Material Science and Engineering with Advanced Research

Importance of Molecular Simulation for Studying Structural Properties

Norma-Aurea Rangel-Vázquez

Instituto Tecnológico de Aguascalientes, Depto. de Metalmecánica, División de Estudios de Posgrado e Investigación

Abstract

The importance of molecular simulation is due to its application in different subjects as such as drug design, computational biology and materials science for studying molecular systems ranging from small chemical systems to large biological molecules and material assemblies.

Some properties of molecular simulation are, quantitative structure-activity relationships (QSARs) which establish a quantitative relationship between chemical structures and their properties (structural and physicochemical), and this contributes to assisting and guiding the design and the selection of potent and safe drug candidates. The molecular electrostatic potential (MESP) is the potential energy of a proton at a particular location near a molecule, which correlates with dipole moment, electronegativity, and partial charges. MESP are valuable in computer-aided-drug-design because they help in optimization of electrostatic interactions between the protein and the ligand. These surfaces can be used to compare different inhibitors with substrates or transitions states of the reaction. FTIR technique is applied to obtain different functional groups present in the molecule or reaction. Besides, we can realize several studies as for example, kinetics, absorption and others.

Keywords: Simulation, QSAR, MESP, FTIR

Introduction

The term computational chemistry is normally used when a mathematical method is sufficiently well developed that it can be used automatically on a computer. Quantum mechanics generation is a mathematical description of the behavior of electrons that has never been found to be wrong. However, the quantum mechanical equations have never been solved exactly for any chemical system other than the hydrogen atom. Thus, the entire field of computational chemistry is built around approximate solutions. Some of these solutions are very crude but are still more accurate than any experiment that has yet been conducted [1].

Molecular simulation encompasses all theoretical methods and computational techniques used to model or mimic the behavior of molecules. The techniques are used in the fields of computational chemistry, drug design, computational biology and materials science for studying molecular systems ranging from small chemical systems to large biological molecules and material assemblies. The simplest calculations can be performed by hand, but inevitably computers are required to perform molecular modeling of any reasonably sized system. The common feature of molecular modeling techniques is the atomistic level description of the molecular systems [2]. Drug design, sometimes referred to as a rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient.

In the most basic sense, drug design involves the design of small molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques. This type of modeling is often referred to as computer-aided-drug-design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as structure-based drug design [3].

Natural products have played an important role in the history of drug discovery and development process by providing novel, clinically useful medicines having various biological activities such as anticancer, antiasthmatic, antifungal, anti-protozoan and antimicrobial activities, among others [4].The development of hydrogels interpenetrating type (IPN: interpenetrated networks), where many natural polymers such as, chitosan, starch, hyaluronic acid, collagen, etc., are taken interest in the field of bioengineering as they are used for synthesis new biocompatible materials for drug delivery [5], which resemble natural living tissue than any other class of materials.

These hydrogels are capable of absorbing large quantities of water or biological fluids due to three-dimensional polymeric networks

of high molecular weight and hydrophilic character possessed, they are insoluble due to the presence of chemical or physical crosslink's that provide the network of a defined structure and physical integrity [6-8]. The hydrophilicity property is due to the presence of hydrophilic functional groups such as: OH, COOH and others.

Hydrogels are materials suitable for medical applications because of their good interaction with the living tissue on one hand and have good biocompatibility properties, mainly because of their soft, elastic consistency and moisture content. Furthermore, inert materials are those cells and proteins that tend not to stick to its surface. And besides, its characteristic swelling in liquid medium gives them the ability to absorb, retain and release under controlled conditions, some organic solutions [9].

Polymers are macromolecules composed of repeating structural units of monomers connected by covalent chemical bonds and this process is known as polymerization. There are many types of polymers including natural and synthetic moiety. Natural polymers such as proteins (collagen, silk and keratin), carbohydrates (starch, glycogen) are widely used materials for conventional and novel dosage forms. These materials are chemically inert, nontoxic, less expensive, biodegradable, eco-friendly and widely available [5-6]. The development of new applications for chitosan and its derivative is mainly due to the fact that these are renewable source of natural biodegradable polymers and also due to chitin and its derivative are the most abundant natural polymers [10].

Naturally occurring cationic polysaccharide known for its biocompatibility and biodegradability is chitosan (QN). The QN is a copolymer of the amino polysaccharide which is obtained by alkaline deacetylation of chitin [11], the main structural material in the exoskeletons of crustaceans and other animal species [7]. This copolymer can be used as basis for the genipin crosslinking which is a natural reactant to conventional crosslinking agents used for the chitosan is an alternative because of its good biocompatibility and absence of toxicity [12].

With this, the IPN of chitosan crosslinked with genipin to form hydrogels which are used as a means of transportation for the delivery of drugs and to assist in the three-dimensional tissue regeneration and organ structures [13]. Under this guideline, it's controlled release of active substances such as metformin used in the prevention of diabetes mellitus type 2, is presented as an alternative solution for drugs that are primarily administered orally or intravenously [14]. With these, recent developments regarding drug administration have facilitated the selection of specific tissues for release.

Nanomedicine, the use of nanotechnology for medical applications, has undergone rapid development in the last several decades. The goal of nanomedicine is to design and synthesize drug delivery vehicles that can carry sufficient drug loads, efficiently cross physiological barrier to reach target sites and provide safe and sustainable cure disease. Numerous organic nanomedicines, including liposomes, drug—polymer conjugates, dendrimers, polymeric micelles and nanoparticles (NPs), have been extensively studied as drug delivery systems [15].

So with the advent of nanotechnology, these applications (hydrogels, IPN) are turning nanomedicine into a billion dollar industry due to the inherent ability of its members to overcome solubility and stability problems, direct the administration of drugs to sites concrete or could even generate multifunctional entities able to diagnose, treat and monitor treatment simultaneously [16].

Geometry Optimization

Geometry optimization is a key component of most computational chemistry studies that are concerned with the structure and/or reactivity of molecules [17]. It is a method to predict the three-dimensional arrangement of the atoms in a molecule by means of minimization of model energy. The phenomenon of binding, that is to say the tendency of atoms and molecules to conglomerate into stable larger structures, as well as the emergence of specific structures depending on the constituting elements, can be explained, at least in principle, as a result of geometry optimization.

Two atoms are said to be linked together by a bond if there is an opposing force against pulling them apart. Associated with a bond is a binding energy, which is the total energy, required to separate the atoms. Except at very high temperature, atoms form bonds between each other and conglomerate into molecules and larger aggregates such as atomic or molecular chains, clusters, and crystals.

Model Energy

A wide range of model energies are in use, depending on the type of system and the desired level of understanding. To obtain quantitatively accurate and chemically specific predictions, one uses ab initio energy surfaces, that is to say surfaces obtained from a quantum mechanical model for the system's electronic structure which requires as input only atomic numbers. For large systems, one often uses classical potentials.

The latter are particularly useful for predicting the 3D structure of systems composed from many identical copies of just a few basic units, such as crystalline clusters, carbon nanotubes, or nucleic acids [18-19]. Long-range interactions (LRIs) play an important role in biological, physical, and chemical processes and were the focus of a recent U.S. Department of Energy, Office of Science workshop and review spanning the biology, chemistry, and physics communities. LRIs are categorized as being long-range electrodynamic, electrostatic, and polar interactions that dominate the organization of small objects at separations beyond an interatomic bond length. They give rise to forces that help systems lower their thermodynamic free energy. They should be distinguished from the basic chemical process of covalent bond formation associated with chemical reactions, and the basic biological processes of metabolism leading to energy production.

In addition, more than a dozen "different" LRIs are typically defined and used by researchers in particular scientific fields, e.g., hydrophobic, hydration, steric, depletion, and other interactions. The impact of these types of particularization in LRIs is closely tied to specific application areas, which while convenient in the

subfields, is an inhibition of the fundamental advancement in the nanoscale science of long-range interactions [20].

Density Functional Theory (DFT)

Molecular modeling and quantum mechanical simulations using the density functional theory play an increasingly important role in fundamental understanding of nanoscale phenomena and as well as in technological applications.

Discovery of the active site of these molecules would be performed by quantum mechanical simulations using density functional theory method [21]. DFT is an approach for the description of ground state properties of metals, semiconductors, and insulators. The success of DFT not only encompasses standard bulk materials but also complex materials such as proteins and carbon nanotubes.

The main idea of DFT is to describe an interacting system of fermions via its density and not via its many-body wave function. For N electrons in a solid, which obey the Pauli principle and repulse each other via the Coulomb potential, this means that the basic variable of the system depends only on three -- the spatial coordinates x, y, and z – rather than 3N degrees of freedom.

The principles characteristics are:

a. The wave function φ of an N-electron system includes 3N variables, while the density, ρ no matter how large the system is, has only three variables x, y, and z. Moving from E[φ] to E[ρ] in computational chemistry significantly reduces the computational effort needed to understand electronic properties of atoms, molecules, and solids.

b. Formulation along this line provides the possibility of the linear scaling algorithm currently in fashion, whose computational complexity goes like $O(NlogN)$, essentially linear in N when N is very large.

c. The other advantage of DFT is that it provides some chemically important concepts, such as electronegativity (chemical potential), hardness (softness), Fukui function, and response function [22].

QSAR Properties

QSAR is the study of the correlation between chemical structure and associated biological activity, with the ultimate goal of predicting the activity of untested chemicals based on structurally related compounds with known activity. Structure-activity relationships (SARs) are qualitative relationships, often in the form of structural alerts that incorporate molecular substructures or fragments related to the presence or absence of activity. QSARs attempt to quantify the relationship between an aspect of chemical structure and an activity or property imparted by that structure.

Chemical structure is often described by descriptors (e.g., electrophilicity, hydrogen bonding, molecular fragments) or physical-chemical properties (e.g., Log P) which are then used to develop a mathematical correlation between a group of structures and a defined activity or endpoint. The mathematical correlations usually take the form of statistical algorithms developed through a variety of techniques (e.g., univariate regression, multiple linear regressions, partial least squares analysis) [23-24].

QSAR methods in drug design are used particularly for the estimation of physicochemical properties, biological effects as well as understanding the physicochemical features governing a biological response. The lipophilicity of a drug is its capacity to be partitioned between a polar phase and a non-polar environment. Lipophilicity is often expressed as the logarithm of the partition coefficient (log P) of a compound measured by distribution between immiscible phases of n-octanol and water.

Experimental methods for log P evaluations include the shake-flask method, reversed-phase high-performance liquid chromatography (RP-HPLC), and the potentiometric method. Besides these experimental techniques, there is a plethora of free and commercial computational tools for log P prediction. Lipophilic parameters are often highly significant in QSAR models. ADME properties of molecules and drug–target interactions are also partly governed by their lipophilic properties. Some important efforts have been made toward a better characterization of the intermolecular forces underlying lipophilicity. LSER analysis is suitable for decomposing lipophilicity in terms of polar and hydrophobic intermolecular forces [25].

For example, in the chitosan, when it is crosslinking with genipin suffers a nucleophilic attack by the primary amine occurs at the carbon atom in genipin, while the secondary amine attacks the aldehyde group. Something similar occurs when chitosan with genipin is applied to absorption of glibenclamide: nucleophilic attack of the amino group of chitosan at the carbonyl of the genipin leads to formation of a stable bond (amide), and an oxygen atom in genipin is replaced by a nitrogen atom from chitosan.

Molecular Electrostatic Potential (MESP)

MESP at a given point $p(x,y,z)$ in the vicinity of a molecule is the force acting on a positive test charge (a proton) located at p through the electrical charge cloud generated through the molecules electrons and nuclei.

Despite the fact that the molecular charge distribution remains unperturbed through the external test charge (no polarization occurs) the electrostatic potential of a molecule is still a good guide in assessing the molecules reactivity towards positively or negatively charged reactants. The MESP is typically visualized through mapping its values onto the surface reflecting the molecules boundaries. The latter can be generated through overlapping the vdW radii of all atoms of the molecule, through algorithms calculating the solvent accessible surface of the molecule, or through a constant value of electron density. The latter will be used here to answer the question of which site in imidazole is particularly attractive to a proton. Imidazole contains two nitrogen atoms both of which might act as proton acceptor sites [26].

The electron density isosurface is a surface on which the molecule's electron density has a particular value and that encloses a specified fraction of the molecule's electron probability density. The electrostatic potential at different points on the

electron density isosurface is shown by coloring the isosurface with contours.

The results of analysis of MESP show that the negative electrostatic potential corresponds to an attraction of the proton by the concentrated electron density in the molecules (from lone pairs, pi-bonds, etc.). In the meantime, the positive electrostatic potential corresponds to repulsion of the proton by the atomic nuclei in regions where low electron density exists and the nuclear charge is incompletely shielded. The calculated partial charges represented as spheres show how the molecule would interact with approaching protons or positive charges. When a unit of positive charge (proton) approaches a positive region of the molecule, the repulsive interaction results in an increasing positive potential energy [27].

Conclusions

Simulation computational is necessary for life of society, especially for many applications in chemistry. For example, the researchers can determine interaction molecules of atom/molecule, surface properties and thermodynamics of inorganic, biological and polymeric systems in certain time period. Something properties includes optimization of geometry is an important part of most quantum chemical calculations for to find the configuration of minimum energy of the molecule. QSAR is a method to correlate the chemical structure of a molecule with its chemical, physical, pharmaceutical, or biological etc. effect. Finally, MESP where show the charge distributions of molecules three dimensionally. These results allow us to visualize the charge distributions can be used to determine how molecules interact with one another.

References

1. Adejoro IA, Oyeneyin OE, Adeboye OO, Obaleye JA. Dichlorobis (N-{4-[(2-pyrimidinyl-kN-amino)sulfonyl}acetamide]copper(II), Containing a Metabolite N-acetylsulfadiazine. J Computational Methods in Molecular Design. 2012; 2(4):142-148.

2. Parsons J, Holmes JB, Rojas JM, Tsai J, Strauss CE. Practical conversion from torsion space to cartesian space for in silico protein synthesis. J Comput Chem. 2005; 26:1063-1068.

3. Wang R, Gao Y, Lai L. Lig Builder: A Multi-Purpose Program for Structure-Based Drug Design. J Mol Model. 2000; 6(7–8):498–516. doi: 10.1007/s0089400060498.

4. Reddy TV, Devi BLP, Prasad RB, Poornima M, Kumar CG. Total synthesis and antifungal activity of (2S, 3R)-2-aminododecan-3-ol. Bioorg Med Chem Lett. 2012; 22:4678–4680. doi: 10.1016/j.bmcl.2012.05.082.

5. Coronado R, Pekerar S, Lorenzo AT, Müller AJ, Sabino MA. Obtención y caracterización de hidrogeles inteligentes del tipo red intepenetrada basados en poli(n-isopropil acrilamida). Suplemento: Rev. LatinAm. Metal. Mater. 2009; 1(S2):65-66.

6. Santoni N, Matos M, Müller KC, Nicola H, Sabino M, Müller A. Caracterización de hidrogeles de quitosano entrecruzados covalentemente con genipina. Rev. Iberoam. Polim. 2008; 9(3):326-330.

7. Berger J, Reist M, Chenite A, Felt BO. Fast-swelling porous starch-g-poly (acrylic acid) superabsorbents. Int. J. Pharm. 2005; 288:197.

8. Geckil H, Xu F, Zhang X, Moon S, Demirci U. Engineering hydrogels as extracellular matrix mimics. Nanomedicine (Lond). 2010; 5(3):469–484. doi: 10.2217/nnm.10.12.

9. Arredondo AP, Londono-Lopez ME. Hydrogels Potentials biomaterials for controlled drug delivery. Rev. Ing. Biomed. 2009; 3(5):83-94.

10. Bansal V, Kumar Sharma P, Sharma N, Prakash Pal O, Malviya R. Applications of Chitosan and Chitosan Derivatives in Drug Delivery. Adv Biolog Res. 2011; 5(1):28-37.

11. Chun Hsu Y, Bai Shuan L, Chen Jung C. Preparation of networks of gelatin and genipin as degradable biomaterials. Mater. Chem. Phys. 2004; 83(2-3):204–208. doi: 10.1016/j.matchemphys.2003.08.027.

12. Butler M, Pudney P, Yiu Fai Ng. Mechanism and kinetics of the crosslinking reaction between biopolymers containing primary amine groups and genipin. J. Polym. Sci. Part A: Polym. Chem. 2003; 41(24):3941-3953. doi: 10.1002/pola.10960.

13. García CR, Mendoza MA. Estudio de las propiedades morfológicas y reológicas de una red híbrida de polímeros sintetizada a partir de tres biopolímeros: gelatina/quitosan/dextran. Rev. Iberoam. Polím. 2010; 11(2):88-109.

14. Arredondo PA, Londoño LM. Hidrogeles. Potenciales biomateriales para la liberación controlada de medicamentos. Rev Ing Bioméd. 2009; 3(5):83-94.

15. Tang L, Cheng J. Nonporous silica nanoparticles for nanomedicine application. Nano Today. 2013; 8(3):290—312.

16. Oropesa NR, Jáuregui HU. Las nanopartículas como portadores de fármacos: características y perspectivas Nanoparticles as drug carriers: characteristics and perspectives. Rev CENIC-Cienc Biológ. 2012; 43(3):1-20.

17. Schlegel HB. Geometry optimization. WIREs Comput MolSci. 2011; 1:790-809. doi: 10.1002/wcms.34.

18. Li D. On the Crystallization of 2D Hexagonal Lattices. Commun. Math. Phys. 2009; 286:1099-1140.

19. Friesecke G, Theil F. Validity and failure of the Cauchy-Born hypothesis in a two-dimensional mass-spring lattice. J. Nonl. Sci. 2002; 12(5):445-478. doi: 10.1007/s00332-002-0495-z.

20. Wen AM, Rambhia PH, French RH, Steinmetz NF. Design rules for nanomedical engineering: from physical virology to the applications of virus-based materials in medicine. J Biol Phys. 2013; 39(2):301–325. doi: 10.1007/s10867-013-9314-z.

21. Varmaghani Z, Monajjemi M, Mollaamin F. Discovery of active site of vinblastine as application of nanotechnology in medicine. NanomedJ. 2014; 1(3):162-170.

22. http://www4.ncsu.edu/~franzen/public_html/CH795Z/lecture/DFT_Method.pdf (Reviewed: 28/02/2015).

23. Katritzky AR, Maran U, Lobanov VS, Karelson M. Structurally Diverse Quantitative Structure–Property Relationship Correlations of Technologically Relevant Physical Properties. J Chem Inf Comput Sci. 2000; 40(1):1–18.

24. Manibusan M, Paterson J, Kent R. (Quantitative) Structure Activity Relationship [(Q)SAR] Guidance Document. Nafta. 2012; 1:186.

25. Bajot F. The Use of QSAR and Computational Methods in Drug Design. In Recent Advances in QSAR Studies. In: Jerzy Leszczynski, Tomasz Puzyn, Mark Cronin, editors. Recent Advances in QSAR Studies: Methods and Applications. Netherlands: Springer Science & Business Media; 2010. p. 261-282.

26. Molecular Electrostatic Potential [Internet]. [cited 2015 Feb 28]; [about 1 p]. Available from: http://www.cup.uni-muenchen.de/ch/compchem/pop/mep1.html.

27. http://www.elmhurst.edu/~chm/vchembook/211elecpotential.html (Reviewed: 28/02/2015).