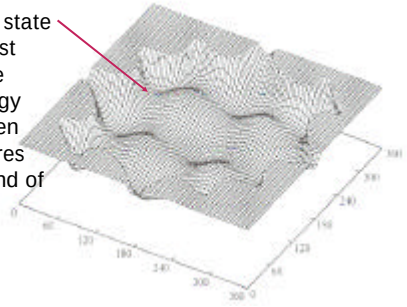
Transition State Modeling

Transition States

- A transition state is the highest point on the lowest energy path between two structures (at either end of a single mechanistic step)



TS Modeling

- When do you need the TS geometry?
  - To better understand reaction mechanism
  - To understand the influence of substituents
  - As input for computation of TS properties at higher levels of theory (quantum mechanics)
- When do you need the TS energy?
  - To determine relative rates of conformational conversion
  - To determine relative reaction rates

TS Modeling by Molecular Mechanics

- Quiz:
  - Given what you know about the molecular mechanics functional form, which of the following are appropriate to do using molecular mechanics?
    - Model relative rates of conformational interconversion
    - Model relative reaction rates involving bond breaking/making
    - Estimate TS geometry for reactions involving bond breaking/making
  - Explain why these are/are not appropriate.

Quiz Answers

- Model relative rates of conformational interconversion
  - This is appropriate, the torsional parameter is parameterized to reproduce the energy as a function of rotation through the entire 360º range
- Model relative reaction rates involving bond breaking/making
  - Inappropriate, most MM forcefields utilize a harmonic stretching potential to represent energy as a function of bond length and vastly overestimate the energies at long bond lengths. Even for relative reaction rates, these energies are likely to give completely unreliable results.
- Estimate TS geometry for reactions involving bond breaking/making
  - Either answer is fine here, we are about to discuss why this is appropriate!

Methods for MM TS Modeling

1. Hold atoms involved in bond making/breaking fixed at TS geometry and work with remainder of structure with MM methods
2. Define TS atom types and develop parameters that alter the potential energy surface so that TS geometry is at a minimum [Houk*]
3. Model starting material and product -> force both toward TS and look for intersections (in terms of geometry) [Jensen]

* Chem. Rev. **1993**, 2439-2461

TS Atoms Fixed

- Requires known TS geometry for model structure (Usually from quantum mechanical calculations)
- Assumes that changes in positions of other atoms (or changes in substituents) does not affect geometry of atoms involved in reaction at the TS

TS Parameterized as Minimum

- Requires known TS geometry
  - Usually from QM
  - This gives references values (r_0, ϕ_0, Θ_0)
- Requires imposed 'stiffness' of TS geometry
  - Gives stretching constants, bending constants, and torsional parameters

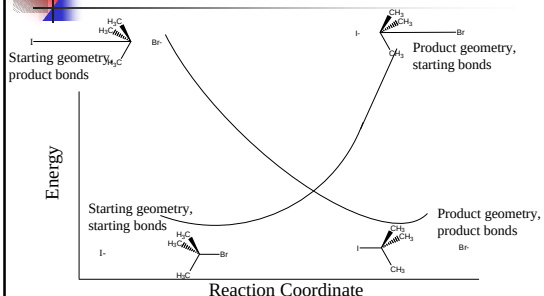
TS by PES Crossing

- Requires general understanding of the reaction coordinate (mechanism) but not the exact TS geometry
- Requires ground state parameters for the starting material and product of a single mechanistic step -> two energies calculated at each position on the PS, one using SM functions, the other using product functions
- Should not assume that the reaction coordinate is exactly straight between SM and product -> example: cyclohexane chair conversion involves twisted TS

Class Exercise

- Compute the geometry of the TS for the S_N2 substitution of methyl bromide with iodide

Approach to Exercise



Rxn coordinate SHOULD involve changes in C-C-C bond angles as well as C-X distances!

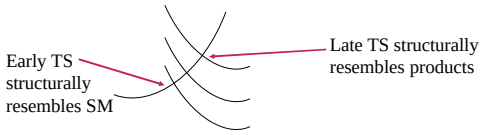
TS Energies

- TS energies are best computed using quantum chemical methods
  - Hybrid QM/MM with reacting centers defined as QM region, remainder as MM region
  - Pure QM, either wavefunction or density functional methods
  - QM using effective core potentials (ECP's) if only valence electrons are involved in the reaction
- TS geometries from PES crossing can be used as initial input for QM methods, which are slow to find TS when initial guess is poor

Comparison of Methods

- Only PES crossing can be done to find an unknown TS geometry
- Both PES crossing and TS with fixed atoms can be done without new parameters
- PES crossing method will be inadequate for rxns (bond breaking) if a pure harmonic bond stretching term is used (MMFF94 does not use a pure harmonic)
- PES crossing is most likely to produce results that agree with Hammond's Postulate

Hammond's Postulate



Reading

- Jensen, F. "Transition Structure Modeling by Intersection Potential Energy Surfaces", J. Comp. Chem., **1994**, 15(11), 1199-1216

Innovative Quiz Answer

- Given what you know about the molecular mechanics functional form, which of the following are appropriate to do using molecular mechanics?
  - Model relative rates of conformational interconversion
  - Model relative reaction rates involving bond breaking/making
- Both appropriate:

$$A \underset{}{\overset{K_{eq}}{\rightleftharpoons}} B$$ can calculate ΔG and that equals $-RT\ln K_{eq}$

$$\log\frac{k_X}{k_H} = s_{rate}\,r \qquad \log\frac{K_X}{K_H} = s_{equilbrium}\,r$$ (Hammett Equations)

For reactions with known reaction constants (for both equilibrium and rate), relative equilibrium constants can be used to derive relative rates