

CHEM 330

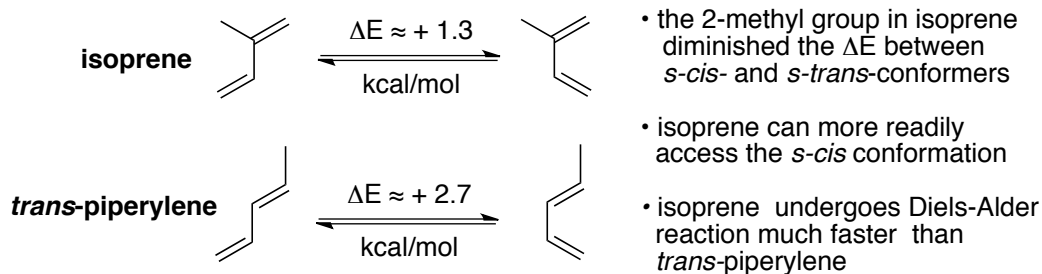
Topics Discussed on Nov. 27

1. Conformational aspects - II:

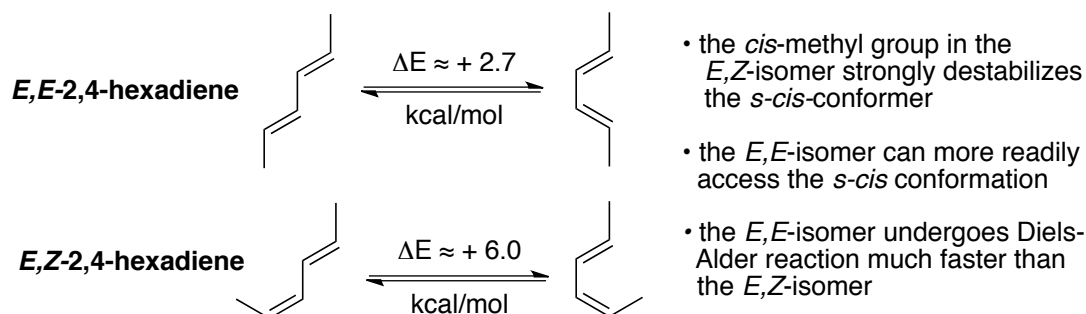
Consequences of the requirement for an *s-cis* diene conformation in a Diels-Alder reaction:

- The more readily an acyclic diene can attain the *s-cis*-conformation, the faster it undergoes Diels-Alder reaction:

i. isoprene vs. trans-piperylene



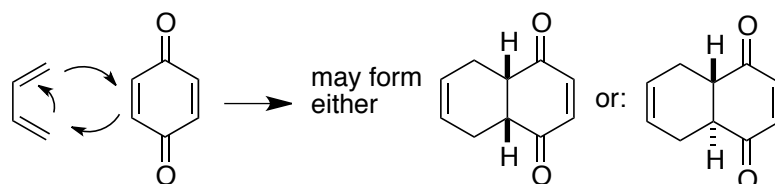
i. E,E- vs. E,Z-2,4-hexadiene



The Diels Alder reaction as a $4\pi + 2\pi$ cycloaddition

2. Stereochemical aspects:

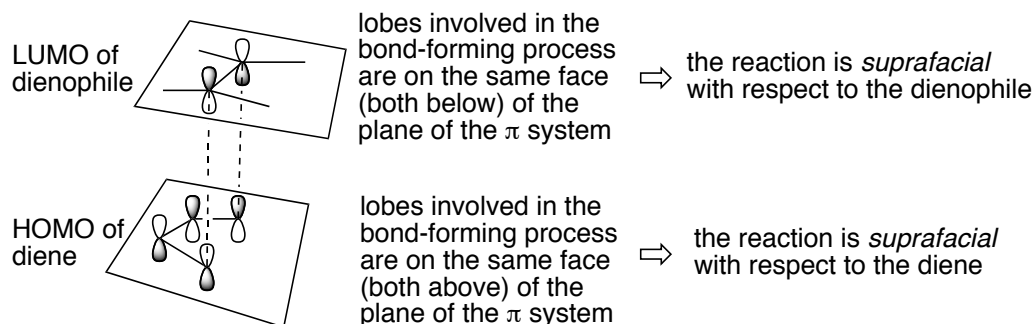
A Diels-Alder reaction leads to a cycloadduct that could be obtained in two diastereomeric forms. Consider the reaction of 1,3-butadiene with 1,4-benzoquinone:



which product does actually form?

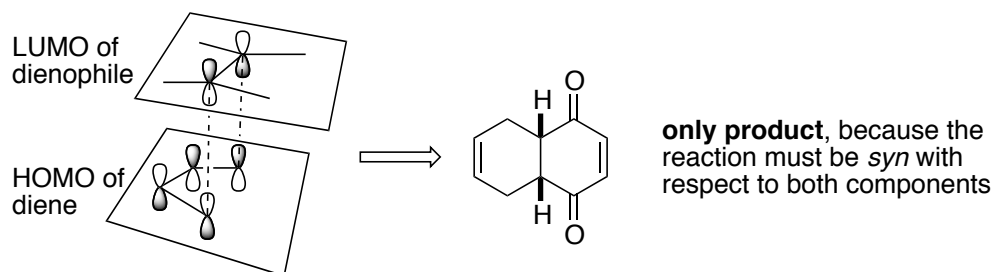
important: we are only concerned about *relative* configurations. i.e., *diastereoselectivity*. obviously, chiral molecules will form as racemates

Addressing the foregoing problem using FMO theory: details of the interaction between the HOMO of the diene and the LUMO of the dienophile:



reminder: constructive orbital interaction requires the overlap of lobes of identical phase

One may thus predict that the reaction will be strictly *suprafacial* (= *syn*) with respect to both diene and dienophile, meaning that each component interacts with the other by utilizing lobes of the p-type orbitals composing the π system that are situated on the *same face* (top or bottom) of the respective molecular planes

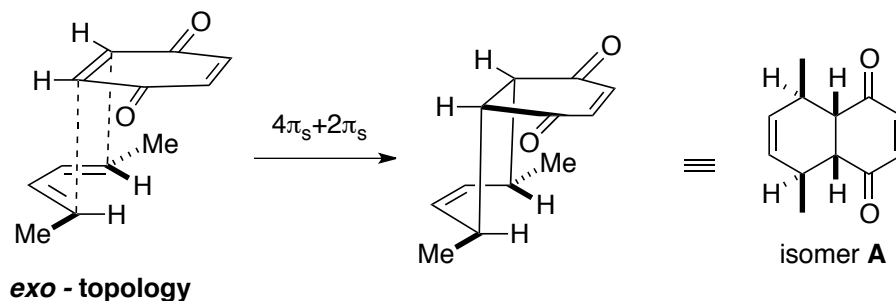


The Diels-Alder reaction (and related processes) as a $4\pi_s + 2\pi_s$ cycloaddition

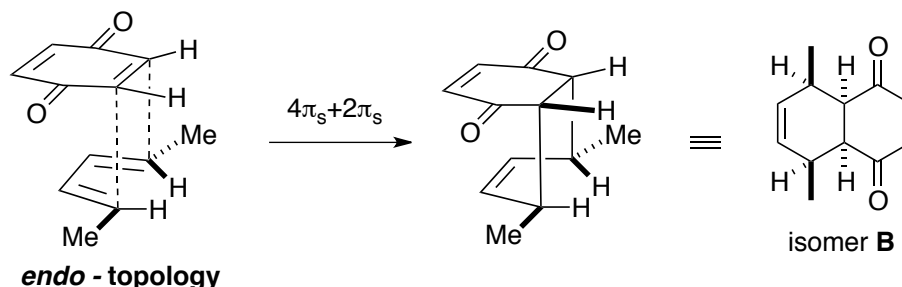
3. Topological aspects of the Diels-Alder reaction:

Principle: a $4\pi_s + 2\pi_s$ cycloaddition can occur with *two* different topologies, leading to two diastereomeric forms of the cycloadduct.

Example: the reaction of benzoquinone (very electron-deficient, highly reactive dienophile) with (*E,E*)-2,4-hexadiene:

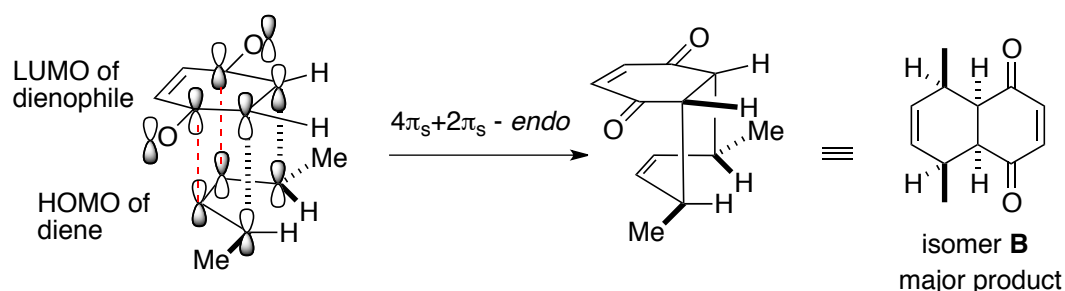


In the *exo* (= "outside") mode of reactivity, the bulk of the dienophile occupies a region of space that is *external* to that occupied by the diene (and viceversa).

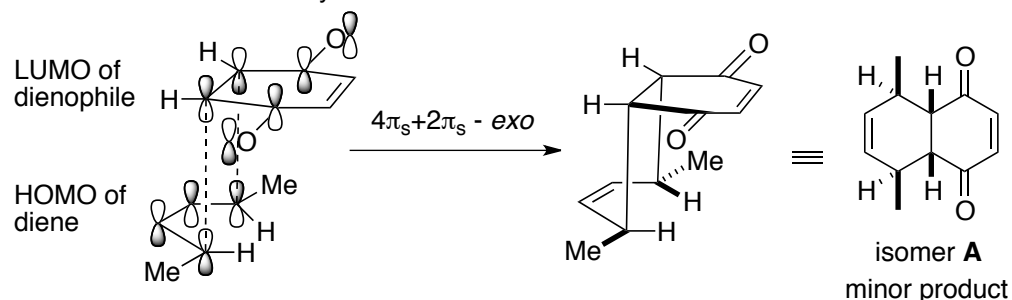


In the *endo* (= "inside") mode of reactivity, the bulk of the dienophile occupies a region of space that is *internal* to that occupied by the diene (and viceversa).

Principle: the *exo* topology is favored on steric grounds (less steric compression), but the *endo* topology is favored on electronic grounds, probably due to **secondary orbital interactions**:



black dashed lines: primary orbital interactions. These are responsible for bond formation.
red dashed lines: secondary orbital interactions. These assist bond formation



no possibility of secondary orbital interactions

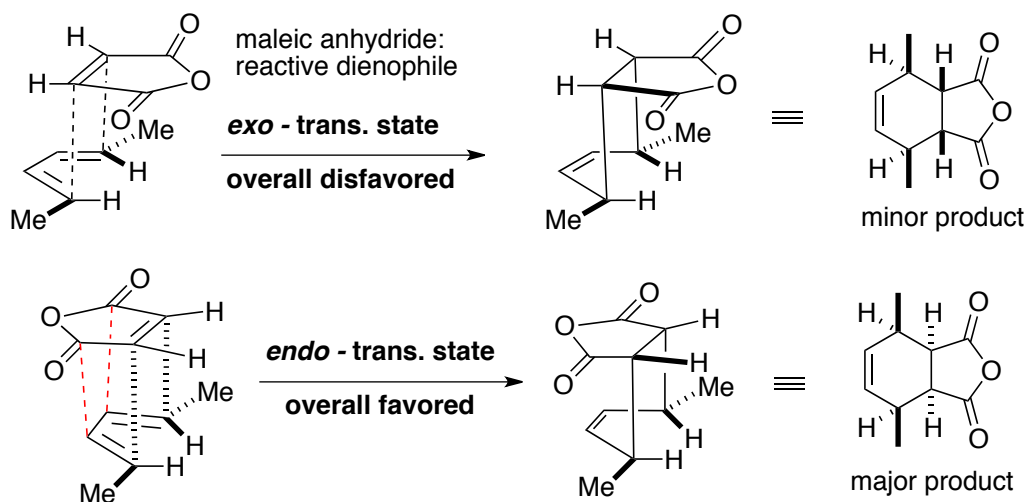
Principle: secondary orbital interactions are believed to promote the cycloaddition process by "compacting" the diene-dienophile complex, and by providing additional electron delocalization. As a consequence, diene and dienophile are "compressed together" during an *endo*-Diels-Alder reaction, and the total electronic energy of the diene-dienophile complex is lowered, resulting in a significant rate acceleration.

note: explanations other than those involving secondary orbital interactions have been advanced for the *endo* preference in Diels-Alder reactions. The relative merits of the various explanations are a matter of scientific controversy.

Description of the Diels-Alder reaction as a $4\pi_s + 2\pi_s$ *endo* cycloaddition

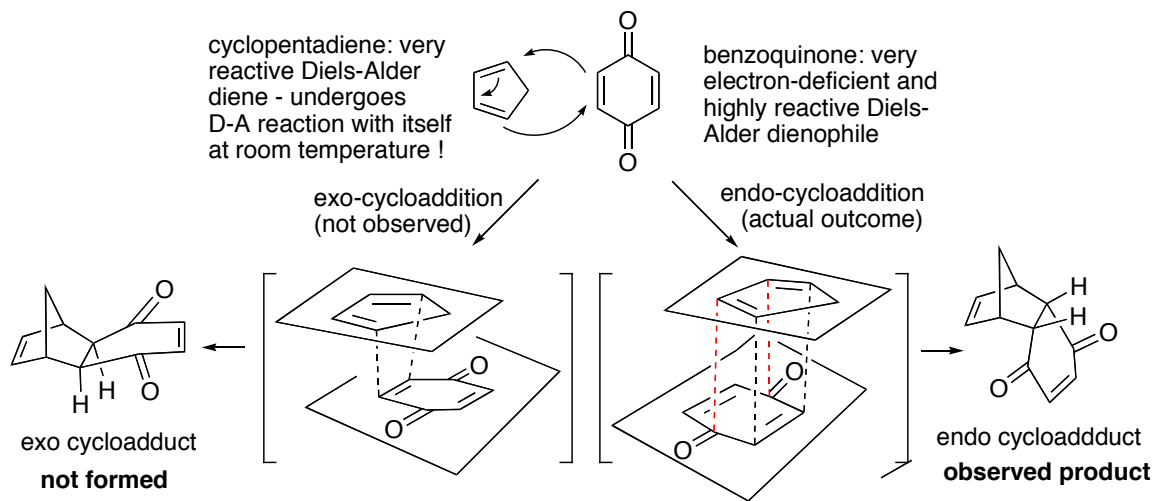
Stereochemical consequences of the *endo* preference of the Diels-Alder reaction:

- The reaction of maleic anhydride (very electron-deficient, highly reactive dienophile) with E,E-2,4-hexadiene:



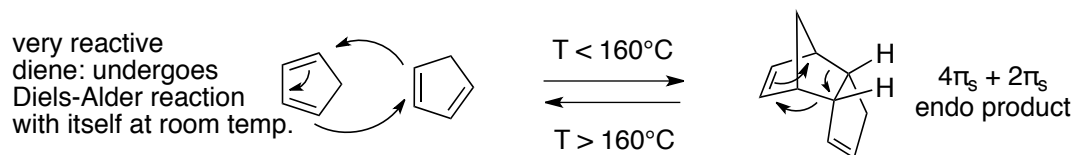
black: primary orbital interaction
red: secondary orbital interaction

- The reaction of benzoquinone (very electron-deficient, highly reactive dienophile) with cyclopentadiene (highly reactive Diels-Alder diene):



black: primary orbital interaction
red: secondary orbital interaction

Reversibility of the Diels-Alder reaction at sufficiently high temperatures: case of cyclopentadiene monomer-dimer equilibrium:



Reversibility of certain Diels-Alder reactions even at / near room temperature: the case of furan

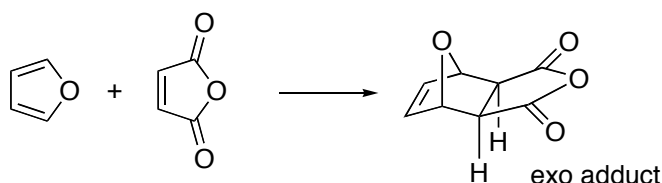


furan

- weakly aromatic character of furan
- slightly positive ΔG for the Diels-Alder reaction of furan with various dienophile
- facile reversibility of the process

Principle: in general, Diels-Alder *endo* cycloadducts are less thermodynamically favorable (= more energetic) than *exo* cycloadducts

Principle: a hypothetically reversible Diels-Alder reaction might produce the more thermodynamically favorable *exo*-cycloadduct: the case of furan + maleic anhydride:

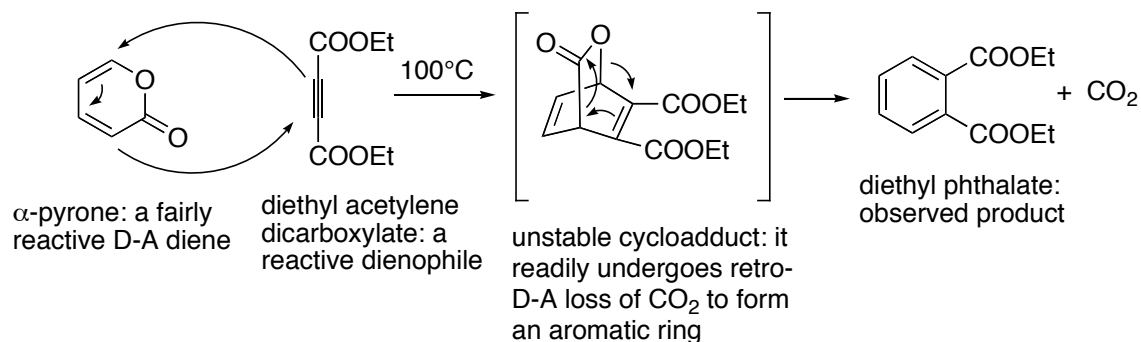


- rapid equilibration of furan and maleic anhydride with the less thermodynamically favorable *endo* adduct at room temperature
- facile reversibility of the process
- accumulation of the more thermodynamically favorable *exo* adduct

The preference for the *endo* topology in the Diels-Alder reaction as a **kinetic** effect

the reversibility of the D-A reaction of furan results in a switch from kinetic to thermodynamic control

Facile occurrence of reverse Diels-Alder reactions that involve the expulsion of a small, highly thermodynamically stable molecule such as SO_2 , CO_2 , N_2 ; e.g.:



Interest of the above reactions in the synthesis of complex aromatic compounds