Chapter 6

Pericyclic Reactions and Tools to determine Reaction Mechanisms

The goal of this chapter:

- draw molecular orbital diagrams of simple organic molecules
- using molecular orbital theory to determine whether a pericyclic reaction is thermally or photochemically allowed
- gain an understanding of kinetic isotope effects and how they and other tools can be used to determine reaction mechanisms

π-MO Diagrams

π-orbitals are “simple”:

- Construct the symmetry allowed combinations of atomic p_z-orbitals
- Substituents are treated as “perturbations”:
  - ➢ Increase/decrease the lobes of the unsubstituted hydrocarbon

The frontier molecular orbitals (FMOs, *i.e.*, HOMO and LUMO) are sufficient

FMOs are powerful: Predict the reaction conditions (thermal, photochemical) and stereoselectivity!

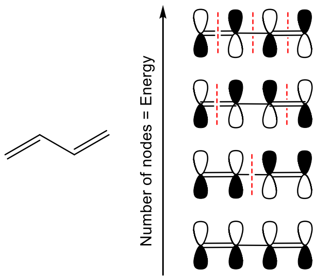
Recall: Energy of the MOs increases with the number of nodes

Example:
Alkenes are straightforward

*General **Hückel** solution for acyclic systems*

n= number of atoms
k = 1, 2 ,3

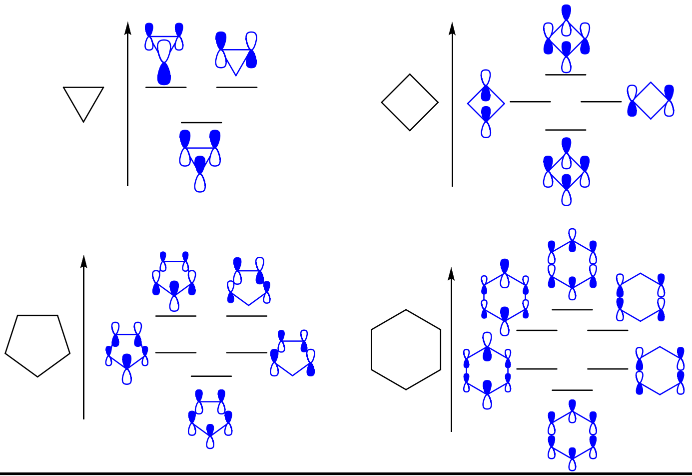
$$\boxed{E_k = \alpha + 2\beta\cos\frac{k\pi}{(n+1)}}$$



π-MO Diagrams of Cyclic Alkenes

Rule of thumb (or of symmetry, see later):
Draw the skeleton structure with a vertex on the bottom

- ➢ The positions of the carbon atoms indicate the spacing of the MOs

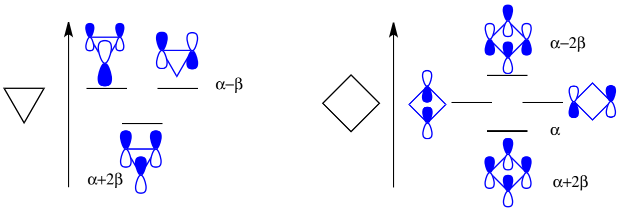


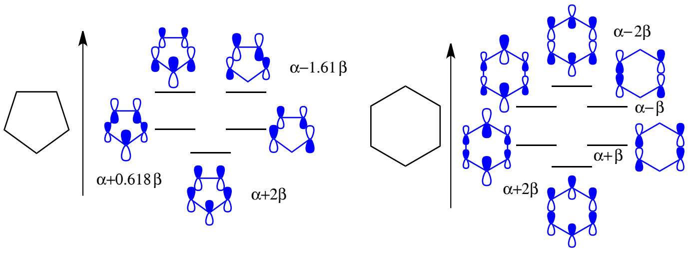
π-MO Diagrams of Cyclic Alkenes

*General **Hückel** solution for cyclic systems*

$$\boxed{E_k = \alpha + 2\beta\cos\frac{2k\pi}{(n)}}$$

n= number of atoms
k = 0, ±1, ±2…±*l* for even *n* *n=2l*
k = 0, ±1, ±2…±*l* for odd *n* *n=2l+1*



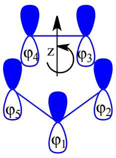


π-MO Diagrams of Cyclic Alkenes

What about the shape (relative signs and sizes) of the lobes?
Group theory gives the shapes:

Example: π-MO of $C_5H_5^-$
Use the pure cyclic groups, i.e., C_5 symmetry and not the full symmetry (D_{5h})
The character table is:

	E	C_5	$(C_5)^2$	$(C_5)^3$	$(C_5)^4$
A	1	1	1	1	1
E_1	1	e	e^2	e^{2*}	e^*
	1	e^*	e^{2*}	e^2	e
E_2	1	e^2	e^*	e	e^{2*}
	1	e^{2*}	e	e^*	e^2



e=exp(2πi/5) = cos(2π/5)+i sin(2π/5) (Euler relation)
Therefore: e ≈ 0.31+0.95i; e* ≈ 0.31-0.95i; e^2 ≈ -0.81+0.59i; e^{2*} ≈ -0.81-0.59i

Pick one p_z (ϕ_1) orbital and perform the symmetry operations

	E	C_5	$(C_5)^2$	$(C_5)^3$	$(C_5)^4$
φ_1	φ_1	φ_2	φ_3	φ_4	φ_5

π-MO Diagrams of Cyclic Alkenes

		E	C_5	$(C_5)^2$	$(C_5)^3$	$(C_5)^4$
A		1	1	1	1	1
E_1	e_1	1	e	e^2	e^{2*}	e^*
	e_1'	1	e^*	e^{2*}	e^2	e
E_2	e_2	1	e^2	e^*	e	e^{2*}
	e_2'	1	e^{2*}	e	e^*	e^2
	$\Gamma\varphi_1$	φ_1	φ_2	φ_3	φ_4	φ_5

"Symmetry adapted linear combinations"
A is simple (the first factor is the normalization):
$\pi^A=(1/\sqrt{5})(1\ \varphi_1+1\ \varphi_2+1\ \varphi_3+1\ \varphi_4+1\ \varphi_5)$
This is the fully symmetric π-orbital (lowest in energy)
The degenerate e_1 and e_1' components of E_1 are:
$e_1= 1\ \varphi_1+(0.3+1.0i)\ \varphi_2+(-0.8+0.6i)\ \varphi_3+(-0.8-0.6i)\ \varphi_4+(0.3-1.0i)\ \varphi_5$
$e_1'= 1\ \varphi_1+(0.3-1.0i)\ \varphi_2+(-0.8-0.6i)\ \varphi_3+(-0.8+0.6i)\ \varphi_4+(0.3+1.0i)\ \varphi_5$
when rounding all numerical values to 1 decimal place.

The linear combinations allow for real valued MOs:

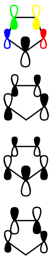
$$e_1 + e_1' \longrightarrow \frac{1}{\sqrt{2^2+2\cdot(0.6^2+1.6^2)}}(2\varphi_1+0.6\varphi_2-1.6\varphi_3-1.6\varphi_4+0.6\varphi_5)$$

$$e_1 - e_1' \longrightarrow \frac{1}{\sqrt{2\cdot(1.9^2+1.2^2)}}(1.9\varphi_2+1.2\varphi_3-1.2\varphi_4-1.9\varphi_5)$$

Applying the same principle to E_2 leads to:

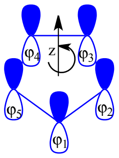
$$e_2 + e_2' \longrightarrow \frac{1}{\sqrt{2^2+2\cdot(1.6^2+0.6^2)}}(2\varphi_1-1.6\varphi_2+0.6\varphi_3+0.6\varphi_4-1.6\varphi_5)$$

$$e_2 - e_2' \longrightarrow \frac{1}{\sqrt{2\cdot(1.2^2+1.9^2)}}(1.2\varphi_2-1.9\varphi_3+1.9\varphi_4-1.2\varphi_5)$$



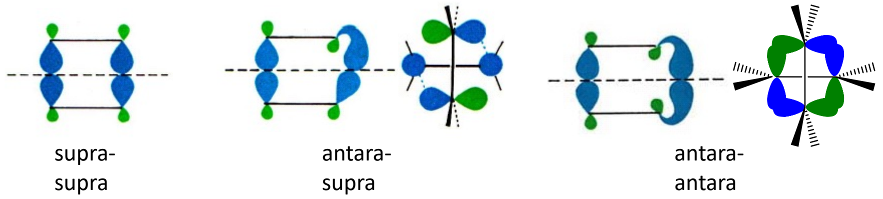
1 net
bonding
interaction

2 net
anti-bonding
interaction



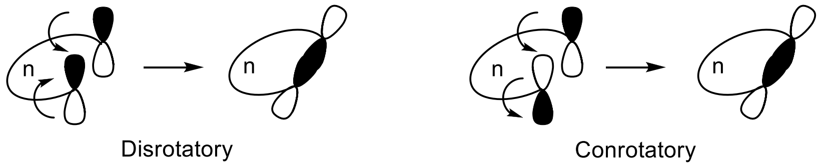
General Definitions for Pericyclic Reactions

Supra- /Antarafacial and Con-/Disrotatory



The components for a reaction are the parts of the molecule that undergo a change during a pericyclic reaction.

Which pericyclic reactions occur in the ground state?
Reactions formally allowed might be geometrically unfavourable



R.B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed.* **1969**, *8*, 781.

General Rules for Pericyclic Reactions

Pericyclic reactions are concerted and hence do not show any (radical) intermediates.

A ground-state pericyclic change is symmetry-allowed when the total number of (4q+2)supra and (4r)antara components is odd.

q and r are integers
Reactions allowed in the ground state are forbidden in the excited state and vice versa.

Conditions:
a) The geometry must be physically realizable
b) Non-participating bonds do not interfere

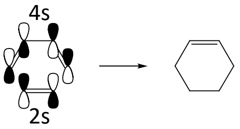
Violations?
There are none!

Pericyclic Reactions

A ground-state pericyclic change is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ electron components is odd.

This means that any 2-, 6-, 10-, 14-electron, etc. suprafacial component is considered, and any 0-, 4-, 8-, 12-electron, etc. antarafacial component is considered when determining if there are an odd number for the reaction under consideration.

Examples:

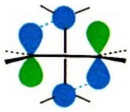


1. Cycloadditions, e.g. Diels-Alder reactions are $4\pi^s + 2\pi^s$
applying the general rule:
1 × 2s component
0 × 4a component
Sum is 1 ⟶ the reaction is **symmetry-allowed** in the ground state

For the $2\pi^s + 2\pi^s$ cycloaddition: 2 × 2s component
Sum is 2 ⟶ the reaction is symmetry-forbidden in the ground state
but the $2\pi^a + 2\pi^s$ cycloaddition:

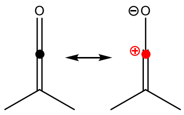
The Rare Case of Thermal [2+2] Cycloadditions

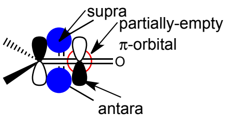
The $2\ \pi^s + 2\ \pi^a$ reaction is symmetry allowed - but does not readily occur:
1 × 2s component, sum is **1**.

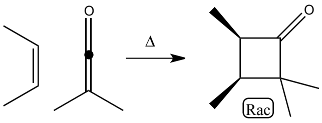


The product would be highly strained, as the two reactants are perpendicular to each other

Ketenes have considerably less steric hindrance and a low lying quasi-empty p-orbital perpendicular to the reacting double bond.
The $2\pi^s + 2\pi^a$ reactions of ketenes are indeed observed experimentally



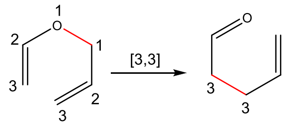




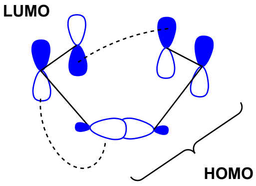
Pericyclic Reactions

A ground-state pericyclic change is symmetry-allowed when the total number of (4q+2)s and (4r)a components is odd.

2. **Sigmatropic rearrangements** are denoted by [i,j], where i and j refer to the position of the new σ-bond relative to the old one



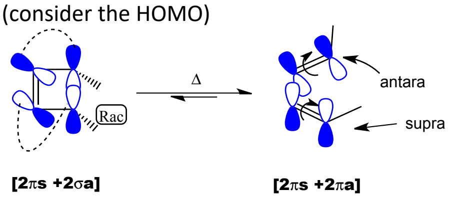
Which frontier orbitals to set up?
One way is to consider a 4s+2s reaction.



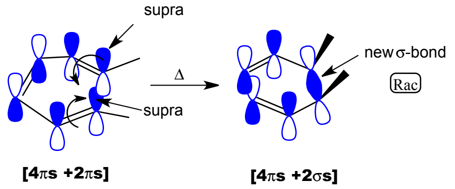
MOs at the Origin of the Woodward-Hoffmann Rules

3. Electrocyclic Ring-opening/closing of cycloalkenes:

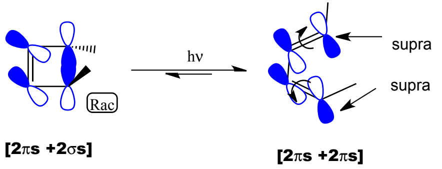
4*n* π conrotatory in the ground-state (consider the HOMO)



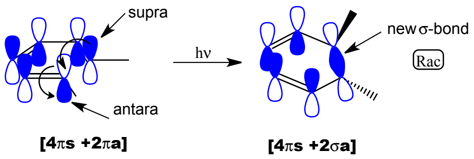
4*n*+2 π disrotatory in the ground-state



4n π disrotatory in the excited state (consider the LUMO)



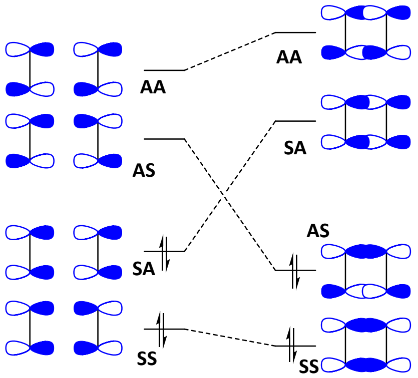
4n+2 π conrotatory in the excited state



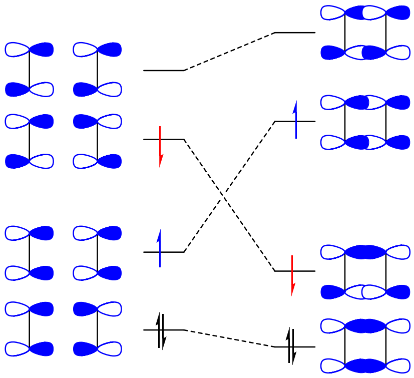
All the reactions are highly stereoselective!

[2+2] Cycloadditions: correlation diagram

MO diagrams give a more complete picture than the simple FMO picture
Example: Why is the 2 π^s, 2 π^s cycloaddition of ethylene forbidden in the ground state but allowed in the excited state?



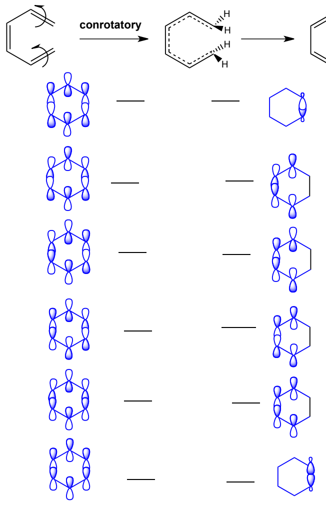
No direct connection between the two ground states

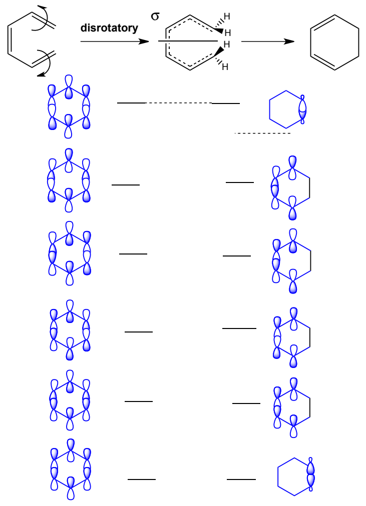


A direct connection between the two excited states exists but is energetically unfavorable

Quiz on correlation diagrams

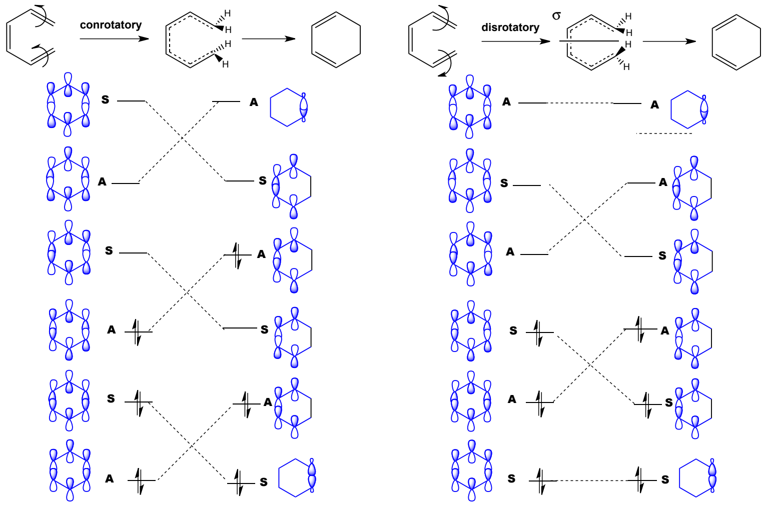
Develop an orbital symmetry correlation diagram for the hexatriene-cyclohexadiene interconversion by considering both conrotatory and disrotatory processes.





Quiz on correlation diagrams

Develop an orbital symmetry correlation diagram for the hexatriene-cyclohexadiene interconversion by considering both conrotatory and disrotatory processes.



Determination of reaction mechanisms

To understand and improve chemical reactions, chemists need to know their mechanisms.

Mechanisms indicate the detailed path followed by all atoms of the species involved in going from reactants to products.

The only way to validate a mechanism or to pick among mechanistic hypothesis is to probe its consistency with respect to experiments; however the entire hypothesized mechanism is not the ultimate truth!

Two of the most common methods to probe reaction mechanisms are described hereafter. Those methods may complement computational investigations (see Chapter **5**).

Kinetic Studies

First tool to determine reaction mechanisms: kinetic studies

➡ Monitor rate of reaction as a function of:

- concentrations of reactants
- solvent
- temperature…

Obtain reaction order, first indication on how many and which molecules are involved in the rate-determining step.

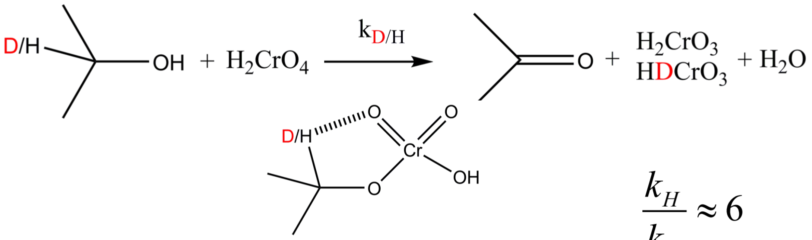
Using appropriate kinetic studies, insight can be gained on the number of reaction steps, of species involved, on activation parameters…

Kinetic Isotope Effects

Kinetic studies: no information on which bond is broken or formed.

➡ Use kinetic isotope effects!

Isotopic substitution can influence reaction kinetics:



$$\frac{k_H}{k_D} \approx 6$$

Reaction with H proceeds 6 times faster than with D!

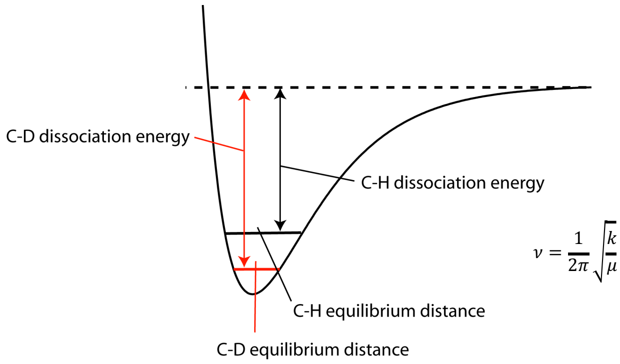
Large effect = direct participation of H in the reaction

Primary kinetic isotope effect

Kinetic Isotope Effects

Isotopes differ in principle only by their mass and have the same chemical reactivity.

However, X-H and X-D bonds have different lengths and dissociation energies!



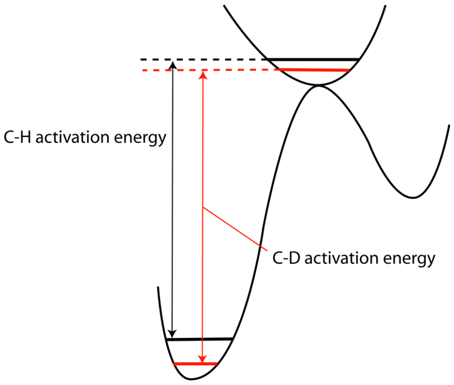
$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}}\ , \mu = \frac{m_1 m_2}{m_1 + m_2}$$

Different mass for D: different vibrational frequency and hence different zero-point energies.

Kinetic Isotope Effects

Difference in ZPE is bigger for larger force constants.

Lower force constant for TS ➡ Difference in activation energy for D and H



Generally:

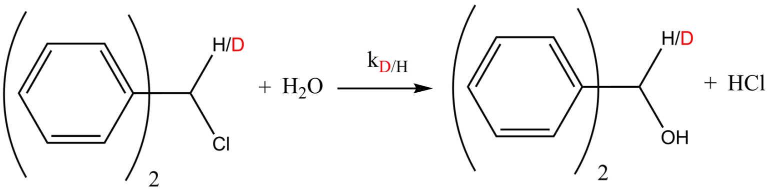
$\frac{k_H}{k_D} > 1$ Force constant of the bond lower for TS than for reactant

$\frac{k_H}{k_D} < 1$ Force constant of the bond higher for TS than for reactant

$\frac{k_H}{k_D} = 1$ Force constant of the bond does not change

Kinetic Isotope Effects

Kinetic isotope effects are not only observed for reactions implying H directly:



$$\frac{k_H}{k_D} = 1.11$$

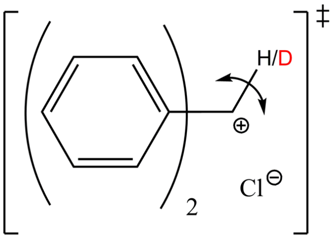
Smaller kinetic isotope effect because H is not directly involved.

Secondary kinetic isotope effect

Here, D is in α position to the reaction center: α-deuterium isotope effect.

Kinetic Isotope Effects

Transition state in this example is similar to carbocation:

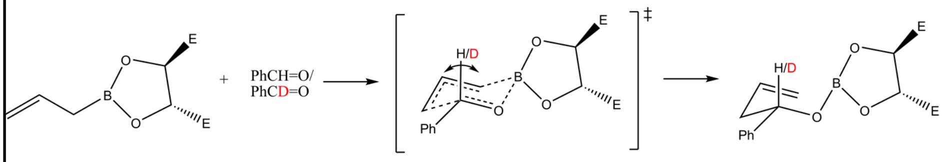


Force constant for out-of-plane bending vibration smaller in TS (sp^2) than in reactant (sp^3):

origin of this α-deuterium isotope effect.

Kinetic Isotope Effects

Example of inverse kinetic isotope effect:



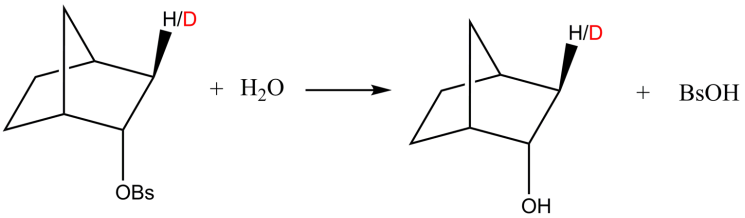
$$\frac{k_H}{k_D} = 0.74$$

Force constant for the indicated bending is higher in the TS: kinetic isotope effect lower than 1!

Change of hybridization at a carbon between TS and reactant can be monitored by isotopic substitution on this C.

Kinetic Isotope Effects

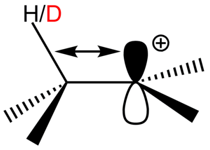
Kinetic isotope effects also occur for D in β position:



$$\frac{k_H}{k_D} = 1.19$$

β-deuterium isotope effect

C-D bond weakened at the TS due to hyperconjugation



For norbornane above, conformation is fixed so that hyperconjugation is maximal.

Kinetic Isotope Effects

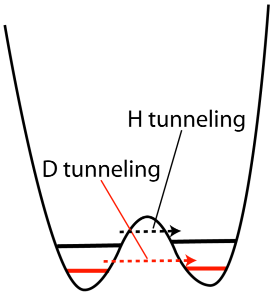
Primary kinetic isotope effects can be greatly enhanced by quantum mechanical tunneling.

$$k = QAe^{-E/RT}$$

$$Q = \frac{e^{\alpha}}{\beta - \alpha}(\beta e^{-\alpha} - \alpha e^{-\beta})$$

$$\alpha = E / RT$$

$$\beta = 2a\pi^2 (2mE)^{1/2} / h$$



Tunneling rate depends exponentially on mass and on barrier width

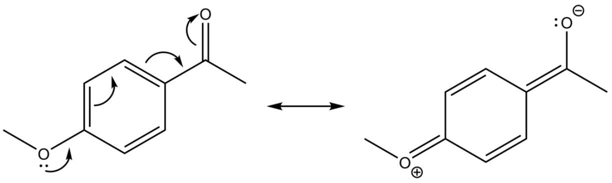
➡ $\frac{k_H}{k_D}$ can reach 50 or more!

Linear Free Energy Relationships

Instead of substituting an atom by a heavier isotope, entire fragments (substituents) can be added or substracted to a molecular system.

Substituents influence reaction rates through:

- Field effects (for charged, dipolar… substituents)
- Inductive effects (for electronegative substituents, etc.)
- Resonance effects (for π substituents, etc.)

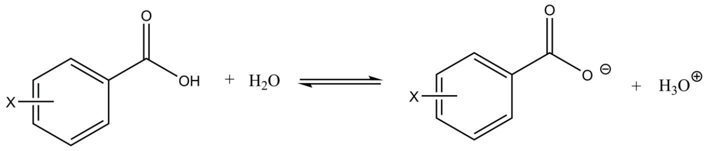


- Polarizability effects
- Steric effects
- Solvation effects

Linear Free Energy Relationships

To quantify the substituent effects, Linear Free Energy Relationships (LFER) can be used.

First, substituents should be characterized. Hammett defined a scale measuring substituent ability to influence acidity of benzoic acid:



X=H is taken as a reference, and all other substituent effects (in meta or para position) are measured relative to it:

$$\sigma_{m/p} = \sigma_{meta/para} = \log\left(\frac{K_X}{K_H}\right)$$

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Linear Free Energy Relationships

During the reference reaction, a negative charge builds up on the acid.

$\sigma_{m/p}$ measures substituent ability to donate or attract electrons and hence to destabilize or stabilize the negative charge.

$\sigma_{m/p} < 0$: electron donating group, destabilize negative charge

$\sigma_{m/p} > 0$: electron withdrawing group, stabilize negative charge

Values for a number of substituents are tabulated.

Note that $\sigma_{m/p}$ reflects the total electron donating/attracting ability, by induction or resonance, but **not** the direct stabilization by resonance of a negative charge!

In the reference reaction, negative charge **cannot** be stabilized directly by resonance.

See for example: D. H. McDaniel, H. C. Brown, *J. Org. Chem.*, **1958**, *23*, 420.

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Linear Free Energy Relationships

Using Hammett constants, the amount of negative or positive charge building up during a reaction can be probed.

For this, the reaction should be performed with different substituents and its kinetics measured.

Then, $\log(k_X/k_H)$ is plotted versus $\sigma_{m/p}$. Usually, a straight line is obtained and the slope ρ can be determined.

$$\log\left(\frac{k_X}{k_H}\right) = \rho\sigma_{m/p}$$

- If $\rho > 1$, the reaction is more sensitive to substituent effects than benzoic acid and more negative charge is building up.
- If $0 < \rho < 1$, the reaction is less sensitive than benzoic acid but still builds negative charge.
- If $\rho = 0$, the reaction show no substituent effect.
- If $\rho < 0$, the reaction builds positive charge.

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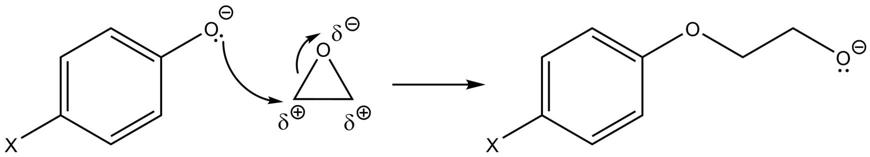
Linear Free Energy Relationships

Caution: ρ directly indicates the sensitivity of a reaction to substituent effects and not the charge!

The molecular structure and the distance between the substituents and the hypothetical location of the charge should always be considered.

Moreover, building up negative charge at the TS also corresponds to a decrease of positive charge at the TS, and vice-versa.



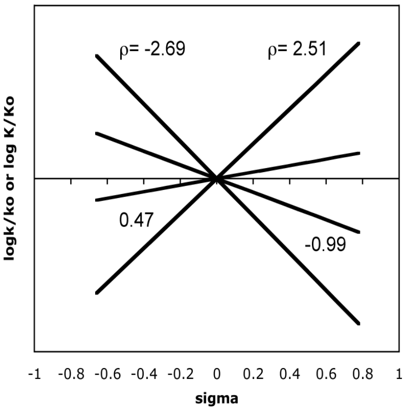
The above reaction gives $\rho = -0.95$. The reaction does not build positive charge but reduce negative charge on O.

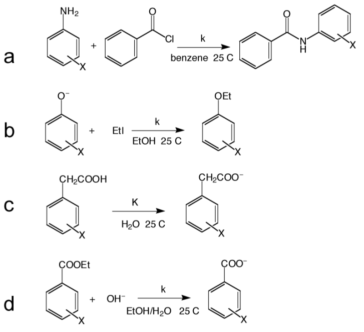
Value of ρ can help discriminate between mechanistic hypothesis with different charges.

Chapter 6

Linear Free Energy Relationships

Assign the following Hammett plots to the following reactions





Linear Free Energy Relationships

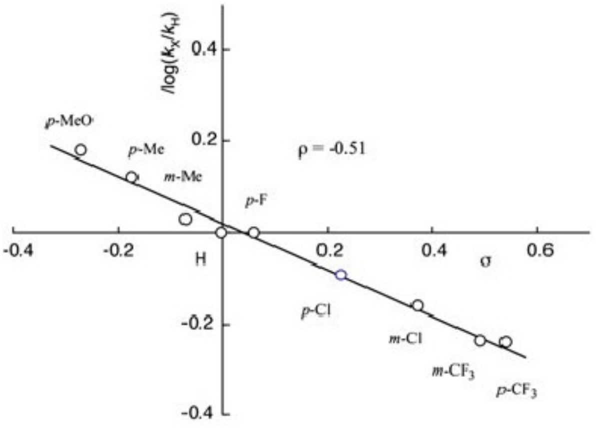
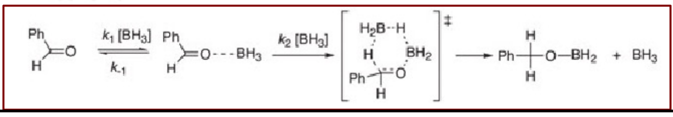


Figure 2. Hammett correlation of the BH_3 reduction of XC_6H_4CHO in THF at 25 °C



Linear Free Energy Relationships

The linearity of $\log\left(\frac{k_X}{k_H}\right) = f(\sigma_{m/p})$ is often observed, but not always.

Deviations from linearity can indicate:

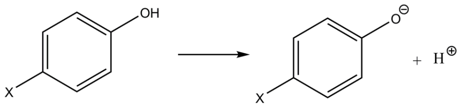
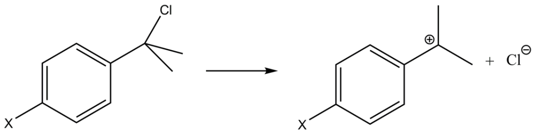
- that substituents induce a change of rate-determining step or of mechanism (abrupt change, curve can be fitted by two straight lines)
- that direct resonance stabilization of a charge is involved (often corresponds to scattered data in Hammett plot)

If direct resonance stabilization is thought to have a role, σ^+ and σ^- Hammett values can be used instead of σ_m and σ_p.

Linear Free Energy Relationships

σ^+ and σ^- are determined with reference reactions by comparison with X=H like $\sigma_{m/p}$.

Hammett plots with σ^+ or σ^- can be more linear, indicating resonance stabilization plays a role in the reaction under study.

Reference reaction	Index	Interpretation
	σ^-	Ability to stabilize a negative charge by resonance
	σ^+	Ability to stabilize a positive charge by resonance

Linear Free Energy Relationships

Different schemes aim at decomposing the Hammett constants to extract information about polarizability, sterics, induction…

For example,

- the Taft parameters are also based on reference reactions to characterize polar and steric effects of substituents

-Swain-Scott parameters characterize nucleophilicity…

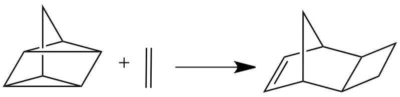
These parameters (and many more) can all be used in kinetic studies to assess the sensitivity of the reaction barrier to different substituent effects.

Outlook

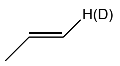
- Exploring reaction mechanisms is experimentally and computationally challenging except for the simplest reactions.
- Simple kinetic studies may help gather basic information about the reaction steps.
- Isotope substitution can provide precious and detailed information regarding bonds being broken and formed. The changes undergo by the molecular system are very small and will unlikely change the mechanism, but measurements may be difficult.
- Linear Free Energy Relationships (LFER) allow to assess substituent effects on the barrier heights and may discriminate between different mechanisms, but they imply significant modifications of the molecular system, which may be practically difficult and influence the mechanism under investigation.
- Many more techniques may be used to investigate a mechanism, notably to capture hypothetical intermediates. Only chemists imagination is a limit!
- Note that the above techniques probe only the rate-determining step.

Mini Quiz 9

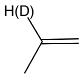
1. **Examine the following pericyclic reaction and characterize it using the electron count and suprafacial/antarafacial terminology. State if the reaction is allowed or forbidden based upon the generalized orbital symmetry rules.**



2. **The following isotope effects are found for the ozonolysis of various deuterium-substituted propenes. What do these isotope effects tell you about the mechanism?**



KIE=0.88



KIE=0.88

Mini Quiz 9

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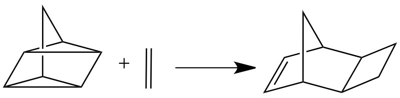

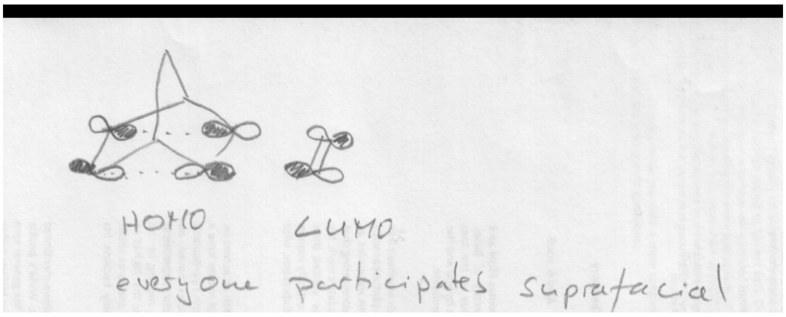

everyone participates suprafacial