

Section: Sat, March 20, 2021 11am-
11:50am

INTRODUCTION TO COMPUTATIONAL CHEMISTRY

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IS THIS THE CLASS YOU ARE LOOKING FOR?

- Computational (not analytical) chemistry is the branch of chemistry that uses computers to solve quantum mechanics equations to solve problems in chemistry such as predicting the structure, properties, and patterns of reactivity of molecules. This course will be a very math-lite survey of what computational chemistry is about and the fundamental balance of computational expediency and accuracy.
- **Prerequisites**
*High school level chemistry/physics in grades 10-12
AP Chemistry and Physics are a huge plus.*

CAN CHEMISTRY BE MADE INTO A QUANTITATIVE SCIENCE?

Every attempt to employ mathematical methods in the study of chemical questions must be considered profoundly irrational and contrary to the spirit of chemistry. If mathematical analysis should ever hold a prominent place in chemistry – an aberration which is happily almost impossible – it would occasion a rapid and widespread degeneration of that science.

Augustus Comte, French philosopher, 1798–1857; in *Philosophie Positive*, 1830.

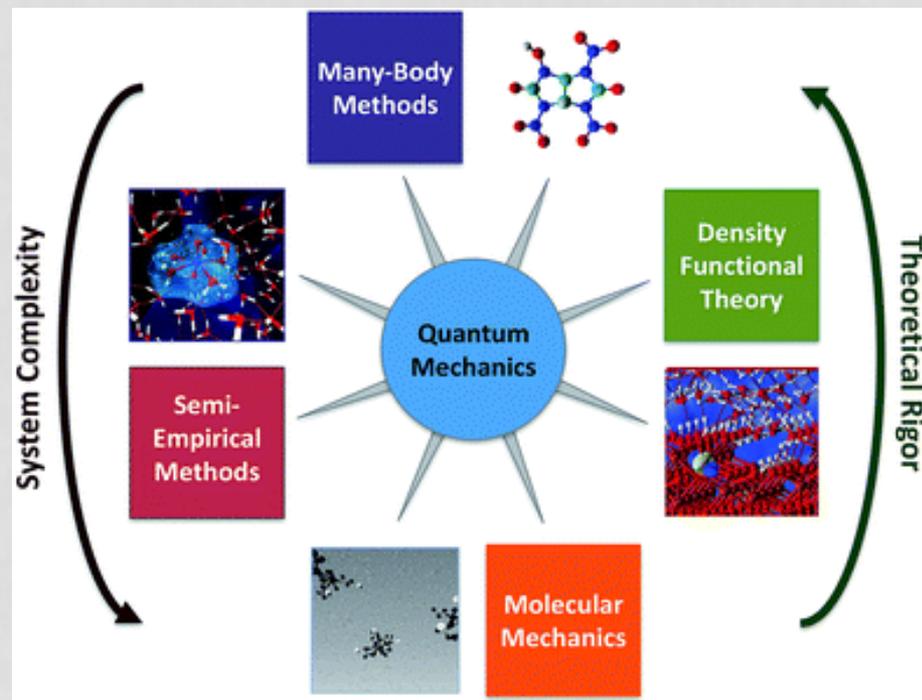
CAN CHEMISTRY BE MADE INTO A QUANTITATIVE SCIENCE?

The more progress the physical sciences make, the more they tend to enter the domain of mathematics, which is a kind of center to which they all converge. We may even judge the degree of perfection to which a science has arrived by the facility to which it may be submitted to calculation.

Adolphe Quetelet, French astronomer, mathematician, statistician, and sociologist, 1796–1874, writing in 1828.

COMPUTATIONAL CHEMISTRY

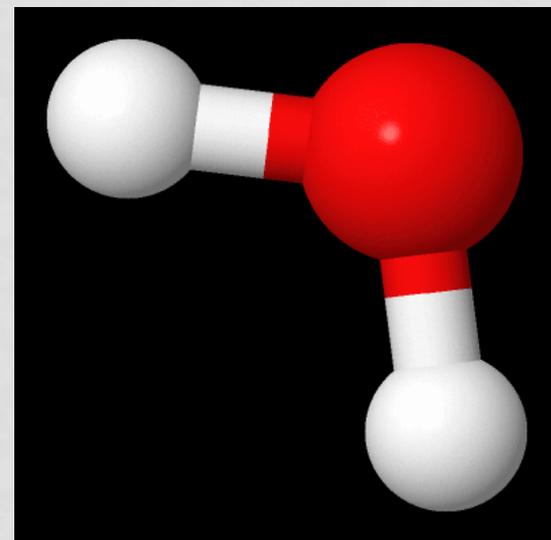
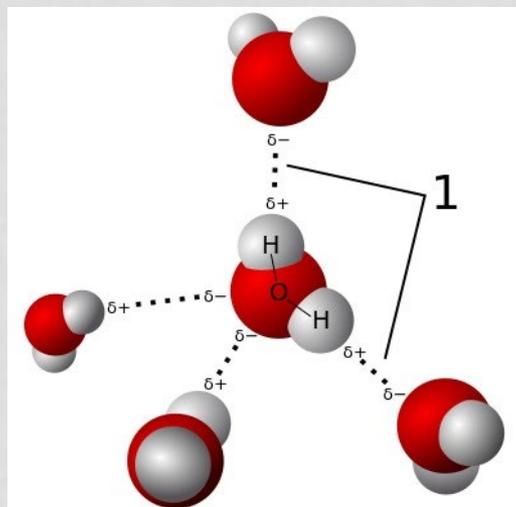
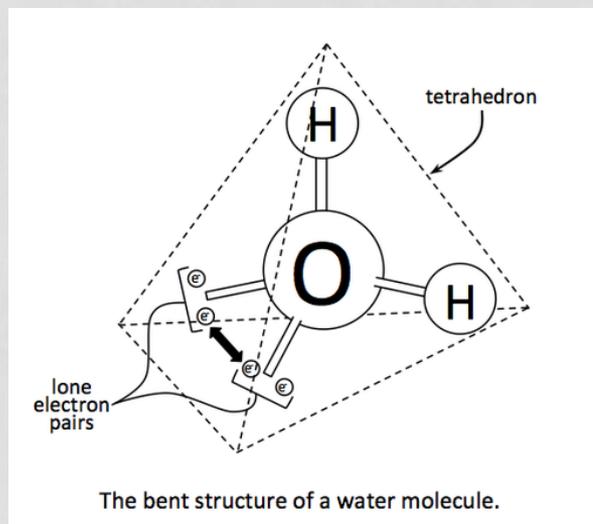
- Computational chemistry is the branch of chemistry that uses computers to solve quantum mechanics equations to solve problems in chemistry such as predicting the structure, properties, and patterns of reactivity of molecules.



Tratnyek, Paul G., Eric J. Bylaska, and Eric J. Weber. *Environ. Sci.: Proc. Impacts* 19, 3 (2017): 188-202.

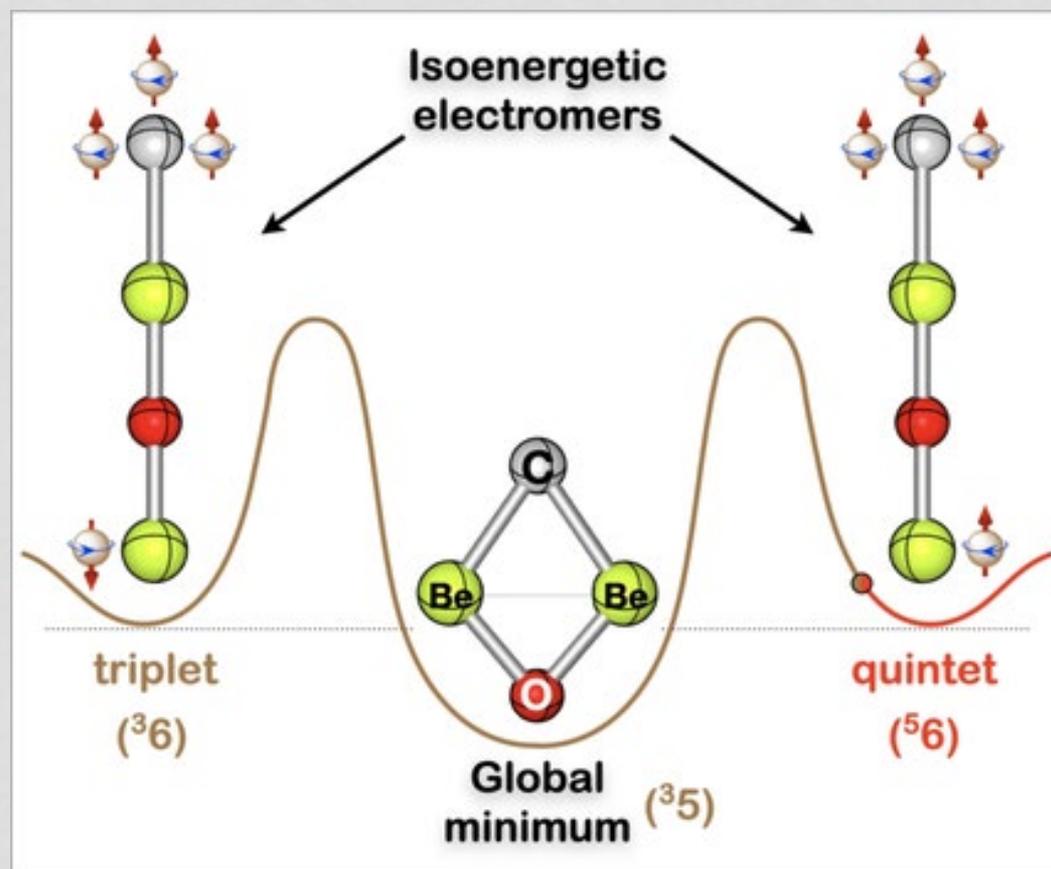
WHAT CAN YOU INVESTIGATE WITH COMPUTATIONAL CHEMISTRY?

- Molecular geometry: what does the molecule look like?



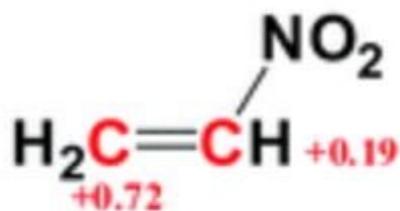
WHAT CAN YOU INVESTIGATE WITH COMPUTATIONAL CHEMISTRY?

- Energies of molecules: What form is favored? What will be the results of a chemical reaction? How fast will it happen?

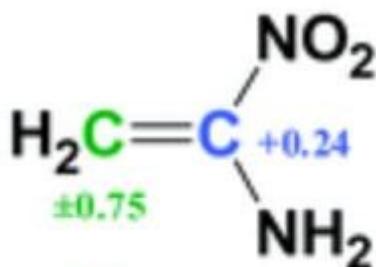


WHAT CAN YOU INVESTIGATE WITH COMPUTATIONAL CHEMISTRY?

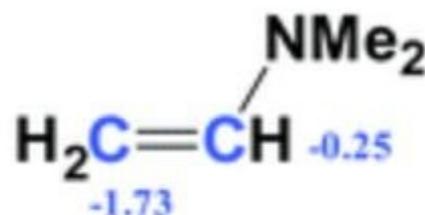
- Chemical reactivity: Where will the reaction happen on the molecule?



$R_k = +n.nn$
electrophilic
center



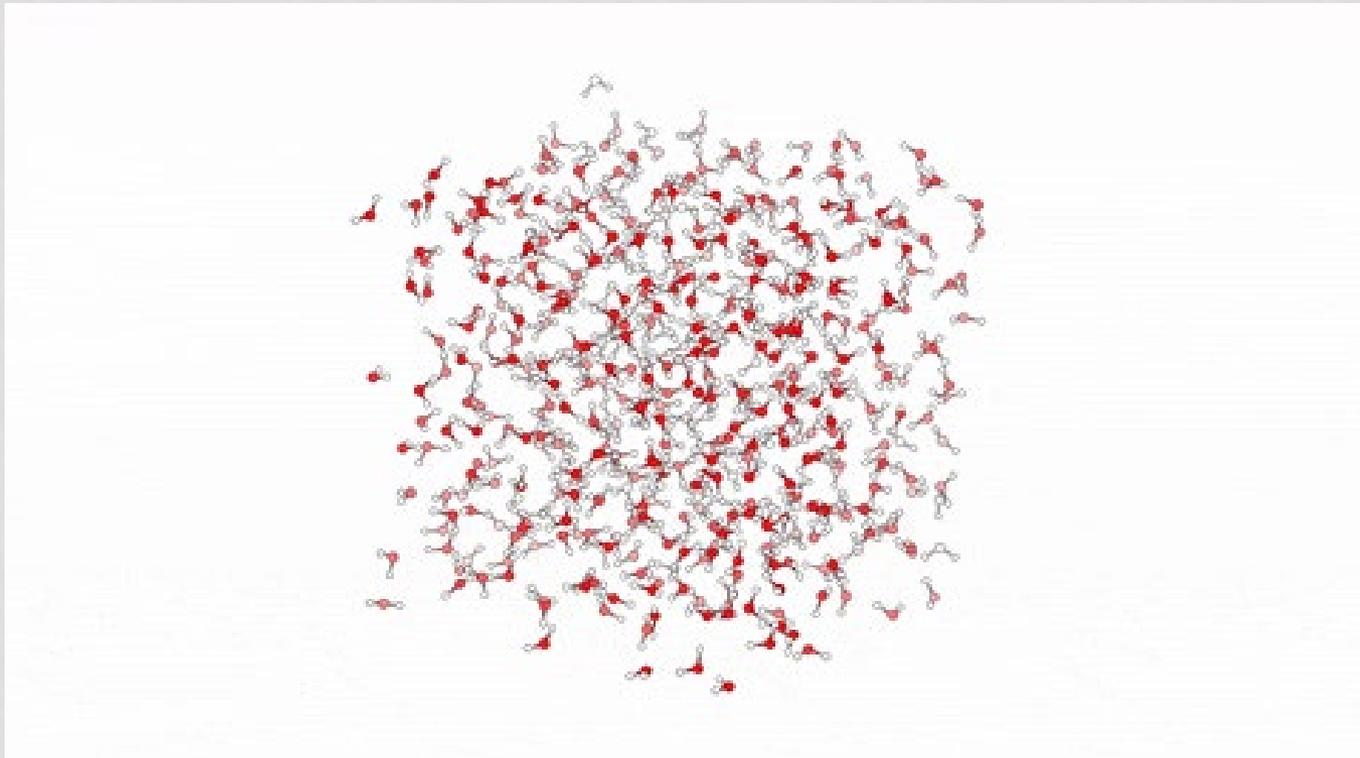
$R_k = \pm n.nn$
ambiphilic
center



$R_k = -n.nn$
nucleophilic
center

WHAT CAN YOU INVESTIGATE WITH COMPUTATIONAL CHEMISTRY?

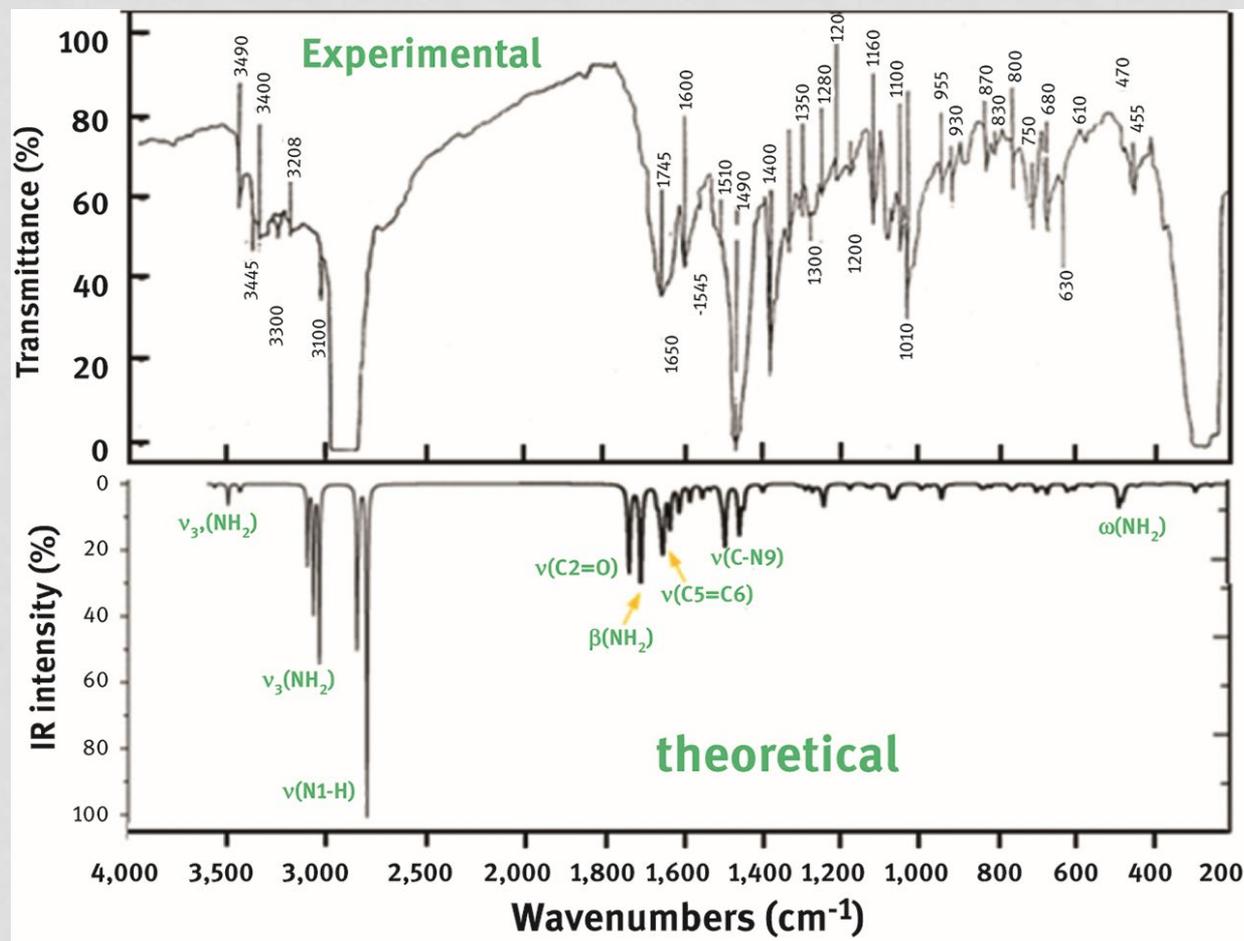
- Molecular dynamics: Where will the atoms go next?



https://en.wikipedia.org/wiki/File:MD_water.gif

WHAT CAN YOU INVESTIGATE WITH COMPUTATIONAL CHEMISTRY?

- Spectroscopy: What will the response of the molecule to radiation or light look like?



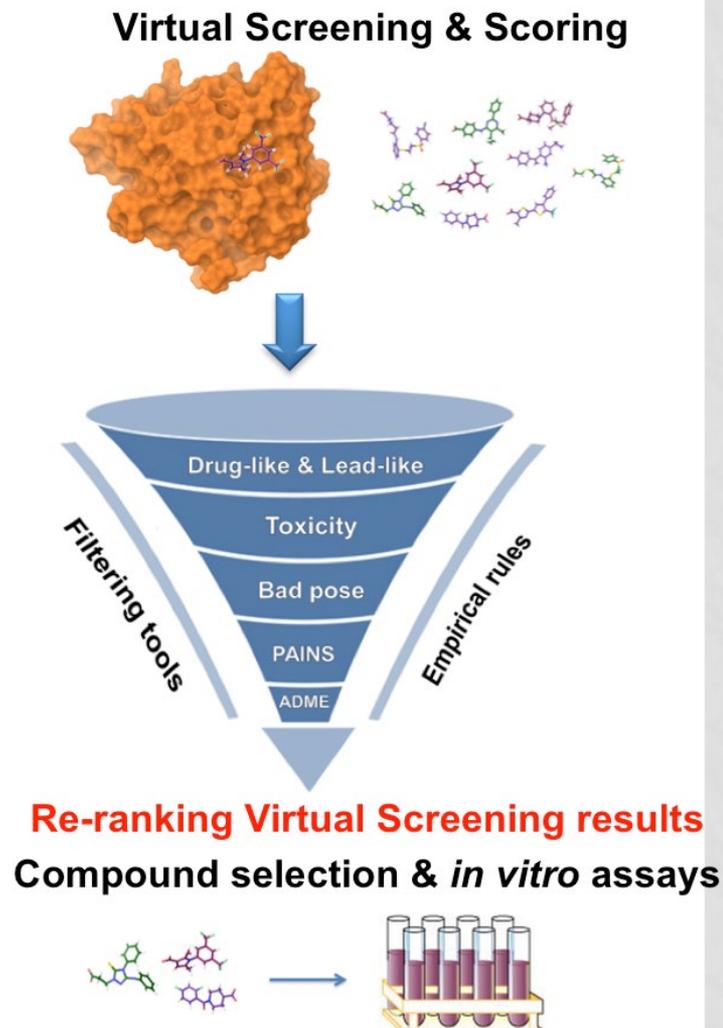
WHAT CAN YOU INVESTIGATE WITH COMPUTATIONAL CHEMISTRY?

- Drug design: Which drug molecule will fit into the protein pocket better?

<https://summerofhpc.prace-ri.eu/re-ranking-virtual-screening-results-in-computer-aided-drug-design/>

Anticancer drugs discovered with computational methods:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7251168/>



CLASSICAL MECHANICS

$$\text{Kinetic Energy} + \text{Potential Energy} = E$$

Classical
Conservation of
Energy
Newton's Laws

$$\frac{1}{2} mv^2 + \frac{1}{2} kx^2 = E$$

$$F = ma = -kx$$

Harmonic oscillator
example.

<http://hyperphysics.phy-astr.gsu.edu/hbase/quantum/schr.html>

SCHRÖDINGER EQUATION

Quantum
Conservation of
Energy
Schrodinger
Equation

In making the
transition to
a wave equation,
physical variables
take the form of
"operators".

The energy becomes
the Hamiltonian operator

Wavefunction

$$H\Psi = E\Psi$$

Energy "eigenvalue"
for the system.

The form of the Hamiltonian
operator for a quantum
harmonic oscillator.

$p \rightarrow \frac{\hbar}{i} \frac{\partial}{\partial x}$
 $x \rightarrow x$
 $H \rightarrow \frac{-\hbar^2}{2m} \frac{\partial^2}{\partial x^2} + \frac{1}{2} kx^2$

$\frac{p^2}{2m} + \frac{1}{2} kx^2$

<http://hyperphysics.phy-astr.gsu.edu/hbase/quantum/schr.html>

WHAT'S A WAVEFUNCTION?



Each "particle" is represented by a wavefunction Ψ (position, time) such that $\Psi^* \Psi =$ the probability of finding the particle at that position at that time.

The wavefunction is used in the Schrodinger equation. The Schrodinger equation plays the role of Newton's laws and conservation of energy in classical mechanics - i.e., it predicts the future behavior of a dynamic system. It predicts analytically and precisely the probability of events or outcome. The detailed outcome depends on chance, but given a large number of events, the Schrodinger equation will predict the distribution of results.

SO WHAT'S THE PROBLEM?

The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble. It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomic systems without too much computation.

Paul Dirac (8 August 1902 – 20 October 1984) was an English theoretical physicist who is regarded as one of the most significant physicists of the 20th century.)

https://en.wikiquote.org/wiki/Paul_Dirac#:~:text=The%20underlying%20physical%20laws%20necessary,too%20complicated%20to%20be%20soluble.

https://en.wikipedia.org/wiki/Paul_Dirac

METHODS TO SOLVE IT:

More expensive, more accurate, more costly

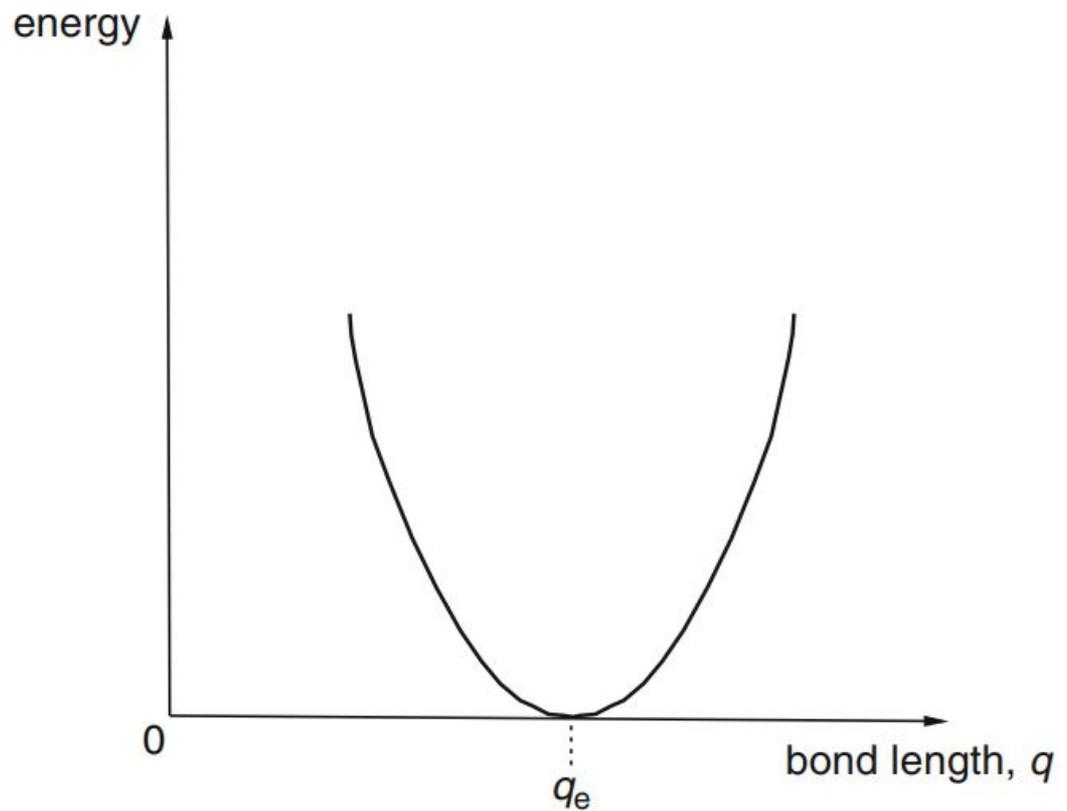
- Molecular mechanics – based on a ball-and-springs model of molecules parameterized against experiment or better calculations
- *Ab initio* (from the beginning) methods – based on approximate solutions of the exact Schrödinger equation without fitting to experiment
- Semiempirical methods – based on approximate solutions of the Schrödinger equation with fitting to experiment (i.e. using parameterization)
- Density functional theory (DFT) methods – based on approximate solutions of the Schrödinger equation, bypassing the wavefunction that is a central feature of *ab initio* and semiempirical methods in favor of the density: exact solution of an approximate form of the problem.
(won't discuss in this class)

THE BORN-OPPENHEIMER APPROXIMATION

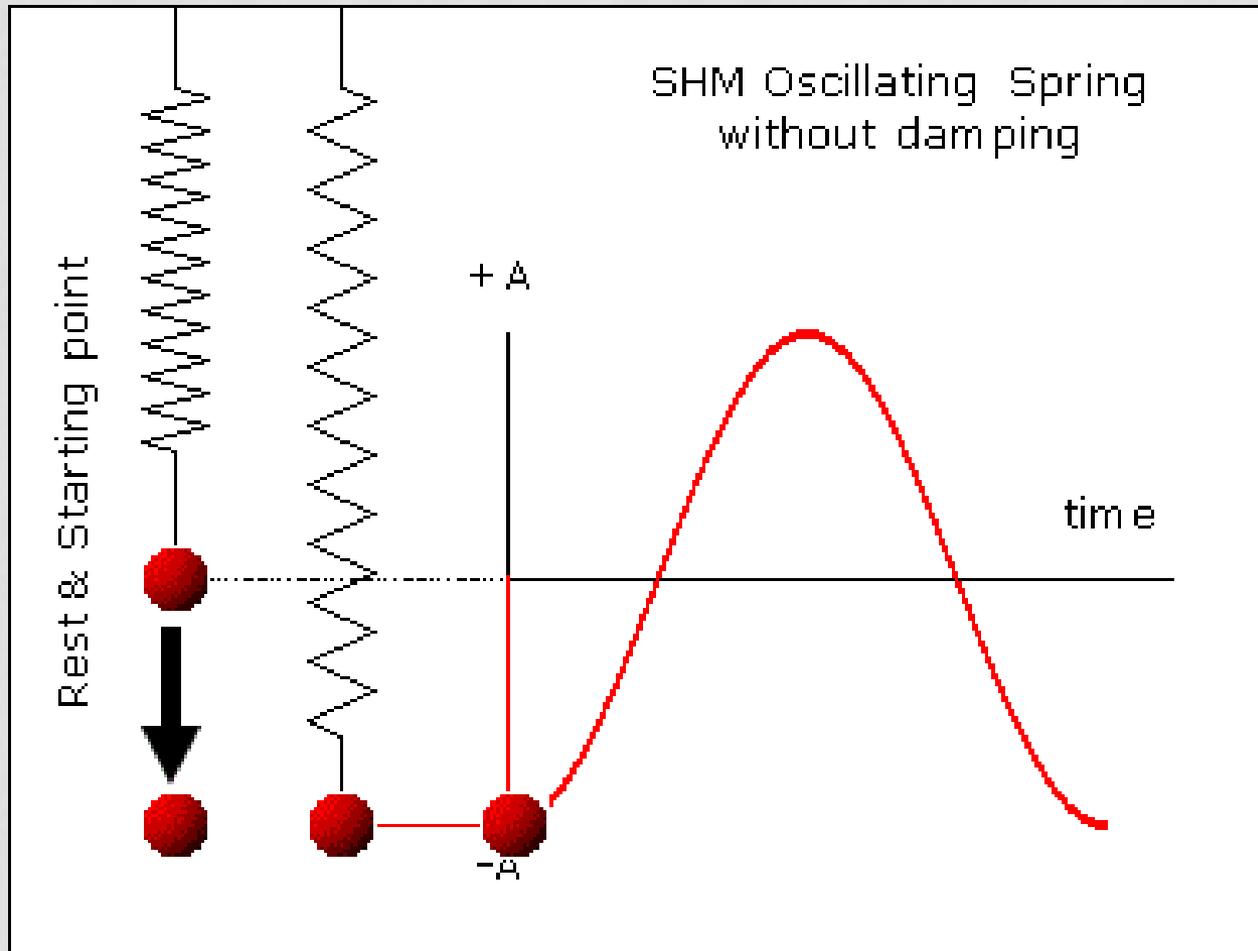
1. Born and Oppenheimer showed in 1927 that to a very good approximation, the nuclei in a molecule are stationary with respect to the electrons. This makes the problem of solving for the energy of a *molecule* a lot simpler as the positions of the nuclei are *parameters* that determine the equation not *variables*.
2. Energy = energy of negative electrons in molecule + constant repulsion between positive nuclei.
3. Molecules have a shape.
4. This is not always be a good approximation, particularly when light and/or excited states involved.

FUNDAMENTAL CONCEPT: POTENTIAL ENERGY SURFACE

Fig. 2.1 The potential energy surface for a diatomic molecule. The potential energy increases if the bond length q is stretched or compressed away from its equilibrium value q_e . The potential energy at q_e (zero distortion of the bond length) has been chosen here as the zero of energy



HARMONIC OSCILLATOR GIF: HOW WELL DO YOU THINK THIS DESCRIBES A MOLECULE?



FUNDAMENTAL CONCEPT: POTENTIAL ENERGY SURFACE

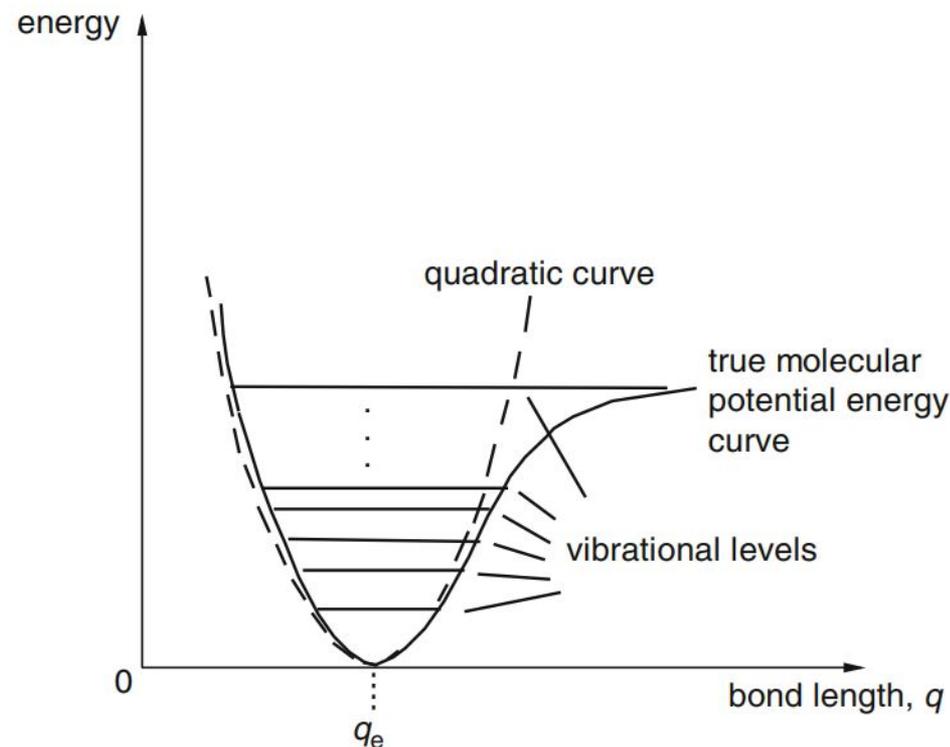
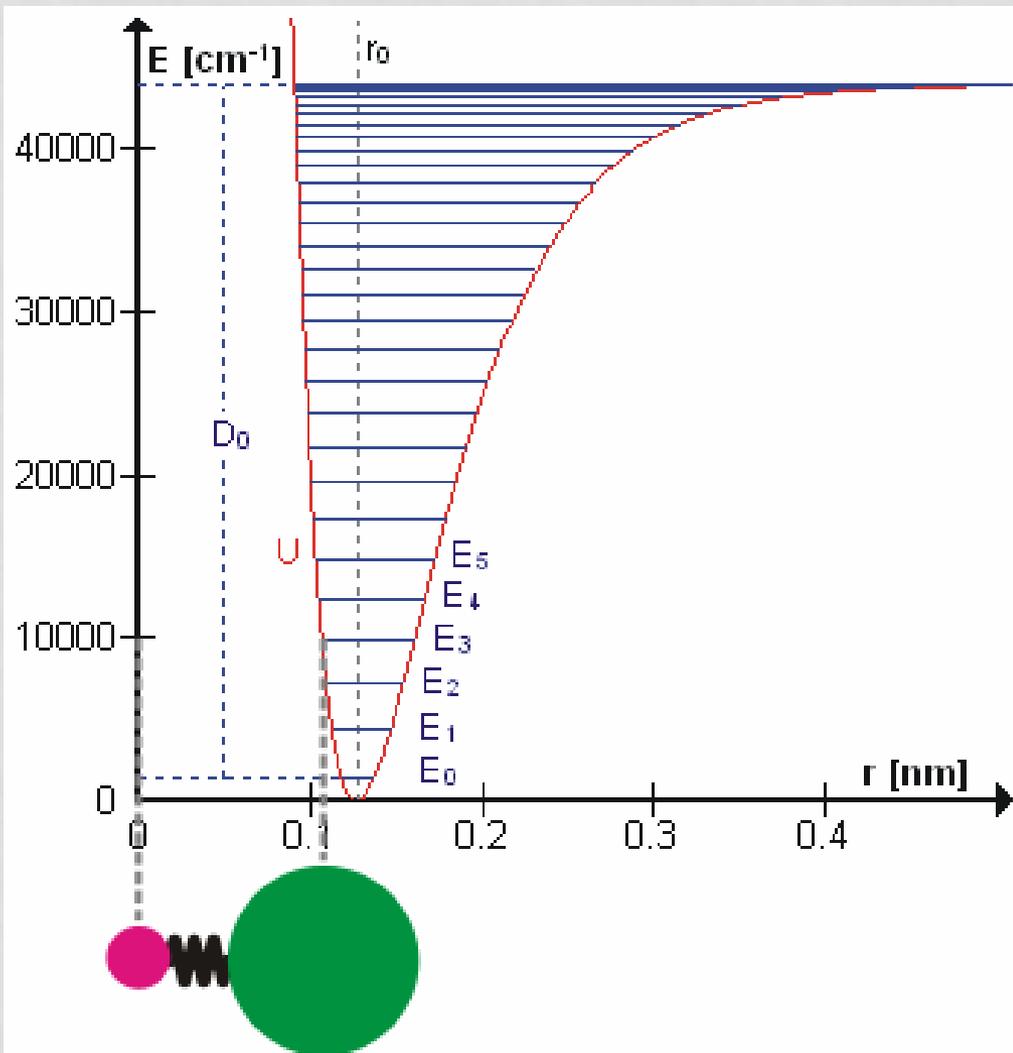


Fig. 2.2 Actual molecules do not sit still at the bottom of the potential energy curve, but instead occupy vibrational levels. Also, only near q_e , the equilibrium bond length, does the quadratic curve approximate the true potential energy curve

ANHARMONIC OSCILLATOR GIF



[https://chem.libretexts.org/Courses/Pacific Union College/Quantum Chemistry/05%3A The Harmonic Oscillator and the Rigid Rotor/5.03 %3A The Harmonic Oscillator Approximates Vibrations](https://chem.libretexts.org/Courses/Pacific_Union_College/Quantum_Chemistry/05%3A_The_Harmonic_Oscillator_and_the_Rigid_Rotor/5.03%3A_The_Harmonic_Oscillator_Approximates_Vibrations)

FUNDAMENTAL CONCEPT: POTENTIAL ENERGY SURFACE

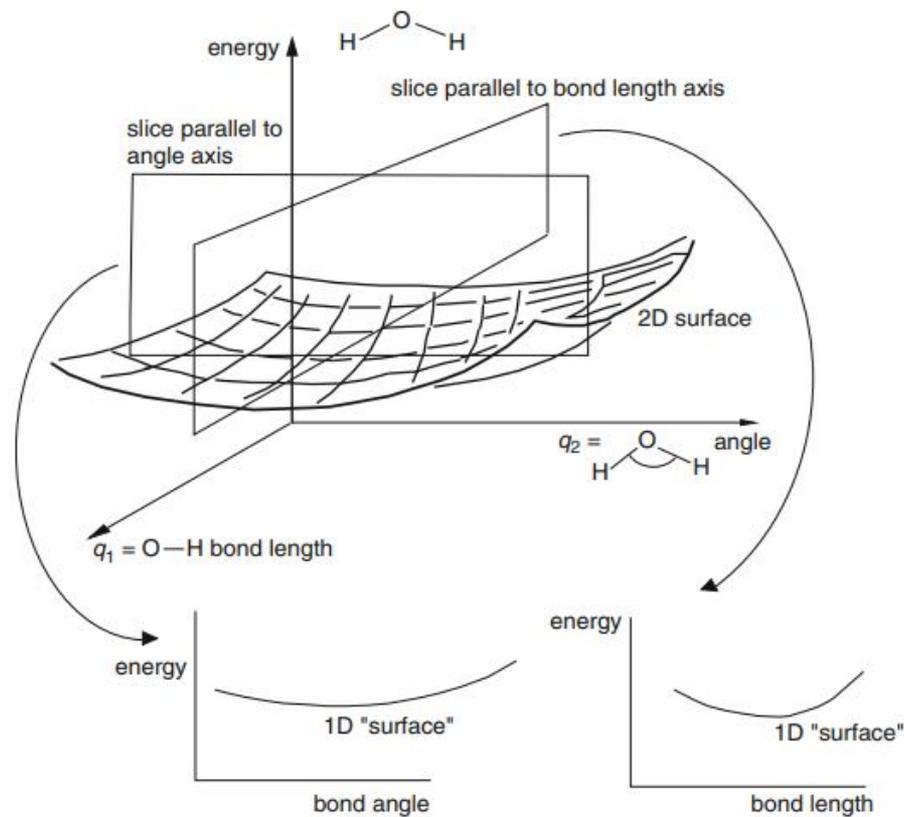


Fig. 2.5 Slices through a 2D potential energy surface give 1D surfaces. A slice that is parallel to neither axis would give a plot of geometry versus a composite of bond angle and bond length, a kind of average geometry

FUNDAMENTAL CONCEPT: POTENTIAL ENERGY SURFACE

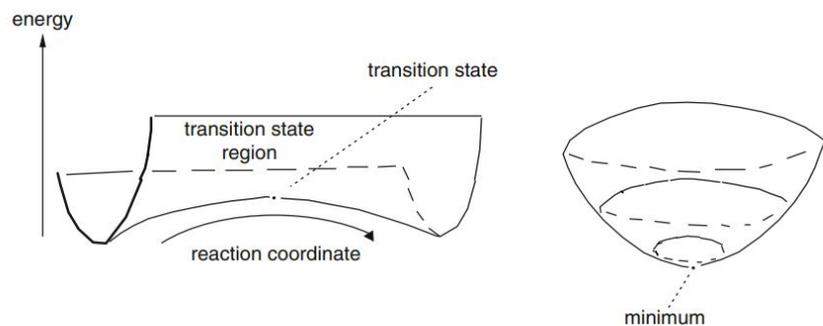
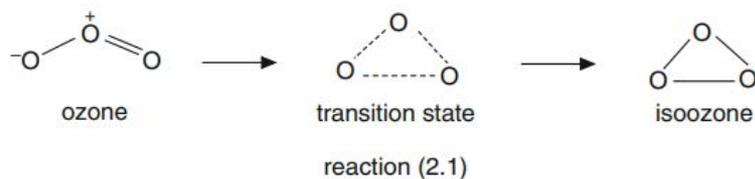


Fig. 2.8 A transition state or saddle point and a minimum. At both the transition state and the minimum $\partial E/\partial q = 0$ for all geometric coordinates q (along all directions). At the transition state $\partial^2 E/\partial q^2 < 0$ for $q =$ the reaction coordinate and > 0 for all other q (along all other directions). At a minimum $\partial^2 E/\partial q^2 > 0$ for all q (along all directions)

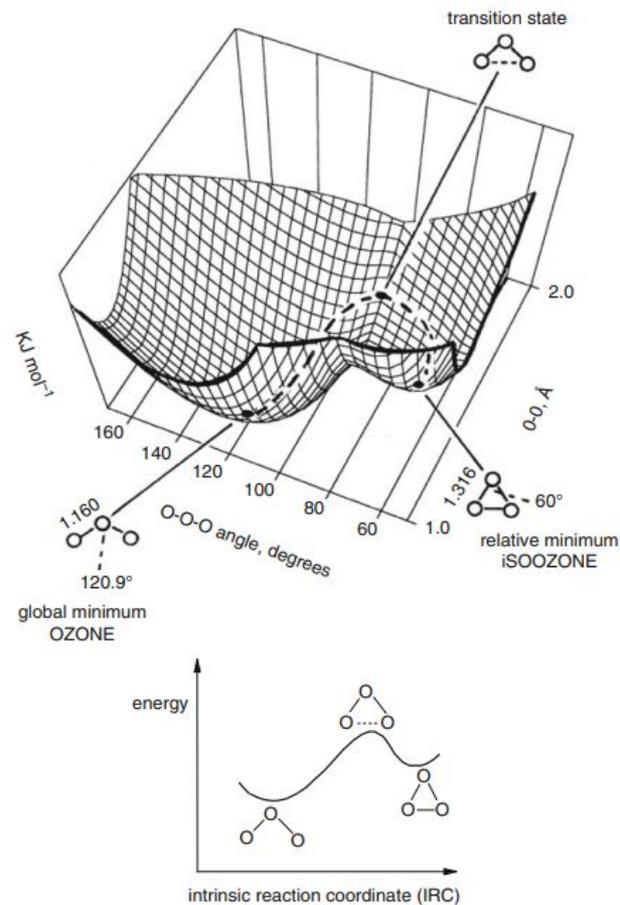
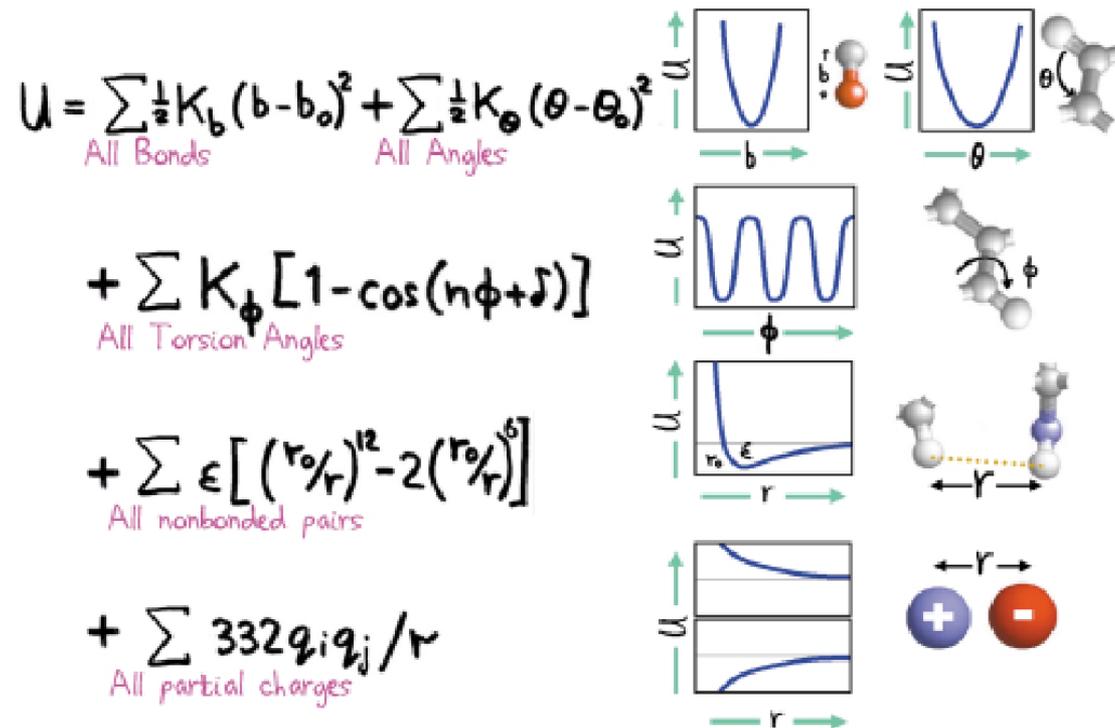


Fig. 2.7 The ozone/isoozone potential energy surface (calculated by the AM1 method; Chapter 6), a 2D surface in a 3D diagram. The *dashed line* on the surface is the reaction coordinate (intrinsic reaction coordinate, IRC). A slice through the reaction coordinate gives a 1D "surface" in a 2D diagram. The diagram is not meant to be quantitatively accurate

CAN IGNORE QUANTUM MECHANICS (KINDA)

Levitt

Nat. Struc. Bio. 2001, 8, 392



CAN COMBINE THEM: QM/MM

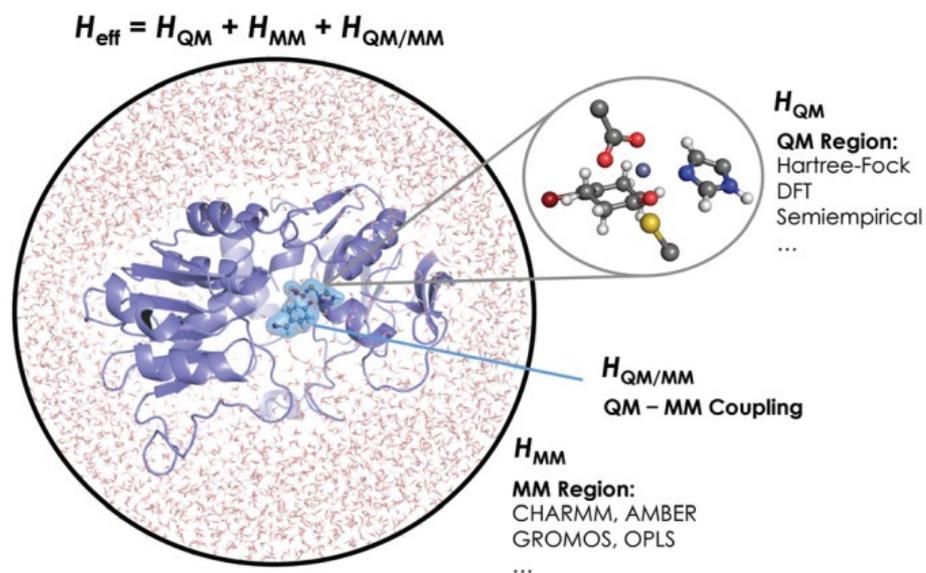


Fig. 4 Schematic representation of the QM/MM treatment of a biocatalytic system.

The Nobel Prize in Chemistry 2013



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A. Mahmoud

Martin Karplus

Prize share: 1/3



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Michael Levitt

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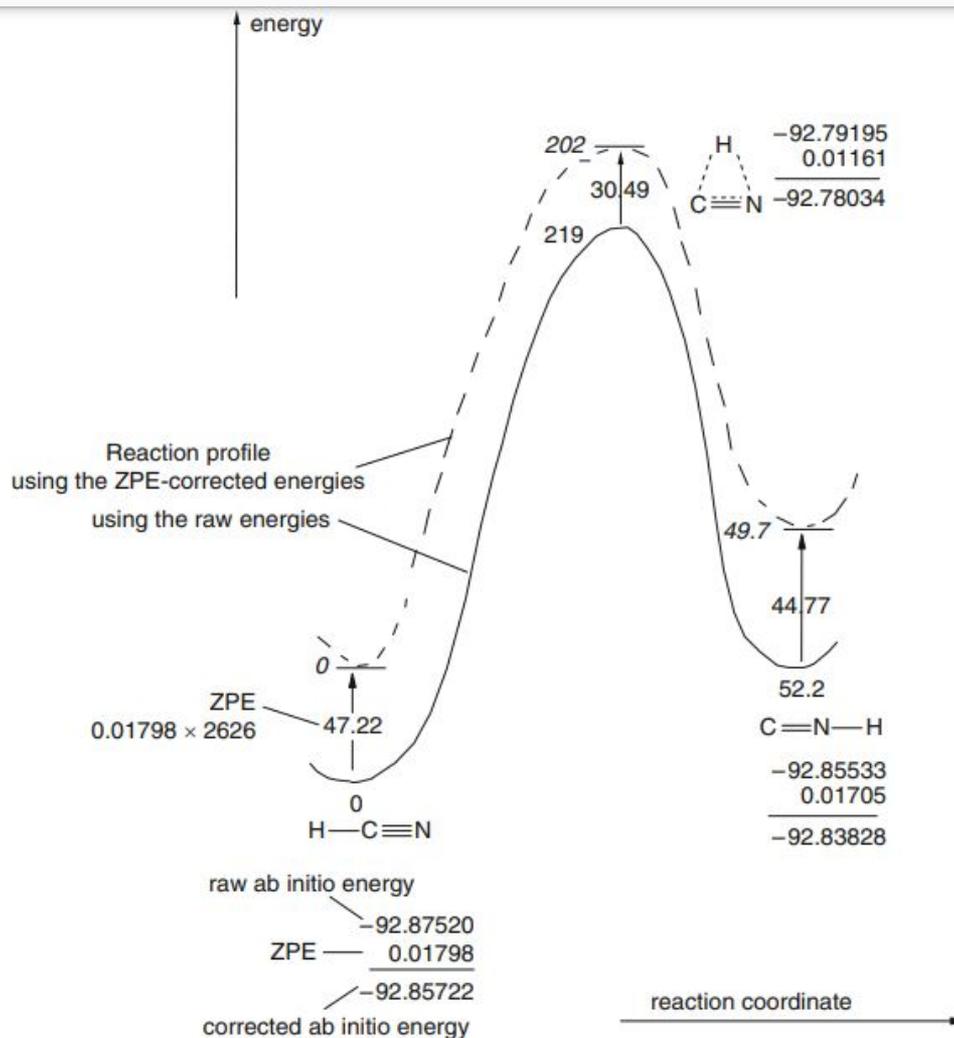
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Arieh Warshel

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Romera-Rivera *et al.*, *Chem. Commun.*, 2017, 53, 284--297

HOW TO USE THE ENERGIES YOU CAN COMPUTE?



REACTION MECHANISM EXAMPLE

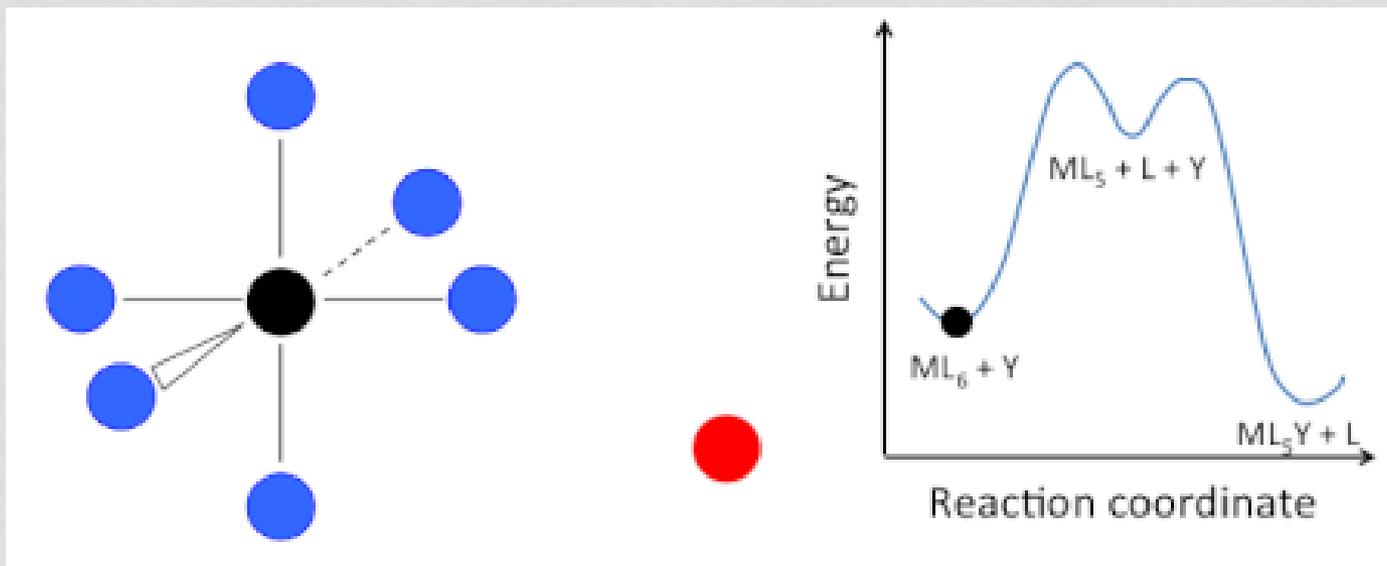


Illustration of the dissociative ligand substitution mechanism for an ML_6 complex. The reaction energy profile is shown at the right..

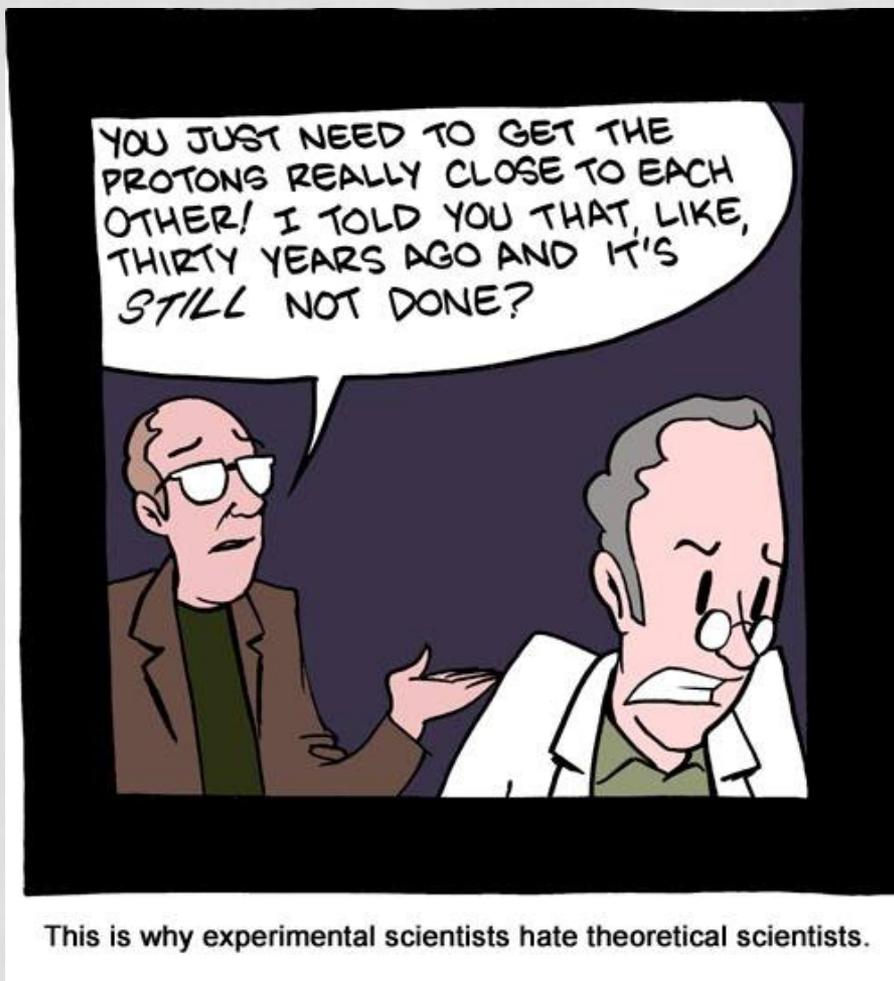
https://en.wikibooks.org/wiki/Introduction_to_Inorganic_Chemistry/Coordination_Chemistry_and_Crystal_Field_Theory

WHAT CAN WE USE COMPUTATIONAL CHEMISTRY FOR?

- Test our ideas before we go to the lab
 - Which compound would be best to test?
- Rational design
 - How does this compound work so we can improve it?
 - Find the slow step of the reaction and screen molecules until find one with the *fastest* slow step
- Interpretations of experiment
 - What did I just measure?
 - What is the best explanation for the observation?
- Save money \$\$\$

Source for most figures and text if not otherwise sourced: Lewars, Errol. ["Computational chemistry. Introduction to the theory and applications of molecular and quantum mechanics."](#) Springer (2011).

WHAT CAN WE USE COMPUTATIONAL CHEMISTRY FOR?



QUESTIONS?

WANT TO GET INVOLVED IN RESEARCH?

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In terms of getting started with computational chemistry research, I would recommend:

1. Taking rigorous courses in high school
2. Getting involved in the Regeneron (formerly Intel?) science fair high school program if possible
3. Getting involved in research in college.
4. Can do some stuff on your own: <http://chemistry.ncssm.edu/>
5. However, some groups do allow high school students e.g.
<http://ffgroup.chem.uci.edu/outreach/>
<https://web.nmsu.edu/~talipovm/doku.php>

Just Google "computational chemistry research high school" for more.