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DOUMI Iman

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Modélisation moléculaire de la solvatation des polymères: Approche théorique

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Mr. LASRI Boumediene	**Pr**	**Université Dr. Tahar Moulay de Saida**	**Président**
Mr. BOUDRAA Kamel Eddine	**MCA**	**Université Dr. Tahar Moulay de Saida**	**Encadreur**
Mr. MESKINE Mohamed	**MCA**	**Université Dr. Tahar Moulay de Saida**	**Examinateur**
Mr. DJAAFRI Tayeb	**MCA**	**Université Dr. Tahar Moulay de Saida**	**Examinateur**

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To my parents who sacrificed their lives to give meaning to mine.

To my brothers: Ali , Mohamed

To my sister: Mariem

And to everyone I love

Thanks :

At the end of the writing of this thesis, I am convinced that the thesis is far from being a solitary work. Indeed, I could never have done this work without the support of a large number of people whose generosity, good humor and interest shown in with regard to my research, I have been able to progress in this delicate phase.

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Introduction

Introduction

Polymers are everywhere, just look around. Our plastic water bottles, the silicone rubber tips on our phone's ear buds. The nylon and polyester in our jacket or sneakers. The rubber in the tires on the family car. If we take a look in the mirror, many proteins in our bodies are polymers, too. Consider keratin (KAIR-uh-tin), the stuff our hair and nails are made from. Even the DNA in our cells is a polymer [1]. The science of polymers leads to the production of new materials. Efforts are always dedicated to understanding these materials and improving their properties to meet industrial needs, but more and more polymers are applied to a wide range of issues, and certainly in terms of development of new materials. They are worth studying because their behavior as materials is different from that of metals and other low-molecular-weight materials. As a result, a large percentage of chemists and engineers are engaged in work involving polymers, which necessitates a formal course in polymer science .

The molecular modeling approach is beneficial in more than one way; On the one hand the theoretical understanding of the modeled material and to test new approaches allowing to better understand the local behavior of this system; on the other hand, to predict the behavior of such material under certain conditions that are sometimes difficult to achieve in the laboratory. Since the beginning of the 90's and with the continuous evolution of computer science (Programming languages and techniques, processors, computing clusters, etc ...), simulation has also made remarkable progress to become a predominant tool in the majority of scientific research projects and more particularly in the science of polymers. It is certain that the molecular modeling methods, describing the materials at the atomic scale due to the different types of interatomic interactions, do not replace the experimental methods but give a complementary tool to a better understanding of the macroscopic or microscopic behavior of the materials and to predict certain physicochemical, optical and thermodynamic properties.

The aim of this work is to solvate two hydrophilic polymers which are poly Methyl methacrylate (PMMA) and poly 2-Hydroxy ethyl methacrylate (PHEMA). The different tools of molecular modeling (molecular dynamics) are used to carry this job. The geometric and energetic parameters of these polymers will help us discuss the stability of these last in isolated case, and in solvent box.

The first chapter is dedicated to a general introduction to the subject. The second chapter reviews the molecular modeling techniques that are widely used in physics, chemistry, the pharmaceutical industry and agro-chemistry. In Chapter 3, theoretical models and methods for the study of solvation of macromolecules are presented. Chapter 4 is reserved for applications of the solvation models of biomolecules studied. And finally, we end with a general conclusion.

References:

[1] SID PERKINS, Explainer _What are polymers _science news for students (OCT 13, 2017)

Chapter I :

Generalities on ***polymers***

I.1 Definitions and basic concepts

By definition, polymers are large molecules made by bonding (chemically linking) a series of building blocks. The word polymer comes from the Greek words “many parts.” Each of those parts is called “monomer” (which in Greek means “one part”). Think of a polymer as a chain, with each of its links a monomer. Those monomers can be simple — just an atom or two or three — or they might be complicated ring-shaped structures containing a dozen or more atoms. They usually consist of several structural units bound together by covalent bonds. For example, polyethylene is a long-chain polymer and is represented by

$$-CH_2-CH_2-CH_2- \text{ or } [-CH_2-CH_2-]_n$$

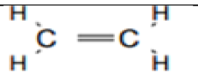
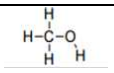
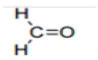
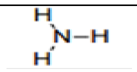
Where the structural (or repeat) unit is $-CH_2-CH_2-$ and n represents the chain length of the polymer [1].

I-2 Molecular architectures and properties of polymers:

I-2.1 functionality:

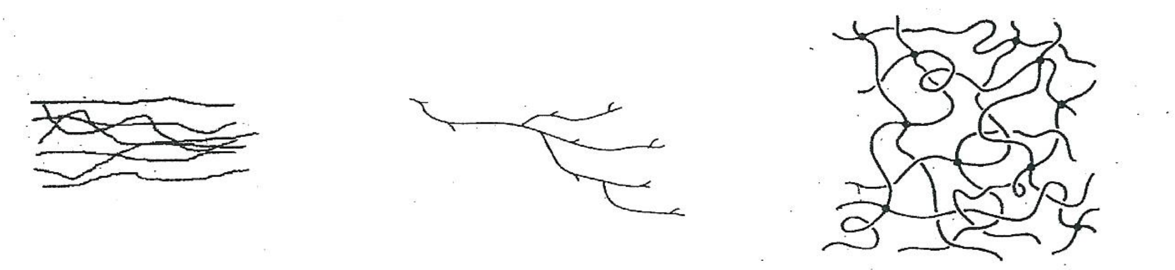
The functionality of a monomer refers to its number of reactive sites which is very important. When a monomer or a set of monomers have an average functionality of less than 2, only compounds of low molecular weight (called oligomers) are formed which cannot be used as materials. On the other hand, a greater or equal functionality 2 allows a linear polymer synthesis. When these are soluble in organic solvents, they are called materials thermoplastics [2]. As will be seen below, the type of polymerization and the functionality of the monomers determine the linear, branched or cross-linked nature of the polymer.

Table I.1: Main functional groups involved in macromolecular chemistry [2]

Groups	*Structures*	*functionality*
Vinyl group		**2**
Hydroxyl group		**1**
Carbonyl group		**2**
Amine group		**1 or 2**

I-2.2 Basic structures of macromolecules:

Depending on the monomer structure and the experimental conditions during the polymerization, the chains can grow with different architectures. Figure I.1 shows the main architectures found in commercial polymers: linear, branched and cross-linked.



Linear Branched Cross-linked

Figure I.1: Main architectures of polymer chains

- *Linear polymers*: (or mono-dimensional) polymers, for which each macromolecular chain consists of a (possibly) high but finite number of monomer units
- *Branched polymers:* (or two-dimensional) in which short branches have developed from the main chains;
- *Cross-linked polymers:* the cross linking corresponds to the formation of chemical bonds in the different directions of space, during polymerization of linear polymers, which leads to the formation of a three-dimensional network [3]

Linear polymers and branched polymers are generally soluble in organic solvents. They can be melted or softened by heating. These are thermoplastic materials.

I-2.3 Amorphous polymers and crystallized polymers:

At the macromolecular scale, the polymers essentially have two different structures; the amorphous state which is characterized by a statistical ball-like structure, in which no large-scale order is distinguished, and the crystalline state which is characterized by a long-range order; the two ordered and disordered states can coexist in a same material which is then semi-crystalline in nature.

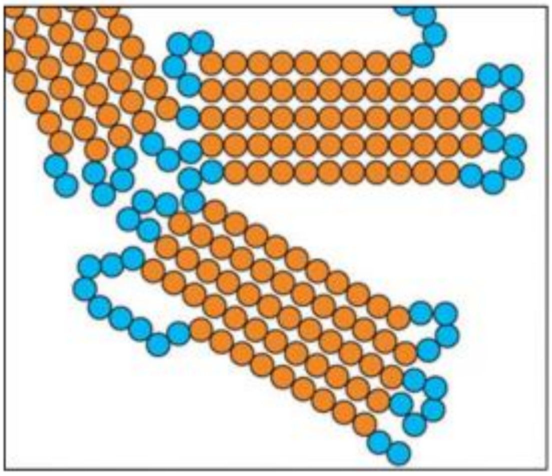


Figure I.2: Schematic representation of a semi-crystalline polymer.

I.3 Polymer classifications

Several classifications of macromolecular compounds may be proposed depending on whether the origin, the type of architecture, the chemical structure of the units or the types of polymerization are chosen as the basis for the classification.

I.3.1 Classifications according to their origin:

Polymers can be classified according to their origin into three categories:

- *Natural polymers:* This kind of polymers is obtained from plant or animal sources. To this category belong all families of proteins (wool, silk, etc.), natural rubber, etc.
- *Artificial polymers:* They are obtained by the chemical modification of natural polymers in order to transform some of their properties, such as cellulose esters (nitrocellulose, cellulose acetate, etc.), have been economically important for a long time
- *Synthetic Polymers:* They are exclusively the results of human creations; they are obtained by polymerization of the monomer of molecules. There is a wide variety of such polymers.

I.3.2 Classifications according to their properties:

- *Thermoplastics:* They are linear polymers, fusible and soluble in solvents organic and they are generally recyclable, that is to say, they allow the heating and cooling several times when molding parts.
- *Thermosets:* They are highly cross-linked and to obtain a cross-linking process was carried out by baking the polymer. The cross-linked sample forms a three-dimensional network, but the networked polymers have their cohesion due to chemical bonds.

There is therefore no solvent for them, no melted phase, so they are insoluble and infusible; these materials are not recyclable [4].

Thermoplastics Thermosets elastomeric

Figure I.3: The main groups of polymers [04].

- *Elastomeric:* They are polymers that can be stretched to at least twice their original length and shrink back to their original size as soon as the stretching force ceases and this without vulcanization. Among the advantages of elastomers, it is necessary to mention an excellent implementation, good mechanical properties, a very low internal heating and a very good resistance to cold [5].

I.4 Configuration and Conformation:

I.4.1 Configuration:

The configuration is the way in which the atoms and lateral groupings are arranged along a chain. It is fixed at the time of synthesis (by means of appropriate techniques) and can only subsequently be modified by chemical reactions, thus excluding physical processes such as thermal and/or mechanical movements or dissolution in a solvent (solvates). The possibility of certain chemical elements to form multiple bonds leads to more possibilities for varying the structure of a polymer. The configuration of the molecules has a decisive influence on the behavior of the polymer [6].

The most subtle of the structural features of polymer chains is called stereo regularity. It plays an important factor in determining the properties of polymers so that in a polymer molecule. Figure I.4 shows a polymer chain in which all carbon chains are in the same plane. Three configurations can be obtained: A polymer molecule is isotactic if all groups are found on the same side of the main chain. In a syndiotactic molecule polymer the additional group R is found alternately on one side and then on the other side of the plane formed by the carbon atoms. A molecule is said to be atactic if the positioning of the additional group R is random on one side and on the other side of the plane formed by the carbon atoms. [7-8]

Two other concept of configuration arises as to the arrangement of the structural units of an asymmetric monomer during the polymerization (eg vinyl chloride or styrene), namely:

1 / Head-to-head arrangement alternating with tail-tail

2 / Head-to-tail arrangement.

In a homopolymer, for example, polypropylene, the sequence of constituent units can be done locally and in different ways (see Figure I.4): the head-to-tail connections ensure the regularity of the chain. In contrast, head-to-head or tail-to-tail sequences are defects in the chain [9]

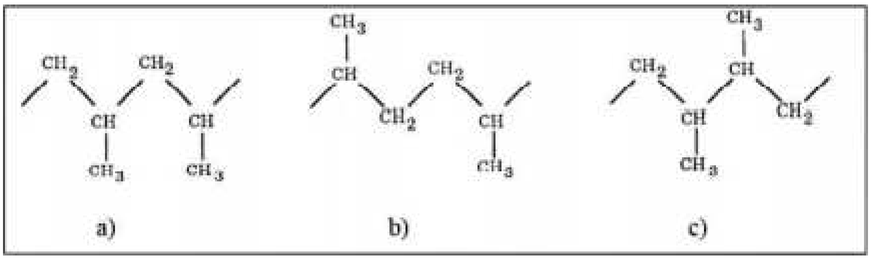


Figure I.4: Sequence of the constituent units in a homopolymeric polypropylene: a) head to tail; b) head to head; (c) tail to tail [9].

I.4.2 Conformation:

Once a polymer molecule has been formed, its configuration is fixed. However, it can take on an infinite number of shapes by rotation about the backbone bonds. The final shape that the molecule takes depends on the intra-molecular and intermolecular forces, which, in turn, depend on the state of the system. For example, polymer molecules in dilute solution melt phase, or solid phase would each experience different forces. The conformation of the entire molecule is first considered for semi crystalline solid polymers. A polymer molecule cannot be expected to be fully extended, and it actually assumes a chain-folded conformation, the most common conformation for amorphous bulk polymers and most polymers in solution is the random-flight (or random-coil) conformation, which is discussed in detail later.

In principle, it is possible for a completely stereo regular polymer in a dilute solution to assume a *planar zigzag* or *helical conformation*; whichever represents the minimum in energy. The conformation of the latter type is shown by biological polymers such as proteins and synthetic polypeptides.

The term “conformation” is used in organic chemistry, one calls conformation of a molecule the different spatial structures that it can take as a result of rotations around one or more simple bonds C-C. The conformation of a molecule can be defined locally and globally:

-The local conformational structure designates the relative orientation of the chain segments and lateral groups. It depends on the local covalent structure and interactions between atoms and "unbound" groups.

- The overall conformational structure is at the scale of the chain, the relative arrangement of the carbon atoms (or oxygen, nitrogen, etc.) constituting the skeleton of the chain. It depends on intramolecular and intermolecular interactions.

I.5 Dimension and molar mass:

I.5.1 Degree of polymerization:

The degree of polymerization (DP)-n in a polymer molecule is defined as the number of monomer repeating units (RUs) in the polymer chain. For example $-(-CH_2-CH_2-)-_n$

Since the minimum length or size of the molecule is not specified, relatively a small compound molecule, only three monomers could be called a polymer. Yet, the term polymer has come into general use to implicate a large molecule (the macromolecule). As a result, the lower molecular weight of products with low degree of polymerization should preferably be called oligomers [10].

I.5.2 Molar mass:

Synthetic polymers never have a uniqueness of the length of the chains, n in A_n is variable within the same sample. As the physical and mechanical properties depend on n, it is necessary to be able to identify this parameter and also to know the distribution of it. There are analytical methods that can be used to find the distribution of the values of n, but we often only evaluate one or two averages that are representative of parameters that govern the behavior of the polymer in its applications. The molar mass of A_n is defined as the product of n and MA, the molar mass of the link calculated from the sum of the atomic weights of the atoms which up.

I.5.2.1 Average mass in number ($\overline{Mn}$)

It is defined as the statistical average molecular weight of all the polymer chains that are present in a polymer sample.

$$\overline{M_n} = \frac{\sum_i^\infty n_i M_i}{\sum_i^\infty n_i} \qquad (I.1)$$

where M_i is the molecular weight of a chain and n_i is the number of chains of that molecular weight. M_n can be predicted by polymerization mechanisms and is measured by methods that determine the number of molecules in a sample of a given weight [11].

I.5.2.2 Average mass by weight (M_w)

The weight average molecular weight is defined by:

$$\bar{M}_w = \frac{\sum_i^\infty w_i M_i}{\sum_i^\infty w_i} \quad (I.2)$$

W_i is the fraction by weight of the polymerization degree chains *i*. by definition $\sum w_i = 1$ (w_i is a fraction) of the average mass by weight so it is equal to the sum of all weighted masses by a coefficient w_i which represents the fraction by weight of the species present. The ratio $\frac{\overline{M_w}}{\overline{M_\iota}}$ which is always greater than 1 makes it possible to characterize the sample polydispersity.

I.5.2.3 Average viscosity mass (M_v)

There is another average which is obtained by viscosity measurements in solution, it is called viscosimetric average and represented by Mv

$$\bar{M}_v = [\textstyle\sum_i w_i M_i]^{1/a} = \left[\frac{\sum_i n_i M_i^{a+1}}{\sum_i n_i M_I}\right]^{\frac{1}{a}} \quad (I.3)$$

For $a = 1$, $M_v = M_w$ and for $a = -1$, $M_w = M_n$. Thus M_v falls between M_w and M_n

The properties of polymers (such as reactivity), which depend more on the number of molecules than on the size of molecules, M_n is inversely a parameter more useful than M_w or M_v, to correlate the properties of polymers (such as viscosity) that are more sensitive to the size of the polymer molecules M_w or M_v are more useful [12].

I.6 Polymerization reaction:

I.6.1 Polycondensation:

Polycondensation is a chemical reaction between basic molecules with different functional groups; this reaction leads to the elaboration of macromolecules called polycondensates [13]. Condensation reactions usually involve monofunctional reagents. In polycondensation, the molecular structure is made from di- or plurifunctional monomers. The chain is constructed by means of condensation reactions between functional groups carried by the monomer molecules and by the polymer molecules in formation. The polycondensation reactions are schematized according to the mechanism illustrated in the figure I.5.

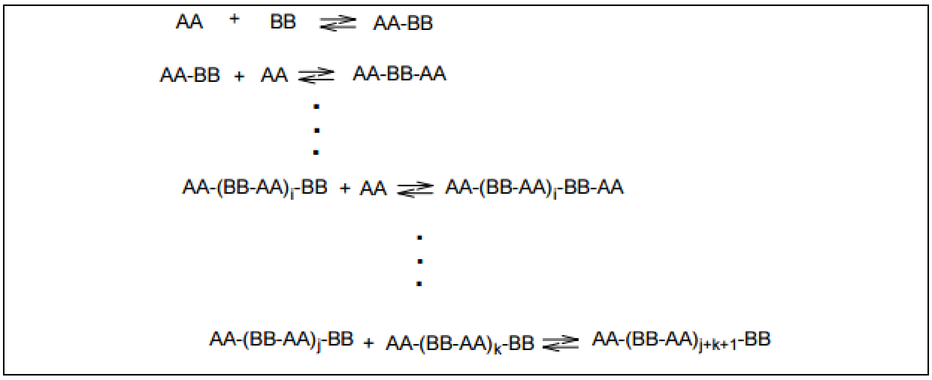


Figure I.5: Diagram of a polycondensation reaction.

Each end-of-chain reaction group retains its reactivity and the building of the polycondensate molecules continues throughout the duration of the reaction.

I.6.2 Chain polymerization:

A chain polymerization reaction is a reaction leading to the formation of polymers by successive additions of monomers on an active end of the macromolecular chain (active center noted *) [14]. It can be schematized by:

$$\mathbf{-M_{an}^{*} + M \longrightarrow -M^{*}_{n+1}}$$

It can be cationic, anionic or radical, depending on the nature of the active species.

I.6.2.1 Anionic polymerization:

The active part is a carbanion (one of the carbon atoms carries a negative charge) or an oxanion (the negative charge is carried by an oxygen atom) associated with a counter ion Me+, positively charged and often metallic. The polymerization can be done by opening a double bond (styrene, dienes, acrylonitrile, vinylpyridine) or a ring (oxirane, lactone, lactam ...). [15]

I.6.2.2 Cationic polymerization:

The part is carbonations, where one of the carbon atoms carries a positive charge, associated with a negatively charged counter-ion. The cationic polymerization requires stabilized carbonations. The monomers can be:

- ✓ Olefins (*iso-butylene*).
- ✓ Vinyl ethers CH2 = CHOR.
- ✓ Unsaturated carbides (*styrenes*, *indene*, *benzofuran*).
- ✓ Heterocyclic compounds (*oxirane*, *tetrahydrofuran*, *cyclosiloxane*).

The R group must be a donor electron (*iso-butylene*, *vinyl ether*) or stabilize the cation by resonance (*styrene*, *indene*) [16].

The active center is a carbanion, the group R tends to be electron acceptor, example: CN-COOR.

I.6.2.3 Radical polymerization:

Radical polymerization is a reaction which, as its name suggests, involves reactive species R * called free radical. This technique is successful in its ease of implementation [17], the reaction time is very short and the formation of high molecular weight polymers is also fast.

a) ***Initiation***: it includes two successive reactions:

The generation of radicals (called primary) using a substance

$$A \longrightarrow 2R^{\circ}$$

- The addition of the primary radical to a first monomer unit M to form the first link of the growing polymer chain.

$$M \longrightarrow MR$$

This step provides the necessary energy for the activation of a certain number of radical chains. It is most often chemical, thanks to the thermal decomposition of an initiator. It can also be photochemical and, in this case, activation is caused by radiation (UV, Gamma, X).

b) ***Propagation:*** The propagation is done by successive additions of monomer molecules on the active part of the growing chain. This reaction is done in a split second and returns to a giant molecule, with a free radical at the end of the chain. A process is now essential that will finish the big chain, the termination reaction [18].

$$RM^{\circ} + M \longrightarrow RM^{\circ}_{2}$$

$$RM^{\circ}_{2} + M \longrightarrow RM^{\circ}_{3}$$

$$R\,M^{\circ}_{n} + M \longrightarrow RM^{\circ}_{n+1}$$

c) ***Termination:*** The termination reaction consists of the destruction of the active center which is located at the end of the growing chain and can, in principle, be done in different ways (shocks on a wall, reaction with impurities, etc.). This reaction can be carried out according to two mechanisms, coupling or disproportionation.

In the case of a polymerization, this reaction stops the growth of macromolecular chains; the macromolecules are thus completed [19].

I.7 Use of polymers:

Here we will list some of the important uses of polymers in our everyday life.

- Polypropene finds usage in a broad range of industries such as textiles, packaging, stationery, plastics, aircraft, construction, rope, toys, etc.
- Polystyrene is one of the most common plastic, actively used in the packaging industry. Bottles, toys, containers, trays, disposable glasses and plates, tv cabinets and lids are some of the daily-used products made up of polystyrene. It is also used as an insulator.
- The most important use of polyvinyl chloride is the manufacture of sewage pipes. It is also used as an insulator in the electric cables.
- Polyvinyl chloride is used in clothing and furniture and has recently become popular for the construction of doors and windows as well. It is also used in vinyl flooring.
- Urea-formaldehyde resins are used for making adhesives, moulds, laminated sheets, unbreakable containers, etc.
- Glyptal is used for making paints, coatings, and lacquers.
- Bakelite is used for making electrical switches, kitchen products, toys, jewellery, firearms, insulators, computer discs, etc.

I.7.1 Commercial Uses of Polymers [20]:

Table I.2: The table below represent some Commercial Uses of Polymers

Polymer	**Monomer**	**Uses of Polymer**
Rubber	Isoprene (1, 2-methyl 1 – 1, 3-butadiene)	Making tyres, elastic materials
BUNA – S	(a) 1, 3-butadiene (b) Styrene	Synthetic rubber
BUNA – N	(a) 1, 3-butadiene (b) Vinyl Cyanide	Synthetic rubber
Teflon	Tetra Flouro Ethane	Non-stick cookware – plastics
Terylene	(a) Ethylene glycol (b) Terephthalic acid	Fabric
Glyptal	(a) Ethylene glycol (b) Phthalic acid	Fabric
Bakelite	(a) Phenol (b)Formaldehyde	Plastic switches, Mugs, buckets
PVC (polyvinyl chloride).	Vinyl Cyanide	Tubes, Pipes
Melamine Formaldehyde Resin	(a) Melamine (b) Formaldehyde	Ceramic plastic material
Nylon-6	Caprolactum	Fabric

References:

[1] SID PERKINS, Explainer _What are polymers _science news for students (OCT 13, 2017)

[2] H. H. Kausch, N. Heymans, C. J. Plummer, P. Decroly, Matériaux polymères: Propriétés mécaniques et physiques, Presses polytechniques et universitaires romandes, vol-14, Lausanne, (2001).

[3] P. Wiess, la chimie des polymères, Université Médicale Virtuelle Francophone, (2010).

[4] Christian Oudet, Polymères structures et propriétés, Masson-Paris (1994)

[5] R. Perrin, J. P Scharff, Chimie industrielle, Dunod, 2ème Ed (1999).

[6] H. H. Kausch, N. Heymans, C. J. Plummer, P. Decroly, Matériaux polymères: Propriétés mécaniques et physiques, Presses polytechniques et universitaires romandes, vol-14, Lausanne, (2001).)

[7] A.Kumar, S. K. Gupta, Fundamentals of Polymer Science and Engineering, Tata Mc Graw-Hill, New Delhi, (1978).

[8] M. Vogel et E. Rossler, J. Chem. Phys. (114), p 5802 (2001).

[9] A. F. Gourgues-Lorenzo, J. M. Haudin, Matérieux pour l'ingénieur, Presses des Mines, (2006).

[10] Manas Chanda, Salil K.Roy, Plastics Technology Handbook, CRC Press, 4éme Edition by Taylor & Francis Group, LLC (2006).

[11] https://www.askiitians.com/iit-jee-solutions-colligative-properties/molecular-mass-of-polymers

[12] Kenny B. Lipkowitz, Thomas R. Cundari, Reviews in Computational Chemistry 25, John Wiley & Sons (2007).

[13] C. Decker, Progr. Polym. Sci. (21), p593 (1996).

[14] E. Maréchal; Polycondensation et polyaddition ; Techniques de l'ingénieur, traité Plastiques et composites ; A M 3 042.

[15] A. Guyot; Polymérisation; Techniques de l'ingénieur, traité Génie des procédés ; J 5 830.

[16] J. Verdu; Polymérisation sous rayonnement principes; Techniques de l'ingénieur, traité Plastiques et composites; A M 3 043

[17] G. Odian; Principle of polymerization; Wiley Interscience (1991).

[18] N. Mohammedi, Mémoire fin d'étude ingénieur physicien; Option : Physique des Matériaux, département de physique ; UABB Tlemcen ; (juin 2005).

[19] A. Ram; Fundamentals of polymer engineering; Ed. Plenum Press; Chapter 2; 14- 28 (1997).

[20]] https://byjus.com/jee/polymers/#Uses-of-Polymers

Chapter II:

Molecular Dynamic

II-1 .Introduction:

The history of molecular modeling has its origins in the middle of the 19th century, when the first two-dimensional molecular structures were put on paper by Johan Josef Loschmidt. A few years later, in the 1860s, Louis Pasteur introduced 3D thanks to his work on chiral molecules. Molecular modeling becomes strongly attached to the forces fields whose concept appears at the beginning of the 20th century and from which will flow the development of molecular mechanics (MM) or empirical force field method in the 1970s by Allinger. From the 1950s, the first computer methods of molecular mechanics were developed such as the Metropolis algorithm and the bases of the Monte Carlo method. Since then, molecular modeling has followed a continuous development of methods, benefiting from the Internet, the popularization of computing and the explosion of computing power. Today, molecular modeling is further accelerated through graphics processors and helps elucidate the function of proteins and the mechanisms of active molecules.

Coming from solid state physics and quantum chemistry, molecular dynamics now has many applications: particle physics, solid state physics, material sciences, mechanics, biology, biochemistry, and organic chemistry [1].

Theoretical methods and computational methods applied in molecular modeling can be relatively simple and usable quickly or else complex and time-consuming. Molecular modeling methods can be classified into three categories [2]: Quantum methods, molecular mechanics and molecular dynamics

II. 2 Quantum mechanics methods

Quantum mechanics is an extension of quantum theory, resulting from the work of Planck, their interpretation by Einstein and their application to the atomic theory by Bohr and Somerfield. It explains the quantification of certain quantities (energy, kinetic momentum) and brings out the Pauli Exclusion Principle. The new conception of particles that follows from the corpuscular wave duality, explained in the works of De Broglie (1923) leads to wave mechanics.

Modeling methods based on quantum mechanics describe the molecular energies of the systems studied using the Schrödinger equation with the molecular orbital formalism (MO). This method has a main advantage, it uses a minimum number of approximations and explicitly considers the electrons of the studied molecule, and its main disadvantage is that this method is usually long and expensive but remains the reference method for calculating molecular properties. These main variants are: Hückel's method which allows interpreting a large part of the chemical reactivity [3]. The self-consistent field methods rely on more elaborate computations than the Hückel method. Two variants are distinct: the ab initio methods are expensive in computation time and semi-empirical methods require experimental data to calculate the most difficult energy terms. The methods on the functional DFT density use an expression of the electronic energy E as a function of the electron density ρ. The size of systems processed by quantum methods is highly dependent on the resources machines and rarely exceeds a hundred atoms [4,5].

II.3 Molecular mechanics:

Many of the problems that we would like to tackle in molecular modeling are unfortunately too large to be considered by quantum mechanics. Molecular mechanics (also known as Force field methods) ignore the electronic motions and calculate the energy of a system as a function of the nuclear positions only. Molecular mechanics is thus invariably used to perform calculations on systems containing significant numbers of atoms. In some cases force fields can provide answers that are as accurate as even the highest-level quantum mechanical calculations, in a fraction of the computer time. However molecular mechanics cannot of course provide properties that depend upon the electronic distribution in a molecule.

That molecular mechanics works at all is due to the validity of several assumptions. The first of these is the Born-Oppenheimer approximation, without which it would be impossible to contemplate writing the energy as a function of the nuclear coordinates at all. Molecular mechanics is based upon a rather simple model of the interactions within a system with contributions from processes such as stretching of bonds. Even when simple functions (Hooke’s law) are used to describe these contributions the force field can perform quite acceptably. Transferability is a key attribute of a force field, for it enables a set of parameters developed and tested on a relatively small number of cases to be applied to a much wider range of problems. Moreover, parameters developed from data on small molecule can be used to study much larger molecules such as polymers [6].

II.3.1 Force field

The force field is the mathematical model representing the potential energy of a molecule in molecular mechanics. The force field is the basis of molecular simulation techniques. A force field consists of several potential energy functions that describe intermolecular and intramolecular interactions:

$\mathbf{E}_{\text{Total}} = \mathbf{E}_{\text{intramolecular}} + \mathbf{E}_{\text{intermolecular}}$ II.1

Interactions between bonded or intramolecular atoms correspond to binding, valence angle, dihedral angle and torsion energy. Interactions between non-bonded or intermolecular atoms such as Van der Waals interactions and electrostatic interactions as well as hydrogen bond energy [7]. The potential representing the hydrogen bonds or the hydrogen bridges are not always described explicitly in the force fields. Other terms may be used to complete the description of a force field such as: cross terms (link - link, link - angle, angle - angle, link - torsion, angle - torsion, ...) and the terms describing the deformation outside the plane. So steric energy is expressed by the following energetic terms [8]:

$\mathbf{E}_{\text{Total}} = \mathbf{E}_{\text{bond}} + \mathbf{E}_{\text{flexion}} + \mathbf{E}_{\text{torsion}} + \mathbf{E}_{\text{VanderWaals}} + \mathbf{E}_{\text{electrostatic}} + \mathbf{E}_{\text{hydrogen}}$ II.2

- The term "link" represents the elongation of links.
- The term "bending" represents the variation of angles.
- The term "Twisting" refers to the torsional energy of the dihedral angles.
- The term "Van der Waals" accounts for non-covalent interaction energies between non-bound atoms.
- The term "electrostatic" accounts for electrostatic interaction energies between atoms.
- The term "Hydrogen" accounts for hydrogen bonds.

It is important to note that force fields are a purely empirical approach. They are set up in such a way that all the different contributions allow reproducing a series of experimental results. Forces fields are calculated, tested and refined from [9-10] and spectroscopic [11] crystallographic data, theoretical chemistry calculations [12] and ab-initio or empirical calculations for fillers [9]. It is thus possible to find fields intended more specifically for modeling small organic molecules, macromolecules, and organometallic complexes [13], or even nucleotides [14].

II-3.1.1 the different energies:

The main energy terms used in molecular mechanics can be expressed as follows:

II-3.1.1.1 Elongation energy (binding):

A quadratic term is used for link elongation interactions:

$E_{bond} = \sum_{bond} k_{bond}\,(r - r_0)^2$ II.3

Where k_{bond} represents the elongation constant for the binding or stiffness considered (in kcal.mol^{-1}Å^{-1}), r is the separation distance between two atoms, r_o is the equilibrium binding length. Interaction between two atoms linked by a covalent bond is comparable to that of two "balls" attached by a spring [15].

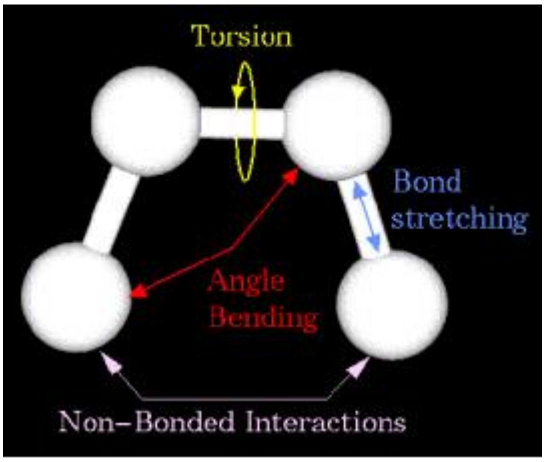


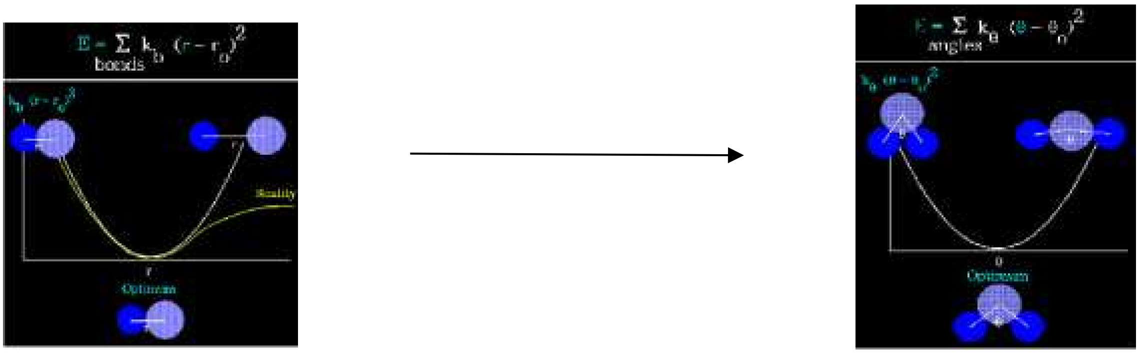
Figure II.1: Link energy

II-3.1.1.2 Bending energy:

This energy is the deformation energy of the valence angles. A harmonic term is chosen to describe the three-body interaction:

$$E_{\text{bending}} = \sum\nolimits_{\text{bending}} k_{\text{bending}}(\theta - \theta_0)^2 \tag{II.4}$$

Where k bending is the bending force constant (in kcal.mol^{-1}), θ is the valence angle between two bonds and θ_0 is the equilibrium binding valence angle.



-a- **-b-**

Figure II.2: Bending energy (a: state 1, b:state 2)

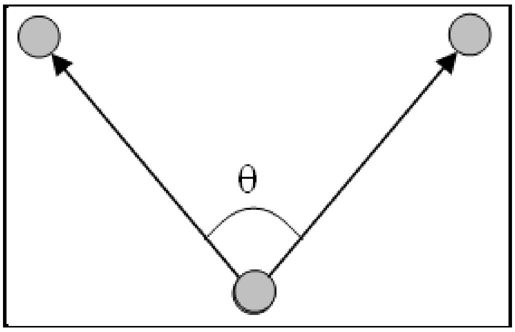


Figure II.3: valence angle between three atoms

II-3.1.1.3 Torsional energy (deformation of the dihedral angles):

The term torsion is of importance in polymers, it is the main term of the mobility of the molecular chains. The term corresponds to the rotation of a connection BC according to the dihedral angle τ formed by four consecutive atoms ABCD is expressed in the form of a periodic function developed in Fourier series, it takes the following form:

$$E_{torsion} = \sum_{n=0} \frac{V_n}{2}[1 + \cos(n\tau + \gamma)] \qquad \text{II.5}$$

The expression of the contribution of each dihedral angle is one (or more) term (s) of a function developed in Fourier series. V_n is an energy term (kcal.mol^{-1}), τ is the torsion angle, γ is the phase factor that represents the angle at which the torsion energy goes through a minimum, and n is the term of multiplicity which determines the number of minima of the function when the angle rotates by 360 °. The torsion energy already takes into account some of the interactions between the unbound atoms since it involves four atoms. These interactions will have to be weighted in the expression of energy terms between unbound atoms.

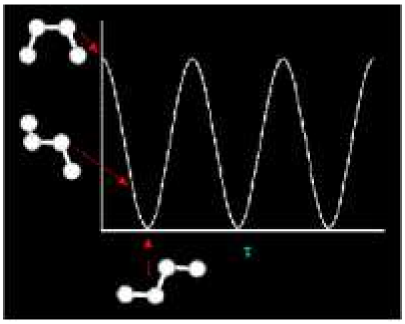


Figure II.4: Torsional energy

II-3.1.1.4 Energy between unbound atoms:

a- 0Electrostatic interaction energy:

Electrostatic interactions take on considerable importance, the electrostatic term (or Coulomb) being taken into account not only the ion - ion interactions where the atoms carry formal charges, but also all other so - called polar interactions. In the latter case, the atoms have partial or point charges. These charges can be adjusted to reproduce the dipole moment of the molecule or the electrostatic potential surface obtained by ab_initio quantum mechanical calculations. The equation that describes this type of interaction is:

$$E_{\text{electrostatic}} = \sum_{i,j} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}^2} \qquad \text{II.6}$$

With E_{elec} electrostatic energy (in kcal.mol^{-1}),

q_i, q_j partial charges borne by the two interacting atoms i and j (in C),

r_{ij} separation distance of the two interacting atoms i and j (in Å),

ε_0 dielectric permittivity of the vacuum**,** [15-17]**.**

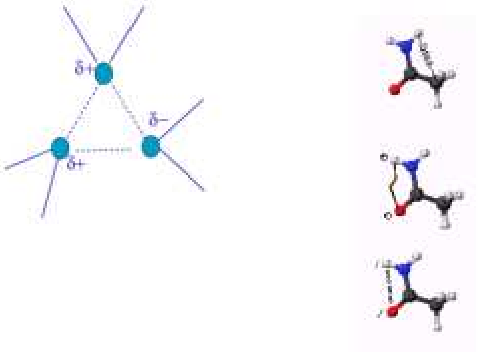


Figure II.5: Electrostatic interaction energy

b- Energy of incorrect dihedral angles:

The energetic term of improper unfixed torsions gives the energetic contribution of the deformations of improper torsions formed by three bonds. An improper twist is for example the angle formed by the ABC and BCD plans defined by the following figure. Improper twists are so called because the four atoms involved are not linearly related. This term serves to maintain the flatness of certain groups such as the carbonyl group:

$$E_{\text{improper}} = \sum_{i=1}^{n} k_w (w_i - w_0)^2 \qquad \text{II.7}$$

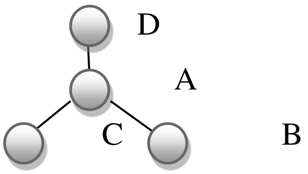


Figure II.6: The improper dihedral angle is defined as the angle between the ABC and BCD planes

Where K_ω represents the torsional constant, ω is the wrong dihedral angle and ω_0 represents the ideal dihedral angle. Improper twists are so called because the four atoms involved are not linearly related. This term serves to maintain the flatness of certain groups such as the carbonyl group [18].

c- Van Der Waals interaction energy:

The interactions of VAN DER WAALS are represented by a potential in 6-12 whose expression is the following:

$$E_{VDW} = \sum_{ij} 4\varepsilon_{ij} \left[\left(\frac{r_0}{r_{ij}} \right)^{12} - \left(\frac{r_0}{r_{ij}} \right)^{6} \right] \qquad \text{II.8}$$

The expression of this energy is in the form of a so-called 6-12 potential (Leonard Jones)

The term power 12 corresponds to the parameters of the repulsive term at short distance (reflection of the repulsion of electric clouds corresponding to the Pauli exclusion rules), that is to say, it comes from because two cores cannot be in the same place at the same time. This notion of superposition of atoms is found within the physics of polymers under the name "excluded volume". As one atom approaches another, the interactions between atoms increase. And this increase will be all the more important as the atoms will be close. The term power 6 is the attractive term at a medium distance (London dispersion forces, Keeson el Debye resulting from the induction and attraction of instant dipoles).

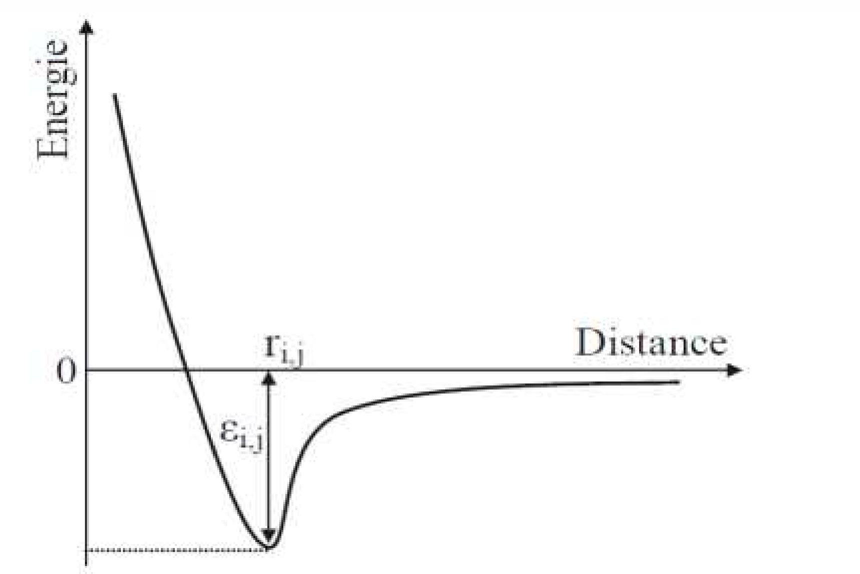


Figure II.7: VdW energy curve

ε_i, represents the depth of the Van Der Waals well, the distance r_i, is the distance between the atom i and j and r_0 is the distance of Van Der Waals. The term $-r_{i,\,j}$ represents the attractive dispersion of London between two atoms and that at r_i, the repulsion due to the exclusion of Pauli [19-20].

d- Energy of the crossed terms:

There are other terms, called cross terms, which describe the interactions between the first three terms, which is why they are also referred to as streitching-bending, torsion stretching, bending-bending. This is particularly so for the elongation-flexing coupling (streitching-bending) which is translated by the following relation:

$$E(1.\theta) = \frac{1}{2}\sum k_{i,j\theta 1}\left(l_{i,j} - l_{0i,j}\right)\left(\theta_{i,j} - \theta_{0i;j}\right) \qquad \text{II.9}$$

K_i, θl is the link-angle coupling parameter with respect to the links i and j and $l_{i,j}=l_i+l_j$ and $l_{0i,j}=l_{0i}+l_{0j}$

e- Hydrogen bonding energy:

I mentioned earlier that molecular mechanics force fields have to be transferable from molecule to molecule, and explained the necessity for non-bonded interactions. These are usually taken to be Lennard-Jones 12–6 type, and they are included between all non-bonded pairs of atoms.

$$U_{L-J}=\frac{C_{12}}{R^{12}}-\frac{C_6}{R^6} \qquad \text{II.10}$$

The Born–Mayer–Huggins potential

$$U_{BMH}=A\exp(-BR)-\frac{C_6'}{R^6}-\frac{C_8}{R^8} \qquad \text{II.11}$$

is sometimes used when dealing with polar species. B is a parameter determined by the size and ‘softness’ of an ion, C6 (not the same as C6 in UL-J) has to do with dipole–dipole interactions whilst C8 is determined by dipole–quadrupole interactions. Some force fields make special provision for hydrogen-bonded atoms; they treat them as non-bonded interactions but soften the Lennard-Jones 12–6 potential for AH B to a 12–10 version

$$U_{HB}=\frac{C_{12}}{{R_{HB}}^{12}}-\frac{C_{10}}{{R_{HB}}^{10}} \qquad \text{II.12}$$

Other authors take the view that hydrogen bonds are perfectly respectable chemical bonds that should be treated just like any other bond. They are therefore given a force constant and so on. It is important to note that force fields are a purely empirical approach. They are set up in such a way that all the different contributions allow reproducing a series of experimental results. A field must therefore always be considered as an indivisible entity and it is excluded from.

So steric energy is expressed by the following equation:

$$E=\overbrace{E_{\text{stretching}}+E_{\text{bending}}+E_{\text{torsion}}}^{\boxed{\text{Energy between linked atoms}}}+\overbrace{E_{\text{vdW}}+E_{\text{elec}}+E_{\text{hydrogen}}}^{\boxed{\text{Energy between unbound atoms}}} \qquad \text{II.13}$$

The term "stretching" represents the elongation of the bonds.

The term "Bending" represents the variation of angles.

The term "Twisting" refers to the torsional energy of the dihedral angles.

The term "VdW" accounts for non-covalent interaction energies between unbound atoms.

The term "Elec" accounts for electrostatic interaction energies between unbound atoms.

The term "Hydrogen" accounts for hydrogen bonds.

It is important to note that force fields are a purely empirical approach. They are set up in such a way that all the different contributions allow reproducing a series of experimental results. A field must therefore always be considered as an indivisible entity and it is excluded from combine terms and / or parameters of two fields in the hope of getting a better set [21]. In addition, the setting is often aimed at allowing the force field to realistically process a particular class of compounds. It is thus possible to find fields intended more specifically for the modeling of small organic molecules and macromolecule [22], nucleotides [23] or even organometallic complexes [22]. It is therefore important first of all to check whether the field chosen is suitable for the system to be studied.

II-3.2 Different fields of forces in molecular mechanics:

Different force fields use the same type of energetic terms but are parameterized in different ways. Force fields in MM can be grouped into three main classes [21]:

- Force fields containing only the harmonic terms.
- Force fields using the terms of higher order (cubic, quadratic ...).
- Strengths suggested by Allinger et al. [22] not only considering the terms of classical molecular mechanics but also chemical effects such as electronegativity

- MM2 (improved hydrocarbon force field) / MM3 / MM4:

Allinger introduced MM2 in 1977 [22-23]. It was designed at the beginning for simple molecules (alkanes, alkenes, non-conjugated alkynes, amines ...), but its improved versions MM3 (1989) [24] and MM4 (1996) [25] allow it to treat organic molecules of more and more complex.

GROMOS:

GROMOS (Groningen Molecular Simulation Program Package) is written by Van Gusteren [26] and is designed specifically for biomolecules in aqueous media to study interactions between water molecules and polar protein groups.

CHARM (Bio +):

Developed by Karplus et al [27], for the calculation of biomolecules. Its concept is similar to that of AMBER. Although at the beginning, this force field is designed for amino acids and proteins, now it deals with other biomolecules.

SPASIBA:

(Spectroscopic Potential Algorithm for Simulating Biomorphic Conforamtional
Adaptability), developed by Gérard Vergoten et al. (1995).

It combines the modified Urey-Bradly-Shimanouchi spectroscopic force field [28] and the AMBER force field. It makes it possible to find structures, conformational energies and vibrational frequencies at the energetic minimum of a molecule [29].

- Emo:

The Emo program (Energy Of Molecule), developed by B. Blaive [30-33], is based on the MM2 force field. It is articulated around three menus:

- Menu 1: entry of the molecule using a keyboard.

- Menu 2: Geometric manipulation on the molecule.
- Menu 3: Minimization of energy by molecular mechanics

AMBER:

(Assisted Molecular Building and Energy Refinement) was developed by P.KOLLMAN in 1981 [34], it also represents a biological force field intended to perform calculations on proteins and nucleic acids and macromolecules in general.

AMBER force field is of the following form [35-36]:

$$E_{tot} = \sum_{\textbf{liaisons}} k(b-b_0)^2 + \sum_{\text{angles}} H(\theta-\theta_0)^2 + \sum_{\text{torsion}}[V_1[1-\cos(\varphi-\varphi_1^0)] + V_2[1-\cos(2\varphi-\varphi_2^0)] + V_3[1-\cos(3\varphi-\varphi_3^0)]] + \sum_{i>j} 4\varepsilon_{ij}\left[\left(\frac{\partial_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\partial_{ij}}{r_{ij}}\right)^{6}\right] + \sum_{i>j}\frac{q_i q_j}{\varepsilon r_{ij}} \qquad \text{II.14}$$

K, H, V_1, V_2, V_3, b_0, θ_0 , φ_1^0, φ_2^0, φ_3^0, ε_{ij}, ∂_{ij}, q_i, q_j, r_{ij} are the potential parameters included in the force field, bond lengths, valence angles, dihedral angles and the distance between two non-bonded atoms i and j respectively [37-38]

OPLS:

The OPLS (Optimized Potentials for Liquid Simulations) program, as its name suggests, is designed to maximize the potential for describing solvation properties. It is written by W. L Jorgensen and J. Tirado Rives [39].

II-3.3 Minimization of potential energy:

In molecular modeling we are especially interested in minimum points on the energy surface. Minimum energy arrangements of the atoms correspond to stable states of the system; any movement away from a minimum gives a configuration with a higher energy. There may be a very large number of minimum of minima on the energy surface. The minimum with the very lowest energy is known as the global energy minimum. To identify those geometries of the system that correspond to minimum points on the energy surface a minimization algorithm is used. There is a vast literature on such methods and so we will concentrate on those approaches that are most commonly used in molecular modeling. We may also be interested to know for example. How do the relative positions of the atoms vary during a reaction? What structural changes occur as a molecule changes its conformation? The highest point on the pathway between two minima is of especial is known as the *saddle point,* with the arrangement of the atoms being the *transition structure*. Both minima and saddle points are stationary points on the energy surface, where the first derivative of the energy function is zero with respect to all the coordinates.

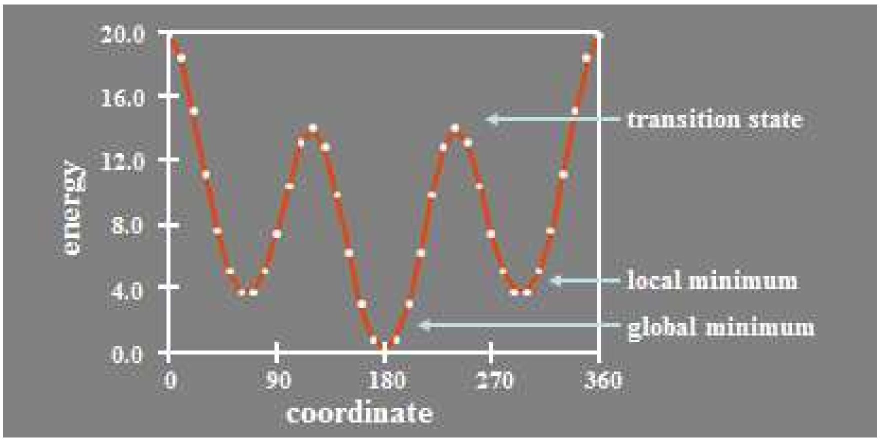


Figure II.8: Global and local minimums representation [30].

The different minimization methods built into the Discover module of Materials Studio 4.0 and 5.0 and the most used are:

- The steepest method or the steep slope "Steepest descent".
- The conjugate gradient method
- Newton Raphson's method

II-3.3.1 Method of steep slope "Steepest descent":

This first-order derivative scheme for locating minima on molecular potential energy surfaces was put forward by K. Wiberg in 1965 [14]. The steepest descents method moves in the direction parallel to the net force, which in our geographical analogy corresponds to walking straight downhill. For 3N Cartesian coordinates this direction is most conveniently represented by a 3N-dimensional unit vector, s_k. thus:

$$s_k = -g_k/|g_k| \qquad \text{II.15}$$

Having defined the direction along which to move it is then necessary to decide how far to move along the gradient. Consider the two-dimensional energy surface of figure II.8. The gradient direction from the starting point is along the line indicated, if we will pass through a minimum and then increase, as shown in this figure. We can choose to locate the minimum point by performing a line search or we can take a step of arbitrary size along the direction of the force.

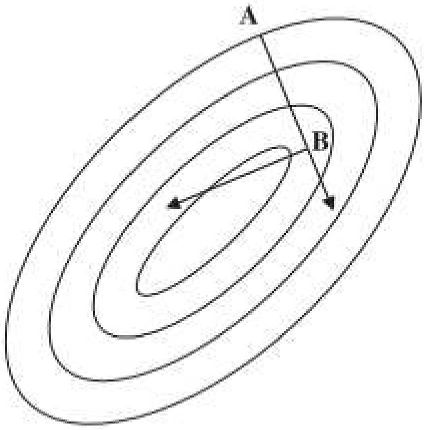


Figure II.9: Steepest descents principle scheme

II-3.3.2 The conjugate gradient method:

This method is based on the same principle as the previous one (direction opposite to the energy gradient). This method is often used following the method of the greatest slope [40]. It finds a minimum in fewer steps than the Steepest Descent method. It requires significant computing times when the structure is far from the minimum. In other words, the minimization begins with a few steps in "Steepest Descent" to get closer to the minimum, and finally to steps in "conjugate gradient" to characterize the minimum potential energy.

II-3.3.3 The Newton-Raphson method:

This so-called Newton-Raphson method is based on the calculation of the second derivative of the energy function with respect to geometric coordinates. . It evaluates the second derivatives of molecular energy with respect to geometric parameters and thus converges more rapidly. Problems can be encountered when the initial conformation is far from the minimum. It requires very important computing times; its application is thus reserved for small systems [41-42]

II-4 Molecular Dynamics:

The first steps of the molecular dynamics could only be made thanks to the arrival of the first computers (1957) [43]. But the first real simulations were made by Raman [44], thanks to his work on the simulation of liquid argon in 1964 with a simulation time of 10-11 s, and then liquid water [45] in 1971. Molecular Dynamics is a method widely used to study molecular systems with large numbers of atoms. This method gives the possibility to observe the behavior of a system as a function of time [46]. Indeed, the total energy of the system is broken down into potential energy described by the force field and kinetic energy related to the temperature of the system. The input of kinetic energy in the form of temperature makes it possible to excite the system and to make it leave the local minimum reached during the minimization. The system that has accumulated enough energy can then explore the conformational space and perform conformational transitions by jumping successive energy barriers [46]. Mechanics and molecular dynamics share the same potential energy function (force field) to describe all the interatomic interactions of the study system. We have therefore used molecular dynamics experiments to obtain stable and low energy structures.

II-4.1 Principle:

Each atom of the molecule is considered as a point mass obeying the law of mass action whose movement is determined by the set of forces exerted on it by the other atoms as a function of time.

$$\vec{F_i} = m_i\vec{a_i} = m_i\frac{d^2\vec{r_i}(t)}{dt^2} \tag{II.16}$$

$\vec{F_i}$: Vector force acting on the atom i.

M_i : mass of the atom i.

$\vec{a_i}$: Vector acceleration of the atom i.

$\vec{r_i}$: The position of the atom i.

Thanks to the velocities and positions of each atom in time, it is possible to evaluate the macroscopic data, such as kinetic energy and temperature. The kinetic energy is calculated according to the formula:

$$E_c = \sum_{i=1}^{N}\frac{|p_i|^2}{2m_i} \tag{II.17}$$

Where p_i is the momentum of the atom i.

The temperature is obtained from the kinetic energy by:

$$E_c = \frac{k_bT}{2}(3N - N_c) \tag{II.18}$$

K_b : Boltzmann constant

N_c : number of constraints

$3N\text{-}N_c$: total number of degrees of freedom.

The force $\vec{F}$ exerted on an atom i in position $r_i(t)$ is determined by derivation of the potential function:

$$\vec{F_i} = -\frac{d\vec{E}(r_i,\ldots,r_n)}{dr_i(t)} \tag{II.19}$$

E: function of the total potential energy of interaction.

r_i : Cartesian coordinates of the atom i.

The velocities of each atom are calculated from the knowledge of atomic accelerations:

$$\vec{a}_i = \frac{d\vec{v}_i}{dt} \qquad \text{(II.20)}$$

And the positions of atoms are calculated from atomic velocities by the relation:

$$\vec{v}_i = \frac{d\vec{r}_i}{dt} \qquad \text{(II.21)}$$

The integration of these equations is done by dividing the trajectory into a series of states separated by very short time intervals whose length defines the integration stepΔt, which leads to a trajectory as a function of time. Knowing the speed and the acceleration of the atom i at time t, we can know its position at time t + Δt:

$$r_i(t + \Delta t) = r_i(t) + v_i\Delta t + {}^{1}\!/_{2}\, a_i\Delta t^2 \qquad \text{(II.22)}$$

II-4.2 Duration of the integration step:

The equations of motion are solved numerically and propagated by relatively fast algorithms. Nevertheless, they impose a severe restriction on the length of the integration step. A time step Δt that is too large introduces significant errors in the evaluation of the energy and can make the simulation diverge. Vibration frequencies must also be taken into account so that Δt is 10 to 20 times smaller than the period of oscillation. In practice, in the organic molecules (polymers), the bonds that vibrate the fastest are the C-H bonds (with a vibration period of the order of 10 fs). The maximum value of Δt must be approximately one-tenth of this period, ie 1 fs [47]. This choice of the time step Δt greatly influences the total simulation time. Indeed, the latter is given by (Δt, Nt), with Nt the number of simulation steps [48-49].

II-4.3 Periodic boundary conditions:

When simulating a system in explicit solvation in a box, the environment of the peripheral atoms is biased because of the edge effects compared to the atoms located in the center of the box. To get rid of it, it is necessary to make sure that the environment of the atoms becomes independent of their position. The periodic boundary conditions of replicating a finite and relatively small set of particles in a central box in the three directions of space (Figure II.10) are used, so that the forces acting on the particles are equivalent. To those of a much larger system and therefore more realistic.

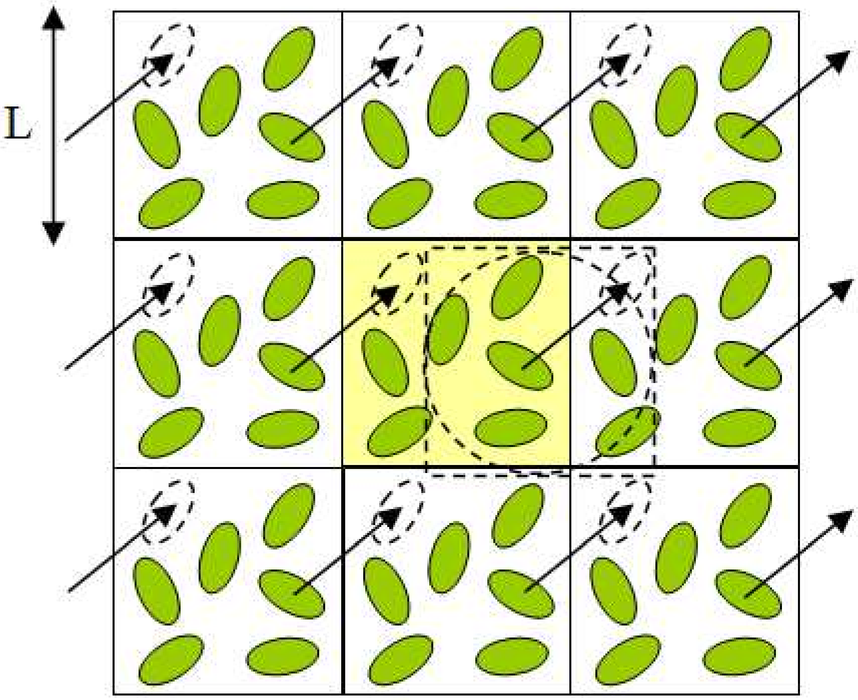


Figure II.10: Periodic conditions illustrated in 2 dimensions with a cubic box [47]

The movements of the atoms in the central box are copied in all the picture boxes. Therefore, if a particle leaves the central box during the simulation, it is replaced by an image particle of an adjacent box on the opposite side. The number of atoms in the central box therefore remains constant. The energy calculations are performed on the molecules of the central box. The unbound interactions of the molecules near the walls of the central box are calculated using the virtual molecules of the contiguous boxes. With the periodic boundary conditions method, larger amplitude fluctuations than can dimensions cannot be studied unless the size of the box is increased. In this case, the number of atoms in the system increases, increasing the number of interactions to calculate [50, 51].

II-4.4 Different sets applied to molecular dynamics:

When the interaction potentials, boundary conditions and initial conditions are set, the molecular dynamics simulation can be started. The system will then evolve over time, and consequently the quantities: number of atoms N, temperature T, pressure P, volume V and energy E will evolve as well. There are several thermodynamic systems, characterized by three independent variables, each defining a representative set (NPT, NVT, NVE, etc.). In order to carry out simulations closer to the experiment, we use tools for regulating the parameters T and P. In our study, the two sets used are NVT and NPT.

II-4.4.1 NVT canonical ensemble:

The number of atoms (N), the volume (V) and the temperature (T) of the system are preserved. The system is in thermodynamic equilibrium and exchanges energy with an external tank called a thermostat. The thermostat serves as a thermal bath, ensuring the stabilization of the average internal temperature of the system around the required temperature (external). The modification of Newton's initial motion equation is therefore necessary to take into account the friction of the system due to the thermostat. The internal energy of the system fluctuates and the quantity conserved over time is Helmholtz's free energy which is the sum of the internal micro canonical energy (NVE) and the energy provided by the thermostat.

$$U_{NVT} = E_{pot} + E_{cin} - T.S \tag{II.23}$$

Where S is the entropy of the system [52].

II-4.4.2 Pressure control (NPT ensemble):

Number of particles N, pressure P and temperature T are constant. In other cases it may be advantageous to simulate at constant pressure rather than at constant volume, it is simulations under iso thermal-isobaric set (NPT). It is a thermodynamic set that represents the real experimental conditions of the laboratory. The canonical set is coupled with a second tank called barostat which maintains a required external pressure. The volume V of the system varies isotropically according to the imposed pressure [53]. There is another variant of this set, it is the set NσT [54], which modifies the dimensions of the simulation box in an anisotropic way (the dimensions and the shape of the box change) under a constraint σ_{ext} imposed (see Figure II.11).

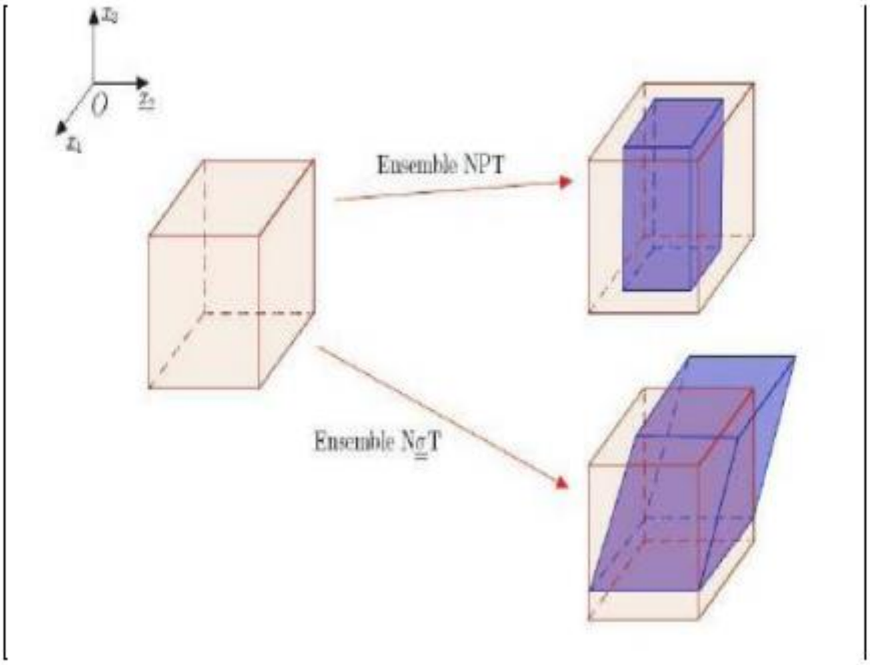


Figure II.11: Deformation of a simulation box in NPT and NσT assemblies [53].

II-4.5 Application and inconvenient of molecular dynamics:

An important application of molecular dynamics is the analysis of normal modes of vibration along the trajectory. Another application is the search and optimization of 3D structures based on crystallography data or Raman scattering spectroscopy (NMR). Another advantage is that it is not limited to harmonic movements around simple minima. It also allows molecules to cross energy maxima and explore other stable conformations. Several efforts have therefore been made to extend the duration of molecular dynamics simulations, the first effort concerns the use of a simplified interaction potential, this simplification shortens the calculation time devoted to the evaluation of the total energy of the system over a simulation. Second effort is the lengthening of the integration step, up to 2fs. Indeed, by the procedure of SHAKE [55]. This algorithm makes it possible to fix the geometry of certain bonds (length of the covalent bond) during a molecular dynamics. Despite these efforts but the molecular dynamics has a number of significant limitations: The first concerns the determination of certain parameters such as the potential barriers of the dihedral angles proves tricky, the second limitation is the size of the systems is also generally limited to tens of thousands of atoms and the third limitation is in the classical treatment of the interactions of the system. Indeed, it is not possible to study the chemical reactions without describing at least a part of the system by the ab-initio methods [56].

References:

[1] bouzid_latifa,modelisation moléculairedes copolymers PMMA-PS,thèse Magister en physique , UNIVERSITE DES SCIENCES ET DE LA TECHNOLOGIE D'ORAN Mohamed Boudiaf (2012)

[2] D. Liotta, Advances in Molecular Modeling, 1, Ed. JAI Press, 1988.

[3] P. A. M. Dirac, Lectures on Quantum Mechanics, Belfer graduate School of Science, Yeshiva University, New York (1964).

[4] B. Minisini, Modélisation et simulation moléculaire d'un matériau nano composite à base de polypropylène chargé de nanoparticules lamellaires, thèse de doctorat, Université du Maine, (2004).

[5] M.O.BENSAID, Étude Des Polymères Par Dynamiques Moléculaire, thèse de doctorat, Université d'Oran des sciences et de la technologie (2015)

[6] Alan Hinchliffe, Molecular Modelling for Beginners, UMIST Manchester, UK(2003)

[7] A. Soldera, N. Metatla, J. Molecular Design (4) ,p 721-736,(2005)

[8] F.Jensen, introduction to computational chemistry, John Wiley & Sons, Chichester (1999)

[9] S. Canneaux, Etude théorique de processus atmosphériques : réaction du radical OH avec l'acétone et capture d'un composé organique volatil par une goutte d'eau, thèse de doctorat, Université de Reims Champagne-Ardenne, (2004).

[10] F. A. Momany, R. F. McGuire, A. W. Burgess, H. A. Scheraga, Energy parameters in polypeptides. VII. Geometric parameters, partial atomic charges, nonbonded interactions, hydrogen bond interactions, and intrinsic torsional potentials for the naturally occuring amino acids, Journal of Physical Chemistry, 79 (22), (1975).

[11] M. J. Sippl, G. Némethy, H. A. Sheraga, Intermolecular potentials from crystal data. 6. Determination of empirical potentials for O-H…O=C hydrogen bonds from packing configurations, Journal of Physical Chemistry, 88, (1984).

[12] O. Ermer, S. Lifson, Consistent force field calculations-III. Vibrations, conformations, and heats of hydrogenation of nonconjugated olefins, Journal of the American Chemical Society, 95, (1973).

[13] N. Allinger, Journal of the American Chemical Society, 99 (25), (1977).

[14] Biosym/MSI, Discover, user guide, ed. Biosym/MSI. San Diego, (1995)

[15] S. J. Weiner, P. A. Kollman, D.T. Nguyen, D. A. Case, An all-atom force field for simulations of proteins and nucleic acids. J. Comp. Chem, (7), 230, (1986)

[16] N. L. Allinger, Calculation of Molecular Structure and Energy by Force-fieldMethods, Rev.Papers (1976).

[17] U. Burkert, N. Allinger ,Molecular Mechanics, ASC Monography, 117, NY (1982)

[18] D. A. Case, D. A. Pearlman, J. W. Caldwell, T. E. Cheatham III, J. Wang, W. S. Ross, C. L. Simmerling, T. A. Darden, K. M. Mer, R. V. Stanton, A. L. Cheng, J. J. Vincent, M. Crowley, V. Tsui, H. Gohlke, R. J. Radmer, Y. Duan, J. Pitera, I. Massova, G. L. Seibel, U. C. Singh, P. K. Weimer et P. A. Kollman, AMBER7, (2002).

[19] Koehl P. and Levitt M. (1999) A brighter future for protein structure prediction. Nature Struct. Biol. 6: 108-111

[20] Etude par modélisation moléculaire des Copolymères PANI-X (X=PMMA, PS) thèse de magister LORF Ahmed

[21] B. R. Brooks, R. E. bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, M. Karplus, J. Comp. Chem, , 4, 187,1983.

[22] I. K. Roterman, M. H. Lambert, K. D. Gibson, H.A. Scheraga, J. Biomol. Struct. Dyn, 7, 421, 1989.

[23] F. A. Momany, R. Ronte, J. Comp. Chem. 13, 888, 1992.

[24] J. C. Smith, M. Karplus, J. Am. Chem. Soc, 114, 805., 1992.

[25] T. Shimanouchi, Pure Appl. Chem, 7, 131. 1963.

[26] H. Dugas, Principes de base en modélisation moléculaire, Aspects théoriques et pratiques, quatrième édition, Librairie de l'Université de Montréal, (1996).

[27] Fabrice Cavillon, Caractérisation de la liaison hydrogène dans des systèmes moléculaires d'intérêt biologique par diffusion de neutrons, thèse de doctorat, Université des Sciences et Technologies de Lille (2008)

[28] Biosym, Molecular Simulations Inc, San Diego, CA, (1999).

[29] W. L. Jorgensen, J. Tirado-Rives, The OPLS Force Field for Proteins, Energy Minimizations for Crystals of Cyclic Peptides and Crambin, Journal of the American Chemical Society, 110 (6), (1988).

[30] A. K. Rappé, K. S. Colwell, W.A. Goddard, and W.M. Ski, UFF, a full periodic table force field for molecular mechanics and molecular dynamics simulations, Journal of American Chemical Society, 114(25), (1992).

[31] M. Karplus, A program for macromolecular energy, minimization, and dynamics calculations J.Comput Chem , (4),p187-217(1983)

[32] P. Derreumaux, M. Dauchez, G. Vergoten, Journal of Molecular Structure, 295(1993).

[33] T. Shimanouchi, Pure and Applied Chemistry, (7), p131 (1963)..

[34] P. K. Weiner, P. A. Kollman, Journal Computational Chemistry, 2, (1981).

[35] W. D. Cornell, P. Cieplak, C. I. Baylyet al , A second generation force field for thesimulation of proteins and nucleic acids. J. Am. Chem. Soc. (117), p5179-5197(1995)

[36] W. D. Cornell, P. Cieplak, C. I. Bayly et al , A second generation force field for the simulation of proteins and nucleic acids, Additions & Correction. J. Am. Chem. Soc. (118),p2309-2309 (1996).

[37] A. Soldera, N. Metatla, J. Molecular Design (4) ,p 721-736,(2005)

[38] A .Soldera, Energetic analysis of the two PMMA chain tacticities and PMA through molecular dynamics simulations, j of polymer (43), p 4269-4275(2002)

[39] M. J. Hwang, T. P. Stockfisch, A. T. Hagler, Journal of the American Chemical Society,p 116, 2515 (1994).

[40] E. Leontidis, J de Pablo, M .Laso, U W. Suter, Adv.Plym.Sci., (116),p 283 (1994).

[41] A. Soldera, Modélisation moléculaire des polymères linéaires, Référence AF6042 (2003)

[42] S. Kirkpatrick, C.D. Gellet, M.P. Vecchi, Science, (220), p671 (1983)

[46] I. Soury-Lavergne Navizet, Modélisation et analyse des propriétés mécaniques des protéines, thèse de doctorat, Université Paris 6 Pierre & Marie Curie, (2004).

[43] B.J. Alder, T. E. Wainwright, J. Chem. Phys, 27, 1208., 1957.

[44] A. Rahman, Phys. Rev, 136, A 405. 1964.

[45] A. Rahman, F. H. Stillinger, J. Chem. Phys., , 5, 3336, 1971.

[47] A. R. Leach, Molecular Modelling: Principles and Applications, Pearson Education Limited, Second Edition, (2001).

[48] L. Verlet, Phys. Rev. 159, 98 (1967).

[49] R. W. Hockney, S. P. Goel, J. W. Eastwood, J. Comput. Phys., 14(2), (1974).

[50] D. Poger, Structure, dynamique moléculaire et sélectivité de métallochaperones à cuivre et à mercure, thèse de doctorat, Université Joseph Fourier – Grenoble I, (2005).

[51] Brahim Khalil Benazzouz, Etude par dynamique moléculaire des propriétés mécaniques et thermodynamiques de l'argile de type kaolinite, thèse de doctorat, l'université Lille Sciences et Technologies(2010)

[52] M. Solar, simulations numériques de dynamique moléculaire du contact normal et tangentiel sur surfaces de polymères amorphes linéaires : vers une meilleure compréhension de la physique locale du contact, Thèse de doctorat, Université de Strasbourg, (2010).

[53] K. Anoukou, Modélisation muliti-échelle du comportement mécanique de nanocomposites polymères à renforts d'argile de type montmorillonite-approche micromécanique et simulation de dynamique moléculaire, thèse de doctorat, Université de Lille 1, (2012).

[54] J. R. Ray, Molecular dynamics equations of motion for systems varying in shape and size, Journal of Chemical Physics, 79(10), (1983).

[55] van Gunsteren and H.J.C. Berendsen ,Algorithms for macromolecular dynamics and constraint dynamics. Mol. Phys. (34) ,p 1311-1327(1977).

[56] S. Aci, Etude par simulation de dynamique moléculaire de la variabilité conformationnelle du dimère de la séquence SL1 du génome de VIH-1, thèse de doctorat,Université D'Orléans, (2004).

Chapter III:

solvation

III-1 Solvent:

Solvents are chemicals that dissolve and dilute other substances without modifying or modifying them. A solvent is liquid in which one or more substances - the solutes - are introduced so as to constitute a homogeneous phase: the solution [1]. The solvent is thus defined not by its chemical structure, but by its physical state - the liquid state - and by the use that is made of it; There is thus an infinite variety of solvents: water, organic compounds (alcohols, acids, hydrocarbons, etc.) are the most traditional, and condensed or pressurized gases, such as ammonia or carbon dioxide [2].

III-1.1 Classification of solvents according to their molecular structure:

- Polar portal solvents (also called protogenic solvents): possessing one or more hydrogen atoms capable of forming hydrogen bonds. For example, water, methanol, ethanol, etc.

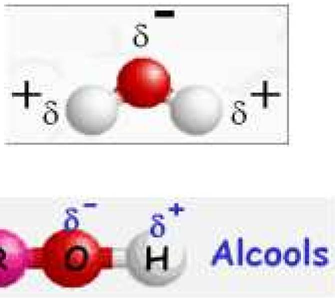


Figure III.1: water, alcohol

- Polar aprotic solvents: having a non-zero dipole moment and devoid of hydrogen atoms capable of forming hydrogen bonds. For example, acetonitrile (CH_3CN), dimethylsulfoxide (DMSO, $(CH_3)_2SO$), tetrahydrofuran (THF, C_4H_8O), etc.

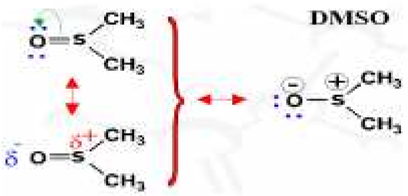


Figure III.2: Dimethylsulfoxide

- Apolar aprotic solvents: having a zero permanent dipole moment. For example, benzene, hydrocarbons: branched or linear alkanes, cyclic alkanes, alkenes, etc.

III-1.2 Classification of solvents according to their composition:

A / Inorganic solvents: These are solvents that do not contain carbon. Water, aqueous solutions containing additives (surfactants, buffer solution ...) and concentrated sulfuric acid are the most well-known inorganic solvents.

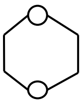
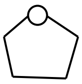
B / Organic solvents: These are solvents containing carbon. They are classified into three families:

- *Hydrocarbon solvents:*
  Aliphatic hydrocarbons: alkanes, alkenes
  Aromatic hydrocarbons: benzene, toluene, xylene.
- *Oxygenated solvents:*
  Alcohols: ethanol, methanol
  Ketones: acetone
  Acids: acetic acid
  Esters: ethyl acetate
  Ethers: ether ... but also glycol ethers
  Other oxygenated solvents: DMF, DMSO and HMPT
- *Halogenated solvents:* Halogenated hydrocarbons (fluorinated, chlorinated, brominated or iodinated): perchlorethylene, trichlorethylene, dichloromethane chloroform, tetrachloromethane (harmful for the ozone layer).

C/ Solvent table:

Table III.1: The table below represent some knowing solvent

Solvent	Chemical formula	T boiling	Dielectric constant	Mass Density
Apolar solvents				
Hexane	C_6H_{14}	69°C	2.0	0,655 $g.ml^{-1}$
Benzene	C_6H_6	80°C	2.3	0,879 $g.ml^{-1}$
Toluene	C_6H_5-CH_3	111 °C	2.4	0,867 $g.ml^{-1}$
Diethyl ether	$C2H_5$-O-C_2H_5	35°C	4.3	0,713 $g.ml^{-1}$
Chloroform	$CHCL_3$	61°C	4.8	1,498 $g.ml^{-1}$
Ethyl acetate	CH_3-COO-C_2H_5	77°C	6.0	0,894 $g.ml^{-1}$

Solvent	Chemical formula	T boiling	Dielectric constant	Mass density
Polar gantry solvents				
1,4-Dioxane		101°C	2.3	1,033 $g.ml^{-1}$
Tetrahydrofuran (THF)		66°C	7.5	0,886 $g.ml^{-1}$
Dichloromethane (DCM)	CH_2CL_2	40°C	9.1	1,326
Acetone	CH_3C0CH_3	56°C	21	0,786 $g.ml^{-1}$
Acetonitrile (MeCN)	$CH_3\text{-}C\equiv N$	82°C	37	0.786 $g.ml^{-1}$
dimethylformamide (DMF)	$HCON(CH_3)_2$	153°C	38	0,944 $g.ml^{-1}$
Dimethyl sulfoxide (DMSO)	CH_3SOCH_3	189°C	47	1.092 $g.ml^{-1}$

Solvent	Chemical formula	T boiling	Dielectric constant	Mass Density
Polar gantry solvents				
n-Butanol	$C_4H_9\text{-}OH$	118 °C	18	0,810 $g.ml^{-1}$
Isopropanol (IPA)	⟍ H_3C CHOH ⟋ H_3C	82°C	18	0,785 $g.ml^{-1}$
Propanol	$C_3H_7\text{-}OH$	97°C	20	0.803 $g.ml^{-1}$
Ethanol	$C_2H_5\text{-}OH$	79 °C	24	0,789 $g.ml^{-1}$
Methanol	$CH_3\text{-}OH$	65 °C	33	0,791 $g.ml^{-1}$
Formic acid	HCOOH	100°C	58	1,21 $g.ml^{-1}$
Water	H-O-H	100°C	80	1,000 $g.ml^{-1}$

Figure III.3: water

Water is the most abundant constituent in living tissues: it represents 60 to 95% of their mass. Its special properties make water an indispensable molecule for life: because of its property of polar molecule, water is an excellent solvent, able to create bridges with other polar molecules.

In addition to its role as a solvent, water is also the substrate and the product of multiple chemical reactions. It is also fundamental in the three-dimensional structure and the assembly of biological molecules. Indeed, folds and assemblies Macromolecular properties are stabilized by the removal of water from non-polar regions (hydrophobic effect) and the creation of hydrogen bonds with certain atoms. Finally, its concentration of hydrogen ions H^+, ie the pH, can modify the ionic state biological molecules, making biological processes very sensitive to these variations [3].

III-2 Solvation:

Solvation is the physicochemical phenomenon observed during the dissolution of a chemical 'solute' compound in a solvent [4].

When introducing a chemical species initially in the solid state (in crystal or amorphous form), liquid or gaseous in a solvent, the atoms, ions or molecules of the chemical species are dispersed in the solution and interact with the solvent molecules. This interaction is called solvation. It is of different nature depending on the solute and the solvent and covers phenomena as different as ion-dipole interactions (solute = Na +, solvent = water), hydrogen bonds (solute = alcohol, solvent = water) or van bonds der Waals (solute = methane, solvent = cyclohexane)

When the solute is in the condensed phase (liquid or solid), the solvation enters the energy balance which involves the separation of molecules or ions in the solute before its dispersion in the solvent. The solute dissolves only if the solute-solvent interactions compensate for the loss of solute-solute and solvent-solvent interactions due to dissolution:

- Either by chemical reaction;
- Either by weakening the bonds sufficiently (for example, the water divides the electrostatic forces by about 80) [5].

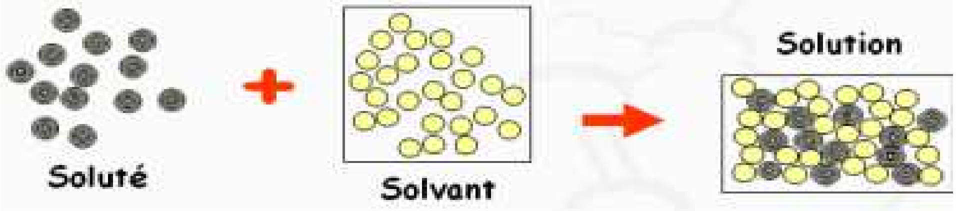


Figure III.4: solvent solute reaction

The liquid which receives is the solvent, the substance which is dissolved therein is the solute, the mixture obtained is the solution, and the operation is commonly called solvation [6].

III-2.1 Solvation layers:

The solvated ion (or molecule) is surrounded by solvent molecules which are directly related to it, which are oriented (in the case of an ion-dipole interaction), and which are only slowly exchanged with molecules outside this first sphere of solvation.

This first sphere is surrounded by other solvent molecules that are not directly ion-bound, that are slightly oriented, that exchange rapidly with solvent molecules from the rest of the solution, and which are slowly exchanged with the molecules of the first sphere.

The rest of the solution consists of solvent molecules that are in the same state that in the absence of solute. Anglo-Saxon literature calls these molecules bulk.

If this structuration of the solution is common to the various solvents and solutes, the number of solvent molecules in each solvation sphere is specific to each type of solution [7].

III-2.2 Number of salvations:

The number of solvation is the number (without units) of molecules of the first solvation sphere or, depending on the case, the total number of molecules of solvent of the two solvation layers. Number of solvation in the first sphere is a fairly easy concept to define, given the stability of solvent-solute interactions. The total solvation number, including the solvent molecules of the second solvation sphere, is more difficult to define. It is most often defined by the method used for the measurement [8]. This disparity, which may seem disruptive in the first instance, reflects the importance of the notion of solvation number in various situations.

The methods for determining solvation numbers are as varied as:

- Theoretical calculations.
- The experimental calculations.

Hydration of biological macromolecules can be studied using several methods that each provides specific, different and complementary information. One can distinguish among these two experimental methods large families of methods:

1. Structural methods (X-ray diffraction crystallography and nuclear magnetic resonance) can detect the presence (for crystallography) and dynamics (for NMR) of specific water molecules around the structure of macromolecules.
2. Thermodynamic methods, based on measurements of microcalorimetry, allow access to the free energy solvation of molecules and its variations during refolding or complexation; these measures of microcalorimetry coupled with volumetric or osmotic pressure approaches can characterize, in terms of number of molecules and energy, the first solvation layers.

Experimental methods for studying hydration are currently becoming more precise. However, they pose difficulties of interpretation, and they do not allow more often than to obtain partial information on the hydration of the biological molecules. It is therefore necessary to consider theoretical methods to study in a more exhaustive way the processes of solvation and to confirm and complete the results of the experimental methods [9].

III-2.3 Study of solvation by theoretical methods:

Theoretical methods such as molecular modeling now make it possible to specify at the atomic level and to better rationalize the structure / function relationship of complex biological systems whose experimental studies are not always simple to implement, nor obvious to interpret. Water plays a very important role in the structure of biomolecular buildings and it therefore appears it is essential to properly represent the solvent around solutes in molecular modeling studies.

Two major strategies stand out for representing the solvent in modeling, the explicit methods, which represent the solvent microscopically, and the implicit methods, which represent the effects of the solvent in a macroscopic way [10].

III-2.3.1 Implicit Solvatation:

(Sometimes known as solvation continuum) is a method of representing solvents as a continuous medium instead of the "explicit" person of the solvent molecules most often used in dynamics and molecular simulations in other applications of molecular mechanics. The method is often used to estimate solute-solvent free energy and interactions in structural chemical processes, such as folding or conformational transitions of proteins, DNA, RNA, and polysaccharides, association of biological macromolecules with ligands, or transport of medications through biological membranes [11].

The implicit solvation model is justified in liquids, where the medium strength potential can be applied to approximate the averaged behavior of many highly dynamic solvent molecules. However, one can also consider the interiors of biological membranes or proteins as media with specific solvation or dielectric properties. These media are continuous, but not necessarily the uniform, since their properties can be described by different analytical functions, such as "polarity profiles" of double lipid layer [12]. There are two basic types of implicit dissolving methods: Accessible Area Based (ASA) models that were historically the first and most recent continuum electrostatic models, although various modifications and combinations of different methods are possible. Accessible area (ASA) method is based on experimental linear relationships between Gibbs transfer free energy and the area of a spacer molecule. This method works directly with the free energy of solvation. The solvent continuum representation also significantly improves the computer speed and reduces statistical errors averaging that result from incomplete sampling of solvent conformations, so that the energy landscapes obtained with the implicit and explicit solvent are different. Although the implicit dissolving model is useful for simulations of biomolecules, this is an approximate method with certain limitations and Problems with parameterization and treatment of ionization effects

Among the implicit methods that allow the calculation of the electrostatic contribution of the free energy of solvation, we distinguish several approaches, of which we will briefly present the fundamental principles:

1. the continuum methods consider the solvent as a continuous medium of high dielectric constant: one finds the methods based on the Poisson-Boltzmann equation, and on the other hand those based on actual pair interactions;
2. the hybrid methods take into account the molecular aspect of the solvent while remaining implicit: we will see on the one hand those of the Langevin dipoles, which treat the solvent as a dipolar fluid, whose equations are based on the polarization properties of the solvent and methods based on the theory of the functional density of liquids, which take into account variations in the density of the solvent [13].

III-2.3.2 Explicit Solvatation: Explicitly treating the solvent, i.e. adding the solvent molecules to the system being studied, is certainly the most rigorous way to understand the behavior of a molecule. However, the computational cost is extremely important since it is necessary to take into account in the calculation of the potential energy function, not only the terms which concern the solute, but also those relating to the solvent, thus resulting in calculation times that are longer than those resulting from a simple implicit treatment of the solvent.

In addition, it is necessary to have the physico-chemical parameters of the solvent molecule calculated specifically for the force field that is used [14].

We used a special solvent type for the MM+ force field: water.

To study a molecule as an explicit solvent, it is necessary to solvate it, that is, to plunge it entirely into a "solvent box". This box of solvent, regardless of its shape (cubic, parallelepiped or truncated octahedral) must have a density very close to the experimental value of the solvent. For this, it is necessary that the number of molecules N of solvent is calculated precisely according to the desired volume of the solvent box:

$$N = \frac{N_0 \times d \times V}{M} \qquad \text{III.1}$$

With N_0: Avogadro number, d: solvent density, V: volume of the solvent box and M: molar mass of the solvent.

For example, in the case of a box of cubic water of 50 A ° edge, the number of molecules of water necessary to have density of water = 1.0 (standard conditions) is:

$$N = \frac{6.02.10^{23} \times 1.0 \times (50.10^{-9})^3}{18.10^{-3}} \qquad \text{III.2}$$

In order to avoid not only that the solvent density in the vicinity of the solute does not vary, but also that the solvent zone is in direct contact with the vacuum (edge effects), periodic boundary conditions are imposed. The solute-solvent system constitutes the primary box which is reproduced as images in all directions of space for a total of [(3 x 9) - 1] = 26 imagery to apply periodic boundary conditions

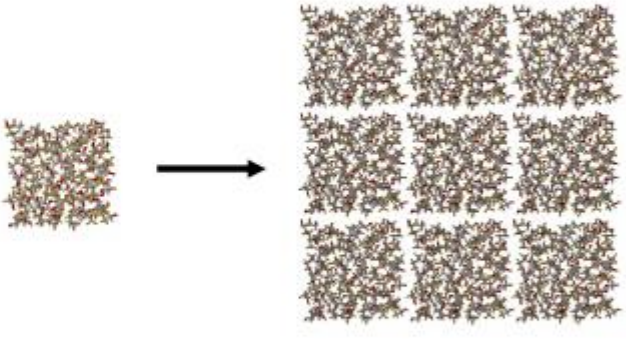


Figure III.5: Creating 26 images around the initial system

It should be noted that, since the solvent molecules are explicitly present, they will directly participate in the evaluation of the energy of the system and therefore the dielectric constant will have a value of 1 [15].

III-3 Poly Methyl Methacrylates:

Poly (methyl methacrylate) (PMMA) is the most important polymer in the polyacrylic category. He is known for its transparency, ease of use and resistance to aging (especially UV light). A large number of alkyl methacrylates which can be considered as poly (methacrylic acid) esters. Indeed, the most important of these polymers is polymethyl methacrylate, which is an important plastic material. As with other linear polymers, the thermal and mechanical properties of polymethacrylates are largely determined by the intermolecular attraction and rigidity of the chain [16].

One of the polymers of importance also obtained by radical route is polymethyl methacrylate (PMMA) obtained by homopolymerization of methyl methacrylate (see Figure III.6). Polymethylmethacrylate is not soluble in water but in organic solvents and it is a thermoplastic resin that softens at temperature (above 110 ° C). It is used mainly for prosthetic bases [17].

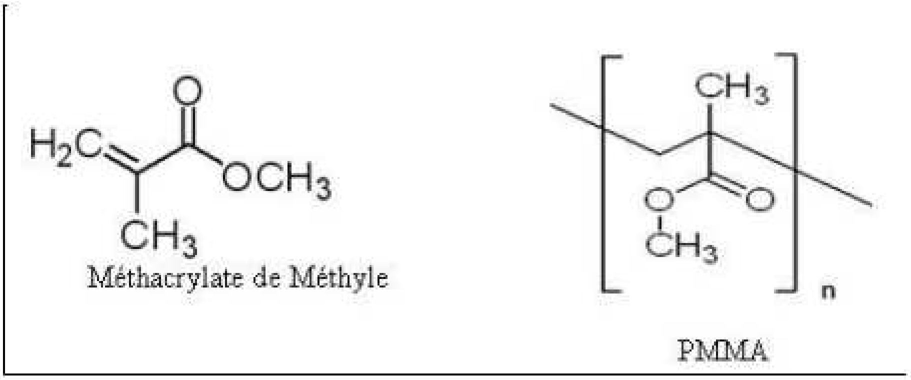


Figure III.6: Chemical structures of the Monomer (MMA) and the Polymer (PMMA) Structures

PMMA is a rigid material with excellent optical qualities. It is used among others in the manufacture of organic contact lenses, designer furniture, safety accessories ... etc. it is known commercially under the name of Plexiglas. Like all materials, PMMA has advantages and disadvantages.

III-3.1 Advantage uses of PMMA:

- Good mechanical qualities

- Good weather stability
- High transparency
- UV resistance

III-3.2 Disadvantages uses of PMMA:

- Low abrasion resistance
- fragile and sensitive to notching

III-3.3 Industrial applications of PMMA:

Due to its transparent properties, lightweight and superior toughness compared to glass, PMMA got popular during World War II. It was extensively used make aircraft windshields, canopies and gun turrets. After this several other commercial applications were developed for PMMA such as glass roofing, façade design, advertising, automotive headlamps, etc. Today various types of acrylic grades are used in wide variety of applications, for example:

Architecture and Construction: Thanks to its excellent impact and UV resistance, PMMA is widely used in window and door profiles, canopies, panels, façade design, etc. It also facilitates light transmission and provides good heat insulation, hence a suitable choice of building green houses. PMMA is also used to build aquariums and marine centers.

Lighting: PMMA sheets are used for designing LED lights where it helps maximize light emitting potential. It is also used for construction of lamps thanks to its transparency and optical properties.

Automotive and Transportation*:* In vehicles, PMMA sheets are used in car windows, motorcycle windshields, interior and exterior panels, fenders etc. Also colored acrylic sheets are used in car indicator light covers, interior light covers etc. It is also used for windows of a ship (Salt resistance) and aviation purposes.

PMMA also open new design possibilities for car manufacturers thanks to its pleasant acoustic properties, outstanding formability and excellent surface hardness.

Electronics: Due to its excellent optical clarity, high light transmission and scratch resistance, PMMA is widely used in LCD/LED TV screens, laptops, smartphones display as well as electronic equipment displays. PMMA also finds used in solar panels as cover materials thanks to its excellent UV resistance and excellent light transmission allowing high energy conversion efficiencies.

Medical and Healthcare: PMMA is a high purity and easy-to-clean material and hence used to fabricate incubators, drug testing devices, storage cabinets in hospitals and research labs. Also, due to its high bio-compatibility, PMMA is also applied as dental cavity fillings and bone cement [19].

III-4 Poly 2-HydroxyEthyl Methacrylate

Poly(2-hydroxyethylmethacrylate) (PHEMA) is a Polymer that well known as hydrogels types. On 1960, Wicherle and Lim were the first introduce the 2-hydroxyethyl methacrylate (HEMA) in contact lenses. PHEMA has stronger mechanical properties than other polymer. It can be strengthened by bulk polymerization, copolymerization with hydrophobic monomers and rigid cyclic monomer modification methods. This polymer also nontoxic and biocompatible the excellent mechanical properties and chemical stability of PHEMA has also by contribution in controlling the optical property of semiconductor nanostructure [20].

Mohar et al. [21], reported that PHEMA able to absorb large amounts (40-45%) of water and have the degree of flexibility similar to the naturally occurring tissue that has higher water content which decreases potential irritation to surrounding membrane and tissues. PHEMA has high solubility in organic solvent such as methanol and ethanol, while it partially soluble in water that leads to the swelling phenomena in water presence. This polymer will become soft and flexible in the swelled state, while quite brittle in the dry state. This PHEMA was chosen as a copolymer. HEMA will provide structural stability and rigidity which in turn reduce the methanol permeability to prevent polymer solubility.

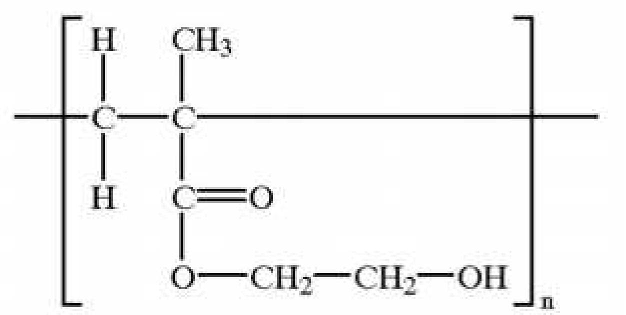


Figure III.7: Chemical structure of the Poly (2-hydroxyethyl methacrylate)

The PHEMA is one of the known polymer in many application such medical, sensor, optical as well as electrochemical devices. This current review paper mainly focus on the application of PHEMA as electrochemical device. The main properties of PHEMA are water insoluble, flexible and capable to form gel membrane. The PHEMA proven can be used to increase the ionic conductivity of the membrane depending on its morphology and structure.

III-4.1Industrial applications of PHEMA:

PHEMA is very important in macromolecular chemistry application. As reviewed, the number of applications of Poly (2-hydroxyethyl methacrylate) has been increase nowadays due to its properties such as easily polymerized, possess a hydrophilic pendant group and enable to form hydrogels:

Hydrogels in the medical field: The use of hydrogels in the medical field is extensive. They can be applied for regeneration of articular cartilage, contact lenses, regenerative medicine and con-trolled drug delivery systems. Hydrogels have the ability to release therapeutic agents in vivo in chosen sites in a controlled space–time frame. The release of bioactive factors is a promising strategy to disease therapy and also enhances tissue regeneration. The hydrogel of poly (2-hydroxyethyl methacrylate) (PHEMA) is one of the most studied polymers in this field of science. It has excellent biocompatibility, has physical properties similar to living tissue and contains hydroxyl functional groups on its surface that can be used for protein bio conjugation.

References:

[1] Moore, J.W., Stanitski, C.L. & Wood J.L). The chemical world: Concepts and applications. (2nd ed.) USA: Harcourt Brace & Company. 1998

[2] Yves GAUTIER, Pierre SOUCHAY .rôle de solvant, p4, 2004 [3]Jacques METZGER Chimie des solutions Dans le chapitre "Propriétés physiques" page : 130-132, 2004

[3] WYPYCH G. "Handbook of solvents". Chem Tec Publishing; William Andrew, 1675 p, 2001.

[4] Solvatation (Yizhak Marcus. Ion solvatation, Ed. J. Wiley & sons limited.), 1985.

[5] Cramer, CJ; Truhlar, DG, "modèles de solvatation pour les énergies libres en solution aqueuse", Chem. Rev, 99, 216, 1999.

[6] M. P. Allen ET D. J. Tidesley. In Computer Simulations of Liquids. Oxford University Press, New-York, 1987.

[7] Bashford, D. and Case, D. A. Generalized born models of macromolecular salvation effects. Annu Rev Phys Chem 51: 129-130, 2000.

[8] Im W, Feig M, Brooks CL. "An implicit membrane generalized born theory for the study of structure, stability, and interactions of membrane proteins". Biophys. J. 85, November 2003

[9] Zhou R. "Free energy landscape of protein folding in water: explicit vs. implicit solvent". Proteins 53 (2): 148–61, November 2003

[10] N. L´evy. Solvatation des macromolécules complexes : une approche fonctionnelle de l’´equation de Poisson-Boltzmann. Thèse de Doctorat, Université d’Evry Val d’Essonne, 2002.

[11] Feig, M. and Brooks, B. R., 3rd. Recent advances in the development and application of implicit solvent models in biomolecule simulations. Curr Opin Struct Biol 14(2): 217-224, 2004.

[12] Roux B, Simonson T. "Implicit solvent models". Biophys. Chem. 78 (1-2): 1– 20, April 1999.

[13] Un Modèle de Solvatation Semi-Implicite pour la Simulation des Macromolécules Biologiques ; Nathalie BASDEVANT (née CAPITAINE) pour obtenir le titre de DOCTEUR de l’UNIVERSITE d’EVRY-VAL-d’ESSONNE, p56, 2003

[14] Colonna-Cesari, F. and Sander, C. Excluded volume approximation to proteinsolvent interaction. Biophys J 57(5):1103, 1990

[15] Eisenberg, D. and McLachlan, A. D. Solvation energy in protein folding and binding, Nature 319(6050): 199-202, 1986

[16] Ferhoum Rabah, Etude Expérimentale et Modélisation Numérique du comportement mécanique du PEHD à l'état vierge et après vieillissement thermique, thèse de doctorat,Université Mouloud Mammeri de Tizi- Ouzou, Juin(2012).

[17] D. Feldman, A. Barbalata, Synthetic Polymers: Technology, Properties and Applications, Chapman & Hall, (1996).

[18] Application of poly (2- hydroxyethyl methacrylate) gel electrolyte in electrochemical device: An Overview. International Journal of Applied Engineering Research ISSN 0973-4562 Volume 11, Number 20 (2016)

[19]https://omnexus.specialchem.com/selection-guide/polymethyl-methacrylate-pmma-acrylic-plastic#Application

[20]Mohan, R., S. Sankarrajan, and G. Thiruppathi, Structural and optical studies of pHEMA encapsulated ZnS:Ni2+ nanoparticles. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2015. 146: p. 7-12

[21] Hodge, R.M., et al., Positronium-salt interactions and ionic conductivity in poly(2-hydroxyethyl methacrylate) gel electrolytes. Polymer, 1999. 40(2): p. 329-335.

Chapter VI:
Results and Discussions

IV.1 Introduction:

Atomistic molecular modelling are a very interesting tool to have preliminary information about blends, phase behavior and compatibility, which exist between polymers. They are an alternative solution to researchers who have not access to experimental. They have reached, recently, a very high level of sophistication, to the point of being able to predict easily several properties with a very high precision, thus anticipating the possible applications of the modelled systems [1-4].

This work consists in studying the solvation of two polymers, by molecular modeling.

IV.2 Polymer identification:

The general molecular structures of the chosen polymers for this study (discussed before) are represented above:

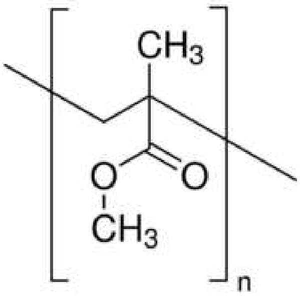


Figure IV.1: n-MMA structure

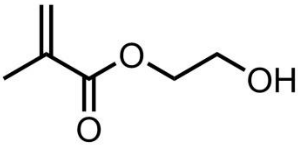


Figure IV.2: n-HEMA structure

For this study, we generate a polymer chain containing 10 Repeat Units (RUs) for each polymer. We optimized the structures by molecular mechanics to obtain starting structures with geometry and a conformation probably the more stable in order to study them by molecular dynamics.

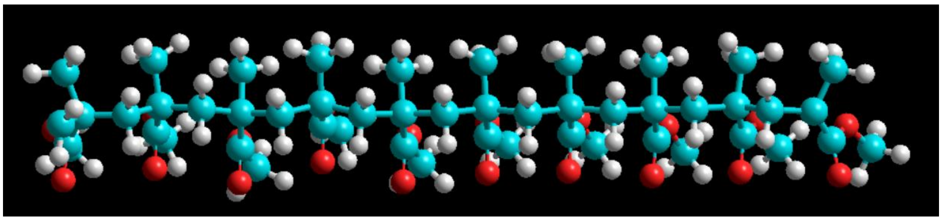


Figure IV.3: PolyMMA structure with 10 RUs (Cyan:Carbon; Red:Oxygen; White: Hydrogen)

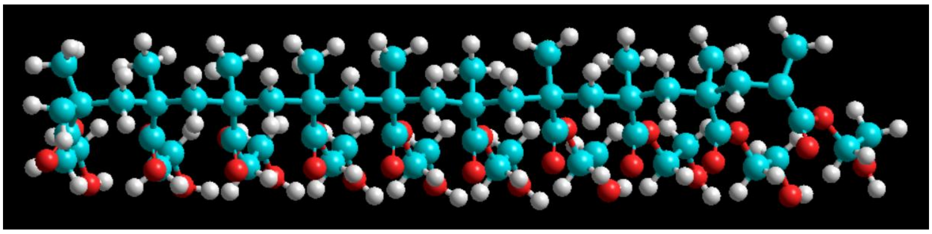


Figure IV.4: PolyHEMA structure with 10 RUs (Cyan:Carbon; Red:Oxygen; White: Hydrogen)

IV.3 Description of the simulation software:

The calculations are performed using *HyperChem* software [5]. *HyperChem* from *Hypercube, Inc.* is a sophisticated molecular modeling environment that is known for its quality, flexibility, and ease of use. Uniting 3D visualization and animation with quantum chemical calculations, molecular mechanics, and dynamics, *HyperChem* puts more molecular modeling tools at fingertips than any other Windows program. *HyperChem* brings in the same interface a set of different tools dedicated to molecular modeling; it allows to really make modeling: it has computational methods (molecular mechanics, semi-empirical, ab-initio, QSAR and conformational research).

ORIGIN 8.0 was used to draw the energy maps. Origin is scientific data processing and analysis software for Microsoft Windows environment developed by *OriginLab* [6]. It allows drawing 2D and 3D graphs and has peak analysis functions. It is also able to import files of various formats such as *Excel*, *ASCII*, *Mathematica* or *SigmaPlot*, and to export the graphs in format JPEG, GIF, Tiff etc.

IV.4 First part: the case of free water

In this part, we present a comparative energy minimization study of the two polymers in the absence of solvent (water) to determine the most stable conformation they can adopt.

IV.4.1 Energy minimization and structure optimization:

Optimization of PMMA and PHEMA by molecular mechanics is done using the mm + force field and Fletcher-Reeves as algorithm (conjugate gradient).

For the PMMA, the starting energy of the brut structure was about 364.109426 Kcal/mol, this energy is converged after 462 steps to reach 102.569635 Kcal/mol.

For the PHEMA, the starting energy of the brut structure was about 524.872829 Kcal/mol, this energy is converged after 791 steps to reach 102.540925 Kcal/mol.

As we can easily see that the two polymer structures have equilibrium energy very close to each other.

Table IV.1: Results obtained after optimization of the different structures:

Molecules	PMMA	PHEMA
Energy (Kcal/mol)	102.569635	102.540925
Bond	15.7596	15.8038
Angle	34.8083	37.0522
Dihedral	-2.75266	-2.89997
Vdw	53.136	50.8921
h-bond	1.6184	1.69278
Electrostatic	0	0

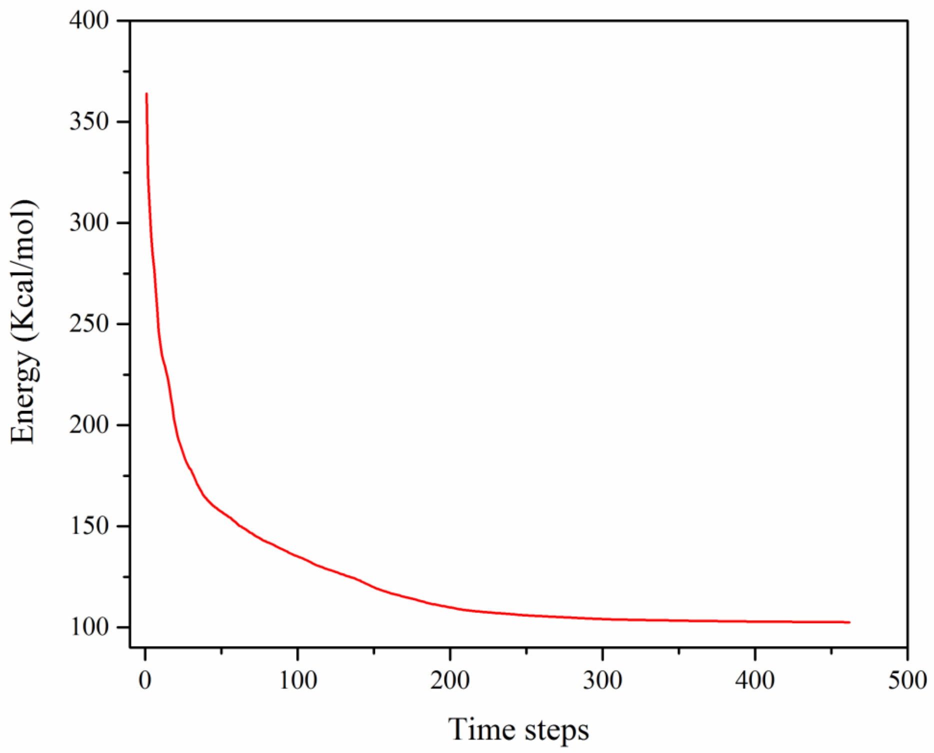


Figure IV.5: Energy minimization of the PMMA structure

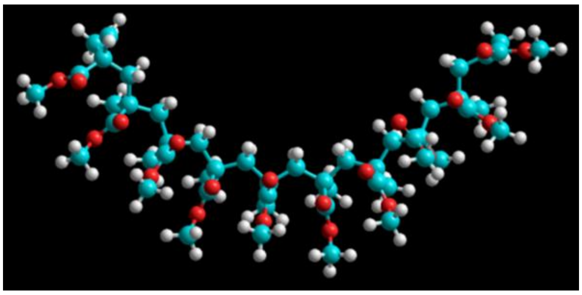


Figure IV.6: The most stable conformation of the PMMA with 10 RUs

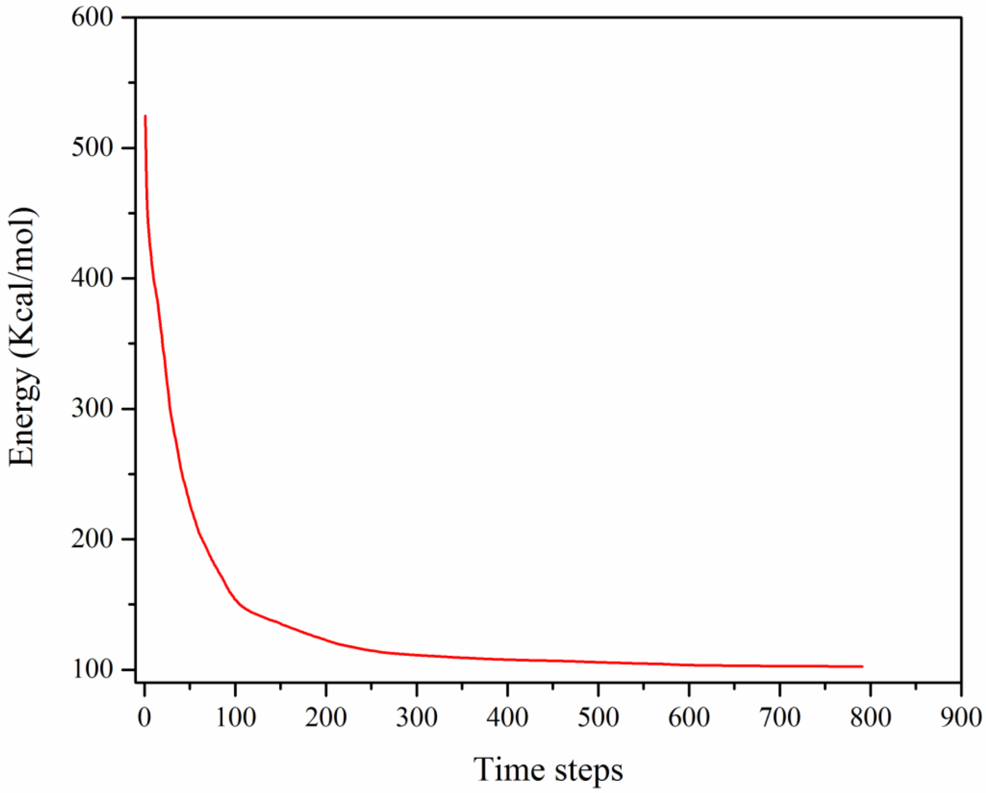


Figure IV.7: Energy minimization of the PHEMA structure

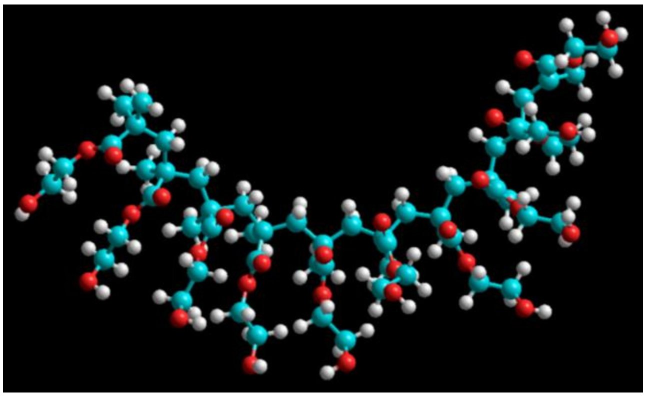


Figure IV.8: The most stable conformation of the PHEMA with 10 RUs

IV.4.2: Relaxing the structures with molecular dynamics:

After performing optimization of the starting structures, it's important to relax the obtained polymer chains. Indeed, in this section we present the molecular dynamic result for the two chosen polymer without solvent. The MD is performed with temperature of 300°K and for a 10 ps simulation time with 0.001 step sizes.

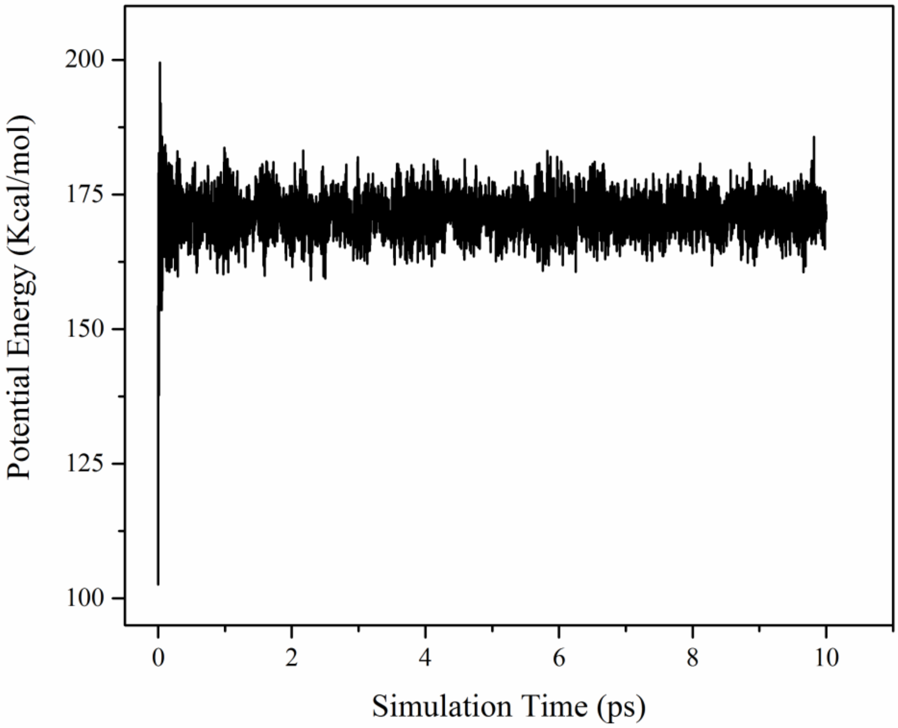


Figure IV.9: Energy equilibration of the PMMA structure after 10 ps

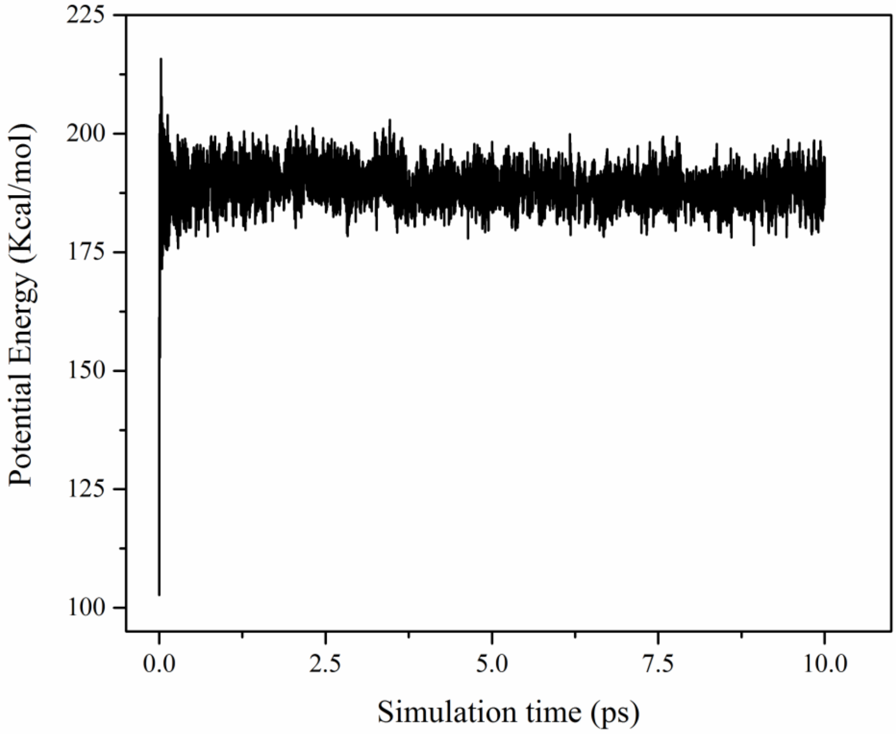


Figure IV.10: Energy equilibration of the PHEMA structure after 10 ps

Table IV.2: Molecular dynamics results for isolated molecules

Molecules	PMMA	PHEMA
Potential Energy (Kcal/mol)	168 ~ 174	185 ~ 192

For the PMMA, the starting energy of the optimized structure was about 102.569635 Kcal/mol, this energy increase and is equilibrated after 10 ps simulations time to stay around 168 ~ 174 Kcal/mol.

For the PHEMA, the starting energy of the optimized structure was about 102.540925 Kcal/mol, this energy increase and is equilibrated after 10 ps simulations time to stay around 185 ~ 192 Kcal/mol.

IV.5 Second part: Solvation of the polymers

The majority of the chemical and biological reactions take place in solution, and the effects due to the solvent can be very important. [5] We can take them into account:

- Either explicitly by placing solvent molecules around the molecule
- Either implicitly, that is, indirectly.

-The explicit solvents:

In this case, a solvation cube is generated around the molecule. That is, "simply" and randomly add a number of solvent molecules corresponding to the density of the solvent. We (the software) create a box with a pre-defined size around the molecule filled with water molecules, this step made in the Hyperchem software. The PMMA and PHEMA are putted into a box with 216 water molecules each.

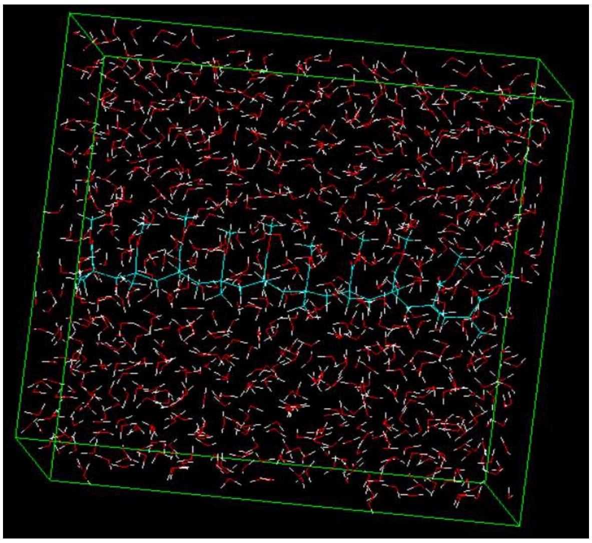


Figure IV.11: PMMA structure (in blue) immersed into 216 water molecules

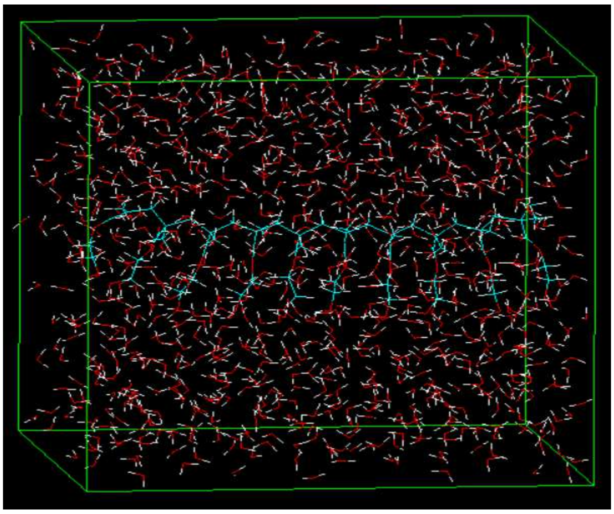


Figure IV.12: PHEMA structure (in blue) immersed into 216 water molecules

IV.5.1 Energy minimization and structure optimization:

The optimization of geometry can be carried out in molecular mechanics (MM), the optimization of PMMA and PHEMA by molecular mechanics using the same parameters used before; That is, the mm+ force field and the Fletcher-Reeves algorithm (conjugate gradient).

For the PMMA cube with water molecules, the starting energy of the brut structure was about 2511.558867 Kcal/mol, this energy is converged after 2140 steps to reach -2244.411297 Kcal/mol.

For the PHEMA cube with water molecules, the starting energy of the brut structure was about 1304.933984 Kcal/mol, this energy is converged after 2530 steps to reach -2367.747188 Kcal/mol. All the results are gathered in the table IV.3.

Table IV.3: Obtained results obtained after optimization

Molecules	PMMA	PHEMA
Energy (Kcal/mol)	-2244.411297	-2367.747188
Bond	27.4509	34.5282
Angle	49.4214	55.3837
Dihedral	2.6097	11.5201
Vdw	-638.219	-693.565
h-bond	2.42858	3.11648
Electrostatic	-1688.1	-1778.73

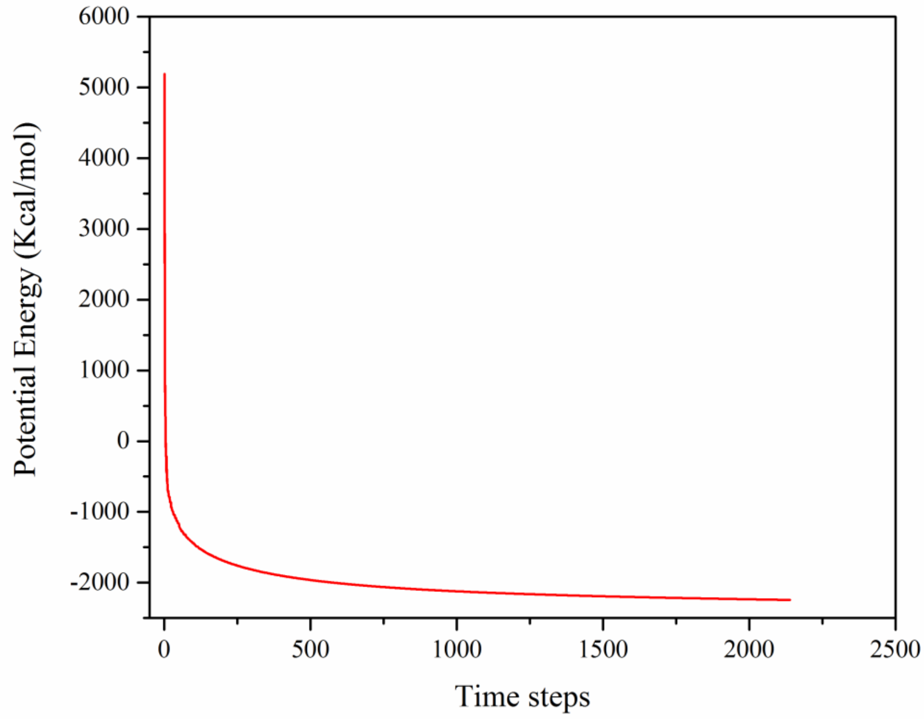


Figure IV.13: Energy minimization of the PMMA structure immersed in water

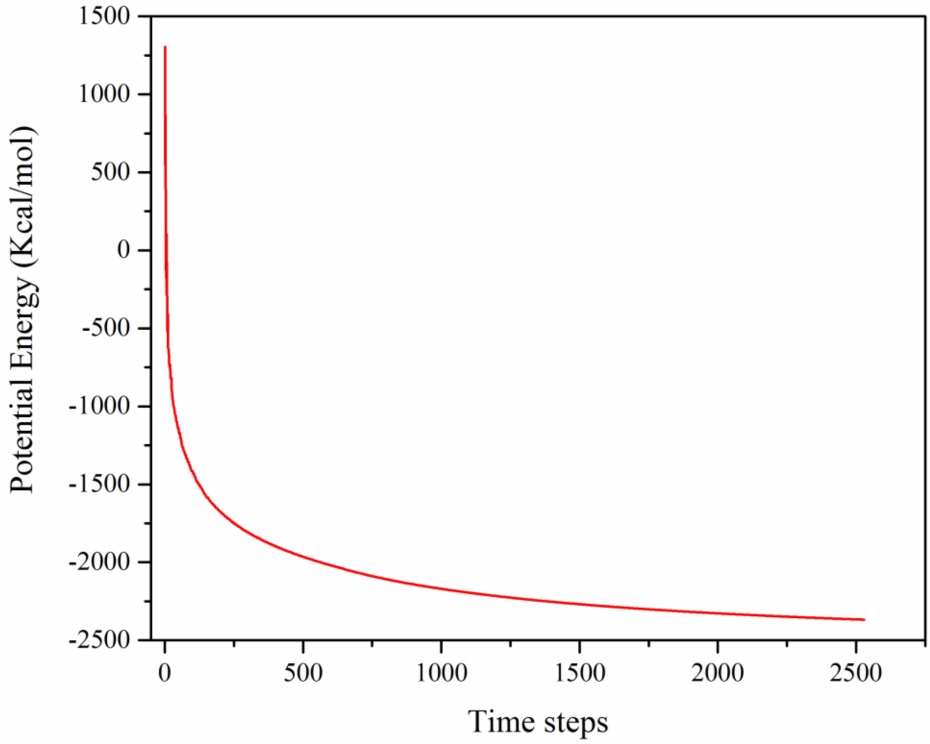


Figure IV.14: Energy minimization of the PHEMA structure immersed in water

IV.5.2: Relaxing the structures with molecular dynamics:

In this section we present the molecular dynamic result for the two chosen polymer immersed in solvent (water). The MD is performed keeping the same parameters used befor. That is, with temperature of 300°K and for a 10 ps simulation time with 0.001 step sizes.

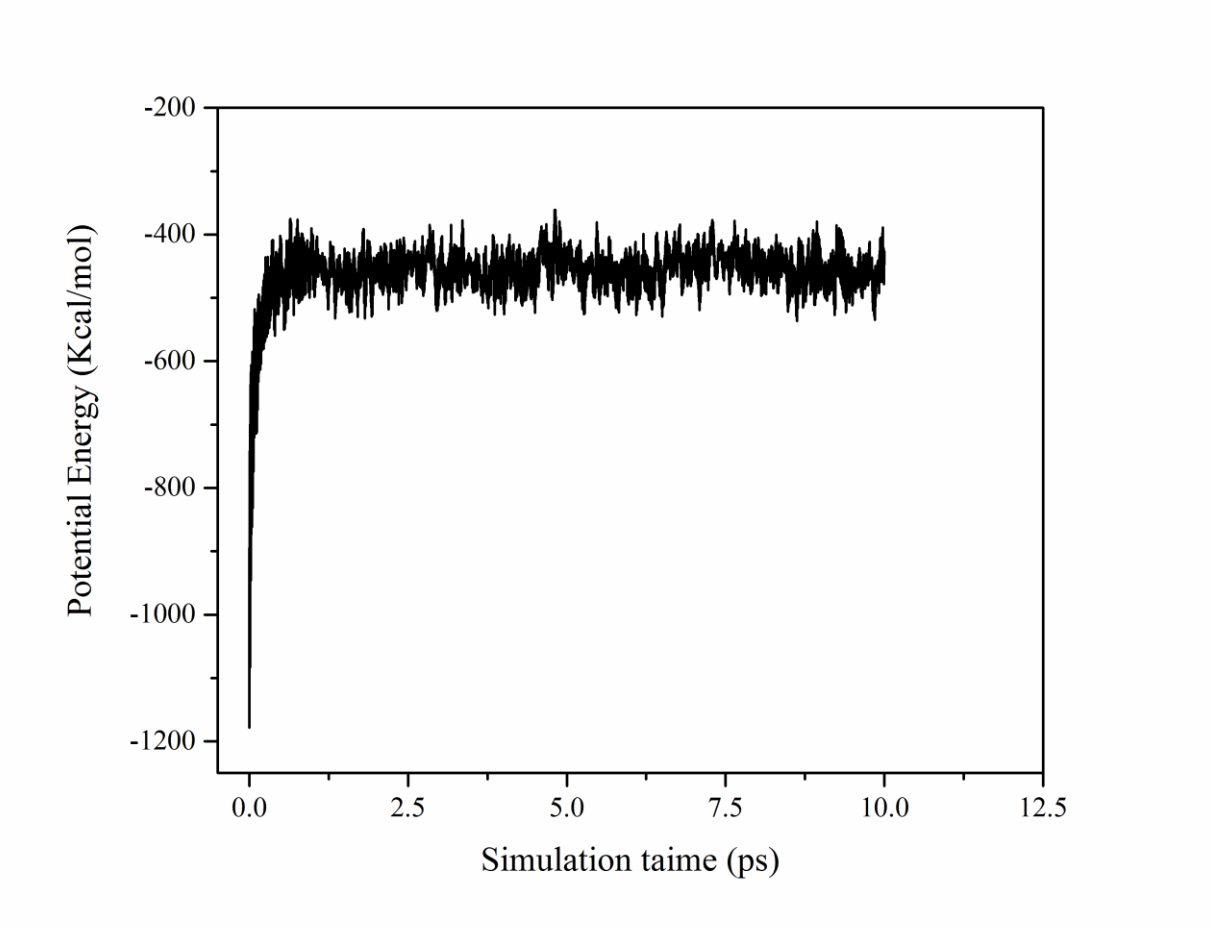


Figure IV.15: Energy equilibration of the PMMA immersed in water with 10 ps simulations time

For the PMMA, the starting energy of the optimized structure was about -2244.411297 Kcal/mol, this energy increase and is equilibrated after 10 ps simulations time to stay around -450 ~ -530 Kcal/mol.

For the PHEMA, the starting energy of the optimized structure was about -2367.747188 Kcal/mol, this energy increase and is equilibrated after 10 ps simulations time to stay around -650 ~ -530 Kcal/mol.

Table IV.4: Molecular dynamics results for immersed polymers in water molecules

Molecules	PMMA	PHEMA
Potential Energy (Kcal/mol)	-530 ~ -450	-650 ~ -530

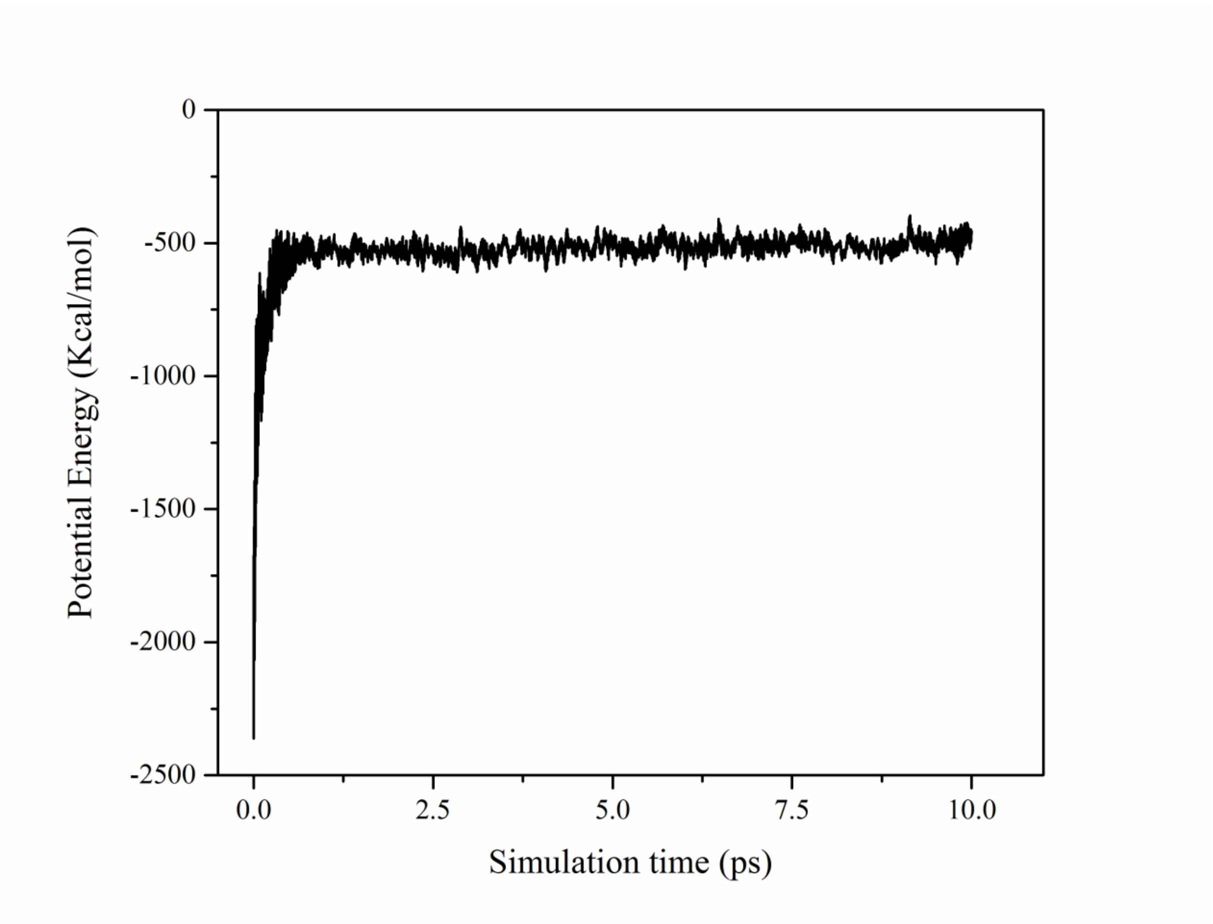


Figure IV.16: Energy equilibration of the PHEMA immersed in water with 10 ps simulations time

IV.6 Qualitative analysis:

According to the obtained results shown in the table IV.5, it is noted that the energy of PHEMA without solvent is low compared to the found energy of PMMA without solvent. In the case where the two molecules are used with solvent, the phenomenon is confirmed; this is due to the polymer chemical structure. Indeed, the PHEMA contain in its structure a chemical group O-H which favors the binding with water molecules what makes the energy is small compared to the one presented by PMMA.

Table IV.5: Different energies obtained after geometry optimization for the different systems.

Molecules		Energy (Kcal/mol)	
		Starting	Final
PMMA	Unboxed	364.109426	102.569635
	Boxed	2511.558867	-2244.411297
PHEMA	Unboxed	524.872829	102.540925
	Boxed	1304.933984	-2367.747188

Reference:

[1] H.Dugas, Principes de base en modélisation moléculaire, Aspects théoriques et pratique, Librairie de l'université de Montréal, Chapitre 3. 1996

[2]Daan Frenkel, Berend Smit Understanding Molecular Simulation: From Algorithms to Applications, ISBN 0-12-267370-0, 1996

[3] Drug Discovery & Development magazine: Vol. 11, No. 2, February, pp. 30-32, 2008

[4] Solvatation (Yizhak Marcus. Ion solvatation, Ed. J. Wiley & sons limited.), 1985

[5] http://www.hyper.com/

[6] https://www.originlab.com/origin

Conclusion

Conclusion

The solvation of polymers as well as the representation of the solvent, whose role is very important in the stabilization and dynamics of polymers, constitutes a major challenge in molecular modeling. This work was devoted to the study by molecular modeling of solvation of two isotactic polymers which are PMMA (Poly Methyl Methacrylate) and PHEMA (Poly Hydroxy ethyl methacrylate). It comprises four chapters:

The first is dedicated to a bibliographical study on polymers by citing some basic definitions to be able to initiate the reader on this subject.

The aspects of molecular modeling are discussed in the second chapter in order to situate molecular mechanics among the modeling methods used for the description of atomic behavior within the molecular structure. The notion of force field, the set of terms of steric energy is defined precisely in the mathematical expression in molecular mechanics. The importance of parametrization justifies the choice of the force field.

Chapter 3 reviews the various existing methods, experimental and theoretical, and also the various existing solvents and their classifications, to study precisely the solvation of macromolecules. The study of the solvation of polymers appears to be essential to rationalize the influence of water on chemical processes and therefore represents a major challenge for physics and modern chemistry.

The last chapter is devoted to the results obtained and to the discussion and interpretation of these.

Polymers are extremely important organic compounds due to their natural abundance and their structural and energy reserve functions. In the organized or disorderly state, understanding of polymer / water interactions is essential for many scientific and technological fields. The complexity of these interactions is due to the presence of very close hydroxyl groups which multiply the hydrogen bond alternatives either intramolecularly or with water.

The calculations carried out with the *Hyperchem* software led us to different energy values (minimization and dynamics -stabilization) for the two PMMA and PHEMA polymers. So the solvent (water) plays a very important role in stabilizing the structures of the polymers.

The prospects we plan to achieve in the future as part of a PhD will be to deepen this study to be able to determine and predict the physical properties of such materials as well as to treat more complex systems and determine the effects of solvent on polymers.

Résumé :

Ce Mémoire traite une étude théorique par dynamique moléculaire de la solvatation dans l’eau de deux polymères acryliques biocompatibles hydrophiles qui sont le PMMA (Poly Méthacrylate de Méthyle) et le PHEMA (Poly 2-Hydroxy Ethyle Méthacrylate). L’étude a été basée sur la comparaison des énergies potentielles des deux polymères dans deux états différents, le premier est un état sec (Sans ajout de solvant-Eau-) et le deuxième état en ajoutant du solvant –Eau- et ceci pour pouvoir déterminer l’effet de l’ajout du solvant –Eau- sur les deux polymères. Il a été constaté que l’énergie du PHEMA sans solvant est inférieure à celle du PMMA. Cet effet est confirmé lors de l’ajout du solvant.

Mots Clés : modélisation moléculaire, solvatation, polymère

Abstract :

This dissertation deals with a molecular dynamics theoretical study of the solvation in water of two hydrophilic biocompatible acrylic polymers which are PMMA (Poly Methyl Methacrylate) and PHEMA (Poly 2-Hydroxy Ethyl Methacrylate). The study was based on the comparison of the potential energies of the two polymers in two different states, the first is a dry state (Without adding solvent-Water-) and the second state by adding solvent -Water- and this to be able to determine the effect of the addition of the solvent -Eau- on the two polymers. It has been found that the energy of PHEMA without solvent is lower than that of PMMA. This effect is confirmed when adding the solvent.

Key words: molecular modeling, solvation, polymer

ملخص :

تتناول هذه الأطروحة دراسة نظرية ديناميكية جزيئية للمحلول في الماء من بوليمرين أكريليك متوافقين مع الماء الحيوي وهما PMMA (Poly Méthyl Méthacrylate) و PHEMA (Poly 2-Hydroxy Méthyl Méthacrylate). استندت الدراسة إلى مقارنة الطاقات المحتملة للبوليمرات في حالتين مختلفتين ، الأولى هي حالة جافة (بدون إضافة مذيب-ماء) والحالة الثانية مضيفة مذيب -الماء وهذا قادر على تحديد تأثير إضافة المذيب-الماء- على كلا البوليمرات. لقد وجد أن طاقة PHEMA بدون مذيب أقل من طاقة PMMA. يتم تأكيد هذا التأثير عند إضافة المذيب.

الكلمات المفتاحية: النمذجة الجزيئية ، الذوبان ، البوليمر