Computational Chemistry (F14CCH)
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Room A49

Module Goals
- Introduce some current methods in computational chemistry
- Hands-on experience with various computational chemistry software packages
- Some background on the theoretical methods
- Some understanding of the capabilities, limitations and reliability of various computational chemistry methods

Some useful texts
- Computational Chemistry (Oxford Chemistry Primer) G. H. Grant and W. G. Richards (Oxford University Press)
- Molecular Modeling – Principles and Applications, A. R. Leach (Addison Wesley Longman)
- Introduction to Computational Chemistry, F. Jensen (Wiley)
- Essentials of Computational Chemistry – Theories and Models, C. J. Cramer (Wiley)
- Computational Chemistry – A Practical Guide for Applying Techniques to Real World Problems, David Young (Wiley)
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<th>Week</th>
<th>Lectures</th>
<th>Labs</th>
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<td>Mon 12pm-1pm</td>
<td>Tue 11am-1pm</td>
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<td>Oct 3rd</td>
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Thereafter, weekly optional open-door Office Hours/Tutorial: Monday 12-1pm

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**What is Computational Chemistry?**

- *Ab initio* quantum chemistry
  - HF, DFT, MP2, CCSD(T)
- Semi-empirical
- Classical/force field based methods
  - Molecular Dynamics simulations
- Docking
- Cheminformatics
- Bioinformatics
What can Comp Chem tell us about?

- Molecular structure
  - Bond length < 0.1Å, bond/torsion angle < 1°
- Spectroscopy
  - UV, IR, NMR, ...
- Energetics
  - cis vs trans
- Thermodynamics
  - Binding, reaction enthalpy < 5 kcal/mol
- Dynamics
Richard Wheatley

Non-covalent bonds
Molecular Simulations

% of bond energy

0
100

Uncertainty in the best calculations

The orbital approximation

Covalent
Van der Waals

H₂H₂O, N₂H₂O, O₂H₂O, COH₂O:
Small organic molecules

Quantum Chemistry
N. A. Besley

Use of computers to study the structure and spectroscopy of molecules

For example;

- New methods to solve the Schrodinger equation
- Electronic spectroscopy of molecules in solution and on surfaces
- NMR of defects in fullerenes and nanotubes

Computational Nanoscience
Elena Bichoutskaia

Like-charged dielectric particles can be strongly attracted!

Implications/Applications

- formation of stable colloidal suspensions
- transportation of pharmaceutical powders
- protein interactions
- self-assembly of macro-anions
- formations of clouds and stars
David Robinson  
Membrane simulations and spectroscopy  

Condensed phase spectroscopy: insights from quantum chemistry  
- Explicit molecular environment \(\rightarrow\) quantitative optical spectroscopy  
- Design novel fluorophores e.g., 5-hydroxy-indole (1000x smaller than GFP): probe function/dynamics of proteins & membranes

Types of Molecular Models

- Wish to model molecular structure, properties and reactivity  
- Range from simple qualitative descriptions to accurate, quantitative results  
- Costs range from trivial to months of supercomputer time  
- Some compromises necessary between cost and accuracy of modelling methods

Plastic molecular models

- Fixed bond lengths and coordination geometries  
- Good enough for qualitative modelling of the structure of some molecules  
- Easy and cheap  
- Provide a good feeling for the 3D structure of molecules  
- No information on properties, energetics or reactivity
Molecular mechanics

• Ball and spring
• Represent equilibrium geometries better than plastic models
• Can compute relative strain energies
• Cheap
• Lots of empirical parameters
  – have to be carefully tested and calibrated
• Limited to equilibrium geometries
• Does not take electronic interactions into account
• No information on properties or reactivity
• Cannot handle making and breaking of bonds

Semi-empirical molecular orbital methods

• Approximate description of valence electrons
• Solve simplified form of the Schrödinger eqn
• Many integrals approximated using empirical expressions with various parameters
• Semi-quantitative description of electronic distribution, molecular structure, properties and relative energies
• Cheaper than \textit{ab initio} electronic structure methods, but not as accurate

\textit{Ab Initio} Molecular Orbital Methods

• More accurate treatment of the electronic distribution using the full Schrödinger equation
• Can be systematically improved to obtain chemical accuracy
• Do not need to be parameterized or calibrated with respect to experiment
• Can describe structure, properties, energetics and reactivity
• Expensive
Molecular Modelling Software

- Many packages; numerous platforms
- Most have graphical interfaces, so that molecules can be sketched and results viewed pictorially
- Will use a few selected packages to simplify the learning curve
- Experience readily transferred to other packages

The Nobel Prize in Chemistry 1998

"for his development of the density-functional theory"
Walter Kohn
1/2 of the prize
USA
University of California
Santa Barbara, CA, USA
b. 1923
(in Vienna, Austria)

"for his development of computational methods in quantum chemistry"
John A. Pople
1/2 of the prize
United Kingdom
Northwestern University
Evanston, IL, USA
b. 1925
d. 2004

Goals of Applied Quantum Chemistry

- Optimize geometries of starting materials, intermediates and transition states
- Determine properties of the optimized geometries: bond lengths, energies, frequencies, electronic spectra, charges etc
- Visualize changes during the course of a reaction, isolate pertinent factors, understand reactions on the molecular level
Tools

Computational methodology (Hartree-Fock, DFT etc), combined with a basis set (STO-3G, 6-31G, etc), as implemented by a software package (GAMESS, Gaussian, HyperChem etc).

Choice of method and basis set determines speed and accuracy of the calculation.
Choice of software determines speed and available options.

Quantum Mechanical Methods

– Molecular Orbital methods (MO) (also known as Ab Initio and First Principles)
  • Bare bones: Hartree-Fock (HF)
  • correlated, perturbational: Møller-Plesset (MP)
  • correlated, configuration interaction: CI
  • multideterminant active space: CAS
– Density Functional Theory (DFT)
– Hybrid DFT/MO methods
– Semi-empirical

Access to software

• Novell windows applications
  – (1) Quantum Chemistry – GAMESS
  – (2) ccp1gui – molecular editor
• Unix cluster
  – (3) GAMESS
  – (4) Molecular dynamics simulations
Assignment 1
Which geometries are adopted?
What are their relative energies?
On smaller fragments, establish:
Influence of level of theory (HF, MP2, DFT).
Influence of basis set.
Influence of functional.
Influence of side chain, R.
Influence of a single hydrogen-bonded water molecule.

Design of investigation (i)
• Choose a relevant small molecule
  – \( \text{H}_2\text{CO} \) or \( \text{HCONH}_2 \) or \( \text{HCONHMe} \).
• Establish accuracy versus time for:
  – Method: HF, MP2, DFT
  – Basis set: STO-3G, 3-21G, 6-31G, 6-31G*
    and/or cc-pvdz, cc-pvtz (consider # basis fns)
  - Functional in DFT: BLYP versus B3LYP
Design of investigation (ii)

• Compare: full versus partial optimization versus single-point energy calculation at higher level of theory, i.e. optimize using Hartree-Fock, and then compute MP2 energies at the minima.
• Consider absolute & relative energies of different conformers eg cis versus trans.
• Use sequential approach: optimize at low level; use optimized geometry as starting geometry for next of theory – don’t try to optimize a poor geometry directly with an expensive method – it will take too long!

Computational studies of …

Assignment 2
Account for zero-point energy.
Characterise stationary points, as minima or transition states.
Investigate vibrational spectra.

Computational studies of …

Assignment 3
How well does the CHARMM molecular mechanics force field model the structure and infrared vibrational spectra of simple peptides?
Influence of context in a peptide chain, e.g., different dipptides, different neighbours, location at different termini.
Influence of timestep.
Influence of length of simulation.
Influence of explicit solvent.
The peptide bond

Phi ($\phi$) – the angle of rotation about the N-C$\alpha$ bond.

Psi ($\psi$) – the angle of rotation about the C$\alpha$-C$\alpha$ bond.

The planar bond angles and bond lengths are fixed.

Structural variation in peptides

- G. N. Ramachandran – first calculations of sterically allowed regions of phi and psi
- Note the structural importance of glycine

Assessment (Coursework)
You must write reports on Three (33% each) experiments:

1. Quantum Chemical study of structure
2. Quantum Chemical study of vibrational spectra
3. Classical molecular dynamics simulations of peptides
Reports + deadlines

• Do not write up in excessive detail
• No programming skills required.
• Deadline for submission of reports (5% penalty per day late):
  – 2 reports by 3pm Thursday 8th Dec, 2011;
  – 1 report by 3pm Thursday 19th Jan, 2012

Time management

“God is having playing a joke at my expense tonight. Its Mark (the one who saw you yesterday about CHARMM); I’ve come to finish off my work so it can be printed off in colour tomorrow - but my server is down. Pardon the expression but FUCK. I can’t access any of my files; I can’t even access groupwise (hence why I’m using a different email address). By the time this is sorted it will be far too late to hand in my coursework. I realise as you said, as long as it is there when you arrive Monday first thing - but is the Cripps Office open at weekends? My report relies heavily on colour.”