

Week 6

Thermodynamics

6.1 Selectivity

- 10/8:
- Lecture 9 recap.
 - Last lecture wrapped up reactive intermediates, focusing specifically on carbenes.
 - Triplet carbenes (Figure 5.15a).
 - More linear.
 - Smaller HOMO-LUMO gap implies 2 SOMOs.
 - React as diradicals.
 - R can be any π -acceptor, such as alkyl, vinyl, aryl, carbonyl, SO_2R , NO_2 , B, etc. groups.
 - Singlet carbenes (Figure 5.15b).
 - More bent.
 - Larger HOMO-LUMO gap.
 - React as cations and anions.
 - R can be any π -donor or σ -EWG, such as halogens, NR_2 , or OR groups.
 - Both types of carbenes...
 - Can be nucleophilic or electrophilic;
 - React by adding into π -systems or inserting into bonds.
 - The mechanisms through which S/T carbenes engage in this reactivity vary slightly.
 - Today: Selectivity.
 - Lecture outline.
 - Thermodynamic selectivity.
 - Kinetic selectivity.
 - Curtin-Hammett kinetics.
 - Kinetic quench.
 - Principle of microscopic reversibility.
 - Reactivity-selectivity principle.
 - Practical aspects of selectivity (deferred to next time).
 - When two products form from a single common intermediate (or starting material), selectivity between these products can arise from **thermodynamic** or **kinetic** factors.

- **Thermodynamic** (selectivity): Selecting for a certain product based on the position of an equilibrium, i.e., the stability of the products.

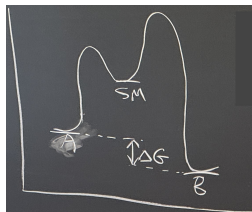


Figure 6.1: Energy variables relevant to thermodynamic selectivity.

- Key words: Thermodynamic = product = equilibrium.
- Relevant reaction coordinate.



- A and B form from a single common starting material (SM).
- The relevant equilibrium constants are K_A and K_B .
- K_A and K_B allow us to define the **selectivity** of this reaction as follows.

$$\text{selectivity} = \frac{[A]}{[B]} = \frac{K_A}{K_B} =: K_{eq}$$

- Energy diagram of a thermodynamically controlled reaction (Figure 6.1).
 - In order for a reaction to be under thermodynamic control, all steps must be reversible, i.e., all intermediates must interconvert.
 - ΔG is the difference in energy between the products.
 - Recall from Gen Chem that $\Delta G = -RT \ln(K_{eq})$ and hence $K_{eq} = e^{-\Delta G/RT}$.
- Thermodynamic selectivity is very useful if all products are at very different energy levels.
- Example: Olefin isomerization can occur with great selectivity because one product can be much more stable than another.
- **Selectivity** (of a reaction): The preference for one product (A) over another (B), where both A and B originate from a single common intermediate or starting material. *Given by*

$$\text{selectivity} := \frac{[A]}{[B]}$$

- **Kinetic** (selectivity): Selecting for a certain product based on the differences in energies of competing transition states, i.e., by reaction rates.

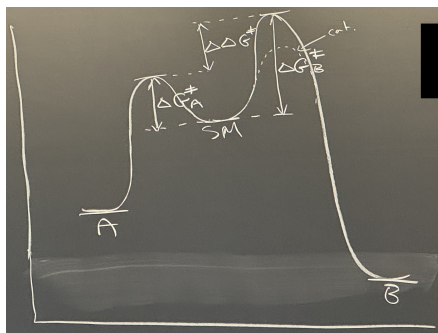


Figure 6.2: Energy variables relevant to kinetic selectivity.

- Key words: Kinetic = transition state = rate.
- Relevant reaction coordinate.



- As before, A and B form from a single common SM.
- The relevant rate constants are k_A and k_B .
- k_A and k_B allow us to define the selectivity of this reaction as follows.

$$\text{selectivity} = \frac{[A]}{[B]} = \frac{k_A}{k_B}$$

- Energy diagram of a kinetically controlled reaction (Figure 6.2).
 - ΔG_A^\ddagger and ΔG_B^\ddagger are the activation energies required to form the transition states from the SM to A and B, respectively.
 - $\Delta\Delta G^\ddagger$ is then the difference between these transition states' activation energies.
 - Recall from Gen Chem that $\Delta\Delta G^\ddagger = -RT \ln(k_A/k_B)$.^[1]
 - Often, k_A/k_B is equal to the relative rate k_{rel} of the two reactions ($SM \longrightarrow A$ and $SM \longrightarrow B$).
 - > If A and B are enantiomers or diastereomers, k_{rel} often equals **er** or **dr**, respectively.
 - > Another consequence of the introduction of k_{rel} is that $k_{\text{rel}} = e^{-\Delta\Delta G^\ddagger/RT}$.
 - Note that *catalyzing* a pathway is a kinetic effect, corresponding to a lower activation barrier.
- In contrast to thermodynamic equilibrium, the products formed here are formed irreversibly and do not interconvert.
- Kinetic control is more common than thermodynamic control.
 - Reactions under thermodynamic control have largely been developed and optimized over the last 100 years, so kinetic control gives us a better handle in modern methods development.
 - Everything about a catalytic cycle is based on kinetics! You're not changing the thermodynamics of CO₂ upcycling; you're making it more energetically feasible.
- **Enantiomeric ratio:** The ratio of the (*S*)-enantiomer to the (*R*)-enantiomer. *Denoted by er*.
 - This is more mathematically useful than the enantiomeric excess (ee), so there's currently something of a push to phase out ee in favor of er.
 - ee is still used primarily for historical reasons.
- **Diastereomeric ratio:** The ratio of one diastereomer to the other. *Denoted by dr*.
- We now discuss a special type of kinetic control called **Curtin-Hammett kinetics**.
- **Curtin-Hammett** (kinetics): A kinetic regime characterized by two starting materials or intermediates that rapidly interconvert, causing the ratio of products (i.e., the selectivity) to depend only on the transition state energies. *Also known as C/H*.

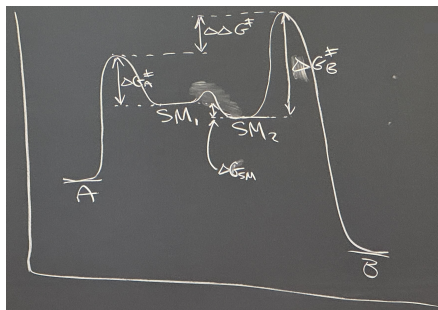
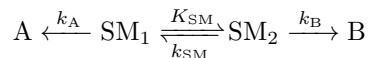


Figure 6.3: Energy variables relevant to Curtin-Hammett kinetics.

¹This can be derived by dividing the Arrhenius equation for one reaction by the Arrhenius equation for the other reaction and rearranging.

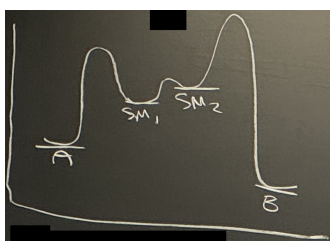
- In particular, the selectivity does *not* depend on the energies of the starting materials.
- Relevant reaction coordinate.



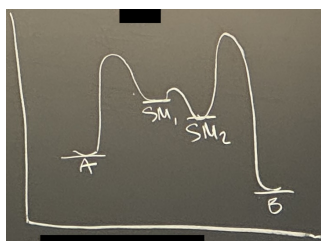
- k_{SM} must be big. Typically, it is approximately ten times faster than k_A or k_B .
- Working out the math, we get

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

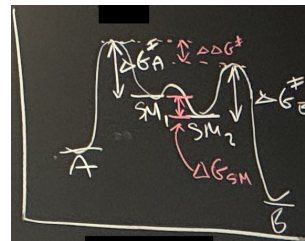
- Indeed, we see that in this regime, the selectivity *mathematically* depends only on the relative energies of the transition states.
- Energy diagram of a reaction under Curtin-Hammett kinetics (Figure 6.3).
- Note that there is only a small energy barrier between SM_1 and SM_2 because we need fast interconversion.
- Observe that the products are formed irreversibly and do not interconvert.
- Indeed, the SMs interconvert freely as long as they stay SMs, but once they go over their barrier to A or B, they do not continue to interconvert.
- Scenarios that manifest Curtin-Hammett kinetics.



(a) More stable reacts more quickly.



(b) Less stable reacts more quickly.



(c) Both react same.

Figure 6.4: Curtin-Hammett scenarios.

1. The more stable starting material reacts more quickly (Figure 6.4a).
 - Let SM_1 be lower energy than SM_2 , and let the $SM_1 \rightarrow A$ transition state have a lower activation energy than the $SM_2 \rightarrow B$ transition state.
 - It follows that SM_1 is thermodynamically favored. This means that we'll see more of it in solution: $[SM_1] > [SM_2]$.
 - The lower activation energy to form A (i.e., $\Delta G_A^\ddagger < \Delta G_B^\ddagger$) implies that A is kinetically favored.
 - The product ratio will not be equal to the starting material ratio.
 - You might not even see SM_2 among the starting materials; you might just think that $SM_1 \rightarrow A + B$.
 - Takeaway: It isn't always obvious when Curtin-Hammett kinetics are in effect.
2. The less stable starting material reacts more quickly (Figure 6.4b).
 - Let SM_1 be higher energy than SM_2 , and let the $SM_1 \rightarrow A$ transition state have a lower activation energy than the $SM_2 \rightarrow B$ transition state.
 - It follows that SM_2 is thermodynamically favored. This means that we'll see more of it in solution: $[SM_2] > [SM_1]$.

- The lower activation energy to form A (i.e., $\Delta G_A^\ddagger < \Delta G_B^\ddagger$) implies that A is kinetically favored.
 - The less stable starting material is kinetically favored to react.
 - Takeaway: All the reactivity goes through SM_1 , even though we might not even see SM_1 ; you might just think that $SM_2 \longrightarrow A + B$.
 - This is classic Curtin-Hammett kinetics, wherein the product we observe is from the starting material we don't observe.
 - Results like this can be confusing because the SM we put in the flask doesn't look like it'd give the product we see.
 - This contrasts with Scenario 1, wherein the SM we see logically leads to our product A, and all we miss is that there's a secret equilibrium that helps us get to B.
3. Both starting materials react equally quickly (Figure 6.4c).
- Let SM_1 be higher energy than SM_2 , and let the $SM_1 \longrightarrow A$ and $SM_2 \longrightarrow B$ transition states have identical activation energies (i.e., $\Delta G_A^\ddagger = \Delta G_B^\ddagger$).
 - We call this **ground state control**.
 - Thus, ΔG_{SM} suddenly predicts our products; not because it actually does but because $\Delta\Delta G^\ddagger = \Delta G_{SM}$.
 - To reiterate: $\Delta\Delta G^\ddagger$ still controls selectivity; it just happens that it equals ΔG_{SM} .
 - Because $\Delta\Delta G^\ddagger = \Delta G_{SM}$, we can work out mathematically that the selectivity happens to be the following (even though we still have C/H kinetics).
- $$\text{selectivity} = \frac{[A]}{[B]} = \frac{[SM_1]}{[SM_2]}$$
- This regime often arises when A and B are really similar and hence have similar transition states (e.g., if A and B are enantiomers or diastereomers with far apart stereogenic centers).
- It's our job as the responsible scientist to account for the full kinetic picture, even when it may not provide us much additional information!
 - Indeed, the reactions that are the most interesting to develop are the ones that fall in this C/H regime because they have the most subtle reactivity.
 - Let's now look at some examples.
 - Pay attention, because this is going to be a super useful skill for grad school and beyond!!
 - Example: Nitrogen rapidly epimerizes while a *tert*-butyl group locks the chair in place.

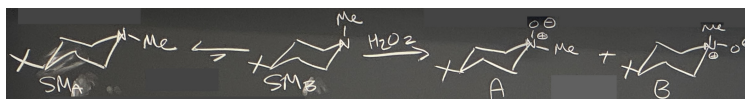


Figure 6.5: Curtin-Hammett kinetics: Kinetically trapping epimers.

- This epimerization (a **nitrogen inversion**) occurs fast relative to product formation.
- It puts SM_A and SM_B in a 98 : 2 ratio.
- Either epimer can react with H_2O_2 to form the *N*-oxo products in a 5 : 95 (A : B) ratio.
- This is an example of Scenario 2 (Figure 6.4b).
 - Your first thought might be that the oxidation occurs with inversion of stereochemistry. This is a great first thought.
 - But then you have to ask about alternate scenarios, and you should think about decoupled Curtin-Hammett steps wherein you're just kinetically trapping the epimers.

- Example: Axial and equatorial tosylates equilibrate before E₂ elimination to form a double bond.



Figure 6.6: Curtin-Hammett kinetics: Elimination.

- Let SM_A be the axial tosylate (on the left), and let SM_B be the equatorial tosylate (on the right).
 - Because of the large steric bulk of the tosylate group and hence its disfavored 1,3-diaxial interactions, SM_A and SM_B occur in a 1 : 14 ratio.
 - However, SM_A has hydrogens antiperiplanar to it, so it reacts faster ($k_{\text{rel}} = 70$).
 - So to recap: SM_B is preferred, but the product comes from SM_A. Therefore, this must be another example of Scenario 2 (Figure 6.4b).
- Example: *trans* and *cis* alkenes react via bromination to form a *trans*- and *cis*-dibromide.

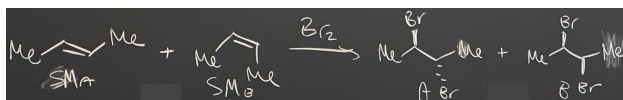


Figure 6.7: Curtin-Hammett kinetics: Bromination of geometric isomers.

- We have a 1 : 1 mixture of SMs, and we form a 1 : 1 mixture of products.
 - Thus, based on the selectivity equation, it looks like this could be a candidate for Scenario 3. However, this is not C/H because the SMs do not interconvert! Rather, this is a case of a kinetic quench, which we'll cover next.
- Learn C/H because we will see a lot of it on PSet 2.
 - Kinetic quench (not C/H).

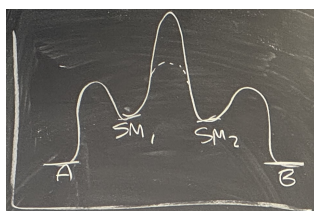


Figure 6.8: Energy variables relevant to a kinetic quench.

- Here, the SM₁ \rightleftharpoons SM₂ interconversion is slower than product formation.
- Thus, the ratio of starting materials equals the ratio of products, as follows.

$$\text{product ratio} = \frac{[A]}{[B]} = \frac{[SM_1]}{[SM_2]}$$

- This is basically a case of two isolated systems (SM₁ \longrightarrow A and SM₂ \longrightarrow B).^[2]

²Could I come up with one-pot reactions where you have two different starting materials under kinetic quench form two different products and then those products react??

- One tricky thing: When the rate of interconversion approximately equals the rate of product formation (Masha shows this regime with the dotted line in Figure 6.8).
 - In this case, the product ratio is difficult to predict!
 - That's real, messy science.
 - When you encounter such a regime, either you change something to make it simpler, or you do a Wendlandt-style deep dive on the full mechanism where you uncover the secrets of the universe and then publish a bunch of *Science* papers.
 - "Alison's the master of these really hairy and difficult kinetic pictures and disentangling them and adding to our understanding of chemistry overall."
- Example of kinetic quench: Protonating two different epimers of an amine.

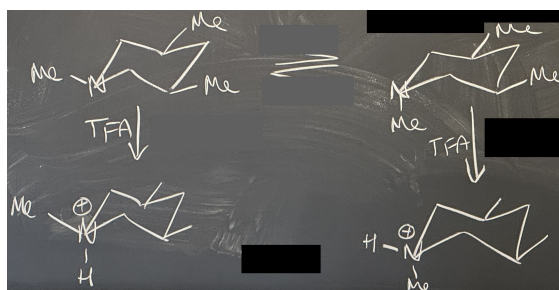
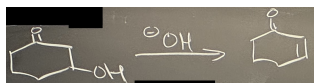


Figure 6.9: Kinetic quench: Protonation.

- The epimer with the equatorial methyl occurs in a $> 15 : 1$ ratio.
- Epimerization occurs relatively slowly, protonation of the equatorial lone pair occurs fast, and protonation of the axial lone pair is even *faster* than protonation of the equatorial one.
 - What is “fast” and “slow” is all relative! Usually, nitrogen inversion is fast, but proton transfer (PT) to nitrogen is even faster.
- However, the product ratio is also $> 15 : 1$, just like the SM ratio. To reiterate, this is because we're not interconverting between our starting materials.
- Moving on, let's discuss the **principle of microscopic reversibility**.
- **Principle of microscopic reversibility:** The lowest energy path connecting two intermediates is the same, regardless of the direction in which the reaction proceeds.
 - Basically, if you propose a mechanism from $A \longrightarrow B$, the same mechanism (in reverse) has to be true for $B \longrightarrow A$.
 - If we proceed through a certain transition state in one direction, we cannot proceed through a different transition state on the way back.
 - Really useful to probe kinetically silent steps.
- A cool example of using the principle of microscopic reversibility to see which mechanism is operative (Figure 6.10).
 - Consider the elimination of a β -hydroxyketone to form an enone (Figure 6.10a).
 - Is the mechanism E_2 (Figure 6.10b) or E_1CB (Figure 6.10d)?
 - How can we determine the better mechanism? Consider the reverse reactions!
 - Retro- E_2 (Figure 6.10c): A one-step forward reaction for E_2 means a one-step reverse reaction, wherein HO^- adds in, the olefin grabs a proton from water, and HO^- leaves.



(a) An elimination reaction.

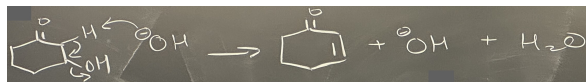
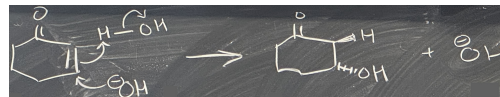
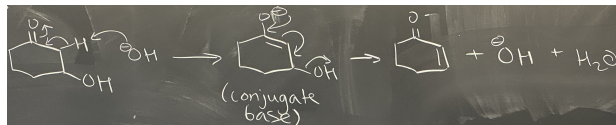
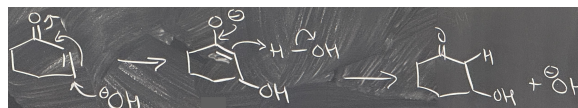
(b) E₂ mechanism.(c) Retro-E₂ mechanism.(d) E₁CB mechanism.(e) Retro-E₁CB mechanism.

Figure 6.10: Microscopic reversibility to differentiate plausible mechanisms.

- Retro-E₁CB (Figure 6.10e): This time, a two-step reverse reaction is implied. First, we kick electron density all the way up to oxygen, and second, we kick arrows back down to grab a proton.
- Which reverse mechanism is more plausible?
 - In Figure 6.10c, we need a termolecular transition state (which is possible, but rare). However, we'd also form only the anti product, and this is flatly inconsistent with experiment.
 - In Figure 6.10e, we have a conjugate addition step followed by an enolate protonation step, both of which are very typical reactions.
 - Molecular orbital theory also implies that the electrons push all the way up through the conjugated system to the oxygen in a concerted step upon nucleophilic addition at the Bürgi-Dunitz angle, like in 5.13!
- Now remember that the more reasonable mechanism must follow the same steps in the forward and reverse direction.
 - Thus, more reasonable in reverse implies more reasonable in forward!
- Conclusion: E₁CB wins!
- **Elimination unimolecular conjugate base:** Just a type of E1 that happens with an acidic proton. Also known as **E₁CB**.
 - You draw the formation of a conjugate base (i.e., the conjugate base of the SM “acid”) followed by the elimination of something.
- That wraps it up for microscopic reversibility; let's now move onto another principle.
- **Reactivity-selectivity principle:** It is often observed that a more reactive reactant, intermediate, or reagent corresponds to a less selective reaction.
 - When we say “more reactive,” we typically mean higher energy, more exothermic, etc.
 - This happens because the transition states to different products tend to resemble this higher energy intermediate per the **Hammond postulate**.
 - It follows since the transition state does not resemble the products that it is less sensitive to differences in product energy, so it is harder for the transition state to differentiate between products, so the reaction is less selective.

- **Hammond postulate:** The transition state is most similar in structure to the higher energy intermediate.
- Example of the reactivity-selectivity principle: Radical halogenation.

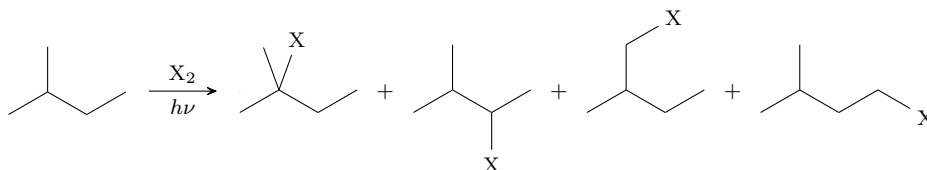


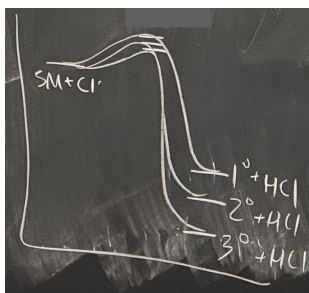
Figure 6.11: Reactivity-selectivity principle in radical halogenation.

- This reaction yields 1 tertiary product, 2 different secondary products, and 1 primary product.
- The reaction in Figure 6.11 forms different product distributions with different halogens.

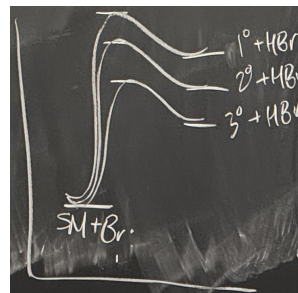
X = Cl (%)	28	35	24	12
X = Br (%)	90	9	< 1	< 1

Table 6.1: Product distribution in radical bromination vs. chlorination.

- Evidently, $\text{Br}\cdot$ is more selective than $\text{Cl}\cdot$.
- Why? Consider BDEs in the selectivity-determining propagation step wherein a halide radical creates an alkyl radical and HCl .



(a) Chlorination energy diagram.



(b) Bromination energy diagram.

Figure 6.12: The Hammond postulate explains the reactivity-selectivity principle.

- In radical chlorination: C-H has a BDE of 98 kcal/mol and H-Cl has a BDE of 103 kcal/mol.
 - Thus, the reaction is exothermic with $\Delta H = -5$ kcal/mol.
 - Then per the reactivity-selectivity principle, we have a high-energy intermediate. This will lead to three energetically close transition states that unselectively determine the product (Figure 6.12a).
- In radical bromination: C-H has a BDE of 98 kcal/mol and H-Br has a BDE of 87 kcal/mol.
 - Thus, the reaction is endothermic with $\Delta H = 11$ kcal/mol.
 - Then per the reactivity-selectivity principle, we have a low-energy intermediate. This will lead to three energetically distinct transition states that resemble the product more and hence selectively determine it (Figure 6.12b).

- The reactivity-selectivity principle is useful to understand and many-times true, but there are also many exceptions.
 - Example exception: If there are more complicated mechanistic relationships between the SMs and transition states.
- See Figure 3.4 of Labalme (2024)!
- Practical aspects of selectivity (will come up on our quals).
 - Numbers worth knowing.
 - We'll go over this in the Lecture 10 recap on Thursday!

6.2 Office Hours (Jonathan)

- Would this similarly predict that H_2O has longer bonds than NH_3 ?
 - Perhaps, but other factors make O–H bonds in water shorter than the N–H bonds in ammonia.
- In what way does the HIA only tell us the *relative* stability?
 - The number doesn't tell us anything on its own, and it's not a very useful number.
 - Essentially, all we can learn from these is which cations are more reactive *relative* to other cations.
- How can Bn-Br be the most stable and most reactive species (Table 4.1)?
 - The benzyl *cation* (not the benzyl bromide) is the most stable because it takes the least energy to create it. We had to put more energy into the other two systems to create carbocations, so they are higher energy and hence less stable.
 - The benzyl cation is most reactive toward solvolysis because it has the highest k_{rel} .
- Mayr electrophilicity?
 - What I wrote down sounds wrong to Jonathan.
 - It has nothing to do with the thermodynamic stability of anything; it's all about rate constants.
 - I can read the paper if I want, but it's probably not too important.