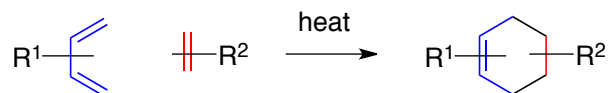# CHEM 330

Topics Discussed on Nov. 25

A typical cycloaddition process leading to C–C bond formation: the **Diels-Alder reaction** between an appropriately substituted 1,3-butadiene and an alkene:

R^1, R^2 : generic substituents connected to any C atom of the reactants

The Diels-Alder reaction as a powerful transformation for the construction of carbon architectures of the type found in molecules of biomedical interest, particularly when combined with the methods discussed earlier in the course

Description of the mechanism of the Diels-Alder reaction as a pericyclic movement of six electrons:
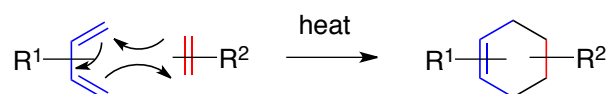
R^1, R^2 : generic substituents connected to any C atom of the reactants

The Diels-Alder reaction as a concerted process; i.e., one that *does not* involve reactive intermediates (ions / radicals), and in which the product forms in a single kinetic step
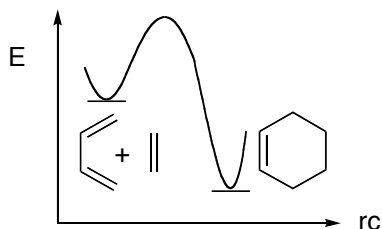
compare the above with the case of other, multistep ring-forming processes such as the aldol-dehydration sequence of a Robinson annulation:
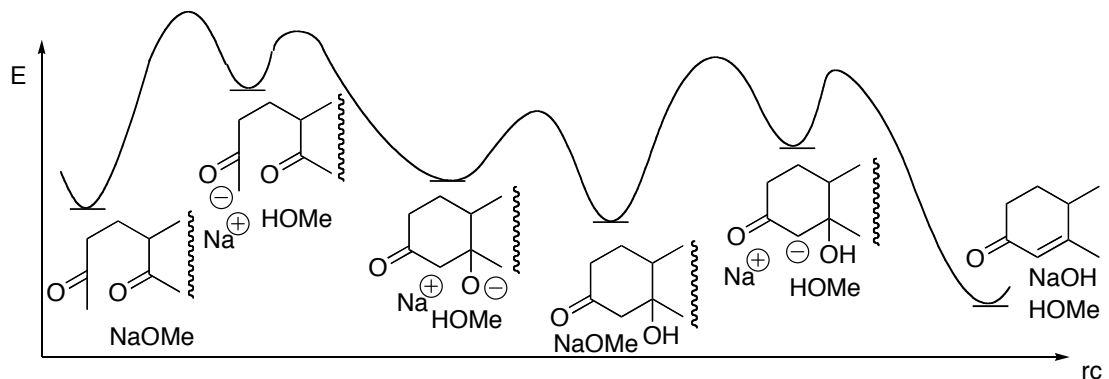
Dienophile: the "diene-loving" olefin that combines with the diene during a Diels-Alder reaction

Cycloadduct: the product of a cycloaddition reaction, e.g., of a Diels-Alder reaction
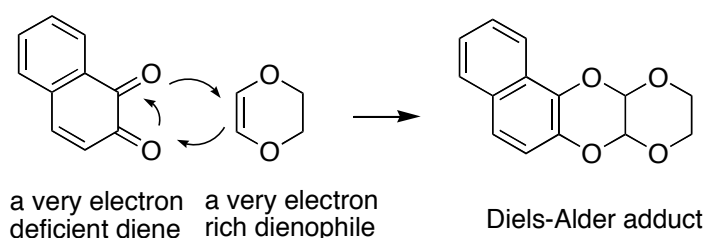
Principle: in a Diels-Alder reaction, and indeed in **any** reaction, electrons must flow from populated $\pi_{C=C}$ molecular orbitals of one component into vacant $\pi^*_{C=C}$ molecular orbital of the other component, and viceversa. Therefore, one can favor the process by creating a "voltage difference" between the components, i.e., by making one component electron-rich and the other electron-deficient

Substitution of Diels-Alder components with electron-donating (OMe, OSiR$_3$, NMe$_2$, alkyl, ...) or electron-withdrawing (C=O, CN, SO$_2$R, NO$_2$, ...) groups in order to make them electron-rich or electron-deficient

Regular demand Diels-Alder reactions: those in which the diene is electron rich and the dienophile is electron-deficient, e.g.:

butadiene: a
fairly electron
rich diene

benzoquinone:
a very electron
deficient dienophile

Diels-Alder
product
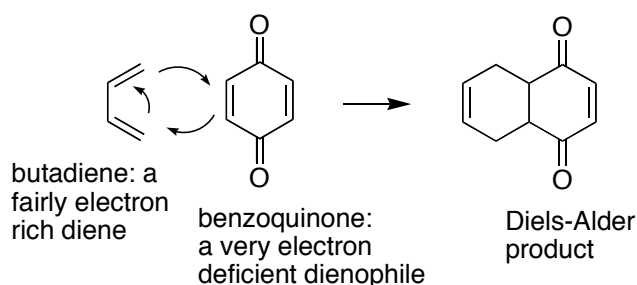
Inverse demand Diels-Alder reactions: those in which the diene is electron-deficient and the dienophile is electron-rich, e.g:

a very electron   a very electron
deficient diene   rich dienophile

Diels-Alder adduct

Historical primacy of regular-demand Diels-Alder reactions

Principle: during a Diels-Alder reaction, electrons must flow from one component of the reaction to the other, through appropriate orbital interactions. Accordingly, all of the following key aspects of the Diels-Alder reaction are defined by the details of how the molecular orbitals of one component interact with those of the other:

     i. **conformational**: which conformation(s) of the diene promote the reaction

     ii. **stereochemical**: relative configurations of newly formed stereocenters

     iii. **topological**: relative faciality of diene / dienophile interaction

     iv. **regiochemical**: relative orientation of diene and dienophile during the reaction
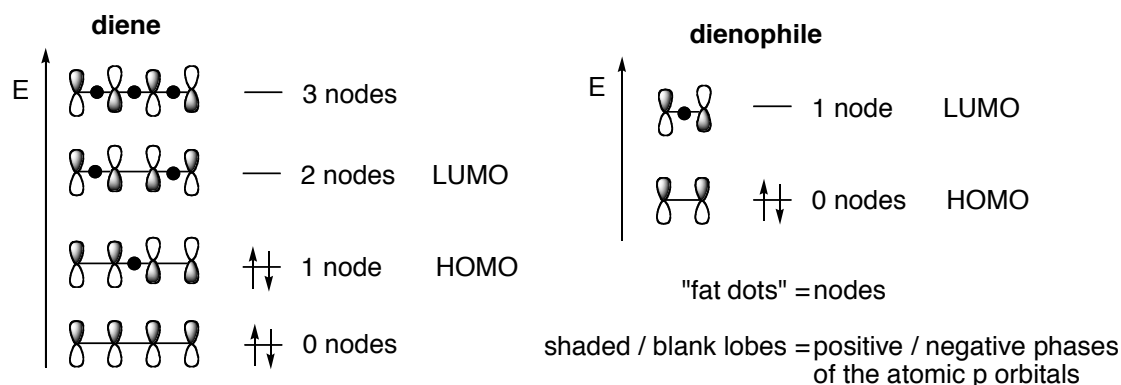
v. **kinetic**: how structure affects reactivity

Principle: the analysis of the interaction between the molecular orbitals of the diene and those of the dienophile during a Diels-Alder reaction is complex, but it may be simplified by considering just the interaction of the **Frontier Molecular Orbitals** (FMO's)

Frontier molecular orbitals: the **H**ighest **O**ccupied **M**olecular **O**rbital (HOMO) and **L**owest **U**noccupied **M**olecular **O**rbital (LUMO) of a molecule

The Fukui principle: in *any* reaction, the molecular orbital-based treatment of chemical reactivity may be simplified by considering just the interaction between the HOMO of the electron-rich component with the LUMO of the electron-deficient component

Frontier molecular orbital (FMO) theory: a simplified treatment of chemical reactivity based on an analysis of HOMO(electron-rich component)-LUMO(electron-deficient component) interaction

Molecular π orbitals of diene and dienophile components of a Diels-Alder reaction:

diene   **dienophile**

E ┃   [orbital diagram] ── 3 nodes   E ┃   [orbital diagram] ── 1 node   LUMO

      [orbital diagram] ── 2 nodes   LUMO   [orbital diagram] ↑↓ 0 nodes   HOMO

      [orbital diagram] ↑↓ 1 node   HOMO

      [orbital diagram] ↑↓ 0 nodes   "fat dots" = nodes

                                                          shaded / blank lobes = positive / negative phases
                                                                        of the atomic p orbitals

Symmetric molecular π orbitals: those in which the component p-type atomic orbitals located at the terminal positions of the π molecular orbital have identical phases

>   For example (molecular orbital diagram above), the LUMO of the diene and the
>   HOMO of the dienophile are symmetric orbitals

Antisymmetric molecular π orbitals: those in which the component p-type atomic orbitals located at the terminal positions of the π molecular orbital have opposite phases

>   For example (molecular orbital diagram above), the HOMO of the diene and the
>   LUMO of the dienophile are antisymmetric orbitals

Key molecular orbital interaction during a regular demand Diels-Alder reaction (=electron rich diene + electron-deficient dienophile): HOMO(diene) – LUMO(dienophile)

The Diels-Alder reaction as one that involves the interaction of 4 π electrons associated with the diene and 2 π electrons associated with the dienophile; therefore, a 4π+2π cycloaddition

FMO analysis of regular-demand Diels-Alder reactions (electron-rich diene reacting with electron-deficient dienophile):

Because electrons must flow from the diene to the dienophile, the most significant orbital interaction will be the one between the HOMO of the diene (populated by electrons that can most readily be displaced toward an acceptor) and the LUMO of the dienophile (vacant orbital that can accommodate additional electrons).

LUMO
of dienophile   bond-forming interactions
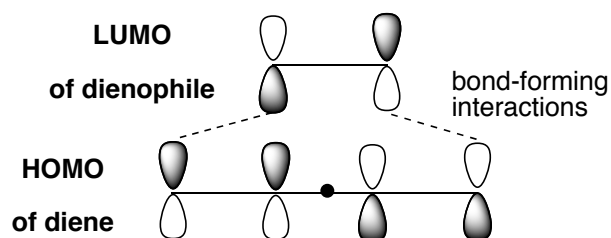
HOMO
of diene

Notice that HOMO$_{(diene)}$ and LUMO$_{(dienophile)}$ are both antisymmetric orbitals.

Moreover, the HOMO$_{(diene)}$ – LUMO$_{(dienophile)}$ interaction causes the termini of the diene to become bonded to the termini of the dienophile. This requires that p orbitals associated \ with the terminal atoms of both components interact through lobes of like phase
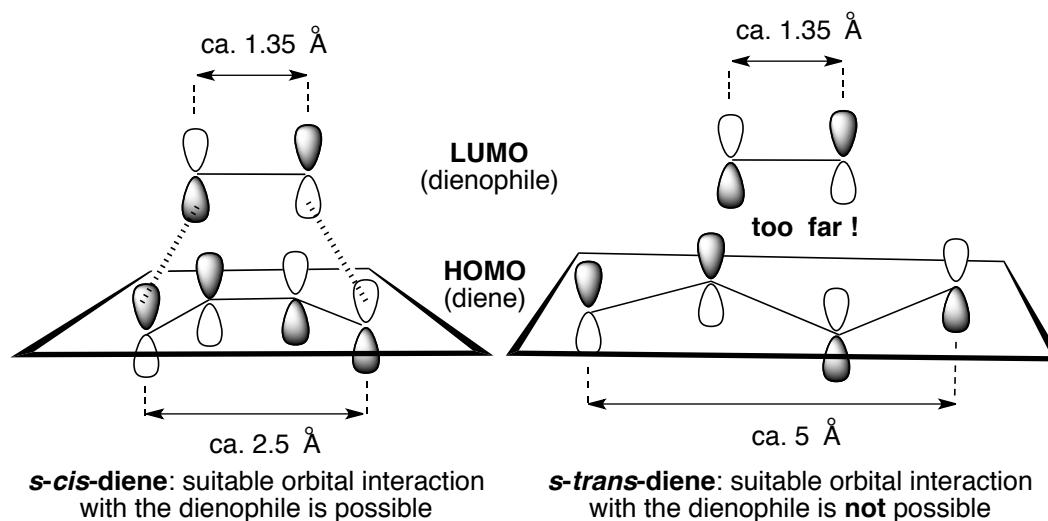
1. Conformational aspects of the Diels-Alder Reaction:

Preference for a planar conformations of dienes to ensure maximum extent of π conjugation

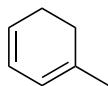The *s-cis* and *s-trans* conformations of a diene:

ΔE ≈ + 2.5 kcal/mol

unfavorable interaction

s-trans conformer
less energetic

s-cis conformer
more energetic

Requirement for an *s-cis* conformation of the diene in order to induce a Diels-Alder reaction:

ca. 1.35 Å

ca. 1.35 Å

LUMO
(dienophile)

too far !

HOMO
(diene)

ca. 2.5 Å

ca. 5 Å

s-cis-**diene**: suitable orbital interaction with the dienophile is possible

s-trans-**diene**: suitable orbital interaction with the dienophile is **not** possible
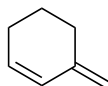
Consequences of the requirement for an s-*cis* diene conformation in a Diels-Alder reaction:

 • Dienes locked in an *s-trans*-conformation cannot undergo Diles-Alder reaction:

undergoes
Diels-Alder
reaction

does not undergo
Diels-Alder reaction
because it cannot
attain an *s-cis* conf.

s-cis-type diene   *s-trans*-type diene