

# 5.53 (Molecular Structure and Reactivity I) Notes

Steven Labalme

September 17, 2024

# Weeks

<b>1</b>	<b>Introduction</b>	<b>1</b>
1.1	Introduction . . . . .	1
<b>2</b>	<b>Bonding Models</b>	<b>7</b>
2.1	Bonding Models 1 . . . . .	7
2.2	Bonding Models 2 . . . . .	14
<b>3</b>	<b>???</b>	<b>21</b>
3.1	Computational Chemistry . . . . .	21
<b>References</b>		<b>27</b>

# List of Figures

1.1	Mechanism depth level 1 (arrow pushing) . . . . .	2
1.2	Arrow types in arrow pushing. . . . .	2
1.3	Mechanism depth level 2 (transition states). . . . .	3
1.4	Mechanism depth level 3 (full reaction coordinate). . . . .	3
1.5	Mechanism depth level 4 (full energy manifold). . . . .	5
1.6	Aspects of mechanism. . . . .	6
2.1	Lewis dot structures. . . . .	7
2.2	MO diagram for H <sub>2</sub> . . . . .	10
2.3	MO diagram for ethylene. . . . .	10
2.4	MO diagram for formaldehyde. . . . .	11
2.5	QMOT diagram for CH <sub>3</sub> . . . . .	12
2.6	QMOT diagram for CH <sub>2</sub> . . . . .	13
2.7	QMOT diagram for formaldehyde. . . . .	14
2.8	Huckel diagram for ethylene. . . . .	15
2.9	Huckel diagram for allyl groups. . . . .	16
2.10	Huckel diagram for benzene. . . . .	16
2.11	Huckel diagram for cyclobutadiene. . . . .	17
2.12	Möbius aromaticity. . . . .	18
2.13	Ring current. . . . .	19
2.14	Banana bonds in cyclopropane. . . . .	19

# 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.

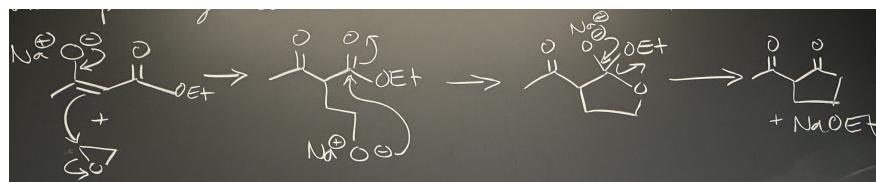


Figure 1.1: Mechanism depth level 1 (arrow pushing).

- 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.

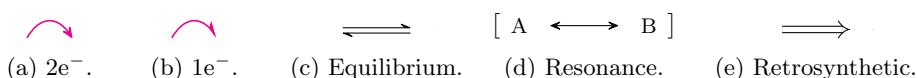


Figure 1.2: Arrow types in arrow pushing.

## 2. Determine the transition-state structures.

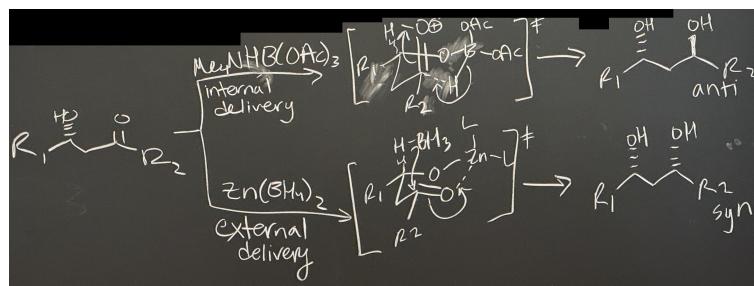
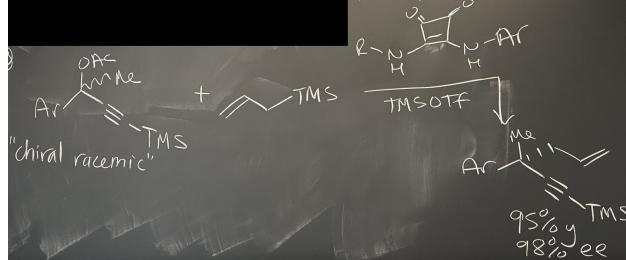


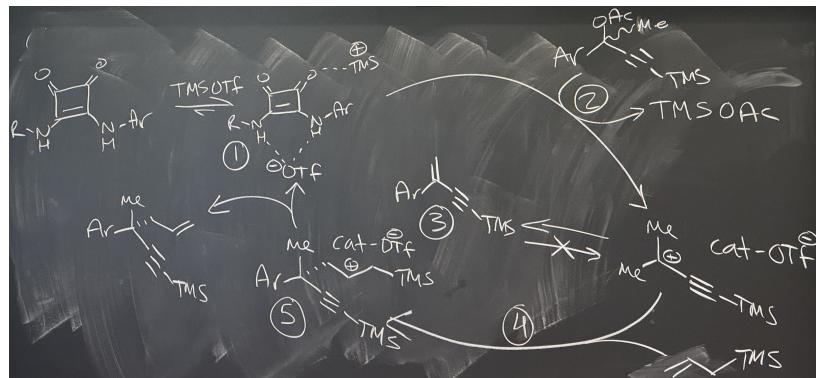
Figure 1.3: Mechanism depth level 2 (transition states).

- 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  $\beta$ -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!!).<sup>[1]</sup>
      - 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):  $\beta$ -silicon effects and  $\alpha$ -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<sub>N</sub>1 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).

<sup>1</sup>KIEs 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.

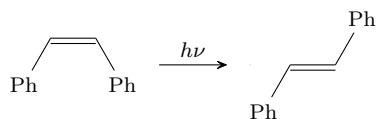


Figure 1.5: Mechanism depth level 4 (full energy manifold).

- 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<sub>N</sub>2 reaction, Br<sup>-</sup> + Me-I → Br-Me + I<sup>-</sup>.



(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.



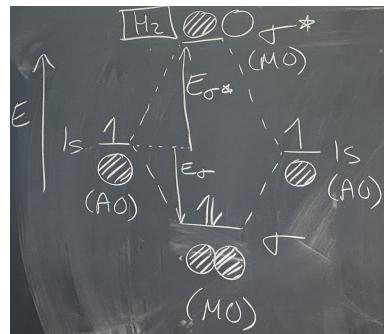
Figure 2.1: Lewis dot structures.

- Developed in 1916 by G. N. Lewis.
  - 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, NH<sub>3</sub> 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  $\theta$ . *Denoted by  $i$ . Given by*

$$1 + i \cos \theta = 0$$
- Example:  $\text{NH}_3$  has a hybridization index of 3.4.
- Example:  $\text{H}_2\text{O}$  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  $\text{H}_2\text{O}$  has longer bonds than  $\text{NH}_3$ ??
- **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  $\sigma$ -bonds.
  - Example:  $\text{ACN}$ . 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.
  - Example: Consider an  $\alpha, \beta$ -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  $\pi$ -networks, but it *can* happen through  $\sigma$ -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.,  $\sigma$ ,  $\sigma^*$ ,  $\pi$ ,  $\pi^*$ ) 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  $\text{H}_2$ .

- 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  $E_\sigma$ .
- The destabilization energy is  $E_{\sigma^*}$ .
- 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  $\sigma$ -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.

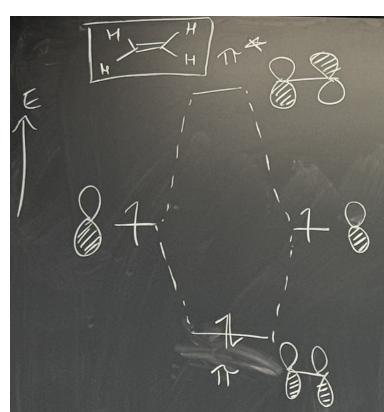
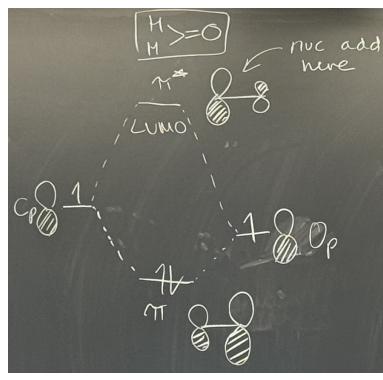


Figure 2.3: MO diagram for ethylene.

- Looking specifically at the  $\pi$ -bond formation.
  - This is why we form a stable  $\pi$ -bond.
  - Example MO diagram: Formaldehyde.
- 
- The diagram illustrates the molecular orbital (MO) formation in formaldehyde (H<sub>2</sub>O). At the top left, the Lewis structure H=O is shown with two lone pairs on oxygen. Below it, two carbon p-orbitals (C<sub>p</sub>) are shown, each with one lobe pointing up and one lobe pointing down. To the right, an oxygen p-orbital (O<sub>p</sub>) is shown with two lobes, both pointing upwards. A horizontal dashed line labeled 'LUMO' represents the lowest unoccupied molecular orbital. Arrows indicate the interaction between the C<sub>p</sub> and O<sub>p</sub> orbitals to form the LUMO. A vertical dashed line labeled 'nuc add here' points to the oxygen atom. At the bottom center, a pi bond (π) is formed by the overlap of the C<sub>p</sub> and O<sub>p</sub> p-orbitals, with two pi electrons represented by arrows in the resulting bonding orbital.
- Figure 2.4: MO diagram for formaldehyde.
- We mix a C<sub>p</sub> AO and a (lower energy) O<sub>p</sub> 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  $\pi$ -orbital is asymmetric because its energetically more similar to O<sub>p</sub> than C<sub>p</sub>.
      - In other words, it's going to look more like the O<sub>p</sub> 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:  $\text{CH}_3$ .

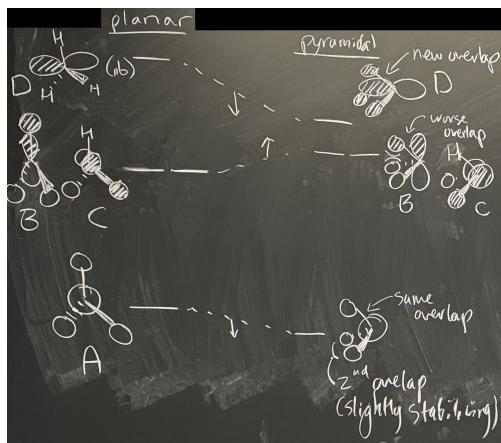


Figure 2.5: QMOT diagram for  $\text{CH}_3$ .

- Key question: What geometry of  $\text{CH}_3$  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  $\text{CH}_3^+$  cation: We have 6 electrons, so we populate the planar orbitals because it's more stable overall.
  - Consider the  $\text{CH}_3^-$  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.
  - NH<sub>3</sub>: 8 electrons, pyramidal.
  - BH<sub>3</sub>: 6 electrons, planar.
  - ·CH<sub>3</sub>: 7 electrons, *slightly* planar.
    - But this is a special case only for ·CH<sub>3</sub>; 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: CH<sub>2</sub>.

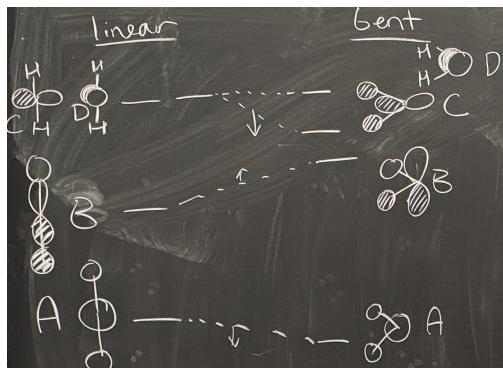


Figure 2.6: QMOT diagram for CH<sub>2</sub>.

- Two geometries: Linear and bent.
- Linear.
  - A. Linear chain of *s*-orbitals with matching phases.
  - B. Linear chain of matching phases orbitals, with *p<sub>x</sub>* 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.
- H<sub>2</sub>O: 8 electrons, bent.
  - Note that this model predicts that H<sub>2</sub>O 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.

- $\text{CH}_2$  (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  $136^\circ$ , and singlet is  $105^\circ$ , 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.

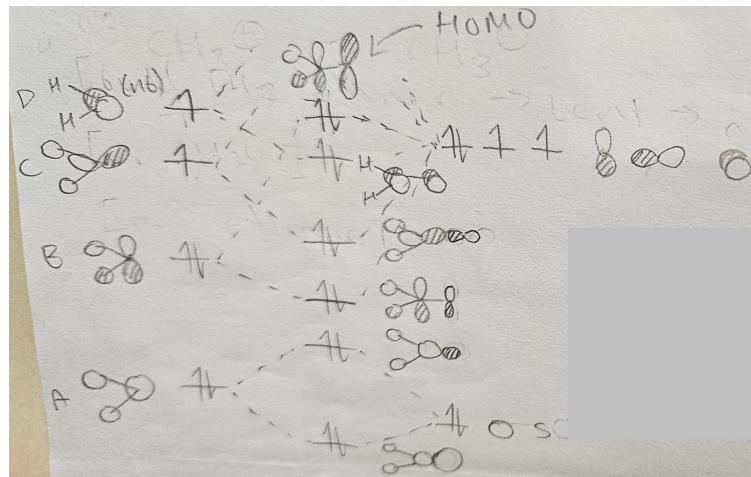


Figure 2.7: QMOT diagram for formaldehyde.

- 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  $\pi$ -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  $\pi$ -system in a planar molecule.
  - Key assumptions.
    - The  $\pi$ -system is independent of the  $\sigma$ -network.
    - You only consider valence electrons.
    - Only neighboring orbitals interact, i.e., only  $\pi$ -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  $\alpha$ .*
  - This is also the energy of an electron in an empty  $p$ -AO.
- Example Huckel diagram: Ethylene.

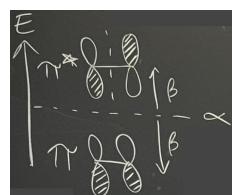
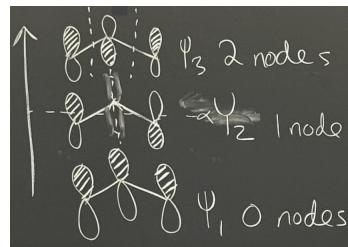


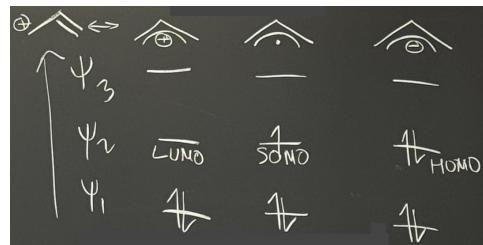
Figure 2.8: Huckel diagram for ethylene.

- Let's first confirm that this diagram meets all four Huckel theory rules.
  - We get two new  $\pi$ -MOs from two  $p$ -AOs.
  - The energy difference from the nonbonding energy level is called  $\beta$ .
  - 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  $\psi_1$ .
  - It has 0 nodes.
- The middle energy orbital is called  $\psi_2$ .
  - To maintain symmetry, we have to delete the middle orbital and give opposite phases.
- The highest energy orbital is called  $\psi_3$ .
  - 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  $\psi_2$ !
  - $\psi_2$  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.

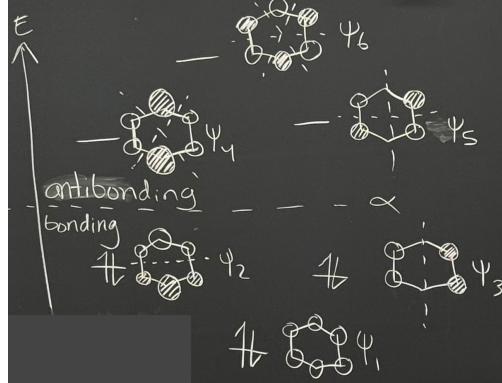


Figure 2.10: Huckel diagram for benzene.

- For cyclic systems, we draw a **Frost circle**.
  - For benzene, the radius of the Frost circle is  $2\beta$ .
- We create  $\psi_1, \dots, \psi_6$ .
  - $\psi_2, \psi_3$  and  $\psi_4, \psi_5$  are degenerate.
  - No electron density on the central  $p$ -orbitals in  $\psi_3$  implies bigger coefficients on the corresponding orbitals in  $\psi_2$ .
    - See Anslyn and Dougherty (2006) for more!!
  - $\psi_4, \psi_5$  have 2 nodes at angles.
  - For  $\psi_6$ , we have 3 nodes through a hexagon, which is alternating shading.
- $\alpha$  is the nonbonding level; higher is antibonding, lower is bonding.
- 6 electrons in benzene's bonding  $\pi$ -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;  $\beta$  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.

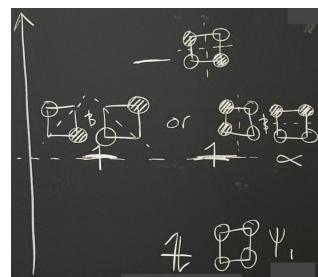


Figure 2.11: Huckel diagram for cyclobutadiene.

- $\psi_1$  has no phase inversion and no nodes.
- There are two different ways to draw the orbitals for  $\psi_2, \psi_3$ .
  - 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.<sup>[1]</sup> 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**.

<sup>[1]</sup>“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  $\pi$ -electrons are aromatic.
  - If you have  $4n$  electrons in a cyclic planar molecule with continuous  $\pi$ -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  $\pi$ -orbitals are pointing toward each other.
  - No phase inversions are allowed; we must connect orbitals without crossing the  $\sigma$ -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.

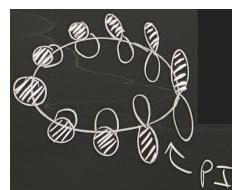


Figure 2.12: Möbius aromaticity.

- 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.

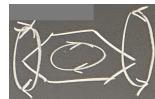


Figure 2.13: Ring current.

- Suppose you have an external magnetic field perpendicular to the  $\sigma$ -plane.
  - This would induce the  $\pi$ -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  $\delta$ ) outside and shielded (lower  $\delta$ ) inside.
  - Cyclohexene: No ring current, so we get a bit of downfield shift for the vinyl protons ( $\delta$  5.6).
  - Benzene: Has a ring current, so we get a noticeable downfield shift ( $\delta$  7.3).
  - [18]annulene: Has a large ring with many  $\pi$ -electrons, so we get a significant downfield shift for the external protons ( $\delta$  9.3) and a significant *upfield* shift for the internal protons ( $\delta$  -2.9).

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

- Example: The dipole aligned up and down in benzene, 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.

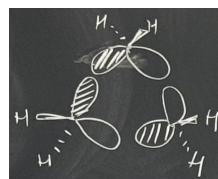


Figure 2.14: Banana bonds in cyclopropane.

- Cyclopropane needs more  $p$ -character because of its  $60^\circ$  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  $\sigma$ -bonds has to go somewhere.
- Group orbitals (HOMO) degenerate.
  - The **Walsh orbitals** have more  $\pi$ -character, so cyclopropane is  $sp^2$ -like.
  - This means it is a good  $\pi$ -donor and a bad  $\pi$ -acceptor.
  - Example of donation: The isopropylcyclopropane cation is very stable because all of the  $sp^2$ -character is getting donated into the carbocation’s empty orbital.
  - What is going on here??
- 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.
  - 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,  $\psi$  is the wave function describing the position of the electron in space, and  $H$  is the **Hamiltonian operator**. *Given by*

$$H\Psi = E\Psi$$
  - $\psi^2$  is the probability of finding an electron in a specific position (i.e., the electron density!).
  - Big  $\Psi$  is the total molecular wave function, and little  $\psi$  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 ( $\phi_1^2, \phi_2^2$ ) are very separate.

# Week 3

???

## 3.1 Computational Chemistry

9/17:

- Lecture 3 recap.
  - Huckel theory: A fast way to draw the MOs of conjugated  $\pi$ -systems.
    - If the conjugated  $\pi$ -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.<sup>[1]</sup>
  - 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.

<sup>[1]</sup>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.<sup>[2]</sup> *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<sub>N</sub>1 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 CDCl<sub>3</sub>!
      - 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.

<sup>2</sup>This 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  $120^\circ$  angle (the **Bürgi-Dunitz angle**), because that’s where it’s easiest to donate into the  $\pi^*$ -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!

# References

- Ajami, D., Oeckler, O., Simon, A., & Herges, R. (2003). Synthesis of a Möbius aromatic hydrocarbon. *Nature*, 426, 819–821. <https://doi.org/10.1038/nature02224>
- Anslyn, E. V., & Dougherty, D. A. (2006). *Modern physical organic chemistry*. University Science Books.
- Labalme, S. (2023). *CHEM 26100 (Quantum Mechanics) notes*. Retrieved September 17, 2024, from <https://github.com/shadypuck/CHEM26100Notes/blob/master/Notes/notes.pdf>
- Takeuchi, S., Ruhman, S., Tsuneda, T., Chiba, M., Taketsugu, T., & Tahara, T. (2008). Spectroscopic tracking of structural evolution in ultrafast stilbene photoisomerization. *Science*, 322(5904), 1073–1077. <https://doi.org/10.1126/science.1160902>
- Wendlandt, A. E., Vangal, P., & Jacobsen, E. N. (2018). Quaternary stereocentres via an enantioconvergent catalytic S<sub>N</sub>1 reaction. *Nature*, 556, 447–451. <https://doi.org/10.1038/s41586-018-0042-1>