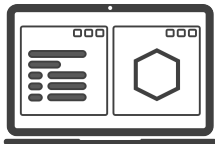


Introduction to Computational Chemistry

Part 2: Reaction Pathways from Scratch

Eno Paenurk & Patrick Finkelstein & Felix Pultar



03.05.2023



- Part 1: Takeoff
- Part 2: Reaction pathways from scratch
- Part 3: Preparing structures
- Part 4: Density Functional Theory
- Part 5: Organometallics
- Part 6: Spectroscopy
- Part 7: Chemical concepts

What you should know already



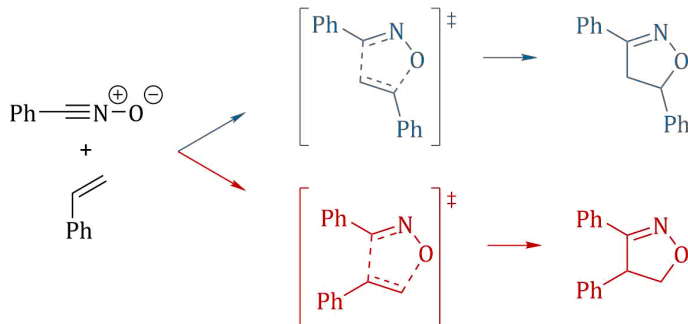
- Access to the cluster
- Navigation in the terminal
- Submission of simple scripts



- Automated calculation of reaction energy profiles (*black box* approach)
- Analysis of the computational pipeline
- Things to consider/potential problems

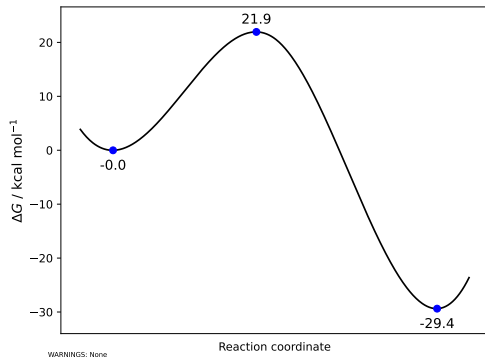
Provide bridge between ChemDraw and other graphical interfaces and QM software that runs in the terminal on Linux clusters.

Example from Last Week

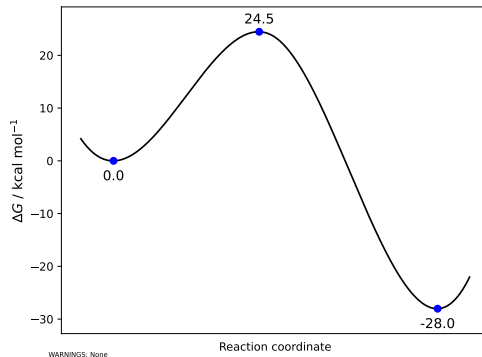


Which pathway will the reaction go?

1,3-Isoxazoline



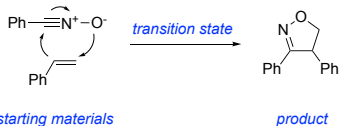
1,2-Isoxazoline



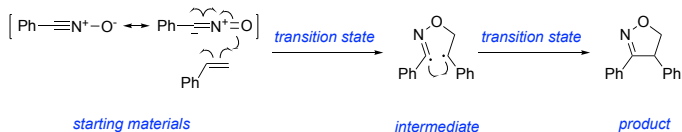
Result: $\Delta\Delta G^\ddagger = 2.6 \text{ kcal/mol}$ (energy barrier), $\Delta\Delta G = 1.4 \text{ kcal/mol}$ (free energy difference)



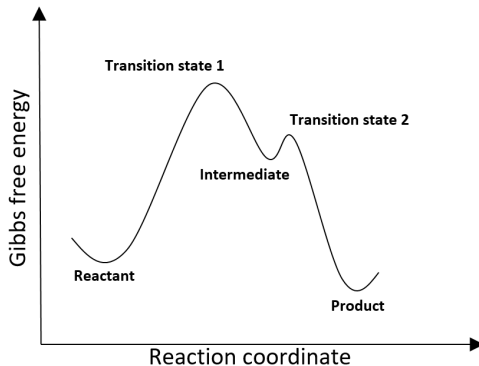
Option 1: concerted (Huisgen)



Option 2: stepwise (Firestone)

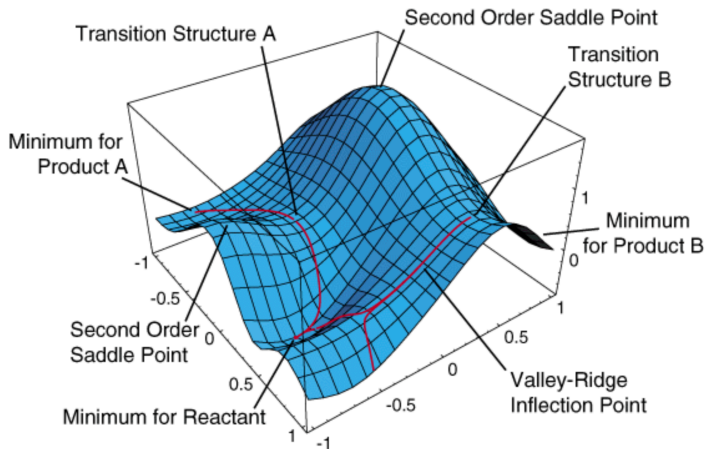


- 1 Consider reasonable mechanisms
- 2 Partition into elementary steps
- 3 Identify relevant intermediates and transition states



- **Reactants and Intermediates:** Local minima on potential energy surface
- **Transition States:** First-order saddle points connecting two minima

Problem: Potential Energy Surface is High-Dimensional



J. Comp. Chem. **2003**, 24, 1514.



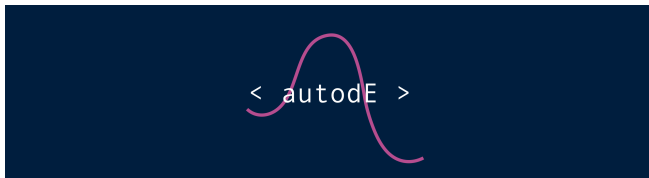
General workflow to compute a reaction profile (**black box today, details in later weeks**):

- 1 Convert 2D ChemDraws to 3D objects (Week 3)
- 2 Geometry optimization (Week 4)
- 3 Frequency calculation and check for *imaginary frequencies* (Week 4)
- 4 Extraction of Gibbs free energy (Week 4)
- 5 Analysis of transition state (Week 4)

Typically *trivial* to localize reactants but *hard* to localize transition states



Most of these steps have been automated for you!



Computational Chemistry Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2021**, 60, 4266–4274

International Edition: doi.org/10.1002/anie.202011941

German Edition: doi.org/10.1002/ange.202011941

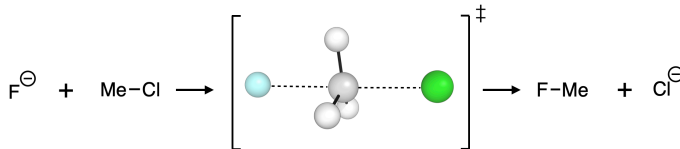
autodE: Automated Calculation of Reaction Energy Profiles— Application to Organic and Organometallic Reactions

*Tom A. Young, Joseph J. Silcock, Alistair J. Sterling, and Fernanda Duarte**

<https://github.com/duartegroup/autodE>



Describe reaction programmatically with Python and SMILES



```
1 import autode as ade
2 ade.Config.n_cores = 4
3
4 rxn = ade.Reaction("CCL.[F-]>>CF.[Cl-]", name='sn2', solvent_name='water', temp=273.15)
5 rxn.calculate_reaction_profile(free_energy=True)
```

SMILES: simplified molecular-input line-entry system (stay tuned!)

<https://duartegroup.github.io/autode/quickstart.html>

Tailored autodE for Euler and Grace: icctools



Import code from icctools

```
from icctools import librxn
```

Define reaction ...

```
rxn_name = "sn2-reaction" # no spaces  
rxn_smiles = "CCL.[F-]>>CF.[Cl-]"  
rxn_solvent = "water"  
rxn_temperature = 273.15
```

... and resources

```
n_cores = 4  
memory_per_core = 1024 # in MB  
method = librxn.Method.XTB
```

Run calculation and print results

```
rxn = librxn.calculate_reaction_profile(rxn_smiles, rxn_solvent, rxn_temperature, rxn_name,  
                                       n_cores, memory_per_core, method)  
librxn.print_results(rxn)
```

Components of autodE Used in this Course



Python module to interface **electronic structure theory** software

- RDKit (Greg Landrum, Riniker Group @ ETHZ)
Cheminformatic toolkit
- xtb (Grimme Group @ University of Bonn)
lmethod: Fast but inaccurate semi-empirical software
- ORCA (Neese Group @ MPI Mülheim)
hmethod: Comprehensive electronic structure software package



Combination of lmethod and hmethod reduces computational cost



- 1 Convert SMILES strings to mathematical graph
- 2 Identify forming and breaking bonds
- 3 Enumerate conformers of **products** and **starting materials**
- 4 Conformer *geometry optimization*
- 5 Localize **TS candidates** via *relaxed scan* along involved bonds
- 6 Enumerate TS conformers and optimize geometries
- 7 Verify transition state by following the reaction coordinate
- 8 *Single point calculation* of stationary points
- 9 *Frequency calculation* (Hessian matrix)
- 10 Extract Gibbs free energy and plot profile

We will deal with many of these concepts in more detail in the following weeks.

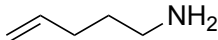


Idea: Encode chemical structure with characters

- Hydrogens, single and aromatic bonds are usually omitted
- Stereocenters, double and triple bonds, cycles, etc. supported



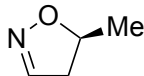
CCCCC



C=CCCCN



C1CCCCC1



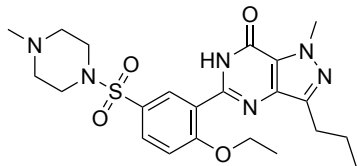
C[C@H]1CC=NO1

<https://www.daylight.com/dayhtml/doc/theory/theory.smiles.html>



Idea: Encode chemical structure with characters

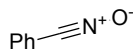
- Hydrogens, single and aromatic bonds are usually omitted
- Stereocenters, double and triple bonds, cycles, etc. supported
- Separation of molecules with ".", reaction arrow with ">>"



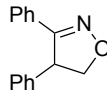
```
CN1CCN(CC1)S(=O)(C2=CC(C3=NC4=C(C(N3)=O)N(N=C4CCC)C)=C(OCC)C=C2)=O
```



+



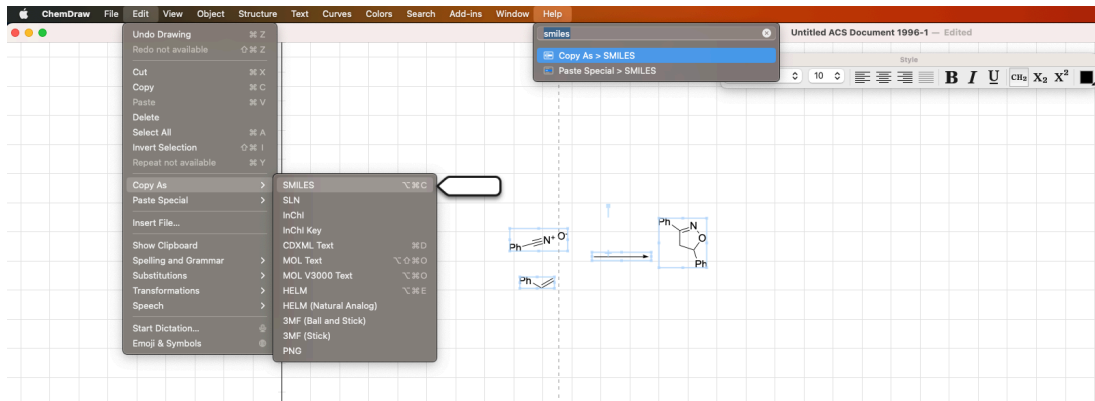
>>



```
C=CC1=CC=CC=C1.[O-][N+]#CC2=CC=CC=C2>>  
C3(C4=CC=CC=C4)=NOCC3C5=CC=CC=C5
```

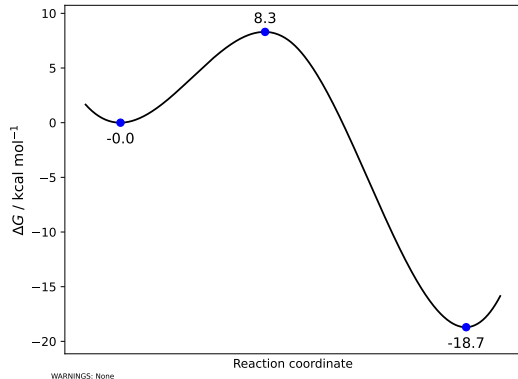
Warning: SMILES can fail for certain types of molecules and organometallics (see Week 3).

Copy & Paste with ChemDraw to SMILES



Advice: Always double-check generated SMILES, e.g., via ChemDraw (Paste Special).

Result of icctools and autode



```
Saving transition state templates in /cluster/home/fpultar/.icc-2023/autode-lib
Using BP86 functional as hmethod
Using 4 cores and 1024 MB of memory per core for sn2-reaction.
Starting from SMILES
```

Energies

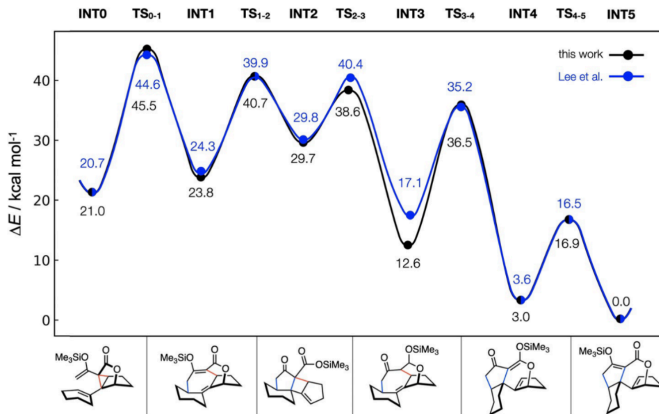
```
ΔE_r (kcal mol⁻¹) = -19.80
ΔE‡ (kcal mol⁻¹) = 4.64
ΔH_r (kcal mol⁻¹) = -18.95
ΔH‡ (kcal mol⁻¹) = 3.40
ΔG_r (kcal mol⁻¹) = -18.71
ΔG‡ (kcal mol⁻¹) = 8.30
```

TS info

```
Number of imaginary freqs = 1
First imaginary freq (cm⁻¹) = -358.9
```

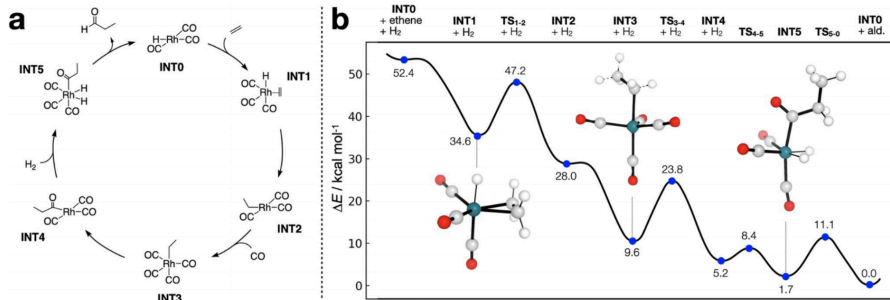
Next week we will also look at the generated 3D structures.

Motivating Example: Ireland-Claisen in Total Synthesis



Duarte, ACIE **2021**, 60, 4266–4274.

Motivating Example: Rh-Catalyzed Hydroformylation



Duarte, ACIE **2021**, 60, 4266–4274.

We encourage you to look at the paper and supporting information to see more examples.



Caveats of Automation

- All steps from SMILES parsing to the final profile are automated
- If any step fails, calculations cannot easily be recovered
- Some errors may be undiscovered (e.g., wrong double bond geometry, wrong TS geometry, ...)

Fix:

- Update software regularly
- Check error files and structures (see exercises and next weeks)
- Check that your generated SMILES actually encode what you think they encode



One calculation for each elementary step

- Many reactions in the lab involve multiple steps
- Submit one calculation for each elementary step (i.e., arrow pushing)

Using adequate methods

- AutodE has reasonable defaults
- But, your systems may require changing these defaults (next weeks!)



Concentration effects

- Gibbs free energy depends on the different concentrations of reactant and product.
- Account for very big excess (e.g., in a catalytic reaction) through a correction term:

$$\Delta G = \Delta G^\circ + RT \ln \frac{[Product]}{[Reactant]}$$

Temperature effects

- Calculate the thermochemical correction at the correct temperature
- Fast and easy calculation once you have the Hessian (see Handout)



Homolytic cleavages:

Can lead to multireference transition states

Potential fix:

Consult your local computationalist





Non-statistical effects

Statistical rate theories may not be adequate to describe the experimental behaviour (see *PCCP*, **2011**, 13, 20906)

Entropic intermediates

If the TS corresponding to the rds of a reaction is not a maximum on the PES but an entropic maximum, it will not be found with the methods we showed (see *JACS* **2012**, 134, 1914)



