$ - Trifluoromethyl sulfone

MFSI - Methyl fluorosulfonyldifluoroacetate

CuI - Copper iodide

KI - Potassium iodide

DMF - Dimethylformamide

HMPA - Hexamethylphosphoramide

NaOH - Sodium Hydroxide

NIS - Nickel sulfide

$[Pb(dba)_2]$ - Bis(dibenzylideneacetone) Palladium

CF_3CO_2H - Trifluoroacetic acid

$Co(OAc)_2$ - Cobalt(II) acetate

NBS - N- Bromosuccinimide

MeCN - Methyl cyanide

n-BuLi - n Butyllithium

CF_3CO_2Na - Sodium trifluoroacetate

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