# Computational Chemistry

Chapter 1

Knowledge is experiment's daughter
Leonardo da Vinci,

- You can **calculate** **molecular geometries**, **rates** and **equilibria**, **spectra**, and **other physical properties**.
- The **tools of computational chemistry** are **molecular mechanics**, **ab initio**, **semiempirical** and **density functional methods**, and **molecular dynamics**.
- **It does not replace experiment, which remains the final arbiter of truth about Nature**.

# What You Can Do with Computational Chemistry

- Computational chemistry (also called molecular modelling; the two terms mean about the same thing) is **a set of techniques for investigating chemical problems on a computer**.
- Questions commonly investigated computationally are:
- Molecular geometry: the shapes of mol. (BL, BA and DA).
- Es of molecules and TSs → which isomer is favored at eq. and how fast a reaction should go.
- Chemical reactivity: nucleophilic and electrophilic sites → enables us to predict where various kinds of reagents will attack a molecule.
- IR, UV and NMR spectra can be calculated.
- The interaction of a substrate with an enzyme.
- The physical properties of substances: depend on the properties of individual molecules and their interactions in the bulk material.

# The Tools of Computational Chemistry

**The main tools available belong to five broad classes:**

**(1) Molecular mechanics:**

- is based on a model of a molecule as a collection of balls (atoms) held together by springs (bonds).
- spring lengths and the angles between them → how much energy it takes to stretch and bend the springs → energy of a given collection of balls and springs (molecule)
- changing the geometry → the lowest energy → geometry optimization
- Molecular mechanics is fast: a fairly large molecule like a steroid (e.g. cholesterol, C27H46O) can be optimized in seconds on a good personal computer.

## (2) Ab Initio calculations

- ab initio, Latin: "from the start", i.e. from first principles"
- are based on the Schrodinger equation.
- The ab initio method solves the Schrodinger equation for a molecule and gives us an energy and wavefunction.
- The wavefunction → electron distribution (and, in theory at least, anything else about the molecule).
- The Schrodinger equation cannot be solved exactly for any molecule with more than one (!) electron.
- Thus approximations are used; the less serious these are, the "higher" the level of the ab initio calculation is said to be.
- Regardless of its level, it is based only on basic physical theory (quantum mechanics) and is in this sense "from first principles".
- They are relatively slow.

## (3) Semiempirical calculations

- are, like ab initio, based on the Schrodinger equation.
- However, more approximations are made in solving it (very complicated integrals are not actually evaluated in semiempirical calculations: a kind of library of integrals that was compiled by finding the best fit of some calculated entity like geometry or energy (heat of formation) to the experimental values, which is called parametrization.
- It is the mixing of theory and experiment that makes the method "semiempirical": it is based on the Schrdodinger equation, but parameterized with experimental values (empirical means experimental).
- They are slower than molecular mechanics but much faster than ab initio calculations. they take roughly 100 times as long as MM, and ab initio calculations take roughly 100–1000 times as long as them.

## (4) Density functional calculations (DFT calculations, density functional theory)

- are, like ab initio and semiempirical calculations, based on the Schrodinger equation
- However, unlike those, DFT does not calculate a conventional wavefunction, but rather derives the electron distribution (electron density function) directly.
- A functional is a mathematical entity related to a function.
- Density functional calculations are usually faster than ab initio, but slower than semiempirical.
- DFT is relatively new (serious DFT calculations goes back to the 1980s, while the ab initio and semiempirical approaches was being done in the 1960s).

## (5) Molecular dynamics (MD) calculations

- apply the laws of motion to molecules.
- Thus one can simulate the motion of an enzyme as it changes shape on binding to a substrate
- or the motion of a swarm of water molecules around a molecule of solute;
- quantum mechanical MD also allows actual chemical reactions to be simulated.

## Putting It All Together

- Very large biological molecules are studied mainly with molecular mechanics, because others would take too long.
- Novel molecules, with unusual structures, are best investigated with ab initio or possibly DFT calculations, since the parameterization in MM or SE methods makes them unreliable for molecules that are very different from those used in the parameterization.
- the structure of large molecules like proteins or DNA → MD. Their motions can be studied with MD.
- Key portions of a large molecule, like the active site of an enzyme, can be studied with semiempirical or even ab initio methods.
- Moderately large molecules like steroids → SE or ab initio calculations.
- MM does not give information on electron distribution, so chemical questions connected with nucleophilic or electrophilic behaviour, say, cannot be addressed by MM alone.

- The energies of molecules can be calculated by MM, SE, ab initio or DFT.
- Reactivity, which depends largely on electron distribution, must usually be studied with a QM method (SE, ab initio or DFT).
- Spectra are most reliably calculated by ab initio or DFT methods, but useful results can be obtained with SE methods, and some MM programs will calculate fairly good IR spectra.
- Docking a molecule into the active site of an enzyme to see how it fits is an extremely important application of computational chemistry (as a guide to designing better drugs)
- This work is usually done with MM, because of the large molecules involved,
- although selected portions of the biomolecules can be studied by one of the quantum mechanical methods.

- Computational chemistry is valuable in studying the properties of materials,
- Computational chemistry is fairly cheap,
- it is fast compared to experiment, and it is environmentally safe (!!! For consumption of energy and the disposal of obsolescent machines).
- It does not replace experiment (to make something – new drugs, new materials – one has to go into the lab).
- However, computation has become so reliable in some respects that, more and more, scientists in general are employing it before embarking on an experimental project,

# Summary

- Calculation of molecular geometries, reactivities, spectra, and other properties.
- MM: based on a ball-and-springs model of molecules
- Ab initio methods: based on approximate solutions of Schrodinger eq.
- SeEm methods – based on approximate solutions of the Schrodinger equation with appeal to fitting to experiment (using parameterization)
- DFT methods – based on approximate solutions of Schrodinger eq., bypassing the WF that is central in ab initio and seEm methods
- MM methods study molecules in motion.
- Ab initio and the faster DFT are used for molecules that are not too big.
- SeEm methods, which are much faster than ab initio or even DFT, can be applied to fairly large molecules
- MM will calculate geometries and energies of very large molecules such as proteins and nucleic acids;
- MM does not give information on electronic properties.

# Questions

- 1. What does the term computational chemistry mean?
- 2. What kinds of questions can computational chemistry answer?
- 3. Name the main tools available to the computational chemist. Outline (a few sentences for each) the characteristics of each.
- 4. Which is the fastest computational chemistry method (tool), and which is the slowest?
- 5. Why is computational chemistry useful in industry?
- 6. Basically, what does the Schrdodinger equation describe, from the chemist's viewpoint?
- 7. What is the limit to the kind of molecule for which we can get an exact solution to the Schr€odinger equation?
- 8. What is parameterization?
- 9. What advantages does computational chemistry have over "wet chemistry"?
- 10. Why can't computational chemistry replace "wet chemistry"?