

# Week 5

## Misc. Reactive Intermediates

### 5.1 Radicals

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

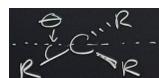
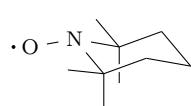


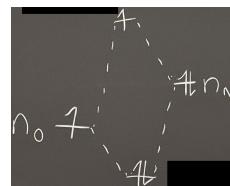
Figure 5.1: Angle of deviation from planarity.

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

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



(a) Structure.



(b) N-O · molecular orbitals.

Figure 5.2: TEMPO.

- Formed by oxidizing 2,2,6,6-tetramethylpiperidine (TMP), a sterically hindered organic base, with  $\text{H}_2\text{O}_2$  in the presence of the tungstate anion ( $\text{WO}_4^{2-}$ ).
- Check: TEMPO *does* have both resonance stabilization (with the adjacent nitrogen heteroatom) and steric blocking (from the adjacent quaternary carbons).
- The MO diagram (Figure 5.2b) reveals that the  $\text{N}-\text{O}\cdot$  bond is an example of a 2c-3e bond.
- The **spin density map** shows that the radical is evenly dispersed on O and N: 50% radical density on O and 50% on N.
- Takeaway: If you want to design your own persistent radical, take something with some resonance, add some steric blockers, and you're good to go!

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



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

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

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

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

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

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

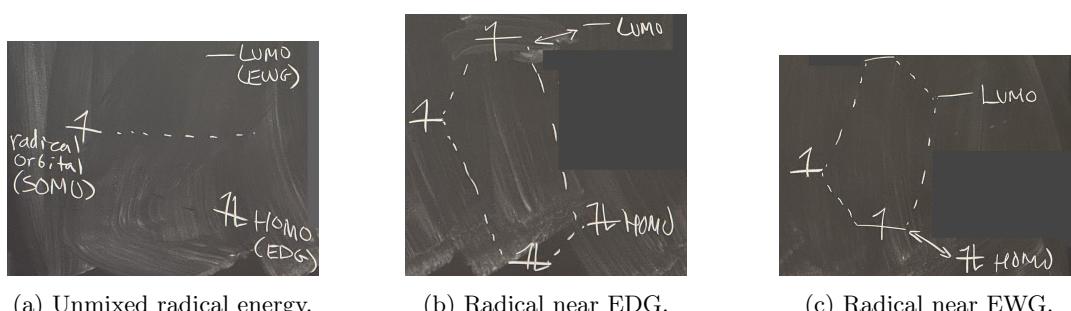


Figure 5.3: Radicals near EDGs and EWGs.

- Both EDGs *and* EWGs can stabilize radicals, despite the fact that radicals are electron deficient.
- Example: A radical  $\alpha$  to a carbonyl (e.g., homolytically cleave one of acetone's C–H bonds).
  - The carbonyl *will* destabilize the radical inductively.
  - However, it *will* also *stabilize* the radical through resonance.
  - The second effect (resonance) is stronger.
- Let's now justify these stabilizing effects using MO theory.
  - Before mixing (Figure 5.3a), a typical radical has energy intermediate between the HOMO of an EDG and the LUMO of an EWG.
  - When a radical's SOMO interacts with the HOMO of an EDG (Figure 5.3b), *two* electrons get stabilized and *one* gets destabilized. It follows that there is a net stabilization of the molecule, as expected.
  - When a radical's SOMO interacts with the LUMO of an EWG (Figure 5.3c), the sole electron present in the system gets stabilized. It follows that there is *still* a net stabilization of the molecule, even here!
- These molecular orbital diagrams reveal two additional attributes of polarized radicals, as well.
  1. EDGs make radicals more nucleophilic.
    - When a radical's SOMO interacts with the HOMO of an EDG (Figure 5.3b), a new radical SOMO (the antibonding orbital) is created.
    - This new SOMO is a better energy match with LUMOs, so the radical electron is more likely to mix with a LUMO since this will lead to greater thermodynamic stabilization of the product than before.
    - In other words, the radical is now more nucleophilic.
  2. EWGs make radicals more electrophilic.
    - When a radical's SOMO interacts with the LUMO of an EWG (Figure 5.3c), a new radical SOMO is once again created, but it is the stabilized bonding orbital this time.
    - This new SOMO is a better energy match with HOMOs, so the radical electron is more likely to mix with a HOMO since this will lead to greater thermodynamic stabilization of the product than before.
    - In other words, the radical is now more electrophilic.
- Synthesis of radicals.
  - Also known as **initiation**, if we're doing a radical chain reaction.
  - Most common way to make a radical: Homolytic cleavage of a weak bond.
    - We'll often use light or heat to give a little burst of energy and break this bond.
  - Commonly used radical initiators.
    - Peroxides are easily broken by light and heat, so we often use them.
      - Example: Organic peroxides react like  $\text{RO}-\text{OR} \xrightarrow[\Delta]{h\nu} \text{RO}\cdot$
    - AIBN.
    - $\text{Br}_2$ .
      - Bromine reacts like  $\text{Br}-\text{Br} \xrightarrow[\Delta]{h\nu} \text{Br}\cdot$
    - Paramagnetic metals, i.e., metals with 1 unpaired electron.
      - Example:  $\mathbf{Cp_2Ti^{III}Cl}$ .
    - Single-electron transfer (SET) or energy transfer (ET).
      - Often done with metals, electrochemistry, or photochemistry.
      - These are increasingly common ways to cycle one-electron oxidation states.
  - Essentially, if we ever need to make a radical, we can choose old-school or new-school based on what we have on hand!

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



Figure 5.4: AIBN as a thermal radical initiator.

- This radical has a very cool design: Under heat or shock, you cleave the N–C bonds to form tertiary radicals that are additionally stabilized by their proximity to a  $\pi$ -system, and release  $N_2$ .
  - You commonly see AIBN used with  $HSnBu_3$  in radical cyclizations.

- **Titanocene monochloride:** An increasingly popular SET agent. Denoted by  $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ .

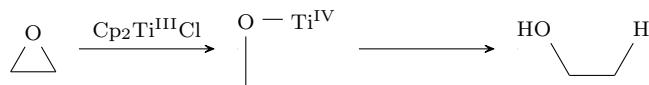
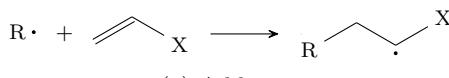


Figure 5.5:  $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$  as an SET radical initiator.

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

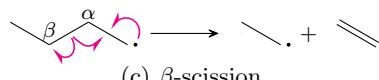
- Radical reactions.



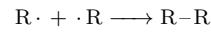
(a) Addition.



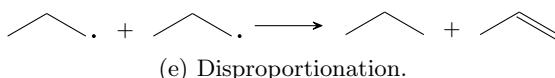
(b) Abstraction.



(c)  $\beta$ -scission.



(d) Coupling.



(e) Disproportionation.

Figure 5.6: Radical reactions.

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

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

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

- **Radical decarboxylation.**

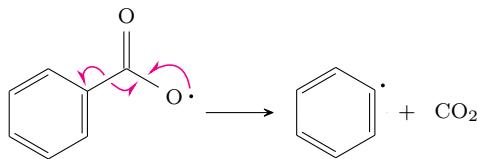


Figure 5.7: Radical decarboxylation.

- Radical decarboxylation can help us generate unstable radicals.
- For example,  $\text{Ph}\cdot$  isn't too stable normally, but we will form it under radical decarboxylation conditions regardless because  $\text{CO}_2$  is a really good leaving group. Basically,  $\text{CO}_2$  helps the thermodynamics work out.
- **Barton deoxygenation.** A method of deleting hydroxyl groups. *Also known as Barton-McCombie deoxygenation.*

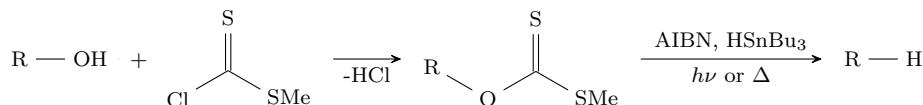


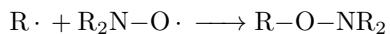
Figure 5.8: Barton-McCombie deoxygenation.

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

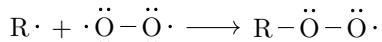
<sup>2</sup>See 5.47 notes for a mechanism.

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

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



– Example: Per MO theory,  $\text{O}_2$  is a ground-state triplet diradical, so it can interact with  $\text{R}\cdot$  and form the peroxide as follows.



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

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

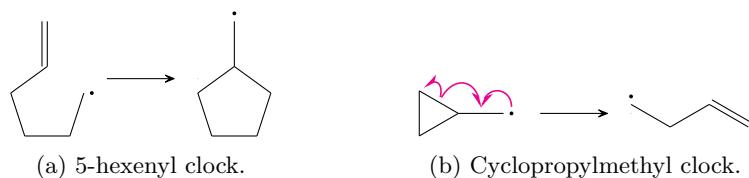


Figure 5.9: Radical clock reactions.

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

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

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

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

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

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

– These are very common kinetic probes for mechanisms!

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

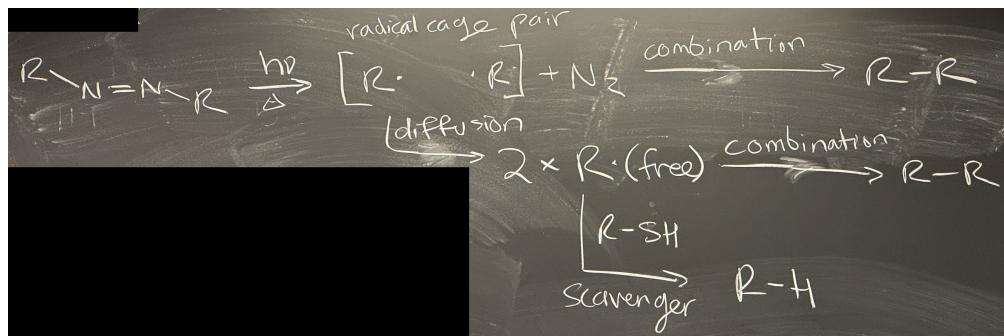


Figure 5.10: Radical cage effect.

<sup>3</sup>This is a type of radical cyclization allowed by Baldwin's rules.

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

- Radical anions and cations.

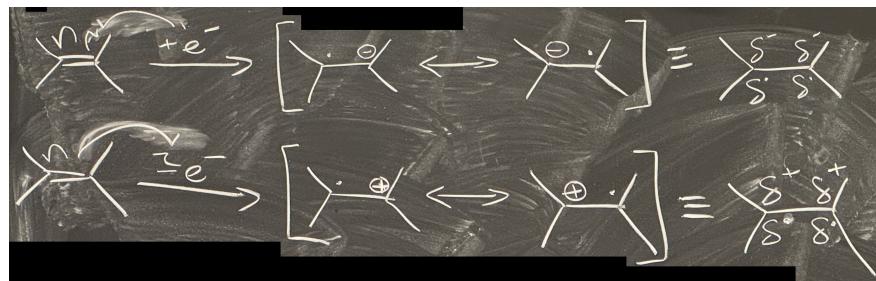


Figure 5.11: Radical ion formation and structure.

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

- Radical ions are common in aromatic rings.

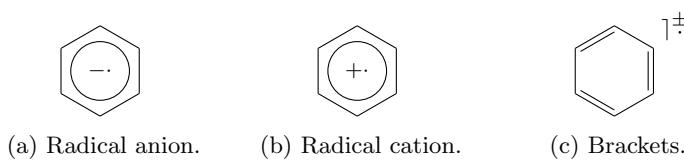
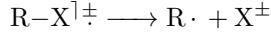


Figure 5.12: Aromatic radical ion notation.

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

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



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

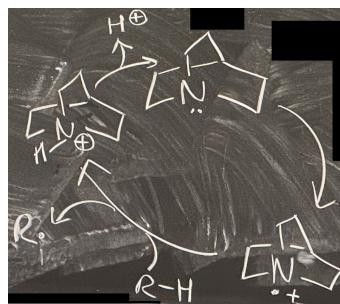


Figure 5.13: Catalysis with radical ions.

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

## 5.2 Carbenes

10/3:

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

- Lecture outline.
  - Orbital structure of carbenes (i.e., the origins of singlet vs. triplet states).
  - Substituent effects on carbene stability and state.
  - Synthesis of carbenes.
  - Carbene reactivity.
  - How carbene orbitals determine the transition-state angle of approach.
- Recall the Walsh diagram for  $\text{CH}_2$ .

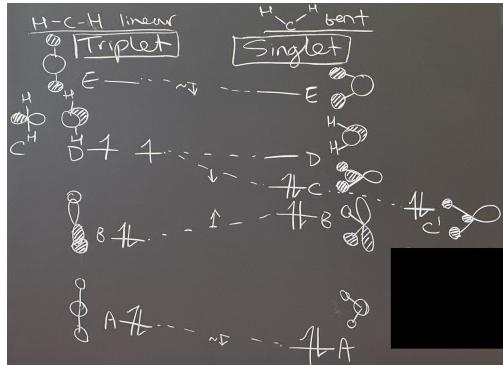


Figure 5.14: Walsh diagram for  $\text{CH}_2$ .

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

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

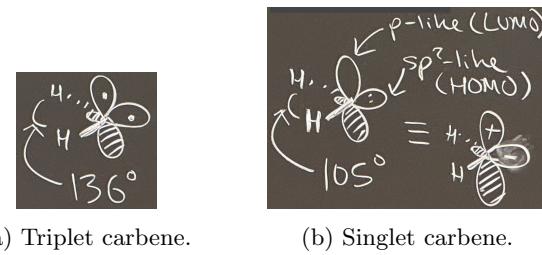
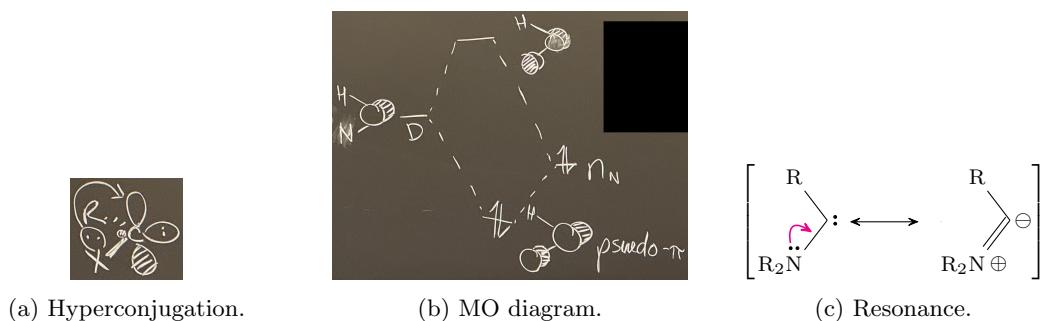


Figure 5.15: Singlet vs. triplet carbene orbitals.

- As we would expect from Figure 5.14, triplet carbenes are more linear and singlet carbenes are more bent.
  - However, the difference isn't as big as we might expect: The actual angles are 136° and 105°.
- We say that triplet carbenes have “diradical character” since we put an unpaired electron in both **C'** and **D**.
- We say that singlet carbenes have “cation + anion character” since we put two paired electrons in the *sp*<sup>2</sup>-like **C'** orbital and none in the *p*-like **D** orbital.
  - Note that this makes **C'** our HOMO and **D** our LUMO.
- Implication: Triplet carbenes react as diradicals, and singlet carbenes react as cations and anions.
- Let's now discuss some ways we can push carbenes to favor the singlet state, or the triplet state.
  - Specifically, we'll discuss the effects of placing  $\pi$ -donors,  $\pi$ -acceptors,  $\sigma$ -EWGs, and multiple bonds (e.g., for conjugation) near the carbene.
  - **Singlet-triplet gap:** The difference in energy between the singlet and triplet states of a carbene.
  - Simple dialkyl carbenes favor the triplet state.
    - Example:  $\text{H}_2\text{C}$ : favors the triplet state by 8.5 kcal/mol.
  - $\pi$ -donor substituents stabilize carbenes and favor the singlet state.

Figure 5.16:  $\pi$ -donor substituents stabilize carbenes and favor the singlet state.

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

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

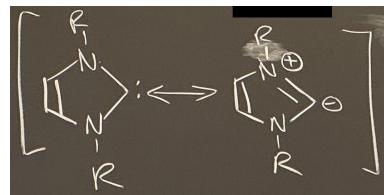


Figure 5.17: *N*-heterocyclic carbene.

- $\sigma$ -EWGs stabilize carbenes and favor the singlet state.
  - A  $\sigma$ -EWG is basically just an electronegative substituent.
  - $\sigma$ -EWGs stabilize carbenes because they stabilize anions.
    - Recall that  $\sigma$ -EWGs also *destabilize* radicals!
  - Example: F<sub>2</sub>C: favors the singlet state by  $\sim 50$  kcal/mol.
- $\pi$ -acceptor substituents stabilize carbenes and favor the triplet state.
  - Examples: Carbonyls, sulfones (SO<sub>2</sub>R), NO<sub>2</sub> groups, boron, etc.
  - These groups mix with **D** just like in Figure 5.16b, except that the new, lower-energy orbital is now empty!
    - This new, lower-energy orbital is our LUMO.
    - Since it has been stabilized, it is now close in energy to the **C'**-orbital.
    - This allows you to release the spin pairing energy by forming the triplet state.
  - These substituents also make carbenes more electrophilic.
- Conjugation stabilizes carbenes and favors the triplet state.
  - Example groups that can conjugate with carbenes: Alkenes, alkynes, and arenes.

- Synthesis of carbenes.

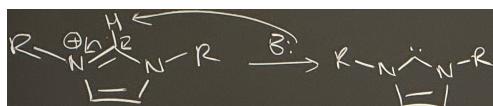
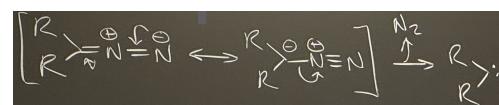


Figure 5.18: Synthesis of carbenes.

- We almost always synthesize carbenes via  $\alpha$ -elimination (Figure 5.18a).
  - If you're forming a carbocation and a carbanion at the same time, you're forming a carbene.
  - We can draw  $\alpha$ -elimination as a concerted or stepwise mechanism.
  - To deprotonate a secondary halide, we need a strong base.
- Aside (practical consideration): Don't run strongly basic reactions in CHCl<sub>3</sub>! Even something like KO<sup>t</sup>Bu can form dichlorocarbenes from chloroform in solution.
- Diazo compounds can also form carbenes pretty easily (Figure 5.18b).
- NHCs can form from an aromatic salt and a strong base (Figure 5.18c).
  - These aren't so much of a recent development anymore; they've definitely left their mark on organic chemistry.
  - These are important catalysts and ligands for transition metal catalysis.
  - If the R-groups are small, then NHCs will dimerize to form a double bond.
- Aside (story): When Masha gave this lecture last year, she talked about how you can put NHCs on quantum dots (to do cool things) in honor of Moungi's Nobel Prize.
- Aside (chemis-tea): On the Nobel Prize.
  - You get a medallion made of solid gold for you to keep and a few (cheaper) replicas to display.
  - You have to pay for the replicas, though. In fact, you have to pay for a lot: They take the expenses for flights, tickets to the gala, etc. out of your Nobel winnings (like 40 grand in total).
  - This was both Moungi's and Schrock's experience, which Masha found out when she had lunch with Schrock last week during his visit.
- Aside (chemis-tea): Get a tungsten wedding ring! Aqua regia will eat a gold or silver wedding band.
- Most synthetically useful reactions involve **carbenoids**, i.e., metal carbenes.
  - We won't talk about carbenoids in here because that's a topic for 5.44 - Organometallics, which we can take next year with Alison if we want.
  - To be clear, we'll only talk about **free** carbenes in this class.
- **Free** (carbene): A carbene that is not bound to a metal.
- We will now begin discussing the reactivity of carbenes.
  - Singlet (cation/anion) and triplet (diradical) carbenes naturally react differently.
  - Carbene reactivity is easier to grasp than the carbene stability stuff from earlier :)

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

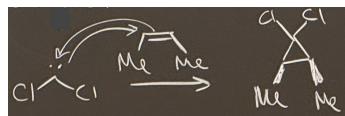
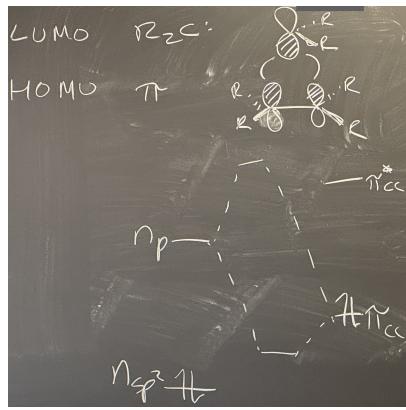
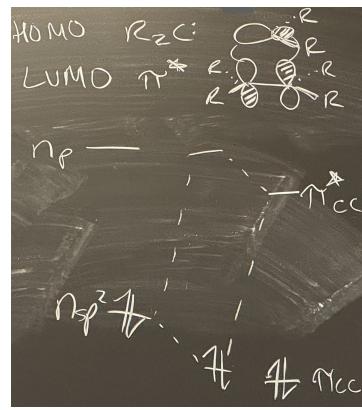


Figure 5.19: Carbene reactions: Chelotropic [2 + 1] cycloaddition.

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



(a) Electrophilic carbenes.



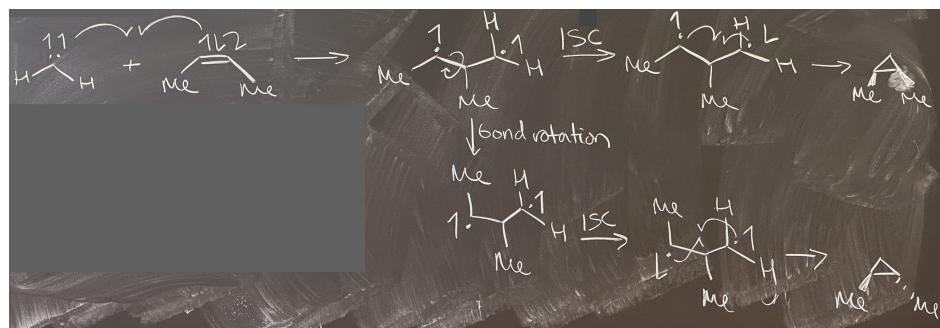
(b) Nucleophilic carbenes.

Figure 5.20: The orbitals behind chelotropic carbene cycloadditions.

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



(a) General form.



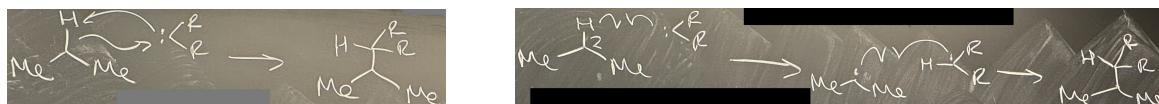
(b) Mechanism.

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

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

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

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



(a) Concerted (singlet carbenes).

(b) Stepwise (triplet carbenes).

Figure 5.22: Carbene reactions: Insertions.

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

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



(a) Expanding benzene.



(b) Expanding pyrrole.

Figure 5.23: Carbene reactions: Ring expansions.

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

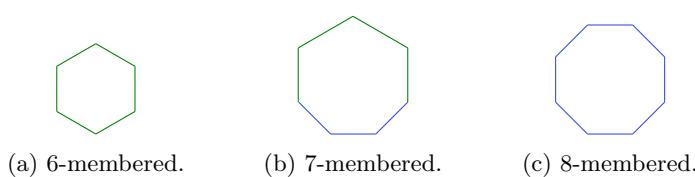


Figure 5.24: Drawing a 7-membered ring.

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

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

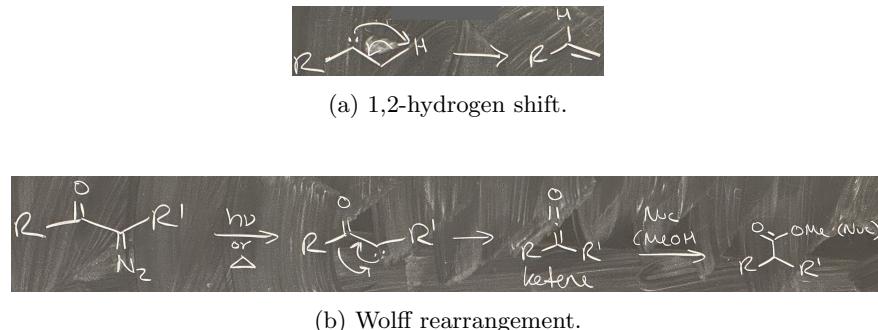


Figure 5.25: Carbene reactions: Rearrangements.

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

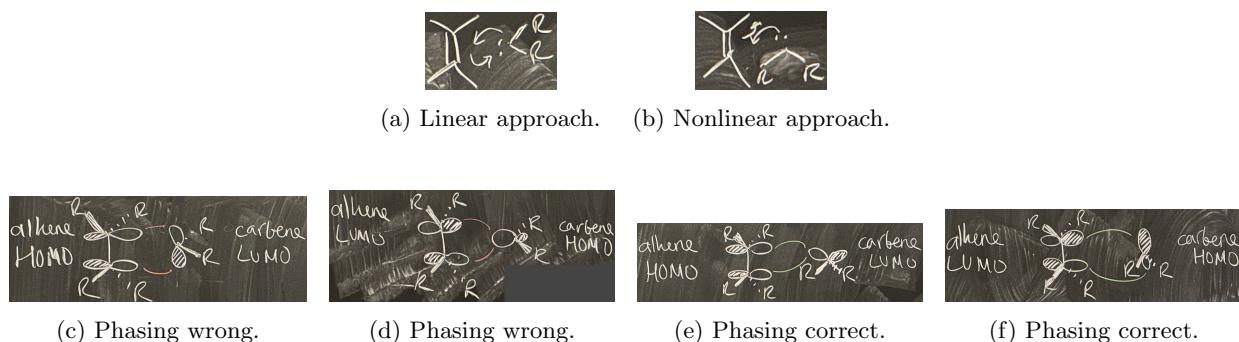


Figure 5.26: Angle of approach in chelotropic [2 + 1] cycloadditions.

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

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