

- Allyl anion: Four electrons, so fill the bottom and middle MOs.
 - Like any carbanion, the allyl anion will react as a nucleophile.
 - If it reacts as a nucleophile, it must react with its HOMO (still the middle orbital!).
- Interesting consequence of this filling: All three allyl species should only react with their middle-energy MO!
 - This would predict that all allyl reactivity occurs at the termini of the allyl group, not the middle carbon, since all of the density of the middle orbital is at the termini and none of it is at the middle carbon.
 - This prediction is experimentally confirmed!
- **Singly occupied molecular orbital:** The molecular orbital in which an unpaired radical electron exists. *Also known as SOMO.*
- An elaboration on why nodes must be placed symmetrically in the MOs of conjugated π -systems (see Figures 2.14 and 2.16 and the associated discussion).
 - Reminder: Everything from here, on, in these notes is beyond the scope of this class!
 - The long-short.
 - The waveforms in Figure 2.14 are *exactly* equal to their corresponding particle-in-a-box wave functions (according to some analyses of quantum mechanics).
 - This relationship can be rationalized intuitively because a conjugated π -system is like an extended, one-dimensional box in which a quantum particle (namely, an electron) lives.
 - The implication is that the molecular orbitals of a conjugated π -system look *exactly* like the particle-in-a-box orbitals, including having nodes in the same places.
 - This actually also means that the individual p -orbitals making up the MOs are different sizes!
 - For example, in the lowest energy MO in Figure 2.14, the two middle p -orbitals will be larger than the two terminal p -orbitals.
 - More relevantly, the HOMO and LUMO in Figure 2.14 will have larger terminal p -orbitals, which explains why dienes react at their ends and not in the middle; we have already seen an example of dienes reacting at their terminal carbons instead of their middle carbons in Figure 2.8.
 - More detail.
 - The exact sizes of each p -orbital in a given MO of a conjugated π -system can be calculated — by hand — using only linear algebra. This calculation is part of something called **Hückel theory**.
 - You can learn about Hückel theory by taking a course in quantum mechanics, inorganic chemistry, or graduate physical organic chemistry.
 - If you are interested in reading more about this now, look through the attached PDF. I'd recommend starting with the diagrams and sine/cosine functions on pages 6.6 and 6.7. Enjoy!

2.13 Diels-Alder - 1

10/4:

- Lecture 12 recap.
 - Pericyclic reactions have concerted and cyclic transition states.
 - Essentially, what unites all of these reactions is that they have electron arrows moving in a ring!
 - All of these reactions are theoretically reversible.
 - Prof. Elkin redraws the prototypical pericyclic reactions from last class.

- Three main classes.
 1. Cycloaddition.
 - Bond types changed: $2\pi \rightleftharpoons 2\sigma$.
 - Nomenclature: $[m + n]$.
 - General form: See Figure 2.8.
 - To reiterate: This reaction can also proceed in reverse, i.e., from right to left!
 2. Electrocyclization.
 - Bond types changed: $1\pi \rightleftharpoons 1\sigma$.
 - Nomenclature: $m\pi$.
 - General form: See Figure 2.10.
 - To reiterate: This reaction can also proceed in reverse, i.e., from right to left!
 3. Sigmatropic rearrangements.
 - Bonds moved: 1σ .
 - Nomenclature: $[m, n]$.
 - General form: See Figure 2.11.
 - To reiterate: This reaction can also proceed in reverse, i.e., from right to left!
- Announcements.
 - Please fill out the feedback survey in Canvas > Announcements.
 - PSet 3 is due today.
 - PSet 4 will be posted today.
 - It is the last PSet before Exam 2.
 - It only covers Diels-Alder content. However, the rest of this unit's content (cycloadditions, electrocyclizations, and sigmatropic rearrangements) *will* be on Exam 2 as well.
 - So to prepare for the exam, continue doing the Recitation Worksheets even after PSet 4!!
- Today: Diels-Alder (lecture 1 of 2).
- Recall from last lecture that a *Diels-Alder reaction* is a $[4 + 2]$ cycloaddition.
 - Specifically, a **diene** reacts with an olefin, which we call the **dienophile**.
 - The simplest Diels-Alder (DA) reaction is drawn in Figure 2.8.
 - This is actually a terrible Diels-Alder reaction because there's a poor HOMO-LUMO energy match (we'll talk more about what that means shortly).
 - The Diels-Alder is a powerful tool to make six-membered rings.
 - We see a lot of six-membered rings in organic chemistry, so the Diels-Alder is very useful.
 - This reaction is very predictable: It is **regioselective**, **stereospecific**, and **reliable**.^[4]
- **Diene**: A compound that contains two conjugated double bonds.
 - The diene is (usually) the HOMO.
 - You can think of it as the nucleophile.
- **Dienophile**: An olefin. *Etymology* from Latin “lover of dienes.”
 - The dienophile is (usually) the LUMO.
 - You can think of it as the electrophile.
- **Reliable** (reaction): A reaction that almost always works if you have the right energy matching.

⁴We'll discuss both regioselectivity and stereospecificity later this lecture, and stereospecificity even further on Monday.

- Let's look at the MO picture for a Diels-Alder reaction.

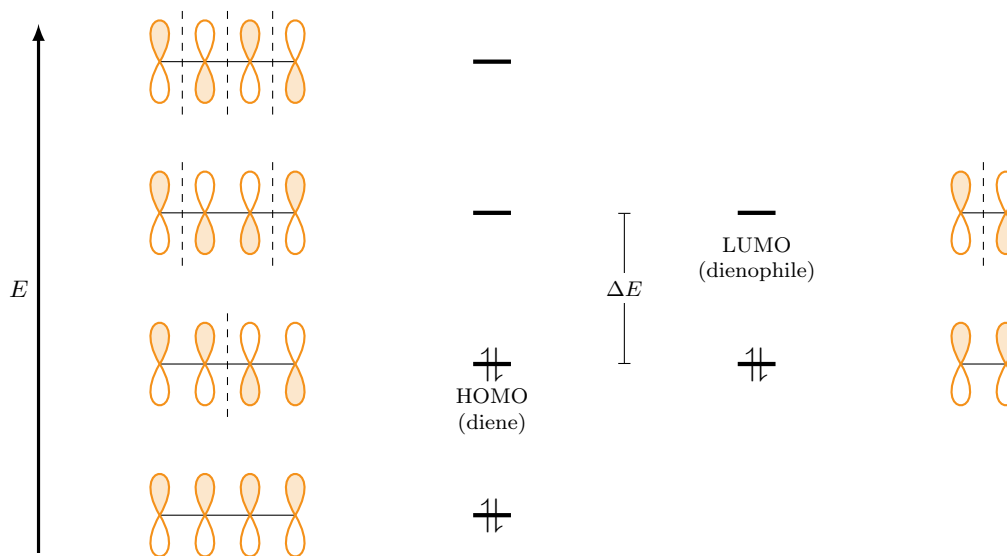


Figure 2.17: Reactive molecular orbitals in a Diels-Alder.

- Recall our diene MOs from last lecture (Figure 2.14).^[5]
 - Specifically, recall that our HOMO has the orbital picture of the second energy level. Since we have said that the diene reacts with its HOMO, this is the important orbital to watch.
 - Recall also our dienophile MOs from last lecture (Figure 2.13).
 - The olefin has two electrons, so its LUMO is the second energy level. Since we have said that the dienophile reacts with its LUMO, this is the important orbital to watch.
 - Initially, we have a poor energy match between HOMO and LUMO (ΔE is large). Therefore, if we want to improve the reaction, we should strive to bring their energies closer together.
 - Two main things to accomplish this goal of bringing HOMO and LUMO energies closer together.
 - Raise the HOMO by adding EDGs to the diene.
 - Lower the LUMO by adding EWGs to the dienophile.
- Example: A Diels-Alder reaction that does work well.

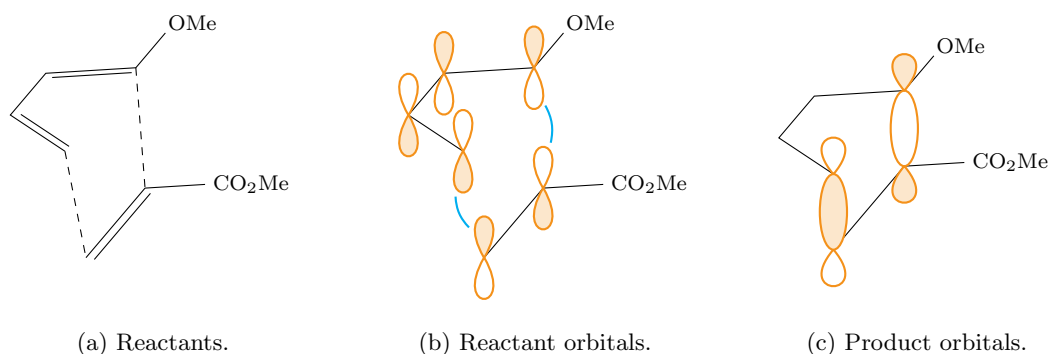


Figure 2.18: Diels-Alder orbitals in 3D space.

⁵Prof. Elkin reviews the three rules for drawing the MOs of conjugated systems; remember these!!

- Let's analyze the new reactants we've drawn (Figure 2.18a).
 - The methoxy-substituted diene is a better nucleophile than 1,3-butadiene because methoxy groups are electron-donating.
 - The ester-substituted dienophile is a better electrophile than ethylene because ester groups are electron-withdrawing.
 - Recall electrophilic aromatic substitution reactions, which tell you what substituents are electron donating vs. withdrawing. Review this 5.12 content!!
- Now let's look at their orbitals (Figure 2.18b).
 - We draw a “perspective picture” of the HOMO and LUMO.
 - Observe that the phases of the HOMO and LUMO match!
 - Specifically, we mean that the lobes connected by the blue lines have the same shading.
 - A note on shading.
 - The *relative* shading between reacting molecules *does* matter because we've got to see overlap between pairs of shaded lobes and pairs of unshaded lobes when we're forming bonds.
 - Thus, while we could invert the shading of every *p*-orbital in Figure 2.18b and be fine, we *could not* invert the shading of just the diene and leave the dienophile unchanged (or vice versa).
- We now redraw the molecules, but after they've formed σ -bonds (Figure 2.18c).
 - As the π -orbitals come together, the middle lobes fuse and become σ -bonds.
 - Implication: You have to have a top-to-bottom approach so that the *p*-orbitals interact and mix. A side-to-side overlap would not form σ -bonds from *p*-orbitals.
- Accelerating Diels-Alder reactions.

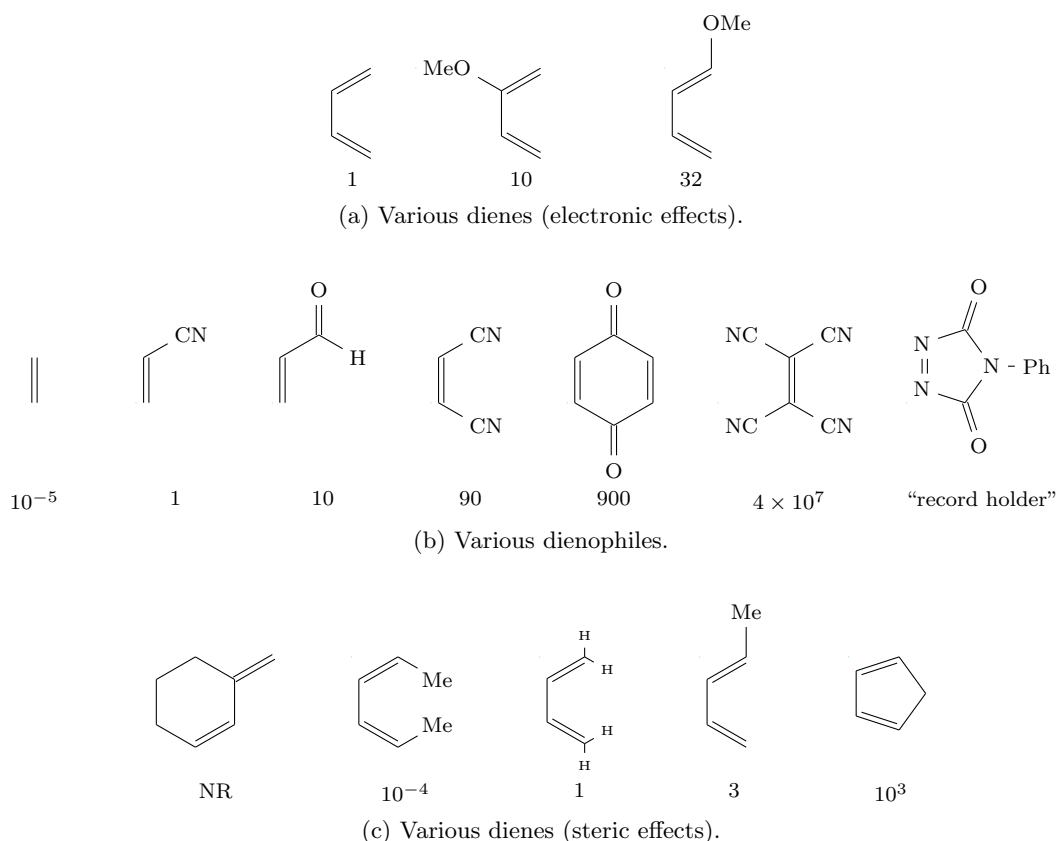


Figure 2.19: The relative rate of reaction of different Diels-Alder substrates.

1. Raise the HOMO by putting EDGs on the diene (Figure 2.19a).
 - Adding a methoxy substituent (an EDG) will increase the rate regardless of the position to which you add it.
 - However, interestingly enough, it will increase the rate *more* when added to some positions over other positions.
 - This is because of the difference between **cross-conjugation** and regular conjugation.
 2. Lower the LUMO by putting EWGs on the dienophile (Figure 2.19b).
 - From left to right, the names of these seven compounds are: ethylene, acrylonitrile, propenal, *cis*-1,2-dicyanoethene, *para*-quinone, tetracyanoethene, and 4-phenyl-1,2,4-triazole-3,5-dione (PTAD^[6]).
 3. Enforce the ***s-cis*** configuration (Figure 2.19c).
 - The leftmost compound is locked in the ***s-trans*** conformation.
 - The next one has a big steric clash between methyl groups, so it's much more stable in the *s-trans* configuration.
 - Buta-1,3-diene likes to be *s-trans* because it still has sterics from the hydrogens.
 - Penta-1,3-diene has the same mild steric preference for *s-trans* as buta-1,3-diene.
 - However, certain stereoelectronic effects (which you'll work out on PSet 4!) promote its reactivity.
 - Essentially, methyl groups are slightly electron-donating.
 - Cyclopentadiene is locked in an *s-cis* conformation.
- **Cross-conjugated** (molecule): A molecule containing multiple olefins that — despite being arranged in a row — do not delocalize efficiently.

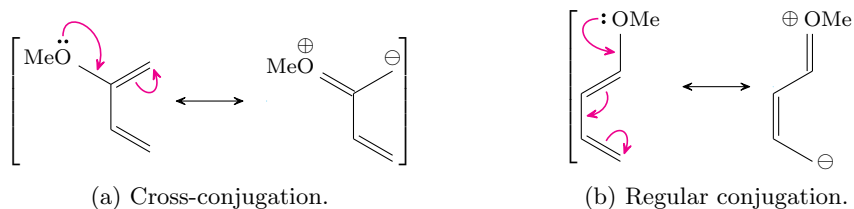


Figure 2.20: Cross-conjugation vs. regular conjugation.

- Notice that for the molecule in Figure 2.20a, we cannot draw a resonance structure that engages the bottom π -bond.
 - In contrast, regular conjugation (Figure 2.20b) disperses the oxygen's electron density across the entire π -system.
- ***s-cis*** (conformer): The rotational isomer of a diene in which the alkenes are *cis* relative to the σ -bond.

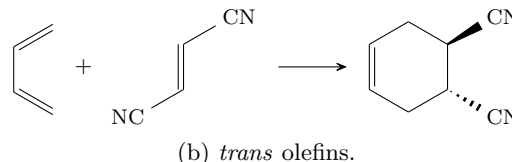
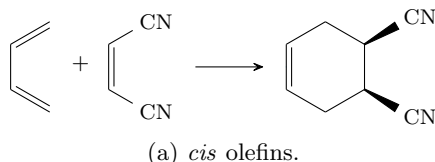
Figure 2.21: *s-cis* diene.

⁶According to Sauer and Schröder (1967), PTAD is approximately 10^5 times faster than tetracyanoethene. This means that it is approximately 4×10^{12} times faster than acrylonitrile!

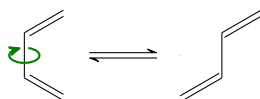
- **s-trans** (conformer): The rotational isomer of a diene in which the alkenes are *trans* relative to the σ -bond.

Figure 2.22: s-*trans* diene.

- Essentially, olefins can be *cis* or *trans*.

Figure 2.23: Reacting *cis* and *trans* olefins in the Diels-Alder.

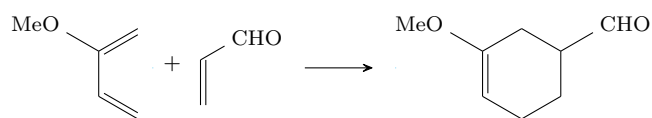
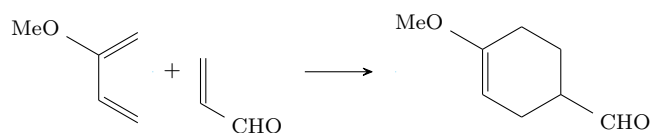
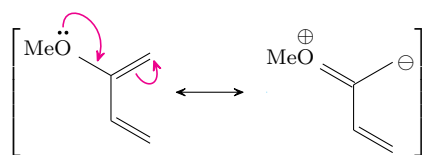
- When you react the *cis*-olefin in a Diels-Alder, you get (exclusively) the *cis*-product.
- When you react the *trans*-olefin in a Diels-Alder, you get (exclusively) the *trans*-product.
- This means that the Diels-Alder is **stereospecific**.^[7]
- On the other hand, dienes can be s-*cis* or s-*trans*.

Figure 2.24: s-*cis* and s-*trans* conformers rapidly interconvert.

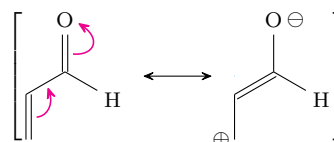
- The “s” stands for “sigma bond.”
- These two diene conformers are not discrete species; rather, they interconvert like the gauche, anti, staggered, etc. conformers of ethane.
- Only s-*cis* dienes react in Diels-Alders, so enforcing that geometry accelerates the reaction.
- **Stereospecific** (reaction): A reaction in which the stereochemistry of the reactants translates directly into a single stereochemical product.
- **Stereoselective** (reaction): A reaction in which when a certain stereochemical product is favored, but a mixture is still produced and the stereochemistry of the reactants doesn’t exert excessive influence.
- **Stereoretentive** (reaction): A reaction in which the exact stereocenters present in the starting material are conserved in the product.
- Does the rightmost diene in Figure 2.19a have to be *trans* at the upper alkene?
 - Yes; we’ll talk about that more next lecture.
- Can you lower the LUMO so much that the Diels-Alder reaction no longer proceeds?
 - Yes! This is related to **inverse electron-demand** Diels-Alder reactions, discussed next Monday.
- Can you have a photochemical Diels-Alder?
 - They’re quite rare, but you can do similar things.
 - Note: Lewis acid acceleration of Diels-Alders will also be discussed next Monday.

⁷Next lecture, you will learn how the Diels-Alder is **stereoselective** but still not **stereoretentive**.

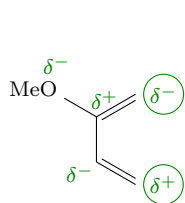
- Regioselectivity.

(a) *meta*-product.(b) *para*-product.

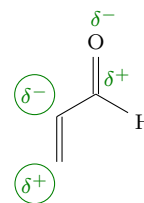
(c) Diene (resonance).



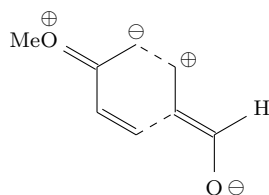
(d) Dienophile (resonance).



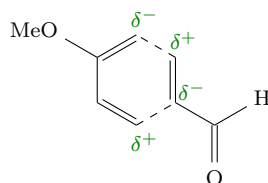
(e) Diene (hyperconjugation).



(f) Dienophile (hyperconjugation).



(g) Resonance matching.



(h) Hyperconjugation matching.

Figure 2.25: Diels-Alder regioselectivity.

– Observation: Depending on how the diene and dienophile are oriented when they react, we could conceivably form two different products (Figures 2.25a-2.25b).

■ These two products are called the *meta*-product and the *para*-product.

- So which product do we actually get?
 - We will determine this by using either *resonance* or *hyperconjugation/partial negative charges* to identify and match the electron-rich and electron-poor sites on our diene and dienophile.^[8]
 - You may use whichever method you prefer since they give the same result, but you should learn both!!
 - The resonance analysis (Figures 2.25c-2.25d).
 - As in Figure 2.20, push arrows as far as we can to get the reactive resonance structure.
 - The hyperconjugation analysis (Figures 2.25e-2.25f).
 - Begin with an atom that we *know* will have a partial positive (δ^+) or partial negative (δ^-) charge.
 - For example, we know that oxygen will be δ^- because it is the most electronegative atom in both structures.
 - Thus, we can label it first in both Figures 2.25e and 2.25f.
 - Then expand out over the rest of the conjugated system, alternating δ^+ or δ^- atom-to-atom.
 - So since oxygen is δ^- , the carbon α to it should be δ^+ , the carbon(s) β to it should be δ^- , the carbon(s) γ to it should be δ^+ , etc.
 - Keep track of the partial charges on the termini of the diene and dienophile (i.e., the reactive sites). These are circled in Figures 2.25e-2.25f.
 - Notice the agreement/consistency between the two methods!
 - Indeed, the carbanion in Figure 2.25c corresponds to a δ^- carbon in Figure 2.25e, and the carbocation in Figure 2.25d corresponds to a δ^+ carbon in Figure 2.25f.
 - Once we have performed either analysis, matching up the negatives on the diene to the positives on the dienophile and vice versa predicts our product!
 - Thus, by both analyses, the *para*-product is favored!
 - This matching of positive and negative charges is indicative of the maxim that “organic chemistry is just magnets everywhere.”
 - Exercise: Try drawing the meta-product, which will force you to put positive near positive and negative near negative.
 - “That’s not fun, that’s not how magnets work.”
- **meta-product:** The product of a Diels-Alder reaction in which the substituents would be oriented *meta* to each other on the six-membered ring, if the six-membered ring were aromatic.
 - **para-product:** The product of a Diels-Alder reaction in which the substituents would be oriented *para* to each other on the six-membered ring, if the six-membered ring were aromatic.
 - Prof. Elkin has many more examples, but will go through them on Monday.

⁸Note that there is also a secret third method: MO theory! See Clayden et al. (2012, p. 890) for how to do this. As we would expect, the predictions we get by both resonance and hyperconjugation match the predictions of MO theory. (Note also that you are not required to learn the MO theory method because it was not covered in class; this comment is purely to point out an interesting connection :)

References

- Clayden, J., Greeves, N., & Warren, S. (2012). *Organic chemistry* (Second). Oxford University Press.
- Sauer, J., & Schröder, B. (1967). Eine studie der diels-alder-reaktions, viii: 4-phenyl-1.2.4-triazolin-dion-(3.5) als dienophil. *Chemische Berichte*, 100, 678–684. <https://doi.org/10.1002/cber.19671000238>