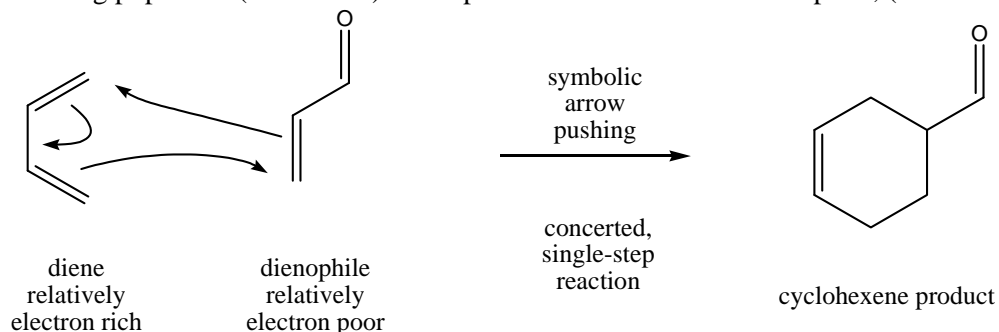


The Diels-Alder reaction is one of the most famous reactions in organic chemistry. The reaction is incredibly useful and typically constructs a cyclohexene ring system with a fair amount of functionality, regioselectivity and stereoselectivity. Two reacting pi components are joined together in a concerted, single-step reaction. One pi component is typically relatively electron rich and referred to as the diene (C=C-C=C). The other component typically has an electron poor C=C double bond, because it is conjugated with an electron withdrawing pi portion (often C=O). This part is referred to as the dienophile, (C=C-C=O).

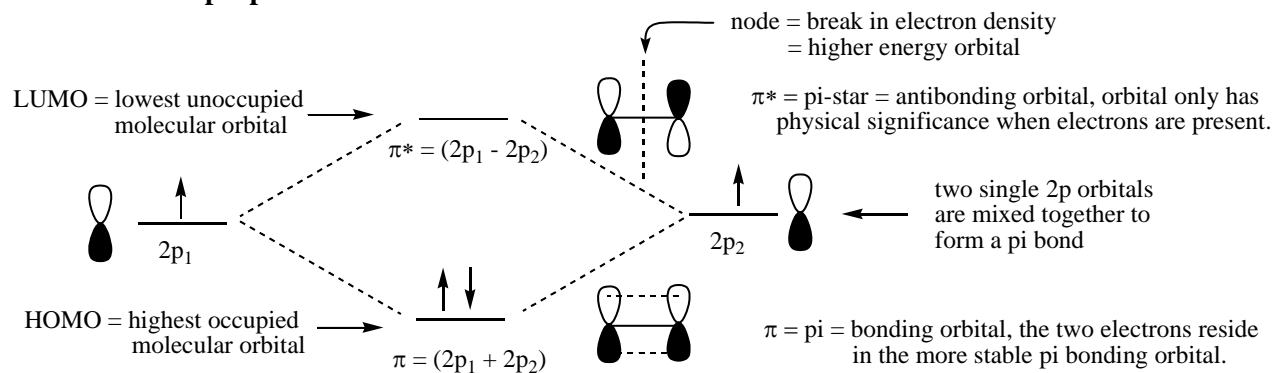


The discoverers of the reaction (in 1928), Otto Diels and Kurt Alder, won a Nobel prize for their work in 1950. However, until the mid 1960s there was no good explanation for how the reaction worked the way it did (a simple, concerted step). In fact, the instructor of an organic course taken in the 1960s by this writer referred to the Diels Alder reaction as a “magic” reaction. The explanation of the Diels Alder reaction (and other related reactions) was ultimately found in molecular orbital theory and won its own Nobel prize in 1981 (Roald Hoffman and Kenichi Fukui).

One possible explanation of the reaction involves looking at two special conjugated, pi-like molecular orbitals, called Frontier Molecular Orbitals (FMOs). One of these is the *highest occupied molecular orbital* (HOMO) on the component referred to as the “diene.” The other is the *lowest unoccupied molecular orbital* (LUMO) on the component referred to as the “dienophile”.

To see how these two important orbitals are created, we begin with the MO construction of a pi bonding orbital ( $\pi$ ) and a pi-star antibonding orbital ( $\pi^*$ ). A pi bond results from the overlap of two 2p orbitals on adjacent bonded atoms. This can simplistically be considered to be the sum of the electron density shown as  $\pi = 2p_1 + 2p_2$  (below). To conserve the number of orbitals, a second mixing of the two 2p orbitals creates a  $\pi^*$  (pi star) antibonding orbital and is also shown, as a subtraction,  $\pi^* = 2p_1 - 2p_2$ . (The actual mathematics is a little more complicated than this.) Addition leads to constructive interference of the 2p lobes producing greater electron density between the bonding atoms, while subtraction leads to destructive interference between the 2p lobes producing no electron density between the bonding atoms (called a node). Since there are only two shared electrons, only the more stable, lower-energy bonding pi orbital is occupied. This is shown below.

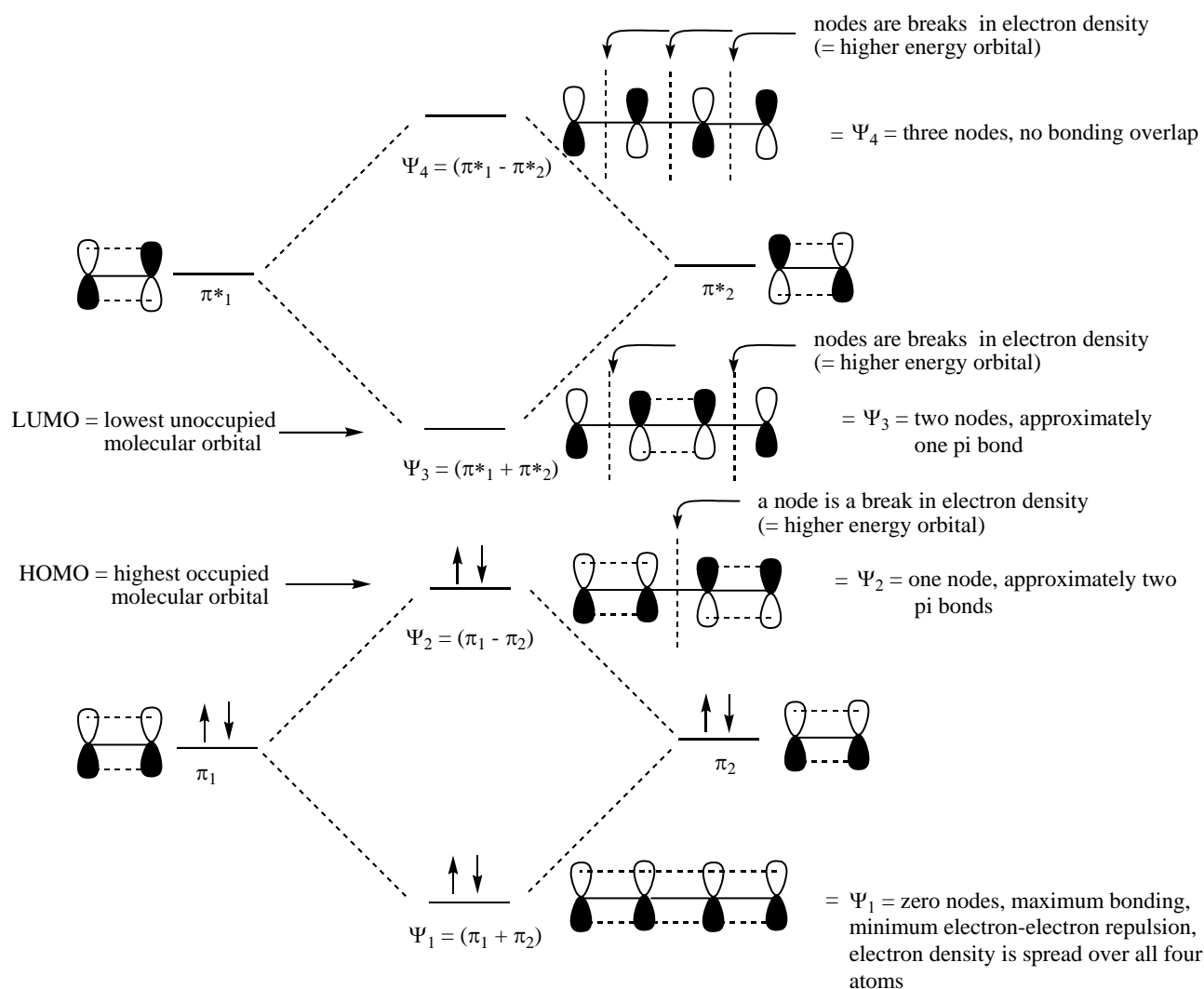
### Picture of a simple pi bond



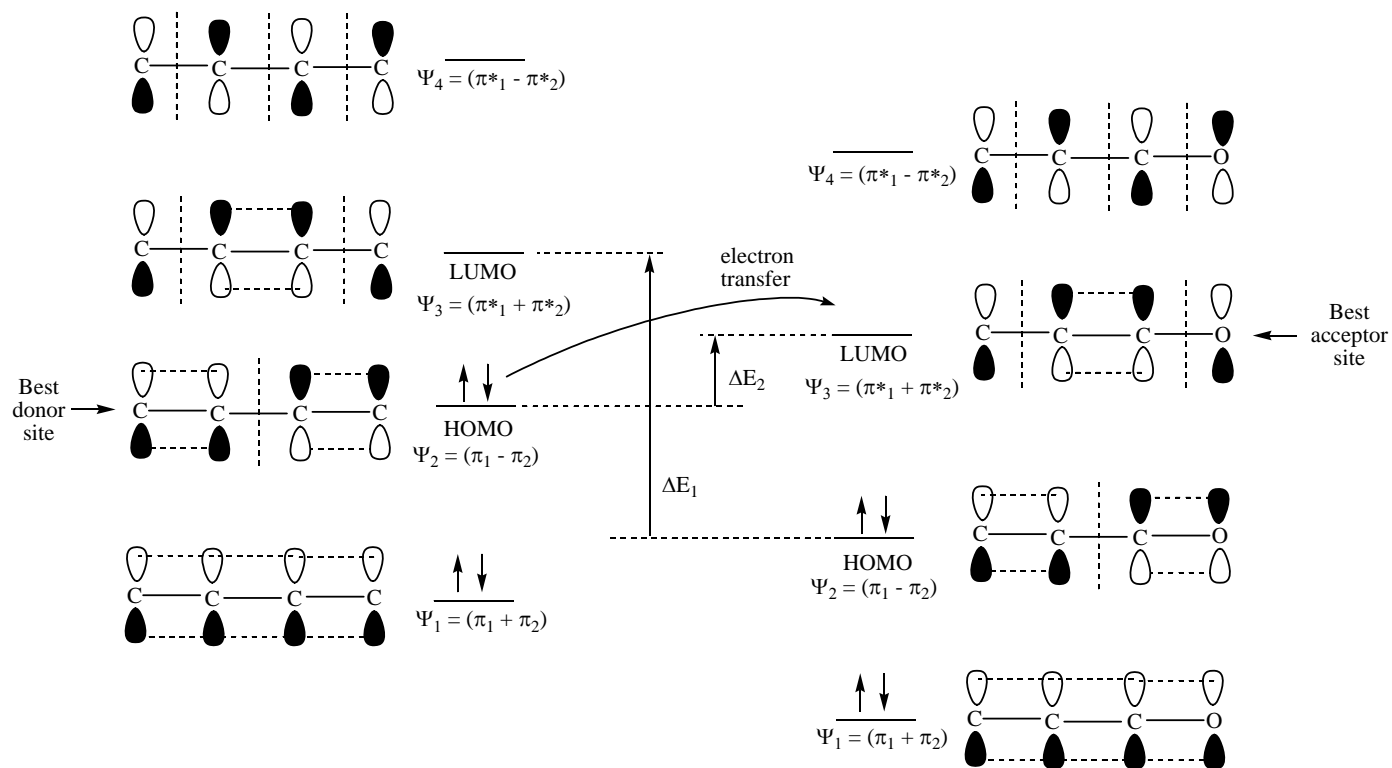
Sigma bonding electrons (not shown) form a lower potential energy (more stable) framework below the pi electrons. The energy gap between the HOMO and LUMO provides the smallest energy difference between a full bonding MO and an empty anti-bonding MO. These orbitals are important in deciding whether and how reactions occur with other pi components.

When two pi bonds are conjugated (adjacent to one another) the pi bond MO picture (above) can be extended by mixing the pi bond parts together and mixing the pi-star anti-bonding parts together. All of the orbitals mix together to some extent, but we only consider the strongest interactions in our explanation. This leads to four new molecular orbitals (usually labeled as  $\Psi_1, \Psi_2, \Psi_3, \Psi_4$ ) of increasing potential energy based on the amount of overlap of electron density (fewer nodes means more stable). The MOs are no longer referred to as pi bonds, but instead symbolized by psi,  $\Psi_n$ , with a subscript number (n) to indicate each MO. This is shown below. Since there are only a total of four electrons from two pi bonds, these are used to fill in  $\Psi_1$  and  $\Psi_2$ , the two most stable MOs in the diagram. That makes  $\Psi_2$  the HOMO and  $\Psi_3$  the LUMO (the frontier molecular orbitals). Notice, too, in the diagram that the  $\Delta E_{\text{HOMO-LUMO}}$  gap of a pi bond is larger than the  $\Delta E_{\text{HOMO-LUMO}}$  in the conjugated pi system of the diene.

### Simple conjugation of two pi bonds, producing four molecular orbitals, (MOs).

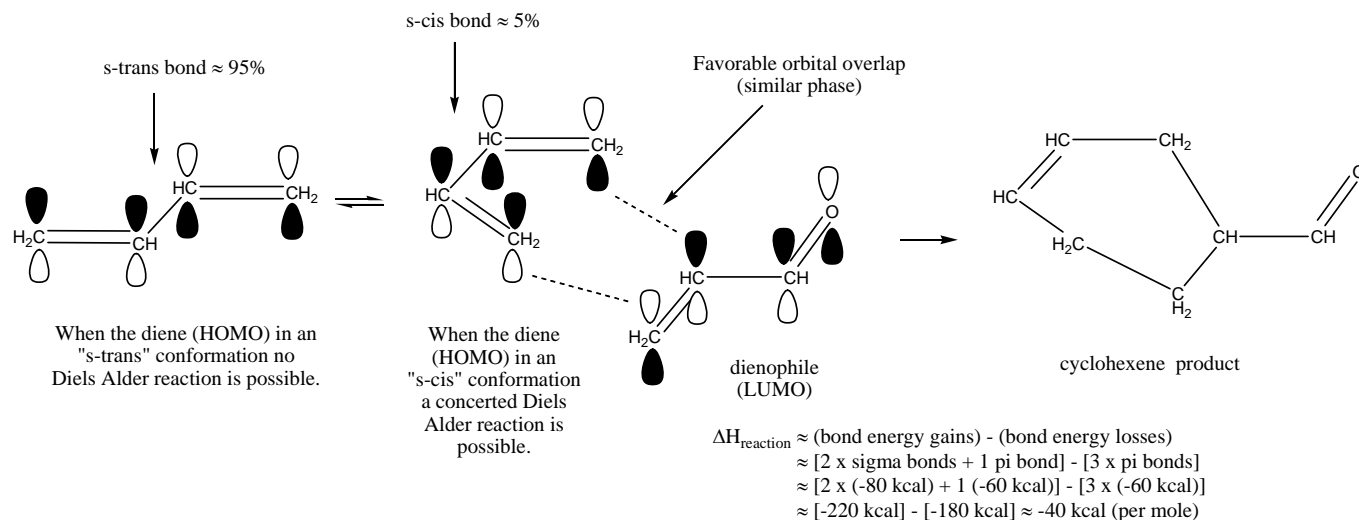


A simple diene and simple dienophile have very similar MO diagrams, except that the dienophile has an electron withdrawing oxygen, which shifts all of the pi-like MOs ( $\Psi_n$ 's) to lower potential energy, PE (see below). The C=C double bond part of the dienophile is relatively electron poor because of being conjugated with the carbonyl pi bond. The diene HOMO is considered to be the best site for electron pair donation (think "like a nucleophile") because of its weaker hold on its pi-like electrons. The dienophile LUMO is considered to be the best site for electron pair acceptance (think "like an electrophile") because of the influence of the oxygen atom's electronegativity on its pi-like orbitals.



The smaller this number ( $\Delta E$ ) the stronger the interaction between the two reacting parts. From above:  $\Delta E_1 > \Delta E_2$ . The most important orbital interactions are the diene HOMO and the dienophile LUMO. An electron pair transfer occurs from diene HOMO into dienophile LUMO. These two orbitals are considered to be the frontier molecular orbitals (FMOs)

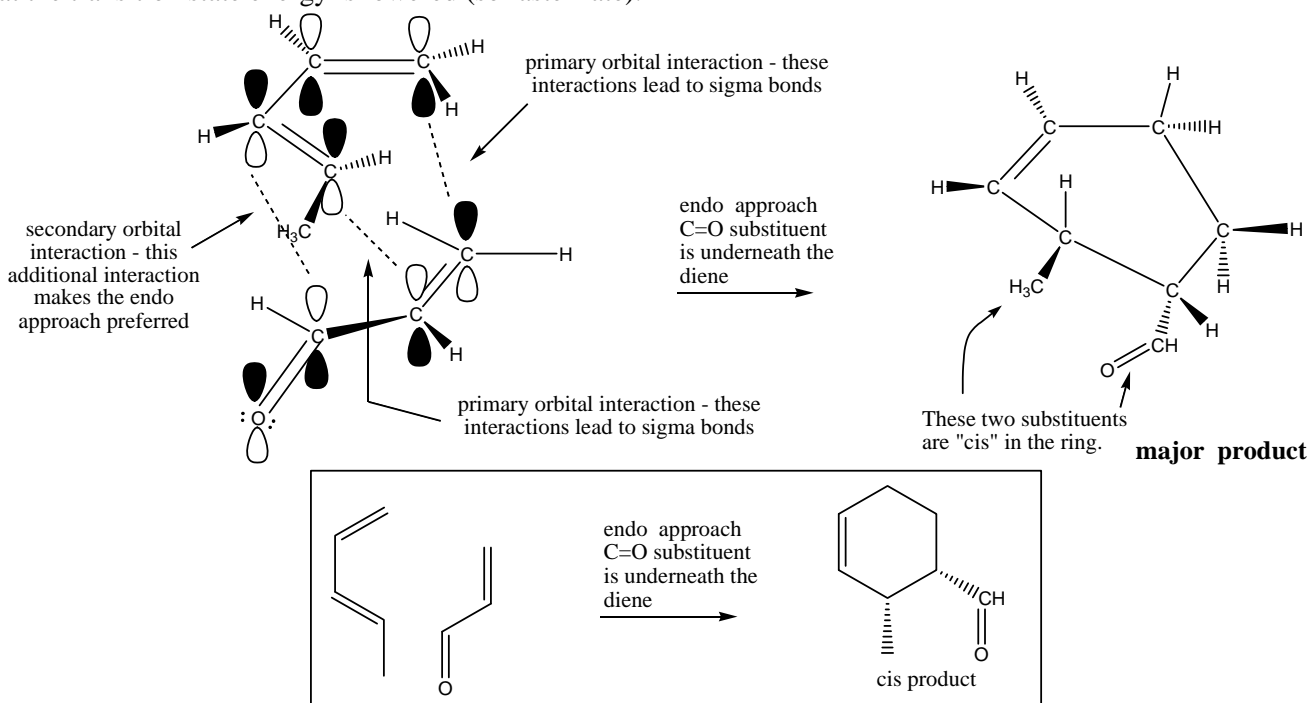
The most important interactions shown above are the HOMO of the diene and the LUMO of the dienophile. These two orbitals are sometimes referred to as the "Frontier Molecular Orbitals." Using just these two orbitals, favorable orbital overlap (similar phase) decides how the diene and the dienophile are joined together. A favorable interaction is possible from either the top or the bottom, and both approaches must be considered. It is essential that the diene be in a s-cis conformation so that both ends of the diene can overlap with the dienophile pi bond orbitals in the concerted transition state (TS) ("s" stands for the single bond, between the two pi bonds). Even though the s-cis conformation only makes up about 5% of the equilibrium mixture, 100% of the Diels Alder reaction proceeds via that conformation.



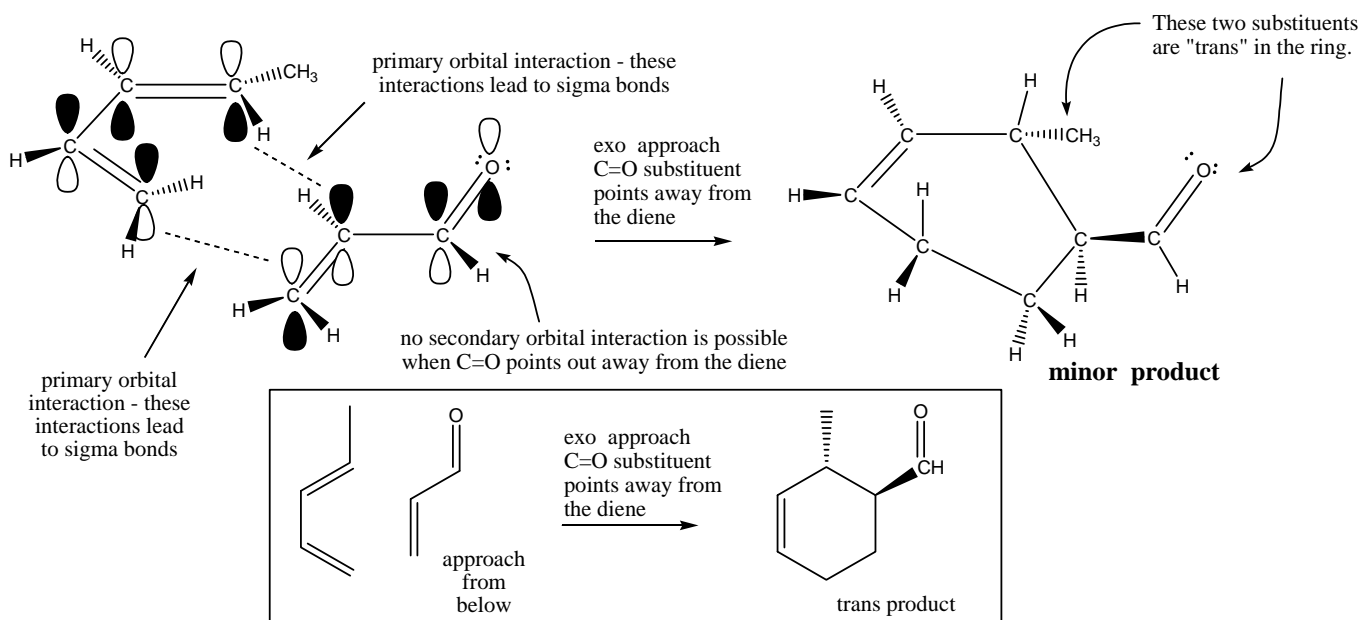
There are a number of features that the above picture does not consider. When there are substituents on the diene and dienophile the regiochemistry and stereochemistry can be somewhat varied. Examples of these two factors are shown below.

### Stereoselective Choices

**Endo Approach by Dienophile** - The diene is modified by an additional substituent to show the result of two different approaches. An endo approach is often the preferred approach because of secondary orbital interactions between the C=O lobes and the back lobes of the diene HOMO. No bonds are formed from these interactions, but it is suggested that the transition state energy is lowered (so faster rate).



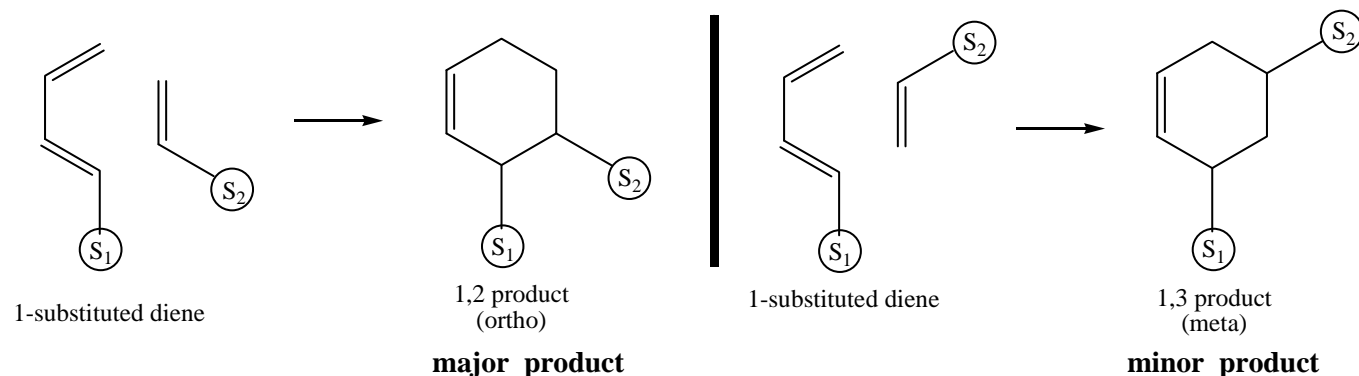
**Exo Approach by Dienophile** - The diene is modified by an additional substituent to show the result of two different approaches. Since the C=O points away from the diene there are no secondary orbital interactions.



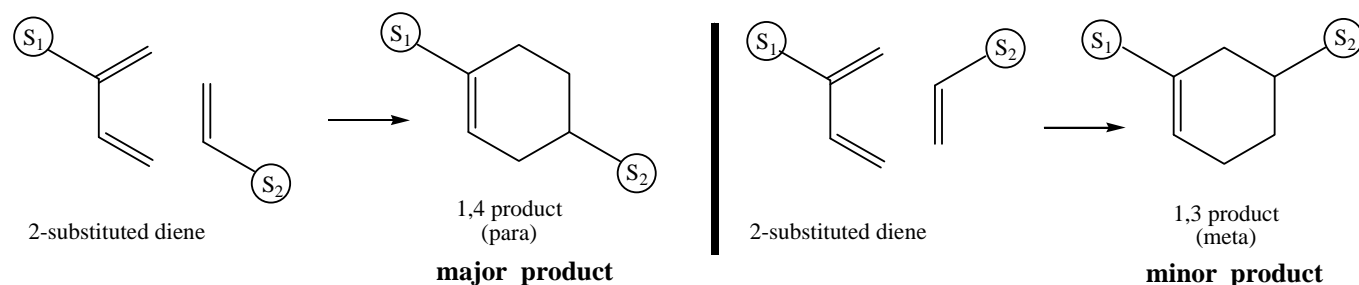
### Regioselective Choices

A single substituent on the diene and a single substituent on the dienophile can lead to two possible products, though one is usually preferred. Two possible arrangements are shown below.

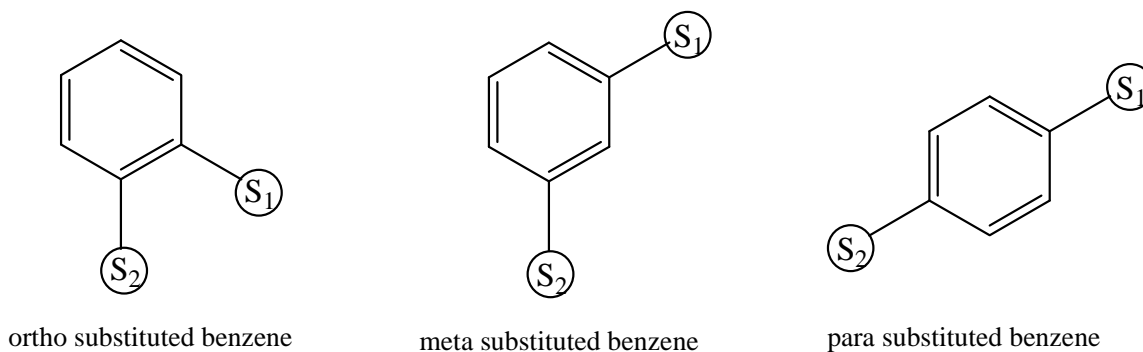
1,2 (“ortho”) patterns (stereochemistry is not indicated)



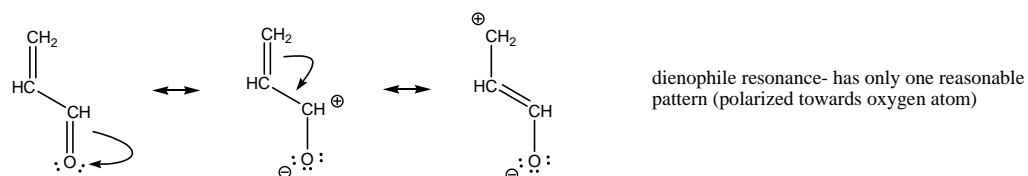
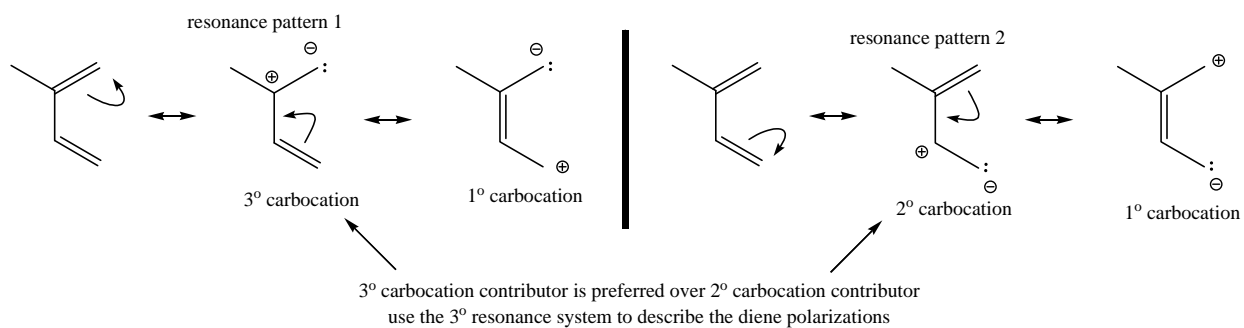
1,4 (“para”) patterns (stereochemistry is not indicated)



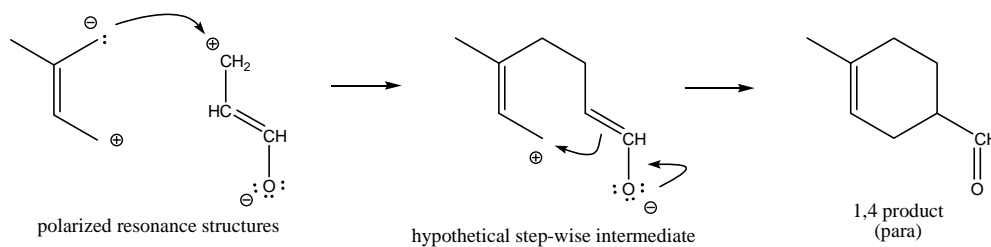
The terms “ortho, meta and para” come from substitution patterns in aromatic rings and are common nomenclature descriptions sometimes used in place of the preferred numerical descriptions.



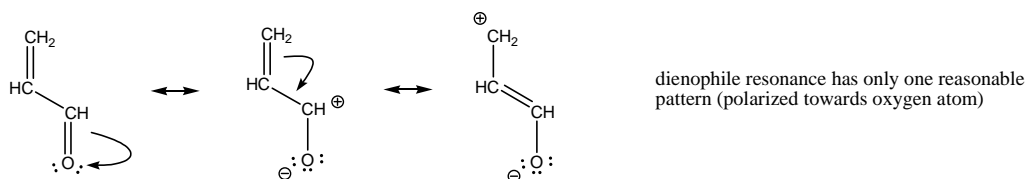
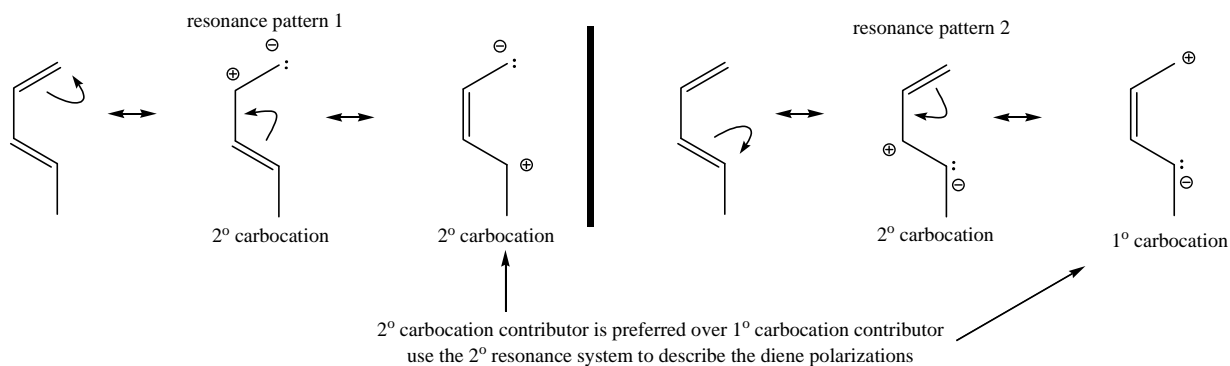
While the Diels Alder reaction is a concerted reaction, having no discrete intermediates, the molecular orbitals do have charge polarizations due to their substituents. If we write these polarizations as the “descriptive” secondary resonance structures, we can gain some insight as to the regioselective choices shown above. Results from other Diels Alder reactions (not shown) suggest that this is not a complete explanation.



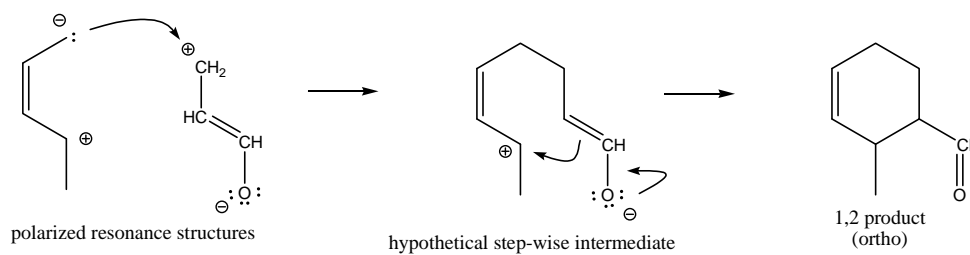
Artificial step-wise approach to Diels Alder product leads to correct prediction of regioselectivity using polarized resonance descriptors.



Similar analysis leads to a prediction of 1,2 regioselectivity in the other example.

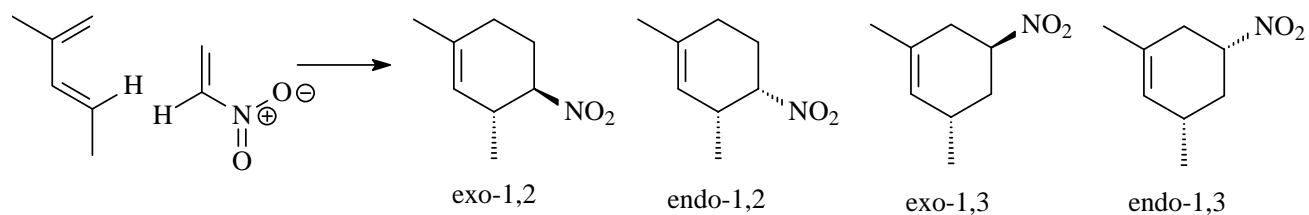


Artificial step-wise approach to Diels Alder product leads to correct prediction of regioselectivity using polarized resonance descriptors.



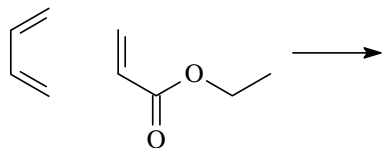
Problem - Predict the major product(s) in each reaction below. If endo and exo products can be distinguished, identify each of these. If regioisomers are possible, show all possible isomers and indicate which is preferred. The first example has been worked as an example and shows the maximum number of possible results.

Example

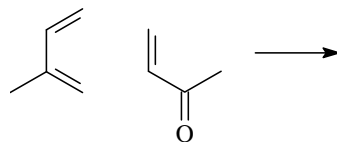


1,2-regioselectivity (pseudo "ortho") is preferred over 1,3-regioselectivity (pseudo "meta") and endo is preferred over exo stereoselectivity so the second structure is the preferred one in this group.

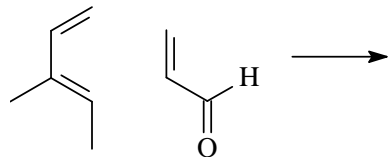
a.



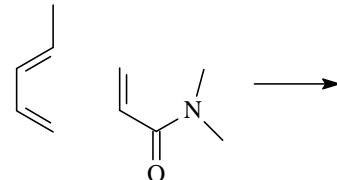
b.



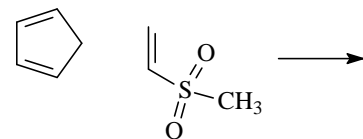
c.



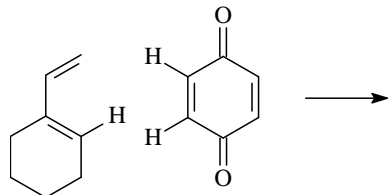
d.



e.



f.



1. Show which Frontier Molecular Orbitals (FMO's) interact most strongly with one another in a reaction of 1-phenylbuta-1E,3-diene and methyl propenoate. Which FMO gives up electron density and which FMO accepts electron density? What are the special designations given to each of these orbitals? Show the appropriate atomic lobes of the interacting atoms in an "endo" transition state and the resulting product. Do likewise for an "exo" transition state and the resulting product. Which one is usually preferred?

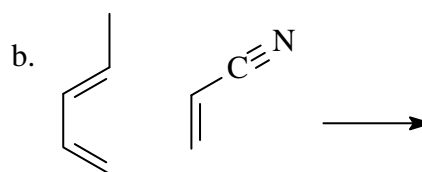
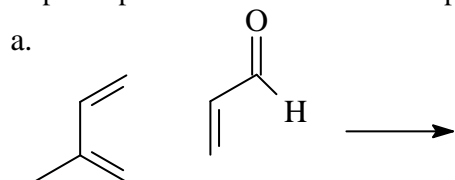
endo TS

product

exo TS

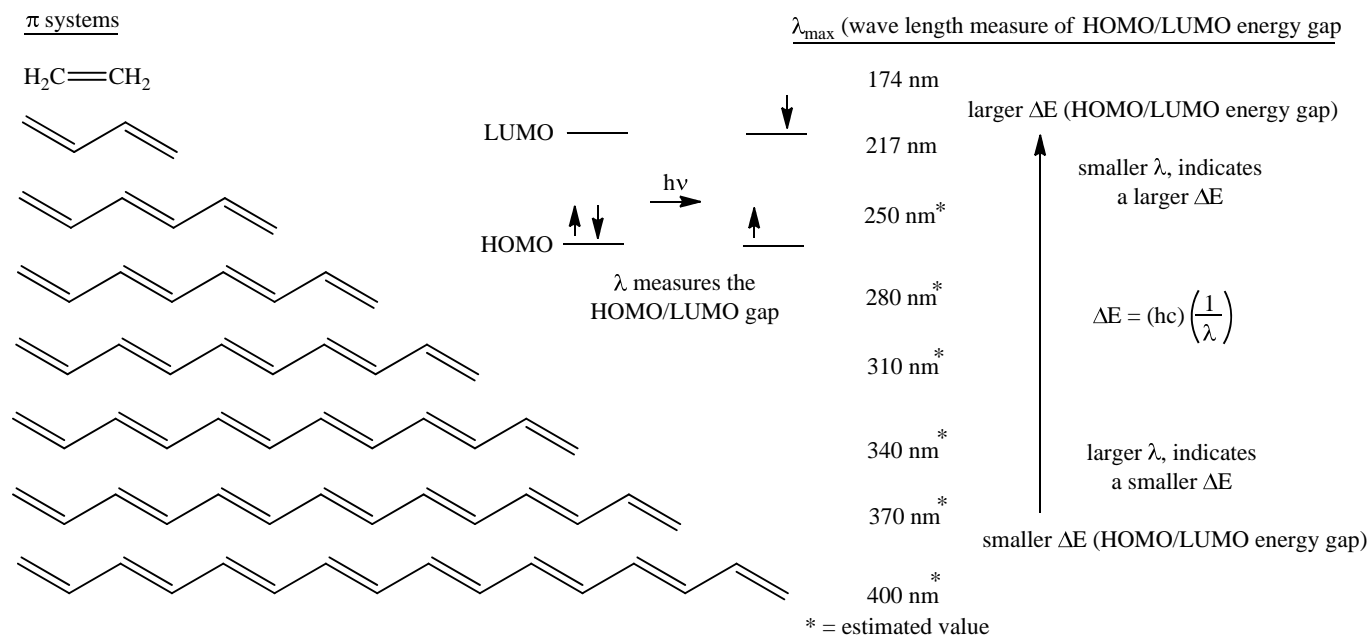
product

2. Use "ionic" structures (not really present, but representations of partial polarizations) to form the bonds in a stepwise process and rationalize and predict the preferred regioselectivity of the two reactions shown below.

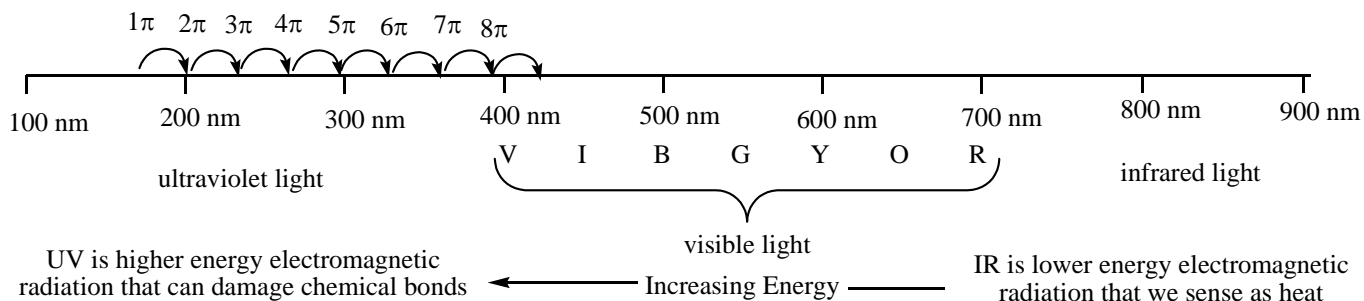




The HOMO/LUMO energy gap can be measured with light (frequency =  $\nu$  or wave length =  $\lambda$ )

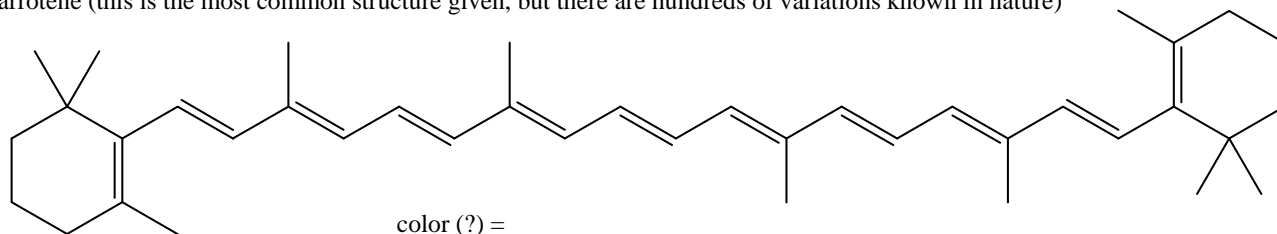


With enough conjugated pi bonds the HOMO/LUMO energy gap is decreased until it begins to absorb in the visible region and parts of the visible spectrum disappear, leaving a residual color to be seen.

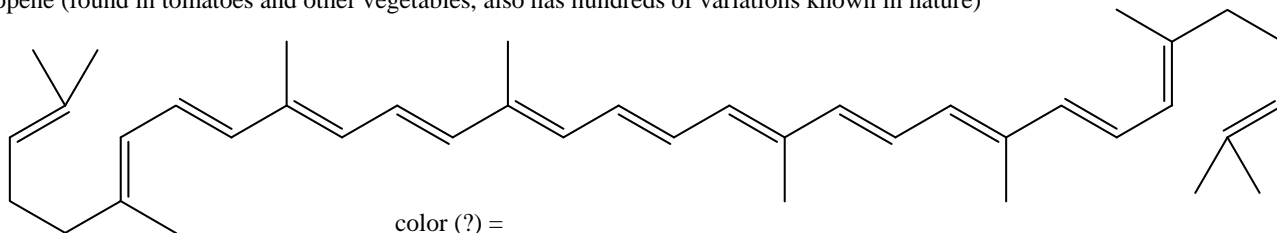


Molecules From Nature having such features. (Probable colors?)

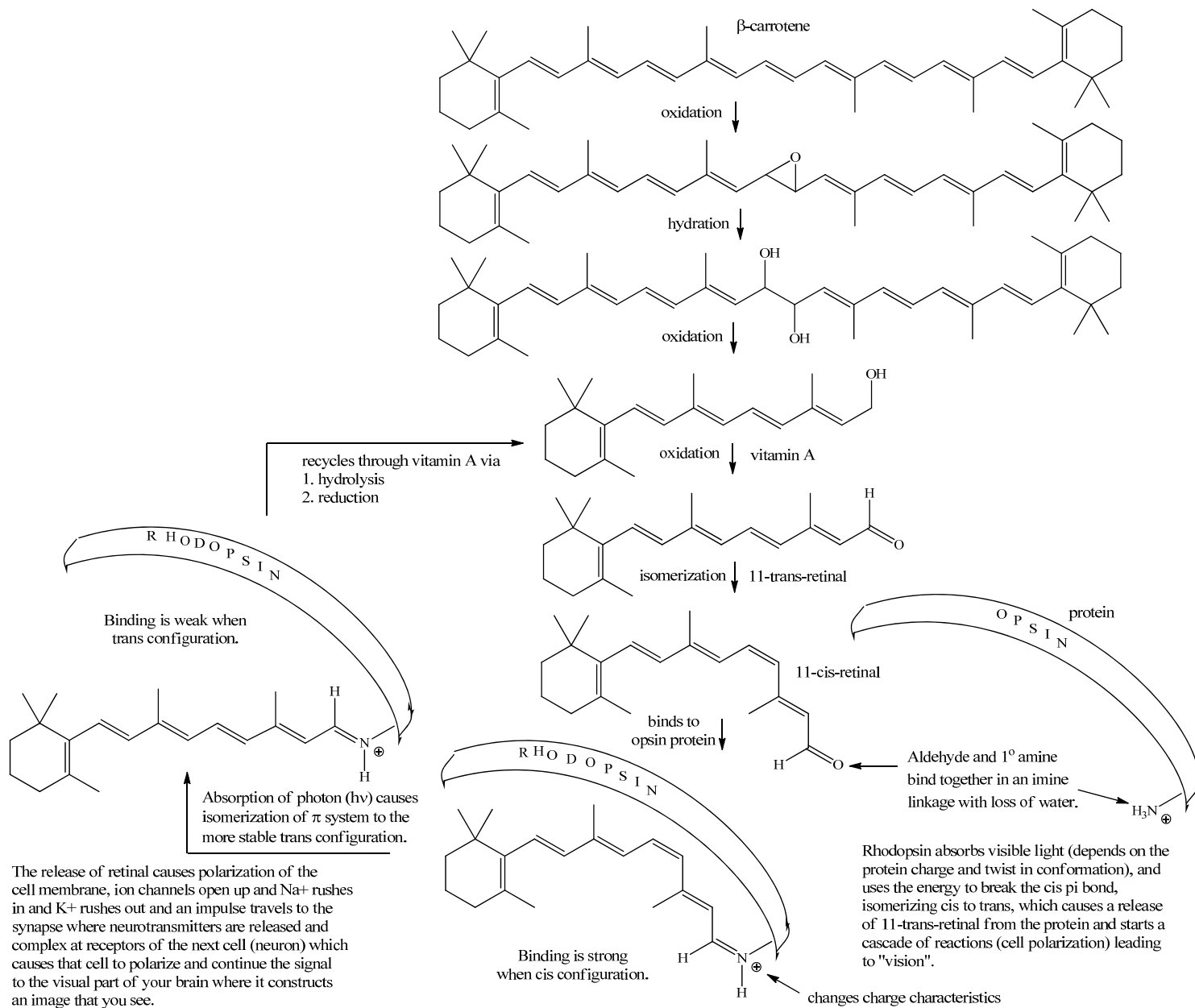
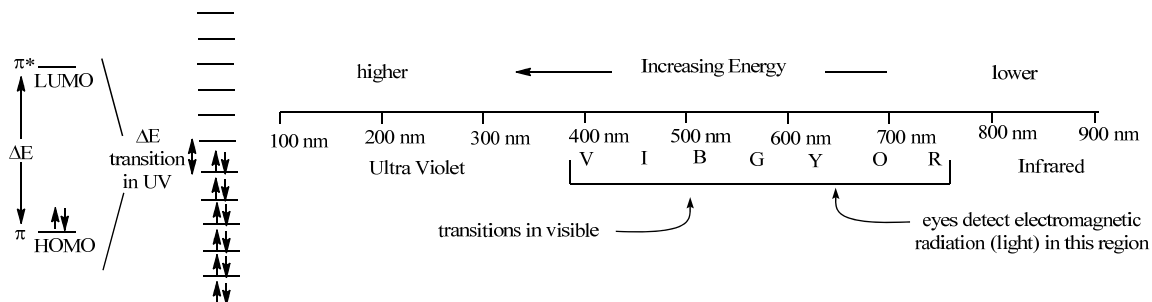
$\beta$ -carotene (this is the most common structure given, but there are hundreds of variations known in nature)



lycopene (found in tomatoes and other vegetables, also has hundreds of variations known in nature)

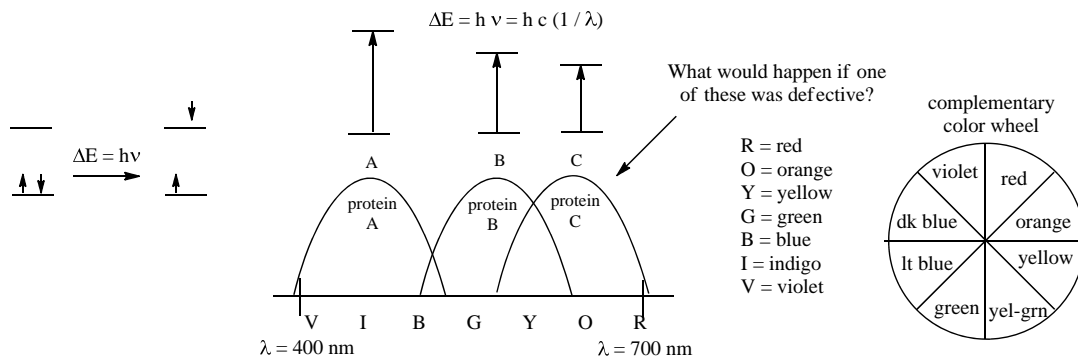


## Why are you supposed to eat your carrots?



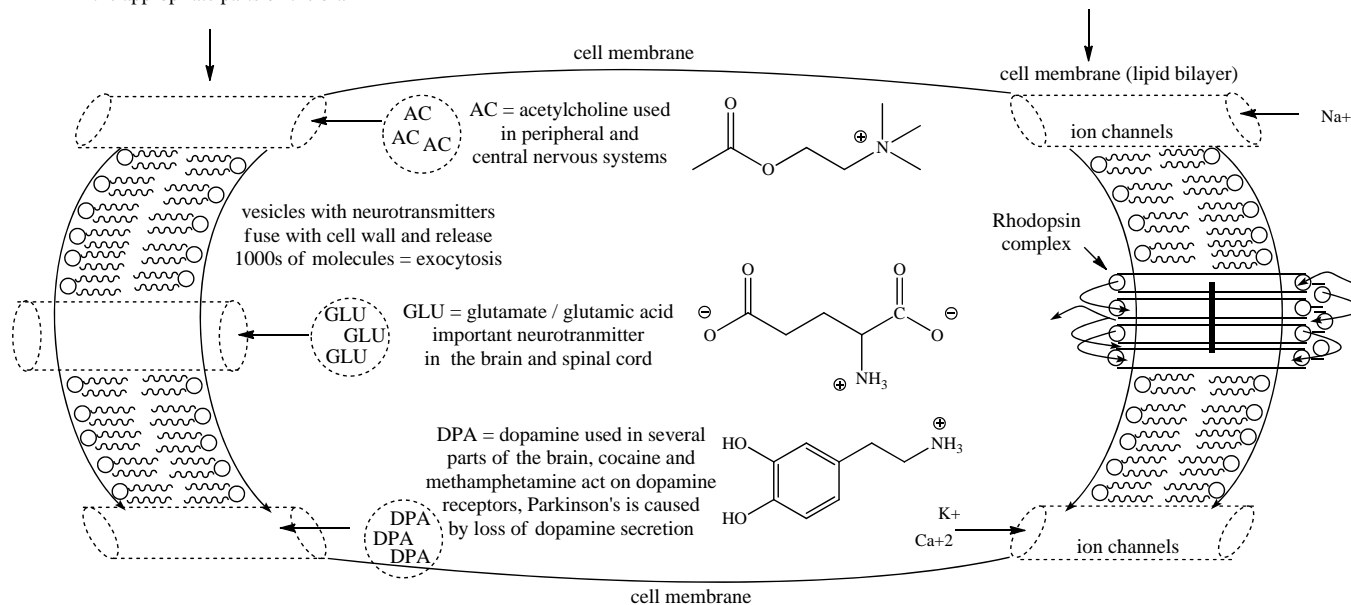
## How does vision work?

Slightly different protein environments, changes HOMO/LUMO gap and what part of visible region gets absorbed. Your genetics determines your protein structure and the colors that you see. Different variations of protein complexes (twisting and charge distribution) absorb different wavelengths of light.

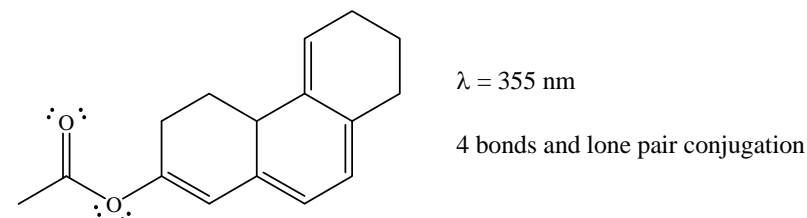
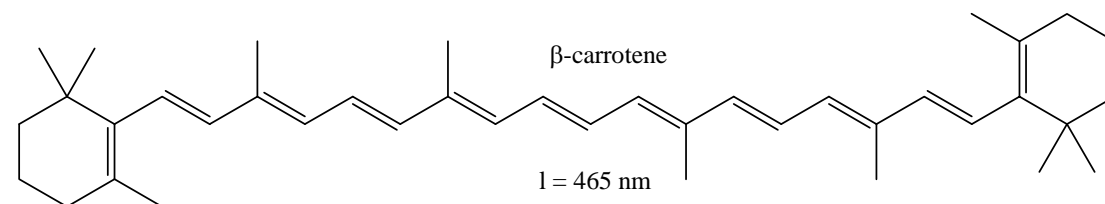
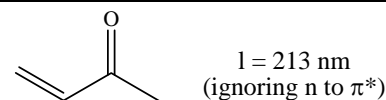
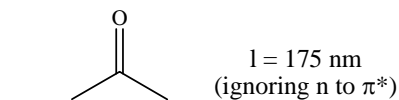
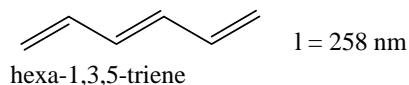
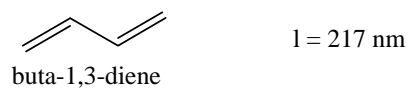


At a synapse, neurotransmitters are released from vesicles, triggering the next neuron to fire and transmit the signal to the appropriate parts of the brain

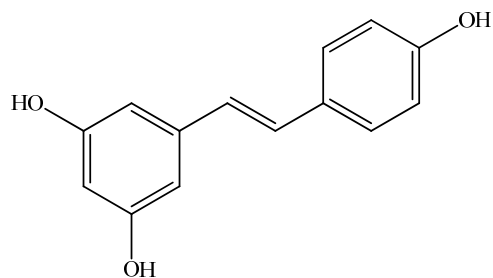
Rhodopsin complex imbedded in cell membrane has retinal bound perpendicular to 7 transmembrane protein helicies. Isomerization triggers cell action potential (polarization) and  $\text{Na}^+$  flows in and  $\text{K}^+$  flows out (1 millisec). In some cells this is followed by  $\text{Ca}^{+2}$  ions efflux (100 millisec).



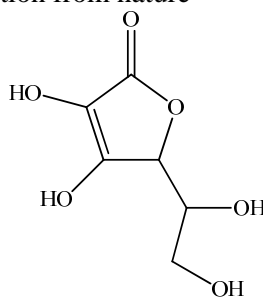
Provide an explanation for the differences in the  $\lambda_{\max}$  (wave lengths) of absorption between 2-propanone and 3-buten-2-one. You will need to build the pi molecular orbitals of each system and point out the HOMO/LUMO gaps that lead to the differing energies for these gaps (draw the pictures using simple pi bonds and shading to indicate the phase of the p orbital overlaps). The hydrocarbon examples are merely provided for comparison and reference.



### Biomolecules offering free radical protection from nature

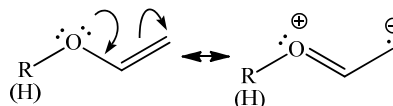


resveratrol - polyphenolic found in red wine, possibly protective antioxidant, mouse studies showed protection from obesity and diabetes, but the mice consumed resveratrol in an amount equivalent to 60 L of wine/day.

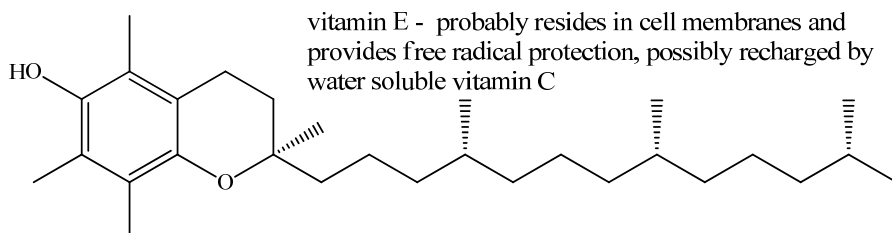


vitamin C - circulates in the blood and provides free radical protection, possibly recharges vitamin E in cell membranes.

Electron transfers are relatively easy from these molecules because of high potential energy HOMOs due to extended conjugation and stabilization of initial cation charge by oxygen lone pair.

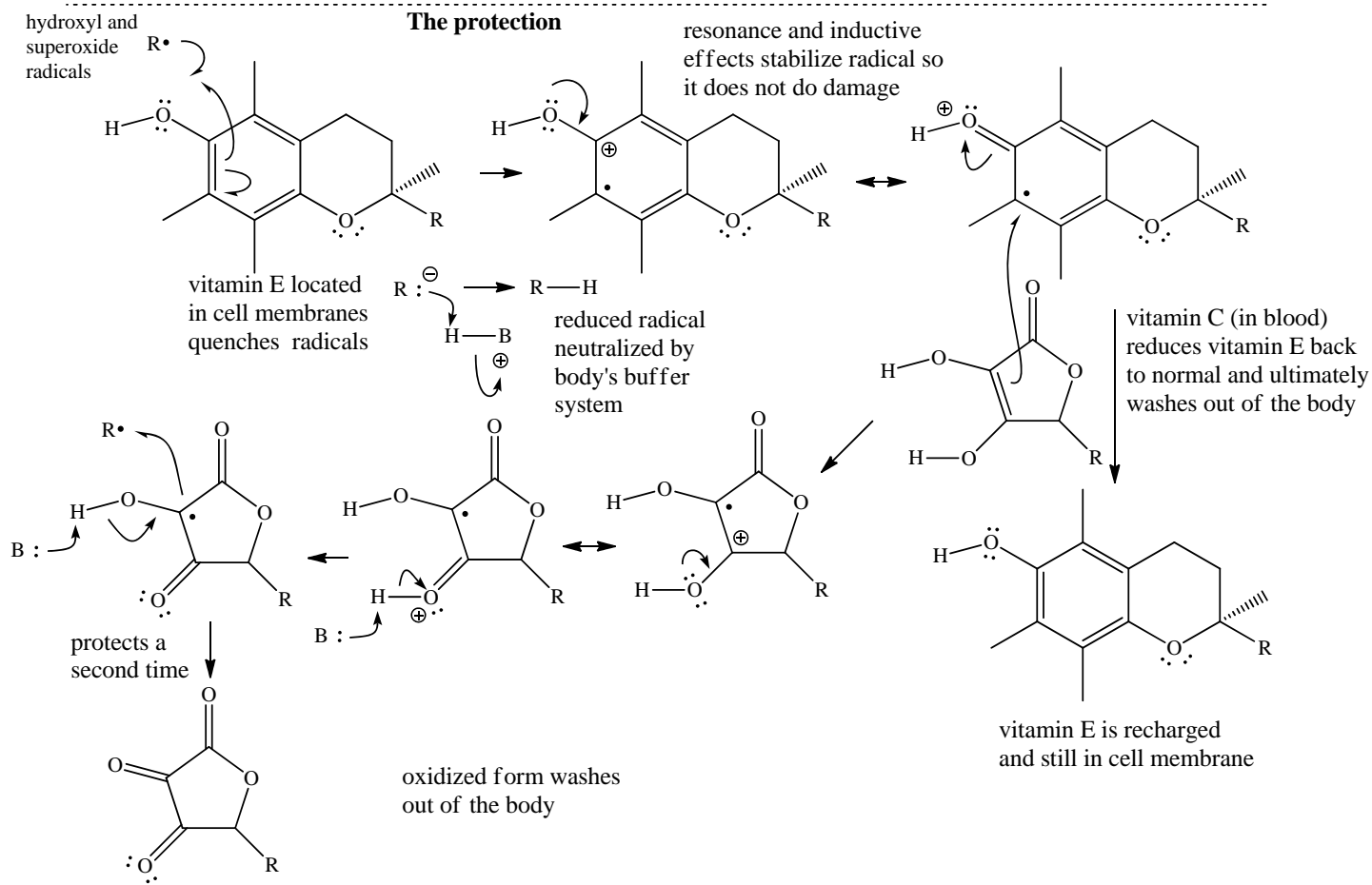
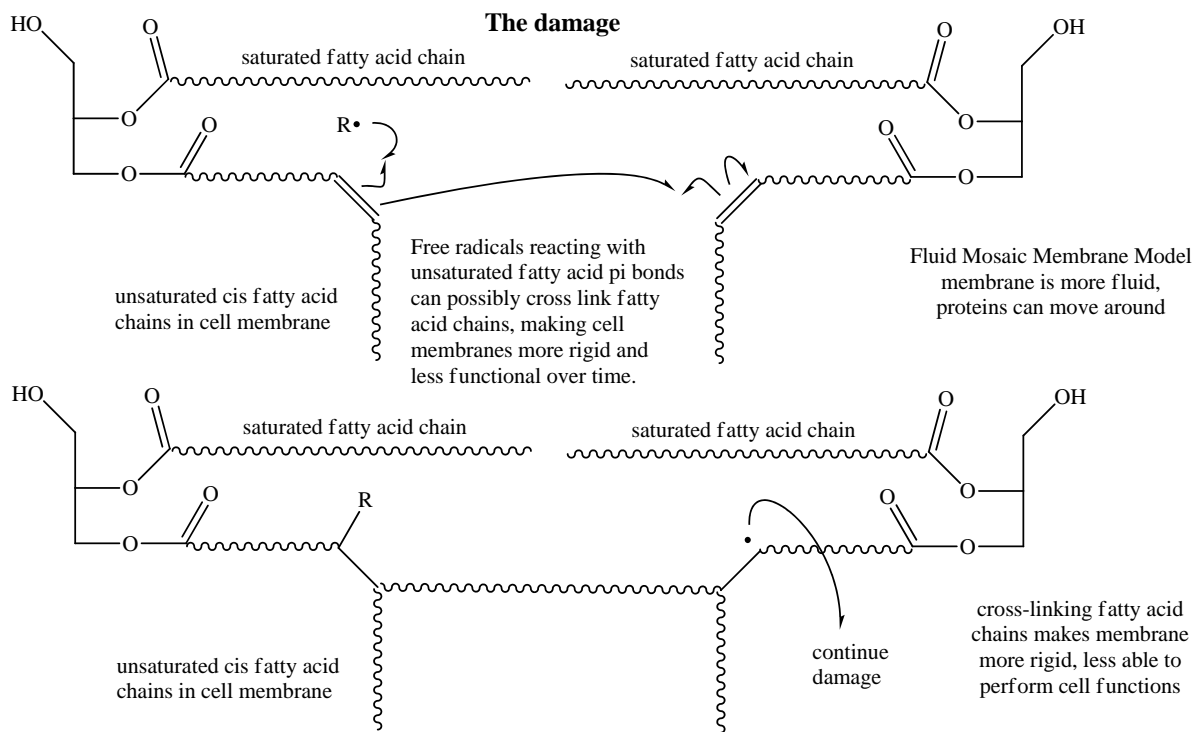


enol pumps up C=C and makes it more electron rich, better able to donate an electron

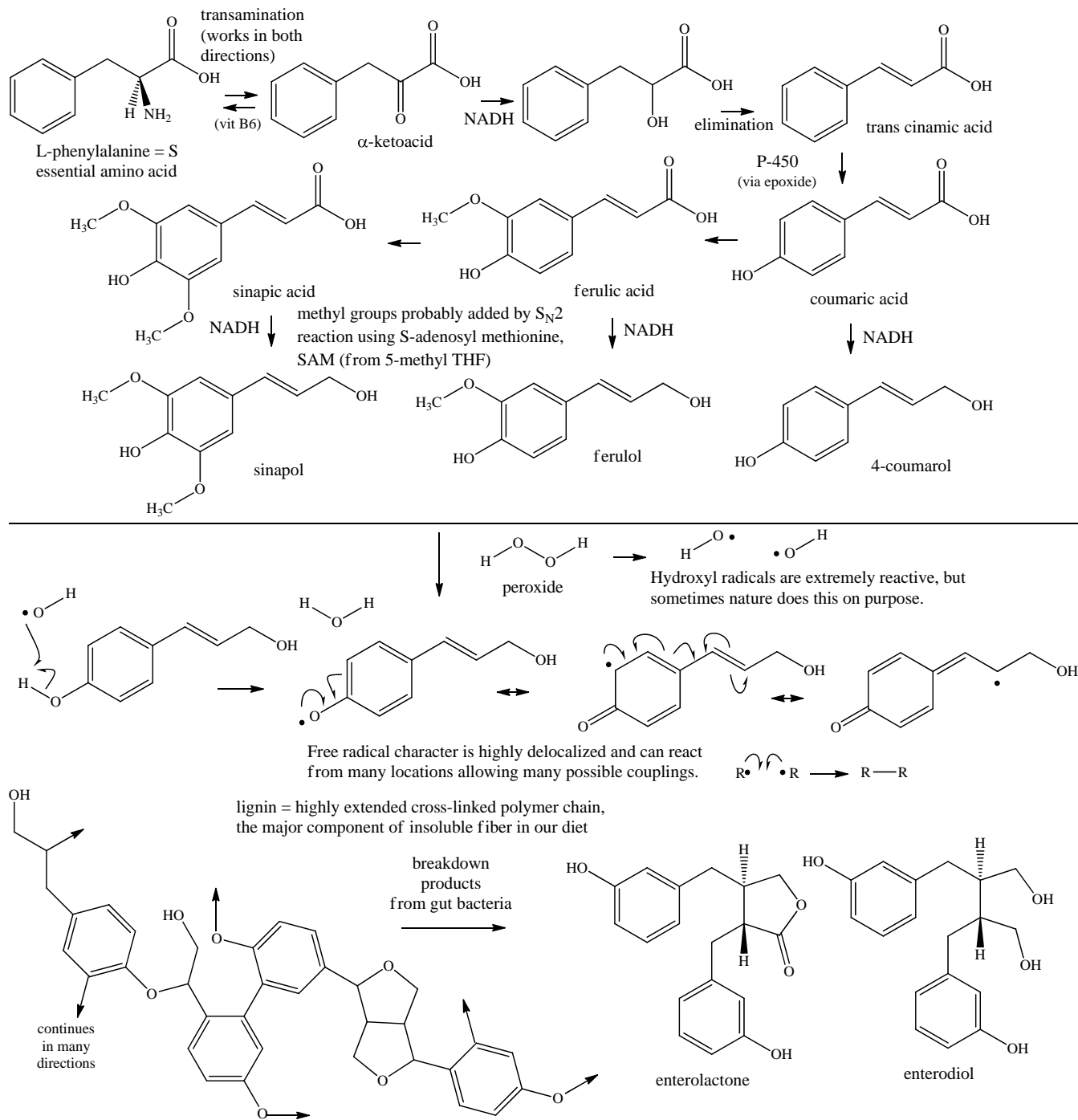


vitamin E - probably resides in cell membranes and provides free radical protection, possibly recharged by water soluble vitamin C

Possible membrane damage from free radicals and possible protection from vitamins E and C.



## Lignin Synthesis (structural support and antioxidant protection for plants)



coumarins (also called coumadins) are also produced by plants (found in cherries, apricots, strawberries, etc.) and can act as anticoagulants (prevents blood clotting). They are hepatotoxic (liver) but some are used as anticoagulants (warfarin) and also used as rat poison (causes rats and mice to bleed).

