

## 2.11 Molecular Orbital Theory - 2

9/30: • Lecture 10 recap: What MO theory can explain.

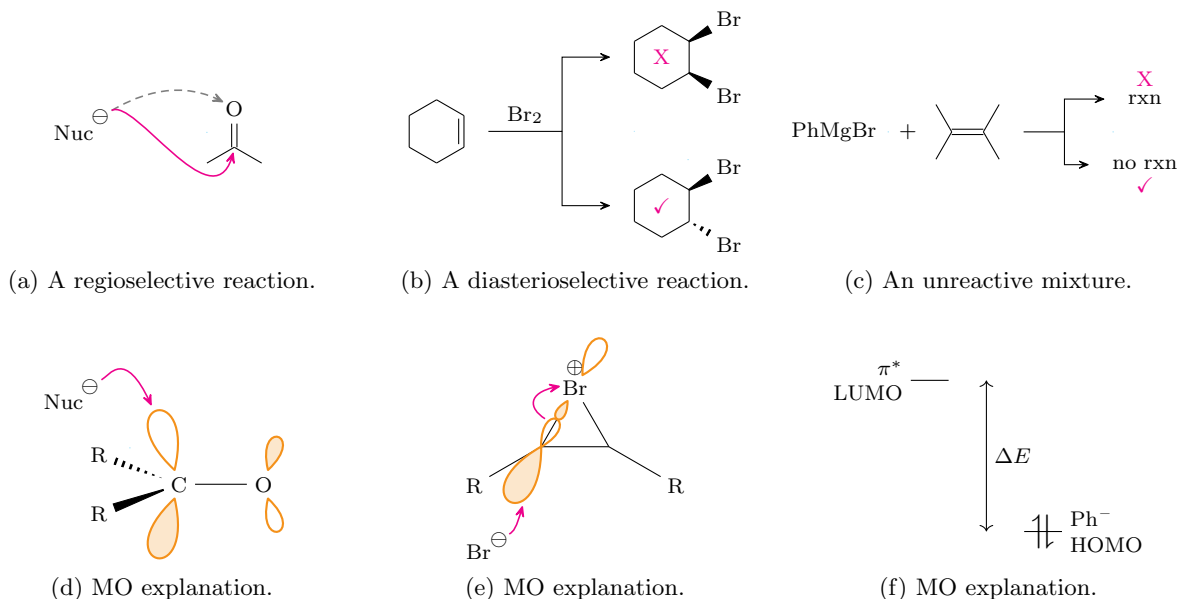


Figure 2.1: MO theory explains these phenomena.

### – Regioselectivity.

- Consider a nucleophile adding into a carbonyl (Figure 2.1a).
  - Experimentally, we observe that the nucleophile attacks the carbon atom (magenta arrow) instead of the oxygen atom (grey dashed arrow).
- To understand why, we must consider the carbonyl's molecular orbitals (Figure 2.1d).
  - Specifically, we must consider the carbonyl's LUMO, since this will be the MO that interacts with the nucleophile's HOMO. Here, the LUMO is the carbonyl's  $\pi^*$ -orbital.
  - The carbonyl's LUMO has big lobes on carbon and small lobes on oxygen; in other words, this LUMO is **polarized** toward carbon.
  - The difference in lobe size explains why the nucleophile attacks carbon instead of oxygen.

### – Diastereoselectivity.

- Consider the bromination of an alkene (Figure 2.1b).
  - Experimentally, we observe that the *anti* adduct is formed instead of the *syn* adduct.
- To understand why, we consider the MOs of the bromonium ion intermediate (Figure 2.1e).
  - For the same reason as before, we must consider the bromonium ion's LUMO. Here, the LUMO is the C–Br  $\sigma^*$ -orbital.
  - The bromonium ion's LUMO has its largest lobe behind carbon.
  - Thus, this is the lobe that will be attacked by the  $\text{Br}^-$  nucleophile. Such an attack is called a “backside attack” and induces the *anti* product.

### – Reactivity.

- Consider a Grignard reagent adding into an olefin (Figure 2.1c).
  - Experimentally, we observe no reaction here.
- To understand why, we must consider the relative energies of the reacting MOs (Figure 2.1f).
  - Essentially, the alkene's LUMO (a  $\pi^*$ -orbital) is much higher in energy than the phenyl anion's HOMO. Thus, the  $\Delta E$  gap is too big, i.e., there is a lack of energy symmetry.
  - Therefore, by Rule 3 from Lecture 10, no reaction occurs.

- Today: More MO theory.
- Lecture outline.
  - The Bürgi-Dunitz angle.
  - Hyperconjugation.
  - The anomeric effect.
  - Stereoelectronic effects and the rate of reaction.
- **Bürgi-Dunitz angle:** The angle at which nucleophiles typically add to carbonyls. *Given by  $107^\circ$ .*

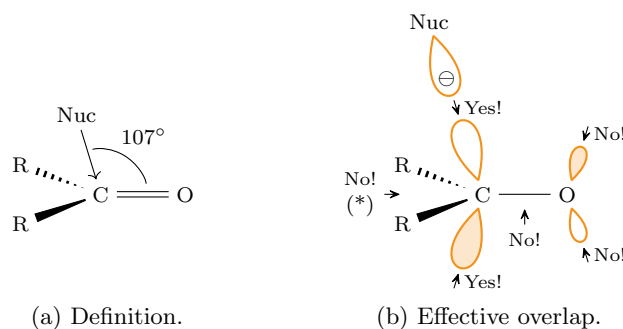


Figure 2.2: Bürgi-Dunitz angle.

- This is the angle between the new C–Nuc bond and the carbonyl's  $\sigma$ -plane (Figure 2.2a).
- Nucleophiles attack at this angle because it's the location of the  $\pi^*$ -lobe on carbon (Figure 2.1d).
- Let's elaborate a bit on Figure 2.1d now (Figure 2.2b).
  - Once again, consider the carbonyl  $\pi^*$ -orbital (its LUMO) and its “butterfly” lobes.
  - The nucleophile must approach the  $\pi^*$ -orbital with the right symmetry. This is why we see its HOMO's lobe approach the carbon atom's  $\pi^*$ -lobe dead-on at exactly the right angle.
    - This angle leads to efficient overlap, and hence an effective sharing of electron density.
    - This is an example of Rule 3 from Lecture 10.
  - Are there any other locations at which we can add into the carbonyl?
    - We can also add into the shaded carbon  $\pi^*$ -lobe on the other side of the  $\sigma$ -plane by reversing the shading of the nucleophile's lobe!
    - However, any other angle of attack will *not* work.
    - Note (\*): A backside attack is good for interacting with the  $\sigma^*$ -orbital, but bad for interacting with the  $\pi^*$ -orbital that we need for carbonyl chemistry.
- **Hyperconjugation:** The mixing of filled and empty orbitals to stabilize a system.
- Example (from 5.12): Stabilizing carbocations.

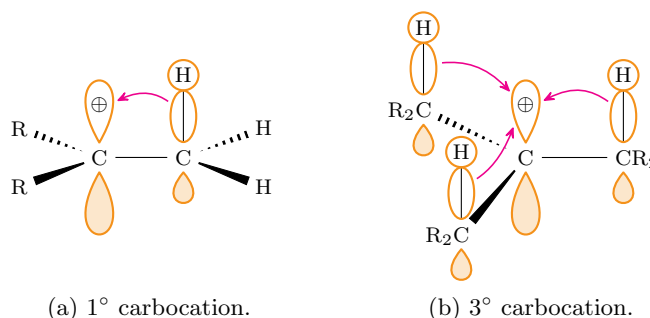
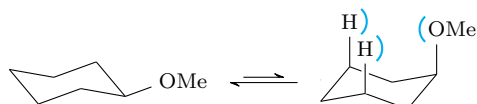


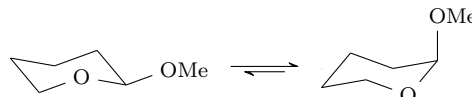
Figure 2.3: Hyperconjugation stabilizes carbocations.

- Consider a primary ( $1^\circ$ ) carbocation (Figure 2.3a).
  - In a carbocation, the positively charged carbon localizes its lack of electron density to an empty  $p$ -orbital.
  - However, adjacent to this empty  $p$ -orbital is a full  $\sigma$ -orbital, namely, the adjacent C–H bond. Moreover, this bond has the right *geometry* to donate into the empty  $p$ -orbital.
  - Thus, the  $\sigma$ -orbital of the C–H bond will donate electron density into the empty  $p$ -orbital, delocalizing both positive and negative charges and thereby stabilizing the system.
- We denote hyperconjugation interactions using a special **notation**; the particular hyperconjugation in Figure 2.3 is denoted  $\sigma_{\text{CH}} \rightarrow p_{\text{C}}$ .<sup>[1]</sup>
- In a tertiary ( $3^\circ$ ) carbocation, we get electron donation from *three* adjacent  $\sigma_{\text{CH}}$  orbitals.
  - These *three* stabilizing interactions explain why  $3^\circ$  carbocations are more stable than  $1^\circ$  ones!
  - Such effects are also why more substituted cations are more stable in general.
- **Hyperconjugation notation:** The concise method for denoting a certain hyperconjugative orbital interaction. *Given by*

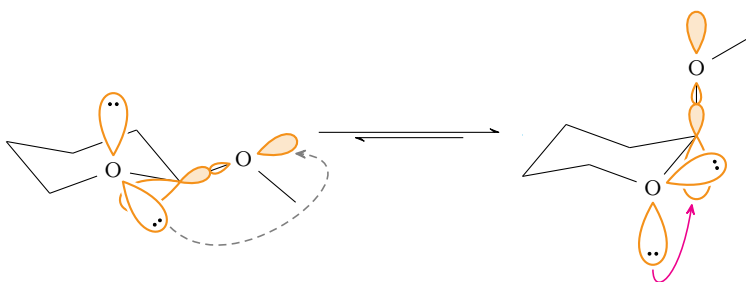
$$\text{orbital}_{\text{atoms}} \rightarrow \text{orbital}_{\text{atoms}}$$
  - The arrow means “donates into.”
    - Indeed, we always write the filled orbital first (before the arrow) and the empty orbital second (after the arrow).
  - Possible orbitals:  $\sigma, \sigma^*, \pi, \pi^*, p, n$ .
    - Note that  $n$  denotes a nonbonding lone pair.
- **Anomeric effect:** The tendency of heteroatom substituents adjacent to heteroatoms in cyclohexane derivatives to prefer the axial orientation.
- Let’s break this rather complicated definition down through an example.



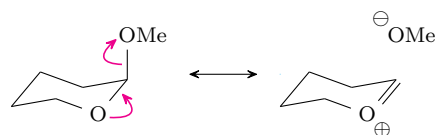
(a) Sterics win in methoxycyclohexane.



(b) Anomeric wins in 2-methoxytetrahydropyran.



(c) MOs explain the anomeric effect.



(d) Resonance explains the anomeric effect.

Figure 2.4: Anomeric effect.

<sup>1</sup>This is pronounced “sigma C–H to  $p$  C donation” or (very explicitly) “sigma see aech to pee see donation.”

- In methoxycyclohexane, the methoxy group prefers to be equatorial to avoid 1,3-diaxial interactions (Figure 2.4a).
  - This leads to a 70 : 30 distribution in favor of the equatorial conformer.
- However, in 2-methoxytetrahydropyran, the methoxy group prefers to be *axial* due to the anomeric effect (Figure 2.4b).
  - This *also* leads to a 70 : 30 distribution, but this time in favor of the axial conformer.
  - Notice how this empirical observation reflects the definition of the anomeric effect: We have a heteroatom substituent (the methoxy group) adjacent to a heteroatom in cyclohexane (the oxygen in the six-membered ring), and it is preferring the axial orientation!
- What causes the anomeric effect? Let's investigate the stabilization of the axial conformer further using molecular orbitals (Figure 2.4c).
  - In 2-methoxytetrahydropyran's equatorial conformation, we get poor overlap between the oxygen lone pair's orbital and the C–OMe antibonding orbital. This poor overlap is due to the *gauche* orientation of said orbitals.
  - In 2-methoxytetrahydropyran's axial conformation, we get really nice overlap between the oxygen lone pair and the  $\sigma^*$ -orbital of the C–OMe bond. This is because both orbitals have large lobes pointing axial down. Because of this favorable geometry,  $n_{\text{O}} \rightarrow \sigma_{\text{CO}}^*$  hyperconjugation occurs.<sup>[2]</sup>
- Another way of showing how the anomeric effect stabilizes the axial conformer is by using resonance diagrams (Figure 2.4d).
  - Indeed, starting from the typical picture, we can push the lone pair into an O=C  $\pi$ -bond and formally break the C–OMe  $\sigma$ -bond.
  - The result is called a **no-bond resonance form**.
  - Something should feel off to you here, though.
    - When you learned to draw resonance structures, you learned that you can't break  $\sigma$ -bonds.
    - However, we are now telling you that sometimes, you *are* allowed to break  $\sigma$ -bonds. This is “next-level resonance structures.”
  - Note that 2-methoxytetrahydropyran doesn't go all the way to the no-bond resonance form, but said resonance form *is* a major contributor.
    - This also means that the no-bond resonance form affects the reactivity of the molecule.
- Both hyperconjugation and the anomeric effect fall under the broader category of **stereoelectronic effects**.
  - Note that they are not the only examples of such effects, though.
- **Stereoelectronic effect:** An effect on structure or reactivity of a molecule caused by the spatial orientation of its orbitals.
  - We've previously learned that everything in Orgo can be explained by steric and electronic effects, but stereoelectronic effects are like a secret third option!
- Let's now look at some more places where stereoelectronic effects crop up.

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<sup>2</sup>Note that there is no particular reason why overlap with a  $\sigma^*$ -orbital, in particular, is stabilizing. Rather, the point is that we have a filled orbital (the lone pair) adjacent to an empty orbital (which just happens to be a  $\sigma^*$  orbital), so hyperconjugation can occur to spread out the negative and positive charges. This delocalization — like any — is then inherently stabilizing.

- Example: Hyperconjugation in noncationic species.

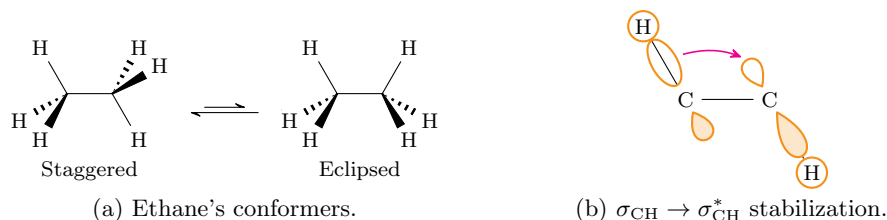


Figure 2.5: Hyperconjugation stabilizes staggered ethane.

- We may have learned that ethane prefers the staggered conformer over the eclipsed conformer (Figure 2.5a) due to sterics.
  - This is not true!
  - We know this because H is really tiny.
- In fact, this preference is due to hyperconjugation, a stereoelectronic effect (Figure 2.5b).
  - Staggered ethane is stabilized by electron donation from the  $\sigma$ -bond of one C–H bond into the adjacent, antiperiplanar C–H bond's  $\sigma^*$  orbital:  $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CH}}^*$ .
  - This is a small interaction, but it occurs six times, once for each C–H  $\sigma$ -bond!
- Takeaway: Electron delocalization is stabilizing, and more delocalization is more stabilizing.
- Example: Stereoelectronic stabilization can accelerate reactions.

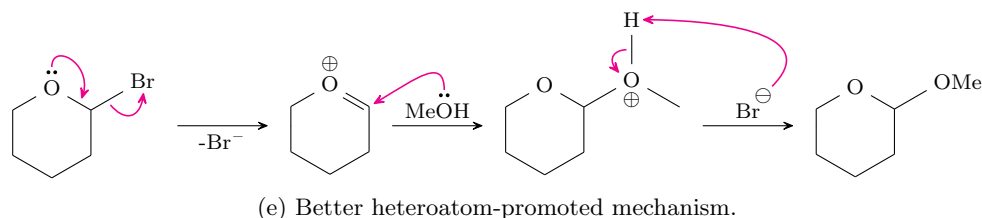
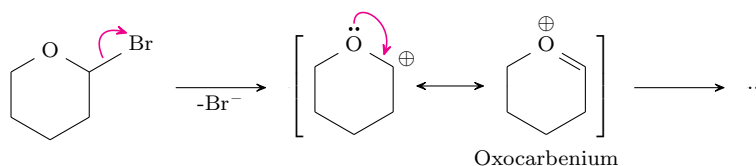
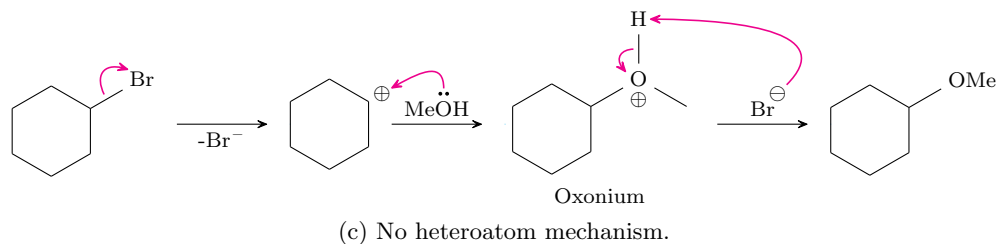
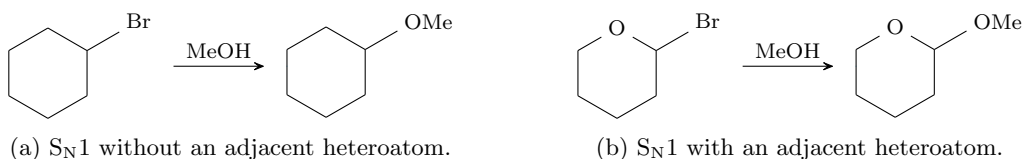


Figure 2.6: Stereoelectronic effects accelerate reactions.

- Consider the  $S_N1$  substitution of bromocyclohexane to methoxycyclohexane (Figure 2.6a), vs. the  $S_N1$  substitution of 2-bromotetrahydropyran to 2-methoxytetrahydropyran (Figure 2.6b).
- Which of these substitutions occurs faster?
- To answer this question, let's look at the mechanism of each (Figures 2.6c-2.6d).
  - Note that in Figure 2.6c, either bromide or another equivalent of methanol can do the final deprotonation of the **oxonium** ion.<sup>[3]</sup>
  - Note that in Figure 2.6d, the fact that the **oxocarbenium** ion obeys the octet rule implies that it is the more stable resonance structure.
- In fact, the oxocarbenium ion is an example of oxygen stabilizing a carbocation through  $n_O \rightarrow p_C$  hyperconjugation.
- This is one example of hyperconjugation in this reaction scheme, but there is another effect as well.
  - In the original 2-bromotetrahydropyran molecule, the oxygen lone pair will also hyperconjugate into the C–Br  $\sigma^*$ -orbital per the anomeric effect.
  - In other words, O mediates the departure of the leaving group through  $n_O \rightarrow \sigma_{CBr}^*$  hyperconjugation.
- Thus, since both hyperconjugative stabilizing effects can (and do!) happen, it is better to say mechanistically that the arrow pushing in the first step happens simultaneously (Figure 2.6e).
  - Indeed, the rule in arrow pushing is “make a bond, break a bond,” so that's what we do.
- We can now complete the mechanism for the heteroatom-promoted reaction (Figure 2.6e).
  - MeOH adds into the  $\pi^*$ -orbital of the oxocarbenium (at the Bürgi-Dunitz angle!), also kicking electrons up to the oxygen in a concerted step.
  - Then we get deprotonation again.
- Now that we've got both mechanisms, let's consider the energy surface in order to compare the rates of reaction.
  - Both reactions will have two-humped energy surfaces, befitting a mechanism with only one true catinoic intermediate.
  - However, in the energy surface for the heteroatom-promoted reaction,  $n_O \rightarrow p_C$  hyperconjugation will stabilize the intermediate and  $n_O \rightarrow \sigma_{CBr}^*$  will stabilize the transition state of the first step, lowering its activation energy!
  - Thus, the heteroatom-promoted  $S_N1$  is faster!
- Takeaway: The overall reaction specifics depend on geometry and orbital overlap.

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<sup>3</sup>Note that — comparing the  $pK_a$  of protonated methanol to HBr — methanol is actually almost a million times more basic than bromide. As such, for every one time bromide does the final deprotonation, methanol will do it to almost a million other oxonium intermediates. However, it can still be useful to think of bromide as *formally* doing the final deprotonation so as to balance the reaction  $C_6H_{11}Br + CH_3OH \longrightarrow C_6H_{11}OCH_3 + HBr$ .