

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.

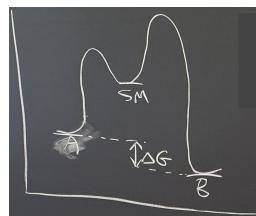


Figure 6.1: Energy variables relevant to thermodynamic selectivity.

- 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.

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

- 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 $\Delta G = -RT \ln(K_{\text{eq}})$ and hence $K_{\text{eq}} = e^{-\Delta G/RT}$.
- 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.

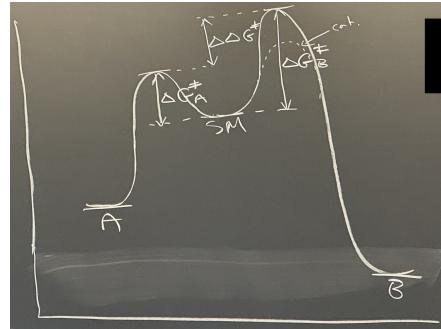


Figure 6.2: Energy variables relevant to kinetic selectivity.

- 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 ($\text{SM} \longrightarrow A$ and $\text{SM} \longrightarrow B$).
 - 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 CO_2 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.

- **Diasteriomic 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.*

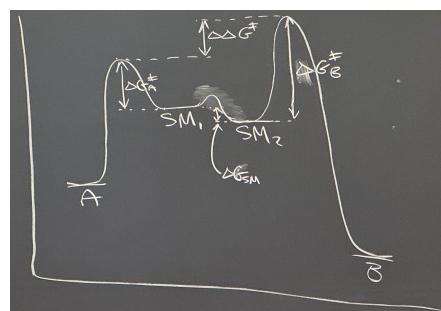
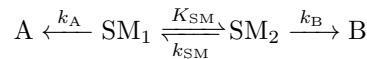


Figure 6.3: Energy variables relevant to Curtin-Hammett kinetics.

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

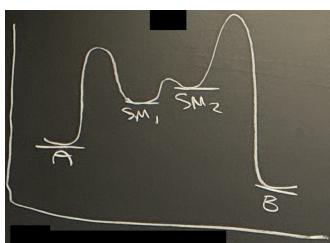
- In particular, the selectivity does *not* depend on the energies of the starting materials.
- Relevant reaction coordinate.



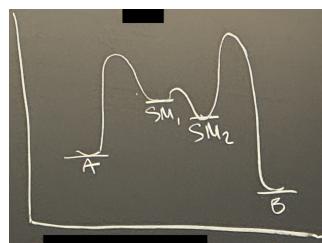
- k_{SM} must be big. Typically, it is approximately ten times faster than k_A or k_B .
- Working out the math, we get

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

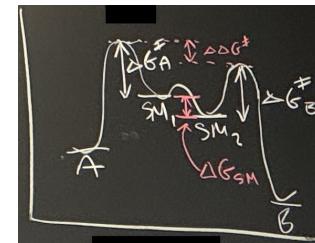
- Indeed, we see that in this regime, the selectivity *mathematically* depends only on the relative energies of the transition states.
- Energy diagram of a reaction under Curtin-Hammett kinetics (Figure 6.3).
 - Note that there is only a small energy barrier between SM_1 and SM_2 because we need fast 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.

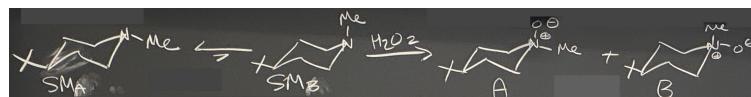


Figure 6.5: Curtin-Hammett kinetics: Kinetically trapping epimers.

- 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.

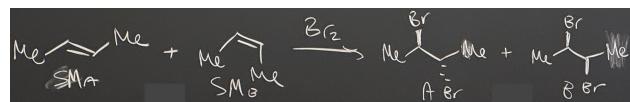


Figure 6.7: Curtin-Hammett kinetics: Bromination of geometric isomers.

- 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).

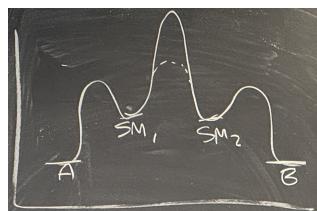


Figure 6.8: Energy variables relevant to a kinetic quench.

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

$$\text{product ratio} = \frac{[A]}{[B]} = \frac{[\text{SM}_1]}{[\text{SM}_2]}$$

- 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.

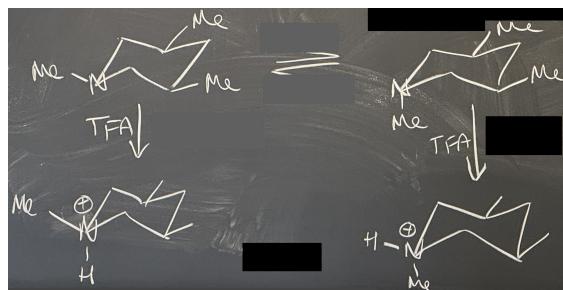


Figure 6.9: Kinetic quench: Protonation.

- 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.

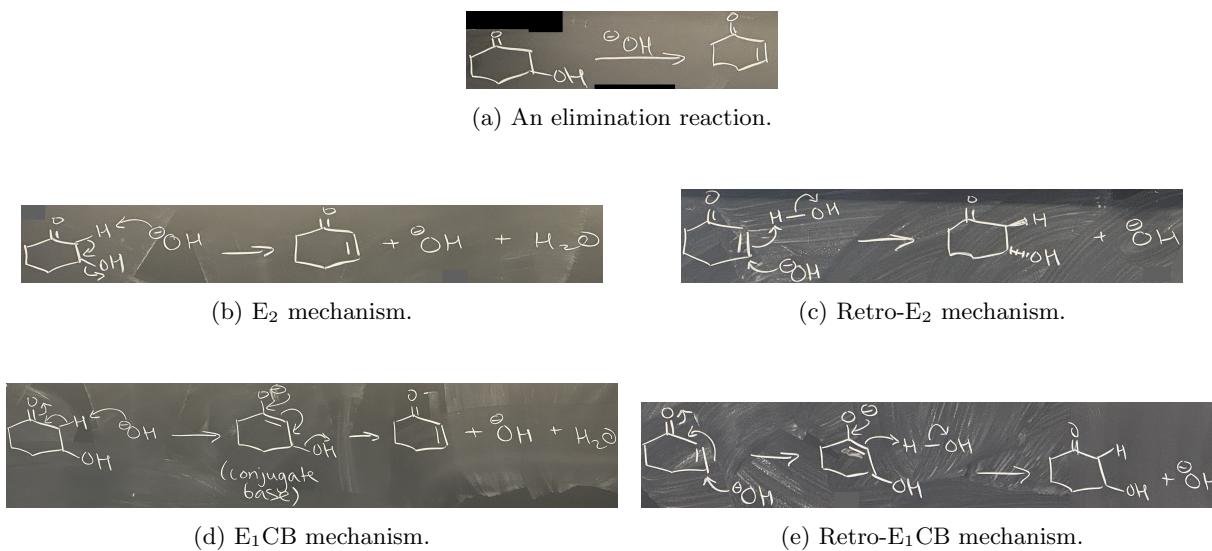


Figure 6.10: Microscopic reversibility to differentiate plausible mechanisms.

- 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.

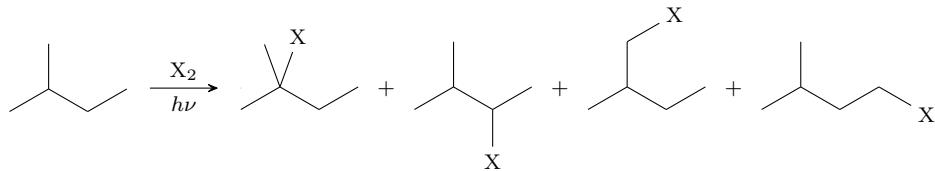


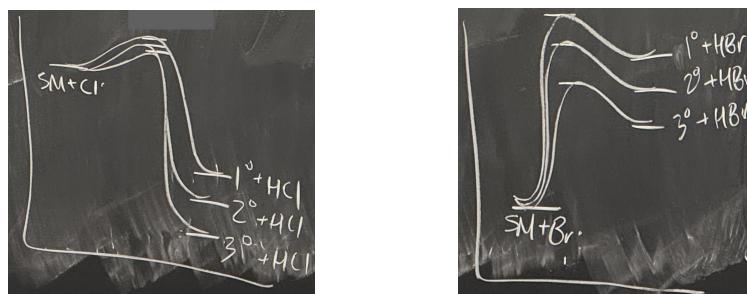
Figure 6.11: Reactivity-selectivity principle in radical halogenation.

- 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.

$\mathbf{X = Cl \ (\%)} \quad $	28	35	24	12
$\mathbf{X = Br \ (\%)} \quad $	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 HX.



(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 $\Delta H = -5 \text{ kcal/mol}$.
 - 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 $\Delta H = 11 \text{ kcal/mol}$.
 - 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 H₂O has longer bonds than NH₃?
 - 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.

6.3 Linear Free Energy Relationships

10/10:

- Masha's perspective on the Nobel Prize.
 - "Very new, very corporate, very Capitalistic science."
 - Oleta Johnson: Justice for Bill DeGrado (other *de novo* protein person, along with David Baker).
- Lecture 10 recap.
 - Two types of selectivity: Thermodynamic (ΔG) and kinetic (ΔG^\ddagger).
 - Curtin-Hammett kinetics.
 - Kinetic quench.
 - Principle of microscopic reversibility.
 - Practical aspects of selectivity.
 - If $\Delta G = 1.4 \text{ kcal/mol}$, then we get a 10 : 1 ratio at room temperature.
 - This free energy difference can be in the rate (ΔG^\ddagger) or products (ΔG).
 - If there's only one thing you learn in this class, let it be these numbers!!
 - It's a super common qual question.

- Lecture 10 continued: Practical aspects of selectivity.
- The kinetic products are typically favored by short reaction times and low temperature.
 - The thermodynamic products are typically favored by long reaction times and high temperatures.
 - Example: If you want a kinetic enolate vs. a thermodynamic enolate, you'll use different conditions.
- All reactions exist on the spectrum of kinetic control to thermodynamic control.
 - At infinite time, all reactions reach thermodynamic equilibrium.
 - Example: All diamond will eventually convert into graphite because diamond is not the thermodynamically stable form of carbon; it's just kinetically locked.
 - Implication: The “diamonds are forever” jingle is not scientifically true!
- Thermodynamic control.
 - Recall from Gen Chem that $\Delta G = -RT \ln(K_{\text{eq}})$.
 - If we plug in the K_{eq} for a 10 : 1 ratio (i.e., $K_{\text{eq}} = 10$), then $\Delta G = 1.4 \text{ kcal/mol}$ at room temperature.
 - Because of the log scale, if $K_{\text{eq}} = 100$, then $\Delta G = 2.8 \text{ kcal/mol}$.
 - Implication: Doubling the energy difference doubles the order of magnitude of the selectivity.
 - We rarely think about the energies behind the data we get in the lab. If we get a 10 : 1 selectivity, it feels like that should be because of a big driving force. But it's actually not: It's just a kcal and a half (remember that bond rotation is 3 kcal/mol, for comparison).
- Kinetic control.
 - Recall from Gen Chem that $\Delta\Delta G^\ddagger = -RT \ln(k_{\text{rel}})$.
 - Examples of k_{rel} : er and dr.
 - To get an ee of 90% (i.e., a 95 : 5 ratio, so er = 19), we only need $\Delta\Delta G^\ddagger = 1.75 \text{ kcal/mol}$ at room temperature.
 - To get an ee of 99.5% (er = 366), we only need $\Delta\Delta G^\ddagger = 3.5 \text{ kcal/mol}$ at room temperature.
 - Implication: The energy required for 0-90 ee is the same as for 90-99.5, so it gets progressively harder to get higher ee's.
- Temperature dependence: Lower temperatures mathematically enable higher selectivity, both thermodynamically and kinetically.
 - Example: 1.75 kcal/mol at -78°C gives us 98% ee.
 - Example: 1.4 kcal/mol at -78°C gives us a 37 : 1 product ratio.
- Rates of completion.
 - A reaction is complete after five half lives (approx 97% yield).
 - A slow reaction (1 day) has a transition state energy of 23 kcal/mol at room temperature.
 - A fast reaction (1 hour) has a transition state energy of 21 kcal/mol at room temperature.
 - Increasing the temperature by 10°C increases the rate by 2-5 times.
 - Implication: A reaction that finishes in 6 hours at room temperature will finish in 17 minutes at 50°C .
 - Essentially, high temperatures can put a lot of energy into our system and really accelerate our reactions.
- This concludes the end of last lecture.

- Today: Linear free energy relationships (LFERs).
- Lecture outline.
 - Types of substituent effects.
 - Hammett plots (definition and special cases).
- LFERs are based on **substituent effects**.
- **Substituent effect:** The effect that a new substituent (Y) can have on a reaction rate (ΔG^\ddagger) or equilibrium (ΔG), relative to a reference substituent (X).
- Examples.
 1. **Inductive effects.**
 2. **Field effects.**
 3. **Resonance effects**
 4. **Polarizability effects.**
 5. **Steric effects.**

- **Inductive effect:** The donation or withdrawing of electrons through σ -bonds.
 - Distance dependence: The closer our EWG or EDG is, the bigger effect it has.
- Example of inductive effects' distance dependence.

Acid				
pKa	4.9	4.2	3.1	0.2

Table 6.2: Inductive effects' distance dependence.

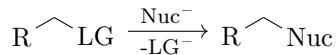
- Let's compare the pK_a 's of propionic acid, 4,4,4-trifluorobutyric acid, 3,3,3-trifluoropropionic acid, and trifluoroacetic acid.
- The trifluoromethyl EWG stabilizes the anion, resulting in a more acidic proton as the EWG gets closer to the site of deprotonation.
- **Field effect:** The donation or withdrawing of electrons through space.
 - Examples: Dipole moments or charges.
- **Resonance effect:** The donation or withdrawing of electrons through π -bonds.
- Example resonance effect: Deactivating a carbonyl.
 - Consider acetophenone vs. the *para*-methoxy analog.
 - The *para*-methoxy group can donate electron density up through the ring and into the carbonyl, making the carbonyl less electrophilic. We can visualize this donation with resonance structures.
 - This is a further example of the resonance saturation effect.
- **Polarizability effect:** The ability of a substituent to distort an electron cloud.
 - An atom's electron cloud can be **hard** or **soft**.
- **Hard** (atom): An atom that is not polarizable; its electron cloud is difficult to distort.
 - Example: Oxygen.
- **Soft** (atom): An atom that is polarizable; its electron cloud is easy to distort.
 - Example: Sulfur.

- **Steric effect:** The ability of a large group to “deflect” reactants.
- Example steric effect: Changing the rate of an S_N2 reaction.

R	H	CH ₃	^t Bu
k_{rel}	1	0.33	3.3 × 10 ⁻⁷

Table 6.3: Steric effects on S_N2.

- Imagine you’re trying to run the following S_N2 reaction.



- Table 6.3 tells us what happens as we change the R group.
 - In particular, *k_{rel}* changes dramatically for bigger groups!
- This concludes our discussion of substituent effects.
 - However, there is still one more major factor that can affect free energy: The solvent.
- **Solvent effect:** The effect on the reaction of changing the solvent.
 - This is *not* a substituent effect, but it can amplify them.
 - You see this a lot, especially in conjunction with field effects and charge.
- What do substituent effects tell us?
 - Identical substituents tend to have similar effects across different reactions and substrates.
 - Examples.
 - NO₂ is almost always an EWG.
 - NR₂ is almost always an EDG.
 - This may be intuitive to us at this point, but it’s not necessarily a given! It’s a blessing that chemistry works out this way.
 - Today, we will discuss a method of quantitatively showing that substituents engender similar effects across reactions and substrates.
 - Substituent effects can tell us a lot about the mechanism and transition states of a reaction.
 - We get mechanistic and transition state information from quantifying how much a substituent “matters,” which we will do with LFERs!
- Let’s now talk about LFERs and the tool through which we visualize them, called a **Hammett plot**.
- Hammett’s program: What did Hammett want to do, and how did he do it?
 - Hammett wanted to study the electronic effects that substituents have on chemical reactions.
 - Initial observation: Substituents thermodynamically favor products with charges that they can help stabilize, and kinetically favor transition states with charges that they can help stabilize.
 - Hammett’s plan: Let’s find a reaction with a product that should obviously be stabilized or destabilized by EWGs and EDGs, let’s vary the EWGs and EDGs on the substrate, and let’s measure the variability in the extent to which the reaction proceeds!
 - The relationship he found happened to be log-linear (hence *linear* free energy relationships), and therefore ended up being very useful.
 - After measuring how each EWG or EDG affected this “reference” reaction, he had a numerical scale on which he could measure EWG/EDG effects on other reactions relative to this reference.
 - Note: Like any relative numerical scale, the origin must be defined arbitrarily. Hammett chose the substituent H as his zero.
 - With this framework, people could measure substituent effects, plot them, and interpret them!

- **Linear free energy relationship:** A correlation of free energy (ΔG or ΔG^\ddagger) to parameters that describe substituent effects. *Also known as LFER.*
 - To reiterate: LFERs quantify the effect of substituents on equilibrium or rate.
- Key aspects of LFERs.
 - EDGs accelerate reactions with positive charge buildup in the transition state, and EWGs accelerate reactions with negative charge buildup in the transition state.
 - This is because if you're building up a charge on the transition state, it's more stabilizing to delocalize that charge across the molecule.
 - Later this lecture, we will look at cases where changing the substituents can change the mechanism. In these cases, Hammett plots give us great insight into reaction mechanism!
- One tool in particular helps us study and visualize LFERs: **Hammett plots**.
- **Hammett plot:** A plot of ΔG or ΔG^\ddagger for a reaction as a function of a **substituent parameter**.
- **Substituent parameter:** A measure of a substituent's ability to stabilize a negative charge. *Denoted by σ_X . Given by*

$$\sigma_X := \log\left(\frac{K_X}{K_H}\right)$$
 - K_H is the equilibrium constant for some reference reaction that creates a negative charge, where the starting material is unsubstituted.
 - K_X is the equilibrium constant for some reference reaction that creates a negative charge, where the starting material has substituent X attached.
 - Higher values of σ_X indicate a stronger ability to stabilize a negative charge.
 - Negative values of σ_X indicate an ability to *destabilize* a negative charge.
 - Alternatively, negative values of σ_X indicate an ability to stabilize a positive charge!
- Hammett quantified how various substituents stabilize the negative charge in benzoate, choosing Figure 6.13 as his reference reaction.

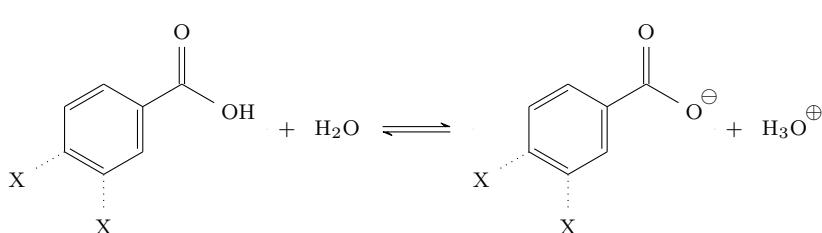


Figure 6.13: Hammett's reference reaction.

- In particular, he looked at the deprotonation of benzoic acid ($X = H$) as a reference reaction, calling its equilibrium constant K_H .
- Then he looked at the deprotonation of substituted benzoic acids, calling their equilibrium constants K_X .
- He defined σ_m to measure the substituent's effect when *meta*-positioned on benzoic acid, and σ_p to measure the substituent's effect when *para*-positioned on benzoic acid.

- σ_m : A measure of a substituent's ability to stabilize (inductively) the negative charge that builds up when a substituted benzoic acid is deprotonated. *Given by*

$$\sigma_m := pK_a(H) - pK_a(X)$$

- Note that the above definition equals $\log(K_X/K_H)$, where the equilibrium constants are K_a 's!
- To measure σ_m , the substituent is *meta*-substituted onto benzoic acid.
 - This way, it *cannot* resonance-delocalize to the *ipso*-position.
- σ_p : A measure of a substituent's ability to stabilize (inductively *and* through resonance) the negative charge that builds up when a substituted benzoic acid is deprotonated. *Given by*

$$\sigma_p := pK_a(H) - pK_a(X)$$

- Note that the above definition equals $\log(K_X/K_H)$, where the equilibrium constants are K_a 's!
- To measure σ_p , the substituent is *para*-substituted onto benzoic acid.
 - This way, it *can* resonance-delocalize to the *ipso*-position.
- Note that we don't use σ_o (i.e., for *ortho*-substituted substituents) because it incorporates steric effects that are hard to decouple.
 - We will discuss methods of quantifying steric effects next lecture!
- Relating the definitions of substituent parameters to LFERs.
 - The change in free energy ΔG of the deprotonation reaction is related to the equilibrium constant K_a , which is related to pK_a .
 - Thus, to measure ΔG , we can measure the pK_a !
- Recap: Why benzoate is a great proxy for measuring a substituent's electronic effects.
 - *meta*- and *para*-positioning decouples the substituent's steric effects from its electronic effects.
 - Benzoic acid is aromatic and conjugated, so even though the *para*-position is farther away from the reactive site, there is a minimal difference in distance dependence between the *meta*- and *para*-positions to interfere with comparing inductive effects.
 - Substituted benzoic acids are readily accessible synthetically.
- Example: σ_p and σ_m values for some common substituents.

X	pK_a	σ_p	σ_m
CH ₃ O	4.5	-0.27	0.10
CH ₃	4.3	-0.14	-0.06
H	4.2	0	0
Cl	4.0	0.24	0.37
NO ₂	3.4	0.81	0.71

Table 6.4: σ_p and σ_m for common substituents.

- We first measure the pK_a 's of the *para*-X substituted benzoic acids (see Figure 6.13).
 - These numbers are reported in the pK_a column in Table 6.4.
 - Plugging them into the definition of σ_p yields the σ_p column in Table 6.4.
 - Examples:

$$\sigma_p(\text{NO}_2) = 4.2 - 3.4 \approx 0.81$$

$$\sigma_p(\text{CH}_3) = 4.2 - 4.3 \approx -0.14$$

- A similar process allows us to measure σ_m .
- Recap: Intuitively interpreting the values of these substituent parameters.
 - When $\sigma = -$, we have an EDG (which makes our substrate less acidic than when X = H).
 - When $\sigma = +$, we have an EWG (which makes our substrate more acidic than when X = H).
 - When σ_p and σ_m differ, the group is inductively an EWG but by resonance an EDG.
 - Example: CH_3O has $\sigma_p = -$ (resonance EDG), but $\sigma_m = +$ (inductive EWG).
- Now that we've established our substrate parameters, let's use them to learn something about the following reaction.

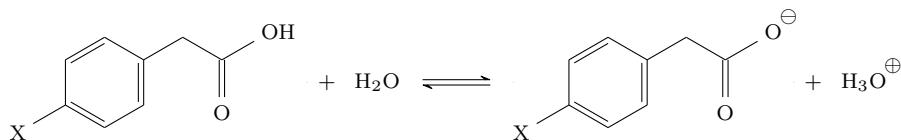


Figure 6.14: The deprotonation of phenylacetic acid.

- In particular, we'll use them to build our first actual Hammett plot.

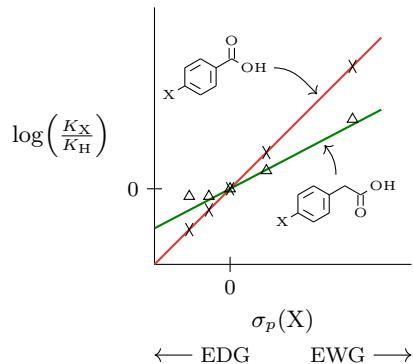


Figure 6.15: Hammett plot for benzoic and phenylacetic acid.

- Measure K_X for the deprotonation of *para*-substituted phenylacetic acid (see Figure 6.14), as X varies over the substituents in Table 6.4.
- Use these values to calculate a corresponding set of $\log(K_X/K_H)$ values.
- Plot these values against the σ_p values in Table 6.4 as the triangles in Figure 6.15.
- Perform a regression to fit this data to the appropriate general Hammett equation.

$$\log\left(\frac{K_X}{K_H}\right) = \rho\sigma_X \quad \log\left(\frac{k_X}{k_H}\right) = \rho\sigma_X$$

- We use the left equation above in the case of ΔG (e.g., this case).
- We use the right equation above in the case of ΔG^\ddagger .
- Recall that σ_X is the substituent parameter.
- ρ is the **sensitivity factor**.
- Performing this analysis, we can determine that $\rho = 0.56$ for phenylacetic acid (green line in Figure 6.15).
 - Naturally, $\rho = 1$ for the reference reaction (red line in Figure 6.15).
 - This means that the reaction in Figure 6.14 is about half as sensitive to substituent effects as the reference reaction (Figure 6.13), which makes sense because the carboxylic acid is no longer conjugated to the substituent-bearing aromatic ring.

- **Sensitivity factor:** A measure of how sensitive a chemical reaction is to changes in substituents. Denoted by ρ .
- Intuitively interpreting the value of ρ .
 - $\rho > 0$: The reaction builds up negative charge in the transition state.
 - Such as the *anion-forming* deprotonations in Figures 6.13 & 6.14!
 - $\rho < 0$: The reaction builds up positive charge in the transition state.
 - $\rho = 0$: The reaction is not sensitive to substituents.
 - $|\rho| < 1$: The reaction is less sensitive to substituents than the reference reaction.
 - Such as the deprotonation in Figure 6.14 where, as mentioned, the reactive site is farther from the substituent.
 - $|\rho| > 1$: The reaction is more sensitive to substituents than the reference reaction.
- Steven: Is the axis labeling correct?
 - Math is definitely not Masha's strong suit.
- To build our intuition and ability to connect ρ values to mechanistic insights, let's look at some examples.

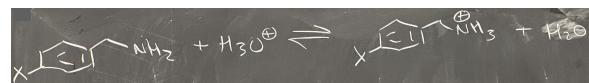
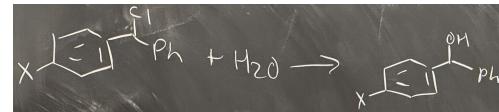
(a) Phenol deprotonation ($\rho = 2.26$).(b) Benzylamine protonation ($\rho = -1.05$).(c) Phenolate attack ($\rho = -0.95$).(d) Nucleophilic substitution ($\rho = -5.09$).

Figure 6.16: Sensitivity factors for simple reactions.

- The deprotonation of *para*-substituted phenols (Figure 6.16a).
 - $\rho = 2.26$.
 - This means that we're building up negative charge in the transition state, and the reaction is more sensitive to X than the reference reaction.
- The protonation of *para*-substituted benzylamines (Figure 6.16b).
 - $\rho = -1.05$.
 - This means that we're building up positive charge in the transition state.
- The ring-opening backside attack of *para*-substituted phenolates on epoxides (Figure 6.16c).
 - $\rho = -0.95$.
 - There's no discrete build up of positive charge in this reaction, but this value indicates that we have a loss of negative charge in the transition state.
- A nucleophilic substitution (Figure 6.16d).
 - $\rho = -5.09$.
 - Since $\rho = -$, we're building up positive charge in the transition state.
 - Since $|\rho| > 1$, we're (significantly) more sensitive to substituents than the reference.

- These two facts can actually help us determine the mechanism of this reaction!
 - There are two possible mechanisms by which this reaction can proceed: S_N1 and S_N2 .
 - The RDS of S_N1 is the departure of the leaving group, and S_N2 is concerted. Importantly, this means that S_N1 mechanisms have a significantly greater buildup of positive charge in the “transition state” since they form a true carbocation.
 - So since substituents have a *significant* effect here, the mechanism of this particular nucleophilic substitution must be S_N1 !
 - If it were S_N2 , we’d expect a small negative ρ .
- Takeaway: Sometimes Hammett plots give us simple insights, and sometimes they are powerful tools to help us probe reaction mechanisms.
 - Usually, we measure ρ and try to propose mechanisms that would be consistent with that ρ value; we do not usually draw the mechanism and guess the ρ .
- While linear Hammett plots can evidently be very helpful, sometimes we get nonlinear relationships. These can also give us important information.
- Example: Consider the following two-step reaction.

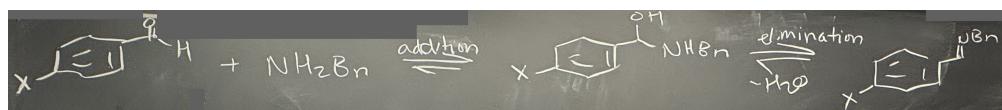


Figure 6.17: Imine formation from a substituted aldehyde.

- This is nucleophilic addition to an aldehyde, forming a hemiaminal, followed by elimination to the imine.
- The Hammett plot for Figure 6.17 is **concave down**.

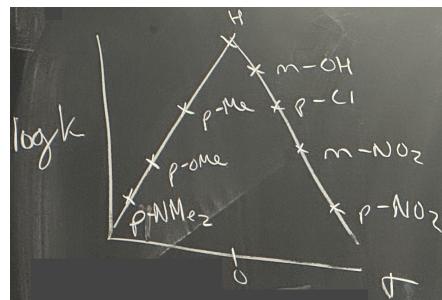


Figure 6.18: Hammett plot for imine formation.

- Notice that this Hammett plot deals with rate (ΔG^\ddagger) because the y -axis is in $\log(k)$, not $\log(K)$.
- Hence, this Hammett plot is under the control of two *kinetic* regimes.
- In the left regime, stronger EDGs decrease the rate of reaction.
 - Stronger EDGs will make the initial carbonyl less electrophilic.
 - Thus, with stronger EDGs, addition becomes the rate-limiting step.
- In the right regime, stronger EWGs decrease the rate of reaction.
 - Stronger EWGs will make the initial carbonyl more electrophilic (speeding up addition), and they will destabilize the positive charge that builds up when the hydroxyl group is protonated before elimination.
 - Thus, with stronger EWGs, elimination becomes the rate-limiting step.

- **Concave down** (Hammett plot): A Hammett plot that indicates a change in rate-determining step as X is varied, but the same overall mechanism.

- It should also make intuitive sense that a concave down plot changes the RDS: We have something of an equilibrium at H and all we need is one step slowed down to be the RDS, so pushing one way slows down one step, and pushing the other way slows down the other step!
- Essentially, regardless of which step is accelerated or slowed down by EWGs/EDGs, what matters is that *one* of the steps will be being slowed down, and *that* step will become rate-limiting.

- Further examples of concave down Hammett plots.



Figure 6.19: More concave down Hammett plots.

- Some can have two conjoined downward-sloped lines (Figure 6.19a).
 - This also corresponds to a change in the RDS, but in this case, *both* steps build up positive charge and hence are decelerated by EWGs.
- Some can be curved down (Figure 6.19b).
 - This corresponds to a more gradual change in RDS.
 - We see this when the transition state “moves” with the substituent changes.
- This concludes our discussion of concave down Hammett plots.
- We now look at another example reaction and its Hammett plot.

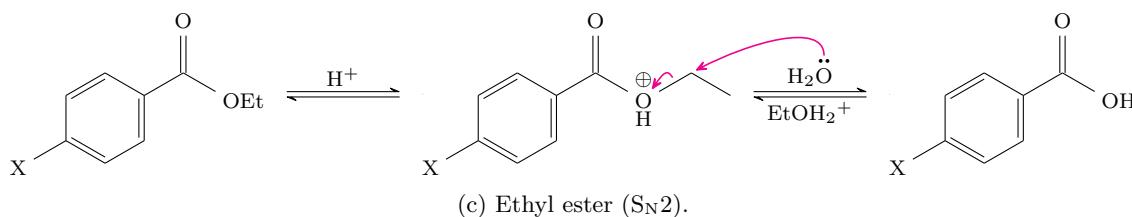
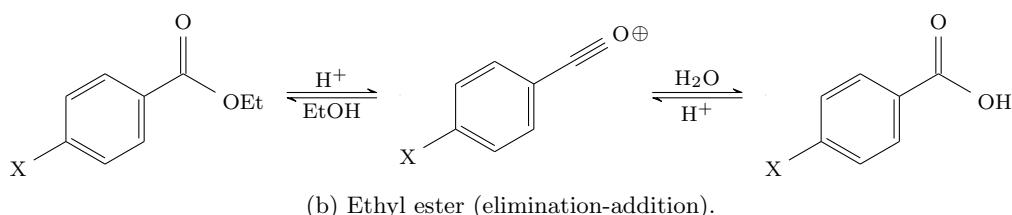
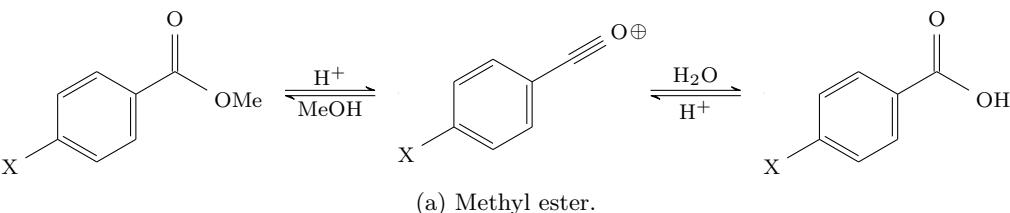


Figure 6.20: Acid-catalyzed ester hydrolysis.

- When a methyl ester hydrolyzes under acidic conditions, there is only one possible mechanism: Protonation of OMe followed elimination of methanol, forming an acylium ion, then addition of water followed by deprotonation to the acid (Figure 6.20a).
 - We call this an “elimination-addition mechanism.”
- However, when an *ethyl* ester hydrolyzes under acidic conditions, it can follow one of two mechanisms.
 1. An analogous elimination-addition mechanism (Figure 6.20b).
 2. Protonation of the ester oxygen followed by an S_N2-type mechanism (Figure 6.20c).
- The Hammett plot for the hydrolysis of a methyl ester is linear - down (Figure 6.21a), but the Hammett plot for the hydrolysis of an ethyl ester is **concave up** (Figure 6.21b).

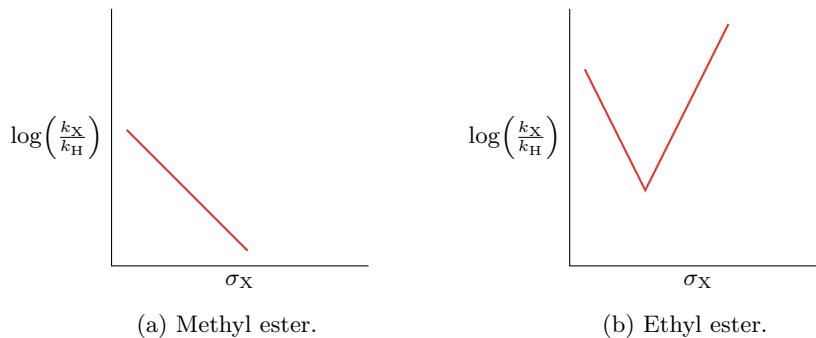


Figure 6.21: Hammett plots for ester hydrolysis.

- The hydrolysis of a methyl ester displays a constant, negative sensitivity factor (Figure 6.21a).
 - This is because the positively charged acylium ion intermediate gets destabilized by stronger EWGs.
- The hydrolysis of an ethyl ester displays a negative sensitivity factor for EDGs, and a positive sensitivity factor for EWGs (Figure 6.21b).
 - When X is an EDG, the acylium ion get stabilized. Weaker EDGs stabilize it less ($\rho = -$), but we still favor the elimination-addition mechanism (Figure 6.20b).
 - When X is an EWG, the carboxylic acid is a better leaving group (6.20c). This corresponds to a positive Hammett slope.
- **Concave up** (Hammett plot): A Hammett plot that indicates a change in mechanism.
 - It should also make intuitive sense that a concave up plot changes the mechanism: Here, both EDGs and EWGs *accelerate* a certain pathway. Thus, it doesn’t matter if they’re slowing the RDS of one mechanism; there’s another that they accelerate!
 - Essentially, regardless of which mechanism is accelerated or slowed down by EWGs/EDGs, what matters is that *one* of the mechanisms is being accelerated, and *that* mechanism becomes operative.
 - Why are neither of these mechanisms addition-elimination?
 - That’s better under basic conditions!
 - Take-home message: Any deviation from linearity in a Hammett plot indicates a change in the RDS or the mechanism.
 - Hammett plots are a very powerful mechanistic tool; think about using them in your final mechanistic proposal!!