

DFT in Organic Chemistry

Tanya Rogova

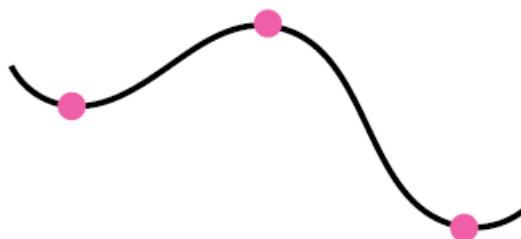
01.04.2020

Why do organic chemists use DFT?

- *DFT offers a balance of computational performance and accuracy*
- *ab initio* HF (almost) never appropriate to study organic reactions and molecules
- Post-HF (MP2, CCSD(T)) only applicable with very small systems

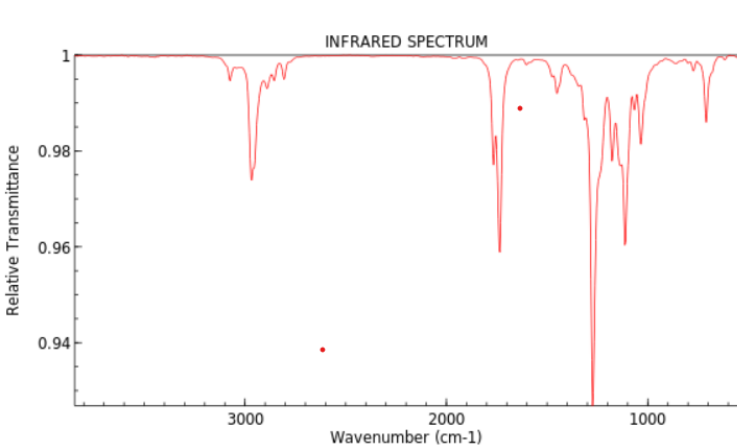
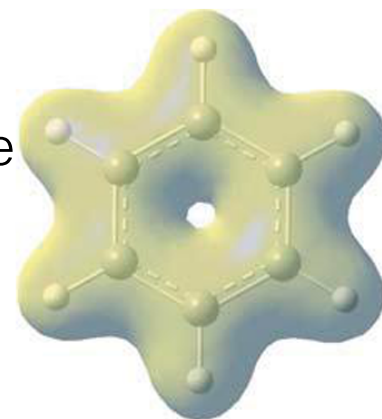
What can DFT be used for?

- Investigate the reactivity of a given molecular system
 - Explore the critical points on the potential energy surface (PES)
 - Kinetic/thermodynamics of a given system
 - Explore possible mechanisms, predict product distribution



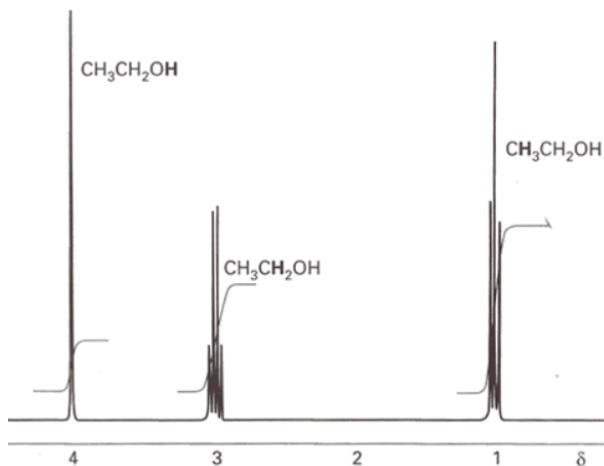
What can DFT be used for?

- Investigate various physical properties of a given molecule
 - Predict spectroscopic data (IR, NMR, etc.)
 - Aromaticity, electrophilicity, reduction potentials, etc.
 - Conformational analysis
 - Optical rotation/circular dichroism predictions
 - Excited-state properties (TD-DFT methods)

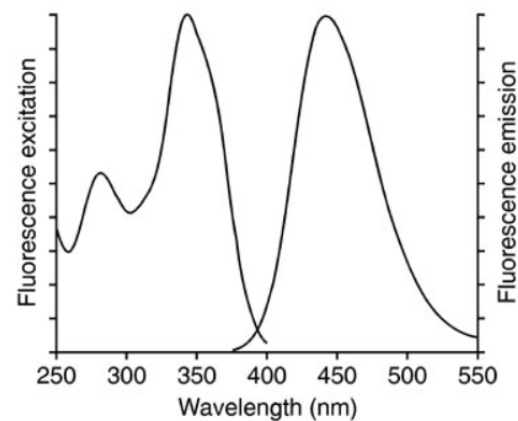


NIST Chemistry WebBook (<https://webbook.nist.gov/chemistry>)

IR

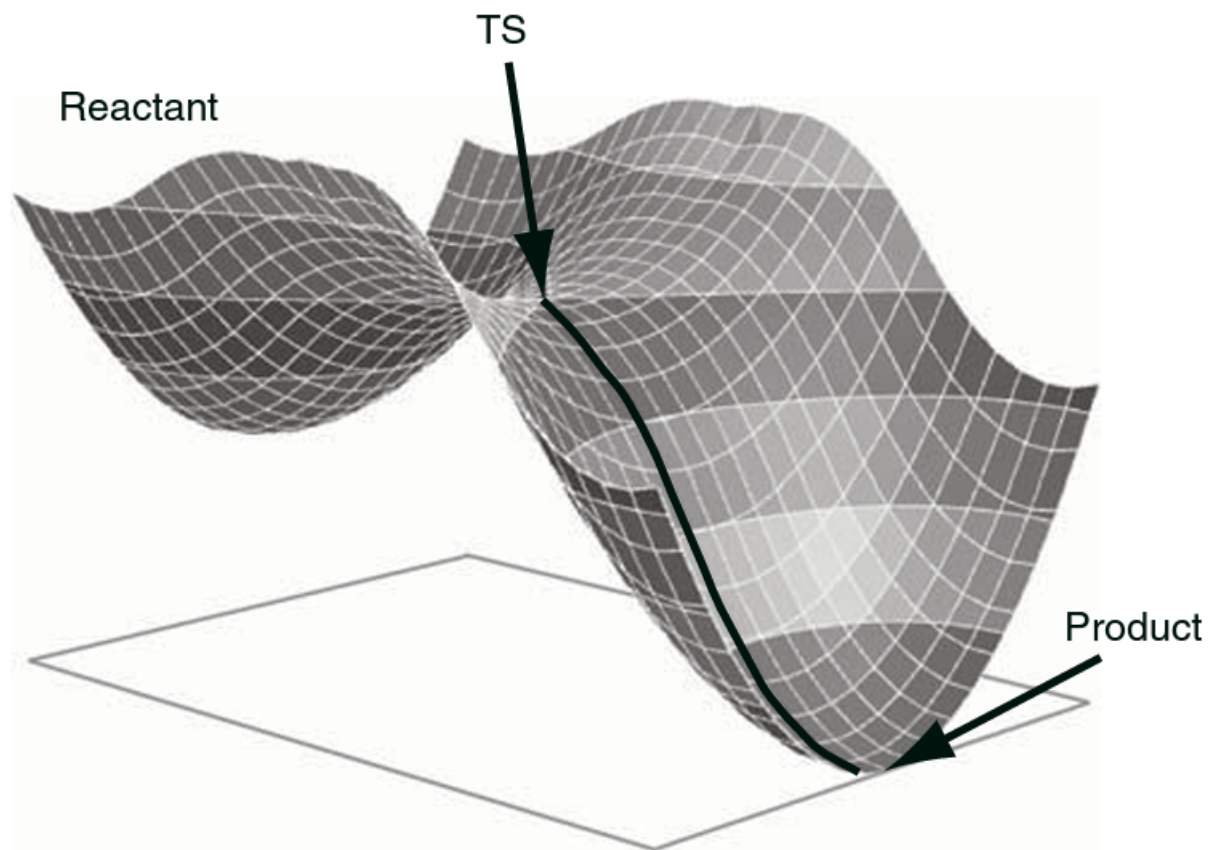


NMR



UV/Vis 4

Potential Energy Surface (PES)

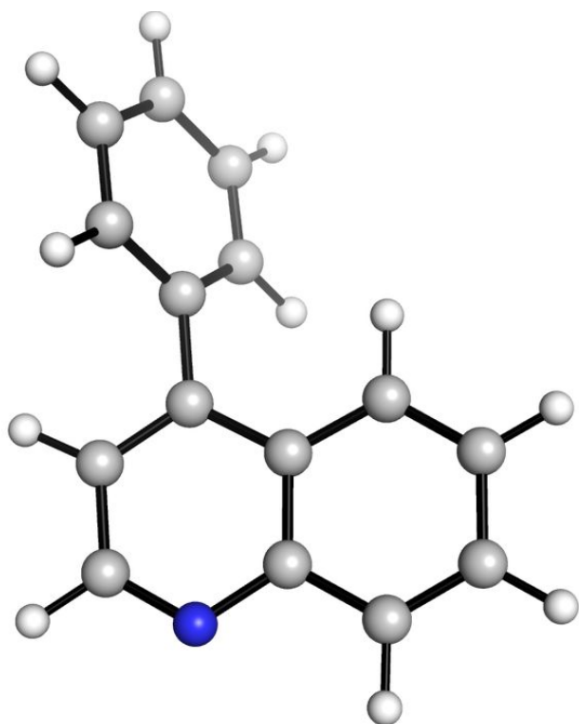


Potential Energy Surface (PES)

- How to identify *critical points* on the PES
 - The gradient vanishes (derivative of E = 0)
- How to characterise a *critical point* on the PES
 - Calculate the matrix of second derivatives at the point of interest
 - Called a **Hessian** $\mathbf{H}_{ij} = \frac{\partial^2 E}{\partial q_i \partial q_j}$
 - These eigenvalues determine normal vibrational modes of the molecule

Interpreting the Hessian

- If all vibrational modes are positive...
- ... then the critical point is a local minimum



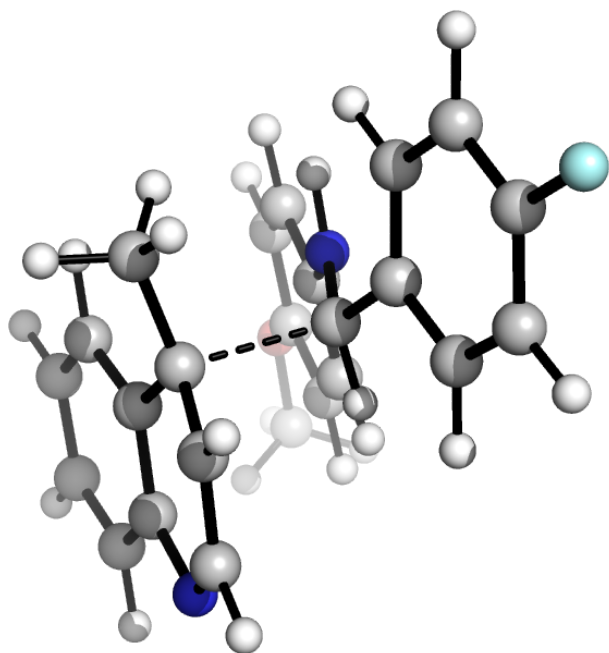
G1:M9:V1 - Vibrations

Harmonic			
	Mode #	Frequency	Infrared
1	1	58.37	0.0300
2	2	76.92	0.4355
3	3	91.39	0.1391
4	4	177.22	6.1212
5	5	185.72	1.2650
6	6	254.48	0.5555
7	7	293.07	1.0384
8	8	314.86	1.9093
9	9	418.74	1.1583

Animate Vibration:

Interpreting the Hessian

- If one vibrational mode is **negative**...
- ... then the critical point is a transition state



G1:M24:V1 - Vibrations

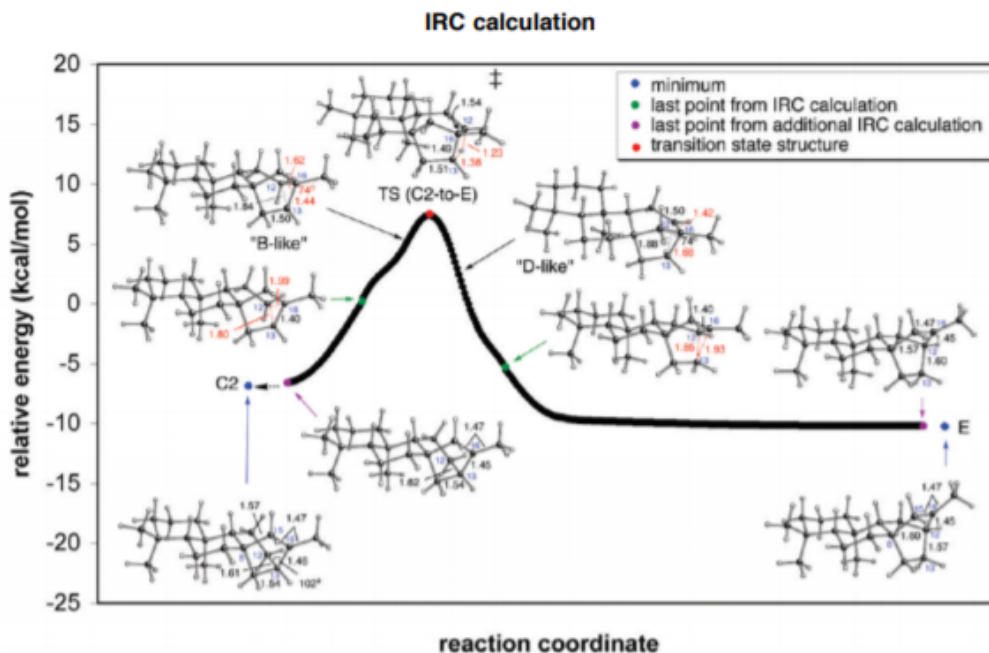
Harmonic

	Mode #	Frequency	Infrared
1	1	-384.87	162.2224
2	2	21.51	1.2211
3	3	31.03	0.2247
4	4	43.76	0.7384
5	5	51.71	0.1278
6	6	57.04	1.1540
7	7	74.03	9.1735
8	8	92.09	1.9174
9	9	97.05	0.1125

Animate Vibration:

Interpreting the Hessian

- Intrinsic Reaction Coordinate (IRC)
 - Steepest descent pathway from the TS to the stationary points
 - Represented using mass weighted coordinates
 - Initial direction given by the eigenvector with the negative eigenvalue



Geometry Optimisation Calculation

- Determine the local minima and saddle points on your PES
- **Step 1:** Initial guess of the molecular geometry
- **Step 2:** Vary the positions of the atoms such that the energy of the molecule decreases.

Geometry Optimisation Calculation

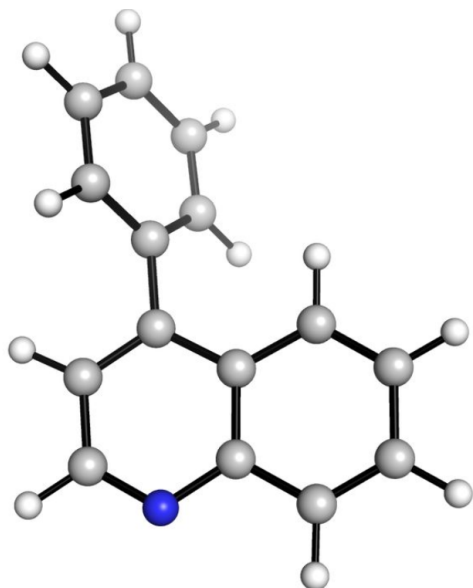
- How do you vary the positions?
- Do you lengthen or shorten the bond lengths?
- By how much should you lengthen or shorten your bond?

This information is determined through the calculation of first and second derivatives of the energy

Geometry Optimisation Calculation

- Do you lengthen or shorten the bond lengths?
 - If the first derivative is **positive**, then the energy will increase with an increase in bond length
- By how much should you lengthen or shorten your bond?
 - Second derivative gives the **curvature of the surface**—an idea by how far you should adjust

Geometry Optimisation Calculation



```
%mem=4GB  
%nprocshared=4  
# freq opt wB97XD/6-31g(d) scrf=(smd,solvent=DiMethylSulfoxide)
```

title

0 1

C	1.351398000	2.566968000	0.029659000
C	2.349818000	0.527065000	0.010016000
C	1.098223000	-0.178785000	-0.050028000
C	-0.123508000	0.612374000	0.009856000
C	0.071192000	1.982147000	0.049641000
H	4.488165000	0.428862000	0.090240000
H	1.432571000	3.652392000	0.039499000
C	3.585500000	-0.174247000	0.050204000
C	1.204615000	-1.600953000	-0.179957000
H	-0.752993000	2.678403000	0.139432000
C	2.413223000	-2.254412000	-0.089785000
C	3.629065000	-1.540934000	0.040320000

Standard Workflow



Submit initial guess of the geometry



Compute the energy and the gradients



Obtain Hessian



Optimisation criteria met?



Yes! Calculation complete.



No. Resubmit new geometry.

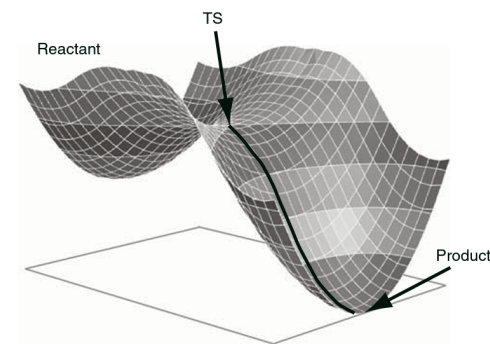
General Tips and Guidelines

- The energy of the system is more sensitive to method than the geometry
 - Geometry optimisation with a lower level method
 - Compute energy using higher-level single point calculation, from the optimised structure
 - Noted as: “ ω B97x-D/6-311++G(d,p)// ω B97x-D/6-31G(d)”

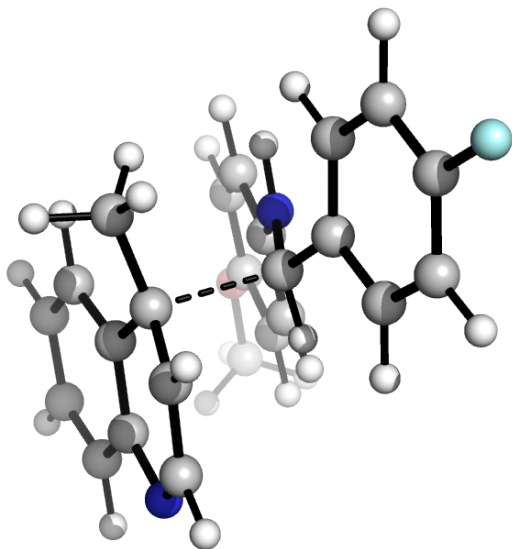
Energy	Geometry
--------	----------

General Tips and Guidelines: TS

- TS optimisations are more challenging
 - Must have an initial good guess (within quadratic region of the critical point)
 - Compute Hessian at the beginning to identify the uphill direction
- Methods to identify the geometry
 - Linear Synchronous Transit method (LST)
 - Quadratic Synchronous Transit method (QST)
 - Then a quasi-Newton method is used to complete the optimisation



General Tips and Guidelines: TS



```
%mem=8GB  
%nprocshared=12  
# freq opt=(ts,calcfc,noeigentest) wb97xd/6-31g(d) scrf=(smd,solvent=DiMethylSulfoxide)
```

title

0 2			
F	-1.33008009	-4.97630457	2.72698241
C	-0.97447200	-3.88987557	2.01196842
C	0.32213533	-3.41351641	2.11967133
C	0.68303639	-2.28927089	1.38531948
C	-0.24082177	-1.64704139	0.54919726
C	0.07453400	-0.40634200	-0.18689000
N	1.37930862	-0.22699912	-0.61867490
C	1.78147510	0.52870758	-1.72745609
C	0.97754880	0.69783444	-2.85580408
C	1.42100304	1.44666301	-3.94566991
C	2.69156544	2.02344873	-3.93312461
O	3.21778958	2.76417963	-4.94281658
C	2.41813450	2.96687189	-6.09342252
C	3.50854890	1.83950906	-2.81176036
C	3.05841686	1.10962291	-1.72446982

Modelling a Chemical Reaction

1. Pick an appropriate model and level of theory
(ex. B3LYP, M06-2X, PBE0, ω B97X-D ...)
2. Chose basis set
(ex. 6-31G(d), def2SVP, aug-cc-pVDZ, ...)



FIG. 3. The alphabet soup of approximate functionals available in a code near you. Figure used with permission from Peter Elliott.

Modelling a Chemical Reaction

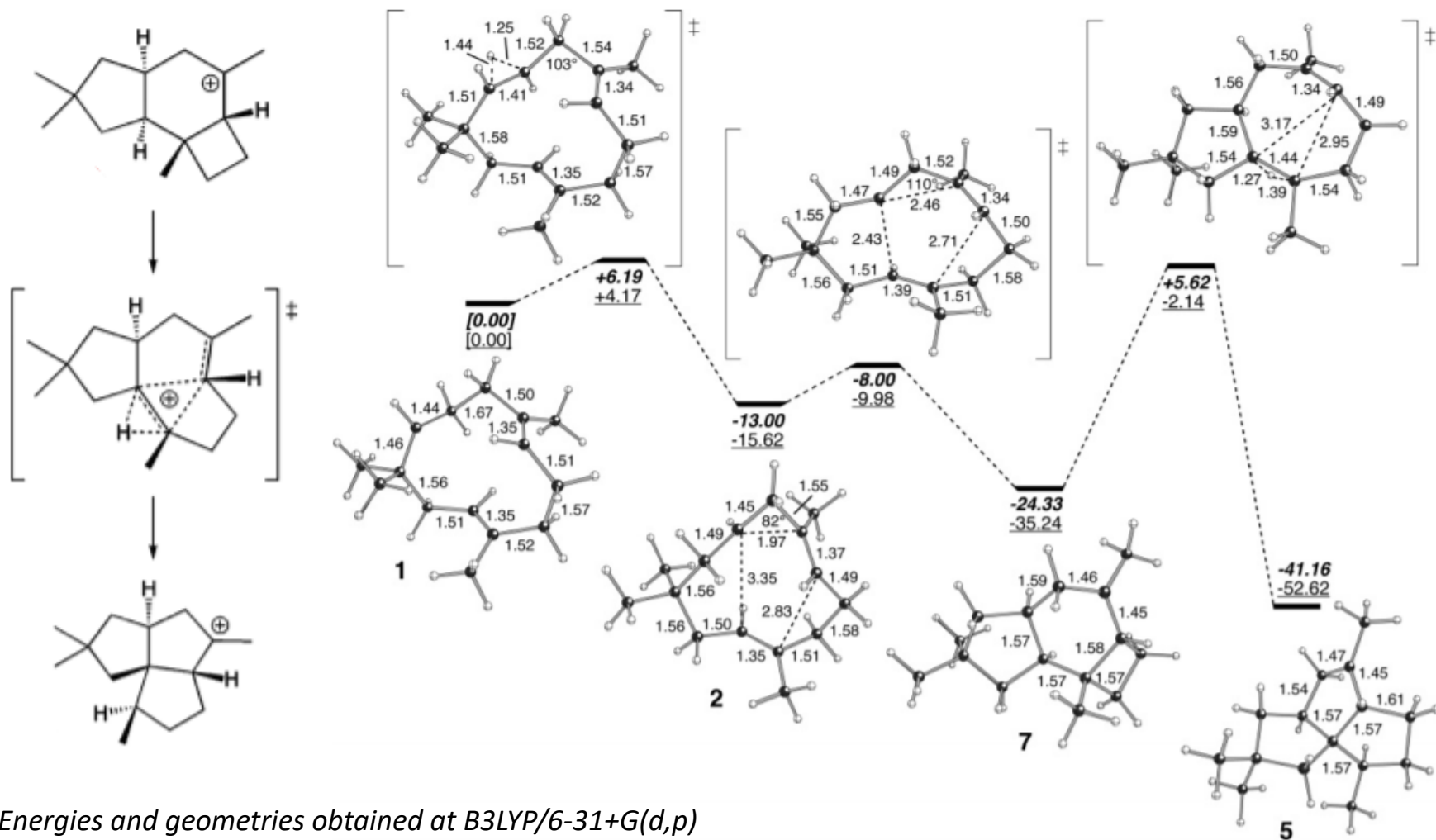
3. Perform a geometry optimisation on desired structure

(Include frequency calculation to determine the identity of the stationary point)

4. Obtain single point energy of the optimised structure at a higher level of theory
5. Determine the relative energies of your system
6. Optional: Perform an IRC calculation

Theoretical Studies on Farnesyl Cation Cyclization: Pathways to Pentalenene

Pradeep Gutta and Dean J. Tantillo*



Energies and geometries obtained at B3LYP/6-31+G(d,p)

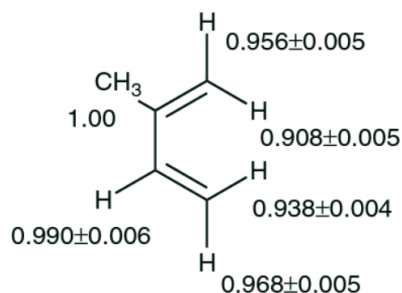
Underlined, single points obtained at mPW1PW91/6-31+G(d,p)

Tantillo, J et al.; *J. Am. Chem. Soc.* **2006**, 6172.

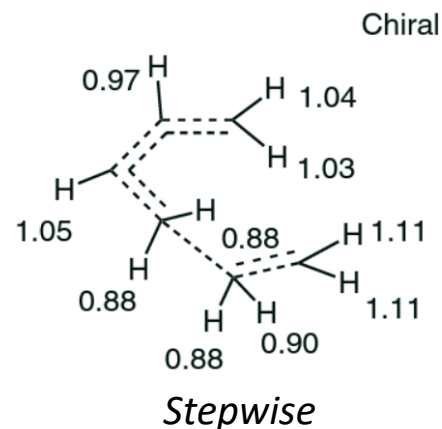
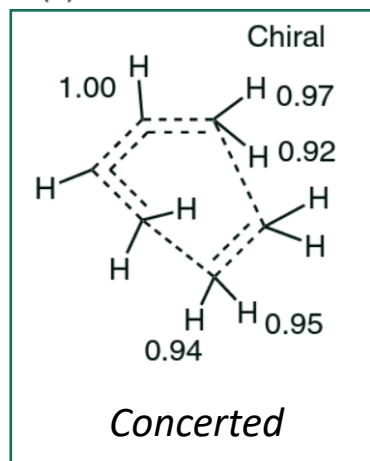
Additional Application: KIE Studies

- Kinetic Isotope Effects (KIE)– another mechanistic study
 - Determine the nature of the transition in pericyclic reactions
- Calculating vibrational frequencies of isotopologues (^2H and ^{13}C)
- *Quiver/THERMISTP* or *ISOEFF* software packages available
 - Gives a more precise calculation of the vibrational frequencies

Experimental Values



Calculated Values



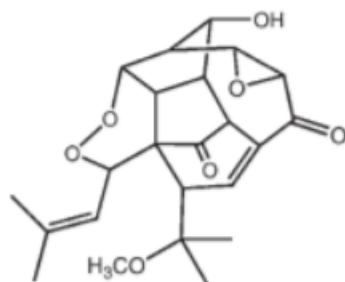
Level of theory: B3LYP/6-31G(d)

Singleton, D.A. et al.; *J. Am. Chem. Soc.*, **1995**, 117, 9357.

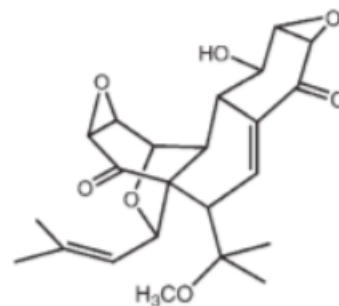
Houk, K.N., Singleton, D.A. et al.; *J. Am. Chem. Soc.*, **1996**, 118, 9984.

Additional Application: NMR Studies

- Predict the NMR spectrum from a proposed structure
- Valuable tool in natural product chemistry



**Hexacyclinol originally
proposed structure**



**Hexacyclinol
revised structure**

Additional Application: NMR Studies

- Three Part Method:
 1. Geometry optimisation/frequency calculation
 - Suggested by Tantillo: B3LYP/6-31+G(d,p) in gas phase
 2. Calculate NMR isotropic shielding constants
 - mPW1PW91 or PBE0 are best with 6-311+G(2d,p) basis set
 - Include implicit solvation model
 3. Adjust chemical shifts with experimentally-derived scaling factors
- Commonly used software: Spartan, CHARMM, TINKER, INSIGHT II, Hyperchem, Macromodel
- Useful resource: <http://cheshirenmr.info/index.htm>

Additional Useful resources

- Bachrach, S. *Computational Organic Chemistry (2nd Ed.)*, Wiley-VCH: Weinheim, Germany, **2014**.
- Koch, W.; Holthausen, M.C. *A Chemist's Guide to Density Functional Theory (2nd Ed.)*, Wiley-VCH: Weinheim, Germany, **2001**.
- Bachrach's blog: <http://comporgchem.com/blog/?cat=52>
- Rzepa's blog: <https://www.ch.imperial.ac.uk/rzepa/blog/?tag=1>

Topics Not Covered

Quantum tunneling effects

Organic Reaction Dynamics
Transition state bifurcation

Benchmarking/calibration

Basis set superposition error

Spin contamination

Solvation models

Time-dependent DFT