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*Theme:*

# *Theoretical study of an inclusion complex (Beta-cyclodextrin/azomethin) using Semi-empirical method*

**Presented by:**

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# ملخص

من خلال هذا العمل، قمنا بدراسة نظرية لظاهرة التداخل بين جزيئتي السيكلودكسترين التي تعتبر جزيئة مضيفة وجزيئة الازوميثين و هي الجزيئة الضيفة. فلقد تتبعنا مسار التداخل بين الجزيئتين باستعمال حسابات الطريقة النظرية PM3 للحصول على المماكبات الأكثر استقرارا. النتائج المتحصل عليها بينت أن هناك احتمالين للتداخل بين الجزيئتين وبالتالي الحصول على معقدين تداخليين. استقرار المعقدين راجع الى انشاء روابط هيدروجينية بين الجزيئتين.



**كلمات مفتاحية:** معقد تداخلي، مضيف، مضيفة، طريقة PM3، الربطة الهيدروجينية.

# Abstract

We are interested in this work to the inclusion complexes phenomena. We chose the azomethine /beta- cyclodextrine as guest and host molecules. A theoretical study was carried out to investigate the inclusion process and localizing the minimum global of the stable complexes. In fact, there was found two possible orientations and we have found two complexes.

The calculation was executed using the semi empirical method PM3. The intermolecular H-bond between the host and guest contribute the stability of the complexes.

**Key words:** inclusion complex, host, guest, PM3 method, H-bon interaction.

# Résumé

Dans ce travail, nous avons étudié le phénomène de complexation entre la béta-cyclodextrine (hôte) et l'azométhine (invité). L'étude théorique qui a été effectué à l'aide de méthode semi empirique PM3 est une investigation de processus de l'inclusion entre les deux molécules pour localiser et déterminer les minimums globaux de complexes. En effet, les résultats obtenus montrent qu'il y a deux orientations possibles pour l'inclusion. Les complexes trouvés sont stabilisés par les liaisons d'hydrogène entre les deux molécules.

**Mots clés :** complexe d'inclusion, hôte, invité, méthode PM3, liaison d'hydrogène

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## List of Symbols and Abbreviations

***αCD*:** alpha-cyclodextrin

**βCD** : beta-cyclodextrin

**γCD :** gamma-cyclodextrin

**CD:** cyclodextrin

**DFT:** Density Functional Theory

**HF:** Hartree-Fock

**HOMO:** Highest occupied molecular orbital

**LUMO:** Lowest unoccupied molecular orbital

**MNDO:** modified Neglect of diatomic Overlap

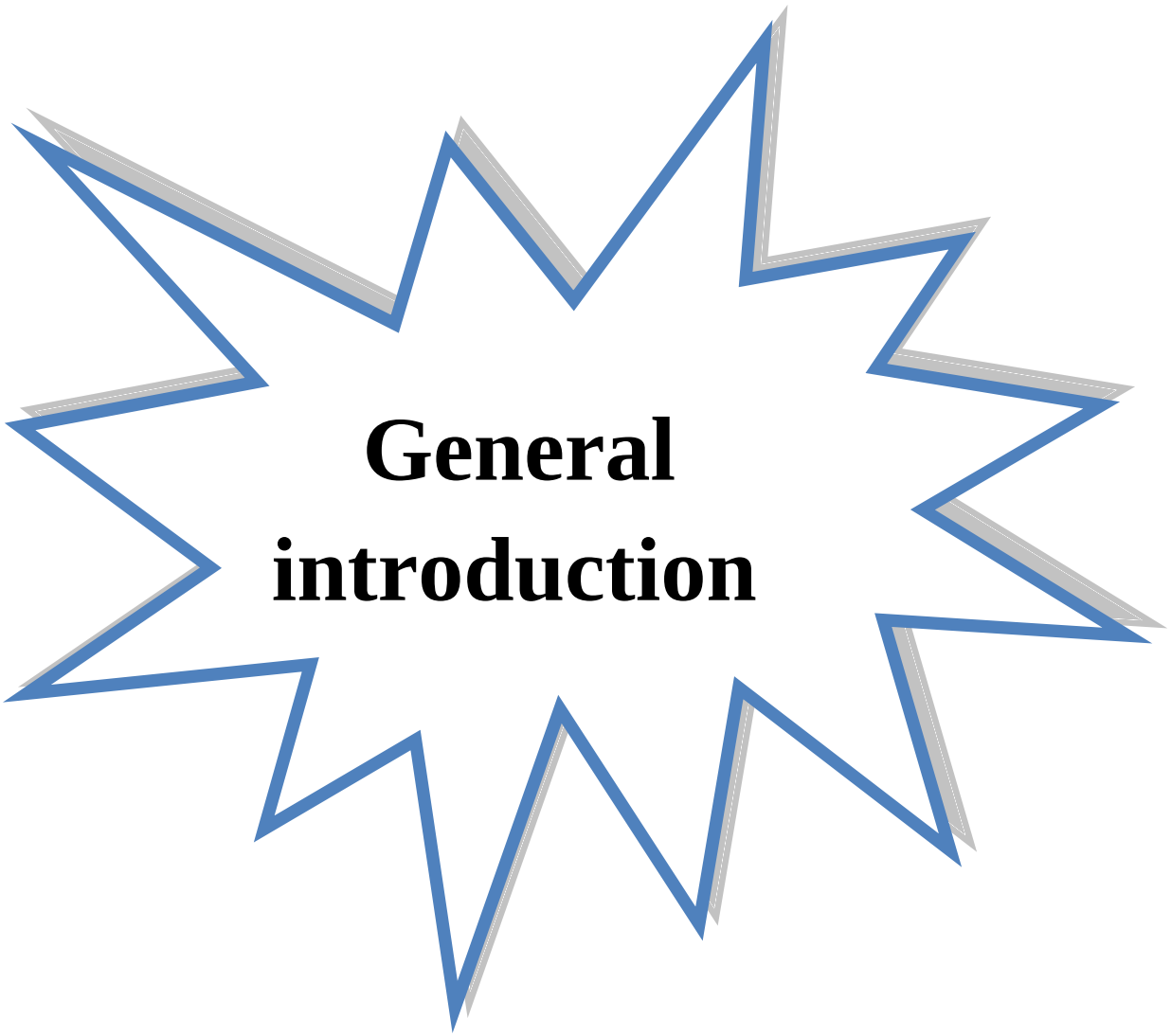
**NDDO**: Neglect of Diatomic Differential Overlap

**INDO:** Intermediate Neglect of Differential Overlap

**CNDO**: Complete Neglect of Differential Overlep

**PM3:** Parameterized Model number 3

**UV:** Ultraviolet.


General
introduction

## General Introduction

Computational chemistry also called theoretical chemistry or molecular modeling is a discipline that allows predicting the structure and reactivity of molecules or systems of molecules to the means of programs. The development of computer tools has made it possible to develop more and more advanced computational techniques, making it possible to study increasingly complex systems **[1, 2]**.

The objectives of molecular modeling are mainly: info graphic; visualization and drawing of molecules from structural data, obtaining information on the dynamic movements of molecules and their energies and qualitative prediction of the properties of molecules **[3]**.

Theoretical studies are currently moving towards rational design "Rational design" which means that knowledge of the relationships between the physico-chemical properties and the molecular structure of known molecules allows scientists to develop new molecules, with a fairly good anticipation [4].

Cyclodextrins, which are natural macromolecules, are used as host molecules able to encapsulate inside their cavities a good number of molecules, called invited. For this reason, the interest of their use has grown steadily in recent years [5].

The use of cyclodextrins in pharmacology is another field of use and not the least.

This use is characterized by the encapsulation of an active substance inside the cavities of the cyclodextrins, and this to ensure either its solubilization and hence its slow and controlled dissolution inside the body, its protection against numerous biological degradation, which is of paramount importance in the field of the pharmaceutical industry, with all that this implies as a use in the medical field [5].

The Schiff bases and their complexes are interesting candidates since they can be easily synthesized and allow a great diversity of coordination. Are intensively studied because of synthetic flexibility, selectivity and sensitivity. They have proved to be very useful in catalysis, in medicine as antibiotics and anti-inflammatory agents, etc...[6].

We investigate in this study the formation of inclusion complexes between cyclodextrin and azomthine. Theoretically, using semi empirical method PM3 to localize the global minimum of favor complex and determine the H-bond rule to create a stable complex.

This work is divided into two parts, in the first part, we present relevant bibliographic studies host and guest molecule next, and we describe the concepts of molecular modelling and their computational methods.

The second part is the calculation part: we present general information about the Schiff base. We will begin with the definition of a Schiff base. And then we will recall the method of formation of Schiff base Characterization classification.

**In the first chapter:** This chapter is divided into two parts:

In the first part, we present general information about cyclodextrin. We will start with history of cyclodextrin and Cyclodextrin Structure, Properties of CDs, modified cyclodextrins, applications of cyclodextrins.

In the second part: we present general information about the Schiff base. We will begin with the definition of a Schiff base, and then we will recall the method of Formation of Schiff bases, Characterization, Classification

**In the second chapter**: we describe, the theoretical methods, we present, the Schrödinger equation, and their approximate solutions we will also present Semi-empirical methods and Principle of semi-empirical methods.

**The third chapter** is computational study of the inclusion complexes between beta-cyclodextrine and azomthin. We presented the different results and discussion. Finally, the general conclusion.

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# Chapter I

## Host and guest molecule

## I. 1. Introduction

Natural or chemically modified cyclodextrins (CDs) are part of the "cage molecules" family. They are known for their ability to increase the solubility of many organic molecules through the formation of compounds, or inclusion complexes. This property gives cyclodextrins a wide field of application in a wide variety of fields ranging from pharmacy to agriculture, including the textile industry, perfume and aroma chemistry, etc **[1].**

## I. 2. Cyclodextrins

### I. 2. 1. History

Cyclodextrins have been isolated for the first time by Villiers **[2]** in 1891, thanks to the experience of the starch degradation by microorganisms strain (Bacillus macerans amylase: cyclodextrinase). Villiers highlights two products (probably the α- and β-cyclodextrin) with physicochemical properties similar to those of cellulose.

Cyclodextrins have been characterized in 1903 by Schardinger **[3]** as cyclic oligosaccharides; this is why they are called Schardinger dextrin in the first publications dealing with cyclodextrins.

In 1938 Freudenberg et al. **[4]** have demonstrated that cyclodextrins are constructed from D-glucose units linked together by α linkages (1 → 4) glucosidic bond. Freudenberg et al. **[5]** have found that the cyclodextrins were capable of forming inclusion complexes and entirely determine the structure of the γ- cyclodextrin. In the 1950, groups of French **[6]** and that of Cramer **[7]** have worked on the synthesis and purification of cyclodextrin complexes.

Freudenberg deposited the first patent on the application of cyclodextrins for the shaping of a biologically active compound in 1953 **[8].** From that time, the study of cyclodextrins takes considerable growth: industrial production, synthesis of cyclodextrins modified synthesis of inclusion complexes.

In the years 1970-80, Szetjli **[9, 10]** also called 'godfather' of cyclodextrins, contributed importance in the field. Since 1970, there were just over 130,000 documents on cyclodextrins (publications, patents, abstracts).

Today, the production of the β-cyclodextrin is greater than 1000 T / year and his ongoing price to drop. Other natural or modified cyclodextrins are produced industrially.

## I. 3. Cyclodextrin Structure

The number of glucose units per CD ring varies from 6-13[9] as the enzyme produces a range of oligosaccharides. **[11]** A five glucose unit CD is unlikely due to ring strain and has not been observed. **[12]** the most common CDs contain 6, 7 and 8 units and are known as αCD, βCD and ϒCD, respectively. The glucose residues are labeled (A-H) in a clockwise direction when facing the primary hydroxyl group side. The structures are shown in **Fig.1** and the approximate dimensions are shown in **Fig.2**.

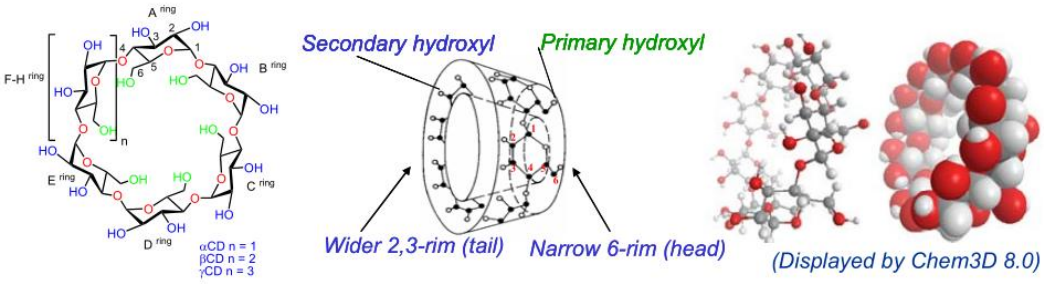



**Figure 1: Schematic representations of the CDs.**

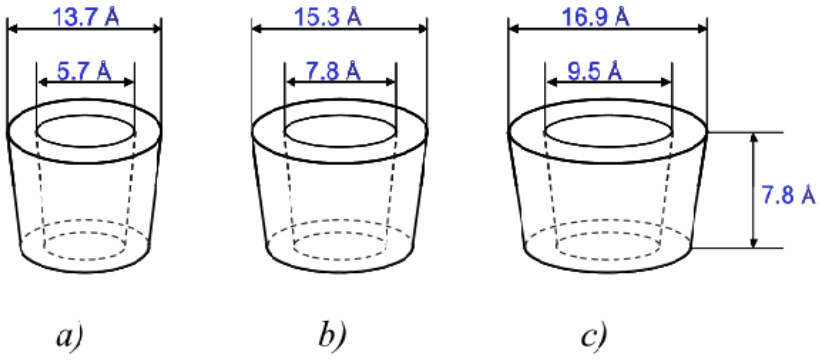



**Figure 2: Dimension of the CDs, a) αCD, b) βCD, c) ϒCD.**

## I. 4. Properties of CDs

The special properties of the -CD derive from the specific distribution of the different functional groups along the internal (hydrophobic) and external surfaces (hyrophile) **[13].**

**Table 1: shows the dimensions and some physicochemical characteristics of the three main cyclodextrins.**

| Cyclodextrin | Mass | Outer diameter (nm) | Cavity Diameter (nm) | | Cavity volume (ml/g) | Solubility H2O (g/kg) | Hydrate (H2O) | |
|---|---|---|---|---|---|---|---|---|
| | | | Inner rim | Outer rim | | | Cavity | External |
| α, (glucose)6 | 972 | 1.52 | 0.45 | 0.53 | 0.10 | 129.5 | 2.0 | 4.4 |
| B; (glucose)7 | 1134 | 1.66 | 0.60 | 0.65 | 0.14 | 18.4 | 6.0 | 3.6 |
| ϒ; (glucose)8 | 1296 | 1.77 | 0.75 | 0.85 | 0.20 | 249.2 | 8.8 | 5.4 |

## I. 5. Modified cyclodextrins

The aqueous solubility of natural CDs is low because of the strong intermolecular hydrogen bond in the crystal lattice **[14]**. Against by hydroxylation or methylation of the hydroxyl groups of β-cyclodextrin improves the solubility and the ability of including parent CD **[15]**. The main types of chemical functionalization performed on cyclodextrins can be classified in the following way **[16,17]**. Etherification (alkyl derivatives and silylated) Esterification (acyl derivatives and sulfonyl) Halogenation Substitution nucleophilic.

## I. 6. Applications of cyclodextrins

### I. 6.1. Cosmetics, personal care and toiletry

In this sector, cyclodextrins involved in the stabilization, odor control and process improvements in the conversion of a liquid component in a solid form. The applications of cyclodextrins in this area include toothpaste, skin creams, liquid and solid fabric softeners,

paper towels, tissues and underarm shields. In fact, the interaction of the guest with CDs produces a higher energy barrier to prevent volatilization, producing lasting fragrance **[18]**.

**I. 6.2. Cyclodextrins in pharmaceutical industry**

Cyclodextrins complexation uses are well known in the pharmaceutical industries that have been certified by several critics in recent years **[19].** Thanks to their non-toxicities, the use of CDs is very important in the bioavailability **[20].** The active stabilization **[21].** Odor or taste masking **[22].** Reducing irritation **[23].** And uses handling equipment **[24].** Then the practical use of natural cyclodextrins as drug carriers is restricted to their low aqueous solubility.

**I. 6. 3. Cyclodextrins in textiles**

The factors that influence the formation and decomposition of inclusion complexes, very important for the use of particularly complex and versatile for selecting the type of cyclodextrin (α, β, γ and δ), constitute the field several studies and are of particular interest to medical textiles with slow-release medicine as well as the influencing factors on the transdermal permeability, very important for the use of cyclodextrins grafted onto textiles, for topical administration drugs **[25].** In 2007, Perrin et al. were discovered another important application of textile finishing products is the use of cyclodextrin as equalizer dye. Given their external and internal polar hydrophobic, cyclodextrins are able to form inclusion complexes with dyes in aqueous media **[26].**

**I. 6.4. Cyclodextrins in environmental**

In the environmental field cyclodextrins play a very important role in terms of solubilization of organic contaminants, enrichment and the removal of organic pollutants and heavy metals from the soil, water and atmosphere **[27].** CDs have been used in water treatment to increase stabilization of the action, encapsulation and adsorption of contaminants **[28].** In 1999, Reid et al. discussed the soil test to determine the bioavailability of pollutants using CD and its derivatives. Cyclodextrins makes three benzimidazole fungicides (thiabendazole, carbendazim and fuberidazole) more soluble in water, which causes the availability of its fungicides to soil. More CDs have the ability to increase the solubility of the hydrocarbon for the biodegradation, bioremediation and reduce the toxicity resulting in increased microbial and plant growth **[29].** Thus 90% of the toxic material is disappear **[30].**

**I. 6. 5. Cyclodextrins in catalysis**

Cyclodextrins and their derivatives are used in the field of catalytic chemistry. For example, Atwood **[31].** Explained the use of α-cyclodextrin in the modified porphyrin

reduction of Mn (III). Ye et al **[32].** Found that the use of a derivative of β-cyclodextrin as a catalyst increases the benzyl alcohol conversion rate to aldehyde.

Because of their steric effects, cyclodextrins plays a significant role in the biocatalytic process by increasing the enantioselectivity. Leventis and Silvius **[33]** have shown that the cholesterol cyclodextrins accelerate the transfer rate between the lipid vesicles.

### I. 6. 6. Cyclodextrins in analysis

In chromatography, cyclodextrins are used extensively in the separation of chiral molecules for their ability to distinguish between the position isomers, functional groups, homologues and enantiomers **[34]**. This property is in fact one of the most useful agents for a range of separations. They are still used as ligands chemically bonded or absorbed in the stationary phase or the mobile phase **[35]**.

Currently, chiral separations are one of the most important areas of application of cyclodextrins and their derivatives **[36]**.

### I. 6.7. Cyclodextrins in polymers, adhesives and coatings

Cyclodextrins are used as additives and blowing agents compatible with hot melt systems. They also increase the stiffness, adhesion of hot melt adhesives and interaction between the associative thickener polymer molecules in emulsion-type coatings such as paints tends to increase viscosity. So, in the literature, CDS can be used to counteract this adverse effect **[37]**.

## II. The invited molecule (azomethine)

### II. 1. Introduction

Hugo Schiff described the condensation between an aldehyde and an amine leading to a Schiff base in 1864 [38]; it represents an important role in different fields of chemistry indeed considerable efforts have been made to develop methods of synthesis of these compounds which have for a very long time aroused very special attention in many on the basis of their importance in the pharmaceutical, biological and industrial fields[39].

### II. 2. Definition

Schiff bases are formed when any primary amine reacts with aldehyde or ketone under specific conditions. Structurally, a Schiff base also called imine or azomethine their structure is shown in **Fig.3** [40].

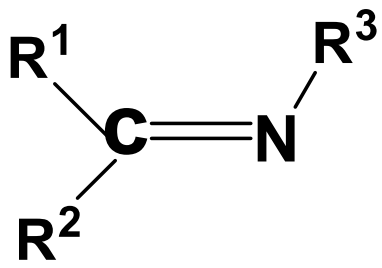


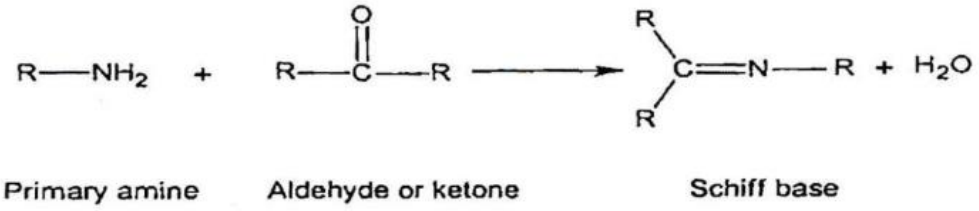

**Figure 3: General basic Schiff structure**

Depending on the nature of the radicals that may be aliphatic as well as aromatic, the linear or cyclical Schiff bases acquire various behaviors in terms of their stabilities, their basicities, their modes of coordination and the diversity of their fields of application [41].

**II. 3. Formation of Schiff bases**

The formation of a Schiff base from an aldehydes (or) ketone is a reversible reaction and generally takes place under acid (or) base catalysis, or upon heating. [42]

**Reaction scheme:**




Then a diagram explains the training mechanism of a Schiff base [43].

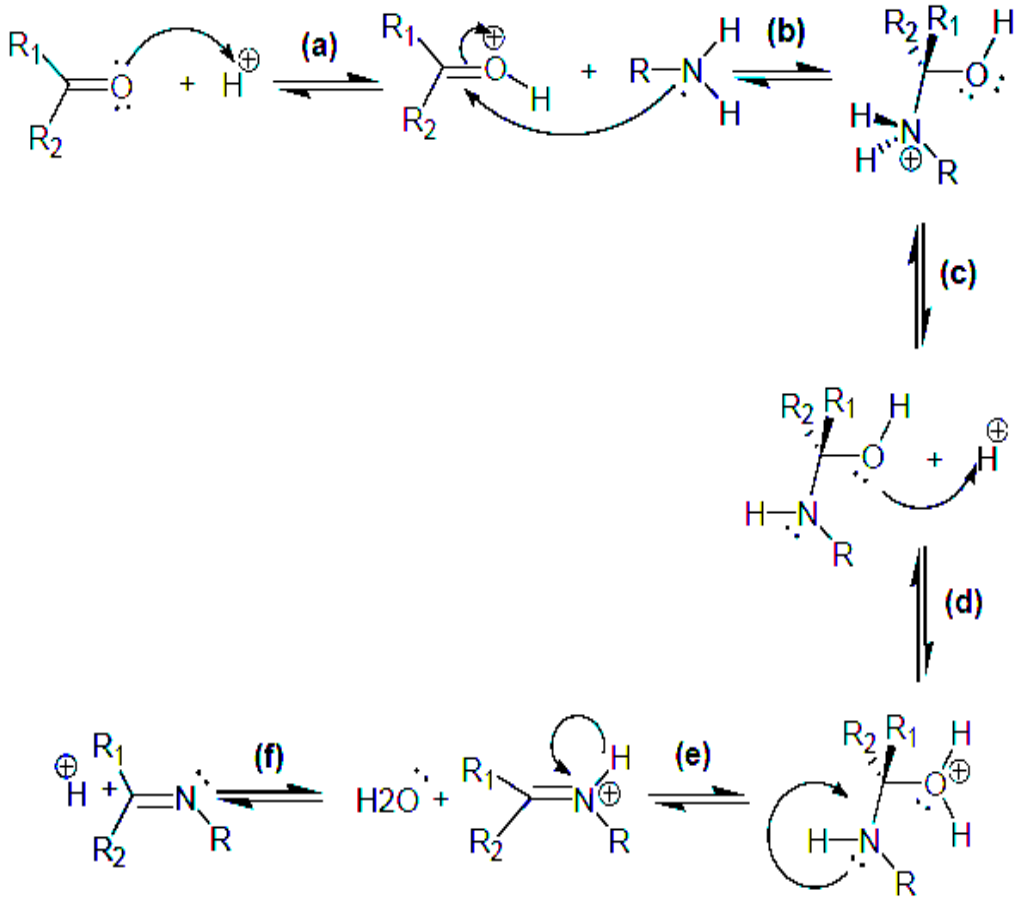



**Figure 4: Schiff Base Training Mechanism**

Activation of the electrophilic character of the carbonylated derivative by protonation of the oxygen atom.

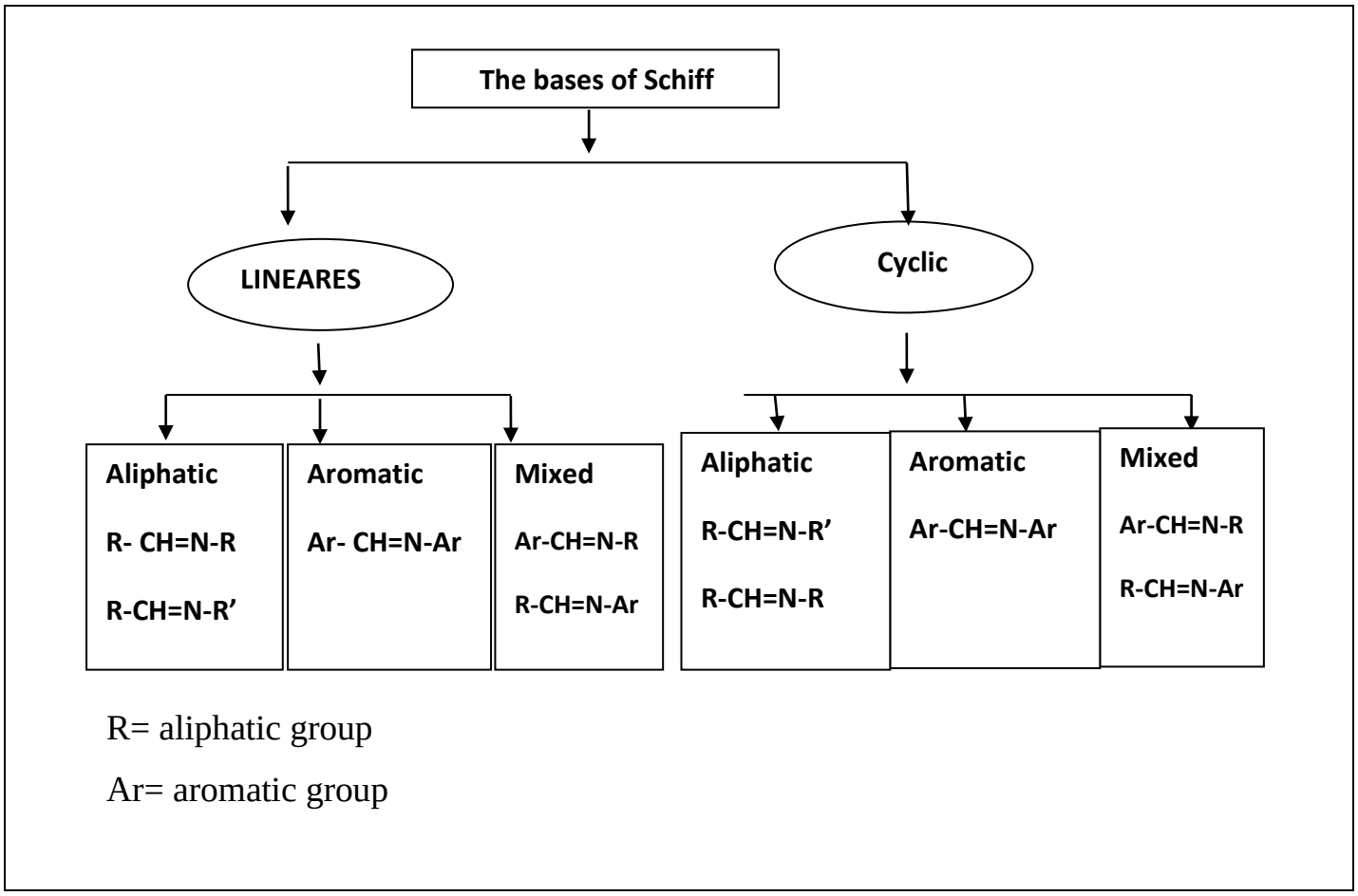
a. Nucleophilic attack of the protonated carbonylated derivative.
b. De-protonation.
c. Protonation of the oxygen atom.
d. Intermolecular removal of water.
e. Deprotonation of imine [44].

**II. 4. Characterisation of the Schiff bases**

The vibration frequencies of the azomethine group (C=N) of the ligands of the Schiff bases are between 1603–1680 cm-1 works, depending on the nature of the different substitutions on the carbon and nitrogen atoms. This property makes infrared spectroscopy a technique of choice for the identification of this grouping the UV-Vis of compounds containing a non-conjugated chromophore is characterized by transition spectra of type n π * in the range 235 –272 nm. The RMN of the H1 proton is also a powerful means for elucidating the structural characteristics in solution [45].

### II. 5. Classification of the Schiff bases

### II. 5. 1. According to their linear or cyclic structures [42]




**Scheme 1:** Basic classification of Schiff according to their linear or cyclic structures

### II. 5. 2 According to the numerous coordination sites

Schiff base ligands can be classified according to several structures: mono, bi, tri, tetra, penta, hexa and heptadentate as follows [46].

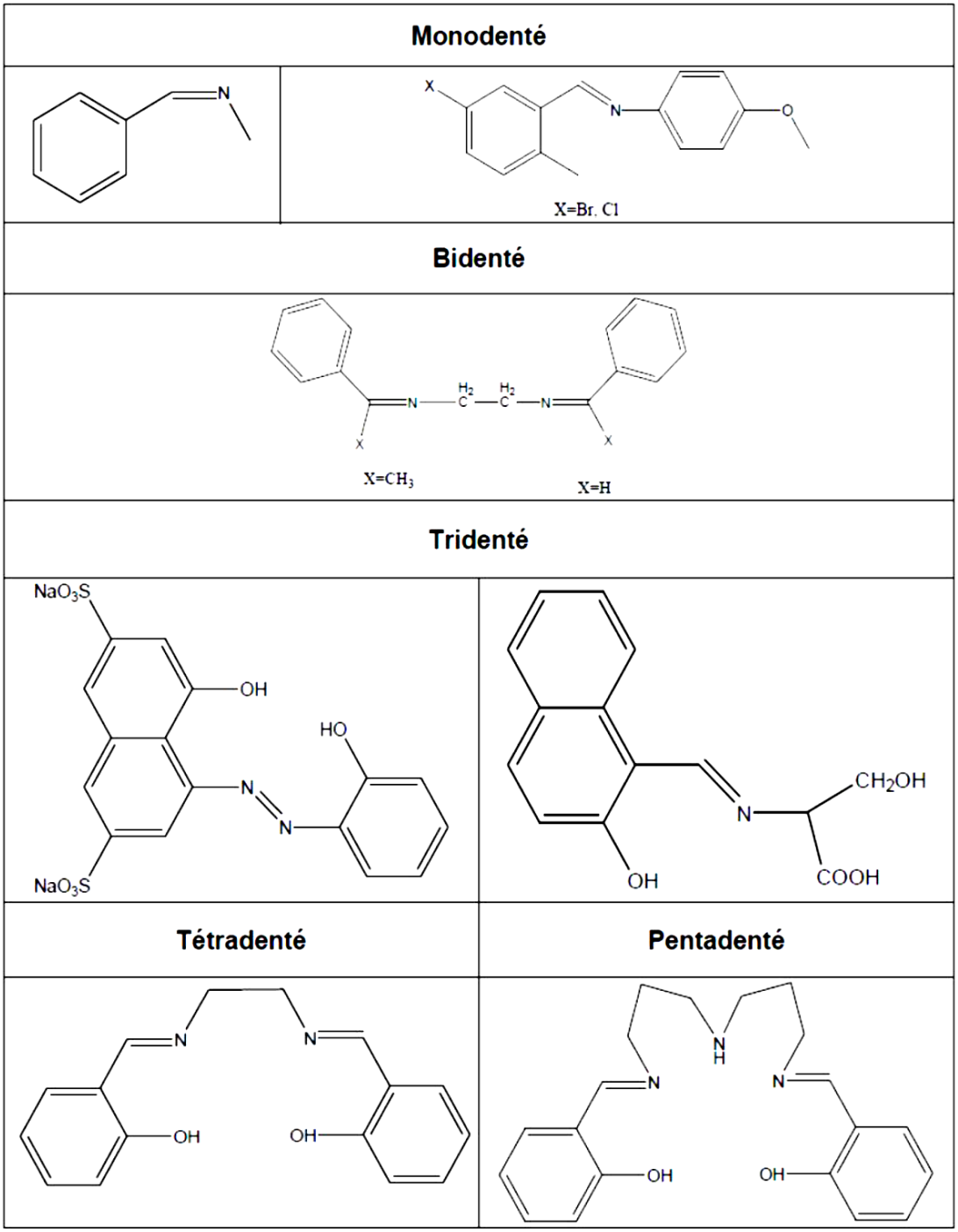



**Figure 5: Basic classification of chiff according to the numerous coordination sites.**

## II. 6. General use

Schiff bases and their complexes have been extensively investigated due to their wide range of applications: in medicine, in crystal engineering, antioxidant agent. Schiff bases and their complexes have been extensively investigated due to their wide range of applications: in medicine, in crystal engineering, antioxidant agent, structural similarities with natural biological enclosures and also due to the presence of azomethine group (-N=CH-) which is important in elucidating the transformation mechanism. Donors and their complexes have

been used as drugs possessing a wide variety of biological activities against bacteria, fungi and a certain type of tumors [46].

### II. 6. 1. Biological activities

The Schiff bases are characterized by an imine-N=CH-group, which helps to clarify the transamination mechanism (is a reversible chemical reaction which consists of the exchange of a primary amine function between an amino acid and a ketoacid) and racemization (is the conversion of a pure enantiomer mixture into a mixture containing more than one of the enantiomers) reaction in the biological system [47].

### II. 6. 2. Antibacterial activity

A bacterial infection is a set of disorders that result from the entry of a pathogenic bacterium into an organism. It can be:

- **Local:** when manifested only at the level where the germs have penetrated.
- **General:** When a germ crosses the barriers of the body at its entrance (skin, mucous membranes) or at the level of the lymph nodes, it enters the blood and spreads through
- **focal:** is the infection in the tissues or organs where germs are brought by the bloodstream. It is throughout the body [48].

The development of new antibacterial drugs enriched by more effective mechanisms of action is clearly an urgent medical need. Schiff bases are identified as promising antibacterial agents [40].

### II. 6. 3. Antifungal activity

Antifungal are substances capable of selectively or not destroying the different fungi encountered in mycology. They are administered locally or generally. They have been used in therapeutics can be classified into two groups according to their origin. These are natural and chemical Antifungal [49]. The most effective research and development antifungal agents are mandatory and some Schiff bases are known to promise antifungal agents. [40]

### II. 6. 4. Antioxidant activity

An antioxidant can be defined as any substance that is able, at a relatively low concentration, to compete with the amount of oxidable substances such as reactive oxygen species (SAR), significantly delays or prevents oxidation of substrates such as lipids, proteins, DNA and carbohydrates. Schiff bases were also presented as promising antioxidants [46].

With other oxidizable substrates and thus delay or prevent oxidation of these substrates. In other words, an antioxidant is a substance that, in low concentration.

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# Chapter II

## Molecular modeling

## II.1. Introduction

Thanks to the computer development of recent years and the rise of parallel computing, intensive. In particular, molecular modeling has become a real challenge.

Indeed, the molecular systems, which are to be studied, tend to become increasingly complex.[1]

Modelling and numerical simulation have become common practices in many scientific and technical fields and in particular in Chemistry. Molecular modelling is defined as an application of theoretical and computational methods to solve problems involving molecular structure and reactivity. [2]

Molecular modelling methods can be grouped into three categories [3]:

- ✓ Quantum methods.
- ✓ Molecular mechanics.
- ✓ Under the term molecular modelling, we find different techniques of visualization, manipulation, analysis and calculation of molecular structures. Molecular dynamics.

Over the past thirty years, the Density Functional Theory has been extensively developed for the study of chemical systems and has established itself as a powerful Alternative to Post HF methods. [4]

## II.2. Theoretical Chemistry

Theoretical chemistry is the study of chemistry through a fundamental theoretical reasoning it is a new discipline, appeared around 1930. Developing slowly until the Second World War, and then more rapidly in the 1950s, it has grown significantly Since 1960 thanks to the progress of computers. Thus, in many scientific universities, this discipline has acquired the same right of place as those much older and traditional of chemistry: physical chemistry, mineral chemistry, organic chemistry [5].

In theoretical chemistry, chemists, physicists and mathematicians develop Algorithms and codes to predict atomic, molecular or other properties, and possibly Chemical reaction paths. Numerical chemists can simply apply existing codes and Methodologies to specific chemical problems. There are two distinct aspects of Digital Chemistry:

- ✓ Studies conducted to find a starting point for laboratory synthesis, or to explain experimental results, such as the position and source of spectroscopic peaks.

- ✓ Studies conducted to predict the possibility of existence for unknown systems or to explore reactive mechanisms that cannot be studied by experimental means. .[6]

**II.3. Molecular modelling Methods**

Molecular modelling is the generic term for methods that simulate the behaviour of a particle system. The size of the system studied can range from a simple diatomic molecule to biological macromolecules of tens of thousands of atoms [7].

Molecular modelling can thus make it possible to describe the electron behaviour of atoms and molecules to explain their reactivities, understand protein-folding processes or explain the importance of certain amino acids in an enzymatic catalytic site.

To carry out this type of study, it is necessary to determine an expression of the interaction energy of the atoms of the molecular system according to their relative positions. To do this, molecular modelling methods use two different approaches to evaluate this interaction energy [8] called: Quantum Mechanics and Molecular Mechanics. The search for stable conformations of a molecule consists in determining the minimum value of this interaction energy corresponding to the global minimum [9].

**II. 4. Quantum chemical methods**

In the early 1900's, revelations of phenomena such as energy quantization and particle- wave duality of light challenged the classic Newtonian understanding of microcosmos.

While, the foundation of quantum mechanics is a product of many great contributions, the most famous and most relevant for chemists is the one made by Erwin Schrödinger in 1926 [10].

He proposed that a physical system is described entirely by a wave function Ψ. It is postulated that Ψ is well behaved and square integrable in real space. While no physical, property can be drawn directly from Ψ

$$p(r) = |\Psi(r)|2dr \ldots\ldots\ldots\ldots\ldots\ldots 1$$

One usually invokes a normalization criterion, since the probability of finding a particle somewhere is 1

$$|\Psi|2d\tau = (\Psi|\Psi) = 1 \ldots\ldots\ldots\ldots\ldots\ldots ...2$$

The wave function is found by solving the eigenvalue problem known as the time-

Independent Schrödinger equation [11]:

$$H\hat{}\Psi = E\Psi \text{ ……...3}$$

This equation can only be rigorously solved for single-electronic systems. The description of more complex systems requires the implementation of a number of approximations. The exact hamiltonian of a system with N nuclei and n electrons, where nuclei are designated by A and B and electrons by k and l, is written:

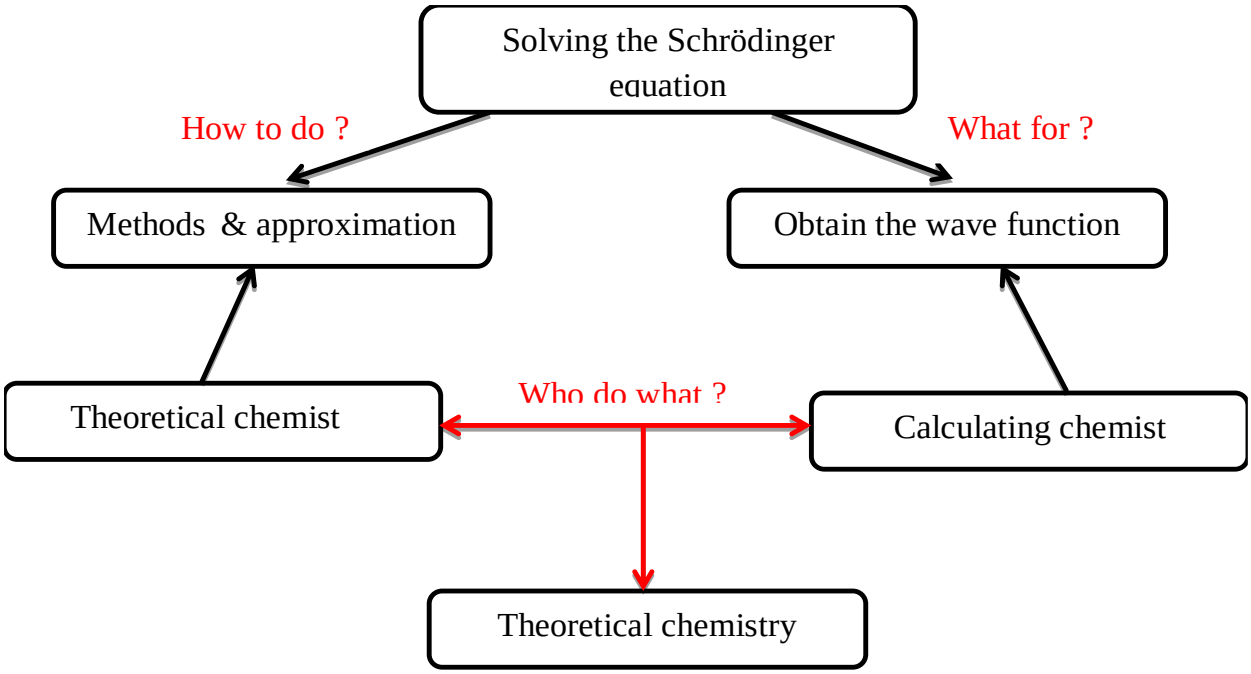
$$\boldsymbol{H = -\sum_{K=1}^{2n}\frac{h^2}{2.m_e}\nabla_K^2 - \sum_{K=1}^{2n}\sum_{A=1}^{N}\frac{e^2}{4\pi\varepsilon_0}.\frac{Z_A}{r_{KA}} + \sum_{K=1}^{2n}\sum_{l>K}^{2n}\frac{e^2}{4\pi\varepsilon_0.r_{Kl}} - \sum_{A=1}^{N}\frac{\bar{h}^2}{2.M_A}\nabla_A^2 + \sum_{A=1}^{N}\sum_{B>A}^{N}\frac{e^2}{4\pi\varepsilon_0}.\frac{Z_A.Z_B}{R_{AB}}}$$

- ✓ Ћ Is the Planck h constant divided by 2π
- ✓ me is the mass of the electron,
- ✓ e is the charge of the electron
- ✓ MA is the mass of kernel A is the distance between electron k and kernel A,
- ✓ R AB is the distance between the nuclei of atom A and atom B whose nuclear

Charges are ZA and ZB, respectively.

$\nabla_K^2$ is the Laplacian of the electron $K^{iéme}$ defined as follows:

$$\nabla_K^2 = \frac{\partial^2}{\partial x_k^2} + \frac{\partial^2}{\partial y_k^2} + \frac{\partial^2}{\partial z_k^2}$$




**Scheme 2 : Ways of solving the Schrödinger equation**

### II. 4. 1. the Born-Oppenheimer approximation

The Born-Oppenheimer approximation is central to Quantum Chemistry and is applied routinely because of its simplicity and high retained accuracy. It states that since electrons move orders of magnitude faster than the heavier nuclei, they can be viewed as moving in a field of fixed nuclear potential.

The purely electronic Hamiltonian reads:

$$H = -\frac{1}{2}\sum_{i=1}^{N}\nabla_i^2 - \sum_{i=1}^{N}\sum_{j=1}^{M}\frac{Z_K}{r_{ij}} + \sum_{i=1}^{N}\sum_{j>1}^{M}\frac{1}{r_{ij}}$$

### II. 4. 2. The Hartree-Fock method

The orbital approximation, introduced by Hartree in 1928 [12], consists of writing the wave function for a poly-electronic system as a monoelectronic spin-orbital product assumed to be normalized

$$\psi_e\,(1,2,3\ldots\ldots n_e) = \varphi(1).\varphi(2).\varphi(3)\ldots\ldots\varphi_{ne}(ne)$$

Knowing that each spin-orbital is the product of an electron$\emptyset_i$ position function and a spin function$\eta_{(si)}$

$$\varphi_i\ (n_i)\ =\ \emptyset_{i_{(ri)}}.\eta\ (s_i)$$

The spinη_((if)) function is associated with two forms: α for spin(1/2) and β(-1/2 ) for spin This concept was then generalised by Hartree and Fock[13], by writing the wave function in the form of a Slater determinant built on the basis of the wave functions of each electron to satisfy the Pauli principle[14], In this case, it is possible to evaluate the best wave function for such a system by minimizing the energy using the variational principle

$$\psi_{(e)}(1,2,3\ldots..n_e) = \frac{1}{\sqrt{n_{e!}}}\begin{bmatrix}\varphi_1(1) & \varphi_2(1)\ldots & \varphi_n(3)\\ \varphi_1(2) & \varphi_2(2)\ldots & \varphi_n(3)\\ \varphi_1(n_e) & \varphi_2(n_e)\ldots & \varphi_{ne}(n_e)\end{bmatrix}$$

- ✓ $\frac{1}{\sqrt{n_{e!}}}$ Est le facteur de normalisation

**II. 4. 3. Post-Hartree-Fock methods**

In digital chemistry, post-Hartree-Fock methods are a set of methods developed to improve (exceed) the Hartree-Fock (HF) method, a self- consisting field method (SCF). They add the electronic correlation, which is a more accurate way to include the repulsions between electrons than in the Hartree-Fock method where they are only averaged.

In general, the SCF procedure requires several assumptions about the nature of the multi-body Schrödinger equation and its set of solutions:

- ✓ Born-Oppenheimer approximation is assumed inherently. The true wave function is also supposed to be a function of the coordinates of each nucleus.
- ✓ Relativistic effects are typically completely overlooked. The motion quantity operator is assumed to be completely conventional.
- ✓ The specific functions of the poly-electronic system are assumed to be monoelectronic wave function products.
- ✓ The base consists of a finite number of orthogonal functions.

The effects of the electronic correlation, beyond that of the exchange energy resulting from the antisymmetry of the wave function, are completely neglected.

For the vast majority of the systems studied, particularly for excited states or processes such as molecular dissociation reactions, the fourth point is by far the most important. Therefore, the term post-Hartree-Fock method is typically used for methods to approximate the electronic correlation of a system.

Usually, Post-Hartree-Fock methods produce better results than Hartree-Fock calculations, although the extra precision entails an additional calculation cost [15],.

### II.4.4. Density Functional Theory

#### II.4.4.1. Historical overview

The purpose of density functional theory is to describe a considering the density ρ(r) as the basic variable. Thus the problem with n electrons is studied in the space of ρ(r) which is dimension 3 instead of the space of dimension 3n of the ψ wave function. The first to express energy as a function of density were L. H. Thomas and E. Fermi in 1927.

In their model, electronic interactions are treated classically and kinetic energy is calculated assuming electronic density Homogeneous. This model was improved by P. A. Dirac in 1930 with an exchange term. A little later, in 1951 J. C. Slater [16]. proposed a model based on the study of an improved uniform gas with local potential.

This method, called Hartree fock slater or Xα, was mainly used in solid- state physics in the 1970s, but DFT [17], establishes a functional relationship between the energy of the ground state and its density.

While the first successful DFT applications for structure research molecular electronics began to appear in the 1990s with the development exchange and correlation functions [18], the most accurate and fastest for calculating the electronic properties of large molecular systems or has been introduced into the Gaussian code.

Finally, we point out that the Nobel Prize was awarded to Kohn and Pople [19], in 1998 as part of the development of this method.

### II. 4. 5. Semi-empirical methods

The semi-empirical methods take up the principle of ab initio methods. However, Unlike the latter, which do not require any experimental endpoints, but only the fundamental laws of quantum mechanics, semi-empirical methods use adjusted parameters with experimental results in order to Simplify the calculations. Taking into account only the

electrons of the valence layer or by neglecting certain integrals, they require shorter calculation times and Provide access to larger systems.

Existing semi-empirical methods include [20]:

- ✓ CNDO: (Complete Neglect of Differential Overlep) Semi-empirical method, it was proposed by Pople, Segal and Santry in 1965. Method with some defects among others: it does not take into account the rule of Hund.
- ✓ INDO: (Intermediate Neglect of Differential Overlap) Proposed by People,

Beveridge and Bosh in 1967. It makes it possible to distinguish between the singulet states and the triplet states of a system by retaining the integrals of exchange.

- ✓ MINDO/3: Proposed by Bingham, Dewar and Lo in 1975.

Parameterization carried out by referring to the experimental results and not to the ab-initio results, moreover the algorithm optimization used is very effective (Davidon- Fletcher-Powel).

However, it overestimates the heat of the formation of unsaturated systems and underestimates molecules containing neighbouring atoms with free pairs: MNDO: (Modified Neglect of Diatomic Overlap) Proposed by Dewar and

Theil in 1977.Methods based on approximation NDDO (Neglect of Diatomic Differential Overlap) which consists in neglecting the differential overlap between Atomic orbitals on different atoms. This method does not treat transition metals and has difficulties for combined systems.

- ✓ AM 1: (Austrin Model 1) Proposed by Dewar in 1985. He attempted to

Correct the defects of MNDO.

- ✓ PM 3: (Parametric Method 3) Proposed by Stewart in 1989. Features many

Points in common with AM1, moreover there is still a debate about the merits Relative parameterisation of each of them.

SAM 1: (Semi-ab-intio Model 1) the most recent method proposed by Dewar in 1993. It includes electronic correlation.

The theoretical Semi empirical methods (PM3, AM1, and MNDO) are Particularly used to obtain the enthalpy of formation of chemical systems.

Dewar's MNDO and AM1 methods were generally applied in the calculations training enthalpy and represent a standard tool for theorists and organic chemistry experimenters. Later, Stewart proposed a mathematical representation in the MNDO method called the PM3 method. Generally, PM3 gives better results than the AM1 method[21].

**Principle of semi-empirical methods:** These methods all have a common objective which is to reduce in a significant proportion the number of integrals to be calculated, and, in particular, that of bioelectronic integrals. They are all based on the following approximations:

1) The orbital base used is the Slater orbitals of the valence layer.
2) All bioelectronic integrals, with three or four centres, are assumed to be null. In addition, some bioelectronic integrals, with one or two centres, are also neglected; their number and nature depend on the method used.
3) The non-bidiagonal terms of the matrix of the heart hamiltonian are estimated by means of empirical relations which are all based on the assumption that these integrals are proportional to the integral coverage of the atomic orbitals concerned.
4) Most mono- or bioelectronic integrals at a centre are often estimated from data from the electron spectra of the atoms or ions of the elements considered.

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# Chapter III

**Computational study of the inclusion complexes . Between beta-cyclodextrin/azomethin**

**Introduction**

Cyclodextrins CDs are cyclic oligosaccharides with truncated shape cone that can be obtained via enzymatic conversion of starch. They are featured by the hydrophilic outer surface and apolar cavity that enable them to form host–guest inclusion complexes with wide range of molecules through the insertion of the hydrophobic portion of the guest molecule inside the apolar cavity, which in turn leads to dramatic changes in the physicochemical properties of the guest molecule [1].

Schiff bases are compound with a functional group that contains a carbon nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group. Azomethine is one examples of a Schiff based compound (Fig8) [2]. According to the previous research [3], azomethine has shown some applications in therapeutic applications to exert anti-tumor activity. In addition, Smith and Chen [4] have demonstrated that azo compounds can be used as chromophores and metalochromic agents. Azomethine (Schiff based) compounds are widely used due to the good mechanical strength [5], attractive thermal stability [6], nonlinear optical materials, optical interconnect, oscillator, amplifier, frequency converter [7] and liquid crystal thermosets (LCTs) [8]. However, poor solubility of these azomethines in organic solvents limits their applications in various fields. Nepal et al. [9] have introduced β-cyclodextrin to the poly (azomethines) to improve the solubility and processability of Schiff bases for various types of applications.

The main objectives of this study are to quantify the nature of non covalent inter molecular interactions especially H-bond interaction between azomethine and β-CD during inclusion complex formation by using semi empirical method PM3.

Experimentally, the inclusion complex is synthesized by Kafirajaa et al [10].

- **Computational details**

The theoretical model of the guest molecule azomethine was studied in the graduation project work of Fahima Senouci, [11]. The host β-CD was retrieved from chem. Office 3D Ultra (version 10, Cambridge software). Fig8

For the complexation process, we followed the method described in literature [12-14]. The glycosidic oxygen atoms of β-CD were placed on the XY plane. Their center is defined as the origin of the coordinates system. The guest molecule was initially placed along the z-axis. Two possible orientation of the guest molecule in the complex were taken into consideration

(complex1: the benzene ring entering into the cavity of β-CD from its wide side, complex 2: the benzene ring entering into the cavity of β-CD from its narrow side). Fig9

The azomethine is a big molecule to include completely in the β-CD cavity. The distance between the sulfonyl groups is 9.93 A° which bigger than the inner diameter of β-CD (7.8 A°). Consequently, the inclusion should be partial to avoid the steric encumbrance.

Then, the guest was moved into the β-CD cavity along the z-axis from 0 to +6 with 1A° step. At each step, the guest was rotated from 0 to 360° with an increment of 10 degrees.

The generated structures at each step and degrees were optimized by PM3 method. It is a powerful tool in the conformational study of cyclodextrin complexes [15-17]. The inclusion process used to localize the minimum energy structures of the complexes.

All calculations were performed using Gaussian 09 program. [18]

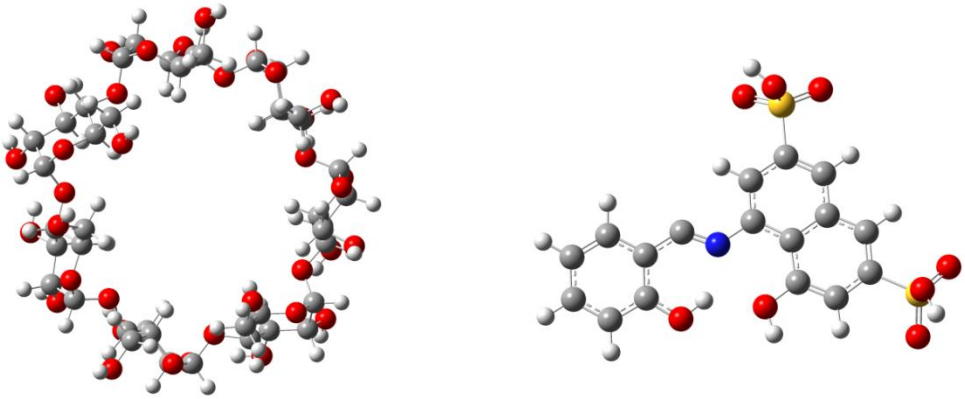


**Figure 6 :** Structures of azomethine and beta cyclodextrin used in the inclusion.

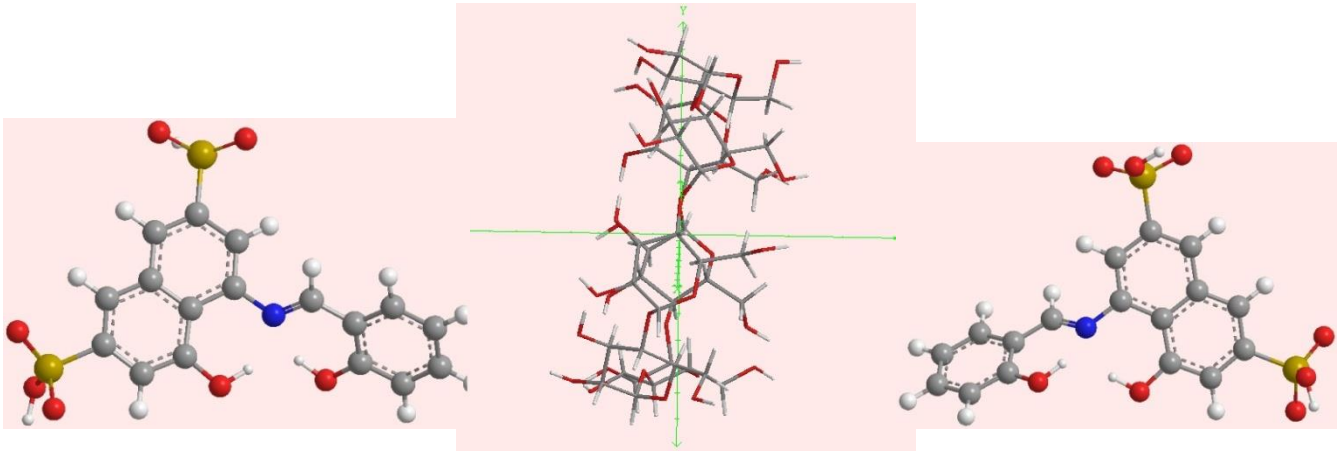


**Figure 7:** Possible orientations for the inclusion process.

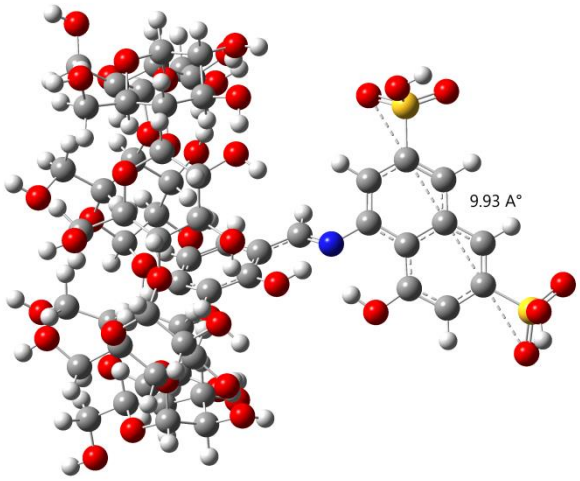



**Figure 8:** comparison between the azomethine size and the cyclodextin's diameter.

### III .3Results and discussion

### III .3.1. Energies and structures

To localize the minimum energies, we should calculate the complexation energy between azomethine and β-CD. E complexation is defined in equation 1.

$$E_{complexation} = E_{complex} - (E_{free\ azo} + E_{free\ \beta\text{-}CD}) \ldots\ldots\ldots\ldots eq1.$$

$E_{complex}$ is the total energy of the complex.

$E_{free\ azo}$ and $E_{free\ \beta\text{-}CD}$ are the energies of free azomethin and free beta-cyclodextrin molecules in the complex.

The results of different calculations are in the following tables.

**Table 2 :** The results of different calculations of complex 1

| Step 6 orientation1 | | | | | | | |
|---|---|---|---|---|---|---|---|
| Degree | $E_{complexation}$ | Degree | $E_{complexation}$ | Degree | $E_{complexation}$ | Degree | $E_{complexation}$ |
| 0 | -0.02237633 | 90 | -0.02472383 | 180 | -0.02201539 | 270 | -0.02173168 |
| 10 | -0.02323847 | 100 | -0.02320333 | 190 | -0.02374958 | 280 | -0.02177384 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 20 | -0.02324656 | 110 | -0.02456346 | 200 | -0.02376929 | 290 | -0.02102854 |
| 30 | -0.02097863 | 120 | -0.02251354 | 210 | -0.02213771 | 300 | -0.02061109 |
| 40 | -0.02133469 | 130 | -0.02291434 | 220 | -0.02263961 | 310 | -0.02166176 |
| 50 | -0.02324072 | 140 | -0.01864598 | 230 | -0.02263961 | 320 | -0.02135224 |
| 60 | -0.02324079 | 150 | -0.02083869 | 240 | -0.02098785 | 330 | -0.021319 |
| 70 | -0.01779046 | 160 | -0.02227603 | 250 | -0.0241349 | 340 | -0.02111441 |
| 80 | -0.0234001 | 170 | -0.02201538 | 260 | -0.02278106 | 350 | -0.02193879 |

| **Step5 : orientation 1** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy |
| 0 | -0.01771522 | 90 | -0.02294019 | 180 | -0.02240737 | 270 | -0.0225559 |
| 10 | -0.01916275 | 100 | -0.02190484 | 190 | -0.02374853 | 280 | -0.02441188 |
| 20 | -0.01810317 | 110 | -0.021536 | 200 | -0.02231875 | 290 | -0.02166164 |
| 30 | -0.0229089 | 120 | -0.01331631 | 210 | -0.02080504 | 300 | -0.02183877 |
| 40 | -0.02974657 | 130 | -0.02323673 | 220 | -0.01885705 | 310 | -0.02183894 |
| 50 | -0.01032466 | 140 | -0.01539034 | 230 | -0.02263886 | 320 | -0.01822396 |
| 60 | -0.02052545 | 150 | -0.02198858 | 240 | -0.02414238 | 330 | -0.02314549 |
| 70 | -0.02206096 | 160 | -0.02082513 | 250 | -0.024195087 | 340 | -0.02135167 |
| 80 | -0.02325749 | 170 | -0.02227629 | 260 | -0.0226392 | 350 | -0.0223014 |
| **Step 4 : orientation 1** | | | | | | | |
| Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy |
| 0 | -0.01988548 | 90 | -0.01640342 | 180 | -0.02388417 | 270 | -0.01786969 |
| 10 | -0.02001607 | 100 | -0.0141858 | 190 | -0.02240668 | 280 | -0.01937676 |
| 20 | -0.01803837 | 110 | -0.01956308 | 200 | -0.01684742 | 290 | -0.01504707 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 30 | -0.021701477 | 120 | -0.02275428 | 210 | -0.02061783 | 300 | -0.0205339 |
| 40 | -0.02079775 | 130 | -0.02314841 | 220 | -0.02004243 | 310 | -0.02166168 |
| 50 | -0.02151272 | 140 | -0.0216436 | 230 | -0.02204081 | 320 | -0.02119334 |
| 60 | -0.01970801 | 150 | -0.01983944 | 240 | -0.02325898 | 330 | -0.02181481 |
| 70 | -0.02112612 | 160 | -0.01321602 | 250 | -0.02161283 | 340 | -0.02177729 |
| 80 | -0.02254718 | 170 | -0.01788676 | 260 | -0.02416184 | 350 | -0.02024975 |

| **Step 3 : orientation 1** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy |
| 0 | -0.01976094 | 90 | -0.0186402 | 180 | -0.02282391 | 270 | -0.01732746 |
| 10 | -0.01931338 | 100 | -0.01443763 | 190 | -0.02305041 | 280 | -0.01132616 |
| 20 | -0.01366078 | 110 | -0.01952916 | 200 | -0.02385379 | 290 | -0.01756317 |
| 30 | -0.01618632 | 120 | -0.01880533 | 210 | -0.02291684 | 300 | / |
| 40 | -0.0179639 | 130 | -0.01797785 | 220 | -0.02026535 | 310 | -0.01891826 |
| 50 | -0.02009813 | 140 | -0.01447905 | 230 | -0.02358363 | 320 | -0.01751234 |
| 60 | -0.01754628 | 150 | -0.01441792 | 240 | -0.02057989 | 330 | / |
| 70 | -0.01432754 | 160 | -0.01356406 | 250 | -0.02057294 | 340 | / |
| 80 | -0.0140652 | 170 | -0.01572643 | 260 | -0.01425117 | 350 | -0.0197459 |

| **Step2 : orientation 1** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | -0.0180799 | 90 | -0.02092433 | 180 | / | 270 | -0.01724889 |
| 10 | -0.02057608 | 100 | / | 190 | / | 280 | -0.023138 |
| 20 | -0.020651741 | 110 | / | 200 | / | 290 | -0.0162215 |
| 30 | -0.016943297 | 120 | / | 210 | / | 300 | -0.01884412 |
| 40 | -0.00116022 | 130 | -0.02618555 | 220 | / | 310 | -0.01360884 |
| 50 | / | 140 | -0.0143164 | 230 | -0.00658409 | 320 | -0.01360885 |
| 60 | / | 150 | -0.01371334 | 240 | -0.0181412 | 330 | -0.01664426 |
| 70 | / | 160 | / | 250 | -0.01964676 | 340 | -0.00339045 |
| 80 | / | 170 | / | 260 | -0.01696175 | 350 | / |

**Table 3 :** The results of different calculations of complex 2

| **Step 6 : orientation 2** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy |
| 0 | -0.01532533 | 90 | -0.0041531 | 180 | -0.01934438 | 270 | -0.0145734 |
| 10 | -0.0107676 | 100 | -0.00561279 | 190 | -0.01046945 | 280 | -0.01648106 |
| 20 | -0.01034175 | 110 | -0.00515679 | 200 | -0.00594511 | 290 | -0.0161116 |
| 30 | -0.01990272 | 120 | -0.01158906 | 210 | -0.00546659 | 300 | -0.01880478 |
| 40 | -0.01854234 | 130 | -0.00059397 | 220 | -0.01437113 | 310 | -0.01269552 |
| 50 | -0.0145518 | 140 | -0.01608791 | 230 | -0.02097049 | 320 | -0.01883527 |
| 60 | -0.01624496 | 150 | -0.01300247 | 240 | -0.01920072 | 330 | -0.00866484 |
| 70 | -0.00850369 | 160 | -0.01076776 | 250 | -0.01869112 | 340 | -0.01224459 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 80 | -0.00892739 | 170 | -0.00911446 | 260 | -0.01185929 | 350 | 0.0061746 |

**Step 5 : orientation 2**

| Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy |
|---|---|---|---|---|---|---|---|
| 0 | -0.01230161 | 90 | -0.00553389 | 180 | -0.00960237 | 270 | -0.00194712 |
| 10 | -0.01176207 | 100 | -0.0154269 | 190 | -0.00330012 | 280 | -0.01846384 |
| 20 | -0.00937703 | 110 | -0.01070371 | 200 | -0.00728594 | 290 | -0.01962789 |
| 30 | -0.00589851 | 120 | -0.01299458 | 210 | -0.020866555 | 300 | -0.01353489 |
| 40 | -0.00952696 | 130 | -0.01263422 | 220 | -0.01893474 | 310 | -0.01353482 |
| 50 | -0.01330886 | 140 | -0.00884931 | 230 | -0.01920829 | 320 | -0.0108769 |
| 60 | -0.00236301 | 150 | -0.015669073 | 240 | -0.01336895 | 330 | -0.01295936 |
| 70 | -0.0152321 | 160 | -0.01300255 | 250 | -0.01323826 | 340 | -0.01061782 |
| 80 | -0.01332643 | 170 | -0.01329692 | 260 | -0.01759754 | 350 | -0.00834234 |

**Step 4 : orientation 2**

| Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy |
|---|---|---|---|---|---|---|---|
| 0 | -0.01220678 | 90 | -0.01876739 | 180 | -0.00974056 | 270 | -0.0224957 |
| 10 | | 100 | -0.01604899 | 190 | -0.01576964 | 280 | / |
| 20 | -0.01204883 | 110 | -0.01638174 | 200 | -0.01557113 | 290 | -0.01002673 |
| 30 | -0.01040872 | 120 | -0.009399025 | 210 | -0.0090838 | 300 | -0.02060478 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 40 | -0.01942328 | 130 | -0.01410293 | 220 | -0.01204955 | 310 | -0.01335565 |
| 50 | -0.00742156 | 140 | -0.00028979 | 230 | -0.00726921 | 320 | -0.01332678 |
| 60 | / | 150 | -0.01803423 | 240 | -0.00884015 | 330 | -0.01318214 |
| 70 | -0.01258429 | 160 | -0.01401887 | 250 | -0.00397481 | 340 | -0.01318212 |
| 80 | -0.01393175 | 170 | -0.01300259 | 260 | -0.01950236 | 350 | -0.0089144 |

| **Step 3 : orientation 2** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy | Degree | Complexation Energy |
| 0 | -0.00774423 | 90 | / | 180 | / | 270 | / |
| 10 | -0.00819408 | 100 | / | 190 | / | 280 | / |
| 20 | -0.00819408 | 110 | / | 200 | / | 290 | / |
| 30 | -0.01671848 | 120 | / | 210 | / | 300 | / |
| 40 | / | 130 | / | 220 | / | 310 | / |
| 50 | / | 140 | / | 230 | / | 320 | / |
| 60 | / | 150 | / | 240 | / | 330 | / |
| 70 | / | 160 | / | 250 | / | 340 | / |
| 80 | / | 170 | / | 260 | / | 350 | / |

From the tables, we can localize the global minimum of each complex using the following curves (Figure 11).

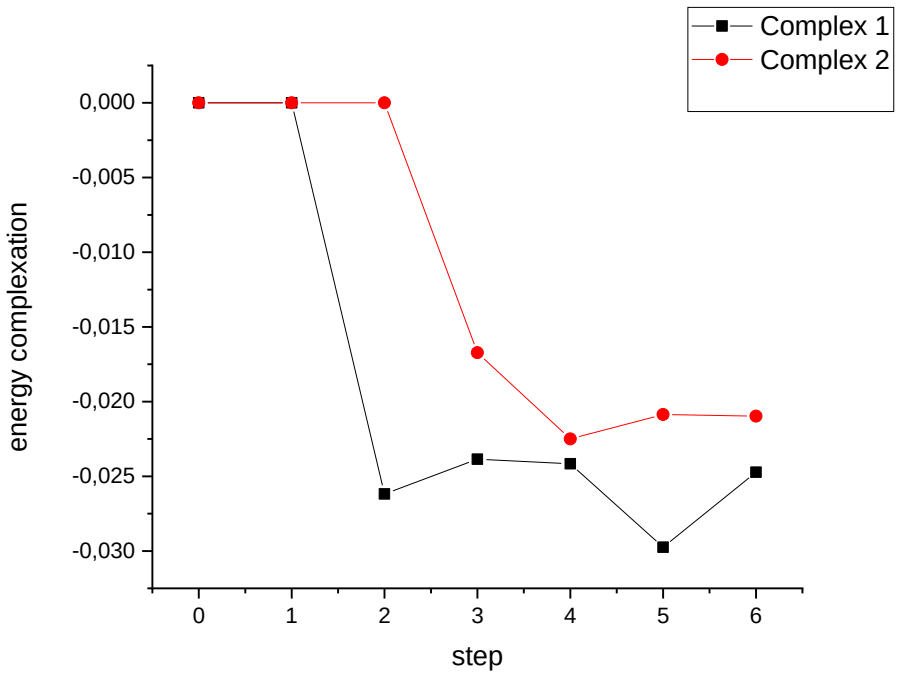



**Figure 9:** Complexation energies profile of the inclusion process.

From the results of the complexation energies showed in Figure 4, it's remarkably that the complex 1 is more favor than the complex 2 (ΔE=0.007248957). The minimum of complex 1 is found at step five at 40 degrees ($E_{complexation}$ =-18.666 Kcal/mol) while, the minimum of complex 2is located at step four at 270 degrees ($E_{complexation}$ =-14.116Kcal/mol).

The structures of the tow complexes have almost the same shape (Figure5). The guest molecule is partially encapsulated in β-CD, due to the volume of the azomethine. The driving forces lead to the inclusion between the host and guest is the H-bond interaction. In the complex 1, one H-bond formed between the Oxygen of the sulfonyl group of azomethin and the Hydrogen of the primary hydroxyl of β-CD. While, there is two H-bonds have been formed in complex 2. The interactions were happened between the Oxygen of the sulfonyl group of azomethine and the Hydrogen of the secondary hydroxyl of β-CD. Also, it found between the hydrogen of sulfonyl group and the oxygen of the secondary hydroxyl of β-CD Complex 2.

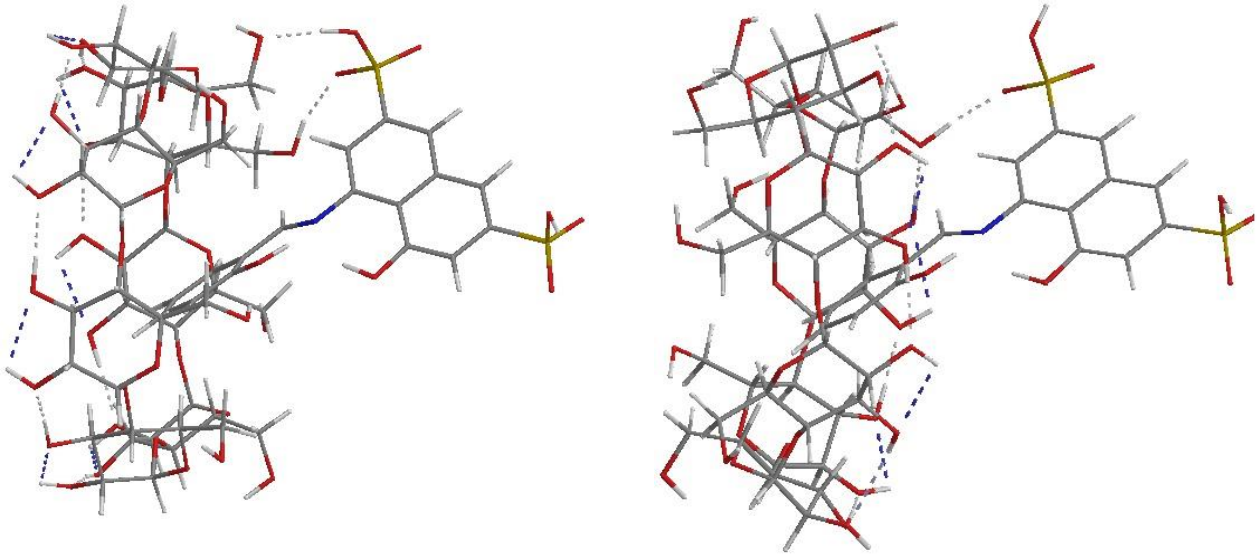
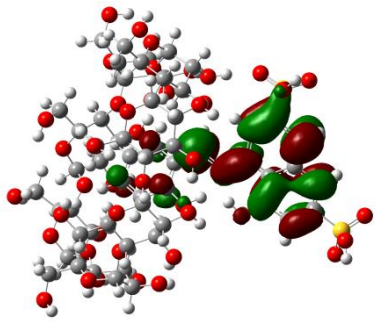
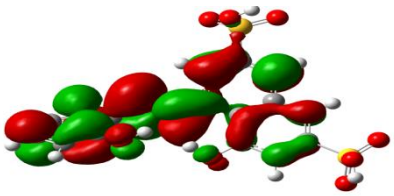
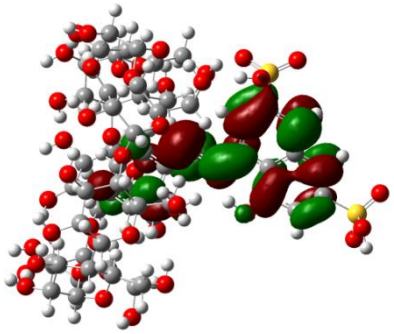


**Figure 10:** mimimum stable complexes, a) complex 1. b) complex 2.

### III .3 .2. frontier molecular orbital and the reactivity descriptors

The frontier molecular orbital (FMO) gives information about the chemical reactivity of the compound [19]. A small energetic gap between HOMO and LUMO allows the electronic transition [20]. In **Figure 4**, we demonstrated the FMO shapes of complexes 1 and 2 with energetic gap values compared by the FMO of guest molecule before inclusion. The quantum molecular descriptors sited in **Table 3** of molecule were calculated using HOMO and LUMO results, such as ionization potential (I), electron affinity (A), electronegativity (χ), hardness (η), chemical softness (S) [21].

| | | |
|---|---|---|
|  |  |  |
| Complex 1 | AZOMETHIN | Complex 2 |
| $E_{LUMO}$ (ev) =-1.87 eV | $E_{LUMO}$ = -2.775ev (B3LYP/6-31G) | $E_{LUMO}$ =-1.72 eV |

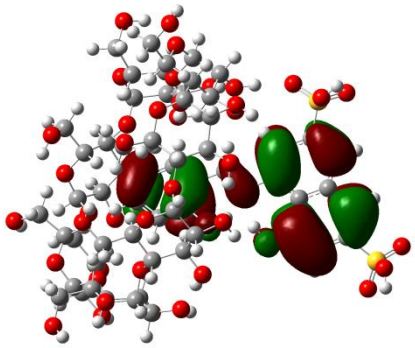
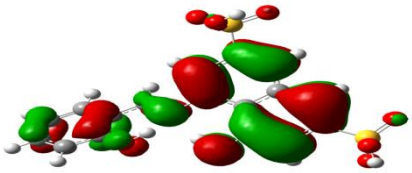
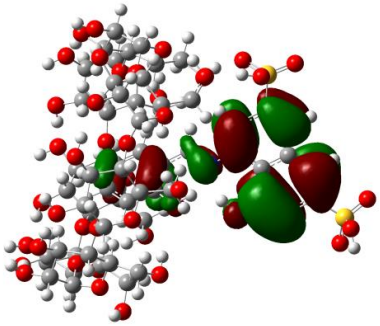
| | | |
|---|---|---|
|  |  |  |
| Complex 1 | Azomethin HOMO | Complex 2 Azomethin |
| $E_{HOMO}$ =-9.18 eV | $E_{HOMO}$ =-6.37 eV (B3LYP/6-31G) | $E_{HOMO}$ =-9.146 eV |

**Figure 11:** Frontier molecular orbital of complex1 and complex2 calculated by PM3 compared to the azomthine before inclusion.

**Table 4:** Quantum descriptor FMO results of complexes 1 and 2 calculated by PM3 method.

| | **Complex 1** | **Complex 2** |
|---|---|---|
| **$E_{HOMO}$ (eV)** | -9.18 | -9.14 |
| **$E_{LUMO}$ (eV)** | -1.87 | -1.72 |
| **$\Delta E = E_{HOMO} - E_{LUMO}$ (eV)** | -7.30 | -7.42 |
| **$I = -E_{HOMO}$ (eV)** | 9.18 | 9.14 |
| **$A = -E_{LUMO}$ (eV)** | 1.87 | 1.72 |
| **$\chi=(I+A)/2$ (eV)** | 5.53 | 5.43 |
| **$\eta=(I-A)/2$ (eV)** | 3.65 | 3.71 |
| **$S=1/\eta$ ($eV^{-1}$)** | 0.27 | 0.2693 |

Table 4 shows that energetic gap of complex 1 and complex 2 is large due to the influence of the interaction with the β-CD. The creation of new links between host and guest modify the electronic character of them.

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# General conclusion

**General conclusion**

In this study, we investigate PM3 calculations of inclusion complexes between beta-cyclodextrine and azomthine. The inclusion process leads to the formation of two complexes 1 and 2. The results showed that the complex 1 is more stable than the complex 2 with a bit difference ΔE=0.0072 Kcal/mol. The guest molecule is partially included in the β-CD. The minimum of both complexes 1 and 2 are localized respectively at step5, 40 degrees and step 4, 270 degrees.

The presence of polar groups as the primary and secondary hydroxyls in beta- CD and sulfonyl groups in azomethin allow the formation of new inter-molecular bonds between them. In fact, it was found a hydrogen bond in complex1 and two hydrogen bonds in complex 2. In addition, these interactions impact to electronic character of the guest molecule.

Finally, this study is the first step in another project to understand and investigate the stabilization of complexes using new DFT methods, NBO analysis, QTAIM analysis and spectroscopic analysis.

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