

Unit 2

Molecular Orbitals and Pericyclic Reactions

2.10 Molecular Orbital Theory - 1

9/27: • See Georgia's notes on Canvas (also included below).

Lecture 10: MO Theory (1/2)

NO 1
DATE 27 Sept 2024

Exam Reflections

- You all did great
- "How did I do?"
 - 90-100 excellent
 - 80-90 good
 - <80 adequate, reach out
- exams hand back in recitations
- these guidelines are exam specific
 - ↳ first exam typically best
- You learned structure determination!

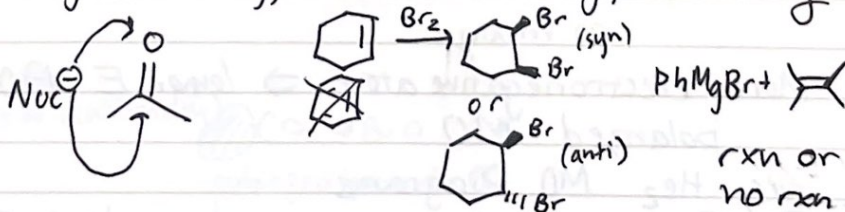
What's Next?

- how do you go from 2D structure to where are e^-
where do they react

Unit 2 Molecular Orbitals & Pericyclic Reactions

- deeper look at e^- movement
- new types of reactions, new class of mechanism
- use molecular orbitals (MO's) to predict reaction outcomes

↳ regioselectivity, diastereoselectivity, reactivity



- MO's provide insight into structure & reactivity

Background/Review & Study

- review gen chem (5.11/5.12) & Orgo I (5.12)
- Clayden: ch. 4, 5, 6

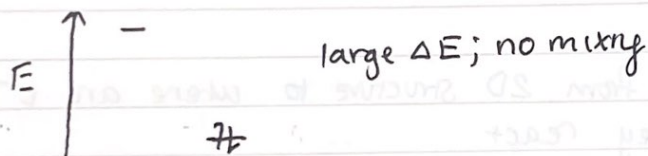
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Lecture 10: (cont)

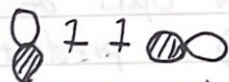
- orbitals are wavefunctions that describe the ability to find an electron in space
- ↳ they interact constructively & destructively

Rules:

- ① # atomic orbitals (AOs) in = # MO's out
- ② interacting orbitals must have similar energy
 - if large ΔE ; no mixing
 - if same E ; best mixing



- ③ interacting orbitals must overlap efficiently and have similar energy symmetry

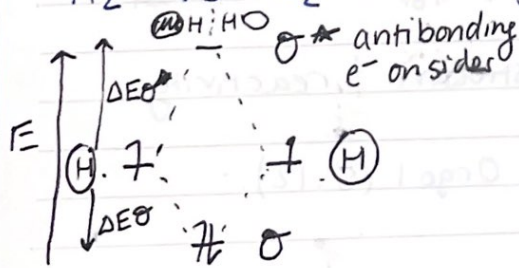


perpendicular orbitals

• poor overlap

• no mixing

- ④ More electronegative atom \Rightarrow lower E AO = more polarized MO

H₂ vs He₂ MO Diagrams

H-O-H

bonding; e⁻ in middleNOTE: $|\Delta E_{\text{bond}}| > |\Delta E_{\text{antibond}}|$

antibonding is more destabilizing than the bonding is stabilizing

H₂ MO more stable than

2 × H• AO

↳ why H₂ bond forms



- antibonding MO filled!
- this is less stable than two individual H atoms
- forming He-He requires filling σ^* (which is more destabilizing) than

• this is the MO explanation for the full octet rule

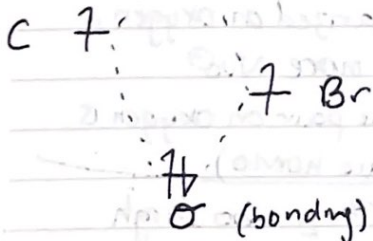
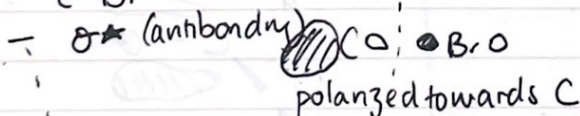
SN₂ MO Picture



Why backside attack?
• identify HOMO & LUMO

HOMO highest occupied MO = nucleophile, filled orbitals, lone pair
LUMO lowest unoccupied MO = electrophile = empty orbitals = π^* or σ^* orbital, cations, C of C-Br bond

MO of C-Br



polarized towards Br

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Lecture 10: (cont)



backside attack because
there is a larger σ^*
lobe there

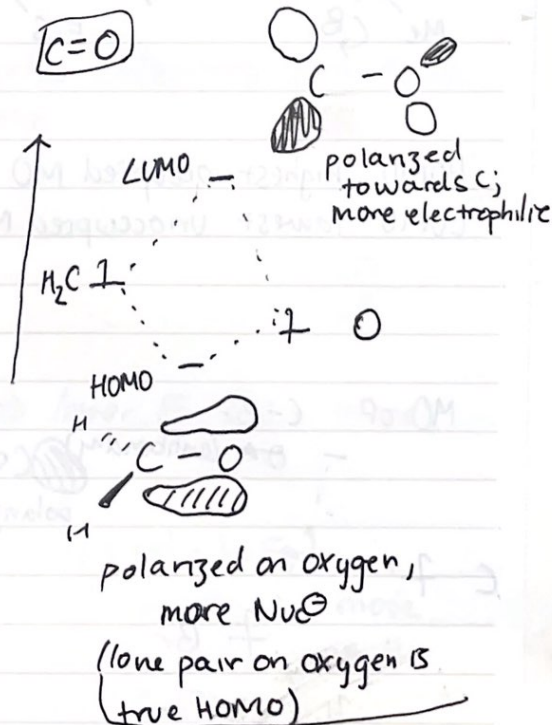
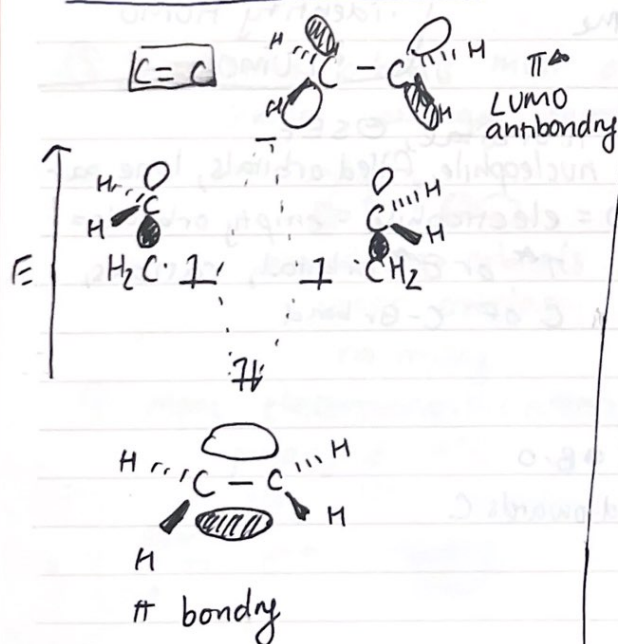
meanwhile



σ bond breaks because σ^* populated

our mechanistic arrows show this

C=C vs C=O MOs



consequences:

C=C less reactive towards Nuc b/c π^* E too high

C=C generally nucleophilic unless somehow polarized
ex: C=C=O

C=O electrophilic on carbon

2.11 Molecular Orbital Theory - 2

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

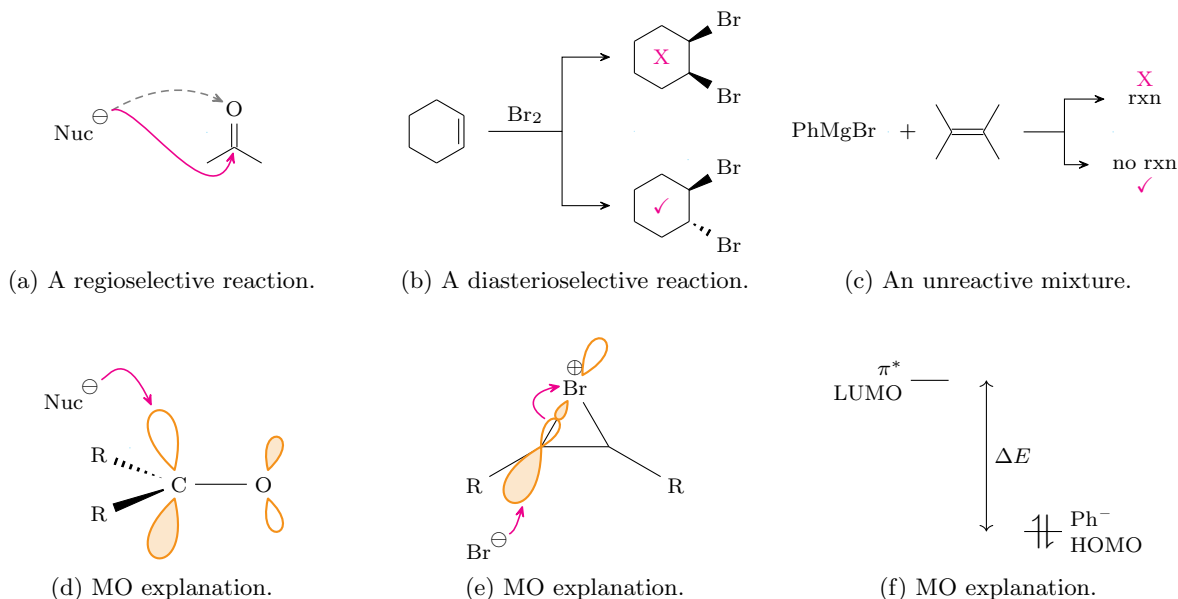


Figure 2.1: MO theory explains these phenomena.

– 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 π^* -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 σ^* -orbital.
 - The bromonium ion's LUMO has its largest lobe behind carbon.
 - Thus, this is the lobe that will be attacked by the 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 π^* -orbital) is much higher in energy than the phenyl anion's HOMO. Thus, the ΔE 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° .*

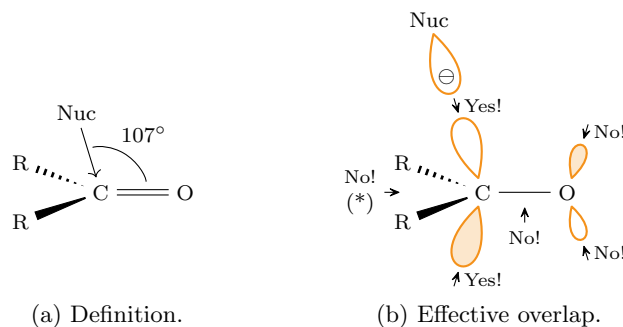


Figure 2.2: Bürgi-Dunitz angle.

- This is the angle between the new C–Nuc bond and the carbonyl's σ -plane (Figure 2.2a).
- Nucleophiles attack at this angle because it's the location of the π^* -lobe on carbon (Figure 2.1d).
- Let's elaborate a bit on Figure 2.1d now (Figure 2.2b).
 - Once again, consider the carbonyl π^* -orbital (its LUMO) and its “butterfly” lobes.
 - The nucleophile must approach the π^* -orbital with the right symmetry. This is why we see its HOMO's lobe approach the carbon atom's π^* -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 π^* -lobe on the other side of the σ -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 σ^* -orbital, but bad for interacting with the π^* -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.

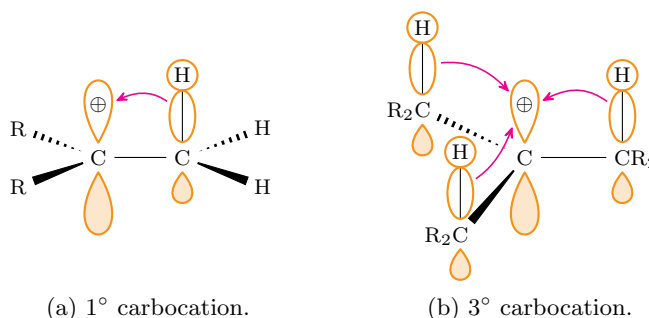
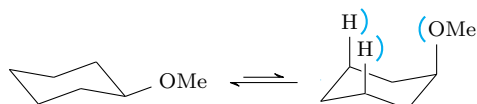


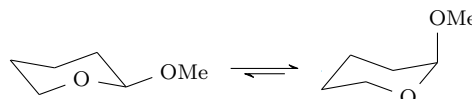
Figure 2.3: Hyperconjugation stabilizes carbocations.

- Consider a primary (1°) 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 σ -orbital, namely, the adjacent C–H bond. Moreover, this bond has the right *geometry* to donate into the empty p -orbital.
 - Thus, the σ -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 $\sigma_{\text{CH}} \rightarrow p_{\text{C}}$.^[1]
- In a tertiary (3°) carbocation, we get electron donation from *three* adjacent σ_{CH} orbitals.
 - These *three* stabilizing interactions explain why 3° carbocations are more stable than 1° 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*

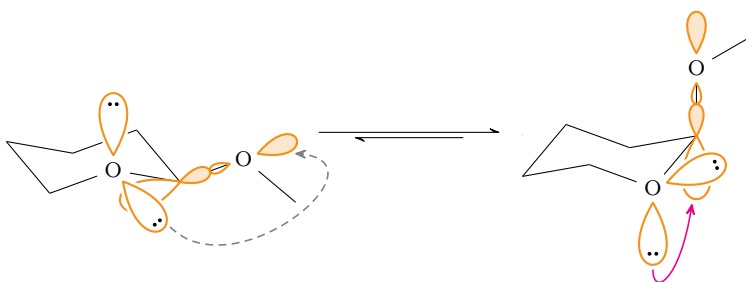
$$\text{orbital}_{\text{atoms}} \rightarrow \text{orbital}_{\text{atoms}}$$
 - The arrow means “donates into.”
 - Indeed, we always write the filled orbital first (before the arrow) and the empty orbital second (after the arrow).
 - Possible orbitals: $\sigma, \sigma^*, \pi, \pi^*, p, n$.
 - Note that 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.



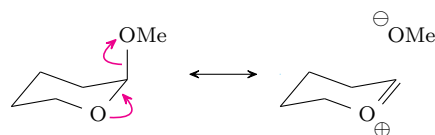
(a) Sterics win in methoxycyclohexane.



(b) Anomeric wins in 2-methoxytetrahydropyran.



(c) MOs explain the anomeric effect.



(d) Resonance explains the anomeric effect.

Figure 2.4: Anomeric effect.

¹This 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 σ^* -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.^[2]
- 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 π -bond and formally break the C–OMe σ -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 σ -bonds.
 - However, we are now telling you that sometimes, you *are* allowed to break σ -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.

²Note that there is no particular reason why overlap with a σ^* -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 σ^* 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.

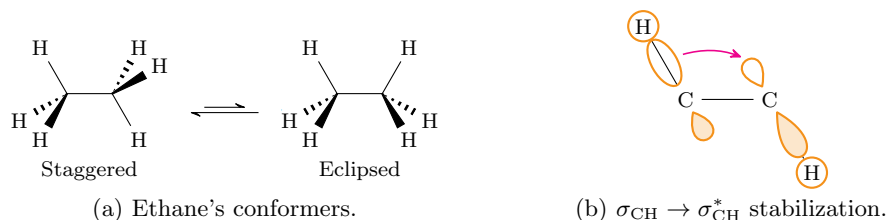


Figure 2.5: Hyperconjugation stabilizes staggered ethane.

- 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 σ -bond of one C–H bond into the adjacent, antiperiplanar C–H bond's σ^* orbital: $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CH}}^*$.
 - This is a small interaction, but it occurs six times, once for each C–H σ -bond!
- Takeaway: Electron delocalization is stabilizing, and more delocalization is more stabilizing.
- Example: Stereoelectronic stabilization can accelerate reactions.

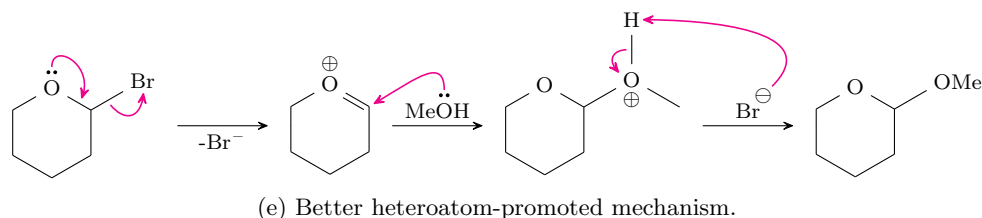
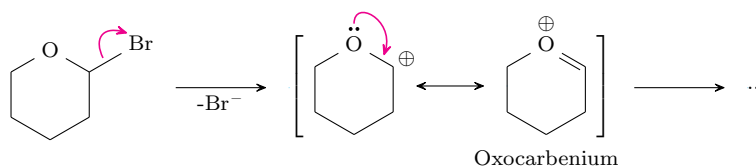
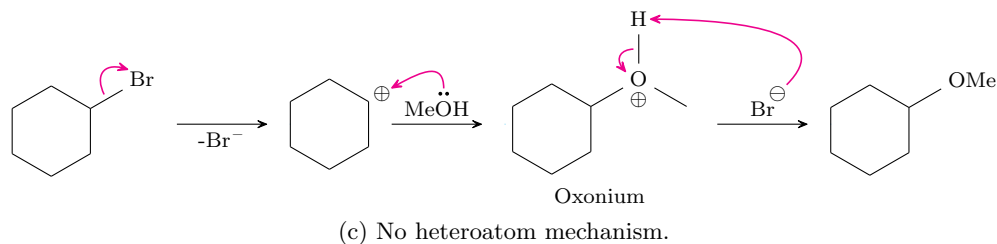
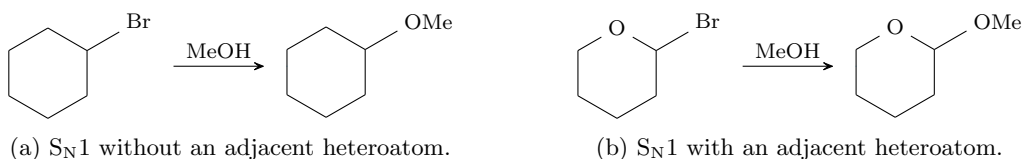


Figure 2.6: Stereoelectronic effects accelerate reactions.

- 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.^[3]
 - 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 σ^* -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 π^* -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.

³Note 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 $C_6H_{11}Br + CH_3OH \longrightarrow C_6H_{11}OCH_3 + HBr$.