

Week 10

Isotope Effects

10.1 Thermodynamic Isotope Effects

11/5:

- Today.
 - Finishing up transition state theory.
 - Then how isotope effects can tell us stuff about reactions.
- Lecture 16 recap.
 - We defined an approach to kinetics.
 - Basically, the $A \rightleftharpoons B$ equilibrium is decided by ΔG via

$$K_{\text{eq}} = e^{-\Delta G/RT}$$

- Then we can determine the rate at which this equilibrium is established via the Eyring equation,

$$k = \left(\kappa \frac{k_B T}{h} \right) e^{-\Delta G^\ddagger/RT}$$

- Qualitative intuition for the relationship between the forms of the Eyring and equilibrium equations: TST is effectively analyzing a quasi-equilibrium between the SMs and the activated complex.
- Lecture 16 continued.
- Let's think about the Eyring equation in terms of the entropies and enthalpies that make up ΔG^\ddagger .

$$k = \kappa \left(\frac{k_B T}{h} \right) e^{-\Delta H^\ddagger/RT} \cdot e^{\Delta S^\ddagger/R}$$

$$\ln k = \ln \left(\kappa \frac{k_B T}{h} \right) - \frac{\Delta H^\ddagger}{R} \left(\frac{1}{T} \right) + \frac{\Delta S^\ddagger}{R}$$

$$\ln \left(\frac{kh}{\kappa k_B T} \right) = -\frac{\Delta H^\ddagger}{R} \left(\frac{1}{T} \right) + \frac{\Delta S^\ddagger}{R}$$

- These manipulations allow us to take the Eyring equation in slope-intercept form, so that we can linearize experimental data and extract from it experimental values for ΔH^\ddagger and ΔS^\ddagger !
 - This process is called forming an **Eyring plot**.
 - If we can acquire data over a minimum temperature range of 30 K, we can extrapolate reasonably accurate data.
- Dick Zare at Stanford has some methods of observing activated complexes, but the main way of learning about them is indirectly through methods such as Eyring plots.

- So using Eyring plots, we can get ΔH^\ddagger and ΔS^\ddagger ... but what do the values of these so-called activation parameters tell us?
- Qualitative interpretation of activation parameters.
 - Typical Eyring plots have a negative slope.
 - This means that we typically have $\Delta H^\ddagger > 0$.
 - This should make sense! Activated complexes have stretched out, weaker, higher energy bonds.
 - The overwhelming majority of Eyring plots have said negative slopes due to said partial bonding.
 - Caveat: $\Delta H^\ddagger < 0$ is physically possible, though uncommon.
 - It corresponds to scenarios in which the activated complex is more enthalpically stable than the starting materials.
 - There will be a question about a system with a negative enthalpy of activation on PSet 3!!
 - Typical Eyring plots imply $\Delta S^\ddagger < 0$.
 - $\Delta S^\ddagger < 0$ corresponds to an associative process.
 - This is because degrees of freedom are being diminished in the activated complex, e.g., restricting rotation due to partial bonding.
 - Example: The activated complex in a Diels-Alder reaction has an entropy of activation (ΔS^\ddagger) of -45 e.u..
 - This is even higher than the 30 e.u. we said we typically get in the van't Hoff analysis because we're restricting even more DOFs here, such as the rotation of dienophile.
 - $\Delta S^\ddagger > 0$ implies a dissociative process.
 - Example: $t\text{BuO}-\text{O}t\text{Bu} \longrightarrow 2 t\text{BuO}\cdot$ has $\Delta S^\ddagger = 11$ e.u..
 - $\Delta S^\ddagger \approx 0$ implies an intramolecular process.
 - Example: 4π retrocyclization of cyclobutene has $\Delta S^\ddagger = -1$ e.u. ≈ 0 e.u..
 - The error bars on these values are probably ≈ 5 e.u., so don't read anything into the above value besides that it's "close to zero."
- Sometimes, big ΔG values (positive or negative) can affect reaction kinetics. Let's look at how.
- The interplay of thermodynamics and kinetics: A justification for the Hammond postulate.
- Let's first build a mathematical model for our justification.

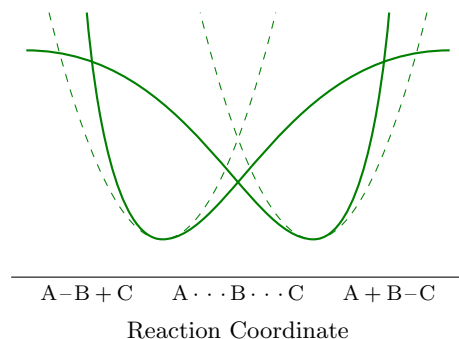


Figure 10.1: Bell-Evans-Polanyi principle: A model to visualize the principle.

- Consider a model reaction $A-B + C \rightleftharpoons A + B-C$.
- $A-B$ has an anharmonic bond energy well, and we can think of the $B-C$ bond energy well as being mirror-reflected.
 - These wells will have a depth on the order of a bond enthalpy, i.e., ≈ 70 kcal/mol.
- The two curves meet when $A-B$ is stretching and $B-C$ is stretching, i.e., in $A \cdots B \cdots C$.
 - This looks a lot like an activated complex!
- The intersection point of these two curves is pretty far down.
 - Recall from Table 9.3 that for an activation energy to be viable, it has to be < 25 kcal/mol.
 - Thus, since the well depth is ≈ 70 kcal/mol and the intersection point is pretty far down, we should be good to go.
- But how do we calculate this intersection point?
 - Although the wells aren't harmonic, we may approximate them reasonably well as parabolas.
 - Then solving for the parabolic curve crossing intersection point is mathematically simple!
- Let's do parabolic curve crossing.

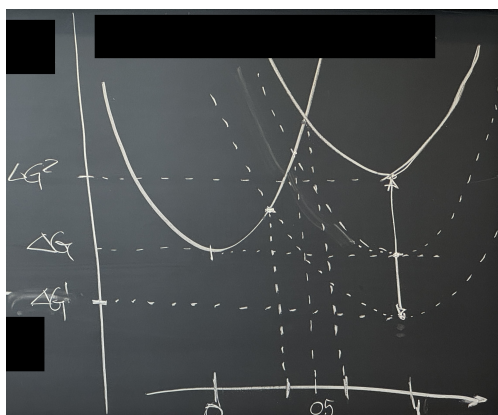


Figure 10.2: Bell-Evans-Polanyi principle: Parabolic curve crossing.

- Both parabolas should have the same curvature.
- Suppose first that the second vertex is lower in energy by ΔG^1 .
 - This implies that the TST happens at less than 0.5 along the reaction coordinate.
 - Implication: Exergonic reactions have TSTs lower in energy than the degenerate reaction, and with a TST more like the SMs (“earlier”).
- If $\Delta G^2 > 0$, endergonic reactions have a TST more like the products (“later”) and higher energy.
- This is all collectively known in the literature as the **Bell-Evans-Polanyi principle**, or alternatively as the **Hammond postulate**.
- Example: Radical halogenation of alkanes.^[1]

	1° C-H	2° C-H	3° C-H
F·	1	1.2	1.4
Cl·	1	3.9	5
Br·	1	82	1600

Table 10.1: Relative reactivity rates in radical halogenation.

¹See Figure 6.12 for where Masha covered this.

- Consider the reaction of $\text{F}\cdot$, $\text{Cl}\cdot$, and $\text{Br}\cdot$ with primary, secondary, and tertiary C–H bonds.
- Specifically, consider the relative rate k_{rel} of these reactions.
- Selectivity indicates that we should radically halogenate the tertiary C–H first.
- Additionally, we observe drastically improved selectivity as we get to heavier halogens. Here's a quantitative explanation for this phenomenon.
 - The reactants are at about 100 kcal/mol because that's the approximate R–H bond enthalpy; see Masha's list!!
 - Then Cl–H is ≈ 103 kcal/mol.
 - For comparison, the H–Br bond dissociation energy is ≈ 87 kcal/mol.
- Alex now essentially redraws Figure 6.12.
- This concludes Lecture 16.
- We now begin Lecture 17: Isotope effects.
- Recall from your previous coursework in quantum mechanics that atomic-scale oscillators have quantized — not classically continuous — energies.

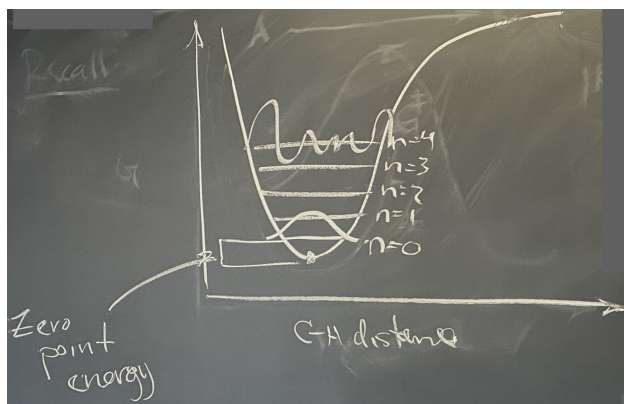


Figure 10.3: Quantum oscillator potential.

- So while we do have a minimum on the potential energy surface, the molecule does not hang out there because this would require that the quantum particle is static (so we'd know its position and momentum, violating Heisenberg uncertainty).
- So at the energy minimum, there is residual energy latent in the system called **zero-point energy**.
- So even in the lowest wave function, there's gonna be some spread of the nuclear position beyond the potential well.
- **Zero-point energy.** Also known as **ZPE**.
- Quantized vibrational energies.

Bond	μ
C–H	0.92
C–D	1.72
^{12}C – ^{12}C	6.00
^{12}C – ^{13}C	6.24

Table 10.2: The reduced mass of common chemical bonds.

- We have that

$$E_n = h\nu \left(n + \frac{1}{2} \right)$$

- Recall that an (asymmetric) molecule has $3N - 6$ vibrational modes.
- This frequency of oscillation (per Hooke's law) is related to the force constant and **reduced mass**.

$$\nu = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}}$$

- Atoms are defined by the number of protons, but we can change the number of neutrons as much as we want! This will change the reduced mass.
- The magnitude of isotope effects is the greatest when the reduced mass changes the most.
- **Reduced mass:** The quantity given as follows, where m_1, m_2 are the masses of two particles in a system. Denoted by μ . Given by

$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

- Looking at the deuterium isotopologue vs. carbon.

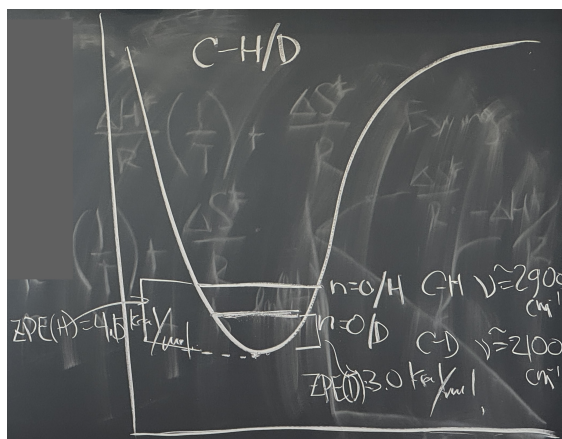


Figure 10.4: Isotopic differences alter the thermodynamic stability of a chemical bond.

- The zero-point energy for the C–D oscillator is less than for the C–H operator.
- Thus, C–H has $\nu \approx 2900 \text{ cm}^{-1}$ and C–D has $\nu \approx 2100 \text{ cm}^{-1}$.
- This means that it will cost more energy to dissociate a C–D bond vs. a C–H bond.
- The potential is defined only by positive and negative charges, so *it's* the same; it's only the isotopes within it that change.
- The zero-point energy of a C–H bond is 4.5 kcal/mol, and the zero-point energy of a C–D bond is 3.0 kcal/mol.
- These 1.5 kcal/mol impact the kinetics reactivity by about sevenfold!

- Equilibrium isotope effects.

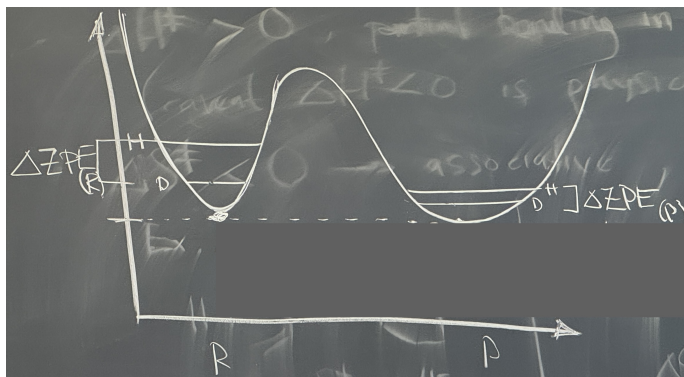


Figure 10.5: Equilibrium isotope effects.

- Consider an energetically degenerate reaction.
- Suppose that the difference in ZPEs is smaller in the products' slack potential.
 - Symbolically, $\Delta \text{ZPE}_{(R)} > \Delta \text{ZPE}_{(P)}$.
- So the effective ΔG for H is greater than the one for D: $-\Delta G_H > -\Delta G_D$.
 - Thus, $k_H/k_D > 1$.
- Example: Equilibrium isotope effects during reductive elimination/oxidative addition at transition metals.

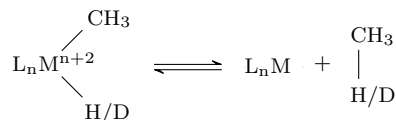


Figure 10.6: Reductive elimination of methane.

- Consider a generic metal-ligand complex (L_nM) undergoing the reaction in Figure 10.6.
- The typical BDE for a M–H bond is 40–80 kcal/mol.
 - The BDE for a methane H_3C –H bond is 104 kcal/mol.
- Since the metal potential is shallower, it is slacker and hence has a lower associated force constant.
 - Symbolically, $k_{\text{M-H}} < k_{\text{C-H}}$.
- Since the ZPE difference is smaller in the more slack potential (per Figure 10.5), it follows that

$$\Delta \text{ZPE}_{\text{M-H/D}} < \Delta \text{ZPE}_{\text{C-H/D}}$$
- Takehome: Deuterated species prefer to be in the well with the stronger force constant.
- Accounting for the anharmonicity^[2] in the potential wells.

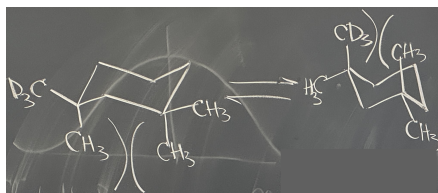


Figure 10.7: Steric isotope effects.

²How is this related to anharmonicity??

- Consider the ring flip of 1,1,3,3-tetramethylcyclohexane, with one of the methyl groups actually a CD₃ group.
- Experimentally, we observe that

$$K = \frac{[\text{CD}_3 \text{ ax}]}{[\text{CD}_3 \text{ eq}]} = 1.042$$

at -100°C .

- It is preferable to have the CD₃ group axial because it is smaller: The lower vibrational amplitude ν for C–D bonds relative to C–H bonds literally shrinks the sterics of the group (Anslyn & Dougherty, 2006, pp. 430, 434).
- How can we link equilibrium isotope effects to kinetics?
 - Like at the beginning of class, we use transition state theory!
 - Indeed, let's apply our understanding of equilibrium isotope effects to the quasi-equilibrium between the starting materials and transition state. This can give us valuable insight into the relative rates of reaction for heavier vs. lighter isotopologues.
- Kinetic isotope effects.

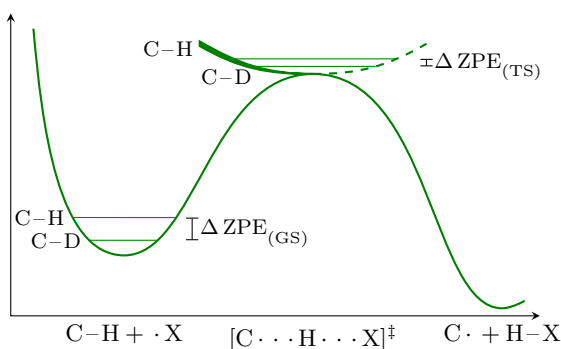
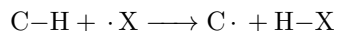


Figure 10.8: Kinetic isotope effects.

- Consider the HAT reaction



- This is a nondegenerate reaction, energetically.
- Recall that transition structures are maxima along one direction, but minima along every other direction in the hyperspace (see Figure 9.4).
 - It follows that ΔZPE is relatively small in the TS, because TS potentials are pretty slack compared with bond potentials.
- The important equation we can write from the above diagram is

$$\Delta\Delta G^\ddagger = \Delta\Delta\text{ZPE} = \Delta\text{ZPE}_{(\text{GS})} - \Delta\text{ZPE}_{(\text{TS})}$$
 - This means that it's easier to take C–H to the transition state than C–D.
 - This is a **normal KIE**, where $k_{\text{H}}/k_{\text{D}} > 1$.
 - This is also primary (1°) because the isotope-sensitive bond is the one being broken/made.
- **Inverse KIEs** involve cases in which $k_{\text{D}}/k_{\text{H}} < 1$.
 - This is also 1° .
- We can also have **secondary** KIEs, where we label a position potentially far from the reactive site.
- Next time: Using KIEs to diagnose reaction mechanisms, single isotopologues under different reaction conditions give us different information, etc. Takeaways: KIEs are super useful.