Conformational Analysis of Contrast Media for X-Ray Diagnostic Radiology

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Thesis Title

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Aim of the study

The development of new contrast media is a long and an incremental process that requires years of research and experimentation. The problem of finding suitable candidate is complicated due to energy considerations and flexibility of the structure. Exploring conformational space enables further studies for investigation of energy relationships, inter-atomic forces inside the molecular system, property space (e.g. lipophilicity) and protein interaction.

The present work is devoted to study the validity and applicability of different computational methods and conformational search techniques for description and analysis of conformational space of the iodinated, non-ionic contrast agent, Iobitridol, in gas phase (in vacuo). It focuses primerly on the capabilities of computational techniques that improves our understanding of geometric issues involved in contrast media characterization. This research work is expected to help in improving the theoretical investigation of geometry dependent property space, i.e. evaluation of average behavior of structural dependent properties, for iodinated non-ionic contrast agents, considering Iobitridol as a model compound presenting this family of molecules.

In addition, this work was extended to study the geometrical implications of steric hindrance imposed by introduction of the iodine atom to the aromatic ring system and its connected side chains. It represents an example of usefulness of the conformational analysis technique, which may serve as a powerful aid in the development of better contrast agents.

Abstract

The conformational analysis of iodinated non-ionic contrast agent, Iobitridol, was carried out using theoretical calculations to explore its conformational space, and to study different aspects connected with application of different search techniques. Monte Carlo (MC), random search (RS) and molecular dynamics (MD) based conformational search techniques were used to extract a reasonable-size sample that adequately represents and has an average behavior of the entire conformational ensemble.

While MC is good for quick search for lowest energy conformer, RS is better in obtaining conformational sample that cover the whole conformational space and MD is the best for investigation of isomeric preferences inside the conformational ensemble at thermal equilibrium. Conformational analysis of the produced gas phase samples reveals that RS and MD methods could sufficiently present the 18 distinct isomeric classes that constitute the total conformational space of the Iobitridol.

RS samples of conformational space of Iobitridol are extensively studied, as it hypothetically cover the total conformational space. They are used to test the suitability of different methods (charge distribution methods, energy calculation methods) for Iobitridol molecular computations and internal structure forces (steric hindrance, resonance interaction), as well as dependances among the internal coordinates (dihedral angles correlations and coincidences).

The atomic partial charge distribution is found to greatly affect the energy calculation for the molecular mechanics based conformational energy distributions. Further energy minimization of conformational sample by the quantum molecular orbital methods is crucial to obtain charge independent as well as energy balanced conformational sample.

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Chapter 1

Introduction and Literature Survey

1-1 Introduction

"*Medical Radiology"* is the branch or the specialized field of medicine that deals with the study and application of radiation technology for diagnostic and therapeutic uses. Whereas, "*Medical Radiography"* is the use of ionizing electromagnetic radiation, such as X-rays, for imaging of human body.

Usually, diagnostic radiology departments of hospitals handle all forms of imaging. It includes the following imaging modalities :

- ***Projection Radiography:*** It is radiographic imaging where a "still image" is made of a bone or organ and shown on film or on a computer screen.
- ***Fluoroscopy*** and ***Angiography:*** They are special applications of X-ray imaging, which utilize fluorescent screens and image intensifier tubes to view movement (of tissue or a contrast agent), or to guide a medical intervention.
- ***Computed Tomography (CT) imaging:*** It uses X-rays in conjunction with computing algorithms to create images of body organs in a series of cross sections or planes.
- ***Medical Ultrasonography:*** It uses ultrasound to visualize soft tissue structures in the body in real time. Ultrasound is limited by its inability to image through air (lungs, bowel loops) or bone.
- ***Magnetic Resonance Imaging (MRI):*** It uses principles of Nuclear Magnetic Resonance. It relies on the fact that different materials resonate at different magnetic field strengths. An advantage of MRI is its ability to produce images in axial, coronal, sagittal and multiple oblique planes with equal ease. MRI scans give the best soft tissue contrast of all the imaging modalities.
- ***Nuclear Medicine (NM) Imaging*** (also called ***Radionuclide Scanning*****):** It involves the administration, into the patient, of radio-labeled pharmaceuticals which has high affinity for certain body tissues. It may use simple radiation detection system, 'Gamma Camera', or make use of advanced computer-based technology; 'Single-Photon Emission Computed Tomography (SPECT)' and 'Positron Emission Tomography (PET)'.

Although Ultrasound and MRI are not technically radiographic techniques (as these disciplines do not use ionizing radiation), however, they were appended to the list of modalities used in diagnostic radiology because they are also medical imaging techniques [Bushburg et al., 2002; Novelline, 1997].

Nowadays, X-rays are a relatively safe method of investigation and the radiation exposure is low. Modern x-ray techniques (both analog film screen systems and digital systems) have significantly more spatial resolution and contrast detail, very tightly controlled x-ray beams with significant filtration and x-ray dose control methods. Thus, scatter or stray radiation is minimized and those parts of a patient's body not being imaged receive minimal exposure. These relatively new radiological techniques provide much safer means of examining internal body structures. However, in pregnant patients, the benefits of the X-ray investigation should be balanced with the potential hazards to the unborn fetus. Although the risk of carcinogenesis above the baseline cancer rate associated with X-ray diagnostic procedures is low and this exact relationship is controversial [Cohen, 2002], X-rays are listed as a carcinogen by the U.S. Government Since 2005 ["Report on Carcinogens", Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program (2005)].

A special exception is the fluoroscopic procedures which pose a potential health risk to the patient. Radiation doses to the patient depend on the size of the patient as well as length of the procedure, with typical skin dose rates quoted as 20–50 mGy/min. Exposure times vary depending on the procedure being performed. While physicians try to use low dose rates during fluoroscopic procedures, the length of a typical procedure often results in a relatively high absorbed dose to the patient [Bushburg et al., 2002; Novelline, 1997].

1-2 Contrast Media

In radiography, contrast is the range between black and white on the final radiograph. High contrast, or narrow latitude, means there is little gray on the radiograph, and there are fewer steps between black and white. Low contrast, or wide latitude, means there is much gray on the radiograph and there are many steps between black and white.

X-ray contrast may be measured by the relative difference in X-ray intensity that exists after a beam pass through a region of interest. The differences in intensity are due to variety of factors in the internal structure that are directly related to X-ray attenuation. These factors include differences in tissue composition, density and path-length. Contrast has many definitions. For a certain position of intensity I, against a background I_o, the X-ray contrast may be defined as the natural logarithm of the intensity ratio [Pettersson, 1998]:

$$\text{Contrast} = \ln (I / I_o) \qquad (1.1)$$

or as the ratio of the intensity difference to the background intensity :

$$\text{Contrast} = (I - I_o) / I_o \qquad (1.2)$$

or as the intensity difference divided by the average intensity :

$$\text{Contrast} = (I - I_o) / \tfrac{1}{2} (I + I_o) \qquad (1.3)$$

A medical contrast medium (or contrast agent) is an exogenous substance used to enhance the contrast of structures or fluids within the body in medical imaging, which allows delineation of internal structures.

Several types of contrast media are in use in medical imaging and they can roughly be classified based on the imaging modalities where they are used :

- ***Radiocontrast Agents:*** Radiography contrast agents are introduced to a certain body organ (tissue) to alter its absorptivity (attenuation ability) to X-rays, so the tissue can be differentiated from the surrounding tissues. Iodine and barium are the most common types of contrast media for enhancing x-ray based imaging methods.

- ***MRI Contrast Agents:*** These are paramagnetic compounds that work by altering the magnetic properties of nearby hydrogen nuclei. This would include gadolinium. In its 3+ oxidation state, the metal has 7 unpaired f-shell electrons, which cause water around the contrast agent to relax quickly, thus enhancing the quality of the MRI scan.
- ***Contrast-Enhanced Ultrasound:*** Microbubbles contrast agents are used to aid the sonography, specifically echocardiograms, for the detection of a cardiac shunt. The bubbles (micro-bubbles filled with gases) are composed of tiny amounts of nitrogen or perfluorocarbons strengthened and supported by a protein, lipid, or polymer shell. The drop in density on the interface between the gas in the bubble and the surrounding liquid strongly scatters and reflects the ultrasound back to the probe. This process of backscattering gives the liquid with these bubbles a high signal, which can be seen in the resulting image [Bushburg et al., 2002; Novelline, 1997].

1-3 Radiographic Contrast Media

Radiocontrast agent is a type of medical contrast media used to improve the visibility of internal body structures in X-ray based imaging techniques such as Radiography (commonly known as X-ray imaging), Fluoroscopy, Angiography, or Computed tomography.

Contrast media may be positive radiographic contrast (***Radiopaque***) agents or negative radiographic contrast (***Radiolucent***) agents. Radiopaque agents have higher atomic number (e.g. barium Z=56 and iodine Z=53) with regard to the tissues (e.g. equivalent atomic number of Fat = 6.46, Water = 7.51, Muscle = 7.64, and Bone = 12.31). Positive contrast agents appear opaque due to their higher absorption of X-rays or other electromagnetic waves and hence the hollow organ or vessel can be more readily seen on the radiographic film. Radiolucent agents attenuate the X-ray radiation less than the surrounding tissues. They may be gas, crystals, air or carbon dioxide (CO_2). Radiolucent

agents are used mainly in the bladder (pneumocystogram) but can also be used in the gastro-intestinal tract (pneumogastrogram, pneumocolon) and in joints (negative arthrogram).

Negative contrast studies show the location, size and wall thickness of the organ. They show marked wall thickening and large luminal filling defects such as masses or foreign bodies, but they give little information about the mucosal surface. Also, smaller filling defects, such as bladder calculi, may be overexposed and small tears in the wall may be missed. Positive contrast studies give little more information than negative contrast studies, and are the best way of detecting a small defect in the wall of the organ, as minor contrast leakage is easily seen.

Modern x-ray imaging procedures (Contrast Enhanced Radiography) based mainly on iodine and barium, i.e. radiocontrast agents are typically iodine or barium radiopaque compounds. An older type of contrast agents, Thorotrast (first introduced in 1932), was based on thorium dioxide, but this was abandoned since it turned out to be toxic radioactive carcinogenic substance.

Barium sulfate is mainly used in the imaging of the digestive system. It is an excellent contrast, relatively cheap, and successfully used for gastrointestinal studies (from esophagus to colon). The substance exists as a water insoluble white powder that is made into a slurry with water and administered directly into the gastrointestinal tract. As the barium sulfate doesn't dissolve, this type of contrast agent is an opaque white mixture. It is only used in the digestive tract; it is usually swallowed or administered as an enema. After the examination, it leaves the body with the feces.

Generally, radiocontrast agents may be administrated through; oral route, rectal route, intravenous route, intra-arterial route, or intra-spinal route. The basic characteristics desirable for a contrast medium are: (1) Satisfactory radiopacity (related to atomic number, material density, and concentration), (2) Stability, (3) Pharmacological inertness, and (4) Minimum sensitizing properties [Bushburg et al., 2002; Dendy and Heaton, 1999; Novelline, 1997].