

5.53 (Molecular Structure and Reactivity I) Notes

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September 7, 2024

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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.

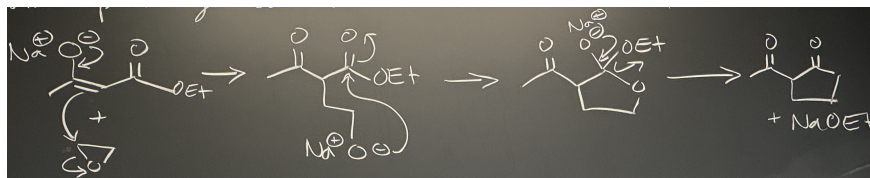


Figure 1.1: Mechanism depth level 1 (arrow pushing).

- 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.

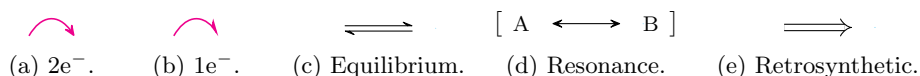


Figure 1.2: Arrow types in arrow pushing.

2. Determine the transition-state structures.

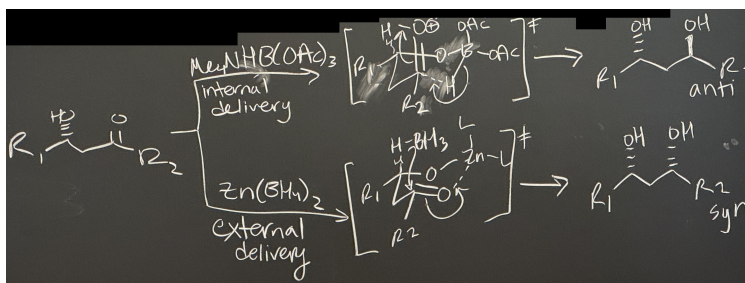
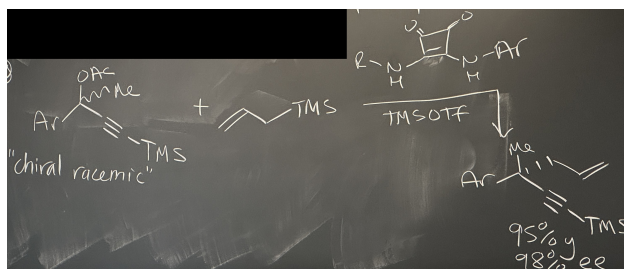


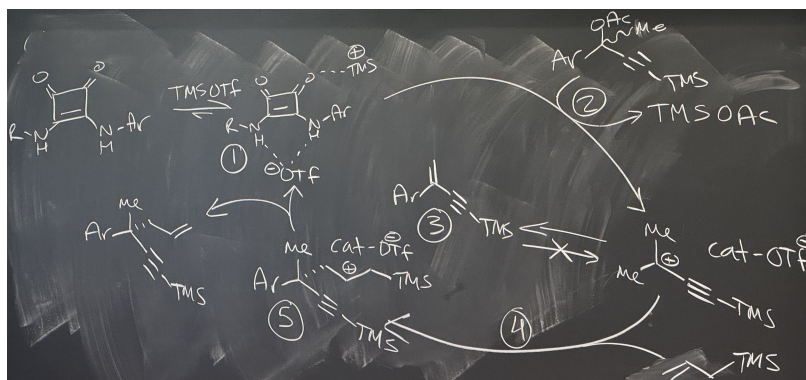
Figure 1.3: Mechanism depth level 2 (transition states).

- 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 20200!!).^[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.

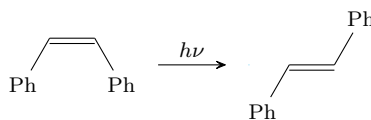
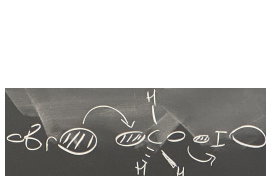


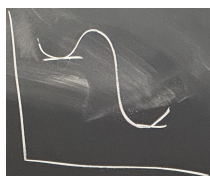
Figure 1.5: Mechanism depth level 4 (full energy manifold).

- 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, $\text{Br}^- + \text{Me-I} \longrightarrow \text{Br-Me} + \text{I}^-$.



(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.

References

- Anslyn, E. V., & Dougherty, D. A. (2006). *Modern physical organic chemistry*. University Science Books.
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- Wendlandt, A. E., Vangal, P., & Jacobsen, E. N. (2018). Quaternary stereocentres via an enantioconvergent catalytic S_N1 reaction. *Nature*, *556*, 447–451. <https://doi.org/10.1038/s41586-018-0042-1>