IMAGES AND COMPUTATIONAL METHODS IN MOLECULAR MODELING EDUCATION

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Abstract

The way as Chemistry is boarded in the schools can contribute for the misconceptions, a time that the concepts are presented of form purely theoretician (and, therefore, tedious for the majority of the pupils), as something that must be memorize and that it is not apply the different aspects of the daily life. So, the aim of this work is to provide the understanding of the chemical world that underlies everything around us by introducing basic chemical concepts and their everyday applications. So that, some specific topics will be presented and they were selected according to their relevance and their ability to be presented in lessons on molecular modeling. This strategy is based on the use of images and free graphics programs employed in chemistry successfully, as the visual effects help the students to "see" abstract descriptions in a concrete form. According to the results obtained by using this methodology, we can conclude that the use of images and computational techniques help the presentation of scientific topics and motivate and facilitate the "chemistry communication".
Key words: *images, visualization, computational techniques, molecular modeling.*

Introduction

Motivation, to be successful, and science education is no exception, has to rely on a rich repertoire of experiences on which to build conceptual learning. These experiences pave the way to meaning making, which in turn supports learning. It also helps to entertain, create or re-create a sense of wonder, which becomes the true incentive for learning.

It is therefore important to think about educational systemic term, not limiting the student's experiences to what can possibly take place in the classroom. The role of alternative learning environments therefore becomes critical as a prelude, a complement a follow-up to the school-based learning process. Experiences come from interaction with a learning environments (Arroio, 2007).

Chemistry involves interpreting observable changes in matter at the concrete macroscopic or laboratory level in terms of imperceptible changes in structure and processes at the imaginary sub-micro or molecular level (Tasker & Dalton, 2006). Chemistry research today is increasingly on phenomena that are understood and communicated by means of visual representations. Visualization tools and high performance computing have changed the nature of chemistry research and have the promise to transform chemistry education. Visualization tools are now beginning to be used in a central way in the introductory chemistry classroom (Jones, 2001). But students must be able to

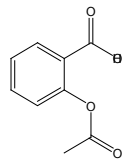
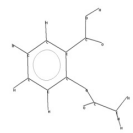
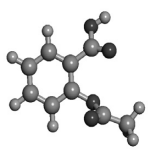
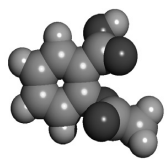
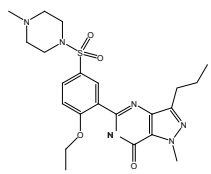
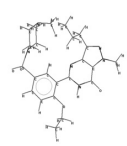
interpret the images to meaning making about that subjects. According to Wu and Shah (2004), three-dimensional (3D) visualization tools enhance student´s understanding of molecular structure.

Ferk and Vrtacnik (2003) emphasize the importance of the correct perception of the 3D molecular structure as the basic step preceding any further mental operations. According to their findings, undergraduate students preferred 3D computerized models or 3D pictures of molecules over other representations.

Computer hardware, scientific visualization, and computational methods of visualization, has enabled multiple conceptual and visual representations of atomic and molecular concepts. Computational research in the sciences makes very effective use of available computing resources in simulating the behavior of complex systems. Routine use of these simulations is possible because of the development of interactive (i.e., real-time, individually controlled) visualizations in three dimensions. The coupling of simulations with visualization presents scientists with a powerful description that matches the three-dimensional dynamic nature of their field. Students have many problems understanding dynamic three-dimensional processes. General chemistry textbooks show several kinds of representations (images) used in different contexts without correlation between these representations or the reason why one was chosen. Some students can switch contexts easily; but most do not integrate the knowledge or extract from them representations to ideas the experts see in them (Reif, 1987; Trunfio, 2003). In order to support students to develop their understanding of chemical subjects this work investigates some chemical representations of theoretical chemical concepts as a visualizing tool.

Molecular Representations

In order to illustrate different representations of a chemical substance, we chose two drugs widely used commercially: acetylsalicylic acid (aspirin) and sildenafil citrate (viagra). Figure 1 displays some molecular representations employed in molecular modeling studies.

Acetylsalicylic acid		
$C_9H_8O_4$		
(a)	(b)	(c)
		
(d)	(e)	(f)
Sildenafil citrate		
$C_{22}H_30N_6O_4S$		
(f)	(g)	(h)

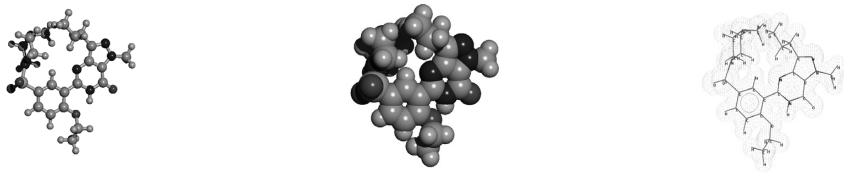


Figure 1. Molecular representations for acetylsalicylic acid and sildenafil citrate.

Figures 1 (a) and (f) are used to illustrate the atomic composition of each molecule; figures 1 (b) and (g) give information about the connection among the atoms inside the molecules in the plane; figures 1 (c) and (h) have the main advantage to show the molecular structure regarding to the localization of each atom in a 3D space; figures 1 (d) and (i) illustrate the same 3D atomic distribution shown in figures 1 (c) and (h), but the atoms and bonds are represented by using balls and sticks, respectively; figures 1 (e) and (j) are useful to demonstrate the volume of the whole molecule from the volume of each atom; figures 1 (f) and (k) also illustrate the molecular volume. From all representations presented by Figure 1 it is possible to say that the teaching of molecular modeling is easily facilitate employing these visualization tools, i.e. the learning process becomes more effective.

Concepts of HOMO and LUMO

In molecular modeling, the energies of the frontier orbitals are important properties in order to understand several chemical and pharmacological processes, for example, studies on the structure–activity relationship (SAR). We can say that the frontier energies are related to the electron-donating and electron-accepting character of a compound and, consequently, on the formation of a charge-transfer complex (CTC) (Honorio, 2003). In medicinal chemistry, several molecular descriptors are used for determining possible interactions between drugs and biological receptors and, consequently, the formation of CTC.

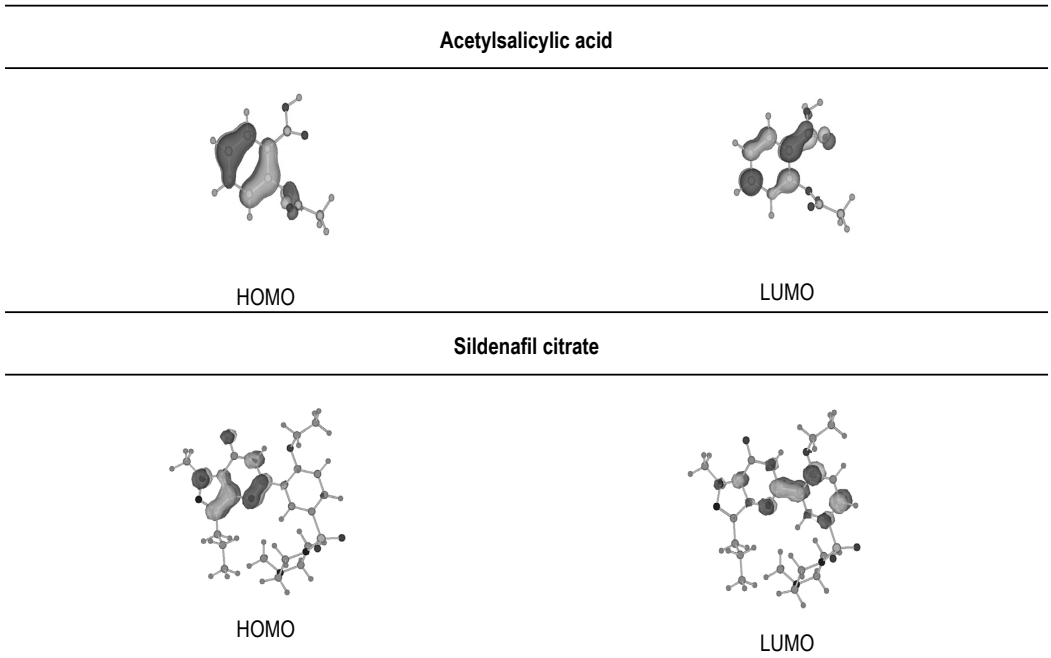


Figure 2. Atomic contribution HOMO and LUMO maps for acetylsalicylic acid and sildenafil citrate.

This procedure involves the transfer of an electron from an orbital localized on the donor to an orbital localized on the acceptor, so it may be expected that the donor will become positively charged and the acceptor negatively charged (Honorio, 2003). In general way, the energy of the highest occupied molecular orbital (E_{HOMO}) measures the electron-donating character of a compound, and the energy of the lowest unoccupied molecular orbital (E_{LUMO}) measures its electron-accepting character (Honorio, 2003). From these definitions, it is possible to note two facts: (a) the greater is the E_{HOMO}, the greater is the electron-donating capability; and (b) the smaller is the E_{LUMO}, the smaller is the resistance to accept electrons. A way to analyze the frontier orbitals is to obtain the atomic contribution maps, which give us important information about sites of reactions. Figure 2 illustrates the HOMO and LUMO maps for two much commercialized drugs (acetylsalicylic acid and sildenafil citrate), which were obtained from a single-point calculation by using the Density Functional Theory (DFT), with B3LYP functional and 6-31G basis set.

From Figure 2 we can notice that the HOMO and LUMO maps of acetylsalicylic acid differ in the contribution of the oxygen atoms, indicating the possible sites of oxidation (HOMO map) or reduction (LUMO map). The same behavior is observed for sildenafil citrate, as different regions contribute for HOMO and LUMO: the main contribution for LUMO is localized at the benzene ring, while the HOMO is mainly formed by the ring containing 5 atoms. The information obtained from HOMO and LUMO plots are important resources of chemical concepts and can be much explored in molecular modeling lessons.

Molecular Electrostatic Potential Maps

Another molecular property very useful to understand several chemical and biochemical processes is the molecular electrostatic potential map (MEPM), which is obtained through the calculation of a set of punctual atomic charges so that they represent the possible best quantum molecular electrostatic potential for a set of points defined around the molecule. In this case, we calculated the MEPM of the two compounds under study by using the DFT methodology (B3LYP and 6-31G basis) and Figure 3 shows the MEPMs obtained.

Figure 3. MEP maps obtained for acetylsalicylic acid and sildenafil citrate.

Analysing Figure 3 we can verify the regions with high electronic density (negatively charged region), as well as the regions with low charge density (positively charged regions), which could explain possible electrostatic interactions between the compounds studied and the respective biological target. The MEPM for the acetylsalicylic acid indicates two regions with high charge density (pink color in Figure 3), and the MEPM for the sildenafil citrate presents five regions with negative charge density. These negative charge regions presented in the MEPM of the two compounds studied could favor the formation of hydrogen bonds between these compounds and the aminoacid residues into the active site of the biological receptor. Therefore, from these images it is possible to discuss several concepts involved in medicinal chemistry and molecular modeling lessons.

PROBLEMS
OF EDUCATION
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Visualization of Protein Structures

Two approaches can be used in molecular modeling and medicinal chemistry lessons: ligand-based drug design (LBDD) and structure-based drug design (SBDD). In the first case (LBDD), only the structure of ligands is used for the molecular modeling. In the SBDD approach, the information about the biological receptor structure is also employed in all steps of the study. Considering our two molecules under investigation in this work (acetylsalicylic acid and sildenafil citrate), the first stage is to collect the information about the receptor structure of each molecule in the Protein Data Bank (PDB, www.rcsb.org). In our study, we found several structures for the biological targets of interest, and we decided to choose the structure with the most resolution. So, for the acetylsalicylic acid, its biological target is the cyclooxygenase-2 and the crystal structure chosen has PDB code 3PGH; for the sildenafil citrate, its biological receptor is phosphodiesterase 5A and the crystal structure chosen has PDB code 1TBF. Several representations (images) for the two macromolecular targets studied can be visualized in Figure 4 (all images were obtained by using Pymol program]).

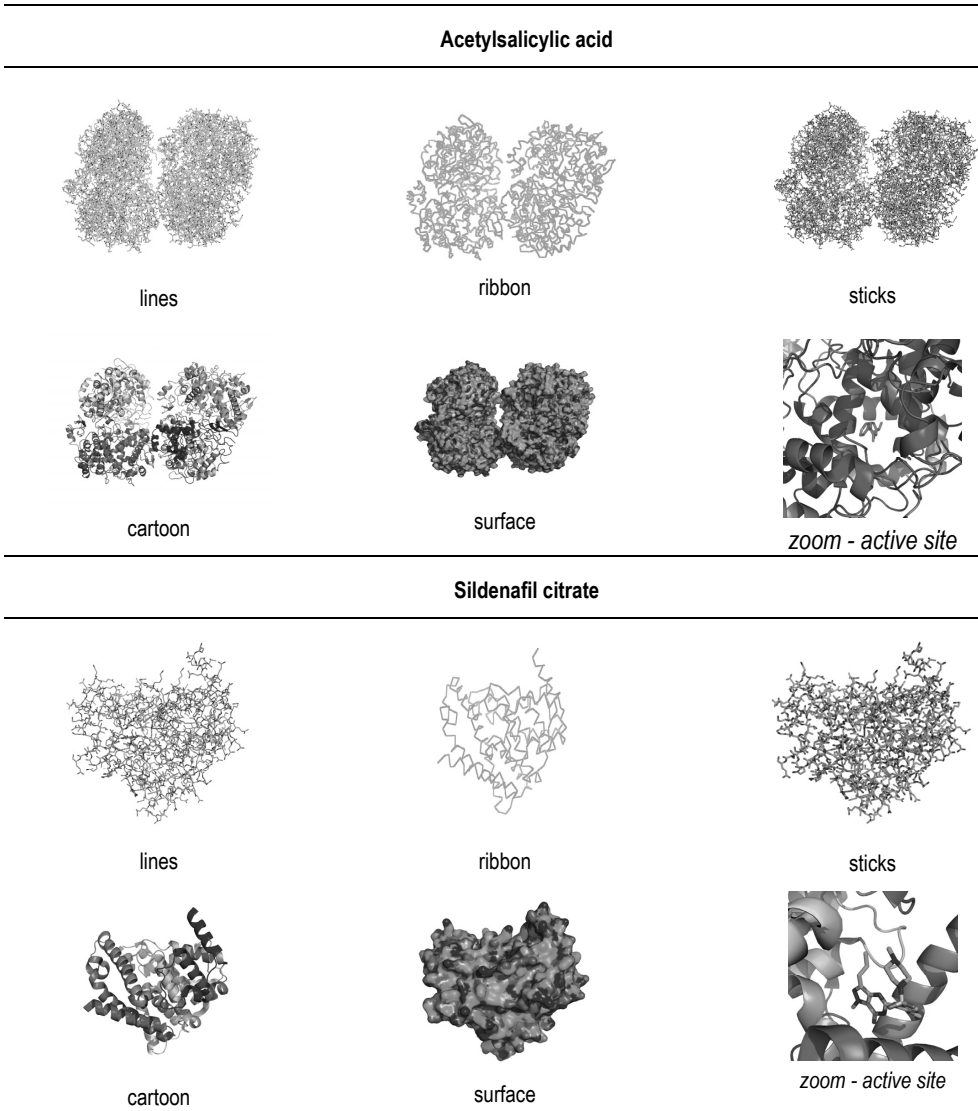

Figure 4. Some representations for the biological target of acetylsalicylic acid and sildenafil citrate.

Figure 4 present several representations of protein structures (lines, ribbon, sticks, cartoon, surface and interaction between a ligand and its biological receptor). These representations can be used according to the objectives of each lesson, i.e. initial concepts on bonds or patterns of secondary and tertiary structure, as well as information about volume and electrostatic properties. Another important topic that can be discussed is the interaction between the ligand and the main residues into the active site, as this subject involves fundamental chemical concepts, for example, intermolecular forces.

Implications

Many topics in chemistry require students to understand chemical structures in three dimensions and molecular visualization can be helpful for learning these dynamic and three-dimensional chemistry concepts. Visualization is not just imagining, but it can be used to convey complex, molecular interactions and dynamic processes that could be really difficult to teach in words. The aim is to understand the concepts underlying the visualization on the image. These advances in molecular modelling and visualization enable students to manipulate a variety of visual representations of abstract concepts, explore these concepts, and, therefore, bring the study of science closer to the doing of science. It is difficult for students to see the connection between the submicroscopic world of atoms, ions, and molecules, and the macroscopic properties of matter.

Spatial relationship in molecular visualizations could be really hard to understand, but with the aid of multiple representations understanding a molecular structure could be easier by comparing these differences. By the way, it is possible to work with the complexity involved in such process when students can understand each variety of representation and the interrelations among them.

According to this data, images and computer provide methods and techniques that help students to see the unseen and on this way it is also possible to make visible data and information that are too far from our sensitivity.

Computational methods are not just a tool for creating beautiful images in order to make a comfortable class. We argue that visualization by computer methods can be done in exploratory perspective as a support for visual thinking and as an interesting cultural tool to communicating chemistry.

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