REVIEW

ABOUT SUPRAMOLECULAR CHEMISTRY - HOW A MODERN AND REVOLUTIONARY SCIENTIFIC CONCEPT CAN BE PRESENTED TO THE STUDENTS AS CHEMISTRY OF EVERY DAY

BOGDAN-CATALIN SERBAN [1, 2], OCTAVIAN BUIU[1], CORNEL COBIANU[1],
MARIUS BUMBAC[3,4], CRISTINA MIHAELA NICOLESCU[4]

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Abstract. *Supramolecular chemistry, one of the topical fields of contemporary chemistry, deals sometimes with subtle interactions, sophisticated molecules, and huge molecular aggregates. Furthermore, many terms such as molecular self-assembly, mechanically-interlocked molecular architectures, container-molecule, and cryptand, may sound abstract and sometimes discouraging. The purpose of this paper is to show how a chemistry teacher can scrutinize supramolecular chemistry in terms of everyday chemistry. Four directions which can help to a better understanding of this domain are identified and analyzed. Simple synthetic procedures for most of the supramolecular receptors, the occurrence of supramolecular chemistry in Nature, the connection between supramolecular chemistry and life itself (self-assembly of nucleic acid bases) are useful examples for emphasizing the versatility of this domain. Last, but not least, the presence of supramolecular chemistry in food, drugs, drinks, tobacco-based products, homecare products, cosmetics, are relevant examples of how this concept is present in everyday life.*

Keywords: *supramolecular chemistry, β-cyclodextrin, molecular recognition*

1. INTRODUCTION

Despite its paramount importance in everyday life, the teaching of chemistry often proves to be a difficult matter. It has a reputation for being an unpopular and even a puzzling science [1, 2]. Sometimes, chemistry (organic chemistry in particular) is often perceived by students as a collection of unrelated letters, graphs, and symbols that require a lot of effort to be understood and assimilated [3, 4]. The main reason for this negative grasp is the lack of ability to abstract. This is a fundamental skill in order to understand the background and logic of chemical process that is macroscopically invisible. Students also fail in connecting the knowledge in chemistry to everyday life. All these aspects are mental barriers that prevent students from learning chemistry [5, 6]. To counteract these drawbacks, the role of teachers is crucial. Beyond their responsibilities and duties, the teachers must find, for all the individual discussed topics, the appropriate strategy in order to present the matter as comprehensible as possible [7].

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[1] National Institute for Research and Development in Microtechnologies, IMT-Bucharest, 077190 Voluntari, Romania. E-mail: bogdan.serban@imt.ro.
[2] Zentiva Romania S.A, 032266 Bucharest, Romania.
[3] Valahia University of Targoviste, Faculty of Sciences and Arts, Department of Sciences and Advanced Technologies, 130004 Targoviste, Romania. E-mail: mariusbumbac@gmail.com
[4] Valahia University of Targoviste, Institute of Multidisciplinary Research for Science Technology, 130004 Targoviste, Romania.

The aim of this paper is to show how a chemistry professor can discuss supramolecular chemistry, a fascinating domain and one of the modern frontiers in chemistry in terms of everyday chemistry. Therefore, the present paper points out different suitable strategies for helping teachers to explain the relevance and importance of supramolecular chemistry.

These strategies relate to the following four directions that we identified, and which can yield to a better understanding of the domain:

a) despite their size and complexity, synthesis of macrocyclic compounds are sometimes facile, starting from simple precursors and using well-known synthetic routes;

b) supramolecular chemistry is more present in Nature than we could imagine and methane hydrate (ice that burns) is a relevant example;

c) self-assembly of nucleic acid bases with hydrogen bonds is a genuine supramolecular chemistry process and does explain the life itself;

d) the presence of supramolecular chemistry in food, drugs, tobacco-based products cosmetics are pertinent examples of how this concept is present in everyday life.

2. SUPRAMOLECULAR CHEMISTRY, MODERN ERA IN MATERIALS SCIENCE

Supramolecular chemistry is one of the most fascinating topics of contemporary chemistry and was defined first in 1978 by Jean-Marie Lehn as the **“chemistry beyond the molecule”** [8]. While “classical” chemistry focuses on the covalent bond, supramolecular chemistry explores the weaker and reversible non-covalent interactions between molecular entities such as hydrophobic forces, hydrogen bonding, π–π interactions, van der Waals forces, metal-ligand coordination, etc. [9]. The pivotal role of supramolecular chemistry in the current research was established by the 1987 Nobel Prize for Chemistry which was awarded to Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen in recognition of their contribution in this field. “Their development and application of molecules with a highly selective structure specific interaction, *i.e*. molecules that can “recognize” each other and choose with which other molecules they will form complexes” were the issues cited as major accomplishments [10].

Nowadays, supramolecular chemistry became even more refined and sophisticated. Thus, the Nobel Prize in Chemistry 2016 was awarded jointly to Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard L. Feringa "for the design and synthesis of molecular machines"[11].

Although it is a relatively new science, supramolecular chemistry has found many applications such as separations through liquid membranes using macrocyclic carriers [12 - 15], separations by solvent extraction [16], masking agents [17], chromatographic separations [18], synergic extractions [19], antioxidant protection [20], sensing [21 - 23], silicon anisotropic etching [24], etc.

The concepts promoted by supramolecular chemistry operates with terms and notions such as molecular self-assembly [25], molecular folding [26], spherical recognition [27], tetrahedral recognition [28], crown-ethers [29], calixarenes [30], host–guest chemistry, mechanically-interlocked molecular architectures, carceplex, cryptands [31].

At first glance, this terminology seems to be abstract, difficult to understand. Furthermore, the complexity of different synthetic and natural supramolecular compounds (e.g., chiral supramolecular complexes as depicted in Fig. 1 or a natural macrocyclic compound such as γ-cyclodextrin - Fig. 2) can discourage the student.

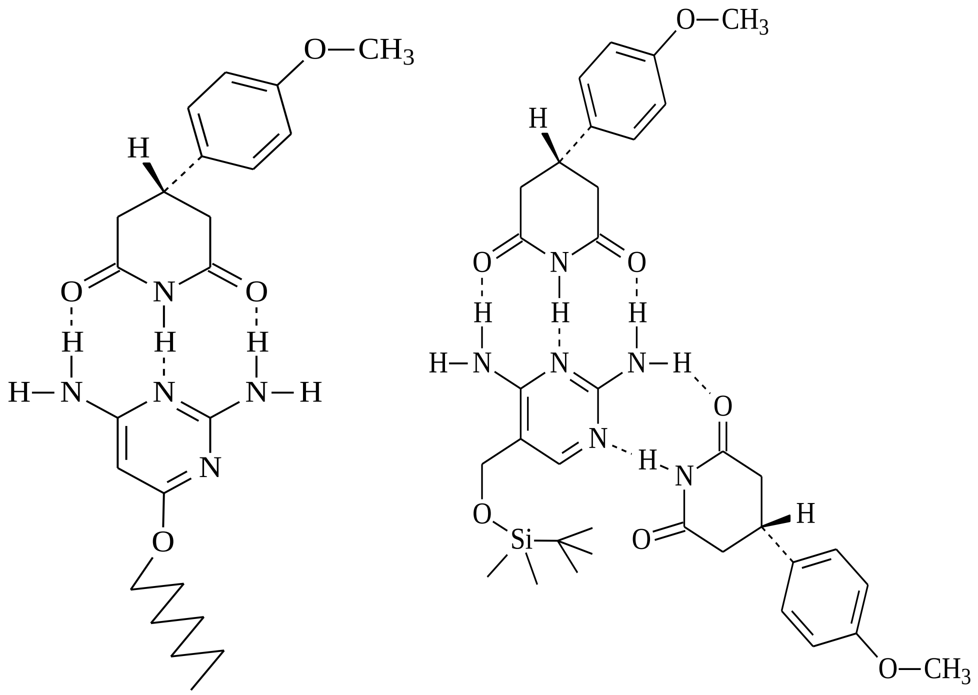


Figure 1. The structures for chiral supramolecular complexes [32].

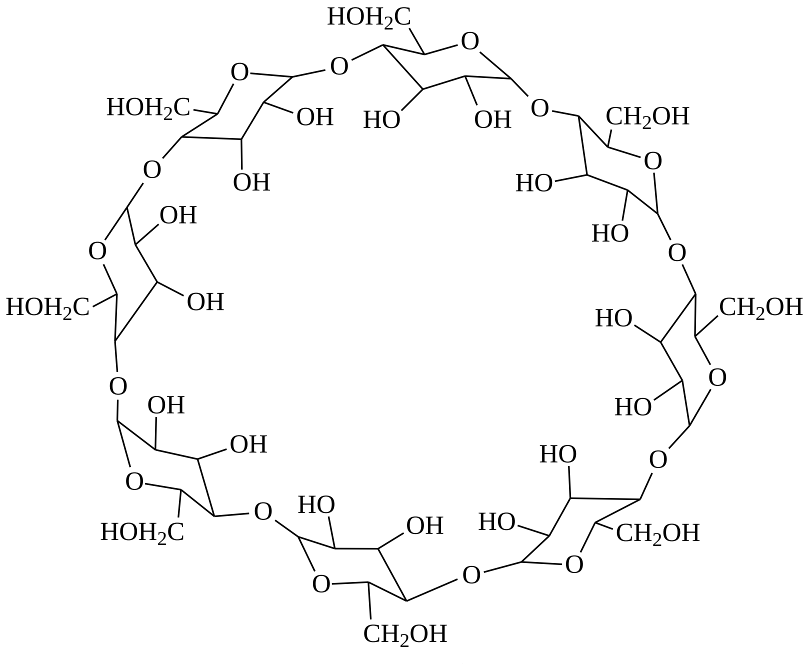


Figure 2. The structure of γ-cyclodextrin.

However, we will see below that supramolecular chemistry is not an incomprehensible topic. Moreover, we "interact" and rely on it when we eat, drink or smoke, use toothpaste or drugs.

3. MACROCYCLIC LIGANDS, COMPOUNDS WITH A SOPHISTICATED MOLECULAR ARCHITECTURE, BUT AVAILABLE ON A LARGE SCALE THANKS TO THEIR SYNTHETIC VERSATILITY

Despite their size and complexity, synthesis of macrocyclic ligands is sometimes versatile, starting from simple compounds, using well-known synthetic pathways and mild conditions [33]. Thus, the synthesis of the different crown–ethers such as 12-crown-4, 15-crown-5, 18-crown-6, are presented in Fig. 3. For instance, diethylene glycol and 1, 2-bis (2-chloroethoxy) ethane (in the presence of NaOH) are necessary for the synthesis of 15-crown-5.

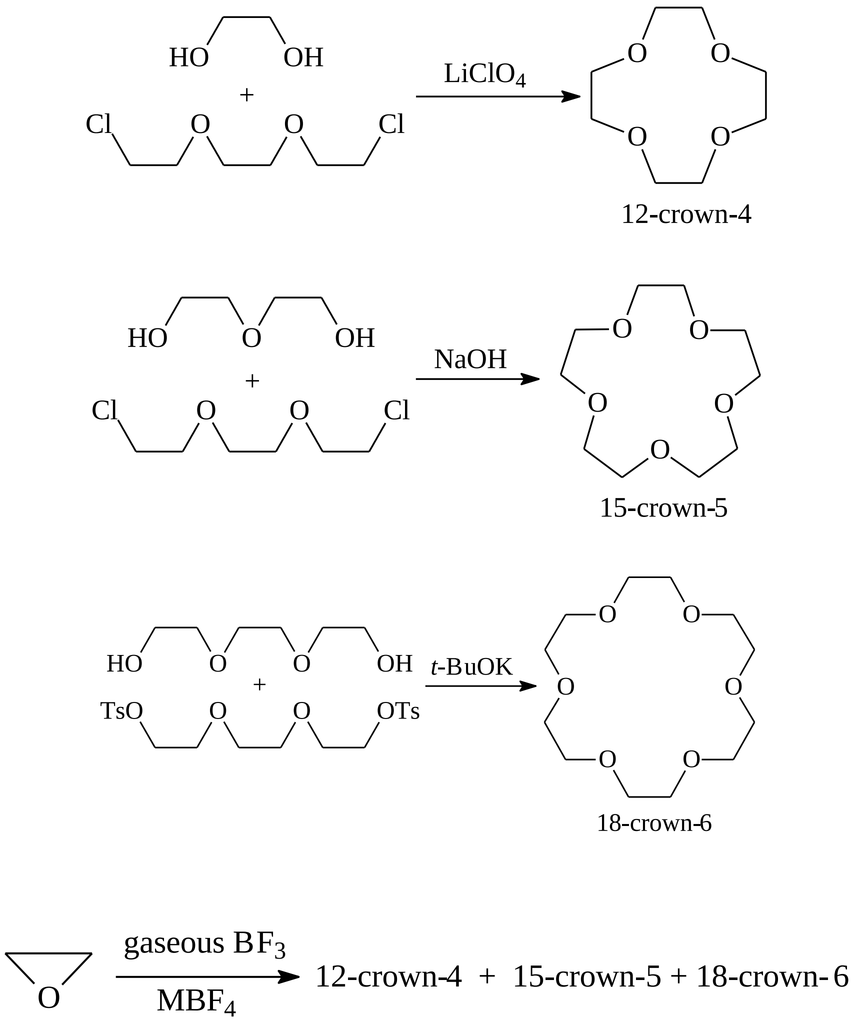


Figure 3. Synthesis of crown-ethers.

The nature of the fluoroborate cation influences significantly the proportion of crown ethers in the final reaction mixture. Along with the crown ethers, variable amounts of linear products are also obtained. The use of alkali metal cations leads to significant improvements in the reaction yield [34, 35].

A complex molecule such as hemicurcubit[12]uril is available from two available precursors, ethyleneurea and formaldehyde, in the presence of HCl [36, 37].

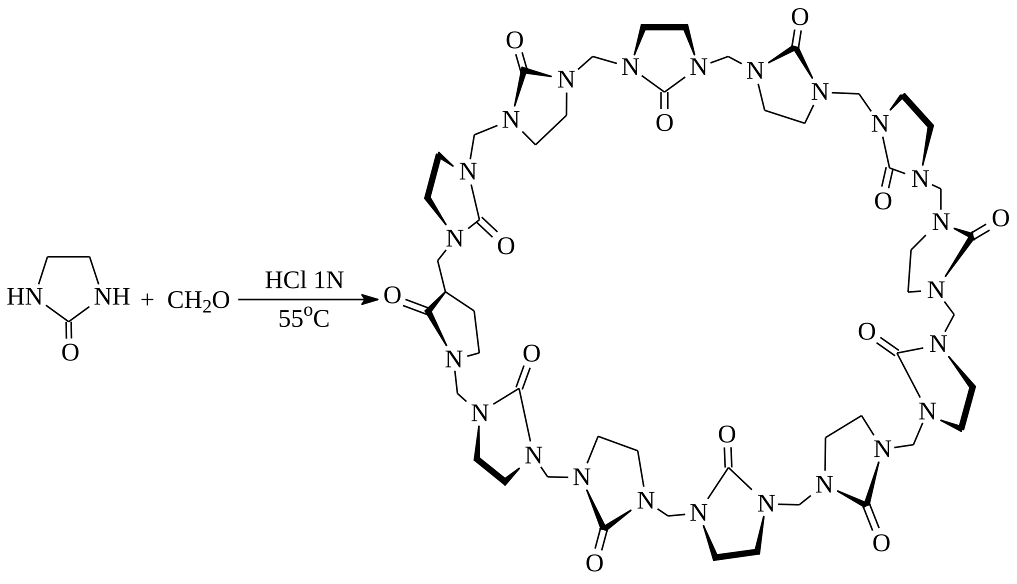
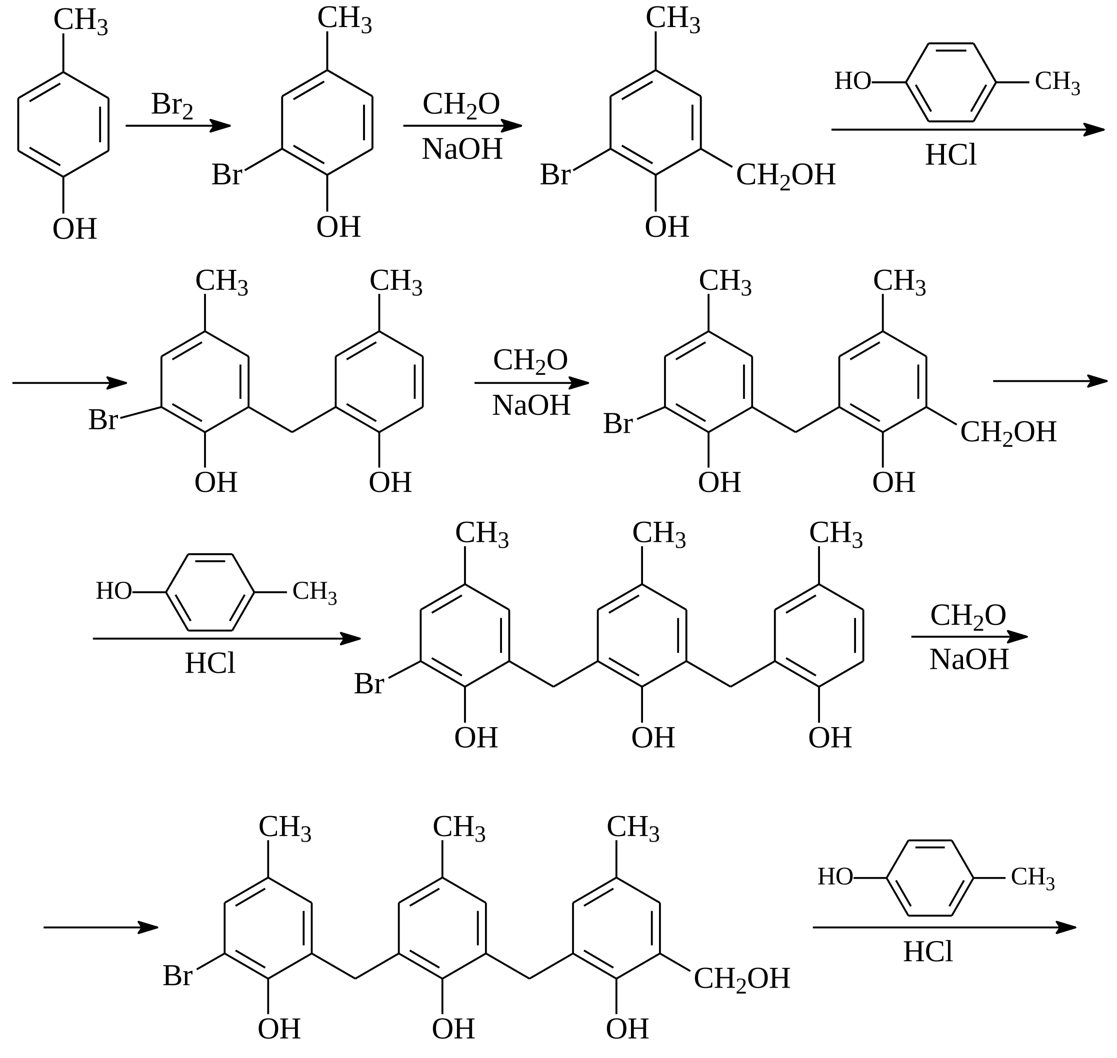


Figure 4. Synthesis of hemicurcubit[12]uril in alternate conformation.

Calixarenes [38] are synthesized in multi-step procedures [39, 40] as depicted in Fig. 5 or in the one-step procedure as depicted in Fig. 6 [41].



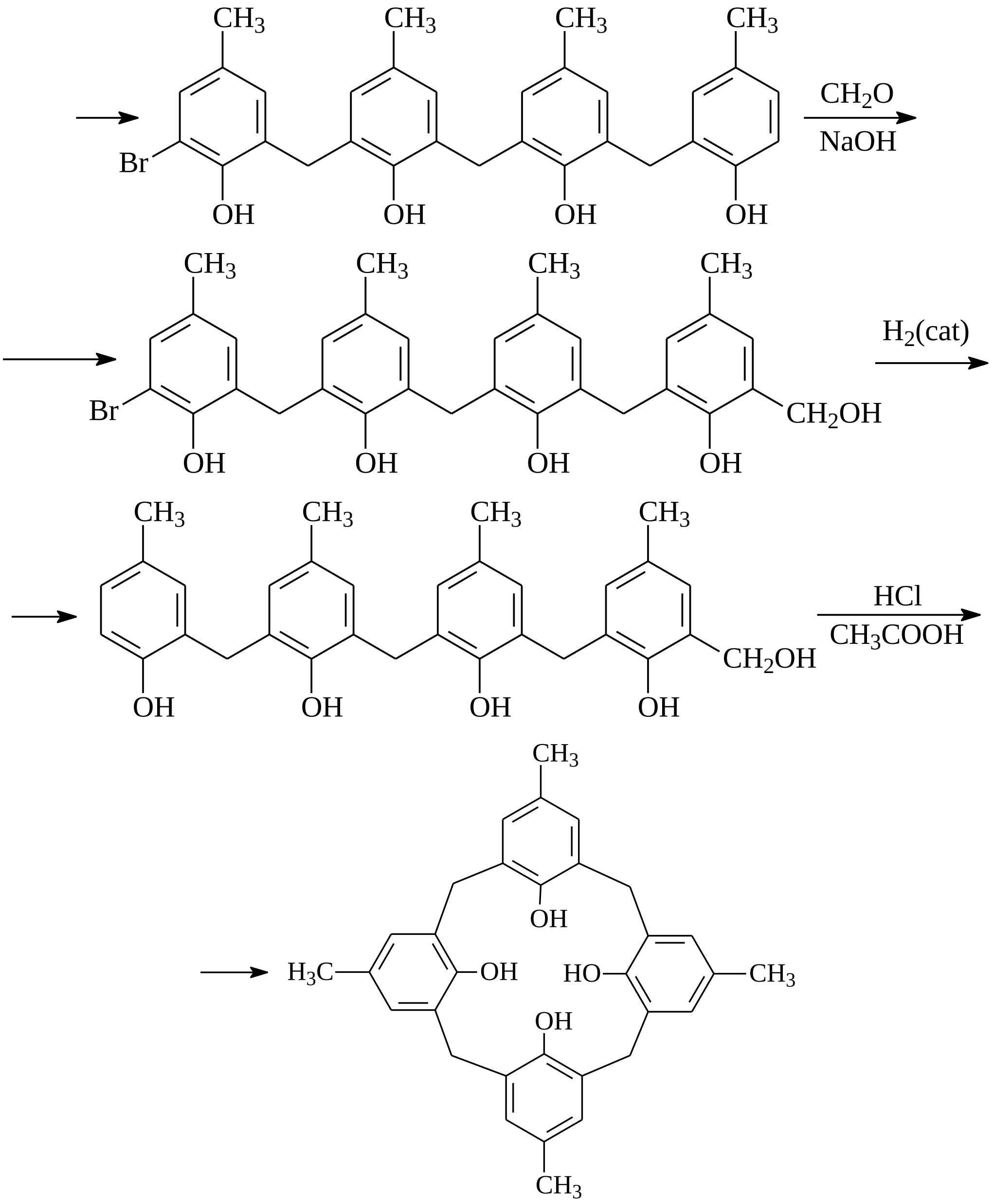


Figure 5. Multi-step synthesis of *p*-methyl calix[4]arene.

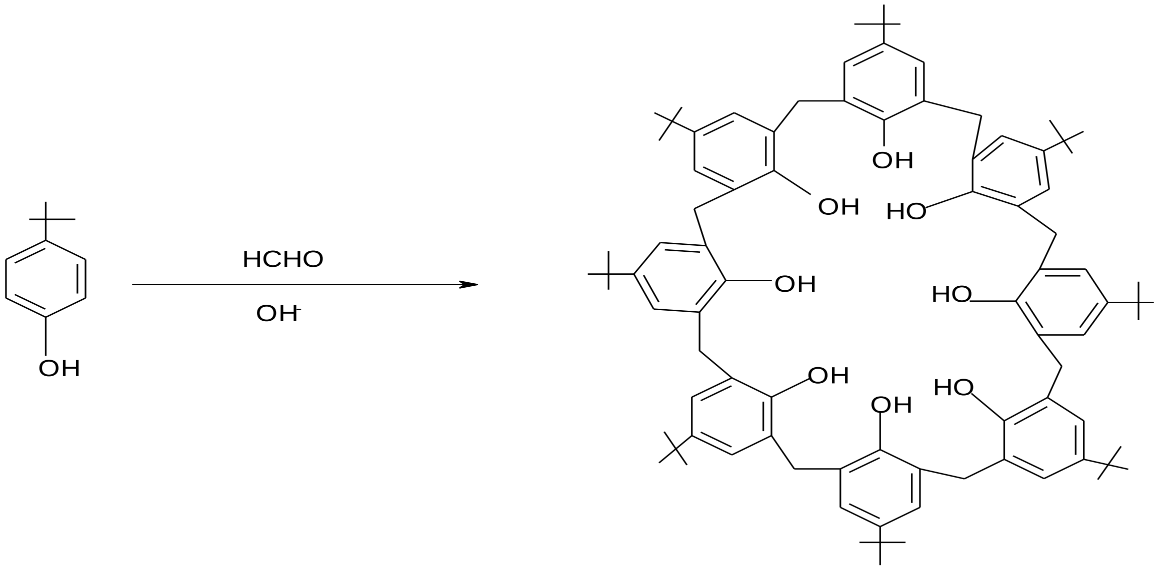


Figure 6. One-step synthesis of *p*-tertbutylcalix[8]arene.

As we can see, despite their complexity, the vast majority of macrocyclic compounds, the core of supramolecular chemistry, are synthesized from simple materials using the traditional methods of organic synthesis.

4. SUPRAMOLECULAR CHEMISTRY - A UBIQUITOUS PHENOMENON IN NATURE

Supramolecular chemistry is more present in Nature than we could imagine, and methane hydrate is a relevant example. Methane hydrate ($CH_4 \cdot 5.75H_2O$), also called ice that burns is a solid compound in which a single molecule of methane is trapped within a crystalline cage formed by frozen water molecules [42].

The supramolecular assembly consists of two components:
a) host molecules of water arranged in a rigid case;
b) methane as guest molecule;

The methane and water molecules are held together in a cage by hydrogen bonds [43].

This intriguing class of compounds has been known since the 1930s, when natural gas companies found that their pipelines were occasionally clogged by a type of gray ice composed of methane and water.

Methane hydrates were later discovered as deposits in permafrost regions (1.4×10^{13} to 3.4×10^{16} m^3) and in submarine sediments in oceans (3.1×10^{15} to 7.6×10^{18} m^3). It is believed that methane hydrate deposits can be encountered on other planets such as Mars [44, 45]. It is important to add that natural gas in hydrates 2 times greater than the total fossil fuel reserves.

By lowering the pressure or raising the temperature, one cubic meter of the methane hydrate break down into the water and about 160 m^3 of gas [46, 47]. Thus, this compound can be viewed as an important source of energy [46, 47].

A major environmental issue related to this natural supramolecular aggregate is the substantial release of natural gas from methane hydrates due to increasing temperature [48].

5. SUPRAMOLECULAR CHEMISTRY - PRESENT IN ALL KNOWN ORGANISMS AND MANY VIRUSES

In 1953, J. D. Watson and Francis Crick predicted the double helical structure and conformation of deoxyribonucleic acid (DNA) using X-ray diffraction patterns of DNA fibers [49]. The double helix arrangement of DNA is stabilized by the hydrogen bonds established between the pairs bases of the two macromolecules. These are, by far, the most important supramolecular structures in the World, explaining the life itself. The four bases of which DNA is composed are adenine (A), thymine (T), guanine (G) and cytosine(C). Complementary base pairing in DNA is C-G (Fig. 7) and A-T (Fig. 8). The four bases of which RNA is composed are adenine (A), uracil (U), guanine (G) and cytosine(C). Complementary base pairing in RNA is C-G (Fig. 7) and A-U (Fig. 9).

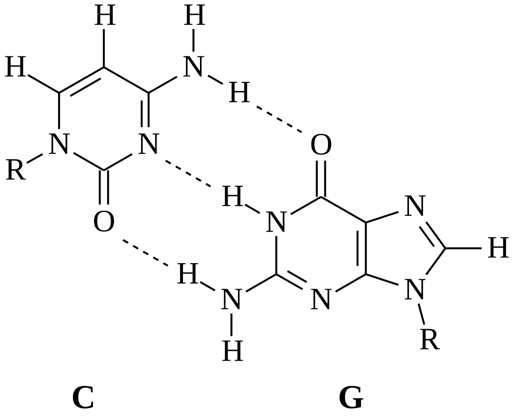


Figure 7. Formation of hydrogen bonds between cytosine and guanine in the DNA or RNA strands.

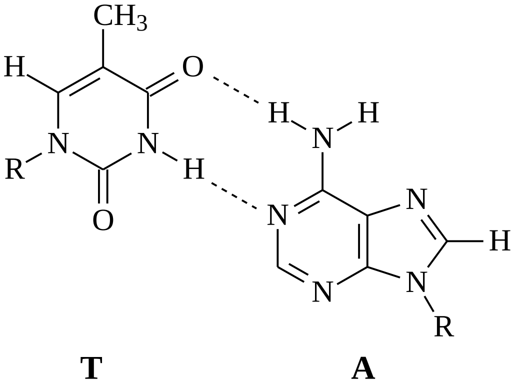


Figure 8. Formation of hydrogen bonds between thymine and adenine in DNA strands.

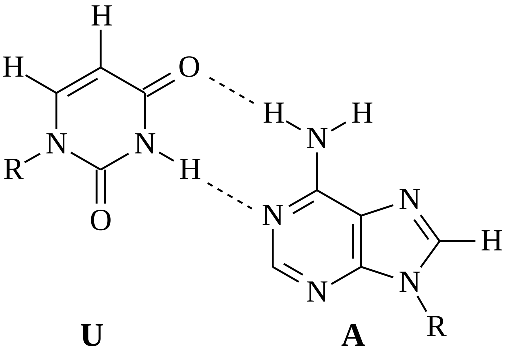


Figure 9. Formation of hydrogen bonds between uracil and adenine in RNA strands.

6. SUPRAMOLECULAR CHEMISTRY – A CONCEPT WITHIN EVERYDAY LIFE

Sometimes, supramolecular chemistry is present in our lives more than we would have expected. In most cases, these applications are related to cyclodextrins. α-, β- and γ-cyclodextrins are non-reducing cyclic oligosaccharides made up respectively of six, seven and eight glucose units linked by α-1,4 bonds. The structure of β- cyclodextrin is shown in Fig.10.

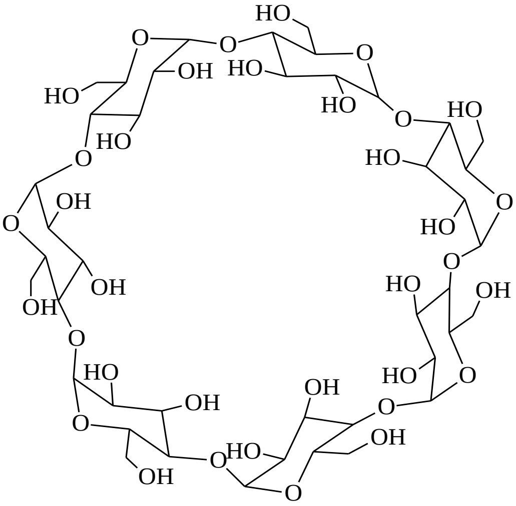


Figure 10. The structure of β-cyclodextrin.

These compounds have relatively hydrophobic toroidal intramolecular cavities and can complex within them a wide variety of chemical species, the phenomenon is known as molecular encapsulation [50].

Cyclodextrins are synthesized by enzymatic hydrolysis of starch in the presence of cyclodextrin glucosyltransferase (CGTase). A mixture of α-, β- and γ-cyclodextrins is formed, as well as traces of cyclodextrins consisting of a larger number of units of glucopyranose [51, 52].

Due to their ability to form stable inclusion complexes as well as the fact that they are non-toxic, non-allergenic and do not pose major health risks at moderate consumption, cyclodextrins have various applications, being used in:

Food industry. Cyclodextrins are used to stabilize food flavors [53 - 57] to mask unpleasant tastes and smells [58 - 61] to improve the quality and technology of food processing [62]. Thus, cyclodextrins can be used as cholesterol sequestrant [63]**,** as protectors from light-induced modifications [64], as protection to heat-induced changes [65] or for improving shelf life [66 - 68]

The tobacco industry. The flavors required in the manufacture of cigarettes are often used in the form of inclusion compounds thereof with cyclodextrins. For instance, menthol can be stabilized as a complex with β-cyclodextrin. Cyclodextrin-based polymers can be used in the manufacture of cigarette filters [69 - 72].

Pharmaceutical industry. Cyclodextrins are widely used in the controlled release of drugs [73 -78]

Agriculture. Insecticides, herbicides, fungicides can be used with multiple advantages in the form of inclusion products with cyclodextrins. Also, cyclodextrins are successfully used to condition fruit ripening agents (ethylene, for instance) [79].

Cosmetics and household products industry. Cyclodextrins are successfully used to condition toothpaste, deodorants. Complexes of cyclodextrins with triclosan, salicylic acid, menthol are used in many personal care products manufacturing. Because of the property of forming inclusion compounds with detergents, they can be used as defoaming agents [80 - 84]. All these applications are summarized in Fig.11.

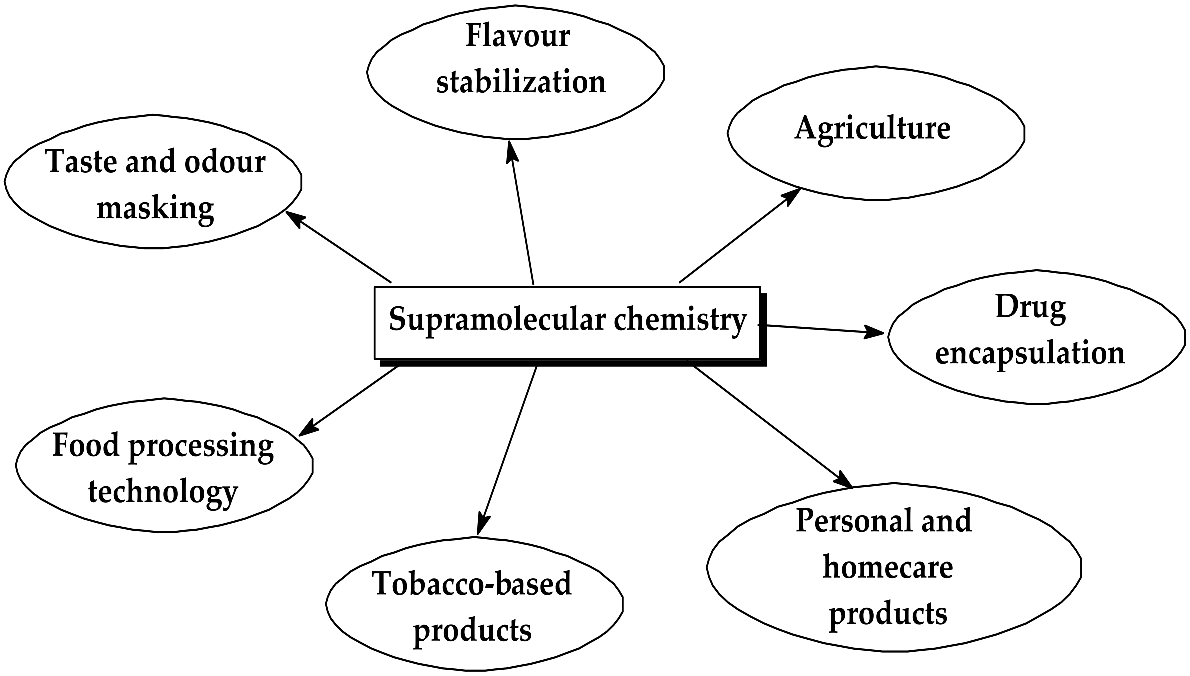


Figure 11. The presence of supramolecular chemistry in everyday life .

7. CONCLUSIONS

Supramolecular chemistry, one of the topical domains of **science**, is the study of entities of greater complexity than individual molecules. The intricate molecular architecture of many supramolecular systems and the terms, principle and notions related to this branch of contemporary chemistry are apparently abstract and sometimes difficult to understand.

The purpose of this paper is to show how a chemistry teacher can explore supramolecular chemistry in terms of every day of chemistry. Four directions helping to a better understanding of this domain were identified and discussed. Simple synthetic procedures for well-known macrocyclic ligands such as crown- ethers, calixarenes, cucurbiturils, the occurrence of supramolecular assemblies such as methane hydrate in Nature, the connection between supramolecular chemistry and life itself (self-assembly of nucleic acid bases) are useful examples in order to point out the versatility of this chemistry field.

Furthermore, the presence of supramolecular chemistry in food, drugs, cosmetics, drinks, tobacco-based products, homecare products are pertinent examples of how this concept is connected with our lives.

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