

5.53 (Molecular Structure and Reactivity I) Notes

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Week 1

Introduction

1.1 Introduction

9/5:

- Normally, only about 20 kids enroll in this class per year. This year, there are 40.
 - This is a typical class for the first-year grad students in OChem, but Elkin asks what made advanced undergrads and second-year grad students enroll, as well as just so many of us overall.
 - Radosevich told all the inorganic kiddos to take this class!
 - Bioinorganic and Organometallics also aren't being offered because everyone's on sabbatical.
- Oleta Johnson came to sit in on Masha's class! Oleta is Masha's "best friend."
- The lecture now begins (on MIT Time).
- Masha will teach the first half of the course; Alex will teach the second half.
 - TF is Jonathan Edward, an Elkin kiddo.
 - He will hold weekly OH, study sessions, grades problems and exams, etc.
 - Has a mastery of the subject material (took 5.53 last year), and unrivaled "approachability."
 - Reach out to Masha or Alex if we have issues with the subject material, our own journeys in grad school or undergrad, etc. It's easier to fix problems early in the semester!
- Overview of the course.
 - 1st half.
 - Basically physical organic chemistry.
 - A deep dive on structure and reactivity.
 - 2nd half.
 - Basically reaction mechanisms.
 - Kinetics, rate laws, kinetic isotope effects (KIEs), methodology experiments, etc.
 - The tools presented herein are broadly applicable to various fields of chemistry.
- This course will teach us to...
 - Propose *reasonable* mechanisms for organic reactions;
 - Scrutinize mechanisms in the literature;
 - That is, figure out if a proposed mechanism is reasonable or not, evaluate the authors' evidence, and identify follow-up experiments that can be run.
 - Design experiments to distinguish and test proposed mechanisms;
 - Conduct our own mechanistic study.

- Masha gives the metacognition spiel again.
 - Know our strengths and weaknesses (correct these by reviewing undergrad notes and Googling).
- Course logistics.
 - 2 exams.
 - Fully online; they are trusting us to work alone on the honor system.
 - 4 problem sets.
 - Posted 1 week before they are due.
 - Encouraged to work collaboratively, but submit our own work.
 - Jonathan and Masha will reserve a study room in which we can collaborate.
 - 1 mechanistic proposal.
 - Engage the literature!
 - Textbook: Anslyn and Dougherty (2006).
 - The standard textbook for PhysOrg (do readings and practice problems as needed).
 - Jonathan is working on a correspondence of lectures to chapters.
 - Reach out to Masha, Alex, or Jonathan if we have any questions!
 - If you ever miss class, post a new topic on the Canvas discussion board asking for notes (and be generous in uploading your own).
- We now begin the course content.
- **Mechanism:** An accounting of all bond-making and bond-breaking events in a reasonable sequence.
 - Mechanisms don't exist in the physical sense; it is more of a *model* of how things proceed.
- Mechanisms exist in four levels of depth.
 1. Describe electron movement via arrow pushing.

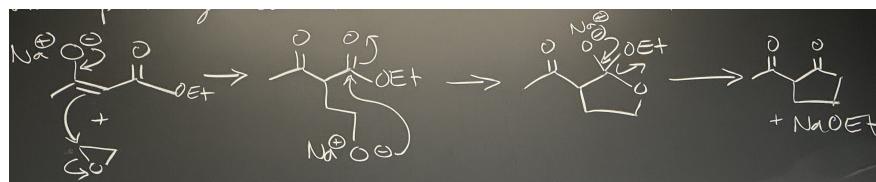


Figure 1.1: Mechanism depth level 1 (arrow pushing).

- Equivalent level: 5.47 & undergrad organic.
- Example: Figure 1.1.
 - In every step that we push arrows, we start at a region of high electron density, we make and break sequential bonds, and we leave the negative charge on an electronegative atom.
 - Once we have completed one step, we can start again from a new region of high electron density, making and breaking bonds, and drawing the product.
 - We repeat this process again and again until we reach the final product.
 - Arrow pushing conserves net neutral charges on molecules.
- Aside: Arrow types.

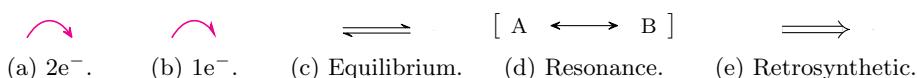


Figure 1.2: Arrow types in arrow pushing.

2. Determine the transition-state structures.

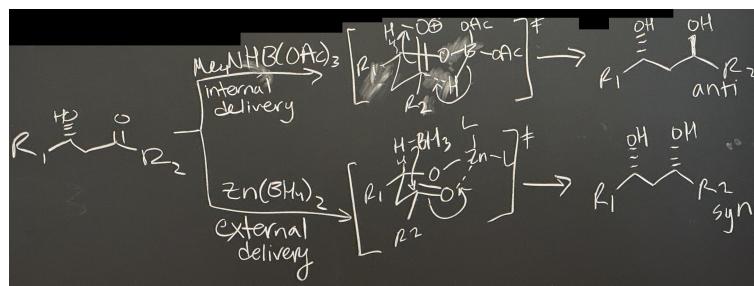
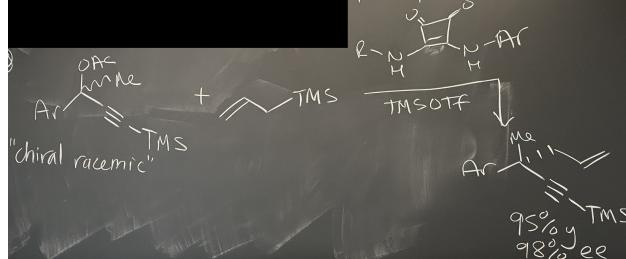


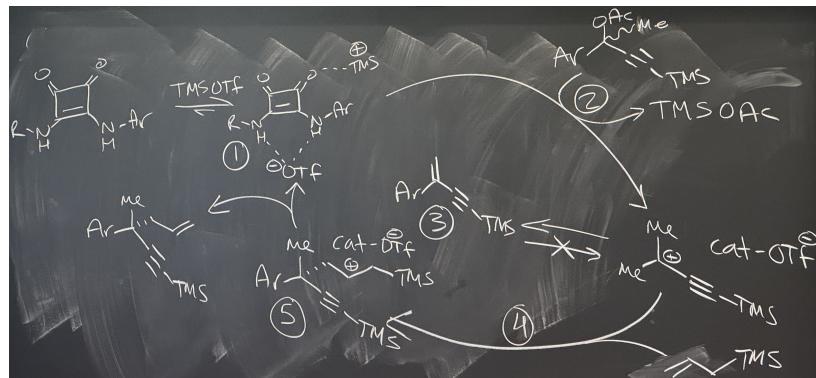
Figure 1.3: Mechanism depth level 2 (transition states).

- Equivalent level: 5.47 & undergrad organic, as well.
- Can't observe these directly — infer from observed selectivities (stereo-, regio-, etc.).
- Example: Figure 1.3.
 - Reacting a β -ketol with two different reducing agents. We can infer the structure of the transition state from the stereochemistry of the product.
 - Internal delivery of tetramethylammonium triacetoxyborohydride yields an *anti*-diol.
 - External delivery of zinc borohydride yields a *syn*-diol.
- Takeaway: We know that in organic chemistry, transition states should have chair-like structures for stability.
- Since we see chair like structures in Figure 1.3, we can infer that these mechanisms are reasonable. Indeed, they have stood for decades!

3. Determine the energy landscape and the full reaction coordinate.



(a) A reaction.



(b) The full reaction coordinate.

Figure 1.4: Mechanism depth level 3 (full reaction coordinate).

- Equivalent level: This class!
- This level of analysis enables us to...
 - Rationally design experiments that improve the reaction (i.e., conduct methods development and catalysis);
 - Discover new mechanistic principles.
- Example: Figure 1.4.
 - Figure 1.4a depicts a curious reaction: Propargyl acetate (with racemic chirality) reacts with an allyl silane under a squaramide catalyst and TMSOTf (a Lewis acid).
 - Even though the starting material is racemic, we get an enantioenriched allylated propargyl acetate (95% yield, 98% ee) as a product.
- The mechanism (Figure 1.4b) proceeds in five steps.
 - (1) Activate the catalyst to form an intermediate.
 - (2) Engage the starting material to form a tertiary carbocation.
 - (3) This carbocation can off-cycle to form an elimination product.
 - (4) Preferably, however, we engage our nucleophile (the allyl silane) to get a new cationic adduct, counterbalanced by the catalyst-triflate complex.
 - (5) The adduct goes on to eliminate our product and regenerate the starting intermediate.
- This mechanism originated from a beautiful mechanistic study by this paper's authors. Let's discuss some of their insights.
 - (1) This complex is the **resting state**.
 - Analytical technique(s): Binding experiments between the catalyst and TMSOTf.
 - This is a thermodynamic insight.
 - (2) This step is the **rate-determining step**.
 - Analytical technique(s): The rate law (a kinetic parameter) and **Hammett plots**.
 - (3) This step is an irreversible side reaction.
 - Analytical technique(s): Competition experiments.
 - Since this step is post-RDS in the mechanism, it is quite difficult to study.
 - Takeaway: It is easy to see things between the resting state and RDS, but everything after the RDS is like magic. These steps are very hard — but very important — to probe. Indeed, knowing how and where side reactions originate provides clues on how to stop them!
 - (4) This step is the **stereo-determining step**.
 - Analytical technique(s): The kinetic isotope effect (review this from CHEM 2020!!).^[1]
 - Revealed that stereoinduction was due to noncovalent interaction (NCIs) between the catalyst and intermediate.
 - Usually, your stereo-determining step is your RDS, but not in this regime. It is very hard to optimize a post-RDS, stereo-determining step.
 - (5) This intermediate is stabilized due to hyperconjugation from silicon.
 - Analytical technique(s): β -silicon effects and α -silicon effects.
- We will learn all of the techniques mentioned above in this class.
- Impact of this paper.
 - It's one of the first enantioselective S_N1 reactions.
 - It has a decoupled RDS and stereo-determining step, but gets high ee regardless.
 - This was an unprecedented result, and it changed the way we as chemists think about optimizing entantioselective reactions.
 - Reference: Wendlandt et al. (2018).

¹KIEs should probably be used in our end-of-class mechanistic proposal, will likely be used in our research, and *can* probe post-RDS steps.

4. Computationally determine the entire multidimensional energy surface.

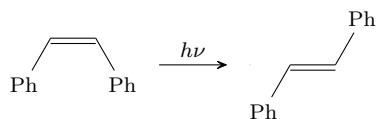


Figure 1.5: Mechanism depth level 4 (full energy manifold).

- Currently only possible for very simple systems.
- Example: Figure 1.5.
 - This is a transformation under light from a *cis*-olefin to a *trans*-olefin.
 - The authors tracked the reaction with femtosecond (10^{-15}) Raman spectroscopy.
 - Reference: Takeuchi et al. (2008).
- Full computational modeling is a pipe dream that would hugely enable our work as chemists.
- **Resting state** (of a catalyst): The state of a catalyst such that if you took an NMR of the reaction mixture at any given time, 95% of the sample would look like this.
- **Rate-determining step.** *Also known as rate-limiting step.*
 - Important because if you can speed it up, you can speed up the whole thing!
- **Rate law:** A measure of how the rate of reaction is influenced by the concentration of different components.
- **Hammett plot:** A mechanistic tool to probe what the rate-determining step is.
- **Stereo-determining step:** The step in a reaction mechanism that sets the stereochemistry of the final product; the ee of this step is the ee of the product.
- Takeaway: Keep in mind these various levels when we're trying to work out a reaction!
- Online tool: Reference Resolver!!
 - Give it the journal, year, and page number, and it brings us to the article.
 - There is a website, but also a browser plugin worth getting.
- Now that we've discussed the kinds of mechanisms, let's talk about what a mechanism can and can't do for us.
- A mechanism *can* tell us...
 - Thermodynamics and equilibria: Identity and structure of the ground state species;
 - Kinetics: Identity and structure of the transition state (TS) structures *relative* to the ground state structures;
 - We can't identify anything about the transition state in absolutes, but we can take educated guesses about intermediates and infer their approximate form.
 - Intermediates: Evidence of reaction intermediates;
 - Example: The tetrahedral intermediate.
 - Such intermediates are often called **metastable**.
 - RDS: Insight into selectivity and RDS's.
- **Metastable** (state): An intermediate energetic state within a dynamical system other than the system's state of least energy. *Also known as unstable equilibrium.*
 - A rectangular prism standing on its end under the force of gravity is metastable.

- A mechanism *cannot* be proven.
 - Mechanisms are hypotheses or proposals that can only be *disproven* or *supported*.
 - This is because experimental data often fits several possible mechanisms; there might be a hidden secret mechanism that we never thought of.
 - In sum, a mechanism is an interpretation that is consistent with *all* the data.
 - If a mechanism doesn't fit our data (even a little bit), either our mechanism is missing something (maybe a little something) or our experiment is flawed (and we need to rerun it or run something else).
- Best practices.
 - The best mechanisms provide *testable* predictions.
 - If a mechanism doesn't provide testable predictions, it is not a useful model.
 - If it's not useful, it's not grounded in good scientific practice.
 - The best experiments disprove a mechanistic proposal.
 - In practice, we list all possible mechanisms and try to disprove them with experiments.
 - When we submit to a journal, we do not say that our mechanism is proven, but we state our reasoning and our reviewers try to think of other mechanisms that could fit the data.
- Aside: Both Alex and Masha care about how scientists actually do science and how science can be done ethically.
 - They want this to be a practical class that would enable us to go in the lab and run any of these experiments.
- We study mechanisms to...
 - Ensure a safe, robust (reproducible), and scalable process;
 - This is especially important in process chemistry.
 - Human consequences of failing at safety, scale, and/or robustness:
 - Your ammonia plant could explode; it is essential to watch any runaway exotherms in a mechanism and control them!
 - Your drug might not make it to market if its synthesis can't be scaled up.
 - Improve reaction features such as yield, selectivity, and greenness;
 - Expand scope and enable predictability;
 - Think about reactions we run daily, such as the Suzuki coupling. It always works, and it's easily applicable in a wide range of settings *because* we understand the mechanism.
 - Understand systems on a molecular level.
 - Masha takes 30 seconds to preach about how mechanisms are critically important knowledge that will be passed down the generations.
- Aspects of mechanism: Consider the S_N2 reaction, Br⁻ + Me-I → Br-Me + I⁻.



(a) Orbitals.



(b) Energy surface.

$$\frac{d[\text{MeBr}]}{dt} = k[\text{MeI}][\text{Br}^-]$$

(c) Kinetics.

Figure 1.6: Aspects of mechanism.

- Three things we can consider in this mechanism are the orbital interactions, the potential energy surface along the reaction coordinate, and the kinetics.

Week 2

Bonding Models

2.1 Bonding Models 1

- 9/10:
- Lecture 1 recap.
 - Aspects of mechanism.
 - Orbitals, energy surface, and kinetics.
 - Masha redraws Figure 1.6.
 - These are the three main pictures that we'll learn about.
 - Today, we'll focus on orbitals.
 - Today: Bonding models.
 - Reading: Anslyn and Dougherty (2006), Chapter 1!!
 - **Bonding:** How electrons are shared between nuclei.
 - This determines all of molecular structure and reactivity (which is the name of this class, and underpins all of organic chemistry!).
 - From bonding, there arise concepts such as nucleophilicity, electrophilicity, etc.
 - There are several levels of bonding theory / models that we'll talk about today.
 - Caveat: *All* of these models are no more than *approximations* of reality that are useful to us.
 - Lecture outline.
 1. Lewis structures.
 2. VSEPR.
 3. Valence Bond Theory (VBT).
 4. Molecular Orbital Theory.
 5. Qualitative Molecular Orbital Theory (QMOT).
 - Lewis structures.



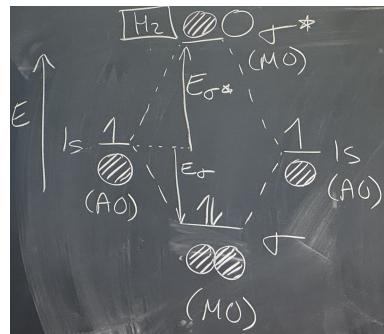
Figure 2.1: Lewis dot structures.

- Developed in 1916 by G. N. Lewis.
 - Chemis-tea: He was nominated 48 times, but never won the Nobel Prize because some people on the review committee didn't like his "interesting personality."
- In this model, we use dots to — on paper — indicate where electrons are in bonds.
- From these **Lewis dot structures**, people developed the "stick structures" that we still use today.
- Lewis structures are very useful in identifying the number of bonds and lone pairs.
- Valence Shell Electron Pair Repulsion (VSEPR).
 - Developed 1939-1957.
 - Key finding: Electrons in bonds repel each other, so you maximize the distance between bonds.
 - This let us go beyond Lewis structures into things like explaining tetrahedral carbon (and its 109.5° bond angles).
 - Issues develop when we try to rationalize other molecules.
 - For example, isobutane has 110.6° Me–C–Me bond angles. The VSEPR purists will cite "sterics."
 - As another example, NH₃ has 107 H–N–H bond angle. The VSEPR purists will cite "lone pair is big."
 - Really, these were just excuses by the VSEPR purists for a bad model, and what we really needed was a new model.
- Valence Bond Theory (VBT).
 - Developed by Linus Pauling, with his seminal paper in 1931.
 - For this work and some other stuff, he won the Nobel Prize in Chemistry in 1954.
 - To be historically accurate, Pauling built off the work of Heitler and London (1926).
 - However, Pauling was the person to both put everybody else's work all together and be visible enough to take the credit.
 - Additional takeaway from Pauling's biography: Don't make your whole life about your work. For example, Pauling was shunned by many of his colleagues after he got into nuclear proliferation, but now we say he was so brave. He even won the Nobel Peace Prize!
 - Takeaway on Pauling vs. Lewis: It pays to not be a jerk. Lewis died via cyanide poisoning (may have been an accident, but was probably suicide).
 - This is a quantum mechanical (QM) description of Lewis structures.
 - Central tenet: Each atom contributes 1 valence electron in a QM-derived atomic orbital (AO).
 - Shows that electrons are delocalized between atoms, and where two electrons overlap and localize is a chemical bond.
 - In other words, electrons are not restricted to tight orbitals.
 - Many concepts arise within VBT until the advent of MO theory.
- VBT was key for many conceptual innovations, such as **hybridization**, **electronegativity**, and **resonance**.
- **Hybridization:** The mixing of orbitals on the same atom to make new orbitals.
 - Specifically, we can take a linear combination of AO waveforms (or AOs).
 - More directional orbitals give you better overlap and therefore stronger bonds.
 - Example: A linear combination $s + p_y + p_x + p_z$ yields four sp^3 -hybridized orbitals. That's four orbitals with uneven lobes. We can draw all of these on top of each other, and from *there*, we get the tetrahedral carbon.

- We always like new models that agree with old models; this is called a **sanity check**.
- We can also calculate something called the **hybridization index**.
- **Hybridization index:** The number i in the following formula, expressed as a function of the experimentally determined bond angle θ . *Denoted by i . Given by*

$$1 + i \cos \theta = 0$$
- Example: NH_3 has a hybridization index of 3.4.
- Example: H_2O has a hybridization index of 4! That's why it has the tiny bond angle. The remaining s -character is localized on the oxygen, and that's why we say that oxygen is electron dense and nucleophilic.
 - Would this similarly predict that H_2O has longer bonds than NH_3 ??
- **Electronegativity:** The power of an atom to attract electrons to itself.
 - There are different scales for this. We probably used the **Pauling scale**, but there is also a **Mulliken scale**.
 - More electronegative atoms have lower energy orbitals.
 - This is summarized via the **inductive effect**.
- **Inductive effect:** The withdrawing of electron density through σ -bonds.
 - Example: ACN . We think about nitrogen having a partial negative charge and carbon having a partial positive charge. This results in a dipole.
 - Takeaway: Dipoles arise from electronegativity in VBT!
- **Resonance:** The superposition of several Lewis structures. *Antiquated mesomerism*.
 - Example: Consider an α, β -unsaturated ketone. Its resonance structure is a zwitterionic intermediate, and a second resonance structure is a different zwitterion. We have three resonance forms, so that predicts more stable than something with less resonance structures. It also identifies our positive and negative reactive sites.
 - Resonance usually happens through π -networks, but it *can* happen through σ -networks.
 - Takeaway: Delocalization of electron density leads to stability.
 - Know your rules for drawing good resonance structures.
 - We only move bonds, not atoms (no nuclear motion).
 - Prefer to have the least separation of charge.
 - Put the more negative charge on the more electronegative atoms.
- Limitations of VBT.
 - Over time, some key experimental findings emerged that VBT couldn't explain. These results motivated people to develop a new model to explain these rare cases.
 - Nowadays, exceptions to VBT are not so rare.
 - Remember: If a model can't explain certain cases, it's not a useful model.
 - Maxim: Not predictive = not useful.
- Here's a list of the limitations of VBT.
 - Doesn't account for unusual stability/instability (e.g., aromaticity and antiaromaticity).
 - No antibonding orbitals (i.e., no explanation of interactions between molecules).
 - When a nucleophile attacks a ketone, the interaction is with the antibonding orbital of the ketone. Forming a new bond involves populating an antibonding orbital.
 - Thursday is all about aromaticity, and modern ways to conceptualize it.

- This leads to the mother of all bonding models, Molecular Orbital Theory.
 - Central tenet: Molecular orbitals (e.g., σ , σ^* , π , π^*) arise from linear combinations of atomic orbitals (in Orgo, this is s & p ; we won't consider d -orbital effects so much).
 - We consider the electronic structure of the whole molecule, not just atoms or bonds.
 - We focus on key molecular orbitals such as the HOMO and LUMO.
 - We also get **group orbitals**: Leads into QMOT, which is MOs for prototypical groups.
- MO theory leads to MO diagrams.

Figure 2.2: MO diagram for H_2 .

- Two atomic orbitals interact to fill two molecular orbitals.
- We fill the bonding orbital with all the electrons that come in (in this case, 2).
- The energy of stabilization is E_σ .
- The destabilization energy is E_{σ^*} .
- Read Anslyn and Dougherty (2006) for more rules.
- Notes.
 - $|E_{\sigma^*}| > |E_\sigma|$. Thus, if the antibonding orbitals get populated, the molecule breaks. This is because of nuclear repulsion.
 - The σ -bond is more stable than the $1s$ orbitals by themselves. This is why the H–H bond forms. This kind of analysis allows us to predict whether or not a bond will form.
- Question for us to consider: Why doesn't He–He form?
 - Because its antibonding MOs would be populated.
- Example MO diagram: Ethylene.

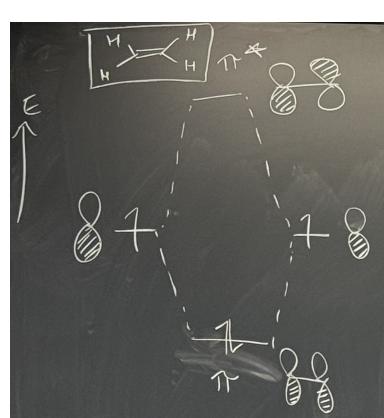
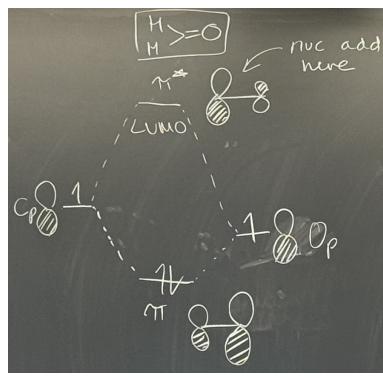


Figure 2.3: MO diagram for ethylene.

- Looking specifically at the π -bond formation.
 - This is why we form a stable π -bond.
 - Example MO diagram: Formaldehyde.
- 
- The diagram illustrates the molecular orbital (MO) formation in formaldehyde (H₂O). At the top left, the Lewis structure H₂O is shown with two hydrogen atoms (H) and one oxygen atom (O). A horizontal arrow labeled 'm' points from the oxygen towards the carbon atom. Below the molecule, several atomic orbitals (AOs) are depicted as pairs of overlapping circles. On the left, there is a C_p AO (one circle with a vertical lobe) and a C₁ AO (two circles, one with a vertical lobe and one with a horizontal lobe). On the right, there is an O_p AO (one circle with a vertical lobe) and an O₁ AO (two circles, one with a vertical lobe and one with a horizontal lobe). Dashed lines connect the C_p AO to the C₁ AO and the O_p AO to the O₁ AO, representing their linear combination. In the center, a horizontal π -orbital is formed by the overlap of the C₁ and O₁ AOs. Above the molecule, a LUMO (lowest unoccupied molecular orbital) is shown as a single circle with a vertical lobe. An arrow labeled 'nuc add here' points to the oxygen atom, indicating where nucleophiles would attack. The diagram also shows the bonding and antibonding orbitals resulting from the overlap of the C_p and O_p AOs.
- Figure 2.4: MO diagram for formaldehyde.
- We mix a C_p AO and a (lower energy) O_p AO.
 - These orbitals interact less well than those in ethylene due to their difference in energy.
 - We benefit from constructive phasing, but the lobes are much bigger on oxygen.
 - In the antibonding orbital, the lobes are much bigger on carbon.
 - Principles revealed by this MO diagram.
 - Closer energy AOs give stronger mixing, resulting in lower energy MOs. Lower energy MOs are more stabilizing.
 - More electronegative atoms have lower energy atomic orbitals.
 - The π -orbital is asymmetric because its energetically more similar to O_p than C_p.
 - In other words, it's going to look more like the O_p orbital.
 - One more way of stating this is that the coefficient of oxygen in the LCAO is bigger.
 - We know that the LUMO (frontier orbital) interacts with nucleophiles. The lobe of the LUMO is bigger on carbon, hence why we react there.
 - Qualitative MO theory (QMOT).
 - All about forming group orbitals for common functional groups or motifs.
 - Essentially, we may not need to calculate MOs for the whole molecule to find out how every carbonyl reacts; we can trust that carbonyl group orbitals are decently conserved.
 - There are a bunch of rules for how to form a QMOT diagram.
 - See Table 1.7 in Anslyn and Dougherty (2006) for building QMOT diagrams.
 - This is the basis of **Walsh diagrams**.
 - We can build group MOs from linear combinations of s & p AOs.
 - **Walsh diagram:** A representation of an MO diagram as a function of geometric distortions.
 - This matters because geometry affects orbital overlap, which can be destabilizing or stabilizing.

- Example QMOT diagram: CH_3 .

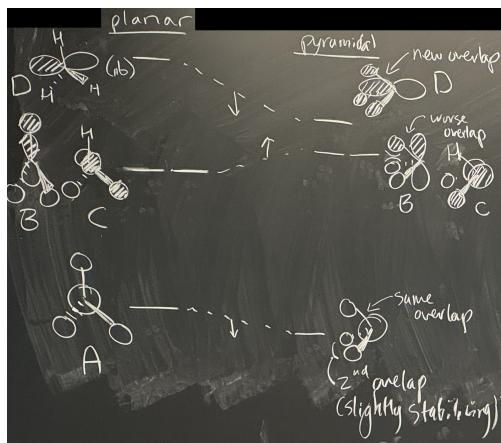


Figure 2.5: QMOT diagram for CH_3 .

- Key question: What geometry of CH_3 is favorable?
- Masha defines axes.
- Undetermined yet if this is a radical, cation, or anion. We'll get there!
- We look at a planar set of orbitals first.
 - A. All phases in sync, all s orbitals.
 - B. Phases align top to bottom with the p_x orbital of carbon.
 - C. Phases align in and out of the board with the p_y orbital of carbon.
 - D. Nonbonding; just the p_z orbital.
- There are also **E**, **F**, and **G** orbitals that are energetically above these, but we won't draw them for now (because we won't fill them with electrons in the carbocation, carbanion, or carbon radical).
 - The **E**, **F**, and **G** orbitals will have the opposite phasing of the lower orbitals!
- We now draw an analogous, pyramidal set of orbitals.
 - A. Overlap is *slightly* more favorable because we have a secondary orbital interaction between the hydrogens now. The C–H overlap stays the same.
 - B. Worse overlap. We're losing a **primary** interaction instead of gaining a **secondary** one, so the energy of **B** actually goes up *more* than **A** went down. We also get some destabilizing secondary interaction between the H orbitals.
 - C. Just like **B**, we get worse primary overlap, and new interfering secondary overlap.
 - D. Gets stabilized the *most* significantly! This is because we've taken something with no bonding interactions and *created* bonding interactions between the p -orbital and the hydrogens.
- Relationship between QMOT and Walsh diagrams: A Walsh diagram is a QMOT diagram with everything connected.
- Now how do we fill electrons?
 - Consider the CH_3^+ cation: We have 6 electrons, so we populate the planar orbitals because it's more stable overall.
 - Consider the CH_3^- anion: We have 8 electrons, so we populate the pyramidal orbitals because *they're* more stable overall.
- This rigorous prediction of conformation is the benefit of this model.
- We can also use this model for other isostructural molecules.

- Examples.
 - NH₃: 8 electrons, pyramidal.
 - BH₃: 6 electrons, planar.
 - ·CH₃: 7 electrons, *slightly* planar.
 - But this is a special case only for ·CH₃; any other radical is pyramidal.
- Primary (orbital interaction): An interaction between orbitals on adjacent atoms in a molecule.
- Secondary (orbital interaction): An interaction between orbitals on atoms that are separated by one other atom in a molecule.
- What is quantitative about QMOT?
 - There is a lot more depth in Anslyn and Dougherty (2006). You can calculate the actual potential energy surface and figure out these conformations exactly.
- Example QMOT diagram: CH₂.

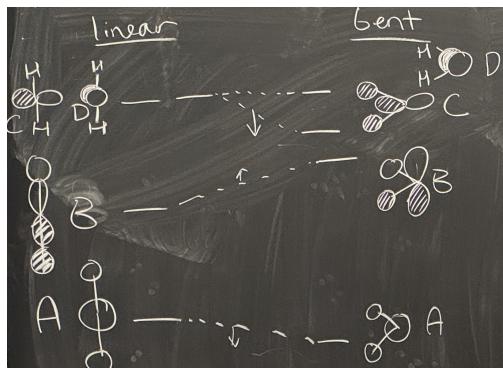


Figure 2.6: QMOT diagram for CH₂.

- Two geometries: Linear and bent.
- Linear.
 - A. Linear chain of *s*-orbitals with matching phases.
 - B. Linear chain of matching phases orbitals, with *p_x* on carbon.
 - C. One of the other *p*-orbitals, with no phasing.
 - D. The last remaining *p*-orbital, again with no phasing.
- Bent.
 - A. Goes down slightly. We kept primary, and added secondary.
 - B. Losing primary overlap and gaining a destabilizing secondary interaction; higher *E* like before.
 - C. Adding *significant* constructive interference. Biggest effect again!
 - D. Staying the same; no bonding interactions to begin or end with. We don't consider secondary interactions when there's no density at all there.
- Example species.
- H₂O: 8 electrons, bent.
 - Note that this model predicts that H₂O has nondegenerate lone pairs, which has been experimentally verified!
 - Bulk water acts as if it has degenerate lone pairs. We can read Anslyn and Dougherty (2006) about this, but otherwise, it's outside the scope of the class.

- CH_2 (a carbene): 6 electrons, a mix of linear and bent!
 - We'll return to carbenes in a few weeks.
 - We'll define **triplet** (2 electrons in different orbitals) and **singlet** (2 electrons in same orbital) carbenes later.
 - Triplet is 136° , and singlet is 105° , so the triplet is more linear and the singlet is more bent! The triplet has reactivity more characteristic of the linear orbital picture, and the singlet has reactivity more characteristic of the bent orbital picture.
 - The triplet is more favored by 9 kcal/mol
- Example QMOT diagram: Formaldehyde.

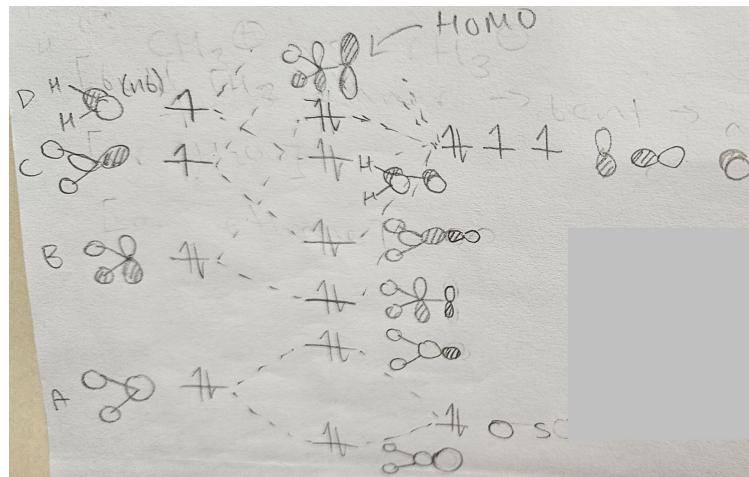


Figure 2.7: QMOT diagram for formaldehyde.

- The HOMO has a larger coefficient on O; this explains why protonation occurs on O and not C!
- Key takeaway: QMOT diagrams and MO diagrams both make the same predictions about the electronic structure and reactivity of formaldehyde (sanity check).
 - Example: They both predict that carbonyls are nucleophilic on oxygen.
 - Example: Orbital mixing is stronger when orbitals are of similar energy.
 - Example: Orbital coefficients are larger on an atom when the MO is closer in energy to the AO that originates with that atom.
 - Example: Orbitals are lower in energy on more electronegative atoms.
 - Etc.

2.2 Bonding Models 2

- 9/12:
- Lecture 2 recap.
 - QMOT for formaldehyde (see Figure 2.7).
 - Recall that the HOMO has a larger coefficient on oxygen, which means that protonation occurs on oxygen instead of carbon.
 - No other topics from Lecture 2 are reviewed.
 - Today: Bonding models (continued).

- Lecture outline.
 - Huckel theory.
 - Aromaticity.
 - Banana bonds.
 - Wave functions.
- **Huckel theory:** A quick way to build MOs for conjugated π -systems.
 - Qualitatively great and quantitatively bad.
 - Quick and dirty, but generates useful predictions.
 - Not *accurate*, but definitely *useful*.
 - It is used to analyze the connectivity and topology of the π -system in a planar molecule.
 - Key assumptions.
 - The π -system is independent of the σ -network.
 - You only consider valence electrons.
 - Only neighboring orbitals interact, i.e., only π -orbitals on adjacent atoms.
 - We ignore orbital overlap and electron repulsion.
 - These are some wild simplifications, but it is quick and useful!
 - Rules.
 - The number of p -AOs you mix equals the number of new MOs you make.
 - The energy of the new MOs is distributed symmetrically around the **nonbonding energy level**.
 - The number of nodes increases by 1 with each energy level.
 - The MOs reflect the symmetry of the molecule.
- **Nonbonding energy level:** The energy of the nonbonding MOs in a Huckel diagram. *Denoted by α .*
 - This is also the energy of an electron in an empty p -AO.
- Example Huckel diagram: Ethylene.

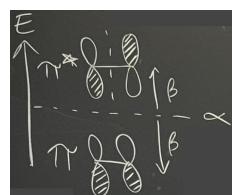
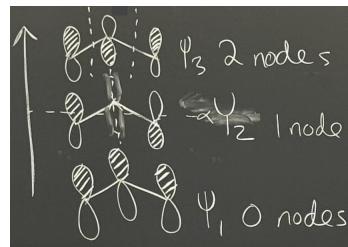


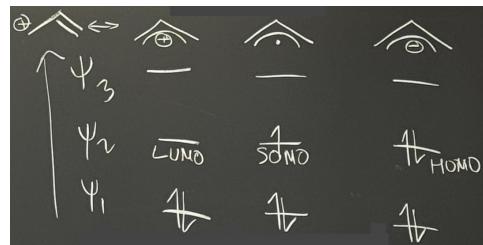
Figure 2.8: Huckel diagram for ethylene.

- Let's first confirm that this diagram meets all four Huckel theory rules.
 - We get two new π -MOs from two p -AOs.
 - The energy difference from the nonbonding energy level is called β .
 - The number of nodes did increase from 0 to 1.
 - The MOs are symmetric.
- Thus, this is a valid Huckel diagram!
- Note: Do remember that symmetric splitting is *not* accurate!
 - On Tuesday, we (correctly) learned that destabilization energy > stabilization energy.

- Example Huckel diagram: Allyl groups.



(a) Diagram.



(b) Filling orbitals.

Figure 2.9: Huckel diagram for allyl groups.

- The lowest energy orbital is called ψ_1 .
 - It has 0 nodes.
- The middle energy orbital is called ψ_2 .
 - To maintain symmetry, we have to delete the middle orbital and give opposite phases.
- The highest energy orbital is called ψ_3 .
 - It has the 2 nodes we expect.
- We now fill electrons for the allyl cation, radical, and anion (Figure 2.9b).
 - These species have 2, 3, and 4 electrons, respectively.
- Now let's look at where each of these species will react.
 - Nucleophiles will attack the LUMO of the cation.
 - Radicals react with their SOMO (singly occupied molecular orbital).
 - Electrophiles will engage the HOMO of the allyl anion.
- But the LUMO, SOMO, HOMO are all ψ_2 !
 - ψ_2 has no density at the middle carbon, so all of these species should only react at the terminal carbons.
 - This prediction of Huckel theory is experimentally confirmed!
 - Intuitively, reacting at the terminals allows you to keep the double bond in play; thermodynamically, you wouldn't want to cleave it by reacting in the middle.

- Example Huckel diagram: Benzene.

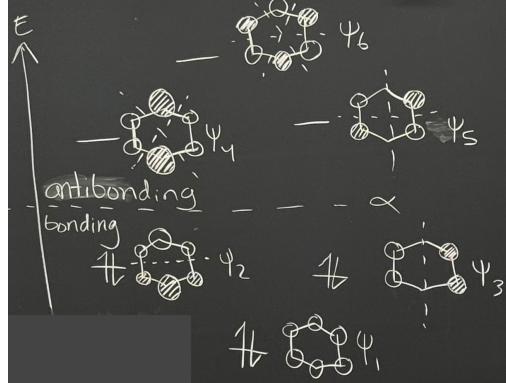


Figure 2.10: Huckel diagram for benzene.

- For cyclic systems, we draw a **Frost circle**.
 - For benzene, the radius of the Frost circle is 2β .
- We create ψ_1, \dots, ψ_6 .
 - ψ_2, ψ_3 and ψ_4, ψ_5 are degenerate.
 - No electron density on the central p -orbitals in ψ_3 implies bigger coefficients on the corresponding orbitals in ψ_2 .
 - See Anslyn and Dougherty (2006) for more!!
 - ψ_4, ψ_5 have 2 nodes at angles.
 - For ψ_6 , we have 3 nodes through a hexagon, which is alternating shading.
- α is the nonbonding level; higher is antibonding, lower is bonding.
- 6 electrons in benzene's bonding π -system yields stabilization.
 - In particular, we observe stabilization relative to three ethylenes: An extra 36 kcal/mol of stabilization!
 - Huckel theory can't really compare energy between two molecules; β is more a qualitative parameter than a quantitative one.
- **Frost circle:** A circle in which we inscribe a regular n -gon with one point down — where n is equal to the number of carbons in the cyclic system — that is used as a guide for drawing Huckel orbitals.
- Example Huckel diagram: Cyclobutadiene.

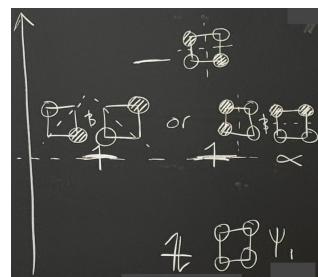


Figure 2.11: Huckel diagram for cyclobutadiene.

- ψ_1 has no phase inversion and no nodes.
- There are two different ways to draw the orbitals for ψ_2, ψ_3 .
 - We can dive deeper into this difference in Anslyn and Dougherty (2006).
 - No extra stability relative to three ethylenes!
 - The model also predicts a ground-state triplet diradical.
 - Indeed, this molecule is highly reactive and dimerizes spontaneously at 35 K.
- We now do a deep dive into aromaticity.
- The history of aromaticity.
 - In 1855, Hofmann (not Hoffmann) coins the term “aromatic” because these compounds were smelly.
 - In 1861, we have Kekulé’s dream of a snake eating its tail.^[1] This inspired a circle of electrons.
 - In 1925, Robinson describes aromaticity as extra stabilization of a molecule.
 - In 1931, Huckel puts forth **Huckel’s rule**.

^[1]“At least, Kekulé said it was a dream!” - Masha. Good use of reasonable doubt and objectivity in her thinking!

- **Huckel's rule:** Cyclic, planar molecules with $4n + 2$ continuous π -electrons are aromatic.
 - If you have $4n$ electrons in a cyclic planar molecule with continuous π -electrons, then you are antiaromatic (extra unstable).
 - Thus, these molecules usually distort out of the plane to break antiaromaticity and become nonaromatic.
 - Both cyclobutadiene and cyclooctatetraene are antiaromatic. Cyclooctatetraene bends into a boat so that its π -orbitals are pointing toward each other.
 - No phase inversions are allowed; we must connect orbitals without crossing the σ -plane.
 - What does this mean??
- Features of aromatic compounds.
 - Aromatic stabilization energy (36 kcal/mol).
 - Equalization of the bond lengths.
 - Essentially, the bond lengths do not alternate but rather share an identical bond order of 1.5.
 - Ring currents and magnetic properties.
 - Those interested in polymer chemistry might be interested in exploiting these properties!
 - Specifically, these are properties that come from a sea of electron density.
 - Benzene vs. hexa-1,3,5-triene.
 - In benzene, all bond lengths are 1.40 Å.
 - In hexa-1,3,5-triene, the single bonds are 1.45 Å, the terminal double bonds are 1.34 Å, and the internal double bond is 1.37 Å.
 - The bond lengths of benzene equalize because benzene has two equally stable major resonance structures.
 - This is why we often draw benzene as a hexagon with a circle in the middle: This is actually the most accurate picture of it!
 - The bond lengths of hexa-1,3,5-triene do *not* equalize because the only resonance structure we can draw of it is a zwitterion, and thus will be a minor contributor.
 - Different kinds of reactivity.
 - Example: Electrophilic aromatic substitution.
 - This is very much distinct from alkene addition chemistry.
- **Möbius aromaticity:** Aromatic rings have one phase inversion (PI), like in a Möbius strip.

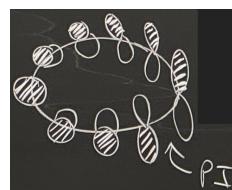


Figure 2.12: Möbius aromaticity.

- This is a different definition of aromaticity.
 - We could research aromaticity for the rest of our lives if we wanted to.
 - There's a whole field of research devoted to it, and we should look into it if we're interested!!
 - A good starting point is Ajami et al. (2003).
- The single phase inversion is called a **Möbius topology**.

- Your PI happens at the sole node.
 - This one node is allowed in Möbius aromaticity, but not in Huckel aromaticity
- The Möbius topology predicts that compounds are aromatic if they have $4n$ electrons and antiaromatic if they have $4n + 2$ electrons.
- To be clear, this content is outside the scope of this class, but Masha wants us to know about it and be able to research it if we so choose.
- Ring current.

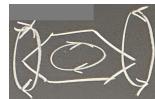


Figure 2.13: Ring current.

- Suppose you have an external magnetic field perpendicular to the σ -plane.
 - This would induce the π -electrons to rotate through their MOs.
 - These rotating electrons would then create an additional magnetic field.
 - This new magnetic field would *reinforce* the external magnetic field outside the aromatic ring and *oppose* the external magnetic field inside the ring.
 - The strength of the induced magnetic field is proportional to the current (i.e., the size of the ring).
- Application (NMR): Ring protons are deshielded (higher δ) outside and shielded (lower δ) inside.
 - Cyclohexene: No ring current, so we get a bit of downfield shift for the vinyl protons (δ 5.6).
 - Benzene: Has a ring current, so we get a noticeable downfield shift (δ 7.3).
 - [18]annulene: Has a large ring with many π -electrons, so we get a significant downfield shift for the external protons (δ 9.3) and a significant *upfield* shift for the internal protons (δ -2.9).

- **Quadrupole:** Two dipoles aligned such that there is no net dipole.

- Example: The dipole aligned up and down in benzene — perpendicular to the σ -plane of the molecule — as opposed to (for instance) the linear dipole in fluoromethane.
- Lots of applications beyond the scope of this class, but we can look into it if we want.

- **Banana bond:** A bent chemical bond that contains an unusually high concentration of p -character.

- The bent p -lobes of banana bonds look like bananas (see Figure 2.14), hence the name.
- Example banana bonds: Cyclopropane.

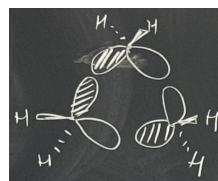


Figure 2.14: Banana bonds in cyclopropane.

- Cyclopropane needs more p -character because of its 60° bond angles; p -character helps bonds bend.
 - Specifically, the C–C bonding orbitals in cyclopropane are sp^5 -hybridized.

- The excess of *p*-character in the C–C bonds means that the C–H bonds of cyclopropane have correspondingly more *s*-character.
 - This makes the C–H bonds in cyclopropane shorter than usual!
 - Indeed, there is something of a “conservation” of bonding character: The *s*-character that’s not in the σ -bonds has to go somewhere.
- Group orbitals (HOMO) degenerate.
 - The **Walsh orbitals** have more π -character, so cyclopropane is sp^2 -like.
 - This means it is a good π -donor and a bad π -acceptor.
 - Example of donation: The dimethylcyclopropyl cation is very stable because all of the sp^2 -character is getting donated into the carbocation’s empty orbital. See Figure 4.4c for more.
- Wave functions.
 - Review Anslyn and Dougherty (2006), Chapters 4 & 14!!
 - Also look up your Gen Chem or Quantum notes if it’s been a while.
 - Is there anything relevant to review in Chapter 4??
 - All bonding theories draw upon QM descriptions of electrons as waves existing in **orbitals**.
- **Orbital:** A wave function that is a specific solution to the **Schrödinger equation**.
 - Masha draws the $1s, 2s, 3s$ orbital penetration graph, as well as what these orbitals look like.
 - Recall that orbitals have **lobes** and **nodes**!
- **Schrödinger equation:** The following equation, where E is the energy of the electron, ψ is the wave function describing the position of the electron in space, and H is the **Hamiltonian operator**. *Given by*

$$H\Psi = E\Psi$$
 - ψ^2 is the probability of finding an electron in a specific position (i.e., the electron density!).
 - Big Ψ is the total molecular wave function, and little ψ is a molecular orbital.
- **Hamiltonian operator:** A representation of all forces acting on the system, such as the kinetic energy of the electron and nucleus, nuclear-nuclear repulsion, electron-electron repulsion, etc.
- Next week, we’ll talk about DFT and approximating solutions to the Schrödinger equation. It will be like an intro to computational chemistry!
- Example: Electron density in H_2 MOs.
 - Masha redraws Figure 2.2 to start, and Figure 7.3 from Labalme (2023).
 - The point is that...
 - The bonding MO has a lot of electron density between the nuclei, even though you still have some at the atoms;
 - The antibonding MO has minimal to no electron density between the nuclei; the AOs (ϕ_1^2, ϕ_2^2) are very separate.

2.3 Chapter 1: Introduction to Structure and Models of Bonding

From Anslyn and Dougherty (2006).

9/23: • Good outline of the purpose of Chapter 1.

- Mostly along the lines of what we’ve talked about in class.

- Why bother with simplistic bonding models if we can just compute everything quantum mechanically nowadays?
 - “A string of computer-generated numbers is just no substitute for a well-developed feeling for the nature of bonding in organic molecules” (Anslyn & Dougherty, 2006, p. 3).
 - “It is still true — and will be true for some time — that descriptive models of bonding that are readily applicable to a wide range of situations are the best way to attack complex problems” (Anslyn & Dougherty, 2006, p. 4).

Section 1.1: A Review of Basic Bonding Concepts

- Vocab for Gen Chem-level quantum mechanics.
 - Most of these I know without review.
- **Spin paired** (electrons): Two electrons in the same orbital with opposite-signed m_s values.
- **Correlation:** The ability of an electron to feel the trajectory of another electron and therefore alter its own course so as to minimize Coulombic repulsions and keep the energy of the system to a minimum.
- The strengths and weaknesses of Lewis structures.
 - Pros: Predict the number of bonds an atom forms, whether it has lone pairs, and whether any double or triple bonds form.
 - Cons: Does not describe the structure or reactivity of any given species.
- Example: Why formal charge is much more a method of “bookkeeping” nowadays than anything accurate.
 - In the tetramethylammonium cation, we put the formal positive charge on the nitrogen.
 - However, computational studies show that since nitrogen is more electronegative than carbon, a δ^- rests on nitrogen in the actual structure, and every carbon shares $\frac{1}{4}$ of the positive charge.
- VSEPR’s geometrically perfect bond angles are only observed in simple, symmetric molecules.
 - However, words like “tetrahedral” and “trigonal” are broadly used to suggest an idea, even when they’re not *strictly* accurate.
- VSEPR “is not based on any first principles analysis of electronic structure theory. It is a simple way to rationalize observed trends” (Anslyn & Dougherty, 2006, p. 8).
 - Indeed, it is not clear that bonding orbitals or lone pairs really *have* any well-defined notion of size.
 - Note that singly occupied orbitals (e.g., radicals) do not have repulsive effects in VSEPR because they are able to bond to doubly occupied orbitals.
- **Steric repulsion:** The buttressing of filled orbitals that cannot participate in bonding, where the negative electrostatic field of the electrons in the orbitals is repulsive.^[2]
- **Hybridization:** The method of adding and subtracting atomic orbitals on the same atom.
 - “Remember that orbitals are mathematical solutions to the Schrödinger equation, and that the addition and subtraction of mathematical equations is just an exercise in algebra. It is a perfectly valid operation to add orbitals as long as one also does the corresponding subtraction” (Anslyn & Dougherty, 2006, p. 9).

^[2]Don’t forget that Alison Wendlandt believes that this definition of sterics is fundamentally flawed, and that overlap is actually beneficial to a point!

- Someday, I should take linear combinations of *s* and *p* wave functions and confirm that they're still orthogonal and in the solution space of the Schrödinger equation!!
 - It's called hybridization because we're literally forming *hybrids* somewhere between the polar extremes of an *s* and *p* orbital!
 - As with VSEPR bond angles, VBT hybridizations deviate from the *sp*, *sp*², or *sp*³ ideal in most organic molecules, but we loosely retain these terms regardless to convey an idea.
- Anslyn and Dougherty (2006) goes over a cool connection between the hybridization index (as defined in class) and experimentally observed ¹H-¹³C NMR coupling.
- The localization of electrons in a chemical bond per VBT is exactly the impression of bonding that is given by a Lewis structure!
- Some useful content on polar covalent bonding that is slightly beyond the scope of the class.
 - “Introducing polarity into a bond strengthens it” (Anslyn & Dougherty, 2006, p. 12).
 - Pauling electronegativity is based on the BDEs of molecules, while Mulliken electronegativity is based on the IEs of atoms.
 - Additional electronegativity scales by Nagle, Allen, Sanderson, Allred-Rochow, Gordy, Yuan, and Parr.
 - Takeaway: Electronegativity is a hard concept to put your finger on!
 - The real use of electronegativity is in comparing *relative* electronegativities, and all scales more or less agree here.
- **Field effect:** The withdrawing of electron density through space, rather than through σ -bonds.
- Additional irrelevant content.
- Application of quadrupoles: Proving that *sp*²-C is more electronegative than H.
- **Resonance energy:** The energy of stabilization imparted by resonance. *Also known as delocalization energy.*
- Why is delocalization stabilizing from the point of view of quantum mechanics?
 - Recall that in the particle in a box, the energy levels are given by
$$E_n = \frac{n^2 h^2}{8mL^2}$$
 - As *L* increases (i.e., as we expand the box/delocalize), the energy goes down.
- Lots more on resonance.

Section 1.2: A More Modern Theory of Organic Bonding

- Molecular orbital theory has the same predictive power as the models in Section 1.1 (Lewis structures, VSEPR, and VBT), but it can better explain certain structural issues and experimental observations, too.
 - MO theory extracts certain key concepts and trends that result from the output of quantum mechanical calculations to lead to a more rigorous, descriptive model of organic bonding than Lewis structures, VSEPR, and VBT can.
- VBT and MO theory are often fairly interconvertable mathematically!
 - Thus, it is *not* necessarily true that MO theory is “better” than VBT.
 - Rather, both models (and any combination thereof) are approximations of the true answer — a full solution to the Schrödinger equation.
- A more detailed analysis of the QMOT examples from class; definitely worth returning to!!

Section 1.3: Orbital Mixing — Building Larger Molecules

- Goes over the mixing of fragments/group orbitals in detail. Relevant to PSet 1!!
- The later sections would likely be quite useful for my development as a chemist, but probably aren't immediately relevant to this course.

2.4 Chapter 14: Advanced Concepts in Electronic Structure Theory

From Anslyn and Dougherty (2006).

Section 14.1: Introductory Quantum Mechanics

- Some basic and some more advanced quantum mechanics, but all stuff with which I am eminently familiar from my undergrad coursework.

Section 14.3: A Brief Overview of the Implementation and Results of HMOT

- **HMOT:** Huckel molecular orbital theory.
- A much more mathematical treatment of Huckel theory, similar to what I saw in CHEM 26100. It does rationalize the benzene coefficients, though, so probably worth returning to!!

Section 14.5: Some Topics in Organic Chemistry for Which Molecular Orbital Theory Lends Important Insights

- More mathematics of aromaticity, cycles, etc. Probably a bit less useful.

Week 3

Applications of Bonding Theory

3.1 Computational Chemistry

9/17:

- Lecture 3 recap.
 - Huckel theory: A fast way to draw the MOs of conjugated π -systems.
 - If the conjugated π -system in question is cyclic, use a Frost circle.
 - Aromaticity.
 - Huckel's definition: $4n + 2$.
 - Möbius's definition: $4n$.
 - Leads to properties like stabilization, quadrupoles, and ring current.
 - Cyclopropane: sp^2 -like banana bonds (the only thing we need to remember from that discussion).
 - Wavefunctions: Solutions to the Schrödinger equation.
- Today: Computational chemistry (an overview).
 - Computational chemistry is typically an entire class!
- Lecture outline.
 - Methods of computational chemistry.
 - Molecular mechanics.
 - Semi-empirical methods.
 - Ab initio methods.
 - Hartree-Fock.
 - Density functional theory (DFT).
 - Best practices for calculations.
 - Properties that are especially easy (or hard) to calculate.
- Why do we do computational chemistry?
 - If we could fully solve the Schrödinger equation, we could know the properties of all of our electrons!
 - However, the Schrödinger equation can only be fully solved (practically) for the simplest systems.
 - For now, at least: People are working on this.
 - As such, we *approximate* solutions instead.

- **Computational chemistry:** The science of approximating solutions to the Schrödinger equation.
 - Computational chemistry can be broken up into two general strategies (**ab initio** and **empirical** methods) and one in-between strategy called **semi-empirical** methods.
- **Ab initio** (methods): Make well-defined approximations to the Schrödinger equation, and then solve the approximations mathematically. *Etymology* from Latin “from first principles.”
 - Essentially, make your math simpler.
- **Semi-empirical** (methods): Replace complicated parts of the Schrödinger equation with experimentally derived parameters, such as bond lengths, vibrational frequencies, and more that we can get from spectroscopy.
 - Essentially, shortcut the hardest parts of solving with experimentally derived features.
- **Empirical** (methods): Approximate molecules with force fields that are experimentally derived, and adjust with further experimental parameters.
 - Essentially, start with reality and derive computational things from that.
- We now look at some commonly derived methods. The following list is sorted from methods with high **accuracy** and low **speed** to methods with low accuracy and high speed.
 - Methods at the high end of accuracy and the low end of speed (ab initio).
 - **Coupled cluster**.
 - **Perturbation theory**.
 - **Density functional theory**.
 - **Hartree-Fock**.
 - Methods in the middle (semi-empirical).
 - **Semi-empirical methods**.
 - Methods at the high end of speed and the low end of accuracy (empirical).
 - **Molecular mechanics**.
- **Speed:** Ease of calculations.
- **Accuracy:** Careful and diligent.
- **Coupled cluster:** Useful for approximately 10 **heavy atoms**. *Also known as CC.*
- **Density functional theory:** Useful for approximately 80 heavy atoms, though we can use more (it just gets slower). *Also known as DFT.*
- **Hartree-Fock.** *Also known as HF.*
- **Molecular mechanics:** Useful for hundreds of heavy atoms. *Also known as MM.*
- **Heavy atom:** Any atom that's not hydrogen.
- In this course, we'll discuss further the bottom four methods in the above list of six.
- Molecular mechanics (MM).
 - Atoms are treated as balls and springs (this is a classical analogy and thus much easier to simulate).
 - We use force fields to describe electrons.
 - These force fields are derived from experimental data, i.e., choose a force field that gives us the bonds we calculate from XRD or the vibrations we see in IR.
 - Very fast; often considered “quick and dirty.”

- Gives us a general picture of what we're thinking about.
- Common application: Very large and flexible systems.
 - Think proteins, polymers, etc.
 - Things that have a lot of degrees of freedom.
 - Very useful for chembio, polymer chemistry, etc.
- Subset application: **Molecular dynamics (MD)**.
 - Simulating movement; uses MM as a basis.
- If you're going to use this method, know that it is (in general) only appropriate for approximating the ground states of molecules (not their transition states).
 - However, MM can be a good starting point for higher-level calculations (i.e., more accurate methods).
 - In Orgo, it's mainly used for first approximations to be refined later (and for heavier stuff).
 - All the same, it is a super useful tool with tons of applications, and its simplicity should not lead us to discount it.
- Running MM.
 - If we have a PC, try clicking the MM2 button in Chem3D (which is part of our ChemDraw package).
 - This may not work on Macs; figure this out!!
 - PerkinElmer (who developed ChemDraw) initially developed their stuff for Macs; Masha's not quite sure where they dropped the ball.
- Semi-empirical quantum mechanical (SQM) methods.
 - Use empirical parameters to simplify *ab initio* calculations.
 - Tries to deliver the best of both worlds (speed and accuracy).
 - We can add corrections for missing phenomena and underestimated features.
 - Theoreticians (developers) will draw the line on accuracy somewhere, and then organic chemists will say, "this model fails here."
 - Once that feedback gets into the literature, theoreticians redefine their line.
 - They might need to account for *d*-orbitals, London dispersion forces (LDFs), flexibility, solvent, or more.
 - Methods of accounting for solvent effects are continuously being optimized.
 - It's important to be on top of the literature here, since things are always getting better!
 - Modern implementations (these are getting fast enough to be usable and really good!).
 - Density function based tight binding (DFTB): Approximate DFT.
 - eXtended Tight Binding (xTB)
 - Developed primarily by the Grimme lab.
 - Basically just adding more parameters.
 - LDFs are becoming increasingly important for selective catalysis, so there's a lot of work to approximate them.
 - Catalysis is not about partial positive and negative charges so much as it is about electrons flopping around to achieve incredible selectivities in next-gen catalysts.
 - Very fast (seconds) and pretty accurate. Increasingly used, especially for ML and data science.
 - Nowadays, if you want to do ML, you need these hundreds of experimental data points.
- Ab initio methods.
 - Background theories (neither is technically true, but it is helpful for speed).

- **Born-Oppenheimer approximation.**

- **Independent electron theory.**

- **Born-Oppenheimer approximation:** Nuclei are way bigger than electrons (have over 1000 times more mass), so they are basically fixed in space relative to the electrons.
 - This means that you can treat the nuclei separately; you can use one approach for the nuclei and an entirely different approach for the electrons.
- **Independent electron theory:** Electron movements are not correlated to each other; all electrons whiz around independently.
 - Making this approximation will cause some issues.
- Hartree-Fock (HF).
 - Treat electrons as a delocalized cloud with independent electron movement.
 - Remember the plum pudding model of the atom? This is not that dissimilar from that.
 - This approximation ignores Coulombic interactions (like LDFs).
 - This becomes very problematic for transition states.
 - HF methods are largely historical today.
 - There are applications where they're still used today, but not in Orgo and not without an understanding of their shortcomings.
- We can run any and all of these computations throughout grad school as MIT students, and we should! They're in our toolbelt now, and we should try them out!!
- Density functional theory (DFT).
 - Instead of calculating wavefunctions, we're going to calculate electron density.
 - We're going to do this using **functionals**.
 - We can include functionals for things like Coulombic interactions, etc.^[1]
 - This is a good workhorse method in organic chemistry.
 - DFT is appropriate for reaction coordinate mapping, transition states, etc.
 - We'll often work with collaborators that can tailor a model to our needs.
 - There are many specific functionals and basis sets.
 - You have to choose the functional (choose what to include), and then choose the basis sets (how much detail do I need for this calculation, e.g., treating polarization, charge, unpaired electrons more accurately).
 - It is best to find a basis set and functional appropriate for our context.
 - Basis sets don't describe all types of elements.
 - Some describe elements 1-30, others do 1-86.
 - Don't be that person who has to redo their entire calculation because they forgot that tin is one of their reagents!
 - We often use **split basis sets** (esp. for transition metals), i.e., certain atoms (i.e., metals) get more functionals.
 - Carbon, hydrogen, and oxygen (CHO) don't need the craziest level of theory to approximate, but that palladium center will!
 - Think about what level of theory you need for each atom.

^[1]Maybe what I can be known for in research is custom building computational tools for specific organic problems, and turning that into a workflow that people do. Maybe that's what ML already is.

- **Functional:** A function of functions.^[2] *Also known as higher-order function.*
- Best practices for running calculations for our own things.
 - This part of the lecture is *critical*; it tells us what we need to know to use computational chemistry.
 - If we want to learn the theory for all of these things, we should read a textbook or take Heather Kulik's class.
 - Use the appropriate level of theory for your needs and capabilities.
 - Questions to ask yourself to assess your needs and capabilities.
 - Do you have a supercomputer? How much time on the supercomputer do you have?
 - When do you need this result by? Is your PI breathing down your neck?
 - What am I trying to model?
 - Is this a thought experiment or something serious?
 - Additional things to consider wrt your needs and capabilities.
 - Consider speed vs. accuracy.
 - You can always start at a lower level theory and then ramp it up if you need more accuracy. This is a great general approach.
 - Consider size and flexibility (no HF on proteins, or MM on methane).
 - Consider “weirdness”: If you've got something that's all inverted and Möbius like, you're gonna need something more tailor-made.
 - Find a *reliable* literature precedent for a similar system.
 - If you want to model a cationic cyclization, use a precedent paper's level of theory.
 - How do I model an iridium catalyst? Find an iridium catalyst paper and go from that!
 - Know how your level of theory works.
 - Does it account for polarizability? Charge? Solvent? *d*-orbitals?
 - It is our responsibility as an experimentalist to know this if we're going to publish it; our PI probably won't be as deep into the nitty-gritty as us.
 - Don't blindly trust calculations.
 - Calculations always give you an answer (unless they fail or don't converge). However, just because you get a number doesn't mean that that number is accurate!
 - Benchmark your calculation with experiments whenever we can. Examples: X-ray structure, ratio of products (we can back-calculate from temperature the activation energy barrier, and from the transition states what ratio of products we expect).
 - Redo a couple of calculations at a higher level of theory to see if you get the same answer.
 - Chris Cramer (a founding father of computational chemistry): “There is no particular virtue to the speed at which a wrong answer can be obtained.”
 - Example of doing calculations wrong: Doing an S_N1 reaction without solvent. These reactions are so solvent-dependent, and there's no gas-phase cation that will replicate this solution-phase reaction.
 - What's easy to calculate?
 - Spectra: IR, Raman, NMR.
 - Masha likes to predict the NMR spectra of wacky intermediates.
 - ChemDraw does this for free.
 - The default solvent is THF; make sure you change it to CDCl₃!
 - MNova's function is better; it's ML-based, but it also costs money to run?? I think Masha has this wrong for MIT students.

²This is the computer science definition; it is largely unrelated to the mathematical definition that is equivalent to linear forms and duals.

- Geometries, conformers, and ground state structures.
 - “Geometry optimization” or “energy minimization” is very common.
 - Draw a 3D structure, give it to our program, move atoms, calculate E , repeat (let the program perturb the atom’s positions a bit) until we reach a *local* minimum.
 - This is what we’ll do on the problem set.
 - If we want to get the *global* minimum, we have to look for lower energy structures (manually, automatically, or a combination of both).
 - We often start at a low level of theory and then refine. Start with a search of the chemical space to find some stable conformers, and then pop that into DFT.
- Frequencies, well-defined transition states, and **single point calculations**.
 - Important because transition states are saddle points on the potential energy surface with 1 imaginary frequency corresponding to the bond-making or -breaking event.
 - If you have a structure that you think is a ground state, you have to prove this.
- **Single point calculation:** Calculating the energy of a structure without any other atoms around.
- Note: Nucleophiles typically come in at a 120° angle (the **Bürgi-Dunitz angle**), because that’s where it’s easiest to donate into the π^* -lobe.
- What’s “hard” to calculate?
 - Caveat: Do your research!!
 - Many applications require specialized approaches.
 - There’s an army of computational chemists who are trying to develop niche methods for our little problem; find them, connect with them, collaborate with them, etc.
 - It is our responsibility to know what part of a certain experiment is difficult.
 - Example: In photophysics, you need to know the limitations of certain parts of our model.
 - The system will not say, “I’m bad at predicting excited states;” you have to know that.
 - Things that require more finessing to study.
 - Open-shell species, e.g., radicals.
 - Transition metals: Heather researches how to model TMs with SQM, etc. This is really important and really hard.
 - “Unusual structures,” e.g., gas-phase plasma nonsense.
 - Thermochemistry.
 - E.g., thermodynamical parameters, calorimetry, etc.
 - There are specific packages that work for this, if we need to look into them.
 - Masha doesn’t know anything about any of this, but recommends that we can learn them!!
 - Solvent effects, LDFs, etc.
 - For these topics, the methods are getting better all the time (which is code for, “the programs don’t work great yet”).
 - **Implicit solvation vs. explicit solvation.**
- **Implicit solvation:** Treat the solvent as a continuous medium.
- **Explicit solvation:** Draw solvent molecules and add them to the calculation.
 - If you think the solvent is stabilizing the transition state in an S_N1 , you need to draw a little THF donating its lone pair to the carbocation.
 - This gets complicated in proteins, where we need to identify how many waters we need to draw to accurately represent water; recent papers suggest that effects matter up to 44 H_2O molecules away!

3.2 Pericyclic Reactions

9/19:

- Lecture 4 recap.
 - Masha redraws the accuracy/speed list of computational techniques.
 - She also rewrites the Cramer quote.
 - Basically, Tuesday was the methods, theory, and applications of computational chemistry.
- Announcements.
 - PSet 1 posted.
 - Conference room booked this afternoon for collaboration on the PSet.
- Today: Pericyclic reactions.
 - Reading: Anslyn and Dougherty (2006), Chapters 15 (pericyclics in general) and 16 (photochemical pericyclics).
 - See Jonathan's reading list!!
- Lecture outline.
 - Pericyclic reaction types and vocabulary.
 - History of pericyclic reactions.
 - Woodward-Hoffmann rules.
 - Dewar-Zimmerman analysis.
 - Frontier molecular orbital theory.
 - Miscellaneous pericyclic reactions.
- **Pericyclic** (reaction): A **concerted** (as opposed to **stepwise**) reaction with a transition state (TS) consisting of a cyclic^[3] array of atoms and orbitals. *Antiquated thermoreorganization*.
 - Informal definition: “If you can draw circle arrows, it’s a pericyclic reaction.”
 - Can be **synchronous** or **asynchronous**.
 - Indeed, sometimes we see asynchronous concerted Diels-Alders! These make us ask, “is the TS truly symmetric, or are some bonds longer or shorter?”
 - There are 5 (main) types of pericyclic reactions. The first three are “the big three,” and the latter two are less common.
 1. **Electrocyclizations**.
 2. **Cycloadditions**.
 3. **Sigmatropic rearrangements**.
 4. **Group transfers**.
 5. **Chelotropic reactions**.
 6. Etc.
 - This lecture assumes that we’ve seen all of these; if we haven’t seen these reactions before in undergrad or if it’s been a while...
 - Read the textbook;
 - Review your notes from undergrad;
 - Do some Googling (the Wikipedia pages are pretty helpful!!);
 - Ideally, do all of the above!

³This stands in contrast to “normal” organic reactions, which prefer to proceed through a *linear* TS.

- **Concerted** (mechanism): A mechanism with no **intermediates**.
- **Stepwise** (mechanism): A mechanism *with* intermediates.
- Concerted and stepwise mechanisms can be differentiated based on their respective energy diagrams.

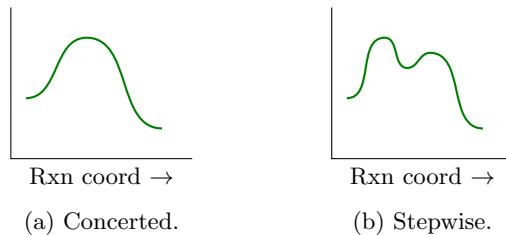
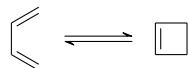


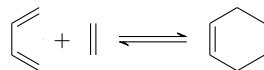
Figure 3.1: Concerted vs. stepwise energy diagrams.

- **Intermediate**: A local ground state structure.
- **Synchronous** (mechanism): All bond-making and -breaking occurs to an equal extent in the TS.
- **Asynchronous** (mechanism): All bond-making and -breaking does *not* occur to an equal extent in the TS.
- David: Would the fact that bond breaking/making happens more sequentially in an asynchronous mechanism imply that these reactions have energy diagrams that differ from the synchronous, concerted ideal of Figure 3.1a?
 - The energy diagram *is* different between synchronous and asynchronous.
 - Look into Dean Tantillo at UC-Davis for more!!
- **Electrocyclization**: A pericyclic reaction in which one π -bond gets converted into one σ -bond or vice versa. *Also known as electrocyclic reaction. Denoted by $m\pi$.*



– Example: We can refer to the above reaction as a “ 4π electrocyclization.”

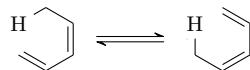
- **Cycloaddition**: A pericyclic reaction in which two or more unsaturated molecules (intermolecular) — or parts of the same molecule (intramolecular) — combine to form a cyclic adduct with a net reduction of bond multiplicity. *Denoted by $[m + n]$.*



– Example: We can refer to the above reaction as a “[$4 + 2$] cycloaddition.”

– This specific cycloaddition is also known as a **Diels-Alder reaction!**

- **Sigmatropic rearrangement**: A pericyclic reaction in which a σ -bond migrates along with a corresponding reorganization of the π -electrons. *Also known as sigmatropic reaction. Denoted by $[m, n]$.*



– Example: We can refer to the above reaction as a “[$1, 5$]-sigmatropic hydride shift.”

- **Group transfer** (reaction): A reaction that transfers atoms from one molecule to another, but in a concerted pericyclic transition state.
 - **Chelotropic** (reaction): A cycloaddition in which two bonds are made to one atom.
 - **Diels-Alder** (reaction): A $[4 + 2]$ cycloaddition.
 - Aside (chemis-tea): One of Steve Buchwald's pet peeves.
 - Don't erase the chalkboard with your fingers; use the eraser.
 - If Steve is on your thesis committee, the first thing he'll tell you is to use the eraser.
 - History of pericyclic reactions.

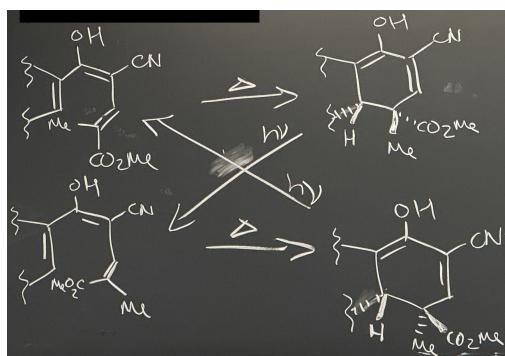


Figure 3.2: First observation of a pericyclic mechanism.

- Long considered to have “no mechanism.”
 - This is because people saw a starting material and a product, with nothing in between.
 - Quote from the ’60s: “No-mechanism is the designation, given half in jest, half in desperation, to thermoreorganization reactions” – von Eggers Doering and Roth (1962).
 - In 1966, Woodward and his army of grad students were synthesizing Vitamin B₁₂. During one particular ring-closing ‘thermoreorganization’ reaction, they noticed that using different geometric isomers as starting materials formed different stereoisomers as products (see Figure 3.2).
 - This gave a hint!
 - Shortly after, Woodward and colleagues made a second (even weirder) observation: In the presence of light, the cyclized products would revert to their starting materials, but to the *opposite* geometric isomer (also see Figure 3.2)!
 - These observations kickstarted a series of studies into the mechanism of such reactions.
 - In time, we came to classify the reaction in Figure 3.2 as a “6π electrocyclization,” governed by the mechanism described as follows.



Figure 3.3: 6π electrocyclization mechanisms.

- During a **thermal** electrocyclization, the termini of the π -systems rotate in opposite directions.
 - Notice how in Figure 3.3a, both *exo* groups rotate down, but the right one rotates clockwise and the left one rotates clockwise.
- During a **photochemical** electrocyclization, the termini of the π -system rotate in the same direction.
 - Notice how in Figure 3.3b, both axial groups rotate clockwise.
- This “rotation” of the π -systems’ termini is classified as **disrotatory** and **conrotatory**, respectively.
 - The disrotatory/conrotatory phenomenon led us to the **Woodward-Hoffmann rules**.
- The fact that Woodward and colleagues’ forward reaction is thermal but reverse reaction is photochemical is what yields the opposite starting material!
- **Thermal** (reaction): A reaction driven by high temperatures.
- **Photochemical** (reaction): A reaction driven by light.
- **Disrotatory** (electrocyclic reaction): An electrocyclic reaction in which the termini of the π -systems rotate in opposite directions.
- **Conrotatory** (electrocyclic reaction): An electrocyclic reaction in which the termini of the π -systems rotate in the same direction.
- **Woodward-Hoffmann rules:** Pericyclic reactions occur by the conservation of orbital symmetry from starting material to product.

Activation	# e⁻	Rotation
Δ	$4n$	con
Δ	$4n + 2$	dis
$h\nu$	$4n$	dis
$h\nu$	$4n + 2$	con

Table 3.1: Woodward-Hoffmann rules.

- These rules are important because they allows us to predict the stereochemistry of our products.
- Nobel prize (1981) to Hoffmann and Fukui.
 - Fukui was jointly awarded this prize for his work on frontier molecular orbital theory, which we’ll talk about later in this lecture.
 - Woodward didn’t win because he had died. It was ok, though, because he had already won the Nobel once; this would have been his second.
 - Aside (chemis-tea): A spat over who invented the Woodward-Hoffmann rules.
 - E. J. Corey claimed credit for giving Woodward the idea for the Woodward-Hoffmann rules in 2004 — see Corey (2004).
 - Then Hoffmann rebuts Corey with a show-me-the-receipts type article — see Hoffmann (2004).
 - Woodward and Corey were both titans in their field at Harvard, both Nobel laureates, but also both big personalities.
 - Aside: Anyone who believes that science is somehow unbaised and empirical has never worked with a real scientist. Masha: “Scientists are some of the most human, emotional colleagues I’ve ever worked with... and I love them, don’t get me wrong.”
- Historical impact: One of the first successful unions of theory and experiment in chemistry.
 - Credited with leading organic chemists to finally accept MO theory.

- Let's now schematize the orbital machinations underlying the Woodward-Hoffmann rules.
- Correlation diagram:** A method of tracking orbital symmetry from starting materials to products in an electrocyclization.
 - Workflow.
 - Draw MOs.
 - Assign symmetry (S = symmetric, A = antisymmetric).
 - Populate with electrons.
 - Correlate orbitals with the same symmetry.
 - We assign symmetry differently depending on whether we're investigating a disrotatory or conrotatory pathway.
 - Disrotatory pathway: Ask yourself, "are the orbitals symmetric with respect to the σ -plane?"
 - Conrotatory pathway: Ask yourself, "are the orbitals symmetric with respect to the C_2 axis perpendicular to the σ -bond that forms in the electrocyclization and lying in the plane of the pericyclic TS?"
 - For clarification on what exactly this all means, we'll look at a few examples. In particular, we'll investigate the favorability of the thermal and photochemical, disrotatory and conrotatory pathways through which the 4π electrocyclization of butadiene could proceed.
- σ -plane: The mirror plane lying perpendicular to the σ -bond that forms in an electrocyclization.
- Example: The possible thermally activated, 4π electrocyclizations of butadiene.

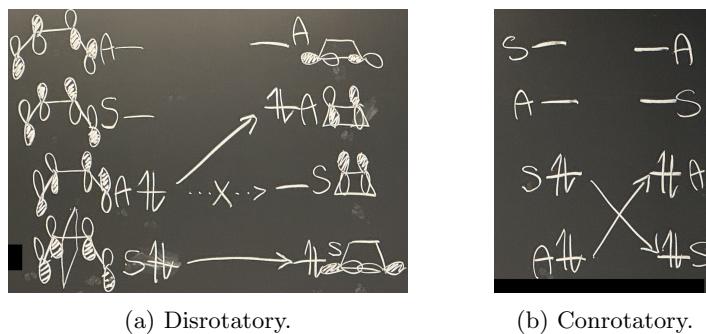


Figure 3.4: Correlation diagrams for butadiene's thermal 4π electrocyclizations.

- We will first apply the correlation diagram workflow to the disrotatory case (Figure 3.4a).
 - Draw MOs for both the starting material and product.
 - Let's begin by drawing the MOs for the starting material.
 - We'll draw four p -orbitals and shade them in to create a conjugated π -system exactly as in Huckel theory.
 - Specifically, notice the no nodes \rightarrow 1 node \rightarrow 2 nodes \rightarrow 3 nodes pattern.
 - Then we draw the product's MOs adjacent.
 - We know that the original four p -orbitals are transforming into a new σ -bond and a new π -bond, so we draw the bonding and antibonding phases of the new σ -bond as well as the bonding and antibonding phases of the new π -bond.
 - Essentially, we are drawing a σ , π , π^* , and σ^* MO.
 - Note that the π and π^* orbitals split less (energetically) than the σ and σ^* orbitals — just like in IChem — because they have less direct overlap; this is why we get the ordering $\sigma \rightarrow \pi \rightarrow \pi^* \rightarrow \sigma^*$ as opposed to $\pi \rightarrow \sigma \rightarrow \sigma^* \rightarrow \pi^*$ or something like that.

2. Assign symmetry to each of our drawn MOs.
 - Since we are looking at the *disrotatory* case, we will look at symmetry with respect to the σ -plane.
 - As a guide, we draw in the σ -plane in the bottom-left MO.
 - This particular MO is clearly symmetric with respect to the σ -plane, so we label it “S”.
 - We then perform this analysis for the remaining MOs, noting them as either symmetric or antisymmetric.
 3. Populate the starting MOs with electrons.
 - 4π electrocyclization, so 4 electrons to fill normally (i.e., per Aufbau, Pauli, and Hund).
 4. Correlate the filled starting MOs to the lowest energy product MOs with matching symmetry.
 - Maxim: An orbital cannot flip its symmetry during an electrocyclization.
 - As such, the lowest energy starting MO (being symmetric) has no problem becoming the lowest energy product MO (which is also symmetric).
 - However, the second-lowest energy starting MO (being antisymmetric) *cannot* become the second-lowest energy product MO because the latter is symmetric. (We say that this transition is formally **forbidden** because symmetry is not conserved.) As such, it must go up in energy to become the third-lowest energy product MO.
 - This population of a higher energy orbital means that the 4π electrocyclization of butadiene is *disfavored* to occur through a thermal, disrotatory pathway.
- We now apply the correlation diagram workflow to the conrotatory case (Figure 3.4b).
1. The MOs will be the same as in Figure 3.4a, so we don’t need to redraw them.
 2. The symmetry must be evaluated with respect to that C_2 axis this time, though, so we have to reassign S or A to each MO.
 - For the MOs as drawn in Figure 3.4a, the C_2 axis we need goes into the plane of the page.
 3. We populate the starting MOs as before.
 4. When we correlate, this time we can fill the bottom two product MOs!
 - We didn’t populate electrons directly across, but we *did* populate the lowest energy orbitals again, so the conrotatory pathway is *favored*.
 - Both arrows involve a conservation of orbital symmetry, so (to reiterate) this reaction is **allowed** (thermally).
- David: Why do we only draw some of the molecular orbitals?



Figure 3.5: MOs relevant to butadiene’s 4π electrocyclization.

- We only consider the orbitals involved in the reaction; considering the whole σ -network would get more complicated without changing our results.
- This is actually an example of why arrow-pushing is useful! Namely, because it shows that the p -MOs we consider in the starting material become the σ - and π -MOs we consider in the product.
- **Photochemical reaction:** A reaction driven by the absorption of a photon, leading to an excited state.
 - Later in this course, we’ll go more into detail on photochemical reactions, but this is the only level of detail we need right now.
 - In the reactions we’ll look at today, one electron is kicked up an energy level with no other changes to the structure.

- Example: The possible photochemically activated, 4π electrocyclizations of butadiene.

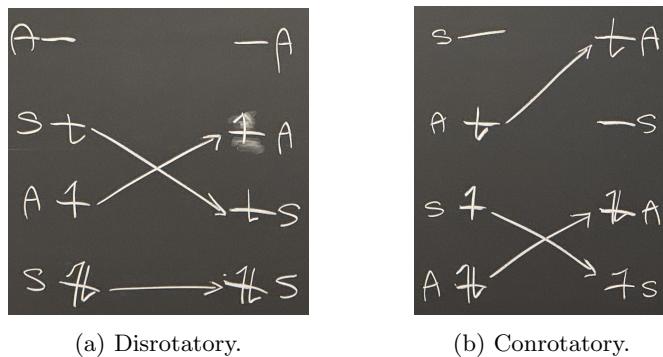


Figure 3.6: Correlation diagrams for butadiene's photochemical 4π electrocyclizations.

- We use the same MOs and symmetries as in the corresponding subfigures of Figure 3.4.
- Differences only start to appear when we populate with electrons.
 - In particular, we excite one electron up a level (without altering its spin) in both sets of starting-material MOs.^[4]
- Disrotatory case (Figure 3.6a).
 - Orbital symmetries are such that we end up with the *same* populations as in the starting material.
 - Therefore, this pathway is allowed/favored.
- Conrotatory case (Figure 3.6b).
 - Orbital symmetries are such that we end up with a *higher-energy* population than in the starting material.
 - Since electrons are in “much higher” energy levels, this pathway is forbidden/disfavored.
- Notice that the photochemical result that disrotatory is favored and conrotatory is disfavored is the opposite of thermal!
 - Thus, we just derived the Woodward-Hoffmann rules (Table 3.1) about what is favored and disfavored!
 - At least we derived the case for 4 electrons.
 - A more general mathematical proof can be done to rigorously verify Table 3.1, but the details are beyond the scope of this class.
 - If you ever forgot the WH rules, just rederive them from first principles :)
- A note on the correlation arrows in Figures 3.4 and 3.6.
 - The uppermost correlation arrow in Figure 3.6b corresponds to an *allowed* but *disfavored* electronic transition.
 - The X'ed-out correlation arrow from A to S in Figure 3.4a corresponds to an explicitly *forbidden* electronic transition.
- The Woodward-Hoffmann rules are one way to look at pericyclic reactions, probably the most complex way.
 - We'll now look at two simpler ways.

⁴I.e., without intersystem crossing to a triplet state.

- Dewar-Zimmerman analysis: Aromatic TS theory.
 - Principle: Reactions that go through aromatic transition states are allowed.
 - We already like 6-membered TS's because they're geometrically stable; 6-membered *aromatic* TS's are even lower energy and more favored!
- Examples of aromatic and antiaromatic transition states.



(a) Aromatic TS in a [4 + 2] cycloaddition.



(b) Antiaromatic TS in a [2 + 2] cycloaddition.

Figure 3.7: Aromatic and antiaromatic transition states.

- Figure 3.7a shows that the transition state in a Diels-Alder reaction is aromatic.
 - This is why the forward Diels-Alder reaction is favored (under thermal conditions).
- Figure 3.7b shows that the transition state in a [2 + 2] cycloaddition is antiaromatic.
 - This is why the forward reaction to cyclobutane is disfavored (under thermal conditions).
- Let's get a little more formal now.
- Rules.
 1. Draw orbitals with any phasing, and decide the reaction topology.
 - By “any phasing,” we do mean that you can take *any* of the MOs you would draw and the Dewar-Zimmerman analysis will still work. So “go crazy,” if you want!
 - Masha does not draw out any examples to inductively prove this to us, but it would probably be a good exercise to do this on my own!!
 - By “reaction topology,” we mean how the two reactants approach each other. Is something coming from the top? The bottom?
 2. Connect orbitals through the reaction topology and count the number of phase inversions (PIs).
 - In other words, count how many lines connect lobes of opposite phases.
 - This will tell us whether we should evaluate the transition state for *Huckel* or *Möbius* aromaticity.
 - Essentially...
 - If there are an *even* number of PIs, having $4n + 2$ electrons will lend *Huckel* aromaticity to the transition state and favor its formation;
 - If there are an *odd* number of PIs, having $4n$ electrons will lend *Möbius* aromaticity to the transition state and favor its formation.
 3. Count the number of electrons.
 - As mentioned above, this number will tell us (depending on whether we're in Huckel-land or Möbius-land) whether the transition state is aromatic.

- To practice using these rules, let's reevaluate the examples in Figure 3.7.

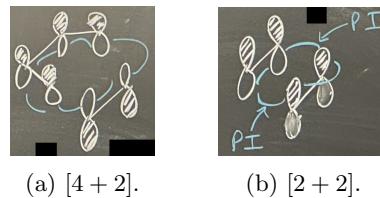
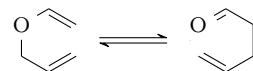


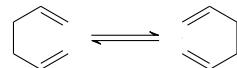
Figure 3.8: Dewar-Zimmerman connections for [4 + 2] and [2 + 2] cycloadditions.

- Example: [4 + 2] cycloaddition (Figure 3.8a).
 1. Draw MOs, and decide the reaction topology.
 - MOs: Let's arbitrarily choose to use the MOs with no nodes for both butadiene and ethene.
 - Topology: Let ethene approach butadiene from the bottom.
 2. Connect orbitals, and count PIs.
 - Connections: We connect all the bottom lobes of butadiene, the two top lobes of ethene, and (since ethene is approaching from the bottom, per the reaction topology) the bottom terminal lobes of butadiene to the top terminal lobes of ethene.
 - The connections are all drawn as blue lines in Figure 3.8.
 - PIs: All of the connected lobes are unshaded, so there are 0 PIs.
 - 0 is an even number, so we are in Huckel-land.
 3. Count the number of electrons.
 - There are $6 = 4(1) + 2 \pi$ -electrons.
 - Therefore, our TS will be *stabilized* by *aromaticity* of the *Huckel* type.
 - Example: [2 + 2] cycloaddition (Figure 3.8b).
 1. Draw MOs, and decide the reaction topology.
 - MOs: We once again choose (arbitrarily) the MOs with no nodes for both ethenes.
 - Topology: The right ethene approaches the left ethene from the bottom.
 2. Connect orbitals, and count PIs.
 - Connections: We connect the bottom lobes of the left ethene to each other and to the top lobes of the right ethene (which are also connected to each other).
 - PIs: This time — because of the way we have drawn the right ethene — we have 2 PIs.
 - 2 is an even number, so we are in Huckel-land.
 3. Count the number of electrons.
 - There are $4 = 4(1)$ π -electrons.
 - Therefore, our TS will be *destabilized* by *antiaromaticity* of the *Huckel* type.
 - The Dewar-Zimmerman analysis is useful for predicting the feasibility of sigmatropic rearrangements.
 - Recall from above that a *sigmatropic rearrangement* involves the migration of a σ -bond along with a corresponding reorganization of the π -electrons.
 - Specifically, in a sigmatropic rearrangement, the total number of π - and σ -bonds does not change.
 - Example sigmatropic rearrangements.
 1. **Claisen rearrangement.**
 2. **Cope rearrangement.**

- **Claisen rearrangement:** A [3, 3]-sigmatropic rearrangement of allyl vinyl ethers to form corresponding γ, δ -unsaturated carbonyls.



- **Cope rearrangement:** A [3, 3]-sigmatropic rearrangement of 1,5-dienes to form other 1,5-dienes.



- We should be familiar with both the Claisen and Cope rearrangements; if we're not, Google them!!
- Example: Dewar-Zimmerman analysis of **suprafacial** and **antarafacial** [1,3]-sigmatropic H shifts.

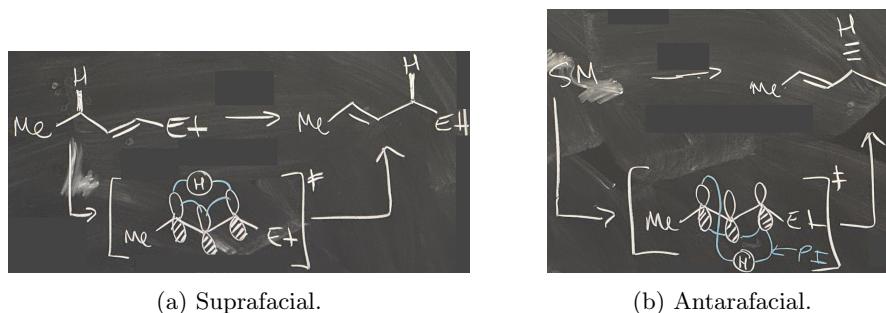


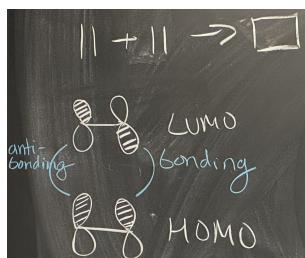
Figure 3.9: Dewar-Zimmerman analysis of [1, 3]-sigmatropic hydride shifts.

– We'll start with the suprafacial case (Figure 3.9a).

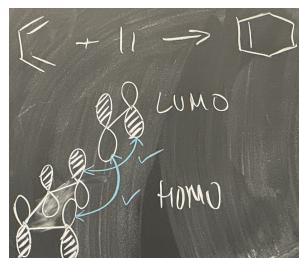
1. Draw MOs, and decide the reaction topology.
 - MOs: We choose the MO with no nodes for the π bonds, and the hydrogen atom's 1s orbital.
 - Notice that we draw a p -orbital for all three carbons involved in the bond breaking/making process in the transition state, not just the two carbons involved in the initial or final bond!
 - Topology: Draw the H atom in the process of migrating.
2. Connect orbitals, and count PIs.
 - Connections: Connect all the top lobes together and to hydrogen.
 - PIs: 0.
 - Even PIs, hence Huckel.
3. Count the number of electrons.
 - We have two electrons in the C=C π -bond, and two electrons in the C–H σ -bond.
 - We also get a clue that there are 4 electrons present because we drew 4 orbitals!
 - Thus, there are $4 = 4(1)$ electrons present.
 - Therefore, our TS will be destabilized by Huckel antiaromaticity.
 - It follows that the suprafacial pathway is (thermally) forbidden.
 - This is an interesting result because at first glance, it "looks" like a nice TS (with the H just bouncing over), but nope! It's not allowed.

- We now move onto the antarafacial case (Figure 3.9b).
 1. Draw MOs, and decide the reaction topology.
 - MOs: Same as in Figure 3.9a.
 - Topology: The H atom is switching faces, so it will have to engage with the top lobe on one side and the bottom lobe on the other side.
 2. Connect orbitals, and count PIs.
 - Connections: We connect the three *p*-orbitals as expected, but note the explicit connection of the top-left *p*-lobe and the bottom-right *p*-lobe to the hydrogen, in accordance with the reaction topology.
 - Note that it doesn't really matter which lobes of the *p*-orbitals we connect because we get the same result either way.
 - PIs: 1.
 - This is our first time having an *odd* number of PIs, so we are now in Möbius-land!
 3. Count the number of electrons.
 - As above, there are $4 = 4(1)$ electrons.
 - However, because we are in Möbius-land, this nevertheless means that our TS will be *stabilized* by *aromaticity* of the *Möbius* type.
 - Thus, “ugly” antarafacial transition states are nevertheless totally allowed!
- Despite the fact that antarafacial [1, 3]-sigmatropic hydride shifts are favored over their suprafacial counterparts, our intuition that the antarafacial transition state would be sterically strained is correct.
 - Indeed, there are examples of [1, 3]-hydride shifts occurring with stereoinversion, but they are rare.
 - Nevertheless, this is a fun and nonintuitive finding!
 - If you are interested, you can look into work on antarafacial [1, 3]-methyl shifts, which are also favored over their suprafacial counterparts!
- Aside: One place where we do see stereoinversions.
 - The keto-enol tautomerization could be thought of as a [1, 3]-sigmatropic hydride shift!
 - Indeed, if it occurs intramolecularly, it would occur with stereoinversion.
 - However, the rate of this intramolecular rearrangement is naturally very slow due to strain, which is why we need a solvent, acid, or base catalyst to do the proton transfer intermolecularly with any appreciable rate.
 - Essentially, the reaction can't really happen intramoleucularly because it'd be forbidden electronically with *cis* hydrogens or very disfavored sterically with *trans* hydrogens.
- **Suprafacial** (sigmatropic rearrangement): A sigmatropic rearrangement in which the bond-breaking and bond-making processes occur on the *same* face of the π -system.
- **Antarafacial** (sigmatropic rearrangement): A sigmatropic rearrangement in which the bond-breaking and bond-making processes occur on *opposite* faces of the π -system.
- Notice how...
 - In Figure 3.9a, the hydride is on the same side of the molecule in both starting material and product, i.e., coming out of the plane of the page;
 - That's why we call this suprafacial!
 - In Figure 3.9b, the hydride is on opposite sides of the molecule in the starting material vs. the product, i.e., coming out of the plane of the page vs. going into the plane of the page.
 - That's why we call this antarafacial!

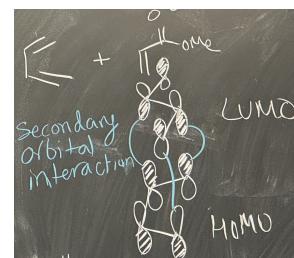
- Frontier molecular orbital theory (FMO).
 - By Fukui, as mentioned above.
 - This is a simplification of some other models in which you only consider the HOMO/LUMO interactions (instead of all MOs).
 - Principle: If the HOMO of the electron-donating species and LUMO of the electron-accepting species mix favorably, then the reaction is allowed.
 - Example: FMO analysis of cycloadditions.



(a) [2 + 2].



(b) [4 + 2].



(c) *endo*-[4 + 2].

Figure 3.10: Frontier molecular orbital analysis of cycloadditions.

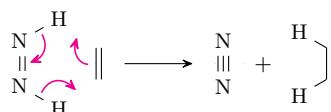
- A [2 + 2] cycloaddition (Figure 3.10a).
 - As in a Dewar-Zimmerman analysis we begin by drawing the HOMO and LUMO of the reactants and deciding the reaction topology.
 - MOs: Recall that for ethene, the HOMO has 0 PIs and the LUMO has 1 PI.
 - Topology: We have decided to have the ‘electron-donating’ ethene attack from the bottom.
 - Then (also as in a Dewar-Zimmerman analysis) we connect lobes and check for bonding and antibonding interactions.
 - Here, we have 1 bonding and 1 antibonding interaction.
 - The presence of an antibonding interaction means that this reaction is forbidden/disfavored.
 - Bonus content: Ketenes engage in [2 + 2] cycloadditions at ambient temperatures!
 - Masha encourages us to look more into this!!
 - A [4 + 2] cycloaddition (Figure 3.10b).
 - Performing an analogous analysis to the above, we observe 2 bonding interactions. This means that this reaction is allowed.
 - A [4 + 2] cycloaddition with a more elaborate dienophile (Figure 3.10c).
 - As in both previous cases, we begin by drawing the HOMO of the ‘electron-donating’ species and the LUMO of the ‘electron-accepting’ species.
 - MOs: Notice that it does not matter that the dienophile’s π -system contains a heteroatom.
 - Topology: This time, we have the dienophile attack from the top.
 - Connecting orbitals.
 - First, observe that we get the same favorable bonding interactions as in Figure 3.10b.
 - In addition, we get a new, secondary orbital interaction if we draw the *endo* transition state.
 - This additional, stabilizing interaction rationalizes why the *endo* transition state is favored in a Diels-Alder reaction!
 - Therefore, this reaction is allowed, and the *endo* product is preferred due to secondary orbital interactions.

- Miscellaneous pericyclics: Group transfer and chelotropic reactions.
- Recall from above that a *group transfer* reaction transfers atoms from one molecule to another, but in a concerted pericyclic transition state.
- Example group transfer reactions.

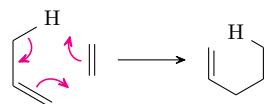
- Diimide reduction.**

- The ene reaction.**

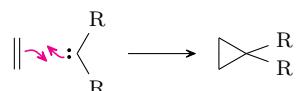
- Diimide reduction:** A group transfer reaction that converts an unsaturated organic compound to a reduced alkane using diimide (N_2H_2).



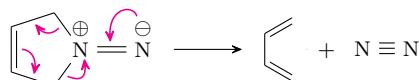
- Remember to draw arrows to the place where you're making the bond, not to an atom unless the electrons are going on that atom!!
- Ene reaction:** A group transfer reaction between an **ene** and an **enophile** that forms a new σ -bond with migration of the ene double bond and a 1,5-hydrogen shift. *Also known as Alder-ene reaction.*



- Ene:** An alkene with an allylic hydrogen.
- Enophile:** A compound containing a multiple bond.
- Moving on, recall from above that a *chelotropic* reaction is a cycloaddition in which two bonds are made to one atom.
- Example chelotropic reactions.
 - Carbene addition.**
 - Certain **cycloreversions**.
- Carbene addition:** The addition of a singlet carbene to an alkene to make a cyclopropane.



- Observe how the two arrows form two σ -bonds to the carbene.
- Cycloreversion:** The reverse of a cycloaddition reaction.



- Since two of the left nitrogen's bonds are being *broken*, this is technically a *retro-chelotropic* reaction.

- Lecture summary: Three models to study pericyclic reactions.
 1. The Woodward-Hoffmann rules.
 - These are all about the conservation of orbital symmetry.
 2. The Dewar-Zimmerman analysis, also known as aromatic TS theory.
 - This is the “I can’t believe it works!” one, where you can draw any phasing and the model still gives you the right answer.
 3. FMO theory.
 - This is where we only look at HOMO/LUMO interactions.
- Matthew: When would you use one model over the others?
 - All three models should always give the same result (otherwise, there’s a problem with the model), but sometimes you care more about one aspect of a reaction or another.
 - For example, if you want to figure out whether you get the conrotatory or disrotatory product, it is easier to use the Woodward-Hoffmann rules.
 - This is because they’re designed specifically for such questions.
 - If you need a quick-and-dirty “is this reaction going to happen,” use FMO.
 - If you want to determine whether a reaction will be antarafacial or suprafacial, use Dewar-Zimmerman.

3.3 Chapter 14: Advanced Concepts in Electronic Structure Theory

From Anslyn and Dougherty (2006).

Section 14.2: Calculational Methods — Solving the Schrödinger Equation for Complex Systems

- 9/23:
- 20 pages on computational methods, but a bit outdated.

3.4 Chapter 15: Thermal Pericyclic Reactions

From Anslyn and Dougherty (2006).

- This whole chapter is a gold mine. Return to!!

Section 15.1: Background

-

Section 15.2: A Detailed Analysis of Two Simple Cycloadditions

-

Section 15.3: Cycloadditions

-

Section 15.4: Electrocyclic Reactions

-

Section 15.5: Sigmatropic Rearrangements

-

3.5 Chapter 16: Photochemistry

From Anslyn and Dougherty (2006).

- Also a treasure trove, though much of this is beyond the scope of the course. However, it is largely within the scope of 5.47, so I should definitely return!!

Section 16.3: Photochemical Reactions

- Recommended readings for this course: Sections 16.3.4-16.3.5.
- The tail-end of 16.3.5 talks a bit about norbornadiene (PSet 1).

Week 4

Ions

4.1 Cations

9/24:

- Lecture 5 recap.
 - Pericyclic reactions: Concerted reactions with a TS having a cyclic array of atoms and orbitals.
 - Three models.
 1. Woodward-Hoffmann rules: Conservation of orbital symmetry.
 2. Dewar-Zimmerman analysis: Aromatic TS theory.
 3. Frontier MO theory: HOMO-LUMO interactions.
 - “No mechanism... half in jest, half in desperation... to the thermoreorganization reactions.”
 - Essentially, pericyclic reactions really led to a new blossoming of organic chemistry, and a series of successful mergers between theory and experiment.
- Announcements: PSet 1 due tomorrow; if late, we'll lose a lot of points.
- Today: Cations (mostly carbocations).
 - This is the first in a series of lectures on functional groups: Cations, anions, radicals, and carbenes.
- Lecture outline.
 - Overview of cation structure and reactivity.
 - Measuring a cation's (thermodynamic and kinetic) stability.
 - Stabilizing cations to promote reactivity.
 - Cation reactions.
 - Nonclassical carbocations.
- There are three phases in a cation's lifetime: Synthesis, stability, and reactivity.

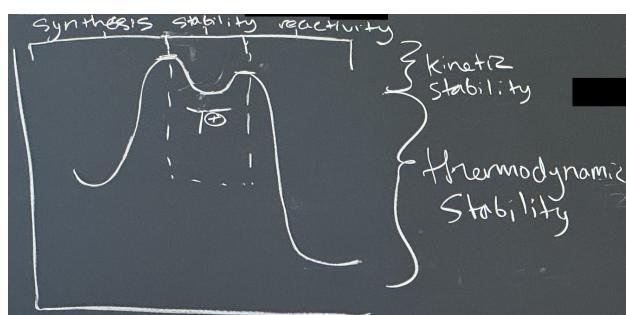


Figure 4.1: Phases in the life of a cation.

- All three phases correspond to specific regions along the reaction coordinate in the energy diagram for a cation-intermediate reaction.
- Stability, in particular, we'll talk about from a kinetic *and* a thermodynamic perspective.
 - Kinetic stability deals with the energy barrier to *form* and to *react* the cation.
 - Thermodynamic stability deals with the energy difference between the cation and the adjacent local ground state structures.
- Cations can have quite “sensitive” energy surfaces, i.e., factors that can stabilize and destabilize cations can have dramatic effects on the synthesis, stability, and reactivity of cations.
- Features that stabilize cations tend to lead to reactions.
 - If you're in the lab, consider stabilizing the cation in order to induce the desired reactivity!
- Cation structure.

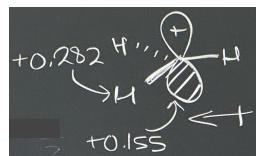


Figure 4.2: Cation structure.

- Figure 4.2 depicts a methyl cation (CH_3^+).
- In general, cations are sp^2 -hybridized, trigonal planar species.
 - Recall that Figure 2.5 explains why cations are trigonal planar instead of pyramidal.
- The cationic charge is delocalized across the entire molecule, not localized on the carbon.
 - Indeed, there is a δ^+ on the H's, too.
 - In fact, the dipole qualitatively points *toward* the carbon.
 - Quantitatively, the **Mulliken partial charges** are +0.155 on C and +0.282 on each H. Together, these partial charges sum to the total charge of +1:

$$1 \times 0.155 + 3 \times 0.282 \approx 1$$

- Experimental evidence for cation formation.

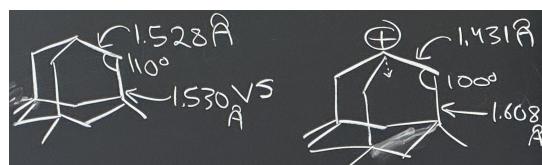


Figure 4.3: Evidence that carbocations exist.

- Experimental evidence primarily comes from some cool adamantane structures.
- For example, consider trimethyl adamantane and its corresponding cation. The cation has structural characteristics indicative of the “flattening” transformation we would expect. Specifically...
 - The adjacent bond angles flatten from 110° to 100° ;
 - The bonds immediately surrounding the cation shrink from 1.528 \AA to 1.431 \AA as the molecular geometry compresses the flattening cation;
 - The bonds α, β to the cation elongate from 1.530 \AA to 1.608 \AA as electron density is removed from them through hyperconjugation and the no-bond resonance form.
- Reference: Laube (1986).

- Moving on, to measure the thermodynamic stability of a cation, we use the **hydride ion affinity**.
- Hydride ion affinity:** The extent to which cations want to bind a hydride in solution. *Also known as HIA. Given by*



- Always measured in the gas phase.
- Only tells you the *relative* stability.^[1]
- Example HIAs.

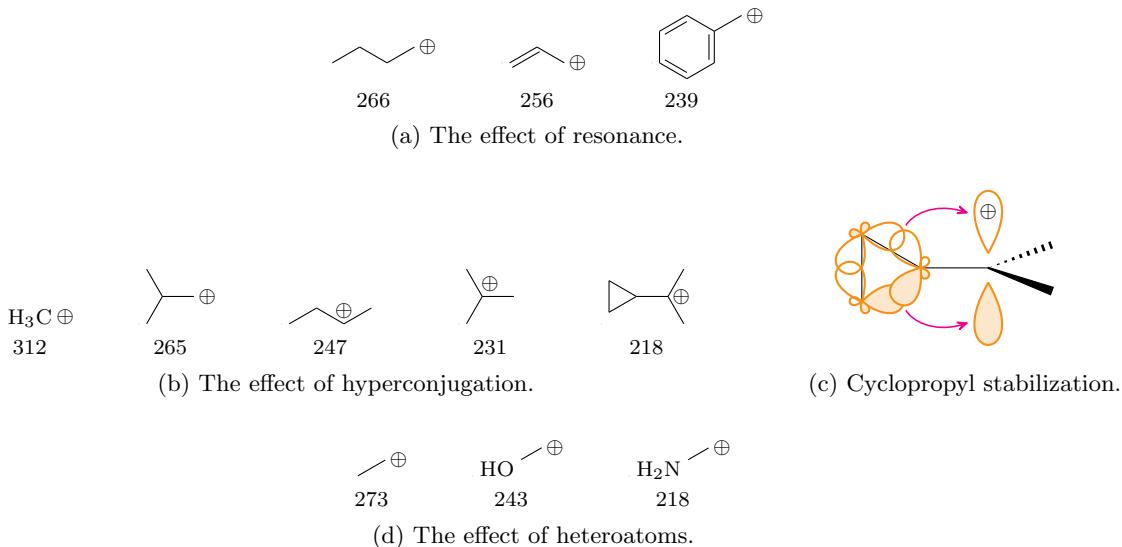


Figure 4.4: Hydride ion affinity examples.

- Alkyl, allylic, and benzylic HIAs (Figure 4.4a).
 - Respectively: 266 kcal/mol, 256 kcal/mol, and 239 kcal/mol.
 - Attributable to resonance delocalization and conjugation.
- Methyl, isobutyl, *sec*-butyl, *tert*-butyl, and dimethylcyclopropyl HIAs (Figure 4.4b).
 - Respectively: 312 kcal/mol, 265 kcal/mol, 247 kcal/mol, 231 kcal/mol, and 218 kcal/mol.
 - Attributable to hyperconjugation.
 - Deeper dive: Hyperconjugation from cyclopropyl rings (Figure 4.4c)
 - This is a follow up to our brief discussion on the same topic in Lecture 3.
 - When this molecule forms, the carbocation's empty *p*-orbital will align with the σ -plane of the cyclopropyl group.
 - With this alignment, *both* adjacent C–C banana bonds can donate into the carbocation through hyperconjugation.
 - The hyperconjugative interaction is so extreme that the barrier to rotation along the bond between the cation and the cyclopropyl group is 13.7 kcal/mol!
 - We can also picture this interaction through no-bond resonance forms that delocalize the positive charge to the back two carbons in the cyclopropyl group.
 - You can look up the crystal structure of this molecule to see the interaction more.
- Ethyl, hydroxymethyl, and aminomethyl HIAs (Figure 4.4d).
 - Respectively: 273 kcal/mol, 243 kcal/mol, and 218 kcal/mol.
 - Attributable to heteroatom stabilization (aka resonance).

¹Relative to what??

- The stability of the carbocation (as discussed above in terms of HIAs) determines how high the local minimum is in the energy diagram in Figure 4.1.
- We now move onto the kinetic stability/reactivity of cations.
- Two ways of measuring this.

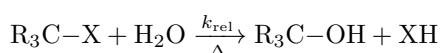
- Rates of **solvolysis**.

- Used all the time.

- Mayr electrophilicity**.

- More niche, but still good to know.

- Solvolysis:** A type of nucleophilic substitution (S_N1 or S_N2) wherein the nucleophile is a solvent molecule. *Given by*

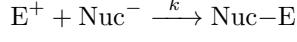


- Rates of solvolysis are reported as a relative rate constant k_{rel} .
- Comparing HIAs to rates of solvolysis.

	Bn-Br	All-Br	<i>i</i> Pr-Br
HIA (R^+)	239	256	249
k_{rel}	100	52	0.7

Table 4.1: HIAs and the rate of solvolysis are not correlated.

- To be clear, we are listing the HIA of the benzyl, allyl, and isopropyl cations.
- Benzyl bromide affords a cation that is both the most stable and the most reactive in the set.^[2]
- Note that in general, solution-phase measures of stability like solvolysis and gas-phase measures of stability like the HIA *don't* correlate. This means that we do have to measure them independently.
- Mayr electrophilicity:** The rate of reaction for various electrophilic and nucleophile pairs. *Given by*



- By Herbert Mayr from 5.47!
 - Mayr defined three parameters (s , N , and E) via the equation
- $$\log k = s(N + E)$$
- s is a nucleophile-specific slope parameter.
 - N is a nucleophile parameter.
 - E is an electrophile parameter.
 - Note that “ Nuc^- ” indicates a nucleophile, just like the more commonly used Nu^- .
 - Mayr has done hundreds of these reactions, measured their rates, had reference nucleophile, etc.
 - His group is still expanding the chart!
 - There's a giant PDF on Mayr's [website](#) that we can download if we want.
 - Reference: Mayr and Patz (1994).

²Clarify??

- Example Mayr electrophilicities.

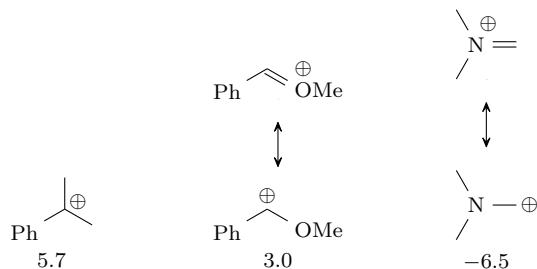


Figure 4.5: Mayr electrophilicity examples.

- To be clear, Figure 4.5 lists the E value for each species.
- Remember that Mayr electrophilicity is reported on a logarithmic scale, so the difference in E between the left two species (approximately 3) corresponds to a difference in reactivity of three *orders of magnitude*.
 - Similarly, the difference in reactivity between the right two species is *nine orders of magnitude*!
- Some of these trends should make sense.
 - For example, it stands to reason that the cation with heteroatom stabilization is the least electrophilic.
 - Observe that our most thermodynamically stable carbocation (the 3° one with extensive resonance into the phenyl ring) is also our most Mayr electrophilic one!
 - This is yet another example of thermodynamics being decoupled from the kinetics of reactivity.
- This concludes our discussion of *measuring* kinetic and thermodynamic stability. Let's now talk about *enhancing* carbocation stability.
- Four ways of doing this.
 1. **Hyperconjugation.**
 2. Heteroatom stabilization.
 3. The β -silicon effect.
 4. The neighboring group effect.
- **Hyperconjugation:** The delocalization of electrons through σ -bonds.



(a) $\sigma_{\text{CH}} \rightarrow p_{\text{C}}$ donation.

(b) No-bond resonance.

Figure 4.6: Stabilizing carbocations: Hyperconjugation.

- Hyperconjugation explains why substituted cations are more stable.
- Recall from 5.13^[3] that the ethyl cation is stabilized by $\sigma_{\text{CH}} \rightarrow p_{\text{C}}$ donation.
- Equivalently, we can say that the ethyl cation is stabilized by **no-bond resonance**.
 - What this really tells us is that the C–C bond is shorter than we'd normally expect, and the C–H bond is longer than we'd normally expect.

³Figure 4.6a is just Figure 2.3a from Labalme (2024a).

- Example HIA differences caused by hyperconjugation (Figure 4.4b).
 - Increasing from no adjacent C–C bonds to three adjacent C–C bonds decreases the HIA from 312 kcal/mol to 231 kcal/mol.
 - Essentially, as we add more R groups, the cation's empty p -orbital gets stabilized by additional adjacent σ -orbitals.
- Matthew: Does hyperconjugation induce a barrier to rotation?
 - There's always some barrier.
 - In a normal alkyl molecule, it's approx 3 kcal/mol.
 - In a hyperconjugated cation, we will see bigger differences.
 - In fact, there's a fascinating example somewhere in the literature of the stereochemistry of a product being determined by geometric constraints caused by hyperconjugation!
 - So all this is to say, yes.
- Heteroatom stabilization.

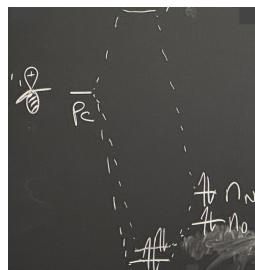


Figure 4.7: Stabilizing carbocations: Adjacent heteroatoms.

- The high-energy empty p -orbital on carbon and low-energy heteroatom lone pair interact to form new bonding and antibonding MOs.
 - The bonding MO will be lower energy than the lone pair AO, so the electrons in that lone pair will be stabilized.
- Nitrogen vs. oxygen stabilization: Rationalizing why nitrogen is more stabilizing in Figure 4.4d.
 - The n_O AO is lower in energy than the n_N AO.
 - This means that there is worse energy overlap between the n_O AO and the p_C AO than between the n_N AO and the p_C AO.
 - The worse energy overlap with oxygen leads to a resultant decrease in MO splitting, and hence less stabilization for the oxygen lone pair than the nitrogen lone pair receives.
- **β -silicon effect:** The stabilization of positive charge at the position β to a silicon atom.
 - Caused by hyperconjugation.
 - Specifically, silicon is a better σ -donor, by which we mean that C–Si bonds are better at sharing their electron density via hyperconjugation than C–C or C–H bonds.^[4]
 - Silicon is better because...
 - Silicon is less electronegative than other common σ -donors;
 - Indeed, $EN_C = 2.55$ and $EN_C = 2.20$, but $EN_{Si} = 1.90$.
 - Thus, C–Si bonds hold their electrons less tightly and hence are happier to share.
 - C–Si bonds holding their electrons less tightly also implies the following.

⁴Note that we do *not* mean that silicon is a better σ -donor ligand, like in inorganic chemistry.

- C–Si bonds are longer;
 - 1.86 Å vs. the 1.54 Å typical of a C–C bond.
 - This allows for greater overlap with the typically lengthy *p*-orbitals.
- C–Si bonds are more ionic;
 - Polarization toward carbon (more ionicness) means that there's more electron density on the carbon (i.e., near the carbocation).
- The σ_{CSi} orbital is higher in energy than σ_{CC} orbital.
 - Thus, like in Figure 4.7, we get closer to the p_{C} energy level and have more effective overlap.
- Example HIA differences caused by the β -silicon effect.

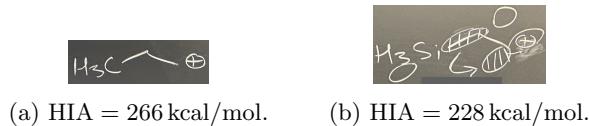


Figure 4.8: Hydride ion affinities subject to the β -silicon effect.

- Changing an alkyl cation to the direct silicon analogue alters the HIA by nearly 40 kcal/mol.
- Examples of how the β -silicon effect alters reactivity.

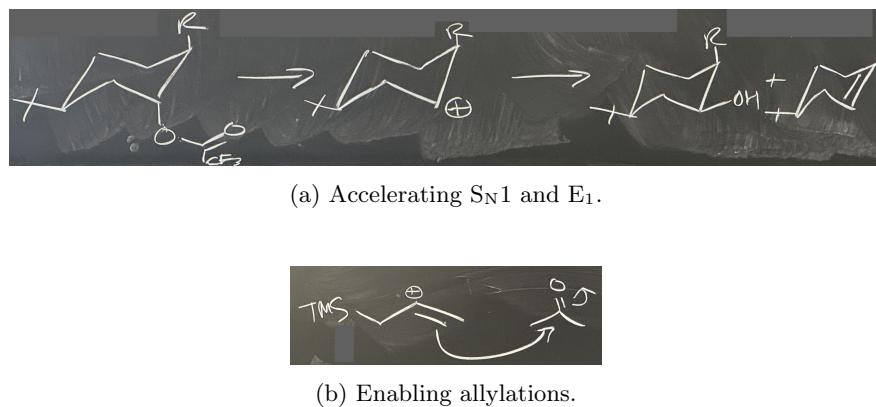
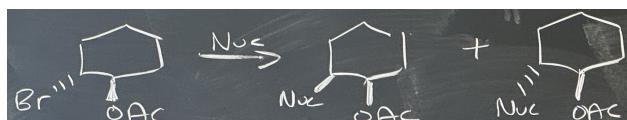


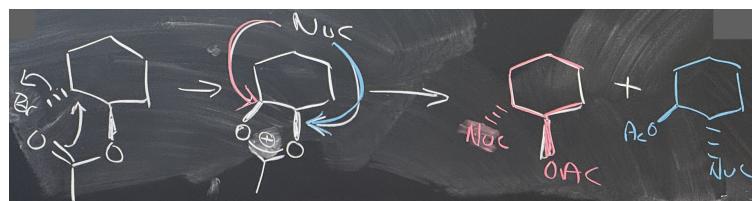
Figure 4.9: The β -silicon effect enables cationic reactivity.

- It can accelerate the departure of a leaving group by orders of magnitude (Figure 4.9a).
 - Suppose we have a trifluoroacetate leaving group on a cyclohexane ring in aqueous solution.
 - Locking F_3CCO_2^- in the axial position with an equatorial *tert*-butyl group aids departure.
 - Specifically, if $\text{R} = \text{SiMe}_3$, the anomeric effect will significantly weaken the C–O bond.
 - Once F_3CCO_2^- leaves, the reaction completes through hydration (S_N1) or elimination (E₁).
 - If $k_{\text{rel}} = 1$ when $\text{R} = \text{H}$, then $k_{\text{rel}} = 2.4 \times 10^{12}$ when $\text{R} = \text{SiMe}_3$.
 - There's a reason this effect has a name: It's huge!
- It enables allylations to happen at all (Figure 4.9b).
 - We do allylations with allyl silane because it's the only way this will work.
 - The allyl group attacks the carbonyl as a nucleophile, forming a secondary carbocation that's stabilized by the β -silicon effect at the indicated position.
 - Note that this reaction is *not* an already-formed carbocation somehow engaging in a nucleophilic attack, despite how it's drawn. Here's a helpful [reference](#) on this type of reactivity.

- Motivating the neighboring group effect.



(a) The possible products of a reaction.



(b) The mechanism of the reaction.

Figure 4.10: The neighboring group effect alters cationic reactivity.

- The reaction in Figure 4.10a is a nucleophilic substitution with an enantiopure starting material, and it has four possible product stereoisomers.
- Through which mechanisms could this reaction proceed?
 - If S_N2: We'll see 100% *syn* and 0% *anti* product because S_N2 is stereospecific.
 - The *syn* product will be enantiopure due to the stereoinverting nature of the attack.
 - If S_N1: We'll see 50% *syn* and 50% *anti*, maybe favoring *anti* a bit due to sterics.
 - Both diastereomers will be enantipure (we're not engaging the acetate's chiral carbon).
 - Observed: We get 0% *syn* and 100% *anti*, and it's a racemic mixture of the *anti* diastereomer.
- What's happening here?!
 - The acyl group is not as innocent as it seems.
 - Per Figure 4.10b, the actual mechanism begins with intramolecular displacement of the bromine to form a resonance-stabilized carbocation. This is followed by a backside attack on either carbon, hence selecting the *anti* product and inducing the racemization.
 - Conclusion: The neighboring group effect makes this reaction *trans*-selective and racemizing.
- Neighboring group effect:** The interaction of a reaction center with either an intramolecular lone pair or an intramolecular pair of π -electrons. *Also known as anchimeric assistance.*
 - Note that the intramolecular pair of π -electrons cannot be conjugated with the reaction center; that's just resonance stabilization of the carbocation then.
- Homoconjugation:** A neighboring group effect in which the neighboring group is a π -system.^[5]
- Example of homoconjugation.



Figure 4.11: Homoconjugation.

⁵This definition is consistent with the definition of homoconjugation as “an overlap of two π -systems separated by a non-conjugating group” because the carbocation counts as a π -system and the carbocation in Figure 4.11 is separated from the π -bond by one methylene group on each side.

- Essentially, the displacement of the tosyl group in Figure 4.11 is much more favorable in the molecule shown than in the saturated analog because a double bond is present nearby (in the unsaturated molecule), and its π -orbitals can donate into the carbocation.
 - Something like 5 orders of magnitude faster.^[6]
 - We're now done with carbocation stability, and we'll begin discussing their synthesis and reactivity.
 - Acidity.

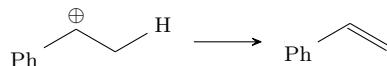
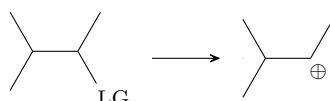
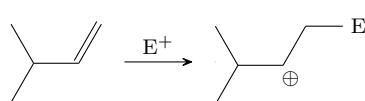


Figure 4.12: Carbocations acidify β -protons.

- Carbocations induce a dramatic acidification of β C–H bonds.
 - Indeed, the pK_a of the proton drawn in Figure 4.12 is $-14!$
 - Additionally, this reaction is just the second step in an E_1 mechanism: Adjacent deprotonation is just elimination!
 - The reaction is purely downhill thermodynamically, and adjacent deprotonation is actually a great perspective to take on E_1 .
 - Synthesis of carbocations: Two main ways.



(a) Ionization.



(b) π -activation.

Figure 4.13: Synthesis of carbocations.

1. Ionization.

- This is just the departure of a leaving group.

2. Activation of a π -system.

- Can be done by an electrophile, such as a proton, metal, etc.
 - Gives the Markovnikov adduct.

• Reactions of cations.



(a) [1, 2]-sigmatropic shift.



(b) General form of a rearrangement.

Figure 4.14: Reactions of cations.

⁶Actually 11 orders of magnitude per Wikipedia.

- Cations most typically appear in elimination (E_1) and capture/substitution (S_N1) mechanisms.
 - Once formed, cations can also do rearrangements, shifts, cyclizations, etc.
 - An important subcategory of cationic shifts is [1, 2]-sigmatropic shifts.
 - These are very common.
 - They are also very fast and very easy to do.
 - The rate of a [1, 2]-sigmatropic hydride shift is $k_{1,2} = 3 \times 10^7 \text{ s}^{-1}$, even at -139°C .
 - The activation energy $\Delta G_{1,2}^\ddagger \approx 3 \text{ kcal/mol}$, which is on the same order of magnitude as bond rotation.
 - If you want these to happen, that's great!
 - If not, you're going to need to think about explicit ways to prevent it by design because [1, 2]-shifts will happen whether or not you want them to — you can't stop it.
 - Migratory aptitude: $s > sp > sp^2 > sp^3$.
 - The probability that a substituent will shift depends on the extent to which there is *s*-character in the bonding orbital of the *mobile* group because more *s*-character leads to better orbital overlap in the transition state (Figure 4.14a).
 - Essentially, the mechanism works by taking hyperconjugation “to the extreme” to move the bond (Figure 4.14a).
 - Two final noteworthy things about shifts.
 - We have a 2-electron Huckel aromatic transition state, so it will be allowed/favored by the Dewar-Zimmerman analysis.
 - We retain the stereochemistry of the migrating group (it's a suprafacial shift).
 - There are many named rearrangements.
 - Examples include the **Wagner-Meerwein rearrangement**, **pinacol rearrangement**, and **semipinacol rearrangement**.
 - We are not a named-reactions class, so we will not discuss these much, but you can look them up if you want.
 - These are all variants on a theme, though.
 - They all follow the general form in Figure 4.14b but with different R and LG groups.
 - The naming generally depends on the *identity* of the R and LG, based on whichever chemist discovered and popularized the class.
 - Nonclassical carbocations.



(a) 3c-2e bonds.



(b) Energy diagrams.

Figure 4.15: Nonclassical cations.

- Consider two cations: The 3° *tert*-butyl cation and a 2° cation on norbornane.
 - Interestingly, HIA = 231 kcal/mol for *both* of these cations!
 - How can they both be equally stable?
 - This question led to the discovery of nonclassical 3c-2e bonds (Figure 4.15a).
 - Essentially, we can draw two no-bond resonance forms for this cation. We move one of the σ -bonds in each of these (which we're not usually supposed to do).
 - Thus, we can draw the real structure with two half bonds.

- Aside (chemis-tea): The debate as to whether the true structure of nonclassical cations was barrierless resonance or an equilibrium between two cations raged in the literature for 70 years (Figure 4.15b).
 - On team resonance: Olah (Nobel prize for this cation work), Wintsein, Schleyer, Saunder.
 - On team equilibrium: H. C. Brown (Nobel prize for unrelated work).
 - Brown just thought this was due to poor techniques.
 - They would go to conferences, sit in the front row, yell at each other; publish snarky papers at each other.
 - Debate era: 1940s-2010s.
 - The debate ended at Science, 2013, 62 with an X-ray structure of the nonclassical cation (which really supported the resonance team). Unfortunately, H.C. Brown died in 2004. Anybody who knew Brown said he wouldn't have accepted this either.
 - “One would have thought that the application of careful experiment and intelligent thought would lead to a rapid solution to the [nonclassical carbocation] problem. This has not been the case” - Brown’s book.
 - Until they could prove the structure of one or both, we couldn’t know. This really drove the development of spectroscopy, NMR, low-temperature analysis of exotic species, etc. Essentially, people work hard when their ego is at stake.
- Takeaway from our discussion of nonclassical cations: Cations exist on a spectrum.

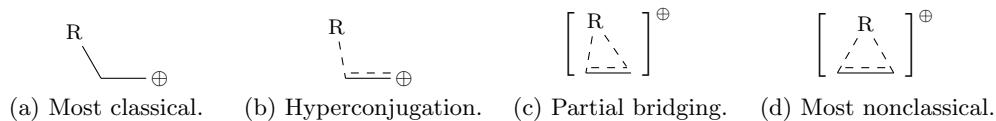


Figure 4.16: A spectrum of cations.

- Most classical: Discrete, trivalent, trigonal carbocations.
 - These rarely exist.
- Next step: Hyperconjugation and resonance.
 - This accounts for most carbocations.
- Next step: Some kind of bridging but asymmetric carbocation.
 - There are some examples.
- Most nonclassical: Bridging, symmetric carbocations (3c-2e).
 - These have to be special cases, such as the norbornane one.

4.2 Anions

9/26:

- Lecture 6 recap: Modes of cation stabilization.
 - Heteroatoms: Through lone-pair resonance.
 - Anchimeric assistance: With neighboring lone pairs (Figure 4.10b).
 - Homoconjugation: With nearby π -electrons (Figure 4.11).
 - Hyperconjugation: With adjacent σ -bonding orbitals. (Figure 4.6a).
- Announcements.
 - Don’t cheat on the PSet.
 - You can probably find papers or the key online, but be responsible academics instead.
 - PSets give you a chance to engage with the material; you will not learn if you cheat.
 - Ask for help if you can’t make the deadline.

- Today: Anions.
 - Lecture outline.
 - Acidity.
 - Gas phase.
 - Solution phase.
 - pK_a 's.
 - Common ones.
 - Solvent effects.
 - Misc. influencing factors.
 - Anion structure and inversion.
 - Synthesis of carbanions.
 - Reactions of carbanions.
 - Kinetic vs. thermodynamic acidity.
 - Thermodynamic stability of an anion.
 - **Acidity** (gas phase): The extent to which anions want to bind a proton in the gas phase. *Given by*
- $$\text{R}-\text{H} \rightleftharpoons \text{R}^- + \text{H}^+ \quad \Delta H^\circ = \text{acidity}$$
- Similarities between this definition and that of the HIA!
 - Acidity is also always measured in the gas phase.
 - It is also more useful as a measure of relative stability.
 - Trends in (gas-phase) acidity are not always the same in solution.
 - Example gas-phase acidities.

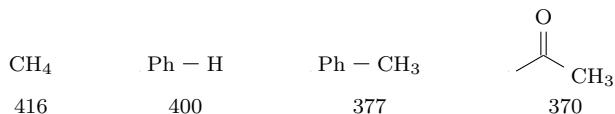


Figure 4.17: Gas phase acidity examples.

- We can intuitively rationalize these with resonance/EWG stabilization of the conjugate base.
 - **Acidity** (solution phase): The extent to which anions want to bind a proton in the solution phase. *Given by*
- $$\text{R}-\text{H}_{(\text{aq})} \rightleftharpoons \text{R}_{(\text{aq})}^- + \text{H}_{(\text{aq})}^+ \quad pK_a = \text{acidity}$$
- A refresher on what exactly “ pK_a ” means.
 - The dissociation of an Arrhenius acid (exemplified by the above chemical equation) obeys the following mass action expression, where K_a is the **dissociation constant**.

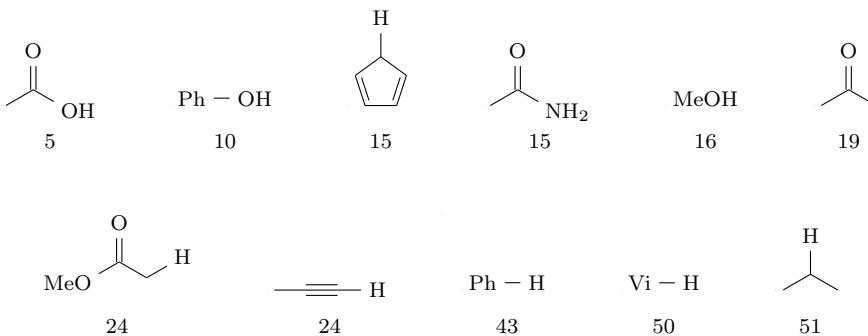
$$K_a = \frac{[\text{R}_{(\text{aq})}^-][\text{H}_{(\text{aq})}^+]}{[\text{RH}_{(\text{aq})}]}$$

- To look at the K_a 's in more human-readable units, we transform them to a log scale using the **p function**:

$$pK_a = -\log K_a \approx \Delta G$$

- Solution-phase acidity is a quantitative measure of anion stability.

- Some pK_a 's to know. (Memorize these!! These are the baseline, and they are a common qual question.).



- These are all measured in H_2O .
- These all come from the [Evans \$pK_a\$ table](#).^[7]
- We should bookmark this page and refer to it regularly when we're trying to work out plausible mechanisms!!
- Solvent effects on the pK_a .

R–H	pK_a (H_2O)	pK_a (DMSO)
H–Cl	–8	1.8
PhCOOH	4.2	11.1
CH ₃ NO ₂	10	17.2
H ₂ O	15.7	32
H ₃ CCN	25	31.3
CH ₂ (CN) ₂	11	11

Table 4.2: pK_a 's in H_2O vs. DMSO.

- The pK_a of H_2O is about 15, so it is hard to get accurate measurements in H_2O for anything less acidic (higher pK_a).
- One solution to this problem is to use DMSO as an alternate solvent.
 - The pK_a of DMSO is ≈ 35 .
 - This allows you to characterize a greater range of things.
 - DMSO is also very polar (like water), minimizing conflicting aggregation effects.
- All data on DMSO acidity comes from the [Bordwell \$pK_a\$ table](#).
- pK_a 's are typically higher in DMSO than in water, as we can see in Table 4.2.
 - This is because H_2O is better at anion stabilization than DMSO, so the equilibrium is easier to access.
 - The trends are not always consistent, e.g., CH₂(CN)₂.
 - When pK_a s are similar in different solvents, this tends to be because the anion is being stabilized internally.
 - For example, the (CN)₂HC[–] anion is stabilized by both resonance and σ -EWG inductive effects. Since it is internally stabilized, its stabilization is less dependent on solvent effects.

⁷Not all of Masha's values match the Evans table (e.g., cyclopentadiene is 18.0, not 15). Whose value should we memorize??

- Factors influencing a compound's solution-phase acidity.

1. Electronegativity.

- More electronegative atoms make acids stronger.
 - This is because electronegative atoms inductively (i.e., through the σ -network) withdraw electron density, stabilizing the negative charge through delocalization.
 - Example: HOAc and TFA have $pK_a = 4.76$ and 0.52, respectively.

2. Hybridization.

- More s -character leads to a stronger acid.
 - Essentially, orbital electronegativity (and hence stability) decreases $s > sp > sp^2 > sp^3$.
 - This is because p -orbitals "feel" the δ^+ nuclear charge less, owing to their node at the nucleus. Therefore, s -orbitals are a better place for δ^- charge to reside in.
 - Example: ---H , Ph-H , and ${}^i\text{Pr-H}$ have $pK_a = 24$, 43, and 51, respectively.
 - This effect also extends to nitrogen.
 - Example: Protonated imines are more acidic than protonated amines because their conjugate bases (the neutral imine and amine) have lone pairs in sp^2 vs. sp^3 orbitals.
 - Example: Piperidine is more basic than pyridine because its lone pair is in a relatively destabilized sp^3 orbital.
 - Good qual question: Use a hybridization argument to differentiate basicities/acidities!!

3. Delocalization and aromaticity.

- A more delocalized anion means a stronger acid.
- Example: Cyclopentadiene and cyclopropene have $pK_a = 15$ and 61 because the former deprotonates to an aromatic anion and the latter deprotonates to an antiaromatic anion.

4. Orbital overlap with adjacent atoms.

- Donation into adjacent d - or σ^* -orbitals stabilizes anions.
- Example: $\text{R}_3\text{P}^+ - \text{CH}_2^-$.
 - This ylide has a relatively stable anion.
 - Ylides are especially stable when the adjacent atom is S or P; such ylides are synthetically useful (e.g., Swern oxidation and Wittig olefination).

- Anion structure.

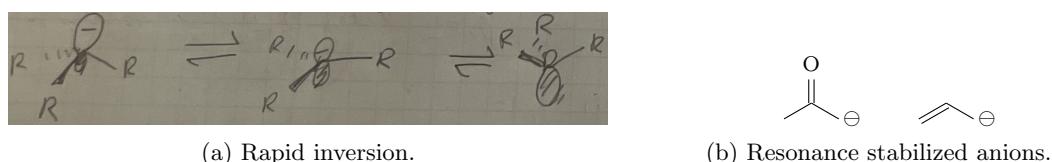


Figure 4.19: Anion structure.

- In general, anions are sp^3 -hybridized, trigonal pyramidal species.
 - Recall that Figure 2.5 explains why anions are trigonal pyramidal instead of planar.
- Inversion is possible through a trigonal planar structure (Figure 4.19a).
 - The inversion barrier for carbanions is an *extremely* low 1-2 kcal/mol.
 - Because of this rapid inversion, anions behave as if they are planar even though they are not!
- Exception: Resonance stabilized anions are *actually* planar (Figure 4.19b).
 - This is because in these cases, the negative charge localizes to a p -orbital to have better overlap with the π -system with which it resonates.
 - This gives the carbanion atom an orbital structure of $sp^2 + p$.

- Some factors can raise the inversion barrier.
 1. Geometric constraints (i.e., incorporation into a small ring) raise the inversion barrier.
 - The planar structure of the ring requires some bond angles (e.g., between the anion lone pair and a substituent) to be larger than in the pyramidal structure.
 - Example: The cyclopropanide anion.
 2. More electronegative substituents raise the inversion barrier.
 - VBT explanation.
 - Electronegative groups prefer to bind to orbitals with more *p*-character (**Bent's rule**) since it's easier to "steal" those electrons because they're further from the nucleus.
 - MO theory explanation.
 - Consider the **D**-MO in Figure 2.5, which is the HOMO for an anion.
 - In the pyramidal structure, the *p*-AO in **D** will hybridize into an *sp*³-orbital, shedding some of its *p*-character. But per the "conservation of bonding character" discussed in Figure 2.14, this *p*-character will infuse the bonds to the (now electronegative) substituents.
 - Electronegative substituents then want this influx of *p*-character, lowering the energy.
 - Is this it, or am I missing something else??
- Other XR₃ structures with 8 electrons.
 - Consider H₃C⁻, H₃N, F₃N, and H₃P.
 - Their respective inversion barriers are 1-2 kcal/mol, 5 kcal/mol, 50 kcal/mol, and 35 kcal/mol.
 - Thus, H₃C⁻ and H₃N are effectively planar, and F₃N and H₃P are pyramidal.
 - F₃N is pyramidal due to its electronegative substituents.
 - H₃P is pyramidal due to the HOMO of P being even more stabilized by its larger 3*p*-orbital.
 - Implication: We can have chirality at P, but rarely at N.
- Synthesis of carbanions: Two main ways.

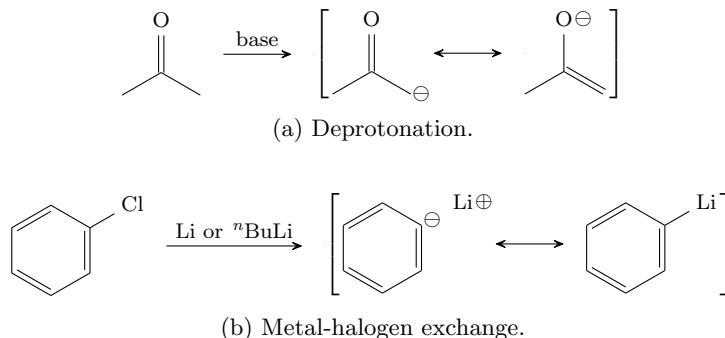


Figure 4.20: Synthesis of carbanions.

- A carbanion created by base deprotonation typically must be stabilized (e.g., by resonance).
- Metal-halogen exchange is typically used to create aryl, vinyl, and primary alkyl anions.
- Proton transfer and lithium-halogen exchange are among the fastest *intermolecular* reactions common in organic chemistry.
 - Some *intramolecular* reactions can be faster, e.g., 1,2-hydride shifts.
 - It is important to know such relative rates for reaction planning.
 - Caveat: Proton transfer from heteroatoms is much faster than proton transfer from carbon ($k_{\text{rel}} \approx 10^6$). This is why we often talk about acidic X-H bonds, e.g., RCOOH.
- Note: B-H bonds are **hydridic** (think inorganic), not protic??

- Reactions of carbanions.

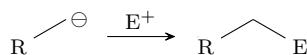
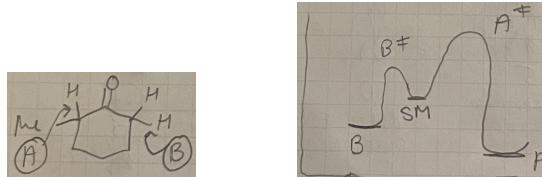


Figure 4.21: Reactions of carbanions.

- Anions are nucleophilic and basic.
- They react with electrophiles, such as protons and metals.
- Kinetic vs. thermodynamic acidity.



(a) Two deprotonation sites. (b) The energy diagram.

Figure 4.22: Energy differences governing kinetic and thermodynamic acidity.

- Rate of deprotonation varies based on whether our base attacks site A or B (Figure 4.22a).
- Site B has less steric clutter, so deprotonation is easier there.
 - This ease of deprotonation manifests as a lower energy B^\ddagger relative to A^\ddagger (Figure 4.22b).
 - To form this enolate, we should use a base such as LDA that is sterically bulky and has essentially irreversible deprotonation, so we will be under kinetic control.
- On the other hand, **Zaitsev's rule** tells us that the tetrasubstituted enolate we obtain by deprotonating at site A is more thermodynamically stable than the trisubstituted one we obtain by deprotonating at site B.
 - This difference in thermodynamic stability manifests as a lower energy A relative to B (Figure 4.22b).
 - To form this enolate, we should use a base such as an amine or alkoxide that has reversible deprotonation, so we eventually form the thermodynamic product.
- Great explanation of this phenomenon in Figures 5.3-5.7 (esp. Figures 5.5-5.6) of Labalme (2024c).
- **Zaitsev's rule:** The more substituted alkene is the more stable one.

Week 5

Misc. Reactive Intermediates

5.1 Radicals

- 10/1:
- Lecture 7 recap.
 - Anion formation: $\text{R}-\text{H} \rightleftharpoons \text{R}^- + \text{H}^+$.
 - pK_a 's are a measure of anion stability.
 - Anions are stabilized by...
 - Electronegative substituents (that withdraw electron density);
 - More *s*-character (to hold the negative charge closer to the positive nucleus);
 - Delocalization/resonance (to spread out the negative charge);
 - Orbital overlap with adjacent atoms (along the lines of reverse hyperconjugation, e.g., in the case of ylides).
 - Anions are pyramids with low inversion barriers, and hence are effectively planar.
 - Today: Radicals.
 - Lecture outline.
 - Structure of radicals.
 - Stability of radicals (thermodynamic and kinetic).
 - Bond dissociation energy.
 - Synthesis of radicals.
 - Radical reactions.
 - Probing radical mechanisms: Radical clocks, traps, and cages.
 - Radical ions.
 - Structure of radicals.

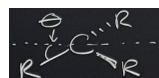
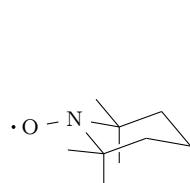


Figure 5.1: Angle of deviation from planarity.

- Most radicals are shallow pyramids with small inversion barriers (< 5 kcal/mol).
 - The methyl radical ($\cdot\text{CH}_3$) is planar by ~ 10 kcal/mol.
 - Recall the discussion of its QMOT diagram (Figure 2.5)!

- As with anions, electronegative substituents raise the inversion barrier.
 - For example, the trifluoromethyl radical ($\cdot \text{CF}_3$) is pyramidal.
- Increasing sterics favor pyramidalization (more p -character)?? Wouldn't bulky groups push apart?
- Consider the angle of deviation θ from planarity.
 - The ethyl radical (1°) has $\theta = 11.9^\circ$.
 - The isopropyl radical (2°) has $\theta = 18.6^\circ$.
 - The isobutyl radical (3°) has $\theta = 24.1^\circ$.
- Thermodynamic stability of radicals.
 - Delocalization stabilizes radicals.
 - Delocalization with neighboring heteroatoms is especially stabilizing!
 - Hyperconjugation stabilizes radicals.
 - Thus, in terms of decreasing stability, $3^\circ > 2^\circ > 1^\circ$.
 - This is analogous to cations.
 - More p -character stabilizes radicals.
 - Thus, in terms of decreasing stability, $p > sp^3 > sp^2 > sp > s$.
 - This is because radicals are inherently electron deficient, so they want to be further from the δ^+ nucleus.
 - This is the opposite of anions!
 - Alternatively: The more s -character, the stronger the bond, and hence the less stable the radical formed by homolytic bond cleavage.
 - We'll formalize this notion with **BDEs** in just a moment.
 - More electronegative atoms destabilize the radical center.
 - Thus, in terms of decreasing stability, $\cdot \text{C} > \cdot \text{N} > \cdot \text{O}$.
 - Larger atomic size stabilizes radicals.
 - Thus, in terms of decreasing stability, $\cdot \text{S} > \cdot \text{O}$.
 - This is because larger atoms are more polarizable.
- Kinetic stability of radicals.
 - Consider a relatively stable radical, such as one that has some resonance stabilization. Suppose we add some steric blocking to it. This yields a **persistent radical**.
- **Persistent radical:** A kinetically stable radical that may even be shelf-stable.
 - These are not thermodynamically stable: It's still a radical, so it doesn't want to exist. But it just won't react with anything.
 - Classic example: **TEMPO**.
 - Persistent radicals are useful for radical traps and other experiments discussed later this lecture.
- **(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl:** A common persistent radical. *Also known as TEMPO.*
Structure



(a) Structure.

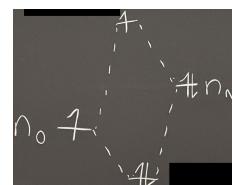
(b) $\text{N}-\text{O}\cdot$ molecular orbitals.

Figure 5.2: TEMPO.

- Formed by oxidizing 2,2,6,6-tetramethylpiperidine (TMP), a sterically hindered organic base, with H_2O_2 in the presence of the tungstate anion (WO_4^{2-}).
- Check: TEMPO *does* have both resonance stabilization (with the adjacent nitrogen heteroatom) and steric blocking (from the adjacent quaternary carbons).
- The MO diagram (Figure 5.2b) reveals that the $\text{N}-\text{O}\cdot$ bond is an example of a 2c-3e bond.
- The **spin density map** shows that the radical is evenly dispersed on O and N: 50% radical density on O and 50% on N.
- Takeaway: If you want to design your own persistent radical, take something with some resonance, add some steric blockers, and you're good to go!

- **Bond dissociation energy:** The energy it takes to symmetrically break a chemical bond. *Also known as BDE. Given by*



- Observe that this definition is analogous to those of HIA and $\text{p}K_a$ from the past two lectures!
- X and Y can be organic groups, hydrogen, heteroatoms, etc.
- The above reaction denotes **homolytic** bond cleavage, as opposed to **heterolytic**.
- BDE is an extremely useful measure of “bond strength.” It’s probably one of the top three key concepts we should take away from Phys Orgo to use in the rest of our careers.
 - Guideline: A weak bond yields a more stable radical.
 - BDE is useful for predicting if a reaction is endothermic or exothermic.
 - One big factor that affects BDE is bond polarity.
 - In general, more polar bonds are stronger.
 - This contrasts with heterolytic cleavage, where polar bonds are easier to cleave.
 - Essentially, acidic bonds are “stronger” even if it’s easier to take off the acidic proton with your own “hands” (reagents) in lab.
 - See Table 5.1 for more.
 - Key point: When we talk about “strong bonds,” just remember that we’re talking about the BDE.

- **Homolytic** (bond cleavage): The breaking of a chemical bond in such a way that an *equal* amount of electron density is left on both products.
- **Heterolytic** (bond cleavage): The breaking of a chemical bond in such a way that an *unequal* amount of electron density is left on both products.
- Let’s look at some example comparisons between $\text{p}K_a$ ’s and BDE’s to see the aforementioned inverse relationship.

	$\text{H}_3\text{C}-\text{H}$	$\text{H}_2\text{N}-\text{H}$	$\text{HO}-\text{H}$	$\text{F}-\text{H}$
$\text{p}K_a$ (H_2O)	48	38	15.7	3.2
BDE (kcal/mol)	105	107	119	135

Table 5.1: BDEs and $\text{p}K_a$ ’s are inversely related.

- As we go to the right, it becomes easier to remove H^+ .
- As we go to the left, it becomes easier to remove $\text{H}\cdot$.

- Some BDEs to know. (Memorize these!! They will likely come up in your Quals!)
 - The effect of bond polarity.
 - C–C: ~ 81 kcal/mol.
 - C–H: ~ 98 kcal/mol.
 - O–H: ~ 105 kcal/mol.
 - The effect of hyperconjugation.
 - Me–H: ~ 105 kcal/mol.
 - Et–H: ~ 100.5 kcal/mol.
 - i Pr–H: ~ 98.1 kcal/mol.
 - t Bu–H: ~ 95.7 kcal/mol.
 - The effect of hybridization.
 - $\text{RC}\equiv\text{C}-\text{H}$: ~ 132.8 kcal/mol.
 - $\text{R}_2\text{C}=\text{CH}-\text{H}$: ~ 111.2 kcal/mol.
 - Ph–H: ~ 112.9 kcal/mol.
 - The effect of resonance.
 - All–H: ~ 88.2 kcal/mol.
 - Bn–H: ~ 88.5 kcal/mol.
 - Note that allyl bonds are broken more easily than benzyl ones because resonance stabilizing the product radical doesn't force you to break aromaticity; indeed, breaking aromaticity is a little less fun than moving a π -bond around.
 - The effect of atomic size and polarizability.
 - Me–I: ~ 57.1 kcal/mol.
 - Me–Br: ~ 70.3 kcal/mol.
 - Me–Cl: ~ 83.7 kcal/mol.
 - Me–F: ~ 110.0 kcal/mol.
 - Peroxides.
 - HO–H: ~ 119 kcal/mol.
 - HO–OH: ~ 51 kcal/mol.
 - t BuOO–H: ~ 88 kcal/mol.
 - t BuO–OH: ~ 44 kcal/mol.
 - t BuO–H: ~ 106 kcal/mol.
- Polar effects on radicals.

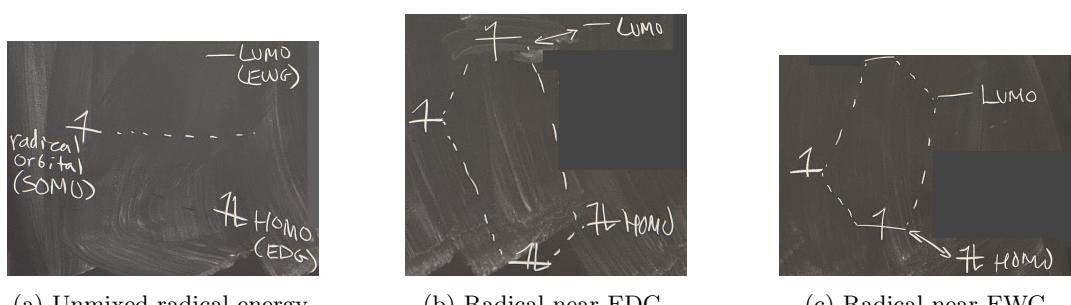


Figure 5.3: Radicals near EDGs and EWGs.

- Both EDGs *and* EWGs can stabilize radicals, despite the fact that radicals are electron deficient.
- Example: A radical α to a carbonyl (e.g., homolytically cleave one of acetone's C–H bonds).
 - The carbonyl *will* destabilize the radical inductively.
 - However, it *will* also *stabilize* the radical through resonance.
 - The second effect (resonance) is stronger.
- Let's now justify these stabilizing effects using MO theory.
 - Before mixing (Figure 5.3a), a typical radical has energy intermediate between the HOMO of an EDG and the LUMO of an EWG.
 - When a radical's SOMO interacts with the HOMO of an EDG (Figure 5.3b), *two* electrons get stabilized and *one* gets destabilized. It follows that there is a net stabilization of the molecule, as expected.
 - When a radical's SOMO interacts with the LUMO of an EWG (Figure 5.3c), the sole electron present in the system gets stabilized. It follows that there is *still* a net stabilization of the molecule, even here!
- These molecular orbital diagrams reveal two additional attributes of polarized radicals, as well.
 1. EDGs make radicals more nucleophilic.
 - When a radical's SOMO interacts with the HOMO of an EDG (Figure 5.3b), a new radical SOMO (the antibonding orbital) is created.
 - This new SOMO is a better energy match with LUMOs, so the radical electron is more likely to mix with a LUMO since this will lead to greater thermodynamic stabilization of the product than before.
 - In other words, the radical is now more nucleophilic.
 2. EWGs make radicals more electrophilic.
 - When a radical's SOMO interacts with the LUMO of an EWG (Figure 5.3c), a new radical SOMO is once again created, but it is the stabilized bonding orbital this time.
 - This new SOMO is a better energy match with HOMOs, so the radical electron is more likely to mix with a HOMO since this will lead to greater thermodynamic stabilization of the product than before.
 - In other words, the radical is now more electrophilic.
- Synthesis of radicals.
 - Also known as **initiation**, if we're doing a radical chain reaction.
 - Most common way to make a radical: Homolytic cleavage of a weak bond.
 - We'll often use light or heat to give a little burst of energy and break this bond.
 - Commonly used radical initiators.
 - Peroxides are easily broken by light and heat, so we often use them.
 - Example: Organic peroxides react like $\text{RO}-\text{OR} \xrightarrow[\Delta]{h\nu} \text{RO}\cdot$
 - AIBN.
 - Br_2 .
 - Bromine reacts like $\text{Br}-\text{Br} \xrightarrow[\Delta]{h\nu} \text{Br}\cdot$
 - Paramagnetic metals, i.e., metals with 1 unpaired electron.
 - Example: $\mathbf{Cp_2Ti^{III}Cl}$.
 - Single-electron transfer (SET) or energy transfer (ET).
 - Often done with metals, electrochemistry, or photochemistry.
 - These are increasingly common ways to cycle one-electron oxidation states.
 - Essentially, if we ever need to make a radical, we can choose old-school or new-school based on what we have on hand!

- **Azobisisobutyronitrile:** A common thermal radical initiator. *Also known as AIBN.*



Figure 5.4: AIBN as a thermal radical initiator.

- This radical has a very cool design: Under heat or shock, you cleave the N–C bonds to form tertiary radicals that are additionally stabilized by their proximity to a π -system, and release N_2 .
- You commonly see AIBN used with HSnBu_3 in radical cyclizations.
- **Titanocene monochloride:** An increasingly popular SET agent. *Denoted by $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$.*

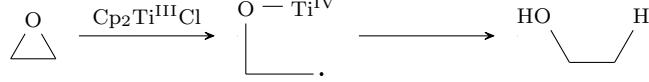


Figure 5.5: $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ as an SET radical initiator.

- For example, $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ can be used for radical-mediated epoxide openings, as shown above.
- Radical reactions.

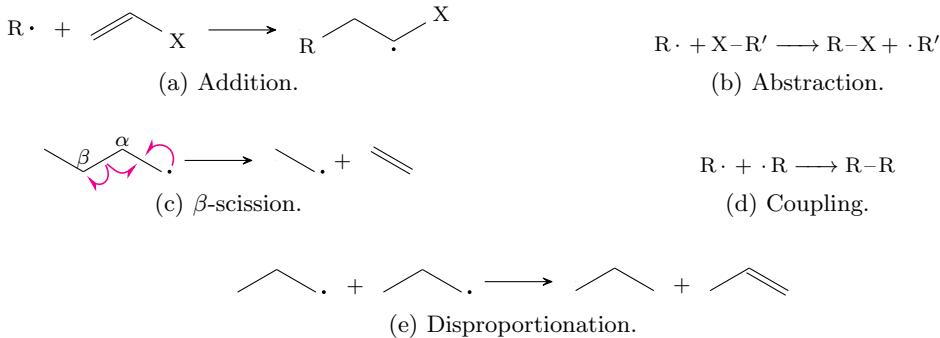


Figure 5.6: Radical reactions.

- Addition to multiple bonds (Figure 5.6a).
 - This can lead to cyclization, quenching, propagation, etc.
 - If it's a cyclization, we follow **Baldwin's rules**.^[1]
- Abstraction (Figure 5.6b).
 - X is a halogen or hydrogen.
- β -scission and fragmentation.
 - In general, β -scission refers to breaking the chemical bond between the carbons α and β to the radical.
 - Fragmentation can be interpreted more broadly.
 - Example: The second step in the cleavage of benzoyl peroxide would count as fragmentation. Formally, this is called **radical decarboxylation**.
- Radical chain propagation.
 - This occurs by one of the above mechanisms.

¹These rules are not covered in this course, but basically, they tell us which radical cyclizations are allowed.

- Polymerization.
 - If this is our goal, great! Radical chain reactions are great for making polymers.
 - If this is not our goal, it's a common side reaction for which we need to watch out.
- Radical coupling/dimerization, i.e., a **termination** step.
 - Two radicals form a bond.
 - ΔH is always negative (from an enthalpic point of view), but sterics can prevent this as with persistent radicals.
- Disproportionation.
 - A reaction in which two radicals form two nonradical products.
 - This is another possible termination step.
- **Barton deoxygenation.**

- **Radical decarboxylation.**

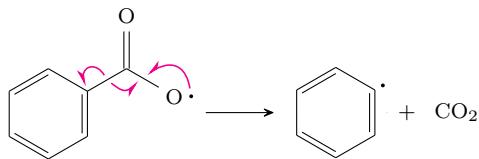


Figure 5.7: Radical decarboxylation.

- Radical decarboxylation can help us generate unstable radicals.
- For example, $\text{Ph}\cdot$ isn't too stable normally, but we will form it under radical decarboxylation conditions regardless because CO_2 is a really good leaving group. Basically, CO_2 helps the thermodynamics work out.
- **Barton deoxygenation.** A method of deleting hydroxyl groups. *Also known as Barton-McCombie deoxygenation.*

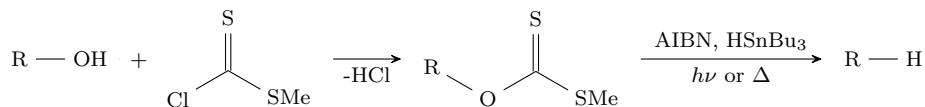


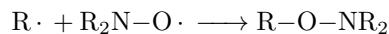
Figure 5.8: Barton-McCombie deoxygenation.

- Masha wanted to include this one named reaction, even though named reactions are not our focus in this class.
- Essentially, we react an alcohol to form a xanthate ester and then cleave it off with radicals.^[2]
- David: Why would you ever choose to use a thermal initiator over a photochemical one?
 - Practically speaking, chemical initiators can be a bit easier to work with in lab because with photochemical, you have to find the exact right wavelength that will activate our initiator and do nothing else in our reaction.
- Radical **clocks** and **traps**.
 - This is the first of many mechanistic experiments we'll cover in this class, so take note of it in case you want to use it in your final project (the mechanistic proposal)!!
 - Radical clocks and traps both test for the presence of radical intermediates.

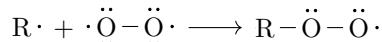
²See 5.47 notes for a mechanism.

- **Radical trap:** A species (often a persistent radical) that can quickly sequester a radical intermediate.

– Example: If we add TEMPO ($\text{R}_2\text{N}-\text{O}\cdot$) to our reaction mixture, any radical intermediate $\text{R}\cdot$ that is formed in solution is likely to react with TEMPO to form a **TEMPO adduct** as follows.



– Example: Per MO theory, O_2 is a ground-state triplet diradical, so it can interact with $\text{R}\cdot$ and form the peroxide as follows.



– Interpret the results of a radical trap experiment with caution — they can't be the basis of our whole argument that something is a radical mechanism; they are just a good first piece of evidence.

- **Radical clock:** A reaction with a known (fast) rate that is used to benchmark a radical reaction of interest.

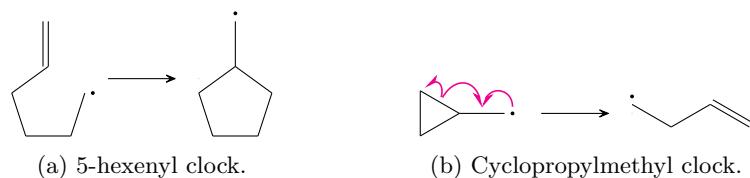


Figure 5.9: Radical clock reactions.

– Method: Synthesize an analogue of your substrate with a certain functional group attached such that if a radical is formed at a certain site, it will react with your new functional group instead of doing the designed reactivity.

– Example: Enable the formation of a 5-hexenyl radical so that it can do a **5-exo-trig cyclization**.^[3]

■ The rate of this reaction is $k = 2.3 \times 10^5 \text{ s}^{-1}$.

– Example: Enable the formation of a cyclopropylmethyl radical so that it can do a radical ring opening and form an olefin.

■ The rate of this reaction is even quicker: $k = 9.4 \times 10^7 \text{ s}^{-1}$.

■ This is gold standard for a mechanistic experiment to prove radical mechanisms.

– These are very common kinetic probes for mechanisms!

- Another mechanistic experiment: The **radical cage effect**.

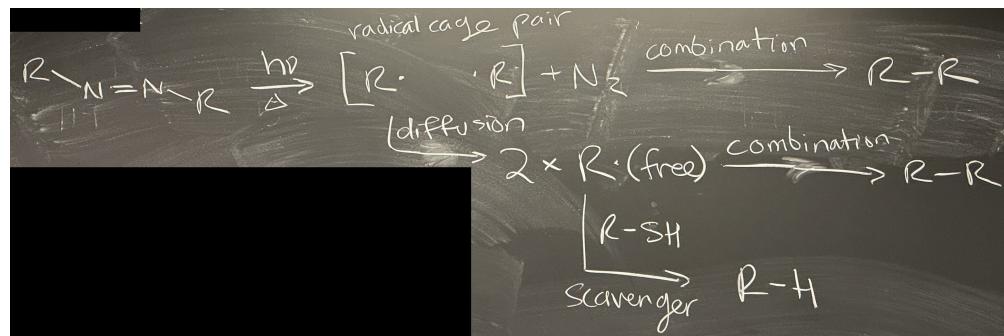


Figure 5.10: Radical cage effect.

³This is a type of radical cyclization allowed by Baldwin's rules.

- Consider a radical initiator of the form R-N=N-R.
 - When it decomposes — either thermally or photochemically — it will form two radicals that are in very close proximity to each other in solution.
 - We call these two radicals a **radical cage pair**, where the “cage” is the surrounding solvent molecules.
 - These radicals can easily recombine within the cage in a radical coupling/dimerization reaction to form R-R.
 - However, they can also diffuse out of the cage, drifting apart to yield 2 R· in solution.
 - These “free” radicals can then combine again to form R-R.
 - Or, alternatively, they can interact with a radical scavenger (such as a thiol^[4]) in solution.
 - Notes on the cage effect.
 - A more viscous solvent makes it harder to escape the cage.
 - A scavenger can differentiate pathways.
 - Stereoretentive radical reactions can occur within a radical cage, because combination within the cage can outcompete stereoinversion.
 - However, if you diffuse out of the cage, forget it.
 - Takeaway: Cages can have stereochemical consequences, such as retention.
 - I need to do more reading on this and figure out exactly what I’m responsible for here!!
- Radical anions and cations.

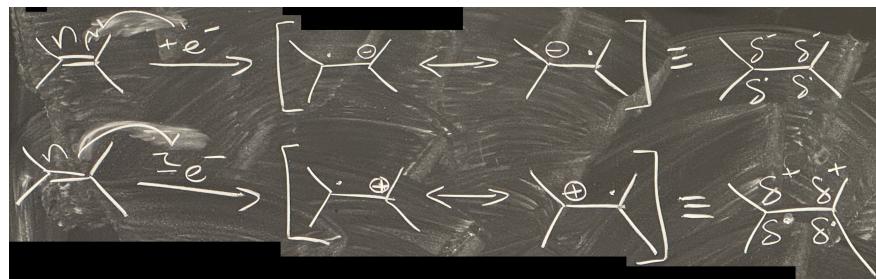


Figure 5.11: Radical ion formation and structure.

- Start with a π -system.
 - When we add an electron to the π -system or subtract one from it, we form a radical ion.
 - These radical ions exist in resonance with each other, giving us partial radical and ion character at both sides of the π -system.
 - Example of radical cations: Mass spec.
- Radical ions are common in aromatic rings.

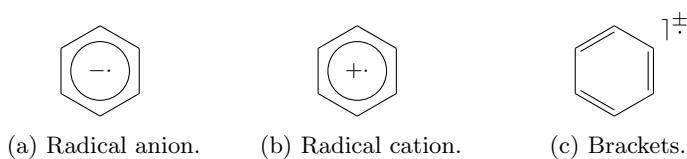
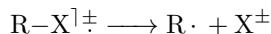


Figure 5.12: Aromatic radical ion notation.

⁴ Alison Wendlandt uses thiols (such as adamantane thiol, AdSH) as HAD sources in her research!

- As such, we have a special notation for them.
 - Use a circle for the π -system, and then write “ \pm ” in the center.
 - Alternatively, we can write the “ \pm ” and “ \cdot ” on top of each other outside a bracket surrounding the species.
- Example of aromatic radical anions: The Birch reduction. See Labalme (2024b).
- Radical ions can undergo **mesolytic cleavage** to generate a radical plus an ion.



- This is what happens in mass spec!
- It’s actually a common phenomenon, even though we often don’t think of it in that much detail.
- Example of radical ions: A plug for using these species in catalysis.

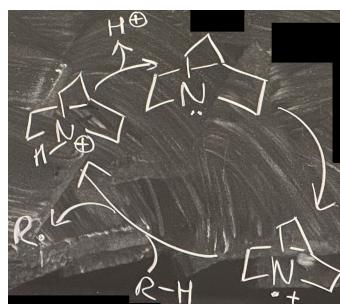


Figure 5.13: Catalysis with radical ions.

- Quinuclidine forms a radical cation, reacts with $\text{R}-\text{H}$ to form $\text{R}\cdot$ and quinuclidinium via an H-atom abstraction (HAA) pathway, and then can reform quinuclidine by loss of a proton. The $\text{R}\cdot$ then goes on to do cool stuff.
- Here, quinuclidine is used as a catalytic initiator!
- Reference: Le et al. (2017).

5.2 Carbenes

10/3:

- Lecture 8 recap.
 - Radicals are shallow pyramids with low inversion barriers.
 - They are stabilized by hyperconjugation and resonance.
 - They are destabilized by electronegative atoms and s -character since they are electron deficient.
 - π -EWGs stabilize radicals *and* make them electrophilic.
 - On the other hand, σ -EWGs (e.g., nearby halogens) *only* destabilize radicals.
 - EDGs stabilize radicals and make them nucleophilic.
 - You can make persistent radicals (i.e., radicals that *persist* over long timeframes/are kinetically stable) by using bulky steric blocking groups to prevent dimerization.
 - Recall that persistent radicals are still not thermodynamically stable.
- Today: Carbenes.
 - This is the last lecture in our “reactive intermediates” series.

- Lecture outline.
 - Orbital structure of carbenes (i.e., the origins of singlet vs. triplet states).
 - Substituent effects on carbene stability and state.
 - Synthesis of carbenes.
 - Carbene reactivity.
 - How carbene orbitals determine the transition-state angle of approach.
- Recall the Walsh diagram for CH_2 .

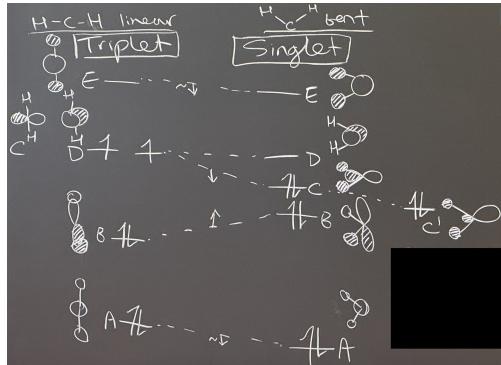


Figure 5.14: Walsh diagram for CH_2 .

- Masha redraws Figure 2.6, but adds a higher-energy **E** orbital that is antibonding.
 - We will soon see that this **E** orbital is the LUMO of a so-called “triplet carbene.”
 - The **E** orbital also goes down in energy slightly when the carbene is bent.
 - Additional change from Figure 2.6: Per QMOT Rule 7 in Anslyn and Dougherty (2006), **C** also goes down a bit more to **C'** via secondary mixing and hybridization to an “ sp^2 -like” orbital.
 - Populating 6 electrons gives us a triplet diradical for linear, and a singlet for bent.
 - The sp^2 -like **C'** ends up being our HOMO for singlet carbenes!
 - Sergei: Why don't secondary bonding interactions stabilize **D**?
 - Because the hydrogen orbitals are in the nodal plane of the constituent p -orbital, so they don't participate in this MO.
 - It's probably a symmetry thing.
 - **Multiplicity:** The following number, where S is the sum of the electron spins m_s . *Given by*
- $$2S + 1$$
- Example: All electrons are paired, save two electrons with parallel spins as in the linear carbene.
 - $S = 1/2 + 1/2 = 1$, so the multiplicity is $2(1) + 1 = 3$. We call this a “triplet.”
 - Example: All spins are paired as in the bent carbene.
 - $S = 0$, so the multiplicity is $2(0) + 1 = 1$. We call this a “singlet.”
 - This proves that our linear form is a **triplet carbene** and our bent form is a **singlet carbene**.
 - **Triplet** (carbene): A carbene with two unpaired electron spins. *Denoted by T.*
 - **Singlet** (carbene): A carbene with all electron spins paired. *Denoted by S.*

- Why would we favor a singlet carbene over a triplet, or vice versa?
 - It comes down to Hund's rule: We pay an energetic penalty for pairing electrons, and we pay an energetic penalty for putting electrons in higher orbitals, so we'll pay whichever is less.
 - Implication: As **C** and **D** get close in energy, we favor the triplet; as **C** and **D** get further apart, the singlet is favored.
- The **C'** and **D** orbitals in singlet and triplet carbenes.

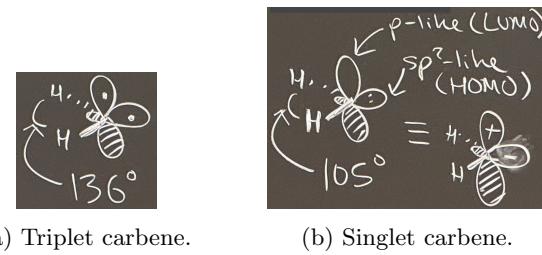
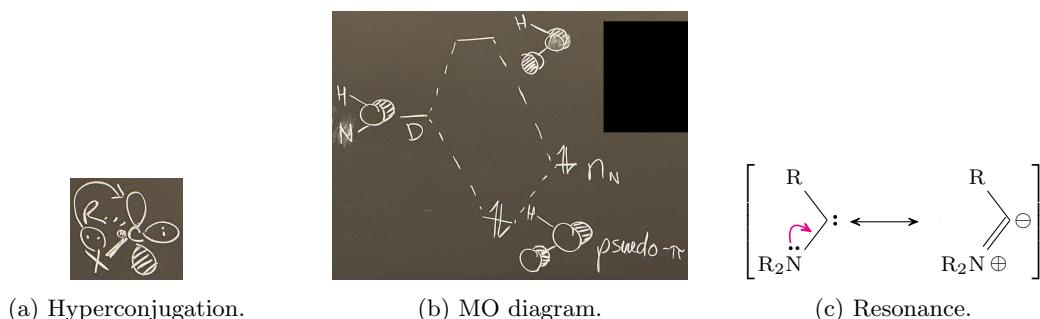


Figure 5.15: Singlet vs. triplet carbene orbitals.

- As we would expect from Figure 5.14, triplet carbenes are more linear and singlet carbenes are more bent.
 - However, the difference isn't as big as we might expect: The actual angles are 136° and 105°.
- We say that triplet carbenes have “diradical character” since we put an unpaired electron in both **C'** and **D**.
- We say that singlet carbenes have “cation + anion character” since we put two paired electrons in the *sp*²-like **C'** orbital and none in the *p*-like **D** orbital.
 - Note that this makes **C'** our HOMO and **D** our LUMO.
- Implication: Triplet carbenes react as diradicals, and singlet carbenes react as cations and anions.
- Let's now discuss some ways we can push carbenes to favor the singlet state, or the triplet state.
 - Specifically, we'll discuss the effects of placing π -donors, π -acceptors, σ -EWGs, and multiple bonds (e.g., for conjugation) near the carbene.
 - **Singlet-triplet gap:** The difference in energy between the singlet and triplet states of a carbene.
 - Simple dialkyl carbenes favor the triplet state.
 - Example: H_2C : favors the triplet state by 8.5 kcal/mol.
 - π -donor substituents stabilize carbenes and favor the singlet state.

Figure 5.16: π -donor substituents stabilize carbenes and favor the singlet state.

- Example π -donor substituents: Neighboring lone pairs from atoms like N/O/X.
 - Additional example: **NHCs**.
- π -donors favor the singlet state because they stabilize cations.
 - Intuitively, we can think of this as the electron density from a π -donor “pushing out” the radical electron from **D** and moving it into **C'**.
- More accurately, molecular orbital theory tells us that π -donors stabilize the high-energy, cationic **D**-orbital through hyperconjugation (Figure 5.16a).
- Formally, this hyperconjugation is manifested as a pseudo- π -bonding interaction (Figure 5.16b).
 - **D** mixes with a nonbonding lone pair n_X to stabilize the lone pair and form a new, higher-energy LUMO.
 - Intuitively, the lone pair is stabilized because it has gotten to delocalize more!
 - This new LUMO is lower than **E** in energy.
 - In the process, **D** is effectively moved way up in energy in the Walsh diagram (Figure 5.14), forcing the carbene’s electrons into **C'**.
- One last way of representing this interaction is via resonance (Figure 5.16c).
 - This resonance structure reveals that the carbene electrons are properly an anion.
- To recap, there are *three* ways we can think about carbene stabilization by π -donors: Hyperconjugation, MO diagrams, and resonance diagrams.

- **N-Heterocyclic carbene: Also known as NHC. Structure**

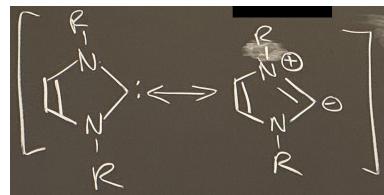


Figure 5.17: *N*-heterocyclic carbene.

- σ -EWGs stabilize carbenes and favor the singlet state.
 - A σ -EWG is basically just an electronegative substituent.
 - σ -EWGs stabilize carbenes because they stabilize anions.
 - Recall that σ -EWGs also *destabilize* radicals!
 - Example: F₂C: favors the singlet state by ~ 50 kcal/mol.
- π -acceptor substituents stabilize carbenes and favor the triplet state.
 - Examples: Carbonyls, sulfones (SO₂R), NO₂ groups, boron, etc.
 - These groups mix with **D** just like in Figure 5.16b, except that the new, lower-energy orbital is now empty!
 - This new, lower-energy orbital is our LUMO.
 - Since it has been stabilized, it is now close in energy to the **C'**-orbital.
 - This allows you to release the spin pairing energy by forming the triplet state.
 - These substituents also make carbenes more electrophilic.
- Conjugation stabilizes carbenes and favors the triplet state.
 - Example groups that can conjugate with carbenes: Alkenes, alkynes, and arenes.

- Synthesis of carbenes.

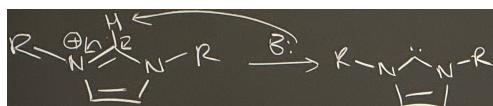
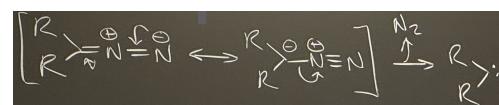


Figure 5.18: Synthesis of carbenes.

- We almost always synthesize carbenes via α -elimination (Figure 5.18a).
 - If you're forming a carbocation and a carbanion at the same time, you're forming a carbene.
 - We can draw α -elimination as a concerted or stepwise mechanism.
 - To deprotonate a secondary halide, we need a strong base.
- Aside (practical consideration): Don't run strongly basic reactions in CHCl₃! Even something like KO^tBu can form dichlorocarbenes from chloroform in solution.
- Diazo compounds can also form carbenes pretty easily (Figure 5.18b).
- NHCs can form from an aromatic salt and a strong base (Figure 5.18c).
 - These aren't so much of a recent development anymore; they've definitely left their mark on organic chemistry.
 - These are important catalysts and ligands for transition metal catalysis.
 - If the R-groups are small, then NHCs will dimerize to form a double bond.
- Aside (story): When Masha gave this lecture last year, she talked about how you can put NHCs on quantum dots (to do cool things) in honor of Moungi's Nobel Prize.
- Aside (chemis-tea): On the Nobel Prize.
 - You get a medallion made of solid gold for you to keep and a few (cheaper) replicas to display.
 - You have to pay for the replicas, though. In fact, you have to pay for a lot: They take the expenses for flights, tickets to the gala, etc. out of your Nobel winnings (like 40 grand in total).
 - This was both Moungi's and Schrock's experience, which Masha found out when she had lunch with Schrock last week during his visit.
- Aside (chemis-tea): Get a tungsten wedding ring! Aqua regia will eat a gold or silver wedding band.
- Most synthetically useful reactions involve **carbenoids**, i.e., metal carbenes.
 - We won't talk about carbenoids in here because that's a topic for 5.44 - Organometallics, which we can take next year with Alison if we want.
 - To be clear, we'll only talk about **free** carbenes in this class.
- Free** (carbene): A carbene that is not bound to a metal.
- We will now begin discussing the reactivity of carbenes.
 - Singlet (cation/anion) and triplet (diradical) carbenes naturally react differently.
 - Carbene reactivity is easier to grasp than the carbene stability stuff from earlier :)

- We'll begin by discussing carbenes' reactivity toward [2 + 1] cycloaddition.
- Singlet carbenes add to alkenes in a concerted and stereospecific fashion.

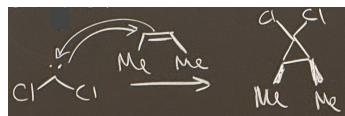
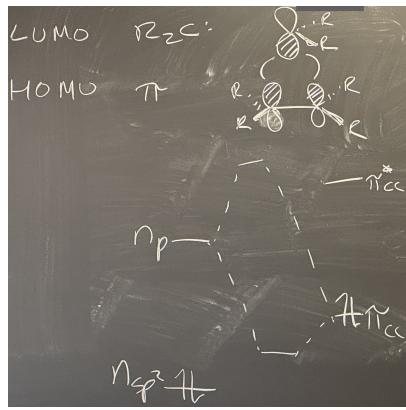
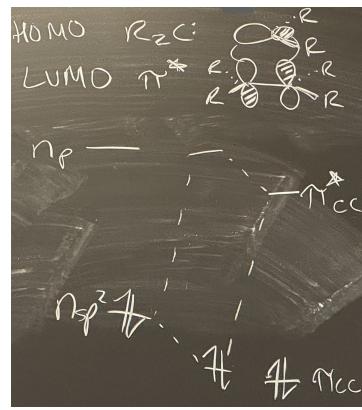


Figure 5.19: Carbene reactions: Chelotropic [2 + 1] cycloaddition.

- Example (Figure 5.19): Dichlorocarbene and 2-butene react to form a 100% *cis*-product.
- This is a chelotropic cycloaddition! Recall that we discussed carbene addition in Lecture 5.
- FMO analysis of this reaction.



(a) Electrophilic carbenes.



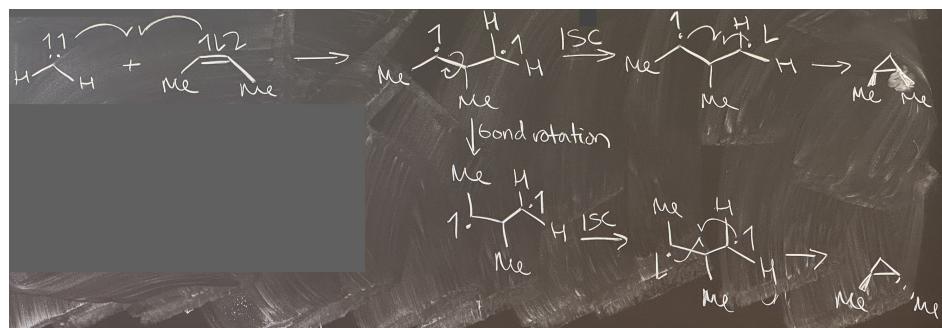
(b) Nucleophilic carbenes.

Figure 5.20: The orbitals behind chelotropic carbene cycloadditions.

- Electrophilic carbenes have low-energy orbitals, so their LUMO engages the alkene's π -HOMO.
- Nucleophilic carbenes have high-energy orbitals, so their HOMO engages the alkene's π^* -LUMO.
- Triplet carbenes also add to alkenes, but in a stepwise and non-stereospecific fashion.



(a) General form.



(b) Mechanism.

Figure 5.21: Carbene reactions: Stepwise [2 + 1] cycloaddition.

- Because the mechanism has changed, this [2 + 1] reaction is no longer chelotropic nor pericyclic.
- The rough product distribution is usually about 30% *cis* and 70% *trans* (Figure 5.21a).
- Let's investigate the mechanism (Figure 5.21b).
 - We begin with two unpaired electrons on the carbene (which have the same spin) and two paired electrons in the π -HOMO of the alkene (which, naturally, have opposing spins).
 - One of the carbene electrons will react with the alkene electron having specifically the *opposite* spin.
 - Postulate: Only radicals with paired spins can react.
 - After the first step, two radicals remain (one from the olefin and one from the carbene).
 - Since they both have the same spin, though, we will need **ISC** to the singlet state before we can proceed.
 - Following ISC, the remaining radicals can react to form a second bond.
 - Alternatively, since ISC takes a bit of time, we can have a bond rotation followed by an ISC, followed by bond formation.
- Takeaway: The *cis*-to-*trans* ratio depends on the relative rates of the bond rotation vs. ISC.
- Hint for the mechanistic proposal!!
 - Suppose you're proposing a mechanistic study of a triplet carbene.
 - We can learn from orthogonal experiments how long a bond rotation takes.
 - Thus, the *cis*-to-*trans* ratio can be a good probe for our triplet lifetime!

- **Intersystem crossing:** A spin flip. *Also known as ISC.*

- We will learn more about this later in the semester!
- Steven: Are ISC and pairing always separate, or can they ever happen together?
 - Pairing involves moving electrons into different orbitals, and spin flipping is just spin flipping; essentially, they're two different kinds of processes, and this is why we draw them separately.
 - You can't pair electrons unless they're spin-flipped (except perhaps in some niche application).
- We'll now talk about carbenes' reactivity toward insertions.

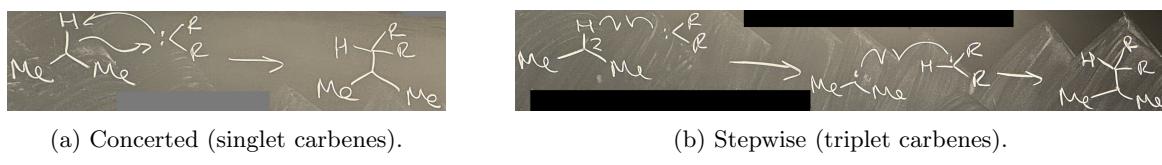


Figure 5.22: Carbene reactions: Insertions.

- These are reactions with C–H bonds.
- Singlet carbenes reacted through concerted mechanisms, and triplet carbenes react through stepwise mechanisms.
 - This means that only singlet carbenes engage in a *true* insertion into the C–H bond.
 - Triplet carbenes, on the other hand, have an H-atom transfer (HAT) followed by radical recombination.
- Aside: HAT refers to hydrogen ($H\cdot$) transfer.
 - It is distinct from proton (H^+) transfer and hydride (H^-) transfer.
 - Know which one you're talking about!

- Moving on from insertions, let's talk about ring expansions.



(a) Expanding benzene.



(b) Expanding pyrrole.

Figure 5.23: Carbene reactions: Ring expansions.

- Benzene as a starting material (Figure 5.23a).
 - This reaction involves addition to an olefin followed by a 6π electrocyclization.
 - Carbenes are so reactive that they can even break aromaticity!
- Pyrrole as a starting material (Figure 5.23b).
 - This reaction involves the same addition to an olefin as before. However, it is then followed by elimination of a chlorine and proton transfer to afford pyridine.
 - This is an example of single-atom editing because it allows us to insert a specific carbon atom into a heterocycle. Single-atom editing is currently blowing up in the literature.
- Steven: Why do we add to the side double bonds in pyrrole instead of the back one?
 - It will be obvious if you draw the product of such an addition: Said product will be much more charge separated.
 - Specifically, if we're going to engage the back π -bond, we have to do so from the resonance structure with a carbanion on one carbon and a positive charge on the nitrogen.
 - Takeaway: The side bonds in pyrrole tend to react more as separate π -systems.
 - This is because the aromatic stabilization of pyrrole is like 17 kcal/mol, i.e., pyrrole is much less aromatic than benzene (35 kcal/mol).
 - Blocking groups might force the second reaction, but it would def give a less stable product.
 - The second reaction would give 4-chloropyridine instead of 3-chloropyridine.
 - We might get a 99 : 1 ratio naturally, but if we put an EWG at the 2-position, that could stabilize a resonance form, giving us 2-EWG-4-chloropyridine.
- Aside: Learning to draw 7-membered ring.

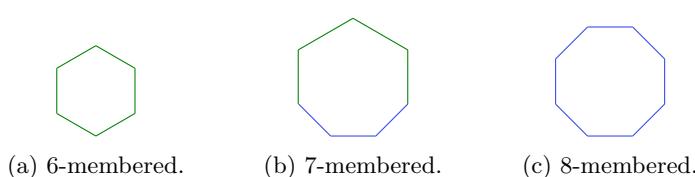


Figure 5.24: Drawing a 7-membered ring.

- On paper, draw half a hexagon and half an octagon. This is easier to read than the “proper” equidistant form, which we should leave that for ChemDraw.

- Masha: “Jonathan [the TF] is like the most brilliant person ever, so whenever I find a chink in the armor, it makes me happy.”
- Lastly, we’ll discuss rearrangements.

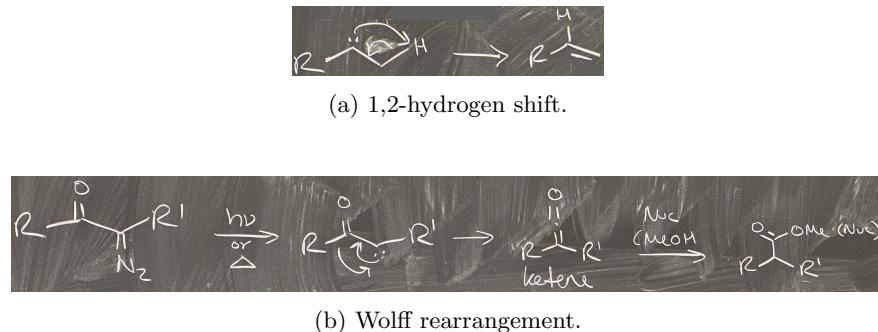


Figure 5.25: Carbene reactions: Rearrangements.

- The most common one is a 1,2-hydrogen shift (Figure 5.25a).
- Then there are a ton of named reactions, e.g., the **Wolff**, **Curtius**, and **Hoffmann rearrangements**.
 - We’ll never run these reactions in our lives, but they teach them all the same regardless... perhaps because they’re mechanistically interesting.
- Example named rearrangement: The Wolff rearrangement (Figure 5.25b).
 - Either light or heat can be used to cleave the diazo functional group to a carbene.
 - Then we get a rearrangement into a ketene.
 - Then a nucleophile attacks the ketene’s central carbon (the electrophilic one) to give a ketone.
 - This rearrangement is useful for lots of things, e.g., a 5.47 problem!
- Angle of approach.

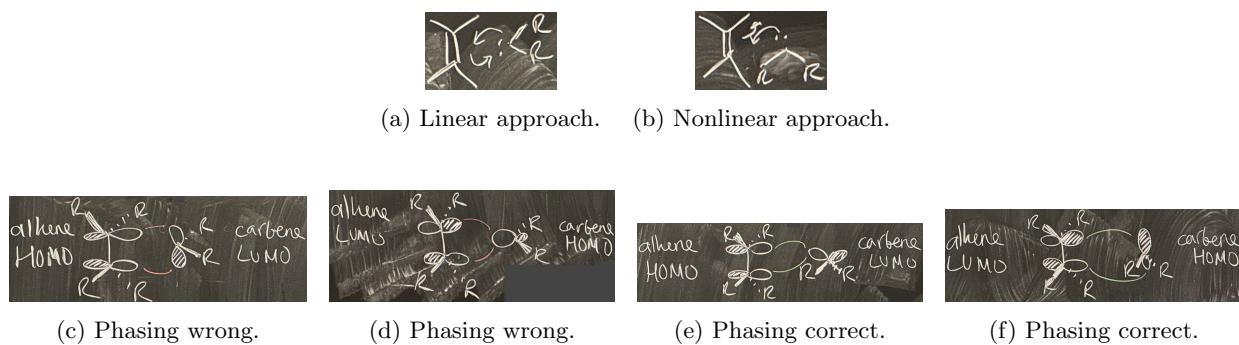


Figure 5.26: Angle of approach in chelotropic [2 + 1] cycloadditions.

- Consider a [2 + 1] with an alkene.
- The mechanism is actually side-to-side per MO theory (Figure 5.26b), not linear and head on as we often draw (Figure 5.26a).
- Linear approach.
 - The alkene and carbene can both be HOMO/LUMO.
 - First, let the alkene be the HOMO and the carbene the LUMO (Figure 5.26c).
 - The phasing is all wrong, because we’ve got a shaded lobe mixing with an unshaded lobe.

- Now consider the alkene LUMO and the carbene HOMO (Figure 5.26d).
 - Here, the phasing is still all wrong, because we're interacting a single carbene lobe with two different shaded π^* -lobes.
- So the phasing is wrong in both cases.
 - Nonlinear approach.
 - Alkene HOMO and carbene LUMO (Figure 5.26e).
 - Good phasing match.
 - Alkene LUMO and carbene HOMO (Figure 5.26f).
 - Good phasing match as well!
 - Conclusion: Nonlinear approach is required!

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.

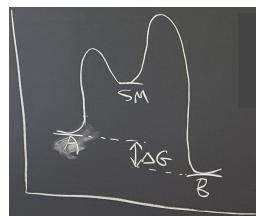


Figure 6.1: Energy variables relevant to thermodynamic selectivity.

- 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.

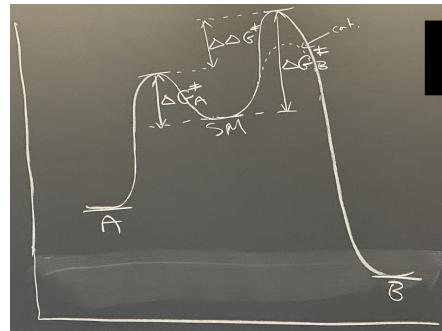


Figure 6.2: Energy variables relevant to kinetic selectivity.

- 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.*

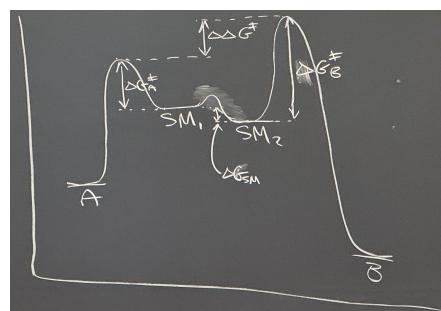
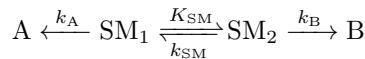


Figure 6.3: Energy variables relevant to Curtin-Hammett kinetics.

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

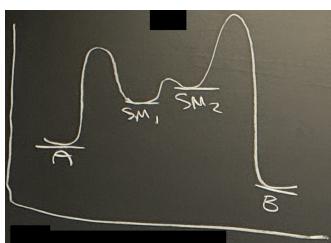
- In particular, the selectivity does *not* depend on the energies of the starting materials.
- Relevant reaction coordinate.



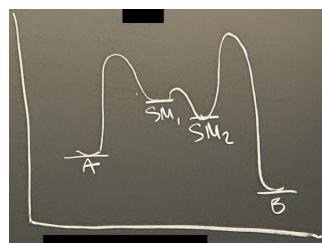
- k_{SM} must be big. Typically, it is approximately ten times faster than k_A or k_B .
- Working out the math, we get

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

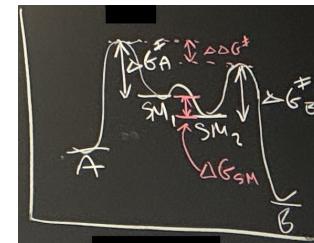
- Indeed, we see that in this regime, the selectivity *mathematically* depends only on the relative energies of the transition states.
- Energy diagram of a reaction under Curtin-Hammett kinetics (Figure 6.3).
 - Note that there is only a small energy barrier between SM_1 and SM_2 because we need fast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

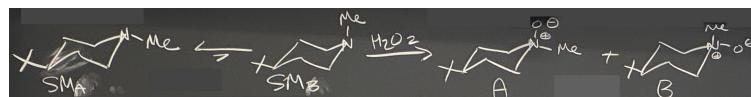


Figure 6.5: Curtin-Hammett kinetics: Kinetically trapping epimers.

- 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.

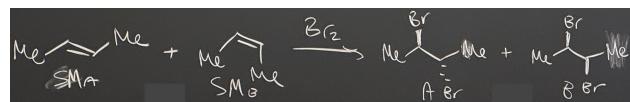


Figure 6.7: Curtin-Hammett kinetics: Bromination of geometric isomers.

- 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).

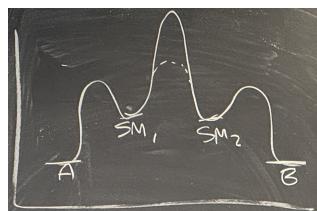


Figure 6.8: Energy variables relevant to a kinetic quench.

- Here, the SM₁ ⇌ 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 → A and SM₂ → 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.

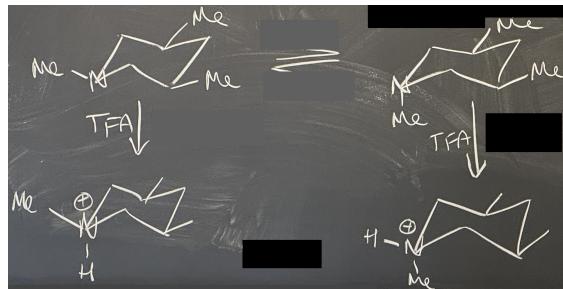


Figure 6.9: Kinetic quench: Protonation.

- 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 E₂ (Figure 6.10b) or E₁CB (Figure 6.10d)?
 - How can we determine the better mechanism? Consider the reverse reactions!
 - Retro-E₂ (Figure 6.10c): A one-step forward reaction for E₂ means a one-step reverse reaction, wherein HO⁻ adds in, the olefin grabs a proton from water, and HO⁻ leaves.

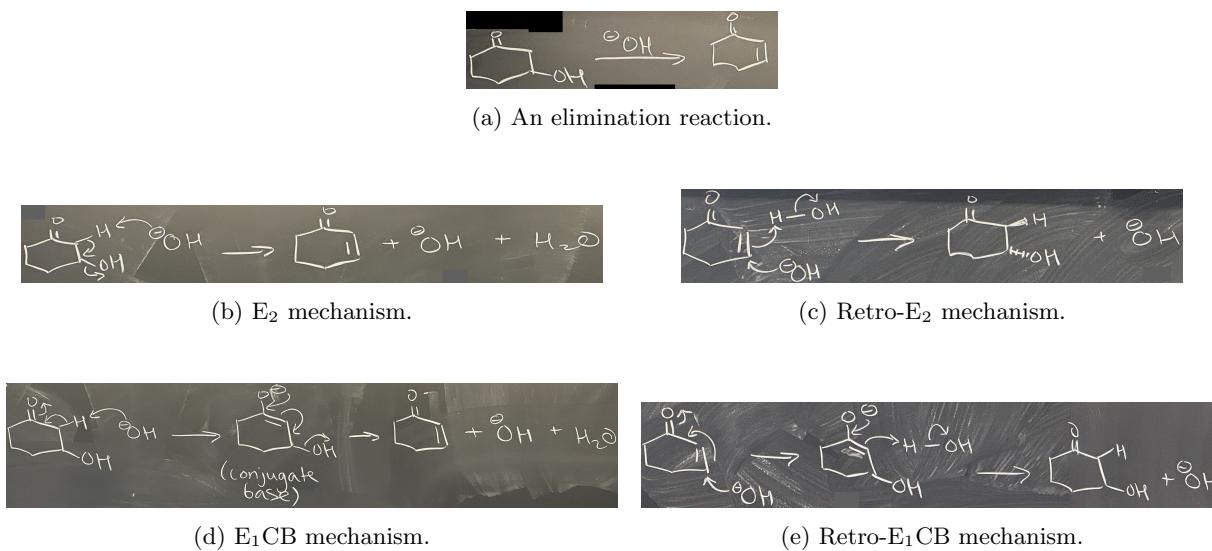


Figure 6.10: Microscopic reversibility to differentiate plausible mechanisms.

- 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.

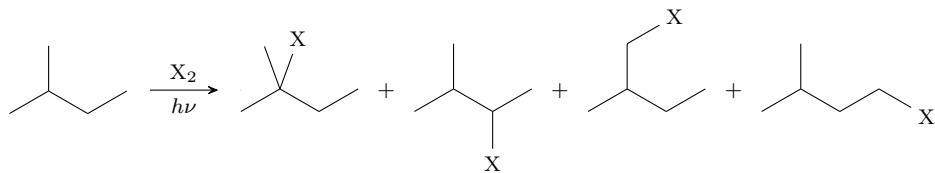


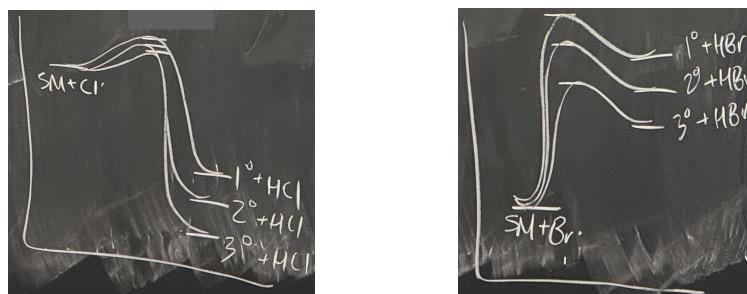
Figure 6.11: Reactivity-selectivity principle in radical halogenation.

- 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.

	$\text{CH}_3\text{CH}_2\text{CH}-\text{CH}_2\text{X}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}-\text{CH}_2\text{X}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}-\text{CH}_3$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{X}$
$\text{X} = \text{Cl} (\%)$	28	35	24	12
$\text{X} = \text{Br} (\%)$	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 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 $\Delta H = -5$ 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 (2024b)!
- 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	<chem>CC(=O)O</chem>	<chem>FC(F)C(=O)O</chem>	<chem>CC(F)(F)C(=O)O</chem>	<chem>CC(F)(F)C(F)(F)C(=O)O</chem>
pK _a	4.9	4.2	3.1	0.2

Table 6.2: Inductive effects' distance dependence.

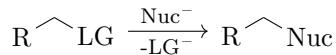
- Let's compare the pK_a's of propionic acid, 4,4,4-trifluorobutyric acid, 3,3,3-trifluoropropionic acid, and trifluoroacetic acid.
- The trifluoromethyl EWG stabilizes the anion, resulting in a more acidic proton as the EWG gets closer to the site of deprotonation.
- **Field effect:** The donation or 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.

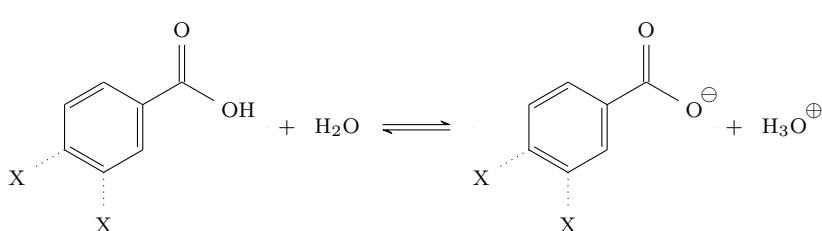


Figure 6.13: Hammett's reference reaction.

- 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.

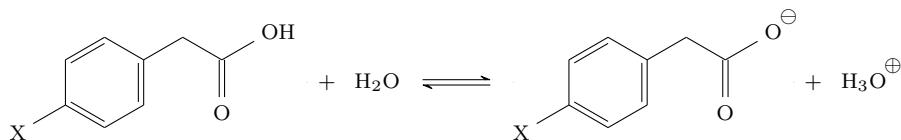


Figure 6.14: The deprotonation of phenylacetic acid.

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

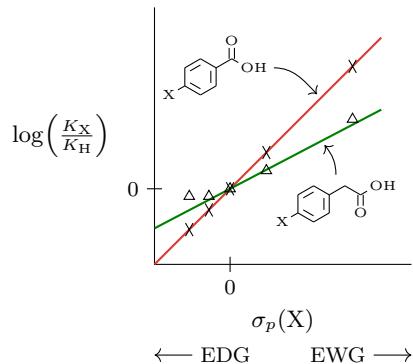


Figure 6.15: Hammett plot for benzoic and phenylacetic acid.

- 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.

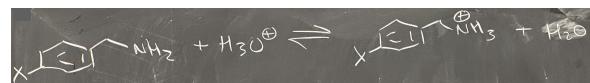
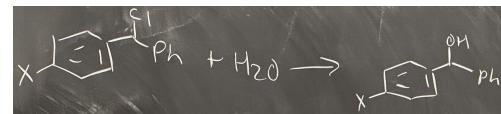
(a) Phenol deprotonation ($\rho = 2.26$).(b) Benzylamine protonation ($\rho = -1.05$).(c) Phenolate attack ($\rho = -0.95$).(d) Nucleophilic substitution ($\rho = -5.09$).

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**.

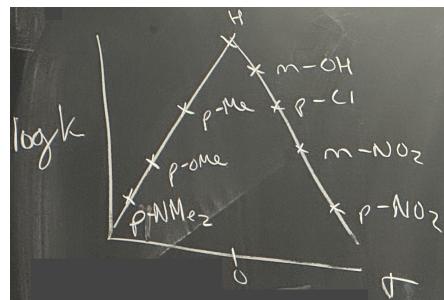


Figure 6.18: Hammett plot for imine formation.

- 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.

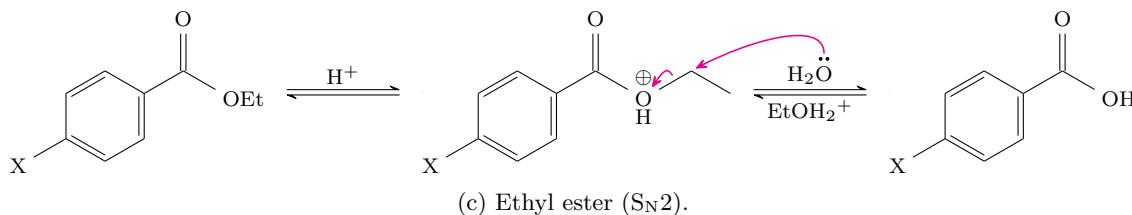
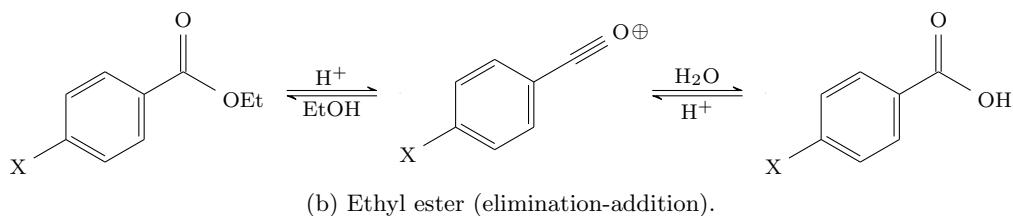
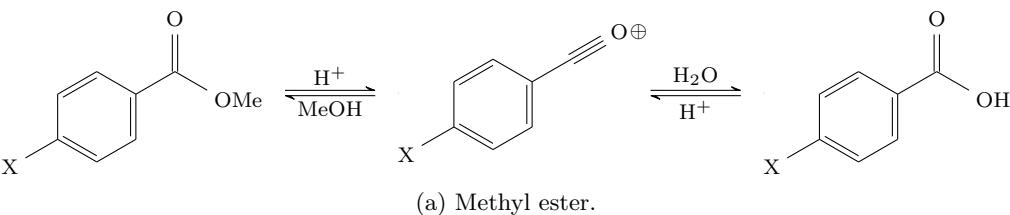


Figure 6.20: Acid-catalyzed ester hydrolysis.

- 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).

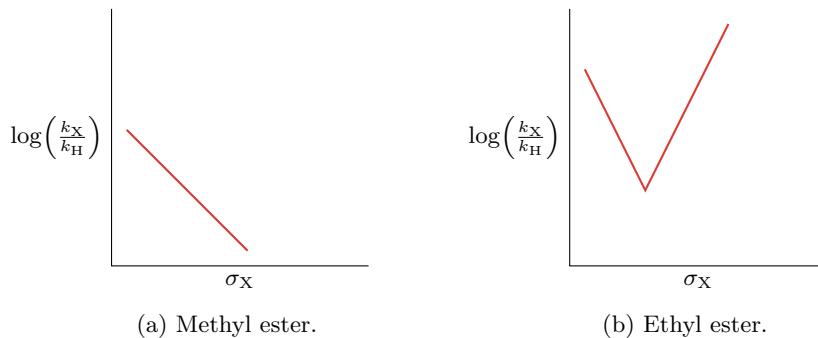


Figure 6.21: Hammett plots for ester hydrolysis.

- 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!!

Week 7

Quantifying Features of Moieties

7.1 Parameters and Linear Regression

10/17: • Lecture 11 recap.

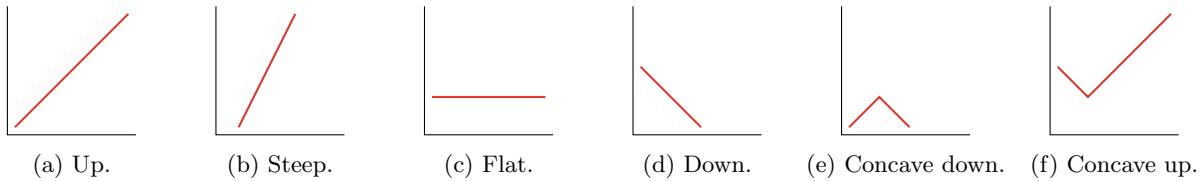


Figure 7.1: Different types of Hammett plots.

- LFERs and Hammett plots let us correlate substituent parameters to changes in the equilibrium (ΔG) or kinetic (ΔG^\ddagger) energies of reaction.
 - These tools come from the observation that substituents exert common influences on reactions.
 - Substituent effects (inductive, field, resonance, polarizability, and steric). Also solvent effects.
 - The different types of Hammett plots.
 - Figure 7.1a: Some negative charge build up in the transition state.
 - Figure 7.1b: More negative charge build up in the transition state.
 - Figure 7.1c: No positive or negative charge build up in the transition state.
 - Figure 7.1d: Some positive charge build up in the transition state.
 - Figure 7.1e: Change in the rate-determining step.
 - Figure 7.1f: Change in the mechanism.
 - Remember that in a Hammett plot, our x -axis is a parameter σ that quantifies electron-donating or electron-withdrawing intensity, and our y -axis is either $\log(k_X/k_H)$ or $\log(K_X/K_H)$.
 - Remember also that stronger EWGs lie to the right, and stronger EDGs lie to the left.
- Announcements.
 - Next week: Masha's last lecture before Alex takes over. It will cover ML.
 - PSet 2: Will be graded by tomorrow or the next day, so we'll be able to study it for the exam.
 - Exam: Live on Canvas on Tuesday. Once downloaded, we'll have 90 mins to take and upload it.
 - Don't cheat; it's not open-book or open-note. Don't take it around anyone else.
 - Take the practice exam under exam-like conditions with a timer and everything.
 - Office hours: Jonathan will hold these virtually on Friday because he's a bit sick currently.

- Today: Continuing our discussion of parameters (such as σ) and linear regression.
- Lecture outline.
 - Defining two new substituent parameters (σ^+ and σ^-).
 - Other electronic parameters (Mayr, Swain-Scott, NBO, Mulliken, NMR, IR, orbital energies).
 - Steric parameters (A-values, sterimol parameters).
 - Stereoelectronic parameters (Taft parameters, Charton parameters).
 - Steric parameters in catalysis (bite angle, cone angle, PBV).
 - Higher-dimensional Hammett plots and the foundations of ML.
- We begin today with a critique of σ_p and σ_m , and the solution developed to address this critique.
- Essentially, chemists noticed that while σ_p and σ_m were good for characterizing electron-withdrawing and -donating character, they did not capture everything.

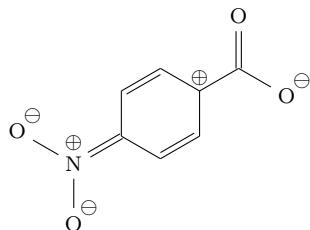


Figure 7.2: Carboxylates do not delocalize efficiently into arenes.

- Importantly, they did not do a great job of capturing resonance effects since the benzoate anion could not delocalize efficiently into the aromatic ring.
 - In general, there is no resonance delocalization of carboxylates into arenes.
 - Recall from last lecture that the substituent can delocalize its charge up to the *ipso*-position; however, the anion can't go in.
- This means that σ_p and σ_m underestimate π -EWG and π -EDG effects.
- As such, later chemists developed scales based on new reference reactions.
 - These new reference reactions generated anions and cations that could resonance-delocalize into the aromatic ring, and hence all the way to the substituent.
 - In particular, two new substituent parameters were developed: σ^- and σ^+ .
- σ^- : A measure of a substituent's ability to stabilize (inductively and through resonance) the negative charge that builds up when a substituted phenol is deprotonated. *Reference reaction*

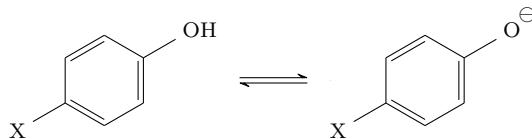


Figure 7.3: Reference reaction for σ^- .

- This is the deprotonation of a phenol, which is nice because phenolates *can* delocalize their anion into the ring and over to the substituent.
 - Thus, this reaction better captures benzylic anion stabilization and π -EWG effects.
- For reference, we set $\sigma^- := 0$ when X = H.

- σ^+ : A measure of a substituent's ability to stabilize (inductively and through resonance) the positive charge that builds up when a substituted cumyl chloride is deprotonated. *Reference reaction*

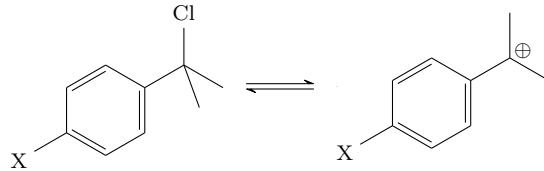


Figure 7.4: Reference reaction for σ^+ .

- This is the ionization of cumyl chloride, which is nice because cumyl groups can delocalize their cation into the ring and over to the substituent.
 - Thus, this reaction better captures benzylic cation stabilization and π -EDG effects.
 - For reference, we set $\sigma^+ := 0$ when $X = H$.
- Now that we have two new substituent parameters, let's compare some of their values with our old substituent parameters.

X	σ_p	σ^-	σ^+
CH ₃ O	-0.27	-0.26	-0.78
CH ₃	-0.14	-0.17	-0.31
H	0	0	0
Cl	0.24	0.19	0.11
NO ₂	0.81	1.23	0.79

Table 7.1: Comparing σ_p with σ^+/σ^- for common substituents.

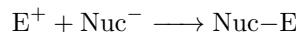
- Misc. observations.
 - σ^- reflects that nitro groups are *six* times better than chlorine, not four times as σ_p suggests.
 - σ^+ is more similar to σ_p for EWGs, and σ^- is more similar to σ_p for EDGs.
 - In the first row, σ^+ deviates (because it captures the π -EDG nature).
 - In the last row, σ^- deviates (because it captures the π -EWG nature).
 - These numbers just quantify our intuition about which groups are stronger, which way (EWG or EDG) the groups are stronger, and why!
- So now that we have several parameters, which one should we use?
 - This is a mechanistic probe; we don't know the mechanism yet!
 - So we plot all of them and see which gives us the best fit to a straight line.
 - This tells us something about the electronics of the transition state.
 - Is it positive? Negative?
 - Is it influenced by π -interactions? σ -interactions?
 - Etc.
- This concludes our discussion of Hammett substituent parameters.

- Let's now discuss some other electronic parameters, including some that describe inductive, resonance, field, and/or polarizability properties.

– What if we want to quantify nucleophilicity or electrophilicity?

- Use Mayr electrophilicity from Lecture 6!

➢ Recall that here, we measure k for the reaction

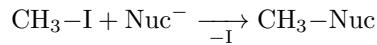


and then set

$$\log(k) = s(N + E)$$

- There are also **Swain-Scott parameters**.
- These are both empirical frameworks that have their own domains of usefulness.
 - These people spent their careers compiling tables of data so that we don't have to!
 - It's super useful.
- What if we want to quantify atomic charges?
 - Look into **natural bond orbital** (NBO), **Mulliken**, etc.
 - Be careful here, though, because the numbers are often in the gas phase, so they may not be useful.
 - Alternatively, the *relative* values may be more useful than the absolute values.
- Another way we can determine electronic effects is with spectroscopic data.
 - NMR shift or IR frequency can be used as a proxy for electronic character.
 - We can calculate the energies of certain bonds, orbitals (e.g., σ, σ^*), lp's, hybrid orbitals, etc.
 - We can also calculate hybridization — the percent *s*-character can easily be calculated exactly.

- **Swain-Scott parameter:** The rate of reaction for various nucleophiles. *Given by*



– Swain and Scott defined two parameters (s and n_x) via the equation

$$\log\left(\frac{k_{\text{nuc}}}{k_{\text{H}_2\text{O}}}\right) = sn_x$$

■ s is the sensitivity.

■ n_x is the substrate constant.

– $k_{\text{H}_2\text{O}}$ indicates that we are setting the hydrolysis of methyl iodide as the reference reaction.

- Besides electronics, the other big thing in chemistry is sterics! The two main steric parameters are...

1. **A-values;**

2. **Sterimol parameters.**

- **A-value** (of an R group): The difference in energy between the axial and equatorial conformers of a mono-R-substituted cyclohexane.

– This is one way of measuring the size of an R group.

– Limitation: When the C–R bond is long.

■ Example: Cl has $A = 0.43$, and I has $A = 0.43$.

■ I is much bigger than Cl, but they have the same A-value because the C–I bond is so long; it doesn't really matter energetically if your I is axial or equatorial since it's far away from the hydrogens.

- **Sterimol parameter:** A parameter that considers the size of the R group in multiple dimensions.

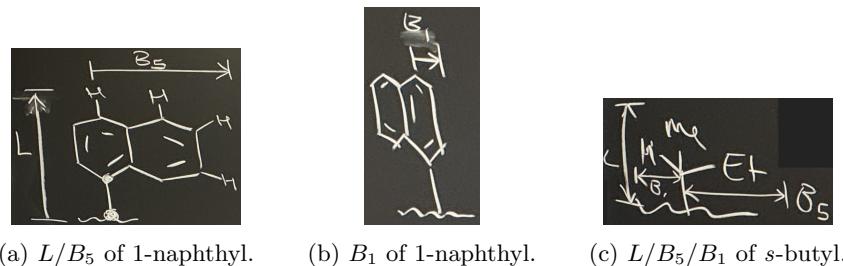


Figure 7.5: Sterimol parameters.

- These are our best steric parameters to date.
 - They are very good at decoupling multiple dimensions of information.
 - They can be calculated by a number of programs and websites.
- Sterimol parameters narrow down what we mean by “size.”
 - For example, it’s hard to say whether a tree or a car is bigger — what do we mean by “big?”
Trees have lots of empty space, cars are more dense, trees have more mass (in general), etc.
 - The same is true of certain R groups.
- Sterimol parameters define the size of a substituent dimension by dimension.
 - L is the length (in Å) from the “parent atom” to the end of the substituent, following the vector connecting the parent atom and the “start of the substituent” (Figure 7.5a).
 - The “parent atom” and “start of the substituent” are the circled atoms in Figure 7.5a.
 - B_5 is the maximum size of the substituent along any vector perpendicular to \vec{L} (Figure 7.5a).
 - B_1 is the minimum size of the substituent along any vector perpendicular to \vec{L} (Figure 7.5b).
 - Figure 7.5b is supposed to be a perspective drawing.
- Masha also draws the sterimol parameters on a *sec*-butyl group (Figure 7.5c).
- Some parameters account for both steric *and* electronic effects.
 1. **Taft parameters.**
 2. **Charton parameters.**
- **Taft parameter:** A measure of a substituent’s ability to electronically activate or deactivate as well as sterically block or expose a reactive site. *Given by*

$$\log\left(\frac{K_X}{K_H}\right) = \rho^* \sigma^* + \delta E_s \quad \log\left(\frac{k_X}{k_H}\right) = \rho^* \sigma^* + \delta E_s$$
 - We can decouple the sterics and electronics by measuring k or K of both pathways.
 - This is some good, honest physical organic chemistry that some people did.
 - $\rho^* \sigma^*$ is the **polar term**.
 - δE_s is the **steric term**
- **Polar term:** The term governing electronics.
- **Steric term:** The term governing a substituent’s ability to block π^* because of its anomalous size.
 - This definition is not necessarily universal; it’s relevant to this reaction, specifically.
 - In some reactions, the ability to block some other antibonding orbital will be more relevant.

- Example: The hydrolysis of a methyl ester under basic and acidic conditions.

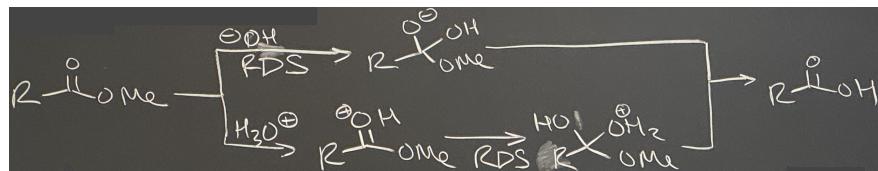


Figure 7.6: Taft parameters characterize ester hydrolysis.

- Under basic conditions, we have basically one step: Addition, then kicking out.
 - The RDS is the hydroxide adding in.
 - There is a negative charge buildup in the transition state.
 - Therefore, the sterics of R can block the addition and the electronics of R might change the carbonyl's electrophilicity. In other words, both the sterics and electronics of R matter.
- Under acidic conditions, we could get protonation of the carbonyl followed by water addition to form the tetrahedral intermediate, and then elimination and deprotonation to the carboxylic acid product.
 - The RDS is the water adding in.
 - There is no charge buildup in the transition state (the charge is already included).
 - Therefore, it's *only* the sterics of R that matter.
- **Charton parameter:** A refinement of E_s with van der Waals radii. *Also known as Charton modification of Taft parameters.*
- Taft and Charton are both a bit historical at this point, but we still need to know them in order to read the literature.
 - Masha's never actually used them, but she does use sterimol.
- We now move onto some steric parameters in catalysis; these were motivated by the need to quantify ligand size.

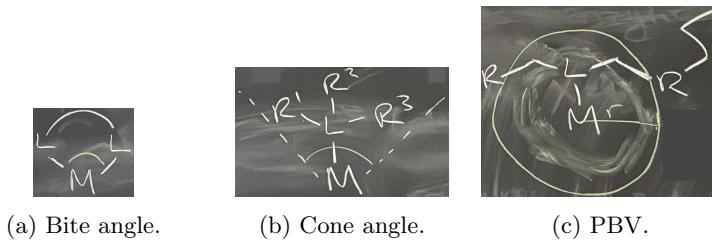


Figure 7.7: Steric parameters in catalysis.

- **Bite angle:** The L–M–L angle for a bidentate ligand. *Schematic Figure 7.7a.*

- To reiterate: Bite angle is a metric of size for bidentate ligands *only*.
- Naturally, bite angle depends significantly on the size of the metal.
 - The example values below are all for the same metal.
 - Historically, bite angles were reported for nickel.
- Examples.
 - DPPM, DPPE, and DPPP ligands have bite angles of 73° , 86° , and 91° .
 - TRANSphos has a 180° angle so that it sits on either side of our catalyst; really useful!
- Bite angle correlates really well to a lot of reactivity, so it's good to know.

- **Cone angle:** The angle from the metal to the outside R groups, where L is a monodentate ligand with three substituents. *Schematic Figure 7.7b.*
 - To reiterate: Cone angle is a metric of size for monodentate ligands only.
 - Cone angle also (naturally) depends on the metal.
 - Examples: Phosphane, trimethylphosphane, and triethylphosphane have 87° , 118° , and 132° .
- **Percent-buried volume:** The percent of the sphere around the metal occupied by the ligand, where the sphere has $r = 3.5 \text{ \AA}$ by default. *Also known as PBV.* *Schematic Figure 7.7c.*
 - The radius can be changed, though, because the ligand should fit mostly in the sphere.
 - Examples: NHC ligands.
 - If $R = \text{Me}, i\text{Pr}, 2,6-i\text{PrPh}$, then $\text{PBV} = 26, 28, 47$.
 - Example of when this is useful.
 - If you want to block your metal, you need bigger R groups.
 - But if you just choose floppy alkyl chains, that might not really block the sphere because they'll just flop away.^[1]
 - We should see these in papers.
 - Use them in our work if we need!
- This is it for regular parameters at this point.
- However, there's one more wrinkle: The case of multidimensional LFERs.

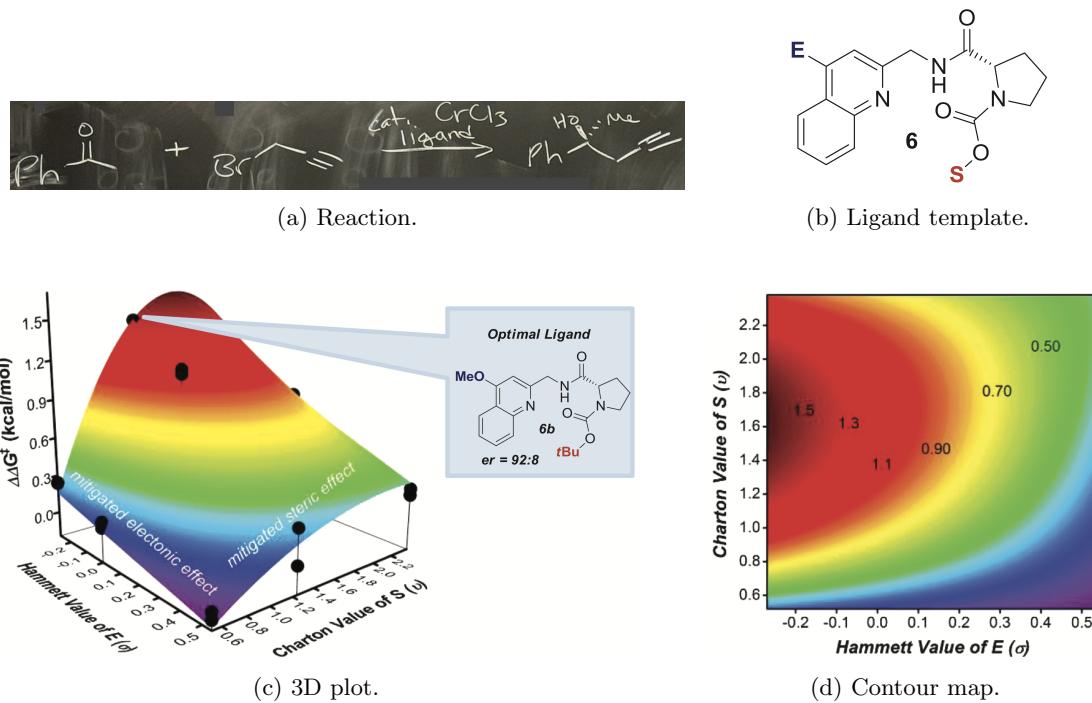


Figure 7.8: Multidimensional LFERs.

¹Sometimes floppiness can be the point, though, as in my research with Santa!

- To make sense of these, we use a higher-dimensional Hammett plot!
 - Even this one step up gets us to multidimensional regression, which is the dawn of ML in chemistry.
 - Back in the day, they called this multidimensional LFERs; today, we call it machine learning (ML).
 - Essentially, some substituents can have synergistic or interdependent effects.
 - To conceptualize this kind of relationship, we model multiple parameters at once.
 - History.
 - This work was pioneered by Matt Sigman at the University of Utah.
 - Now a lot of other people have jumped in: Abby Doyle, Connor Coley, Masha, etc.
 - “As this field gets bigger and bigger and hypier and hypier, no one should forget Matt. Don’t come for Matt.”
 - Example: Catalytic CrCl₃ gets chelated to an asymmetric ligand (Figure 7.8b), and then enantioselectively combines two things (Figure 7.8a).
 - Three variables to consider: Two independent variables, and one dependent variable.
 - The authors varied the size of the substituent S, and measured its size with a Charton parameter, ν .
 - Simultaneously, they varied the electronics of the substituent E, and measured its EWG/EDG character with a Hammett parameter, σ .
 - They measured the ee, from which they could calculate er, k_{rel} , and finally $\Delta\Delta G^\ddagger$.
 - This all results in a 3D plot (Figure 7.8c).
 - The general shape is a sheet that’s going up and down.
 - The contour map might be a bit easier to visualize (Figure 7.8d).
 - High ee toward the left and low ee toward the right.
 - We can also describe all this with an equation.
- $$\Delta\Delta G^\ddagger = -1.20 + 1.22E + 2.84S - 0.85S^2 - 3.79ES + 1.25ES^2$$
- The **cross terms** (ES and ES^2) in this equation are particularly important; they are a mathematical demonstration of the interdependency between sterics and electronics.
 - Thus, the $\Delta\Delta G^\ddagger$ depends on ligand sterics, electronics, and how those interact with each other.
 - The original constant doesn’t have chemical meaning, then electronic parameter, then two steric parameters, then two cross terms.
 - What’s happening here in chemical terms is that electron-poor ligands are not very sensitive to sterics, but electron-rich ligands are.
 - Note the difference in the curves in the back of the 3D plot and the front of the 3D plot. The back one (high EDG) is much more dependent on sterics! We want mid-sterics for highest ee.
 - The front one isn’t great.
 - So the best ligand is when E is very electron-donating (OMe) and S is big but not too big (^tBu; not something huge like adamantyl).
 - Reference: Harper and Sigman (2011).
- Overall guide/overview to building your own multidimensional free energy relationship with more parameters: Santiago et al. (2018).
 - A very accessible read!

7.2 Office Hours (Jonathan)

- 10/18:
- What content will the exam cover?
 - Everything through Hammett plots.
 - PSet 2, Q4?
 - It is, indeed, a singlet carbene because the oxygen's π -donor ability travels through the π -network.
 - The product only has *two* stereocenters! The 3-membered ring is symmetric.

Week 8

Molecular Relations & Quantification

8.1 Machine Learning

- 10/22:
- Lecture 12 recap.
 - Different electronic parameters capture different features of molecules.
 - Electronic parameters.
 - Hammett parameters (σ).
 - Examples include σ_p , σ_m , σ^+ , and σ^- .
 - Nucleophilicity and electrophilicity.
 - Examples include Mayr and Swain-Scott.
 - NMR or IR shifts.
 - You can also parameterize via the energy of certain electrons (e.g., σ , σ^* , lp, etc.).
 - Steric parameters.
 - A values: Historic.
 - Sterimol (L , B_1 , and B_5): Common.
 - Taft (E_s) and Charton for stereoelectronic.
 - Bite angle, cone angle, and PBV for sterics in catalysis.
 - Why do we use parameters?
 - Correlating parameters to reaction outcomes (e.g., rate, selectivity, etc.) lets us...
 - Predict reaction outcomes;
 - Design better catalysts;
 - Learn something about the reaction mechanism (this is especially important for this class).
 - Announcements.
 - Don't forget the exam!
 - This is Masha's last lecture. Fill out the teaching evaluations for Masha and Jonathan at the end of the course! Masha's evals will influence her tenure decision, and Jonathan's could help win him a teaching award.
 - Today: More complex relationships between the input parameters from last time and our output.
 - This is machine learning (ML)!
 - Masha will focus on the applications of ML to organic chemistry, but please read more about the math and other applications if you're interested!
 - There will be a lot of vocab in this lecture, starting with the definition of **AI**.

- **Artificial intelligence:** The development of computer systems able to perform tasks that normally require human intelligence. *Also known as AI.*
- Examples of such tasks.
 - Speech recognition, decision making, visual perception.
 - Not just things like calculus, but things that require a “greater” level of intelligence.
- Under the umbrella of AI falls **ML**.
- **Machine learning:** A subfield of AI that allows computer systems to learn and adapt without explicit instructions or programming. *Also known as ML.*
 - ML is characterized by the computer system being able to do things that we didn’t explicitly program it to do.
- In the context of ML, we also have an explicit definition of **learning**.
- **Learning:** A computer program is said to form some experience (E) with respect to a task (T) and a measure of performance (P ; aka the “performance metric”), if its performance on T — as measured by P — improves with E .
 - This gets into the Turing test, and what it really means to know and to learn and to be conscious. This is more the realm of philosophy, and we won’t get into that.
 - It’s not like it did great from the beginning; it’s that it had to get better with more experience.
- Reviews on the subject of ML in chemistry.
 - A great one to start for organic chemists: Williams et al. (2021). Four big-name corresponding authors.
 - Tobias Gensch: He’s new, but we’ll know him soon.
 - Sigman: The pioneer of multivariate linear regression.
 - Doyle: First to publish ML in chemistry; her 2018 *Science* paper — Ahneman et al. (2018) — exploded the field.
 - Anslyn: Wrote our textbook; the gold standard of Phys Orgo.
 - Any review published by Doyle or Sigman will be great to read.
 - There are also great reviews from Connor Coley, Bill Green, and Klavs Jensen.
- Types of learning: **Supervised** and **unsupervised**.
- **Supervised** (learning): ML that has **labeled** training data.
 - This type of ML analyzes the labeled data and then makes a guess on unlabeled data. After the model guesses, we evaluate its performance.
 - Example: Show my model 100 reactions (with their yields labeled), and then have it guess the yield of a new reaction it’s never seen before.
 - This is called “supervised” learning, because after the model guesses, *we* need to show it the right answer (i.e., the label).
 - Example: Spam filters.
 - These separate spam from “ham,” the technical term for good emails.
 - We train such models by showing them a bunch of spam emails and a bunch of ham emails so that they “learn” what spam looks like.
 - The model looks for typos, weird email addresses, requests for money, etc.
- **Labeled** (training data): A set of data in which each data point (or datum) has an input and output label.

- **Unsupervised** (learning): ML that has **unlabeled** training data.
 - This type of ML tries to uncover relationships between data and find patterns.
 - This is “unsupervised” because there is no right answer, no guidance, no yield.
 - A common approach: **Clustering**.
 - Example: Netflix recommends movies that are similar to each other (i.e., which share common actors, common runtime, common genre labels, common people who have watched them, etc.).
- **Clustering:** Grouping together similar data.
- A really common approach is to do both of these at once in **semi-supervised** learning, our secret third option.
- **Semi-supervised** (learning): ML that splits data into a small labeled dataset and a big unlabeled dataset.
 - We group data together and assign a label to the group.
 - Example: Image classification, i.e., to answer the question, “which photos are of the same animal?”
 - An unsupervised ML finds similar images, and then a few of those get labeled “cat,” so the whole group gets labeled “cat.”
 - This is how self-driving cars and Captcha work. When you help Captcha find all the images with stairs, you’re (nonconsensually) providing labels to help train image recognition models!
- We’ll focus on supervised learning for the rest of today.
- Two types of supervised learning: **Classification** and **regression**.
- **Classification:** The output/label is a category.
 - There are a finite number of options.
 - Example: Photos are “cat,” “dog,” or “human.”
- **Regression:** The output/label is a continuous number.
 - There are an infinite number of options.
 - Example: We could model the cost of a house as a function of house properties (e.g., the year it was built, the year we’re trying to buy it, the cost of the surrounding homes, the neighborhood school system, etc.).
 - Example: Model ΔG as a function of reaction parameters.
 - This is Hammett plots! That was linear regression, so that’s why we call this, “regression.”^[1]
 - Far more common in chemistry.
 - Formal definition: A statistical technique for determining the relationship between independent or explanatory variables (x) and dependent or response variables (y).
- **Linear regression:** Describe the relationship between x and y as a straight line.
 - Fitting to $y = mx + b$.
 - Example: $\log(k_X/k_H) = \rho\sigma$.
 - Some people don’t call this ML; they call this “statistics.” But that distinction is really only fought over by people who care about semantics or credit. So you may hear some strong opinions in the field (e.g., Sigman doesn’t call it ML), but it’s just labels at the end of the day (in Masha’s opinion).

¹Is there a “second time you hear it” effect in psychology that mimics ML? Unlikely to place emphasis on something the first time we hear it (e.g., Dad saying that there are crazy jobs for smart people/Maya telling me about the email tracker), but more likely when we hear it again (e.g., Carina Hong’s job/Dylan Miars telling me about the email tracker). Relation to retention in learning!

- **Multivariate** (linear regression): Multiple x and y variables.
 - This is all the work of Matt Sigman, building off of his classic Hammett paper (Figure 7.8) that we reviewed last lecture.
- The ML workflow: Here are the steps if you want to go into lab and plan a project.
 0. Know or define your goal and application.
 - Why do you want this model?
 - What do you want it to do?
 - Why do you want to use it?
 - Why would anyone care about it?
 - A model that can predict yield to a decimal point will need tens of thousands of data points.
 - If you want a model to help you refine a ligand for a reaction that you've already studied pretty well, that's a good use.
 - ML is fundamentally an engineering solution, so you better have a practical use for this tool you've built.
 1. Data collection.
 - How much data?
 - Labeled or unlabeled?
 - Will this data come from the literature or from experiment?
 - This is an especially relevant consideration in chemistry.
 - Be aware of bias; we, as a field, tend to overreport high-yield reactions and underreport low-yield reactions. So if we train a model based just on the literature, it will think all chemical reactions are high yield.
 - The adage here: Garbage in = garbage out.
 - If you train a model on bad data, you're going to have a bad model.
 - So we can go into the lab and get a bunch of low-yield reactions and feel good about it, which almost never happens!
 - Warning: If you go to Reaxys and dump a bunch of data into a model, the error rate is 30-60% (typos and such).
 - Notoriously, the patent database used to be 60% wrong due to bad data-scraping.
 2. Parameterization.
 - Categorical descriptors (common for solvents, salts, and additives).
 - Tell your model that these 10 were run in toluene, these 10 in DCM, etc. That's a common category approach.
 - Chemically meaningful parameters.
 - This is all of last lecture: σ values, sterimol values, etc.
 - These are chemically meaningful because they capture a feature important to reactivity.
 - Graph networks: Atoms are nodes, bonds are edges, etc.
 - Molecular fingerprints: Lists of functional groups.
 - Example: My molecule contains a ketone, an ester, two methynes, etc.
 - SMILES, or its derivatives: This is how ChemDraw encodes molecules.
 - Example: Cyclohexane is “C1CCCCC1”.
 - This string is just text, so then we can use LLMs.
 - Masha doesn't think these work that well, but they do exist.
 - Most ML papers mess up by this point: They either got bad data, or misrepresented it.
 - Most ML applications use millions or billions of datapoints, so chemistry is a bit unique in that it uses dozens of data points. How to make that tenable is a big question in both the chemistry and computer science communities!

3. Data preprocessing: Cleaning up the data for modeling.

- Technique: Normalization.
 - Make all parameters lie in the range of 0-1.
 - To do this, just divide by the maximum value.
 - Example: Sterimol values of 1, 4, and 8 become 0.125, 0.5, and 1; charge values of 0.01, 0.04, and 0.08 become 0.125, 0.5, and 1.
 - Normalization helps us make sure that the model doesn't think sterimol values are 100 times more important than charge. Essentially, it prevents bias toward parameters with large values.
- Technique: Reduce the number of parameters (if needed).
 - Sigman recommends 8 data points per single parameter.
 - If we have more parameters than data points, we have an **overfit** model (see Figure 8.1c), and that is no good.
- The simplest model architecture (Occam's razor) is the best model.

4. Data sampling: Splitting data into **training**, **validation**, and **test** sets.

- We also sometimes have an **out-of-sample** set.
- So we have a model, but just like in science, we need the model to make useful predictions for it to be a good model.
- In the validation set, the model is going to show us its performance.
 - Example: If linear regression does 70% right and multivariate linear regression does 90% right, we go with the multivariate architecture.
- Then the performance of the model that we report is the performance on the final (test) set.
- Overexposing your model to the test set invalidates the model; this is called **data leakage**.
- Note: Chemists tend to mix up the “validation” and “test” sets in their writing.
 - Just make sure that we have real evidence that the model works on *unseen* data.
 - If you see people say, “we used the validation set to test the model, and then applied the model to the test set,” that’s not a bad thing; that’s just a semantic error.

5. Training and testing: Evaluate the performance of different model architectures based on **metrics**.

- Example metrics: Accuracy, percent data explained, R^2 , RMSE (root-mean-square error).
- Here, we run control and baseline models to predict the average and mode.

6. Interpretation and prediction: Use the trained model to predict reaction results, guide catalyst design, or present mechanistic hypotheses.

- Best practice: Test the model experimentally.
- Relating back to Point 0: Make sure the model is worth making.
 - Make sure you use it for something cool; you don’t need a chainsaw to hammer in a nail.

- **Parameterization:** Converting chemical information to **machine-readable** formats.
- **Machine-readable** (input): A number, binary value, graph representation, etc.
- **Training** (set): The set on which the model learns the trends.
 - Roughly 70% of the data.
- **Validation** (set): The subset of the training set that help you choose between model architectures.
- **Test** (set): The set on which we evaluate the model performance.
 - Roughly 30% of the data.
 - The actual numbers here are up to you! People do everything from 90 : 10 to 60 : 40.
 - We really only want to use the test set once or twice.

- **Out-of-sample** (set): A set that helps us further validate generalizability or **extrapolation**. *Also known as experimental validation* (set).
- **Data leakage**: The mixing of data between the test set and the training set. *Also known as poor data hygiene.*
- **Extrapolation**: The ability to make predictions beyond the training set.
- Memo: Extrapolation vs. **interpolation**?
 - There definitely is a difference.
 - For an example of true extrapolation, see Sigman's paper on extrapolating a model trained on ligands with ee below 80% to find ligands with ee beyond 80%.
- Don't report your training set performance!
- **Overfit** (model): A model that can predict the training set, but not new data.
 - Such models cannot generalize, and they definitely cannot extrapolate.
 - See Figure 8.1c.
- There are actually three types of fitting.

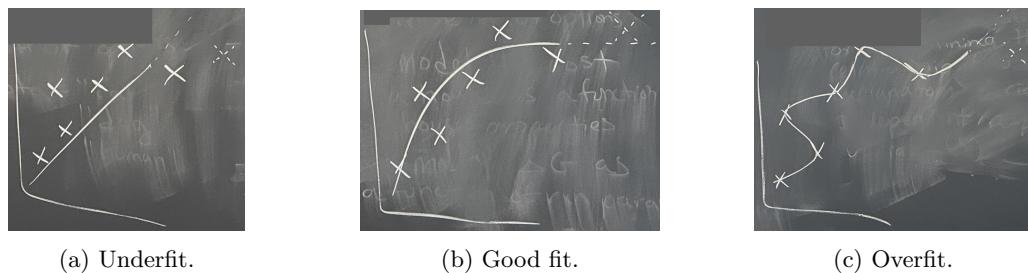


Figure 8.1: Fitting machine learning models.

- Figure 8.1a: Underfitting.
 - Doesn't generalize to new data.
- Figure 8.1b: Good fitting.
 - Generalizes well to new data.
- Figure 8.1c: Overfitting.
 - Doesn't generalize at all to new data.
 - This is tempting to chemists, because it gives them a good-looking model. But that's not actual model; that's fraud!
- Model architectures.

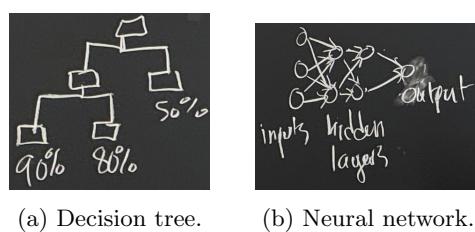


Figure 8.2: Machine learning model architectures.

- These exist on a spectrum from models with low complexity and high interpretability to models with high complexity and low interpretability.
 - Lowest complexity and highest interpretability: Linear regression.
 - k -nearest neighbors (knn).
 - Basic idea: Our ligand is close to something with high ee, so we'll probably get high ee, too.
 - Decision trees (Figure 8.2a).
 - Answer questions such as, "high electronegativity or low electronegativity," and correlates that to ees.
 - Random forest.
 - A subset of decision trees.
 - Make a lot of trees and average the result.
 - Called a "forest" because there are many trees!
 - Highest complexity and lowest interpretability: Neural networks (Figure 8.2b).
 - Like the brain: Inputs, through hidden layers, that converge on an output.
 - This year's physics Nobel Prize went to neural networks; Masha's not quite sure how these are physics, but they really have changed their game.
 - They're very powerful, but extremely complex (so often overfit and not very interpretable).
 - Called "black box models."
 - Not good for mechanisms!
- Masha also has some additional notes on model architectures that she will post on Canvas.

8.2 Noncovalent Interactions

10/24:

- Logistics.
 - Alex has led this class for several years at this point, and it is his favorite one to teach!
 - Goal for the remainder of the semester: Build out an increasingly deep foundation on molecular reactivity.
 - Thus far, we've learned about the intrinsic reactivity of certain things (e.g., carbenes); from now on, though, Alex will expand beyond intrinsic properties to talk about how molecules behave not only in isolation, but with other molecules and how these bits of reactivity manifest (sometimes in statistical ways).
 - A lot of stuff going forward may be review from physical chemistry, advanced organic, etc. This is not a problem! That's a feature of the graduate curriculum.
 - Especially if you've seen it before, be more inquisitive this time! Once you're familiar, be incisive.
 - If it's new, that's why we're here! Learn it now.
 - This should be an interactive lecture: Alex will pose questions and call on people if answers are not forthcoming.
 - The class style will be chalk-talk. The majority of what we need to know goes on the board, but not all!
 - If he riffs and says something exciting, write it down! It will not be in the notes, though.
 - 2 PSets and 1 exam this half-semester as well.
 - Exam 1 will likely be returned before next Tuesday.
 - Class begins at 10:35 on the dot, and Alex will talk until (not past) noon if he has enough to say.
- Alex is quite funny!

- We've learned a bit thus far about how molecules adopt their equilibrium shape (e.g., with Walsh diagrams).
 - Electronic control elements define intrinsic properties, which can tell us a great deal about reactivity.
 - Frontier MOs are very important, "as Ken Fukui and Roald Hoffmann taught us."
 - We will now layer on top additional forces that give us greater insight into how molecules behave when in proximity to others.
 - Unless you're a microwave spectroscopist, most of the chemistry we're interested in happens in a condensed medium.
- Later on: How these interactions affect a system, and how stimuli can modify that system.
- At the end of the class: Photochemistry and electron transfer, if we move apace.
- Today: **Noncovalent interactions**.
 - We'll list a bunch of forces; a not super fun lecture. But we'll reference all these forces going forward.
- **Noncovalent interaction:** An interaction between atoms (stabilizing or destabilizing) that does not occur pairwise through a covalent bond. *Also known as NCI.*
 - These are enthalpic and entropic forces that modulate molecular interactions.
- **Electrostatic** (interaction): A charge-charge interaction. *Also known as ion-ion interaction.*
 - Even in organic chemistry, a lot of charge densities can be generated.
 - Example: Ammonium ion held near a carboxylate.
 - To learn something about the overall energy of a system subject to this interaction, use **Coulomb's law**.
- **Coulomb's law:** If a charge q_1 is held a distance r from a charge q_2 , the energy of the system is given as follows. *Given by*

$$E = \frac{q_1 q_2}{4\pi\epsilon r}$$

Schematic



Figure 8.3: Schematic of an electrostatic interaction.

- ϵ is the **dielectric constant**.
- What's important here is that $\Delta E \propto 1/r$.
 - Not all forces have this energy relationship!
- **Dielectric constant:** The ability of a medium to isolate two static charges from each other. *Denoted by ϵ .*
 - This is *distinct* from ϵ_0 , which is the ability of a *vacuum* to isolate two static charges from each other!
 - Anslyn and Dougherty (2006) refers to the permittivity of the medium as ϵ_μ , and uses ϵ to denote ϵ_μ/ϵ_0 .

- Example of electrostatic interactions.

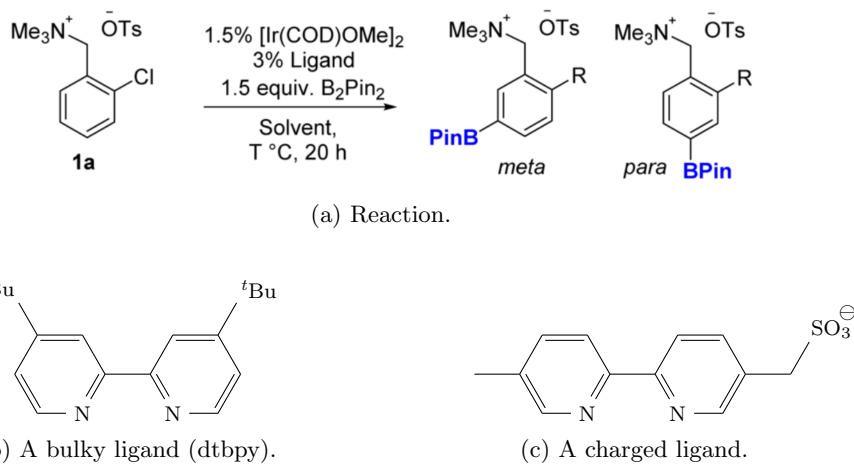


Figure 8.4: Electrostatic interactions in catalysis.

- A chloroarene bearing a pendant ammonium ion is subjected to catalytic borylation conditions (Figure 8.4a).
 - When a particular ligand is employed (Figure 8.4b), the catalyst delivers the Bpin to the position remote from the charged group (*para*) favorably over the *meta*-position in a 2 : 1 ratio.
 - However, use of a complementarily charged ligand (Figure 8.4c) led to the complete inverse regiochemistry — and with an improved selectivity of 10 : 1!
 - The dielectric can also modify this: More polar solvents with higher dielectrics erode selectivity.
 - Reference: Davis et al. (2016).
- Also out of the Phipps lab at Cambridge!

- **Charge-dipole (interaction):** An NCI between a point charge and a dipole. *Given by*

$$E = \frac{\mu q_2 \cos(\theta)}{4\pi\epsilon r^2}$$

Schematic



Figure 8.5: Schematic of a charge-dipole interaction.

- μ is the **dipole moment**.
- We can number charges q with subscripts or superscripts.
- Again, higher dielectrics screen the charge better.
- Here, $\Delta E \propto 1/r^2$.
- Example: The attraction between a carbonyl and a Li^+ ion, e.g., carbonyl activation by a Lewis acid!
- **Dipole moment:** A measure of the separation of positive and negative electrical charges within a system; that is, a measure of the system's overall polarity. *Denoted by μ . Units D “debye”*

- These are both great, but many organic molecules are uncharged.
- **van der Waals** (interaction): An NCI between uncharged molecules.
 - Can be either attractive *or* repulsive.
 - Several subsets.
 - I.) **Dipole-dipole interactions.**
 - II.) **Dipole-induced dipole interactions.**
 - III.) **Dispersion forces.**
- **Dipole-dipole** (interaction): An NCI between two dipoles fixed in the same plane and parallel. *Given by*

$$E = -\frac{\mu_1 \mu_2 (3 \cos^2 \theta - 1)}{4\pi \epsilon r^3}$$

Schematic

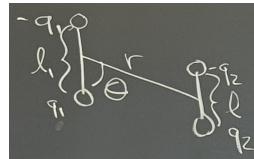


Figure 8.6: Schematic of a dipole-dipole interaction.

- Here, $\Delta E \propto 1/r^3$!
- If the dipoles align, this can stabilize the system, building up hierarchical interactions that can even lead to self-assembly (e.g., in the case of polymers).
- Example: Solid-state NMR with **magic angle spinning**.
- See Anslyn and Dougherty (2006, p. 168).
- **Magic angle spinning:** When you optimize the dipole-dipole interaction energy expression to have $E = 0$ by setting $\theta = 54.7^\circ$ (aka, the “magic angle”).

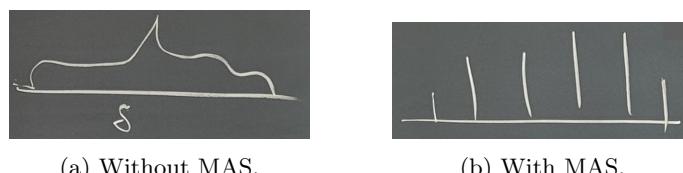


Figure 8.7: Magic angle spinning.

- Essentially, a “normal” solid-state NMR spectrum has a bunch of the anisotropy and broad linewidths.
- However, suppose we fix the sample in the magnetic field at 54.7° . Then we spin the crap out of it ($\approx 10\,000$ rpm). In this case, you get really fantastic tight lines from which you can read out the chemical shift tensor.
- David: Why is there only one θ in Figure 8.6?
 - Look at an intro physics or linear algebra textbook.
 - There are more degrees of freedom that we can introduce, but this is all we need for right now. If the dipoles are not parallel or in the same plane, the equation gets more complicated but the critical $\Delta E \propto 1/r^3$ relation always remains true.

- **Dipole-induced dipole** (interaction): An NCI in which one dipole induces a dipole in a **polarizable** molecule, and the two attract. *Also known as Debye force. Given by*

$$E = \frac{\mu^2 \alpha}{r^6}$$

- Example: Taking a polar molecule (like water) and bringing it close to something polarizable like an arene, so that the two attract.
- See Anslyn and Dougherty (2006, pp. 187–88).
- **Polarizability**: The susceptibility of an atom or molecule's electron cloud to being pushed around or distorted. *Denoted by α .*
 - α is called the **polarizability tensor**.
 - Indeed, polarizability can be quantified as a tensor (not a vector).
 - See Anslyn and Dougherty (2006, pp. 24–25).

- **Disperson** (interaction): An NCI between the quantum-mechanically arising, correlated motions of electrons between molecules. *Also known as London force. Given by*

$$E = \frac{\alpha_1 \alpha_2}{r^6}$$

Schematic



Figure 8.8: Schematic of a dispersion interaction.

- Any single electron induces a small correlation, but many electrons can induce some big correlations in bigger molecules.
 - Longer molecules also maximize dispersion forces.
- Governed by the Pauli exclusion principle: We can't fit more than two electrons into the same orbital, so electrons will still not “hop” between molecules.
- Example of dispersion forces: Silylenes.

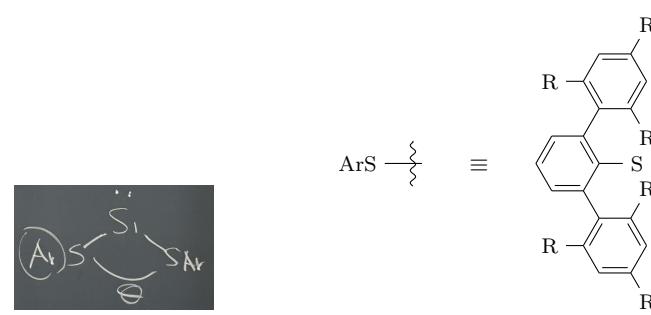


Figure 8.9: Dispersion forces bend silylenes.

- Silylenes are the silicon analog of carbenes (Figure 8.9a).
 - We've already talked about carbene bending in this course.
 - Here's an additional note, though: There are both electronic *and* steric reasons why a carbene would bend at a certain angle, since the electronic preference for some angle has to overcome the steric clash.
 - The same is true of silylenes.
- Consider a silylene with two terphenyl thiolate ligands (Figure 8.9b).
 - Such ligands are a lot to look at, but they're really easy to make.
 - When $R = Me$, $\theta \approx 90.5^\circ$.
 - Note that this is a smaller angle than either singlet or triplet carbenes (see Figure 5.15) because the heavier **cogeners** of carbon tend to be more bent.
 - When $R = iPr$, $\theta \approx 84.8^\circ$.
 - Thus, when the terphenyl thiolate ligands are bulkier, the silylenes are *more* bent!
 - Steric repulsion is being overcome somehow.
- Why this counterintuitive result?
 - Steric interactions are not necessarily repulsive! We've all been lied to.
 - Why? Recall the **Lennard-Jones potential**.
 - At large distances, two atoms have an energy as if they're not interacting at all.
 - As you bring them together, you get a stabilizing interaction until the nuclei begin repulsing, giving you an equilibrium bond distance.
 - Implication: Things must be *very* close together to get steric repulsions; there are bonding interactions that occur at far greater systems.
 - Steric properties of molecules are not always repulsive.
 - This is a universe-level phenomenon that matter tends to condense.
 - This is a profound insight that is animating a lot of method development in organic chemistry right now.

- **Cogeners:** Chemical substances related to each other by origin, structure, or function.
- **Lennard-Jones (potential):** A mathematical energy potential that fairly well approximates the energy of two binding atoms as they are brought closer together. *Given by*

$$E \propto \frac{A}{r^{12}} - \frac{B}{r^6}$$

Graph

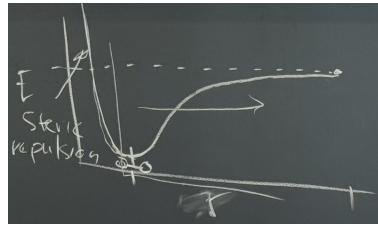


Figure 8.10: Lennard-Jones potential.

- Most Lennard-Jones potentials have the 12-6 form transcribed above.
- This concludes our discussion of van der Waals interactions.

- **Quadrupole:** Something that has the shape/topology of a d -orbital.
- Examples of quadrupoles.

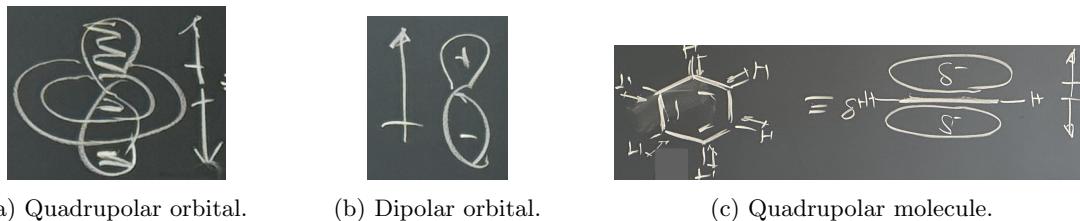


Figure 8.11: Quadrupole examples.

- A d_{z^2} orbital has two dipoles that cancel each other out (Figure 8.11a).
 - In contrast, dipoles are like p -orbitals (Figure 8.11b).^[2]
 - Note that orbitals aren't polar; these analogies are given to illustrate phasing properties.
- You don't need a d -orbital to have a quadrupole, though — they exist in organic chemistry, too!
- Example of quadrupolar molecules in organic chemistry: Benzene (Figure 8.11c).
 - All C–H bonds have dipoles that cancel each other out.
 - However, the net transfer of electron density increases the electron density in the π -cloud, even as it depletes the electron density at the hydrogens.
- Example of quadrupolar molecules in organic chemistry: CO_2 .
- Just like we have charge-dipole interactions, we can have **charge-quadrupole** interactions.
- **Ion-quadrupole** (interaction): An NCI between a cation and the face of a quadrupole.
 - Different atoms in the periodic table have different electronegativities, which we know thanks to Linus Pauling's building on Dmitri Mendeleev's foundation.
 - These are most commonly encountered when we have an arene and we bring in an ion on top.
 - Leads to a net-stabilizing interaction between the ion and the charged molecule.
 - See Anslyn and Dougherty (2006, pp. 181–83).
- Example: K^+ and benzene.

Figure 8.12: Ion-quadrupole interaction of K^+ and benzene.

- These two species' gas phase binding enthalpy is $\Delta H = -19 \text{ kcal/mol}$.
- For comparison, the gas phase binding enthalpy of K^+ and H_2O is $\Delta H = -18 \text{ kcal/mol}$.
 - This shows that ion-dipole and ion-quadrupole interactions are about similarly intense, even though benzene doesn't really have charged regions.
 - This is surprising, in Alex's opinion.
- Reference: Sunner et al. (1981).

²Alex drew the dipole arrow in the inverse direction here by accident.

- Example: Ions and benzene.

M^+	$-\Delta H$
Li^+	38.3
Na^+	28.0
K^+	19.2
NH_4^+	19.3
NMe_4^+	9.4

Table 8.1: Ion-quadrupole interactions with benzene.

- Ion-quadrupole interactions are subject to a size dependence.
- Specifically, harder ions bind better to quadrupoles, and softer ones binds worse.
- This is consistent with the inverse distance dependence in all of our interaction equations.^[3]
- See Dougherty (1996), specifically the section entitled “The Fundamental Interaction: Gas-Phase Studies” and refs. 2-7 cited therein.
- Example: The effect of arene substituents on ion-quadrupole interactions.
 - Look it up if we’re so inclined!!
 - Alex goes deep into this topic many years, “but this year, I’m like f it.”
 - Reference: Mecozzi et al. (1996).
 - By Dennis Dougherty, of Anslyn and Dougherty (2006)!
- Example: Cation- π interactions in biology.
 - Proteins stabilize charged species within them, even when solvated in a high dielectric (H_2O) at physiological pH ($pH \approx 7$). How do they do this?
 - Water is great at solvating charged species, so to incorporate charged species, proteins have to pay a desolvation penalty.
 - Proteins definitely don’t work by allowing water inside them: In fact, enzymes and proteins adopt a tertiary structure that often excludes water into the bulk.
 - Thus, the solution is that proteins use ion-quadrupole interactions (with aromatic residues).
 - Takeaway: Nonpolar, hydrophobic arenes can stabilize cations even in aqueous media.
 - Example: Would benzene or a carboxylate anion stabilize the trimethylammonium cation more?
 - Gas phase: The binding of trimethylammonium to benzene ($\Delta H = -19$ kcal/mol) is far more stabilizing than its binding to acetate ($\Delta H > 100$ kcal/mol).
 - In water: There is so much dielectric stabilization that binding to benzene is weaker ($\Delta H = -5.5$ kcal/mol), and binding to acetate doesn’t do that much at all ($\Delta H = -2.2$ kcal/mol).
 - Corollary: Proteins can take carboxylic acids and modulate their pK_a over multiple log-units via enclosure in a hydrophobic environment.
 - Aside: This is a case of a biological phenomenon being explained by physical chemistry.
 - If you believe that biology lends greater insight into the physical world, good for you!
 - Alex, personally, would rather just look at physical systems though.
 - Reference: Dougherty (1996).
 - By Dennis Dougherty again!

³Note: HSAB (as a polarizability- and dispersion-directed phenomenon) does indeed favor the binding of “soft” benzene to “soft” ions, but the fact that we see this relationship here implies that electrostatics (i.e., classical ion-quadrupole attractions) are *more* active in determining benzene’s affinity for cations (Dougherty, 1996, pp. 163–64).

- **Apparent** (interaction): An NCI that is frequently alluded to in the literature, real, and yet has no fundamental physical basis.

- This is Alex's term; we won't hear about "apparent" interactions anywhere else.
- Several subsets.

I.) **π - π interactions.**

II.) **Hydrogen bonds.**

- **π - π** (interaction): An NCI between two (typically aromatic) π -systems.

- The physical basis for such interactions is probably very complex.
- See Anslyn and Dougherty (2006, p. 184).

- There are three main types of π - π interaction geometries.

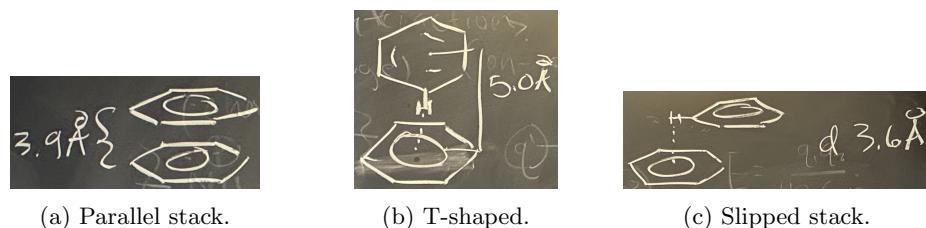


Figure 8.13: π - π interaction geometries.

1. The **parallel stack** of two centroids.
 2. The **T-shaped geometry**.
 3. The **slipped stack geometry**.
- **Parallel stack** (geometry): A π - π interaction geometry in which the two centroids stack their π -systems on top of each other.
 - The equilibrium distance is about 3.9 Å.
 - Important for electronic transport through adjacent π -systems, but not relevant to us today.
 - Energy: $\Delta H = -1.7 \text{ kcal/mol}$.
 - **T-shaped** (geometry): A π - π interaction geometry in which a region of negative electrostatic potential (the face of one ring) is in contact with a region of positive electrostatic potential (the edge of the other). *Also known as edge-to-face.*
 - The equilibrium distance is about 5.0 Å.
 - Energy: $\Delta H = -2.6 \text{ kcal/mol}$.
 - This is more stable than the π -stack!
 - **Slipped stack** (geometry): A π - π interaction geometry consisting of coplanar π -systems with a dislocation between the centroids. *Also known as displaced.*
 - The equilibrium distance is about 3.6 Å.
 - Energy: $\Delta H = -2.6 \text{ kcal/mol}$.
 - Thus, this geometry is still more stable than the conventional parallel stack.
 - Implication: There's nothing intrinsic about arenes that makes them want to π - π stack, and this phenomenon will be generalized to other types of species.

- There are two main models through which to view the phenomenon of π - π interactions.
 1. The **Wheeler-Houk model**.^[4]
 2. The **Grimme dispersion model**.^[5]
 3. As a possible third, Brent Iverson (UT-Austin) has many beautiful papers on π - π stacking.
 - The papers are a bit pedantic, but “I’m [Alex is] a pedant.”
- **Wheeler-Houk** (model): A model of π - π stacking predicated on direct interactions.
 - Wheeler and Houk found (computationally and experimentally) that it’s not the π -faces that interact, but the substituents on the arene that have a quadrupolar interaction with the other arene below.
 - Their model works for substituted arenes.
 - Reference: Wheeler and Houk (2008).
- **Grimme dispersion** (model): A model of π - π stacking which posits that more extended π -systems facilitate and maximize dispersion.
 - This model is more descriptive as we get to larger π -systems.
- This concludes our discussion of π - π interactions; we now move onto hydrogen bonding.
- **Hydrogen bond**: An NCI between a donor of the form A–H and an acceptor of the form B. *Schematic*

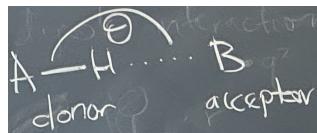


Figure 8.14: Schematic of a hydrogen bond.

- This is a really ill-defined suite of physical phenomena that — all the same — we humans can classify really well.
 - There is (at least) an electrostatic component, an ion-dipole moment, some covalency, etc.
 - Review (the sacred text of hydrogen bonds): Steiner (2002).
 - There is a continuum of hydrogen bonds — from strong to moderate to weak — that is characterized by the distance between the H-bond donor and acceptor as well as the angle, resulting in an energy of stabilization.
 - Strong: 1.2-1.5 Å and $\theta = 175^\circ - 180^\circ$, $\Delta E = 14 - 40$ kcal/mol.
 - Large degree of covalency.
 - Moderate: 1.5-2.2 Å and $\theta = 130^\circ - 180^\circ$, $\Delta E = 4 - 15$ kcal/mol.
 - More electrostatic in nature.
 - Weak: 2.3-3.2 Å and $\theta = 90^\circ - 150^\circ$, $\Delta E < 4$ kcal/mol.
 - Even 4 kcal/mol can upend selectivity.
 - Thus, even these are important!

⁴“HOWK”

⁵“shteh-FAHN GRIM-uh,” a professor at the University of Bonn.

Week 9

Reaction Energetics

9.1 Equilibria

10/29:

- Lecture 14 continued: Examples of hydrogen bonds.
- Alex reviews strong, moderate, and weak hydrogen bonds (see Figure 8.14 and discussion).
- Canonical hydrogen bonds.
 - Those in the bifluoride anion (HF_2^-).
 - Held together by such a strong hydrogen bond that it is stable and isolable.
 - Energy on the order of 39 kcal/mol.
 - Those between H_2O and H_3O^+ .
 - Relatively strong, persistent in solution, etc.
 - Energy on the order of 33 kcal/mol.
 - Those between H_2O and H_2O .
 - The loss of the charge leads to a significant decrease in strength.
 - Charge-assisted hydrogen bonds are typically stronger!
 - Energy on the order of 5 kcal/mol.
 - Fluoroform (CHF_3) in water.
 - Energy on the order of 3 kcal/mol.
- Geometric parameters relevant to hydrogen bonding (find these in crystallographic/biological databases).
 - Donor-acceptor bond length, and donor-acceptor bond angle.
- The prevalence of different kinds of hydrogen bonds vs. the bond angle.

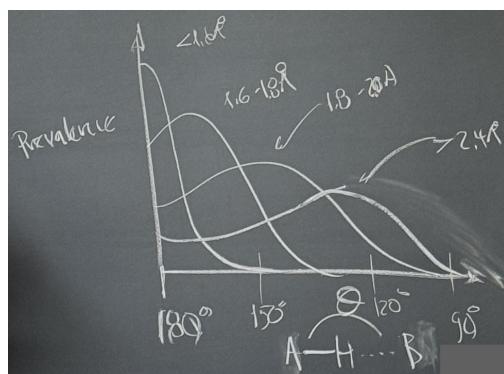


Figure 9.1: Stronger hydrogen bonds are more linear.

- We can think of this plot like a histogram.
- Takeaway: Stronger bonds are more linear, and weaker bonds are more bent.
- As the bond gets weaker, the molecules begin to explore a larger cone of orientations.
- Example: H-bonding in carbonyl species.

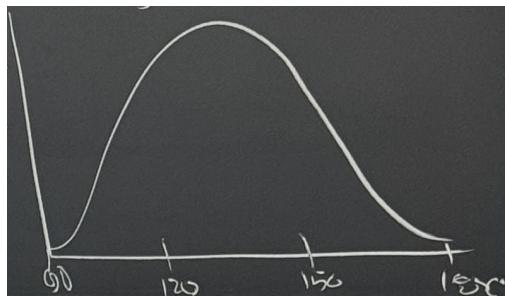


Figure 9.2: Carbonyl hydrogen bonds reflect O(sp^2) hybridization.

- We're looking at the carbonyl C=O⁺–H bond angle.
- These bonds cluster around an area consistent with protonation of one of the lone pairs.
- This indicates that protons' mobile electron density is held to static carbonyl electron density.
- What about thiocarbonyls? What if we replace oxygen with its heavier sulfur analog? This may be on PSet 3!!
- Aside: Anslyn and Dougherty (2006) replaced a much older, worse book.
 - An ambitious book due to its breadth, but may alight or mangle details for a given topic.
 - Suffice to say, it's the best book we've got.
- **Hydrophobic effect:** It is energetically costly to solvate nonpolar molecules in H₂O.
 - Dennis Dougherty's opinion: The hydrophobic effect is the most powerful force in biological chemistry.
- Illustrating the hydrophobic effect.

Solute	$\Delta G_{\text{tr}}^\circ$ (kcal/mol)	ΔH	$-T\Delta S$
PhH	4.62	0.50	4.12
PhMe	5.47	0.41	5.06
<i>n</i> -hexane	7.78	0.00	7.78

Table 9.1: Hydrophobic effect examples.

- Defined by the energy penalty $\Delta G_{\text{tr}}^\circ$ to put a given solute in water.
- To put *n*-hexane into water, it costs about $\Delta G_{\text{tr}}^\circ = 7.78$ kcal/mol.
 - We can actually parse this in terms of its specific enthalpy and entropy.
 - $\Delta H = 0.00$. It's a wash in terms of dipole effects and energy interactions and everything.
 - $-T\Delta S = 7.78$. It's all in the entropy.
- It's every so slightly more favorable to put benzene or toluene in water thermodynamically.
- Chemists are pretty good at estimating enthalpy, but pretty bad with entropy.
 - Alex's goal for this class: We should all leave with a better understanding of entropy.

- Conclusion: The energetic penalty is mostly entropic.
 - If we put a hydrophobic link in the water, it disrupts the water's ability to randomly hydrogen bond with itself.
 - Less ability to H-bond means less dynamic and more ordered water, driving the hydrophobic effect. This is the best hypothesis we have so far; it's still hard for Alex to wrap his head around.
 - There's many chemists who study water, still!
- References.
 - Southall et al. (2002).
 - Grunwald and Steel (1995).
- We've indicated a couple of instances here where knowing a molecule's structure is not enough to predict its reactivity!
 - *n*-hexane reacts differently as its own system vs. in H₂O.
 - We need to appreciate with greater clarity how thermodynamics operate in chemical systems.
- We now begin Lecture 15.
- Today: Reaction energetics.
 - Goal for the next two lectures: Understand how differences in free energy impact...
 - 1) Equilibria (today);
 - 2) Kinetic rates (next time).
- Overview concepts.
 - Consider a reaction

$$A \rightleftharpoons B$$
 - How do we understand such a reaction on a systems level, rather than on a molecular basis?
 - A good place to start is with a reaction coordinate diagram.
 - What we put on the *y*-axis will matter quite a bit.
 - We'll stick with ΔE (generic energy change) for now, and then get to ΔG .
 - The *x*-axis is the reaction coordinate along an arbitrarily defined interval 0-1.
 - The minima relative heights of the energy minima for A and B give us information about the position ΔG_{rxn} of the equilibrium.
 - This same formalism (with ΔG^\ddagger) allows us to learn about the rate as well.
- Recall gas phase dissociation.

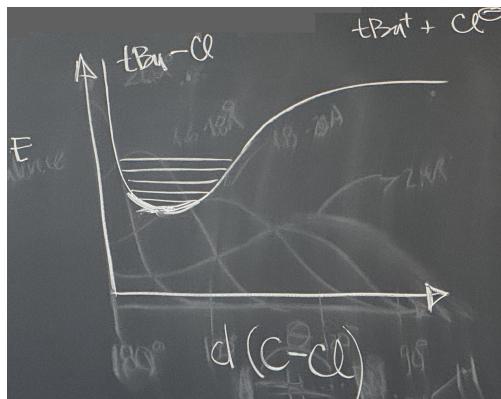


Figure 9.3: Energy diagram for the gas-phase dissociation of *t*-butyl chloride.

- Consider $t\text{Bu}-\text{Cl}$.
- The energy diagram is just Lennard-Jones, again.
- The vibrations of the C–Cl bond along this potential surface are quantized. If you add enough energy, the ions can ping apart into $t\text{Bu}^+$ and Cl^- .
- Most reactions do not occur in the gas phase, though; they occur in condensed media.
- In the condensed phase, dissociation looks a bit different.

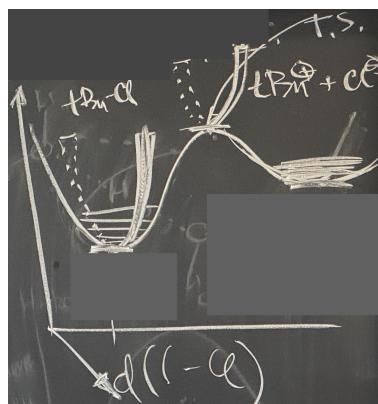


Figure 9.4: Energy diagram for the condensed-phase dissociation of *t*-butyl chloride.

- Bonds are still stable, but the ions will now be stabilized by the condensed media.
- There is a transition state along the potential energy surface.
 - This corresponds to some bond length where the atoms are separating but not yet solvated.
- Degrees of freedom of a molecule: $3N - 6$ or $3N - 5$ degrees of vibrational freedom.
 - Bear in mind that any potential energy surface that we draw is just a cut of the real surface.
 - These graphs help by zooming in on a given reaction coordinate. We get to define this though; there's nothing intrinsic about one reaction coordinate over any other.
 - Additional degrees of freedom may be represented as orthogonal paraboloids.
- The total derivative of the multidimensional potential energy surface $dE/dr = 0$ at local minima.
- Let r be the variable corresponding to our choice of reaction coordinate.
 - $\partial^2 E / \partial r^2 > 0$ at stable structures along the reaction coordinate.
 - $\partial^2 E / \partial r^2 < 0$ at the TS along the reaction coordinate.
- TS's have to be **first-order saddle points**.
- **First-order saddle point:** A point on a multidimensional surface that is a minimum along all the orthogonal vectors except one, on which it is maximized.
 - In our case, the one vector along which the saddle point is maximized is the reaction coordinate.
- Sergei: Why does the energy keep going up as the ions get farther apart? Shouldn't it just stop?
 - The other well *will* be anharmonically a well due to electrostatic interactions.
 - It might keep going up very shallowly, but it will still keep going up.
 - You can think of this as a residual effect of the solvated ions tugging on each other; even when solvated, opposite charges attract per the laws of physics, and it's more stable for them to be a meter apart than 2 meters apart.

- We now look at two-state systems.
 - This is a system in which two states A and B are in equilibrium via $A \xrightleftharpoons{K} B$.
 - K is defined by $K = [B]/[A]$.
 - Energetically, $\Delta G = -RT \ln K_{\text{eq}}$ and hence $K_{\text{eq}} = e^{-\Delta G/RT}$.
- Example: The two chair conformations of methylcyclohexane.
 - At 300 K, $K_{\text{eq}} = 19/1$ in favor of the equatorial position.
 - Here, $\Delta G = 1.74 \text{ kcal/mol}$ (this is the A-value for a Me group!).
- We can generalize this to useful energies.

Species		ΔG_{rxn} (kcal/mol)		
[A]	[B]	$-78^\circ\text{C} = 195\text{ K}$	$rt = 300\text{ K}$	$100^\circ\text{C} = 373\text{ K}$
1	1	0	0	0
1	2	0.27	0.41	0.51
1	10	0.89	1.37	1.71
1	100	1.78	2.74	3.41

Table 9.2: Free energy differences required for a given product distribution at different temperatures.

- Different ratios of products have different ΔG_{rxn} .
- The ΔG_{rxn} values are also different at different temperatures.
- Takeaways.
 - The position of an equilibrium is temperature dependent.
 - The energy differences needed to drive reactions significantly to completion are very small.
- Bond enthalpies are huge; the chemistry that we do in the condensed phase is *so* subtle.
 - Designing new reactions requires mastering subtle energies.
- The partition of species is given by Boltzmann distributions at different temperatures; this explains the table.
 - Essentially, per the Maxwell-Boltzmann distribution, higher temperatures lead to increasing thermal populations of excited states, so it takes a bigger energy difference to maintain selectivity.
- A quantitative analysis of equilibria (ΔG°) is constituent of both...
 - An enthalpy component (ΔH°);
 - Units: kcal/mol.
 - Coming from bond strengths and NCIs.
 - $\Delta H > 0$ is endothermic; distinct from endergonic ($\Delta G > 0$).
 - $\Delta H < 0$ is exothermic; distinct from exergonic ($\Delta G < 0$).
 - An entropy component (ΔS°).
 - Units: e.u. = cal/(mol K).
 - Entropy units are a measure of disorder.
 - This is a reflection of Boltzmann's law on microstates, $S = R \ln \Omega$, where Ω is the number of microstates available.

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

- Theoretically, begin finding a linear equation of the form $y = mx + b$ where m and b correspond to ΔH° and ΔS° , and y and x correspond to observables. In particular, we find

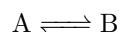
$$\begin{aligned} -RT \ln K_{\text{eq}} &= \Delta H^\circ - T\Delta S^\circ \\ R \ln K_{\text{eq}} &= -\Delta H^\circ \left(\frac{1}{T} \right) + \Delta S^\circ \end{aligned}$$

- Note that the first equality comes from the fact that the quantities on both sides of the equation equal ΔG° .
- So we experimentally measure K_{eq} at a range of temperatures and then use linearization to determine ΔH° and ΔS° .
- These are super fun and satisfying to do because when it works, you can just read out the chemical potential directly from an observable.
- Massive caveat: There are a limited range of temperatures under which an equilibrium can be established.
 - So we're only assaying an extremely small temperature range.
 - Thus, small systematic errors can lead to wide variation in the extrapolated values. So we need to treat these analyses with care.
- Moving on, consider a bimolecular reaction.
 - For example, consider oxidative addition of an aryl chloride to a palladium catalyst.
 - Two things become one in this step.
 - The reaction enthalpy will obviously depend on the bonds broken and formed, but what will be the qualitative sense of entropy?
- Qualitative prediction of equilibria.
 - How do we estimate the position?
 - Proton-transfer values can be helpful.
 - $\text{AH} + \text{B} \longrightarrow \text{A}^- + \text{HB}^+$.
 - Proton affinity and acidity report indirectly on the stability of the conjugate bases.
 - $pK_a = -\log K_a$, so $\Delta G = -1.4pK_a$. “A log unit gives 1.4 kcal/mol.” Therefore, we can know something about the energetics by looking at this reactive intermediate!
 - We can also follow H-atom transfers.
 - Look at alkane transfers; $\Delta \text{BDE} = \Delta H$.
 - Hydride ion affinity can also help us; these values are tabulated with respect to cation stability.
 - How do we estimate the entropy?
 - A fragmentation releases about 30 e.u., and a joining of a catalyst to a molecule costs about 30 e.u.. 30 e.u. times 300 K gives you about 9 kcal/mol! So the new bonds formed must exceed 9 kcal/mol.
 - You can't just do bonds formed and broken; “nah, man; you need 9 kcal/mol; that's real energy!”

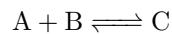
9.2 Transition State Theory

10/31:

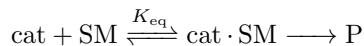
- Lecture 15 continued.
- Consider a simple equilibria of the following form.



- We can characterize it by $\Delta G = -RT \ln K_{\text{eq}}$.
- We can parse ΔG in terms of ΔH and ΔS using the van't Hoff analysis.
- We now show that $\ln K_{\text{eq}}$ (and hence K_{eq}) is unitless for this equilibrium.
 - Units of ΔG : kcal/mol.
 - Units of T : Temperature.
 - Units of R : kcal/(mol K).
 - Therefore, $\ln K_{\text{eq}}$ is unitless since all units cancel in the equivalent fraction $\Delta G/RT$.
 - It follows that K_{eq} is unitless.
 - We can also see this from the fact that the two molarity units cancel.
- We can also characterize the equilibrium constant as $K_{\text{eq}} = [B]/[A]$.
- We can have much more complex equilibria, too, such as multicomponent equilibria.
- Consider the following associative equilibrium.



- Here,
- Hence, K_{eq} has units of M^{-1} .
- This implies that ΔG is concentration dependent!
 - This is a profound statement.
- Consequence: A catalyst operating on a starting material.



- Example: TM catalyst on organic substrate, enzyme on a biological substrate.
- Assume: $K_{\text{eq}} = 100$ and 1 mol% catalyst.
- Let's think about this reaction sequence.
 - Consider the percent of catalyst bound by the starting material, i.e.,

$$\frac{[\text{cat} \cdot \text{SM}]}{[\text{cat}]_T}$$

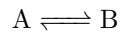
where $[\text{cat}]_T$ is the total amount of catalyst, bound and unbound.

- During the course of the reaction, the position of the equilibrium will decay. At some point, there will be more catalyst than SM!
- Case A (near 1 M SM): On a potential energy surface, $\text{cat} \cdot \text{SM}$ (the catalyst resting state) is lower in energy than the complex.
- Case B (low SM concentration): Less $\text{cat} \cdot \text{SM}$ at equilibrium. So potential energy surfaces are *not* static; they can depend on concentrations.
- It's not K_{eq} changing, but that Q is concentration dependent?? But Q can change ΔG , sure.

- So how do we standardize conditions to standard states?

– Use ΔG° , ΔH° , and ΔS° !

- Defining a standard state.



– Consider a simple two-state equilibrium to start, like the above.

– Define the equilibrium constant K_{eq} as before.

$$K_{\text{eq}} = \frac{[B]_{\text{eq}}}{[A]_{\text{eq}}}$$

– We now define another ratio at some arbitrary time t with some non-equilibrium concentrations.

$$Q = \frac{[B]_t}{[A]_t}$$

– Then we can define the free energy ΔG of a system at any time point with respect to the equilibrium!

$$\Delta G = -RT \ln \left(\frac{K_{\text{eq}}}{Q} \right) = \Delta G^\circ + RT \ln Q$$

■ This value tells us the tendency of the reaction to proceed to equilibrium under *any* conditions.

■ You can also think of this as the driving force at a given time point.

■ This *rigorously* tells us that $\Delta G = 0$ at equilibrium.

– We can also define the standard state

$$\Delta G^\circ = -RT \ln K_{\text{eq}}$$

in which $Q = 1$.

■ This value tells us about the tendency of the reaction to proceed to equilibrium under *standard* conditions.

- Example: Assume $K_{\text{eq}} = 3$ in a simple equilibrium $A \rightleftharpoons B$.

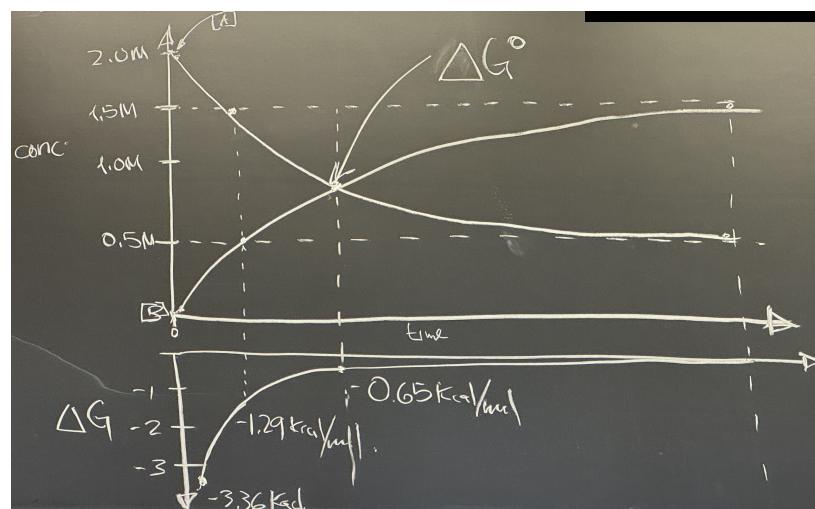


Figure 9.5: A time course vs. free energy.

- Let $[A]_0 = 2 \text{ M}$ and $[B]_0 = 0 \text{ M}$.
- Then in the end, $[A]_{\text{eq}} = 0.5 \text{ M}$ and $[B]_{\text{eq}} = 1.5 \text{ M}$.
- Consider a time course, i.e., how the concentrations change in time.
- After mixing the compounds, as quickly as we can get to the NMR, we take a time point.
 - So $[A]_1 < 2 \text{ M}$ and $[B]_1 > 0 \text{ M}$ slightly.
 - Suppose that specifically, $[A]_1 = 1.98 \text{ M}$ and $[B]_1 = 0.02 \text{ M}$.
 - Then $Q_1 = 0.01$, so $\Delta G_1 = -3.36 \text{ kcal/mol}$.
- Now underneath, we plot the free energy vs. time.
- $[A]$ decreases to equilibrium and $[B]$ increases to equilibrium over time.
- Second time point.
 - Suppose that specifically, $[A]_2 = 1.5 \text{ M}$ and $[B]_2 = 0.5 \text{ M}$.
 - Then $Q_2 = 0.33$, so $\Delta G_2 = -1.29 \text{ kcal/mol}$.
- Third time point.
 - Suppose that specifically, $[A]_3 = 1 \text{ M}$ and $[B]_3 = 1 \text{ M}$.
 - Then $Q_3 = 1$, so $\Delta G_3 = -0.65 \text{ kcal/mol}$.
- Fourth time point.
 - Suppose that specifically, $[A]_{\infty} = 0.5 \text{ M}$ and $[B]_{\infty} = 1.5 \text{ M}$.
 - Then $Q_{\infty} = 3$, so $\Delta G_{\infty} = 0 \text{ kcal/mol}$.
- The third time point is ΔG° since $Q = 1$!
 - So standard conditions start to tell us a bit about how the reaction goes.
- This concludes Lecture 15.
- Today: Transition state theory.
- Empirical observation: The rate of the reaction is proportional to the following.

$$\text{rate} = Ae^{-E_a/RT}$$

- This is the **Arrhenius law**.
- Even before we knew what atoms were, we could track the process of a reaction.
- What unified and predicted the Arrhenius law was a theoretical development from the 1930s called Transition State Theory.
- Two key assumptions.
 1. A so-called “activated complex” may be viewed as being in quasi-equilibrium with the starting material.
 - Essentially, reformulate $A \longrightarrow B$ as

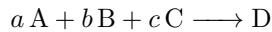


- This allows us to bring to bear our mathematical treatment of equilibria on a kinetic argument.
 - Call the quasi-equilibrium constant K^\ddagger , where
- $$K^\ddagger = \frac{[\text{TS}]}{[A]}$$
2. Any molecule that makes its way to the transition state will then proceed onto the product barrierlessly.

- Thus, we can say that the rate of reaction is given by the following.

$$\text{rate} = \frac{d[B]}{dt} = k^\ddagger[\text{TS}] = K^\ddagger k^\ddagger [\text{A}]$$

- This winds up being useful for a variety of reasons.
- In particular, we can extrapolate this simple analysis to other processes with higher molecularity.
- Example: We can learn the stoichiometry of the rate law just by analysis of the reaction equation. Consider

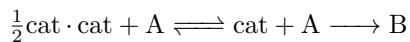


- Then

$$K^\ddagger = \frac{[\text{TS}]}{[\text{A}]^a [\text{B}]^b [\text{C}]^c}$$

$$[\text{TS}] = K^\ddagger [\text{A}]^a [\text{B}]^b [\text{C}]^c$$

- This means that
- So we can learn about the components of the transition structure just by inspecting the rate law.
- Example: Multistep sequences.



- Imagine if the catalyst can either bind to A or off-cycle by dimerizing.
- This tells us something about the potential energy surface.
- The overall rate-determining energy span covers not just the forward direction, but the off-cycling!
- This means that the catalyst has fractional order in the rate law.

$$\text{rate} = k[\text{A}][\text{cat}]^{1/2}$$

- Note that $k = K^\ddagger k^\ddagger$.
- This tells us something about the transition state structure relative to the ground state, so knowing what the ground state is is essential.
- If we have a minor equilibrium on the other hand, then

$$\text{rate} = k[\text{A}][\text{cat}]$$

- Note that the transition state structure has a lifetime on the order of bond vibrations.
- Sergei: All the k's?

- K : Equilibrium constant.
- K^\ddagger : Equilibrium constant to the transition structure.
- k : Experimental or apparent rate constant.
- k^\ddagger : Kinetic efficiency of the transition structure proceeding to product.
- κ : We'll get there.
- k_B : The Boltzmann constant.

- Recall $t\text{BuCl} \longrightarrow t\text{Bu}^+ + \text{Cl}^-$.

- The rate for the formation of the product is given as

$$\text{rate} = \frac{d[B]}{dt} = K^\ddagger k^\ddagger [A]$$

- The facility with which the reaction proceeds is mostly C–Cl bond cleavage, so k^\ddagger must largely be proportional to a fudge factor κ (the transmission coefficient) times ν (the frequency associated with the relevant bond).

$$k^\ddagger = \kappa\nu$$

- In reality, this frequency will be the “imaginary frequency” at the transition state, not any real-numbered frequency.
 - The point: There is a derivation in statistical mechanics through which we can more formally think about this.

- We get

$$K^\ddagger = \left(\frac{k_B T}{h\nu} \right) e^{-\Delta G^\ddagger / RT}$$

➤ h is Planck’s constant.

- Then we bring this together with the above to get

$$\text{rate} = \frac{d[B]}{dt} = \left[\kappa \left(\frac{k_B T}{h} \right) e^{-\Delta G^\ddagger / RT} \right] [A]$$

- From here, we can get the **Eyring equation**:^[1]

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

- David: Does the Eyring equation condense into the Arrhenius equation?
 - Short answer: No, but they’re close.
 - Devil’s in the details: It depends on what exactly is meant by “activation energy.” Additionally, in real life, the activated complex *can* rebound back into the starting material.
- The Eyring analysis allows us to predict a rate constant from an energy barrier, and vice versa.
- A few useful points.

ΔG^\ddagger (kcal/mol)	k (s^{-1})	$\tau_{1/2}$ (s)
3	3.8×10^{10}	1.8×10^{-11}
10	2.7×10^5	2.5×10^{-6}
15	5.9×10^1	1.2×10^{-2}
20	1.3×10^{-2}	55
25	2.7×10^{-6}	70 h
30	5.8×10^{-10}	38 y

Table 9.3: Relating the energy barrier to the rate.

- Let’s define ΔG^\ddagger (in kcal/mol at 298 K), the rate constant k (in s^{-1}), and the half-life $\tau_{1/2}$ (in s).
 - Example of a 3 kcal/mol process: Ethane bond rotation.
- Begin to internalize common kcal values!!
 - Print out a list and put it next to tooth-brushing mirror.

¹See CHEM26300Notes for the derivation.

Week 10

Isotope Effects

10.1 Thermodynamic Isotope Effects

11/5:

- Today.
 - Finishing up transition state theory.
 - Then how isotope effects can tell us stuff about reactions.
- Lecture 16 recap.
 - We defined an approach to kinetics.
 - Basically, the $A \rightleftharpoons B$ equilibrium is decided by ΔG via
$$K_{\text{eq}} = e^{-\Delta G/RT}$$
 - Then we can determine the rate at which this equilibrium is established via the Eyring equation,
$$k = \left(\kappa \frac{k_B T}{h} \right) e^{-\Delta G^\ddagger / RT}$$
 - Qualitative intuition for the relationship between the forms of the Eyring and equilibrium equations: TST is effectively analyzing a quasi-equilibrium between the SMs and the activated complex.
- Lecture 16 continued.
- Let's think about the Eyring equation in terms of the entropies and enthalpies that make up ΔG^\ddagger .

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

- These manipulations allow us to take the Eyring equation in slope-intercept form, so that we can linearize experimental data and extract from it experimental values for ΔH^\ddagger and ΔS^\ddagger !
 - This process is called forming an **Eyring plot**.
 - If we can acquire data over a minimum temperature range of 30 K, we can extrapolate reasonably accurate data.
- Dick Zare at Stanford has some methods of observing activated complexes, but the main way of learning about them is indirectly through methods such as Eyring plots.

- So using Eyring plots, we can get ΔH^\ddagger and ΔS^\ddagger ... but what do the values of these so-called activation parameters tell us?
- Qualitative interpretation of activation parameters.
 - Typical Eyring plots have a negative slope.
 - This means that we typically have $\Delta H^\ddagger > 0$.
 - This should make sense! Activated complexes have stretched out, weaker, higher energy bonds.
 - The overwhelming majority of Eyring plots have said negative slopes due to said partial bonding.
 - Caveat: $\Delta H^\ddagger < 0$ is physically possible, though uncommon.
 - It corresponds to scenarios in which the activated complex is more enthalpically stable than the starting materials.
 - There will be a question about a system with a negative enthalpy of activation on PSet 3!!
 - Typical Eyring plots imply $\Delta S^\ddagger < 0$.
 - $\Delta S^\ddagger < 0$ corresponds to an associative process.
 - This is because degrees of freedom are being diminished in the activated complex, e.g., restricting rotation due to partial bonding.
 - Example: The activated complex in a Diels-Alder reaction has an entropy of activation (ΔS^\ddagger) of -45 e.u.
 - This is even higher than the 30 e.u. we said we typically get in the van't Hoff analysis because we're restricting even more DOFs here, such as the rotation of dienophile.
 - $\Delta S^\ddagger > 0$ implies a dissociative process.
 - Example: ${}^t\text{BuO}-\text{O}{}^t\text{Bu} \longrightarrow 2 {}^t\text{BuO}\cdot$ has $\Delta S^\ddagger = 11\text{ e.u.}$
 - $\Delta S^\ddagger \approx 0$ implies an intramolecular process.
 - Example: 4π retrocyclization of cyclobutene has $\Delta S^\ddagger = -1\text{ e.u.} \approx 0\text{ e.u.}$
 - The error bars on these values are probably $\approx 5\text{ e.u.}$, so don't read anything into the above value besides that it's "close to zero."
- Sometimes, big ΔG values (positive or negative) can affect reaction kinetics. Let's look at how.
- The interplay of thermodynamics and kinetics: A justification for the Hammond postulate.
- Let's first build a mathematical model for our justification.

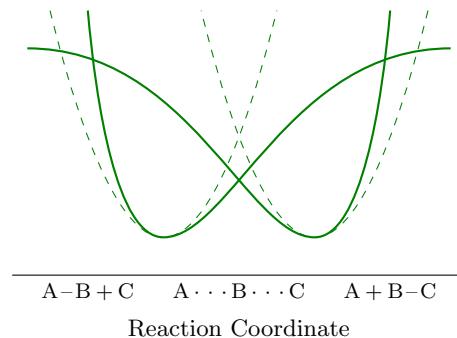


Figure 10.1: Bell-Evans-Polanyi principle: A model to visualize the principle.

- Consider a model reaction $A-B + C \rightleftharpoons A+B-C$.
- $A-B$ has an anharmonic bond energy well, and we can think of the $B-C$ bond energy well as being mirror-reflected.
 - These wells will have a depth on the order of a bond enthalpy, i.e., ≈ 70 kcal/mol.
- The two curves meet when $A-B$ is stretching and $B-C$ is stretching, i.e., in $A \cdots B \cdots C$.
 - This looks a lot like an activated complex!
- The intersection point of these two curves is pretty far down.
 - Recall from Table 9.3 that for an activation energy to be viable, it has to be < 25 kcal/mol.
 - Thus, since the well depth is ≈ 70 kcal/mol and the intersection point is pretty far down, we should be good to go.
- But how do we calculate this intersection point?
 - Although the wells aren't harmonic, we may approximate them reasonably well as parabolas.
 - Then solving for the parabolic curve crossing intersection point is mathematically simple!
- Let's do parabolic curve crossing.

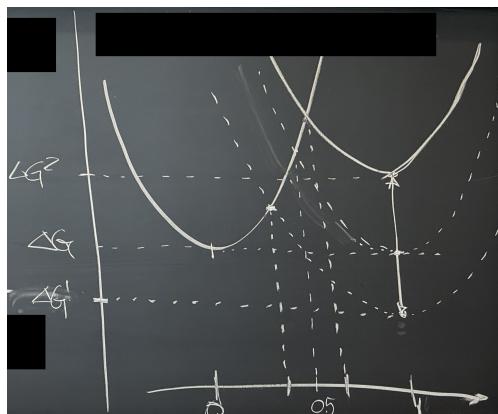


Figure 10.2: Bell-Evans-Polanyi principle: Parabolic curve crossing.

- Both parabolas should have the same curvature.
- Suppose first that the second vertex is lower in energy by ΔG^1 .
 - This implies that the TST happens at less than 0.5 along the reacton coordinate.
 - Implication: Exergonic reactions have TSTs lower in energy than the degenerate reaction, and with a TST more like the SMs ("earlier").
- If $\Delta G^2 > 0$, endergonic reactions have a TST more like the products ("later") and higher energy.
- This is all collectively known in the literature as the **Bell-Evans-Polanyi principle**, or alternatively as the **Hammond postulate**.
- Example: Radical halogenation of alkanes.^[1]

	1° C-H	2° C-H	3° C-H
F·	1	1.2	1.4
Cl·	1	3.9	5
Br·	1	82	1600

Table 10.1: Relative reactivity rates in radical halogenation.

¹See Figure 6.12 for where Masha covered this.

- Consider the reaction of $\text{F}\cdot$, $\text{Cl}\cdot$, and $\text{Br}\cdot$ with primary, secondary, and tertiary C–H bonds.
- Specifically, consider the relative rate k_{rel} of these reactions.
- Selectivity indicates that we should radically halogenate the tertiary C–H first.
- Additionally, we observe drastically improved selectivity as we get to heavier halogens. Here's a quantitative explanation for this phenomenon.
 - The reactants are at about 100 kcal/mol because that's the approximate R–H bond enthalpy; see Masha's list!!
 - Then Cl–H is ≈ 103 kcal/mol.
 - For comparison, the H–Br bond dissociation energy is ≈ 87 kcal/mol.
- Alex now essentially redraws Figure 6.12.
- This concludes Lecture 16.
- We now begin Lecture 17: Isotope effects.
- Recall from your previous coursework in quantum mechanics that atomic-scale oscillators have quantized — not classically continuous — energies.

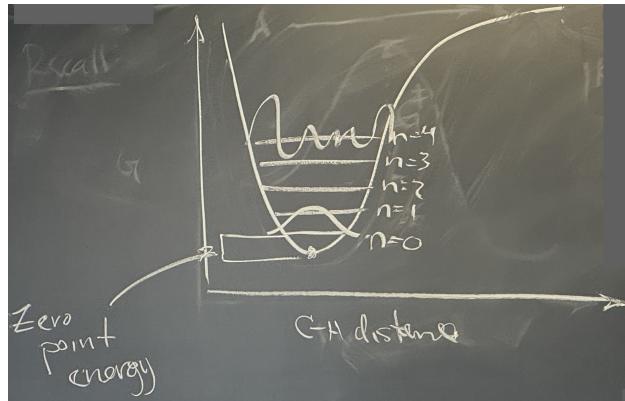


Figure 10.3: Quantum oscillator potential.

- So while we do have a minimum on the potential energy surface, the molecule does not hang out there because this would require that the quantum particle is static (so we'd know its position and momentum, violating Heisenberg uncertainty).
- So at the energy minimum, there is residual energy latent in the system called **zero-point energy**.
- So even in the lowest wave function, there's gonna be some spread of the nuclear position beyond the potential well.
- **Zero-point energy.** Also known as **ZPE**, E_0 .
- Quantized vibrational energies.

Bond	μ
C–H	0.92
C–D	1.72
^{12}C – ^{12}C	6.00
^{12}C – ^{13}C	6.24

Table 10.2: The reduced mass of common chemical bonds.

- We have that

$$E_n = h\nu \left(n + \frac{1}{2} \right)$$

- Recall that an (asymmetric) molecule has $3N - 6$ vibrational modes.
- This frequency of oscillation (per Hooke's law) is related to the force constant and **reduced mass**.

$$\nu = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}}$$

- Atoms are defined by the number of protons, but we can change the number of neutrons as much as we want! This will change the reduced mass.
- The magnitude of isotope effects is the greatest when the reduced mass changes the most.

- **Reduced mass:** The quantity given as follows, where m_1, m_2 are the masses of two particles in a system. *Denoted by μ . Given by*

$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

- Looking at the deuterium isotopologue vs. carbon.

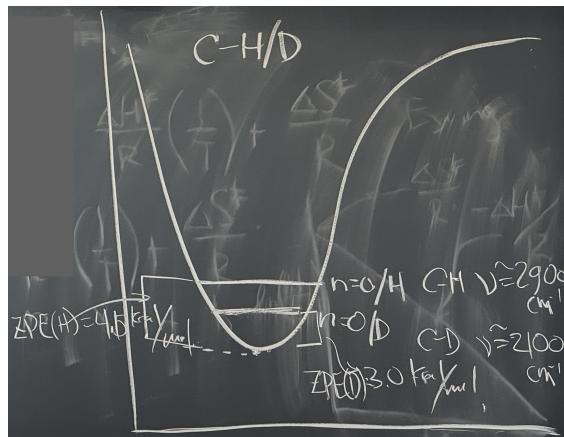


Figure 10.4: Isotopic differences alter the thermodynamic stability of a chemical bond.

- The zero-point energy for the C–D oscillator is less than for the C–H operator.
- Thus, C–H has $\nu \approx 2900 \text{ cm}^{-1}$ and C–D has $\nu \approx 2100 \text{ cm}^{-1}$.
- This means that it will cost more energy to dissociate a C–D bond vs. a C–H bond.
- The potential is defined only by positive and negative charges, so it's the same; it's only the isotopes within it that change.
- The zero-point energy of a C–H bond is 4.5 kcal/mol, and the zero-point energy of a C–D bond is 3.0 kcal/mol.
- These 1.5 kcal/mol impact the kinetics reactivity by about sevenfold!

- Equilibrium isotope effects.

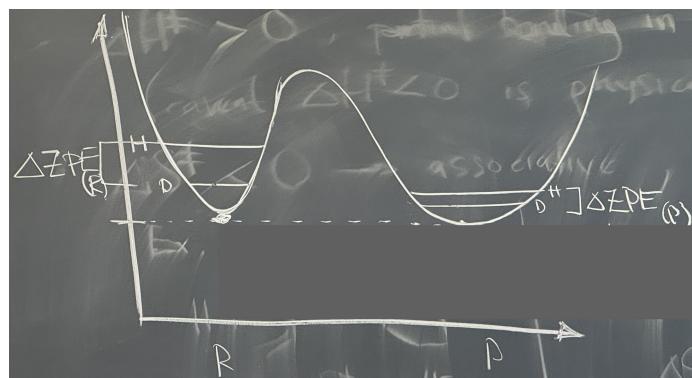


Figure 10.5: Equilibrium isotope effects.

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

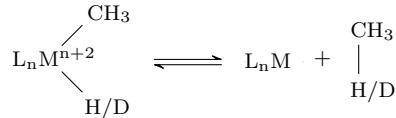


Figure 10.6: Reductive elimination of methane.

- Consider a generic metal-ligand complex (L_nM) undergoing the reaction in Figure 10.6.
- The typical BDE for a M–H bond is 40–80 kcal/mol.
 - The BDE for a methane $\text{H}_3\text{C}-\text{H}$ bond is 104 kcal/mol.
- Since the metal potential is shallower, it is slacker and hence has a lower associated force constant.
 - Symbolically, $k_{\text{M}-\text{H}} < k_{\text{C}-\text{H}}$.
- Since the ZPE difference is smaller in the more slack potential (per Figure 10.5), it follows that

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

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

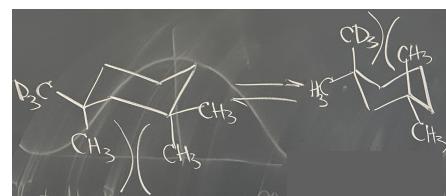


Figure 10.7: Steric isotope effects.

²How is this related to anharmonicity??

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

- Experimentally, we observe that

$$K = \frac{[\text{CD}_3 \text{ ax}]}{[\text{CD}_3 \text{ eq}]} = 1.042$$

at -100°C .

- It is preferable to have the CD_3 group axial because it is smaller: The lower vibrational amplitude ν for C–D bonds relative to C–H bonds literally shrinks the sterics of the group (Anslyn & Dougherty, 2006, pp. 430, 434).

- How can we link equilibrium isotope effects to kinetics?

- Like at the beginning of class, we use transition state theory!
- Indeed, let's apply our understanding of equilibrium isotope effects to the quasi-equilibrium between the starting materials and transition state. This can give us valuable insight into the relative rates of reaction for heavier vs. lighter isotopologues.

- Kinetic isotope effects.

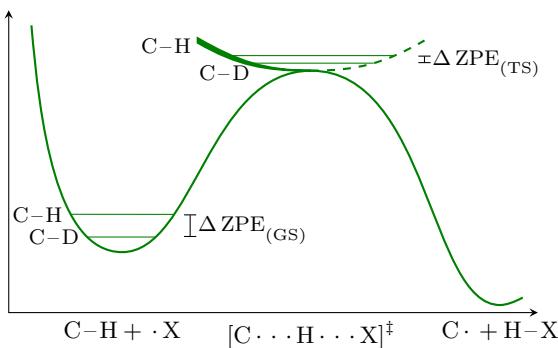


Figure 10.8: Kinetic isotope effects.

- Consider the HAT reaction



- This is a nondegenerate reaction, energetically.

- Recall that transition structures are maxima along one direction, but minima along every other direction in the hyperspace (see Figure 9.4).

- It follows that ΔZPE is relatively small in the TS, because TS potentials are pretty slack compared with bond potentials.

- The important equation we can write from the above diagram is

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

- This means that it's easier to take C–H to the transition state than C–D.

- This is a **normal KIE**, where $k_{\text{H}}/k_{\text{D}} > 1$.

- This is also primary (1°) because the isotope-sensitive bond is the one being broken/made.

- **Inverse KIEs** involve cases in which $k_{\text{D}}/k_{\text{H}} < 1$.

- This is also 1° .

- We can also have **secondary KIEs**, where we label a position potentially far from the reactive site.

- Next time: Using KIEs to diagnose reaction mechanisms, single isotopologues under different reaction conditions give us different information, etc. Takeaways: KIEs are super useful.

10.2 Theory of Kinetic Isotope Effects

11/7:

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

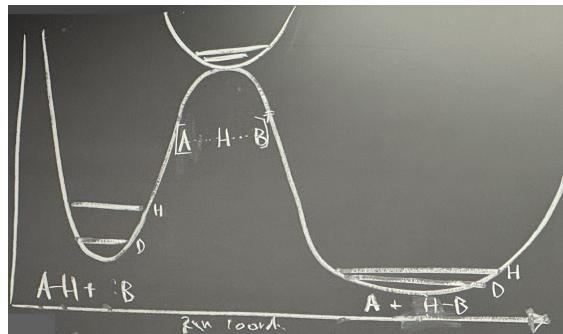
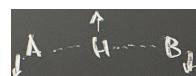


Figure 10.9: Atom-transfer potential energy surface.

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



(a) Asymmetric stretch.



(b) Symmetric bend.



(c) Symmetric stretch.

Figure 10.10: Atom-transfer vibrational modes.

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

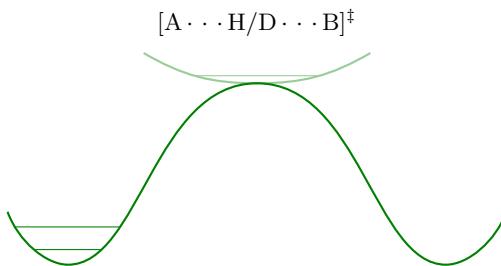


Figure 10.11: Thermoneutral kinetic isotope effects.

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

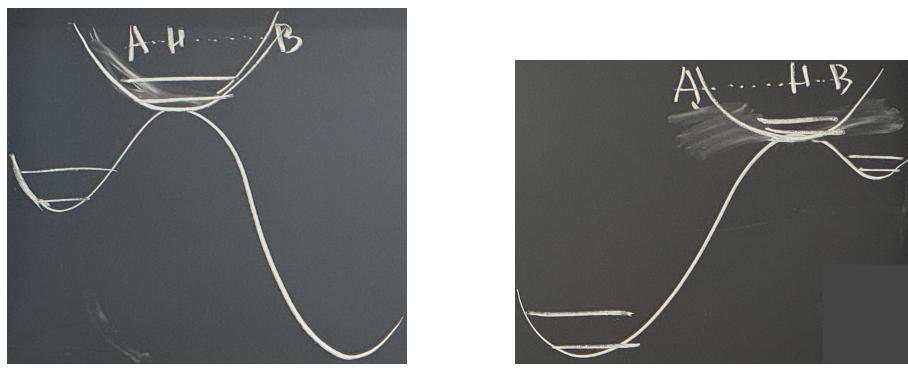


Figure 10.12: Thermodynamically asymmetric kinetic isotope effects.

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

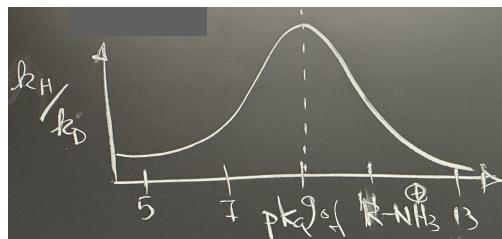


Figure 10.13: Variation in kinetic isotope effects with thermodynamic asymmetry.

- Consider the following acid-base deprotonation.

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

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



Figure 10.14: Nonlinear transition state.

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

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

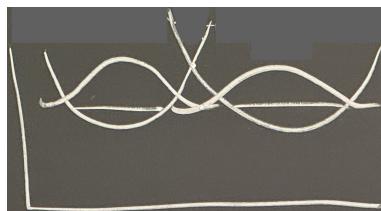


Figure 10.15: Intramolecular HAT can proceed through (rather than over) potential barriers.

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

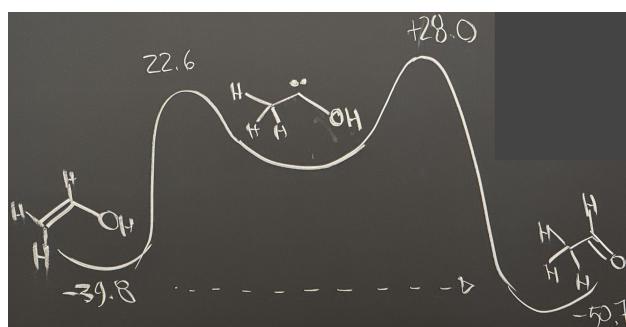
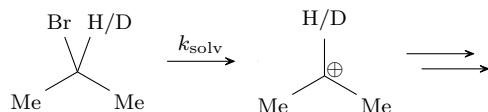


Figure 10.16: Quantum tunnelling can influence product selectivity.

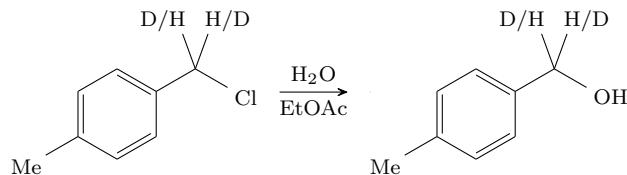
- The reactant is methylhydroxycarbene.
 - The adjacent π -donor makes this carbene a ground-state triplet.
 - This carbene becomes either acetaldehyde or vinyl alcohol.
 - The competing mechanisms are O–H and C–H migration to the carbene center.
 - The driving force for formation of vinyl alcohol is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



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

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

– Consider the solvolysis of a benzyl chloride derivative.



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

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

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

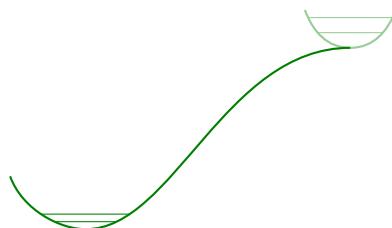
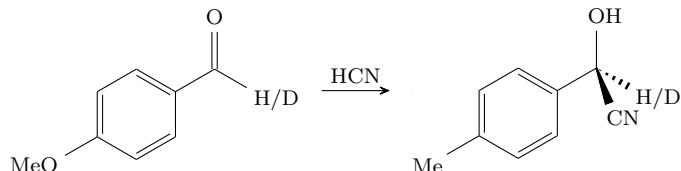


Figure 10.17: Inverse α -secondary kinetic isotope effect.

- Consider the reaction of anisaldehyde to the corresponding cyanohydrin.

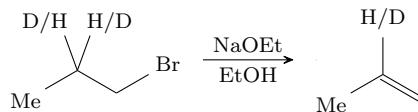


- Isotopically label the aldehyde H/D.
- Burgi-Dunitz trajectory to tetrahedral intermediate, which will be thermodynamically uphill.
- Here, we have an sp^2 SM going to an sp^3 TS.
- More steric bulk in TS leads to more energetic penalty to wagging, leads to tighter well at the top near the TST.
- So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

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

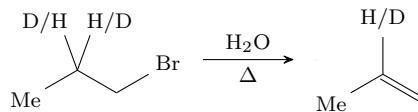
- We now move onto β -secondary KIEs.
- Example: Labeling β to the “active site.”

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



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

– Consider the E_1 dehydrohalogenation of 1-propylbromide.



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

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

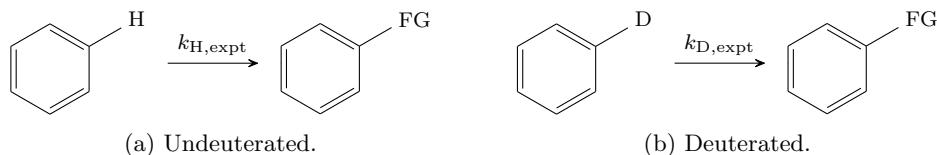


Figure 10.18: Independent absolute rate measurement of kinetic isotope effects.

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

Week 11

Kinetics

11.1 Experimental Determination of Kinetic Isotope Effects

11/12:

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

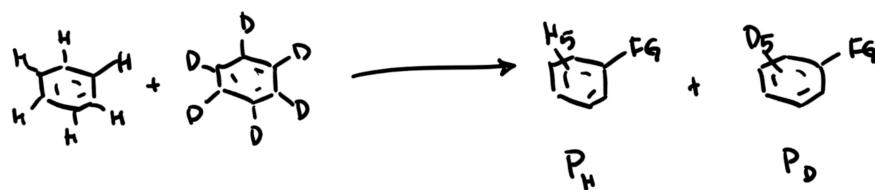


Figure 11.1: Competition experiment (intermolecular).

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

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

$$C := \frac{[P_H]}{[SM_H]}$$

$$R := \left(\frac{[SM_D]}{[SM_H]} \right)_t$$

$$R_0 := \left(\frac{[SM_D]}{[SM_H]} \right)_0$$
 - C is the conversion.
 - From the definition, we can tell that it is a number between 0 and 1.
 - R gives the isotopic enrichment at any moment t .
 - R_0 is the initial isotopic enrichment.
- Thus, we can do some algebra to get a correction term that allows us to calculate the KIE from any time point.

$$\frac{R}{R_0} = (1 - C)^{k_D/k_H - 1}$$

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

- Takeaways.
 - If we can extract both the conversion C and isotopic composition R/R_0 , we can extract the KIE accurately.
 - If we run these reactions in replicates, we can get *very* accurate KIEs!
- Note that at high conversions, the ratio of the deuterated to protonated starting materials goes to infinity. Symbolically,

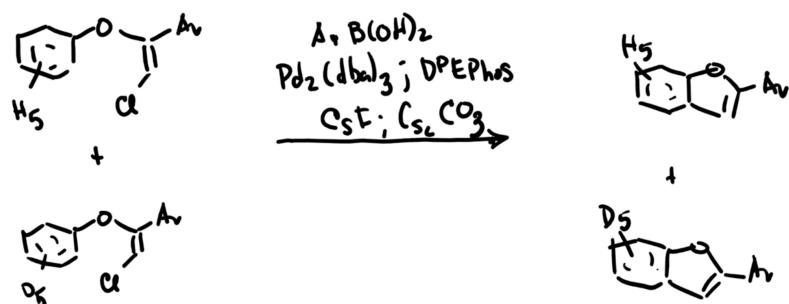
$$\frac{[SM_D]}{[SM_H]} \rightarrow \infty$$
 - Implication: As we get higher and higher conversions, we'll eventually reach a point where we only have a few molecules of starting material left, and almost all of them are the deuterated ones.
 - This high-conversion exaggeration makes measurement easier.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

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

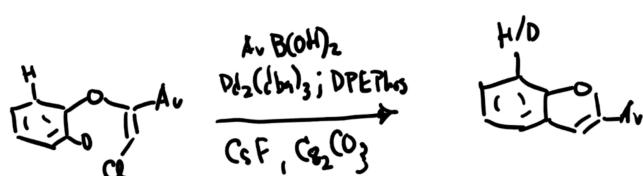


Figure 11.2: Assigning peaks on a potential energy surface by using kinetic isotope effects.

- Consider the reaction of H₅- and D₅-isotopologues run both under a palladium-catalyzed arylation.



- Meant to be a Suzuki coupling (there's a boronic acid in there), but that ended up being irrelevant to the chemistry.
- In reality, the observed products are ring-closed.
- We have *no* intermolecular KIE (that is, $k_H/k_D = 1.0$).
 - This means that the rate of reaction is *not* determined by the presence or absence of heavy isotopes.
 - It follows that C–H/D cleavage is *not* the rate-determining step!
- What does this mean in terms of the potential energy surface?
 - It means that the largest peak (the RDS) does *not* involve C–H/D cleavage, but one of the other peaks could.
- Reference: Simmons and Hartwig (2012).
- Subtopic 2.2: Intramolecular competition.
- Example: Kinetic isotope effects can probe post-rate determining steps!
 - Consider the same palladium-catalyzed arylation, but our substrate has one H and one D that can be cleaved.



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

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

- General structure of intramolecular KIEs.

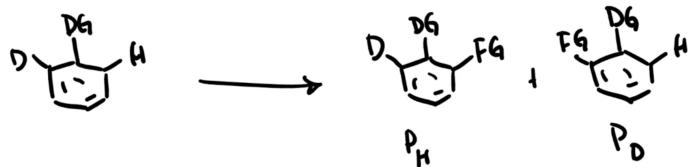


Figure 11.3: Competition experiment (intramolecular).

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

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

at *any* conversion.

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

- To recap.

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

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

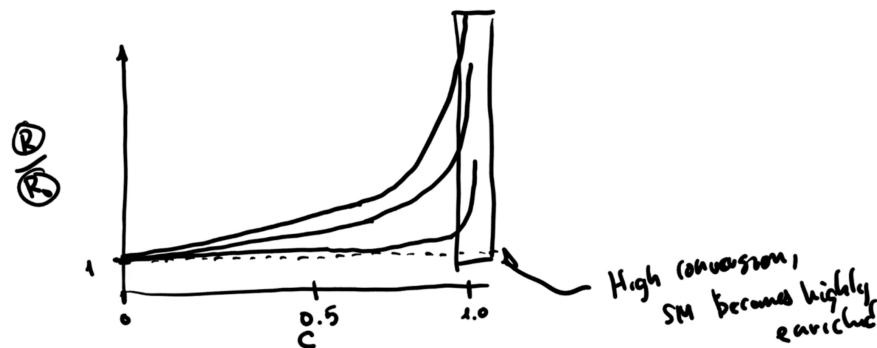


Figure 11.4: Isotopic enrichment at high conversions.

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

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

Table 11.1: Isotopic enrichment at high conversions.

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

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

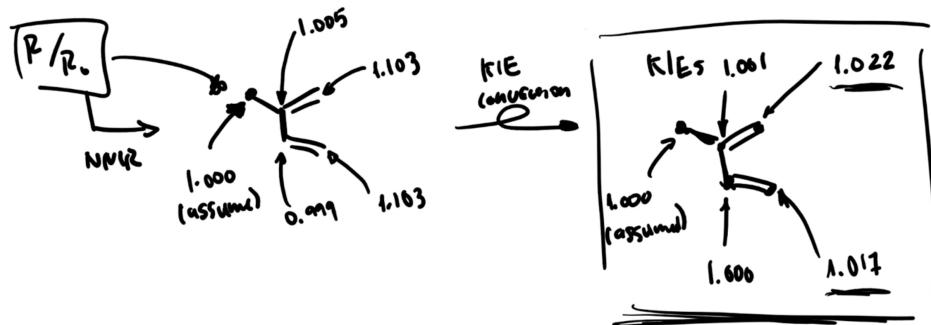
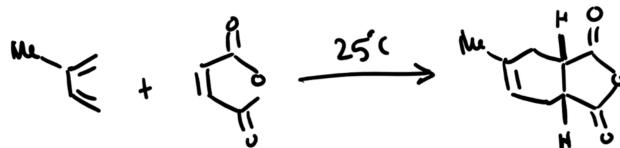


Figure 11.5: Singleton method for intermolecular heavy atom kinetic isotope effects.

- Consider the following Diels-Alder reaction.



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

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

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

- Limitations of the Singleton method.

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

- The results can be difficult to interpret.
 - Any individual number might not be too helpful, but with modern quantum mechanical calculations, we can match our results to a DFT-computed potential energy surface!
 - This will show that one pathway has a better experimental match with KIEs.
 - This is good evidence for a mechanistic course!!
- Natural abundance experiments can be run in both inter- and intramolecular modes.
- Example: Measuring heavy atom kinetic isotope effects (aka “natural abundance experiments”) in an intramolecular mode.

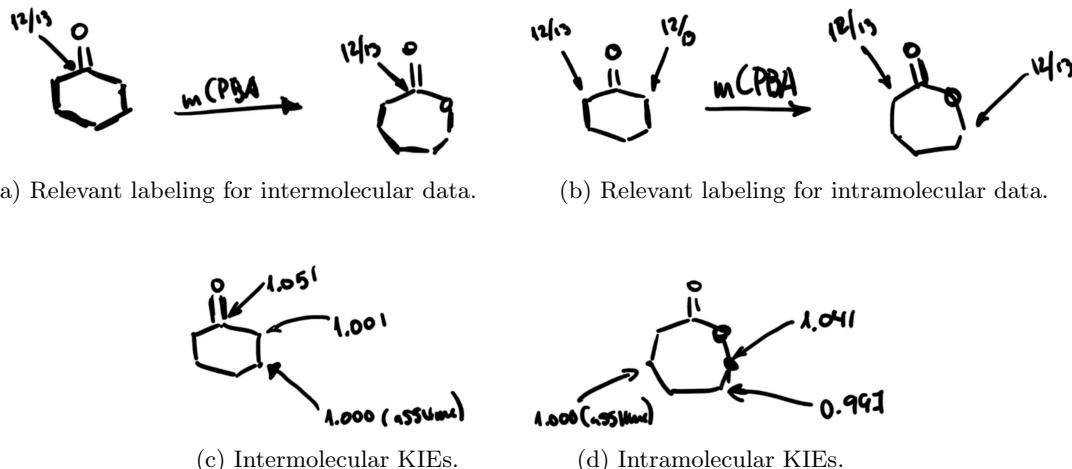
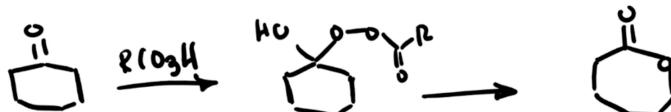


Figure 11.6: Singleton method for intramolecular heavy atom kinetic isotope effects.

- Consider the Baeyer-Villiger reaction.



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

- Intramolecular variant: Consider the labeling at the α -positions.
 - Isotopic enrichment of the product, here, is conversion-independent (because it's post-RDS).
 - We assume that the β -position has an isotopic enrichment of 1.000.
 - The resultant significant isotopic fractionation of the product ($KIE = 1.041$) implies that the migration step occurs after the RDS, and involves the α -position.
- It is somewhat counterintuitive that hemiacetal formation (typically fast) would be rate-limiting!
- Reference: Singleton and Szymanski (1999).
- Takeaways from today.
 - We get deep and important information about reaction courses, rate-determining steps, etc. from isotope effects.
- Next time: Kinetics and kinetic rate laws.

11.2 Kinetic Rate Laws

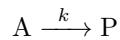
11/14:

- Today: Experimental kinetics, rate laws, etc.
 - This topic will proceed through the next several lectures.
 - Today, we'll focus on general background.
 - This will probably be review for many people, but it's *important* review and good for general understanding.
- How can we experimentally determine the rate at which a reaction occurs? By measuring the kinetics.
- The goal of a kinetics experiment is to characterize the mechanism of a given transformation.
 - Kinetics help us rule out possibilities.
 - We can experimentally determine the **rate law** and see if it fits a proposed arrow-pushing mechanism.
- We begin with some definitions.
- **Rate law:** A mathematical expression for the reaction rate, involving a **rate constant** as well as the concentrations of the involved species scaled by exponents. *General form*

$$\text{rate} = k[A]^x[B]^y[C]^z$$

- Note that the above general form pertains to a reaction $A + B + C \longrightarrow P$.
- These exponents give us information on the composition of the transition state structure relative to the ground state. Remember that we can't directly observe the activated complex, so we need techniques like this!
- Specifically, the values of the exponents tell us the number of A's, B's, and C's in the transition state structure during the RDS.
- **Rate constant:** A proportionality constant that relates the rate of reaction to the concentrations of the starting materials. *Denoted by k .*
 - Falls out of our discussion of transition state theory.
- Example: $\text{rate} = k[A]^1$.
 - The number of molecules of A in the transition state is the same as in the ground state.

- Example: rate = $k[A]^2$.
 - There are twice as many A's in the transition state vs. the ground state.
 - It is important to note that this is *relative* to the ground state; $x = 2$ does *not* necessarily imply that there are specifically two molecules of A in the transition state, only that there are twice as many in the ground state.
 - This is similar to how we were always referencing ground states in Transition State Theory.
- We can have **zeroeth-, first-, second-**, etc. order reactions.
- Example: rate = $k[A][B]$.
 - There are an equal number of molecules of A and B in the transition state.
 - This reaction may be said to be “first order in A” and “first order in B” but “second order overall.”
- **Rate:** The growth in the concentration of the product(s) as a function of time; equivalently, the decay of the starting material as a function of time.
- **Half-life:** The time at which $[A]_t = [A]_0/2$.
- Topic I: Simple kinetic rate laws.
- The simplest case is zero-order kinetics.



- Note that this reaction need not have a single-step mechanism.
 - The rate law looks like the following.
- $$\text{rate} = \frac{d[P]}{dt} = -\frac{d[A]}{dt} = k$$
- Specifically, this is a **differential rate law**.
 - The important thing is that the rate is independent of $[A]$.
 - This case is surprisingly common!
- We don't typically measure rate directly (though we can with calorimetry; we'll talk about this more later).
 - More typically, we measure concentrations.
 - To relate measured concentrations to rates, we need **integrated rate laws**.
 - Alex derives the integrated rate law for zeroeth-order kinetics.

$$\begin{aligned} -\frac{d[A]}{dt} &= k \\ \int_{[A]_0}^{[A]_t} d[A] &= \int_0^t -k dt \\ [A]_t - [A]_0 &= -kt \\ [A]_t &= -kt + [A]_0 \end{aligned}$$

- This integrated rate law tells us that a plot of $[A]_t$ vs. time should be linear with slope $-k$.
- Correlated with this would be the increase in $[P]$ with slope k .
- Equally common is first-order kinetics.
- The differential rate law here is

$$\text{rate} = k[A]$$

- The integrated rate law may be derived from here.

$$\begin{aligned} -\frac{d[A]}{dt} &= k[A] \\ \int_{[A]_0}^{[A]_t} \frac{d[A]}{[A]} &= \int_0^t -k dt \\ \ln([A]_t) - \ln([A]_0) &= -kt \\ [A]_t &= [A]_0 e^{-kt} \end{aligned}$$

- This tells us that a plot of $[A]_t$ vs. time will follow a nonlinear decay, i.e., the rate of reaction will slow down over time as the concentration of A is depleted.
 - We can also linearize this plot by taking $\ln([A]_t)$ vs. time, and know that the slope will be $-k$ and the y -intercept $\ln([A]_0)$.
- Aside: Many of these linearization methods come from a time when we didn't have computers, so linearization was computationally necessary to extract things like rate constants.
 - In the computer age — where manipulating vast datasets is easy — linearization is antiquated.
 - But it still gives us a good intuitive appreciation for trends.
- The half-life of a first-order reaction is given by

$$t_{1/2} = \frac{\ln(2)}{k}$$

- We can derive this by substituting $[A]_{t_{1/2}} = [A]_0/2$ into the integrated rate law.
- Importantly, the half-life does not depend on $[A]$!
 - On a plot, this means that each time a half-life elapses, the concentration of [A] has halved.
 - First-order reactions move faster at the beginning than at any other time, so if you go into lab and your reaction is not working early on, it's not then just going to start working later! You should probably cut your losses and change something.
 - Also tells you how many half-lives you'd need in order to achieve a certain desired conversion.

- Next up is second-order kinetics.
 - There are two situations here.
- Situation 1: Consider a reaction of the following form.



- The differential rate law here is

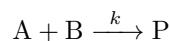
$$\text{rate} = k[A]^2$$

- The integrated rate law may be derived from here.

$$\frac{1}{[A]_t} = kt + \frac{1}{[A]_0}$$

- A raw plot of this data is pitched down steeper in the beginning than a first-order plot.
- We can also linearize once again.
- Note that if we take natural logs (instead of plotting regular or linearized), the data will *look* first-order early on and then diverge from linearity at higher conversions.
 - This reveals a challenge: For rigorous determination of reaction orders, we need to follow the kinetic course over many, many half-lives.

- Situation 2: Consider a reaction of the following form.



- The differential rate law here is

$$\text{rate} = k[A][B]$$

- Deriving the integrated rate law.

- If $[B]_0 \neq [A]_0$, then we can scale $[B]$ by $[A]$:

$$[B]_t = [B]_0 - ([A]_0 - [A]_t)$$

- We can then drop this substitution into the differential rate law, go through the integration, and arrive at

$$\frac{1}{[B]_0 - [A]_0} \left(\ln \frac{[B]_t}{[A]_t} - \ln \frac{[B]_0}{[A]_0} \right) = kt$$

- We can linearize by plotting $\ln([B]_t/[A]_t)$ vs. time.

- The y -intercept defines our initial concentrations.
- The slope is of the form $([B]_0 - [A]_0)k$.

- In situation 2, deriving k through linearization would require the simultaneous tracking of $[A]$ and $[B]$. But this comes with experimental challenges.

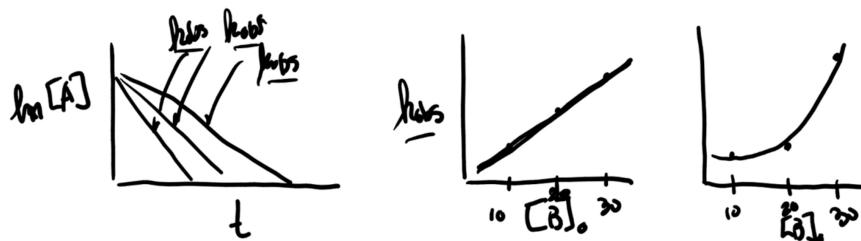


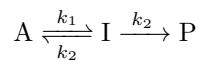
Figure 11.7: Experimentally measuring the rate constant for a two-component second-order reaction.

- Thus, we use a simplification: Pseudo-first order kinetics.
- Here, we simplify our analysis by changing the reaction conditions. Specifically, we want to do this in such a way that the concentration of one component in this overall second-order reaction is constant with respect to time.
- Most typically, this is done by using one reagent in a large excess so that changes in its concentration are negligible. Mathematically, the assumption is that if $[B]_0 \gg [A]_0$, then $[B]_t \approx [B]_0$.
- When we do this, we say that we're running the reaction "pseudofirst in A."
- Essentially, we've changed the rate law into

$$\text{rate} = \frac{d[P]}{dt} = k[A][B] \approx \underbrace{k[B]_0[A]}_{k_{\text{obs}}}$$

- Practically, in order for the condition to be fulfilled, we need at least a 5 times excess of B; 10 times is better.
- When doing this in the lab, run the experiment with $[B]_0$ equal to several different multiples of $[A]_0$ — e.g., $10[A]_0$, $20[A]_0$, and $30[A]_0$ — and extract k_{obs} for each of them.
 - Then plot k_{obs} vs. $[B]_0$ and extract k (if the reaction is first-order in B).
 - If the reaction is second order in B, fit your data to $k_{\text{obs}} = k[B]^2$.

- Let's now discuss the kinetics of multistep chemical processes.
- Example: Consider a mechanism of the following form.



- The overall differential rate law here is

$$\text{rate} = \frac{d[P]}{dt} = k_2[I]$$

- The issue here is that we can't easily measure $[I]$ directly! Thus, we need to measure it indirectly from what we know about the action of A on the system.
- Two main assumptions are used to solve for $[I]$: The **steady-state approximation** and the **quasi-equilibrium assumption**.
- Steady-state approximation:** If $[I] \ll [A]$, then $d[I]/dt \approx 0$. Also known as **SSA**.

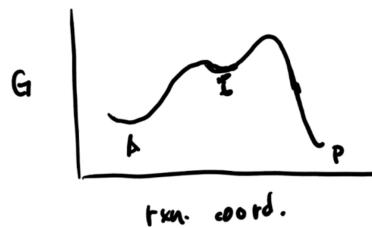


Figure 11.8: Steady-state approximation potential energy surface.

- On a reaction coordinate diagram, this condition looks like A having to proceed *uphill* through I to the product.
- In rate law nomenclature, we want $k_{-1} \gg k_1$.^[1] This defines an endothermic equilibrium.
- Quasi-equilibrium assumption:** $A \rightleftharpoons I$ is reversible and remains in equilibrium throughout the process.

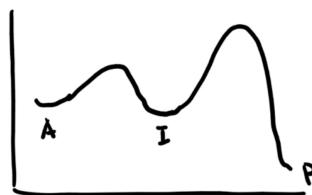


Figure 11.9: Quasi-equilibrium assumption potential energy surface.

- On a reaction coordinate diagram, this condition looks like A and I reaching a finite equilibrium before product conversion.
- Here, we expect $[I]$ to build up during the reaction!
 - Thus, the steady-state approximation is not applicable in this case.
- Reference: Raines and Hansen (1988).
 - A very lucid description of these two approximations by a colleague, Ron Raines!

¹HWE as final mechanistic proposal??

- Let's try applying the steady-state approximation to our model reaction.
 - We begin by writing an expression for all the ways that the concentration of I can change.

$$\frac{d[I]}{dt} = k_1[A] - k_{-1}[I] - k_2[I]$$

- Then applying the SSA, we obtain

$$0 = k_1[A] - k_{-1}[I] - k_2[I]$$

- Rearranging then allows us to solve for [I].

$$[I] = \frac{k_1[A]}{k_{-1} + k_2}$$

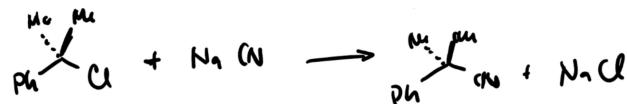
- We can then substitute this expression of observables back into our rate law, arriving at

$$\text{rate} = \frac{d[P]}{dt} = k_2[I] = \frac{k_1 k_2 [A]}{k_{-1} + k_2} = k_{\text{obs}}[A]$$

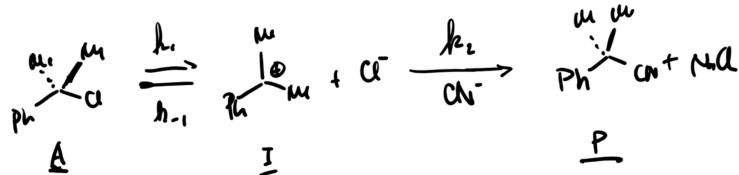
where $k_{\text{obs}} = k_1 k_2 / (k_{-1} + k_2)$.

- Example: Seeing the chemistry in all this math.

- Consider the following reaction.



- Using our knowledge of organic chemistry, we can propose the following $\text{S}_{\text{N}}1$ mechanism.



- Mathematically, the growth in product comes from the reaction of the intermediate with the cyano nucleophile.

$$\frac{d[\text{P}]}{dt} = k_2[\text{I}][\text{CN}^-]$$

- Now as before, write an expression for $d[\text{I}]/dt$.

$$\frac{d[\text{I}]}{dt} = k_1[\text{A}] - k_{-1}[\text{I}][\text{Cl}^-] - k_2[\text{I}][\text{CN}^-]$$

- Apply the SSA and solve for I .

$$[\text{I}] = \frac{k_1[\text{A}]}{k_{-1}[\text{Cl}^-] + k_2[\text{CN}^-]}$$

- Dropping this back into our rate law yields

$$\frac{d[\text{P}]}{dt} = \frac{k_1 k_2 [\text{A}][\text{CN}^-]}{k_{-1}[\text{Cl}^-] + k_2[\text{CN}^-]}$$

- This is a wild rate law for a sophomore organic transformation!

- We can simplify the above rate law in some limiting cases.
 - We do this by finding extrema that simplify the denominator.
- Limiting case #1: $k_{-1}[\text{Cl}^-] \gg k_2[\text{CN}^-]$.

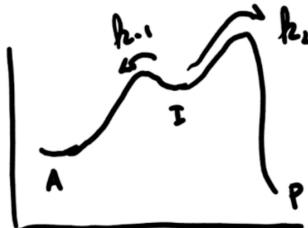


Figure 11.10: Potential energy surface for an $\text{S}_{\text{N}}1$ with a late rate-determining step.

- What does this case mean, physically, though?
 - In terms of the potential energy surface, it means that the return of I to A is faster than the conversion of I to P.
 - This implies that the second step is rate-determining.
- Mathematically, we can drop the $k_2[\text{CN}^-]$ term out of the denominator to simplify the rate law to

$$\frac{d[\text{P}]}{dt} = \frac{k_1 k_2 [\text{A}][\text{CN}^-]}{k_{-1}[\text{Cl}^-]} = k_{\text{obs}}[\text{A}][\text{CN}^-][\text{Cl}^{-1}]$$
 - This means that the reaction is inverse order in Cl^- , hence inhibited by the addition of exogenous chloride.
 - However, it is also first-order in $[\text{A}]$ and $[\text{CN}^-]$.
- Limiting case #1: $k_2[\text{CN}^-] \gg k_{-1}[\text{Cl}^-]$.



Figure 11.11: Potential energy surface for an $\text{S}_{\text{N}}1$ with an early rate-determining step.

- Physical interpretation.
 - In terms of the potential energy surface, it means that the conversion of I to P is faster than the return of I to A.
- Mathematically, we can drop the $k_{-1}[\text{Cl}^-]$ term out of the denominator to simplify the rate law to

$$\frac{d[\text{P}]}{dt} = \frac{k_1 k_2 [\text{A}][\text{CN}^-]}{k_2[\text{CN}^-]} = k_1[\text{A}]$$
 - This reflects the sophomore-organic understanding of $\text{S}_{\text{N}}1$ as a reaction in which the RDS depends only on $[\text{A}]$.

- But how could the rate not depend on CN^- at all? If there's no CN^- , the reaction won't proceed at all!
 - The trick is that we have zeroeth-order dependence on the rate in the limit of large CN^- concentrations, and first-order dependence at very small CN^- concentrations.
 - Entering this so-called **saturation regime** is very common.
 - As CN^- is consumed, we transit along this curve and eventually enter a different kinetic regime!
 - Not a different mechanism, but yes a change in the RDS.
 - Takeaway: The kinetic rate law depends on the conditions!
- Always having to derive the rate law is a bit laborious, so here's a rule of thumb/cheat code (in the context of the SSA).
 - The rate can be expressed as the product of all of the forward rate constants and concentrations, over the sum of the rate constants and concentrations of the ways that the intermediate can react.
 - Alex uses this shortcut to rederive the rate laws for the two previous applications of the SSA.
- Caveat: In order for the SSA to work, it can only be applied to *one* intermediate.
 - Otherwise, the math breaks down.
 - So for a multistep process in which I changes appreciably, we need to use the quasi-equilibrium assumption.
- Using the quasi-equilibrium assumption.
 - We know that

$$K_{\text{eq}} = \frac{[\text{I}]}{[\text{A}]}$$

- Additionally, we know that

$$K_{\text{eq}} = \frac{k_1}{k_{-1}}$$

- Thus, substituting back into the original rate law gives

$$\text{rate} = k_2[\text{I}] = \underbrace{k_2 K_{\text{eq}}}_{k_{\text{obs}}} [\text{A}]$$

Week 12

Experimental Kinetics

12.1 Kinetics of Catalytic Reactions

11/19:

- Last week's lectures.
 - Very simple kinetic scenarios.
 - Linearizations allows us to extract essential kinetic parameters for reactions.
 - Kinetic descriptions for multistep processes.
 - Steady-state approximation, quasi-equilibrium approximation.
- Today: Kinetics of Catalytic Reactions.
- Catalysts speed up the rate of reaction without altering the thermodynamics.
- Consider the following balanced chemical reaction.



- Since the catalyst appears on both sides of the reaction, we typically write it over the arrow.
- This notational simplification alides a great deal of multistep complexity.
- Consider a hypothetical potential energy surface.

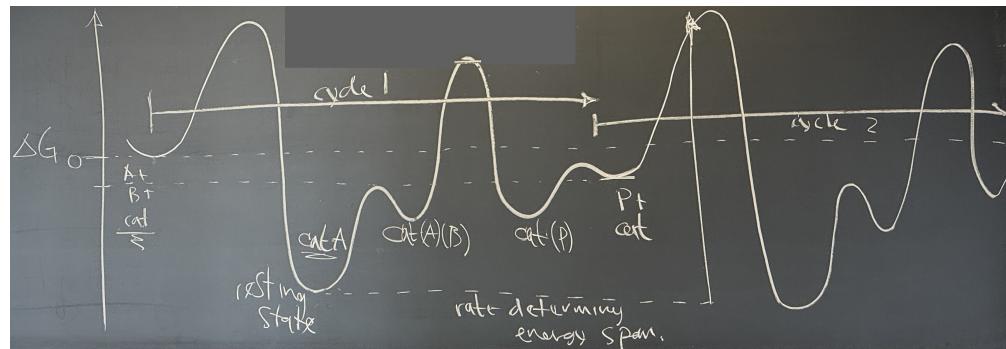


Figure 12.1: Model catalytic potential energy surface.

- Define a reference energy as zero; suppose the starting materials ($A + B + \text{cat}$) begin here.
- Suppose, then, that they proceed through a multistep potential energy surface along our reaction coordinate.

- If this were a stoichiometric reaction, the first step would be rate-determining (highest energy barrier), and the first intermediate would be the product (lowest energy species).
 - But we're catalytic, so we have to consider cycles 2, 3, ...
 - These cycles are driven forward by the ever-so-slight difference in energy ΔG between starting materials and products.
- The “first intermediate” is actually the catalyst **resting state**.
 - Indeed, the thing that we throw in may not be the dominant species in solution!
 - It could be $\text{cat} \cdot (\text{A})$, $\text{cat} \cdot (\text{A})(\text{B})$, or $\text{cat} \cdot (\text{P})$!
- Similarly, the difference in energy between the lowest valley and highest peak is the **rate-determining energy span**.
- Reference (good description of rate-determining energy span): Kozuch and Martin (2011).
- Because continuous potential energy surfaces are not great representations, we typically view catalysts as acting in **catalytic cycles**.

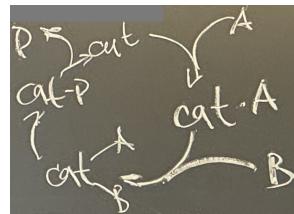


Figure 12.2: Model catalytic cycle.

- This is not that uncommon a catalytic cycle to find!
- Let's now do a kinetic analysis of this model catalytic cycle, using some of the tools developed last lecture.

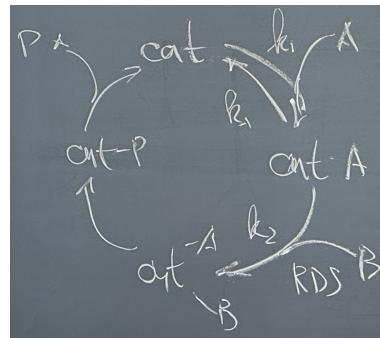


Figure 12.3: Model catalytic cycle (kinetic analysis).

- Assume that the first step is a reversible binding to A.
- Recall that the rate-determining step follows the resting state. Thus,

$$\text{rate} = \frac{d[\text{P}]}{dt} = -\frac{d[\text{A}]}{dt} = k_2[\text{cat} \cdot \text{A}][\text{B}]$$

- We can then apply our rule of thumb for the steady-state approximation.

$$\text{rate} = \frac{k_1 k_2 [\text{A}][\text{B}][\text{cat}]}{k_{-1} + k_2 [\text{B}]}$$

- Going forward, it will be useful to define the total concentration of catalyst

$$[\text{cat}]_T := [\text{cat}] + [\text{cat} \cdot A] + [\text{cat} \cdot AB] + [\text{cat} \cdot P]$$

- To derive the rate law for Figure 12.3 in terms of $[\text{cat}]_T$ — an observable — we'd need a system of equations.
- Let's now consider a different (simpler) catalytic cycle to develop some core ideas.

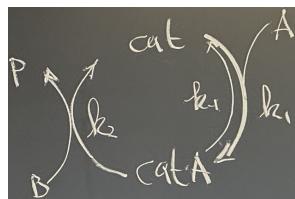
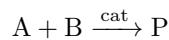


Figure 12.4: Model two-step catalytic cycle (kinetic analysis).

- This cycle pertains to a reaction



- If the second step is rate-determining, then

$$\text{rate} = k_2[\text{cat} \cdot A][B]$$

- It will also be useful to have the assumption

$$[\text{cat}]_T = [\text{cat}] + [\text{cat} \cdot A]$$

- Let's now evaluate this catalytic cycle using the quasi-equilibrium assumption.

- Warning: Lots of algebra coming up!
 - Squiggly lines on the board mean abbreviations.
- The quasi-equilibrium assumption tells us that

$$K = \frac{k_1}{k_{-1}} = \frac{[\text{cat} \cdot A]}{[\text{cat}][A]}$$

- We first solve for the concentration of the catalyst.

$$[\text{cat}] = \frac{[\text{cat} \cdot A]}{K[A]}$$

- We can drop this into our expression for the total catalyst.

$$[\text{cat}]_T = \frac{[\text{cat} \cdot A]}{K[A]} + [\text{cat} \cdot A]$$

- We can factor out the $[\text{cat} \cdot A]$'s.

$$[\text{cat}]_T = [\text{cat} \cdot A] \left(\frac{1}{K[A]} + 1 \right)$$

- Rearrange this to solve for $[\text{cat} \cdot A]$.

$$[\text{cat} \cdot A] = \frac{[\text{cat}]_T}{1/K[A] + 1}$$

- Remove this fractional denominator via multiplication by a clever form of 1 (namely, $K[A]/K[A]$).

$$[\text{cat} \cdot A] = \frac{K[A][\text{cat}]_T}{1 + K[A]}$$

- We can now drop this back into the rate expression to get an expression for the rate in terms of the overall catalyst concentration, which is more useful because that's an observable (we know how much we put in!).

$$\text{rate} = \frac{k_2 K[A][B][\text{cat}]_T}{1 + K[A]}$$

- Note that we could also write the K 's above as K_{eq} 's.

- Let's now derive an analogous expression for the catalytic cycle in Figure 12.4, but this time under the steady-state approximation.

- We initially obtain

$$[\text{cat} \cdot A] = \frac{k_1[A][\text{cat}]}{k_{-1} + k_2[B]}$$

- Rearranging yields

$$[\text{cat}] = \frac{[\text{cat} \cdot A](k_{-1} + k_2[B])}{k_1[A]}$$

- Using the fact that $[\text{cat}] = [\text{cat}]_T - [\text{cat} \cdot A]$, we obtain

$$\frac{[\text{cat} \cdot A](k_{-1} + k_2[B])}{k_1[A]} = [\text{cat}]_T - [\text{cat} \cdot A]$$

- We get rid of the denominator by multiplying both sides by $k_1[A]$, collect a couple of terms, and rearrange into

$$[\text{cat} \cdot A](k_1[A] + k_{-1} + k_2[B]) = k_1[A][\text{cat}]_T$$

- Then divide both sides by the term in parentheses on the left.

$$[\text{cat} \cdot A] = \frac{k_1[A][\text{cat}]_T}{k_1[A] + k_{-1} + k_2[B]}$$

- This substitution can now be dropped back into our rate law.

$$\begin{aligned} \text{rate} &= k_2[\text{cat} \cdot A][B] \\ &= \frac{k_1 k_2 [A][B][\text{cat}]_T}{k_{-1} + k_2[B] + k_1[A]} \end{aligned}$$

- We now multiply by another clever form of 1 (namely the inverse of k_{-1} on both top and bottom).

$$\text{rate} = \frac{\frac{k_1}{k_{-1}} k_2 [A][B][\text{cat}]_T}{1 + \frac{k_2}{k_{-1}} [B] + \frac{k_1}{k_{-1}} [A]}$$

- This is known as the **one plus rate form** of the rate law because of the “1+” in the denominator.

- We can now compare the two rate laws we've derived.

- We do this by assuming that $k_{-1} \gg k_2$, which is exactly the scenario in which the quasi-equilibrium assumption would apply!
- We approach a limit where we can ignore the k_2/k_{-1} term in the denominator, and $k_1/k_{-1} = K_{\text{eq}}$ (as established previously).

- Let's consider some limiting scenarios.

- This will help us partially eliminate complexity.
- First, let's consider the scenario in which

$$1 \gg \frac{k_2}{k_{-1}}[B] \approx \frac{k_1}{k_{-1}}[A]$$

- In this case, the denominator vanishes and the simplified rate law is

$$\text{rate} = \frac{k_1}{k_{-1}}[A][B][\text{cat}]_T$$

- Since this constraint implies that $k_{-1} \gg k_2$, the second step must be rate-determining.
- It also follows that $[\text{cat}]_T \approx [\text{cat}]$, and hence the resting state of the catalyst is the unbound catalyst!
- We can also say that the second step is **turnover-limiting**.

- Second, let's consider the scenario in which

$$\frac{k_2}{k_{-1}}[B] \gg \text{others}$$

- By "others," we mean the other two terms in the denominator.
- In this case, the simplified rate law is

$$\text{rate} = k_1[A][\text{cat}]_T$$

- This constraint implies that the first step is rate-determining.
- Hence, the reaction with B (zero-order) is post-rate limiting.
- It follows additionally that once again, the resting state of the catalyst is the unbound catalyst!

- Third, let's consider the scenario in which

$$\frac{k_1}{k_{-1}}[A] \gg \text{others}$$

- In this case, the simplified rate law is

$$\text{rate} = k_2[B][\text{cat}]_T$$

- Zero-order dependence on [A] implies that the catalyst is fully saturated with [A].
- Hence, the second step is rate-determining and the resting state is the bound catalyst.

- Fourth, everything matters.

- This scenario is not limiting but is, unfortunately, common.
- This implies a kinetic pathway in which all species are at roughly similar energies with roughly similar transition structures.
- This is often a good thing for catalysis, but we'll get there.

- Aside: The one plus rate form.

$$\text{rate} = \frac{c_1[A][B][\text{cat}]_T}{1 + c_2[A] + c_3[A][B] + c_4[P]}$$

- The rate law takes on the above general structure.
- We have a constant (the "kinetic term") c modified by the concentrations of the inputs in the numerator, collectively referred to as the potential terms (because they reflect something about the TST with respect to the ground state).

- The denominator — the **adsorption term** — consists of all the forms that the catalyst can take.
- What do the constants tell us?
 - c_1 tells us about the naked catalyst.
 - $c_2[A]$ can tell us about the $\text{cat} \cdot A$ complex.
 - $c_3[A][B]$ can tell us about the $\text{cat} \cdot AB$ complex.
 - $c_4[P]$ can tell us about the $\text{cat} \cdot P$ complex.
- Goal of this exercise: Gain intuition for the algebra.
 - The best kineticists can easily see the chemistry in rate laws the way that most organic chemists can see it in Lewis structures.
 - Donna Blackmond at Scripps is one of Alex's favorite kineticists.
 - Similarly, spectroscopists can see chemistry in derivative waveforms; “what a power to have!”
- How do we increase the rate, i.e., max out the rate law?
 - We want to get the denominator to go away.
 - This gives Scenario 3, in which all of the substrate is bound to the catalyst and it's doing it's thing as fast as it can.^[1]

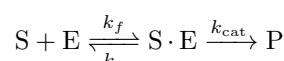
$$\text{rate}_{\max} = k_2[B][\text{cat}]_T$$

- Let's plop rate_{\max} into our steady-state approximation rate law, and multiply it by $1 = k_{-1}/k_{-1}$.

$$\text{rate} = \frac{\text{rate}_{\max} k_1[A]}{k_{-1} + k_2[B] + k_1[A]}$$

- Now define
- $$\frac{1}{K_m} = \frac{k_1}{k_{-1} + k_2[B]}$$
- It follows that
- $$\text{rate} = \frac{\text{rate}_{\max}[A]}{K_m + [A]}$$
- Under the quasi-equilibrium assumption, we can assume something else.
- $$\text{rate} = \frac{\text{rate}_{\max} K_{\text{eq}}[A]}{1 + K_{\text{eq}}[A]}$$
- Now define
- $$K_D = \frac{1}{K_{\text{eq}}}$$
- as the dissociation constant for the $\text{cat} \cdot A$ complex.
- It follows that
- $$\text{rate} = \frac{\text{rate}_{\max}[A]}{K_D + [A]}$$
- K_m takes us into **Michaelis-Menten kinetics**.

- Defined in the early twentieth century to guide our emerging understanding of biochemical kinetics.
- Using the historical nomenclature (substrate and enzyme), we have



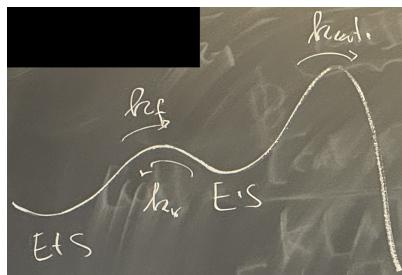
¹Why should this scenario give the fastest rate??

- There is a relationship here to saturation kinetics, defined in the limiting scenarios with Figure 12.4.
- Michaelis and Menten talked about a kinetic velocity v_{\max} where we go from asymptotic speed down to a first-order dependence on $[S]$.
- Other relevant expressions:

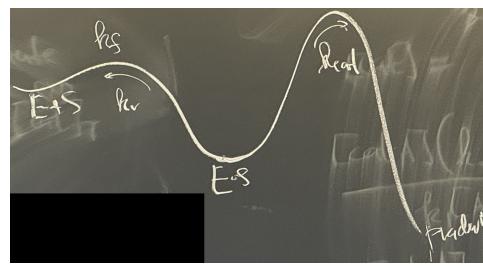
$$K_m = \frac{k_r + k_{cat}}{k_f} \quad v = \frac{v_{\max}[S]}{K_m + [S]}$$

- If $K_m = [S]$, then $v = v_{\max}/2$.
- We can experimentally determine the Michaelis constant by assaying a bunch of different initial rates at different concentrations.

- What's the point of Michaelis-Menten kinetics?



(a) Zeroeth-order.



(b) First-order.

Figure 12.5: Michaelis-Menten kinetic regimes.

- Enzymes can be characterized according the Michaelis constant K_m and the intrinsic rate constant k_{cat} .
- When we're zeroeth order in the substrate, we have one kinetic regime.
- When we're first-order in the substrate, we have a kinetic regime that's more like quasi-equilibrium!
- How well the enzyme binds the substrate is a measure of how efficient the catalyst is.

- When $k_r \gg k_{cat}$,

$$K_m \approx \frac{k_r}{k_f} = K_D$$

- This ratio measures how well the enzyme binds to the substrate.

- When $k_{cat} \gg k_r$,

$$K_m \approx \frac{k_{cat}}{K_m} =: \text{specificity constant}$$

- These ratios can be analyzed as the specificity constant for a specific enzyme.
- Describes an enzyme's preference (both in terms of binding and reactivity) for one substrate over another.

- Example: Fumerase (responsible for redox transport).

- $K_m = 5 \times 10^{-6}$, and $k_{cat} = 8 \times 10^2$, so SC is 10^7 .

- Example: Carbonic anhydrase.

- $K_m = 2.6 \times 10^{-2}$, and $k_{cat} = 4 \times 10^5$, so SC is 10^8 .

- So for great catalysis, you want the catalyst to find substrate quickly and immediately turn it over.
 - These two catalysts operate near the diffusion limit (which is ideal); they are near-perfect.
- References.
 - Knowles (1991).
 - A beautiful piece of literature; the touchstone for biological catalysis, per Alex.

12.2 Techniques for Kinetics Determinations

11/21:

- Today: Experimental techniques for kinetic determination.
 - In contrast to last time's algebra, we'll figure out today that many of those algebraic techniques were unnecessary.
 - Many techniques of kinetic analysis can be done with just a few observational experiments.
 - Goal of today: Convince us that kinetic analysis can be easy... and even fun!
- Consider the following reaction from last time.



- Recall from last time that kinetics can be used to elucidate the transition state structure.
- Recall from last week that linearizing data can give us the reaction order.
- However, we can access rate constant data without regression by using the **method of initial rates**.
- **Method of initial rates:** Assume that rate = $k[A]^a[B]^b[\text{cat}]^c$, take time courses, and make plots as in Figure 11.7 to extract k .

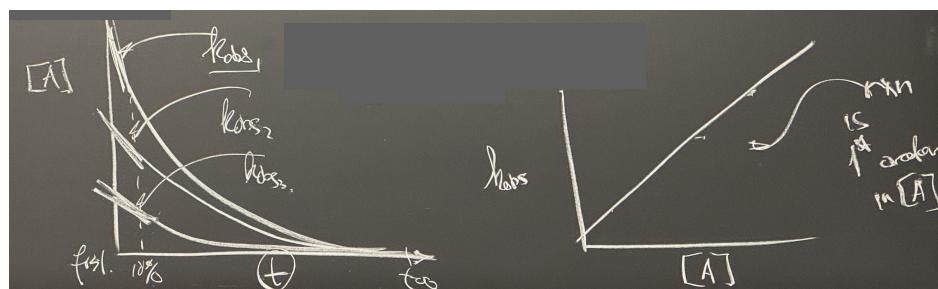


Figure 12.6: Method of initial rates.

- Begin by taking a time course for $[A]$.
- We can extract k_{obs} from initial slopes

$$-\frac{d[A]}{dt} = \frac{d[P]}{dt} = k_{\text{obs}}$$

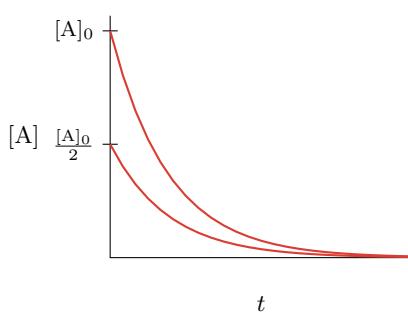
- if we're in a regime where all of the other concentrations are basically constant.
- If we consider the first, say, 10% of the reaction, then this approximate initial slope gives us k_{obs} directly.
- We can vary the initial concentration of $[A]$ to get multiple values of k_{obs} .
- Then — as in Figure 11.7 — we can plot k_{obs} vs. $[A]$ to learn the order of our reaction.

- The time domain matters a lot.
 - If $t \in [10^2 \text{ s}, 10^6 \text{ s}]$, we're in the “conventional” range for reaction speed.
 - Techniques like NMR are applicable here. These can allow us to assign concentration and structure in one experiment.
 - UV-Vis can also be good here.
 - FT-IR is also nice; it's very fast.
 - GC-MS is another recommended one in the conventional time domain.
 - If $t \in [10^{-3} \text{ s}, 10^1 \text{ s}]$, our reactions are too fast to pull out an aliquot.
 - As such, we need stopped flow kinetics.
 - If $t \in [10^{-12} \text{ s}, 10^{-6} \text{ s}]$, our reactions are too fast for mechanical injection into a compartment.
 - As such, use **flash photolysis**: Flash a light and follow the course with (typically) UV-Vis.
- How can we directly read out rate data from a reaction?
 - Calorimetry: The flow of heat from the vessel is directly related to the rate.
 - Mass transport and gas flow: Also good direct measurements.
- Usefulness of the method of initial rates.
 - Pros.
 - No complex math.
 - Direct access to k_{obs} .
 - Easy.
 - You've already got the starting materials, so just set up one more reaction!
 - Useful for trickier reactions with more complex kinetic scenarios, e.g., heterogeneous catalysis.
 - Cons.
 - Prone to error ($\pm 10\%$ at best).
 - We've got only a few data points from a short window in which not much has happened.
 - The first 10% of the reaction course may not be representative of the entire reaction.
 - In fact, there are many cases where the first 10% is patently *not* representative of the entire reaction (see Figure 12.8).
 - Example: A burst of speed at the very beginning due, for example, to a catalyst turning over very quickly because there's a large amount of it unbound early on.
 - Example: An **induction period** before the reaction begins in earnest.
 - Can be labor intensive.
 - We need several measurements of k_{obs} ; two measurements define a straight line, technically, but at least three are needed to be experimentally viable.
- Alex has personally done such initial rate experiments, despite the difficulties. But in the computer age, the method of initial rates has been outpaced by **whole-reaction kinetics**.
 - We can take a bunch of data points, and the computer can just fit it to a curve.
 - We can then transform this into a linear plot of $d[A]/dt$ vs. $[A]$.
 - Curve fitting via polynomial regression: Fit

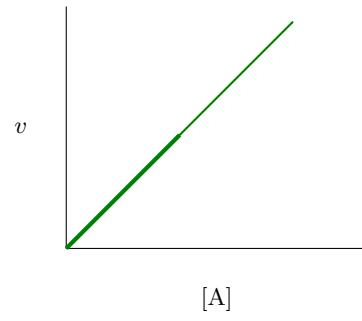
$$[A]_t = f(t) = a + bt + ct^2 + dt^3 + et^4 + ft^5 + \dots$$

- If we have enough terms, we can fit basically anything!
- And polynomials are nice because they're easily differentiated.
- Computers can do all this.

- How can we account for saturation kinetics?
 - Recall that as $[A]$ decreases, we sometimes switch kinetic regimes.
 - Such data may be hard to manipulate via linear regression.
 - This can be easier to look at on a rate vs. concentration plot than a concentration vs. time plot.
 - Note that on a rate vs. concentration plot, reactions with induction periods show up as humps.
 - This is because the reaction takes a bit to get going (i.e., during the induction period), then accelerates to normal, and then tapers off.
 - We can still polynomial fit these!
- Experimental chemistry offers all manner of complex kinetics, not just simple integrated rate laws.
 - So we need powerful techniques.
- To solve these challenges, use reaction progress kinetic analysis (RPKA).
 - Developed by Donna Blackmond (Scripps) — a modern genius of reaction kinetics.
 - She has a few valuable, albeit impenetrable, pieces of literature.
 - Blackmond (2005).
 - Blackmond (2015).
 - This method does not shoehorn reactions into models that they don't fit.
 - Two relevant techniques.
 - Same excess experiment.
 - Different excess experiment.
- Same excess experiment.



(a) Concentration vs. time plot.



(b) Rate vs. concentration plot.

Figure 12.7: Same excess experiment.

- Recall Figure 12.4, and the corresponding rate law

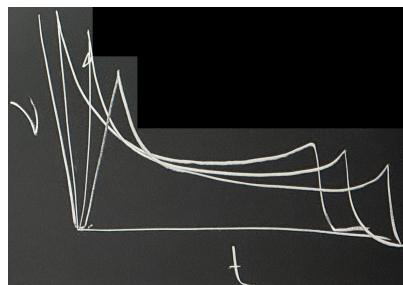
$$\frac{d[P]}{dt} = \frac{k_1 k_2 [A][B][\text{cat}]_T}{k_{-1} + k_2[B] + k_1[A]}$$

- Via the stoichiometry of $\text{A} + \text{B} \xrightarrow{\text{cat}} \text{P}$, we know that the following equality holds.

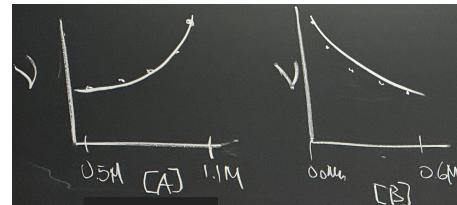
$$[B]_t = \underbrace{[B]_0 - [A]_0}_{\text{"excess"}} + [A]_t$$

- Note that “excess” refers to how much more B there is, relative to A. Because A and B both have coefficients of 1 in the balanced chemical equation, the excess is constant throughout this reaction.
- This substitution also allows us to define reaction progress in terms of only one variable!
- We now run two experiments (Figure 12.7a).
 - Experiment 1: Run the experiment with $[A]_0 = 0.1 \text{ mmol}$ and a small excess $[B]_0 = 0.12 \text{ mmol}$.
 - Then the excess is 0.02 mmol.
 - Experiment 2: Run the experiment with $[A]_0 = 0.05 \text{ mmol}$ and $[B]_0 = 0.07 \text{ mmol}$.
 - The excess is the same as last time: 0.02 mmol!
- If the reaction is behaving in a well-defined way, we should see overlay via visual inspection of the rates in the derivative plot (Figure 12.7b).
 - Thus, we can assay whether the rates of two experiments are the same by whether or not the lines visually overlay.
 - Overlay is commonly the case, but in cases where we *don't* get overlay, we get something really illuminating.
- In what cases does a same excess experiment produce lines that do not overlay?
 - Experiment 2 can proceed in a way such that it doesn't overlay.
 - Case 1: The reaction beginning from 50% conversion is faster. What could explain this?
 - Product inhibition.
 - This is a big one!
 - For example, molecules of the catalyst could be held up by strong binding to the product.
 - Catalyst decomposition.
 - Both of these possibilities suggest new experiments.
 - Start at 50% completion but add 50% product and look for overlay! This would provide evidence for a product inhibition pathway.
 - We could also think about varying catalyst percentage to provide evidence for a decomposition pathway.
 - Case 2: The reaction beginning from 50% conversion is slower. What could explain this?
 - Slow pre-equilibria.
 - For example, there could be an increase in the effective catalyst concentration with time. This could happen if we need, for instance, a retro-dimerization to get the catalyst to its active state.
 - The product could improve rate via some kind of autocatalysis.
 - This is rare, but not impossible.
- The value of visually inspecting rate vs. concentration plots is that they pop out relationships that are otherwise difficult to pull from curves.
 - For example, we may only get a small difference in concentration vs. time curves toward the end of our time courses! This is easy to miss if we're not looking super closely.
- Different excess experiment.
 - Hold the concentration of one of the reagents steady, and change the excess of the other.
 - What if we get overlay here?
 - Then we learn that the rate does not vary with excessive concentrations of B.
 - This means that the reaction is zero-order in B!

- What does no overlay mean?
 - There's a kinetic dependence on B.
 - Mathematically, $v \approx k_{\text{obs}}[A][B]$.
 - Thus, $v/[B] \approx k_{\text{obs}}[A]$!
 - Manipulating the exponent of [B] then allows us to read out the order of B from what exponent gives us a linear plot with overlay
- Note that overlay yes/no is a binary judgement.
 - But how do we know whether something is overlaying? How close does it have to be before we say, “yes, we're seeing overlay?”
 - There's some room for interpretation here.
- Implication from excess experiments: Only these two experiments tell us everything we need to know, even in wildly complex scenarios.
- A Blackmond paper exemplifying the power of excess experiments: Hein et al. (2011).



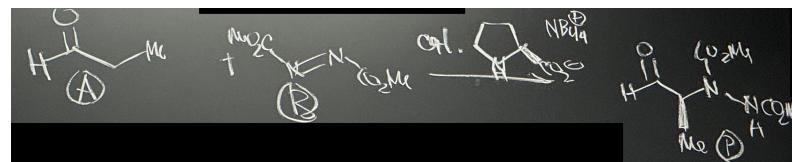
(a) The time course.



(b) The experimental data.

Figure 12.8: A complex time course.

- This paper blew Alex's hair back when he read it.
- The reaction is nominally pretty straightforward: Aldehyde plus azodicarboxylate in the presence of a chiral proline anion organocatalyst, stereoselectively yielding an α -amination product.



- This is literally the same type of reaction as in Figure 12.4.
- The rate was measured via calorimetry in a relevant concentration domain (we didn't have to do weird flooding as with Figure 11.7).
- Result: We have a complex positive order in [A], and a complex *inverse* order in [B] (i.e., at higher concentrations of B, the reaction goes slower).
- The time course (rate vs. time) is fast acceleration, then slowing down, then speeding up, then dead.
 - Here, the full rate course data is *essential* to figuring out what's going on. We would be so wrong it's not even funny if we tried to do method of initial rates here!
 - As an experimentalist, Alex would first think that his calorimeter is horribly broken. But this is rigorous at different concentrations; this *is* the kinetics!
- You can simulate time courses using software packages like COPASI.

- The full mechanism that Blackmond and colleagues ended up determining.

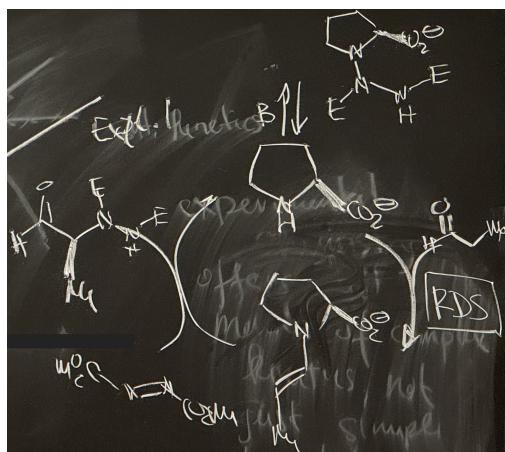


Figure 12.9: Mechanism underlying an example complex time course.

- This involves an off-cycle equilibrium of the catalyst being sequestered by one of the reagents.
- Formation of the enamine is rate-determining.
- How important is this whole paper? Alex doesn't know. The beauty of the process may be lost on you if you're a synthetic organic chemist and only care about getting the product.
- Challenges with RPKA: Measuring rates directly is difficult, and converting concentration data to rate data propagates some error.
- Spiritual successor to RPKA: Variable time normalization analysis (VTNA).



Figure 12.10: Variable time normalization analysis.

- Reference: Work by Jordi Burés.
 - Initial set of papers: Burés (2016).
 - A really useful tutorial: Nielsen and Burés (2019).
- Collect concentration vs. time data (e.g., via GC-MS aliquots as per usual).
- Change the total catalyst concentration $[cat]_T$ and look how the rates change.
- Key insight: $[cat]_T$ is basically constant during the reaction, so just treat it as a parameter of the system.
- Normalize to $[cat]^n$ by varying n until you get overlay and call that the order!

- Using VTNA, you can also normalize not only to something that's constant, but to something that's variable.

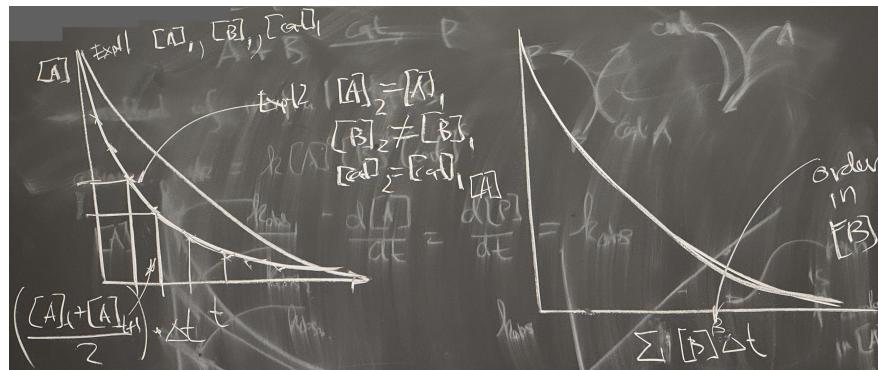


Figure 12.11: Variable time normalization analysis (different excess experiment).

- Do a different excess experiment.
- Experiment 1: Run it with $[A]_1$, $[B]_1$, and $[cat]_1$.
- Experiment 2: Keep $[A]_2 = [A]_1$ and $[cat]_2 = [cat]_1$, but change $[B]_2 \neq [B]_1$.
- $[B]$ is being consumed during the reaction, so it's changing in a stoichiometric fashion.
- Use the trapezoid rule to integrate under the Experiment 2 curve. Then plot $[A]$ vs. our new time-normalized x -axis, and vary β until we get the correct reaction order.

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