

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 .

$$\begin{aligned} k &= \kappa \left(\frac{k_B T}{h} \right) e^{-\Delta H^\ddagger / RT} \cdot e^{\Delta S^\ddagger / R} \\ \ln k &= \ln \left(\kappa \frac{k_B T}{h} \right) - \frac{\Delta H^\ddagger}{R} \left(\frac{1}{T} \right) + \frac{\Delta S^\ddagger}{R} \\ \ln \left(\frac{k h}{\kappa k_B T} \right) &= -\frac{\Delta H^\ddagger}{R} \left(\frac{1}{T} \right) + \frac{\Delta S^\ddagger}{R} \end{aligned}$$

- 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 $\Delta S^\ddagger = 11\text{ e.u.}$
 - $\Delta S^\ddagger \approx 0$ implies an intramolecular process.
 - Example: 4π retrocyclization of cyclobutene has $\Delta S^\ddagger = -1\text{ e.u.} \approx 0\text{ e.u.}$
 - The error bars on these values are probably $\approx 5\text{ e.u.}$, 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.

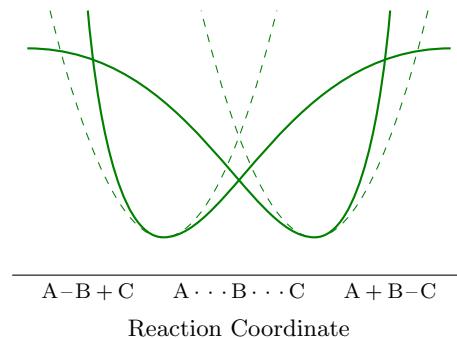


Figure 10.1: Bell-Evans-Polanyi principle: A model to visualize the principle.

- 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.

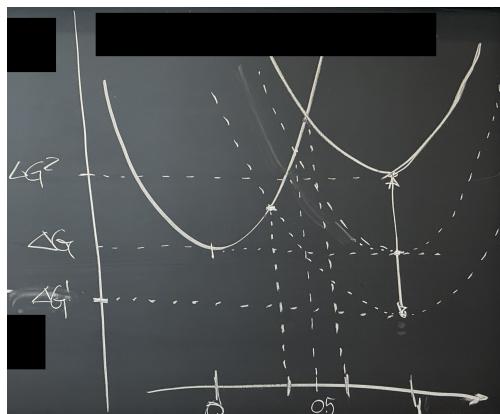


Figure 10.2: Bell-Evans-Polanyi principle: Parabolic curve crossing.

- 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 reacton 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.

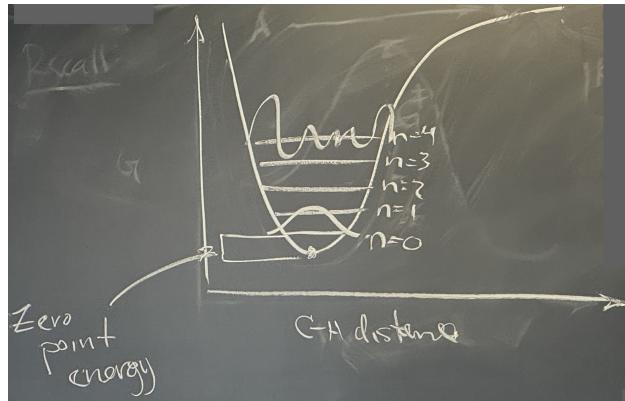


Figure 10.3: Quantum oscillator potential.

- 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**, E_0 .
- Quantized vibrational energies.

Bond	μ
C–H	0.92
C–D	1.72
$^{12}\text{C}–^{12}\text{C}$	6.00
$^{12}\text{C}–^{13}\text{C}$	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.

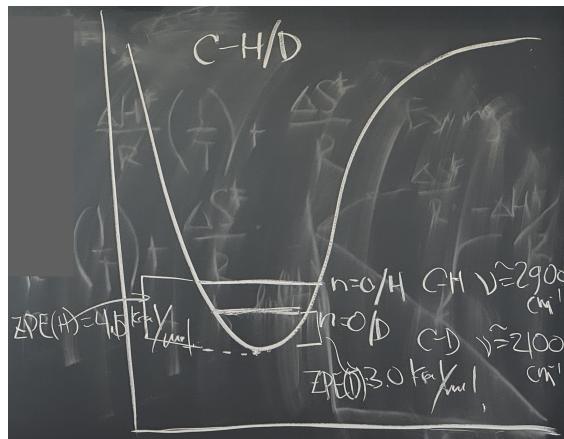


Figure 10.4: Isotopic differences alter the thermodynamic stability of a chemical bond.

- 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.

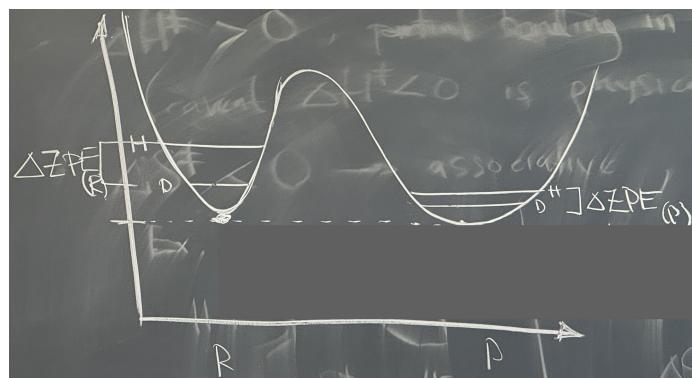


Figure 10.5: Equilibrium isotope effects.

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

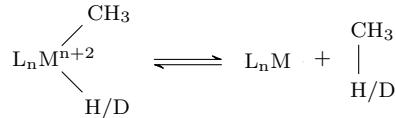


Figure 10.6: Reductive elimination of methane.

- 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 $\text{H}_3\text{C}-\text{H}$ bond is 104 kcal/mol.
- Since the metal potential is shallower, it is slackier and hence has a lower associated force constant.
 - Symbolically, $k_{\text{M}-\text{H}} < k_{\text{C}-\text{H}}$.
- Since the ZPE difference is smaller in the more slack potential (per Figure 10.5), it follows that

$$\Delta \text{ZPE}_{\text{M}-\text{H}/\text{D}} < \Delta \text{ZPE}_{\text{C}-\text{H}/\text{D}}$$

- Takehome: Deuterated species prefer to be in the well with the stronger force constant.
- Accounting for the anharmonicity^[2] in the potential wells.

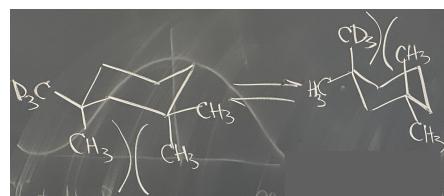


Figure 10.7: Steric isotope effects.

²How is this related to anharmonicity??

- Consider the ring flip of 1,1,3,3-tetramethylcyclohexane, with one of the methyl groups actually a CD_3 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 CD_3 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.

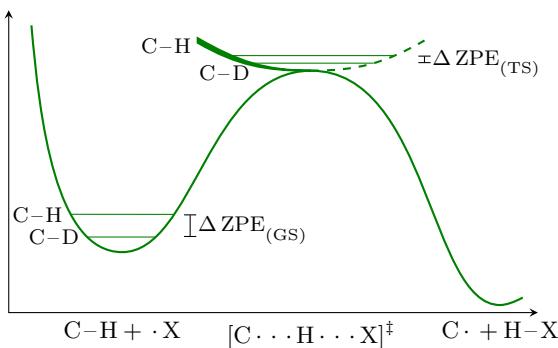


Figure 10.8: Kinetic isotope effects.

- 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

$$\Delta\Delta G^\ddagger = \Delta\Delta ZPE = \Delta ZPE_{(\text{GS})} - \Delta ZPE_{(\text{TS})}$$

- 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.

10.2 Kinetic Isotope Effects

11/7:

- Lecture 17 recap.
 - Potential energy surfaces remain unperturbed when switching between isotopologues because the potentials are defined by the electrostatic charge densities of the relevant nuclei.
 - However, the energetic position within the well of the vibrational wave functions varies with the reduced mass.
 - C–H/D isotope effects lead to six- or sevenfold selectivity differences.
- A note on the thermodynamic population of various energy levels.
 - Almost all molecules reside at the zero-point energy E_0 , so only considering ΔG 's and ΔG^\ddagger 's between zero-point energies *is* a good approximation.
- Today: Finalizing some of the descriptive aspects of isotope effects, especially in the transition state structure.
- Consider an atom-transfer reaction, like in Figure 10.8.

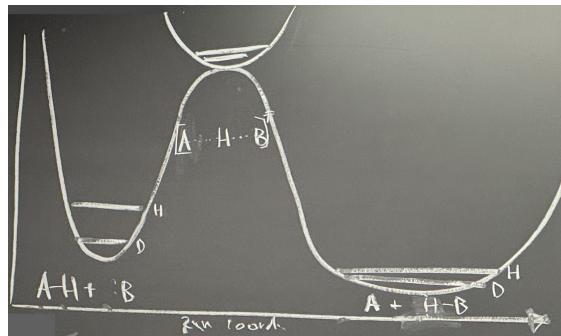
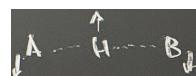


Figure 10.9: Atom-transfer potential energy surface.

- We may think of either an acid-base deprotonation or an HAT; it really doesn't matter.
- The ensemble $[A \cdots H \cdots B]^\ddagger$ is the transition structure.
 - It lives at a saddle point, so all of its vibrational modes live in the orthogonal potentials.
 - Since the TS is triatomic and linear, it has $3N - 5 = 4$ vibrational modes.
 - More specifically, it has 3 different *kinds* of vibrational modes, since the bending mode can happen in two orthogonal directions.
- In the parlance of vibrational spectroscopy, the molecular motion in the transition state is the extreme of the **asymmetric stretch**.



(a) Asymmetric stretch.



(b) Symmetric bend.



(c) Symmetric stretch.

Figure 10.10: Atom-transfer vibrational modes.

- This asymmetric stretch corresponds to the reaction coordinate.
 - This is the vibrational mode along which we're minimizing.
 - No vibrational value that we assign to this mode.
 - Downwards concavity at this point means all frequencies are imaginary.
 - If you use DFT to compute force constants in the TS (which we always should), it will tell us that the force constants are imaginary.
- The other modes include the **symmetric bending mode**.
 - This does modify the KIE. It contributes, but it a minor way that we'll discuss later.
- Then there's the **symmetric stretch**.
 - This mode most dramatically affects KIEs; in fact, it is the primary determinant of the KIE because it is the stretch affected when you switch isotopes.
- If the H or D atom is completely stationary in the TS, the isotopic sensitivity of the transition state goes to zero! Here are the conditions under which this happens.

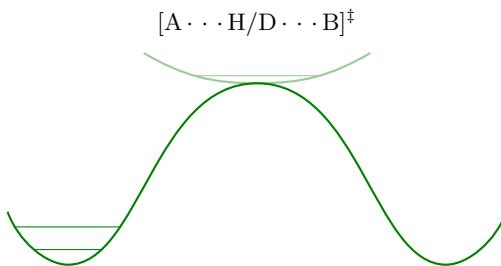
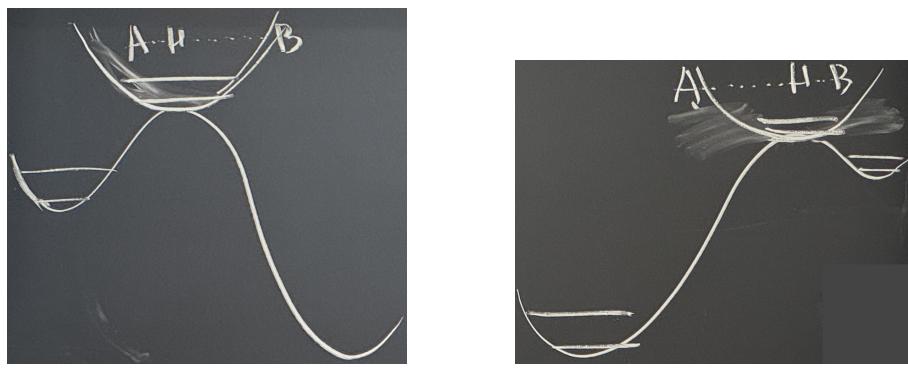


Figure 10.11: Thermoneutral kinetic isotope effects.

- The reaction has to be thermoneutral.
- A and B need to be identical (or at least have the same mass).
 - A thermoneutral HAT between atoms of very different masses gives some interesting KIEs.
 - This would be very devious to put on the exam!!
- With zero difference in zero-point energy between A–H and A–D in the transition state but still a good difference in the starting materials, it follows that $\Delta\Delta G^\ddagger$ should be fairly large.
 - Hence the kinetic isotope effect is pretty large in this regime.
- What about when the TST is asymmetric?



(a) Exergonic.

(b) Endergonic.

Figure 10.12: Thermodynamically asymmetric kinetic isotope effects.

- Consider an exergonic reaction (Figure 10.12a).
 - Per the Hammond postulate, the transition state will resemble the starting materials.
 - Thus, the difference in energy ΔE between the A–H and A–D transition states should be quite similar to the respective ΔE in the starting materials.
 - Hence, $\Delta\Delta G^\ddagger$ smaller, so the KIEs are less than maximal.
- Consider an endergonic reaction (Figure 10.12b).
 - Per the Hammond postulate, the transition state will resemble the products
 - Thus, ΔE will be nonzero (as it is in the products).
 - Hence, $\Delta\Delta G^\ddagger$ is once again smaller than its thermoneutral maximum, so the KIEs are correspondingly smaller than maximum.
- Takeaway: Kinetic isotope effects can give us a window in the precise atomic composition and orientation of the transition structure.
- We can measure the extent to which the magnitude of a kinetic isotope effect varies with thermodynamic asymmetry.

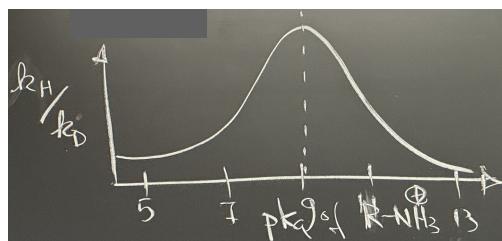


Figure 10.13: Variation in kinetic isotope effects with thermodynamic asymmetry.

- Consider the following acid-base deprotonation.

$$\begin{array}{c} \text{D/H} & \text{H/D} \\ \diagdown & \diagup \\ \text{Me} & \text{NO}_2 \end{array} + \text{R}-\text{NH}_2 \longrightarrow \begin{array}{c} \text{Me} & \text{NO}_2 \\ \diagdown & \diagup \\ \text{NO}_2 & \text{NH}_3^+ \end{array}$$

 - $pK_a \approx 9$ for a nitroalkane.
 - For nitroethane, specifically, $pK_a = 8.5$.
- We then vary R to change the pK_a of the conjugate acid of our amine base.
 - Our dependent variable is the relative rates k_H/k_D of deprotonation of the isotopologues.
- The result is a plot with a peak (greatest KIE) at $pK_a \approx 9$.
- Takeaway: This experimentally confirms that when we tune into a thermoneutral reaction, we get higher KIEs.
- Reference: Dixon and Bruice (1970).
- What happens in a nonlinear transition-state structure?



Figure 10.14: Nonlinear transition state.

- We get increasing contributions from the isotopically sensitive bending modes!
- This tends to decrease the $\Delta\Delta G^\ddagger$ from the ground state to the transition structure.

- This means that 1° KIEs can be much smaller.
 - Typical range: 1.5-3.5.
- Implication: A typical C–H stretching mode — via $R_3C-H \rightleftharpoons R_3C \cdots H$ — has $\nu \approx 2900\text{ cm}^{-1}$, whereas a typical C–H wagging mode — via $R_3C-H \rightleftharpoons R_3C-H\ddownarrow$ — has $\nu \approx 1350\text{ cm}^{-1}$.
- Aside: A reaction that has an anomalous KIE as a result of quantum tunnelling.

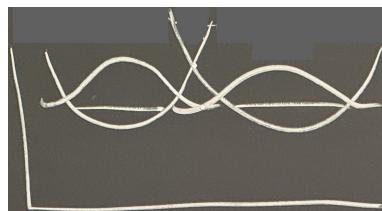


Figure 10.15: Intramolecular HAT can proceed through (rather than over) potential barriers.

- Consider the following intramolecular HAT within the tri-*t*-butylphenyl radical.
-
- One of the methyl groups is perdeuterated to CD_3 .
 - Here, $k_H/k_D \approx 13000$. Why such a big effect?
 - The only thing that moves along the reaction coordinate is the proton or deuteron.
 - However, it does not have to move *over* the potential barrier here; rather, it can quantum tunnel through it!
 - This is because per Figure 10.15, we get a spread of the vibrational wavefunctions (as we discussed in Figure 10.3). Thus, the hydrogen can migrate along the reaction coordinate *through* the potential barrier by just decreasing its wave function on one side and increasing it on the other!
 - Therefore, TST is not applicable here because the first assumption of TST (establishment of a quasi-equilibrium between the SMs and TST) is not met.
 - Reference: Brunton et al. (1976).
 - These tunnelling reactions are not all that rare.
 - Here's some new evidence that a reaction has its product selectivity determined by quantum tunnelling.

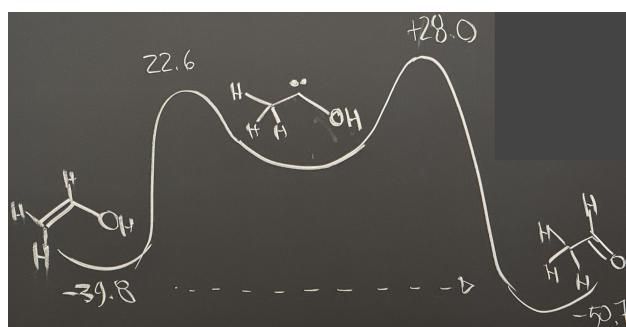
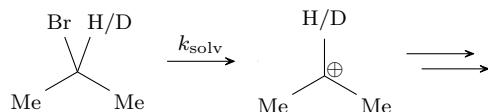


Figure 10.16: Quantum tunnelling can influence product selectivity.

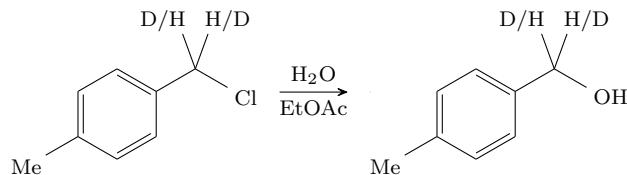
- The reactant is methylhydroxycarbene.
 - The adjacent π -donor makes this carbene a ground-state triplet.
 - This carbene becomes either acetaldehyde or vinyl alcohol.
 - The competing mechanisms are O–H and C–H migration to the carbene center.
 - The driving force for formation of vinyl alcohol is -39.8 kcal/mol .
 - The transition state stability for this migration is $+22.6 \text{ kcal/mol}$.
 - The driving force for formation of acetaldehyde is -50.7 kcal/mol .
 - The transition state stability for this migration is $+28 \text{ kcal/mol}$.
 - Per transition state theory, 5 kcal/mol should lead to a *devastating* selectivity for vinyl alcohol.
 - Experimentally, however, we observe *exclusive* formation of acetaldehyde.
 - Note that this reaction is carried out molecule-by-molecule in a matrix at 11 K ; i.e., the system is very cold, and every methylhydroxycarbene molecule is isolated from every other and hence allowed to react independently.
 - Additionally, $t_{1/2}(\text{H}, 11 \text{ K}) \approx 1 \text{ h}$ and $t_{1/2}(\text{D}, 11 \text{ K}) \rightarrow \infty$.
 - Therefore, the mechanism must be quantum tunnelling.
 - Reference: Schreiner et al. (2011).
- David: Why would we not get competitive keto-enol tautomerization?
 - At 11 K , there's not enough energy for keto-enol tautomerization (even though there is a thermodynamic driving force).
 - Additionally, keto-enol tautomerization is an intermolecular process, and everything is site isolated in the matrix.
 - Recall that we don't see uncatalyzed keto-enol tautomerization because it's Woodward-Hoffmann forbidden (see Figure 3.9b).
 - This is a good question, because this experiment does rely on zero tautomerization.
 - Kwanwoo: Temperature dependence of these quantum mechanical effects?
 - Quantum tunnelling is temperature independent in ways that transition state theory isn't.
 - A related constellation of isotope effects without primary-ness: Secondary (2°) isotope effects.
 - Let's establish the basics through an example.
 - Consider the solvolysis of isopropyl bromide via an $\text{S}_{\text{N}}1$ -like mechanism.



- We assume that k_{solv} is the RDS, and everything else is fast.
- Recall that $\nu_{\text{C}-\text{H}} \approx 2900 \text{ cm}^{-1}$.
 - In the cation, it's not all that different: $\nu_{\text{C}^+-\text{H}} \approx 2800 \text{ cm}^{-1}$.
 - The scissoring bend mode — which brings the proton or deuteron closer to one methyl group or the other — is approximately 1340 cm^{-1} .
 - In the cation, it's also not all that different: 1350 cm^{-1} .
 - However, the out-of-plane bending mode changes quite a bit: 1340 cm^{-1} to 800 cm^{-1} .
 - This is the Andy Streitwieser analysis of secondary KIEs: The out of plane bending modes are dominant.

- Example: A normal α -secondary kinetic isotope effect.

– Consider the solvolysis of a benzyl chloride derivative.



- Isotopically label the two hydrogens on the active-site carbon.
- Through kinetic analysis,^[3] we can confirm an S_N1 mechanism.
- Experimentally, we observe that the α -2° KIE has $k_H/k_D = 1.30$.
- Let's justify this number.

- The sp^3 -like starting material goes through an sp^2 -like transition state.
- This means that we're going to a more slack potential, where the out-of-plane bending can happen more freely.
- Thus, the H/D spacing will be tighter in the TS than the ground state, explaining our *normal* KIE (as opposed to an *inverse* KIE).
- The number will have a smaller magnitude, however, because it is a secondary effect stabilizing and destabilizing our species, not an atom directly involved in the process.

- Example: An inverse α -secondary kinetic isotope effect.

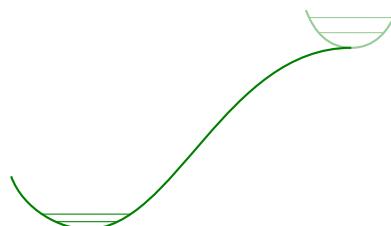
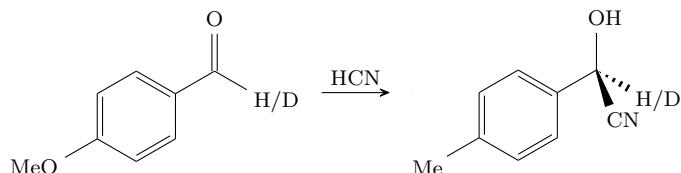


Figure 10.17: Inverse α -secondary kinetic isotope effect.

- Consider the reaction of anisaldehyde to the corresponding cyanohydrin.

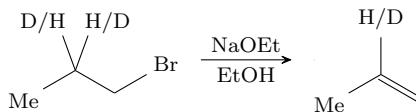


- Isotopically label the aldehyde H/D.
- Burgi-Dunitz trajectory to tetrahedral intermediate, which will be thermodynamically uphill.
- Here, we have an sp^2 SM going to an sp^3 TS.
- More steric bulk in TS leads to more energetic penalty to wagging, leads to tighter well at the top near the TST.
- So we're going from a well with small differences in ZPE to a well with big ZPE differences.
- This penalizes access to the TST with hydrogen, giving us an inverse KIE of 0.7.

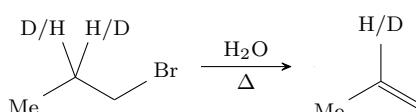
³“We'll get into this in a few lectures” — is this not just Hammett plots??

- We now move onto β -secondary KIEs.
- Example: Labeling β to the “active site.”

– Consider the base-mediated elimination (E_2 dehydrohalogenation) of 1-propylbromide.



- We label β to the bromide.
- Displacement of the bromide is concommittant with C–H cleavage at the β -position, so we should see a large KIE.
 - Indeed we do: $k_H/k_D = 6.7$.
 - So frankly, this is a 1° KIE.
- Example: A real normal β -secondary kinetic isotope effect.
- Consider the E_1 dehydrohalogenation of 1-propylbromide.



- Here, rate-limiting loss of Br gives a cation intermediate.
 - There is no change in hybridization at the β -position.
 - However, we do have a donor-acceptor interaction. Indeed, there is symmetry-allowed $\sigma_{C-H/D} \rightarrow p_C$ mixing.
 - This depopulates the β -bonding orbital.
 - Depopulating this orbital leads to weaker bonds, smaller force constants, and a more slack potential in the transition state.
 - So if we're going to a more slack potential, we get normal KIEs.
- Indeed, $k_H/k_D = 1.4$.
 - This kinetic isotope effect is greater than 1 for all the reasons we've talked about.
 - However, the C–H/D bond is not being cleaved in the transition state, so the magnitude is still relatively small.
- Secondary KIEs are usually smaller because they're not at the reactive center.
 - Secondary KIEs will rarely be bigger than 1.5 or smaller than 0.7.
- All of this is a prelude to what he actually wants to talk about: This lecture's content, which will mostly become next lecture's content.
- Experimental determination of KIEs.
 - Nicely summarized in a paper 10-12 years ago by Eric Simmons (now at BMS) and John Hartwig.
 - Read this before next time in order to dialogue about what's going on!!
 - Reference: Simmons and Hartwig (2012).

- First and least interesting method: Independent absolute rate measurement.

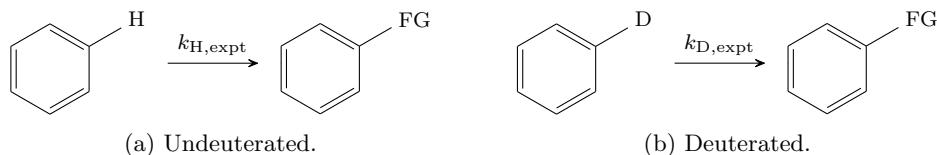


Figure 10.18: Independent absolute rate measurement of kinetic isotope effects.

- Consider the functionalization of an arene, one sample deuterated and the other not.
 - First measure k_H , and then measure k_D . Take the ratio of these independently measured rate constants as your KIE.
 - This works and people do this, but a few things make it difficult.
 1. Absolute (as opposed to relative) determinations of rate constants are prone to error.
 - You have error associated with the determination of each of each.
 - Your KIE is only as good as the accuracy of each independent KIE, so we get propagation of error.
 2. Despite our best attempts, there will be small variations in the way these reactions are executed (e.g., different concentrations, different temperatures, etc.), contributing to our error.
 3. Only reports on reactions when RDS is isotope-sensitive.
 - Only really useful if the bond with the isotope is sensitive to cleavage in the RDS.
 - So good when the initial transition state structure is rate-determining and isotopically sensitive.
 - What if the first step is rate-determining, but not isotopically sensitive? In this case, our rate analysis is useless because everything else is post-rate limiting.
 - So these are difficult experimentally and “blind” to post-rate limiting steps.
 - Next time: Stuff that allows us to see post-rate limiting transformations.