Week 14

???

14.1 Kinetic Resolution and Related Asymmetric Processes

- Announcements.

    - Today: Last Tuesday's lecture.

        ■ Next time: Electron Transfer.

    - Exam 2 tomorrow.

        ■ Format like the practice exam.
        ■ Administered remotely.
        ■ Work alone, and closed note (honor code).
        ■ Available for 48 hours: Start of Wednesday til end of Thursday.

    - Do the teaching evaluations for both Alex and Masha!!

- Today: Kinetic selectivities.

- Consider a starting material (SM) that can evolve to a product A or B.
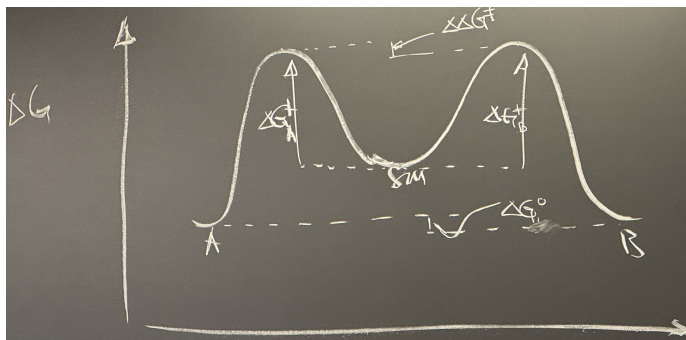

Figure 14.1: Thermodynamic vs. kinetic selectivity energy diagram.

    - We can map this reaction onto a potential energy surface.

    - If A and B are free to reversibly interconvert, then we can explain the product distribution in terms of the $\Delta G°$ between A and B.

        ■ In particular, $\Delta G = -RT \ln K_{eq}$ where $K_{eq} = [A]/[B]$.

- Today, we'll consider the case in which A and B do *not* reversibly interconvert.
    - In this case, what's important is the $\Delta\Delta G^{\ddagger}$ between the transition states.
    - Here, the selectivity is given as the ratio of the rate constants:

$$\text{selectivity} = \frac{[\text{A}]}{[\text{B}]} = \frac{k_{\text{A}}}{k_{\text{B}}} = \frac{\text{e}^{-\Delta G_{\text{A}}^{\ddagger}/RT}}{\text{e}^{-\Delta G_{\text{B}}^{\ddagger}/RT}} = \text{e}^{-\Delta\Delta G^{\ddagger}/RT}$$

    - Note that $k_{\text{A}}/k_{\text{B}} = k_{\text{rel}}$. This quantity is important for determing dr's, er's, etc.
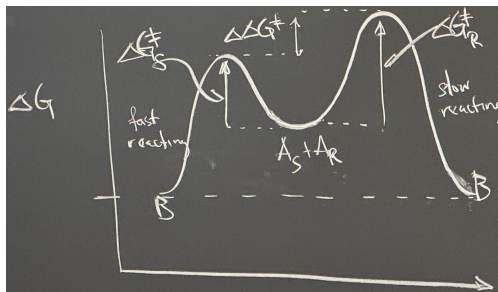- A case in which kinetic selectivity is important: Catalytic kinetic resolution.

Figure 14.2: Catalytic kinetic resolution energy diagram.

- A is our starting material, a chiral racemic compound.
    - Thus, we can denote the starting materials as $\text{A}_{\text{S}} + \text{A}_{\text{R}}$.
    - As enantiomers, A_{R} and A_{S} have identical free energies.
- cat* is a **homochiral** catalyst.
- Then resolution to a product B can happen two different ways: Through a transition state that consumes the (S)-enantiomer, and through a transition state that consumes the (R)-enantiomer.
- When a homochiral catalyst acts on two enantiomers, it forms two different, diastereomeric adducts: $\text{A}_{\text{S}} \cdot \text{cat}^{*}$ and $\text{A}_{\text{R}} \cdot \text{cat}^{*}$.
    - Unlike enantiomers, diastereomers *are* different compounds that may have two different energies.
- What we've indicated in Figure 14.2 is that the (S)-enantiomer is converted faster than the (R)-enantiomer.
- Thus,

$$k_{\text{rel}} = \frac{k_{\text{fast}}}{k_{\text{slow}}} = \text{e}^{-\Delta\Delta G^{\ddagger}/RT}$$

    - In the literature, k_{rel} is sometimes referred to as an **S-factor** (for "selectivity factor").
- Reference: Sheldon (2001).

- **Homochiral** (catalyst): A chiral catalyst of which we're using only a single enantiomer.

- There are many catalytic kinetic resolutions in the literature.

- Radosevich developed one in grad school, when he was roughly our age!
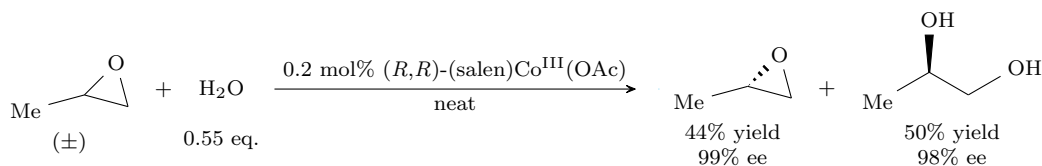
- Example catalytic kinetic resolution.

Figure 14.3: Hydrolytic kinetic resolution.

- Take propylene oxide (racemic) and 0.55 eq. of water.
- React them, neat, in the presence of a small amount of homochiral catalyst.
  - The structure of this complex is totally irrelevant to our aims, but we can look it up in the reference if we're curious.
  - This is our homochiral catalyst that will act on the two relatively inexpensive starting materials.
- We run this reaction neat, and recover one enantiomer of our starting material in nearly quantitative yield with near perfect ee.
- We also obtain a ring-opened *vic*-diol in nearly quantitative yield with near perfect ee.
- $k_{rel} \approx 500$ here!
- Reference: Tokunaga et al. (1997).
- This is a **hydrolytic kinetic resolution**.
  - This is a very useful reaction for the resolution of terminal epoxides — and access to terminal 1,2-diols — because there exists no method to synthetically prefer a single enantiomer.
  - Propylene is so small that even the best chiral epoxidation catalysts aren't very selective here, so it's better to do a racemic epoxidation and then this.
- Great atom economy.

- In a kinetic resolution like the above, the percent ee of both starting material and product is subject to change over time.

- To see this, let's build a theoretical model for a catalytic kinetic resolution.

$$A_S + cat^* \xrightarrow{k_{fast}} P \qquad\qquad A_R + cat^* \xrightarrow{k_{slow}} P$$

- The net transformation involves the above two chemical reactions.
- We can write differential rate laws for each enantiomer

$$\frac{d[A_S]}{dt} = -k_{fast}[A_S][cat^*] \qquad\qquad \frac{d[A_R]}{dt} = -k_{slow}[A_R][cat^*]$$

  - The consumption of the fast-reaction enantiomer will deplete [A].
- Assuming $[cat^*]$ is approximately constant throughout the reaction, each of these differential rate laws can be independently integrated to

$$\ln\left(\frac{[A_S]}{[A_S]_0}\right) = -k_{fast}[cat^*]t \qquad\qquad \ln\left(\frac{[A_R]}{[A_R]_0}\right) = -k_{slow}[cat^*]t$$

- Then, the key thing to note here is that for a racemic mixture, $[A_S]_0 = [A_R]_0$.
- Thus, we can make this substitution and divide the above two integrated rate laws to get

$$k_{rel} = \frac{k_{fast}}{k_{slow}} = \frac{\ln([A_S]/[A_S]_0)}{\ln([A_R]/[A_S]_0)}$$

- This is a useful result, but we can make it even better. We'll start with a couple of definitions.

- **Conversion**: The ratio of how much of a reactant has reacted. *Denoted by c. Given by*

$$c := 1 - \frac{[A_S] + [A_R]}{[A_S]_0 + [A_R]_0} = 1 - \frac{[A_S] + [A_R]}{2[A_S]_0}$$

- **Enantiomeric excess**: A measurement of the degree to which a sample contains one enantiomer in greater amounts than the other. *Denoted by ee. Given by*

$$ee := \frac{[A_S] - [A_R]}{[A_S] + [A_R]}$$

- We can now do some algebra.

  - Indeed, it follows from the above definitions that

$$1 - ee = \frac{2[A_R]}{[A_S] + [A_R]} \qquad\qquad 1 + ee = \frac{2[A_S]}{[A_S] + [A_R]}$$

  - Then we can derive the following interesting relatinoships.

$$\frac{[A_R]}{[A_S]_0} = (1 - c)(1 - ee) \qquad\qquad \frac{[A_S]}{[A_S]_0} = (1 - c)(1 + ee)$$

  - We can now know the extent to which a reaction has evolved to consume one enantiomer or the other as a function of observables!

- Thus, we may define $S = k_{\text{rel}}$ as a function of conversion and ee.

  - For recovered starting material,
$$S = \frac{\ln[(1 - c)(1 - ee)]}{\ln[(1 - c)(1 + ee)]}$$

  - For the product,
$$S = \frac{\ln[(1 - c)(1 + ee)]}{\ln[(1 - c)(1 - ee)]}$$

- These relations allow us to relate conversion to ee for a catalyst of a given, set selectivity S. Specifically, we can parametrically plot ee as a function of conversion.

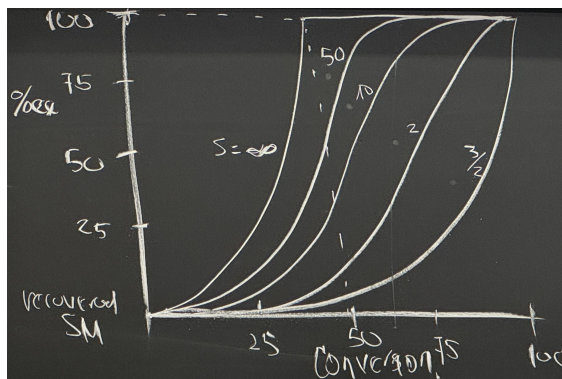- Let's first do this for the percent ee in the recovered starting material.

Figure 14.4: Starting material ee vs. conversion in a catalytic kinetic resolution.

- Consider first what happens in the limit that our selectivity factor is very large, i.e., that $\Delta\Delta G^{\ddagger} =$ large.
- If $S = \infty$, then 50% conversion will get us all we need.
  - ■ This is because at this point, the enantiomer we don't want to recover will have been fully consumed.
- As the S-factor drops, we need higher conversions to get better ee's in the recovered starting material.
- What's cool about this is we can still get high ee's with bad catalysts... at the expense of conversion.
  - ■ Essentially, with bad catalysts, we'll recover *less* enantiopure starting material (because some of it will have been consumed at higher conversions), but we *can* still recover essentially enantiopure starting material.
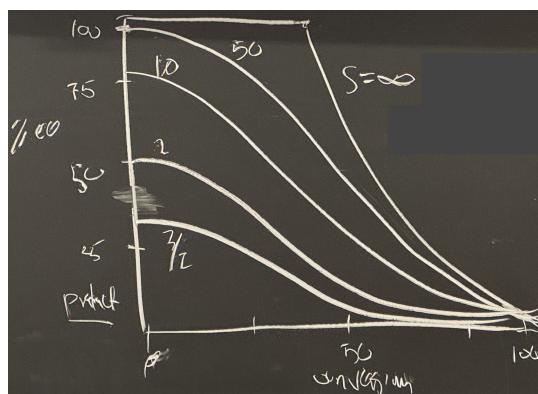
• For the product.

Figure 14.5: Product ee vs. conversion in a catalytic kinetic resolution.

- If $S = \infty$, the product will be enantiopure up until we begin converting some of the other enantiomer.
- If $S = 50$, we start at near-optimal purity, and then our bias will erode.
- What this implies is that for the purpose of kinetic resolution of the product, we need very good catalysts.
- That's what's remarkable about the Jacobsen catalyst: It's extremely selective for both the starting material *and* product.

• Let's now enter into some more complex kinetic regimes.

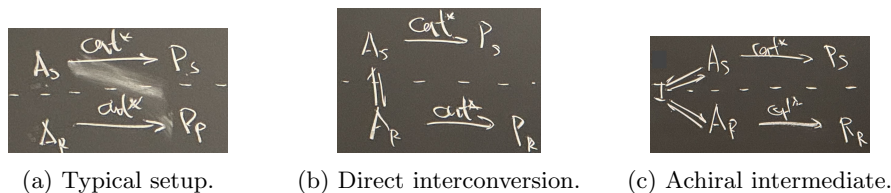(a) Typical setup.   (b) Direct interconversion.   (c) Achiral intermediate.

Figure 14.6: Dynamic kinetic resolution models.

- As we've depicted it in Figure 14.2, our starting materials are equal in energy and not interconverting.
  - ■ We can conceptualize this scenario as having a mirror plane between our starting materials and products that we *never* cross (Figure 14.6a).
- But what about when the starting materials do interconvert?
  - ■ There are two ways in which this can happen: We can cross the mirror plane directly (Figure 14.6b), or through an achiral intermediate (Figure 14.6c).
- The 50% mass balance limit that is otherwise imposed is now lifted!
- Now our catalyst can sample both enantiomers via the epimerization.
- A_S interconverts with A_R, subject to a kinetically selective catalyst.

• Enantiomers under fast equilibrium are still under kinetic control, but with 100% theoretical yield.
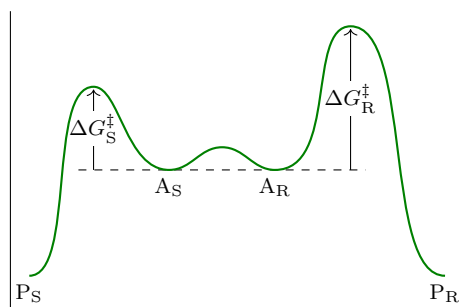

Figure 14.7: Dynamic kinetic resolution energy diagram.

- This is known as a **dynamic kinetic resolution**.

• Example dynamic kinetic resolution: Interconversion of chiral β-ketoesters prior to asymmetric hydrogenation.
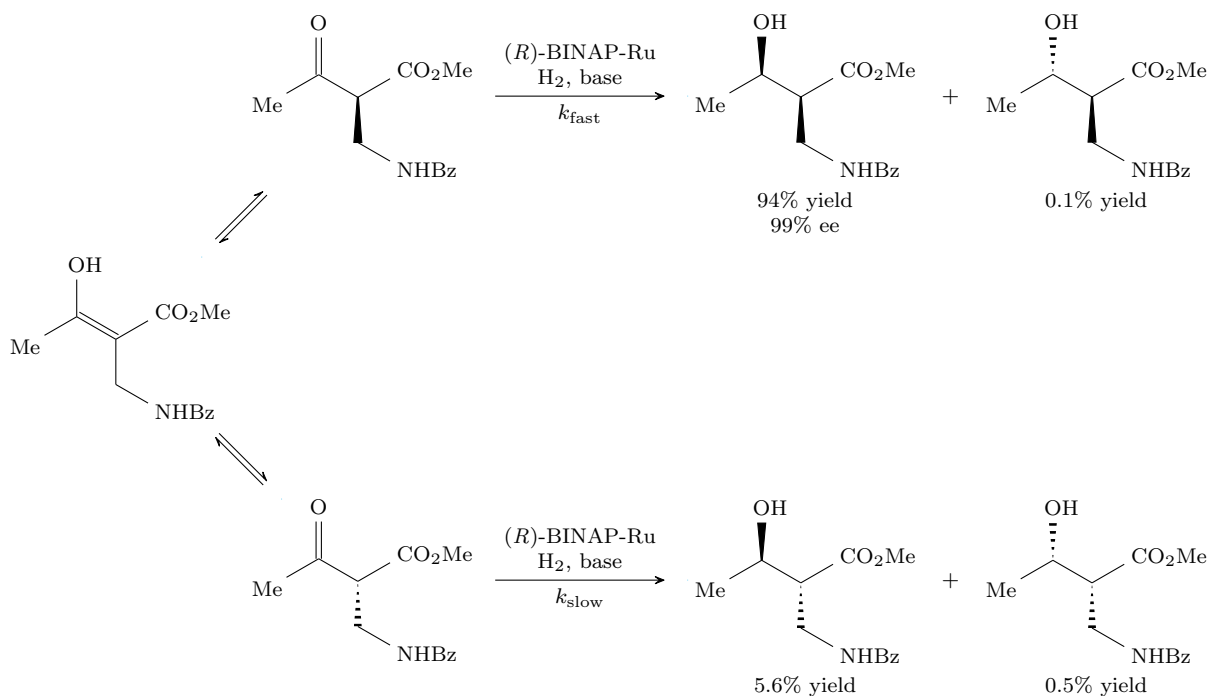

Figure 14.8: Noyori asymmetric hydrogenation.

- Consider a racemic sample of α-alkylated β-ketoester.
- Subject it to hydrogenation under **Noyori conditions**.
    - Both enantiomeric starting materials may become a *syn* or *anti* diastereomers.
    - Thus, in principle, you'd get a mess.
- Our mess is slightly alleviated by the fact that $k_{\text{fast}}/k_{\text{slow}} = 15$ for the ruthenium-BINAP catalyst.
    - This is about $2\,\text{kcal/mol}$ of difference.
    - However, per Figure 14.5, this S-factor is not great.
- Our saving grace is the dynamic nature of this reaction.
    - When we actually run the experiment, we get fast enolization and interconversion through an achiral intermediate because of the base[1] in solution and the acidic α-proton.
    - Indeed, if the rate of enolization/racemation is denoted by k_{rac}, we have $k_{\text{rac}}/k_{\text{fast}} \approx 100$!
- Thus, we get 94% yield of one stereoisomer in 99% ee.
- Reference: Noyori et al. (1995).
    - See Table 3, Figure 19, and the associated discussions.
    - The whole paper is a good review of this chemistry, though.

- **Noyori asymmetric hydrogenation**: The asymmetric hydrogenation of a ketone using a homochiral ruthenium-BINAP catalyst, hydrogen gas, and a base.

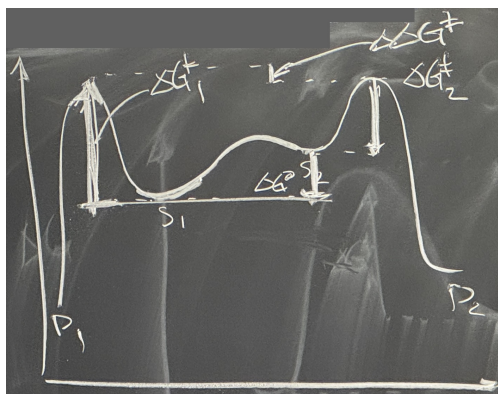- A related kinetic selectivity: Curtin-Hammett kinetics.

Figure 14.9: Curtin-Hammett selectivity derivation.

- Instead of (R)- and (S)-enantiomers, which rigorously have the same energy, we can consider other interconverting species with different energies.
- We can quantitate — with rate laws — the formation of the products.

$$\frac{\mathrm{d}[\text{P}_1]}{\mathrm{d}t} = k_1[\text{S}_1] \qquad\qquad\qquad \frac{\mathrm{d}[\text{P}_2]}{\mathrm{d}t} = k_2[\text{S}_2]$$

- Then taking a ratio gives

$$\frac{\mathrm{d}[\text{P}_1]}{\mathrm{d}[\text{P}_2]} = \frac{k_1[\text{S}_1]}{k_2[\text{S}_2]}$$

- Note that

$$\frac{[\text{S}_1]}{[\text{S}_2]} = K_{\text{eq}}$$

so

$$\frac{\mathrm{d}[\text{P}_1]}{\mathrm{d}[\text{P}_2]} = \frac{k_1}{k_2} K_{\text{eq}}$$

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[1]It appears from the paper that there may not be a base; this may just be keto-enol tautomerization.

- Thus, with Arrhenius,

$$\frac{\mathrm{d}[\mathrm{P}_1]}{\mathrm{d}[\mathrm{P}_2]} = \frac{\mathrm{e}^{-\Delta G_2^{\ddagger}/RT}}{\mathrm{e}^{-\Delta G_1^{\ddagger}/RT}} \mathrm{e}^{-\Delta G^{\circ}/RT} = \mathrm{e}^{(\Delta G_1^{\ddagger} - \Delta G_2^{\ddagger} - \Delta G^{\circ})/RT}$$

- And then referencing Figure 14.9, we can see pictorially that

$$\Delta G_1^{\ddagger} - \Delta G_2^{\ddagger} - \Delta G^{\circ} = \Delta\Delta G^{\ddagger}$$

- Thus,

$$\frac{\mathrm{d}[\mathrm{P}_1]}{\mathrm{d}[\mathrm{P}_2]} = \mathrm{e}^{\Delta\Delta G^{\ddagger}/RT}$$

  if we have a fast equilibrium $\mathrm{S}_1 \rightleftharpoons \mathrm{S}_2$ (10 times faster than P_1 or P_2 formation).
- Essentially, if we have this fast starting equilibrium, then the product ratio is under kinetic control.

- Now suppose we drop S_2 down in free energy and leave the rest of the diagram unperturbed.

  - This change in one variable is compensated for by a change in the other variable, and we remain under kinetic control.

- Alex briefly discusses kinetic quench.

- Curtin-Hammett example 1 (Figure 6.4a).

  - P_1 is kinetically favored.
  - $[\mathrm{S}_1] > [\mathrm{S}_2]$.
  - Here, the $\mathrm{S}_1/\mathrm{S}_2$ ratio is irrelevant to product formation. This is "invisible" C/H kinetics. Mathematically,

$$\frac{[\mathrm{S}_1]}{[\mathrm{S}_2]} \neq \frac{[\mathrm{P}_1]}{[\mathrm{P}_2]}$$

- Curtin-Hammett example 2 (Figure 6.4b).

  - P_1 is kinetically favored.
  - $[\mathrm{S}_1] < [\mathrm{S}_2]$.
  - This is "classic" C/H kinetics.
  - Great example of this in Landis and Halpern (1987).
  - This scenario is actually pretty common.

- Curtin-Hammett example 3 (Figure 6.4c).

  - Here, $\Delta G_1^{\ddagger} = \Delta G_2^{\ddagger}$.
  - This scenario is pretty uncommon, but it is possible.
  - In this case, the equilibrium ratio *does* reflect the product ratio.

- Takeaway: It is far more likely that your equilibrium ratio of intermediates has no bearing on your ratio of products.

14.2 Exam 2 Review Sheet

12/4:
- Noncovalent interactions.

    - Quadrupoles preferentially bind hard, positively charged ions.
    - The strongest hydrogen bonds have short bond lengths and are nearly linear; vice versa for weak.
    - There is an energetic penalty to mixing polar and nonpolar solvents. The penalty is mostly entropic, because putting a hydrophobic link in the water disrupts the water's ability to randomly hydrogen bond to itself. Less H-bonding means more ordered, less entropic water.

- Transition states are first-order saddle points on a hypersurface defined by vibrational DOFs.

    - $\Delta G = -RT \ln K_{\text{eq}}$.
    - $\Delta G^{\ddagger} = -RT \ln k$.
    - $\Delta\Delta G^{\ddagger} = -RT \ln(k_{\text{A}}/k_{\text{B}})$

- **van't Hoff analysis**: Experimental determination of ΔH° and ΔS°.

$$-RT \ln K_{\text{eq}} = \Delta H^{\circ} - T\Delta S^{\circ}$$

$$R \ln K_{\text{eq}} = -\Delta H^{\circ}\left(\frac{1}{T}\right) + \Delta S^{\circ}$$

- Fragmentations give $9\,\text{kcal/mol}$, or $30\,\text{e.u.}$ at $300\,\text{K}$.

- Transition state theory.

    - General form.

$$\text{A} \underset{}{\overset{K^{\ddagger}}{\rightleftharpoons}} [\text{TS}] \xrightarrow{k^{\ddagger}} \text{B}$$

    - Postulates.
        1. Activated complex is in quasi-equilibrium with starting material.
        2. Any molecule that makes its way to the transition state will then proceed onto the product barrierlessly ($\kappa = 1$).
    - The number of times a starting material appears in the TS is it's order in the rate law.
    - Eyring equation:

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

        ■ Linearization (for experimental determination of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$):

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

    - Hammond postulate.

- Isotope effects.

    - QMech foundation:

$$E_n = h\nu\left(n + \frac{1}{2}\right) \qquad\qquad \nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}}$$

    - $\text{C}-\text{D}$ lower by $1.5\,\text{kcal/mol}$.
    - Equilibrium isotope effect:

$$\frac{K_{\text{H}}}{K_{\text{D}}}$$

  - C−D bonds hold onto their electrons more tightly.
  - Kinetic isotope effect.

$$\text{KIE} = \frac{k_\text{H}}{k_\text{D}}$$

  - Asymmetric stretch is the reaction coordinate.
    - Symmetric stretch is the important orthogonal vector.
    - Under thermoneutral conditions with identical atoms on either side, KIE = max because the symmetric stretch has no isotopic sensitivity.
  - Bent transition states have more contributions from bending mode isotopic sensitivities, but smaller overall sensitivities (1.5-3.5).
  - Quantum tunnelling can give anomously large KIEs.
  - Secondary isotope effects at the α-position largely governed by out-of-plane bending modes.
    - Going to a slacker potential: Normal 2° KIE.
    - Going to a stiffer potential: Inverse 2° KIE.
  - Secondary isotope effects at the β-position governed by hyperconjugation, or actually primary because involved (e.g., E_2).
  - Experimental determination.
    - Independent absolute rate measurement.
    - Intramolecular competition experiment.
      - Correction: If

$$C := \frac{[\text{P}_\text{H}]}{[\text{SM}_\text{H}]_0} \qquad R := \left(\frac{[\text{SM}_\text{D}]}{[\text{SM}_\text{H}]}\right)_t \qquad R_0 := \left(\frac{[\text{SM}_\text{D}]}{[\text{SM}_\text{H}]}\right)_0$$

  then

$$\text{KIE} = \frac{k_\text{H}}{k_\text{D}} = \frac{\ln(1 - C)}{\ln\left[(1 - C) \cdot \frac{R}{R_0}\right]}$$

    - Intramolecular competition can probe post-rate-determining steps.
      - Extract KIE from the product ratio at *any* conversion.
  - Heavy-atom KIEs.
    - Extracted at high conversions.
    - Choose a reference atom, take NMRs at high conversion, plug into conversion formula to get KIEs.
    - Can tell you what sites are involved in the RDS!
    - Conversion-*dependent* isotopic enrichment is affiliated with the RDS.
    - Conversion-*independent* isotopic enrichment is affiliated with post-RDS steps.

- Rate laws.

  - Zeroeth-order, first-order, and second-order integrated rate laws.
  - k_obs vs. swamping concentrations to determine k.
  - SSA.
    - If A is more stable than B, the SSA is valid.
    - If I is depleted faster than it is formed, the SSA is valid.
  - QEA.
    - Only valid when $k_{-1} > k_2$.
  - Limiting cases.

- The saturation regime.

- Defining the total concentration of the catalyst is often useful.

- Michaelis-Menten kinetics.

- Blackmond's work.

  - Same-excess experiment and visual overlay.
  - Different excess experiment.

- Kinetic resolution.

  - Relations between conversion and ee.

  - Dynamic kinetic resolution: Going through an intermediate or other interconversion.

  - Curtin-Hammett kinetics.