Methods of Computational Chemistry

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Molecular modeling method

The three dimensional shape of both ligand and target site may be determined by X-ray crystallography or computational method.

The most common computational methods are based on either molecular or quantum mechanics.

Both this approaches produce equation for total energy of the structure.

Computational method

- There are two main types method depending on the starting point theory.

- Classical method :-

  Are those method use Newton mechanics to model molecular system.

- Quantum chemistry method:-

  Which makes use of Quantum mechanics to model the molecular system. This method used different type of approximation to solve Schrödinger's Equation.

- **Classical Methods**

  1. Molecular Mechanics
  2. Molecular Dynamics.

- **Quantum Mechanics Methods**

  1. Semi empirical Methods.
  2. *Ab initio* Methods.
  3. Density functional Theory.

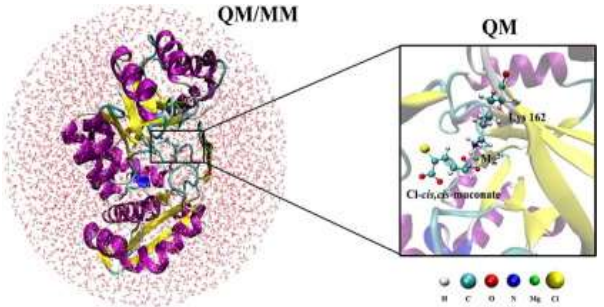
What is Computational Chemistry?

Application of computational methods and algorithms in chemistry

- Quantum Mechanical
  i.e., via *Schrödinger* Equation
  also called *Quantum Chemistry*
- Molecular Mechanical
  i.e., via *Newton*'s law F=ma
  also *Molecular Dynamics*
- Empirical/Statistical
  e.g., *QSAR*, etc., widely used in clinical and medicinal chemistry

$$-i\hbar\frac{\partial}{\partial t}\Psi = \hat{H}\Psi$$

Focus Today



Differences Between Molecular Mechanics & Quantum Mechanics

Molecular Mechanics Vs Quantum Mechanics

A. Quantum mechanical methods

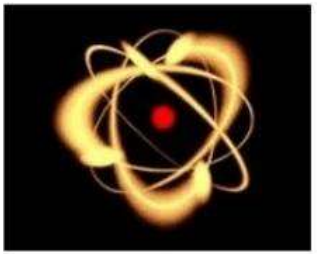
- **deal with electrons in a system, and**
- **the calculations are very MUCH time consuming.**

B. Molecular mechanics (force-field methods) on the other hand

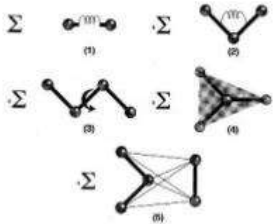
- **ignore the electronic motions and**
- **calculates the energy of the system as a function of the nuclear position only.**
- **the calculations are very LESS time consuming.**

However, molecular mechanics cannot provide answers that rely on the electronic distribution of a molecule.

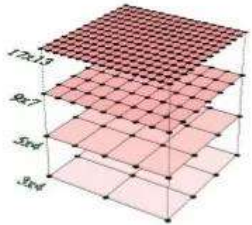
Computational Chemistry



Quantum Mechanics (QM)



Molecular Mechanics (MM)



Hybrid QM / MM

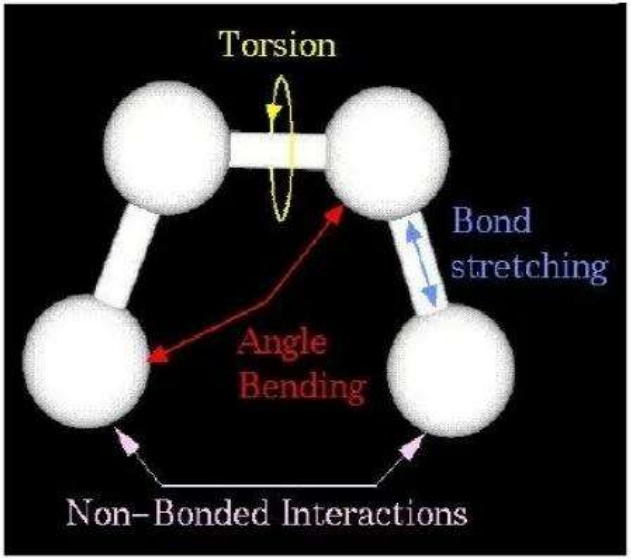
Semi-empirical (SE)

Molecular Mechanics

- Molecular mechanics programs use equations based on classical physics to calculate force fields.
- Atoms treated as spheres, bonds as springs and electron are ignored.
- It assume that the total potential energy (E_{total}) of molecule is given by sum of all the energies of attractive and repulsive forces between atom in structure.

The molecular mechanics equation

$$E = E_B + E_A + E_D + E_{NB}$$



E_B = The energy involved in the deformation bond either by stretching or compression.

E_A = The energy involved in the angle bending .

E_D = The torsional angle energy.

E_{NB} = The energy involved in the interaction between atoms that are not directly bonded.

Force Field

- Force field refers to calculation of the interaction and energies between different atoms between bond stretching, angle bending, torsional angle and non-bonded interaction.
- Force field ignores the electronic distribution while Quantum mechanics considers electronic distribution of molecule.

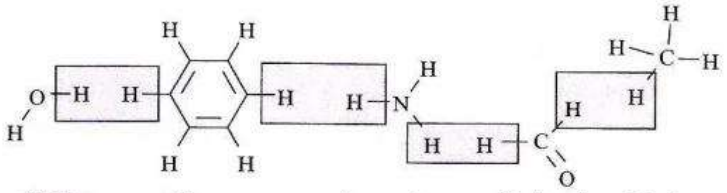
Classical empirical force field

1) AMBER(Assisted Model Building and energy Refinement)
2) CHRAM (Chemistry at Harvard Macromoleculer Mechanics)
3) CVFF(Consistent Valence Force Field)

Molecular Model Using Molecular Mechanics

- The molecular models are created by either using an existing commercial force field computer program or assembling a model from structural fragments held in the database of molecular modeling program.

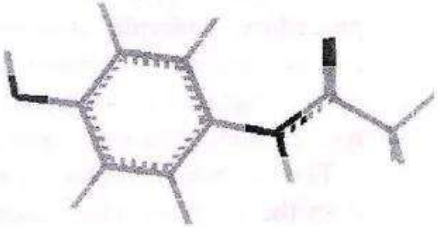
Step 1: the selection of the structure fragments from the database of the INSIGHT II program. The molecule with the relevant functional group and/or structure is selected.

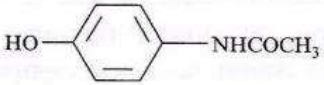


The INSIGHT II models of these structures.

Step 2: The fragments are linked together. Fragments are joined to each other by removing hydrogen atoms (See shaded boxes in step 1) at the points at which the fragments are to be linked. The bonding state of each atom is checked and, if necessary adjusted.

Step 3: the force field of the model is minimized to give the final structure.





An outline of the steps involved using INSIGHT II to produce a stick model of the structure of paracetamol

Molecular Dynamics

- Molecular dynamics is a molecular mechanics program designed to mimic the movement of atoms within a molecule.
- Molecular dynamics can be carried out o a molecule to generate different conformation which on energy minimization, give a range of stable conformation. Alternatively bonds can be rotated in a stepwise process to generate different conformation.
- Molecular dynamics can also be used to find minimum energy structures and conformational analysis.

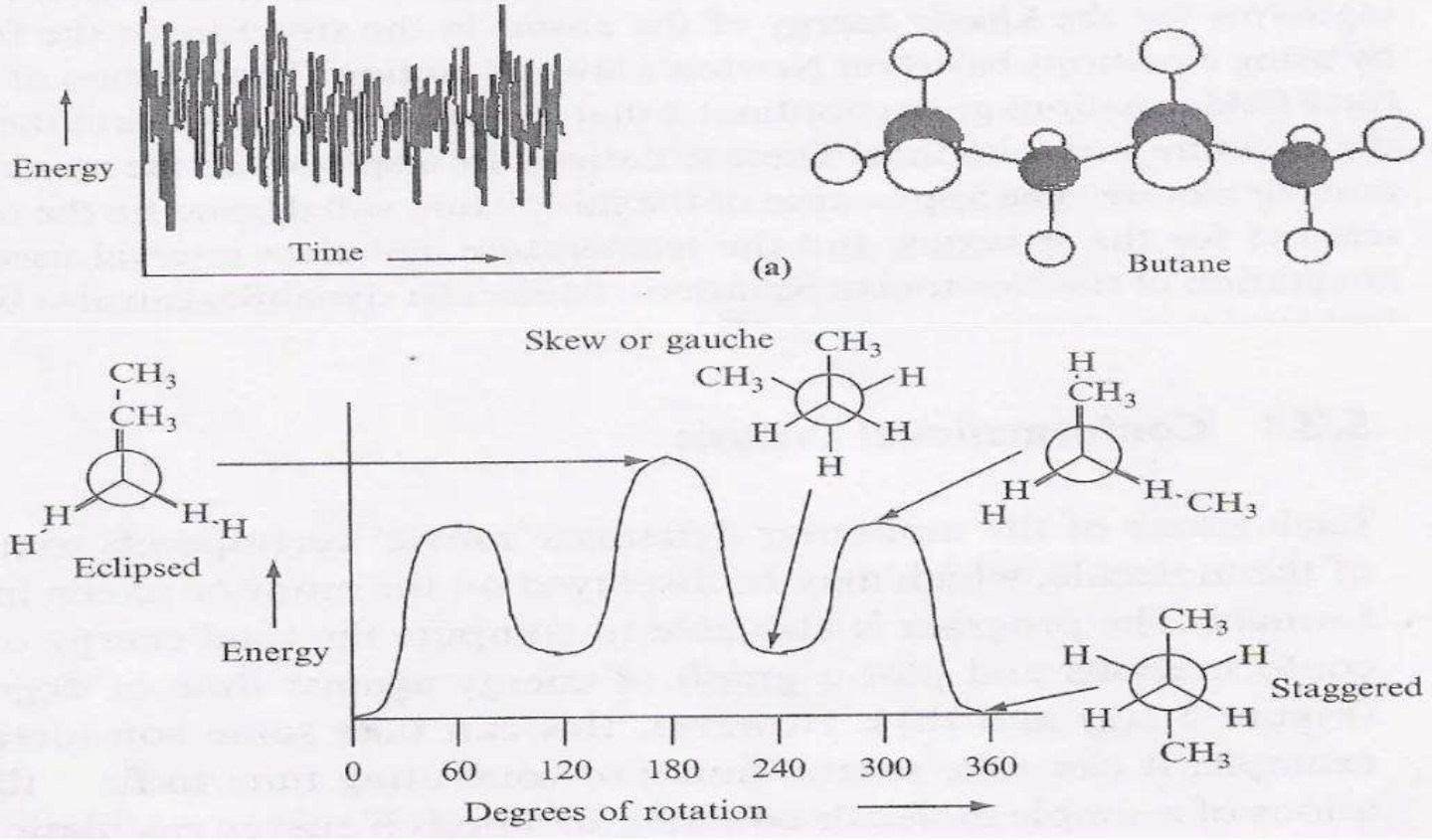


Fig-: Plot of change in the energy with the rotation about C_2-C_3 bond In butane

Quantum mechanics

- Quantum mechanics is based on arrangement of electrons of molecule and interaction of those electron with electron and nuclei of other molecule.
- It based on the realization that electron and all material exhibit wavelike properties.
- The Quantum mechanics based on finding solution to Schrödinger wave equation.

Schrödinger's Equation

- The Schrödinger equation is the basis of quantum mechanics and gives a complete description of the electronic structure of a molecule. If the equation could be fully solved all information of a molecule could be determined.

$$H\psi = E\psi$$

Where

H=Hamiltonian operator

Ψ =wave fuction

E =Energy system

To solve schrodinger equation was found to difficult. Hydrogen-total energy of hydrogen (E) can be described as the sum of kinetic energy and potential energy of its two component i.e. proton and electron.

Schrödinger equation for this relationship can written,

$$H\psi=(k+v)=E\psi$$

Where as
K = kinetic energy
V = potential energy

- Describes both the wave and particle behavior of electrons.
  - The wave function is described by ψ while the particle behavior is represented by E.
  - In systems with more than one electron, the wave function is dependent on the position of the atoms; this makes it important to have an accurate geometric description of a system.

Quantum Mechanics Method

1. *Ab inito* method
2. Semiemperical method
3. Density functional theory

Ab Initio method

- *Ab initio* translated from Latin means from "first principles".
- This refers to the fact that no experimental data is used and computations are based on quantum mechanics.
- It derived directly from theoretical principle.

Different Levels of *Ab Initio* Calculations

1. Hartree-Fock (HF)

2. Density Functional Theory (DFT)

Hartree-Fock (HF)

- The simplest *ab initio* calculation.
- It based on Central field approximation.
- The major disadvantage of HF calculations is that electron correlation is not taken into consideration.

Density Functional Theory

- Considered an *ab initio* method, but different from other *ab initio* methods because the wave function is not used to describe a molecule.
- Density functional theory in which total energy is expressed in term of total electron density is used.
- DFT methods take less computational time than HF calculations and are considered more accurate.

Semi Empirical Method

- Semi-empirical quantum methods, represents a middle road between the mostly qualitative results available from molecular mechanics and the high computationally demanding quantitative results from *ab initio* methods.
- Semi empirical methods use experimental data to parameterize equations.
- Like the *ab initio* methods, a Hamiltonian and wave function are used.
- Less accurate than *ab initio* methods but also much faster.
- Capable of calculating transition states and excited states.

Choice of Method

The method of calculation based on what calculation needs to done and size of molecule.

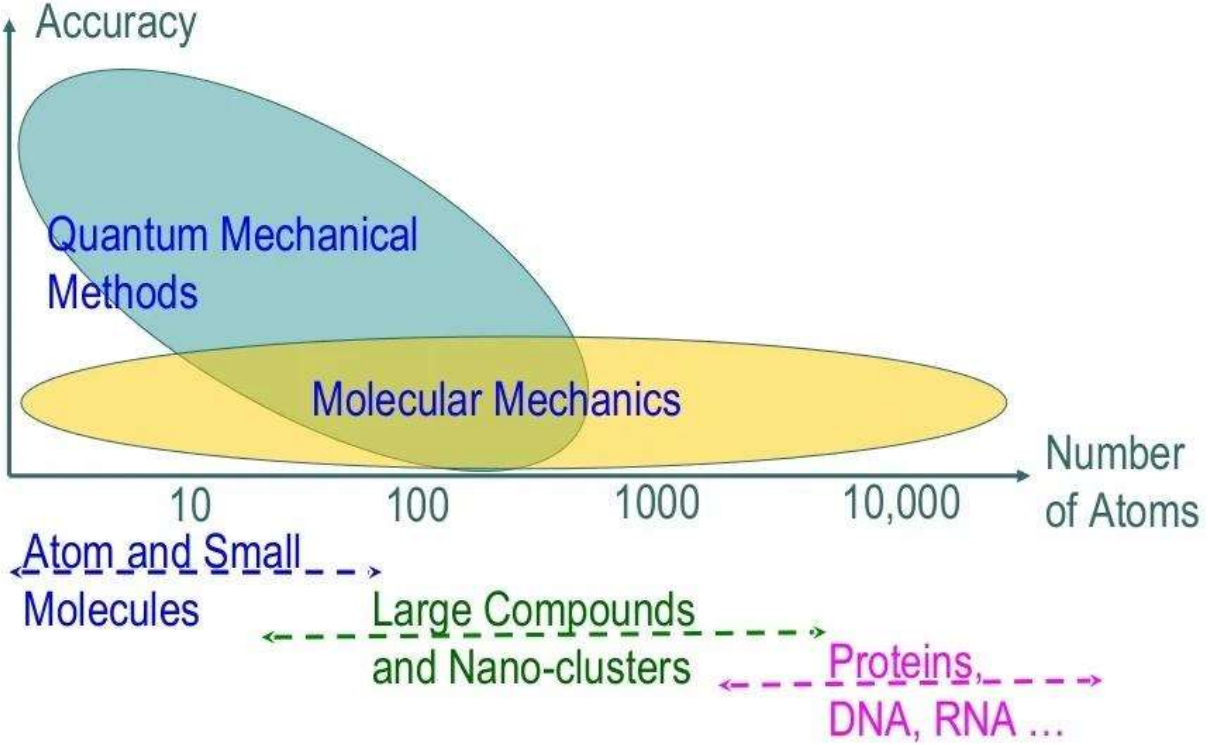
Molecular mechanics useful for

- Energy minimization
- Identifying stable conformation
- Energy calculation for specific conformations
- Studying molecular motion
- Studying different conformation.

Quantum mechanics method are suitable for calculating,

- Molecular orbital energies
- Heat formation for specific conformation
- Dipole moment
- Bond dissociation energy
- Transition-state geometries and energies

Computational Cost vs. Accuracy

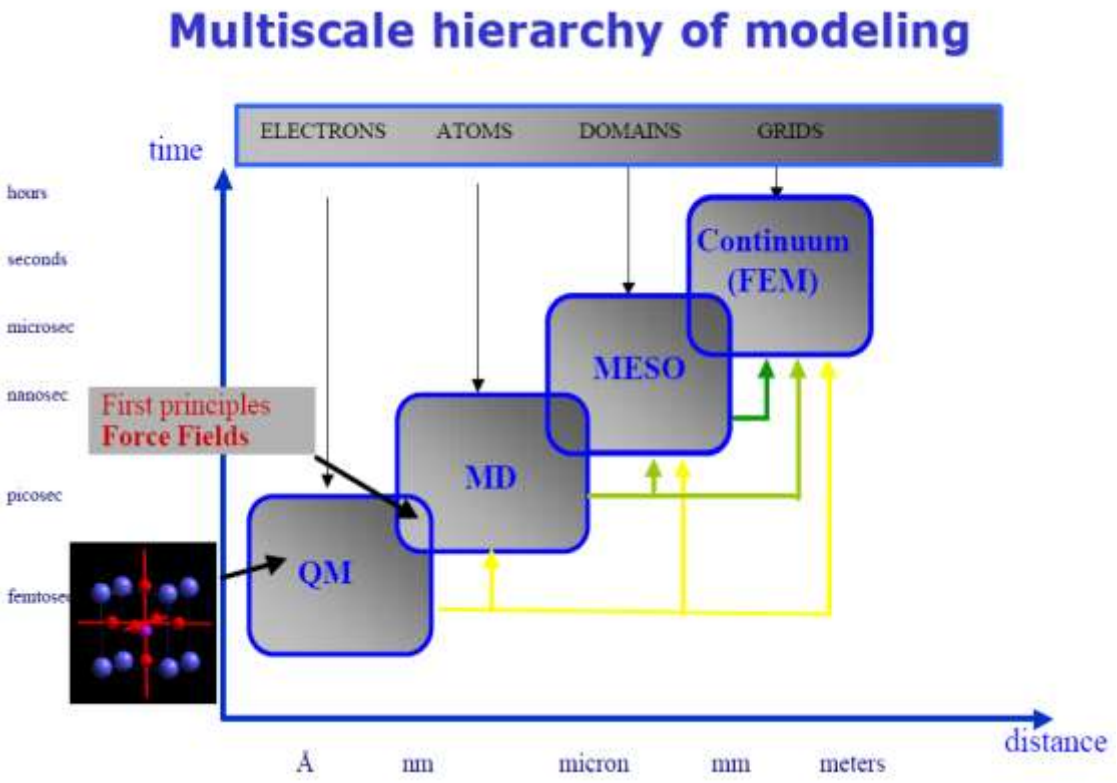


Quantum Mechanics vs. Molecular Mechanics

Quantum Mechanics	Molecular Mechanics
1. Correctly describes the Bond- breaking and Bond-forming	1. Does not properly describe the Bond-breaking and Bond-forming
2. Application limited to Hundreds of Atoms	2. Can treat more than 10,000 Atoms

Quantum mechanics	Molecular mechanics
1) More expensive	1) Less expensive
1) More time	2) Less time
1) More computing power	3) Less computing power
4) Used for small molecule	4) Used for large molecule
5) It can calculate electronic properties like electron density	5) It cannot calculate electronic properties like electron density
6) Application limited to hundreds of atom	6) Applicable to more than ten thousands of atoms

Multiscale Hierarchy of Modeling



How Big Systems Can We Deal with?

Assuming typical computing setup (number of CPUs, memory, disk space, etc.)

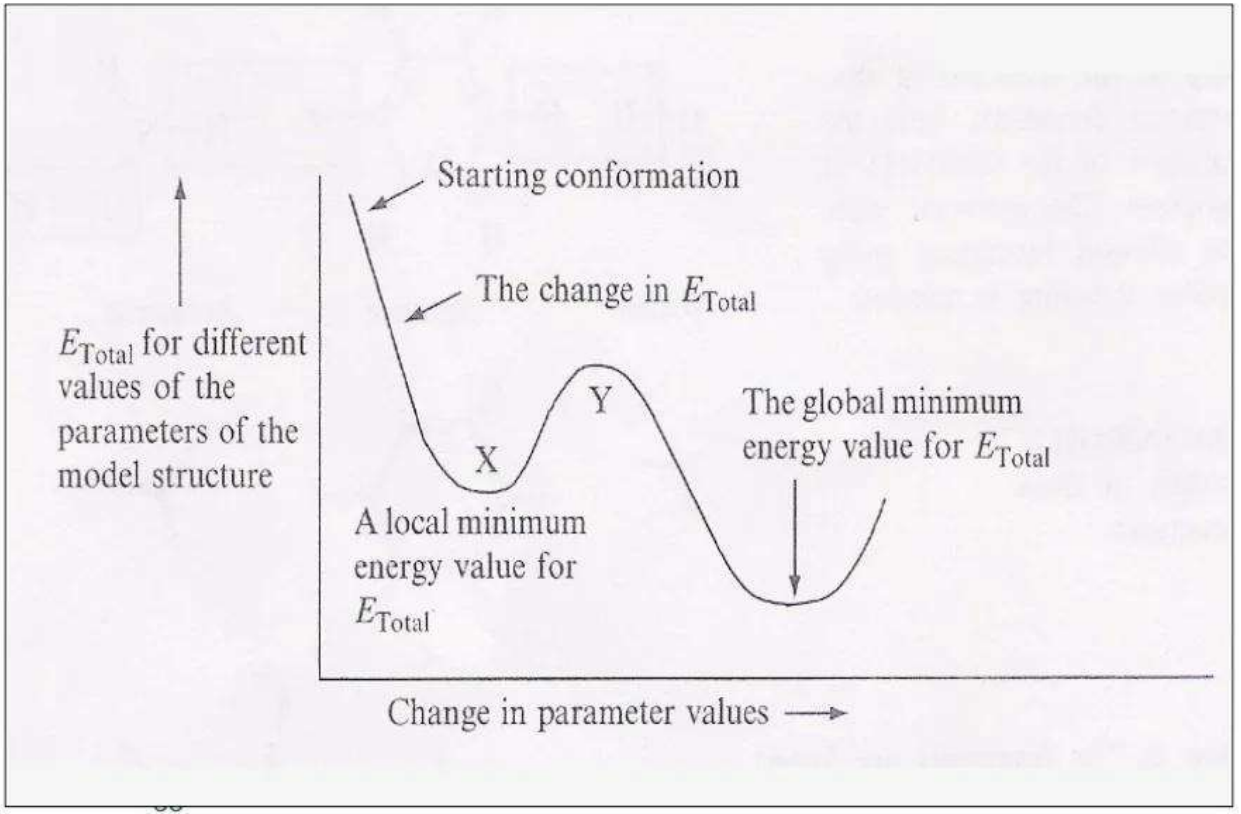
- Ab initio method: *~100 atoms*
- DFT method: *~1000 atoms*
- Semi-empirical method: *~10,000 atoms*
- MM/MD: *~100,000 atoms*

Energy minimization

- Energy minimization produces the nearest stable conformation to the structure presented and not necessarily the global conformation.

- Energy minimization involved alteration of bond length, bond angle, torsion angle and non-bonded interaction .

Energy minimization



Moleculer mechanics energy minimization

- Molecular mechanics is an approach of energy minimization that find stable, low energy conformation by changing the geometry of a structure.

Type of algorithms

1)Steepest Descent procedure

2)Conjugate gradient procedure

3)Newton –Raphson procedure

Selection of energy minimization algorithms

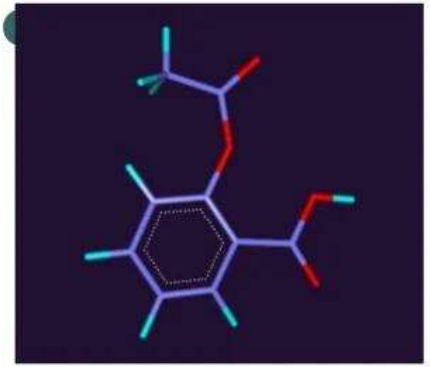
- The selection of energy minimization algorithms depends on size of system and current state of optimization.
- When molecule having larger than 200 atoms then conjugate gradient procedure.
- When molecule having less than 200 atoms then newton-raphson procedure.
- When molecule having larger than 10Kcal/mol/A then Steepest Descent.

Computer graphics

In Moleculer modeling, data produced are converted as visual image on a computer

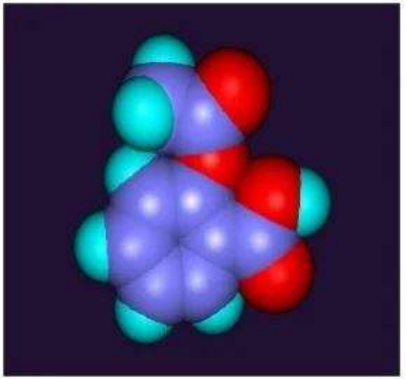
Images displayed as,

- Space fill model
- Ball and stick model
- CPK model
- Mesh model
- Ribbon model

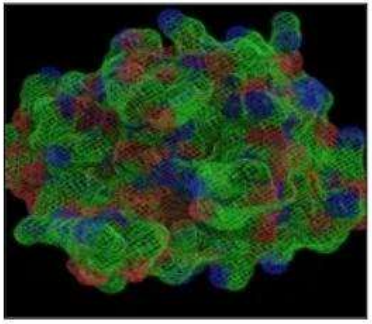


Stick model

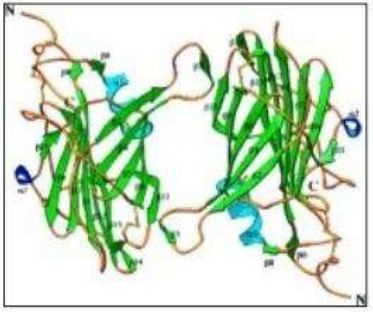
Ball and stick model



CPK model



Mesh representation of Aspirin



Ribbon representation of dihydrofolate reductase