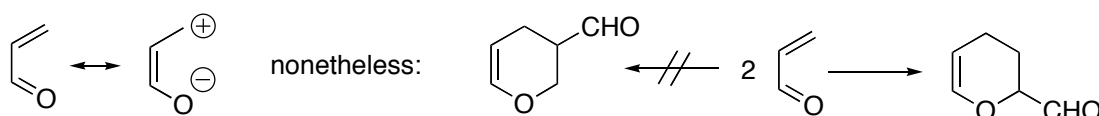


CHEM 330

Topics Discussed on Dec. 2

4. Regiochemical aspects of the Diels-Alder reaction – II

Principle: regiochemical predictions based on atomic polarity are rooted in a coarse approximation of what actually happens when molecular orbitals interact. Although the vast majority of Diels-Alder reactions of interest in the synthesis of biologically active substances follow the above trends, exceptions are known. An example is shown below. Details of such exceptional cases are beyond the scope of CHEM 330.

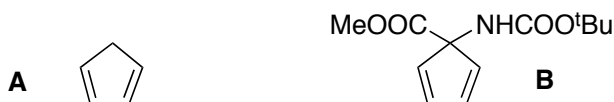


5. Kinetic aspects:

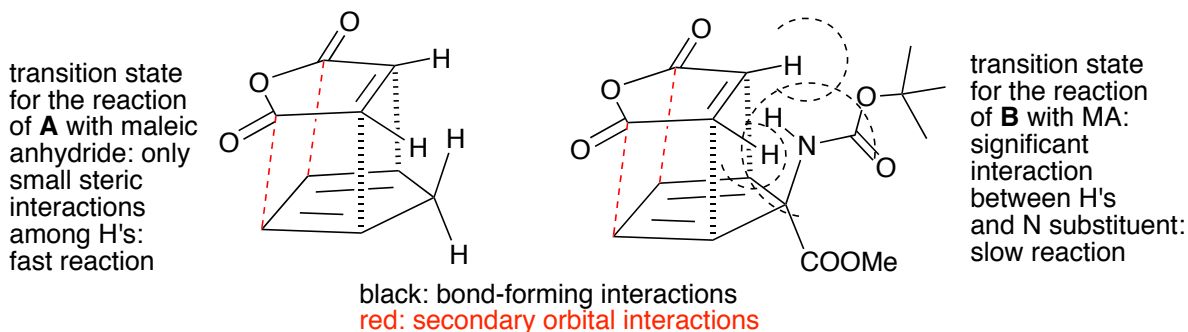
Key factors that affect the rate of a Diels-Alder reaction: steric and electronic effects

Steric effects: nonbonded (=steric) interactions between diene and dienophile (particularly among substituents on one and substituents on the other) retard the rate of a Diels-Alder reaction

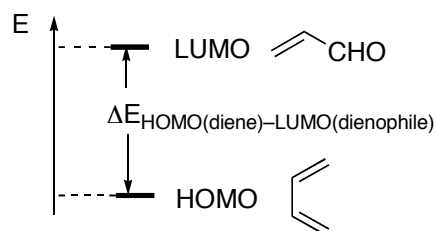
Example: cyclopentadiene, **A**, vs. substituted analog **B**. The dienic systems of the two molecules are virtually identical from an electronic standpoint.



Yet, plain cyclopentadiene, **A**, reacts much faster with, e.g., maleic anhydride than **B**. Such a rate difference is attributable to steric effects:



Electronic effects: in a Diels-Alder reaction, electrons from the HOMO of the electron-rich component must flow into the LUMO of the electron-deficient component. To do so, electrons from the HOMO of one component must "jump the gap" that separates them from the LUMO of the other component (the HOMO-LUMO gap). For instance, in the regular demand Diels-Alder reaction between butadiene (e^- rich diene) and acrolein (e^- deficient dienophile):

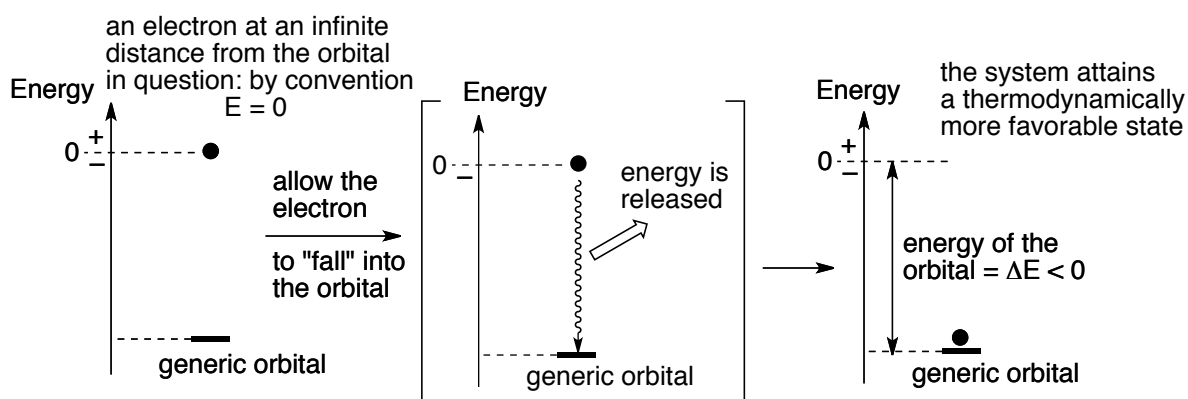


Principle: the rate of a Diels-Alder reaction increases with decreasing $\Delta E_{\text{HOMO-LUMO}}$

Principle: to narrow the HOMO-LUMO energy gap, one may, somehow:

- (i) increase the energy of the HOMO while keeping the LUMO energy constant
- (ii) decrease the energy of the LUMO while keeping the HOMO energy constant
- (iii) simultaneously increase the energy of the HOMO and decrease that of the LUMO

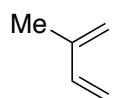
Reminder: the energy of an orbital is defined as the amount of energy that is *released* when an electron, originally at an infinite distance from that orbital, "falls" into, and populates, it. Thermodynamic conventions thus require that orbital energies be expressed as *negative* numbers:



Frequent use of the electron-volt (eV) energy unit to express orbital energy (1 eV \approx 23.5 kcal/mol \approx 98.3 kJ/mol!)

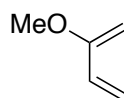
Modulating the HOMO-LUMO gap during a regular demand Diels-Alder reaction: increasing the energy of the HOMO_(diene) by the introduction of electron-donating groups (Me, OMe, NMe₂, OSiMe₃, etc.)

Example: isoprene vs. 2-methoxybutadiene. Both Me and MeO groups are electron-donating, but MeO is more so than Me (recall Friedel-Crafts chemistry....!). If one estimates (MNDO, a particular method to calculate molecular properties) the HOMO energy of the two dienes, one finds that the HOMO of 2-methoxybutadiene (MB) is higher in energy than that of isoprene (IP):



isoprene

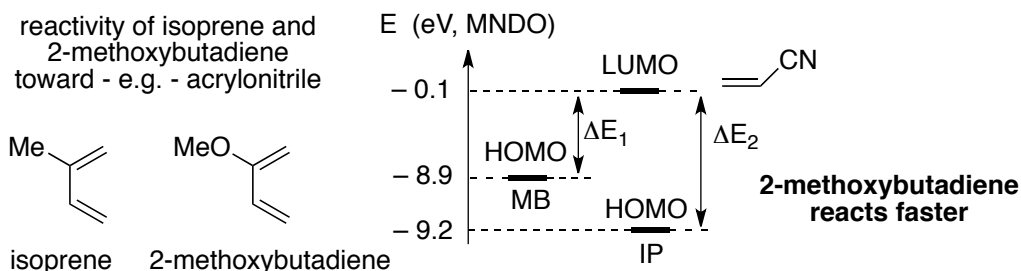
$$E_{\text{HOMO}} = -9.2 \text{ eV (MNDO)}$$



2-methoxybutadiene

$$E_{\text{HOMO}} = -8.9 \text{ eV (MNDO)}$$

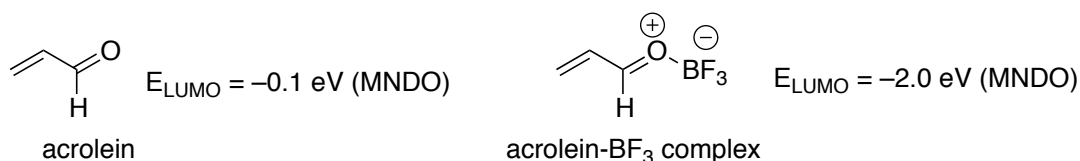
Relative rate of the Diels-Alder reaction of acrylonitrile with isoprene vs. 2-methoxybutadiene: steric factors / barriers are essentially equivalent for the two reactions, yet 2-methoxybutadiene reacts faster, because of a smaller HOMO-LUMO gap:



Modulating the HOMO-LUMO gap during a regular demand Diels-Alder reaction: decreasing the energy of the LUMO_(dienophile) by the introduction of multiple electron-withdrawing groups (CHO, COR, COOR, COCl, CN, SO₂R, NO₂, etc.)

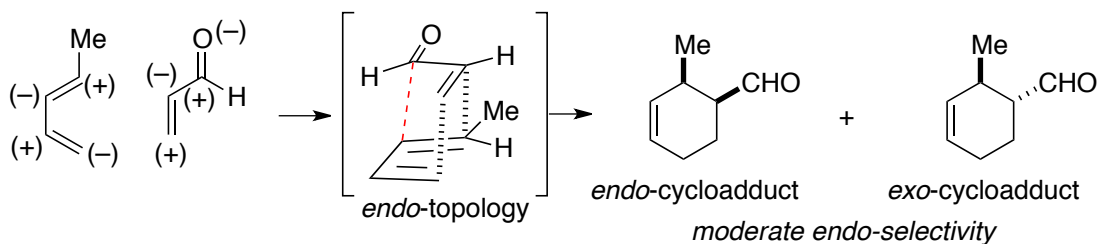
Decreasing the energy of the LUMO_(dienophile) through coordination with an appropriately selected Lewis acid:

Example: effect of Lewis acid coordination on the LUMO energy of acrolein. If one estimates (MNDO, see above) the LUMO energy of free acrolein vs. the complex of acrolein with BF₃ (a commonly used, oxophilic Lewis acid), one finds:



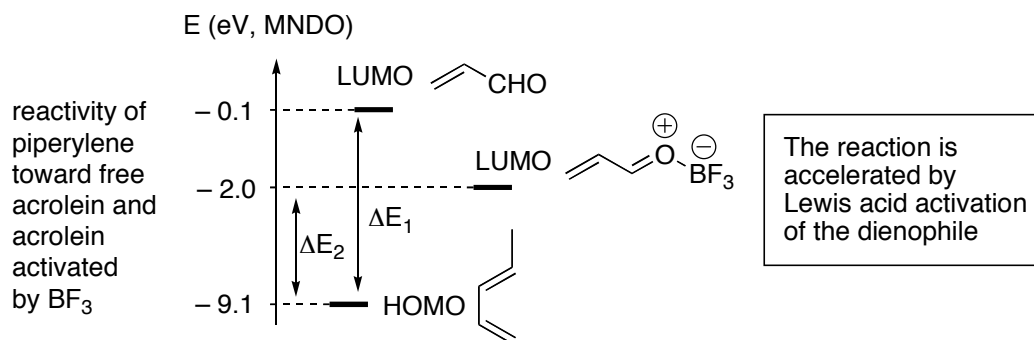
The reaction of 1-methylbutadiene (piperylene) with free acrolein vs. acrolein-BF₃ complex:

Free acrolein reacts slowly with piperylene to give the product of *endo* cycloaddition with moderate selectivity:



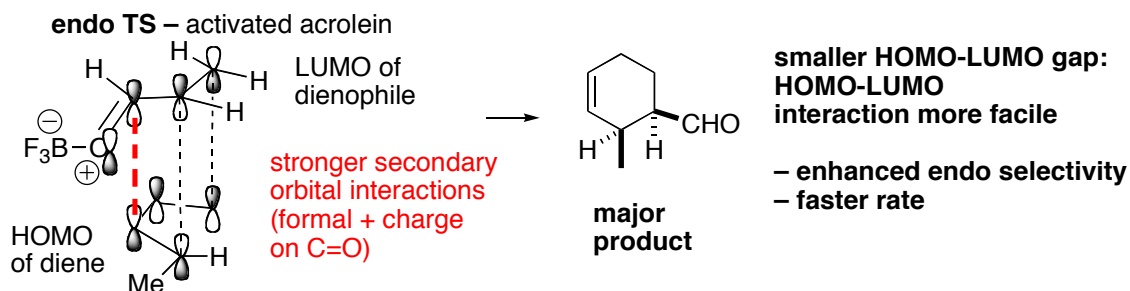
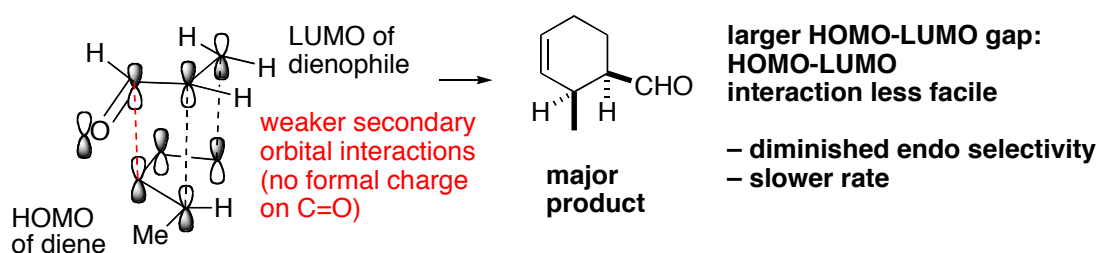
In contrast, the acrolein-BF₃ complex reacts rapidly with piperylene to give the *endo*-cycloadduct with virtually complete selectivity.

The faster reaction rate is attributable to a much smaller HOMO-LUMO gap:



The greater *endo*-selectivity is attributable to much stronger secondary orbital interactions, also resulting from a smaller HOMO-LUMO gap:

endo TS – free acrolein



Conclusion: Lewis acid activation of the dienophile (lowering of LUMO energy) increases both the rate and the *endo*-selectivity of Diels-Alder reactions