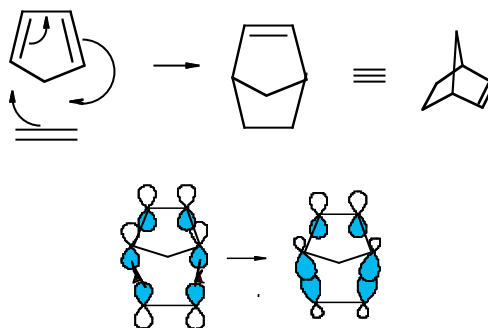


Molecular Modeling: Diels Alder Reactions

See: http://en.wikipedia.org/wiki/Diels_Alder

The following reaction of ethene and cyclopentadiene illustrates the *Diels Alder* addition of an alkene (the dienophile) to a diene. Otto Paul Hermann Diels and Kurt Alder first documented the novel reaction in 1928 for which they were awarded the Nobel Prize in Chemistry in 1950. The reaction is a concerted, stereospecific reaction that involves conservation of orbital symmetry, *i.e.* each orbital of the starting material must be converted to an orbital of the same symmetry to form product. Molecular orbitals interact to form bonds where there is orbital overlap of like colored (shaded) orbital lobes combining to form the new bonds. The link between molecular orbital theory and experimentation was established by Roald Hoffman and Bob Woodward.¹ It led to a Nobel Prize for Roald Hoffman and Kenichi Fukui in 1981.

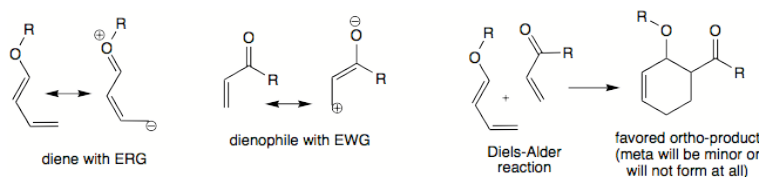
1. Hoffman, R.; Woodward, R. B. *J. Amer. Chem. Soc.* **1965**, *87*, 4388.



The *Diels Alder* reaction is classified as a pericyclic [4+2] cycloaddition, in which a conjugated diene with 4 π electrons and an isolated alkene with 2 π electrons add together in a single step without intermediates by a cyclic redistribution of bonding electrons. This process is very useful in organic synthesis because it forms two carbon-carbon bonds in one step; it is one of the few methods available for directly forming cyclic structures, and it is a relatively “green” reaction where there are no by-products and can be conducted either with a minimal amount of solvent or in certain cases without any solvent.

If unsymmetrically substituted dienes and dienophiles are reacted, *pseudo*-ortho and para orientations are favored in the products over meta. Regioselectivity of substituents in the product can be explained by the fact that a diene with an electron-donating group (ERG) and dienophile with an electron-withdrawing group (EWG) direct product formation, increase the rate of reaction, and govern the product's stereochemistry. Electron donating-withdrawing can be viewed as a push-pull effect which activates both the diene and dienophile. But, if they are reversed: *i.e.* diene has an EWG and dienophile has an ERG, they are de-activated, and the reaction slows dramatically and may not occur.

The highest occupied molecular orbital (HOMO) of the diene will donate electron density to the lowest unoccupied molecular orbital (LUMO) of the dienophile, resulting in a cyclic, nonpolar transition state and cyclic product. The strongest interaction takes place between the HOMO of diene and LUMO of dienophile. Carbons that have the highest difference in two frontier orbitals will bond, which directs the orientation of substituents and the formation of the major product in the reaction.

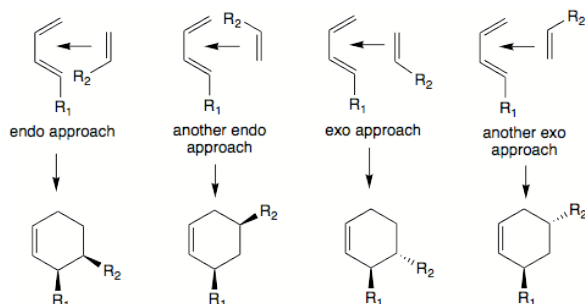


The preferred orientation in the product can be ascribed to the partial positive and negative charges in the diene and dienophile. A carbon with a partial negative charge will interact most readily with carbon bearing a partial positive charge. Therefore those two carbons will attract and direct the relative orientation of substituents. The partial positive/negative charges can be determined by drawing resonance contributors for diene and dienophile, which takes into account the ERG and EWG substituents of the diene and dienophile.

The stereochemistry of substituents in the starting material is retained in the product. This means that if a *cis*-dienophile is reacted, both of the *cis*-substituents will end up on same side (face) of the product ring. *Trans*-dienophile will yield a

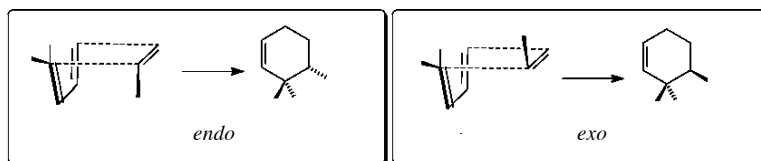
product where both of trans-substituents (that came originally from the dienophile) will be on different sides of the product ring. The same principle applies to dienes: trans-trans or cis-cis 1,4-substituents will end up on the same side of the ring, whereas trans-cis 1,4-substituents will be oriented towards different faces of the ring.

In addition to the *pseudo* ortho/meta/para selectivity, the diene and dienophile orders themselves in different ways in the transition state so that its stereochemistry is either *exo* or *endo*, which produce different products. To determine which is *endo* and which is *exo*, the two molecules are oriented parallel to each other, so that the diene's single bond (the one that connects two double bonds) is parallel to dienophile's double bond. It makes no difference whether the dienophile is positioned above or below the diene. The single substituent (or cis-substituents on the dienophile) is oriented to point in the direction of diene's π -system. This is the *endo* transition state (pictured below). If these substituents are pointed away from the diene, this would be the *exo* transition state.

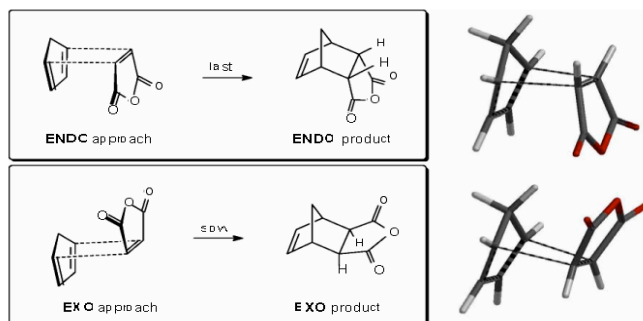


The **endo** rule states that the kinetic product, the one that forms fastest, results from a transition state in which the dienophile's substituent is "**endo**" with respect to the diene. This transition state has the lower energy of activation, E_a .

Compare the two approaches below. Notice the orientation of the substituent relative to the diene. The *endo* approach places the substituent over (or *cis* to) the diene, *exo* is away.



When both the diene and dienophile are cyclic, two products form with different stereochemistries, called *exo*- and *endo*-adducts. They are named from their respective transition states. An example is provided by the reaction of cyclopentadiene and maleic anhydride illustrated below:



The two different products both contain a new bicyclic structure. The *endo* and *exo* labels describe the orientation of the OC-O-CO) relative to the saturated carbon bridge. An *endo* substituent points back towards the alkene bridge. An *exo* substituent points away from the bridge.