Week 11

Kinetics

11.1 Experimental Determination of Kinetic Isotope Effects

11/12:

- Lecture 18 recap.
  - The physical basis and mechanistic interpretation of kinetic isotope effects.
  - We also began discussing independent absolute rate measurement.
    - Alex reviews the discussion associated with Figure 10.18.
- Today: Experimental determination of KIEs.
  - All of these examples are pulled from Simmons and Hartwig (2012).
- Topic 2: Competition experiments.
  - Can be run a couple of different ways.
  - Most simple/natural progression from independent absolute rate measurement: Intermolecular competition.
  - Then there is intramolecular competition.
- Subtopic 2.1: Intermolecular competition.

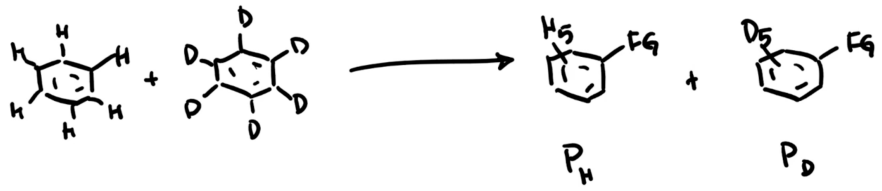


Figure 11.1: Competition experiment (intermolecular).

  - Instead of running the protonated and deuterated substrates independently, throw them into the same pot at the same time.
  - Take half an equivalent of the normal substrate and half an equivalent of the perdeuterated substrate.
    - It doesn't have to be half an equivalent, but this makes the analysis easier.
    - We also don't have to use the perdeuterated substrate, but it's often the easiest to make.
  - We then measure the ratio of undeuterated functionalized product vs. the deuterated functionalized product.

  - We can then extract our KIE from the $[P_H]/[P_D]$ ratio.
  - Caveat (this reaction is frequently run incorrectly in the literature!): We have to account for the fact that the concentrations of the starting materials are changing throughout.
    - Indeed, the product and starting material are highly dependent on the conversion.
    - The ratio of the products is equal to the ratio of the starting materials at high conversion.
    - However, if we only run the reaction to low conversion, we can assume that the concentration of the starting material hasn't changed too much! Thus, the product ratio will reflect the actual KIE.
  - We can quantify products by NMR, LC-MS, GC-MS, etc.!
    - So this reaction is experimentally simple to do because products are easy to quantify.
  - We can measure extremely small KIEs because our product-detection methods are so good!
  - There is a contrasting paradigm in which we run to large conversions and characterize the remaining starting material ratio at the end.
    - We'll get there later in the lecture.

- We have to apply a correction for conversion to extract the KIE at any conversion.
  - Define

$$C := \frac{[P_H]}{[SM_H]_0} \qquad R := \left(\frac{[SM_D]}{[SM_H]}\right)_t \qquad R_0 := \left(\frac{[SM_D]}{[SM_H]}\right)_0$$

    - C is the conversion.
      - ➢ From the definition, we can tell that it is a number between 0 and 1.
    - R gives the isotopic enrichment at any moment t.
    - R is the initial isotopic enrichment.
  - Thus, we can do some algebra to get a correction term that allows us to calculate the KIE from any time point.

$$\frac{R}{R_0} = (1-C)^{k_D/k_H - 1}$$
$$\text{KIE} = \frac{k_H}{k_D} = \frac{\ln(1-C)}{\ln\left[(1-C)\cdot\frac{R}{R_0}\right]}$$

  - Takeaways.
    - If we can extract both the conversion C and isotopic composition R/R_0, we can extract the KIE accurately.
    - If we run these reactions in replicates, we can get *very* accurate KIEs!

- Note that at high conversions, the ratio of the deuterated to protonated starting materials goes to infinity. Symbolically,

$$\frac{[SM_D]}{[SM_H]} \to \infty$$

  - Implication: As we get higher and higher conversions, we'll eventually reach a point where we only have a few molecules of starting material left, and almost all of them are the deuterated ones.
  - This high-conversion exaggeration makes measurement easier.
  - Indeed, at ultra-high conversions, we can get extremely accurate measurements for even very small KIEs!

- Example: Kinetic isotope effects can narrow down which steps are or are not rate-determining.

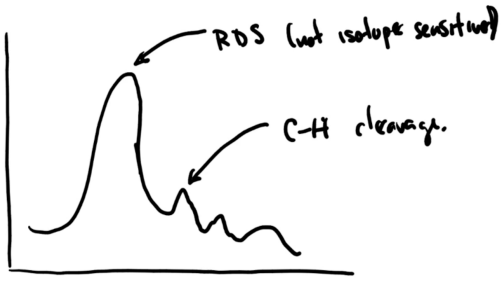
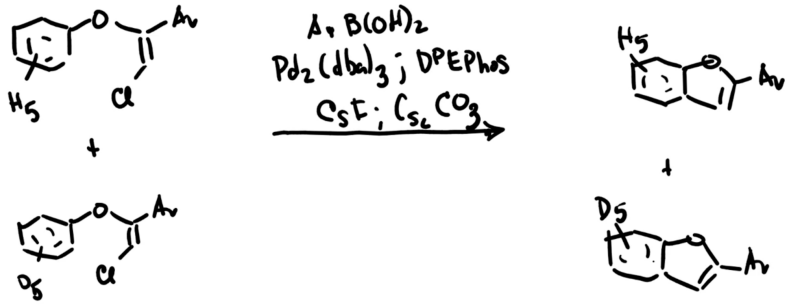


Figure 11.2: Assigning peaks on a potential energy surface by using kinetic isotope effects.

  - Consider the reaction of H_5- and D_5-isotopologoues run both under a palladium-catalyzed arylation.

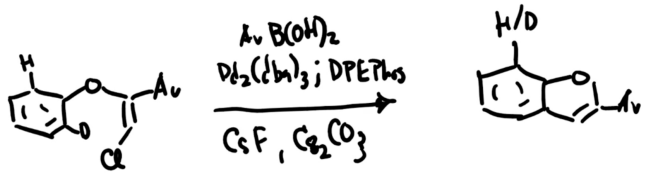


    - Meant to be a Suzuki coupling (there's a boronic acid in there), but that ended up being irrelevant to the chemistry.
    - In reality, the observed products are ring-closed.
  - We have *no* intermolecular KIE (that is, $k_H/k_D = 1.0$).
    - This means that the rate of reaction is *not* determined by the presence or absence of heavy isotopes.
    - It follows that C–H/D cleavage is *not* the rate-determining step!
  - What does this mean in terms of the potential energy surface?
    - It means that the largest peak (the RDS) does *not* involve C–H/D cleavage, but one of the other peaks could.
  - Reference: Simmons and Hartwig (2012).

- Subtopic 2.2: Intramolecular competition.

- Example: Kinetic isotope effects can probe post-rate determining steps!

  - Consider the same palladium-catalyzed arylation, but our substrate has one H and one D that can be cleaved.



  - Then you can quantify the amount of H vs. D at the *ortho*-position in the product and extract an intramolecular KIE of 4.

  - Thus, we have probed a post-rate determining step!
  - In this case, oxidative addition to the sp^2-Cl is believed to be rate-determining; but we can still use this intramolecular KIE to learn something useful for mechanistic analysis or further reaction development.
  - Reference: Simmons and Hartwig (2012).

- General structure of intramolecular KIEs.

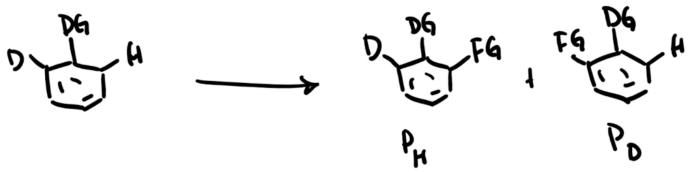


Figure 11.3: Competition experiment (intramolecular).

  - We design a symmetric reactant with a donating group, an H on one side, and a D on the other side.
  - Then the KIE can be rigorously extracted from

$$\text{KIE} = \frac{[\text{P}_\text{H}]}{[\text{P}_\text{D}]}$$

    at *any* conversion.
  - We get to use any conversion because the reaction does *not* enrich the isotopic composition.
    - The (local) concentrations of H and D are fixed by the synthesis of the molecule!
  - This method gets us an "intrinsic" KIE, even for post-rate limiting steps.

- To recap.
  - Independent, intermolecular, and intramolecular.
  - The results depend heavily on the conditions we use!

- Topic 3: Heavy atom KIEs.
  - We'll talk a bit more about the measurement of extremely small KIEs here.
  - The most common heavy atoms to investigate are $^{12}\text{C}/^{13}\text{C}$.
    - However, it can also be N, O, P, Cl, etc.
  - The magnitude tends to be small because of the smaller change in reduced mass (see Table 10.2).
  - Example: $^{12}\text{C}/^{13}\text{C}$ KIEs tend to be 1.0-1.05.
    - 1.05 is large, even — by $^{12}\text{C}/^{13}\text{C}$ standards, that is!
  - Because we have a small enrichment that is difficult to measure, it is very important to use sensitive methods.
  - This also means that we can pretty much only measure *primary* heavy atom KIEs; secondary heavy atom KIEs are usually too small to measure.
  - Reference: Dale et al. (2021).
    - Alex highly recommends to learn more about all aspects of heavy atom KIEs.

- We experimentally measure heavy atom KIEs using a series of experiments developed in the '90s.
- The most common is the Singleton Method for KIE determination.
  - This is a determination done at the natural abundance of the various isotopologues.
- Singleton's key insight #1: ^{13}C is a naturally occurring (typically 1.1% abundance) heavier isotope of ^{12}C.
  - It follows that every molecule is already labeled with this heavy isotopologoue, and already labeled at every position.
- Singleton's key insight #2: ^{13}C can be measured via ^{13}C NMR for quantitation.
- Both of these insights are important because ^{13}C precursors are few and far between, and they're expensive! Labeling a certain position can be very difficult (and expensive).
- Singleton's key insight #3: Recall that $R/R_0 = (1-C)^{1/\,\mathrm{KIE}\,-1}$. As $C \to 1$, R/R_0 becomes very sensitive to the KIE.

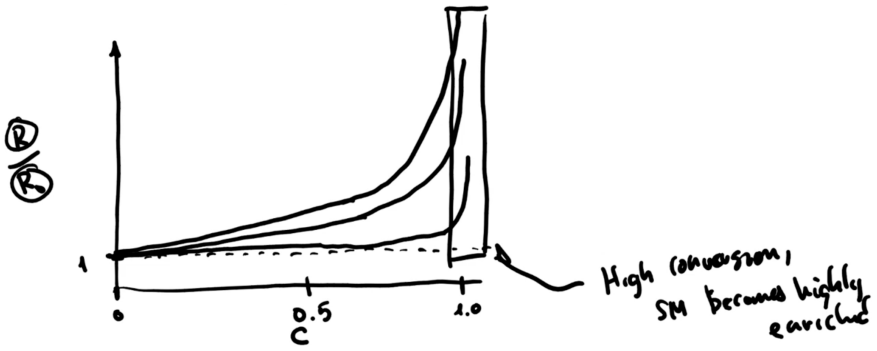


Figure 11.4: Isotopic enrichment at high conversions.

  - We can visualize this relationship through a series of plots of R/R_0 vs. C.
    - If we run a reaction with a KIE of 1.0, we'll have $R/R_0 = 1$ at any $C \in [0, 1)$.
    - If we run a reaction with even a KIE of 1.1, we'll get enrichment in the slower-reacting isotope later on that leads to larger KIEs!
  - Takeaway: At sufficiently high conversions, the starting material becomes highly enriched in the slow-reacting isotopologue.
- Numerical data in support of Figure 11.4.

C	R/R_0
0.5	1.03
0.75	1.07
0.9	1.12
0.99	1.25

Table 11.1: Isotopic enrichment at high conversions.

  - Suppose the light over heavy rate constant ratio ($k_\mathrm{L}/k_\mathrm{H}$) is fixed equal to 1.05.
  - We can get extremely accurate KIE measurements for even very such a small intrinsic KIEs, provided again that we run to sufficient converions.

- Example: Measuring heavy atom kinetic isotope effects for an intermolecular reaction.

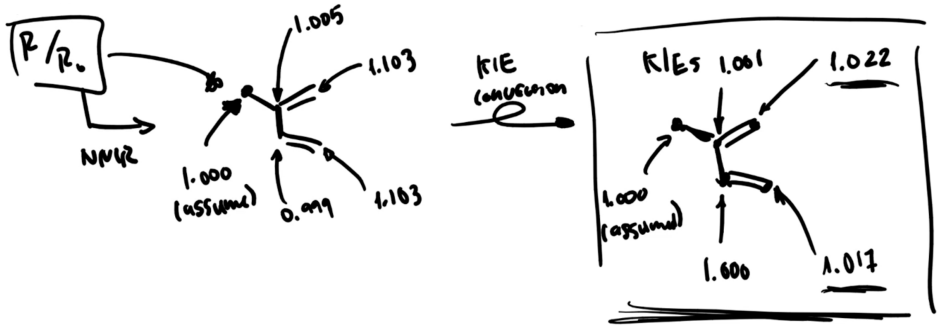
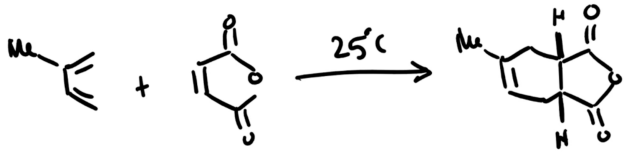


Figure 11.5: Singleton method for intermolecular heavy atom kinetic isotope effects.

  - Consider the following Diels-Alder reaction.



  - It was run to a conversion of 98.9%.
  - We then looked at the R/R_0 ratio in the diene starting material.
    - We do this with NMR measurements.
    - Assume that there is a position in the molecule (e.g., the remote methyl) that is not isotopically sensitive, and hence has KIE = 1.000.
      - ➢ If we pick our site well, this is a reasonable assumption.
    - We then measure the raw integrals at the other sites.
    - Take these integrals, put them back into the equation we derived previously to obtain the KIE ratio.
      - ➢ Example:

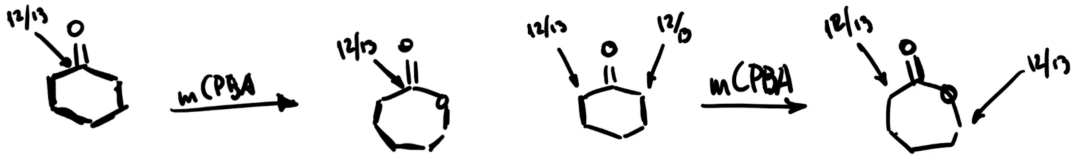
$$\text{KIE} = \frac{k_\text{H}}{k_\text{D}} = \frac{\ln(1-0.989)}{\ln\left[(1-0.989)\cdot\frac{1.103}{1.000}\right]} = 1.022$$

  - Conclusion: The biggest KIEs are at the terminal methyl groups (as expected from the Woodward-Hoffmann rules; this is another confirmation!), and we get a slight improvement in rate on the side near the methyl group.
    - It would probably be prohibitive to label each position in the diene, but just a good mathematical knowledge of conversions gets us everything we need.
  - Reference: Singleton and Thomas (1995).

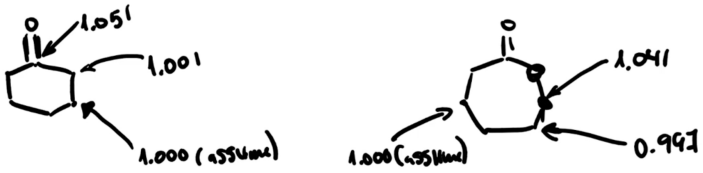
- Limitations of the Singleton method.
  - We need a large amount of sample.
    - This is because we're running the reaction to high conversion, but need to isolate the starting material.
    - So in order to get accurate NMRs, we need sufficiently high concentrations of the sample.
    - We can run Diels-Alders on nearly mole scales, and potentially isolate grams; that's why the previous example worked.
  - The reaction must be irreversible.
    - It it isn't, we're going to get equilibrium isotope effects mixed in.

- The results can be difficult to interpret.
  - Any individual number might not be too helpful, but with modern quantum mechanical calculations, we can match our results to a DFT-computed potential energy surface!
  - This will show that one pathway has a better experimental match with KIEs.
  - This is good evidence for a mechanistic course!!
- Natural abundance experiments can be run in both inter- and intramolecular modes.

- Example: Measuring heavy atom kinetic isotope effects (aka "natural abundance experiments") in an intramolecular mode.



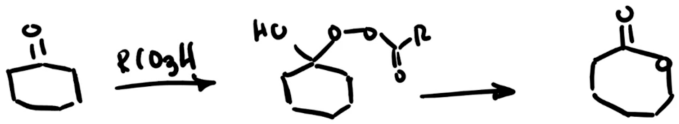
(a) Relevant labeling for intermolecular data. (b) Relevant labeling for intramolecular data.



(c) Intermolecular KIEs. (d) Intramolecular KIEs.

Figure 11.6: Singleton method for intramolecular heavy atom kinetic isotope effects.

- Consider the Baeyer-Villiger reaction.



  - A ketone reacts with a peracid.
  - The mechanism is believed to proceed through a hemiacetal, followed by ring expansion to the lactone.
- So we have a two-step mechanism.
  - We can probe the first step with natural abundance KIE to determine whether or not hemiacetal formation is rate-determining.
  - Simultaneously (in the same pot/set of experiments), we can probe the second step with an intramolecular heavy atom KIE.
- Intermolecular variant: Consider the labeling at the *ipso*-position.
  - Run this reaction to a known conversion, quantitate that conversion well, isolate the starting material, and quantitate its $^{12}C/^{13}C$ well (using, e.g, mass spec).
  - Isotopic enrichment of the starting material, here, is conversion-dependent (because it's affiliated with the RDS).
  - We assume that the β-position has an isotopic enrichment of 1.000.
  - The resultant significant isotopic fractionation of the starting material (KIE = 1.051) implies that the initial conversion of the ketone to the acetal is rate-determining.

  - Intramolecular variant: Consider the labeling at the α-positions.
    - Isotopic enrichment of the product, here, is conversion-independent (because it's post-RDS).
    - We assume that the β-position has an isotopic enrichment of 1.000.
    - The resultant significant isotopic fractionation of the product (KIE = 1.041) implies that the migration step occurs after the RDS, and involves the α-position.
  - It is somewhat counterintiutive that hemiacetal formation (typically fast) would be rate-limiting!
  - Reference: Singleton and Szymanski (1999).

- Takeaways from today.
  - We get deep and important information about reaction courses, rate-determining steps, etc. from isotope effects.

- Next time: Kinetics and kinetic rate laws.