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Antibacterial activity of synthesized organic compound

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Dedicate

I dedicate this work to my dear mother who has always supported me at every step, as well as all my family.

Bouhadja Samah

Dedicate

I dedicate this humble work.

To my angel in life...to the meaning of love, to the meaning of tenderness and devotion...to the smile of life and the secret of existence to those whose prayers were the secret of my success and whose tenderness was a surgical balm to my most precious loved onesDear mother.

To my brothers (Mohammed and Abou Bakr) and sisters and my twin Amina, May God give you a firm side, my support, and the shoulder on which I lean

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Senouci Karima

Contents

List of Figures

List of Table

Abbreviations list:

Generalities :

H : hour
% : percentage
Anti: opposite side
° C : Degree Celsius
g : Grams
Δ: differentiel
m_{exp}: Experimental mass
m_{theo}: Theoretical mass
pH : Hydrogen potentiel
vivo: phenomenon observed in the organism
in vivo: practicing experiments within living beings, organisms
in vitro: Any experimental activity realized on micro-organisms, organs, or cells outside their natural context
C : Concentration (mol/l)
V : Volume (ml)
y : réactionyield(%)
T : température (°C)
PS : polystyrene
PVC : polyvinyl chloride.
PG: Swollen breast of polymer.
PS: Solid weight of polymer.
+++ : Very soluble.
++: Soluble.
+: Almost soluble.
-: No soluble.
nM : number of moles of monomer
nA : number of moles of acetone
R=(nM /nA) : molar ratio
nP : number of moles of polymer
m_i: initial mass
m_f: final mass
P/F: monomer/formaldehyde.
P/A: monomer/acetone.

Solvants :

EtOH : Ethanol
CHCl3 :Chloroforme
CH2Cl2 : Dichloromethane
THF :Tetrahydrofurane
CCl4 : Tetrachloromethane
DMSO :Dimethylsulfoxyde
CH3-COOOH :acide peracetic

Techniques d'analyse :

IR : Infrared
RMN : Nuclear magnetic resonance

GERMES :

E Coli : Escherichia Coli
KP :Klebsiella Pneumoniae

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Organic chemistry[1] is the chemistry of carbon compounds. These compounds also include, in decreasing quantities, the elements hydrogen, oxygen, nitrogen, and halogens. The elements sulfur, phosphorus, and certain metals are also found in organic molecules.

One of the most prominent studies in the science of organic chemistry is the study of macromolecules which are big molecules formed from smaller building blocks characterized by their unique structural and functional properties.

Macrocycles such as calixarenes[2], a class of macrocycles consisting of phenolic repeating units linked by a methylene bridge, have garnered considerable interest due to their applications in various fields.

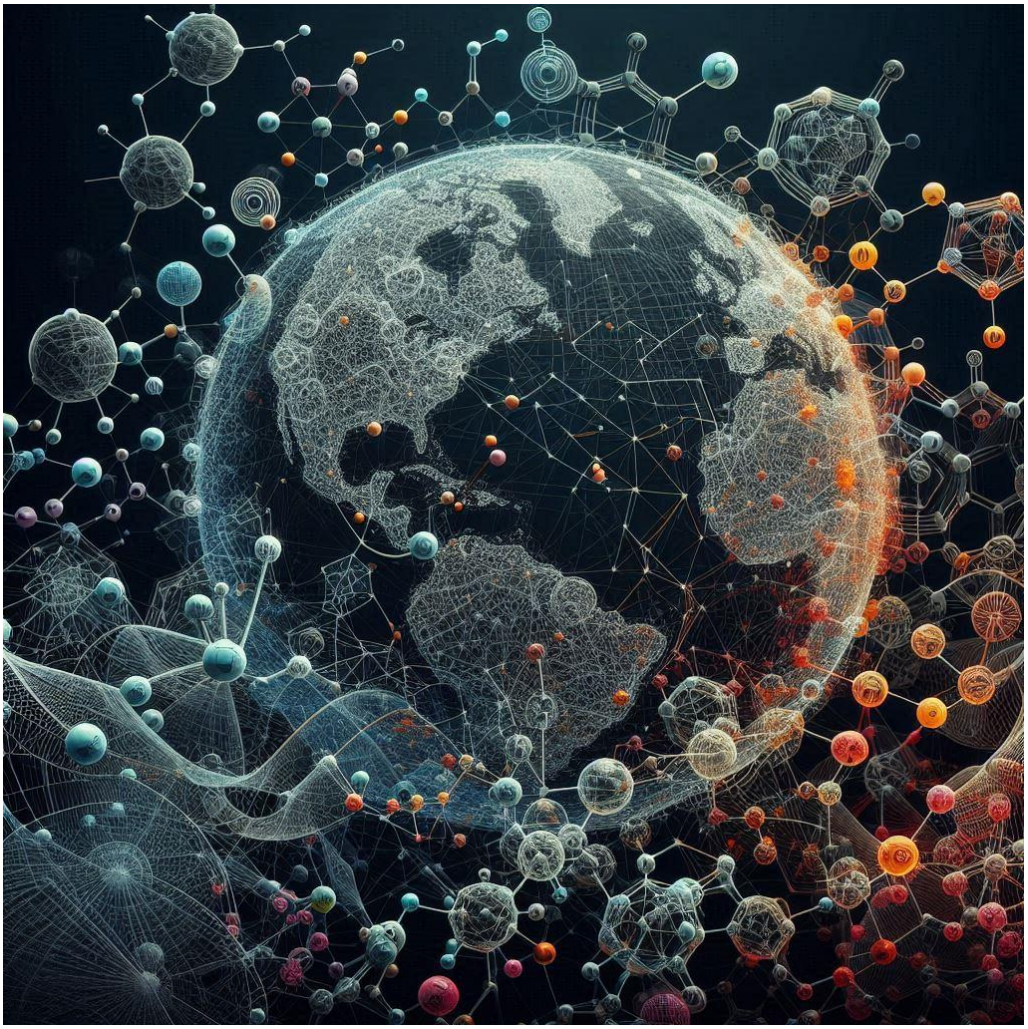
The overall objective of this project is to study the synthesis, characterization, and applications of calixarenes and other organic compounds specifying our study ontestingthe antibacterial activities of these compounds. The work presented in this study is divided into two parts:

1. **bibliographical review:** In this research section we will provide a general description of macromolecules, their general formulary, their classification, and applications moving to basics and fundamentals on calixarenes then discussing the main bases of the antibacterial activity.
2. **Experimental review:** In this part, we will present methods of synthesis of phenolic compounds and other organic compounds, as well as their spectroscopic characterization and antibacterial activity test results.

[1] C. ouahes, 'Chimie organique sciences biomédicales et sciences de la nature', 'Office des publications universitaires 1, place centrale de Ben Aknoun (Alger)', 1988.
[2]SuwabunChirachancai, Kahji Tashiro, 'Handbook of benzoxazine resins', 'Supramolecular chemistry of benzoxazines' (2011), 'Calixarene', 'journal of inorganic biochemistry', (2023).

Part I: bibliographic Review

Chapter 01:*General information onMacromolecules*



I. History:

The historical development of macromolecular science and its impact on various fields of research:

In Eighth Century: Research on naturally occurring polymers such as proteins, cellulose, and starch led to the development of the idea of macromolecules. The chemical structure of these substances was not fully understood by scientists at the time.

In 19th century: The study of macromolecules advanced significantly as a result of the growth of organic chemistry. Due to the discovery of cellulose in 1833, French scientist Anselme Payen initiated the scientific investigation of polysaccharides. German chemist Emil Fischer made significant advances to our knowledge of proteins and their structures in the later part of the 19th century, Cellulose, as the essential building block of cell walls, is the most abundant natural organic polymer. Already in 1838, cellulose was discovered, isolated, and named as such by Anselme Payen[3]

Emil Fischer is credited as the creator of the field of primary natural product chemistry, which includes peptides, proteins, purines, and carbohydrates. He developed asymmetric syntheses, protecting-group chemistry, the assignment of configuration, and the stereochemistry of carbohydrates[4].

Early in the 20th century, the study of macromolecules underwent a radical change with the discovery of synthetic polymers. The development of plastics began in 1907 when Leo Baekeland created backelite, the first synthetic polymer. The structure of macromolecules was also the subject of developing hypotheses at this time, such as Hermann Staudinger's theory that polymers are made up of long chains of repeating units.[5]

Mid-20th Century: The 1953 discovery of DNA's structure by James Watson and Francis Crick marked a turning point in the field of macromolecular biology. It made the molecular basis of genetics clear and opened the path for advances in molecular biology[6].

The Late 20th Century to the Present: The study of macromolecules has continued to evolve rapidly with the development of advanced analytical techniques and technologies.These include electron microscopy, nuclear magnetic resonance (NMR)

[3] Anna F. Lehrhofer, Takaaki Goto, Toshinari Kawada, Thomas Rosenau, Hubert Hettegger, 'The in vitro synthesis of cellulose-A mini-review' *Carbohydrate Polymers* (Volume 285), 119222, , (2022) .
[4] Horst Kunz Prof. DR, 'Unequalled Classicit, Master of Organic chemistry Research, and Inspired Trailblazer of Biological Chemistry' A journal German Chemical Society, (2002).
[5]Ben-AimRogerI, Christophe Chassanieux, Hervé Lefebvre, Sagarario Pascual, 'L'indispensable en Polyméres', (2008).
[6] James D. Watson, 'The Double Helix : The Discovery of the Dna' The Atlantic, , (1968).

spectroscopy, and X-ray crystallography, which have allowed scientists to see and comprehend macromolecule structures at the atomic level[7].

Recent developments have allowed the integration of macromolecules structures at the microscopic level for use for applications in drug delivery, diagnostics, and therapeutics. This includes the design of polymer-based nanoparticles and nanocomposites with enhanced properties for targeted delivery and controlled release[8].

II. Stepgrowth of polymerization:

Step growth polymerizations are of industrial importance. Monomers having two different groups of atoms such as ester or amide can join to form condensation polymer with the release of small molecules such as water, ammonia, etc. Polyesters and polyamides are important commercial polymers. Step growth polymerization reactions are condensation polymerization of difunctional monomers.

The stoichiometric associated with the formation or not formation small molecules during the reaction. Polyester and polyamides are industrially important polymers by step growth polymerization. Phenol and aldehyde reaction is step growth polymerization. Chain Polymerization is an addition polymerization of olefinic monomers. Styrene reaction is a chain polymerization[9].

III. The origin of the word polymer:

The word "Polymer" is derived from the Greek words "Poly" meaning man and "Meros" meaning parts or units. It is defined as a high molecular weight compound formed by the combination of a large number of one or more types of low molecular weight molecules. Giant In other words, polymers are giant, high molecular weight molecules called "macromolecules" that are formed by combining a large number of small molecules called "monomers" and the reaction by which the monomers combine to form polymers is known as " Polymerization". However if a simple molecule is X, then the molecule $X_n$is represented by the formula $(X\text{-}X\text{-}X\text{-}X\text{-}X)_n$[10].

[7] Harumi Sato, YukihiroOzaki, 'Sepectroscopic Techniques for Polymer Characterization methods, instrumentation, application' Page 5, (2022).
[8]Abid Haleem, Mohd Javaid, Ravi Pratap Singh, Shanay Rab, Rajiv Suman, 'Application of nanotechnology in medica filed: a brief review' Global Health Journal Pages 70-77, (2023).
[9]MuralisrinivasanNatamaiSubramanian , 'Basics of Polymer Chemistry' Page 81, (2022).
[10] A.K. Pahari, B,S. Chauhan, 'Engineering Chemistry' Page 49, (2006).

IV. Definitions:

POLYMER—a large molecule made up of smaller repeating units.

MONOMER—the building units.

HOMOPOLYMER—when all the monomers are the same.

COPOLYMER—a polymer composed of different monomers BLENDS—a mixture of polymers.

Figure 1: fundamental definitions of polymers[11].

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IV.1. Macrocycle:

A long closed chain of atoms[12] linked together by covalent bonds or coordination bonds; by extension, molecule which contains such a chain.

IV.2. Oligomer:

The term "Oligomer[13]" is from Greek, Oligos meaning several or a few and Meros meaning a part or repetition it was originally introduced into scientific literature by I.Gelferich in 1930, it was used to describe chemical substances occupying an intermediate position between monomer (low-molecular-mass compounds) and polymers (high-molecular-mass compounds).

The definition by IUPAC Commission on the nomenclature:"A substance composed of molecules containing a few of or more species of atoms or groups of atoms 'Base Units' repetitively linked to each other. The Physical properties of an oligomer vary with the addition or removal of one or few of the base units from its molecules.

IV.3. Pre-polymer :

[11] Paul C. Painter, Michael M. Coleman, 'Essentials of Polymer Science and Engineering. Page 2, (2009).
[12]Journal official, 'Macrocycle, n.m.' France Terme, ministére de la culture, (2019).
[13] Semjon M Mezhikouski, 'Physico-Chemical Principles for Processing of oligomeric blends' Page 1-2, (1998).

A macromolecule[14] or oligomer that has the ability to join several monomeric units into at least one chain of the final macromolecule by entering further polymerization through reactive groups.

V. The difference between Polymer and Oligomer:

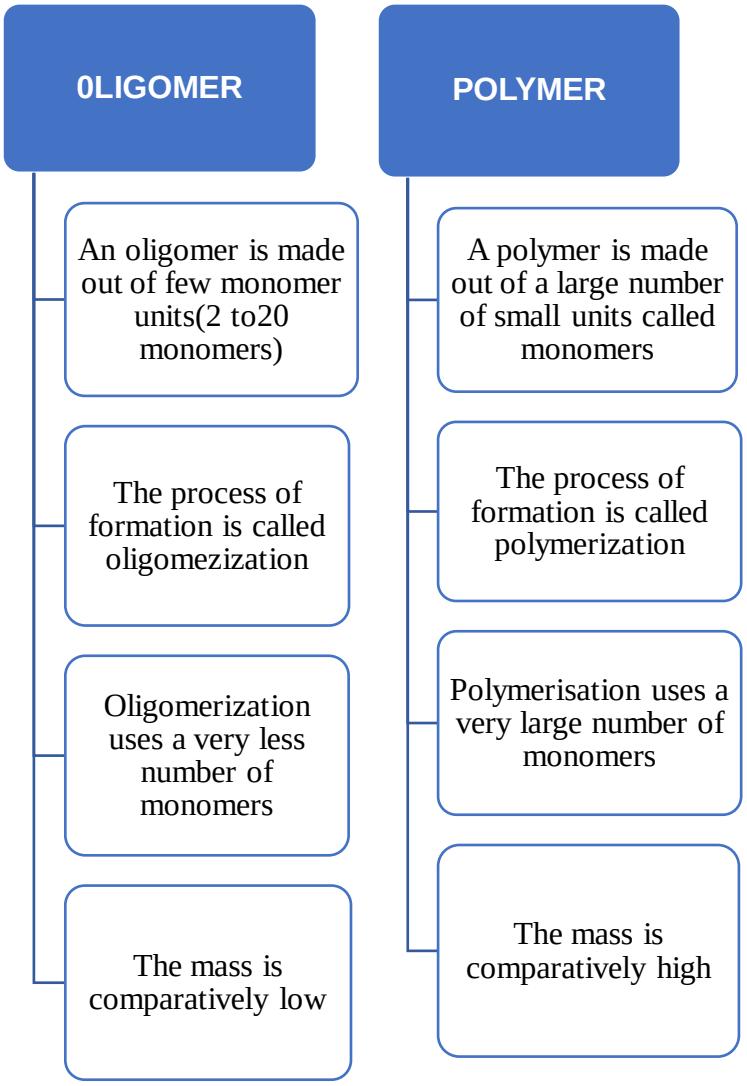


Figure 2: The difference between oligomer and polymer[15, 16].

Polycondensation :

[14] A. D. Jenkinks, P. Kratochivil, R. F. T. Stepto and U. W.Suter, 'Glossary of basic terms in polmer science' International Union of pure and applied chemistry. Macromolecular division commission on macromolecular nomenclature. Volume 68 Page 2290, (1996).
[15]Madhusha, 'Diffrence between Oligomer and Polymer' PEDIAA, (2017).
[16]Ben-Aim Roger I., Christophe Chassanieux, Hervé Lefebvre, Sagrario Pascual, 'L'indispensable en Polyméres',Page 11, (2008).

Polycondensation [17] is the term used to describe polymers formed as a result of reactions involving the condensation of organic materials in which small molecules are split out.

Polycondensation also involves different groups in monomers, producing thermoplastic or thermosetting resins. It produces thermoplastic resins and thermosets by reacting polyfunctional monomers, resulting in a highly cross-linked structure.

Polycondensation[18] is another technique used to synthesize polymers. The reason for the name derives from the elimination of a molecule of water from reactants at each polymerization step. This technique may be applied to multifunctional units to produce thermoset polymers. A classical example of polycondensation leading to thermoset polymers is the copolymerization between phenol and formaldehyde (Conley and Bieron, 1963). Formaldehyde is able to bridge together two aromatic rings, and since the functionality of a ring is five (one carbon is linked to the hydroxyl group) the cross-links between rings are ensured by a relatively low content of formaldehyde as shown in the following figure :

VI. Polymerclassification:

VI.1. ORIGINE OF POLYMERS: There are three different origins[19] of polymers:

VI.1.1. Natural polymers : These can be found in nature; such as cellulose, starch, proteins, natural rubber, and natural silk.

VI.1.2. Semi-synthetic Polymers : These are chemically modified natural polymers such as hydrogenated, halogenated or hydrohalogenated natural rubber, esters and ethers of cellulose such as cellulose nitrate, methyl cellulose, etc.

VI.1.3. Synthetic Polymers : These are synthetically prepared polymers. For examplepolyethylene, polystyrene, polyesters, phenol-formaldehyderesins, etc.

VI.2. Classification according to thermal response :

VI.2.1. Thermoplastic polymers :A thermoplastic[20] is a linear or branched polymer that is softened by heating and hardened by cooling within a specified temperature range. Unlike thermosets, the softening and hardening process can be repeated indefinitely. As a result, thermoplastic waste can be recovered and recycled. They are easy to process, as

[17]A . D. Sarkar M.Eng., B. Sc., 'Mould and core material for the steel foundry', 1967. 'Polycondensation', results in engineering, (2023).
[18] L. Boogh, R. Mezzenga, 'Comprehensive composite materials', 'Polymer matrix composites', 2000. 'Polycondensation', results in engineering, 2023.
[19] A.K. Pahari, B.S. Chauhan, 'Engineering Chemistry' Page 49, (2006).
[20] Ben-Aim Roger I, Christophe Chassanieux, Hervé Lefebvre, Sagrario Pascual, 'L'indispensable en polyméres',Page 110, (2008).

simple heating transforms them into viscous liquids, and after solidification, they can be used to make a variety of objects. These amorphous or semi-crystalline polymers,such as polyethylene (PE), polyvinyl chloride (PVC) and polystyrene (PS), are formed using a variety of techniques, including injection moulding, injection blow moulding, extrusion and rotational moulding. In most cases, the formed polymer returns to its partially crystalline or amorphous state after cooling.

VI.2.2. Thermosetting polymers : The formation of thermosettingpolymers is an irreversible process. Thermosetting are typically hard and rigid. They tend to have higher temperature resistance when exposed to heat and will not creep or warp at higher temperatures compared to thermoplastics. Thermosetting typically are used for structural applications where high strength and stiffness are required to resist high loads[21]. Thermosetting[22] polymers are obtained in soluble and fusible forms in the early stages of their synthesis but become insoluble and infusible on further heating. The process involves chemical reactions that lead to further growth and cross-linking of the polymer chain molecules, producing giant molecules. Examples of this are phenolic resins and urea-melamine resins.

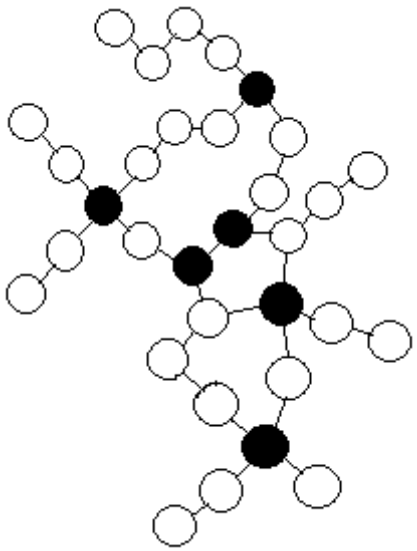


Figure 3: An example of a thermosetting polymer.

VI.2.3.Elastomerpolymers :

[21]Mariam Al Ali AlMaadeed, Deepalekshmi Ponnamma, Ali Alaa El-Samak , 'Polymer science and innovative applications : materials, techniques, and future developments'(2020).
[22] A.K. Pahari, B.S. Chauhan, 'Engineering Chemistry', (2006).

Elastomers[23] are linear or branched polymers transformed by vulcanisation into a three-dimensional, The term vulcanisation is equivalent to the term cross-linking, but is specifically reserved for elastomers (natural or synthetic neoprene rubber, silicones, etc.), they weakly cross-linked, infusible, and insoluble network. They differ from thermosetting in rubbery elasticity, large reversible deformations, and high elongations. They have a low glass transition temperature, making them flexible but limited by their covalent three-dimensional structure.

VI.2.4. Thermoplastic elastomers:

A thermoplastic elastomer[24] is a linear or branched polymer that combines the elasticity of an elastomer with the mouldability of a thermoplastic. Thermoplastic elastomers are usually block copolymers (or homopolymer and/or copolymer mixtures) whose structure in the solid state is always the result of the combination of at least two distinct, non-mixable phases: a soft phase (glass transition temperature between -90°C and -40°C) combined with a rigid phase (glass temperature or melting temperature above 90°C). It is therefore a multiphase material, or the rigid phase is dispersed in the soft phase.

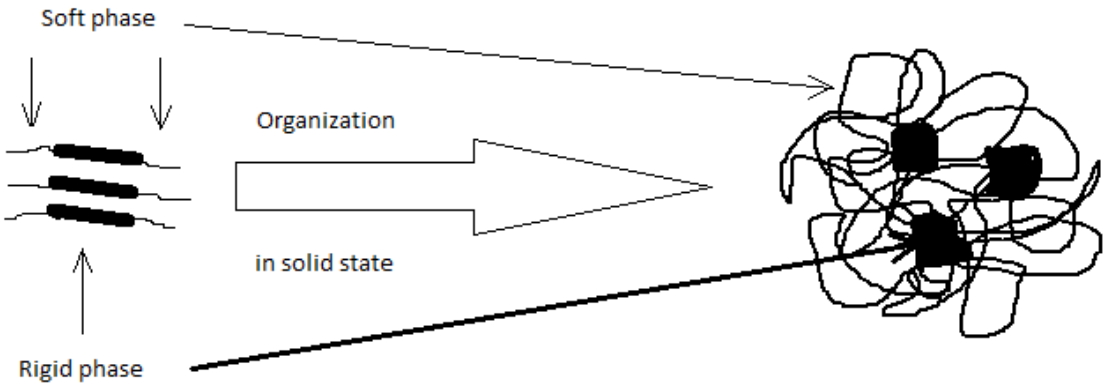


Figure 4: Physical characteristics (thermoplastic elastomers).

Thermoplastic elastomers have a number of advantages over vulcanized elastomers:

- Easier and quicker to format.
- Larger range of potentially available materials.
- Recycling possible.

VII. Polyphenoles:

[23] Hasini. A, ' What is the Diffrence Between Resol and Novolac' PEDIAA, (2023).
[24]Ben-Aim Roger I., Christophe Chassanieux, Hervé Lefebvre, Sagrario Pascual, 'L'indispensable en Polyméres', Page 111-112, (2008).

VII.1. Introduction :

Polyphenols[25] are a class of substances that are found in plants and are renowned for having antioxidant qualities. The basic structure of polyphenols consists of one or more aromatic rings with hydroxyl (-OH) groups attached to them as shown in Figure , which helps to neutralize free radicals (which are highly reactive molecules that can cause damage to cells and contribute to various diseases, including cancer, heart disease, and Alzheimer's disease, etc.).

Other polymerised forms, such as tannins and lignins, are also present. Some are responsible for the flavour, colour and antioxidant properties of the fruits, vegetables, seeds and nuts that we consumed.

Polyphenols[26] are becoming increasingly important, particularly because of their health benefits. In fact, their role as natural antioxidants in the prevention and treatment of cancer is increasing.

VII.2. Phenolic resins in chemistry:

Phenolic resin[27], synthesised from phenol and formaldehyde, continues to grace the resin industry more than a century after it was first developed, due to its versatile properties and performance in a wide range of applications.

The production and commercial use of phenolic resin spread rapidly around the world following its first commercial production in Germany in 1909. Excellent mechanical properties, flexibility, low cost, high thermal stability, and water and chemical resistance have made it the material of choice for applications in the aerospace industry, as adhesives in particle board production.

The synthesis of phenolic resins can be accomplished either through basic (resols) or acid catalysis (novolacs). The reaction occurs in two stages, regardless of the kind of catalyst: the addition of formaldehyde to the phenol followed by the condensation of the formed monomers.

VII.3. Choice of catalysis (comparison between acid catalysis and basic catalysis):

[25] Chandrabhan Verma, Wiley, 'Science and Engineering of Polyphenols fundamentals and industrial scale applications' Page 3, (2024).
[26] Christophe Hano, DuangyaiTungmunnithum, Plant Polyphenols, More than just simple Naturel Antioxidants: Oxidative stress, Agining and Age-Related Diseases' MDPI, (2020).
[27] P. R. Sarika , Paul Nancarrow, Abdulrahman Khansaheb and Taleb Ibrahim, 'Bio-Based Alternatives to Phenol and Formaldehyde for the Production of Resins', polymers, MDPI, (2020).

By comparing the two catalysis[28] systems, it appears that the macromolecular structures of the solids are more branched than those of the novolacs and therefore a greater networking density of the final networks, the addition will immediately follow the condensation and will lead to more linear polymers.

Table 1: Comparison between Resol and Nolvolac[29]**.**

RESOL	NOVOLAC
Resol resins are a subset of phenolic resins characterized by their highly cross-linked, three-dimensional structure and are formed in an alkaline environment	Novolac resins are a subset of phenolic resins characterized by linear or lihtly branched structures and are formed in acidic environment
Have a cross-linked, three-dimensional structure	Exhibit a linear or lightly branched chemical structure
Feature a high degree of cross-linking	Feature a lower level of cross-linking
Offer high rigidity and hardness when cured	Provide relatively lower rigidity and hardness when cured
Typically require higher curing temperatures	Can cure at lower temperatures
Less flexible	Higher flexible
Has applications in phenolic laminates, brake linings, and abrasive products	Commonly used in adhesives, coatings, and specific molding compounds

VII.4. Synthesis method of Phenol-formaldehyde:

Phenol-formaldehyde resin is synthesized from phenol and formaldehyde by acidic or basic catalytic reactions.

The structure and properties of phenol formaldehyde resin are highly dependent on the reaction conditions, the type of catalysts and the reaction conditions, the type of catalyst and the molar ratio of the reactants.

Phenolic resins are classified as Novolac or Resol resin based on the pH and phenol to formaldehyde ratio used in the reaction. Resol type resins are formed under basic conditions when the molar amount of formaldehyde exceeds that of phenol.

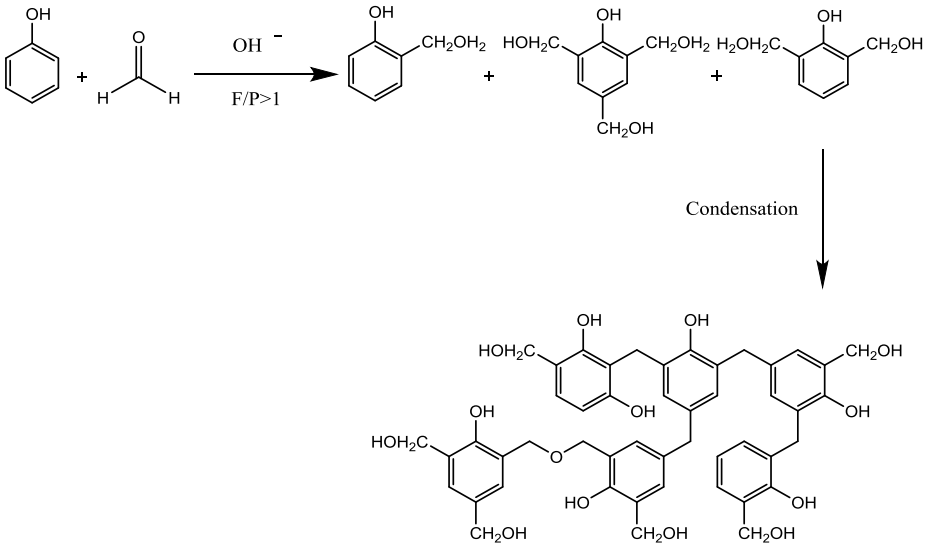
[28] Nathanael Chaussoy, 'These de Doctorat de L'universite De Lyon opérée au sein de sein de Lyon, Ecole Doctorale N° 34 Matériaux de Lyon' ' Synthése et Caractérisations de Résines Thermostables pour Matériaux Composites Carbonés' Page 115, (2021).

[29] Hasini. A, ' What is the Diffrence Between Resol and Novolac' PEDIAA, (2023).

They are thermosetting resins with methylol and hydroxyl groups capable of forming a cross-linked network without the need for network without the use of additional hardeners. This in itself represents a significant environmental advantage over novolac resins, since most curing agents used have toxic effects.

When the resin is prepared under acidic conditions andwithan excess of phenol compared to formaldehyde, a novolac type resin is formed.will be formed. Compared to Resol resins, the shelf life and stability of Novolacresinsishigher.However, an additional catalyst is required to cure novolac resins.

- Resolresin synthesis:



- Novolac resin synthesis:

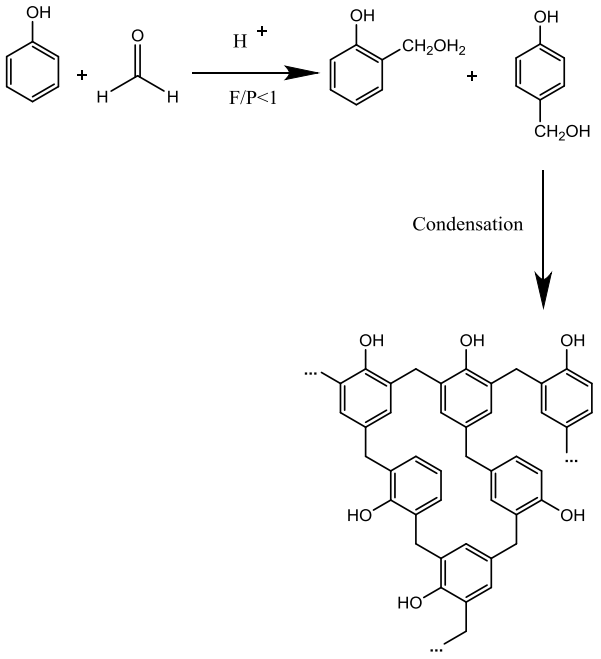


Figure 5: Schematic representation[30] of resol and novolac resin synthesis**.**

VIII.Gran method and Gran titration :

VIII.1. Titration of a Moderate, Weak or very Weak Strength Acid with a Strong Base. Methods of Schwartz and Gran(theory)[31] :

Titration is a method used to determine the concentration of components in a sample or a physicochemical parameter. Potentiometric titration is often used for measuring acidity constants in chemistry and biochemistry. The Gran method, a widely cited scientific paper, is used to study its advantages and limitations. The Gran plot methodology, developed by Schwartz, is a powerful tool for determining titration end points and acidity constants simultaneously. Applications include evaluating the autoprotolysis constant of water and determining equivalence point and acidity constant in potentiometric titrations. The paper also discusses various bibliographic and experimental systems.

Gran presented his paper at the International Congress of Analytical Chemistry in 1952, which was published in The Analyst. The paper, along with four other papers, included discussions with chemists like Lindsey, Sillen, Bishop, and Johansson. The paper's success and widespread applicability were influenced by Gran's meticulous work on the method. By modifying data analysis, Gran plot methodology can be extended to acidic or basic analyte solutions that would be difficult to treat by conventional equations. Schwartz later showed

[30] P. R. Sarika , Paul Nancarrow, Abdulrahman Khansaheb and Taleb Ibrahim, 'Bio-Based Alternatives to Phenol and Formaldehyde for the Production of Resins', polymers, MDPI, (2020).
[31] Julia M, Davinia Barrios R, Agust G, Asuero, 'Determination of the end point in potentiometric titration: Gran and Schwartz Methods' Journal of Laboratory Chemical Education, 6(4), Page 79, (2018).

how the equation could be cast in a form that didn't require prior knowledge of the acidity constant, making it more useful for numerical analysis.

X- Applications of polymers :

Table 2: Examples of some polymer and their applications[32].

Material	Typical Use
Cellulose nitrate	Eyeglass frames
Phenol–formaldehyde	Telephone handsets, knobs, handles
Cellulose acetate	Toothbrushes, packaging
Poly(vinyl chloride)	Raincoats, flooring
Urea–formaldehyde	Lighting fixtures, electrical switches
Ethyl cellulose	Flashlight cases
Polyacrylonitrile	Brush backs, displays
Poly(vinyl acetate)	Flashbulb lining, adhesives
Polystyrene	Kitchenwares, toys
Nylon (polyamide)	Gears, fibers, films
Poly(vinyl acetal)	Safety glass interlayer
Poly(vinylidene chloride)	Auto seat covers, films, paper, coatings
Polyester (cross-linkable)	Boat hulls
Polyethylene (low density)	Squeezable bottles
Fluoropolymers	Industrial gaskets, slip coatings
Silicone	Rubber goods
Cellulose propionate	Automatic pens and pencils
Acrylonitrile-butadiene-styrene copolymer	
Polyurethane	Luggage, radio and television cabinets
Polypropylene	Foam cushions
Polyphenylene oxide	Safety helmets, carpet fiber
Polyimide	Battery cases, high temperature moldings
	Bearings, high temperature films and wire coatings
Polybutene	Films
Thermoplastic polyester	Electrical/electronic parts
Nitrile barrier resins	Containers

[32] Robert O. Ebewele, 'Polymer Science and Technology, (2000).

Chapter 02: *Chemical data for calixarene*

I. History:

The story of calixarene started when Adolf von Baeyer published two papers[33] in ChemischeBerichte in 1872 dealing with the results of mixing aldehydes and phenols in the presence of strong acids. Specific examples of these reactions are discussed in the second paper, including the reaction of benzaldehyde and pyrogallol. In the third paper[34], the reaction with formaldehyde is presented, the only results of these studies were brittle solids "cement-like"or viscous liquids (black, resinous tar) that seemed to have no practical use. advanced chemical techniques were not available to identify this material[35].

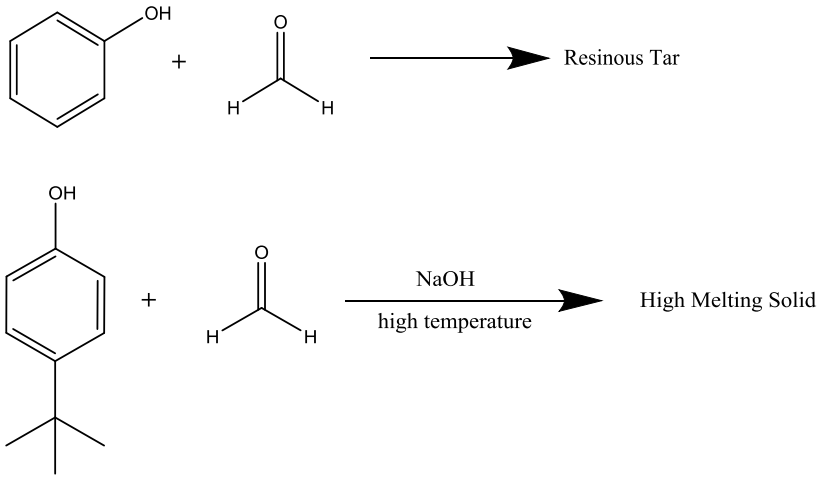


Figure 6: reactions of phenol with formaldehyde.

Intending to develop a synthetic substitute for shellac. Leo Baekland[3637] discovered that heating Baeyer's resinous tar turned it into a hard brittle.On 18 February 1907, he filed for a patent on this process for making a material that he eponymously called Bakelite. With this, the age of modern synthetic plastics had begun.[38]

[33] A. Baeyer, Ber, Ueber die Verbindungen der Aldehyde mit den phenolen., ***Berichte der deutschenchemischen Gesellschaft***, 5, 280-282, (1872).
[34] A. Baeyer, Ber, Ueber die Verbindungen der Aldehyde mit den Phenolen und aromatischenKohlenwasserstoffen, ***Berichte der deutschenchemischen Gesellschaft***, 5, 1094- 1100. (1873).
[35]V. Jacques, H. Jack, Calixarenes in the Nanoworld., Ed hardcover, p 1-19,(2007).
[36]***L. H Baekeland, Method of making insoluble products of phenol and formaldehyde, UNITED STATES PATENT OFFICE, US942699A, (1909).***
[37] Anonyme Wikipedia, **Bakelite,**https://en.wikipedia.org/wiki/Bakelite.

[38] J. L. Meikle, American Plastic: A Cultural History, Ed: Rutgers University Press, p 58-59, (1995).

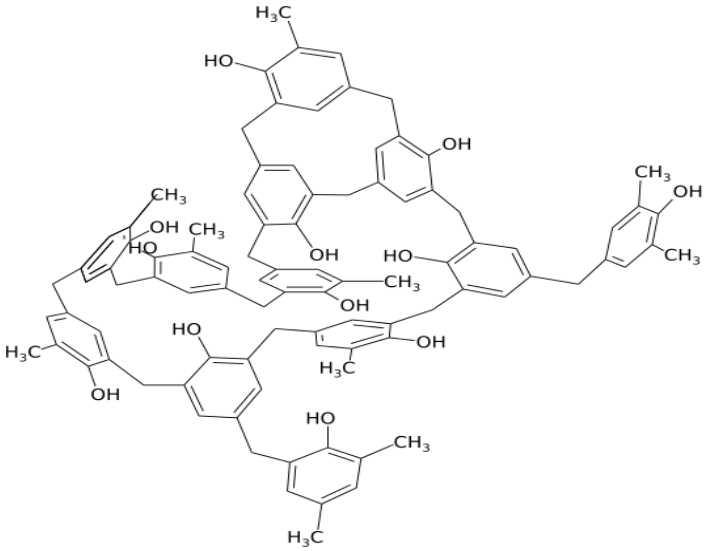
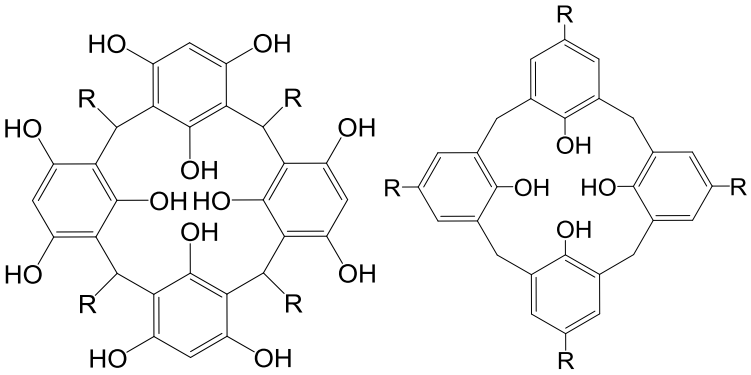


Figure 7: the 3D Chemical formula of the structure of Bakelite.

In the 1940s, Zinke and Ziegler[39] assigned cyclic tetrameric structures to the products of the base-induced reaction of p-substituted phenols with formaldehyde I, while Niederl and Vogel[40] did the same for the products from the acid-catalyzed reaction of resorcinol with aldehydes II. The more recent research by Gutsche[41] and Högberg[42] has shed light on these base- and acid-induced processes, which are increasingly recognized as highly effective methods for synthesizing calixarenes.



II I

[39] A. Zinke, E. Ziegler, Zur Kenntnis des Härtungsprozesses von Phenol-Formaldehyd-Harzen, X. Mitteilung, Berichte der deutschenchemischen Gesellschaft (A and B Series), 77(3-4), 264–272 (1944).

[40] B. J. Niederl, H. J. Vogel, Aldehyde—Resorcinol Condensations, *J. Am. Chem. Soc*, 62, 9, 2512–2514, (1940).

[41] C. D. Gutsche, B. Dhawan, et al : Calixarenes. 4. The Synthesis, Characterization, and Properties of the Calixarenes from p-tert-Butylphenol, J. Am. Chem. Soc, 103, 3782-3792, (1981).

[42] A. G. Sverker Hoegberg, Cyclooligomeric phenol-aldehyde condensation products. 2. Stereoselective synthesis and DNMR study of two 1,8,15,22 tetraphenyl[14]metacyclophan-3,5,10,12,17,19,24,26-octols *J. Am. Chem. Soc*, 102, 6046–6050, (1980).

II. General information on Calixarenes.

II.1. Definition:

The molecule basket now called calixarenes are macrocyclic compound (cyclic oligomer) based on phenolic units bound to each other with bridging groups, calixarenes are named after the Greek word calix or chalic because this type of molecule resembles a vase (or cup), and arene from the aromatic building block, with defined upper and lower rims and a central annulus with hydrophobic cavities.[43,44]

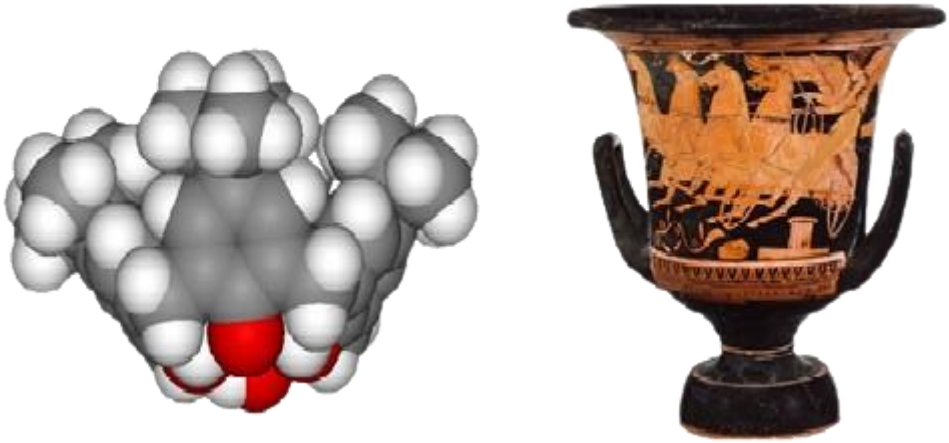
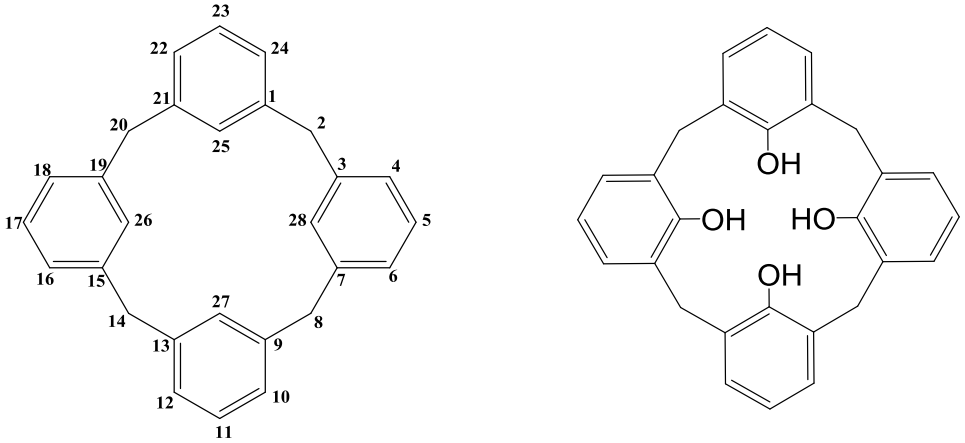


Figure 8:3D representation of a cone-shaped structure resembling a Greek vase.

II.2. Nomenclature:

In the IUPAC system ofnomenclature, a specific member of this group (as represented by structure 1) is named and it is numbered as shown in Figure 12; hydrocarbon cyclo[oligo[(1,3-phenylene) methylene][45]

[43]C. D. Gutsche, in Calixarenes: An Introduction, The Royal Society of Chemistry, Ed 2, p 24, (2008).
[44]C. D.Gutsche, Calixarenes revisited, Ed: The Royal Society of Chemistry.(1998).
[45]IUPAC, Glossary of class names of organic compounds and reactivity intermediates based on structure, 67,1323, (1955).



1 2

Figure 9:poly-aryl m-methylen-brided macrocyclic compounds.

An alternative nomenclature for this type of ring structure was suggested by Cram and Steinberg[46], according to which 1 is named [l.l.l.l]metacyclophane. Several research groups have reported syntheses of the tetrahydroxy derivatives of 1 (as represented by structure 2)and have named them in various ways. For the convenience of written and verbal discussion,C. David Gutsche[47] decided to name him "calixarenes".

The term ”calixarene” originated to describe the conical shape of cyclic tetramers and now includes all compounds derived from phenol, pyrogallol, and resorcinol. 'Calixarene' specifically denotes the unsubstituted core structures. The macrocycle's size is indicated by a number in brackets between 'calix' and 'arene', and the nature and positions of substitutions on the aromatic rings are specified with corresponding numbers and descriptors.

The cyclic tetramer composed of p-tert-butylphenol units and methylene units, for example, is named 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetrahydroxycalix[4]arene; in abbreviated fashion referred to as p-tert-butylcalix[4]arene.

[46]J. D. Cram, H. Steinberg, Macro Rings. I. Preparation and Spectra of the Paracyclophanes. Journal of the American Chemical Society, 73(12), 5691–5704, (1951).
[47]C. D Gutsche, The calixarenes. In: Structural Chemistry. Topics in Current Chemistry, vol 123. Springer, Heidelberg, (1984).

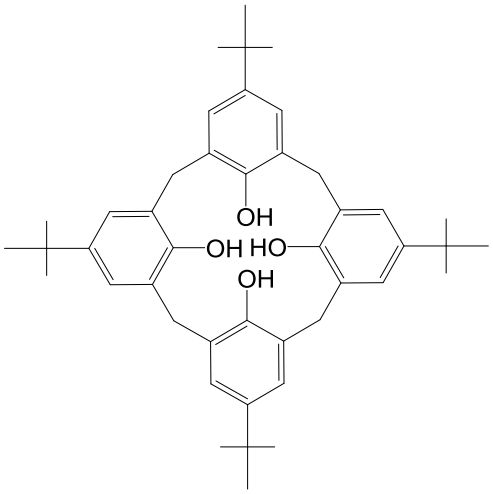


Figure 10: Structure of p-tert-butylcalix[4]arene

Calixarenes are compounds synthesized from phenols, resorcinol, or pyrogallol and are named accordinglyas phenol-derived calixarenes, calixresorcinarenes, and calixpyrogallolarene.

Calixarenes, named after the Greek word for a type of vase, traditionally have their structures depicted with OH groups pointing downwards (endo) and p-substituents upwards (exo). Consequently, the endo face is referred to as the "lower rim" and the exo face as the "upper rim," as shown in Figure 15

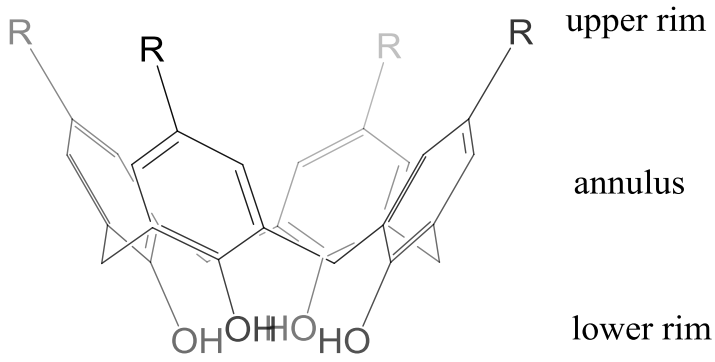


Figure 11:conformations of a typical calix[4]arene.

However, for larger calixarenes lacking distinct "upper, wide" or "lower, narrow" rims, the designation relies solely on the cyclic structure itself, irrespective of orientation or shape. the "endo rim" corresponds to the lower, narrow rim, and the "upper, wide rim" is termed the "exo rim The phenol-derived and resorcinol-derived calixarenes can be distinguished by referring to the former as endo-OH calixarenes, meaning the OH groups are

oriented toward the annulus, and the latter as exo-OH calixarenes, where the OH groups are oriented away from the annulus[48]. In calix[4]arenes, adjacent nuclei are termed "proximal" or (1,2), while the opposite ones are "distal" or "diametrical" (1,3) positions.[49]

II.3. Conformationnel représentationand nomenclature:

Cornforth [50] first recognized the calixarenes as capable of assuming four conformations, with various numbers of aryl groups projecting upward ('u') or downward ("d") relative to an average plane defined by the bridge methylene groups. These were later named by Gutsche[51] as 'cone' (u,u,u,u), 'partial cone' (u,u,u,d), '1,2-alternate' (u,u,d,d), and

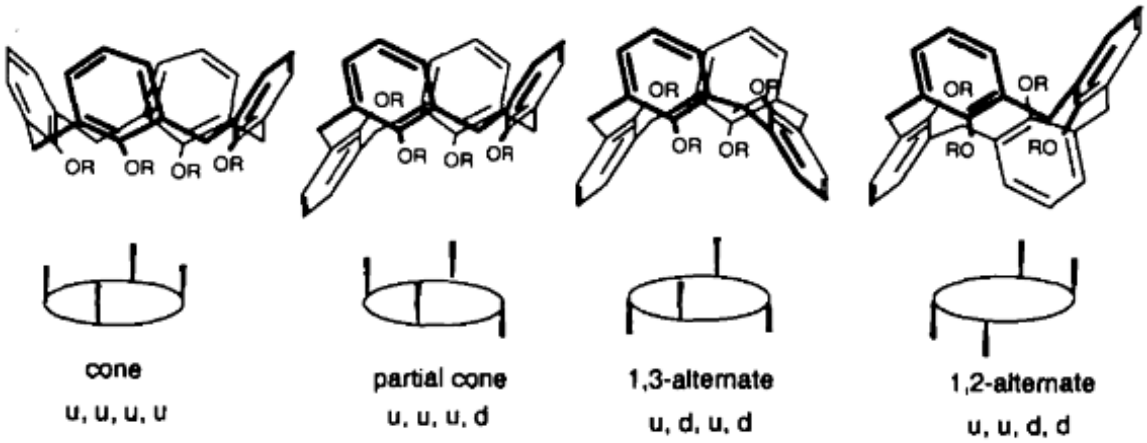


Figure 12: Calix[4]arenederivative conformations.

'1,3-alternate' (u,d,u,d). As the number of aryl groups in a cyclic array increases (as n increases), the number of possible conformations also increase. for exempl: calix[6]arenes have eight, calix[8]arenes have sixteen, etc.

Additionally, with all of the calixarenes, there can be departures from the true "up/down' orientations. The aryl rings can project outward (o), and the more flexible the system is, the greater the likelihood of aryl residues projecting outward.

The number of possible conformers for calixarenes increases significantly with the addition of more rings. Representing them in a simple pictorial or linear fashion becomes a challenging task. The "up, down, out" designations work well for calix[4]arenes, calix[5]arenes, and to some extent calix[6]arenes. However, beyond this point, these

[48]Carl David Gutsche,Calixarenes: An Introduction, The Royal Society of Chemistry, Ed 2, pp. 24-26,(2008).
[49]ROCCO UNGARO, Calixarenes in Action, World scientific, pp. 1-10, (2000).
[50] J. W. CORNFORTH, P. D'ARCY HART, et al, ANTITUBERCULOUS EFFECTS OF CERTAIN SURFACEACTIVE POLYOXYETHYLENE ETHERS, J. Pharmacol, 10, 75, (1955)
[51]Carl David Gutsche,Calixarenes: An Introduction, The Royal Society of Chemistry, Ed 2, pp. 77-115, (2008).

designations become imprecise. When it comes to calixarene derivatives such as ethers and esters, the "up" and "down" designations must consider the method of substitution.

To do this, the Cahn-Ingold-Prelog priority rules are used to select a reference aryl group. For instance, a p-tert-Bu-ArOMe ring takes precedence over a p-tert-Bu-ArOH,ring takes precedence over a p-tert-Bu-ArOH ring takes precedence over a p-MeArOH ring, an ArSO, ring takes precedence over an ArCO ring, etc.

When two or more aryl rings are identical, the one surrounded by the most higher priority aryl rings is selected the reference group is denoted by a bold-faced or underlined u or d (or both) and canbe arbitrarily assigned an 'up' orientation in most instances.

To designate the other aryl groups in the cyclic array, proceed around the ring along the pathway that encounters the groups of higher priority using the "outward exploration concept" of the Cahn-Ingold-Prelog rules. An example is shown in Figure 16, where the priority of the rings is established by OBz>OPr> H. and the aryl ring syn to the reference ring takes precedence over the aryl ring anti to the reference ring.[52]

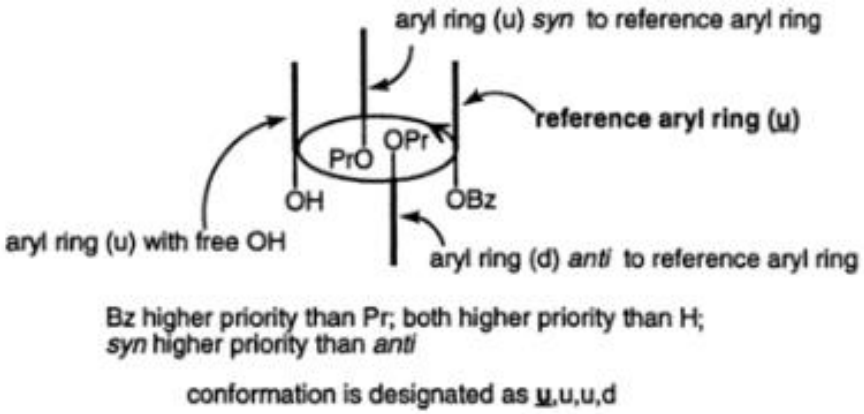


Figure 13: designation of an O-substituted calix[4]arene.

Scrutinizing their 1H and 13C NMR spectra can readily ascertain their identity. Of particular significance are the ^{1}H and^{13}C NMR profiles of the bridging methylene groups, which exhibit distinct characteristics for three out of four conformations (refer to Fig 18). While the 1,2-alternate conformation is less frequent, its NMR pattern is akin to that of the partial cone.

Nonetheless, differentiation between these two conformations can be achieved by examining the aromatic region of the spectrum. A useful correlation "rule" has been

[52] C. D. Gutsche, in Calixarenes Revisited, Ed: The Royal Society of Chemistry, pp. 41-78, (1998).

introduced by De Mendoza and colleagues[53], which allows for the analysis of the ^{13}C NMR spectra of calixarenes with their conformation." The resonance resulting from the bridge methylene carbon has been demonstrated to be approximately δ 31 when two adjacent aryl groups are in the syn orientation (i.e. both "up" or both "down") and approximately δ37 when they are in the anti-orientation (i.e. one group "up" and the other group "down"). This De Mendoza rule has been effectively utilized not only for calix[4] but also for Calix(5)- and calix[6]arenes[54]

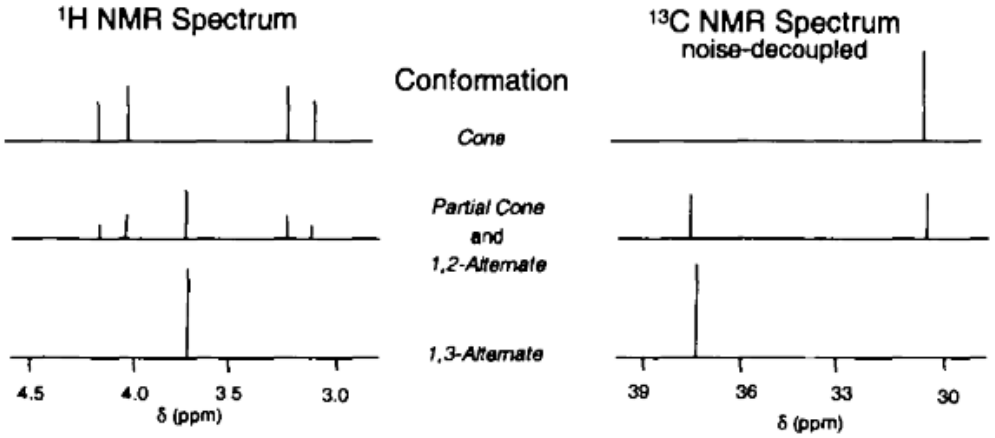


Figure 14: The ^{1}H and ^{13}C NMR spectra of the four different shapes of calix[4]arenes by analyzing their signal patterns.

III. The Synthesis of symmetrically andasymmetrically substituted calix(4)arenes in Base-induced:

III.1. One step:

Preparing p-tert-butylcalix[4]arene has been unpredictable, with inconsistent yields even under identical reaction conditions. The reasons for this variability are still unknown. A reliable set of guidelines was established after examining the impact of different amounts of base under varying temperatures. The technique, devised by Zinke [55] and refined by Cornforth[56] and Gutsche[57],

[53]C Jaime, J. Mendoza, et al., Carbon-13 NMR chemical shifts. A single rule to determine the conformation of calix[4]arenes J. Org. Chem. 56, 3372-3376, (1991).
[54]ROCCO UNGARO, Calixarenes in Action, World scientific, pp. 1-10, (2000).

[55]A. Zinke and E. Ziegler, Zur Kenntnis des Härtungsprozesses von Phenol-Formaldehyd-Harzen, X. Mitteilung, Berichte der deutschenchemischen Gesellschaft., 77, 264, 272, (1944).

[56]J. W. Cornforth, E. D. Morgan, et al,Preparation of antituberculouspolyoxyethylene ethers of homogeneous structure Tetrahedron, 29, 1659,(1973).

III.2. Multi-step:

III.2.1. Convergent StepwiseSyntheses (Fragment Condensation Procedure):

Calix(4)arenes featuring various phenolic units in a specific sequence can be synthesized through a stepwise process in this procedure, the last step involves the cyclization of a monohydroxymethylated linear tetramer

Böhmer [58] expanded on his research on the effects of hydrogen bonding in polyphenolic systems by searching for cyclic oligomers with chemically more interesting functionality. This led him to investigate a "3 + 1" approach, as depicted in Figure 2.5.

Interestingly, incorporating hetero atoms and functional groups as p-substituents can impact the yield. To improve the yields, excess TiCl4 has been used as a catalyst.

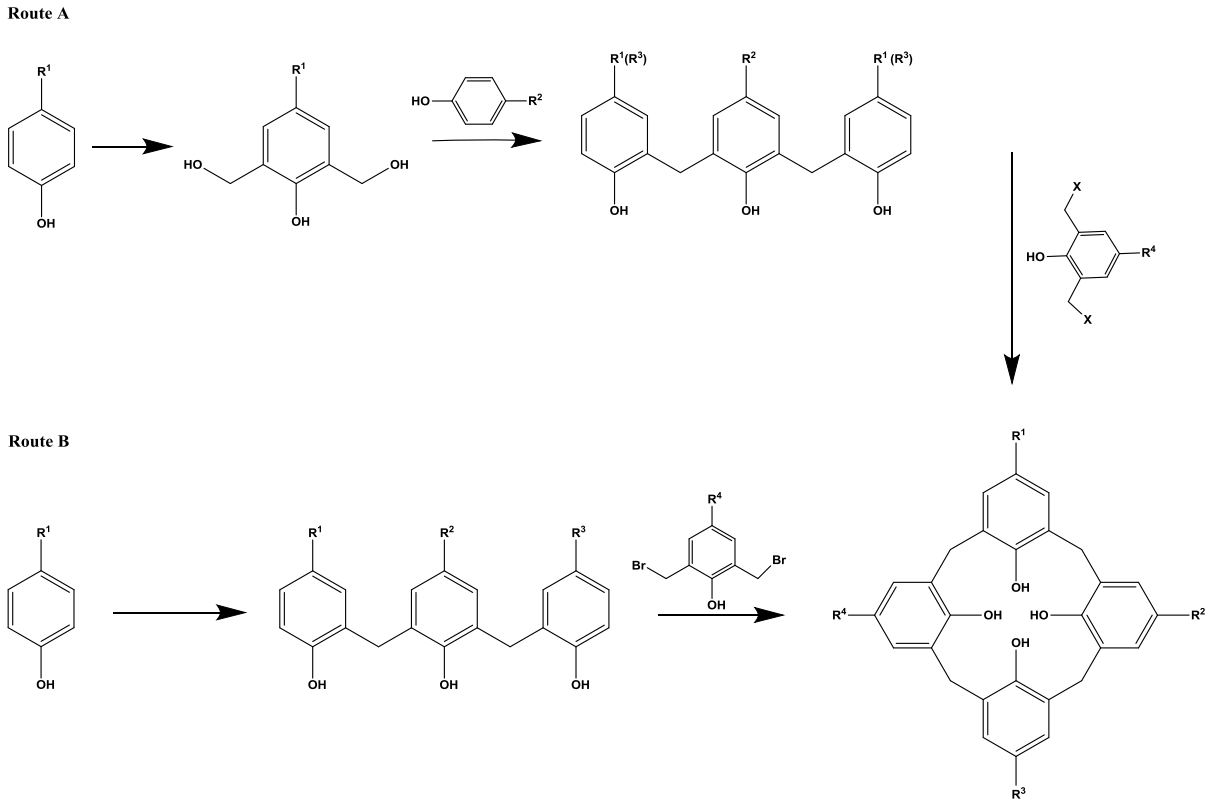


Figure 15: the convergent fragmentation condensation"3 + 1"

[57] C. D. Gutsche, M. Iqbal, *p-tert*-BUTYLCALIX[4]ARENE,*Org. Synth.68*, 234, (1990).
[58] V. Böhmer, P. Chhim, & H. Kämmerer, A new synthetic access to cyclic oligonuclear phenolic compounds. Die MakromolekulareChemie: Macromolecular Chemistry and Physics, 180(10), p 2503-2506,(1979).

Additionally, Böhmer and coworkers[59] have extensively studied the complementary "2+2" procedure, as shown in Figure 2.6. For instance, p-chlorocalix[4]arene can be obtained from the condensation of p.p'-dbromodiphenylmethane using this procedure.

To obtain a definite product, a necessary condition in this case is $R^1 = R^2$ or $R^3 = R^4$. The condensation is carried out in dioxane, using TiC14 as a catalyst

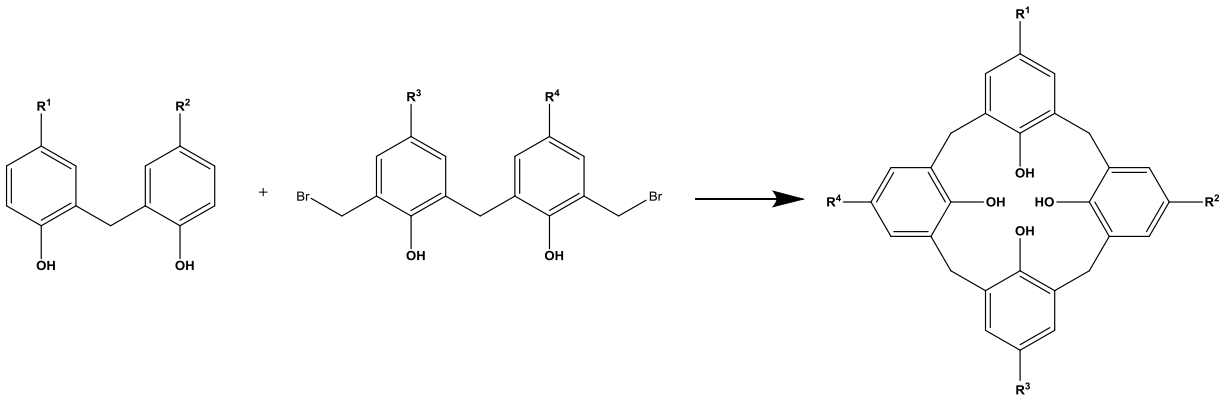


Figure 16: the convergent fragmentation condensation"2 + 2"

III.2.2. Non-Convergent StepwiseSyntheses:

The Hayes and Hunter method[60], illustrated in Figure 1.1, is a classic example of using a blocking group to protect a reactive site, which is then removed to allow for reaction. They selected a bromine atom as the protecting group and incorporated it in the initial step of the process by adding it to one of the ortho-positions of p-cresol.

[59] V. Böhmer, L. Merkel and U. Kunz, Asymmetrically-substituted Calix(4)arenes, J. Chem. Soc. Chem. Commun, 896, (1987).
[60] B. T. Hayes, R. F. Hunter, Phenol-formaldehyde and allied resins VI†: Rational synthesis of a 'cyclic' tetranuclear p-cresol novolak, J. appl. chem., 8, 743-748, (1958).

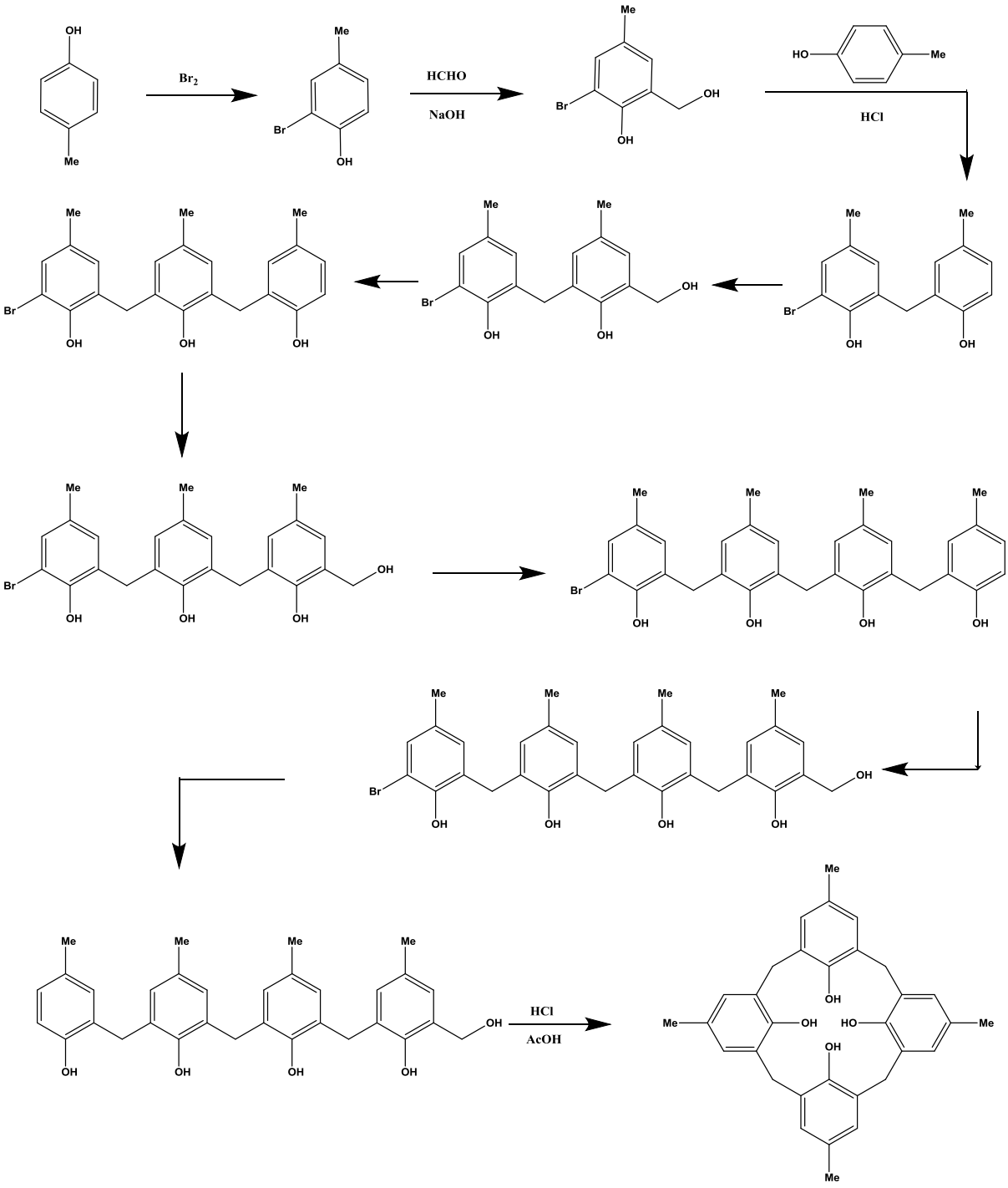


Figure 17: Hayes and Hunter Stepwise Syntheses of a calix[4]arene.

IV. Reactivity of Calixarenes :

Many reactions of calixarenes have been extensively documented. To enhance the characteristics of calixarenes, modifications are made to both their narrow and wide rims.

The functionalization of calix[4]arene is one of the key features that makes it more special when compared with other macrocycles, There are two primary locations for modifying a calixarene: the phenolic hydroxy groups (which allow for the creation of ethers and esters)[61] and the p-positions (which facilitate electrophilic and ipso-substitution)[62,63]. Each of these can be addressed separately. Additionally, reactions may be performed on the methylene bridges, the aromatic system of the phenolic units as a whole (through oxidation or hydrogenation), or through the replacement of the OH function with other groups like S or N.

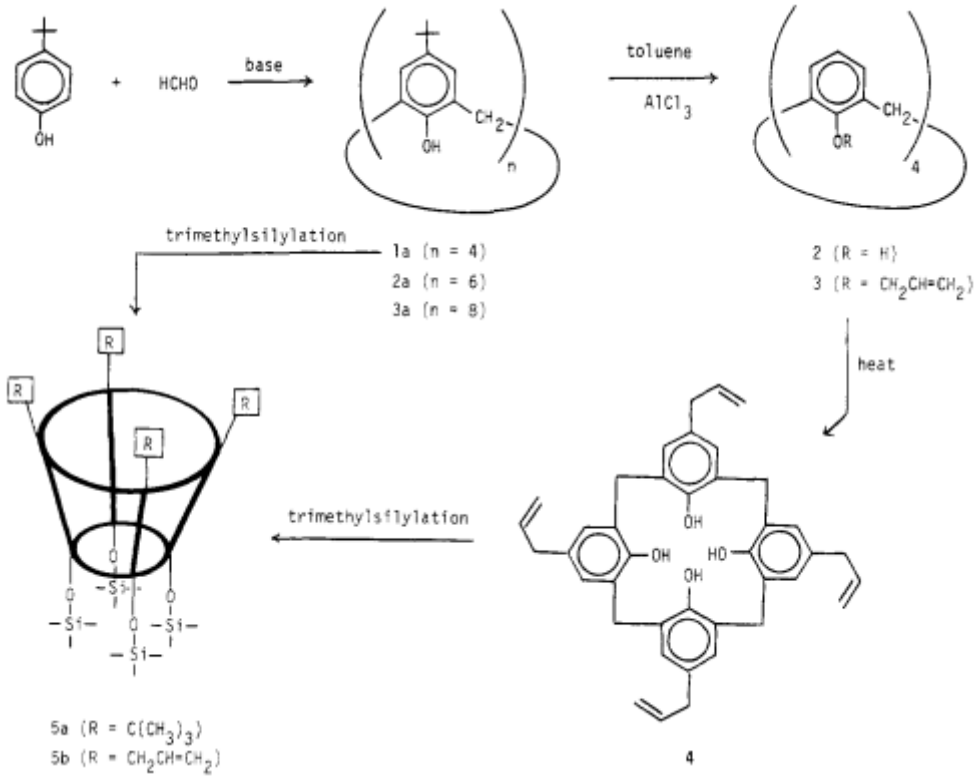


Figure 18: The functionalization of calix[4]arene[64].

[61] F. Arnaud-Neu, E. M. Collins, et al, Synthesis, x-ray crystal structures, and cation-binding properties of alkyl calixaryl esters and ketones, a new family of macrocyclic molecular receptors, J. Am. Chem. Soc. 111 (23), 8681-8691, (1989).
[62]Y.-S. Zheng, Z.-T. Huang, SYNTHESIS OF p-ALKYLCALIXARENES BY FREDELCRAFTS ALKYLATION, Synth. Commun. , 27, 1237 -1245, (1997).
[63]Y. Morzherin, D. M. Rudkevich, W. Verboom, D. N. Reinhoudt, ChlorosulfonylatedCalix[4]arenes: Precursors for Neutral Anion Receptors with a Selectivity for Hydrogen Sulfate, J. Org. Chem, 58, 7602-7605, (1993).
[64]C. David Gutsche, Jeffrey A. Levine, Calixarenes. 6. Synthesis of a FunctionalizableCalix[4]arene in a Conformationally Rigid Cone Conformation, J. Am. Chem. SOC., 104, 2653-2655, (1982).

V. Applications of calixarenes:

Analytical applications of calixarenes

Calixarenes are used in High-Performance Liquid Chromatography (HPLC)[65] due to their ability to interact with a wide range of molecules,[66]

Calix[n]arenes as Organocatalysts

Calix[n]arenes are important platforms for the construction stable, easy-to-handle, and recyclable catalysts that facilitate various chemical transformations.[67] described in 2019, proved to be an effective catalyst for synthesizing a series of polysubstituted pyridines and bis-pyridines from aromatic aldehydes, malononitrile, 1,3-diketones, and arylamines in water.[68]

SupramolecularChemistry:

They are renowned for their role in host-guest interactions, where they can encapsulate smaller molecules or ions within their hydrophobic cavities, Calixarenes are used in, molecular sensing, Solar Energy Conversion in Photoelectrochemical Cells[69], functional materials, and molecular machines due to their reversible and dynamic interactions with guest molecules.[70]

Biomedical Applications:

Calixarenes are utilized in biosensing, bioimaging, and drug/gene delivery[71] systems. Some derivatives also exhibit biological activities, making them potential therapeutic agents.[72]

[65] . Maciej Barc, MagdalenaSliwka-Kaszynska, Preparation and evaluation of 1,3-alternate 25,27-bis-(pentafluorobenzyloxy)-26,28-bis-(3-propyloxy)-calix[4]arene-bonded silica gel high performance liquid chromatography stationary phase . J. Chromatogr. A, 1216 3954–3960, (2009).
[66]B Mokhtari ; K Pourabdollah ; N Dalali, Analytical applications of calixarenes from 2005 up-to-date, J Incl Phenom Macrocycl Chem 69:1–55, (2011).
[67] N. Alishahi, I. Mohammadpoor-Baltork, et al, Calixarene Based Ionic Liquid as an Efficient and Reusable Catalyst for One-Pot Multicomponent Synthesis of Polysubstituted Pyridines and Bis-pyridines, ChemistrySelect, 4, 5903–5910, (2019).
[68] J B Simões, D L da Silva et al , Calix[n]arenes in Action: Recent Applications in Organocatalysis, Eur. J. Org. Chem. (38), 1-24, (2022)
[69]Dr. C Decavoli, Dr. L Chiara, et al, Calix[4]arene-Based Sensitizers for Host-Guest Supramolecular Dyads for Solar Energy Conversion in Photoelectrochemical Cells.Volume2022, Issue34, (2022).
[70]R Nag, CP Rao Calixarene-mediated host-guest interactions leading to supramolecular assemblies: visualization by microscopy,Chemical Communications (Cambridge, England), 58(41):6044-6063, (2022).
[71]Giulia Neri, Enza Fazio, and Carmelo Corsaro,Role of Calixarene in Chemotherapy Delivery Strategies, Molecules, 26, 3963, (2021).
[72]Pan YC, Hu XY, Guo DS. Biomedical Applications of Calixarenes: State of the Art and Perspectives. AngewandteChemie (International ed. in English). 60(6):2768-2794, (2021).

Chapter 03:*Antibacterial Activity*

I. Historic:

The discovery of bacteria, one of Earth's most prevalent life forms, can be traced back to 1677 when Antonie van Leeuwenhoek [73] a Dutch naturalist, first observed these microscopic organisms, He used a simple single-lens microscope he designed himself and referred to them as "animalcules" due to their minuscule size and active movements.

In the 19th century, Christian Gottfried Ehrenberg[74] introduced the term "bacteria" for these organisms. Subsequently, Robert Koch[75] established that bacteria can cause diseases, marking a pivotal moment in the development of modern germ theory.

While most bacteria are innocuous and play a vital role in ecological processes supporting higher life forms, some can cause diseases in humans, animals, or plants.

II. Bacteriadiffinition:

Bacteria[76] live in many different environments around the world. They live almost everywhere, including inside our bodies. Most bacteria do not harm humans, but some can infect humans and cause disease. In fact, bacteria have caused some of the most devastating diseases in human history, such as bubonic plague and dysentery

Bacteria are single-celled and prokaryotic, which means they have no nucleus and are much simpler than eukaryotic cells. Also, unlike eukaryotic cells, most bacteria have a cell wall. The composition of the cell wall varies, and this variation helps scientists tell bacteria apart. Gram staining helps scientists distinguish between types of bacteria based on the components of their cell walls. It is often used as a diagnostic test to determine which type of bacteria is causing an infection. Although bacteria are diverse, they come in three main shapes: rod, sphere, and curved.

[73] A. V. Leewenhoeck, Observations, Communicated to the Publisher by Mr. Antony van Leewenhoeck, in a Dutch Letter of the 9th of Octob. 1676. Here English'd: concerning Little Animals by Him Observed in Rain-Well-Sea. and Snow Water; as Also in Water Wherein Pepper Had Lain Infused, Philosophical Transactions of the Royal Society of London, 12(133-142), 821–831, (1966).
[74] C.G. Ehrenberg, DieInfusionsthierchenalsvollkommeneOrganismen. Ein Blick in das tiefereorganische Leben der Natur. Ed : Leipzig: Verlag von Leopold Voss(1838).
[75]R. Koch, Investigations Into the Etiology of Traumatic Infective Diseases, Ed: New Sydenham Society, p 35-37, (1880).
[76] Sarah Appleton, Margot Willis, National Geographic Society, 'Bacteria Encyclopedic Entry', (2023).

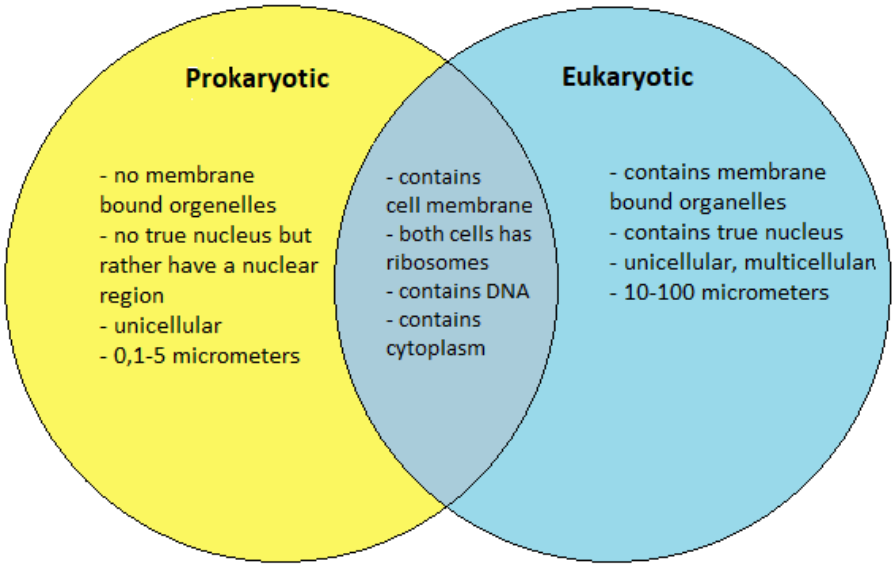


Figure 19: Schematic comparison between a prokaryotic cell and a eukaryotic cell.[77]

Bacterial infections can be caused by ingestion, inhalation it can spread throughout the body through the bloodstream. Toxins produced by bacteria cause illness by attaching to cellular structures. Improved hygiene and antibiotics have helped to reduce bacterial infections. through, targeting specific bacteria and killing cell walls, DNA or ribosomes. Overuse can lead to resistance, making infections harder to treat. Most bacteria are not harmful as they contribute to our microbiome, which helps us stay healthy.

III. Classification:

Bacteria [78] are classified and identified to differentiate between strains and to categorize them according to criteria significant to microbiologists and other scientists. Bacteria are indeed classified based on numerous characteristics, such as cell shape (Morphology), the nature of multicellular aggregates, motility, spore formation, and reaction to the Gram stain[79]. The latter, which indicates fundamental differences in cell wall structure, divides most bacteria into two major groups: Gram-positive and Gram-negative bacteria.

[77] Anonymous, https://study.com/skill/practice/comparing-the-components-of-prokaryotes-eukaryotes-questions.html.
[78]AnnonymeKadner, Robert J. and Rogers, Kara. "bacteria". ***Encyclopedia Britannica***, (2024), https://www.britannica.com/science/bacteria.
[79] H. C. Gram, "über die isoliertefärbung der schizomyceten in schnitt- und trockenpräparaten". fortschritte der medizin, 2(6), 185-189, (1884).

Gram-positive bacteria: Have a thick peptidoglycan layer in their cell wall and retain the crystal violet stain, appearing purple under a microscope (such us Staphylococcus aureus).

Gram-negative bacteria: Have a thin peptidoglycan layer and an outer membrane, do not retain the crystal violet stain, and appear red or pink after counterstaining with safranin (for example *Escherichia coli*).

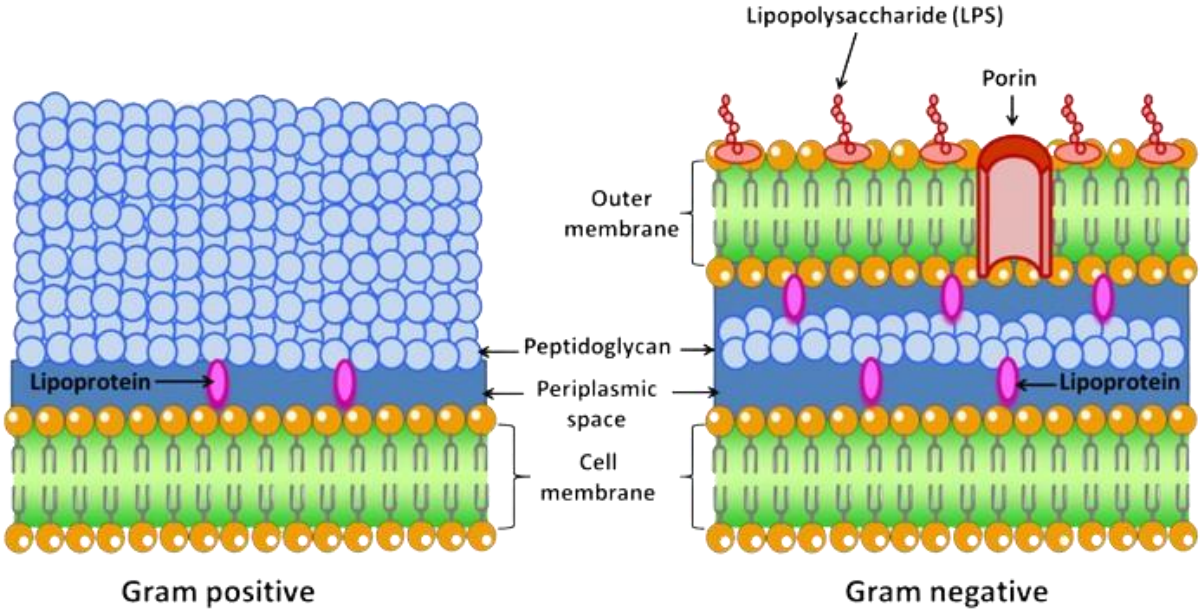


Figure 20: Differences between Gram-negative and Gram-positive bacteria.

IV. Types of certain bacteria:

IV.1. *E coli* (*Escherichia coli*):

V. Escherichia coli (E. coli) is a gram-negative, oxidase-negative bacterium found in the digestive tract of humans and other organisms. It produces Shiga-like toxins, similar to those produced by Shigella dysenteriae. The optimum temperature for growth is 37°C. Cooking destroys shigatoxin-producing E. coli if food is thoroughly cooked. Pathogenic strains are grouped into pathovars or pathotypes[80].

[80] Agence nationale de sécurité sanitaire alimentation, environnement, travail (anses), 'Escherichia coli entérohémorragiques (EHEC)', (2019).

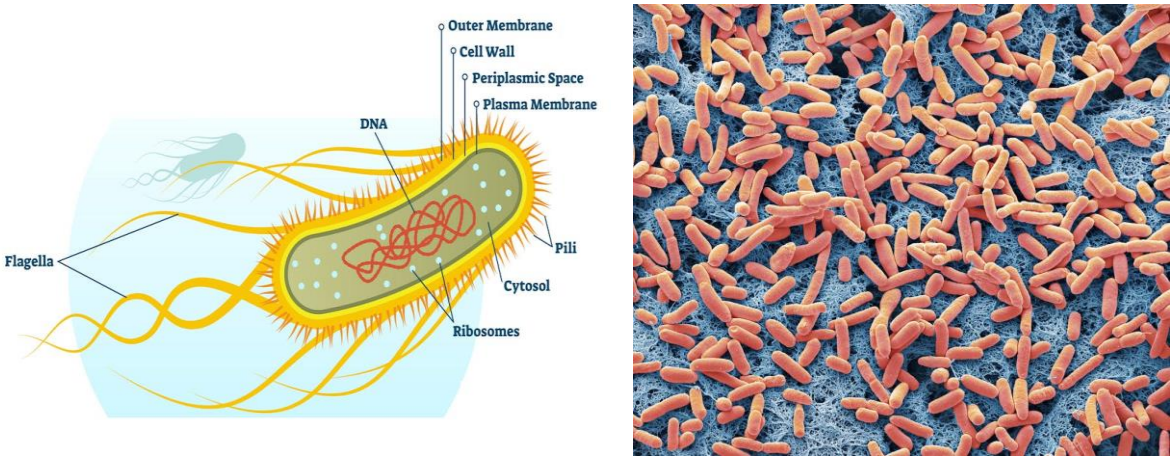


Figure 21: Cellular structure of *Escherichia coli*[81].

V.1. *KP bacteria* (*Klebsiella pneumoniae*):

Klebsiella pneumoniae [82] belongs to *klebsiella*. In 1882 German physician K. Friedlander was the first to isolate *K. pneumoniae* from the lungs of patients who died of pneumonia, and this bacterium was initially named Friedlander's bacillus. The biological shape of *K. pneumoniae* is a short and thick bacillus with a size of 0.5–0.8×1–2 μm, arranged separately, in pairs or short chains.

Klebsiella pneumoniae, is a Gram-negative bacterium, causes various infections, including bacteremia, pneumonia, and urinary tract infections. Hypervirulent strain, resistant to antibiotics, increases siderophore production, enhancing bacterial growth efficiency.[83]

It can cause both nosocomial and community-acquired pneumonia is sometimes called Friedlander's pneumonia.Its incidence and location Usually lobar, with upper lobes most common[84].

[81] Megan Keller, Tobias Dorr, 'E. coli is one of the most widely studied organisms and that may be a problem for both science and medicine', The conversation (an independent source of news and views from the academic and research community), (2023).
[82] Qinqin pu, Min wu, 'Molecular medical microbiology (third edition), Klebsiella pneumoniae', (2024). Chapters and articles From 'Infectious diseases (fourth edition)', (2017).
[83] Rim Abbas, Mohamed Chakkour, Hiba Zein El Dine, Eseiwi Folorunsho Obaseki, Soumaya T. Obeid, Aya Jezzini, Ghassan Ghssein and Zeinab Ezzeddine, 'General overview of klebsiella pneumonia: Epideemiology and the role of siderophores in its pathologenicity', MDPI, volume 13, (2024).
[84] Carol F. Farver,'Pulmonary pathology (Second Edition)', (2018). Chapters and articles, Bishoy Moher Zaki, Ayman El-Shibiny, 'Progress in molecular biology and translational science' (2023). From the laboratory rabbit, guinea pig, hamster and other rodents', (2012).

V.1.1. Pulmonary infection of*klebsiella pneumonia*:

Klebsiella pneumonia[85], a common ventilator-associated pneumonia, is often caused by immunocompromised patients due to age, ethanol abuse, or diabetes. It produces lobar pneumonia, hemorrhagic necrosis, microabscesses, and cavity formation.

V.2.*Listera* :

Listeria are Gram-positive microorganisms found in water, plants, and mammalian habitats, includes pathogenic and non-pathogenic species. Pathogenic species cause disease in animals, while non-pathogenic species cause diseases in humans. L. monocytogenes is a major food-borne pathogen, affecting soft cheese brands. Modern food production must ensure product safety.[86] It is a Gram-positive rod that is typically of 0.5–2 μm in length. It is non-spore-forming, and is not encapsulated. *Listeria* can appear coccoid and motile depending upon the growth temperature. They have an optimum growth temperature of 30–37°C.[87]

Listeria monocytogenes causes listeriosis, a foodborne illness causing gastroenteritis and spreading beyond the intestines. Pregnant women are 10 times more likely to contract the infection.[88]

V.2.1. The disease:

Listeriosis [89] is a bacterium-induced disease caused by the bacterium L. monocytogenes, causing outbreaks worldwide. There are two main types: non-invasive and invasive. Non-invasive listeriosis, a mild form, affects healthy individuals with symptoms like diarrhea, fever, headache, and muscle pain. Invasive listeriosis, a more severe form, affects high-risk populations like pregnant women, cancer patients, elderly, and infants. Diagnosisisbased on clinicalsymptoms and bacteriadetection.

[85] Richard L, Kradin M.D., D.T.M. and amp, H., 'Understanding pulmonary pathology', (2017). Chapters and articles, Bishoy Moher Zaki, Ayman El-Shibiny, 'Progress in molecular biology and translational science', (2023). From the laboratory rabbit, guinea pig, hamster and other rodents (2012).
[86] Martin Wagner, Andreas Bubert, 'Encyclopedia of food micribiology', 'Listeria, detection by commercial enzyme immunoassays', (1999). From 'Encyclopedia of biological chemistry (third edition), (2021).
[87] Carl A, Batt, 'Encyclopedia of food microbiology', 'Listeria, introduction', (1999), From 'Encyclopedia of biological chemistry (third edition), (2021).
[88]Siweifreng, ya-ting wang, 'Molecular medical microbiology (thied edition), 'Pathogenicity islands: origins, structure, and roles pathogenesis', (2024). From 'Encyclopedia of biological chemistry (third edition), (2021).
[89] 'Organization mondiale de santé (OMS)', 'Listériose', (2018).

V.3.*Acinetobactrie*:

Acinetobacter[90] is a genus created in 1954 by Brisou and Prevot to group together the montionless*Achromobacter* (in Greek, Akinetos means motionless). *Acinetobacter* are defined as Gram-negative. As their name suggests, they are immobile, unsporulated , and associated in pairs or in short chains[91].

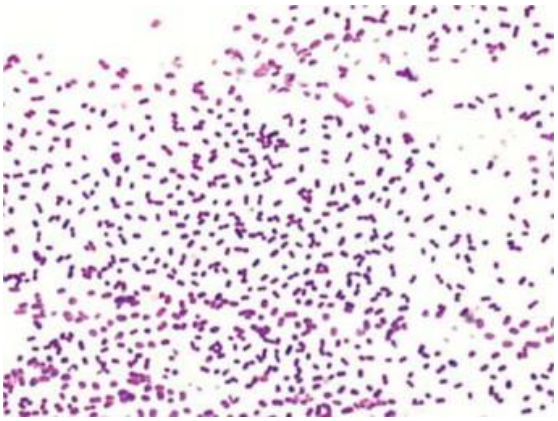


Figure 22: representative figure of acinetobacter.

VI. Antibacterial activity :

VI.1. A study tested the antibacterial activity of B. auriculata root extracts[92] :

A study was conducted to determine the antibacterial activity of P. auriculata root extracts against 150 *E. coli* strains from patients in the Mthata region, Eastern Cape, South Africa. The ethanolic extract showed the highest antibacterial activity. The aerial parts of the plant were dried and extracts were prepared in solvents such as ethanol, petroleum ether and chloroform. The presence of alkaloids and phenolic compounds in the plant may be responsible for its antibacterial activity. The root extract of P. auriculata also showed potential for plasmid curing. The ethanolic extract showed the highest curing efficiency in *K. pneumoniae* and *E. coli.*

VII. Definition of "Bacteriostatic" and "Bactericidal" activity:

The definitions of bacteriostati[93] and bactericidal appear to be straightforward: "bacteriostatic" means that the agent prevents the growth of bacteria (it keeps them in the stationary phase of growth), and "bactericidal" means that it kills bacteria. In reality,

[90] Nadia Hidri, 'Identification d'Acinetobacter spp. Au laboratoire', 'revue francophone des laboratoire, journals and books', Volume 2012, page 37-42, (2012).
[91] Nadia Hidri, 'Identification d'Acinetobacter spp. Au laboratoire', 'revue francophone des laboratoire, journals and books', Volume 2012, page 37-42, (2012).
[92] Khalida Bloch, Sougata Ghosh, 'Recent frontiers of phytochemicals', 'Therapeutic phytochemicals from plumbago auriculata: a drug discovery paradigm', (2023). Chapters and articles. From: Journal of molecular liquids, 'Antibacterial', (2022).
[93] G. A. Pankey, L. D. Sabath, 'Clinical relebance of bacteriostatic verus bactericidal machanisms of action in the tratment of gram-positive bacterial infections', volume 38, Page 864-870, (2004).

there are not 2 pure categories of antimicrobial agents (one that only kills bacteria and another that only inhibits growth). Rather, those agents that are called "bactericidal" usually do not kill all organisms within 18–24 hours of testing, and most so-called "bacteriostatic" agents kill some bacteria within 18–24 hours of testing, often more than 90–99% of the inoculum,but not enough (>99.9%) to be called "bactericidal.". The in vitro microbiological determination of whether an antibacterial agent is bactericidal or bacteriostatic can be influenced by growth conditions, bacterial density, test duration, and the extent of bacterial reduction. The clinical definition is even more arbitrary. Most antibacterial agents are better described as potentially both bactericidal and bacteriostatic.

VIII. Methods of Obtaining Polymers with Antibacterial Properties:

In 1965, polymers with antimicrobial[94] properties were synthesized by Cornell. Since the 1980s, host defense polymers and synthetic polymer disinfectants have served as models for developing peptide-mimetic antimicrobial polymers. In 1984, cationic antibacterial polymers based on poly (vinyl benzyl ammonium chloride) gained interest as effective agents.

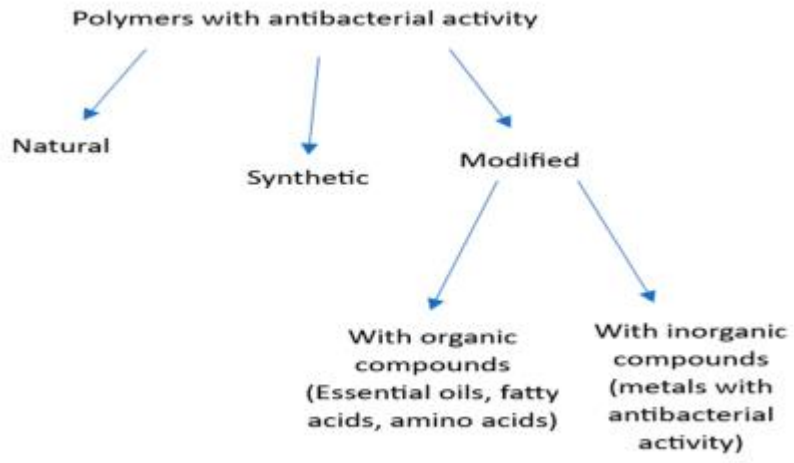


Figure 23: Polymer modification pathways(polymers with antibacterial activity).

IX. Biological activity of phenolic compounds:

Phenolic compounds[95] include a wide range of natural products produced mainly by plants, but also by microorganisms and marine organisms that have the capacity to produce them.They are one of the main classes of compounds formed in plants as part of their

[94] Monika Parcheta, Magdalena Sobiesiak, 'Preparation and functionaisation of polymers with antibacterial properties, Review of the recent developments', 'Materials', MDPI, 16, 4411, Page (2023).
[95] Marcos Soro-Hernandez, Mariana Palma Tenango, Rosario Garcia-Mateos, 'Phenolic compouds : Biological activity', 'IntechOpen', (2017).

response to biotic or abiotic factors, and their structure varies from compounds of low molecular weight, such as phenolic acids, phenylpropanoids or stilbenes, to those of higher molecular weight, for example the polyphenols known as tannins.

Nowadays, interest in these compounds has increased mainly due to their diverse chemical structure and wide biological activity, valuable in the prevention of some chronic or degenerative diseases.

X. The antibacterial properties of Calix[n]arenes:

As previously mentioned, one of the most fascinating features of calixarenes is their numerous functionalizable positions, making them widely applicable in various fields. Calixarenes have demonstrated significant potential in a variety of biological applications, particularly as antivirals, antibacterials, and antifungals.

Since the 1950s, researchers have been focusing on functionalizing calixarene crowns with various functional groups, some of which are already known to possess biological activity.

In 1955, Cornforth[96, 97] reported the initial direct antibacterial effect of calixarene. Their research involved the assessment of the calixarene derivative, (HOC 12.5 EO) on mice infected with tuberculosis revealing significant effectiveness against the infection.

Mourer and colleagues[98] also studied a large series of calixarenes variously substituted in the upper and/or lower rim. Their initial study focused on tetra-para-guanidino-ethylcalix[4]arene, which exhibited significant antibacterial activity against several bacterial strains and clinical isolates. They found that switching from the monomer to cyclotetramer resulted in very good activity against Gram-positive and Gram-negative bacteria.Additionally, they systematically evaluated the cellular toxicity of calixarenes intended for biological research, and their studies concluded that most calixarene structures do not demonstrate in vitro cellular toxicity.

[96]J.W Cornforth, P.D. Hart, Antituberculous Effects of Certain Surface-Active Polyoxyethylene Ethers. Br. J. Pharmacol. Chemother. 10, 73–88,(**1955)**,
[97] J.W Cornforth, E.D Morgan, et al, Preparation of AntituberculousPolyoxyethylene Ethers of Homogeneous Structure, Tetrahedron 29, 1659–1667, (**1973)**,
[98]M.Mourer, M. Grare, et al, In Vitro Activity of Para-Guanidinoethylcalix[4]Arene against Susceptible and Antibiotic-Resistant Gram-Negative and Gram-Positive Bacteria. J. Antimicrob. Chemother, 60, 575–581, (2007).

Many studies propose modifying the calixarene structure with positively charged groups (such as ammonium, guanidinium, imidazolium, etc.) to effectively target the bacterial cell wall with an original mechanism of action based on electrostatic interactions.[99]

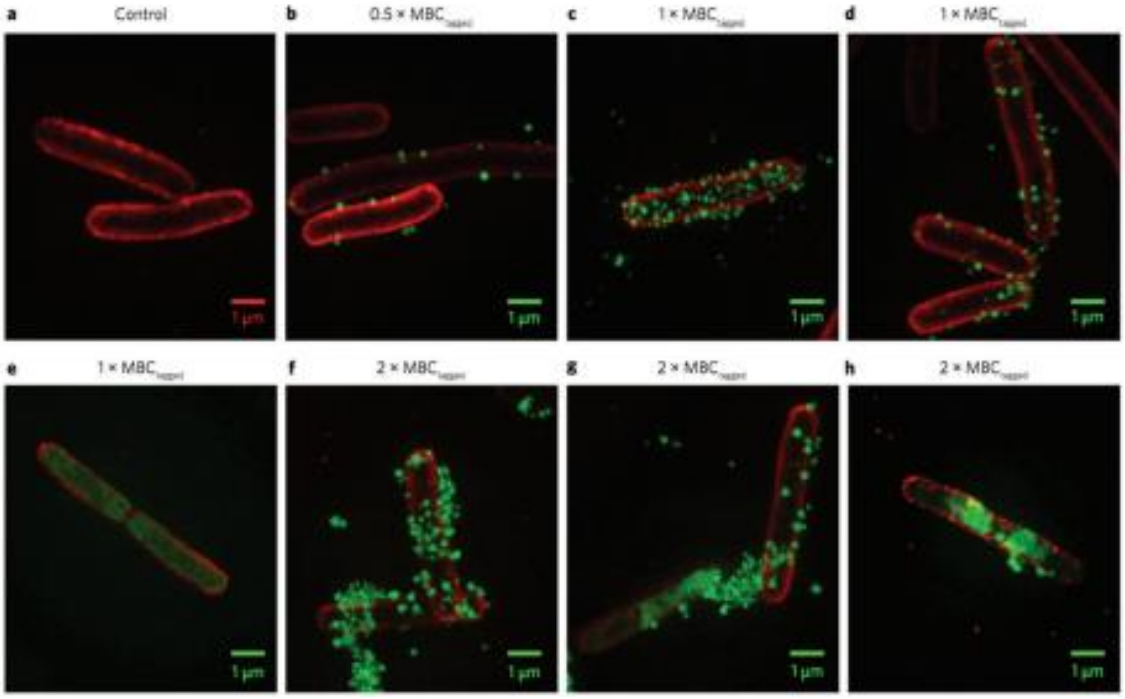


Figure 24: 3D-SIM super resolution fluorescence images of an antibacterial polymer particle with *E. coli* cells. The particles are tagged with AF488 (green) and the *E. coli* cell membrane is dyed with FM4-64FX (red). Control *E. coli* (a), polymer at half the MBC (b).

[99]Mourer, M.; Regnouf-de-Vains, J.-B.; Duval, R.E. Functionalized Calixarenes as Promising Antibacterial Drugs to Face Antimicrobial Resistance. ***Molecules***, ***28***, 6954,**(2023).**

Part II: Experimental part.

Chapter 01:*different materials and products used*

I. Introduction:

In this section, we study and synthesis of macromolecules by polycondensation reaction of monomers with or without protection. then we made quaternization reaction to the amine functions in these polymers.

The first chapter deals with the different devices used.

In the second chapter, we have studied and synthesized macromolecules with IR spectroscopic characterizations.

The third chapter is devoted to the study of the antibacterial activities of different molecules.

II. Definitions:

II.1.The definition of spectroscopy:

Spectroscopy[100] is the study of a physical system by means of electromagnetic radiation with which it interacts or emits. Spectrometry is the measurement of this radiation to obtain information about a system and its constituents.

II.2.PH (potential of hydrogen):

The pH[101] is the concentration of H^+ or $H3O^+$ ions in the solution. If the pH is greater than 7, the solution is basic, if the pH is equal to 7, the solution is neutral and if the pH is less than 7, the solution is acidic.

III. Description of different materials used:

III.1. Infrared spectroscopy:

Infrared[102] (IR) spectroscopy is an absorption method widely used in qualitative and quantitative analyses. The infrared region of the spectrum includes electromagnetic radiation that can change the vibrational and rotational states of covalent bonds in organic molecules.

Organic compounds have distinct infrared spectra, which can be utilized to identify unknowns by the interpretation of distinctive absorbances and comparison with spectral libraries.

[100] Manon Leconte, 'THEME 4 SPECTROSCOPIES', 'Montrouge', Chapitres du thème Spectroscopies d'absorption, Page 1, 2021-2022.
[101] Anonym https://www.ipgp.fr/~losno/Manips/pH/appareilsdemesure.
[102] American Chemical Society (ACS), 'Infrared pectroscopy', DOI: 10.1021, (2017).

Infrared spectroscopy (IR) relies on the considerably smaller energy absorbances that occur between distinct vibrational and rotational states, in contrast to UV and visible spectroscopy, which uses higher energy absorbances from electronic transitions. A common method of interpreting IR spectra is to consider two regions: the functional group frequency region (3600–1200 cm^{-1}) and the "fingerprint" region (1200–600 cm^{-1}).

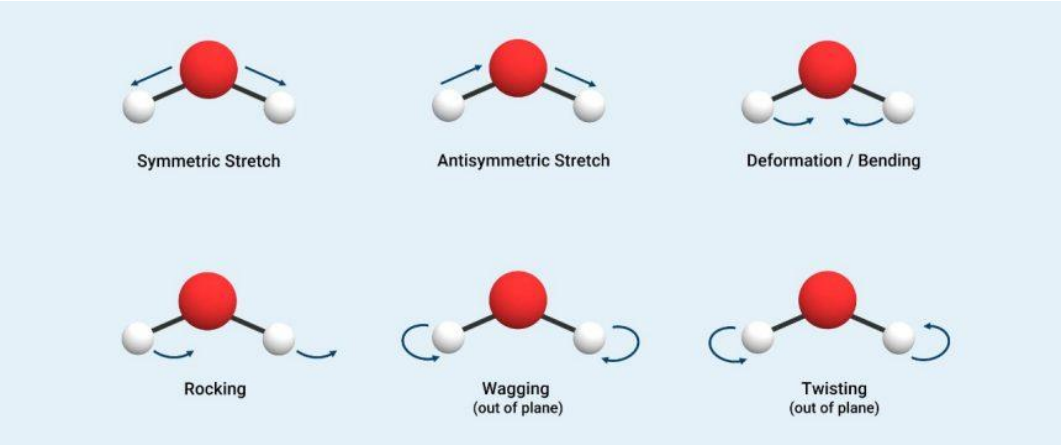


Figure 25: An example of the different types of vibration in infrared spectroscopy of H_2O molecule[103].

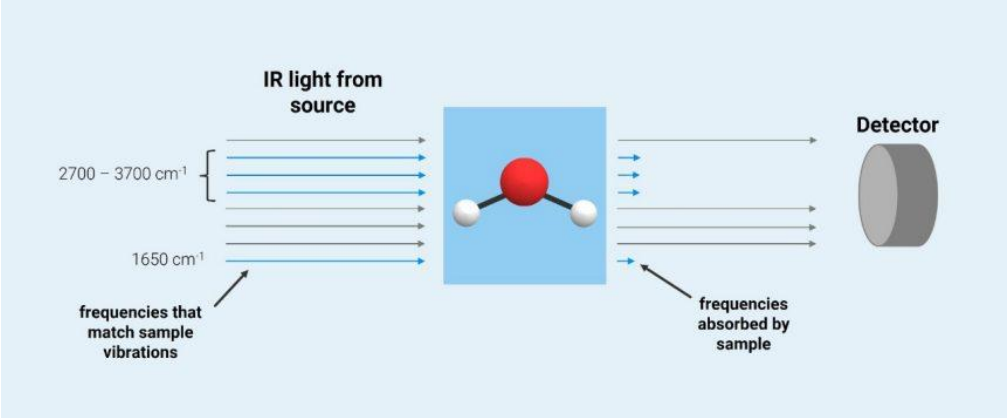


Figure 26: An illustrated example of principle of IR absorption with an example of a water molecule[104].

[103] Anonym 'Gide de la spectroscopie infrarouge' https://www.bruker.com/fr/products-and-solutions/infrared-and-raman/ft-ir-routine-spectrometer/what-is-ft-ir-spectroscopy.
[104] Anonym 'Gide de la spectroscopie infrarouge' https://www.bruker.com/fr/products-and-solutions/infrared-and-raman/ft-ir-routine-spectrometer/what-is-ft-ir-spectroscopy.

III.1.1. PH meter role:

A pH meter is a device for measuring the pH of a solution. It consists of two components: an electronic box that displays the pH value and an electrode that measures this value.

Figure 27:pH meter machine.

III.2. Kofler bench:

III.2.1. Presentation of the Kofler bench :

The Kofler bench[105] is a plate made of a metal alloy covered with anti-corrosion steel. The power supply heats one end to around 260°C. The other end is not heated, so there is a temperature gradient along the plate.

III.2.2. Utilization role :

The Kofler point of fusion is a quick and simple measure of pureness in laboratories. A pure product has a net point of fusion, with a solid-liquid transition occurring within a degree interval, while an impure product has a less net transition.

[105] Anonym https://culturesciences.chimie.ens.fr/thematiques/chimie-experimentale/techniques-d-analyse/utilisation-du-banc-kofler-pour-mesurer-une.

Figure 28: Koflerbenchrepresentation.

IV. Materials and glasswarethat are used:

Beakers.

Burette.

Crystallizer.

Dean-Stark.

Erlenmeyer flask.

Filter paper.

Funnel.

Magnetic stirrer bar.

Oil bath.

Pipette with Pipet Bulb.

Petri dishes.

Retort stand with a clamp.

Spatula.

There-neck round-bottom flask.

Volumetric Flask.

Watch class**.**

Wash bottle.

Electronic Balances.

Heating Magnetic Stirrers.

pH meter.

Thermometer.

IV.1. The Chemistry products:

Acetone Molar mass :58.080g·mol−1 Density:0.7845g/cm3 Boiling point: 56,08˚C Melting point: 94,9˚C  Biochemopharm	***Hydrochloric acid(35-38%):HCl*** Molar mass :36.46 g·mol−1 Density:1,19g/cm3 Boiling point: 61˚C Melting point: 30˚C  BIOCHEM Chemopharma
Acetic Anhydride Molar mass : 102.08 g·mol−1 Density: 1.08g/cm3 Boiling point: 139.8˚C Melting point: 73.1˚C  SARL EXPERLAB	**Glacial Acetic Acid** Molar mass : 60.05 g·mol−1 Density:1.048g/cm3 Boiling point: 117.9˚C Melting point: 16.6˚C  BIOCHEM Chemopharma
Ammonium Hydroxide 25%: NH_4OH Molar mass :35.05 g·mol−1 Density:0.910 g/cm3 Boiling point: 37.7˚C Melting point: 57.5 °C  Panreac	**Ortho-Aminophenol** Molar mass: 109.13 g·mol−1 Density: 1.328 g/cm3 Boiling point: 164˚C Melting point: 174˚C  BIOCHEM Chemopharma
Chloroforme: $CHCl_3$ Molar mass :119.37 g·mol−1 Density:1,48g.cm^{-3} Boiling point: 61.15˚C	**Potassium hydroxide: KOH** Molar mass :56.105 g·mol−1 Density: 2.12 g/cm3 Boiling point: 1.327˚C

Melting point: 63.5˚C  Riedel-de Haen	Melting point: 410˚C 
Dichloromethane: CH_2Cl_2 Molar mass : 84.93 g·mol−1 Density:1.3266g/cm3 Boiling point: 39.6˚C Melting point: 96.7˚C  SIGMA-ALDRICH	**Para-Aminophenol** Molar mass: 109.128 $g.mol^{-1}$ Density: 1.13 g/cm^3 Boiling point:284 °C Melting point: 187.5 °C  SIGMA-ALDRICH
Ethanol 96% Molar mass : 46.069 g·mol−1 Density :0.78945g/cm3 Boiling point: 114.14˚C Melting point: 78.23˚C  BIOCHEM Chemopharma	**Sulfuric acid: H_2SO_4** Molar mass :98.079 g·mol−1 Density :1.8302g/cm3 Boiling point : 337˚C Melting point : 10.31˚C  BIOCHEM Chemopharma
Formaldehyde(37-41%) Molar mass :30.026 g·mol−1 Density:0.8153 g/cm3 Boiling point: 19˚C Melting point: 92˚C  BIOCHEM Chemopharma	**Tetrachloromethane: CCl_4** Molar mass : 153.81 g·mol−1 Density : 1.8567g/cm3 Boiling point: 76.72˚C Melting point: 22.92˚C 

General conclusion

General Conclusion:

In conclusion, this study has explored the synthesis and characterization of a number of organic compounds, including novel calixarene-based macromolecules, and evaluated their potential as antibacterial compounds. The spectroscopic characterization technique infrared (IR) demonstrated that we have obtained the necessary compounds, which show the purity of their synthesis.

The antibacterial activity testing against [IIQ, IIIQF] revealed high efficacy results, with [*E. coli* (23.25 ± 0.42 mm), *KP*(19.69 ± 0.21 mm), *Listeria*(16.32 ± 0.32 mm) and *Acinetobacter baumannii* **(**15.33 ± 0.15 mm) results of IIQ and *KP***(**15.55 ± 0.92 mm)inhibitory effects]. These outcomes suggest that [IIQ and IIIQF] exhibits potential as an effective antibacterial compounds.

Future studies could focus on potential improvements or modifications of these compounds to improve their efficacy in pharmaceutical fields.

Finally, this project contributes to the understanding of macromolecules, calixarenes as promising candidates to combat bacterial infections as novel antimicrobial agents in pharmaceutical and biomedical applications.

Summary :

Our project is based on the study of macromolecules, calixarenes, their structure and antibacterial activity, which showed promising results such as the activity of the monomer orto-amino phenol quaternary with (*Echerichia coli*) (23.25 ± 0.42 mm) and 4-(Dimethylamino)benzoic acidwith formol (15.55 ± 0.92 mm) with (*Klebsiella pneumonia*).
We have structurally modified monomers, macromolecules to enhance their antibacterial properties. Our findings confirm the potential of these compounds as effective agents against bacterial pathogens, highlighting their role in combating antibiotic resistance. This research not only contributes to the field of macromolecular chemistry but also holds important implications for future therapeutic developments in antibacterial agents.

Résumé :

Notre projet est basé sur l'étude des macromolécules, des calixarènes, de leur structure et de leur activité antibactérienne, qui a montré des résultats prometteurs tels que l'activité du monomère orto-amino phénol quaternaire avec (*Echerichiacoli*) (23,25 ± 0,42 mm) et de l'acide 4-(Diméthylamino)benzoïque avec formol (15,55 ± 0,92 mm) avec (*Klebsiella pneumonia*).
Nous avons modifié la structure des monomères et des macromolécules afin d'améliorer leurs propriétés antibactériennes. Nos résultats confirment le potentiel de ces composés en tant qu'agents efficaces contre les bactéries pathogènes, illustrant leur rôle dans la lutte contre la résistance aux antibiotiques. Cette recherche contribue non seulement au domaine de la chimie macromoléculaire, mais elle a également des implications importantes pour les futurs développements thérapeutiques en matière d'agents antibactériens.

ملخص :

يعتمد مشروعنا على دراسة الجزيئات الكبيرة، الكاليكسارين، وتركيبها ونشاطها المضاد للبكتيريا، والتي أظهرت نتائج واعدة لقد قمنا بتعديل هيكلي للمونومرات والجزيئات الكبيرة لتعزيز خصائصها المضادة للبكتيريا. تؤكد النتائج التي توصلنا إليها إمكانات هذه المركبات كعوامل فعالة ضد مسببات الأمراض البكتيرية مثل نشاط مونومرات أورتو-أمينو-فينول quaternary مع (*Echerichia coli*)(23.25 ± 0.42 مم) و4-(ثنائي ميثيل امينو) حمض البنزويك مع الفورمالدهيد (15.55 ± 0.92 مم) مع (*Klebsiella pneumoniae*).مما يسلط الضوء على دورها في مكافحة مقاومة المضادات الحيوية. لا يساهم هذا البحث في مجال كيمياء الجزيئات الكبيرة فحسب، بل يحمل أيضًا آثارًا مهمة للتطورات العلاجية المستقبلية في العوامل المضادة للبكتيريا.