

The University of Oklahoma Alternative Textbook Grant Course Lecture Slides Set

Advanced Organic Chemistry I

Mechanism and Reactivity



Fall 2024 / Chem 5400
Yuanning Feng | 冯元宁
The University of Oklahoma
Norman / Oklahoma / United States





Alternative Textbook Grant Disclosure



- The Alternative Textbook Grant (ATG) is an initiative of OU Libraries. Its primary goal is to compensate instructors for the work required to abandon costly, course materials in favor of open educational resources or other course materials free to students.
- All the course materials of this course will be free.
- Any commercial textbooks are not required. You can get an A just based on the lecture slides and assignments. I will share them digitally on Canvas.
- Following the rule of ATG, free materials can be only used with in the course and will be published by OU.



Course Information



Instructor: Yuanning Feng

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**Lecture: 25 September – 6 December
Monday and Wednesday 11:30-12:55 PM
Astellas Conference Room | SLSRC 3410/3430**

Office Hours: By Email Appointment

Credit Hours: this is a two-credit hour course starting in September 2024



Reference Books



"Organic Chemistry" Reference Book

K. P. C. Vollhardt & N. E. Schore, "Organic Chemistry – Structure and Function", 4th Ed. W. H. Freeman and Company

"Advanced Organic Chemistry" Reference Books

- 1. F. A. Carey & R. J. Sundberg, "Advanced Organic Chemistry Part A: Structure and Mechanisms", 5th Ed. Springer, 2007.**
- 2. J. March, "Advanced Organic Chemistry", 4th Ed. John Wiley & Sons, 1992.**
- 3. E. V. Anslyn & D. A. Dougherty, "Modern Physical Organic Chemistry", University Science Books, 2006.**



Keys to Effective Learning/Performance



- Be interactive to the **questions** on the class. Keep thinking while listening
 - What is a question on the class?
- Take good class notes and study them.
- Interrupt and ask **questions** during the lecture
- Solve homework problems and assigned exercises.
Discuss actively with your classmates.
Present your answers and thoughts to others
The exams will draw heavily from this material.
- Find a good topic for the **presentation**, make fruitful slides and present it clearly. Learn from others' presentations too.



Key Words



1. Valence bond theory and hybrid orbital theory
2. Electronegativity, resonance, conjugation, hyperconjugation
3. The basic concepts of molecular orbital theory and the construction of molecular orbitals
4. Hückel molecular orbital theory
5. Perturbative molecular orbital theory
6. Aromaticity and antiaromaticity

Goal

Be able to skillfully use different theories and methods to describe the structure of organic compounds and explain the physical properties and chemical reaction properties of compounds.



Recap the History



Leucippus (Greek Philosopher): the universe is composed of atoms and voids

Empedocles (Greek Philosopher): fire, earth, air, water and forces

17th – 18th century: the hook-and-eye model of “molecules”

Avogadro (1811): The smallest particles of gases are not necessarily simple atoms, but are made up of a certain number of these atoms united by attraction to form a single molecule. [elementary molecule (atoms), compound molecules, composite molecules]



Recap the History



Kekule (1865): benzene structure (carbon atoms are tetravalent) (**A. S. Couper; A. M. Butlerov; A. C. Brown; J. J. Loschmidt**)

van't Hoff and ***Le Bel*** (1884): carbon atoms are tetrahedral

Lewis (1916): a shared electron-pair bond (octet rule or the rule of 8)

London and ***Heitler*** (1927): valence bond treatment of H_2 using quantum mechanics

Pauling (1931): "*The Nature of the Chemical Bond*" (hybridization theory)

Hund & Mulliken (1930s) **Molecular Orbital Theory** and Methods (linear combinations of the atomic orbitals)



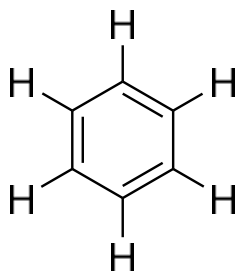
(1828 –1886) Russian Chemist

Structural theory (chemical structure with its modern meaning) (1860)



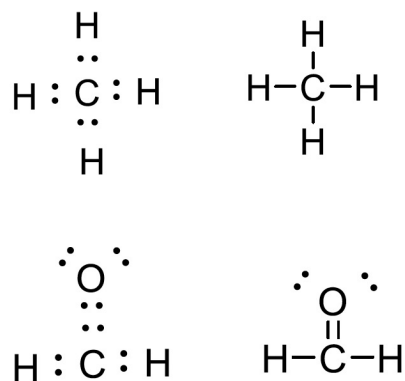
Butlerov Building, Kazan University

Kekule structure of benzene



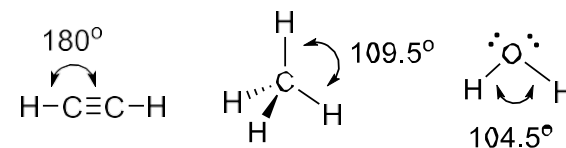
The structure does not provide detailed understanding of the nature of chemical bond

Lewis structures of molecules



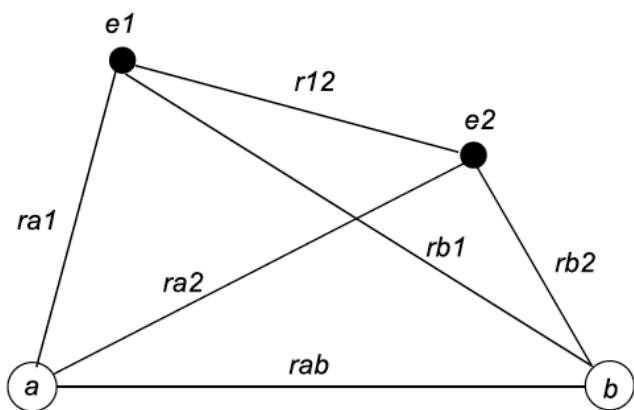
The structure does not tell the geometry, orbital and electron distribution of chemical bond

Valence shell electron pair repulsion (VSEPR) theory



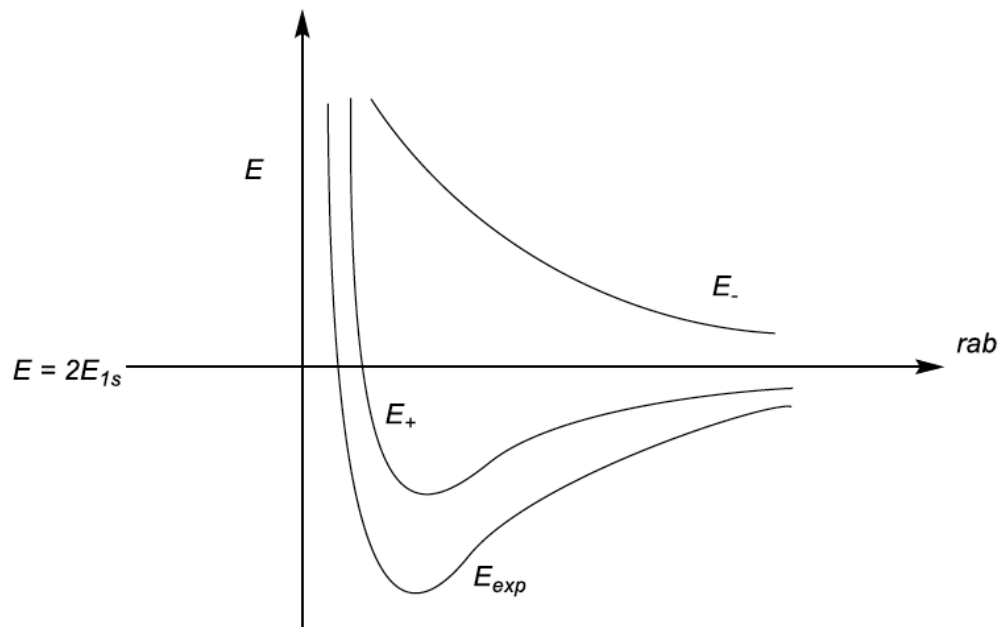
The theory explains the molecular geometry

Valence bond model of an H_2 Molecules (Heitler & London, 1927)

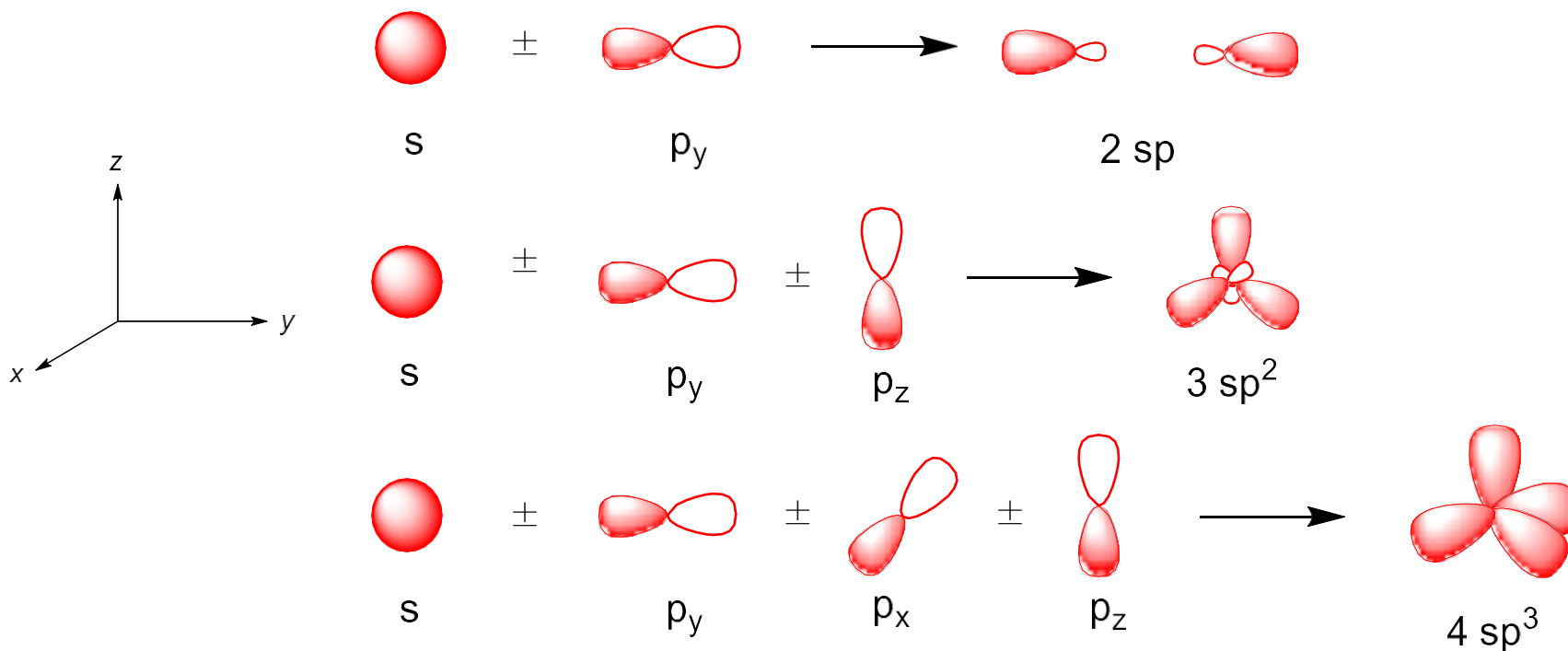


$$\psi_I(1,2) = 1s_a(1)1s_b(2)$$

$$\psi_{II}(1,2) = 1s_b(1)1s_a(2)$$



Hybridization Theory



One s orbital is combined with one, two, and three p orbitals to produce sp, sp², and sp³ hybrid orbitals.

Bonding Orbital



Antibonding Orbital

Bonding Orbital

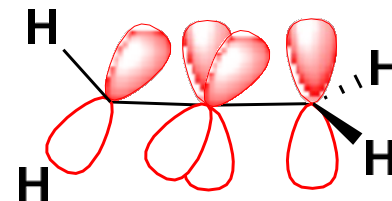
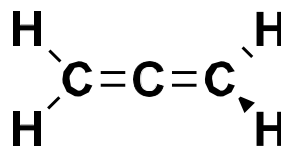
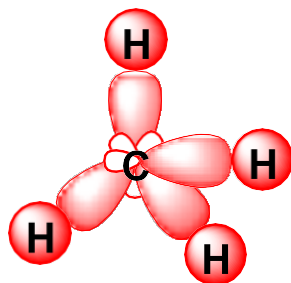
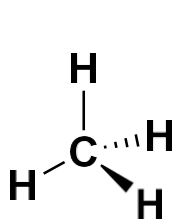


Antibonding Orbital

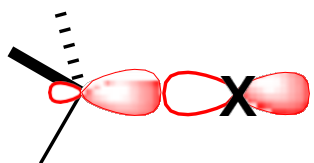
Bonding Orbital



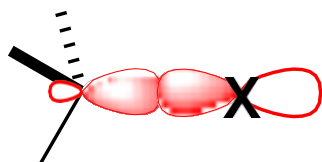
Antibonding Orbital



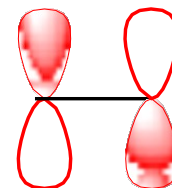
**Question: Is it due to orbital hybridization that...
...a molecule has a specific geometry?**



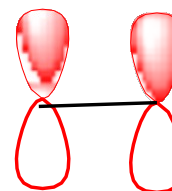
Antibonding



Bonding

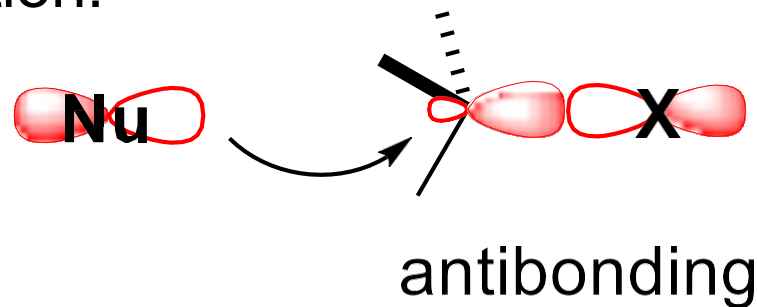
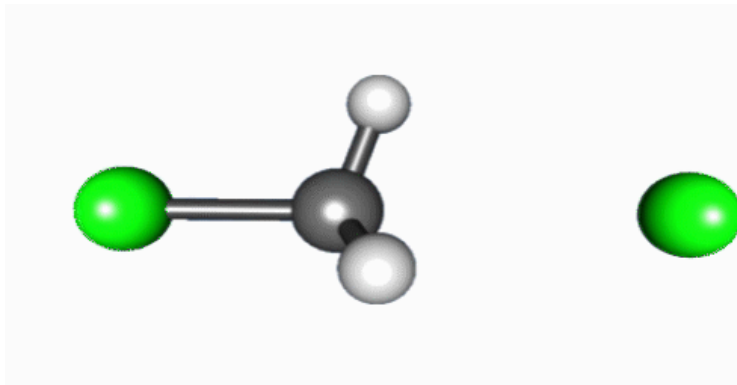


Antibonding



Bonding

Nucleophilic substitution reaction:





Electron Negativity



Pauling vs Mulliken

Atoms: Increases from left to right and decreases from top to bottom in the periodic table

Carbon atoms in different hybridization states:

$\text{Csp} > \text{Csp}^2 > \text{Csp}^3$

Organic groups:

**$\text{NH}_3^+ > \text{OH} > \text{NO}_2 > \text{NH}_2 > \sim \text{CF}_3$
 $> \text{C}\equiv\text{N} \sim \text{C}\equiv\text{CH} > \text{Ph} \sim \text{CH}=\text{CH}_2$
 $\sim \text{CCl}_3 \sim \text{CHCl}_2 > \text{CH}_2\text{Cl} > \text{CH}_3$**

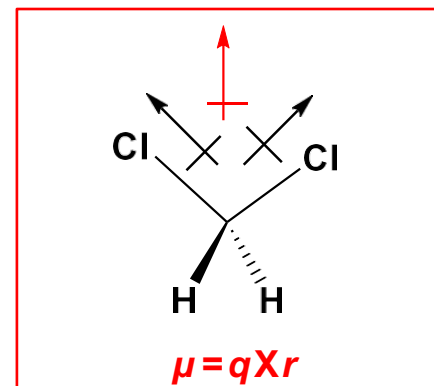
Atom	Original Pauling ^b	Modified Pauling ^c	Mulliken ^f
H	2.1	2.20	2.17
Li	1.0	0.98	0.91
Be	1.5	1.57	1.45
B	2.0	2.04	1.88
C	2.5	2.55	2.45
N	3.0	3.04	2.93
O	3.5	3.44	3.61
F	4.0	3.98	4.14
Na	0.9	0.93	0.86
Mg	1.2	1.31	1.21
Al	1.5	1.61	1.62
Si	1.8	1.90	2.12
P	2.1	2.19	2.46
S	2.5	2.58	2.64
Cl	3.0	3.16	3.05
Ge	1.8	2.01	2.14
As	2.0	2.18	2.25
Se	2.4	2.55	2.46
Br	2.8	2.96	2.83
Sn	1.8	1.96	2.12
I	2.5	2.66	2.57

Carey & Sunderberg
Adv. Org. Chem. p11

Bond Dipoles and Molecular Dipoles

The polarity of a chemical bond (bond dipole) is related to the electronegativity of the atoms that make up the bond.

An electronegativity difference of more than 1.7 is an ionic bond.



Polarity of organic molecules (dipole moment of the molecule)...

...relates to the size and direction of all bond dipoles in the molecule.

(Question: Is the polarity of a molecule the same as the polarity of a chemical bond?)

(Question: Are the polarity and reactivity of molecules the same?)

H. Mayr, M. Breugst, A. R. Ofial **Farewell to the HAHB Treatment of Ambident Reactivity.**
Angew. Chem. Int. Ed. **2011**, 50, 647–650.

Polarizability (hardness / softness)

Hardness = $\eta = (\text{IP} - \text{EA})/2$;

Softness = $\sigma = 1/\eta = 2/(\text{IP} - \text{EA})$

(IP, ionization potential; EA, electron affinity)

Hardness: $\text{F}^- > \text{Cl}^- > \text{Br}^- > \text{I}^-$;

$\text{F}^- > \text{HO}^- > \text{H}_2\text{N}^- > \text{H}_3\text{C}^-$;

$\text{HO}^- > \text{HS}^-$;

$\text{H}^+ > \text{Li}^+ > \text{Na}^+ > \text{K}^+$

Covalent radius and van der Waals radius are ...

...very important in steric effects and stereoelectronic effects.

Some Keywords in π Systems

Resonance

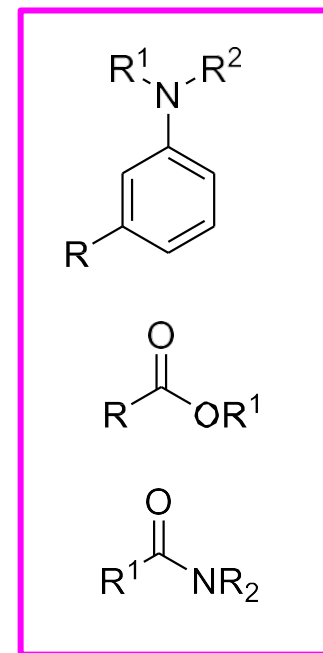
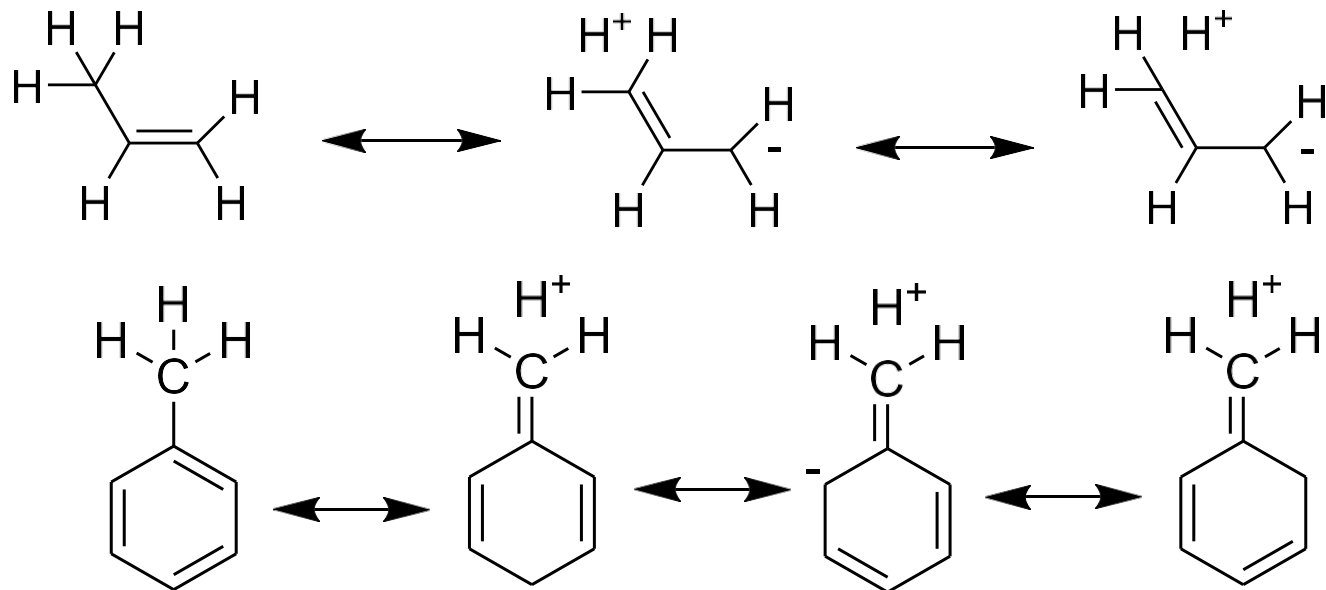
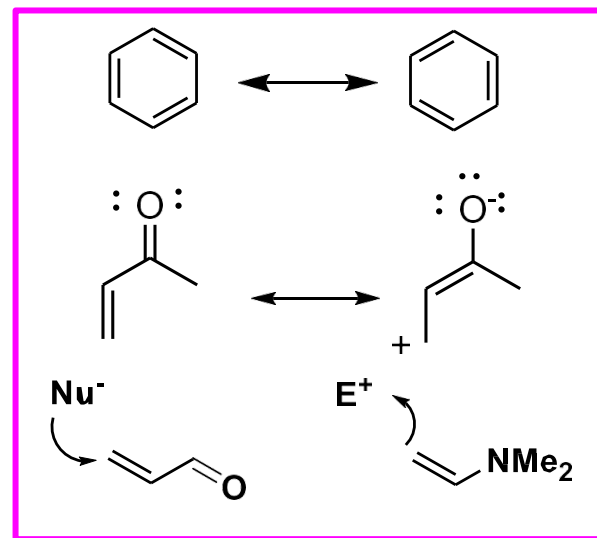
Delocalization

Conjugation

Hyperconjugation

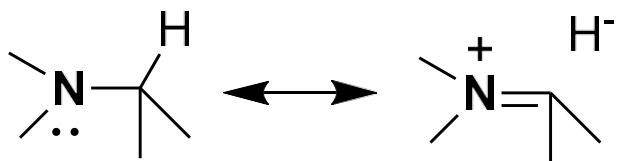
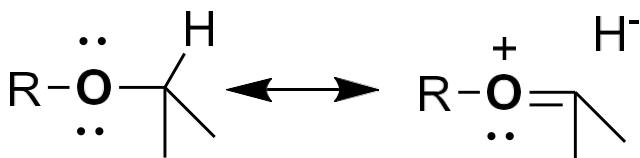
C-H σ bond – empty π^*

Group Discussion

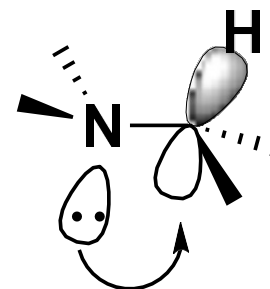


Hyperconjugation

$n - \sigma^*$



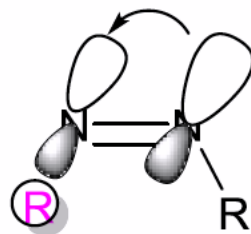
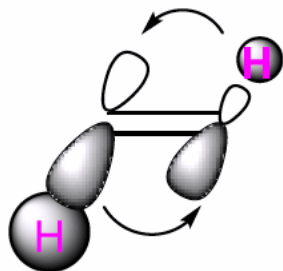
Stereoelectronic effect



Antiperiplanar

Evidences: bond lengths / IR and ^1H NMR signal changes

Hyperconjugation across the double bond ($\sigma - \sigma^*$ and $n - \sigma^*$)



Double Bond:

Shorter in Length

More Overlapping

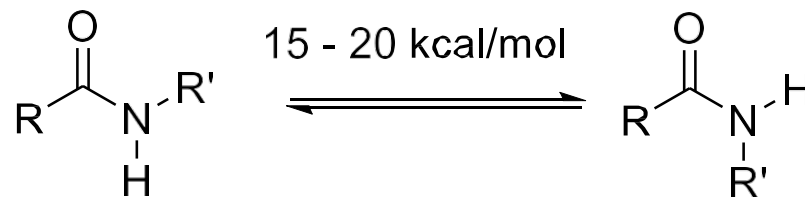
...results in...

Stronger Hyperconjugation

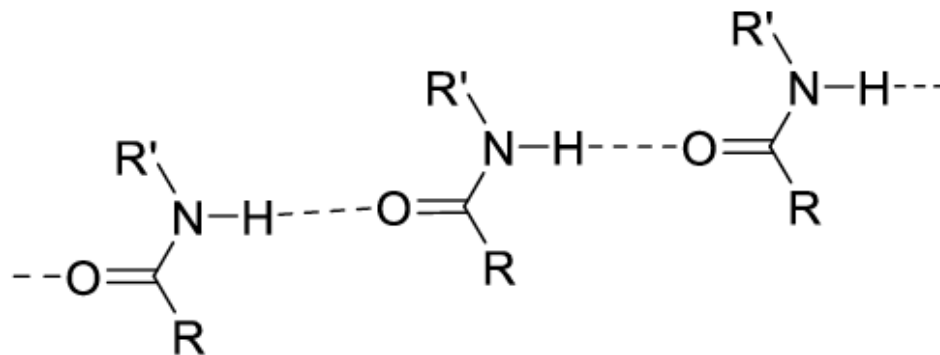
Question: What is hyperconjugation in carbonyl compounds?

Based on the following experimental facts and theoretical calculation results, the most reasonable structural description formula is proposed for RCONHR'

1. The rotation energy barrier for the chemical bond between the carbonyl carbon and nitrogen atoms in the amide is 15–20 kcal/mol



2. Can form strong hydrogen bonds between molecules



3. Calculations show that the N atom does not carry more positive charge than the general amino N atom, and the O atom does not carry more negative charge than the carbonyl O atom of ketone compounds.



Molecular Orbital Theory



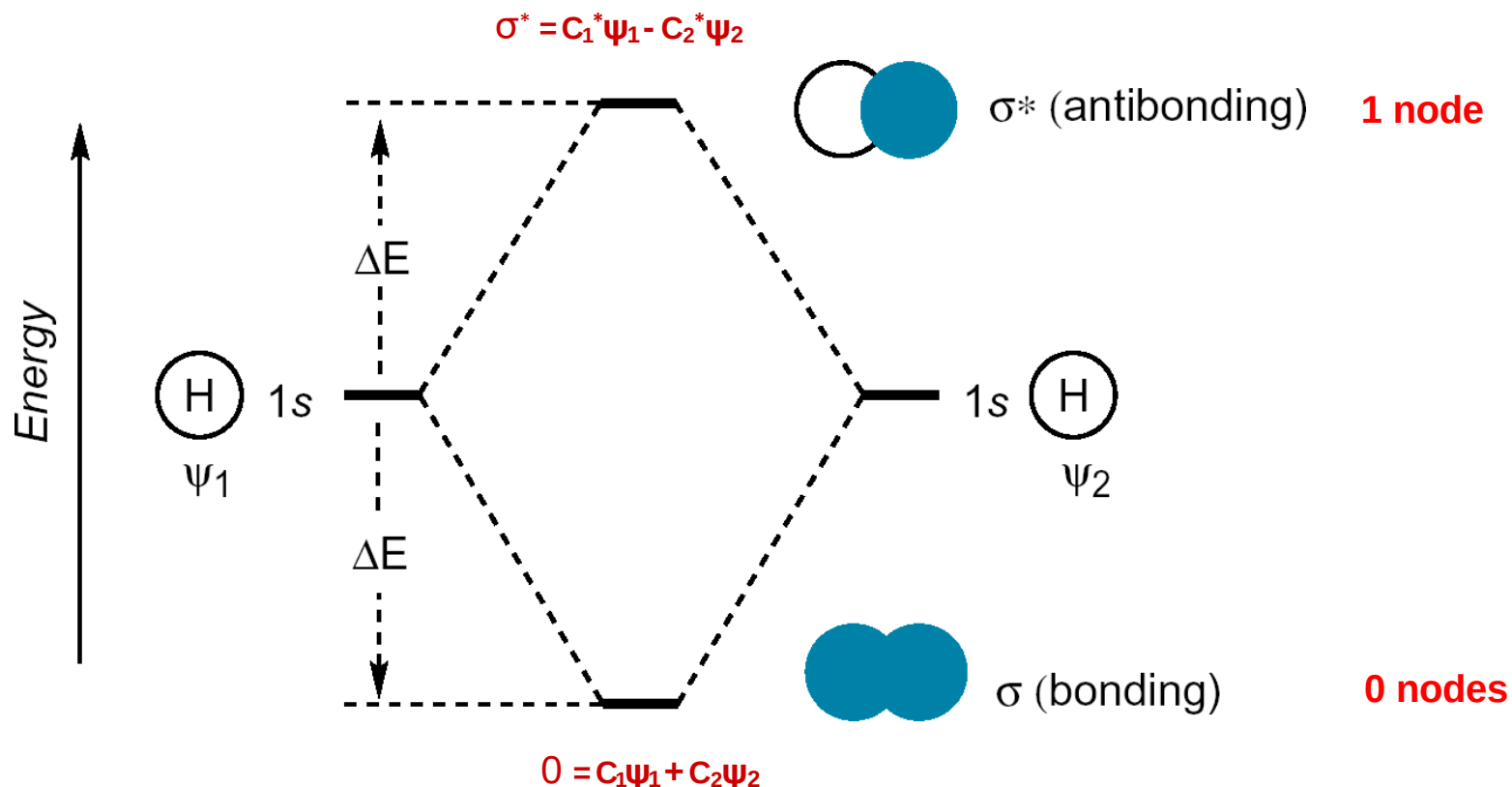
1. Linear combinations of atomic orbitals form molecular orbitals, and n atomic orbitals combine to form n molecular orbitals.
2. Bonding orbitals, antibonding orbitals, and nonbonding orbitals.
3. The energy of the bonding orbitals is lower than that of the atomic orbitals of which they are composed, and charges accumulate between the nuclei.
4. The energy of antibonding orbitals is higher than the energy of the atomic orbitals that compose them. The wave function of antibonding orbitals has one or more nodes between the nuclei, and the internuclear charge decreases.
5. Orbitals with similar energies overlap more strongly than orbits with widely different energies.
6. Symmetry matching.

Molecular orbital calculations give ...

...the structure, energy and electron density of a molecule

Molecular orbital of hydrogen molecule (H—H bond)

The linear combination of the 1s orbitals of two hydrogen atoms creates two molecular orbitals, one bonding orbital, and one antibonding orbital





Fundamental Rules

1. Consider **valence** orbitals only.
2. Form completely **delocalized MOs** as linear combinations of s and p orbitals.
3. MOs must be either **symmetric or antisymmetric** with respect to the symmetry operations of the molecules.
4. **Compose MOs for structures of high symmetry and then produce orbitals for related but less symmetric structures by systematic distortions of the orbitals for higher symmetry.**
5. Molecules with similar molecular structures, such as CH_3 and NH_3 , have qualitatively similar MOs, the major difference being the number of valence electrons that occupy the common MO system.
6. The total energy is the sum of the molecular orbital energies of individual valence electrons.
7. **If the two highest energy MOs of a given symmetry derive primarily from different kinds of AOs, then mix the two MOs to form hybrid orbitals.**
8. When two orbitals interact, the lower energy orbital is stabilized and the higher energy orbital is destabilized. The out-of-phase or antibonding interaction between the two starting orbitals always raises the energy more than the corresponding in-phase or bonding interaction lowers the energy.



Fundamental Rules

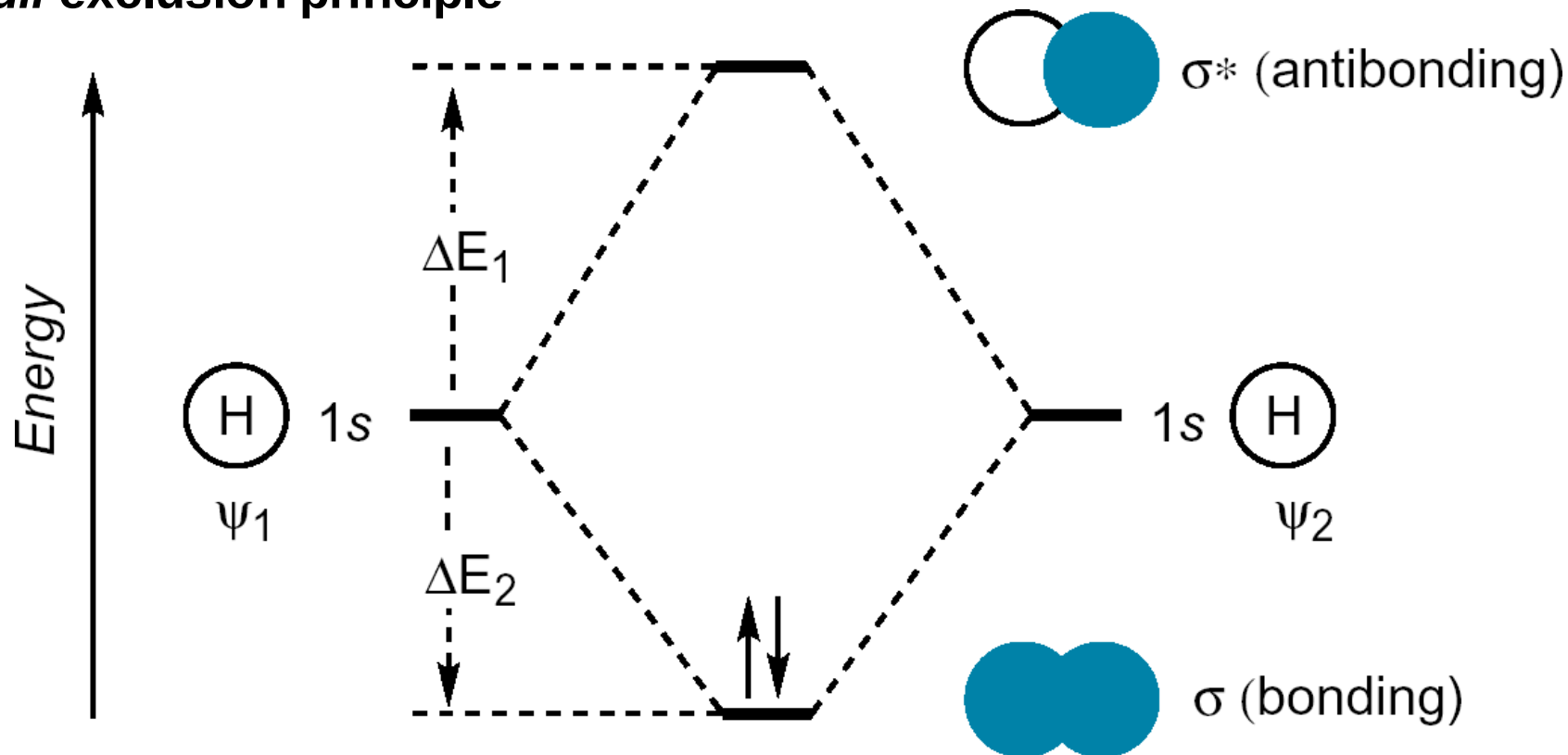
9. When two orbitals interact, the lower energy orbital mixes into itself the higher energy one in a bonding way, while the higher energy orbital mixes into itself the lower energy one in an antibonding way.
10. The smaller the initial energy gap between two interacting orbitals, the stronger the mixing interaction.
11. The larger the overlap between interacting orbitals, the larger the interaction.
12. **The more electronegative elements have lower energy AOs.**
13. A change in the geometry of a molecule will produce a large change in the energy of a particular MO if the geometry change results in changes in AO overlap that are large.
14. The AO coefficients are large in high energy MOs with many nodes or complicated nodal surfaces.
15. Energies of orbitals of the same symmetry classification cannot cross each other. Instead, such orbitals mix and diverge.

Energy Level Diagram of Hydrogen Molecule

Fill one electron from each hydrogen atom into a new molecular orbital

Aufbau principle

Pauli exclusion principle

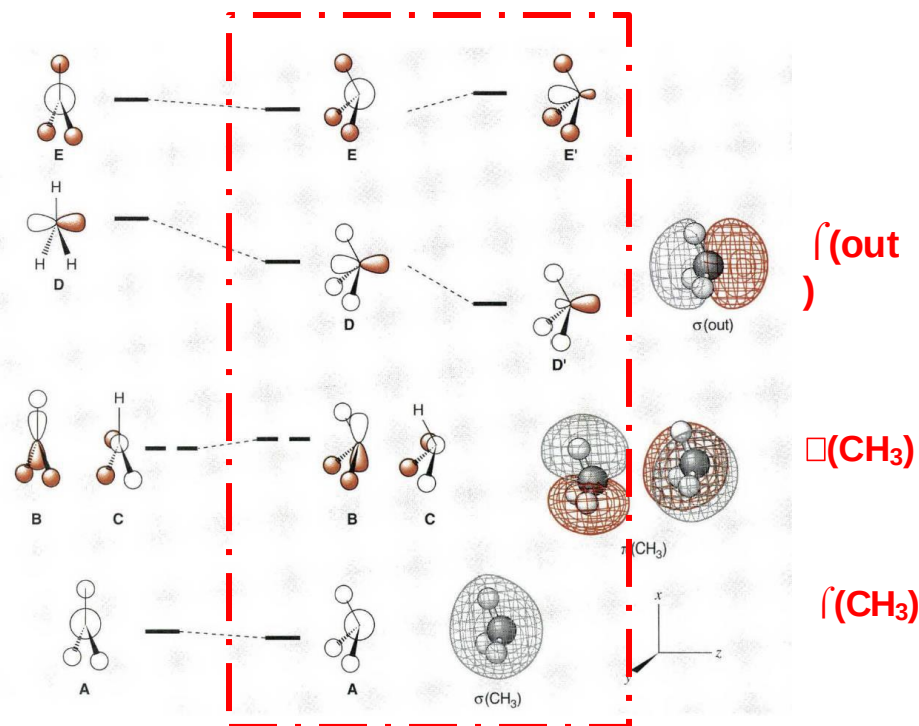
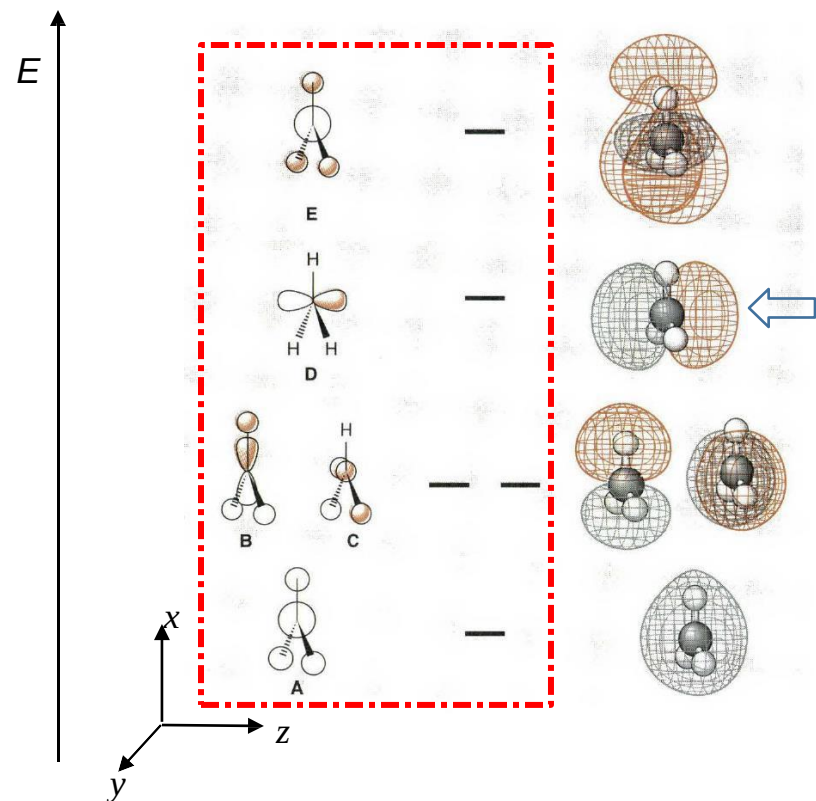


Walsh Diagram

The "group" orbital of
planar CH_3



The "group" orbital of
pyramid CH_3





The Hückel MO Method



Applicable only to **planar** conjugated molecular systems:
e.g., linear conjugated alkenes; aromatic compounds

Applying approximation:

1. Planar conjugated system;
2. Only $2p_z$ orbitals are considered;
3. Adjacent p_z orbitals have interactions;
4. It is stipulated that the orbit overlap integral S is equal to 0;
5. Neglect electron-electron repulsion



Applications of Hückel's MO Theory

1. Aromaticity and Antiaromaticity

$4n+2$ aromaticity; $4n$ antiaromaticity

2. Electrocyclization Reaction

Woodward & Hoffmann Rules

3. Cycloaddition Reaction

Prediction of regioselectivity and stereochemistry

4. Rearrangement Reaction

Prediction of response

5. Molecular Hardness

$$\eta = (IP - EA)/2 = (E_{\text{HOMO}} - E_{\text{LUMO}})/2$$

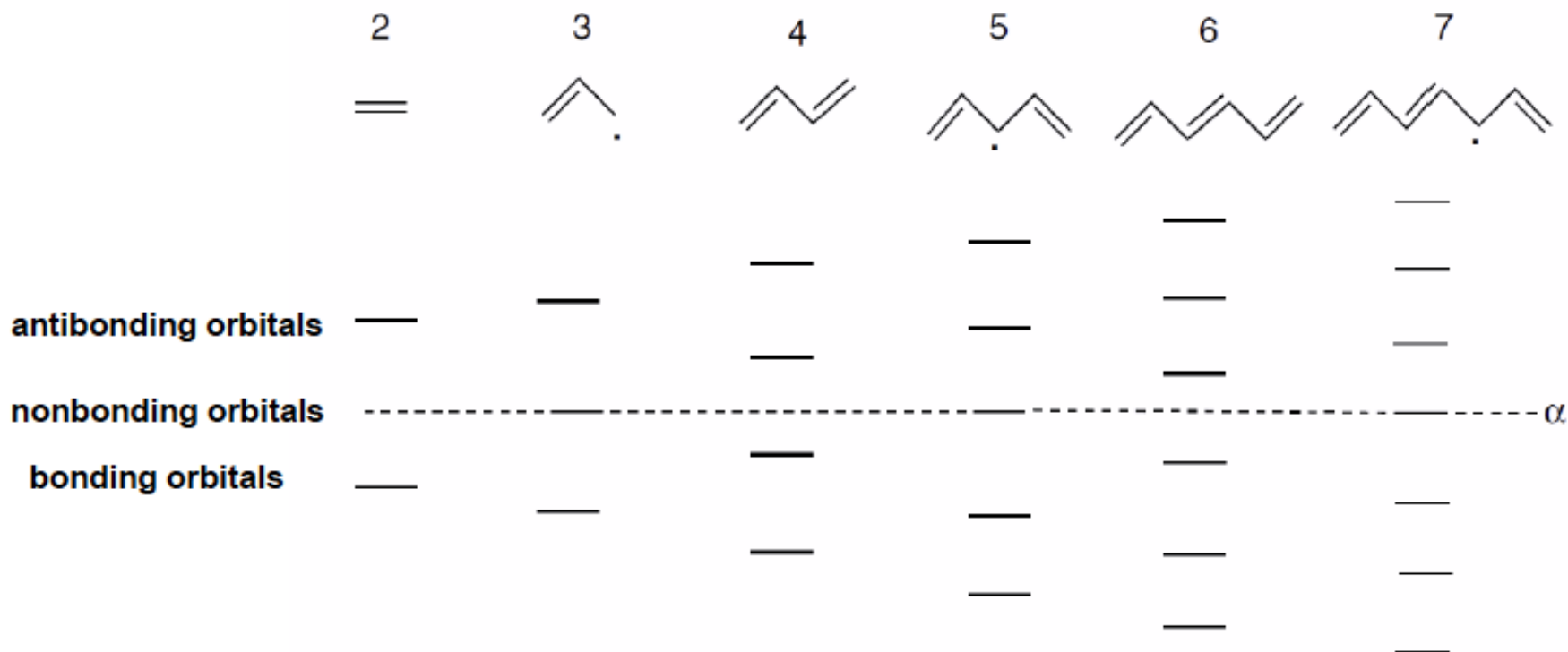
H. Mayr, M. Breugst, A. R. Ofial **Farewell to the HAHB Treatment of Ambident Reactivity.**
Angew. Chem. Int. Ed. **2011**, 50, 647–650.

The energy of the j th π orbital of...
... a fully conjugated linear polyene

$$E_j = \alpha + m_j \beta = \alpha + 2\beta \cos\left(\frac{j\pi}{n+1}\right)$$

α , Coulomb integral (binding of an electron in a $2p_z$ orbital)
 β , Resonance integral (energy of an electron distributed over two or more overlapping $2p_z$ orbitals)

HMO orbital diagram for polyenes ($n = 2 \sim n = 7$)





Orbital Coefficient of 1,3,5-Hexatriene



The contribution of each atomic orbital to HMO (orbital coefficient) in a linear conjugated alkene composed of n atoms

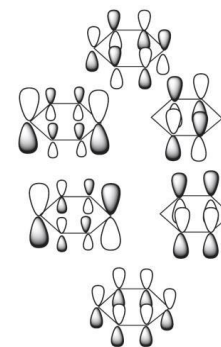
$$C_{rj} = \left(\frac{2}{n+1}\right)^{1/2} \sin\left(\frac{rj\pi}{n+1}\right)$$

Energy Levels and Atomic Coefficients for HMOs of 1,3,5-Hexatriene

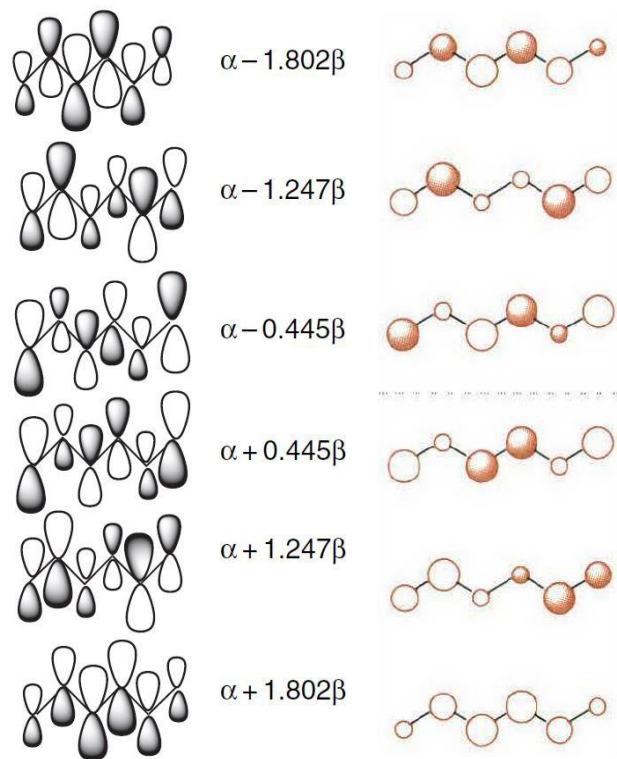
π orbital m_j	c_1	c_2	c_3	c_4	c_5	c_6
Ψ_1 1.802	0.2319	0.4179	0.5211	0.5211	0.4179	0.2319
Ψ_2 1.247	0.4179	0.5211	0.2319	-0.2319	-0.5211	-0.4179
Ψ_3 0.445	0.5211	0.2319	-0.4179	-0.4179	0.2319	0.5211
Ψ_4 -0.445	0.5211	-0.2319	-0.4179	0.4179	0.2319	-0.5211
Ψ_5 -1.247	0.4179	-0.5211	0.2319	0.2319	-0.5211	0.4179
Ψ_6 -1.802	0.2319	-0.4179	0.5211	-0.5211	0.4179	-0.2319

Group Discussion: How to draw them?

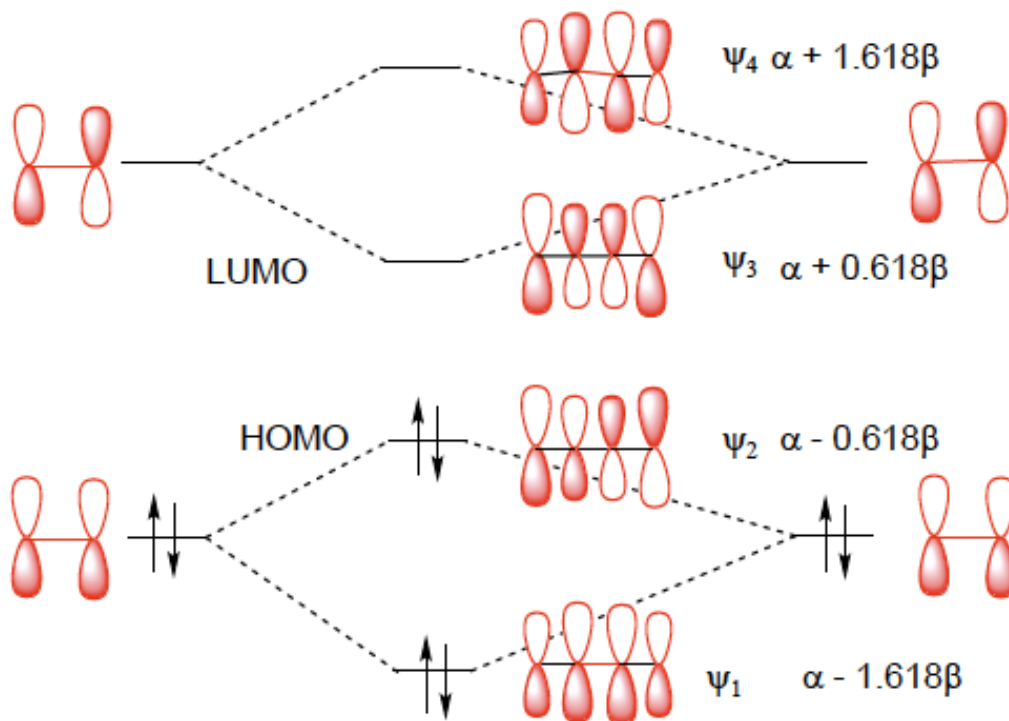
Using this style



π molecular orbital of 1,3,5-hexatriene

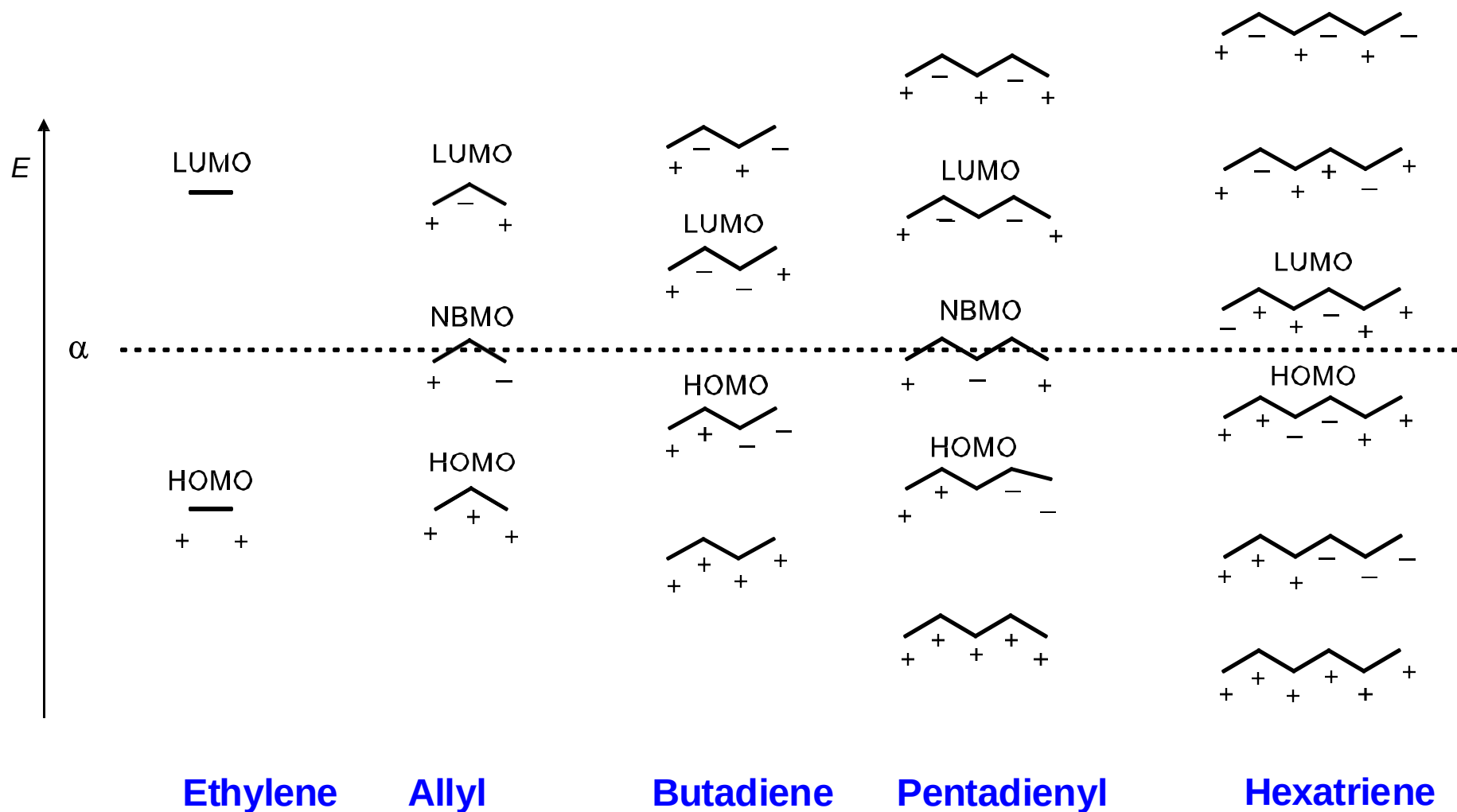


Constructing the π molecular orbital of 1,3-butadiene from the π orbital of ethylene



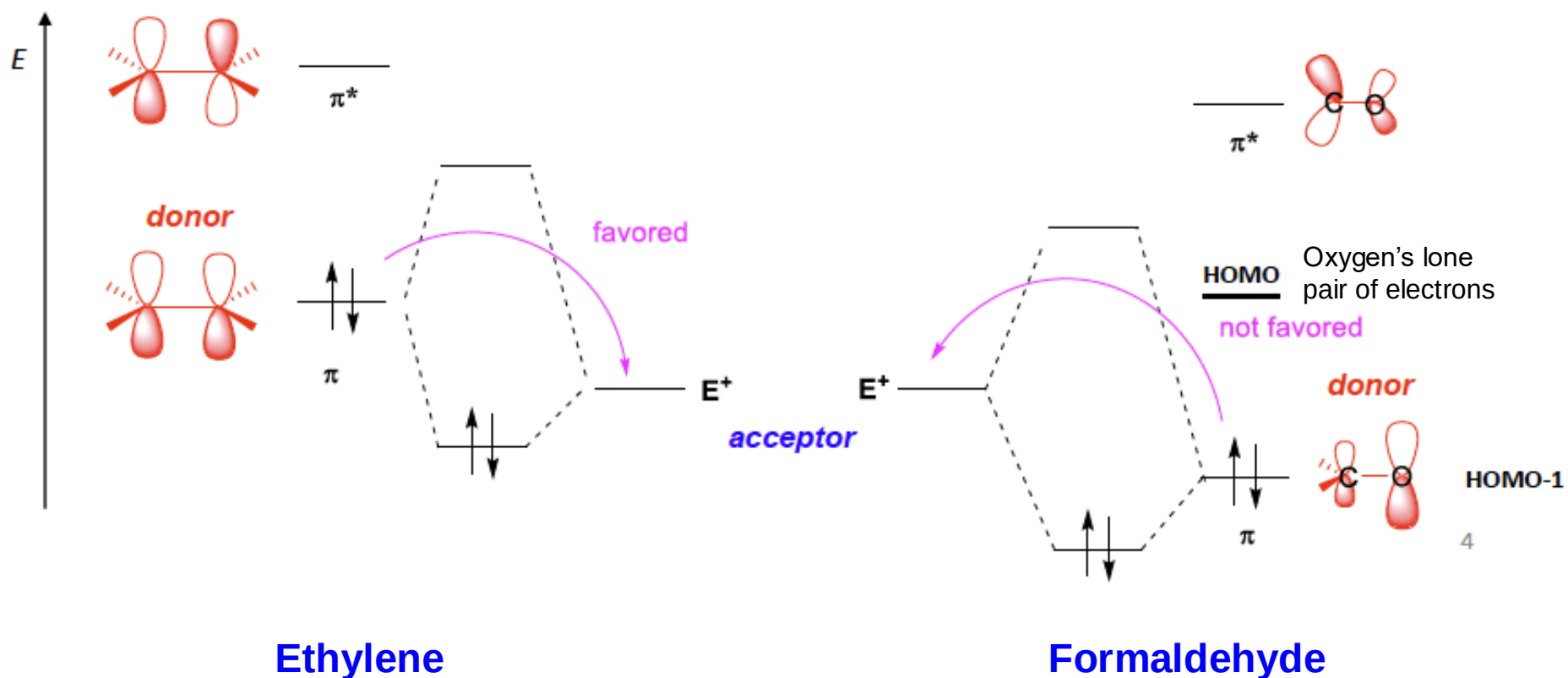


Nodes in Linear Conjugated Alkenes HMO



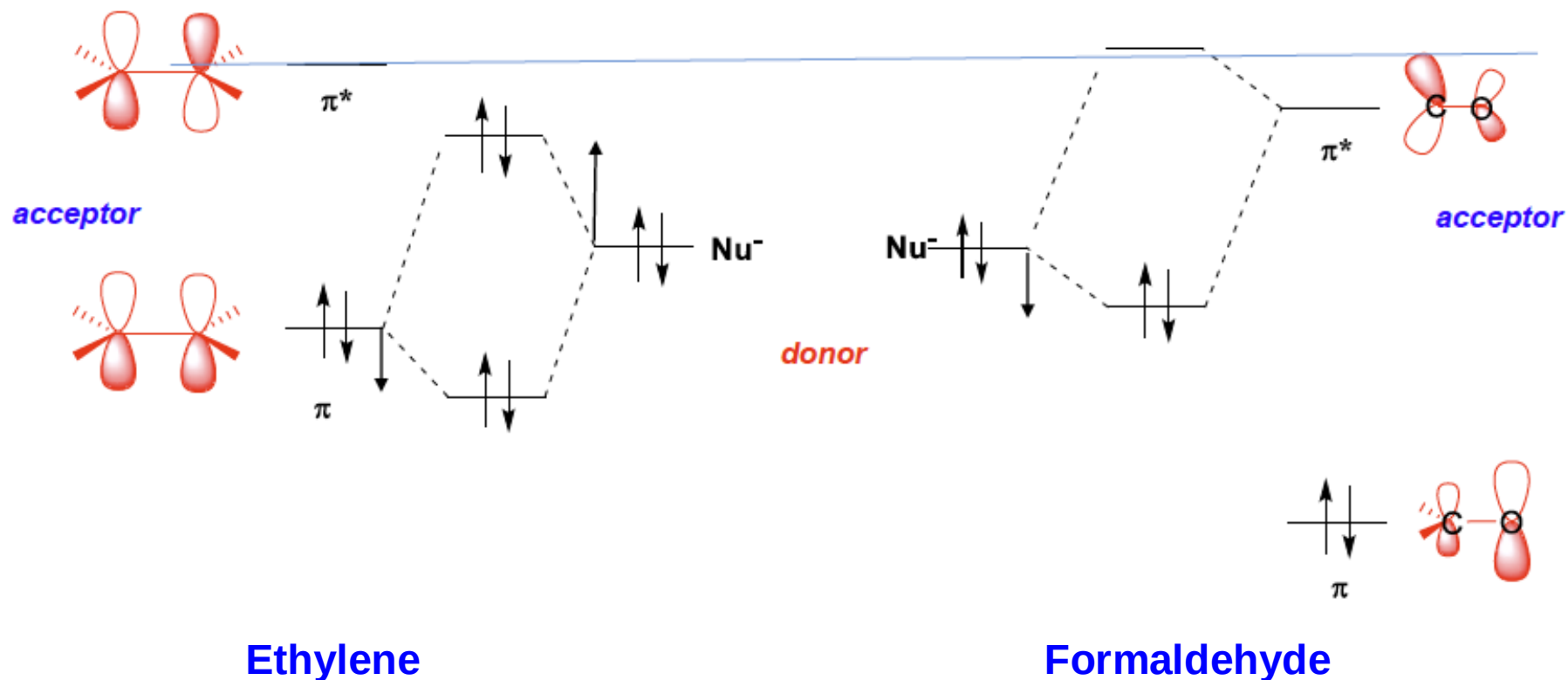
Comparison between a related system and a known MO pattern
Interactions are strongest between orbitals that are close in energy

Ethylene compared to formaldehyde: reaction with electrophile E^+



Comparison between a related system and a known MO pattern
Interactions are strongest between orbitals that are close in energy

Ethylene compared to formaldehyde:
reaction with the nucleophile Nu^-



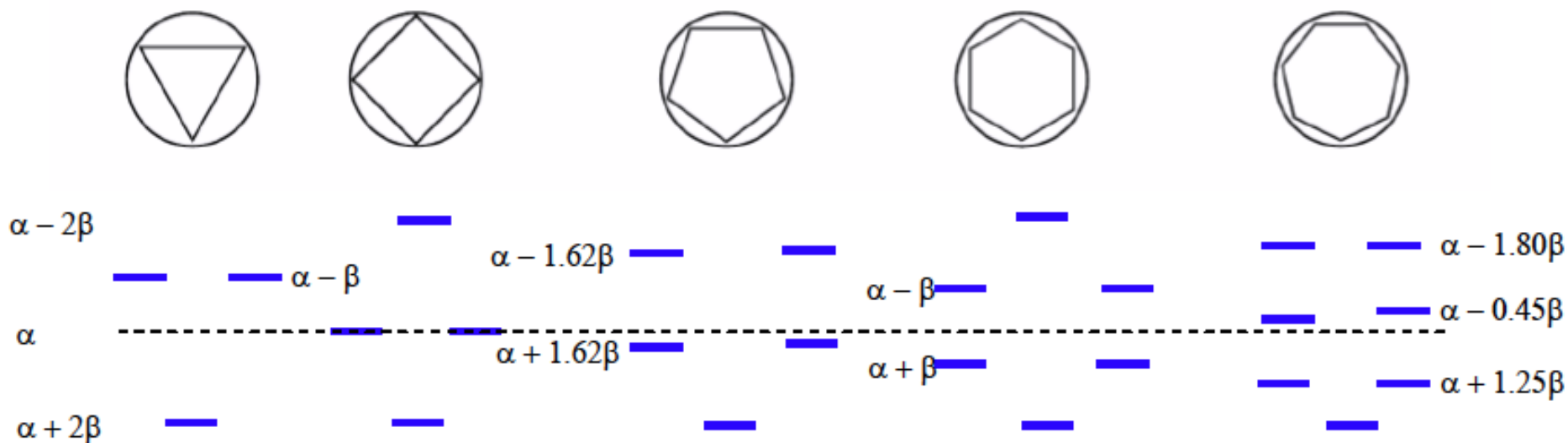
The energy of the j th π orbital of ...
...a fully conjugated monocyclic polyolefin

$$E_j = \alpha + m_j \beta = \alpha + 2\beta \cos\left(\frac{2j\pi}{n}\right)$$

α , Coulomb integral (binding of an electron in a $2p_z$ orbital)
 β , Resonance integral (energy of an electron distributed over two or more overlapping $2p_z$ orbitals)

$j = 0, \pm 1, \pm 2, \dots$ up to $n/2$ (for even) or $(n-1)/2$ (for odd)

Frost's circle mnemonic for HMOs of cyclic polyenes

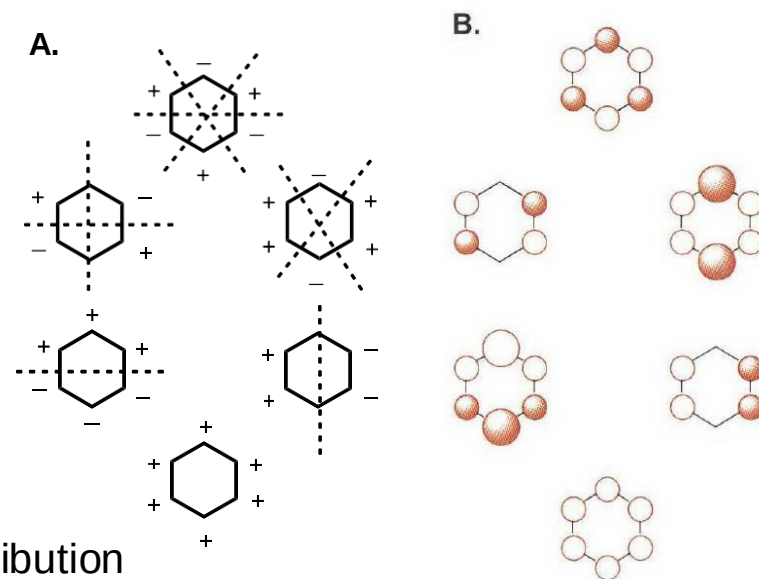


MO: Molecular Orbital / AO: Atomic Orbital

$$\text{MO} \quad Y_i = \sum_k c_{ik} y_{ik} \quad (y_{ik} = \text{AO})$$

$$\text{For each MO} \quad \sum_k c_{ik}^2 = 1$$

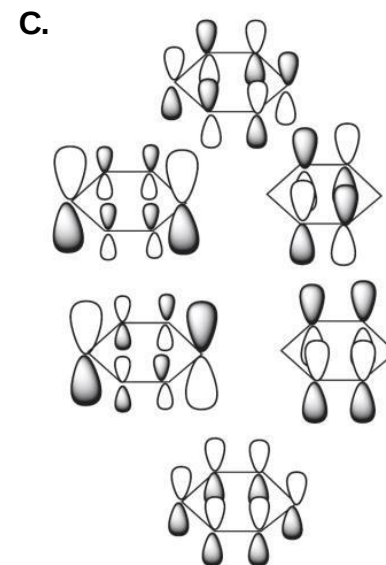
$$\text{For each AO} \quad \sum_i c_{ik}^2 = 1$$



For each pair of degenerate molecular orbitals, the contribution of each atom is consistent, which is the sum of the squares of the atomic coefficients

The symmetry of the molecular orbitals is either consistent with the symmetry of the molecule or antisymmetric

	c_1	c_2	c_3	c_4	c_5	c_6
Y_1	0.4083	0.4083	0.4083	0.4083	0.4083	0.4083
Y_2	0.0000	0.5000	0.5000	0.0000	-0.5000	-0.5000
Y_3	0.5774	0.2887	-0.2887	-0.5774	-0.2887	0.2887
Y_4	0.0000	-0.5000	-0.5000	0.0000	0.5000	-0.5000
Y_5	0.5774	-0.2887	0.2887	-0.5774	-0.2887	0.2887
Y_6	-0.4083	-0.4083	-0.4083	-0.4083	-0.4083	-0.4083



Some Keywords in π Systems

Resonance

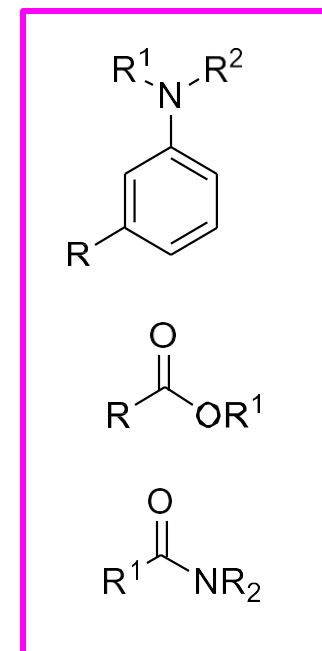
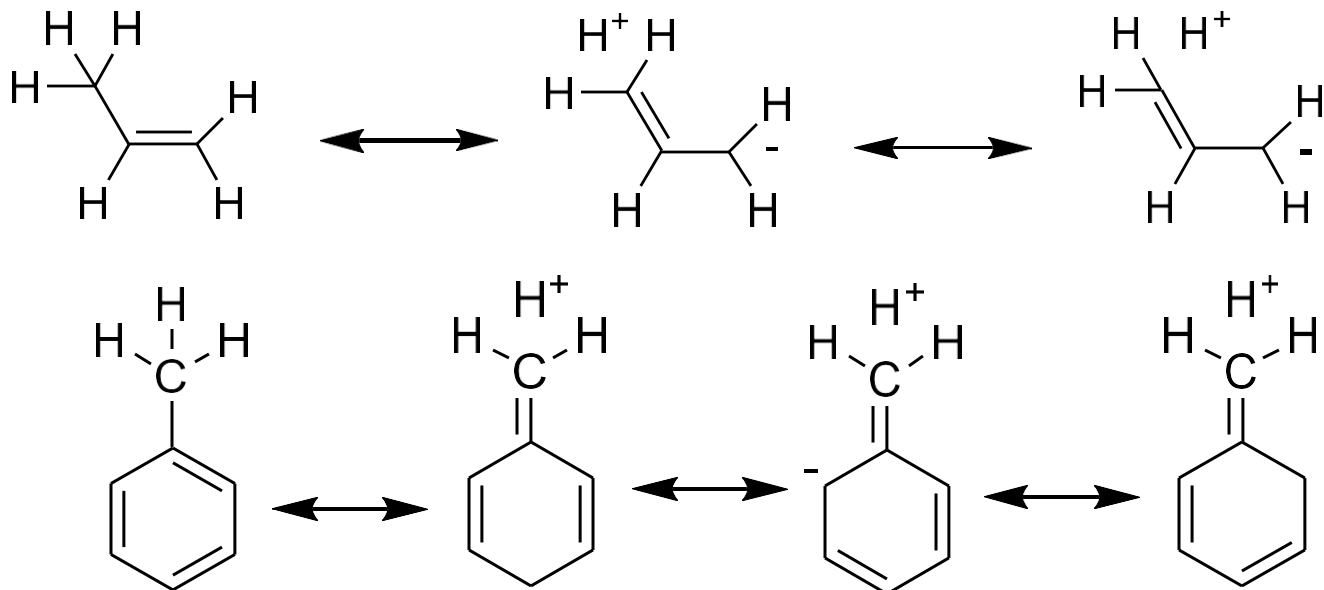
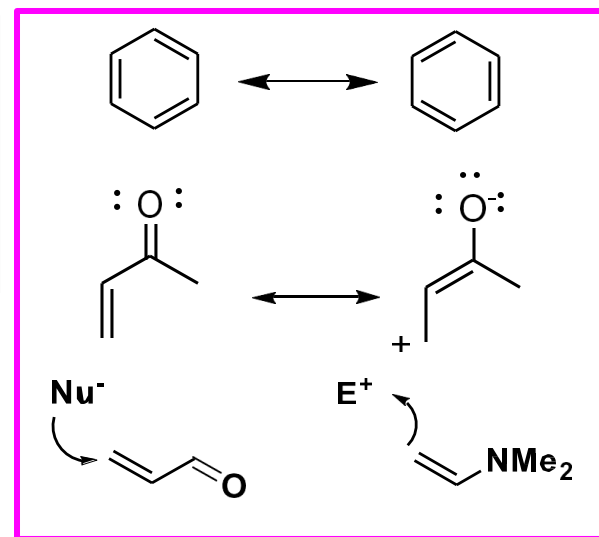
Delocalization

Conjugation

Hyperconjugation

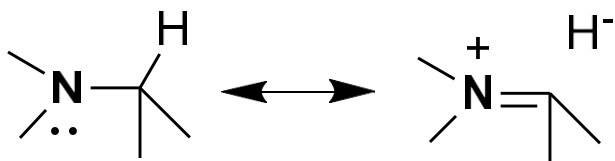
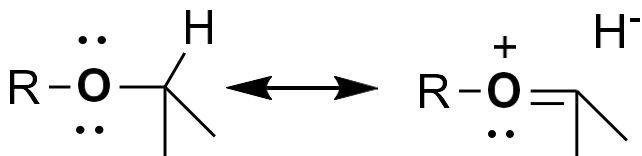
C-H (σ bond – empty p^*)

Group Discussion

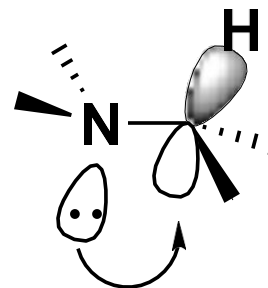


Hyperconjugation

$n - \sigma^*$



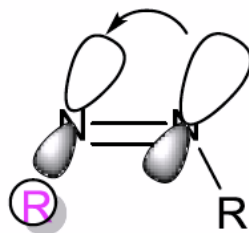
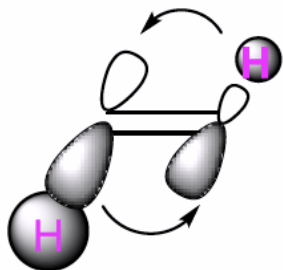
Stereoelectronic effect



Antiperiplanar

Evidences: bond lengths / IR and ^1H NMR signal changes

Hyperconjugation across the double bond ($\sigma - \sigma^*$ and $n - \sigma^*$)



Double Bond:

Shorter in Length

More Overlapping

...results in...

Stronger Hyperconjugation

Question: What is hyperconjugation in carbonyl compounds?

Some Keywords in π Systems

Resonance

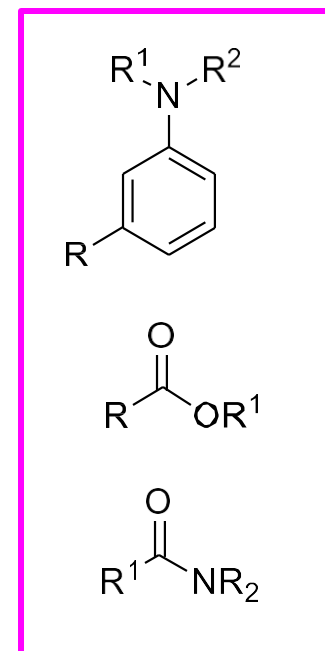
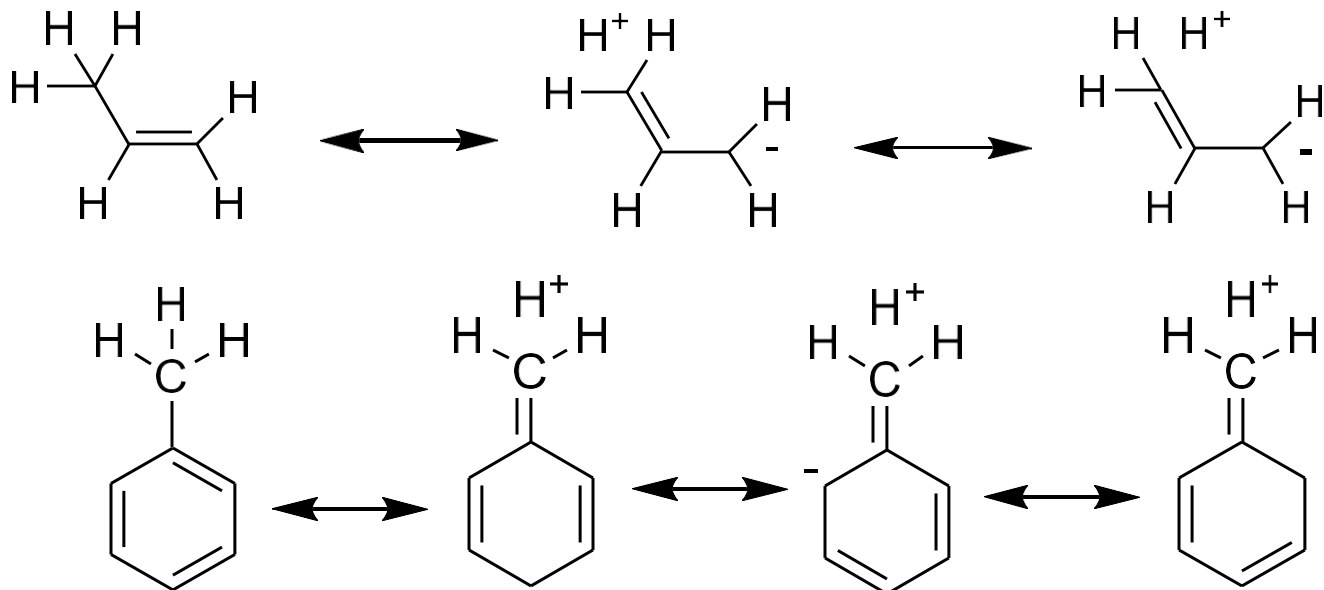
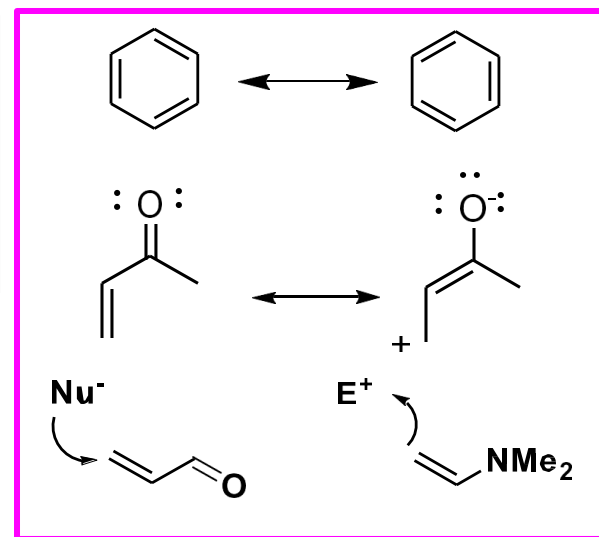
Delocalization

Conjugation

Hyperconjugation

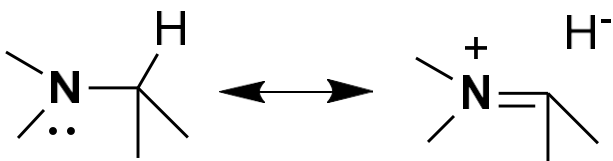
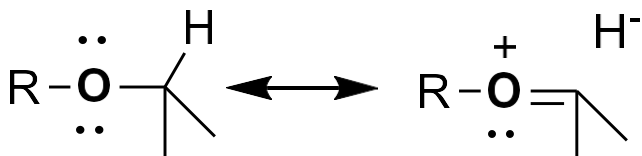
C-H (σ bond – empty p^*)

Group Discussion

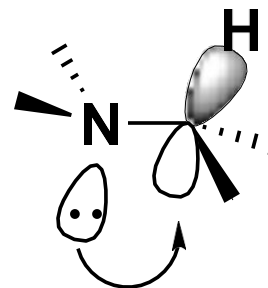


Hyperconjugation

$n - \sigma^*$



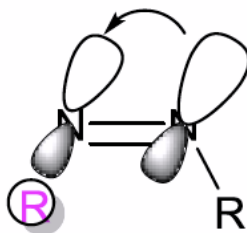
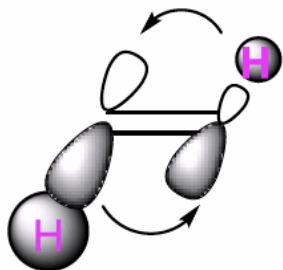
Stereoelectronic effect



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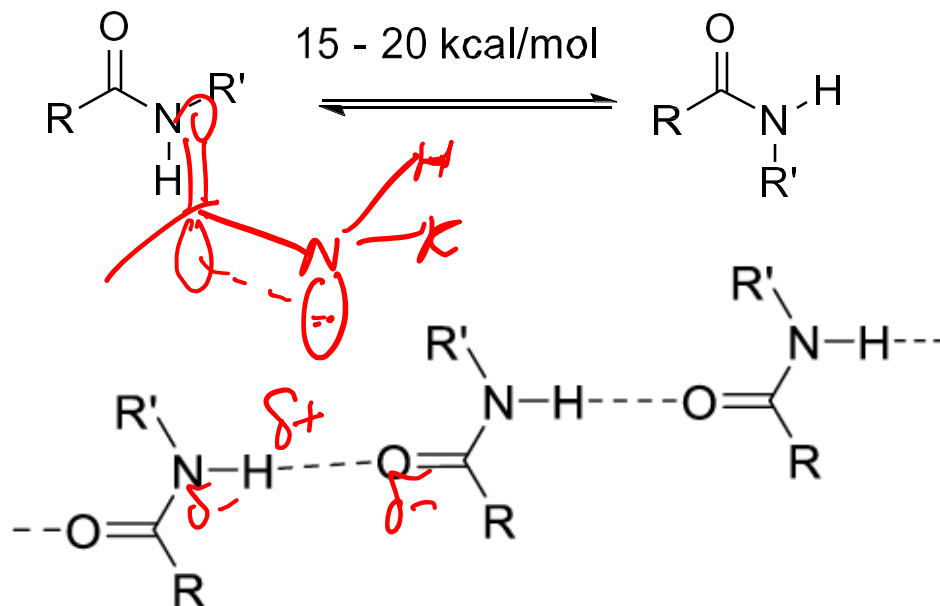
...results in...

Stronger Hyperconjugation

Question: What is hyperconjugation in carbonyl compounds?

Based on the following experimental facts and theoretical calculation results, the most reasonable structural description formula is proposed for RCONHR'

1. The rotation energy barrier for the chemical bond between the carbonyl carbon and nitrogen atoms in the amide is 15–20 kcal/mol



2. Can form strong hydrogen bonds between molecules

3. Calculations show that the N atom does not carry more positive charge than the general amino N atom, and the O atom does not carry more negative charge than the carbonyl O atom of ketone compounds.

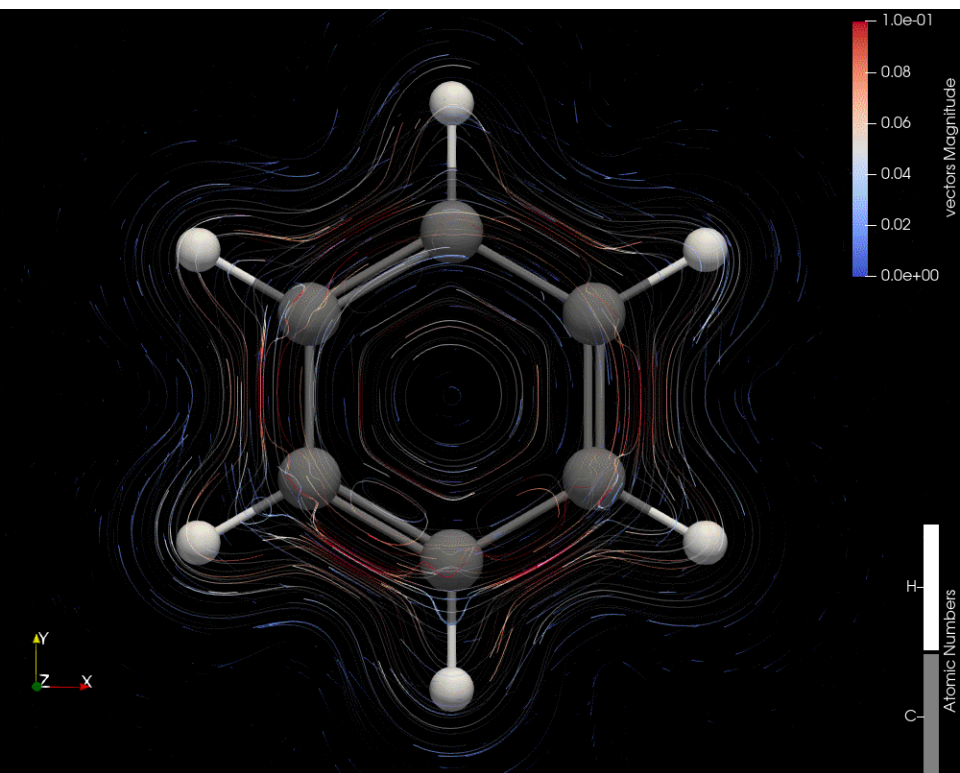


Aromaticity Criterion

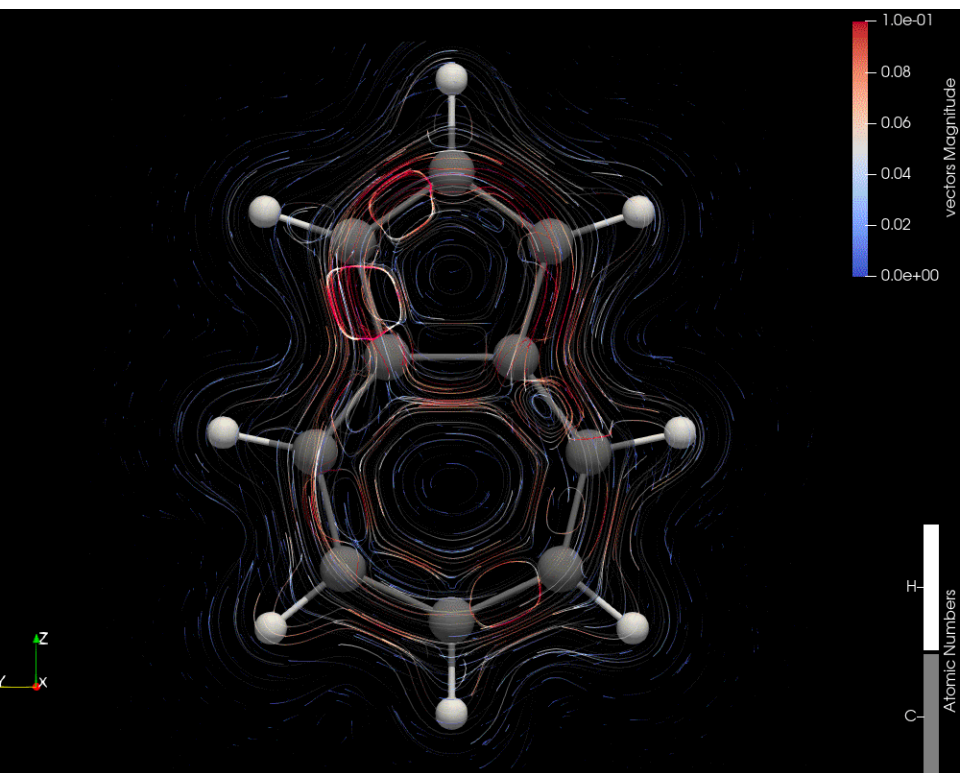
- | | | |
|---|---|---|
| 1. Planar cyclic conjugated system | } | Simply structural and electronic numerical criteria |
| 2. $4n + 2$ n electrons | | |
| 3. Chemical bond length between single and double bonds (delocalization, averaging) | | Structural criterion |
| 4. Aromatization energy (additional conjugation or delocalization stabilization energy) | | Thermodynamic criterion |
| 5. NMR spectroscopy (diamagnetic ring current) | } | Criteria by electronic and magnetic properties |
| 6. NICS value (calculated value of the magnetic field at the center of the ring) | | |
| 7. Magnetic induced current | | |
| 8. Chemical reaction (easy to substitute, difficult to add) | | Reactivity criterion |

NICS (nucleus independent chemical shift) value: negative: aromaticity; positive: antiaromaticity.

Benzene



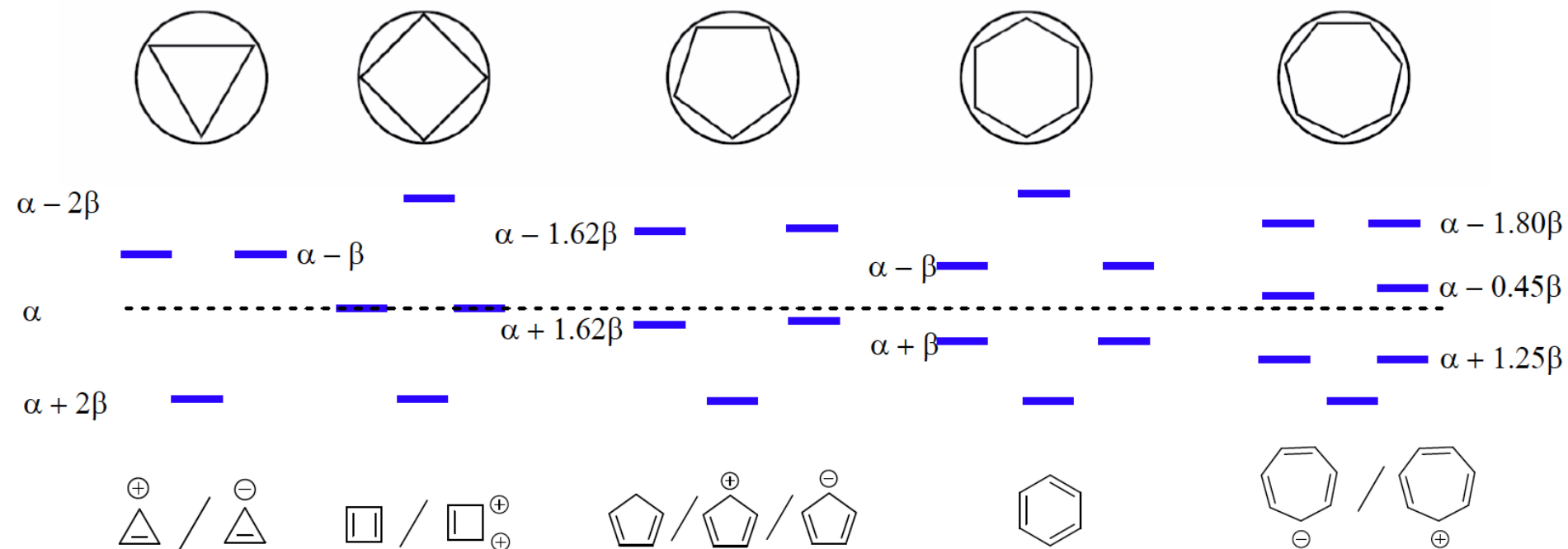
Azulene



Calculate level: B3LYP/6-311G(d) with GIMIC (gauge including magnetically induced current method)

Frost's Circle Mnemonic

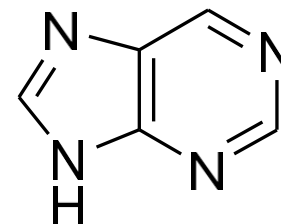
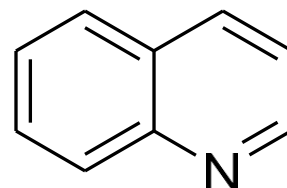
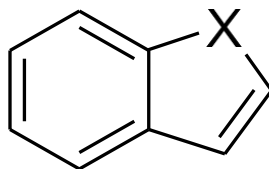
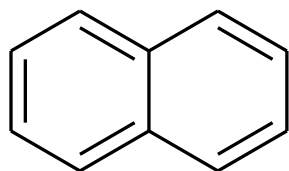
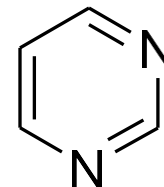
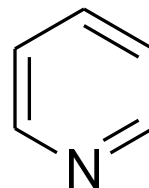
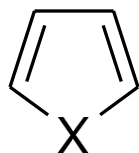
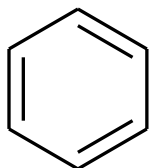
for Hückel's MOs of cyclic polyenes



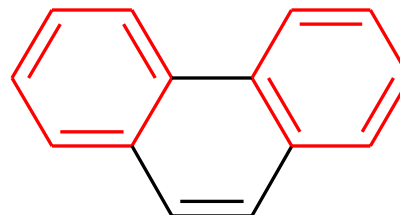
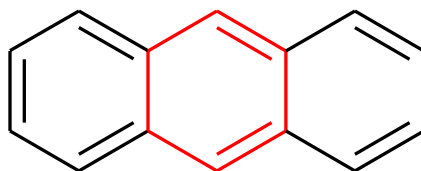
Prediction of aromaticity based on electron filling and energy of planar monocyclic polyolefins.

Comparison of $(4n+2)\pi$ and $4n\pi$ systems

Examples of Aromatic Compounds



X = O, S, NH



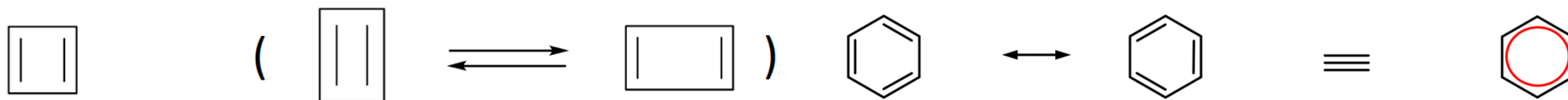
Antiaromaticity is a chemical property of ...

...a **cyclic** molecule with a **π electron** system that has **higher energy**...

...i.e., it is **less stable** due to the presence of...

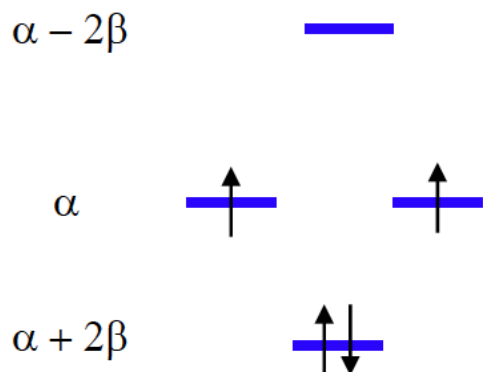
... **$4n$** delocalized (π or lone pair) electrons in it...

... as opposed to aromaticity.



Cyclobutadiene

Benzene

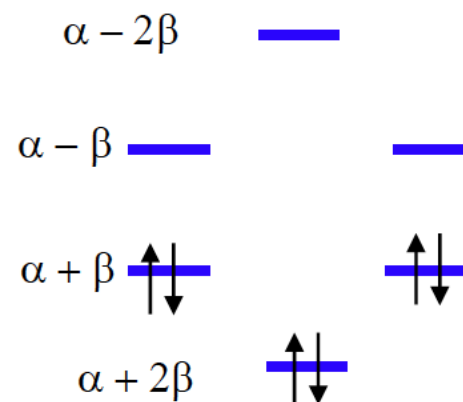


$$\Delta H_f = 114 \pm 11 \text{ kcal/mol}$$

Total destabilization energy
= 87 kcal/mol

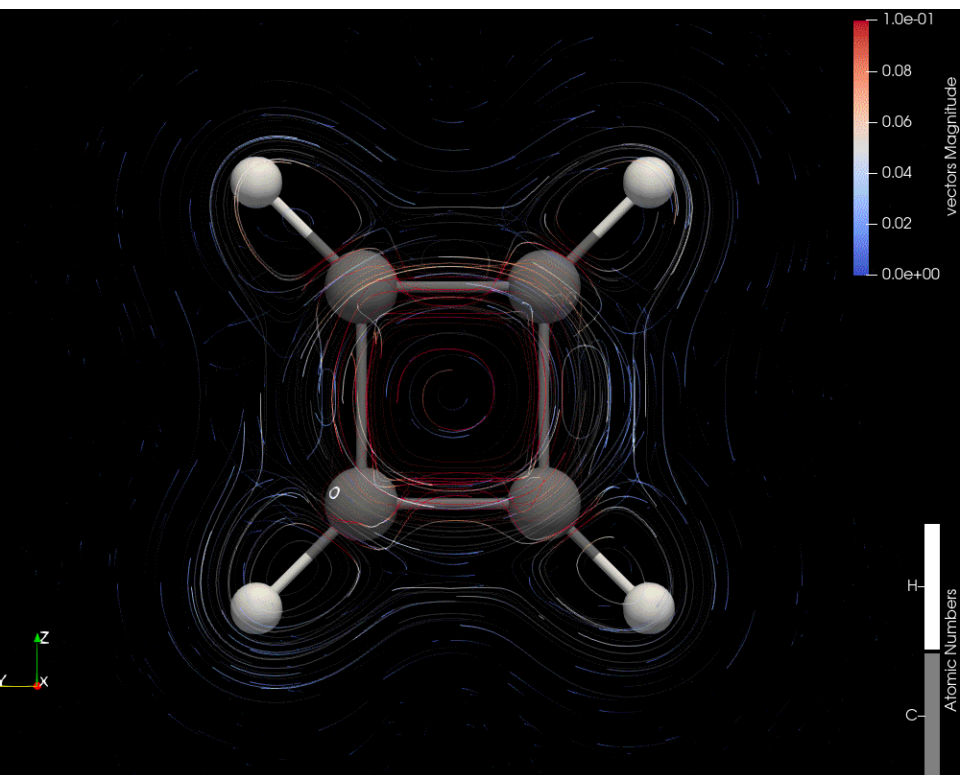
Ring tension: 32 kcal/mol
Antiaromatic: 55 kcal/mol

$$E = 4\alpha + 4\beta$$

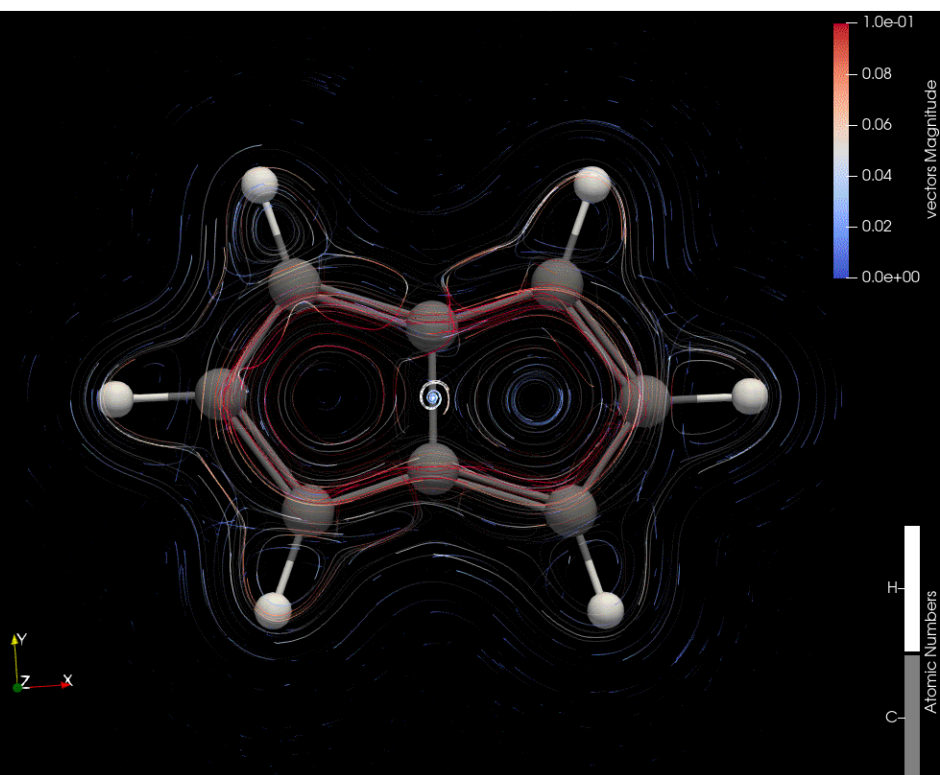


$$E = 6\alpha + 8\beta$$

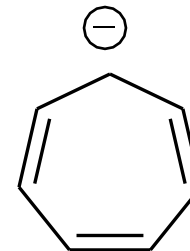
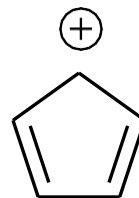
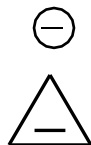
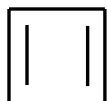
Cyclobutadiene



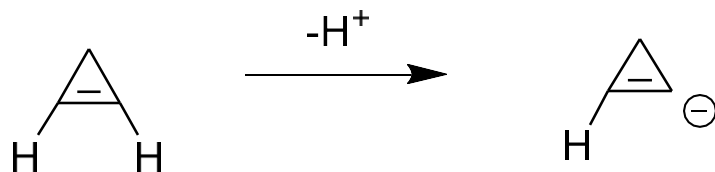
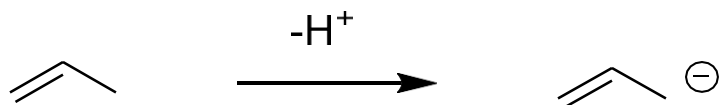
Pentalene



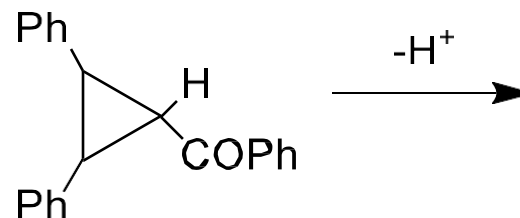
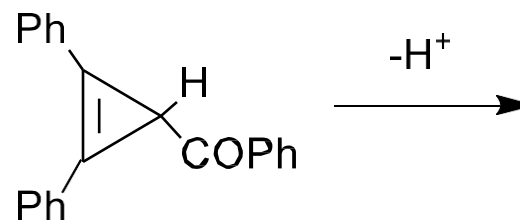
Calculate level: B3LYP/6-311G(d) with GIMIC (gauge including magnetically induced current method)

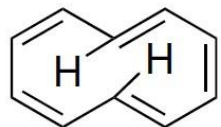


Questions: which one is easier?



Questions: which one is easier?



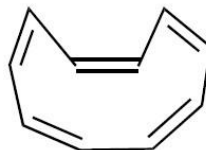


Z,E,Z,Z,E



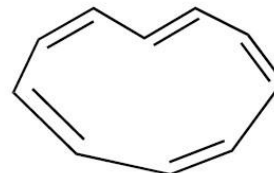
twist

E,Z,Z,Z,Z-



boat

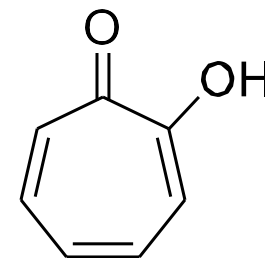
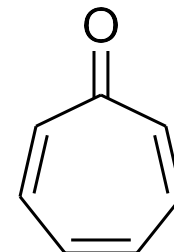
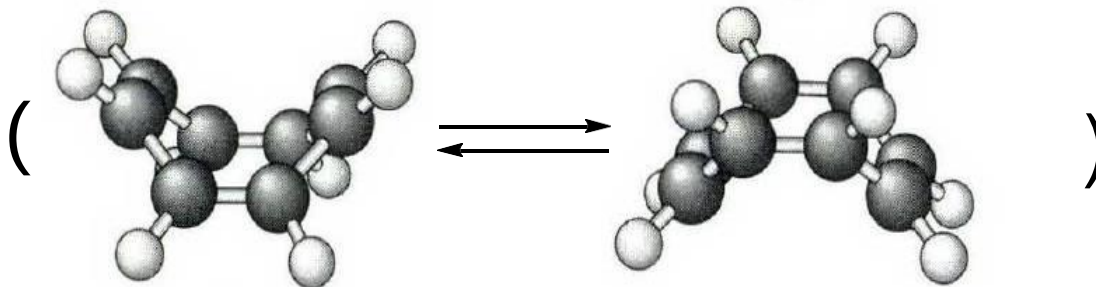
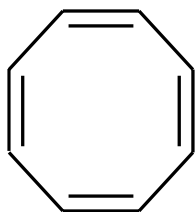
Z,Z,Z,Z,Z-



heart

E,Z,Z,Z,Z-

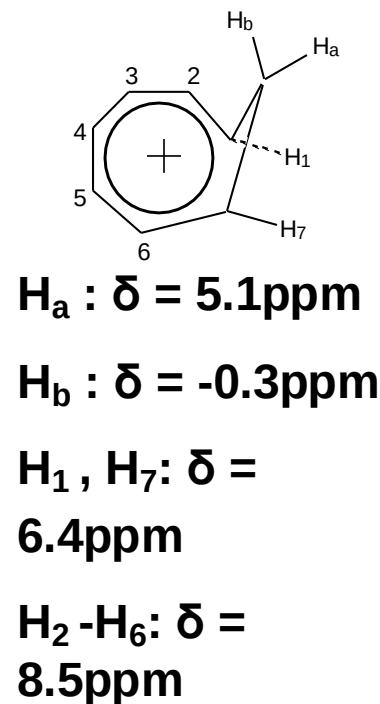
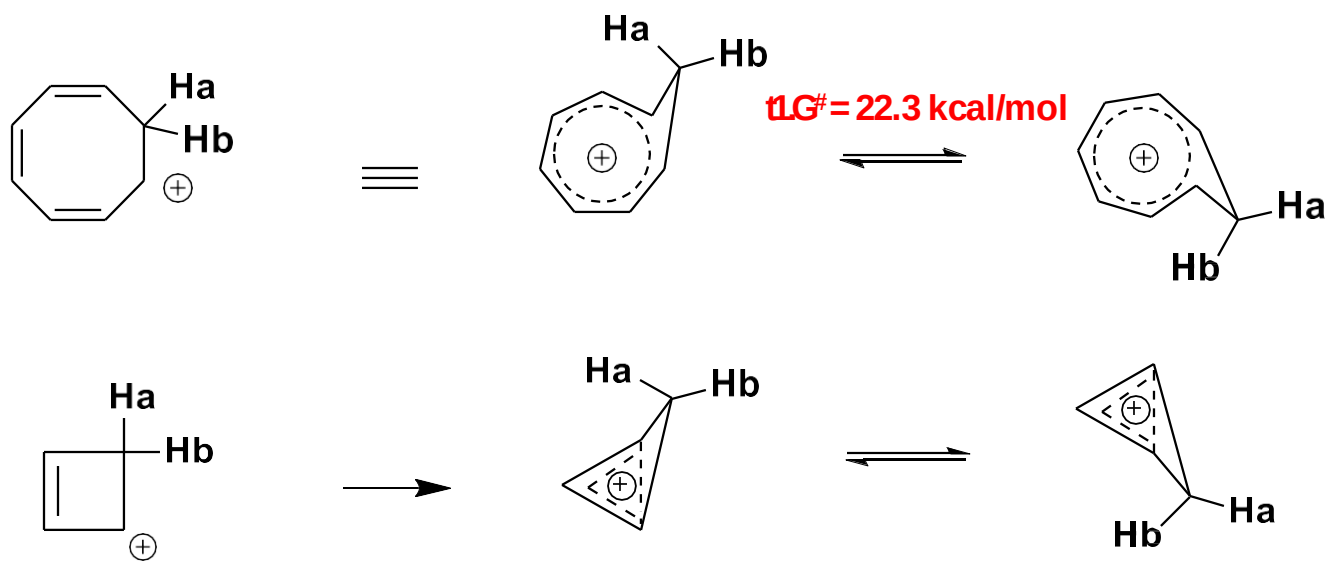
**Repulsion
between two
hydrogen atoms**



**Substitution
reactions can
occur, but
the bond
lengths are
alternating,
uneven, and
nonaromatic.**

Non-planar molecules: HMO theory does not apply

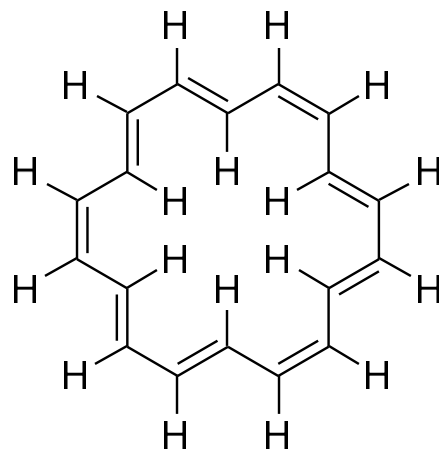
- Homoaromatic compounds refer to a type of compound that contains one or several sp^3 carbons in its conjugated ring system. In order for the p orbital to become a closed ring, the sp^3 carbon is forced to be almost perpendicular to the ring plane.



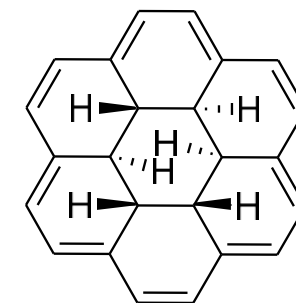
VT ^1H - and ^{13}C - NMR spectra of [18]annulene

Two multiplets at 9.25ppm (12H) and -2.9 ppm (6H) at **-60 °C**.

A singlet at 5.45ppm at **120 °C**.



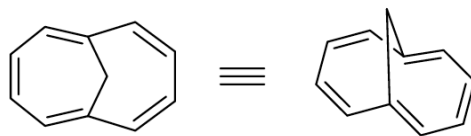
[18]annulene



H_{core} -6 - -8ppm

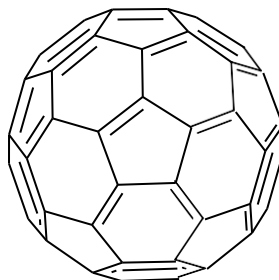
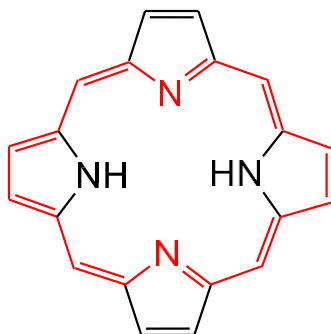
$\text{H}_{\text{periphery}}$ 9.5 ppm

One carbon at 126 ppm at **60 °C**.

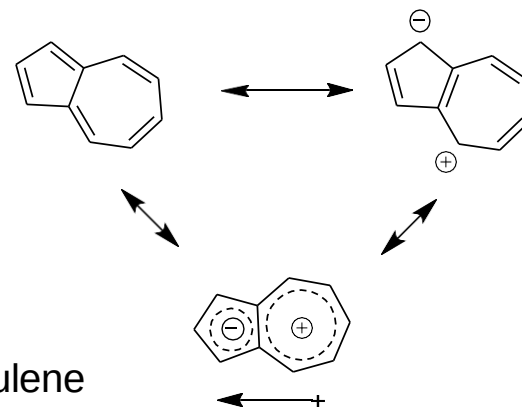


Two carbons at 128 and 121ppm at **-70 °C**.

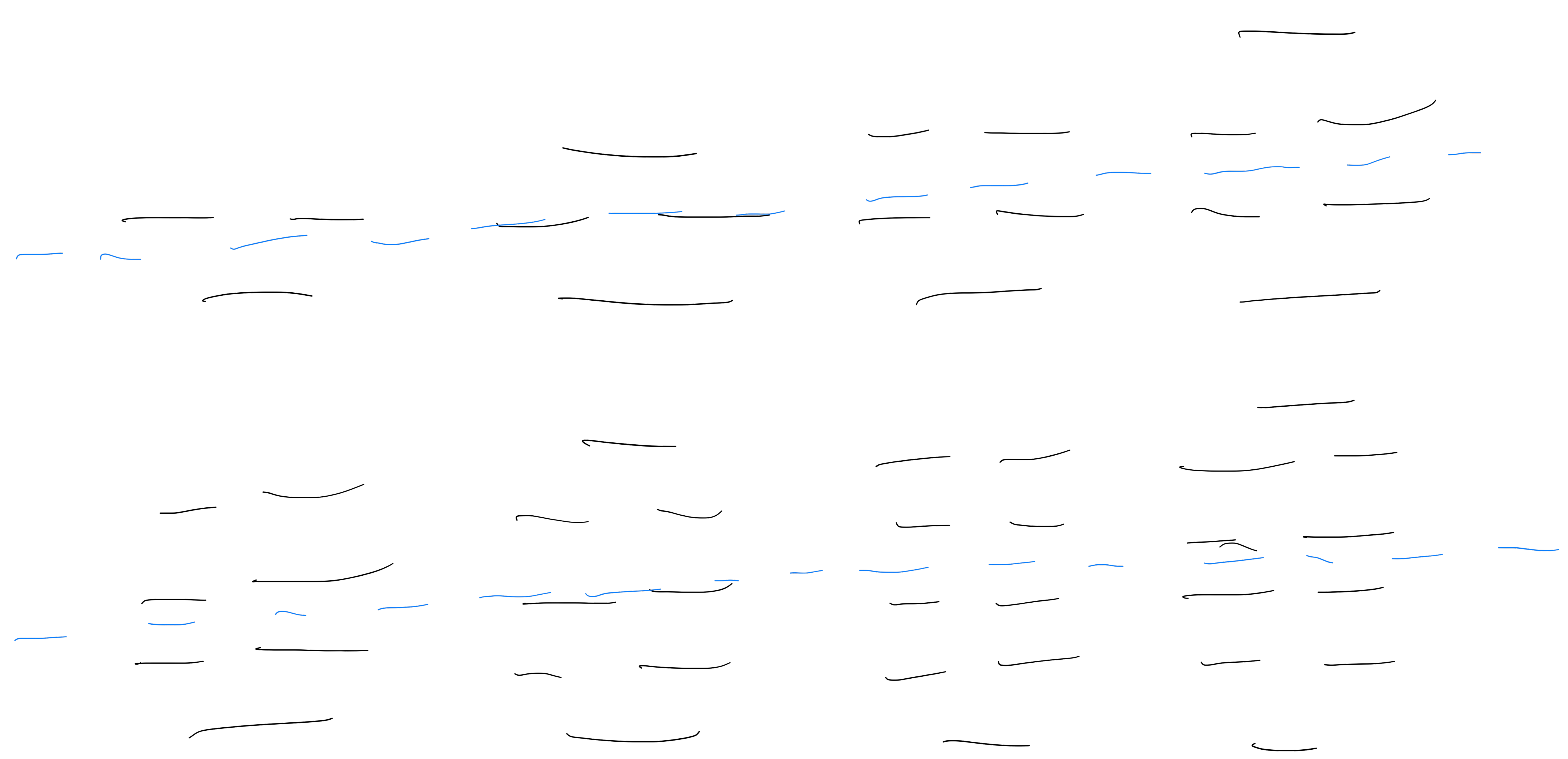
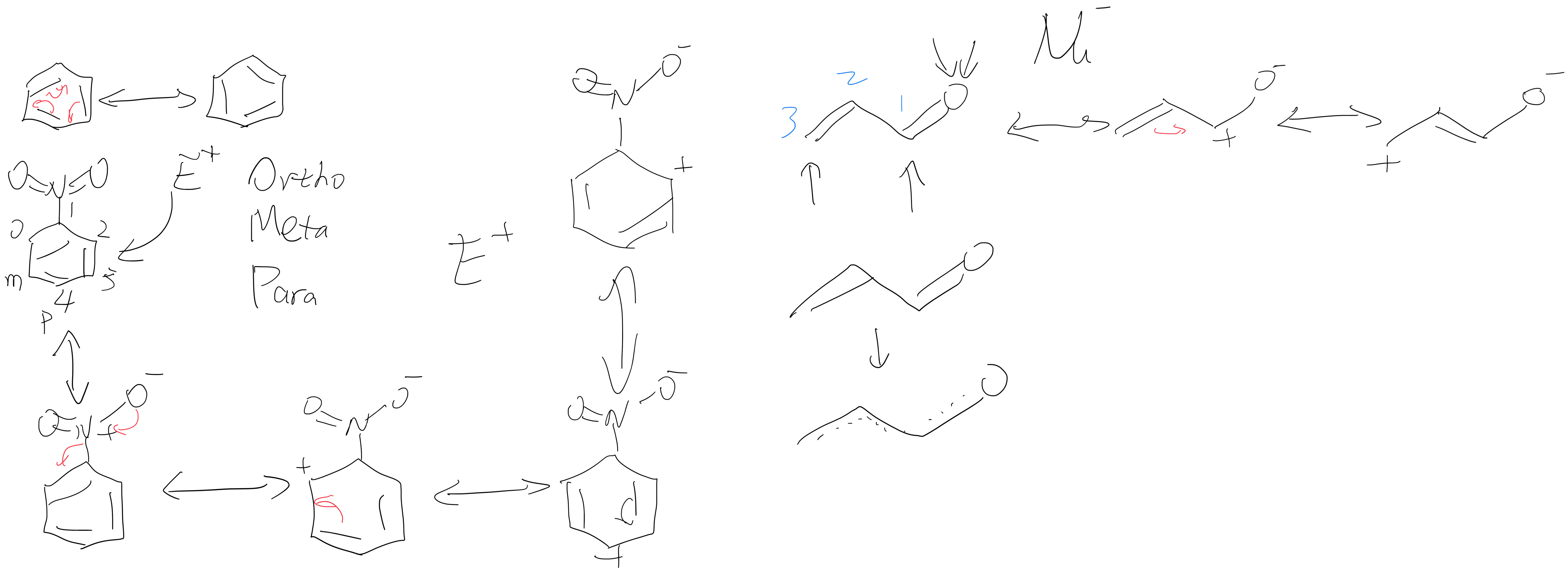
Why?



1,6-methano-[10]annulene



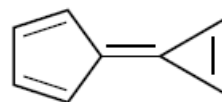
azulene



Q1

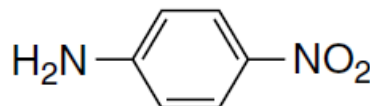
Suggest an explanation for the following observations:

- a. Although the hydrocarbon calicene has so far defied synthesis, but it has been estimated that it would have a dipole moment as large as 5.6 D.



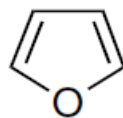
calicene

- b. The measured dipole moment of 4-nitroaniline (6.2 D) is larger than the value calculated using standard group dipoles (5.2 D).

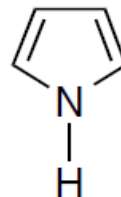


4-nitroaniline

- c. The dipole moments of furan and pyrrole are in opposite directions.



furan

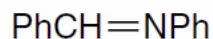


pyrrole

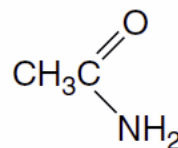
Q2

Predict the preferred site of protonation for each of the following molecules and explain the basis of your prediction.

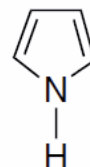
a.



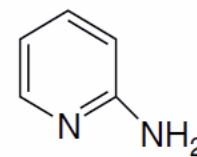
b.



c.

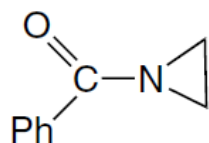


d.

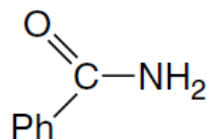


Q3

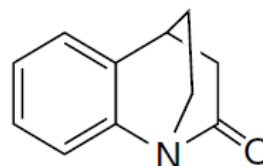
Account for the substantial differences in relative rates of alkaline hydrolysis for the following pairs of carboxamides.



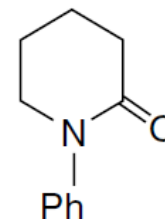
$10^5 >$



and

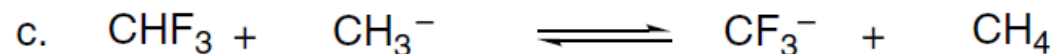
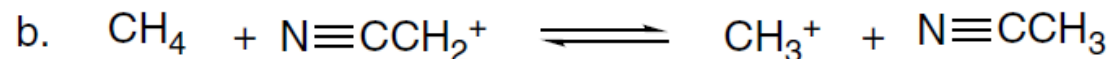
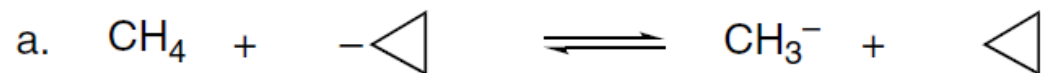


$10^3 >$



Q4

Predict whether the following gas phase reactions will be thermodynamically favorable or unfavorable. Explain your answer.



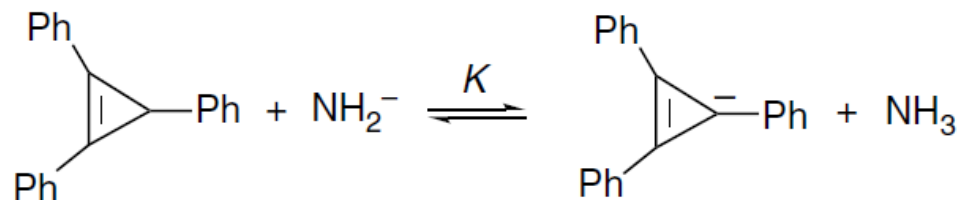
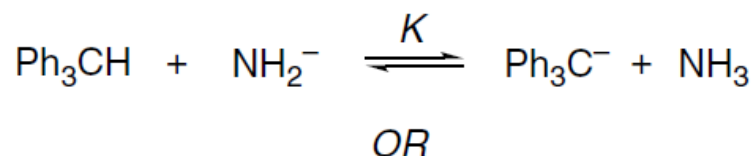
Q5

For each reaction, predict which compound would react faster (k) or give the more complete (K) reaction. Explain the basis for your prediction.

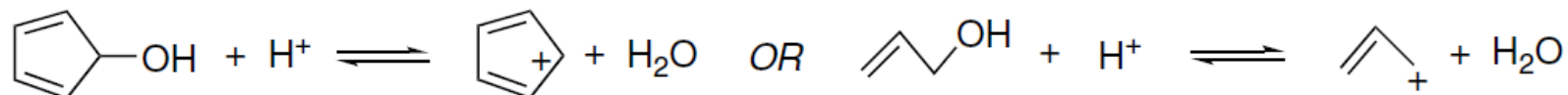
a.



b.



c.

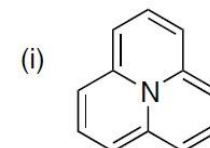
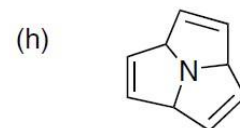
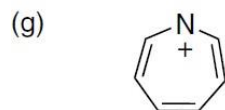
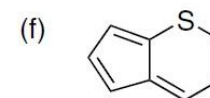
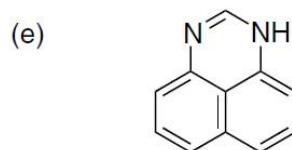
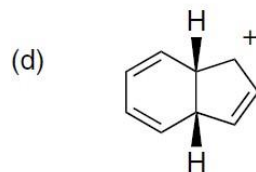
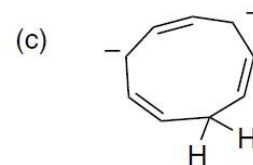
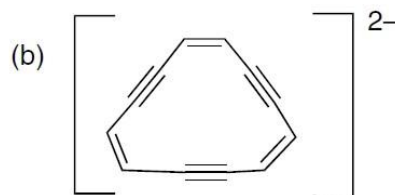
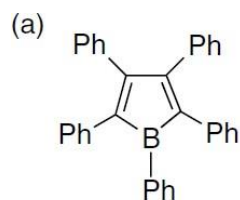


Q6 : Apply molecular orbital theory to CH_3^+ (6e), BH_3 (6e) and NH_3 (8e)

Fill in the electrons and describe the molecular structures of CH_3^+ , BH_3 and NH_3 ?

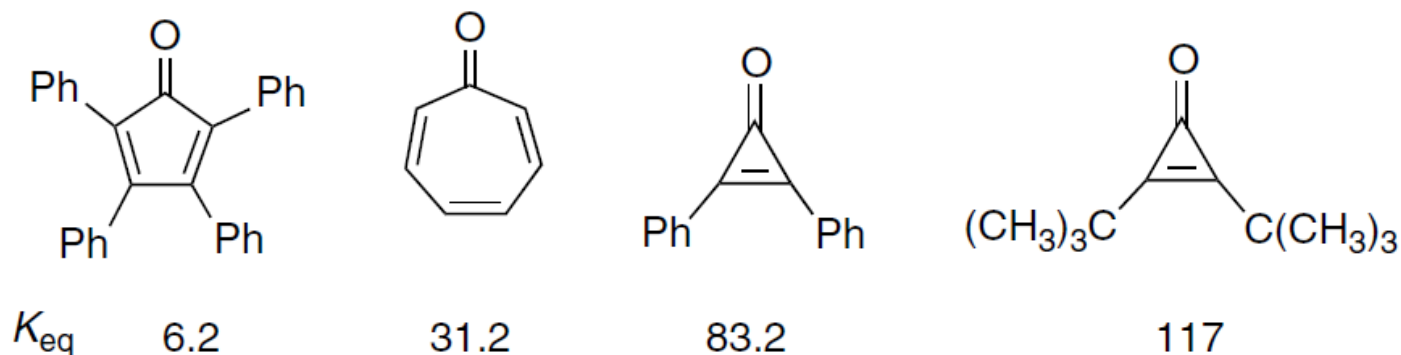
Q7 : Use valence bond theory and molecular orbital theory to discuss the reaction between enamine and allyl cation.

Q8 : Figure out the following compounds are aromatic, non-aromatic or antiaromatic? Why?



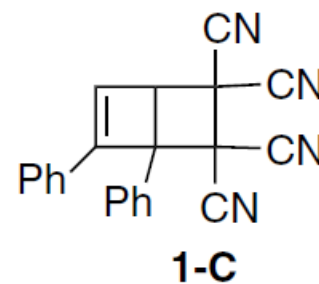
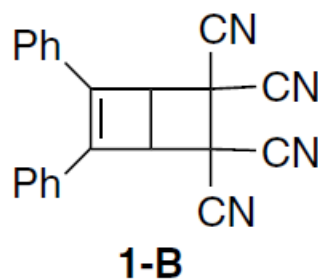
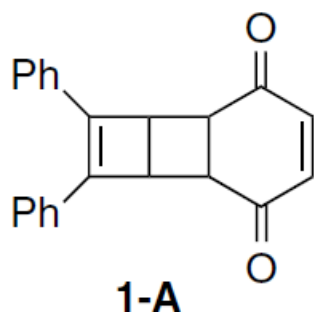
Q9

The relative basicity of carbonyl oxygens can be measured by studying the strength of hydrogen bonding with a hydrogen donor such as phenol. The K_{eq} for 1:1 complexation of the following substituted cyclenones was determined. What conclusions do you draw from these data?



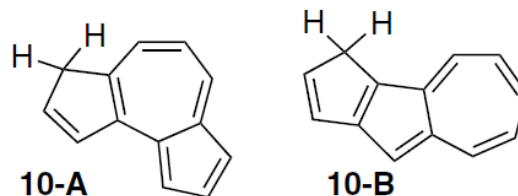
Q10

The reaction of 1,2-diphenylcyclobutadiene (generated in situ by oxidation of its iron tricarbonyl complex) with *p*-benzoquinone yields adduct **1-A** as the exclusive product. A completely analogous structure is obtained using maleimide as the dienophile. However, with the more reactive dienophiles tetracyanoethylene and dicyanomaleimide, two isomeric adducts of type **1-B** and **1-C** are found in a 1:7 ratio in each case. Discuss these results and explain how they relate to the issue of a square versus a rectangular structure for the cyclobutadiene ring.

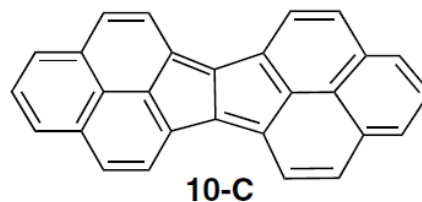


Q11: Explain the following phenomena

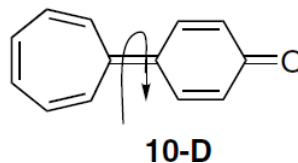
- a. Hydrocarbon **10-A** ($pK \approx 14$) is considerably more acidic than **10-B** ($pK \approx 22$).

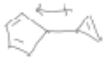


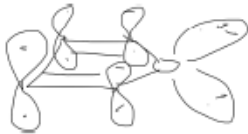
- b. Hydrocarbon **10-C** has an unusually small separation of its oxidation and reduction potentials, as established by electrochemical measurements. It is both easily reduced and easily oxidized. Both mono- and dications and mono- and dianions can be readily formed.

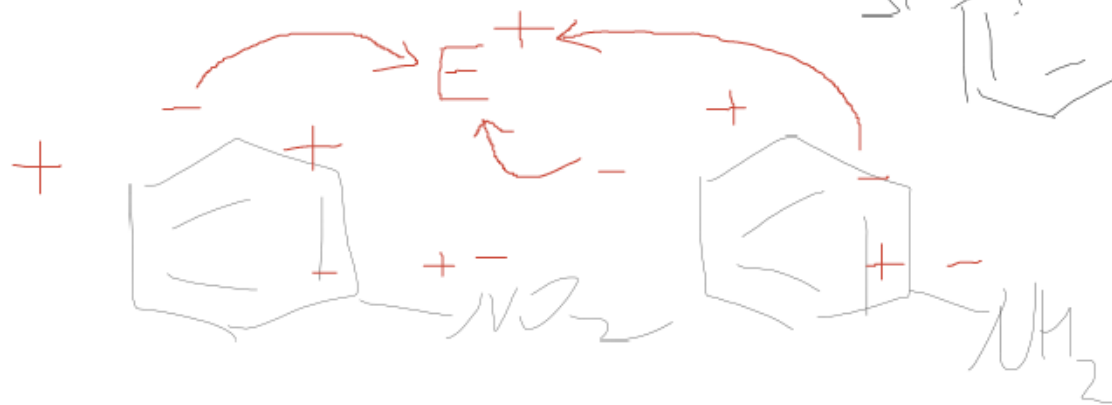
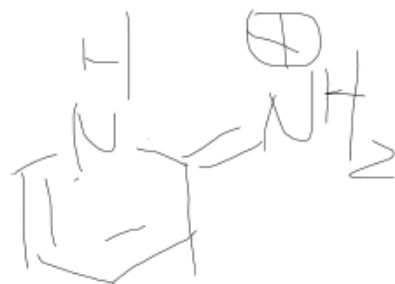
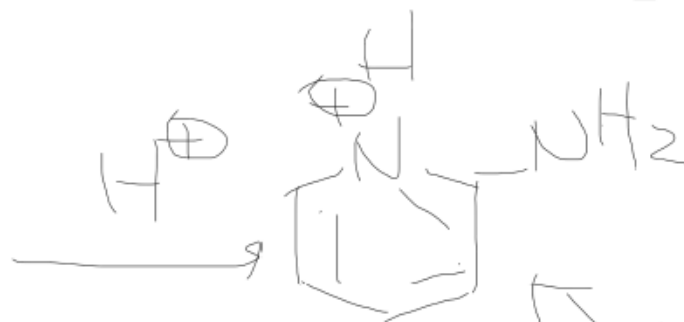
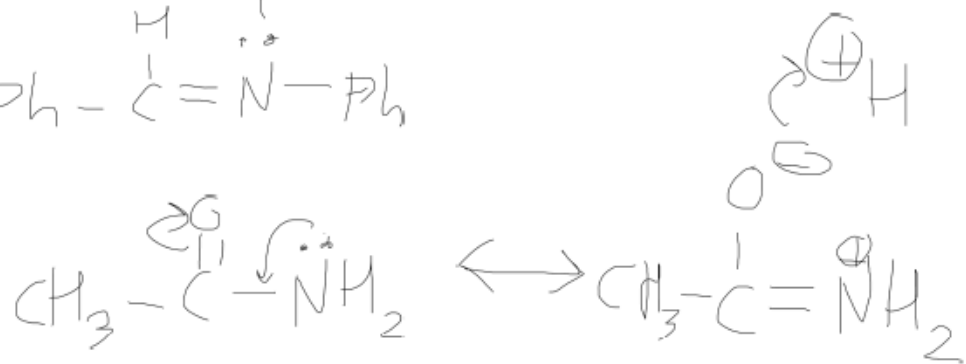
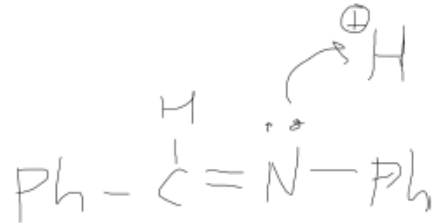


- c. The barrier for rotation about the marked bond in **10-D** is only about 14 kcal/mol.













Nobel Prize on Chiral / Asymmetric Catalysis



The Nobel Prize in Chemistry 2001

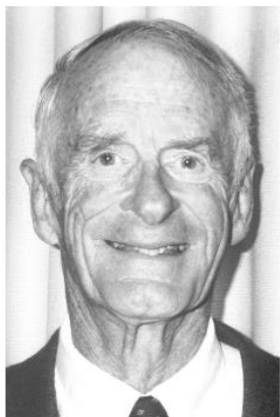


Photo from the Nobel
Foundation archive.

William S. Knowles

Prize share: 1/4



Photo from the Nobel
Foundation archive.

Ryoji Noyori

Prize share: 1/4



Photo from the Nobel
Foundation archive.

K. Barry Sharpless

Prize share: 1/2

The Nobel Prize in Chemistry 2001 was divided, one half jointly to William S. Knowles and Ryoji Noyori "for their work on chirally catalysed hydrogenation reactions" and the other half to K. Barry Sharpless "for his work on chirally catalysed oxidation reactions"

The Nobel Prize in Chemistry 2021



© Nobel Prize Outreach. Photo:
Stefan Bladh.

Benjamin List

Prize share: 1/2



© Nobel Prize Outreach. Photo:
Risdon Photography

David W.C. MacMillan

Prize share: 1/2

The Nobel Prize in Chemistry 2021 was awarded jointly to Benjamin List and David W.C. MacMillan "for the development of asymmetric organocatalysis"



Definitions of Key Words

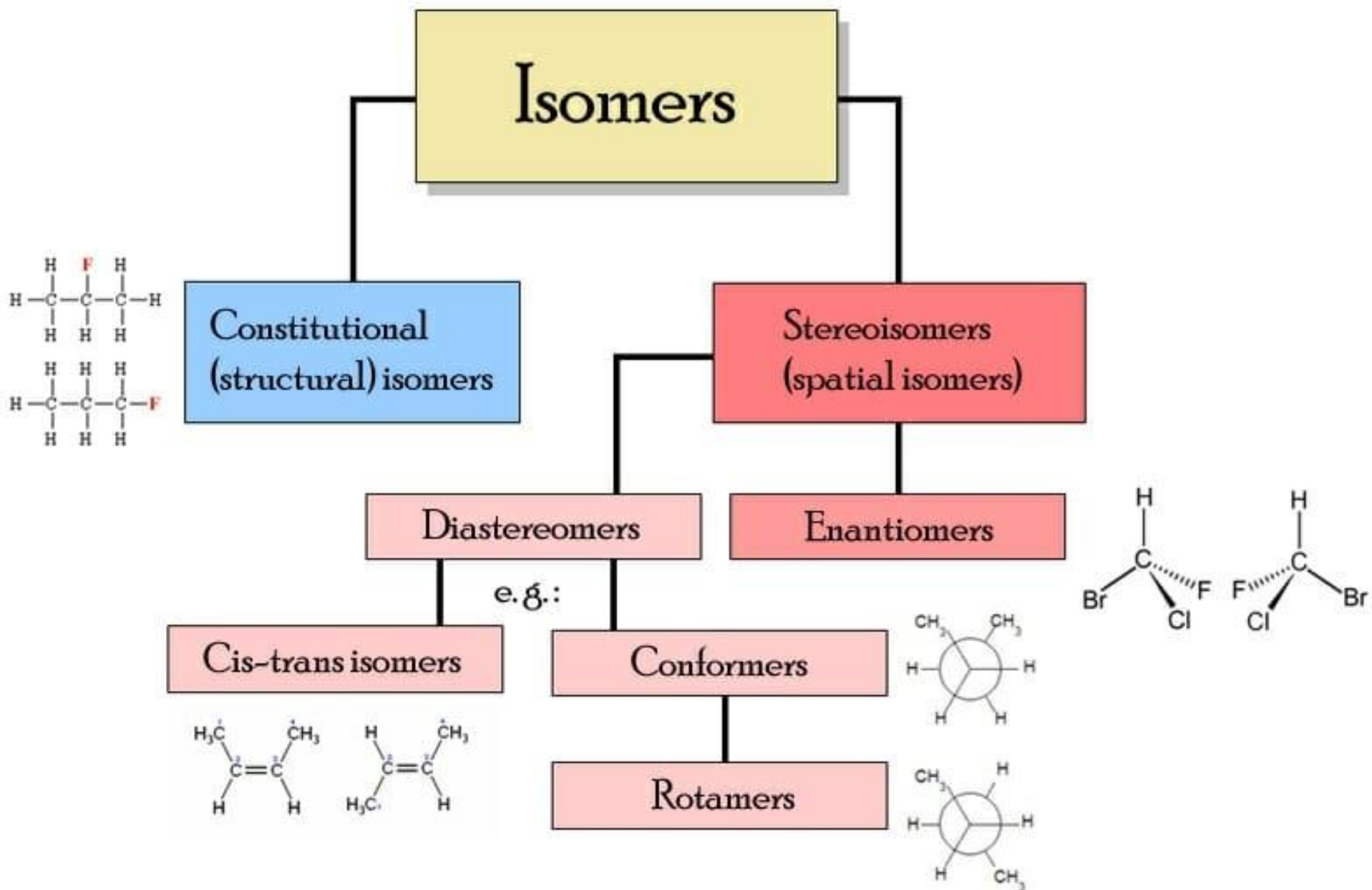


Stereochemistry: Stereochemistry in its broadest sense describes how the atoms of a molecule are arranged in **three-dimensional** space. In particular, stereoisomers are molecules that have identical connectivity (**constitution**) but differ in three-dimensional structure. Stereoisomers differ from one another in **configuration** at one or more atoms.

Configuration: Organic molecules are given structures with different shapes through the **breakage** and **reorganization** of **chemical bonds**.

Conformation: Organic molecules are given structures with different shapes through the **rotation** of one or more **single bonds**.

Classification of Isomers



What have higher energy barriers?

What can not be rotated?

Geometrical
Isomers

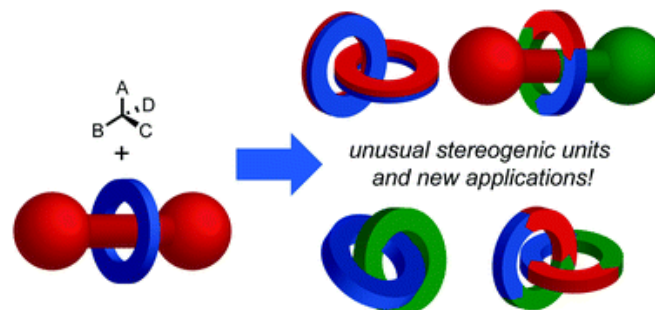
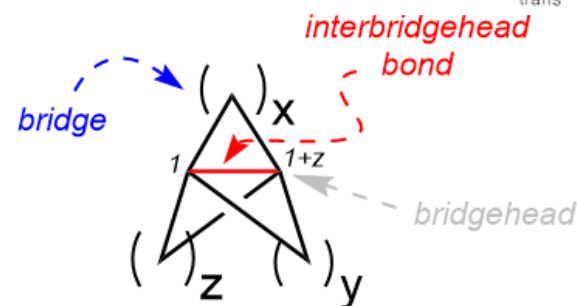
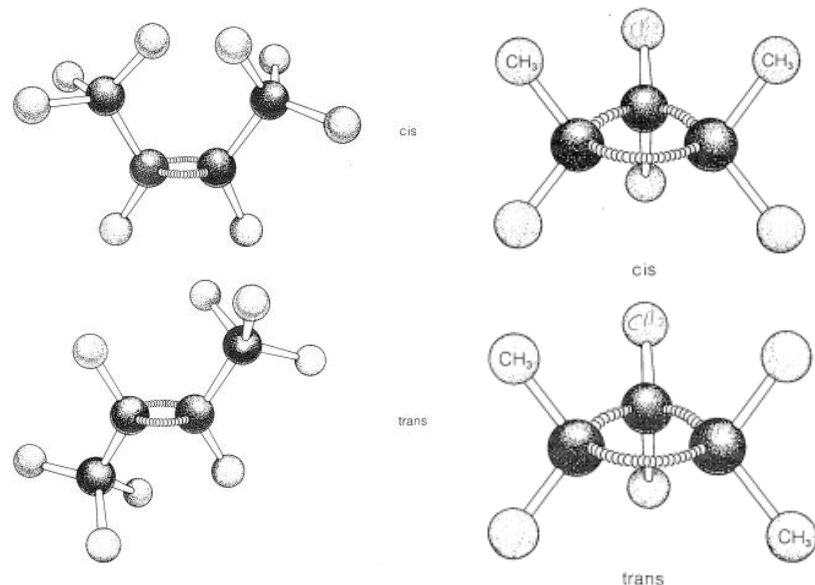
1. Double bonds
2. Fused rings

Chiral
Isomers

3. Chiral Center
Tetrahedral atoms (sp^3)
4. Chiral Axis
Allenes
Spiro compounds
Atropisomer
5. Chiral Plane
Helicene
Propellane

Mechano
stereoisomers

6. Knots
7. Links / Catenanes
8. Rotaxanes



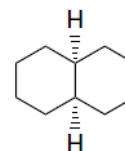


Cahn-Ingold-Prelog Priority Rules

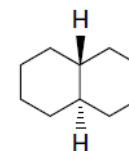


- The rules for establishing priority of different substituents are as follows:
 1. First, assign priority based on the atoms bonded directly to the asymmetric center such that **higher atomic number has higher priority** than lower atomic number.
 2. Second, for cases where two directly-bonded atoms are **isotopes**, assign priority to the one with **higher atomic mass**.
 3. Third, for cases where two substituents are the same atom, proceed outward to **neighboring atoms** in the substituent groups and assign priority based on the **first point of difference**.
 4. Where **double or triple bonds** are encountered, these are treated by assuming that each such bonded atom is **duplicated or triplicated**.

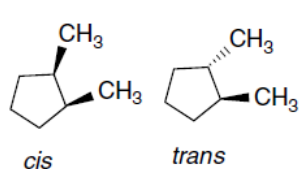
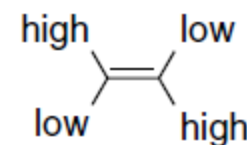
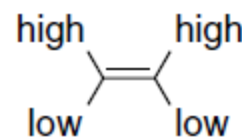
- **Cis**: Same group **same** side
- **Trans**: Same group **opposite** sides
 - *Cis/Trans* denotation considers the **main chain** as the “same group”
- **Z**: Higher priority are **together**
- **E**: Higher priority are **opposite**



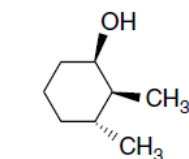
cis-decalin
cis-decahydronaphthalene



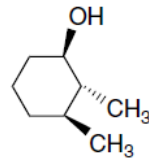
trans-decalin
trans-decahydronaphthalene



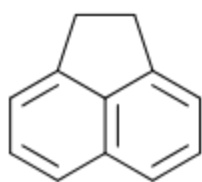
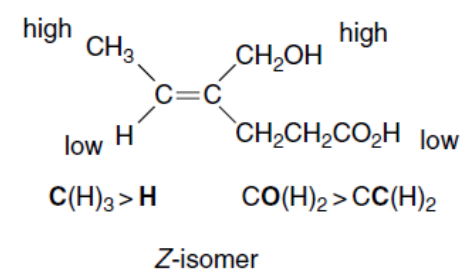
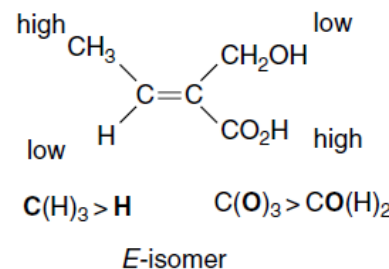
cis
stereoisomers of
1,2-dimethylcyclopentane



cis,trans-2,3-dimethyl-
cyclohexanol



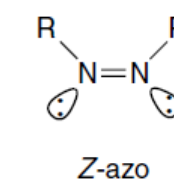
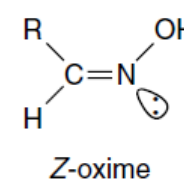
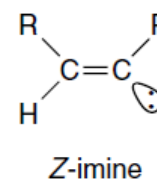
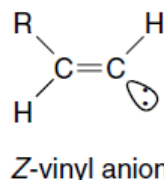
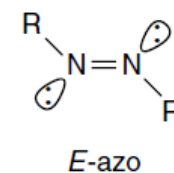
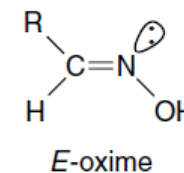
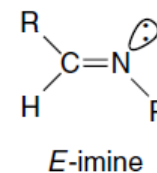
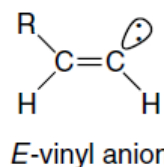
trans,cis-2,3-dimethyl-
cyclohexanol



Acenaphthene

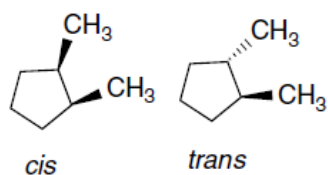
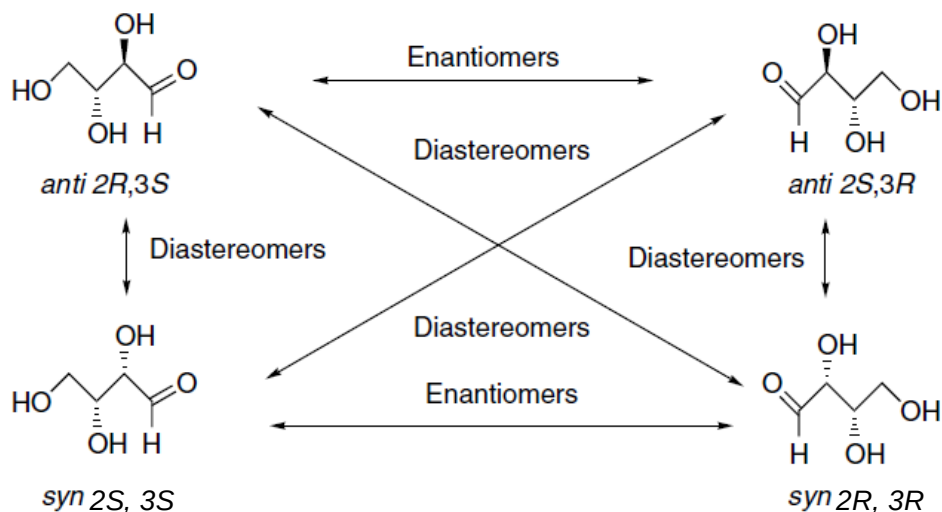


Norbornane

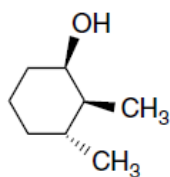


Farthest or Nearest? *Syn/Anti* Denotation

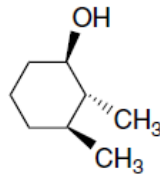
- Two adjacent substituents pointed in the same direction (in or out) are **syn**, whereas those pointed in opposite directions are **anti**.
- But how to define “adjacent”?



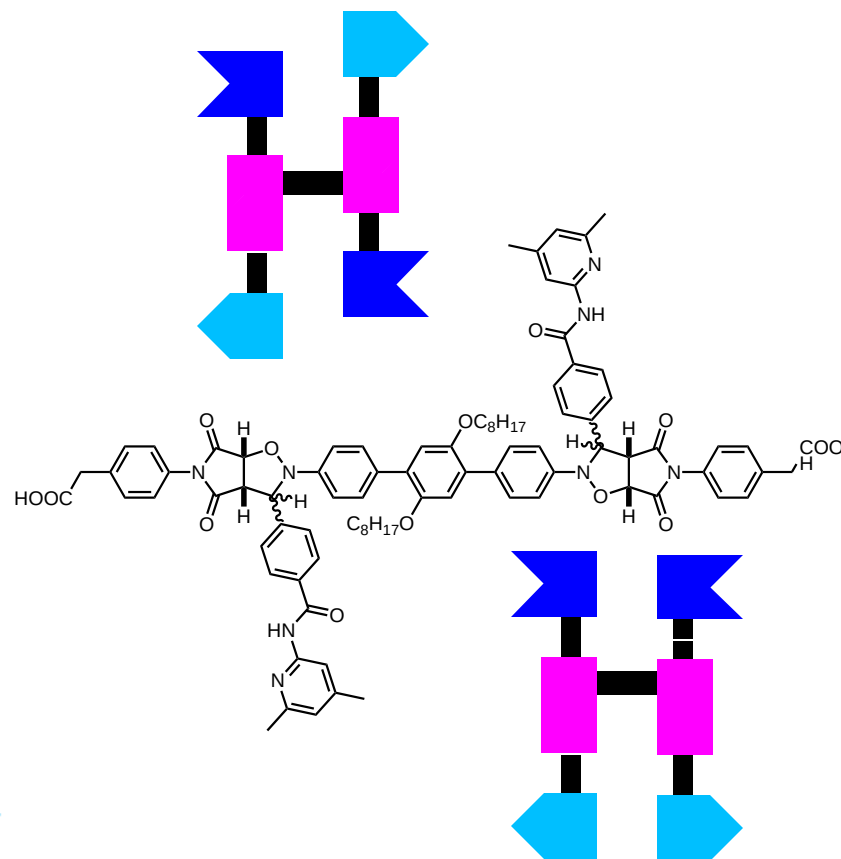
stereoisomers of 1,2-dimethylcyclopentane



cis,trans-2,3-dimethylcyclohexanol



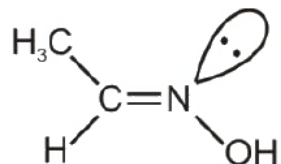
trans,cis-2,3-dimethylcyclohexanol



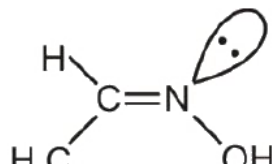
Tricky *Syn/Anti* Situations

Aldoxime: *Syn* isomer: In which hydrogen and –OH are on same side.

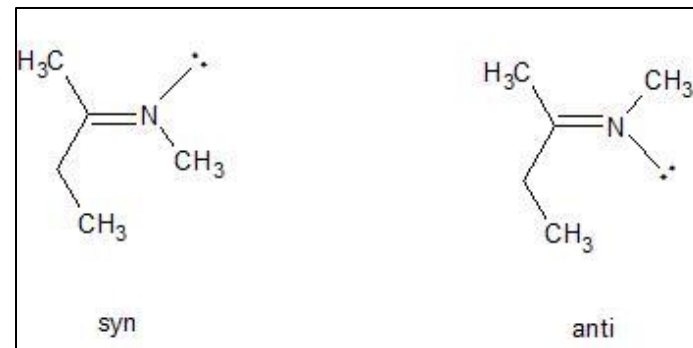
Anti-isomer: In which hydrogen and –OH are on opp. Side.



Syn-oxime

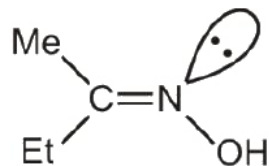


Anti-oxime

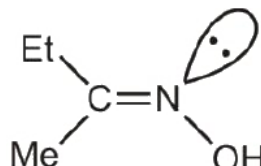


Ketoximes

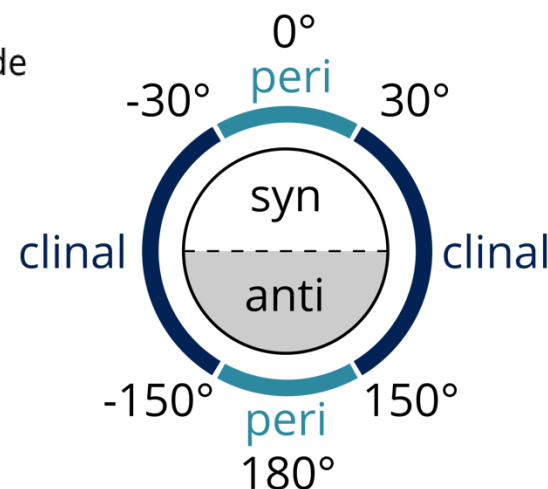
The *z*-oxime has hydroxyl group and the group with higher priority on same side while '*E*' –oxime has it on opposite sides.



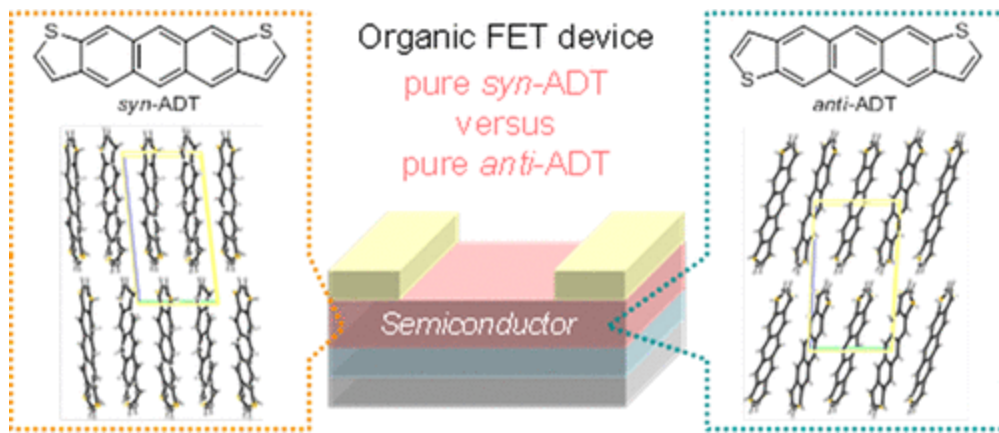
Syn-(*z*)



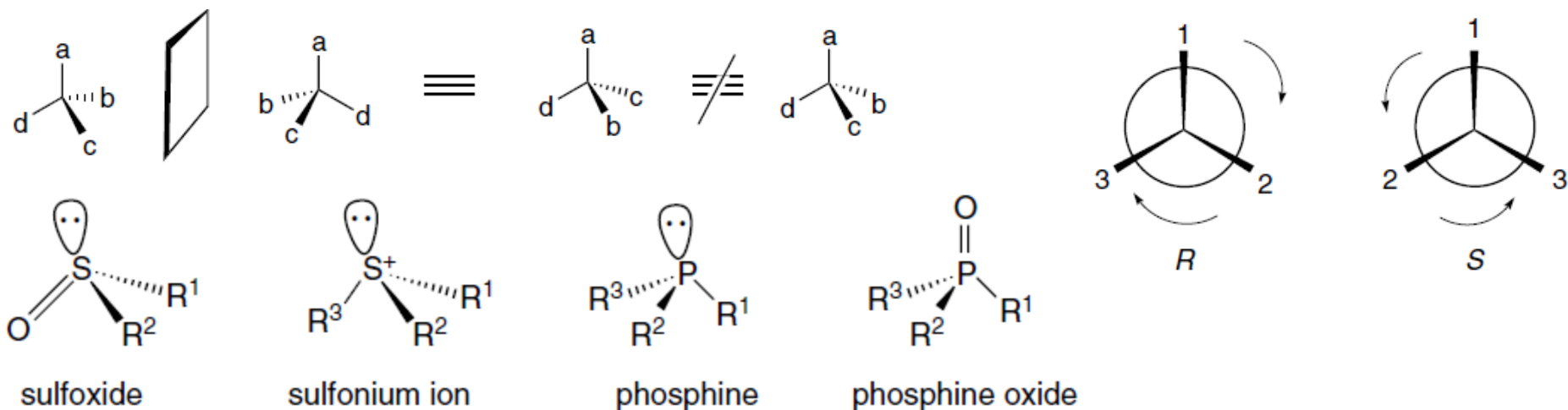
(Anti (*E*))



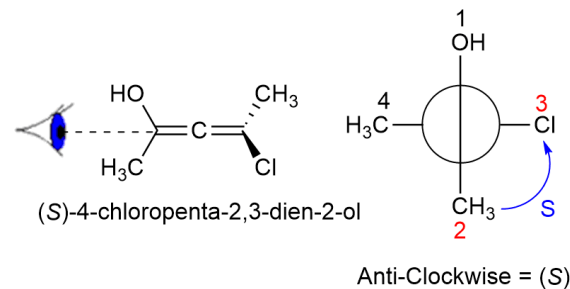
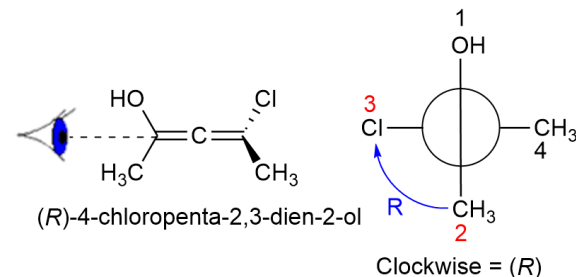
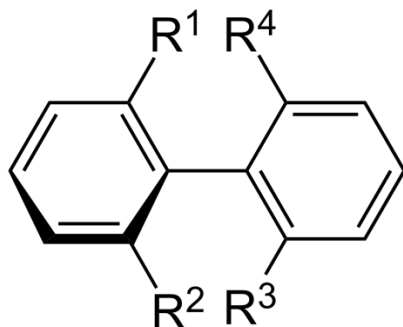
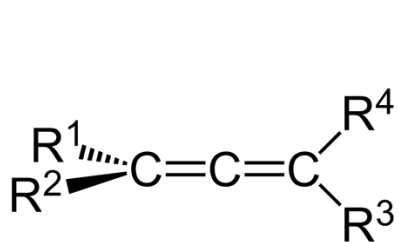
For a Klyne–Prelog System



**Constitutional or
Configurational Isomers?**

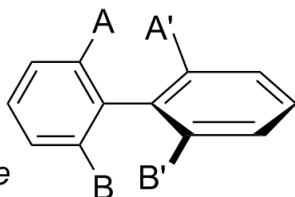
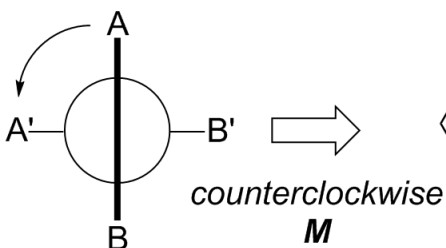


- The molecule is then viewed opposite from the **lowest-priority group**, that is, the group is placed **behind the stereocenter** and away from the viewer.
- Two arrangements are possible for the other three substituents. The groups can **decrease in priority** in either a clockwise or a counterclockwise direction.
- The **clockwise** direction configuration is assigned **R** (for rectus) and the **counterclockwise** direction is assigned **S** (for sinister).

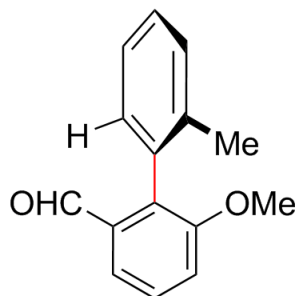


Allenes

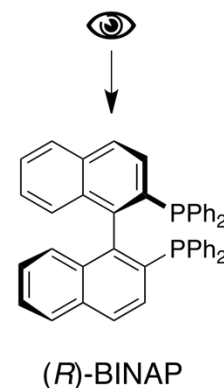
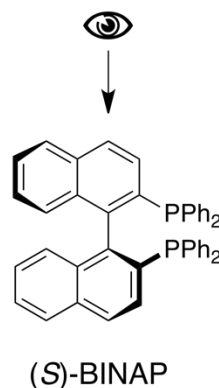
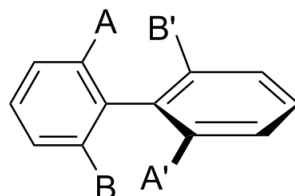
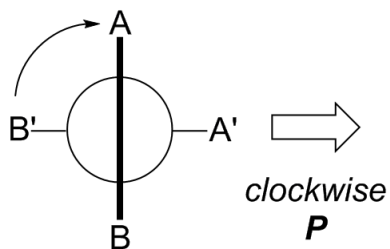
Binaryl Atropisomers



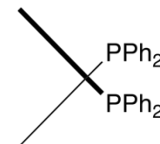
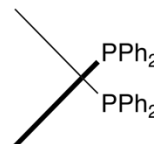
example:



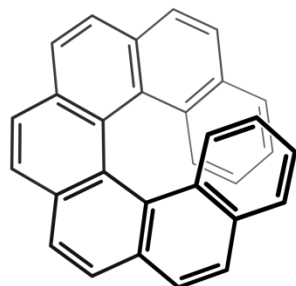
M counterclockwise



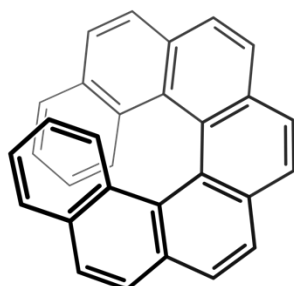
***R*, *P* or Δ for clockwise**
***S*, *M* or Λ for counterclockwise**



Helical Chirality



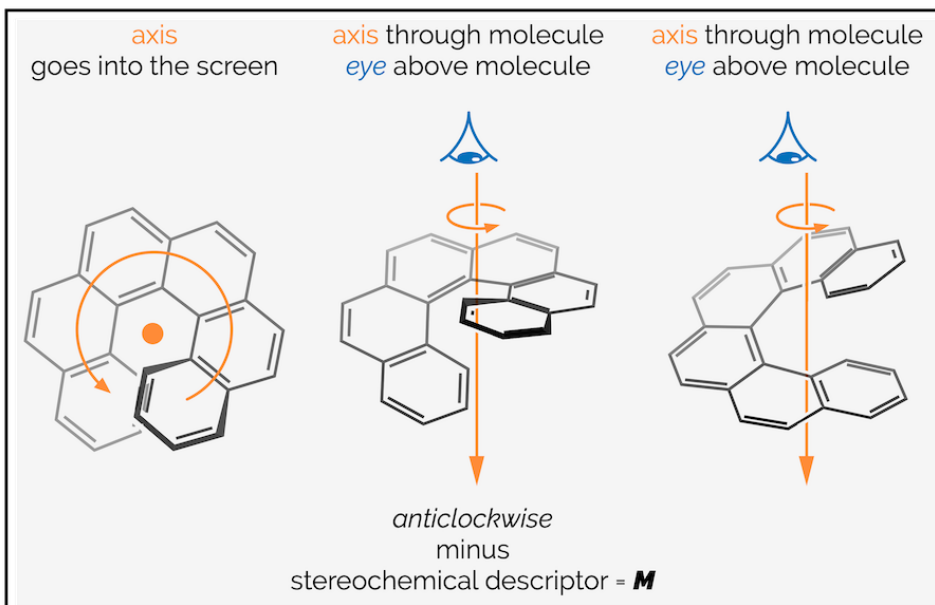
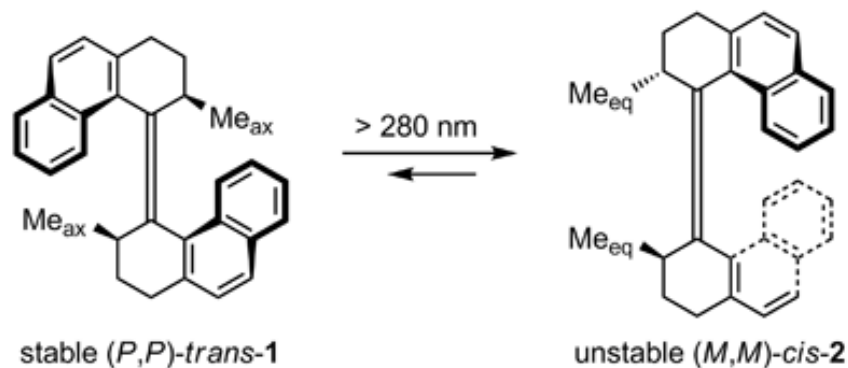
P or Δ



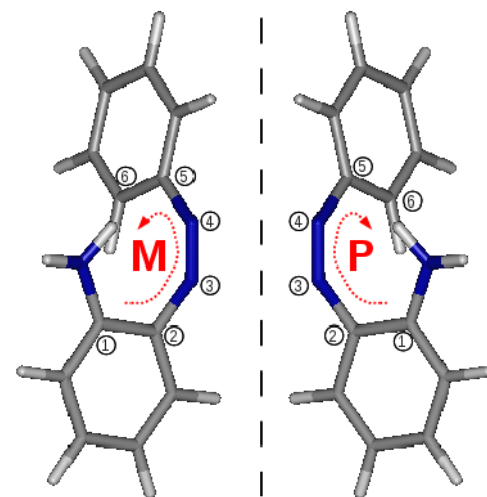
M or Λ

P or Δ for clockwise
M or Λ for counterclockwise

A Feringa's Molecular Motor



Helix in a single ring



Chirality in Biomolecules

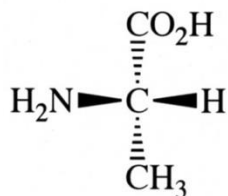
Amino Acid

L: Left-Handed

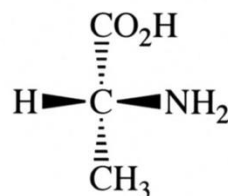
D: Right-Handed

L = ?

D = ?

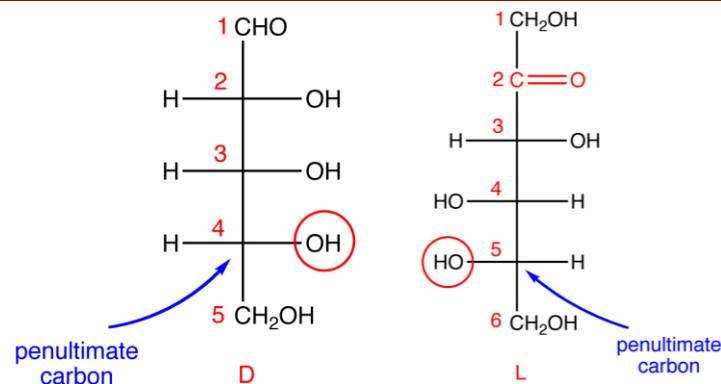


L-Alanine

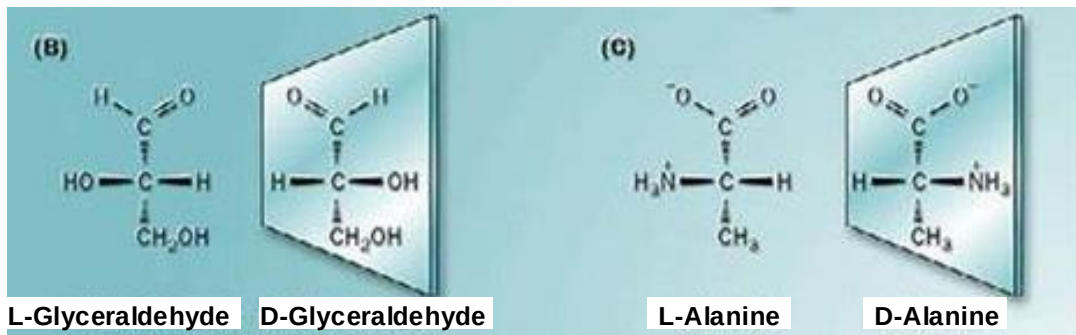


D-Alanine

Mirror



Monosaccharide

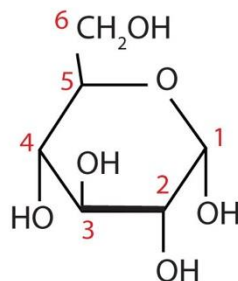
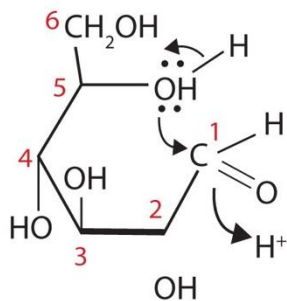
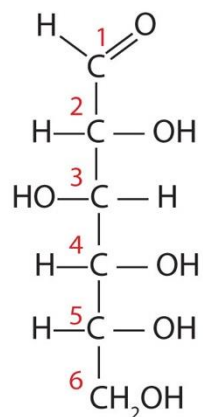
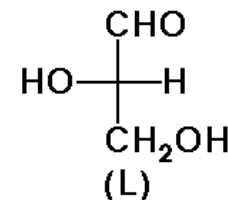
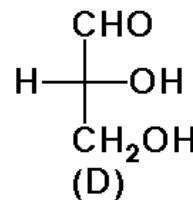
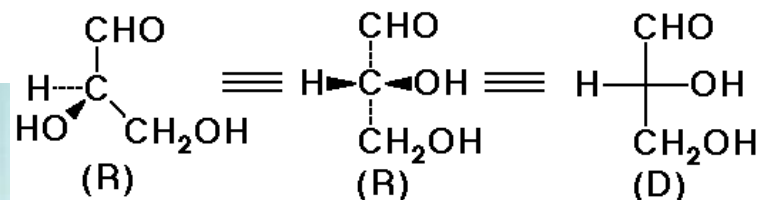


L-Glyceraldehyde

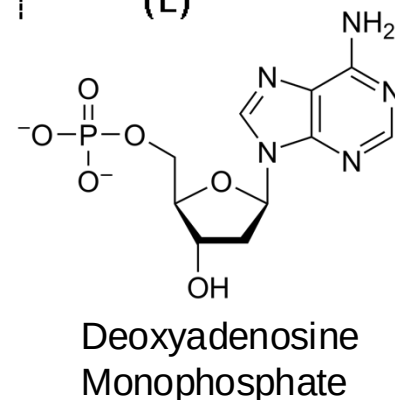
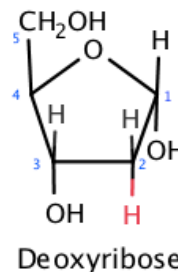
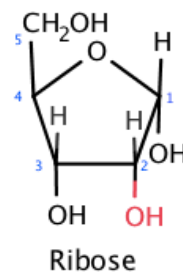
D-Glyceraldehyde

L-Alanine

D-Alanine

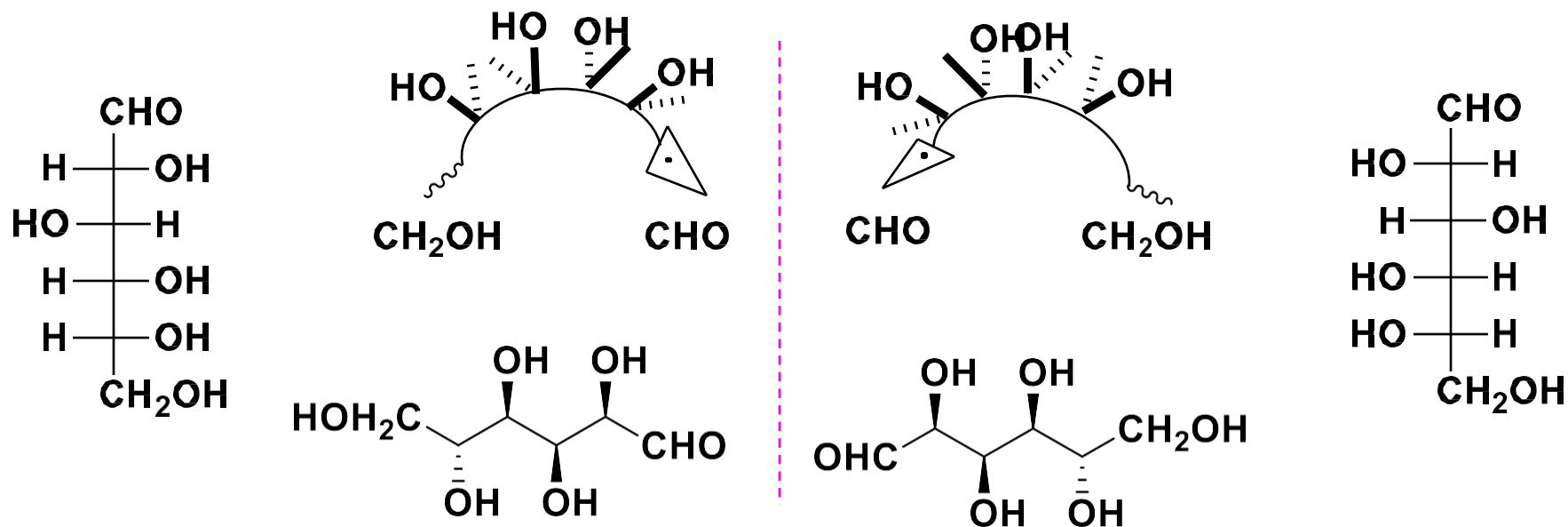


Nucleotide



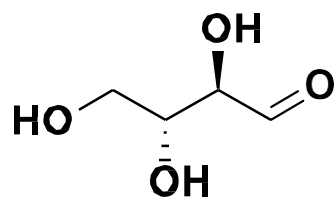


Conversion between Sawtooth and Fischer

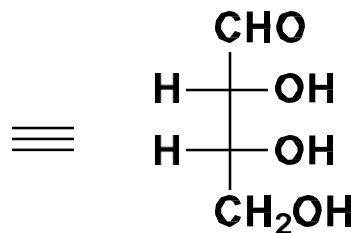




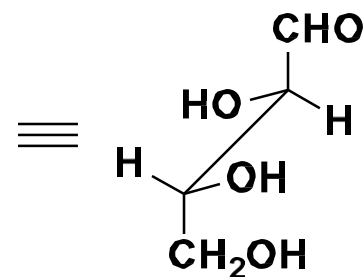
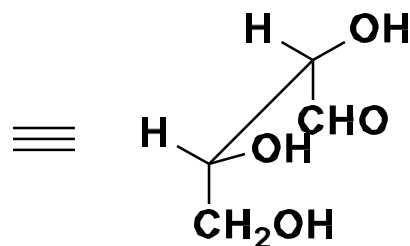
Sawtooth / Fischer / Newman Projections



anti 2R,3R



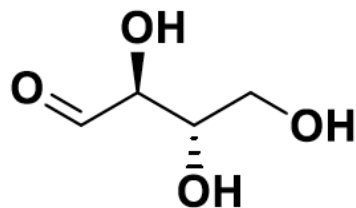
D-erythrose



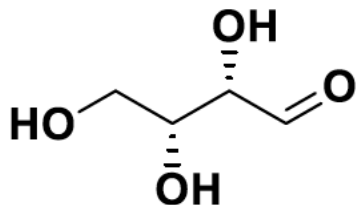
|||

Flash Quiz

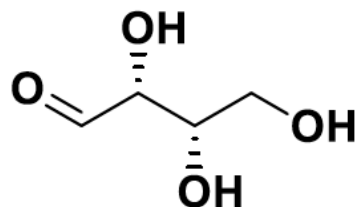
3 isomers
3 projections



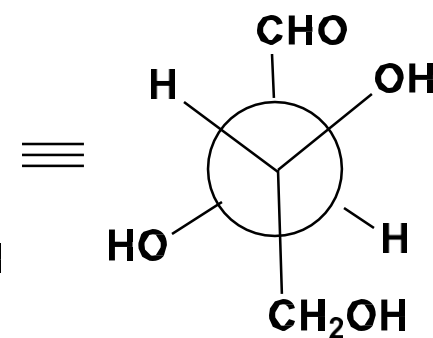
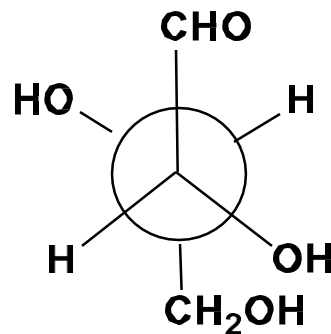
anti 2S,3S



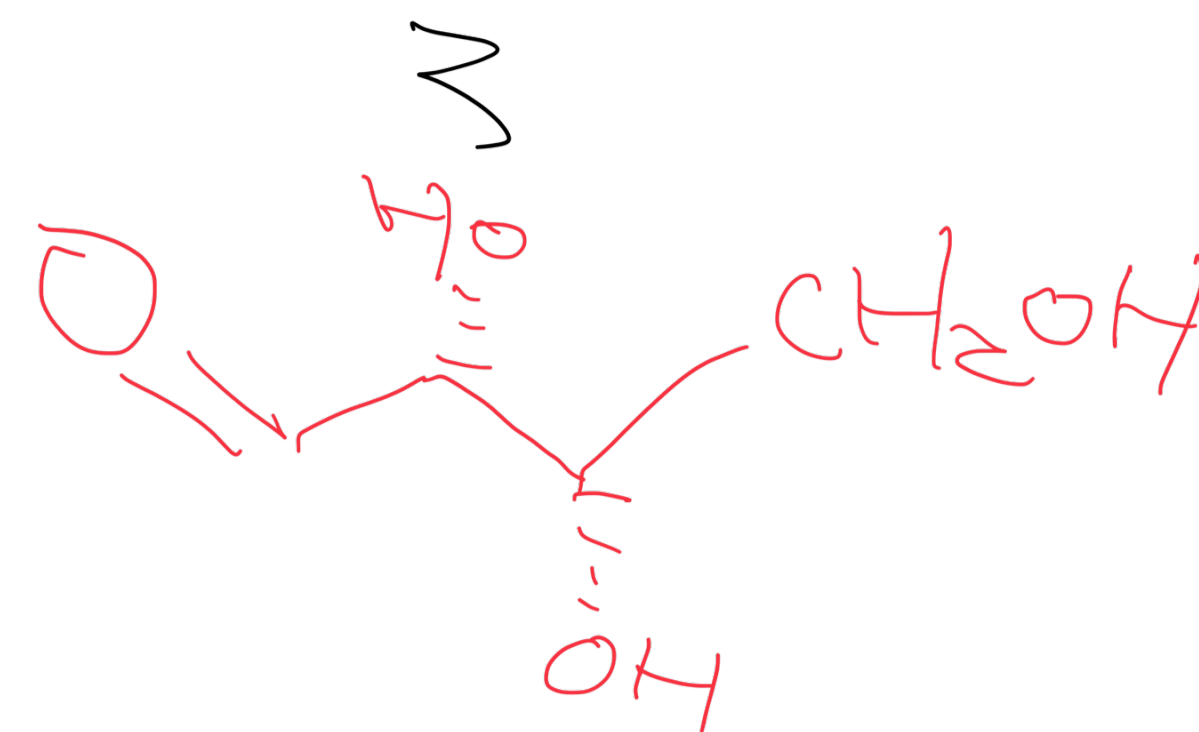
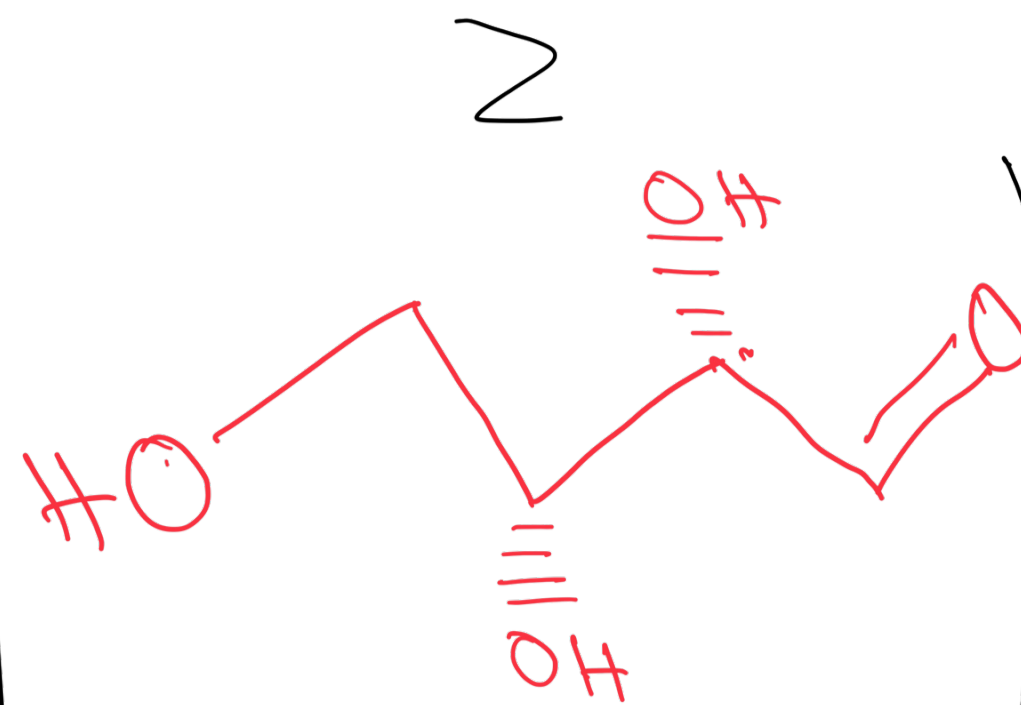
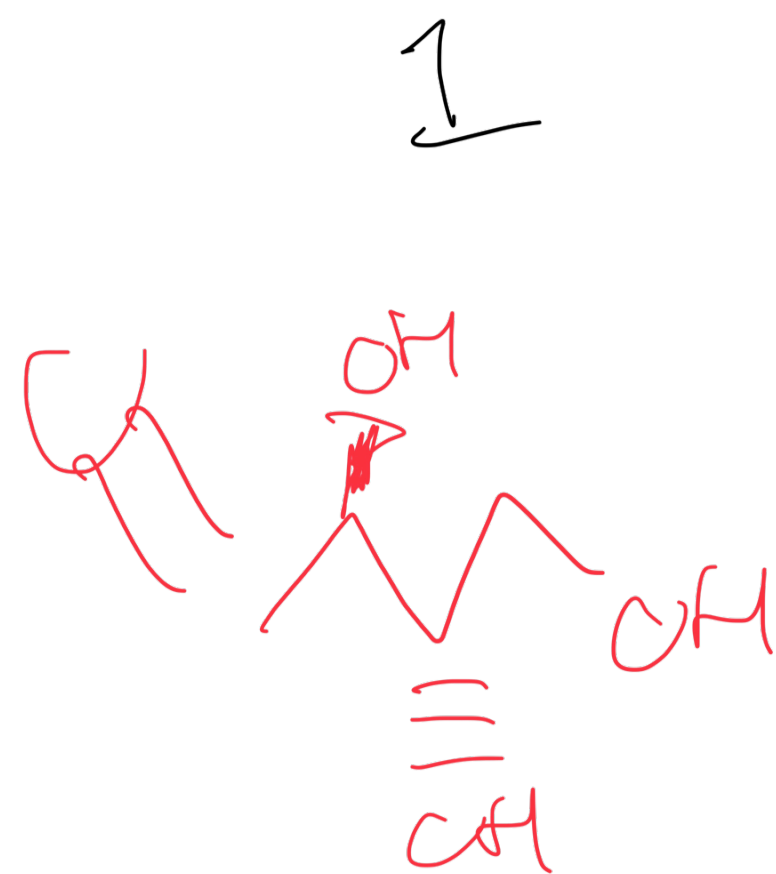
syn 2S,3R



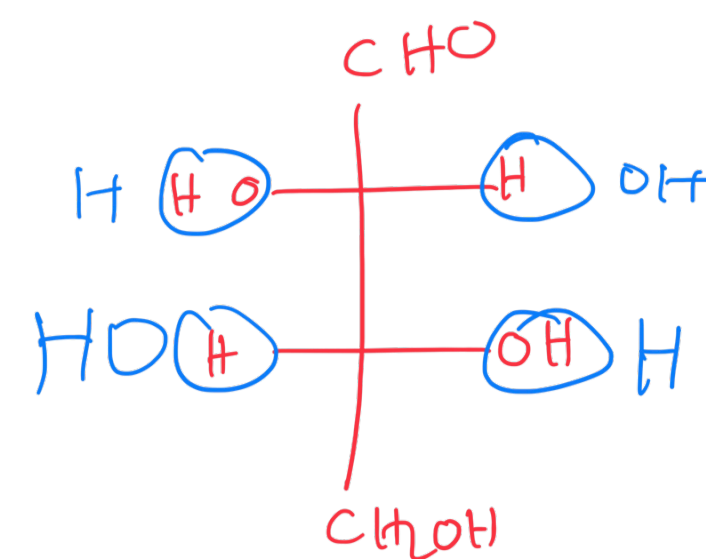
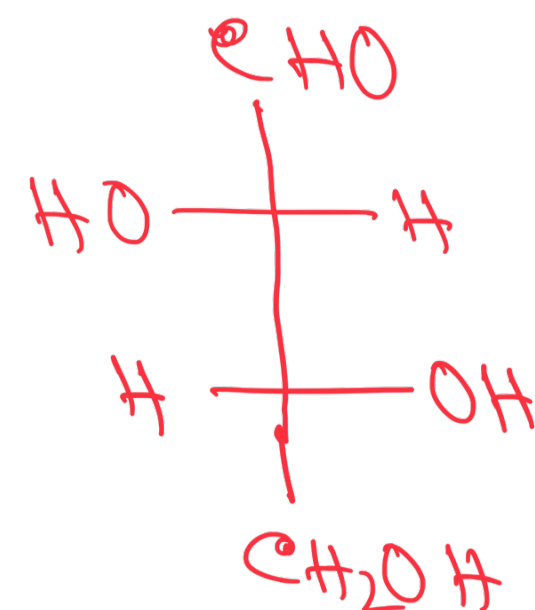
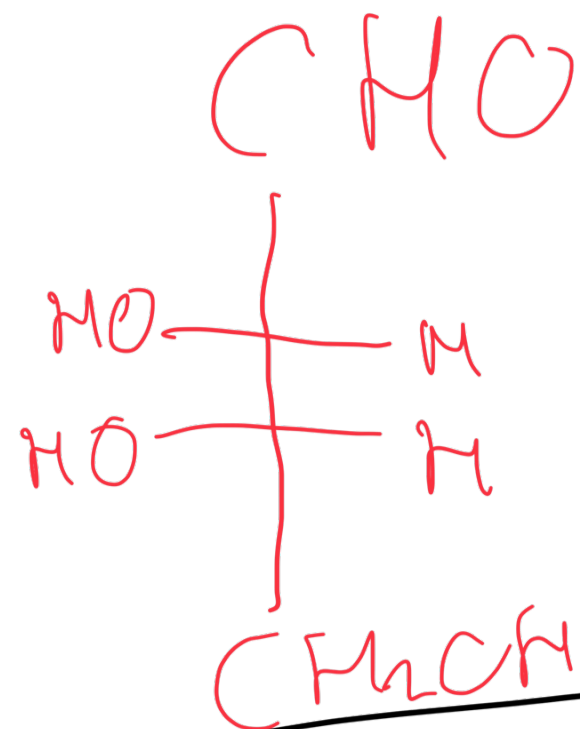
syn 2R,3S



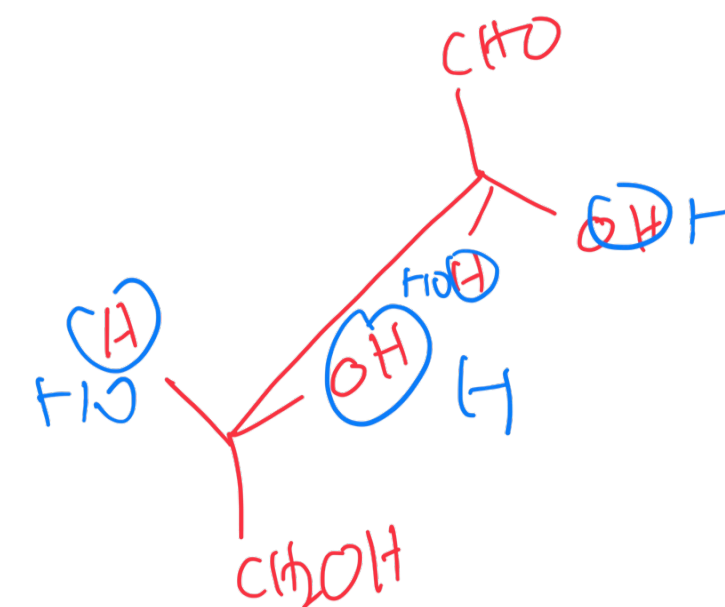
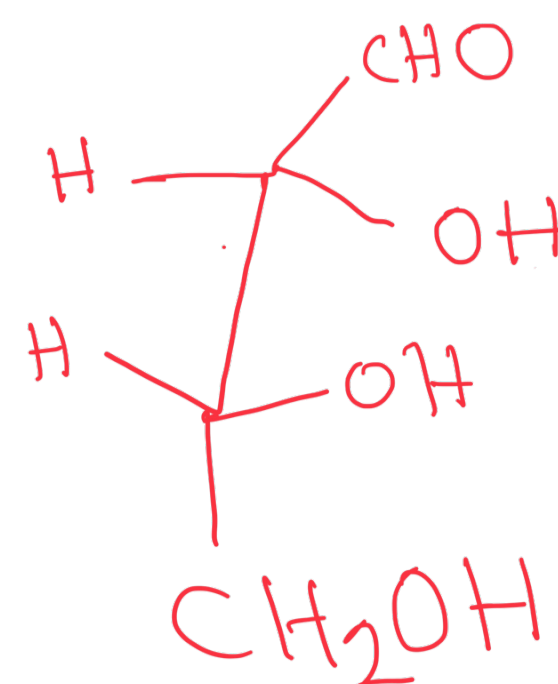
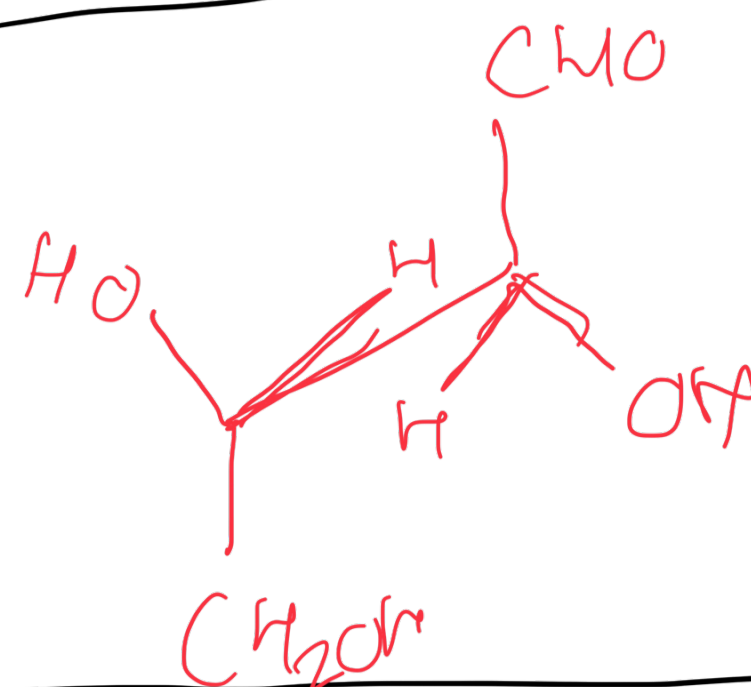
Original



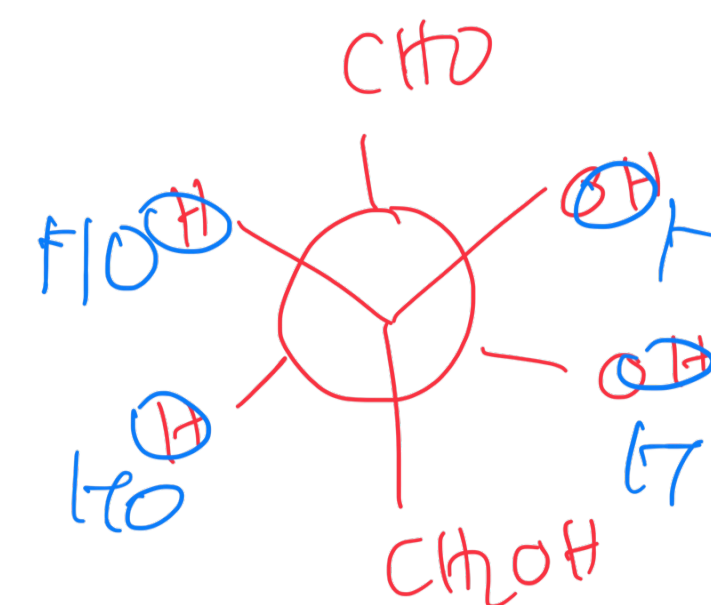
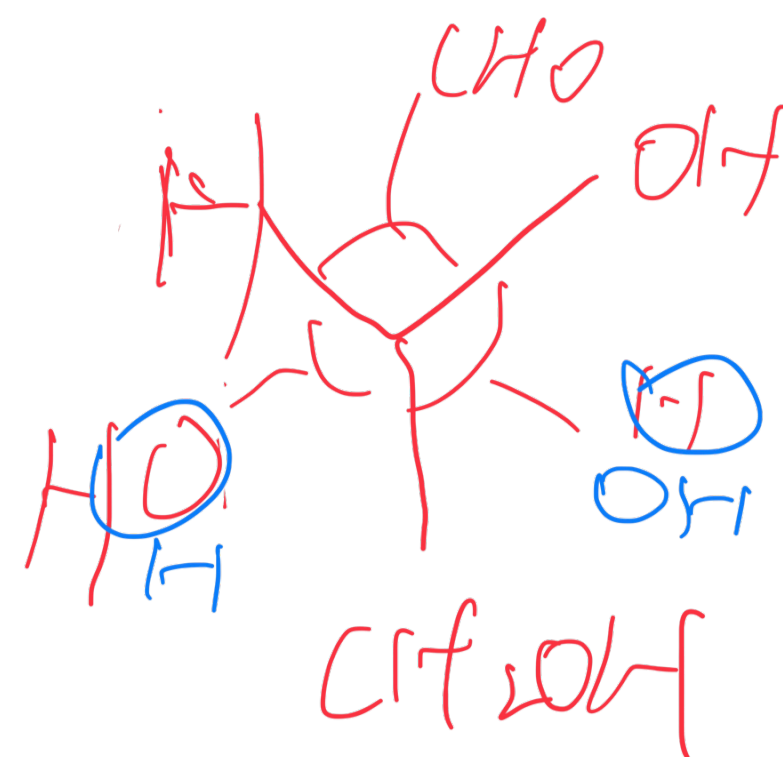
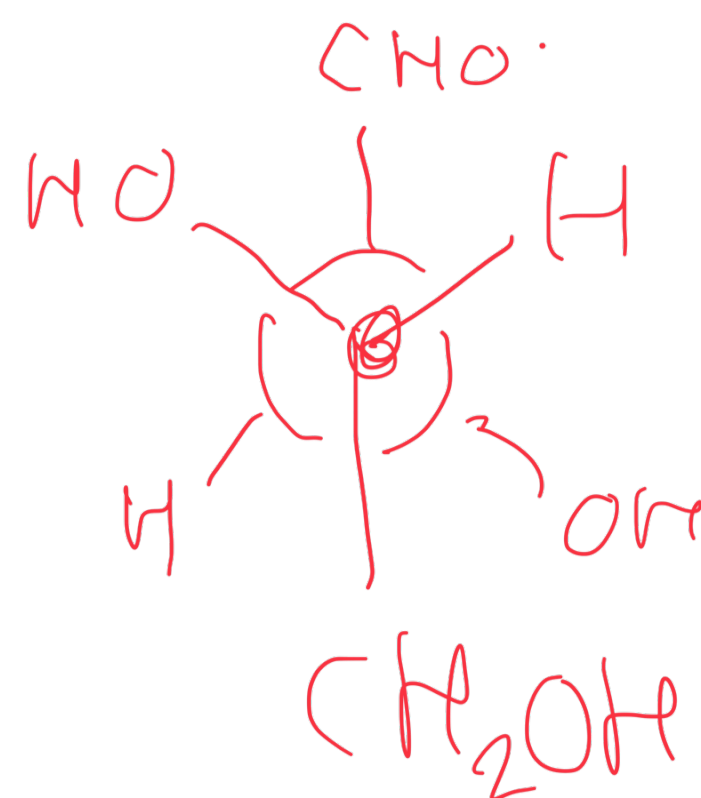
Fischer



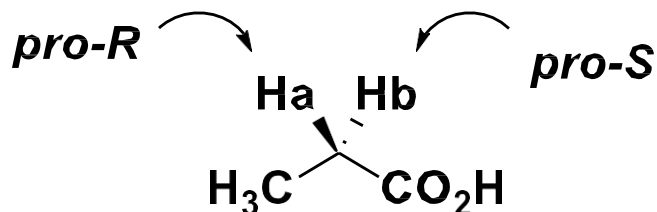
3D



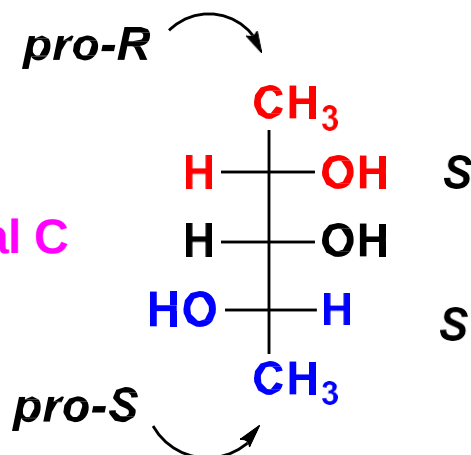
Newman



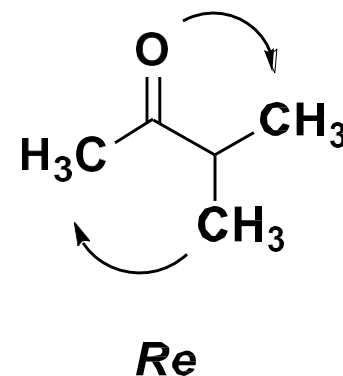
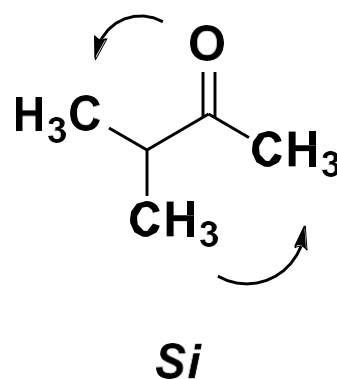
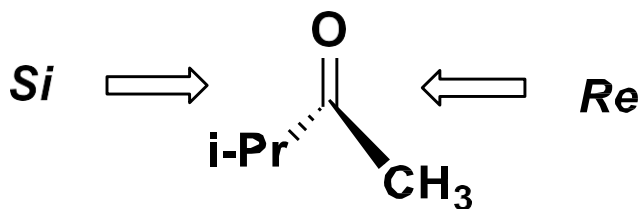
• Prochiral Center



3- Achiral C



• Prochiral Face

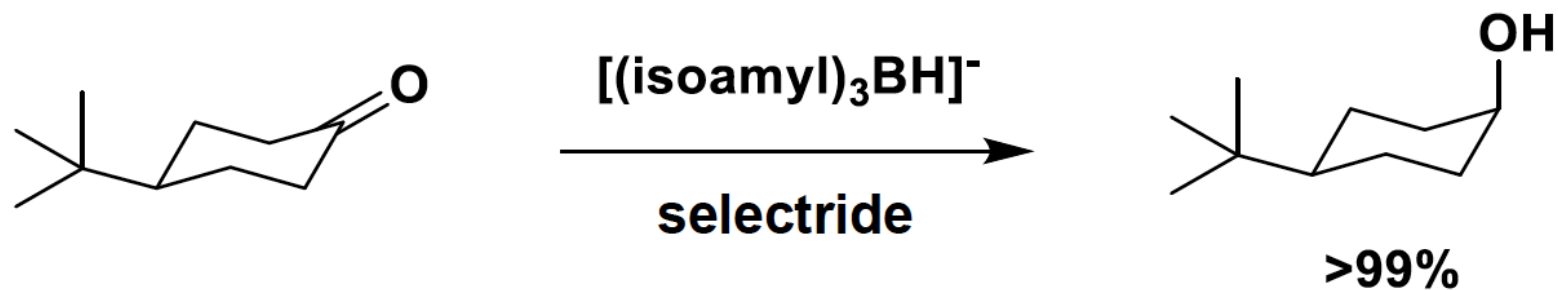
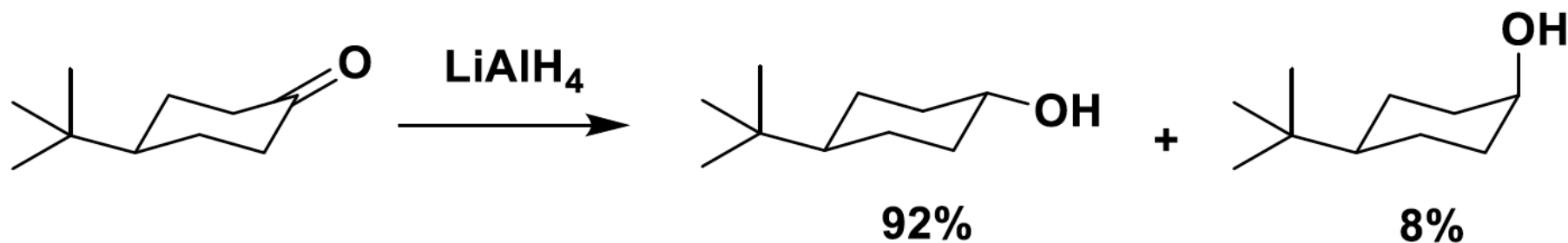
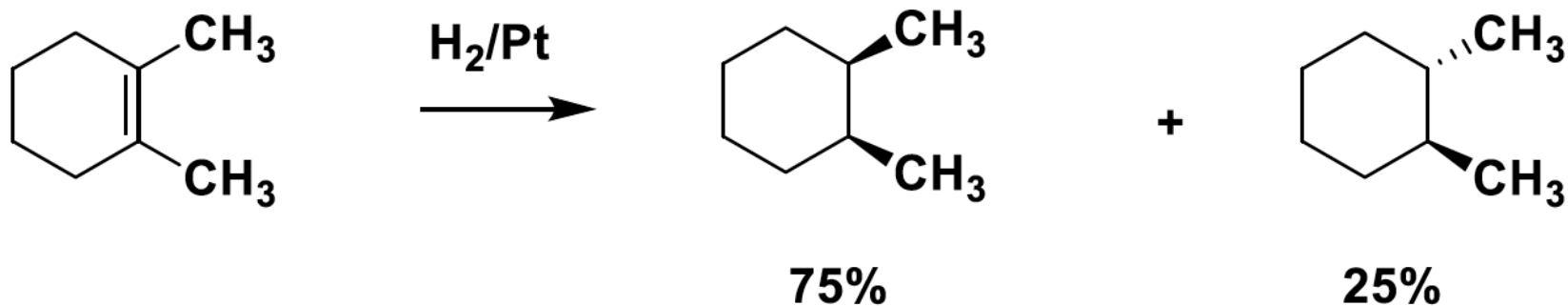


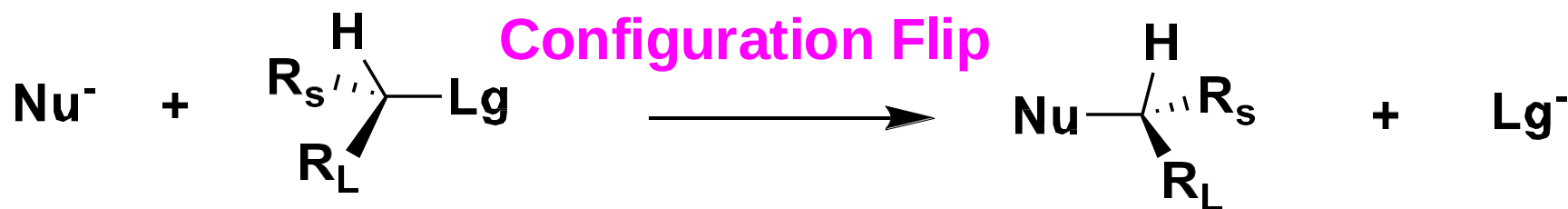
An achiral object which is capable of becoming chiral ...

...in two desymmetrization steps is sometimes described as prochiral.

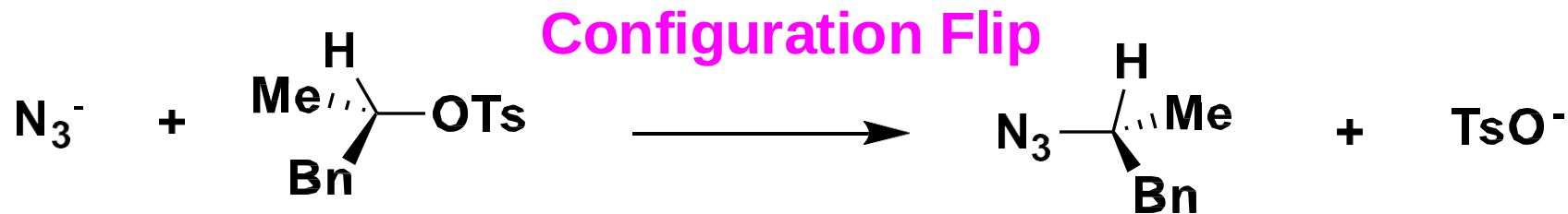
Desymmetrization Reactions —

Reactions that convert prochiral compounds into chiral compounds

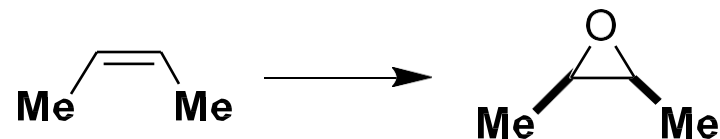
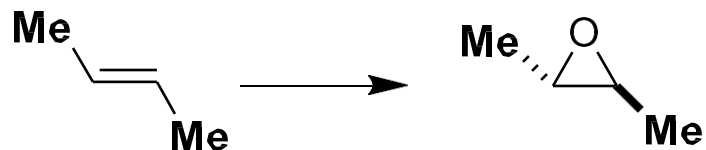




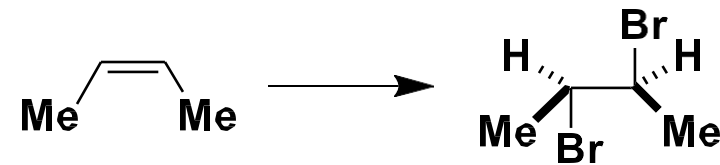
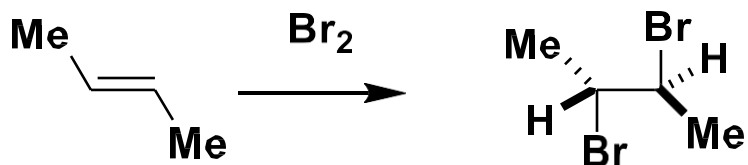
Example:



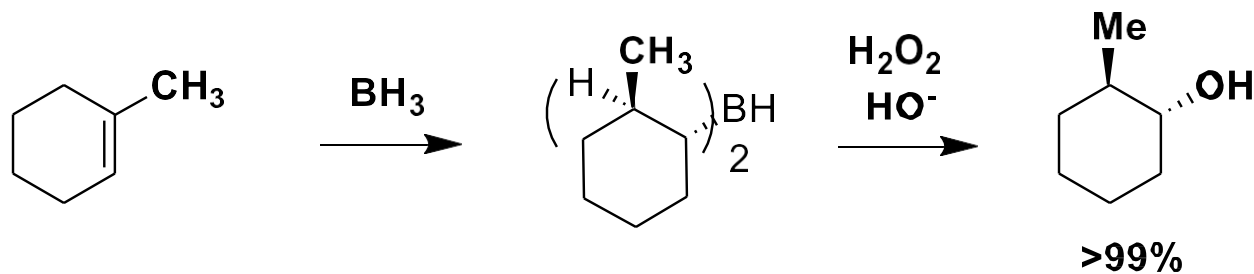
Epoxidation



Bromination

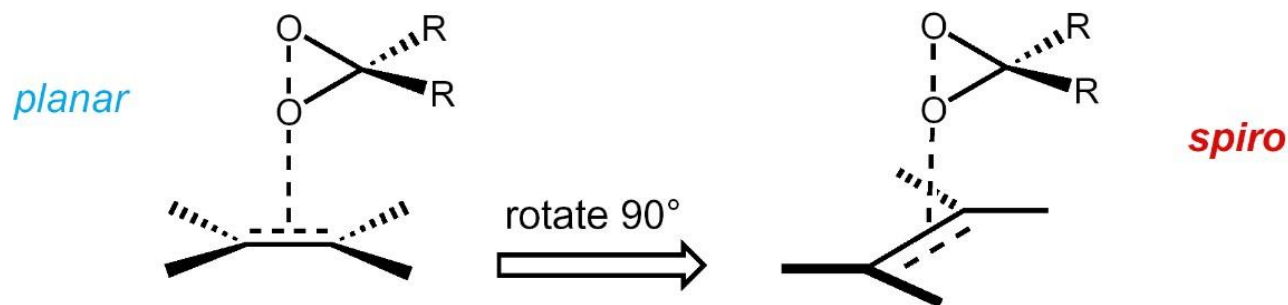


Hydroboration



Epoxidation Using Dioxiranes

Transition State for the Dioxirane Mediated Olefin Epoxidation

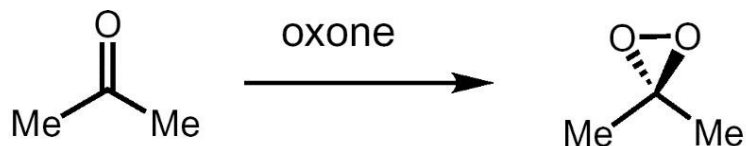


stabilizing $O_{lp} \rightarrow \pi^* C=C$

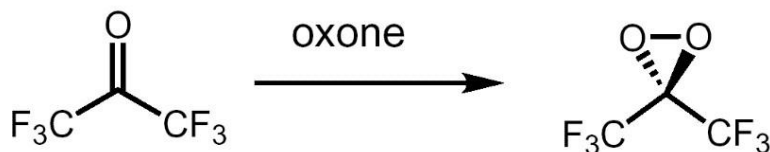
cis olefins react ~10 times faster than *trans*

Houk, *JACS*, **1997**, 12982.

Useful dioxirane synthesis



co-distill to give
~0.1 M soln of
dioxirane in acetone

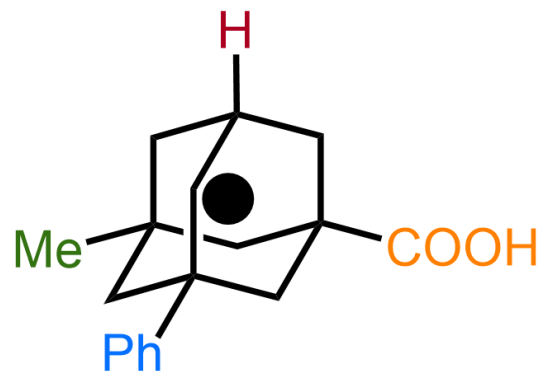


co-distill to give
~0.6 M soln of dioxirane
in hexafluoroacetone

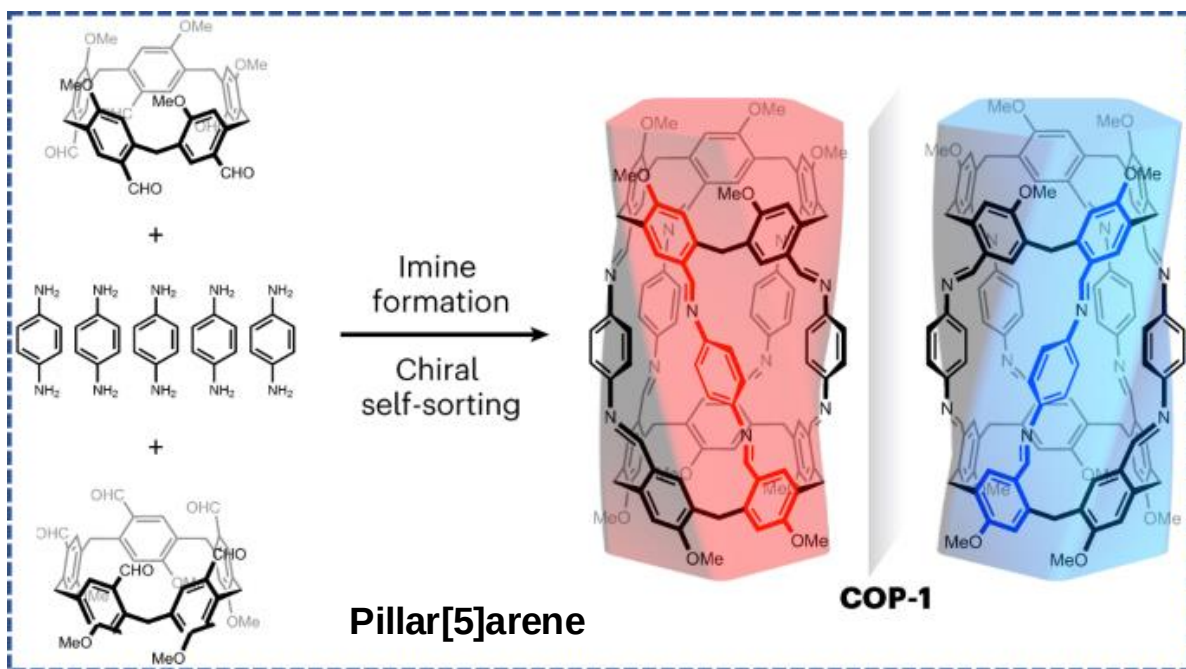
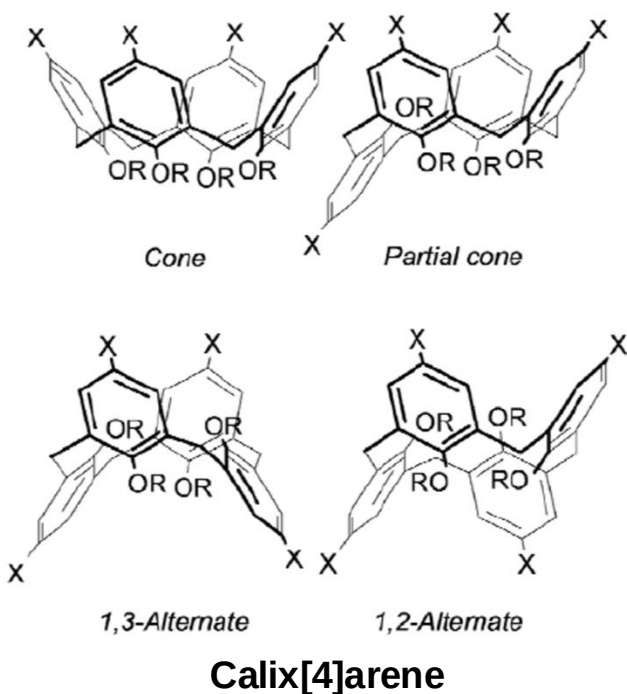
Curci, *JOC*, **1980**, 4758 & **1988**, 3890;
JACS **1991**, 7654.

• Stereogenic “Center”?

Group of “real” stereogenic centers



Adamantane
Derivative



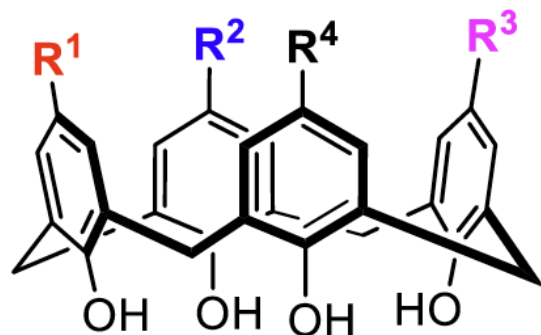
Mislow, K.; Siegel, J. [Stereoisomerism and Local Chirality](#). *J. Am. Chem. Soc.* **1984**, 106, 3319–3328

Synthesis of Covalent Organic Pillars as Molecular Nanotubes with Precise Length, Diameter and Chirality. *Nat. Synth.* **2023**, 2, 395–402

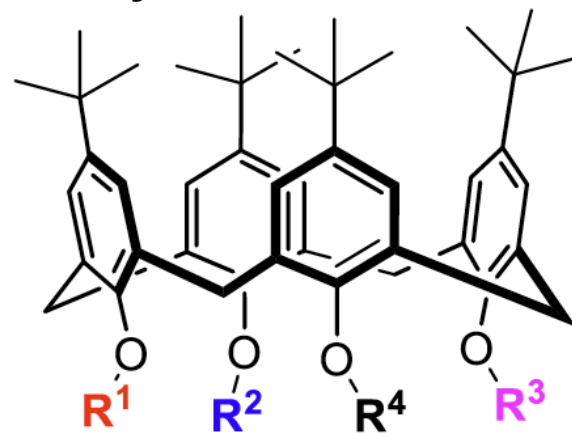
Inherent Chirality

Originated from Inherently Chiral Macrocycles

Calixarenes

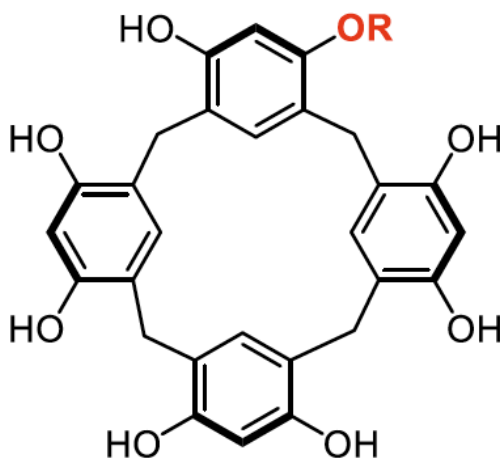


C_1

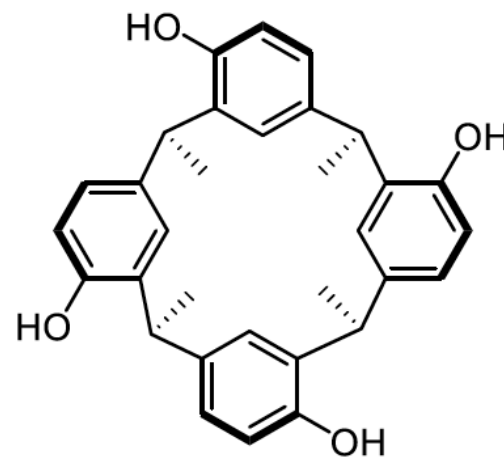


C_1

Resorcinarenes

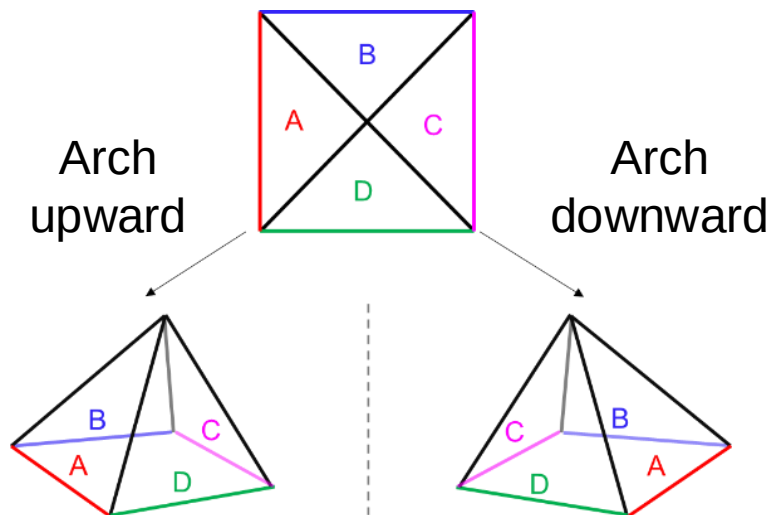


C_1



C_4

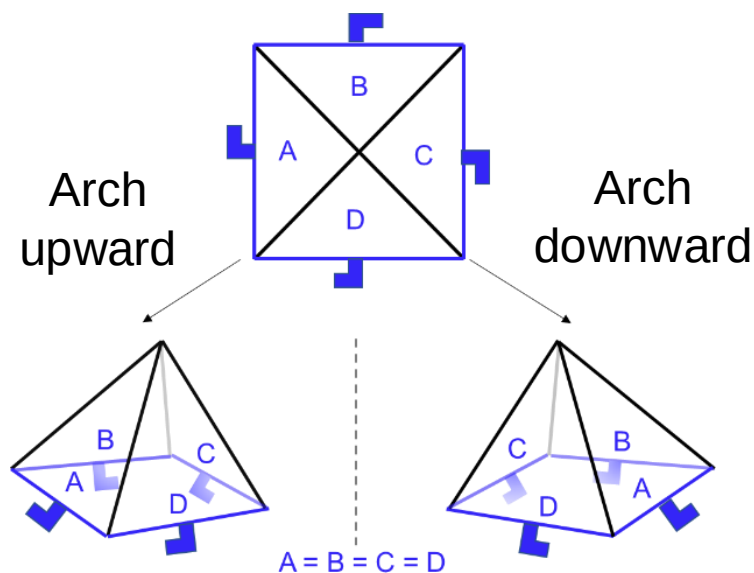
Transformation from 2D to 3D
intrinsically chiral objects
containing only C_1 symmetry



Inherent chirality is a property of molecules and complexes whose lack of symmetry does not originate from a classic stereogenic element, but is rather the consequence of the presence of a curvature in **a structure that would be devoid of symmetry axes in any dimensional representation.**

Mandolini, L. Schiaffino, L. et al. *New. J. Chem.* **2004**, 28, 1198-1199.

Transformation from 2D to 3D
intrinsically chiral objects
containing C_4 symmetry



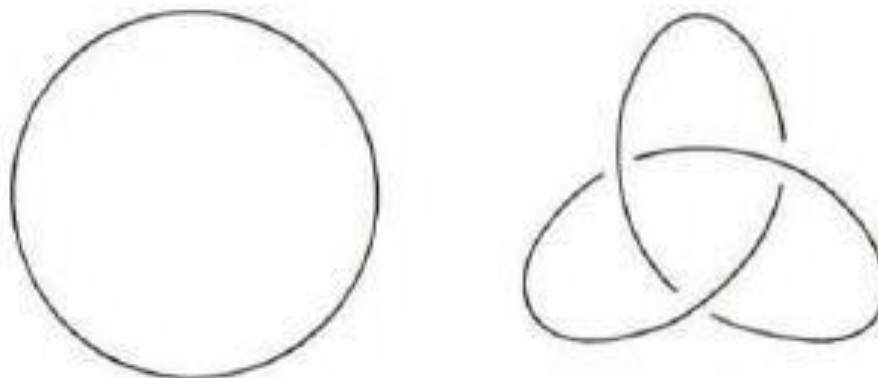
Inherent chirality arises from the introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bidimensional representation.

Szumna, A. *Chem. Soc. Rev.* **2010**, 39, 4274-7285.

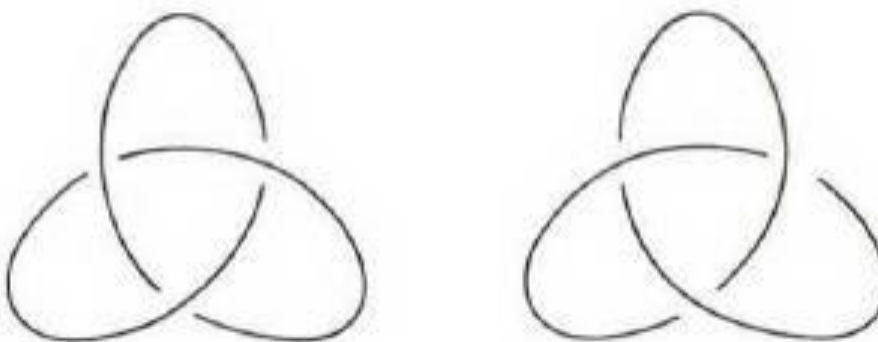
Note: intrinsic chirality is not limited to cyclic molecules!

Topological stereoisomers

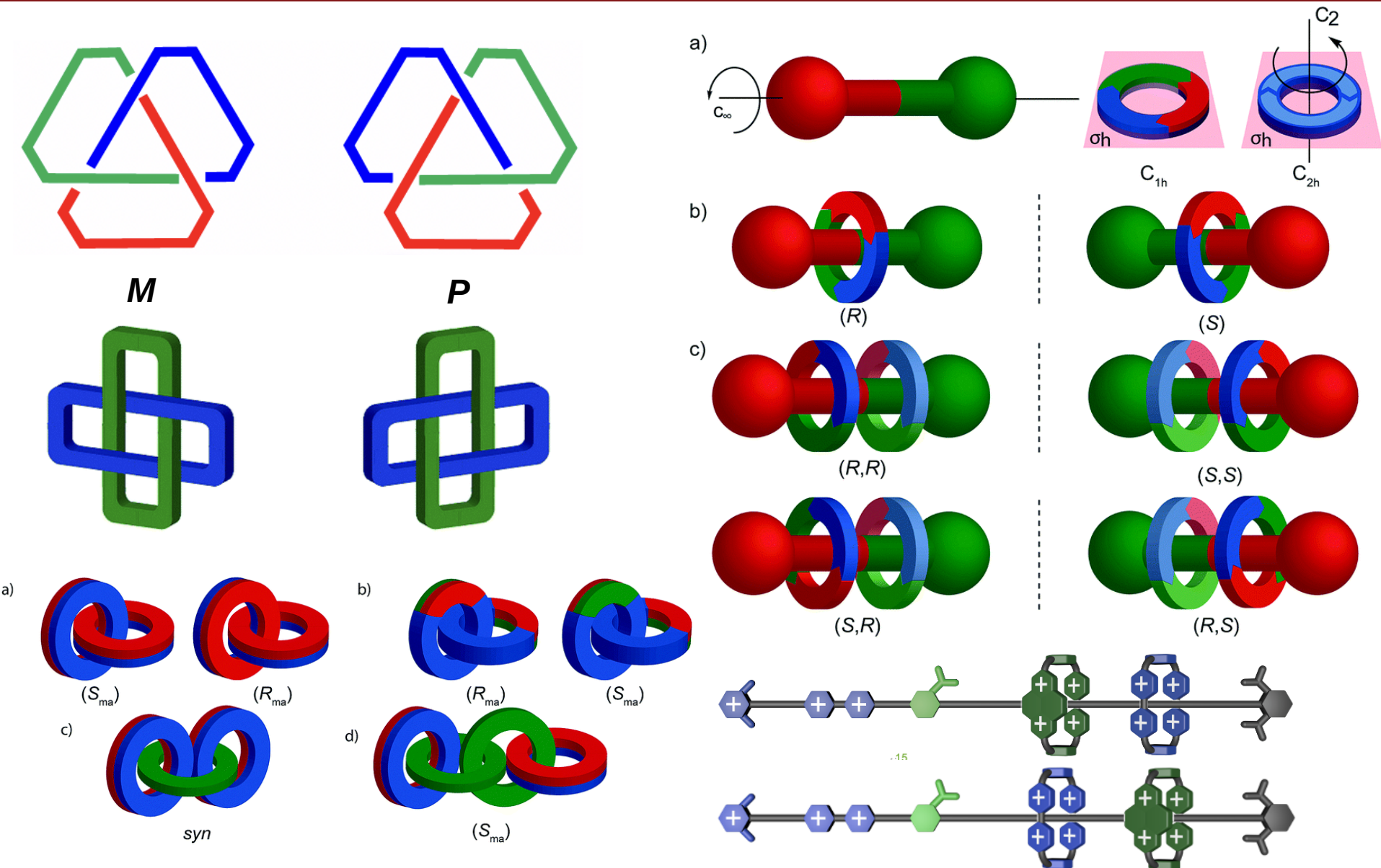
A.



B.



Topological enantiomers

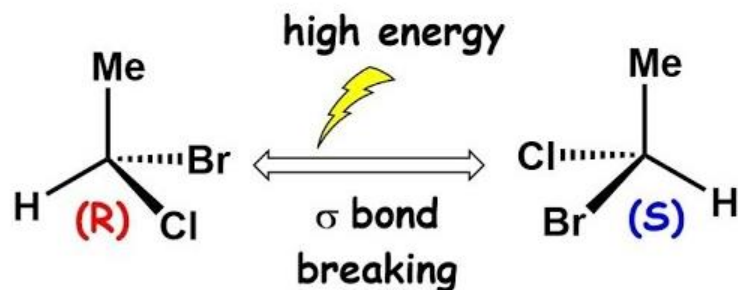




Key Words Discussion

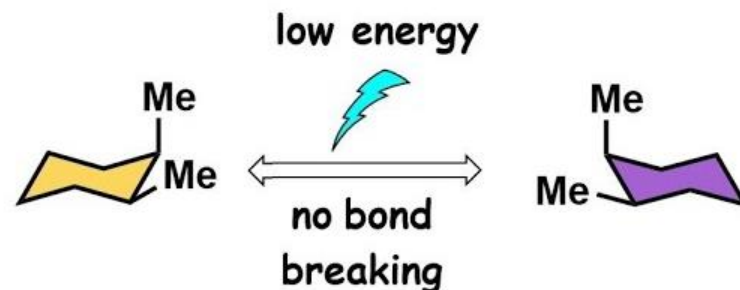


- **Racemic Mixture, Racemate**
- **Meso Compounds**
- **Optically Active Compounds**
- **Enantiomer**
- **Enantiomeric Purity**
- **Single Enantiomer**
- **Enantiomerically Pure or Enantiopure**
- **Enantiomeric Excess, E.E. Value**
 - $R\%-S\%$ or $(R-S)/(R+S) \times 100\%$
- **Enantiomeric Ratio**
 - $R:S$ or $S:R$



**Configurational
isomers**

VS

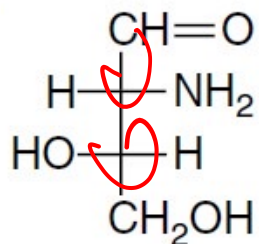


**Conformational
isomers**

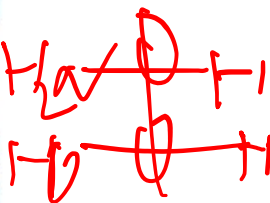
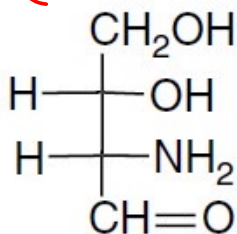
Conformation: Organic molecules are given structures with different shapes not through the breakage and reorganization of chemical bonds, but through the **rotation** of one or more **single bonds**.

Q1 Indicate which of the following 6 pairs of compounds are enantiomers, diastereomers, structural isomers or identical compounds.

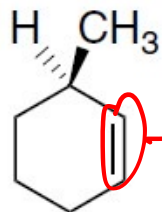
a.



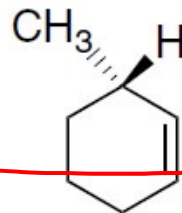
and



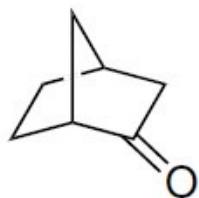
b.



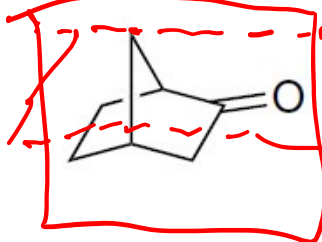
and



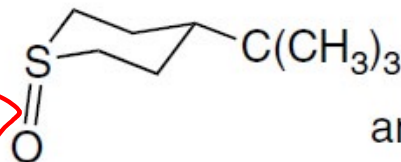
c.



and



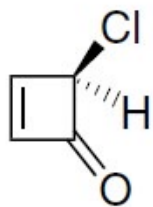
d.



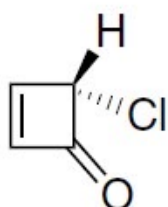
and



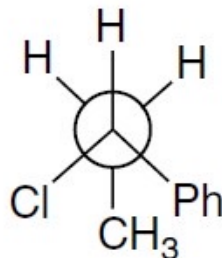
e.



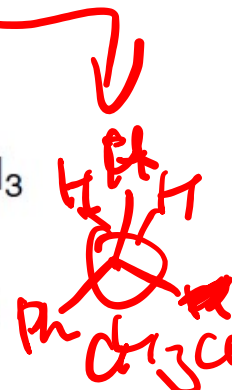
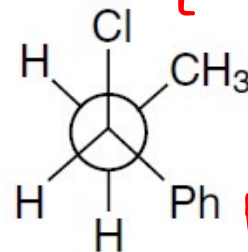
and



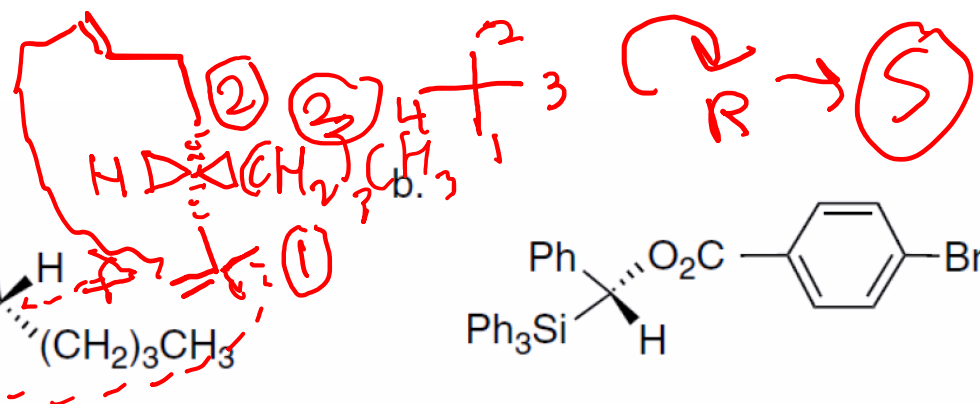
f.



and



Q2 Indicate the stereoconfiguration of the following compounds.



a.

b.

c.

d.

e.

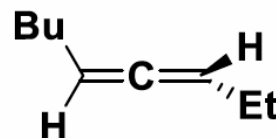
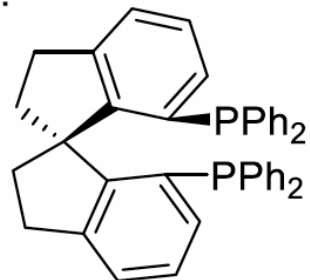
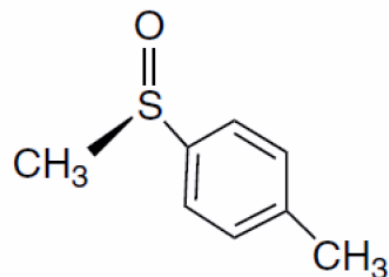
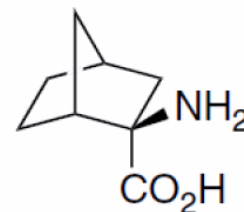
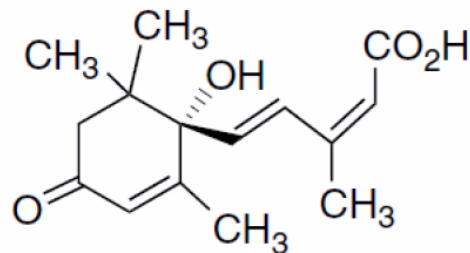
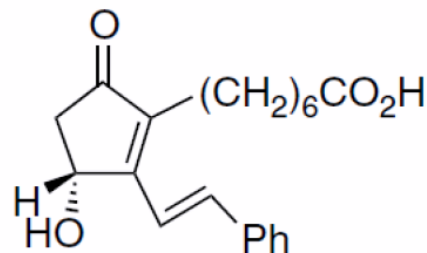
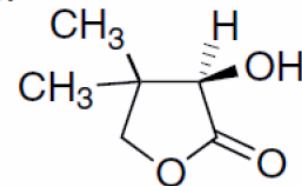
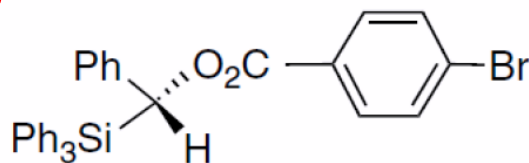
f.

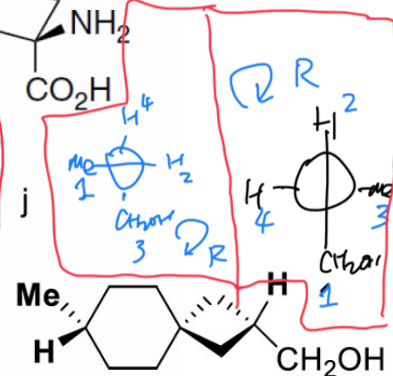
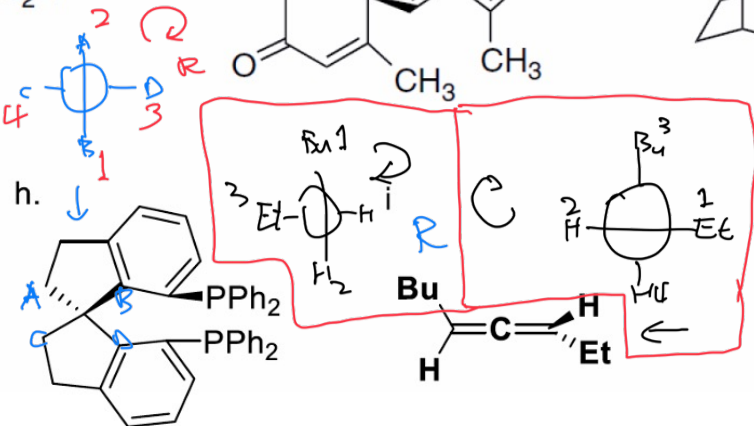
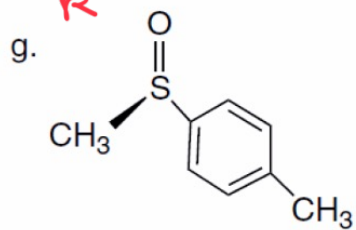
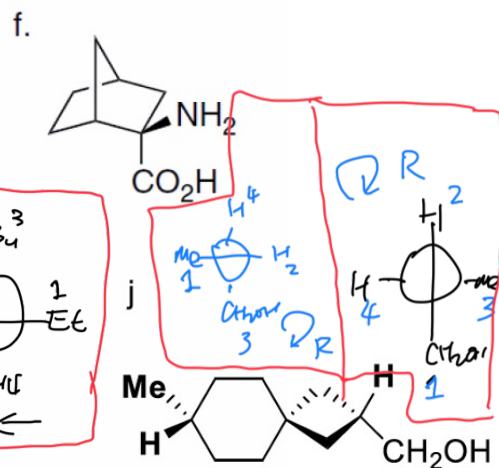
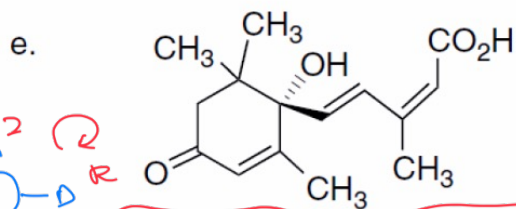
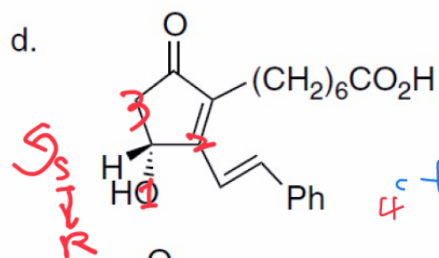
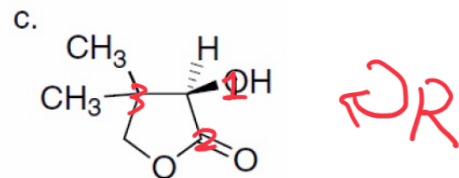
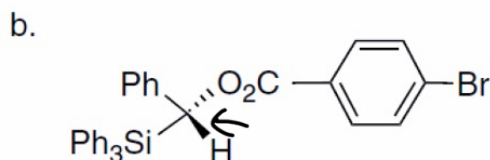
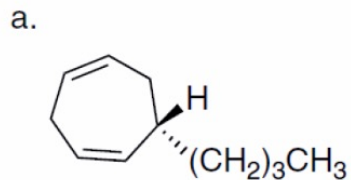
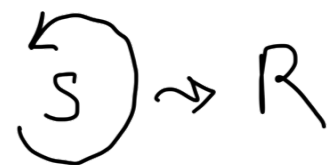
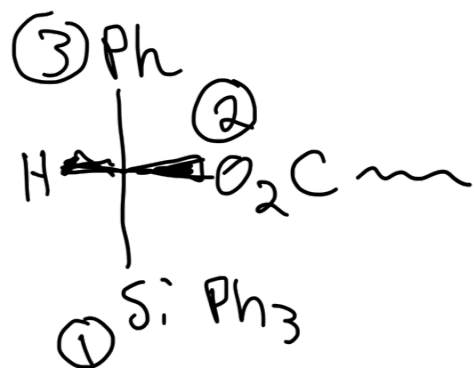
g.

h.

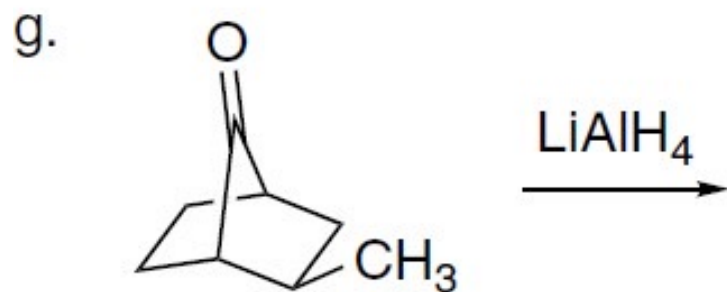
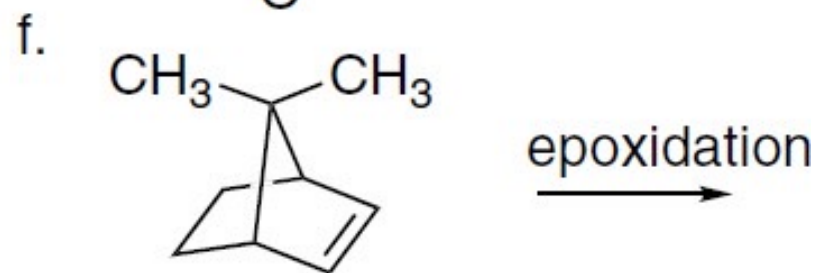
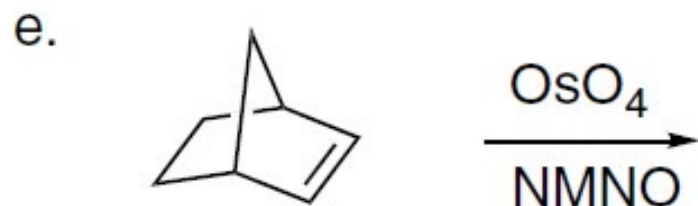
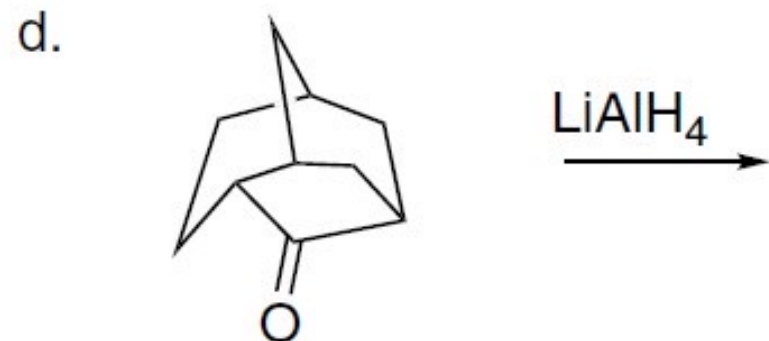
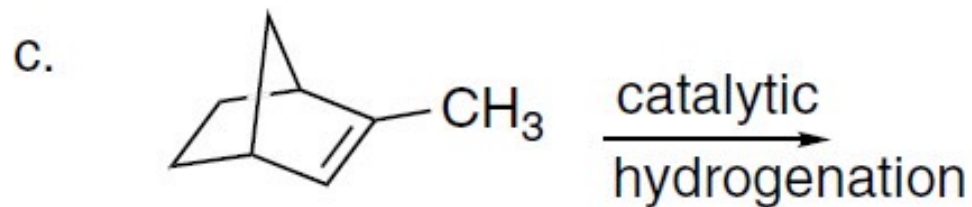
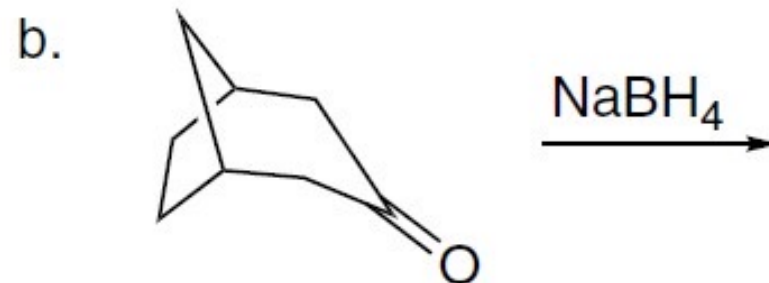
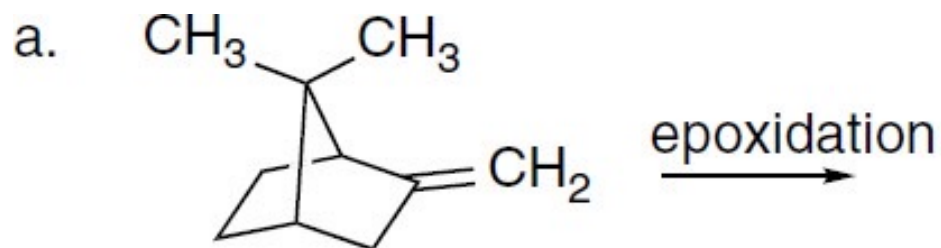
i.

j.

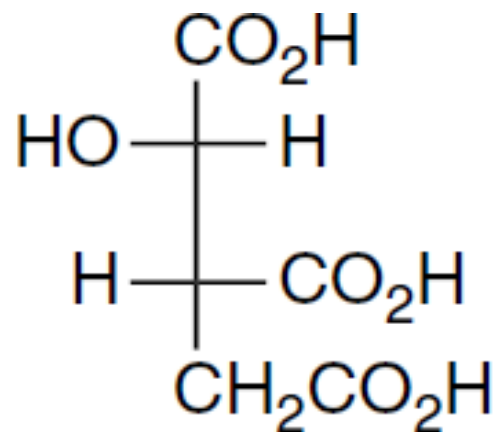
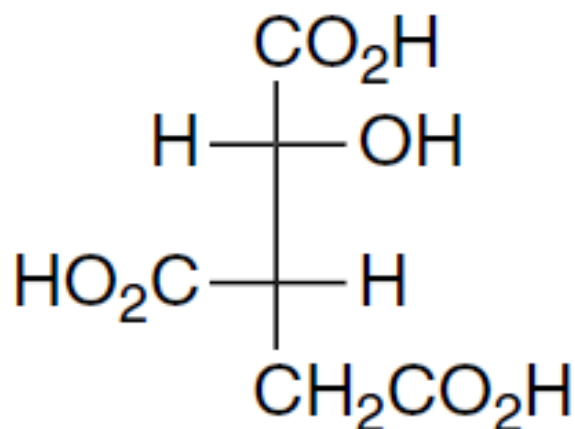




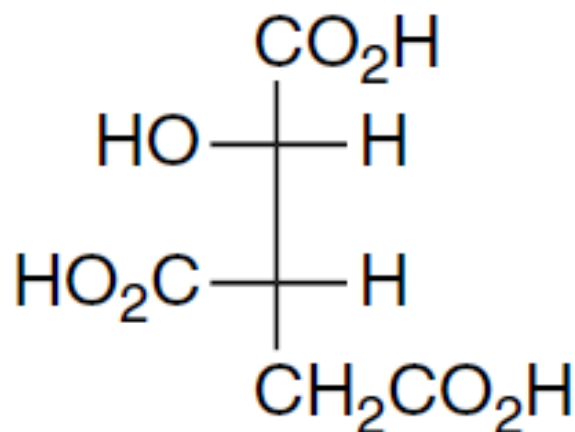
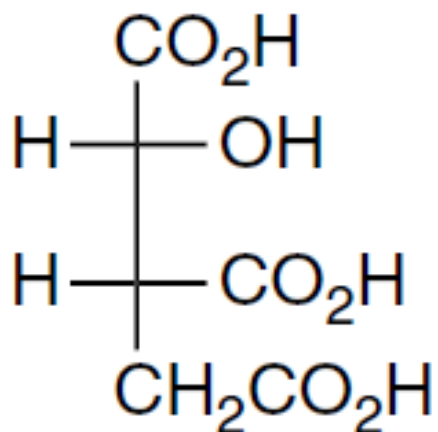
Q3 Predict the stereochemistry of the following reactions.



Q4 Point out the stereoconfiguration of the following compounds and convert it into a sawtooth structure.

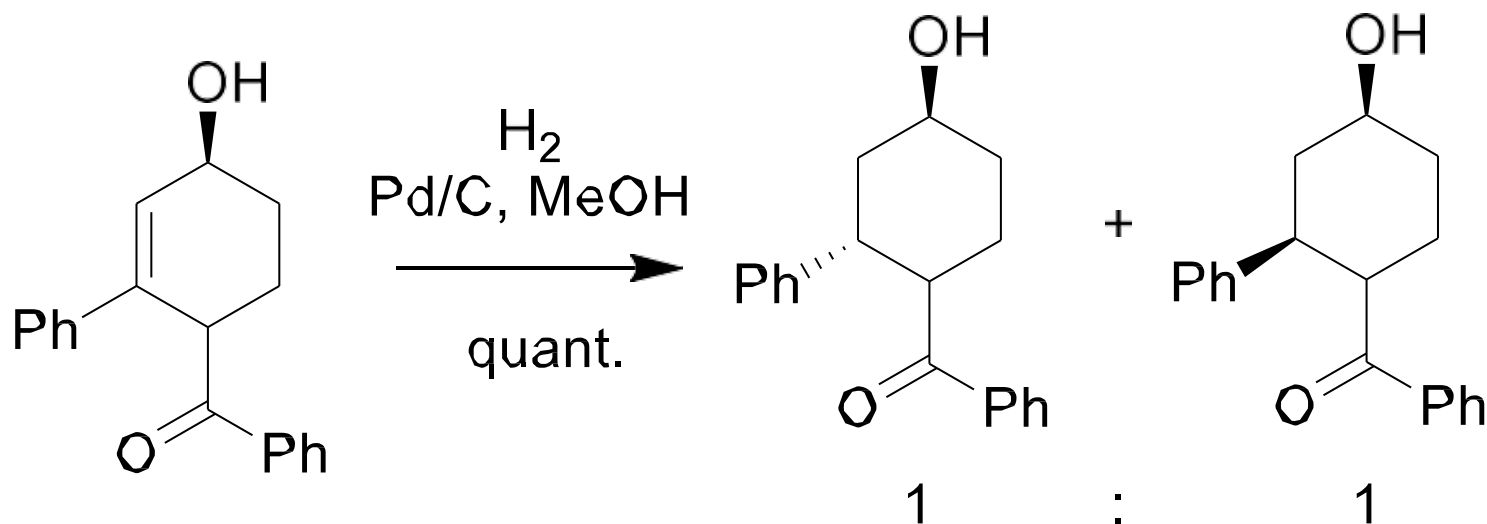
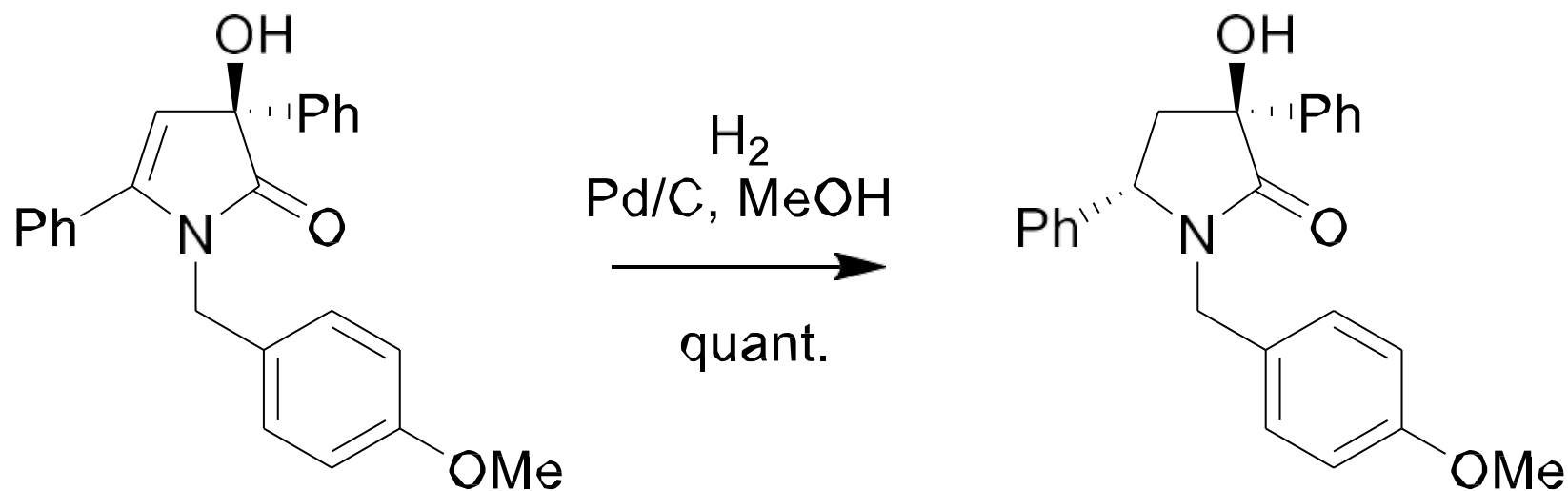


isocitric acids



alloisocitric acids

Q5 Give your interpretation of the stereochemical (diastereoselective) results for the following reactions.



The two enantiomers of bisfunctionalized fullerene adduct **5** were named *trans*-3 (*R*,*RR*,^{*f,s*}*A*)-**5** and *trans*-3 (*S*,*SS*,^{*f,s*}*C*)-**5**. The “*trans*-3” description indicates the relative arrangement of addends proposed by Hirsch and co-workers¹⁰ and used commonly in fullerene chemistry (**Fig. S91** and **Fig. S92**) with “*trans*” indicating the addends are on opposite hemispheres of the fullerene. Next, the descriptors *R/S* for the orientation of the addends are given to the quaternary carbon of the substituents using standard stereochemistry Cahn-Ingold-Prelog (CIP) priority rules. In “^{*f,s*}*X*”, the superscript “*f*” indicates that the descriptor refers to a fullerene and the superscript “*s*” for the systematic numbering.¹¹ The descriptor “*X*” can be either *A* for anticlockwise direction, or *C* for clockwise direction, which is determined by the direction of the preferred helical numbering path leading to the lowest set of locants for the addends (Figure 5). The two enantiomers of trisfunctionalized fullerene adduct **4** were named *e,e,e* (*R*,*R*,*R*,*R*,*R*,*R*,^{*f,s*}*A*)-**4** and *e,e,e* (*S*,*S*,*S*,*S*,*S*,*S*,^{*f,s*}*C*)-**4** in a similar fashion. “*e,e,e*” being the substitution pattern and the rest following the same naming system as above.

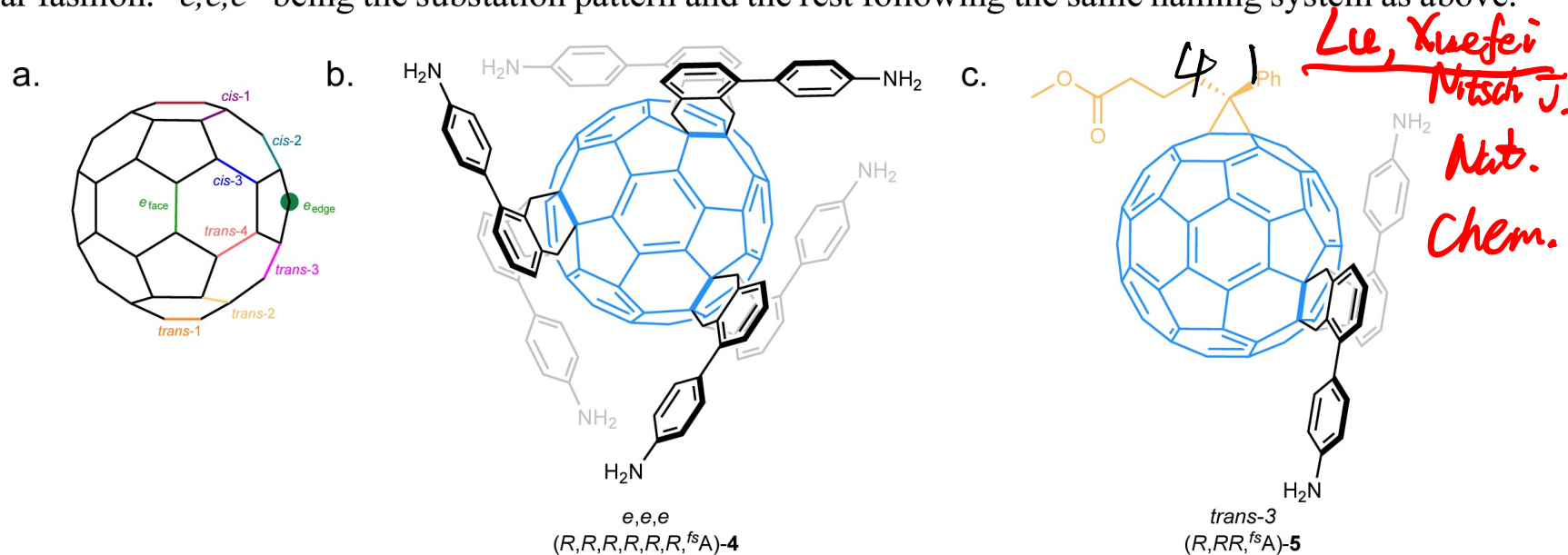


Fig. S105: (a) Relative arrangement of addends. Top bond (red) indicates highest priority substituent. (b) structure of *e,e,e* (*R*,*R*,*R*,*R*,*R*,*R*,^{*f,s*}*A*)-**4**. (c) structure of *trans*-3 (*R*,*RR*,^{*f,s*}*A*)-**5**.

The two enantiomers of bisfunctionalized fullerene adduct **5** were named *trans*-3 (*R,RR,^{f,s}A*)-**5** and *trans*-3 (*S,SS,^{f,s}C*)-**5**. The “*trans*-3” description indicates the relative arrangement of addends proposed by Hirsch and co-workers¹⁰ and used commonly in fullerene chemistry (Fig. S91 and Fig. S92) with “*trans*” indicating the addends are on opposite hemispheres of the fullerene. Next, the descriptors *R/S* for the orientation of the addends are given to the quaternary carbon of the substituents using standard stereochemistry Cahn-Ingold-Prelog (CIP) priority rules. In “^{f,s}*X*”, the superscript “*f*” indicates that the descriptor refers to a fullerene and the superscript “*s*” for the systematic numbering.¹¹ The descriptor “*X*” can be either *A* for anticlockwise direction, or *C* for clockwise direction, which is determined by the direction of the preferred helical numbering path leading to the lowest set of locants for the addends (Figure 5). The two enantiomers of trifunctionalized fullerene adduct **4** were named *e,e,e* (*R,R,R,R,R,R,^{f,s}A*)-**4** and *e,e,e* (*S,S,S,S,S,S,^{f,s}C*)-**4** in a similar fashion. “*e,e,e*” being the substitution pattern and the rest following the same naming system as above.

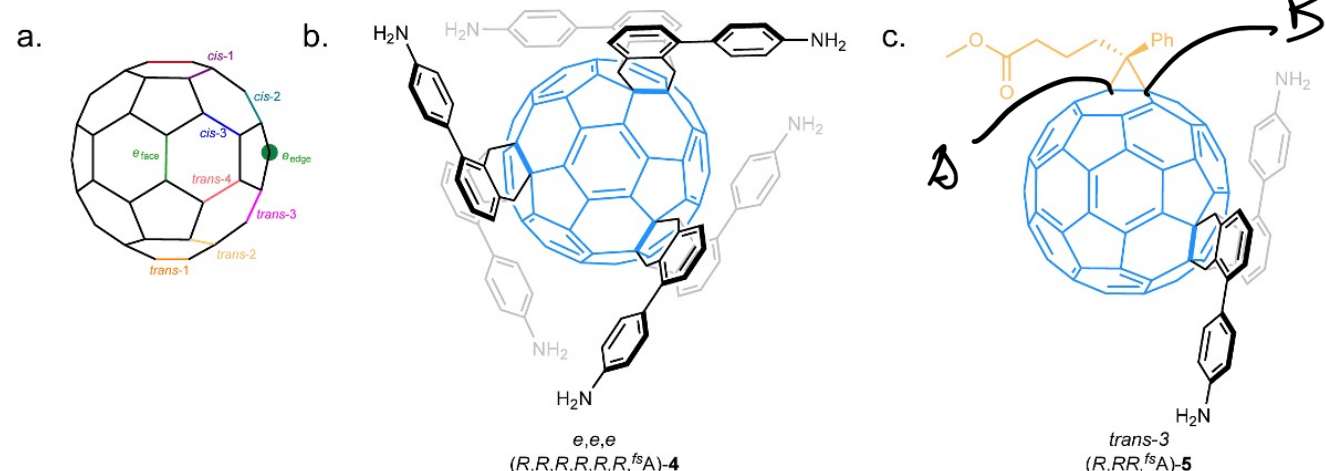
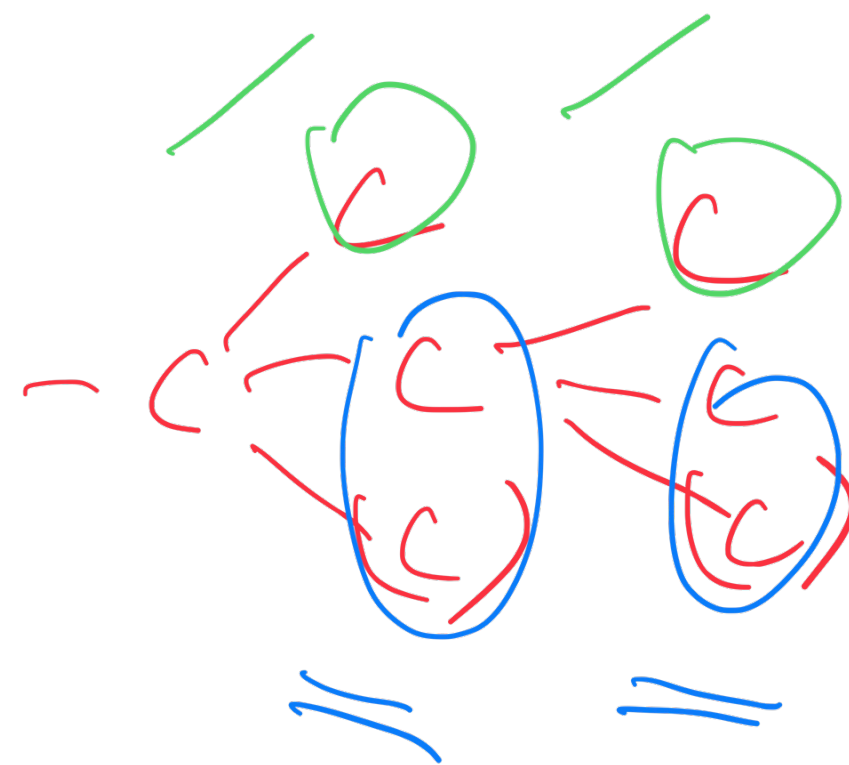
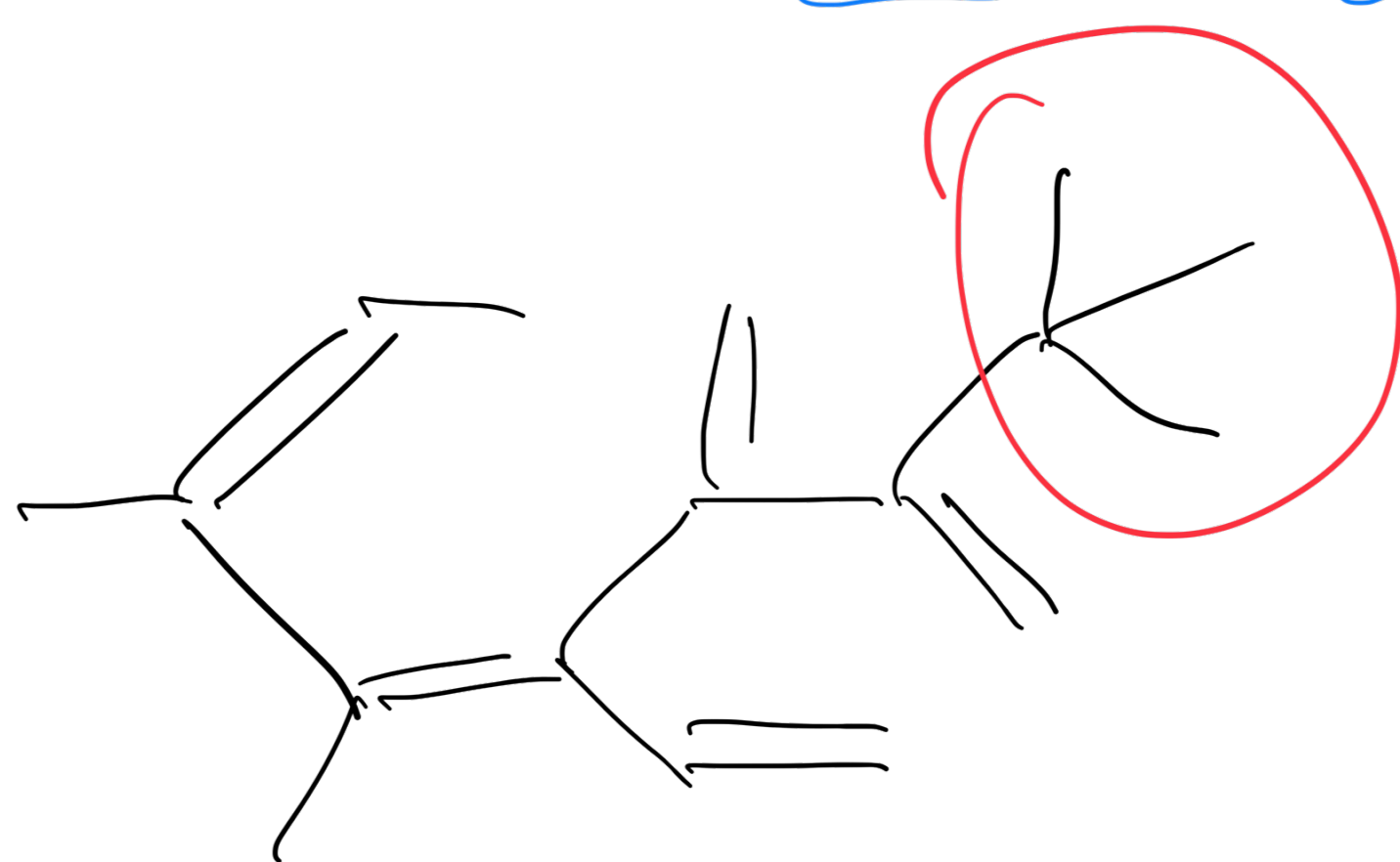
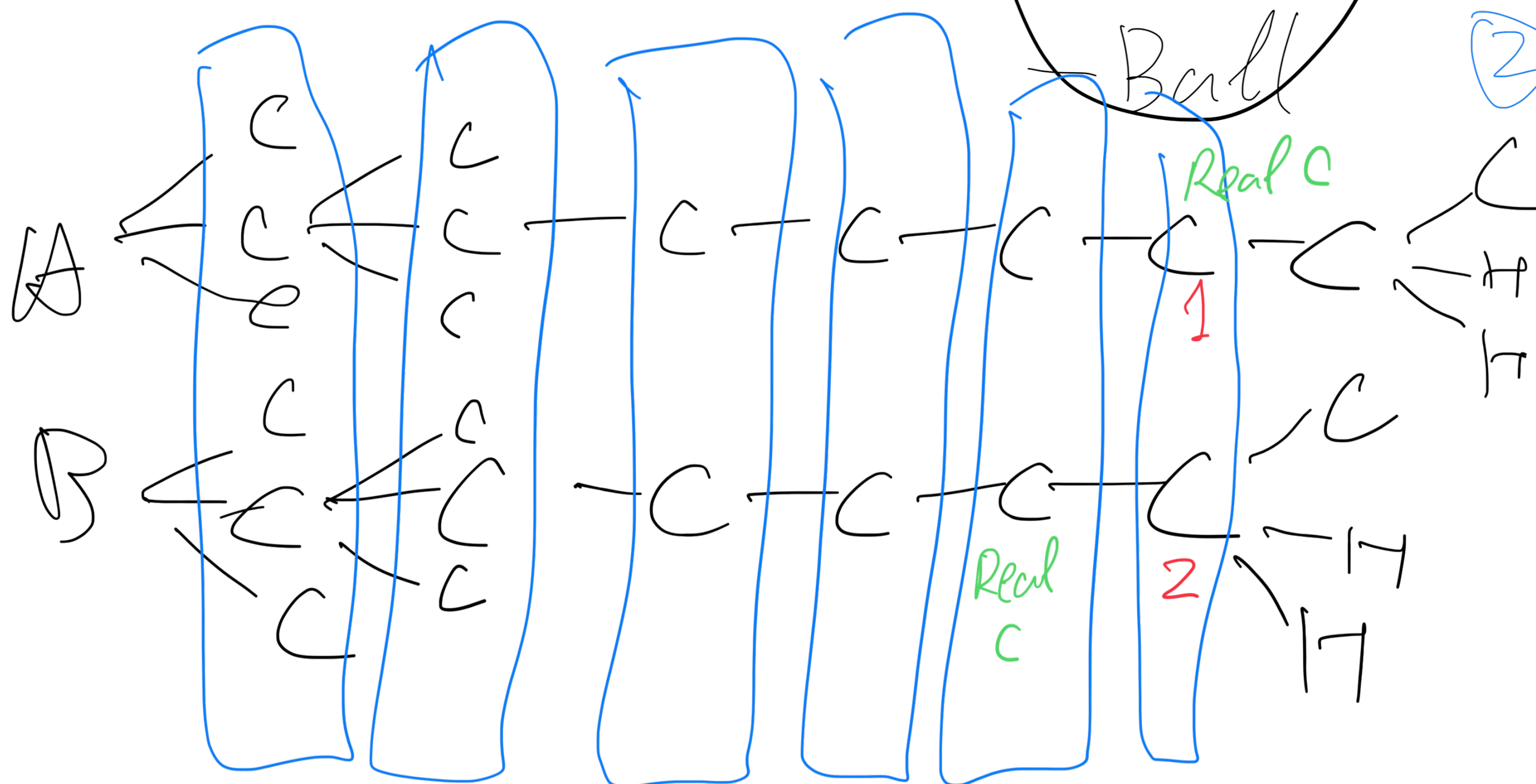
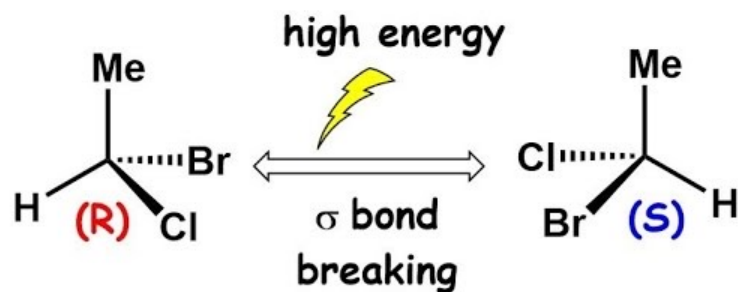


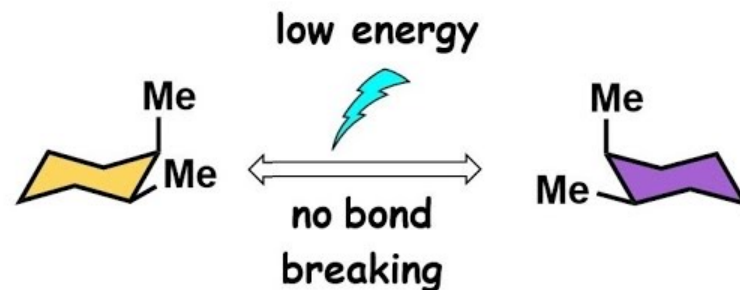
Fig. S105: (a) Relative arrangement of addends. Top bond (red) indicates highest priority substituent. (b) structure of *e,e,e* (*R,R,R,R,R,R,^{f,s}A*)-**4**. (c) structure of *trans*-3 (*R,RR,^{f,s}A*)-**5**.





**Configurational
isomers**

VS



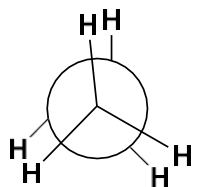
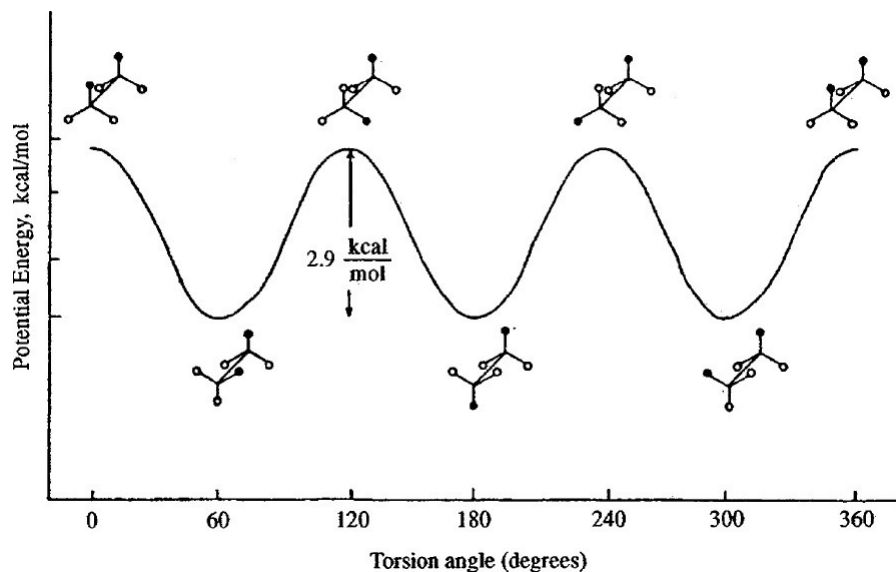
**Conformational
isomers**

Conformation: Organic molecules are given structures with different shapes not through the breakage and reorganization of chemical bonds, but through the **rotation** of one or more **single bonds**.

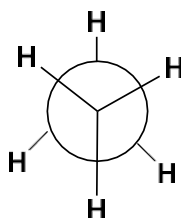
The Conformation of Acyclic Compounds

Taking ethane and propane as examples

Potential energy as a function of torsion angle for ethane

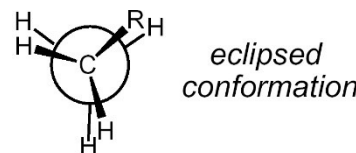


0°, 120°, 240°



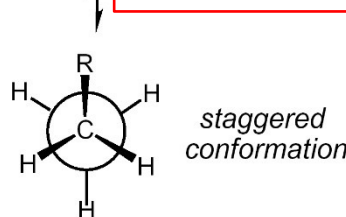
60°, 180°, 300°

The free rotation of the C-C bond in ethane requires about 3 kcal/mol of energy, while propane needs to overcome about 3.4 kcal/mol of energy.



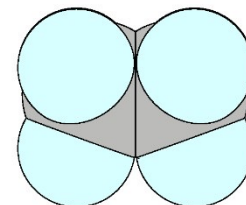
$$\Delta E = +3.0 \text{ kcal mol}^{-1} \text{ (R = H)}$$

$$\Delta E = +3.4 \text{ kcal mol}^{-1} \text{ (R = Me)}$$

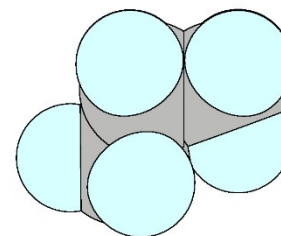


Staggered conformation isomer is stable

CPK (space-filling) models for ethane and propane



Van derWaals radii of vicinal hydrogens do not overlap in ethane



In propane there is a discernable interaction



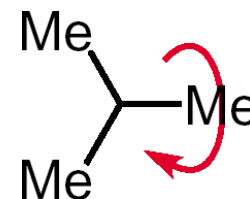
Energy Barriers Analysis



- Decomposition of the effects of adjacent hydrogen atoms and hydrogen atoms, hydrogen atoms and methyl groups in overlapping formulas

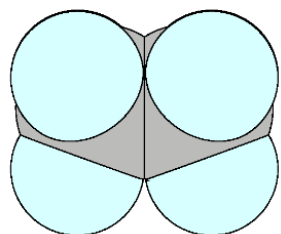
Structure	Eclipsed atoms	1'E (kcal / mol)
ethane	3 (H $\leftrightarrow$ H) interaction	+1.0 kcal / mol
propane	2 (H $\leftrightarrow$ H) interaction 1 (H $\leftrightarrow$ Me) interaction	+1.0 kcal / mol +1.4 kcal / mol

Question: Can you calculate the rotational energy barrier for the C-C bond in 2-methylpropane?

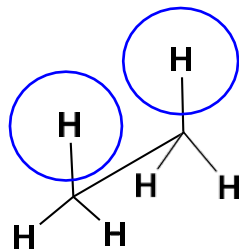


Why do ethane and propane adopt fully crossed conformations?

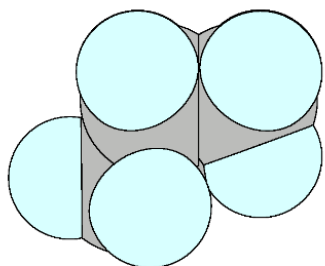
Or why are the fully crossed ethane and propane conformations the most stable?



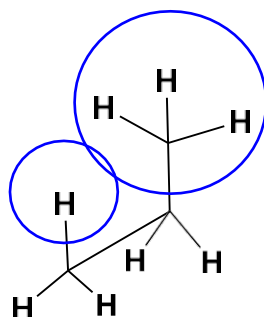
Van der Waals radii of vicinal hydrogens do not overlap in ethane



There is hyperconjugate stabilization in the full crossover!



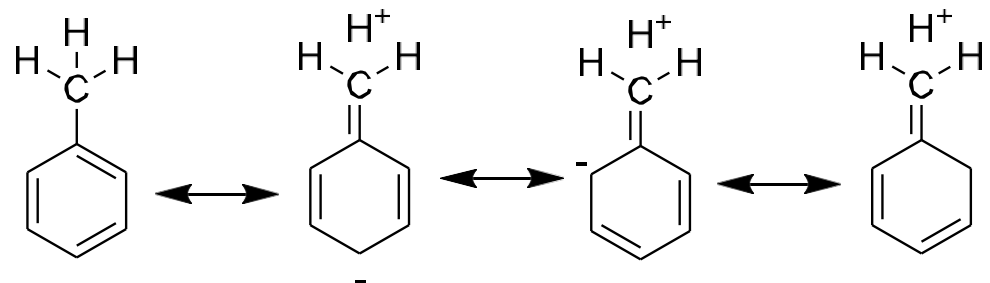
In propane there is a discernable interaction



Let's review the superconjugation effect we talked about before:

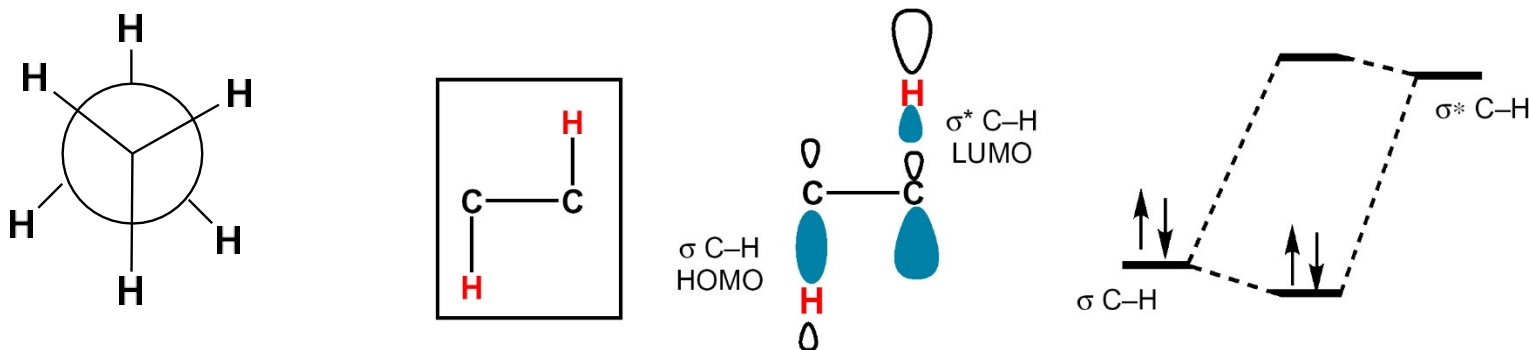
C-H bond – empty re*

The overlapping formula of ethane has unfavorable factors such as the repulsion of bonding electrons and the repulsion of hydrogen nuclei. But not a van der Waals effect!

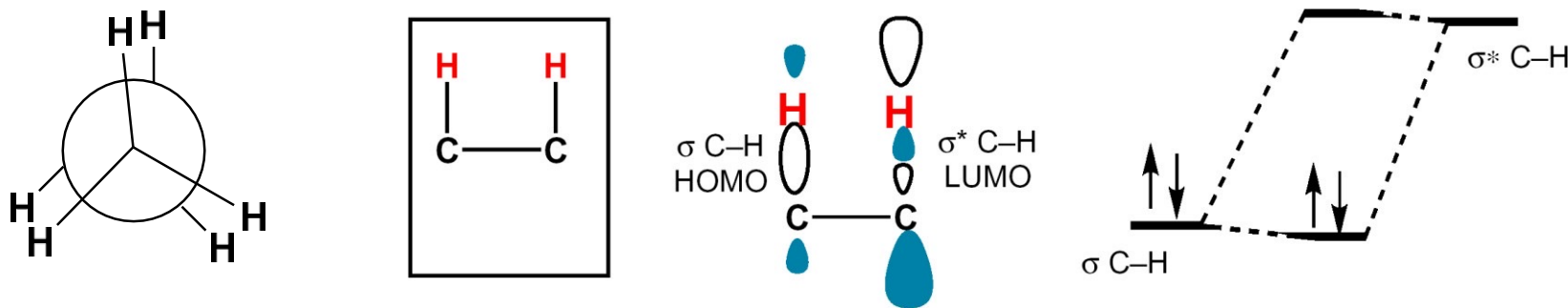


The *trans* coplanarity maximizes the hyperconjugation of σ C-H HOMO with the adjacent σ^* C-H LUMO. Hyperconjugation reduces the energy of σ C-H HOMO and obtains hyperconjugation stabilization energy.

In the staggered conformation there are 6 *anti-periplanar* C-H Bonds



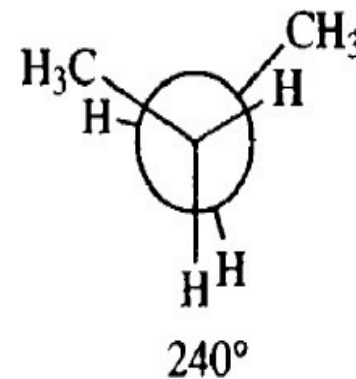
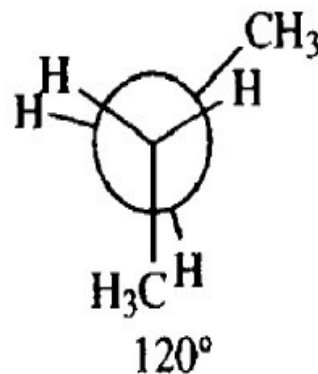
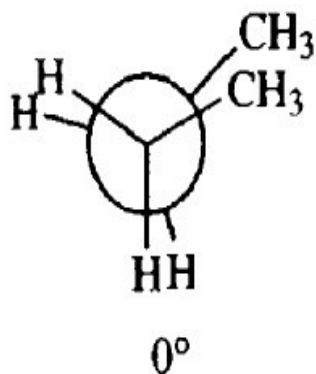
In the eclipsed conformation there are 6 *syn-periplanar* C-H Bonds



Butane — More Conformational Isomers

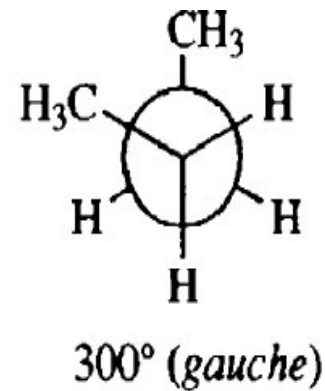
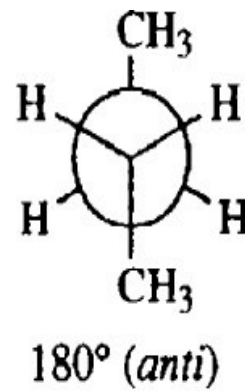
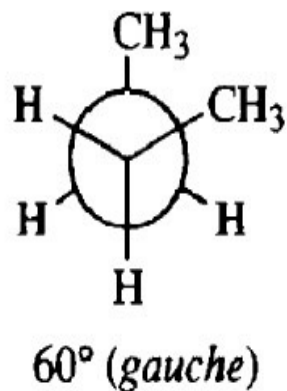
Eclipsed conformations

Torsion angle



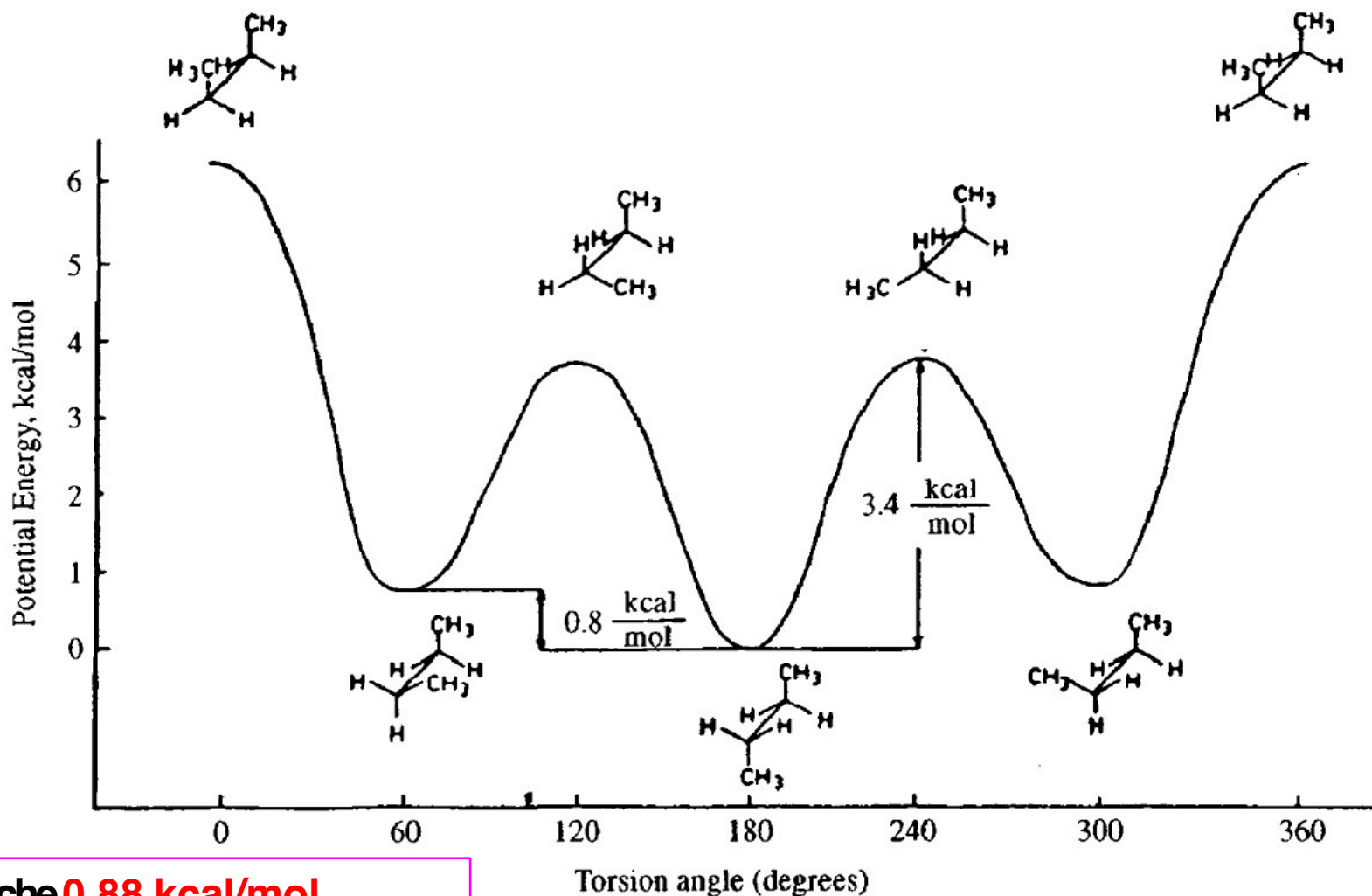
Staggered conformation

Torsion angle



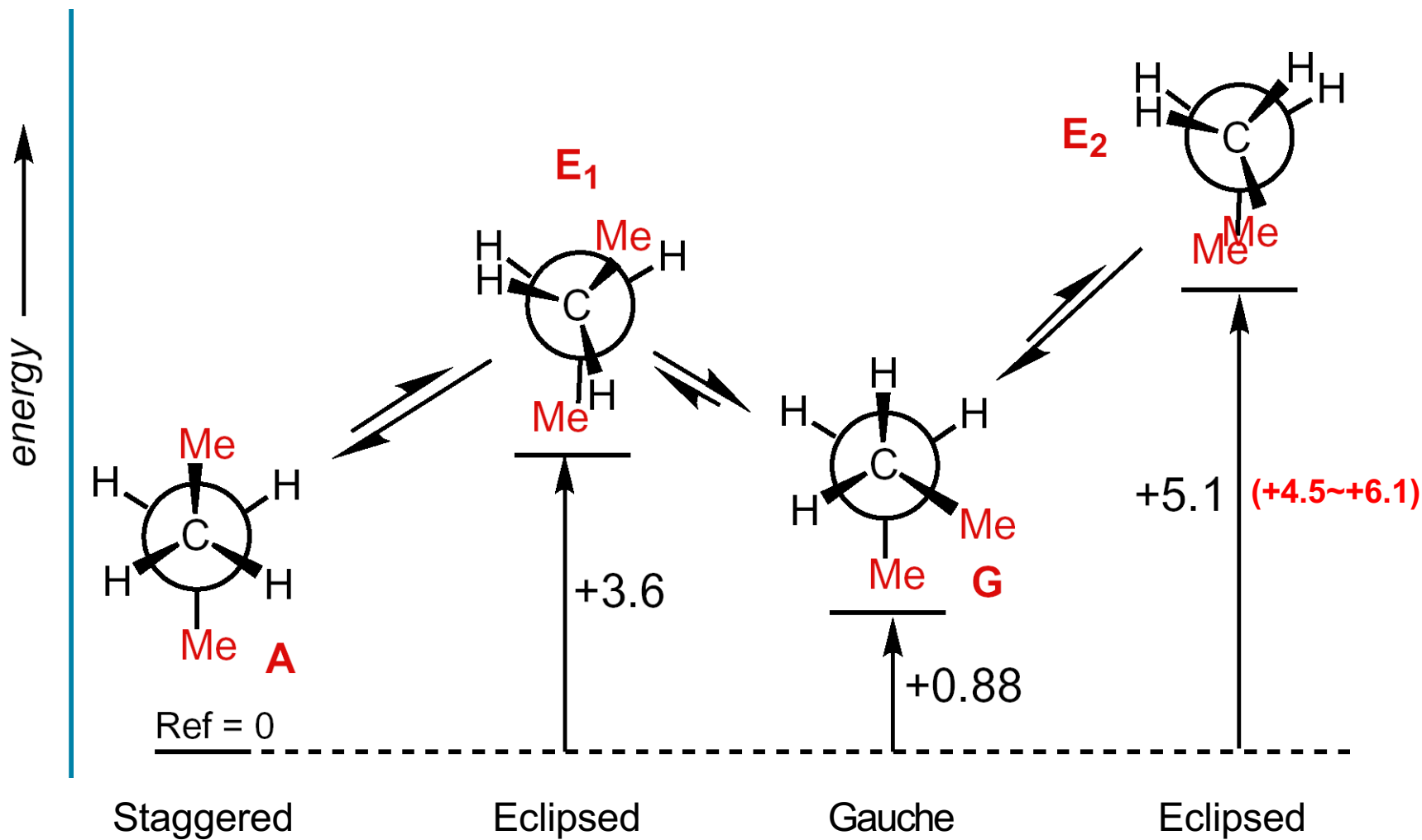
n-Butane Torsional Energy Profile

Potential energy diagram for rotation about the C(2)-C(3) bond in *n*-butane

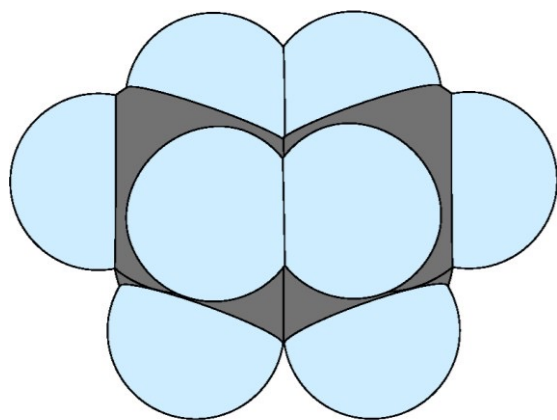
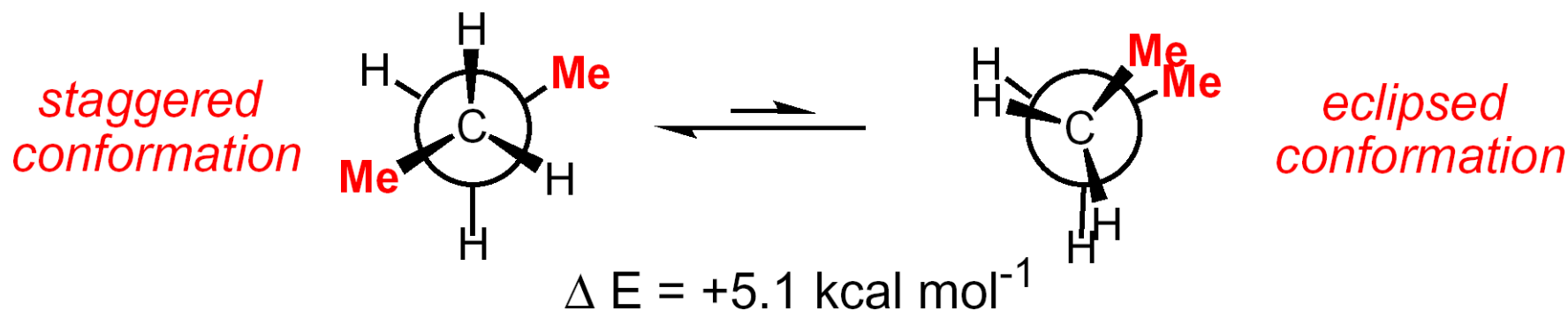


Gauche **0.88 kcal/mol**

n-Butane Torsional Energy Profile



n-Butane Torsional Energy Profile

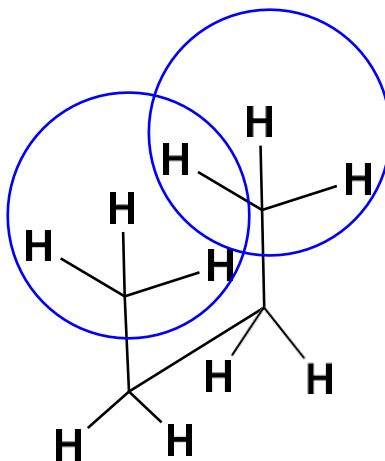


Eclipsed Butane conformation

$$2 (\text{H} \leftrightarrow \text{H}) + 1 (\text{Me} \leftrightarrow \text{Me}) = +5.1$$

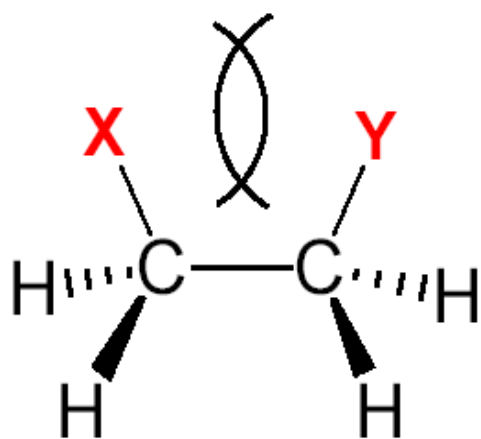
$$1 (\text{Me} \leftrightarrow \text{Me}) = +5.1 - 2 (\text{H} \leftrightarrow \text{H})$$

$$1 (\text{Me} \leftrightarrow \text{Me}) = +3.1$$



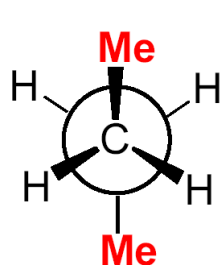
- From the energy barriers of different conformers of ethane, propane and butane, the effects of adjacent positions H—H, H—CH₃ and CH₃—CH₃ in the overlay formula can be estimated

Hierarchy of Eclipsing Interactions



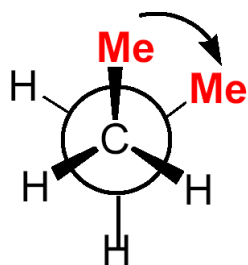
X—Y	$\delta E \text{ kcal mol}^{-1}$
H—H	+1.0
H—Me	+1.4
Me—Me	+3.1

Conformers' Names



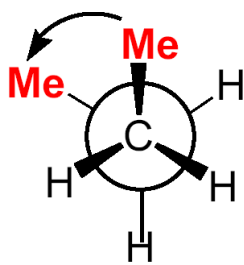
trans or t
or (anti)

70%



gauche(+)
or g^+

15%



gauche(-)
or g^-

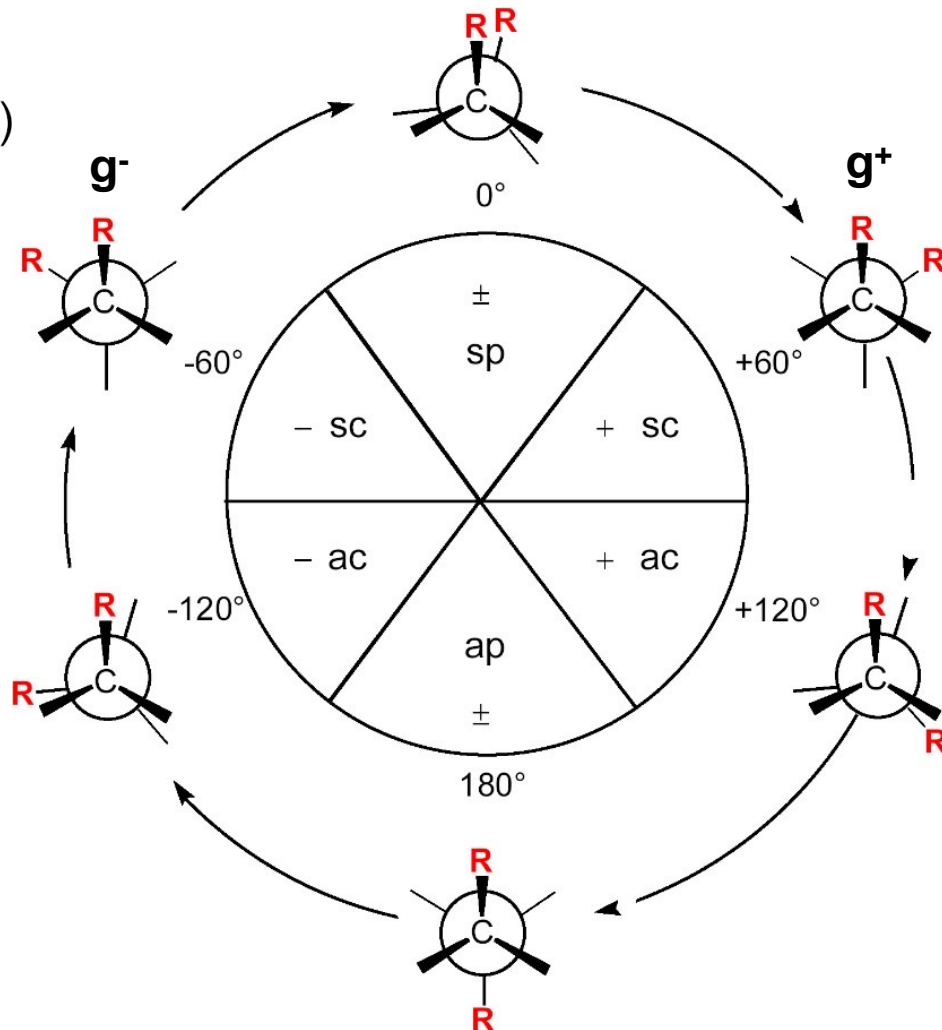
15%

sp: syn periplanar

sc: syn-clinal

ap: anti periplanar

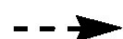
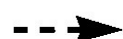
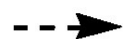
ac: anti-clinal



Conformers' Names

Energy Maxima

Energy Minima



Torsion angle

Designation

Symbol

n-Butane Conformer

$0 \pm 30^\circ$

$\pm$ syn periplanar

$\pm$ sp

E₂

$+60 \pm 30^\circ$

+ syn-clinal

+ sc (g+)

G

$+120 \pm 30^\circ$

+ anti-clinal

+ ac

E₁

$180 \pm 30^\circ$

antiperiplanar

ap (anti or t)

A

$-120 \pm 30^\circ$

- anti-clinal

- ac

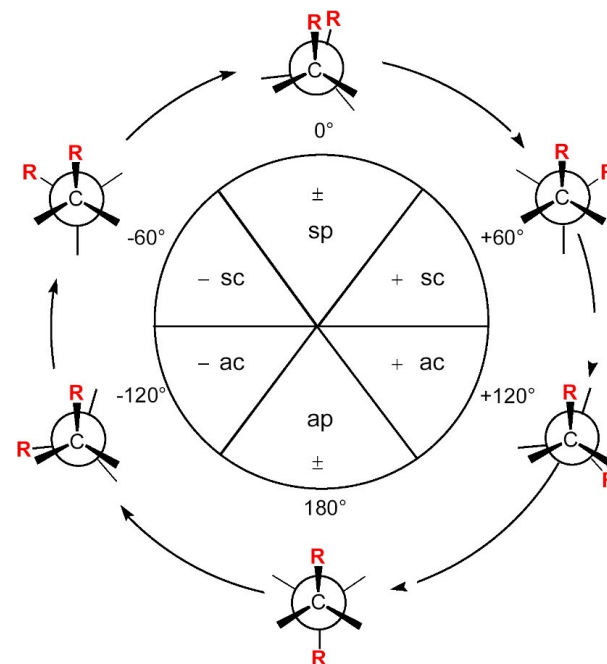
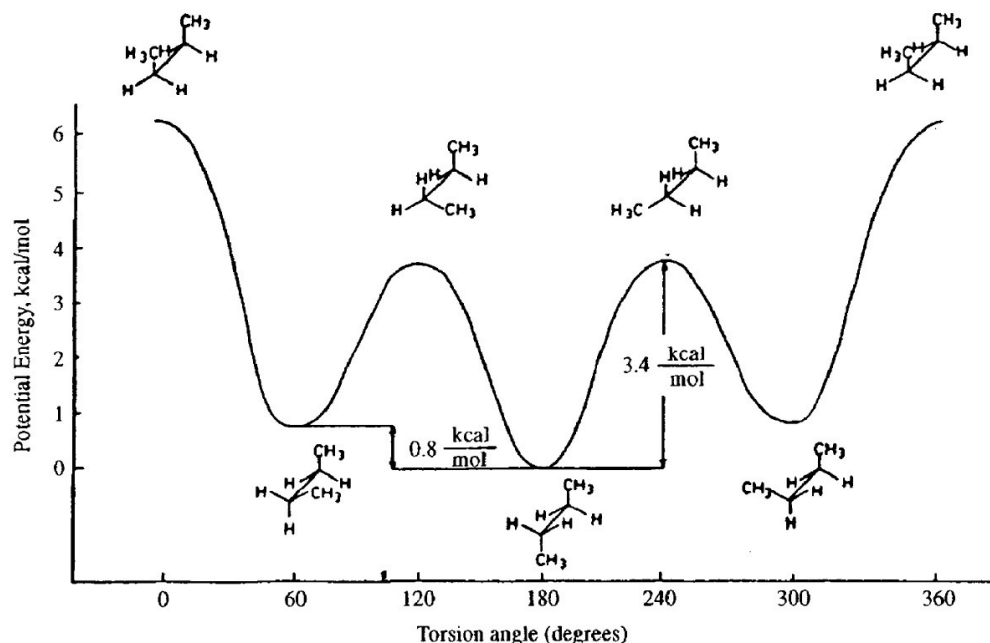
E₁

$-60 \pm 30^\circ$

- syn-clinal

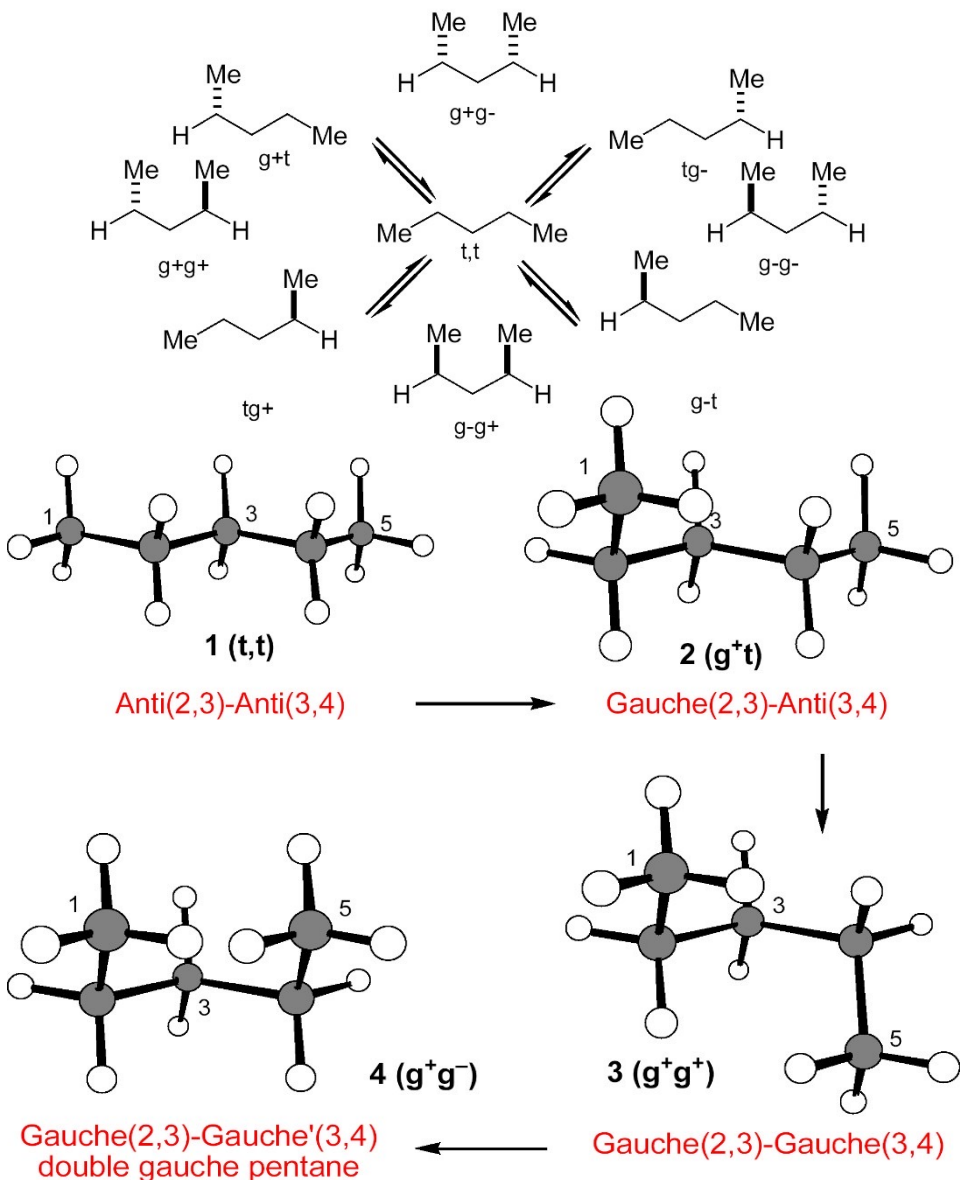
- sc (g-)

G



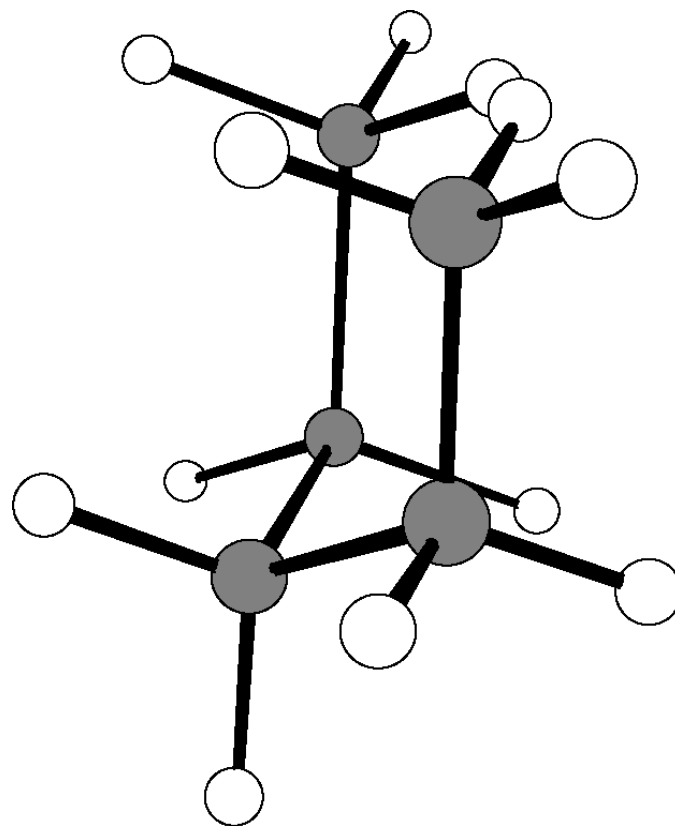
Conformers of *n*-Pentane

Rotation about both the C₂-C₃ and C₃-C₄ bonds in either direction (+ or -):

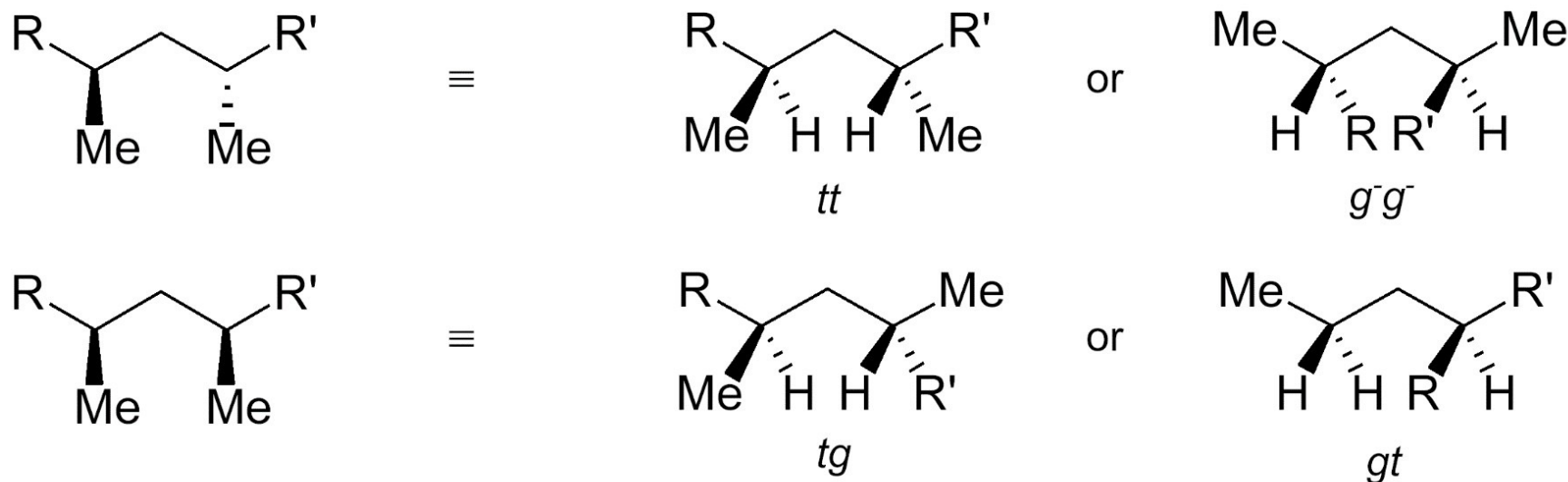


The double-gauche pentane conformation

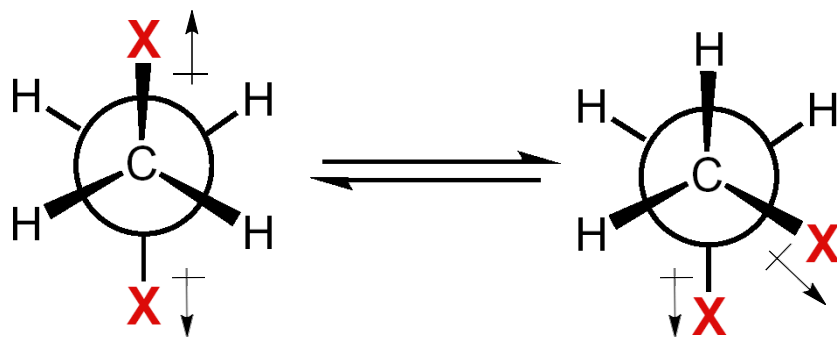
The new high-energy conformation: (g⁺g⁻)



The *syn*-Pentane Interaction – Consequences



- Compounds containing the above fragments should avoid *g⁺g⁻* the most unstable *n*-pentane conformation structure



X = Cl; $\Delta H^\circ = + 0.9\text{--}1.3$ kcal/mol

X = Br; $\Delta H^\circ = + 1.4\text{--}1.8$ kcal/mol

X = F; $\Delta H^\circ = - 0.6\text{--}0.9$ kcal/mol

1,2-dibromoethane and **1,2-dichloroethane** mainly adopt **trans cross conformation**.

As the **polarity of the solvent increases**, the number of ortho cross conformations gradually increases.

However, **1,2-difluoroethane** adopts an **ortho-cross conformation**!

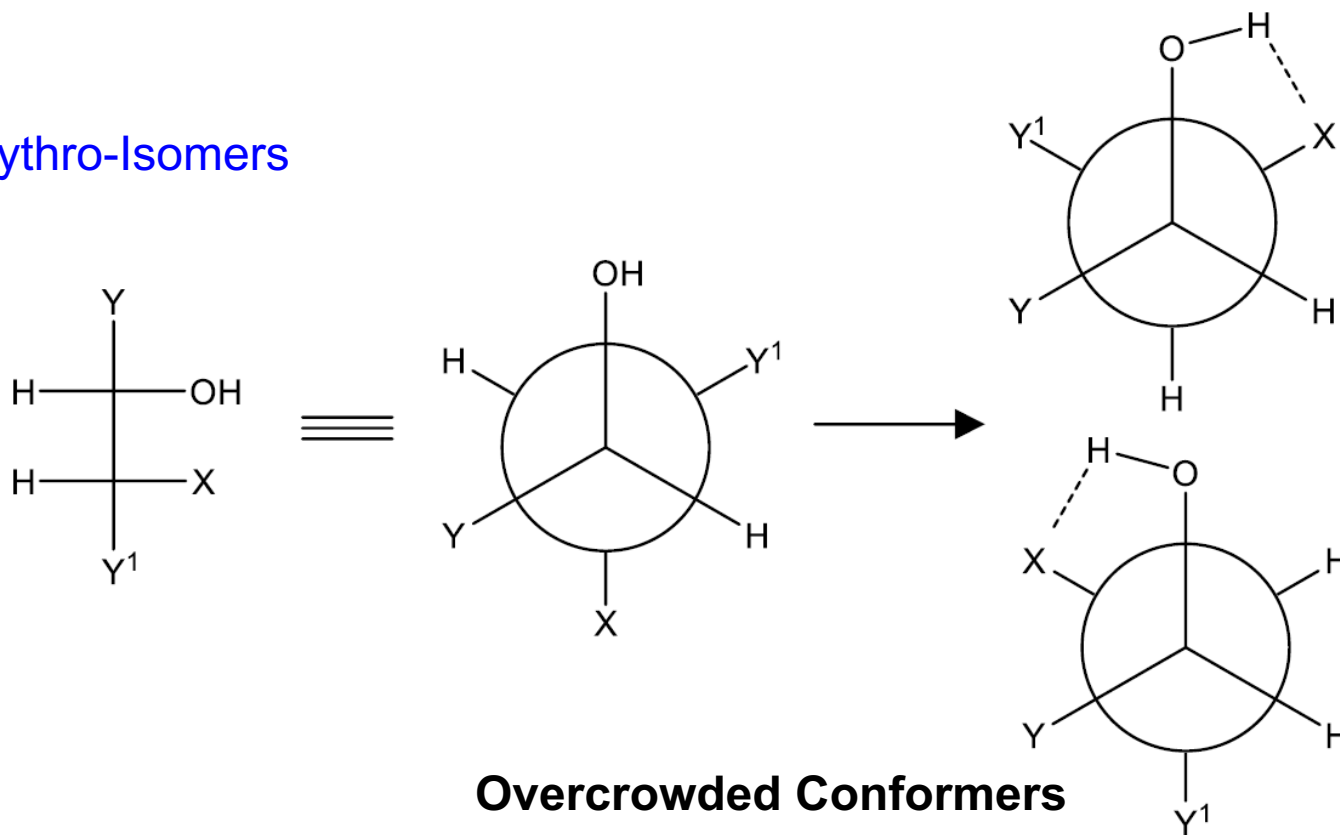
Comprehensive consideration:

polar covalent bond-polar covalent bond repulsion, or dipole-dipole repulsion;
the effect of (polar) solvents on dipole-dipole interactions; Van der Waals repulsion;

hyperconjugation; high electron demand of fluorine atoms.

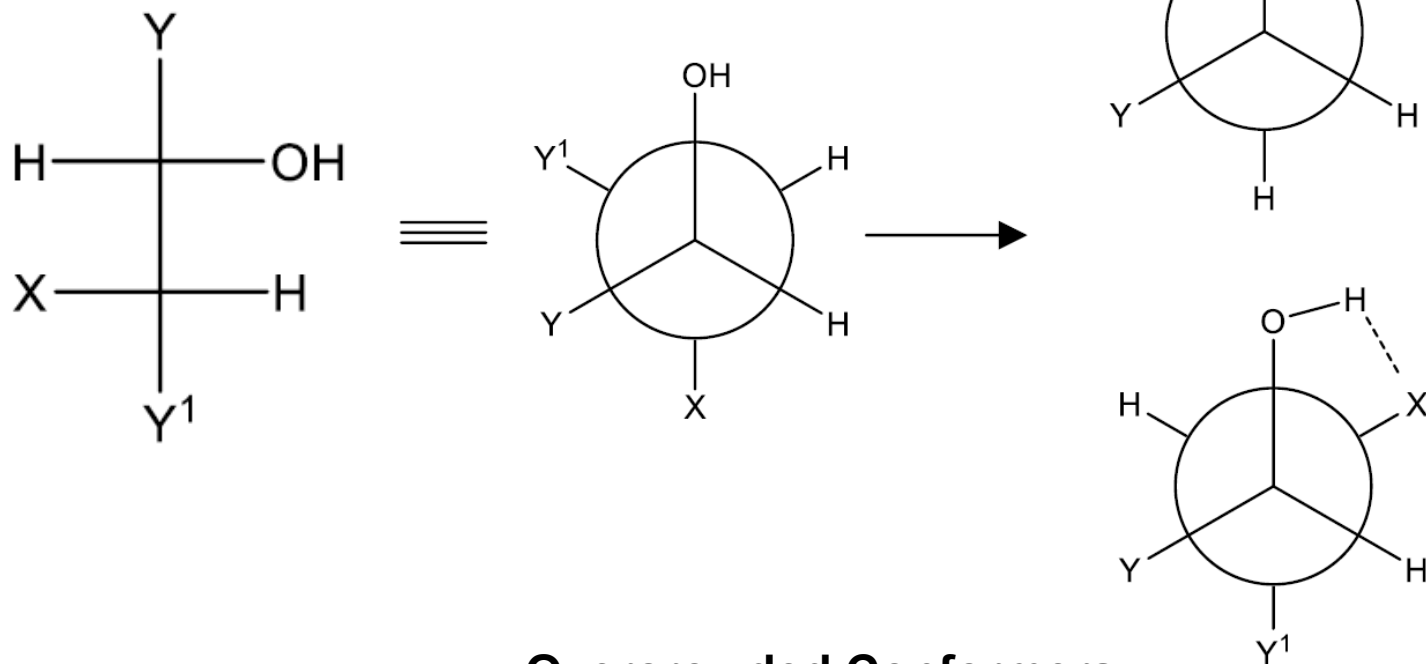
- For erythro and threo isomers, when the substituents on adjacent carbon atoms may be associated with hydrogen bonds, the conformational stability can be divided into several situations:
- $X=F$, OH , OR , NH_2 , Cl , COR , etc., that is, it has a lone pair of electrons.
- Y , Y^1 is a hydrocarbon group

Erythro-Isomers



- Hydrogen bond energy: 5-6 kcal/mol. As long as Y and Y¹ are not too crowded, intramolecular hydrogen bonds are always relatively stable. In the preferred conformation of the Su-type structure, the distance between X, Y, and Y¹ is farther than in the erythro-type structure, which is more stable.

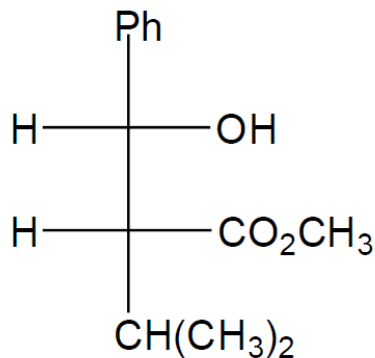
Threo-Isomers



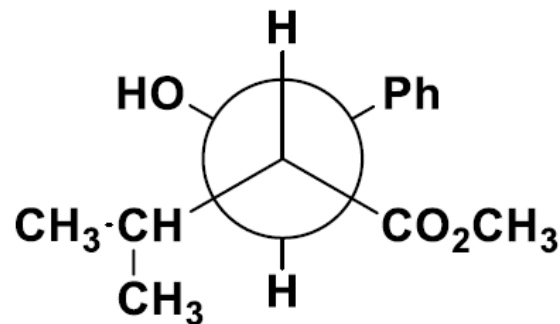
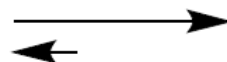
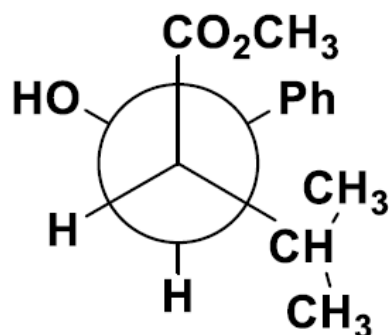
Overcrowded Conformers

When Y and Y1 are both Large

Both erythro and threo isomers tend to use Y and Y1 are mainly in opposite positions

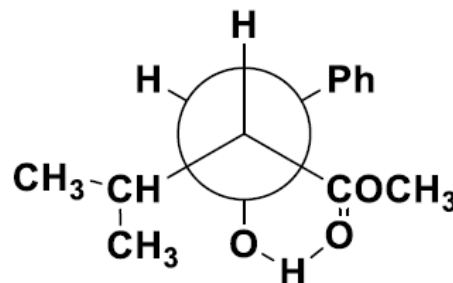
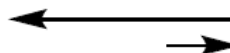
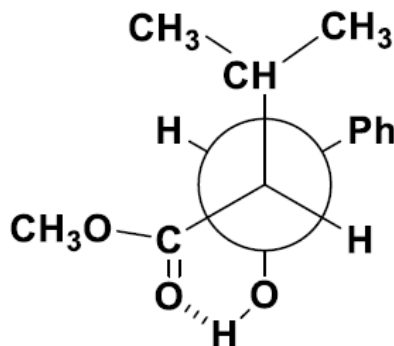
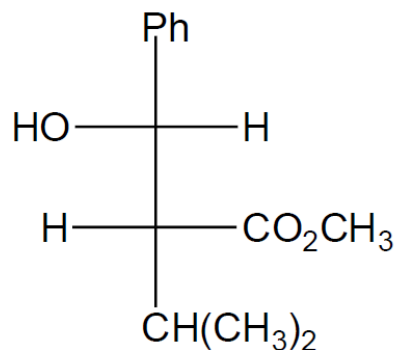


Erythro-Isomers



**Favorable Conformer
But no H-Bonds**

Threo-Isomers



**Favorable Conformer
Also forming H-Bonds**

• Conformations of compounds with polar single bonds and functional groups

Alkanes ^a	Barrier (kcal/mol)	Heteroatom compounds	Barrier (kcal/mol)
CH ₃ –CH ₃	2.9] 0.5	CH ₃ –NH ₂ ^c	2.0] 1.0
CH ₃ –CH ₂ CH ₃	3.4] 0.5	CH ₃ –NHCH ₃ ^c	3.0] 1.4
CH ₃ –CH(CH ₃) ₂	3.9] 0.5	CH ₃ –N(CH ₃) ₂ ^c	4.4] 3.6
CH ₃ –C(CH ₃) ₃	4.7	CH ₃ –OH ^d	1.1
(CH ₃) ₃ C–C(CH ₃) ₃	8.4 ^b	CH ₃ –OCH ₃ ^d	4.6

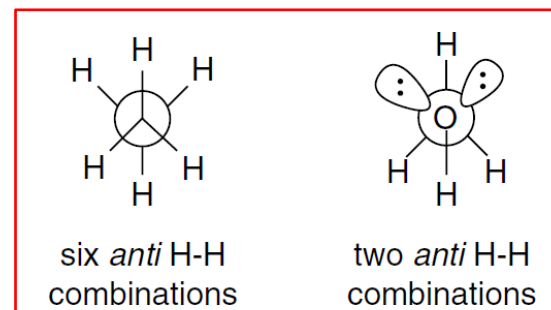
a. Taken from the compilation of J. P. Lowe, *Prog. Phys. Org. Chem.*, **6**, 1 (1968).

b. Footnote 9, J. E. Andersen, A. de Meijere, S. I. Kozhushkov, L. Lunazzi, and A. Mazzanti, *J. Org. Chem.*, **68**, 8494 (2003).

c. M. L. Senent and Y. G. Meyers, *J. Chem. Phys.*, **105**, 2789 (1996).

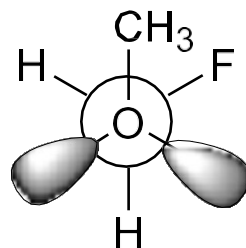
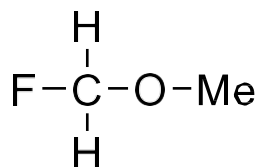
d. V. Pophristic, L. Goodman, and N. Guchhait, *J. Phys. Chem. A*, **101**, 4290 (1997).

The amount of hyperconjugation effect determines the rotation energy barrier

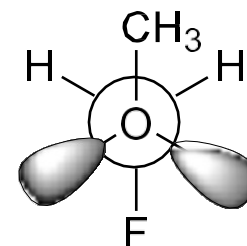
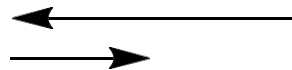


Compounds with Polar Single Bonds

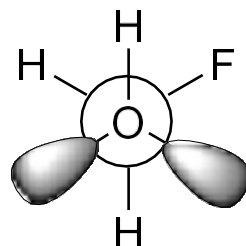
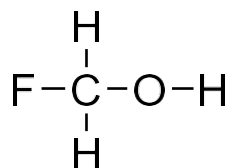
Stereoelectronic effect



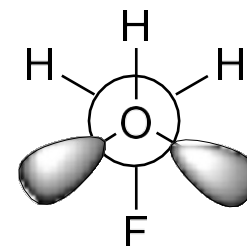
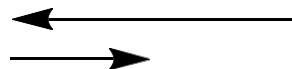
gauche



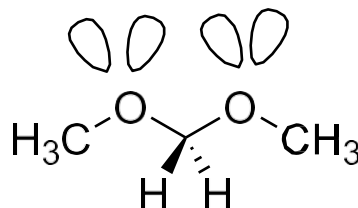
anti



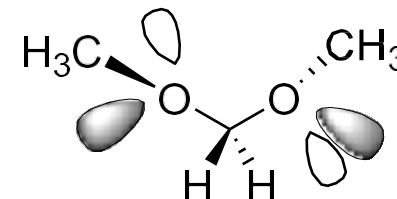
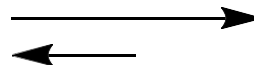
gauche



anti



anti, anti



gauche, gauche

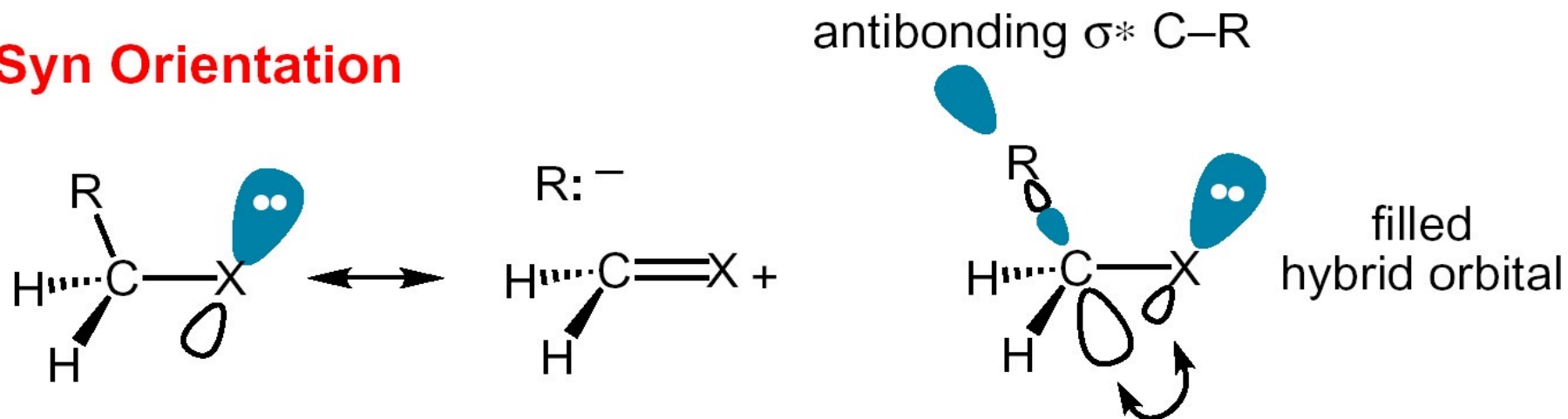
$\text{lpe}_\text{O} - \sigma^*_{\text{C-O}}$



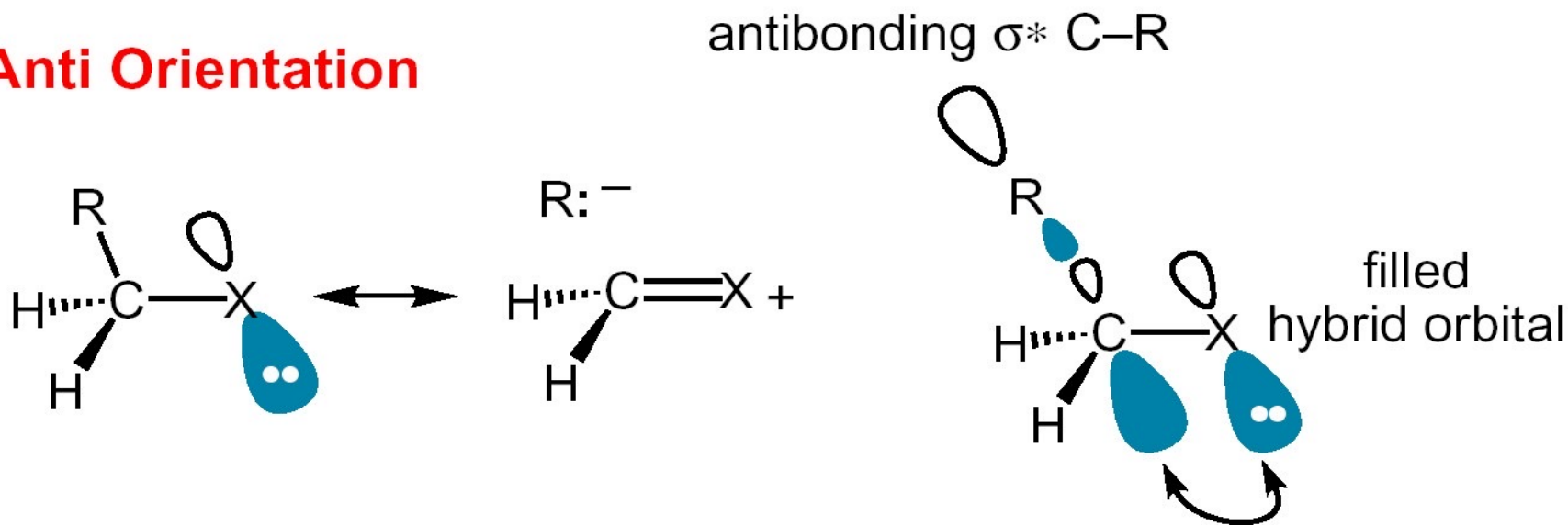
Hyperconjugation effect between n electrons and σ^* C-R of heteroatoms in non-cyclic compounds



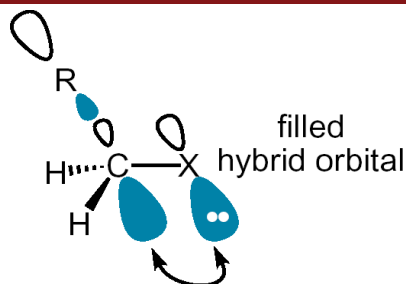
Syn Orientation



Anti Orientation



For *trans-coplanar* conformers, the overlap of lone pairs with σ^* C-R orbitals is preferable



Change in Structure

Spectroscopic Probe

- Shorter C–X bond
- Longer C–R bond
- Stronger C–X bond
- Weaker C–R bond
- Greater e-density at R
- Less e-density at X

X-ray crystallography

X-ray crystallography

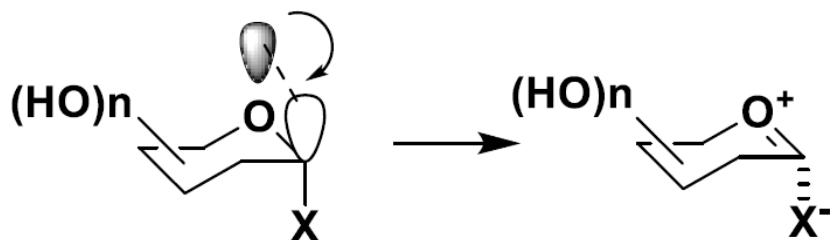
Infrared Spectroscopy

Infrared Spectroscopy

NMR Spectroscopy

NMR Spectroscopy

Typical Anomeric Effect

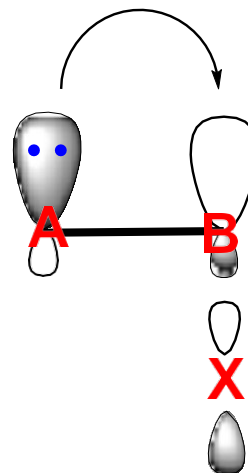


Electron Donors: $nC- > nN > nS > nO > \sigma C-S > \sigma C-H > \sigma C-C > \sigma C-O > \sigma C-F$

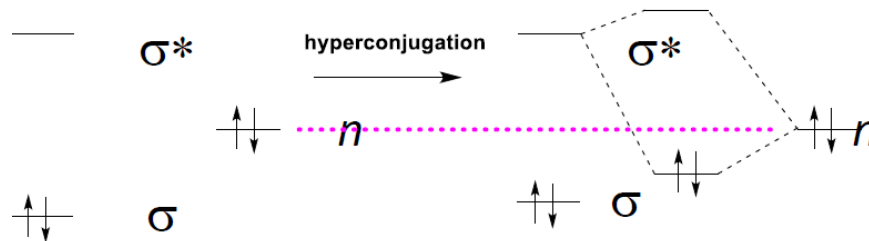
Electron Acceptors:

$\sigma^* C-Br (C-Cl) > \sigma^* C-S > \sigma^* C-F > \sigma^* C-O > \sigma^* C-C > \sigma^* C-H$

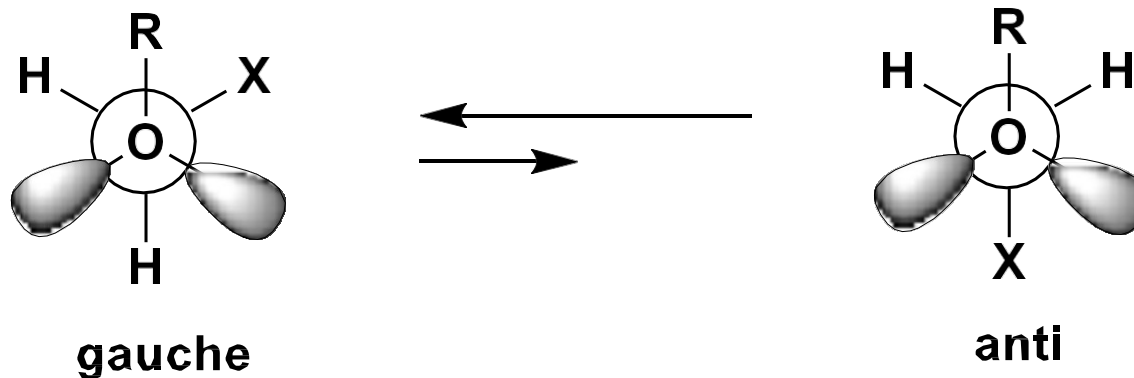
Broadly Anomeric Effect



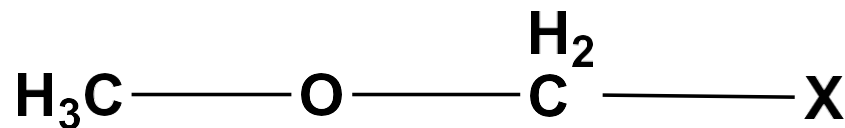
MO Analysis of Hyperconjugation



Stereoelectronic effect

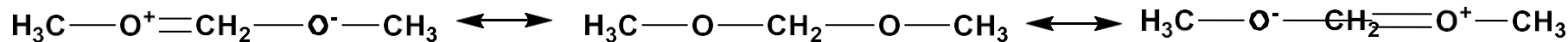


Bond lengths in R-O-CH₂-X compounds



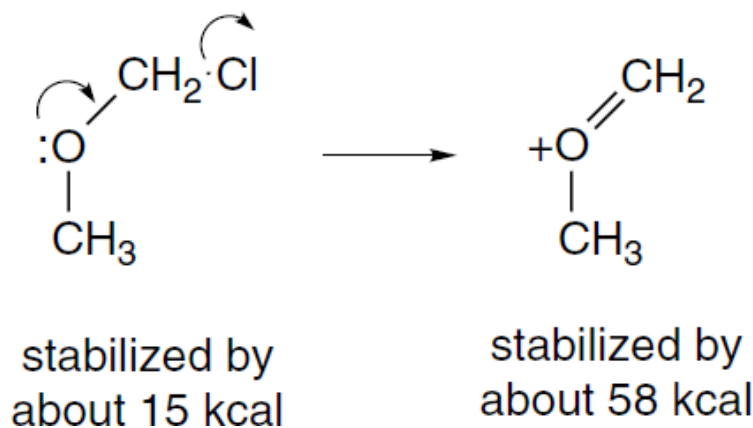
X = F	1.424	1.362	1.385
X = Cl	1.421	1.362	1.822
X = OMe	1.432	1.382	1.382

Standard Bond Lengths	
C-F	1.379
C-Cl	1.767
C-O	1.426



Hyperconjugations in α -halo Compounds

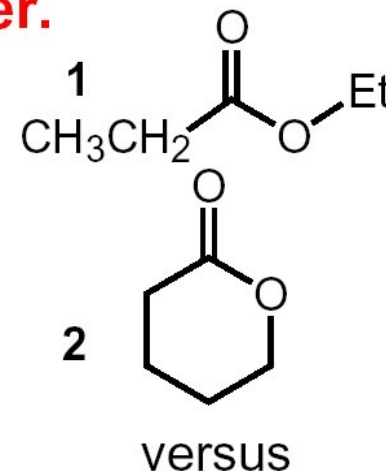
- Hyperconjugative stabilization in compounds does not mean that these compounds are inactive or unreactive.
- In fact, the hyperconjugation stabilization energy is reflected in the weakening of the carbon-halogen bond, which is easily dissociated in polar solvents, and the generated oxonium ions obtain more stabilization energy.



- The reactivity of α -halo acid ester, α -haloamine and α -haloether is relatively high.

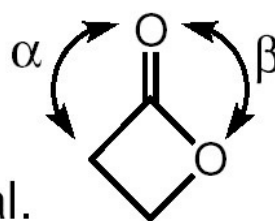
Esters versus Lactones: Questions to Ponder.

Esters strongly prefer to adopt the (E) conformation while small-ring lactones such as **2** are constrained to exist in the (Z) conformation.
following:

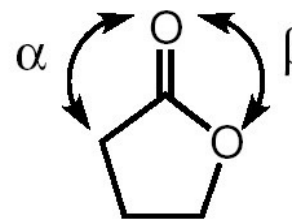


- 1) Lactone **2** is significantly more susceptible to nucleophilic attack at the carbonyl carbon than **1**? Explain.
- 2) Lactone **2** is significantly more prone to enolization than **1**?
In fact the pK_a of **2** is ~25 while ester **1** is ~30 (DMSO). Explain.

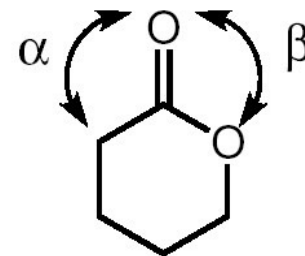
- 3) In 1985 Burgi, on carefully studying the X-ray structures of a number of lactones, noted that the O-C-C (α) & O-C-O (β) bond angles were not equal.
Explain the indicated trend in bond angle changes.



$$\alpha - \beta = 12.3^\circ$$



$$\alpha - \beta = 6.9^\circ$$



$$\alpha - \beta = 4.5^\circ$$



- ◆ **Conformational Analysis of Small Rings**
 - ◆ **Conformational Analysis of Cyclopentane and Cyclohexane**
 - ◆ **Conformational Analysis of Medium Rings**
 - ◆ **Conformational Transmission in Polycyclic Rings**
-
- Three Types of Strain:
 - **Prelog Strain:** *van der Waals interactions*
 - **Baeyer Strain:** *bond angle distortion away from the ideal*
 - **Pitzer Strain:** *torsional rotation about a sigma bond*



Combustion Heat and Ring Strain of Cycloalkanes



Eliel, E. L., Wilen, S. H. *Stereochemistry of Organic Compounds*
Chapter 11, John Wiley & Sons, 1994.

Baeyer Strain for selected ring sizes

size of ring	Heat of Combustion (kcal/mol)	Total Strain (kcal/mol)	Strain per CH ₂ (kcal.mol)	"angle strain" deviation from 109°28'
3	499.8	27.5	9.17	24°44'
4	656.1	26.3	6.58	9°44'
5	793.5	6.2	1.24	0°44'
6	944.8	0.1	0.02	-5°16'
7	1108.3	6.2	0.89	
8	1269.2	9.7	1.21	
9	1429.6	12.6	1.40	
10	1586.8	12.4	1.24	
11	1743.1	11.3	1.02	
12	1893.4	4.1	0.34	
13	2051.9	5.2	0.40	
14	2206.1	1.9	0.14	
15	2363.5	1.9	0.13	

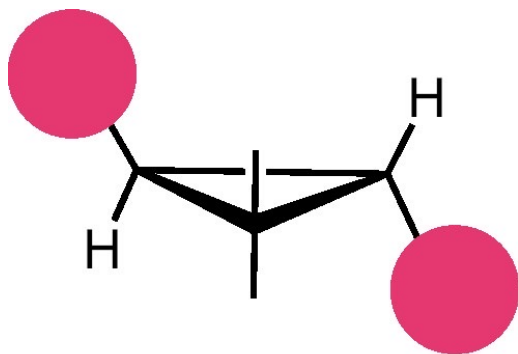
Why is the angular tension of cyclopropane much greater than that of cyclobutane, but the total tension is only slightly greater than that of cyclobutane?



Ring Sizes and Strains



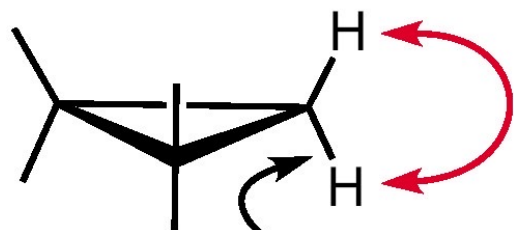
- Baeyer “angle strain” is calculated from the deviation of the **planar bond angles from the ideal tetrahedral bond angle**.
- Discrepancies between calculated strain/ CH_2 and the “angle strain” results from **puckering** to minimize van der Waals or eclipsing torsional strain between vicinal hydrogens.
- Why is there an increase in strain for medium sized rings even though they also can access puckered conformations free of angle strain?
- The answer is **transannular strain- van der Waals interactions** between hydrogens across the ring.



■ Necessarily *planar*.

■ Substituents are therefore eclipsed.

■ Disubstitution prefers to be *trans*.



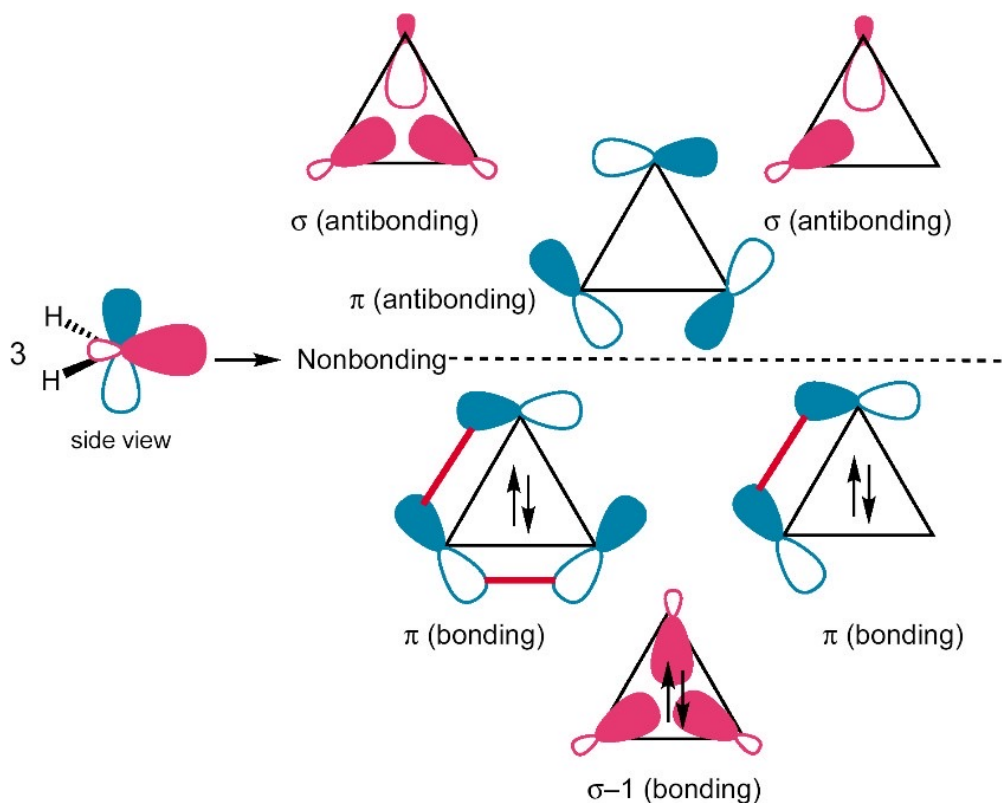
$$\phi = 120^\circ$$

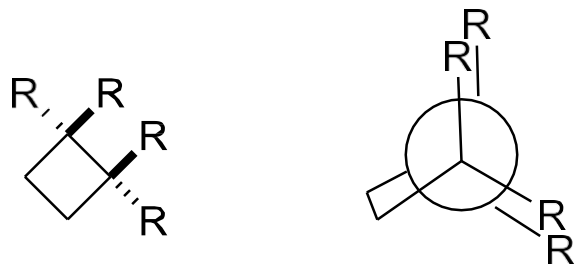
$$\nu = 3080 \text{ cm}^{-1}$$

■ Almost sp^2 , not sp^3

Walsh Model for Strained Rings

- Rather than σ and σ^* C-C bonds, cyclopropane has sp^2 and p-type orbitals instead.

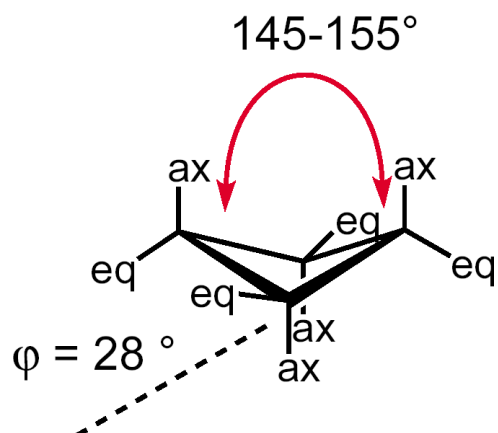




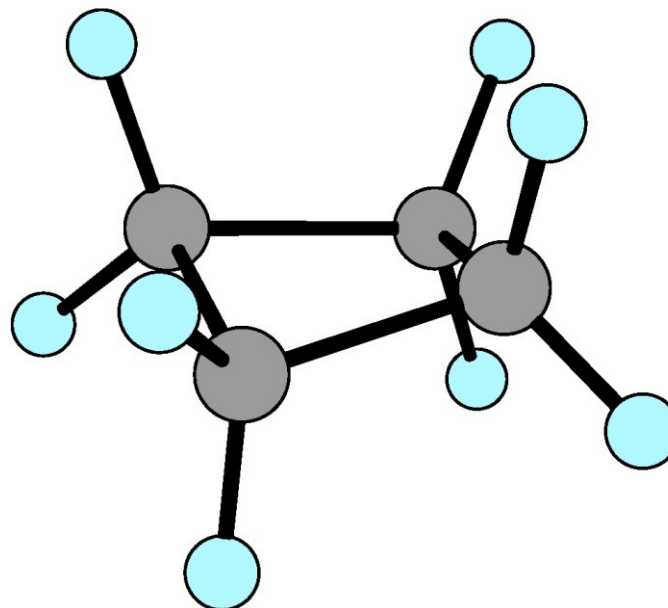
■ Eclipsing torsional strain overrides increased bond angle strain by puckering.

■ Ring barrier to inversion is 1.45 kcal/mol.

Flat Conformer

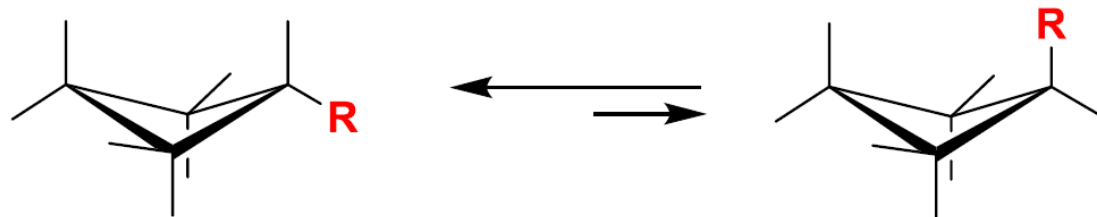


Folded Conformer
(wing-shaped molecules)



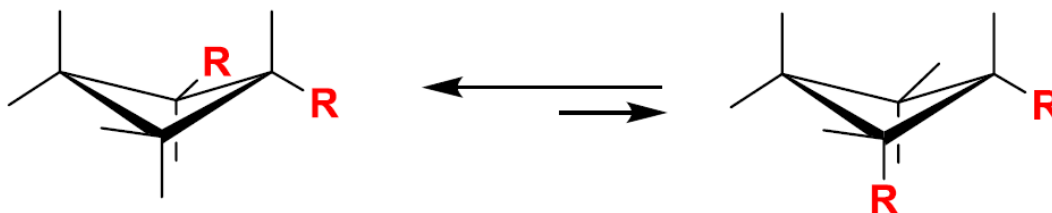
(MM2)

Mono-Substituted



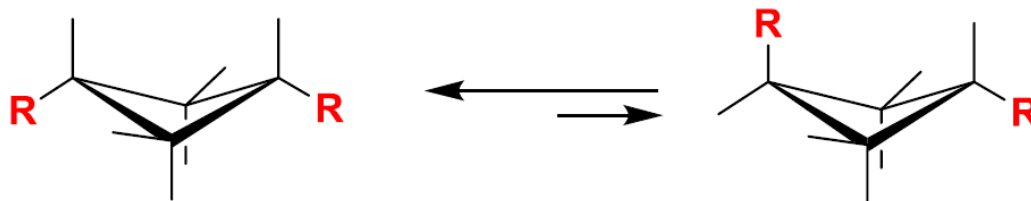
■ $\Delta G = 1$ kcal/mol favoring R = Me equatorial

1,2-Di Substituted



■ 1,2 Disubstitution prefers *trans* diequatorial to *cis* by 1.3 kcal/mol for diacid (roughly equivalent to the cyclohexyl analogue.)

1,3-Di Substituted



■ 1,3 Disubstitution prefers *cis* diequatorial to *trans* by 0.58 kcal/mol for di-bromo cmpd.

Cis-Conformer

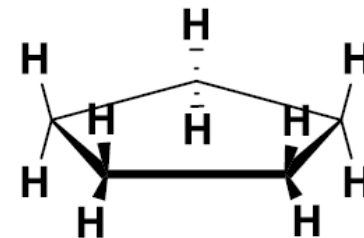
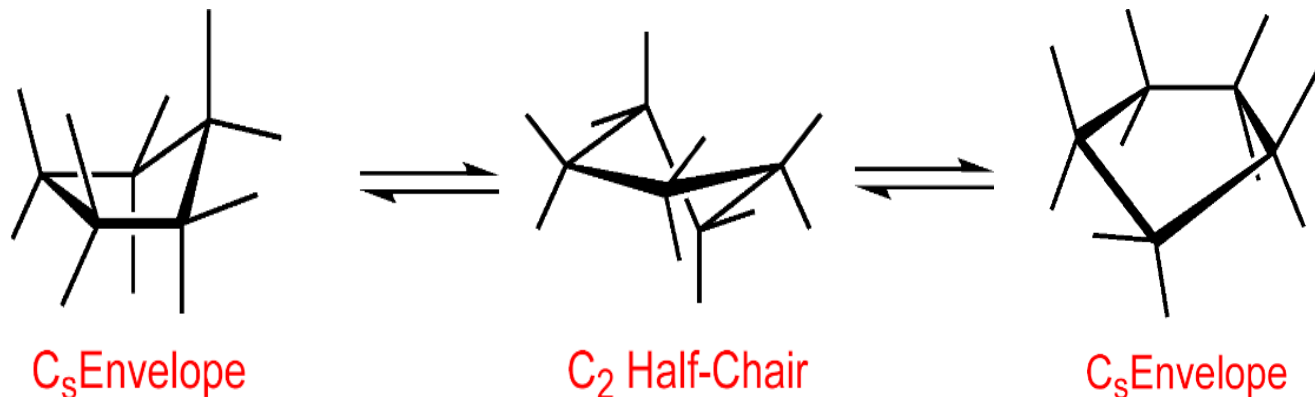


Flatter Geometry



More Stable

Cyclopentane – Two Conformers



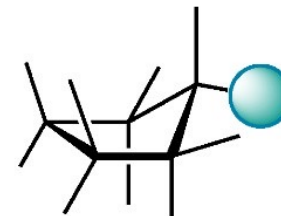
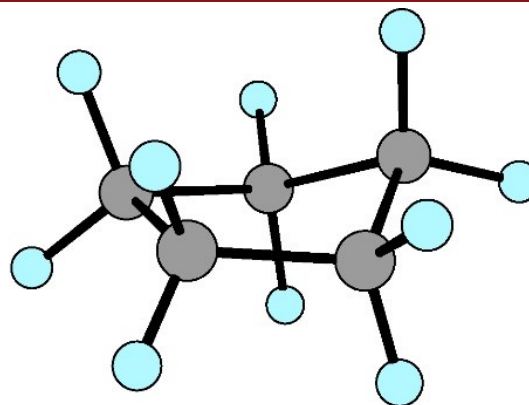
- There are two lowest energy conformations (10 envelope conformations C_s envelope and 10 half-chair conformations C_2 half-chair). The envelope conformation is only 0.5 kcal/mol more stable than the half-chair conformation. There is conformational fluidity. The two conformations flip rapidly, and there always seems to be a carbon atom protruding from or out of the ring.
- Since there is no "naturally stable" conformation, once a substituent is introduced, cyclopentane will adjust its conformation to reduce torsional tension and give a relatively stable conformer.

Planar cyclopentane is unstable. Although it has no angular tension, it contains 10 pairs of H-H overlapping formulas and has huge torsional tension, reaching 10 kcal/mol.

Conformers of Substituted Cyclopentane

Monosubstituted cyclopentane:

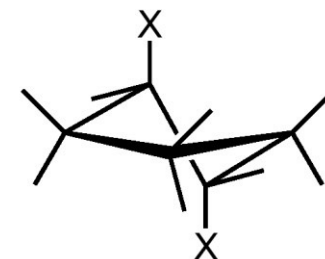
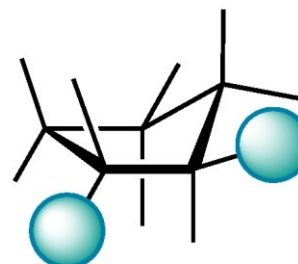
C_s Envelope
(MM2)



■ A single substituent prefers the equatorial position of the flap of the envelope (barrier ca. 3.4 kcal/mol, R = CH₃).

1,2-Disubstituted cyclopentane:

■ 1,2 Disubstitution prefers *trans* for steric/torsional reasons (alkyl groups) and dipole reasons (polar groups).

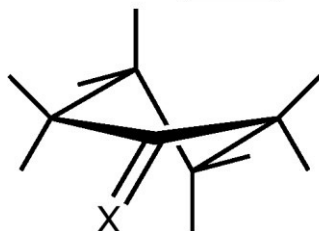


1,3-Disubstituted cyclopentane:



■ 1,3 Disubstitution: **Cis**-1,3-dimethyl cyclopentane 0.5 kcal/mol **more stable** than trans.

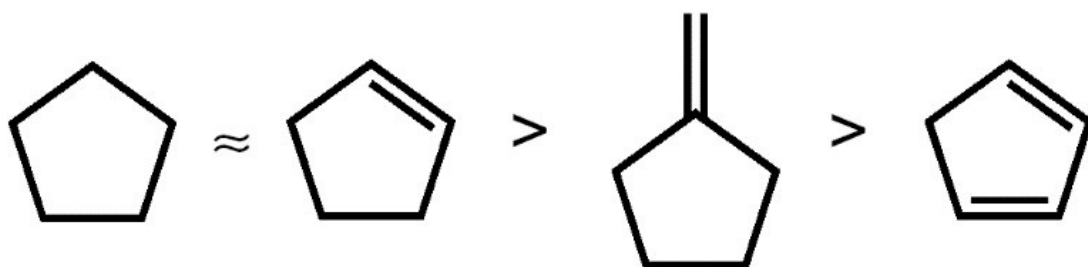
Double bond
Substituted
cyclopentane:



■ A carbonyl or methylene prefers the planar position of the half-chair (barrier 1.15 kcal/mol for cyclopentanone).

The fluidity of the conformation makes it difficult to determine the structure using NMR!

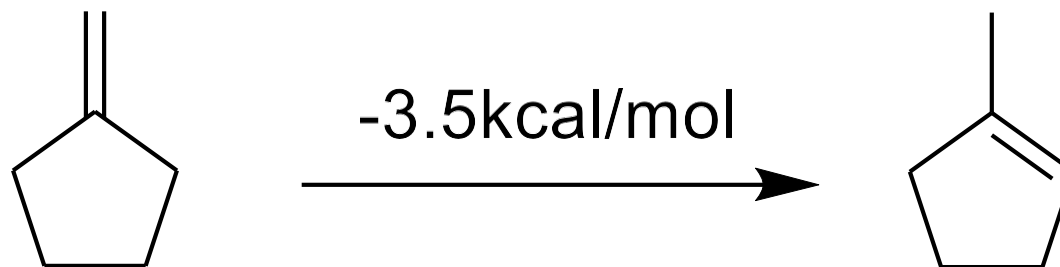
Strain trends:



The decrease in overlap (torsion) tension compensates for the increase in angular tension

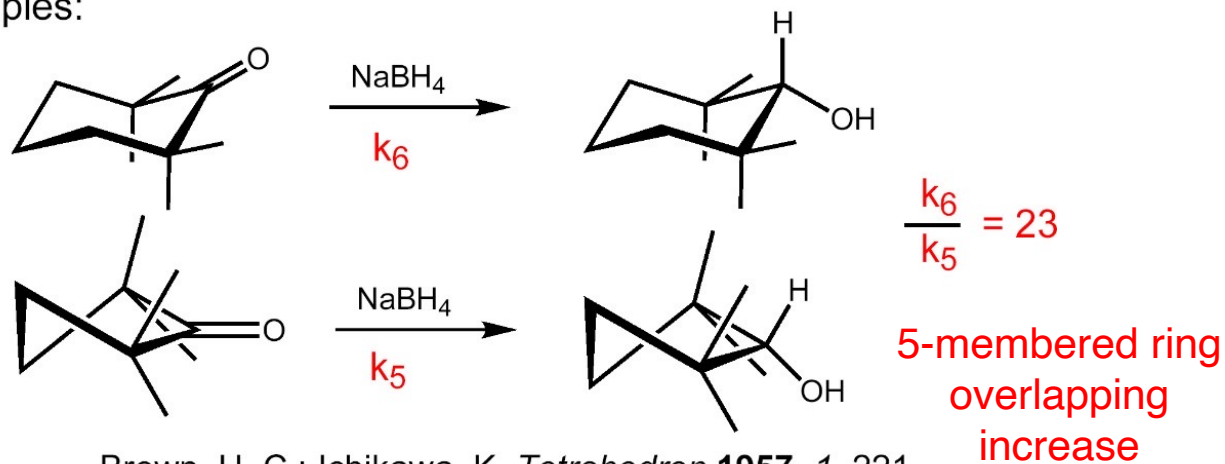
Compared to cyclohexane derivatives, the corresponding cyclopentane prefers the introduction of double bonds outside the ring to reduce overlapping effects, or overlapping (twisting) tension

Example:

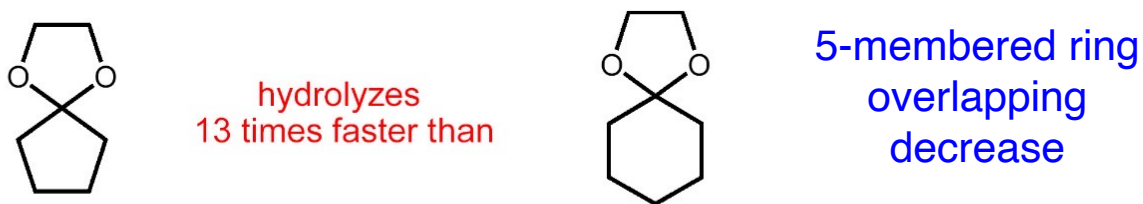


“Reactions will proceed in such a manner as **to favor the formation or retention of an exo double bond in the 5-membered ring** and **to avoid the formation or retention of the exo double bond in the 6-membered ring systems.**”

Examples:

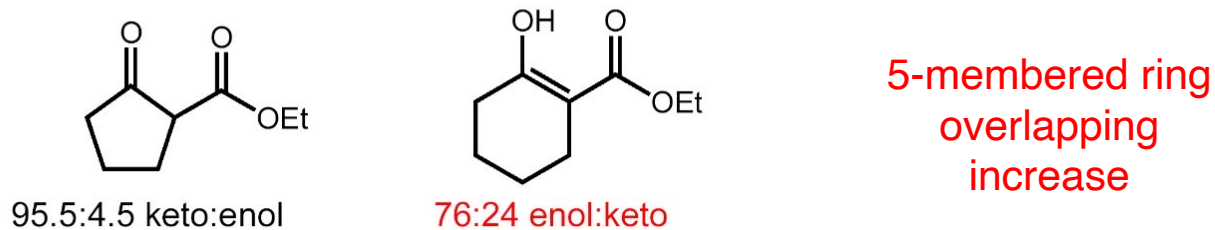


Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, 1, 221.

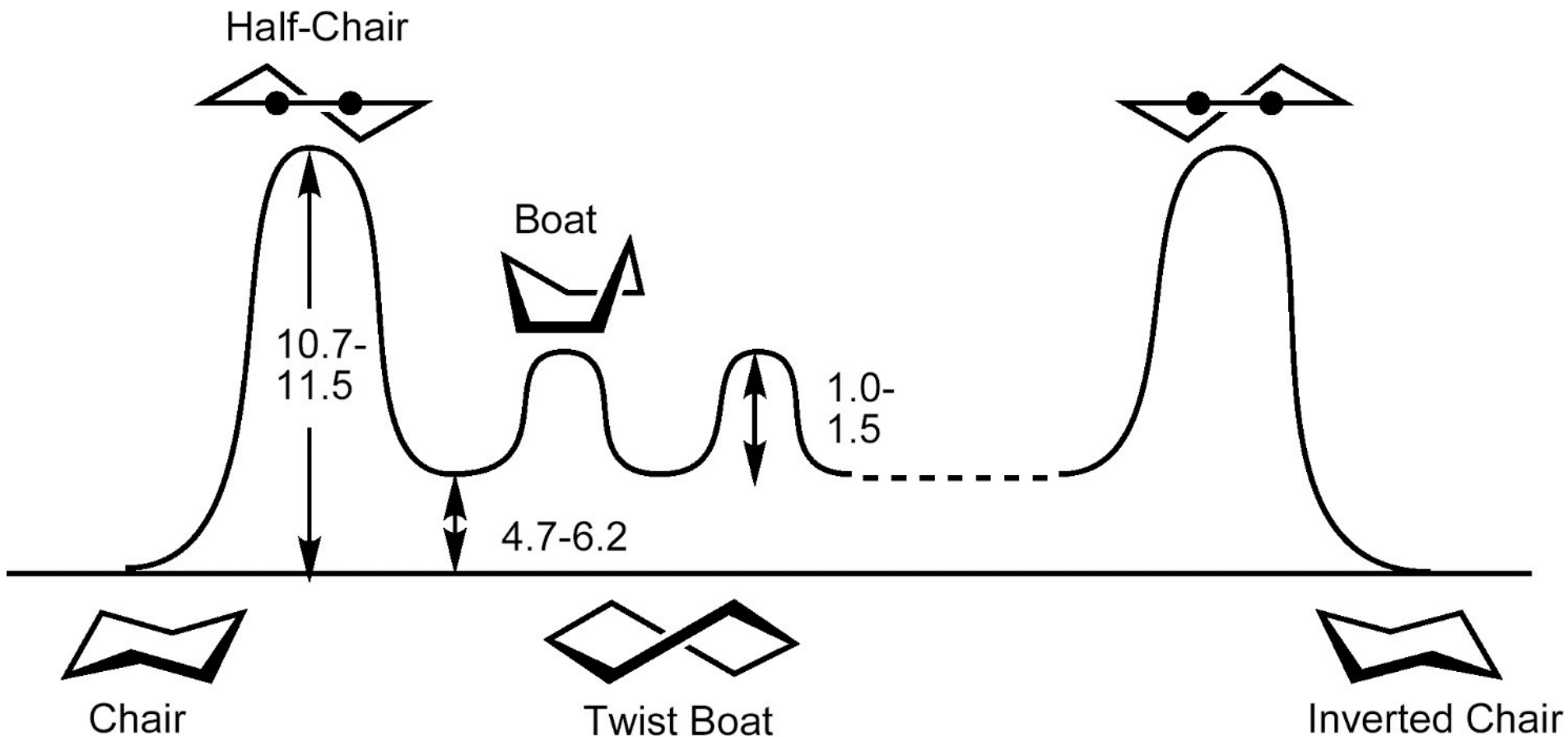


Conan, J-Y.; Natat, A.; Priolet, D. *Bull. Soc. Chim., Fr.* **1976**, 1935.

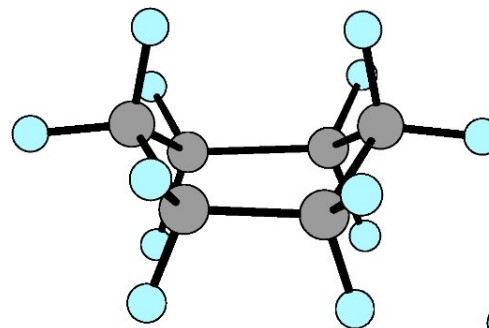
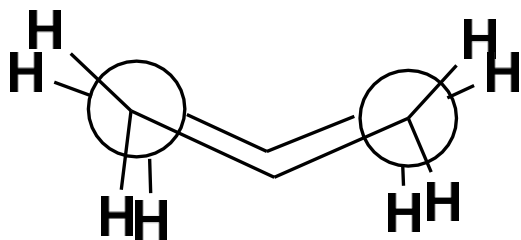
H. C. Brown,
J. H. Brewster,
H. Shechter,
J. Am. Chem. Soc.
1954, 76, 467



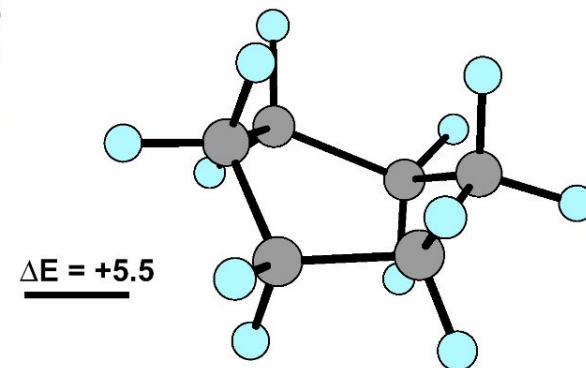
Brown, H. C.; Brewster, J. H.; Shechter, H. *JACS* **1954**, 76, 467.



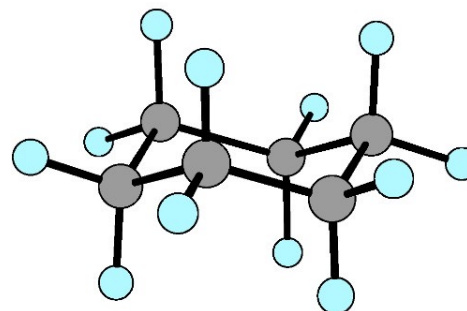
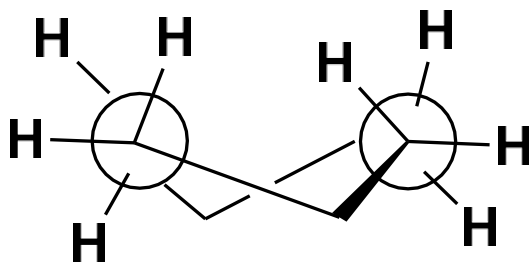
Cyclohexane Energy Profile (kcal/mol)



$$\Delta E = +6.5-7.0$$

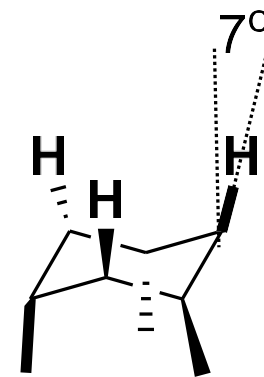
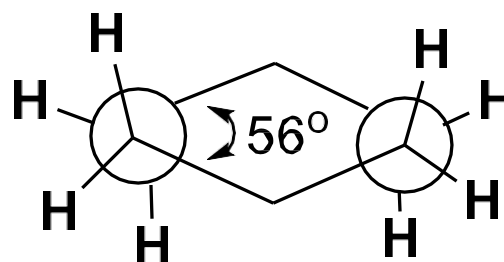
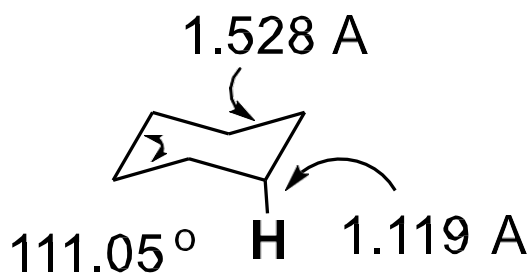


$$\Delta E = +5.5$$

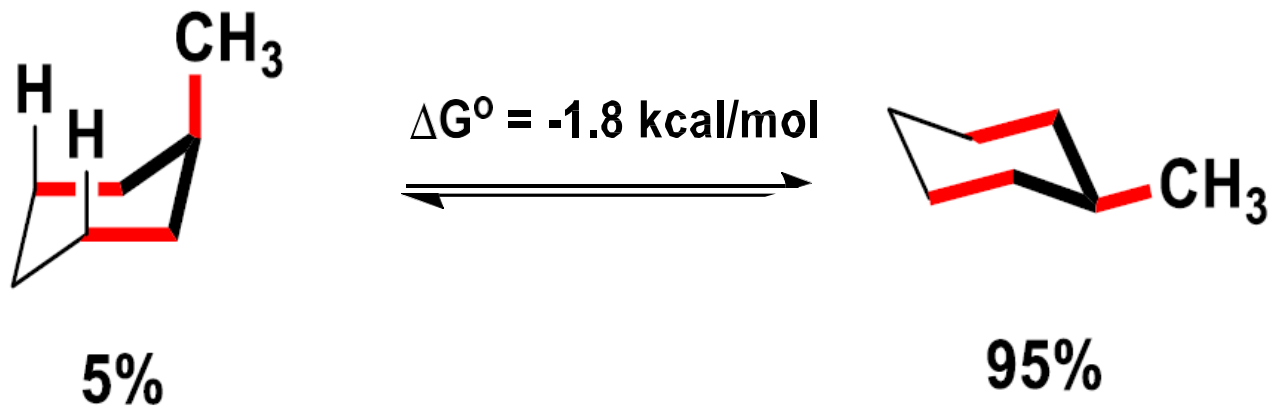


The barrier: +10.7-11.5

$$E = 0$$

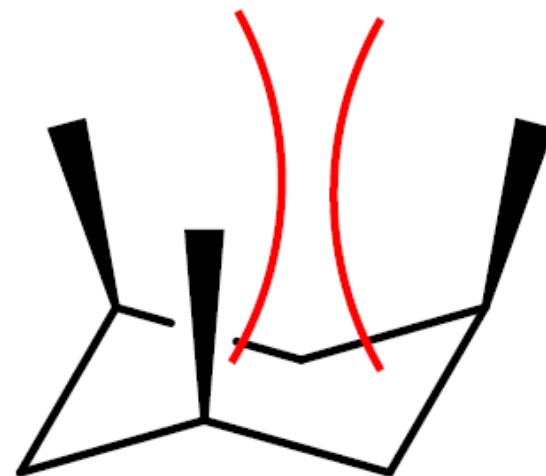
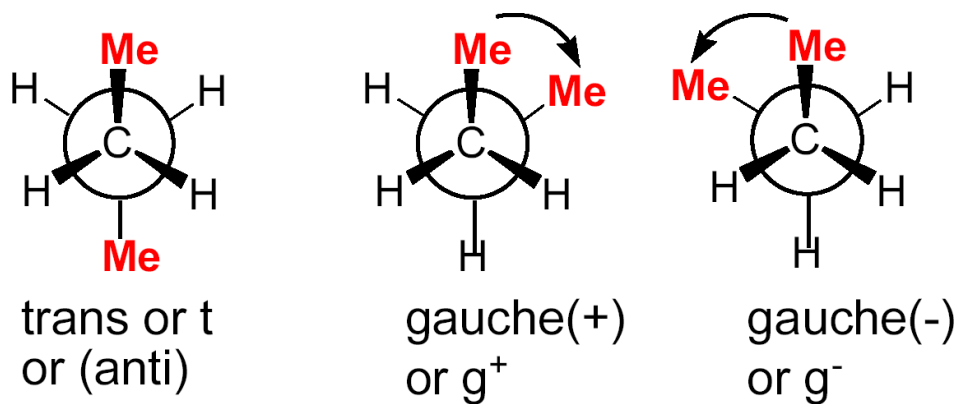


Substituted Cyclohexane



1. gauche butane interactions;

2. 1,3-diaxial interactions



Conformational Free Energy (A value) ($-\Delta G_c$): the preference of the substituent for the equatorial (e) position



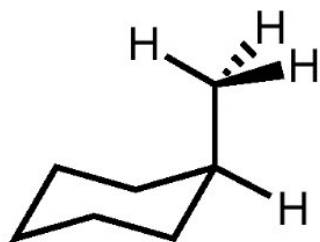
A Value with Various Substituted Groups



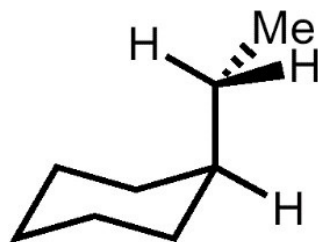
Substituent	$-\Delta G_c$	Substituent	$-\Delta G_c$
F	0.26 ^b	C ₆ H ₅	2.9 ^e
Cl	0.53 ^b	CN	0.2 ^b
I	0.47 ^b	CH ₃ CO ₂	0.71 ^b
CH ₃	1.8 ^c	HO ₂ C	1.35 ^d
CH ₃ CH ₂	1.8 ^c	C ₂ H ₅ O ₂ C	1.1–1.2 ^d
(CH ₃) ₂ CH	2.1 ^c	HO (aprotic solvent)	0.52 ^d
(CH ₃) ₃ C	> 4.7 ^d	HO (protic solvent)	0.87 ^d
CH ₂ =CH	1.7 ^e	CH ₃ O	0.60 ^d
HC≡C	0.5 ^f	O ₂ N	1.16 ^b

- a. For a more extensive compilation see E. L. Eliel, S. H. Wilen, and L. N. Mander *Stereochemistry of Organic Compounds*, Wiley, New York, 1993, pp. 696–697.
- b. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, **3**, 140 (1971).
- c. N. L. Allinger and L. A. Freiburg, *J. Org. Chem.*, **31**, 804 (1966).
- d. J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).
- e. E. L. Eliel and M. Manoharan, *J. Org. Chem.*, **46**, 1959 (1981).

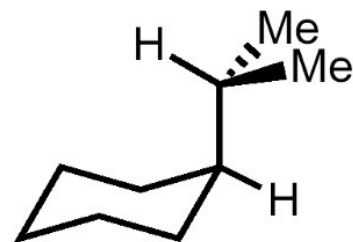
A Value, Size Matter?



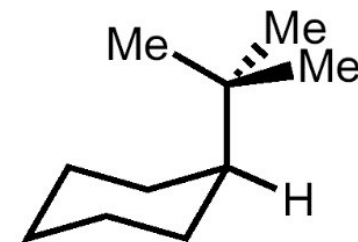
A-Value 1.74



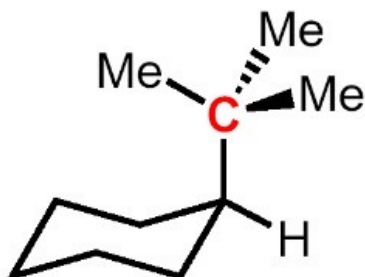
1.80



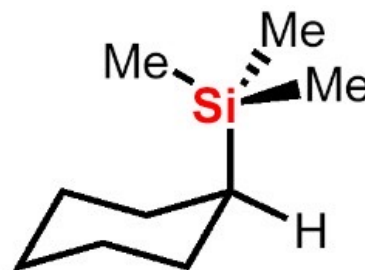
2.15



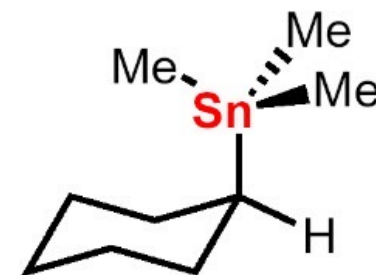
5.0



A-Value 5.0

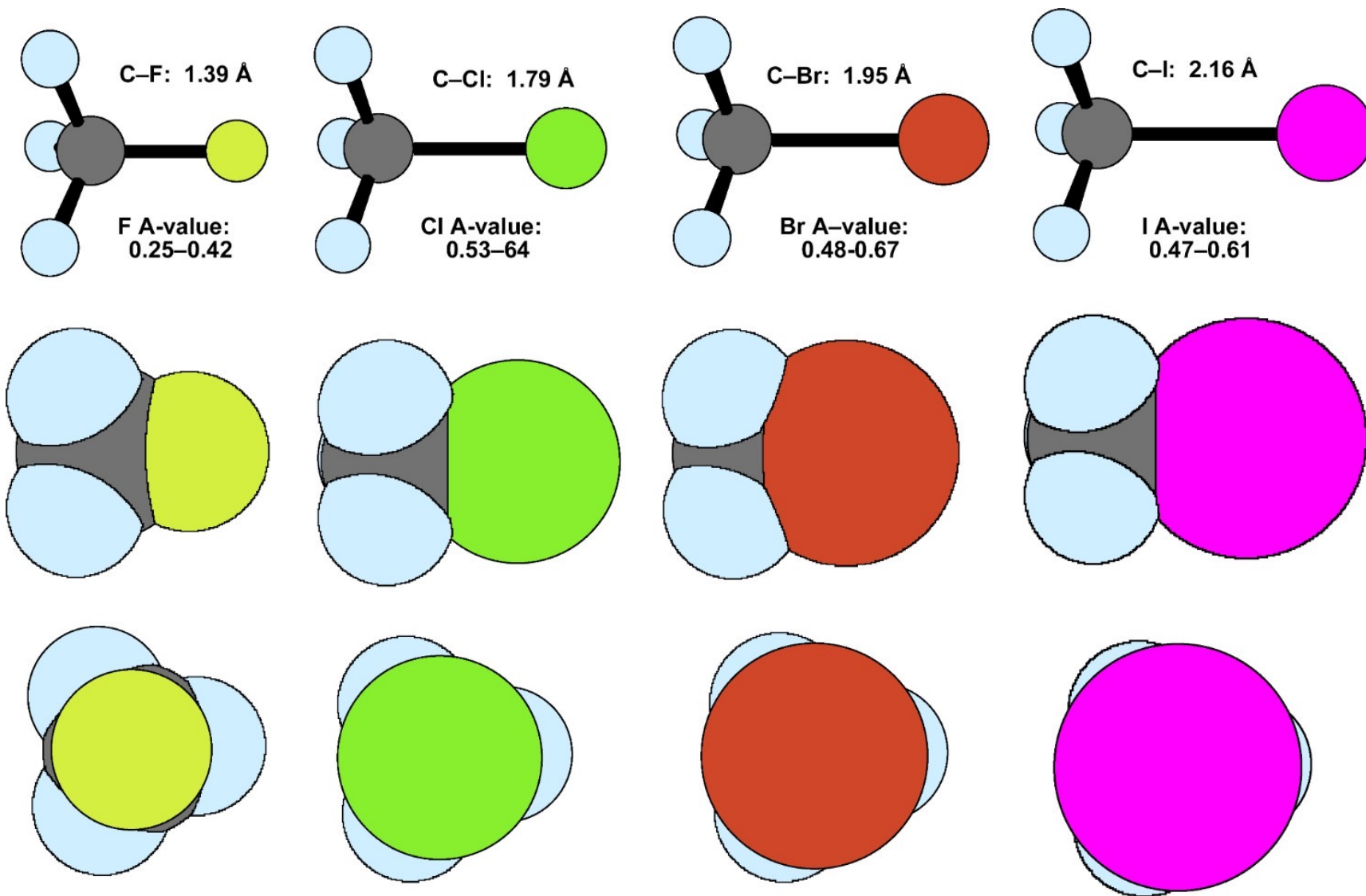


2.5



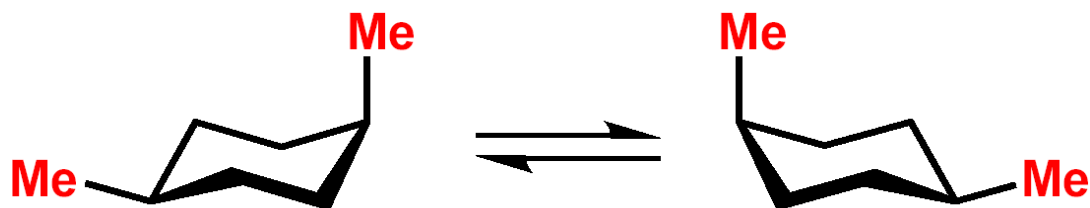
1.1

A Value, Size Matter?

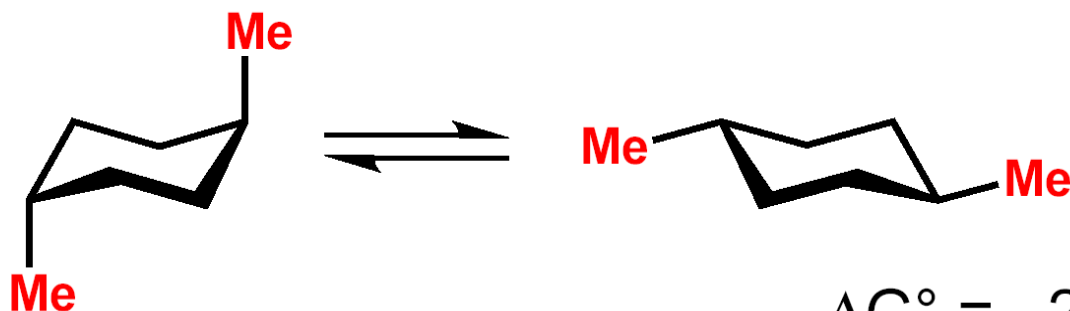


1,4-Disubstitution Cyclohexane

Cis → Always (a,e)



$$\Delta G^\circ = 0 \text{ kcal/mol}$$



$$\Delta G^\circ = -2(1.74) = -3.48 \text{ kcal/mol}$$

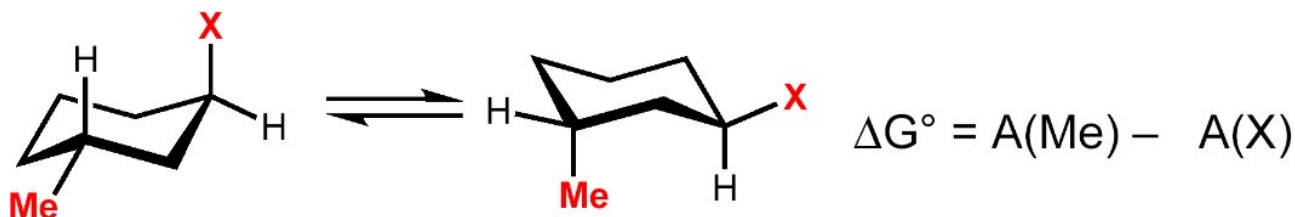
Trans → Highly prefer (e,e)

1, 4 Disubstitution: A values are roughly additive.

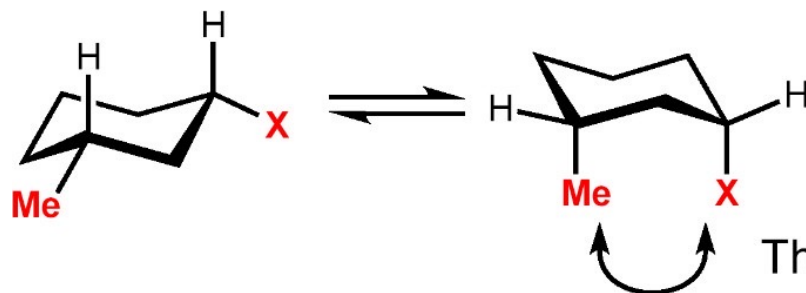
As long as the substituents on the ring do not interact in either conformation, their A-values are roughly additive.

1,3-Disubstitution Cyclohexane

trans(a,e)
X group determine
the preferable
conformer



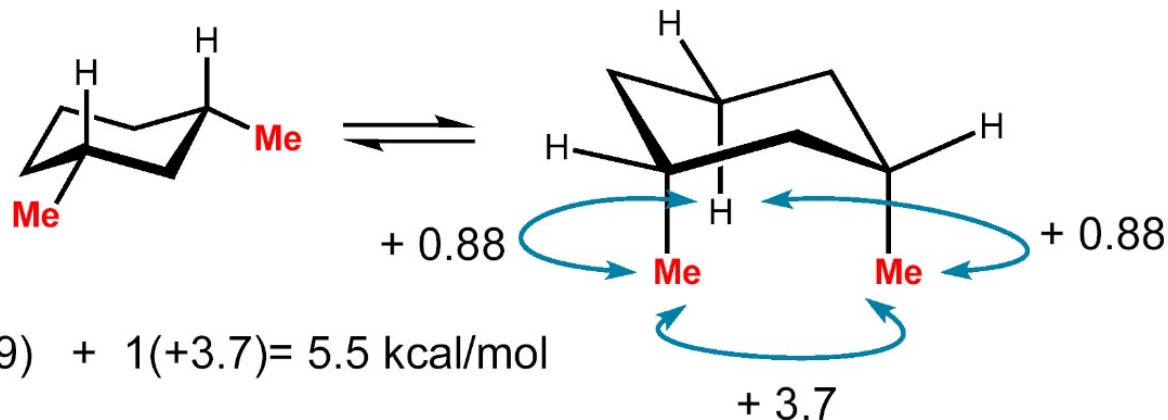
1,3-Disubstitution: A Values are only additive in the *trans* diastereomer.



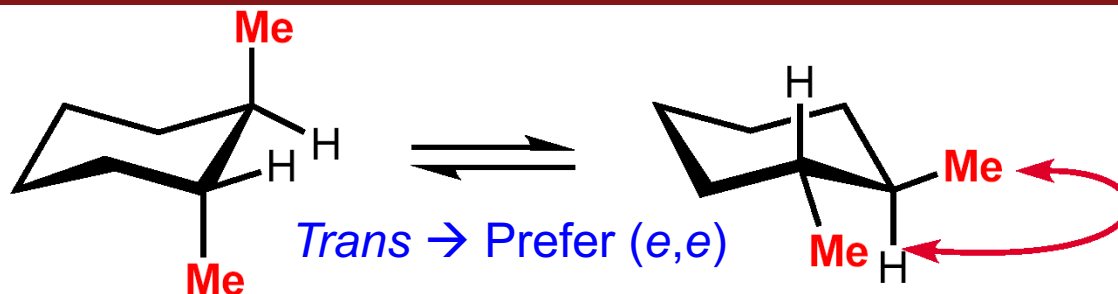
**A Values are not
additive in the *cis*
diastereomer as a
result of the new
interaction**

The new interaction!

Cis → Prefer (e,e)



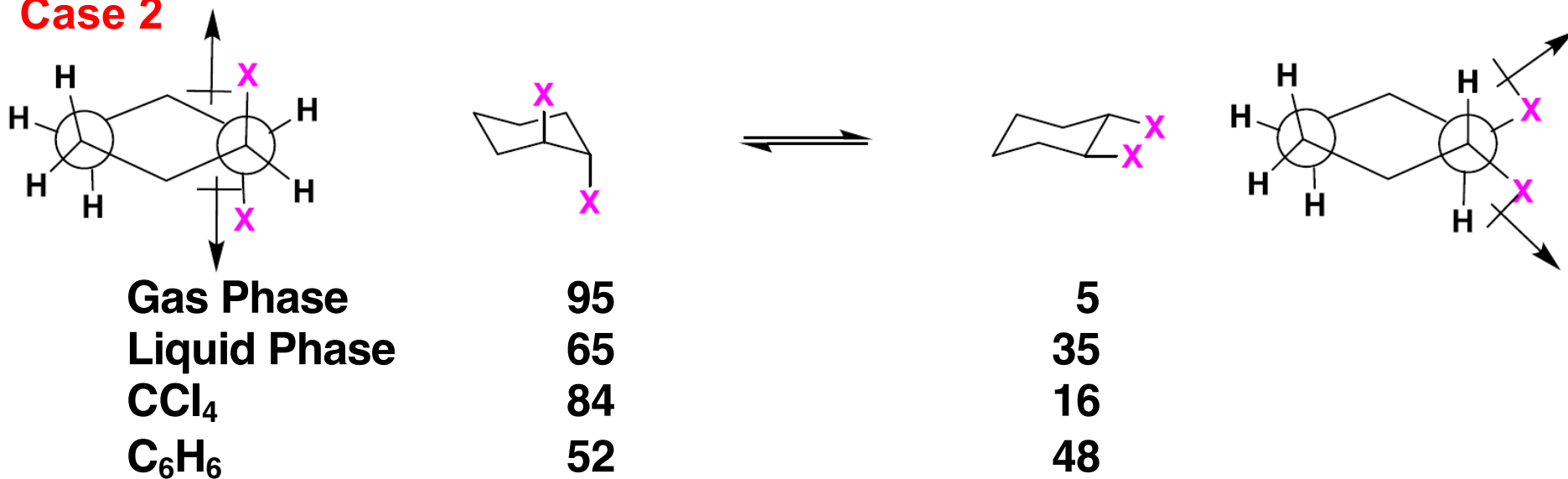
Case 1:



The prediction: $\Delta G^\circ = 1 \text{ gauche butane} - 2A(\text{Me})$

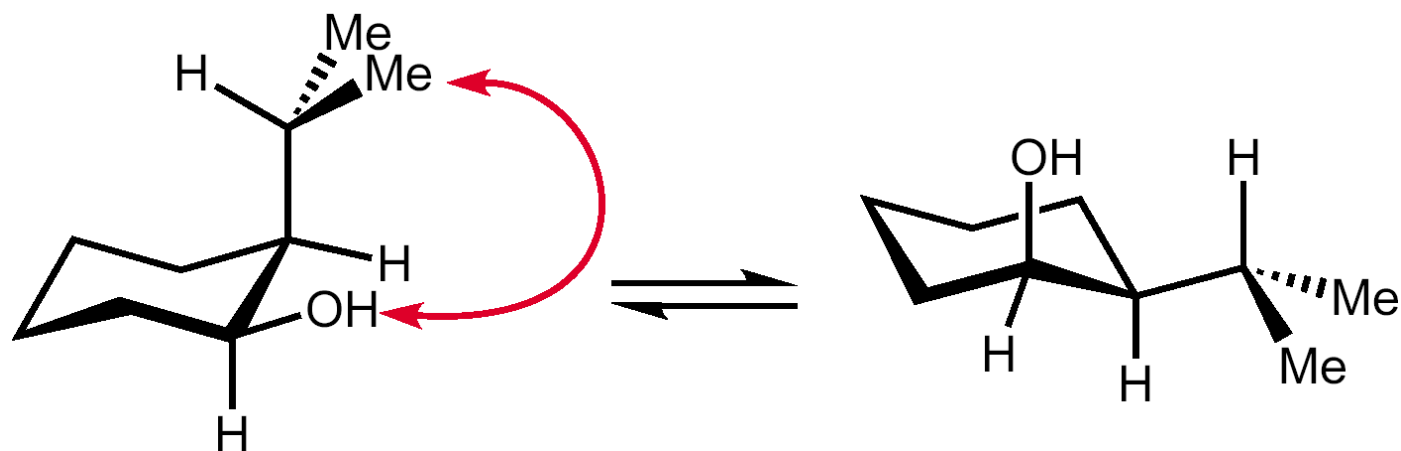
$$-\Delta G^\circ = +0.88 - 2(1.74) = +2.6 \text{ kcal/mol}$$

Case 2



In a pure solution, the intermolecular interaction increases and the intramolecular repulsion decreases; in a solvent, the polarity of the solvent increases, increasing the interaction between the molecule and the solvent, reducing its own dipole repulsion, and increasing the stability of the *ee*-conformer.

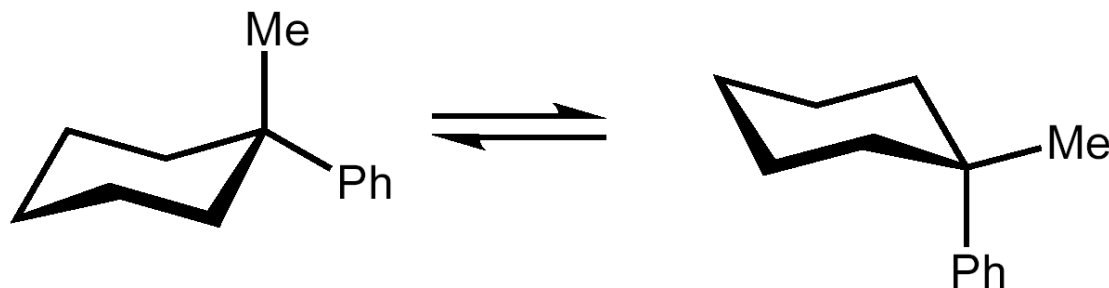
- *Cis* → Always (a,e)
BUT...



The conformer which places the **isopropyl group equatorial** is **much more strongly preferred** than would be suggested by A-Values. This is due to a syn pentane OH / Me interaction.

1,1-Dimethylcyclohexane

- Always (a,e)
BUT...



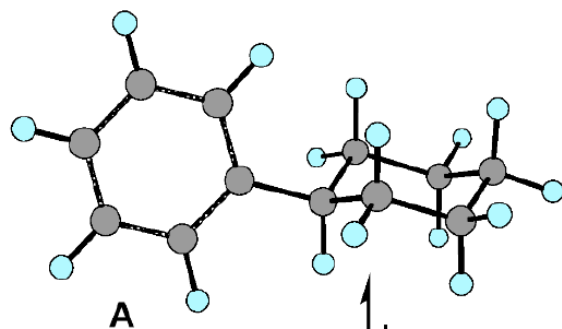
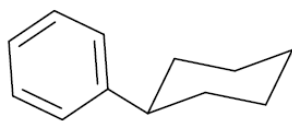
The prediction: $\Delta G^\circ = A(\text{Ph}) - A(\text{Me})$

$$\Delta G^\circ = +2.8 - 1.7 = +1.1 \text{ kcal/mol}$$

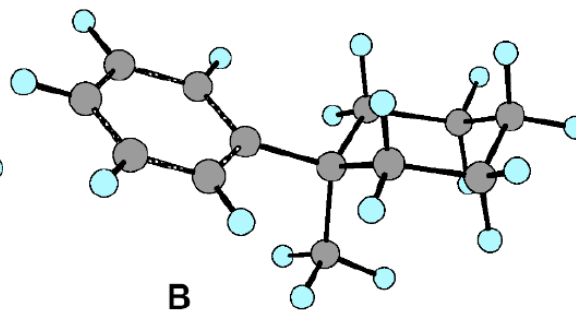
Observed: $\Delta G^\circ = -0.32 \text{ kcal/mol}$

Hence, when the two substituents are mutually interacting you can predict neither the magnitude or the direction of the equilibrium.

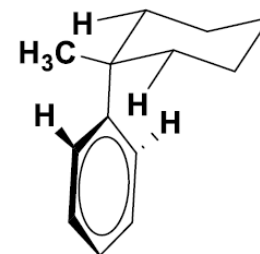
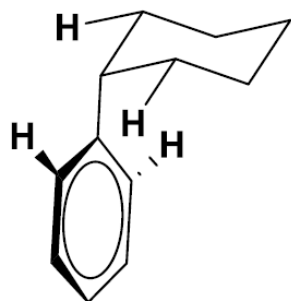
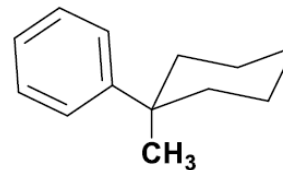
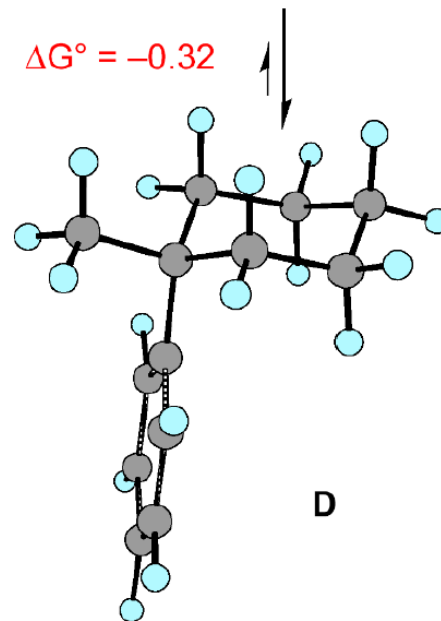
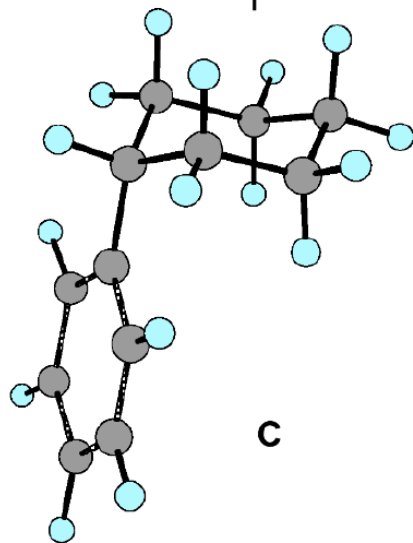
Group Discussion: Let's analyze this case.



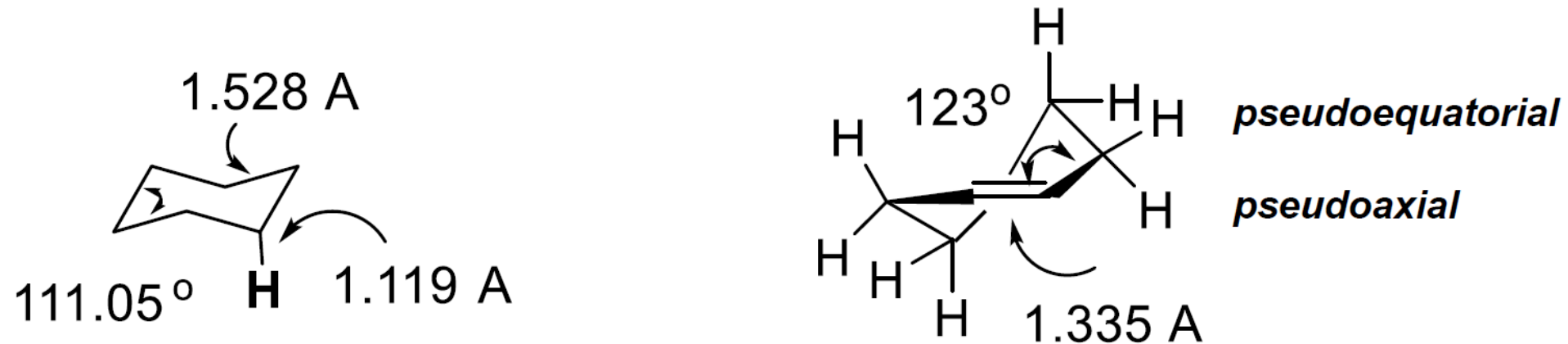
$$\Delta G^\circ = +2.8$$



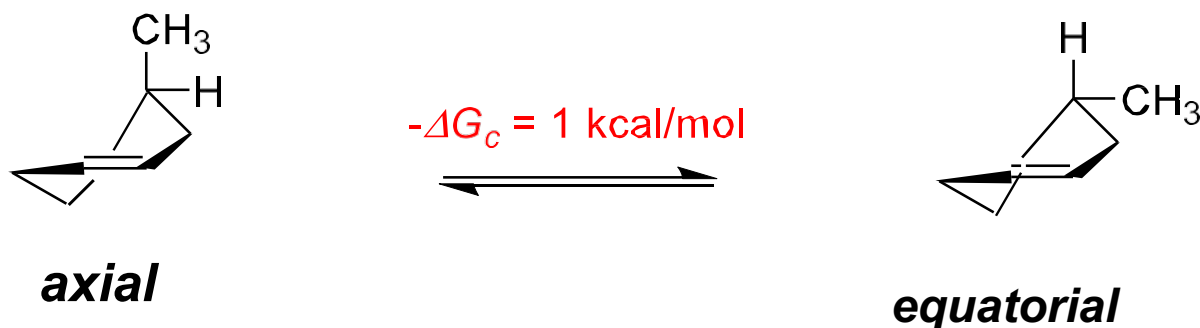
$$\Delta G^\circ = -0.32$$



Note the difference in the Ph substituent in A & B.

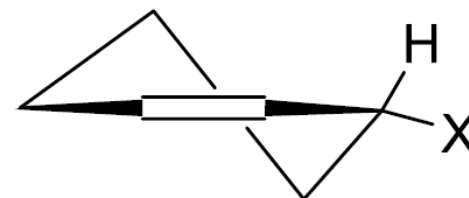
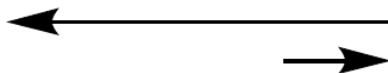
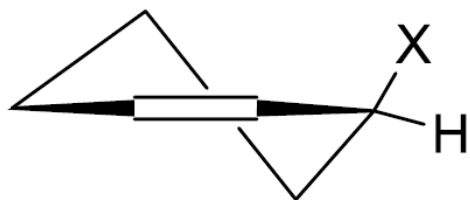
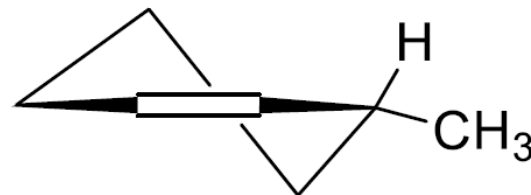
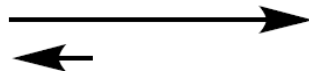
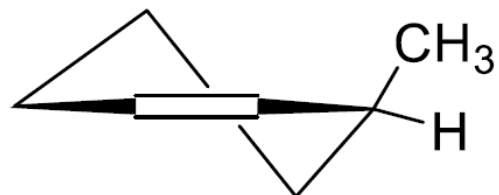


Ring Flipping Energy
10.3 kcal/mol > 5.3 kcal/mol



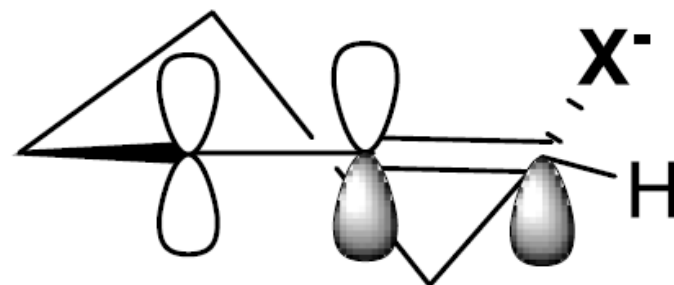
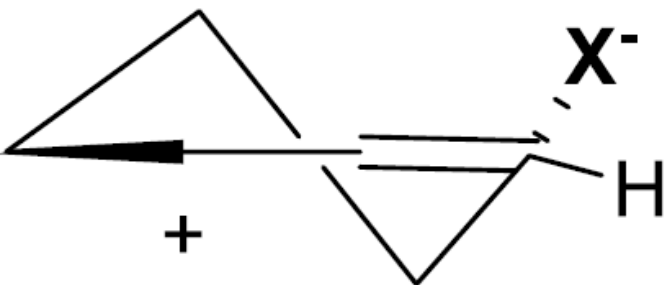
The energy difference between the two is small
1,3-vertical bond has less repulsive effect

3-Substituted Cyclohexene



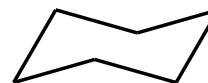
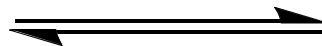
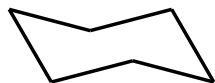
$X = \text{OH}, \text{OCH}_3, \text{OAc}, \text{Cl}, \text{Br}$

Hyperconjugation Effect



Ring Strain

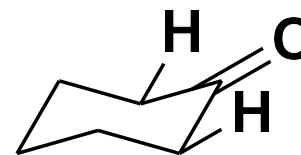
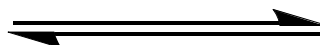
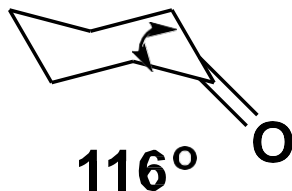
0.1 kcal/mol



Ring Flipping
Energy Barrier

10.3 kcal/mol

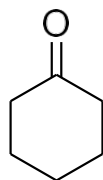
4.0 kcal/mol



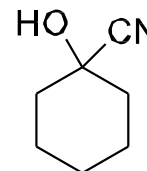
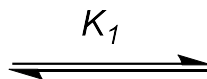
4.0 kcal/mol

Ring tension leads to high reactivity

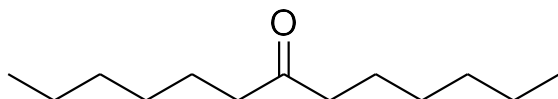
Ring tension (internal energy) release + steric effect



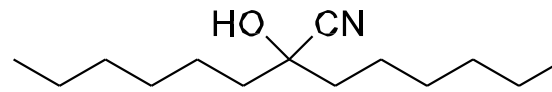
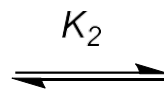
+ HCN



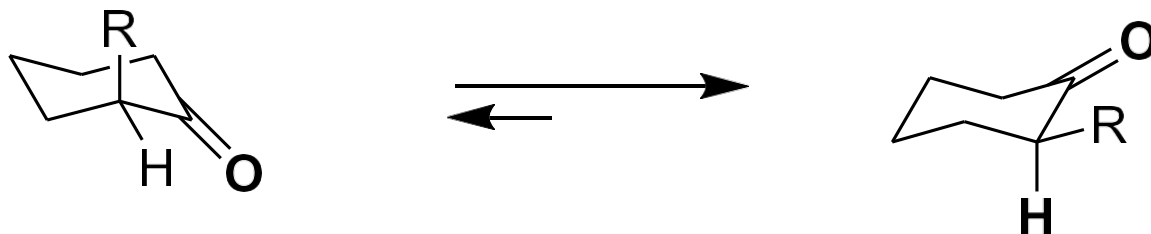
$K_1 / K_2 = 70$



+ HCN



2-Alkylcyclohexanone

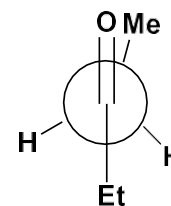
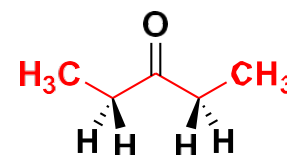


Ratio

R = Me	10%
R = Et	15%
R = CHMe ₂	30%

90%
85%
70%

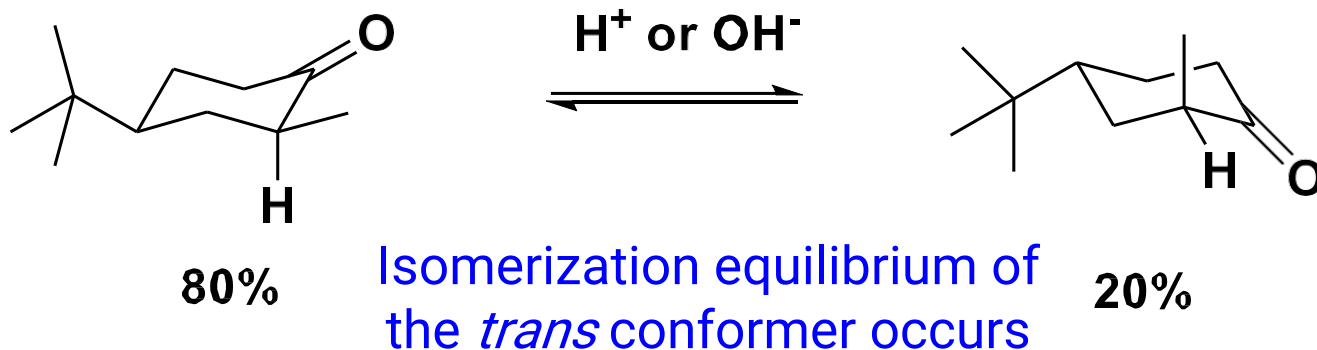
Review



Eclipsed

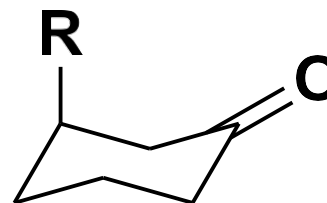
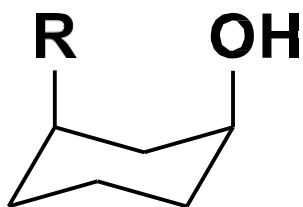
The *ap*
conformer
is
preferable

The *e*-bond stabilization comes from the favorable electronic effects and avoidance of the repulsion of the 1,3-vertical bond

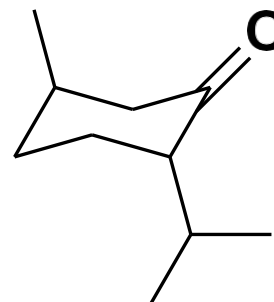
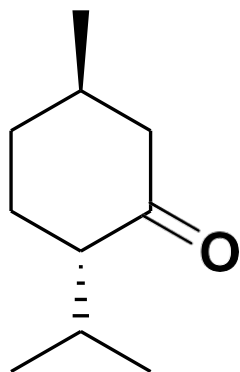


3-Alkylcyclohexanone

In 3-alkylcyclohexanone, due to the lack of 1,3-repulsion, the α -bond conformation is also more stable than the α -bond conformation of cyclohexane. This phenomenon is also called the 3-alkyl ketone effect.

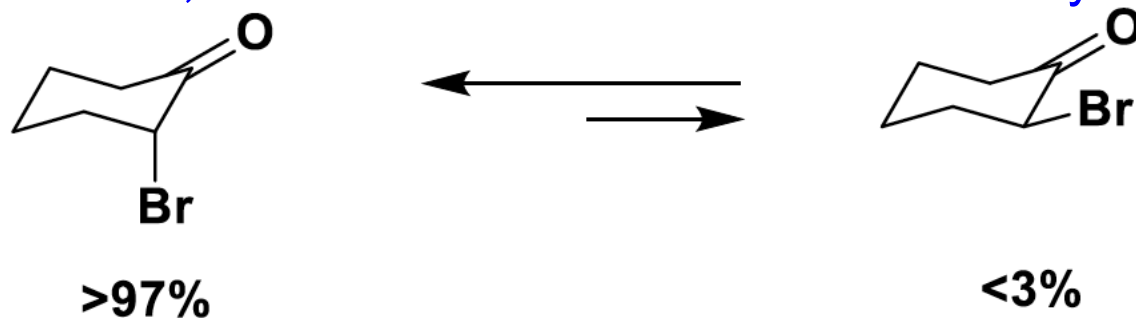


Due to the 2-isopropyl effect and 3-methyl effect of menthone, α,α bonds dominate in low-polarity solvents.



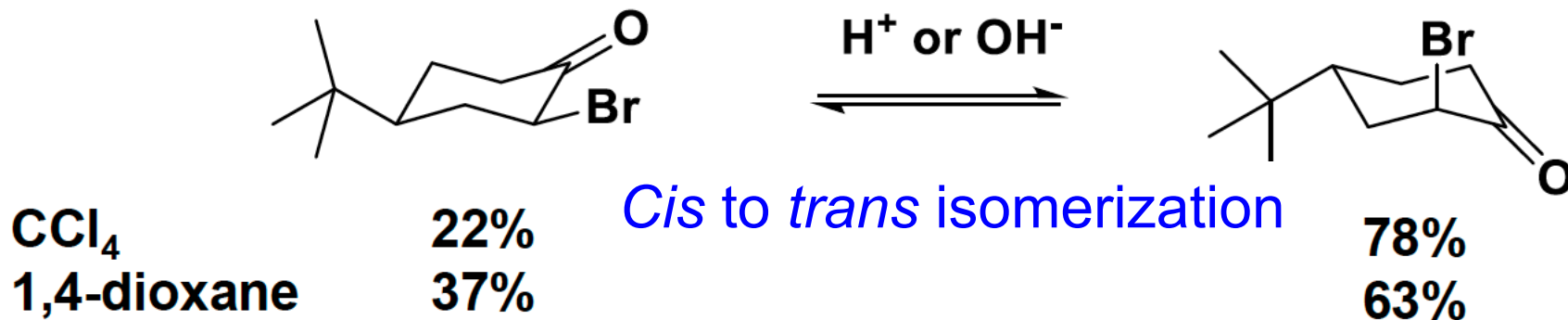
2-Halogenated Cyclohexanone

When there is a polar group (such as halogen) at the 2-position of cyclohexanone, the steric repulsion caused by the partial overlap of the substituent and the carbonyl group has an almost parallel dipole interaction between C-X and C=O, and the e-bond conformation Stability is reduced.

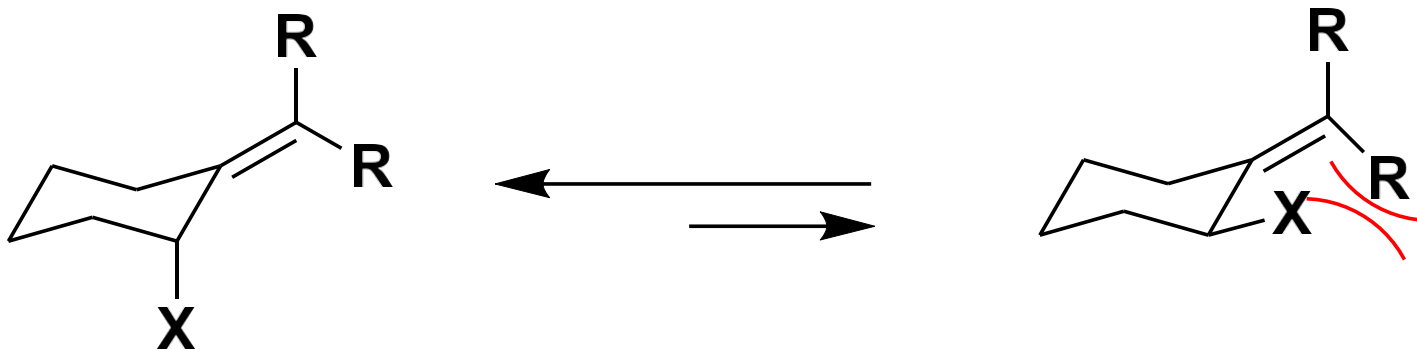


The dipole effect is related to the polarity of the solvent. If the polarity of the solvent is large, the intramolecular dipole effect will be weakened, so the proportion of the conformation is also related to the solvent.

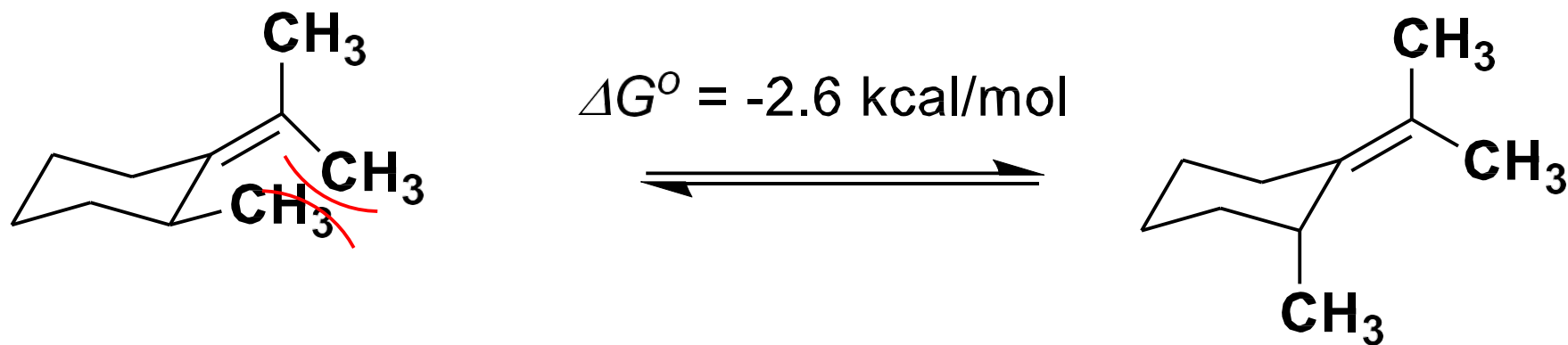
For example, when 2-bromocyclohexanone is isomerized under acid or base catalysis, the proportion of a-bond conformation in polar solvents decreases.



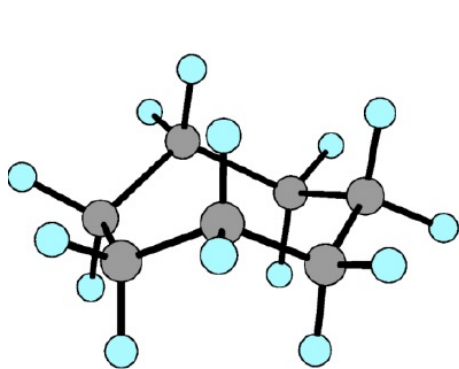
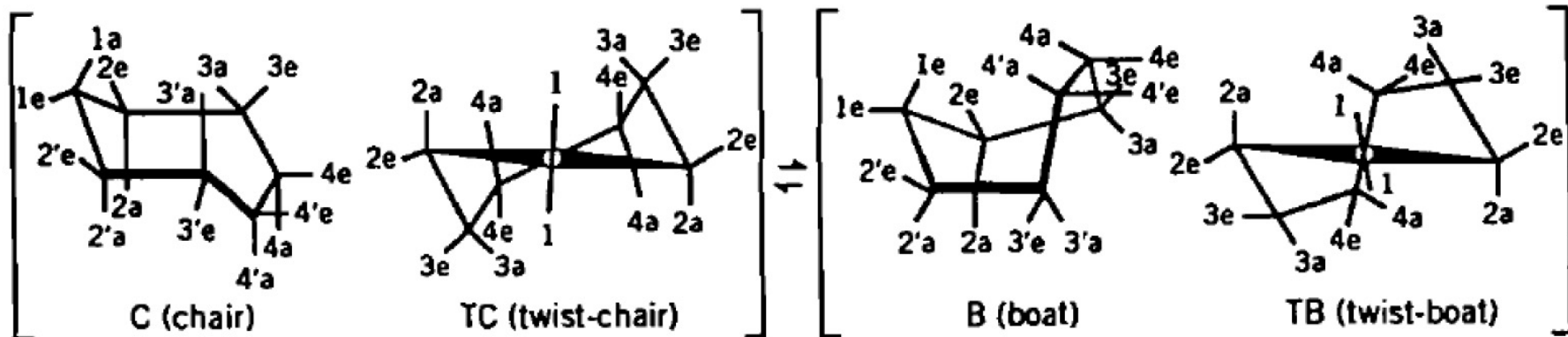
1,3-Allylic Strain



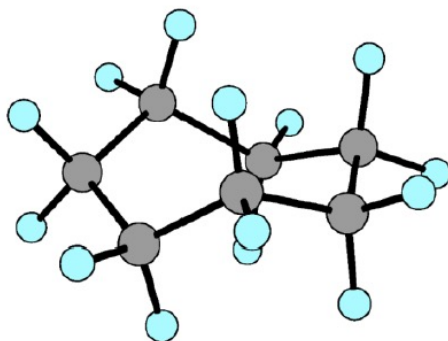
A-(1,3) strain



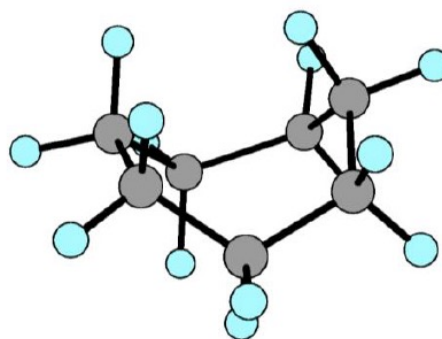
Cycloheptane



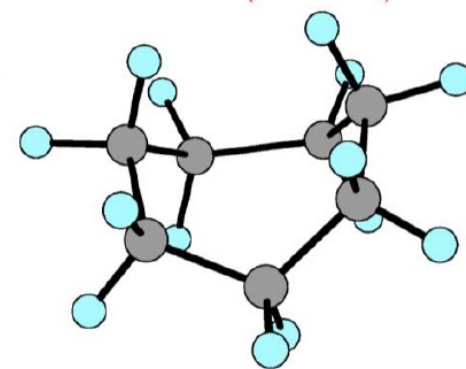
Chair (2.16 kcal/mol)



Twist-Chair (0 kcal/mol)

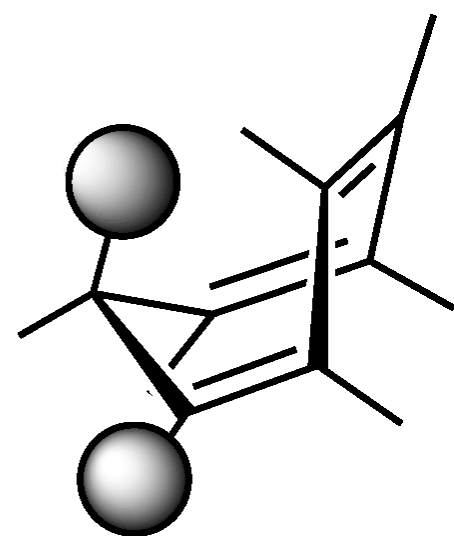
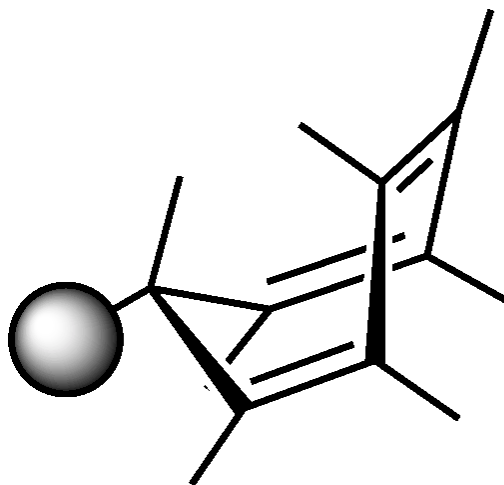
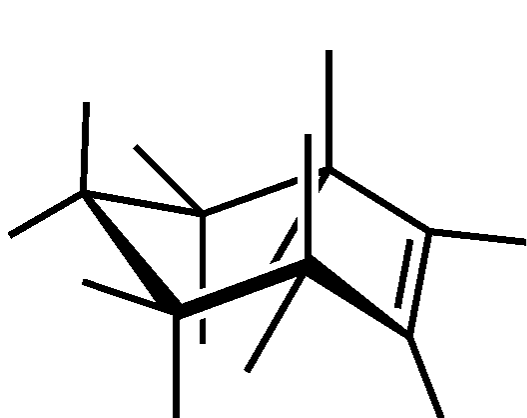


Boat (3.02 kcal/mol)

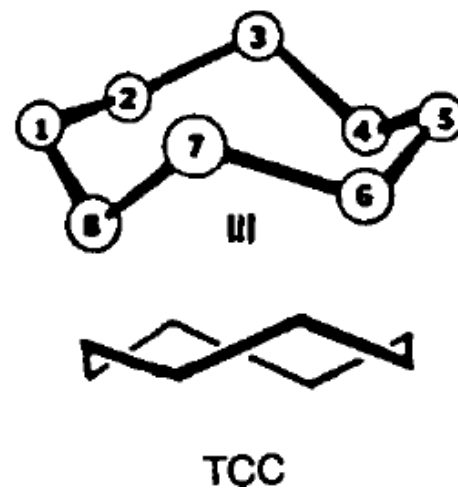
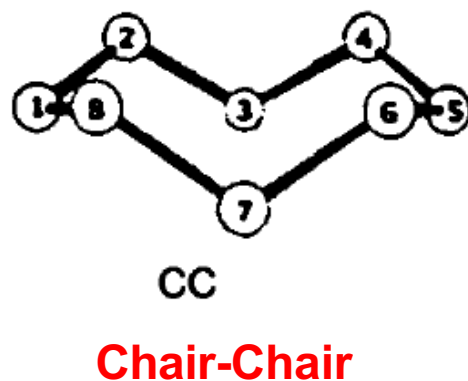
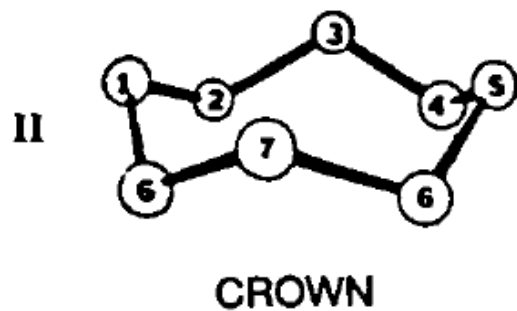
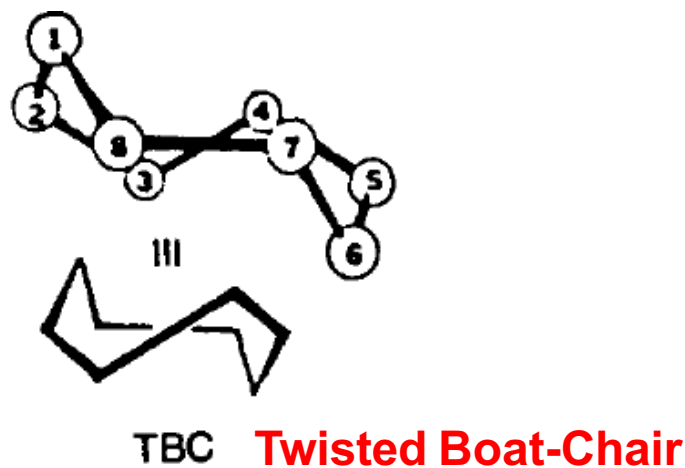
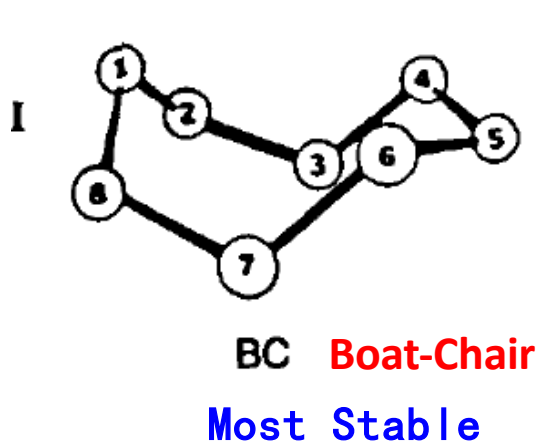


Twist-Boat (2.49 kcal/mol)

Olefins are preferentially orientated to eliminate eclipsing interactions.

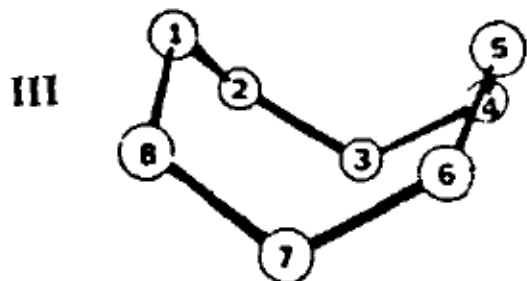


Cyclooctane

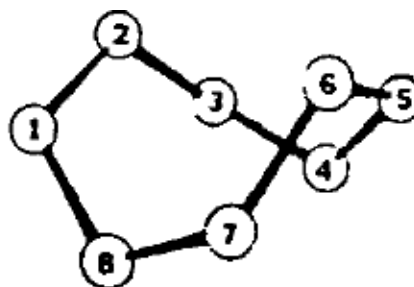


Twisted Chair-Chair

Cyclooctane



BB **Boat-Boat**

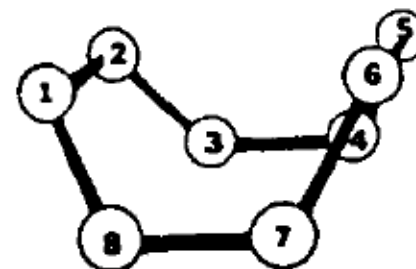


III



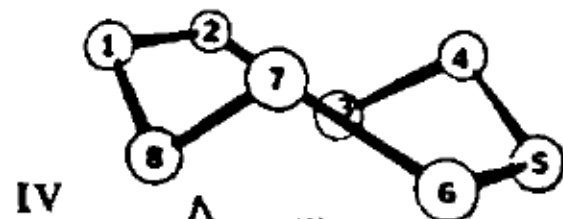
TB

Twisted Boat

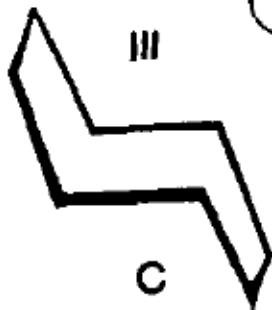


B

Boat

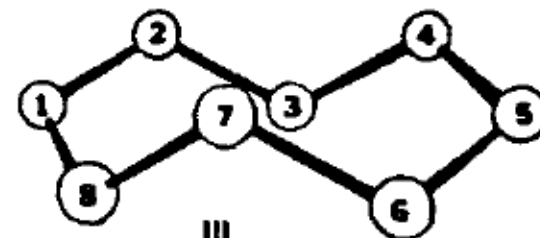


III



C

Chair

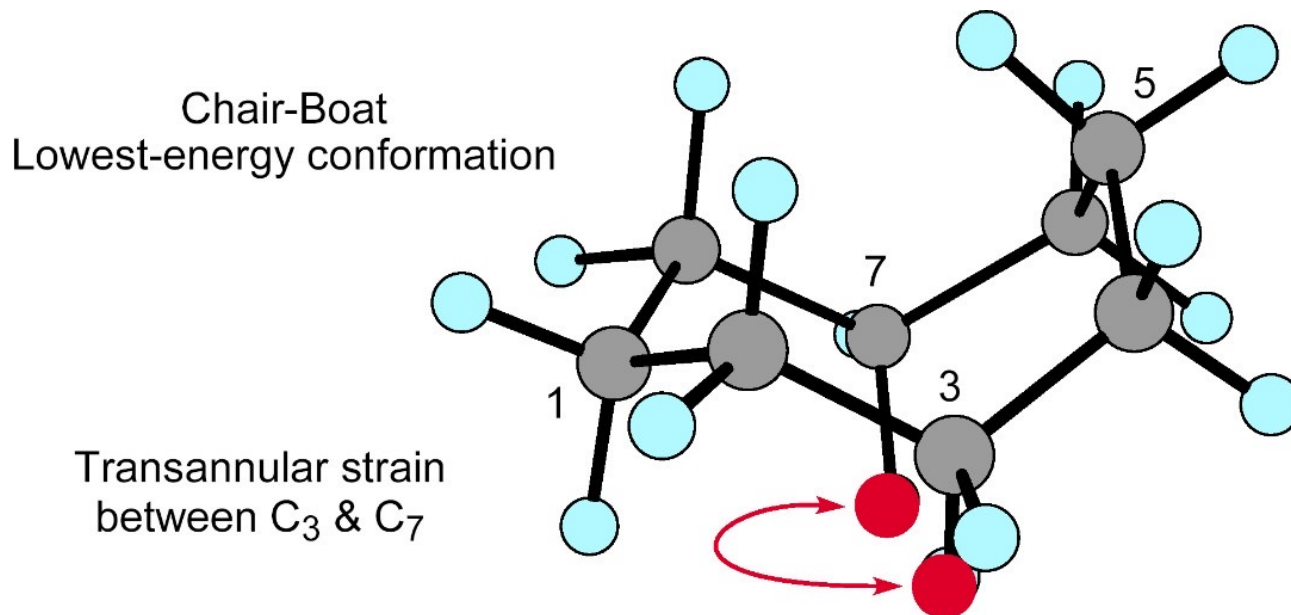


III



TC

Twisted Chair

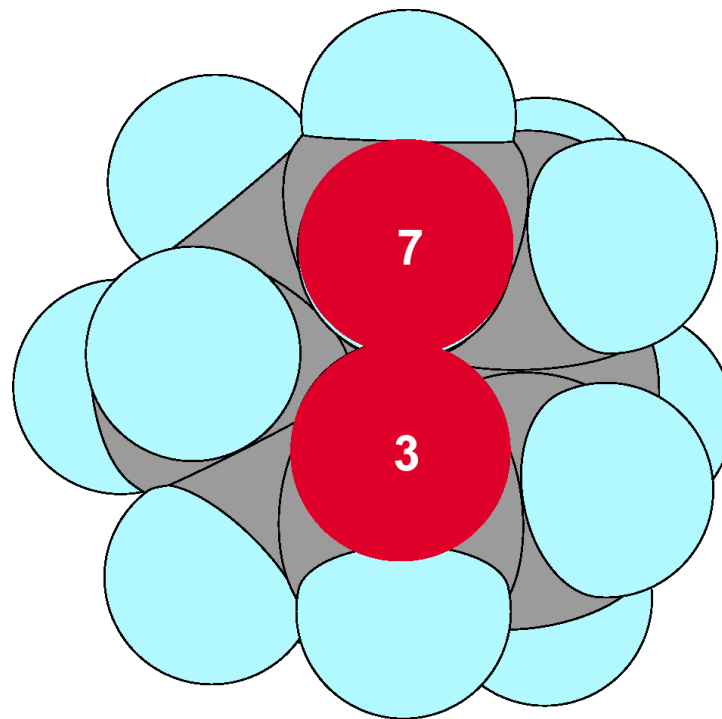
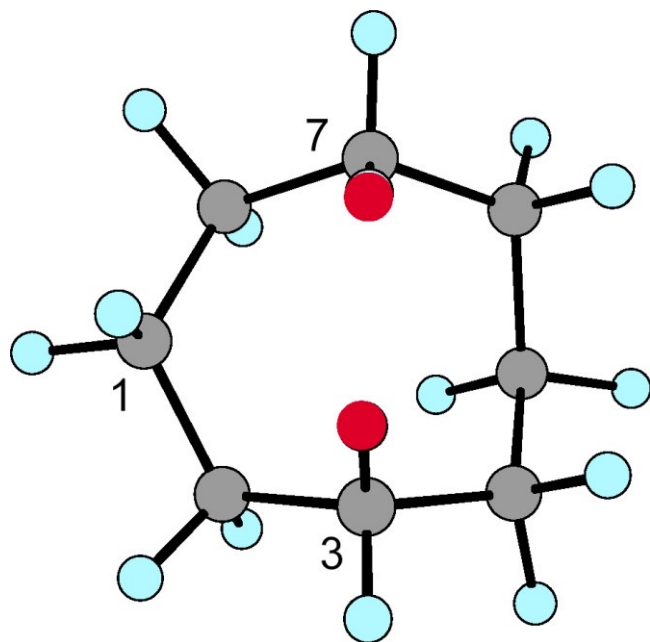


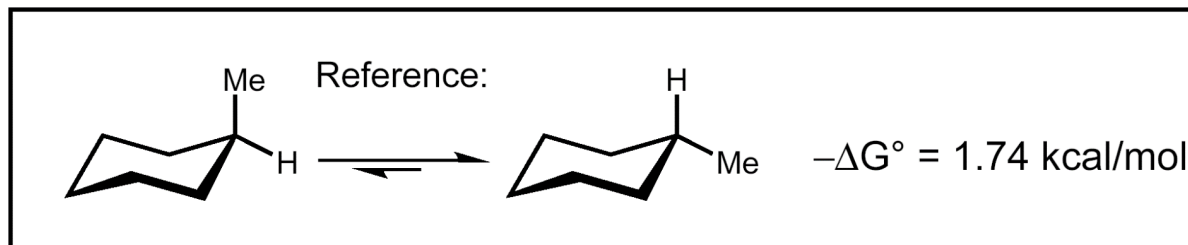
Ring strain originates in eclipsing interactions and transannular van der Waals interactions

Methyl position	1	2	3	4	5
ΔG $\frac{\text{(pseudoeqatorial)}}{\text{(pseudoaxial)}} \text{ (kcal/mol)}$	1.8	2.8	>4.5	-0.3	6.1

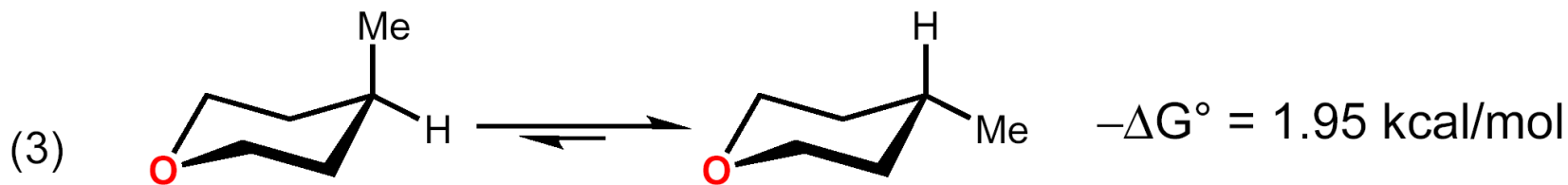
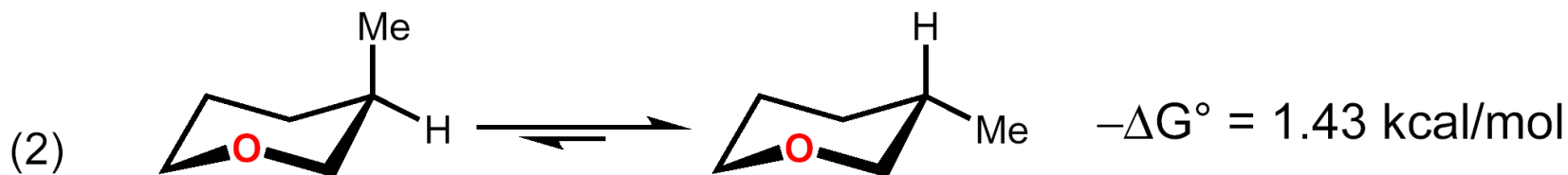
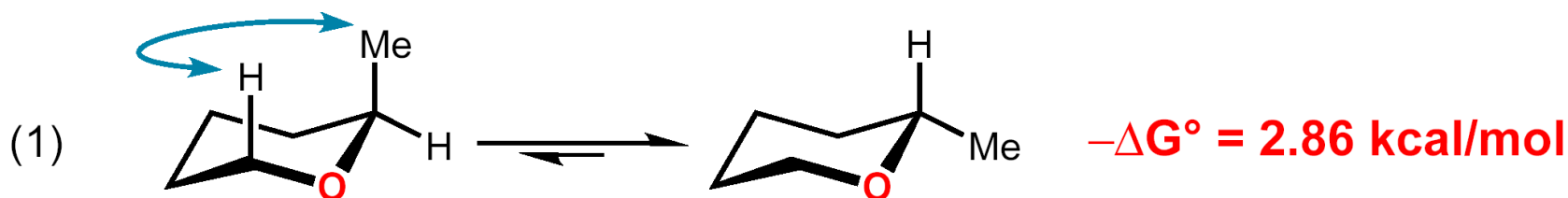
Monosubstituted Cyclooctane

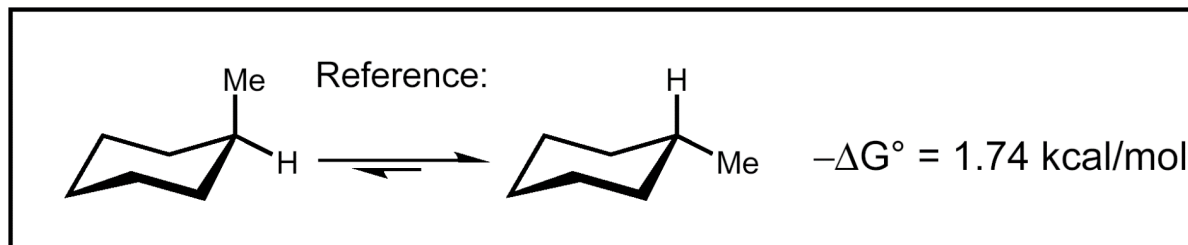
Underside view of boat-chair C3 & C7 eclipsing interactions



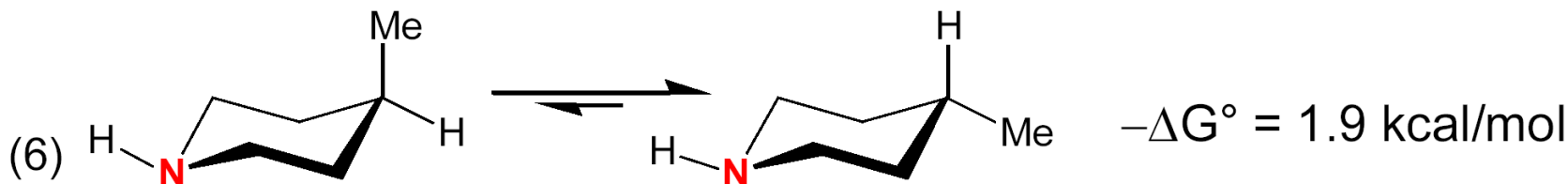
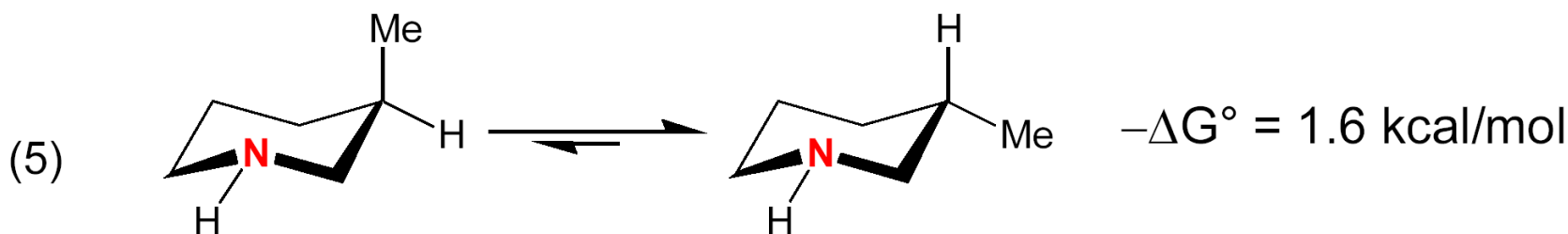
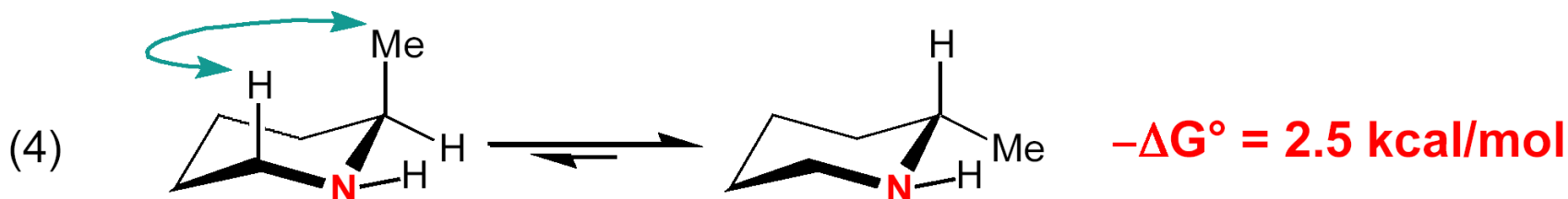


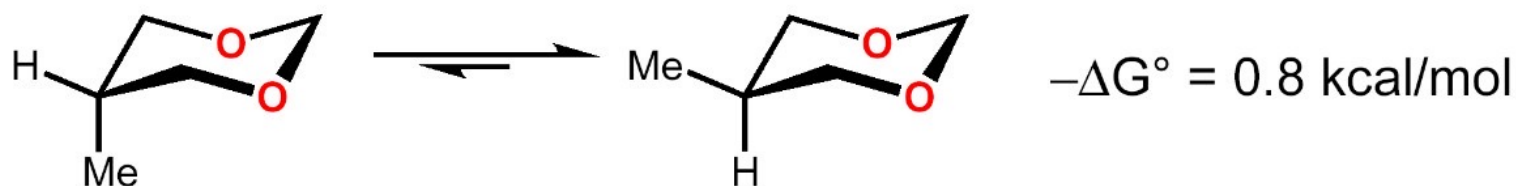
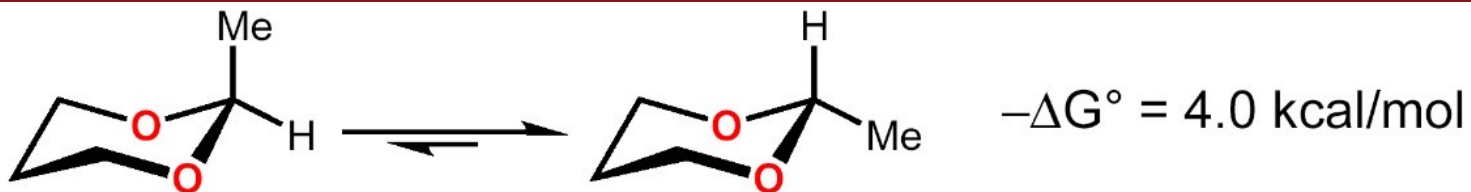
A-values at the 2-position in both the O & N heterocycles are larger than expected. This is due to the shorter C-O (1.43 Å), and C-N (1.47 Å) bond lengths relative to carbon (C-C; 1.53 Å). The combination of bond length and bond angle change increase the indicated 1,3- diaxial interaction.



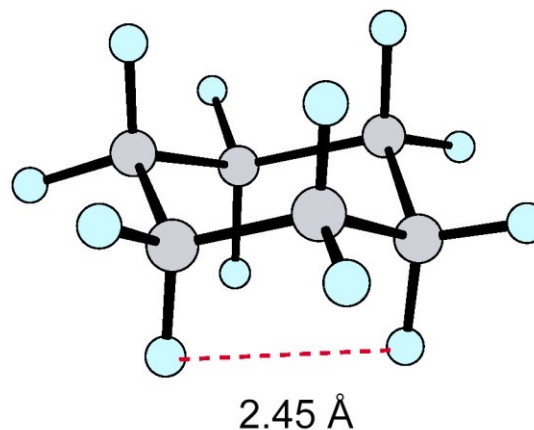
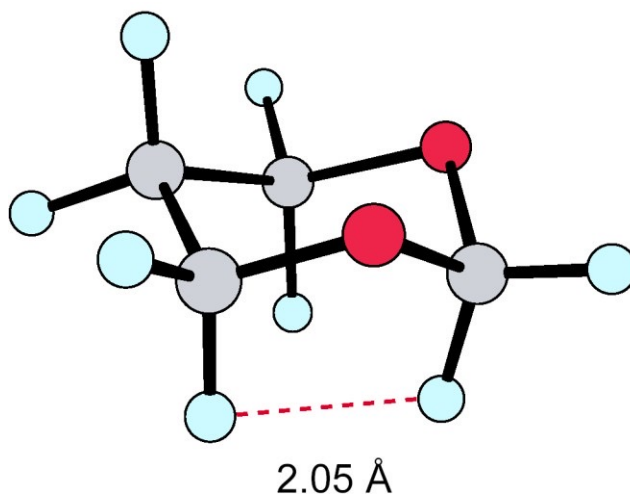


The A-values at the 2-position in both the O & N 6-membered heterocycles are larger than those found in cyclohexane.

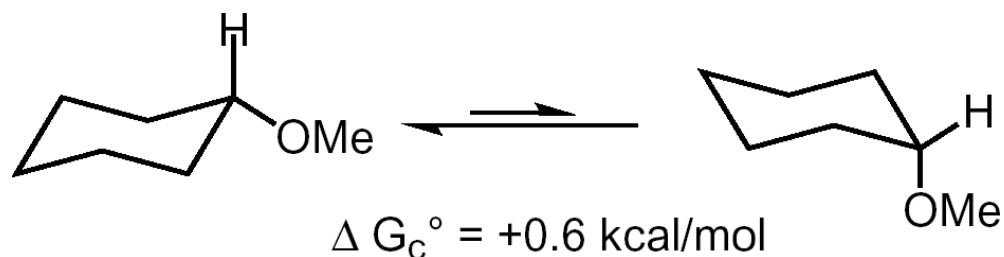




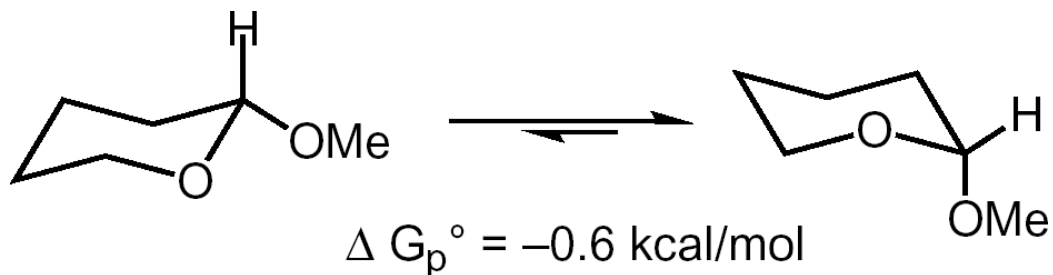
The indicated distance is 2.05 Å. The analogous H-H distance in Cyclohexane is 2.45 Å



It is not unexpected that the methoxyl substituent on a cyclohexane ring prefers to adopt the equatorial conformation.



What is unexpected is that the closely related 2-methoxytetrahydropyran prefers the axial conformation.



That effect which provides the stabilization of the axial OR conformer which overrides the inherent steric bias of the substituent is referred to as the anomeric effect.

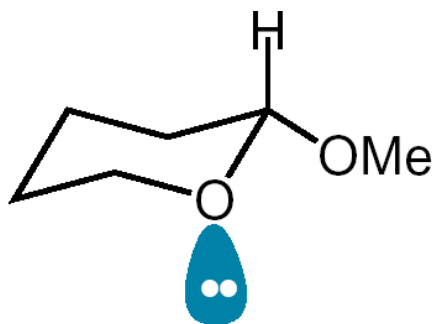
Let anomeric effect = A

$$\Delta G_p^\circ = \Delta G_c^\circ + A$$

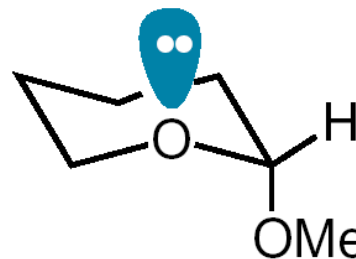
$$A = \Delta G_p^\circ - \Delta G_c^\circ$$

$$A = -0.6 \text{ kcal/mol} - 0.6 \text{ kcal/mol} = -1.2 \text{ kcal/mol}$$

Principal HOMO-LUMO interaction from each conformation is illustrated below:



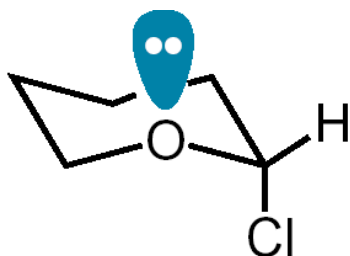
axial O lone pair $\leftrightarrow$ σ^* C-H



axial O lone pair $\leftrightarrow$ σ^* C-O

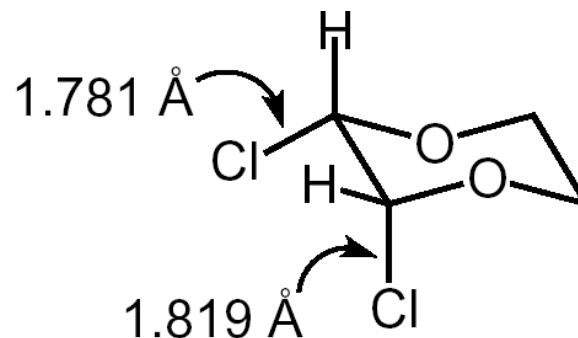
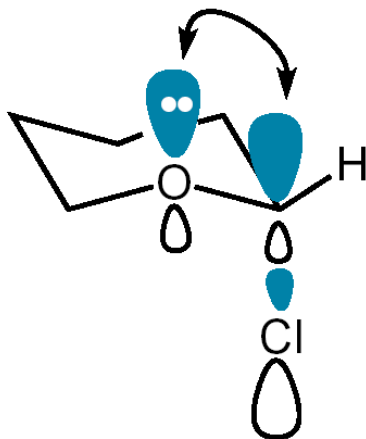
Since the antibonding C-O orbital is a better acceptor orbital than the antibonding C-H bond, the axial OMe conformer is better stabilized by this interaction which is worth ca. 1.2 kcal/mol.

Other electronegative substituents such as Cl, SR etc. also participate in anomeric stabilization.

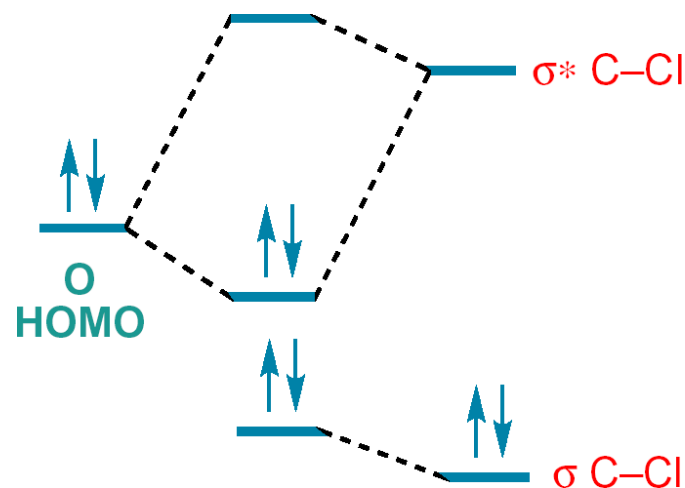


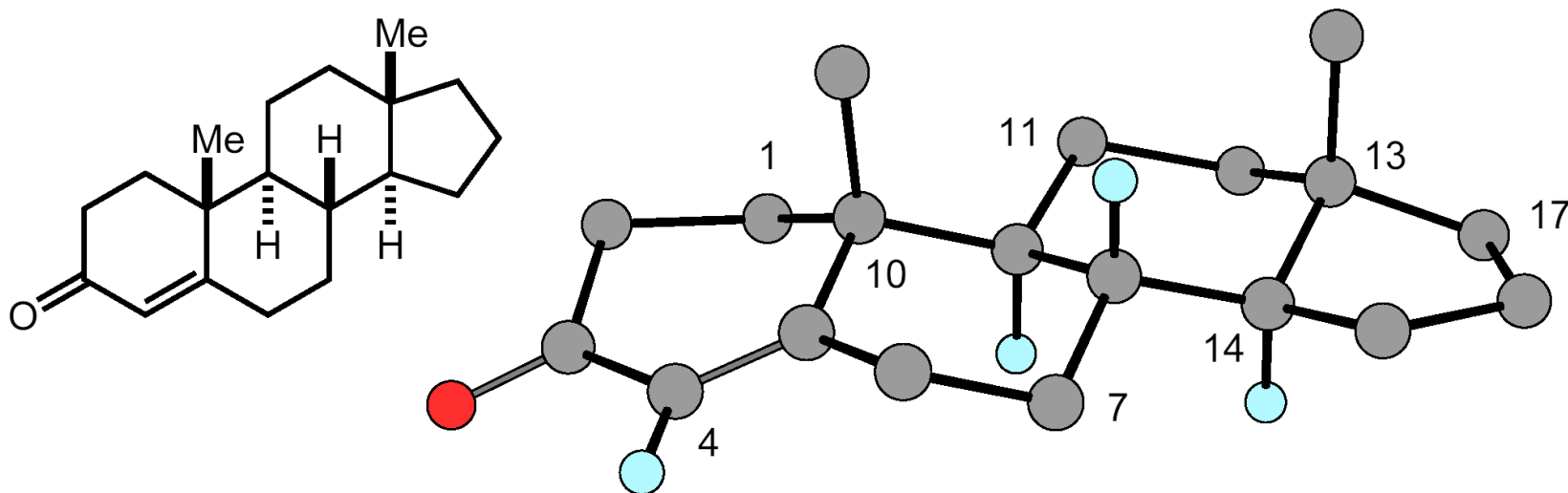
This conformer
preferred by 1.8 kcal/mol

axial O lone pair $\leftrightarrow$ σ^* C-Cl



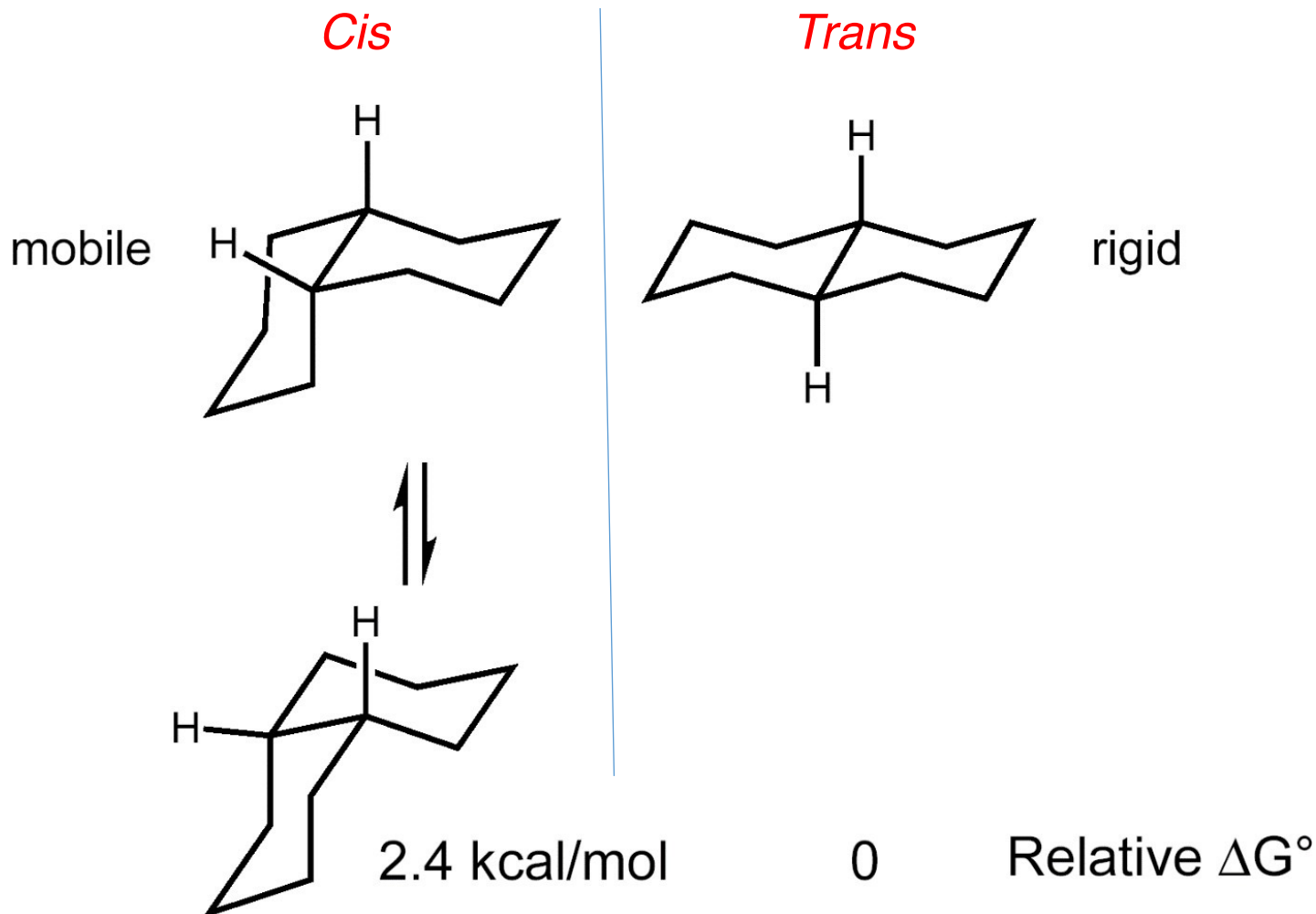
Why is axial C-Cl bond longer ?





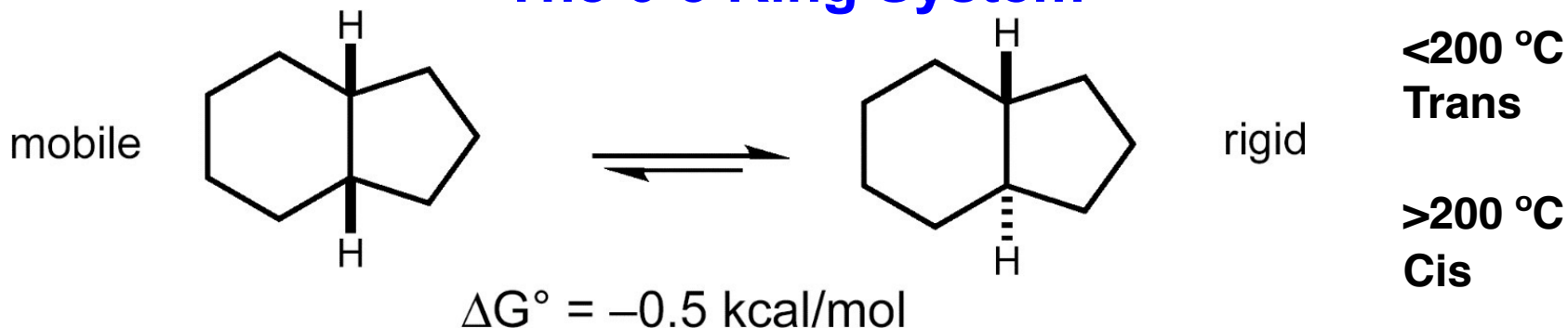
The steroid nucleus provided the stimulation for the development of conformational analysis, particularly of polycyclic ring systems. D. H. R. Barton was awarded a Nobel prize in 1969 for his contributions in this area.

Decalin Ring System (6/6)

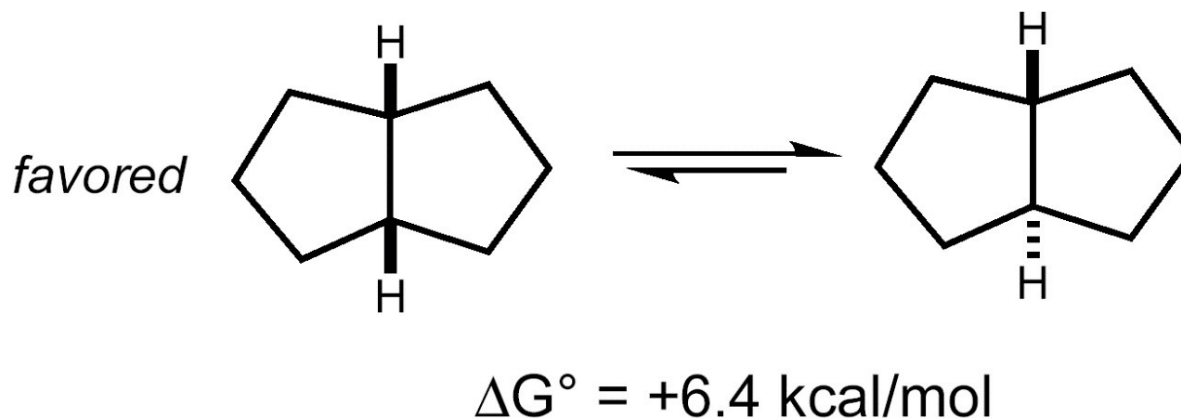


Hydrindane Ring System

The 6-5 Ring System

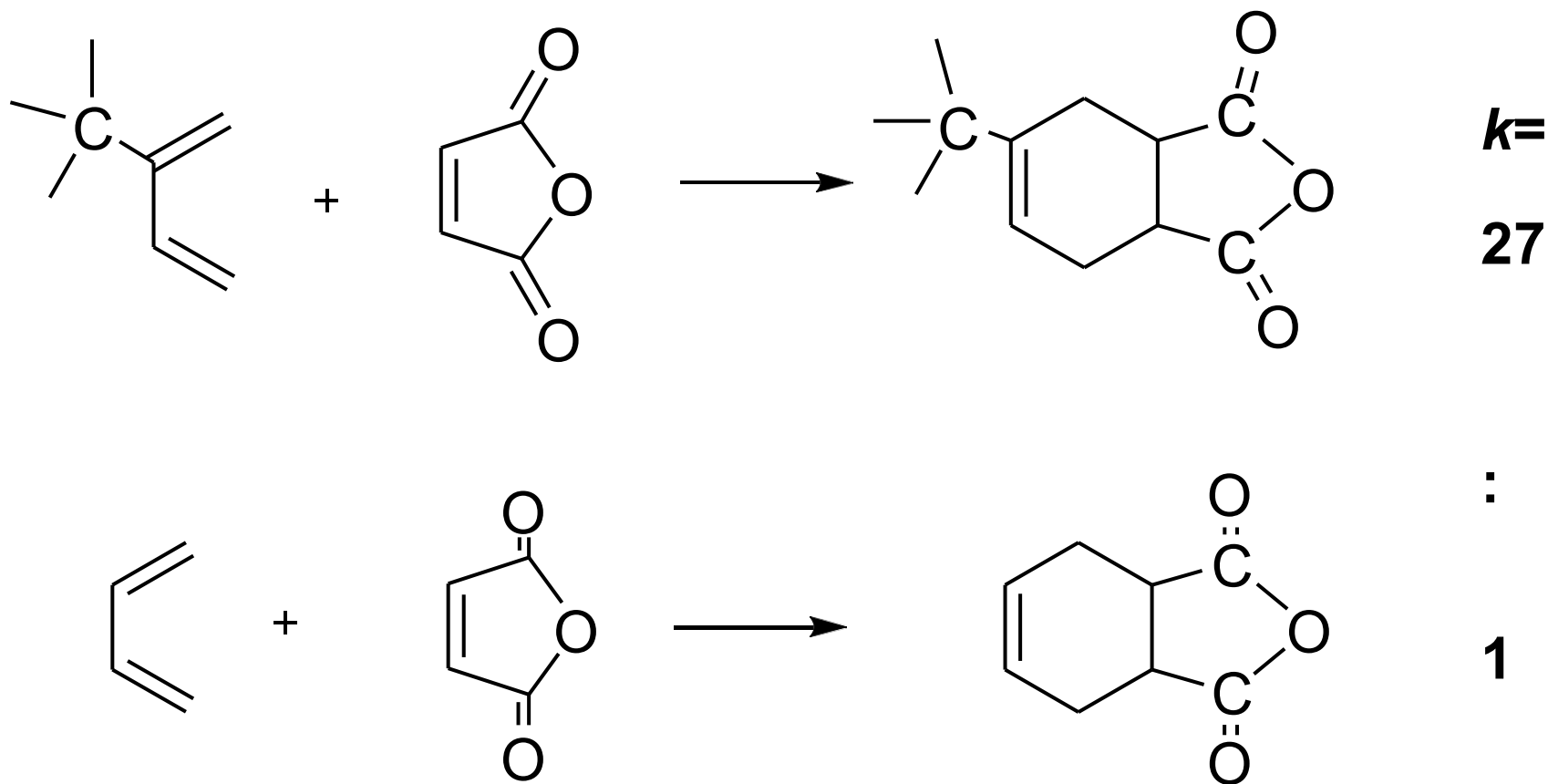


The 5-5 Ring System

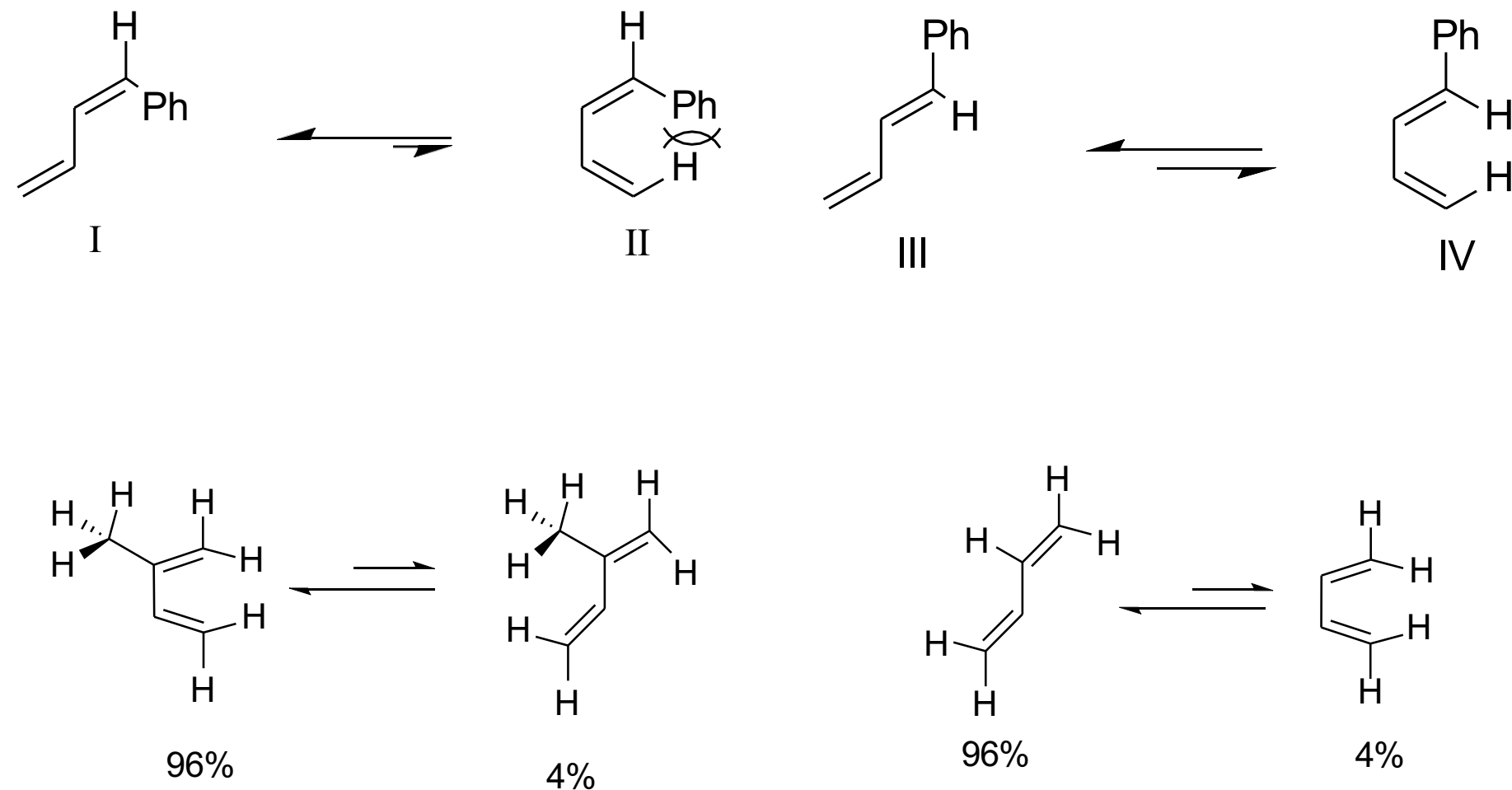


The turnover to favor the cis fusion results from the entropic preference for the less ordered *cis* isomer.

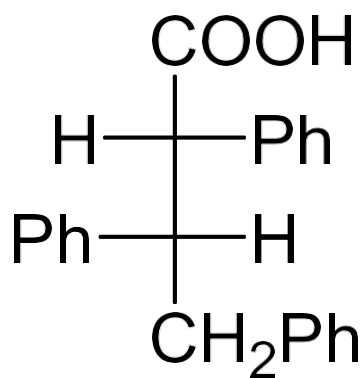
Example 1: D–A cycloaddition



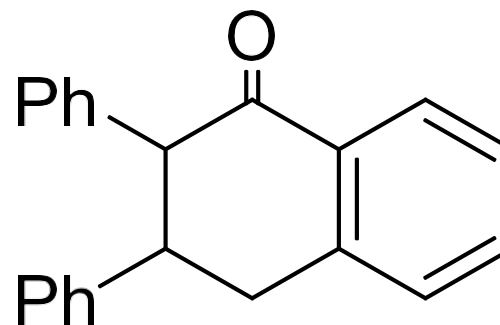
In the D–A reaction, the diene must be transformed from *s-trans* to *s-cis*



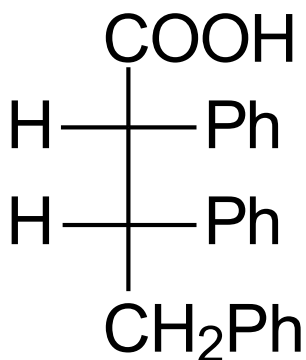
Example 2: F-C Reaction



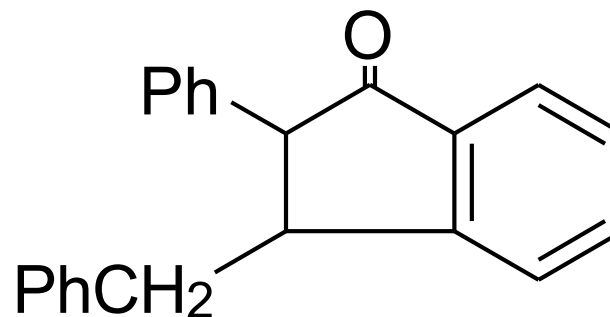
threo



2,3-Diphenyl-1,2-dihydro-1-naphthalenone



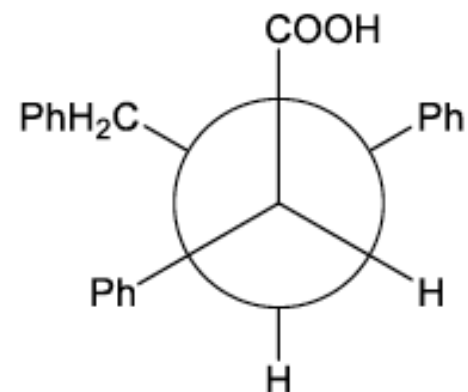
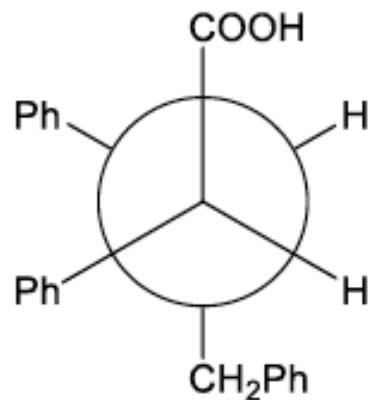
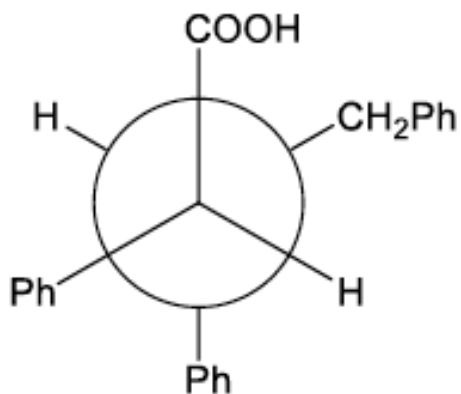
erythro



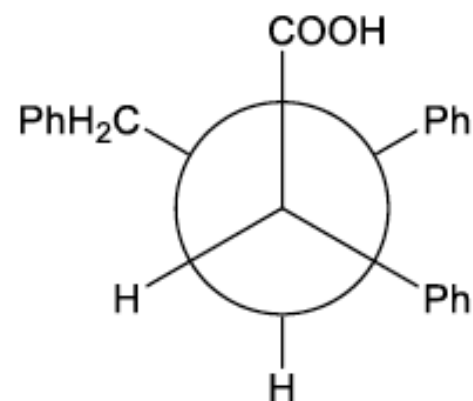
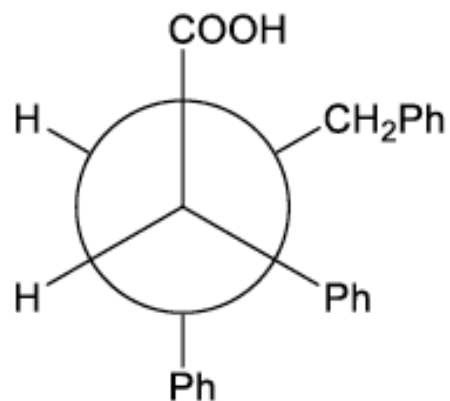
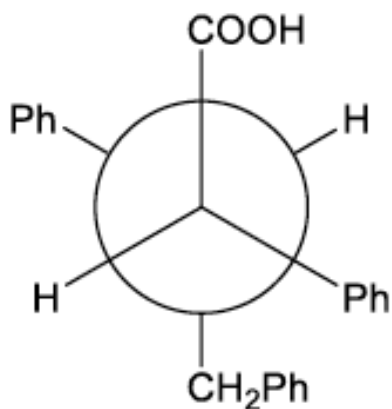
2-phenyl-3-benzyl-1-indanone

Dominated Conformation Directed the Product

threo

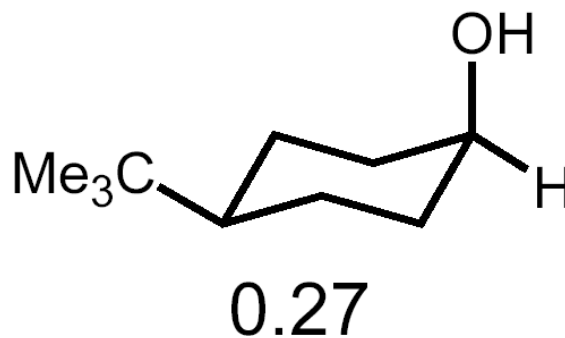
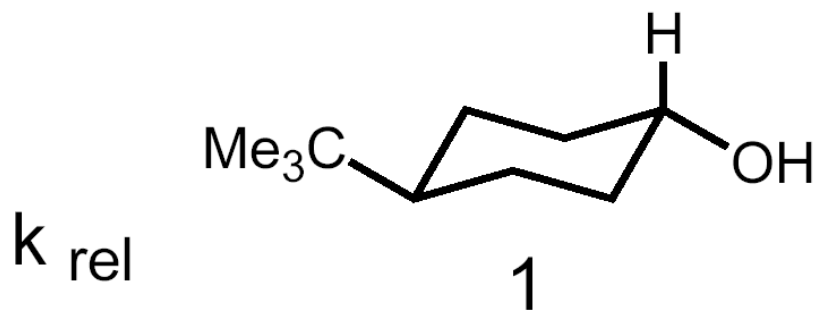
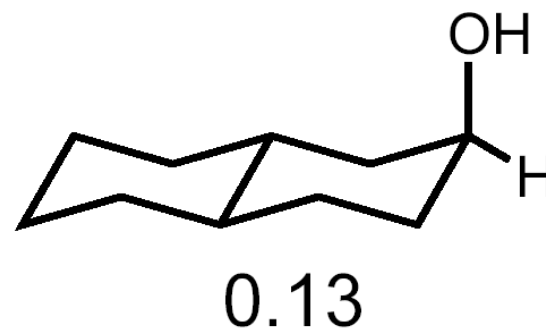
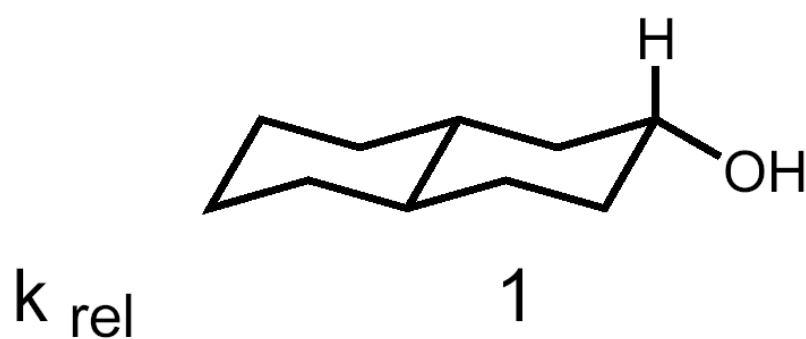


erythro

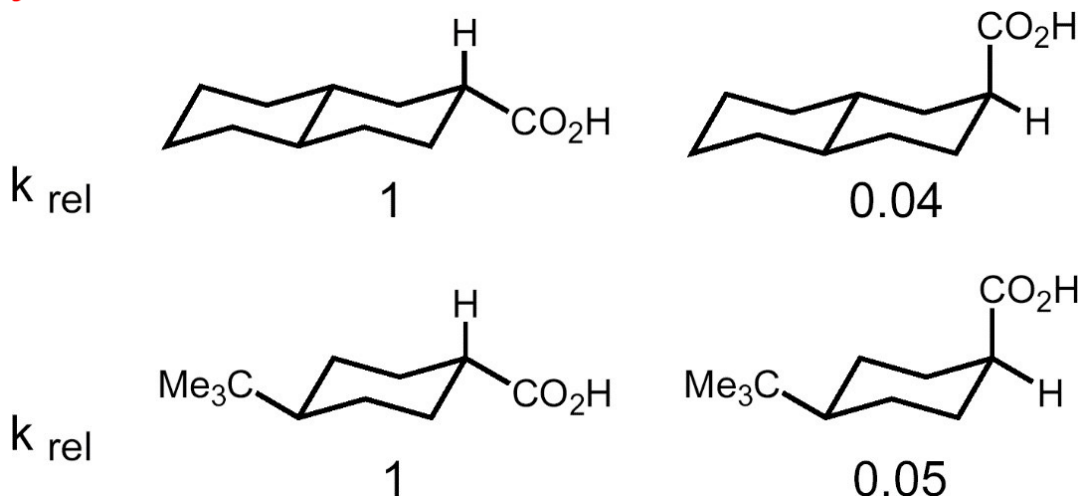


Different reactivity for axial and equatorial substituents
Axial substituents are more hindered, thus less reactive in many transformations

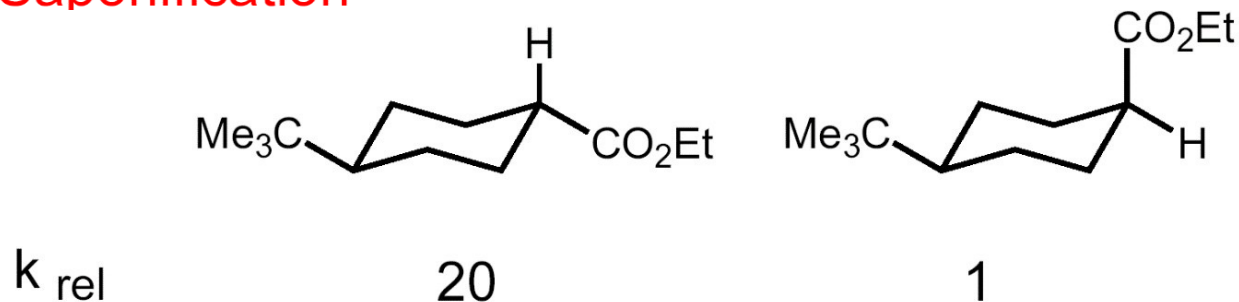
Acetylation with $\text{Ac}_2\text{O}/\text{Py}$



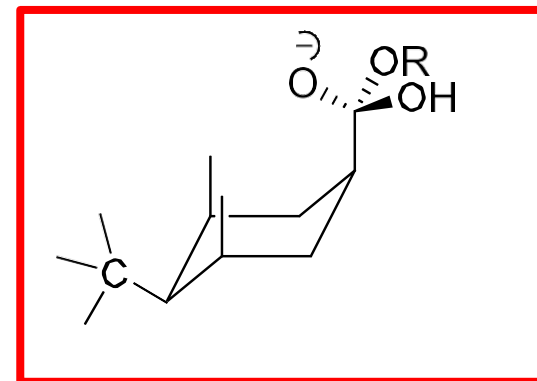
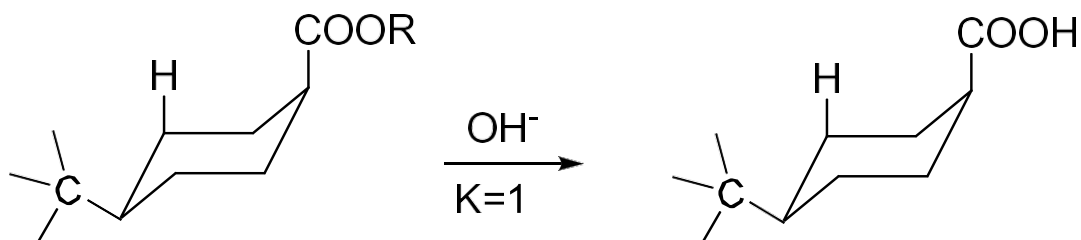
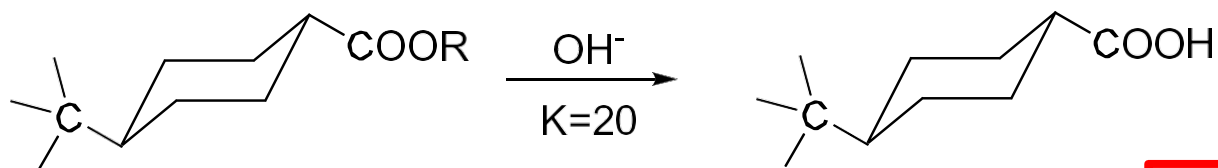
■ Acid-catalyzed esterification



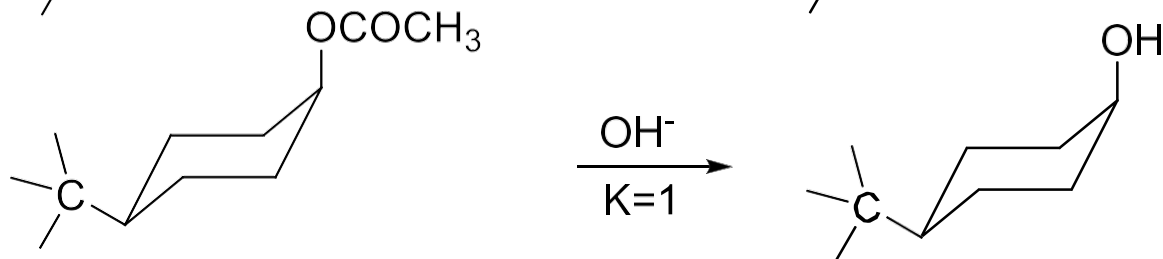
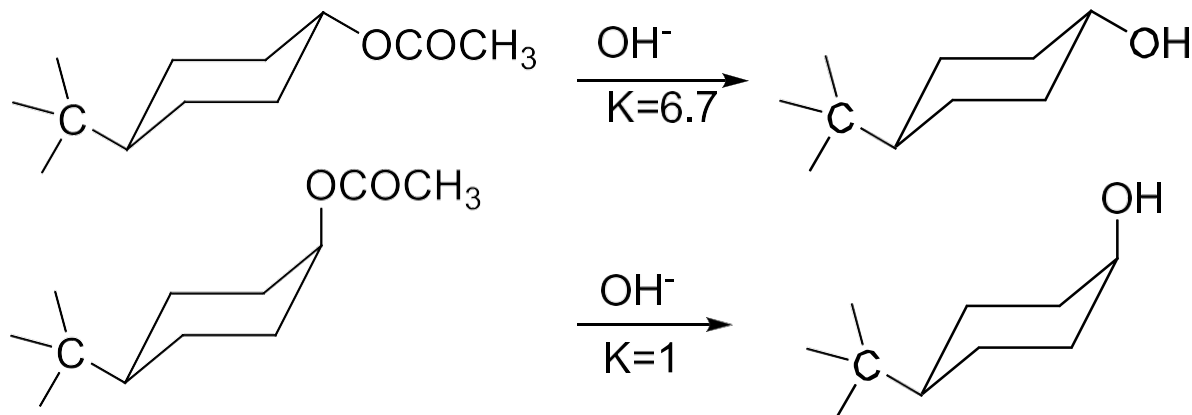
■ Ester Saponification



For a more detailed discussion of this topic see:
 Eliel, E. L., S. H. Wilen, et al. (1994). *Stereochemistry of Organic Compounds* pp 720-726



The α -bond ester intermediate changes from sp^2 to sp^3 , the 1,3-repulsion is greater than that of the reactant, and the activation energy is higher.

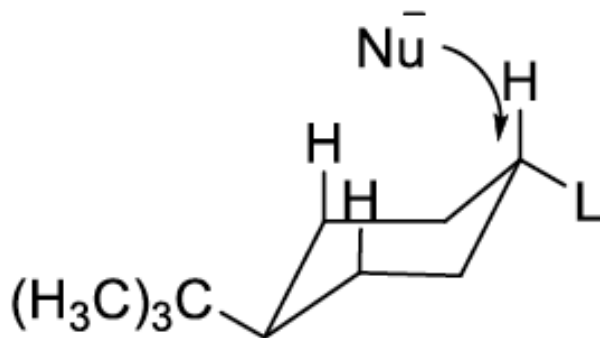


The carbonyl group is one atom away from the ring, so the effect of steric repulsion is smaller than in the top example.

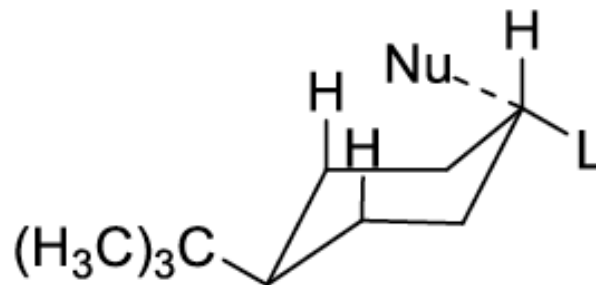
The axial diastereomer is not always slower reacting!

S_N2 Reaction

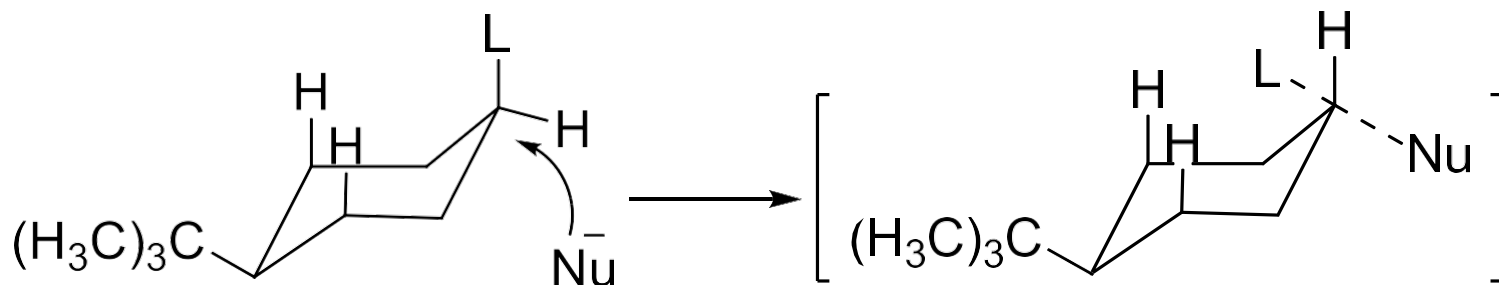
If the Nu^- is greater than L



e-conformer / lower energy / ground state



higher energy / transition state

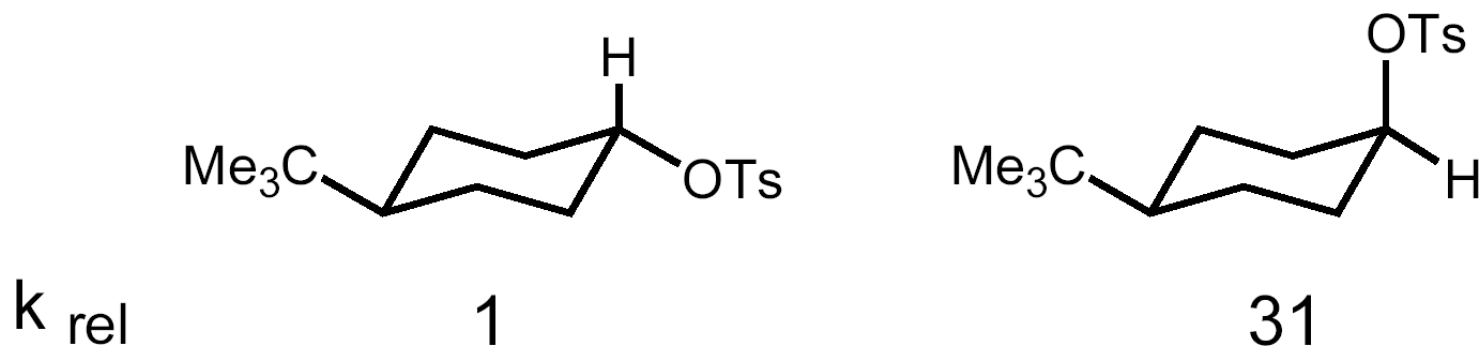


a-conformer / higher energy / ground state

lower energy / transition state

The axial diastereomer is not always slower reacting!

S_N2 Reaction



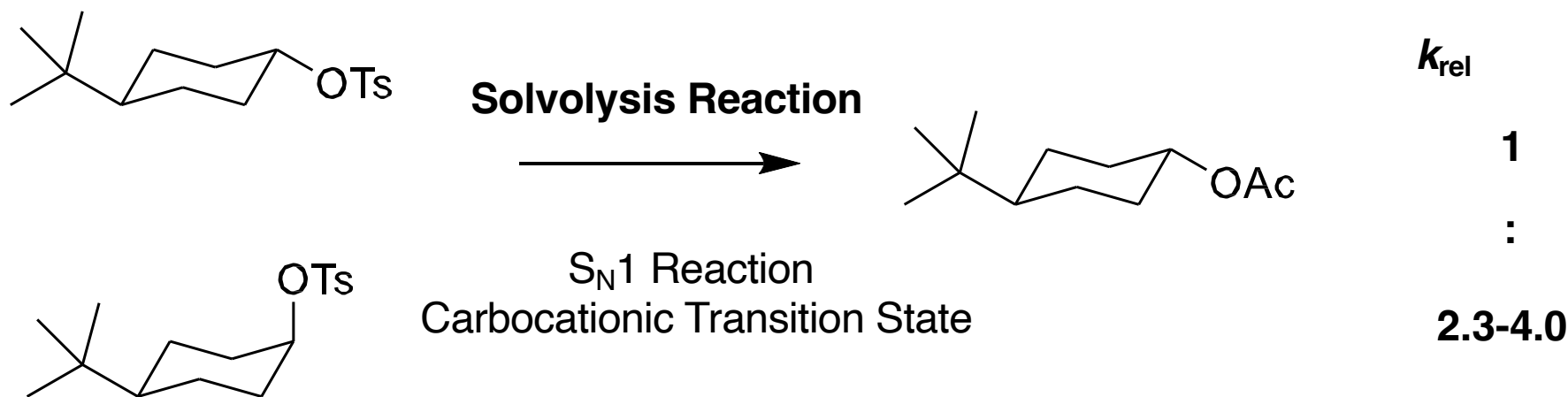
The axial diastereomer is not always slower reacting!

S_N1 Reaction

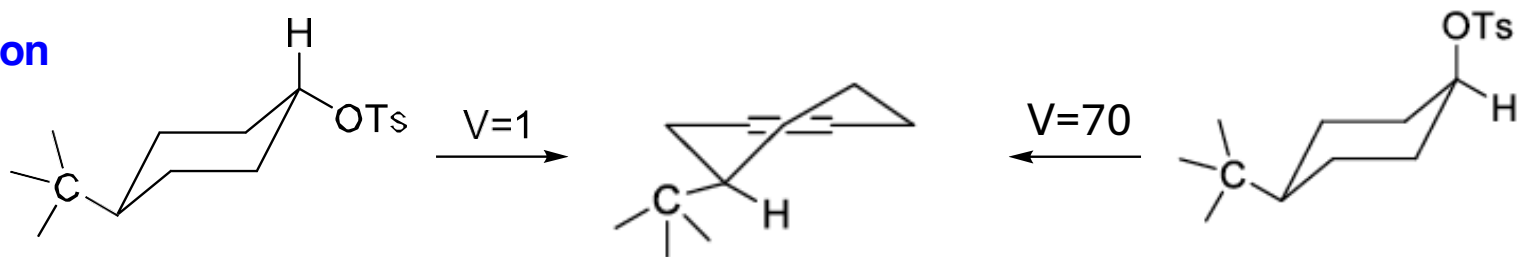
Because the ground state energy of the a-TsO substitution raw material is higher than that of the e-TsO ground state,

In the solvolysis reaction of 4-tert-butylcyclohexane toluenesulfonate

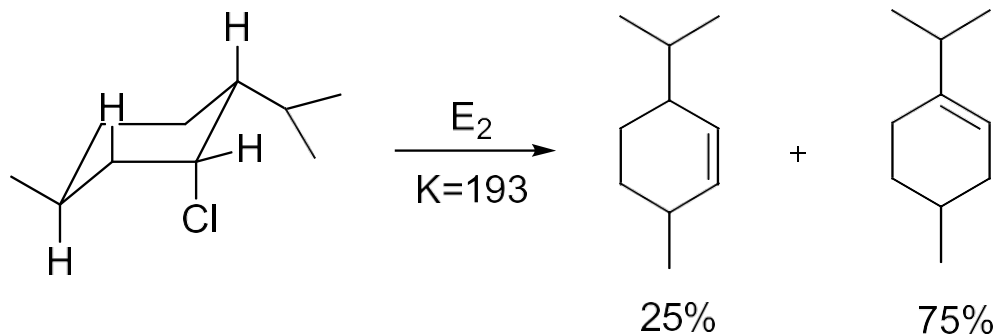
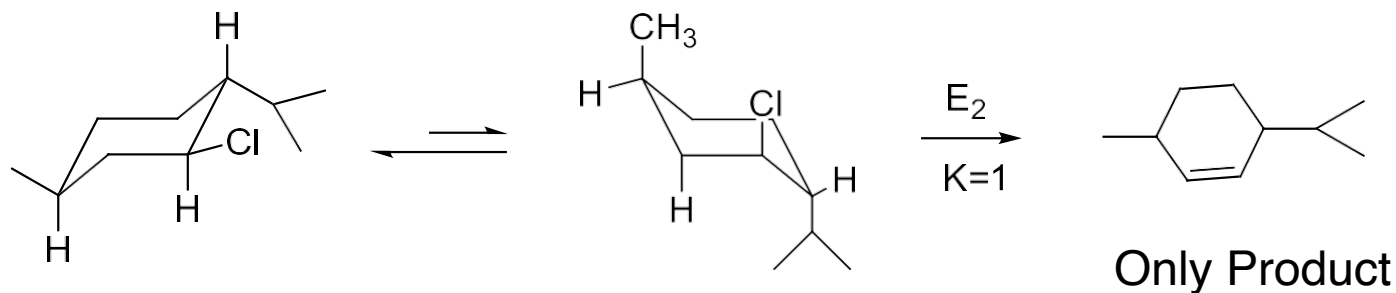
$$k_{\text{cis}}/k_{\text{trans}} = 2.3-4.0$$



E₂ Elimination

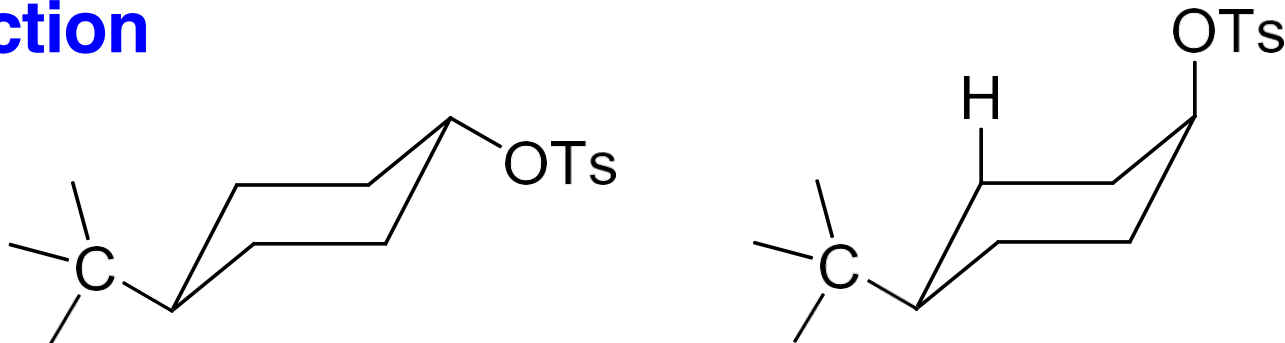


The transition from a stable conformation to an unstable conformation requires high energy and the reaction is slow.



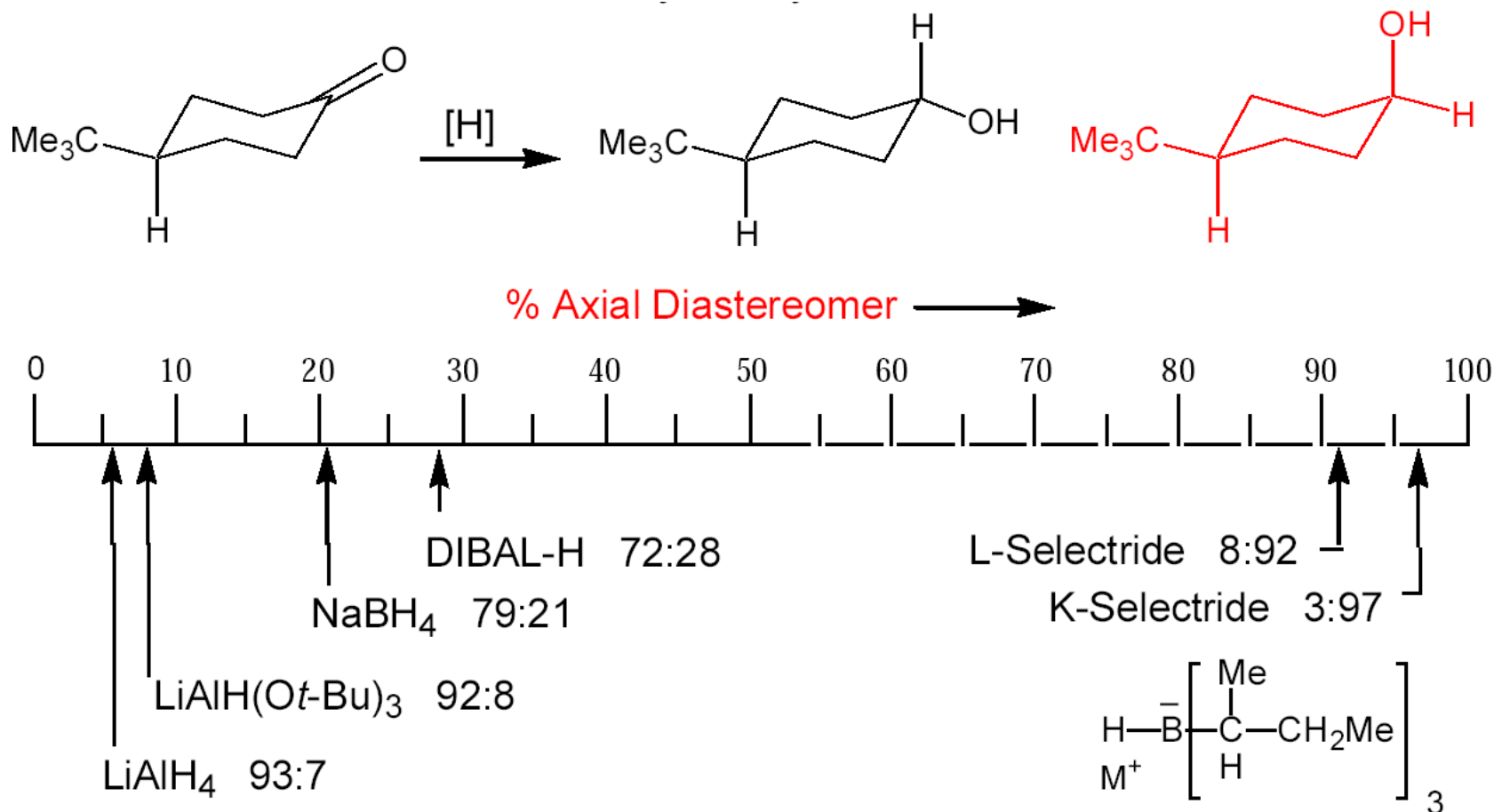


E₁ Reaction



E₁ elimination generates carbocation intermediates. When a-bond and e-bond reactants generate carbocations, the transition state energy is basically equal, but the energy of **a-bond** reactants is **higher** than that of **e-bond** reactants. Therefore, the energy barrier between a-bond reactants and the transition state is smaller, and a-bond reactants are more likely to undergo E₁ reactions.

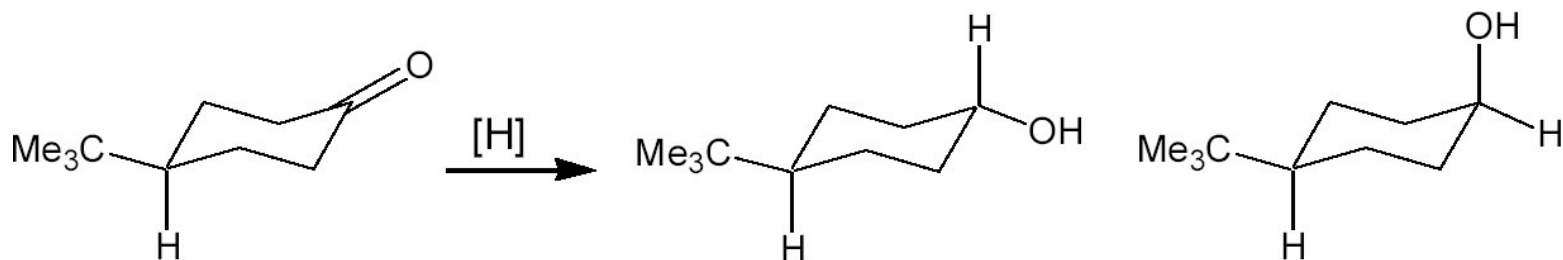
Stereoselective Reductions: Cyclic Systems



Summary: Increasing bulky hydride reagents prefer to attack from the equatorial C=O face.

Stereoselective Reductions: Cyclic Systems

The most stereoselective Reductions



Reagent

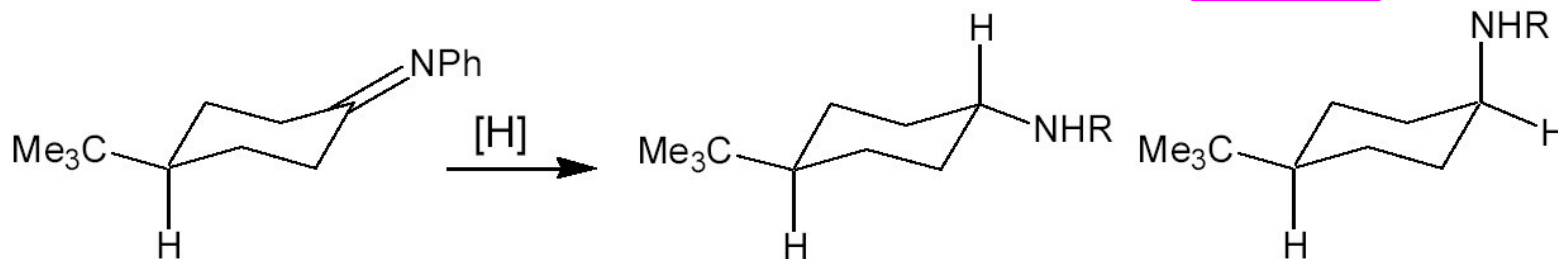
Ratio

KBH(s-Bu)₃

03 :97

Li in NH₃

99 :01



(R)

Reagent

Ratio

Ganem, *Tet. Let* **1981**, 22, 3447

R = Bn

LiBH(s-Bu)₃

03 :97

Hutchins, *JOC* **1983**, 48, 3412

R = Ph

LiBH(s-Bu)₃

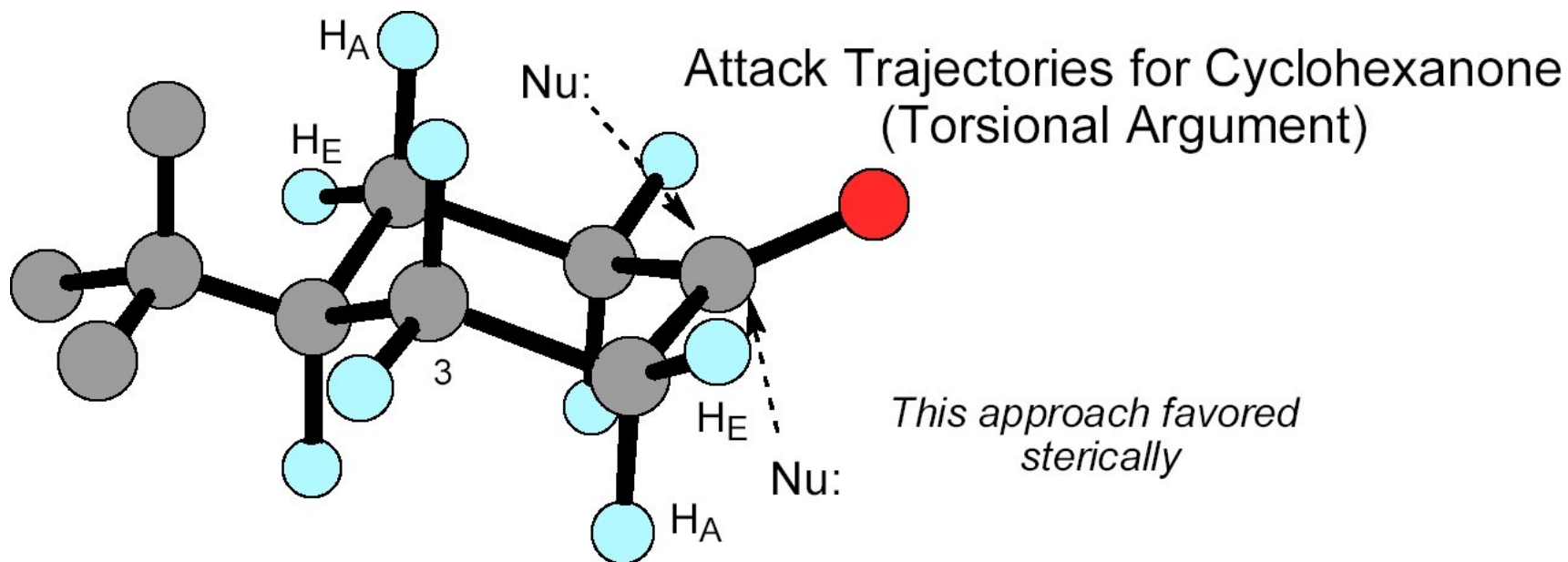
01 :99

private communication

Al/Hg/MeOH

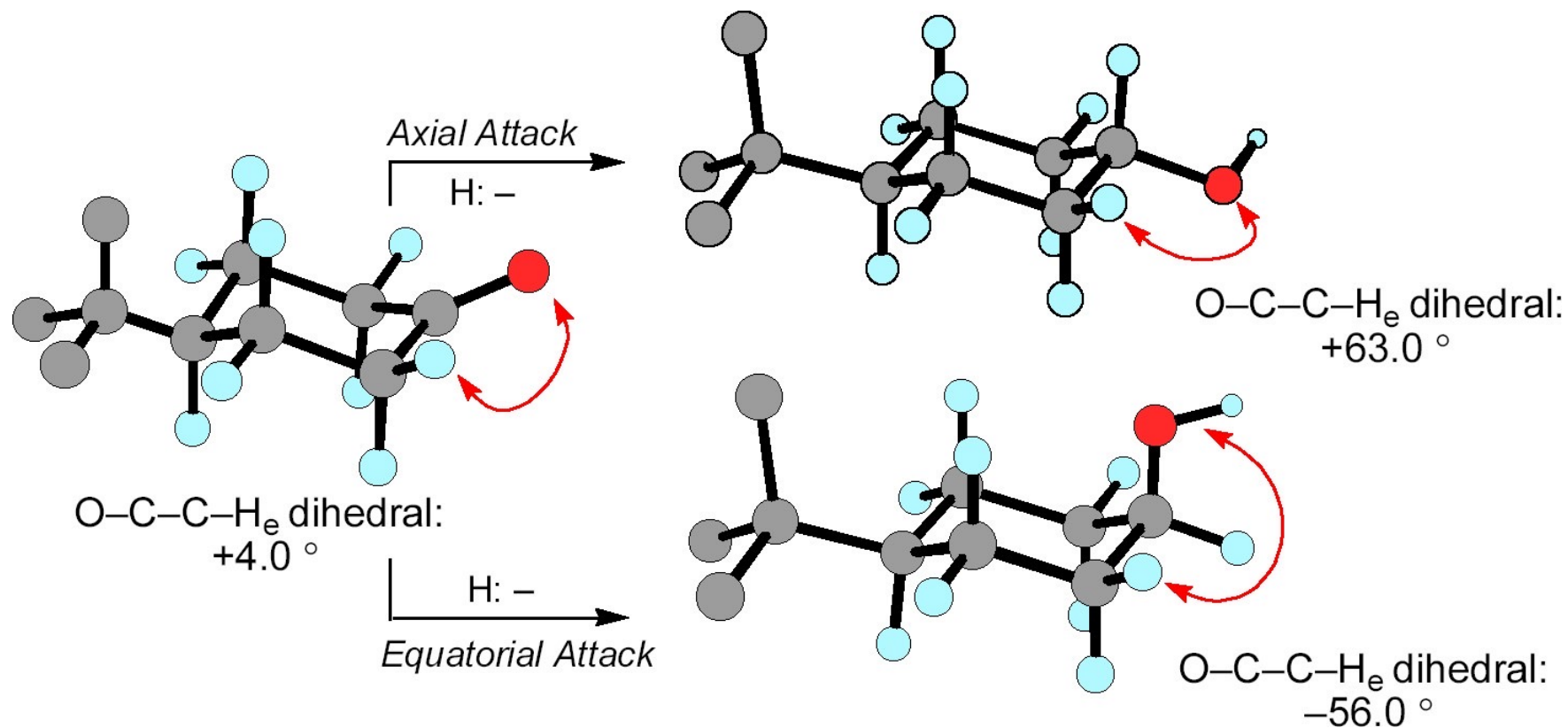
~90 :10

Torsional Effect



The steric hindrance encountered by Nu-attack from the axial C=O face by the axial ring substituents (hydrogens in this case) at the 3-positions is more severe than the steric hinderance encountered from Nu-attack from the equatorial C=O face.

The reaction transition state do not undergo a fully overlapping



The reaction transition state undergoes a fully overlapping



The Issues Associated with the Reduction Process



- **Steric Effects:** Attack across equatorial C=O face sterically more favorable.
- **Torsional Effects:** However, attack across the axial face of the C=O group avoids development of eclipsing interactions in the transition state. (Note the dihedral angle sign changes between reactants & products shown above). These “torsional effects” favor axial attack.

Prediction For “small” hydride reagents such as LiAlH_4 , torsional effects are felt to be dominant and this explains the predisposition for axial attack.

Prediction For “large” hydride reagents such as H-BR_4 , steric effects now are dominant and this explains the predisposition for equatorial attack.

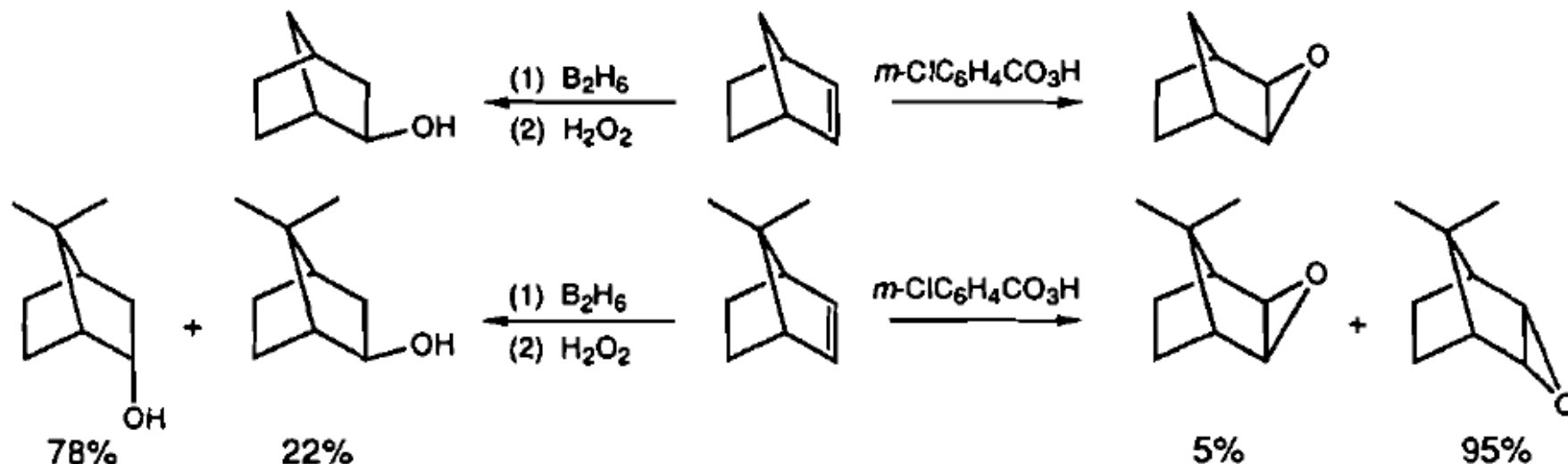
Leading References:

J. I. Seeman, *J. Chem. Ed.* **1986**, 63, 42-48.

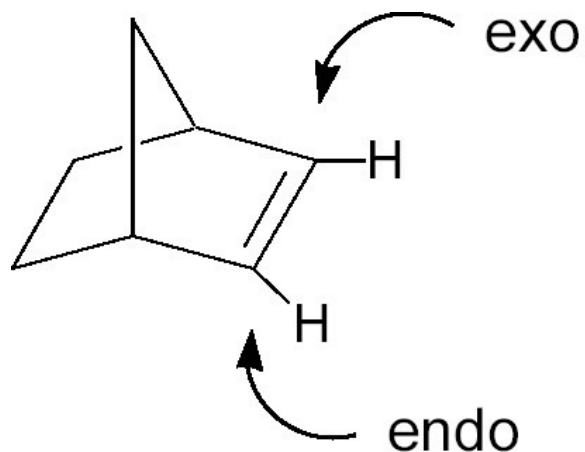
J. I. Seeman, *Chem Rev.* **1983**, 83, 83-134.

See also Eliel, pp. 647-655

Stereoselective epoxidation and hydroboration



Olefin Addition



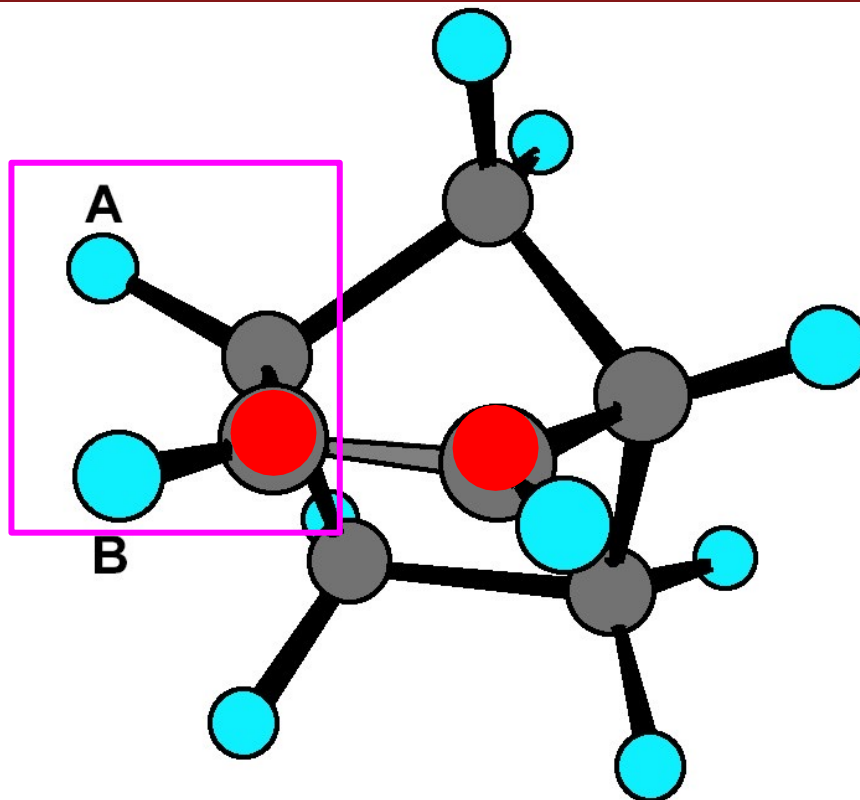
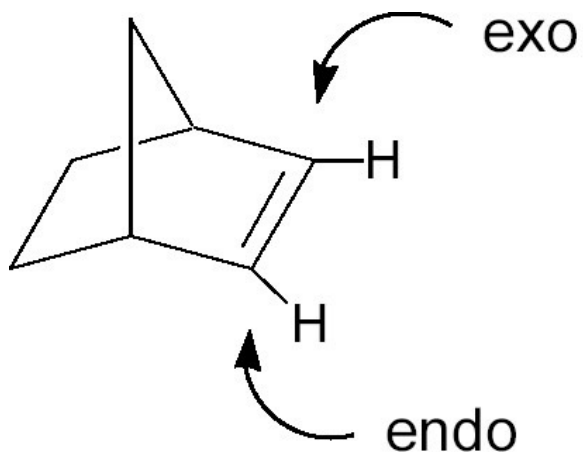
Highly exo selective for electrophilic, nucleophilic and cycloaddition reactions

Rate enhancement due to strain

Addition from exo face avoids eclipsing A & B hydrogens (better hyperconjugative stabilization of transition state).

P. R. Schleyer, *J. Am. Chem. Soc.* 1967, 89, 701.

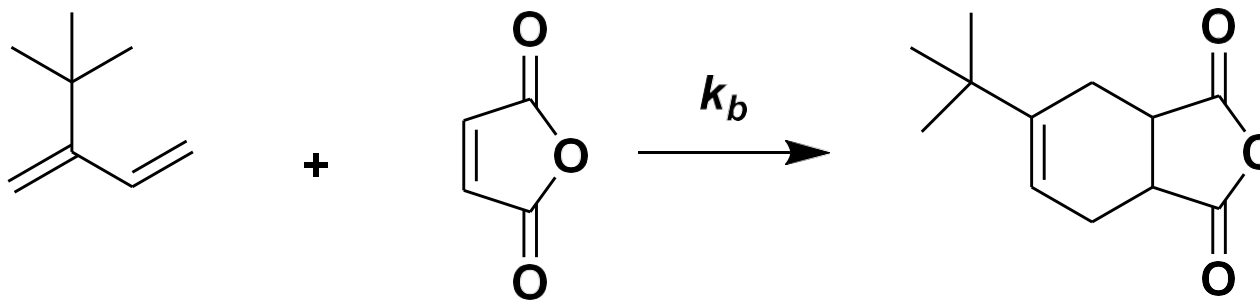
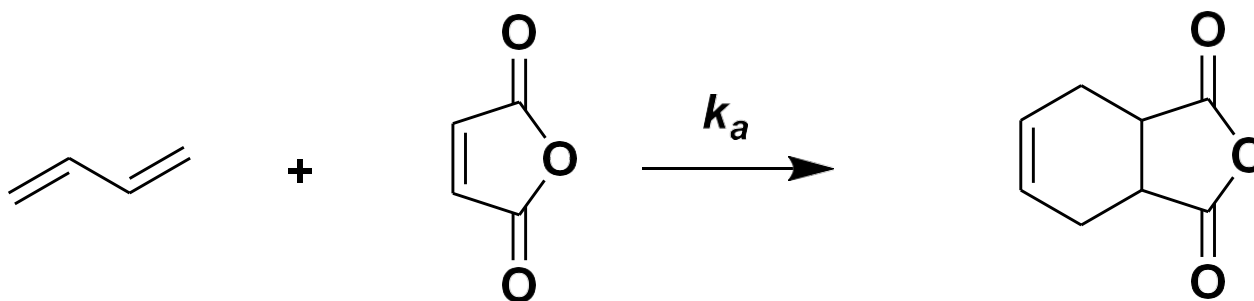
Olefin Addition



Highly exo selective for electrophilic, nucleophilic and cycloaddition reactions

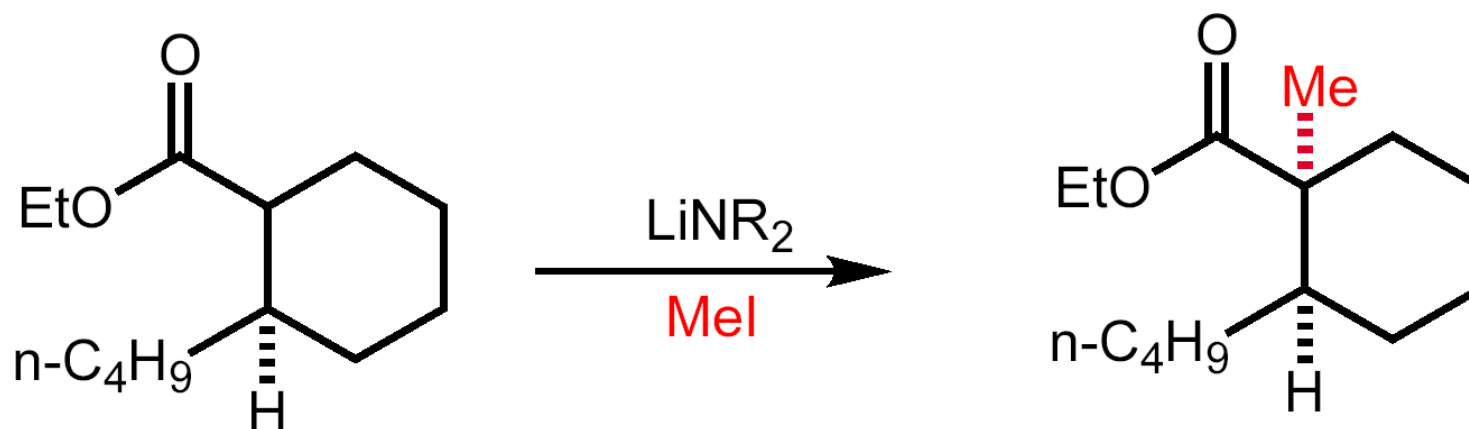
Rate enhancement due to strain

1. Can you explain the different rate of the reactions?



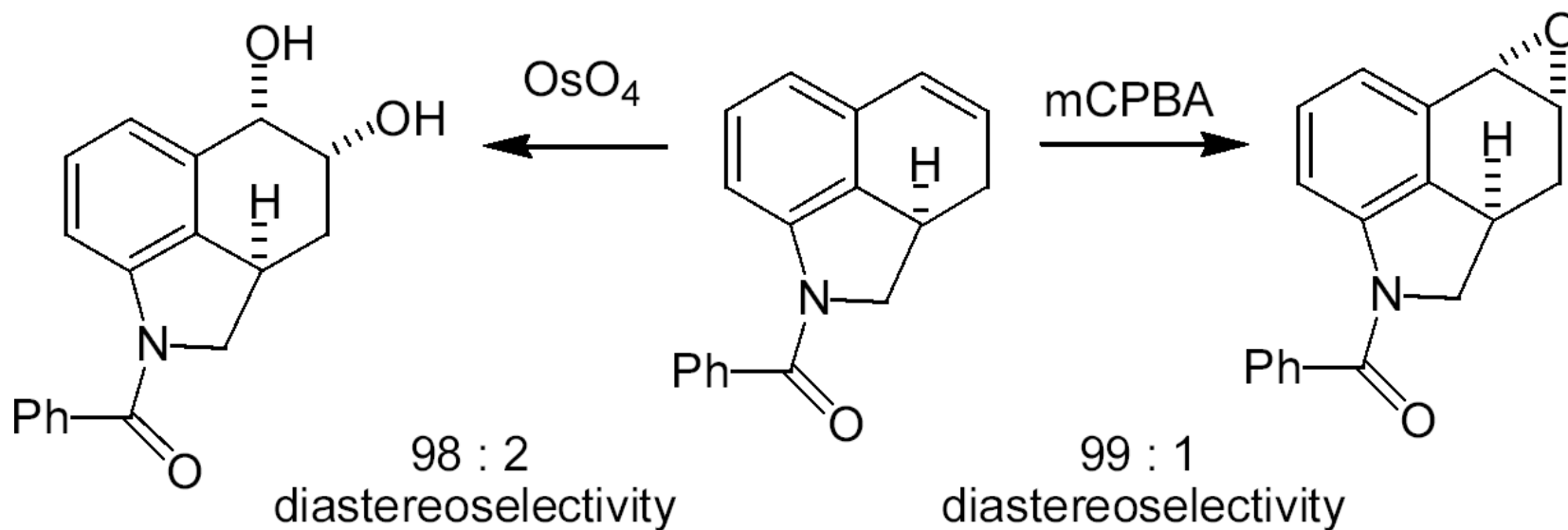
$$k_b : k_a = 27 : 1$$

2. Can you rationalize the stereochemical outcome of this reaction?



diastereoselection 89:11

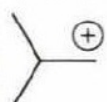
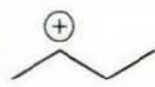
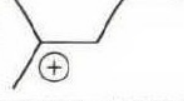
3. How do we account for the high selectivities in the oxidation of the indicated olefin?

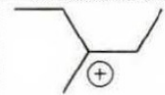
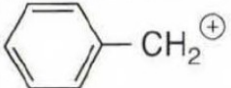
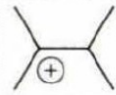
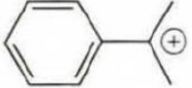
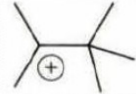
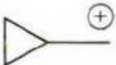
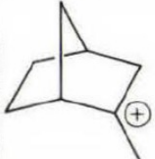
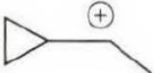


Note: Nitrogen protecting group does not affect selectivities.

Stability of Carbocations

Gas Phase Hydride Ion Affinities (HIA) / kcal/mol

CH_3^+	312		256
C_2H_5^+	273		236
$\text{CH}_3\text{CH}_2\text{CH}_2^+$	266		225
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2^+$	265		225
	265		248
	246		225
	247		212
	231	$\text{HC}\equiv\text{C}-\text{CH}_2^+$	270
	229	$\text{H}_2\text{C}=\text{CH}^+$	287
	228	$\text{H}_2\text{C}=\text{C}^+-\text{CH}_3$	258

	227		234
	226		220
	224		287
	231		249
	225		230
NH_2CH_2^+	218		218
HOCH_2^+	243		201
FCH_2^+	290		258
NCCH_2^+	318		



Substituent Effect



- **Electronic effects:**

- Resonance, conjugation and hyperconjugation,
- Delocalization of electrons
- Stereoelectronic effect
- Polar effect or electrostatic effect
 - Inductive effect
 - Field effect
- Polarizability effect

- **Steric effects:**

- Nonbonding interactions
- Configurations and conformations
- Structural specificity effects
 - Hydrogen bonding
 - Adjacent group participation effects



Electricity (Electronic Effects) of Substituents



ERG/EDG: Electron
Releasing/Donating Group

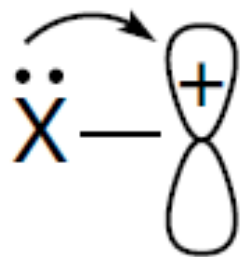
EWG: Electron
Withdrawing Group

<u>Substituent</u>	<u>Resonance</u>	<u>Polar</u>
<u>Alkyl</u> CH ₃ , C ₂ H ₅ , (CH ₃) ₃ C, etc	ERG	ERG (small)
<u>Vinyl and aryl</u> CH ₂ =CH, C ₆ H ₅ , etc	ERG or EWG	EWG (small)
<u>Ethynyl</u> HC≡C, etc	ERG or EWG	EWG
<u>Alkoxy, Acyloxy, Amino, Acylamido</u> RO, RCO ₂ , R ₂ N, RCONH, etc	ERG	EWG
<u>Carbonyl</u> HC=O, RC=O, ROC=O, R ₂ NC=O, etc.	EWG	EWG
<u>Halogens</u> F, Cl, Br, I	ERG	EWG
<u>Polyhaloalkyl</u> CF ₃ , CCl ₃ , etc.	EWG	EWG
<u>Other Nitrogen Groups</u> CN, NO ₂ , R ₃ N ⁺ , etc.	EWG	EWG
<u>Sulfur Groups</u> RS RSO RSO ₂	ERG ERG EWG	EWG EWG EWG
<u>Silyl Groups</u> R ₃ Si	ERG	ERG

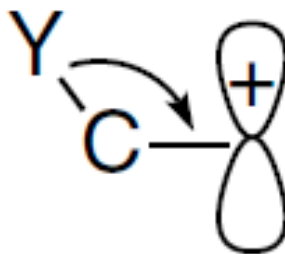
Resonance effects and polarity effects
can be consistent or opposite.

Molecular structure: electronic effects of substituents

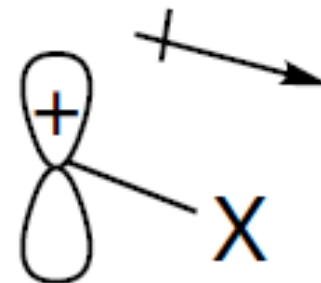
Dipole (polarity), conjugation, aromaticity, hyperconjugation (stereoelectronic effect)



π -donor



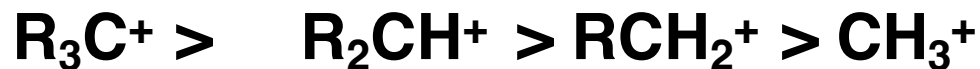
β -hyperconjugation



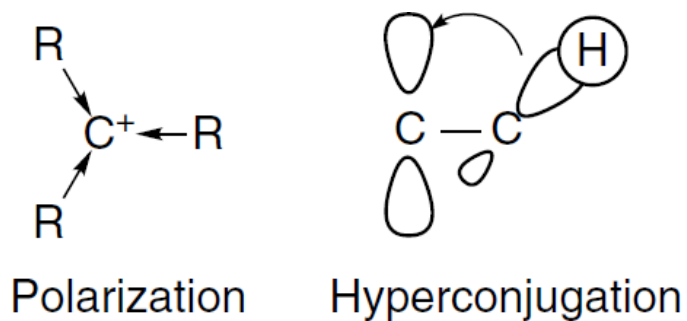
α -polar

Molecular structure: steric effects

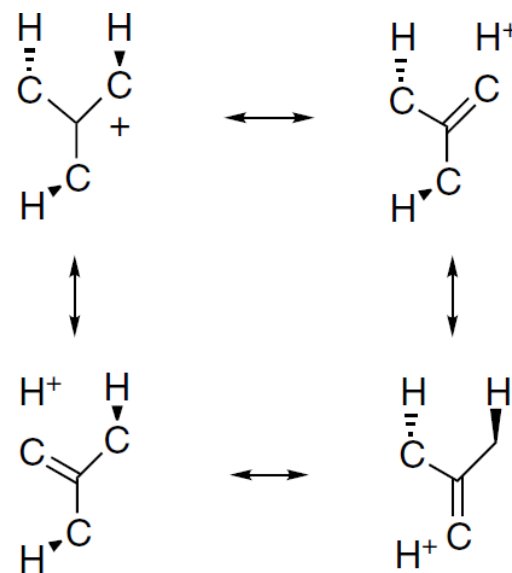
External conditions: solvent effects

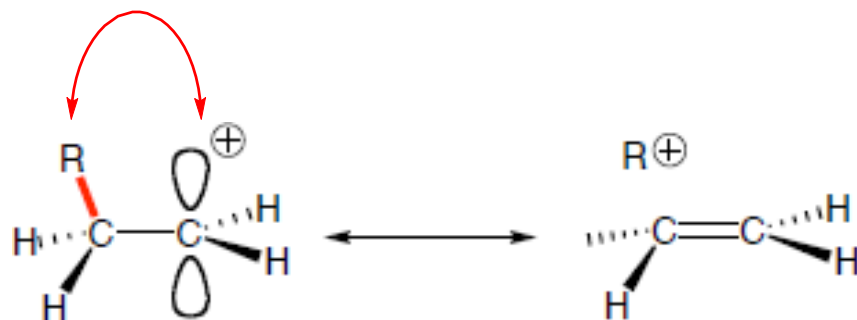


Example: CH_3^+ (0.0 kcal/mol) < $CH_3CH_2^+$ (40 kcal/mol) < $(CH_3)_2CH^+$ (60 kcal/mol) < $(CH_3)_3C^+$ (85 kcal/mol)



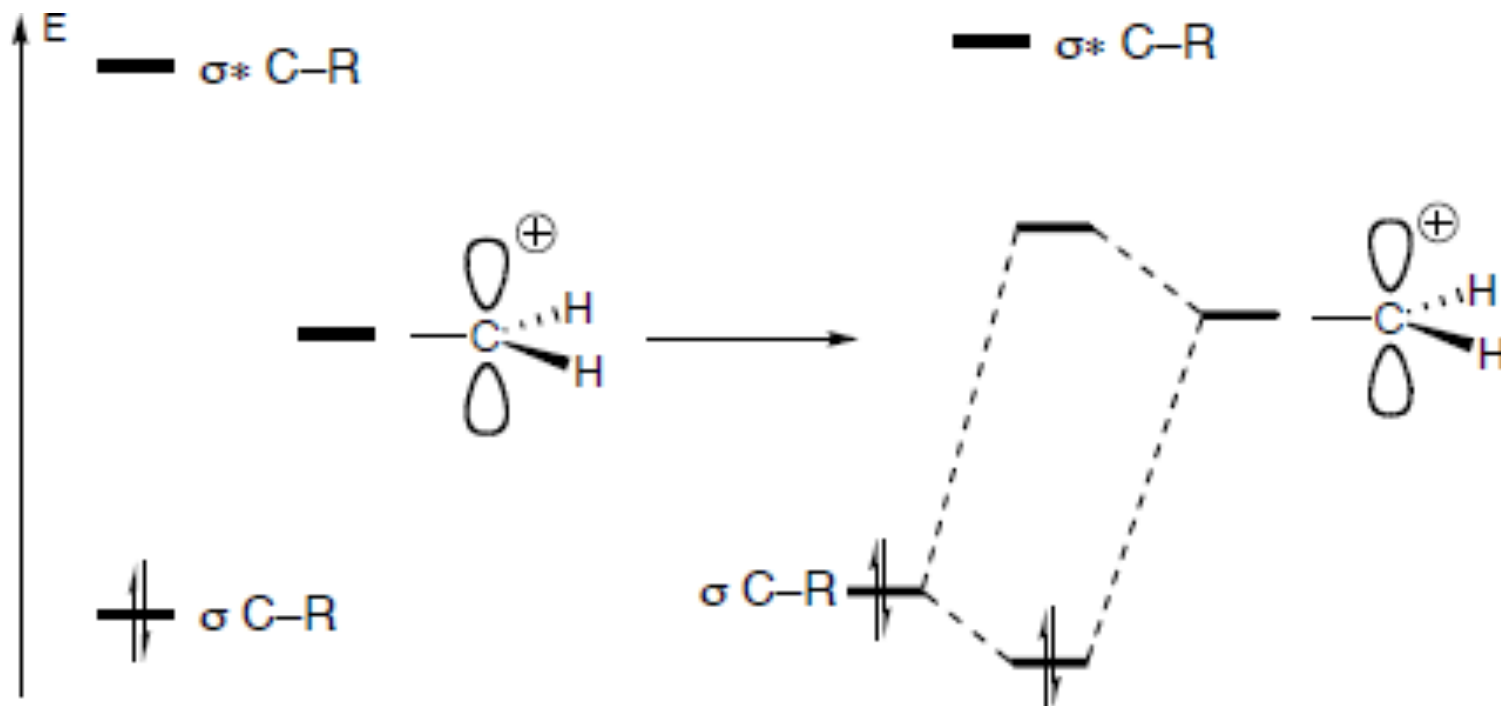
Alkyl groups have consistent polar and resonance effects as EDGs





**Syn-planar orientation
between interacting orbitals !**

MO Description:

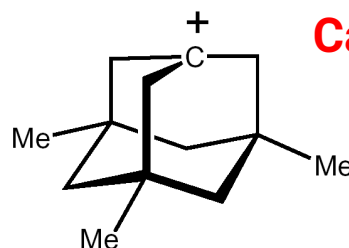
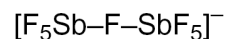
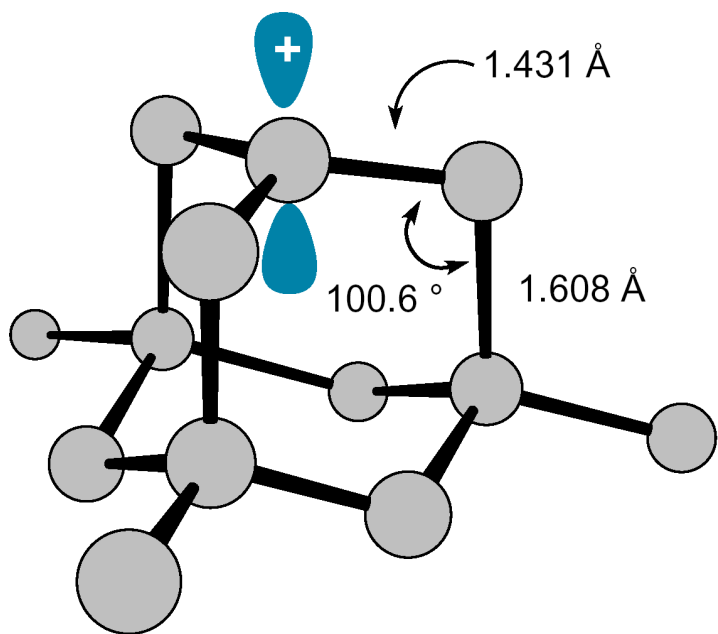


The linear combination of filled s C-R orbitals and empty p_z orbitals brings stabilization

Evidence for Hyperconjugation in Carbocation

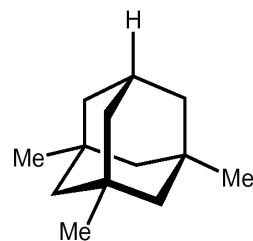
Bonds participating in the hyperconjugative interaction. e.g. C-R, will be lengthened while the C(+)-C bond will be shortened.

First X-ray Structure of an Aliphatic Carbocation



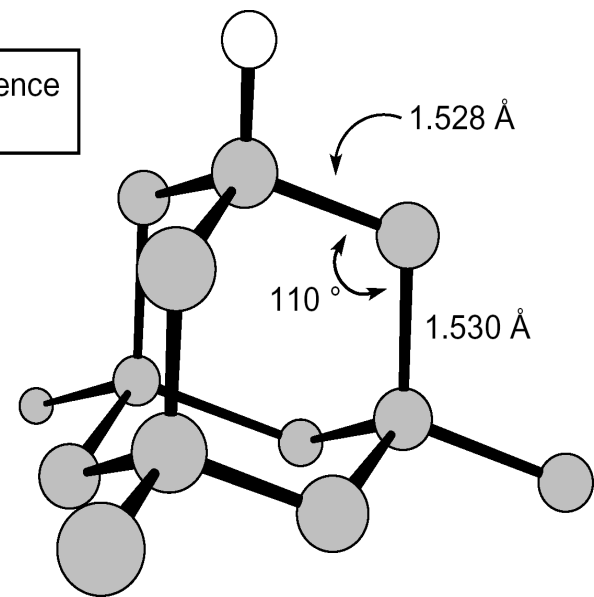
Carbocation planarization tendency

The Adamantane Reference (MM-2)



Changes in bond length and bond angle

Group discussion: Can you predict the structure of 1-methylcyclohexylcarbocation?



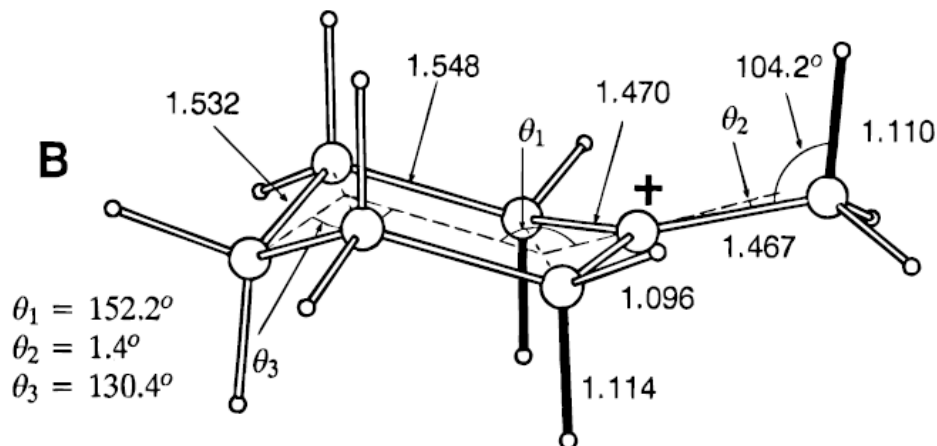
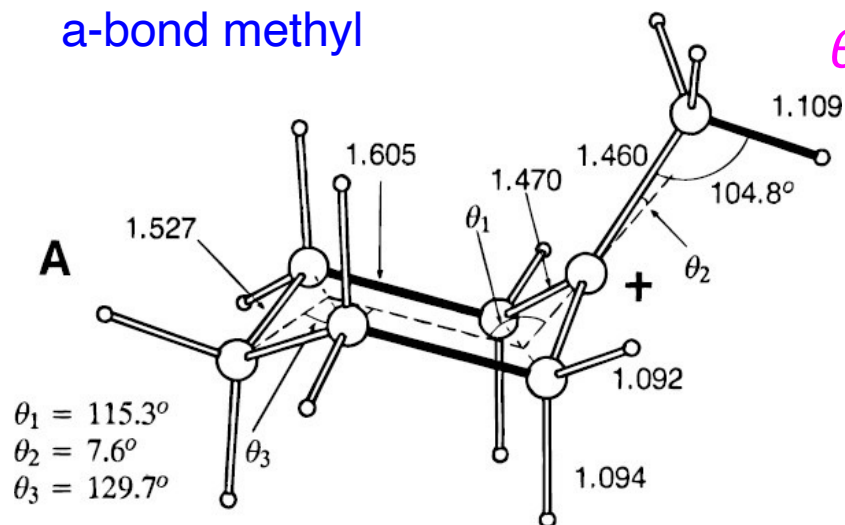
1-Methylcyclohexylcarbocation

Slight coning occurs

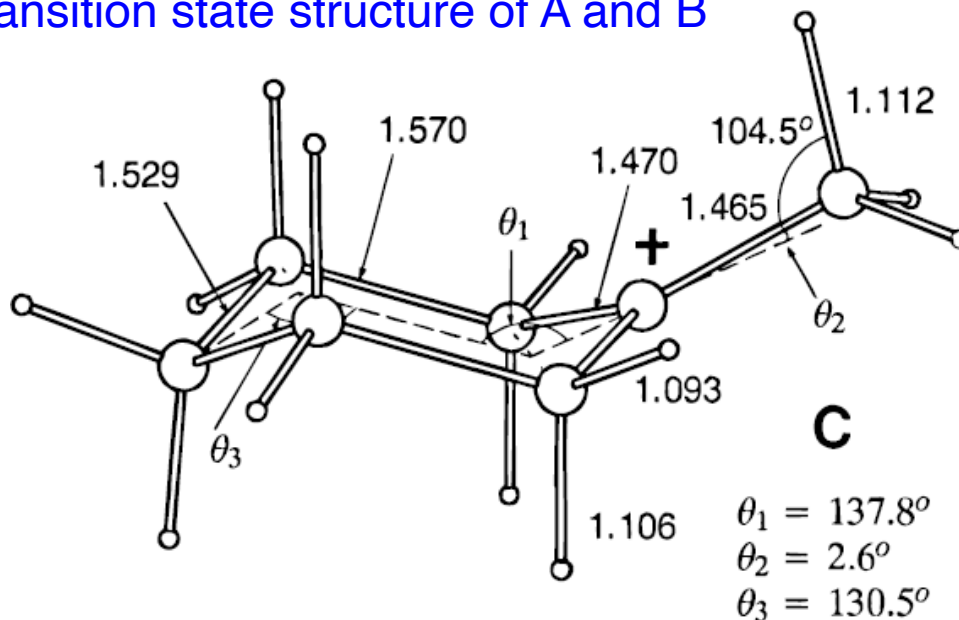
$\theta = 7.6^\circ$ and 1.4°

a-bond methyl

e-bond methyl

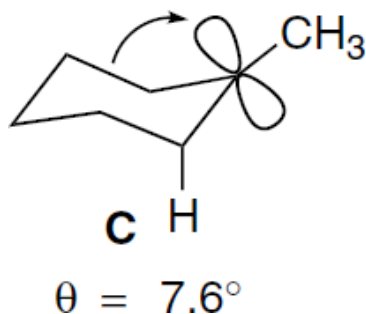


Transition state structure of A and B

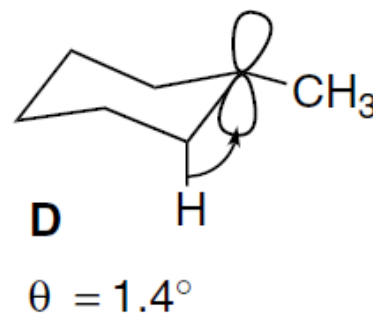


Hyperconjugation in 1-Methylcyclohexylcarbocation

Methyl group in a-bond:
Hyperconjugation of C-
C bond with p orbital

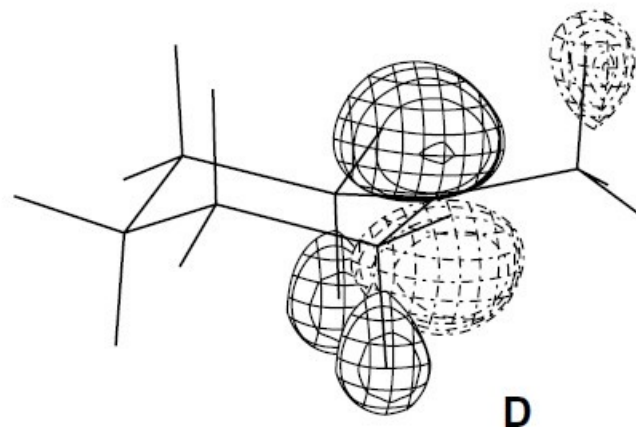
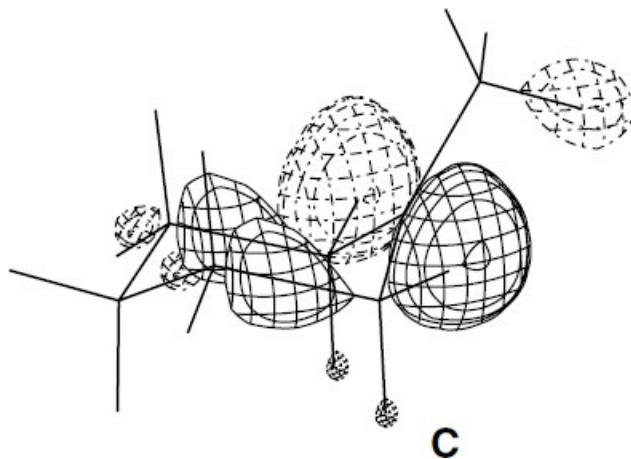


Methyl group in e-bond:
C-H bond and p orbital
are hyperconjugated



Slight coning occurs
 $\theta = 7.6^\circ$ and 1.4°

θ = Deviation of $-\text{CH}_3$ from the plane of
 $\text{C}(1)-\text{C}(2)-\text{C}(6)$ of the cyclohexane ring



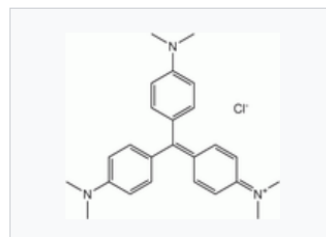
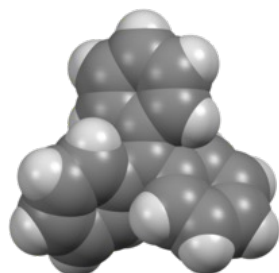
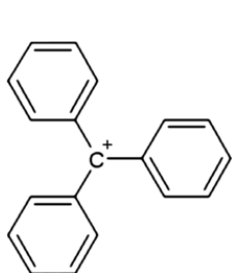
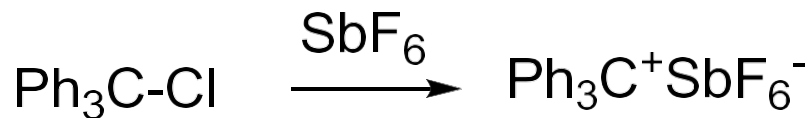
Experiments show that the 1-methylcyclohexyl carbocation of the methyl group in the e bond is slightly more stable (1 kcal/mol), and the energy of the transition state changing between the two is also very low.

J. Am. Chem. Soc. **1996**, 118, 3761.

Aromatic Carbocations

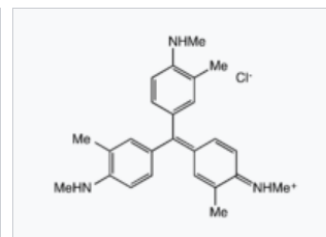
Carbocations attached to aromatic rings have increased stability due to delocalization of conjugation

Many benzyl cations can be used to form antimony hexafluoride salt (SbF_6^-) in solution

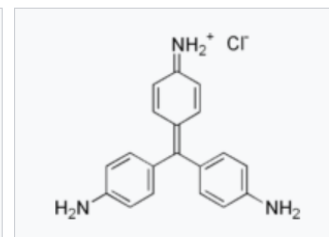


Crystal violet.

Triarylmethane dyes

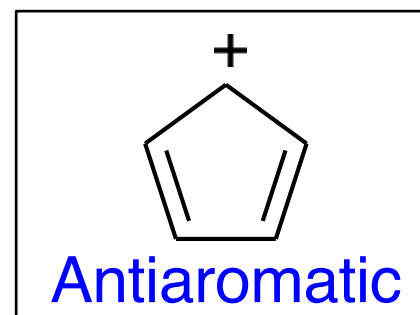
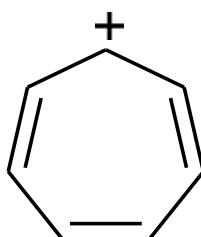


New fuchsin dye.

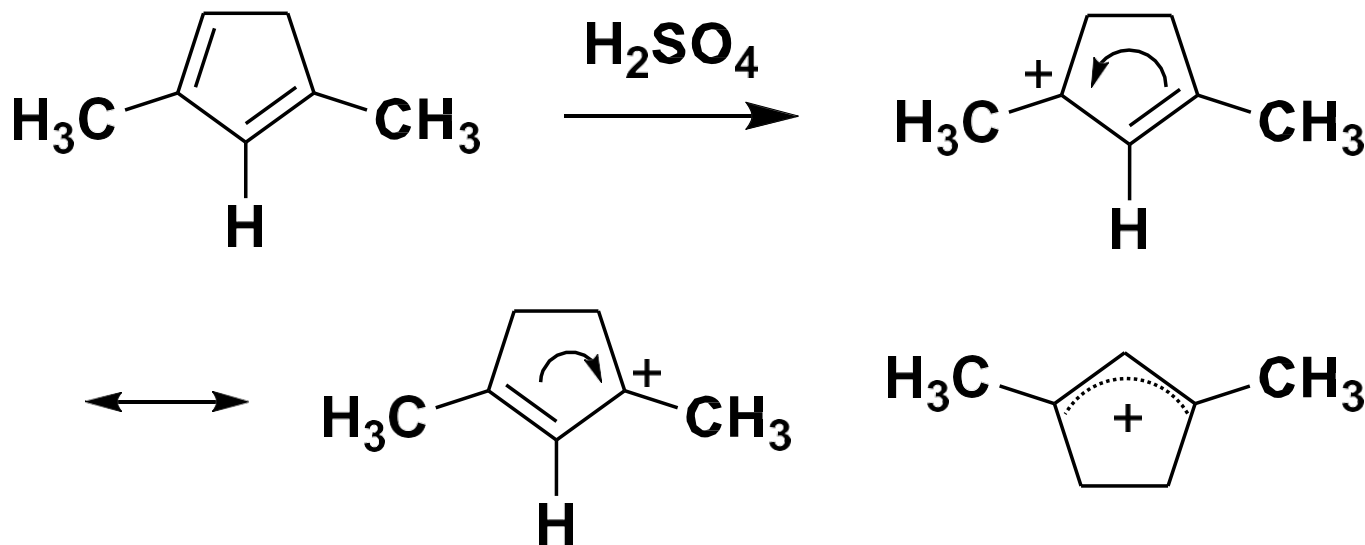


Pararosaniline

Stabilization by making $4n+2$ aromaticity

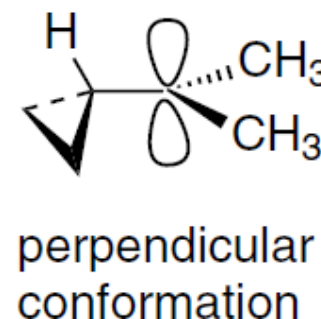
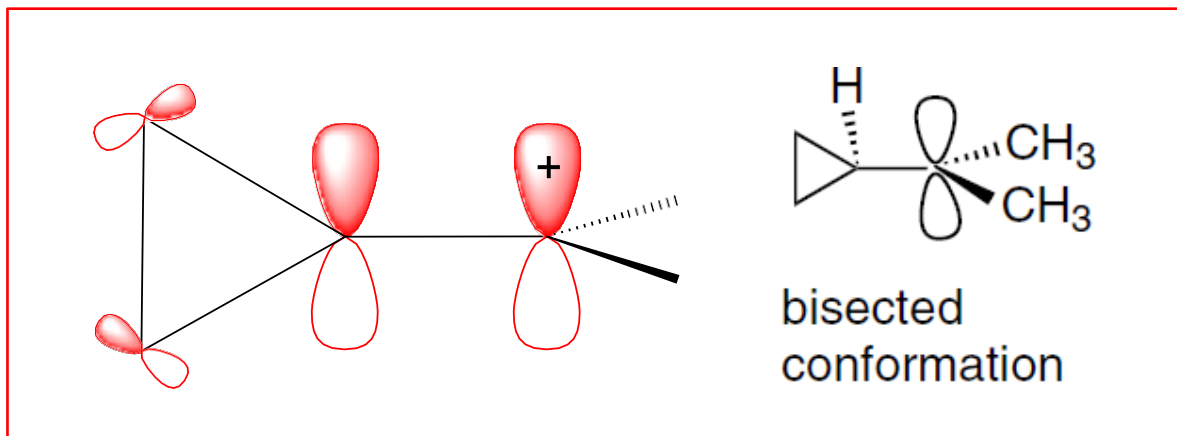


A carbocation conjugated to a double bond has increased stability due to delocalization of conjugation

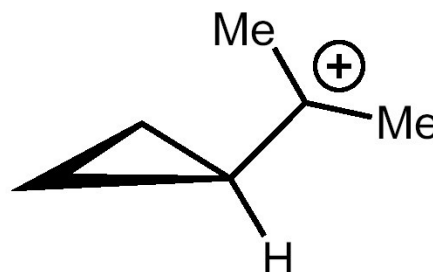


NMR Spectrum showed only three hydrogens, six methyl protons, four methylene protons, and one methine proton, proving that the positive charge was delocalized.

The stability of the cyclopropylmethyl carbocation is due to the conjugation of the empty p orbital of the carbocation with the bonding orbital on the carbon atom in cyclopropane.



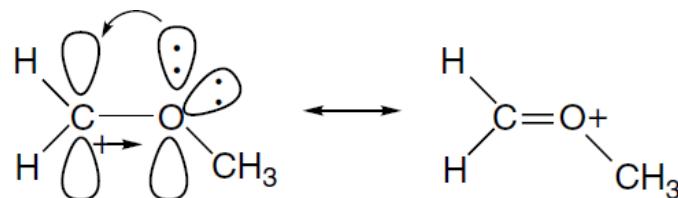
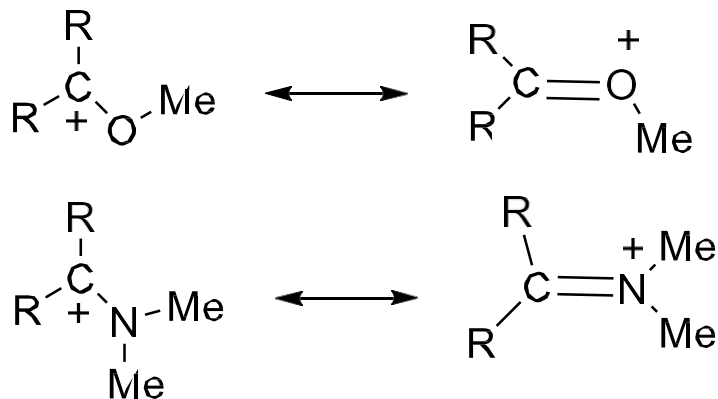
A rotational barrier of about 13.7 kcal/mol is observed in following example:



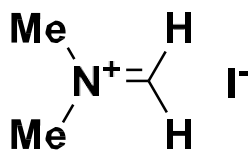
NMR in super acids
 $\delta(\text{CH}_3) = 2.6$ and 3.2 ppm

Research shows that the p empty orbital is parallel to the cyclopropyl C2-C3 bond.
 This stability is unique to cyclopropane.

- The lone pair of electrons of the heteroatom plays a resonance stabilizing role in the carbocation.

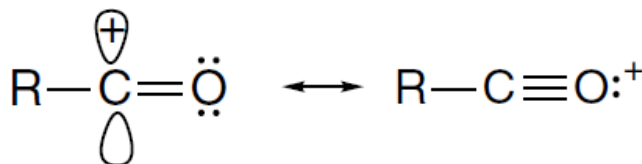


Alkoxy and amino groups are resonated EDGs



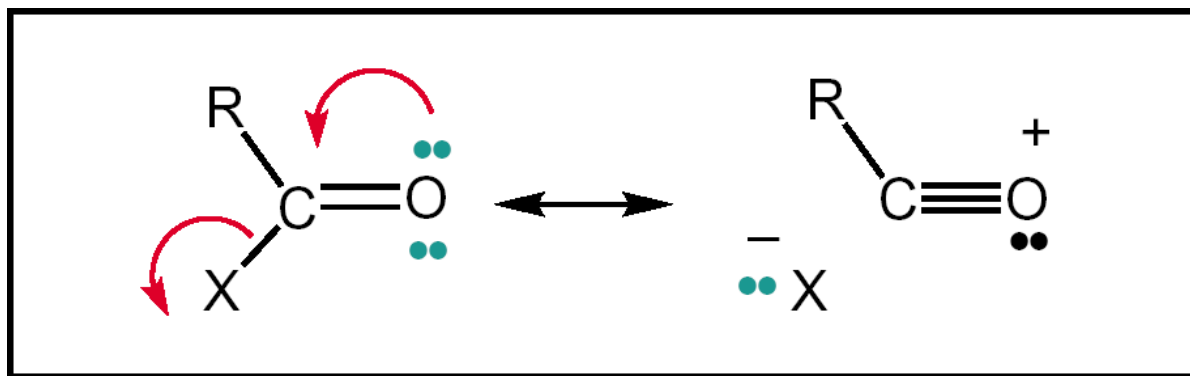
Eschenmoser salt (iminium salt)

Very useful aminoalkylating reagent in organic synthesis

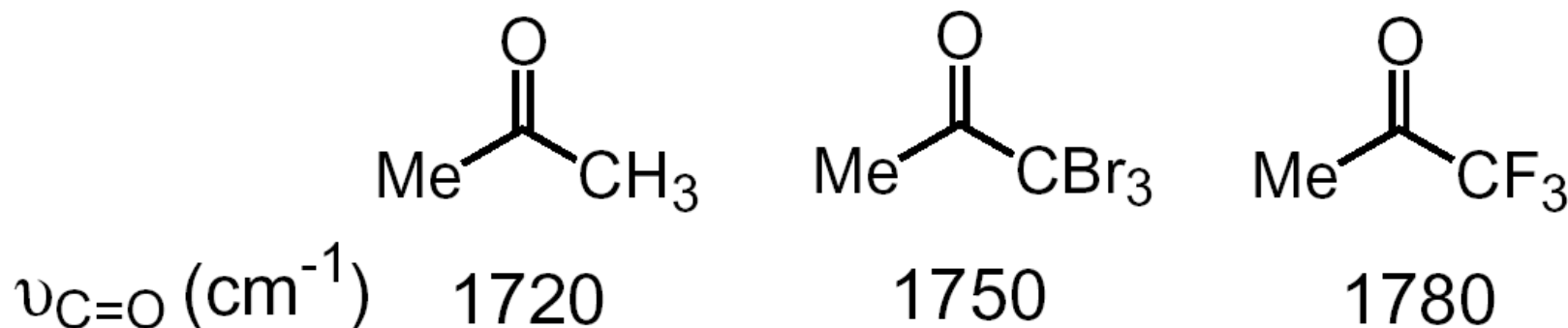


Simple acylcations have been prepared both in solution and in the solid state.
The stability of MeCO^+ is similar to $t\text{-Bu}^+$.

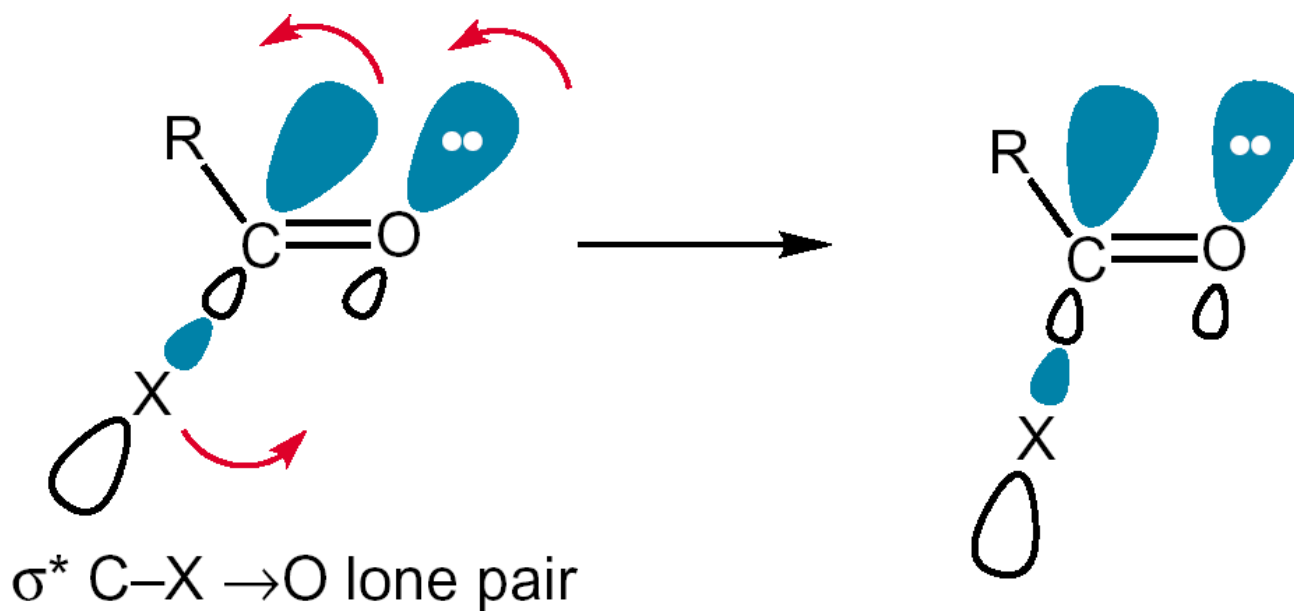
Do the following valence bond resonance structures have meaning?



Prediction: As X becomes more electronegative, the IR frequency should increase

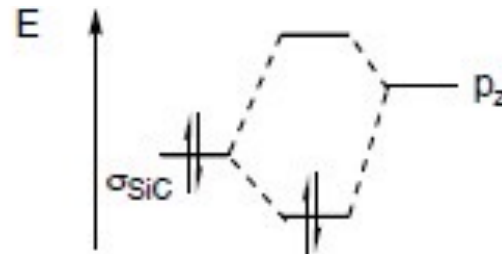
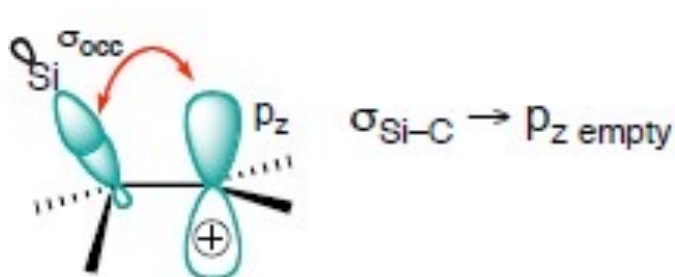
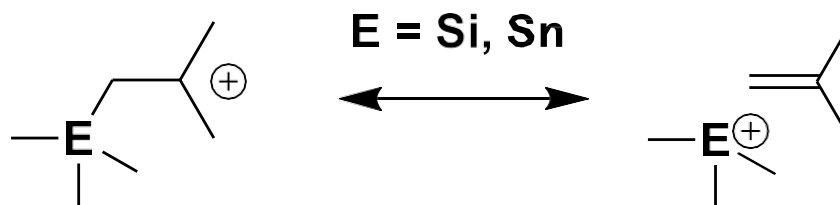


Prediction: As the indicated π -bonding increase, the X-C-O bond angle should decrease. This distortion improves overlap !

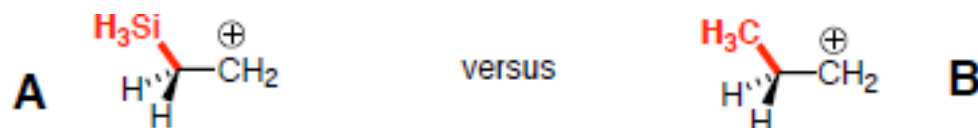


Evidence for this distortion has been obtained by X-ray crystallography

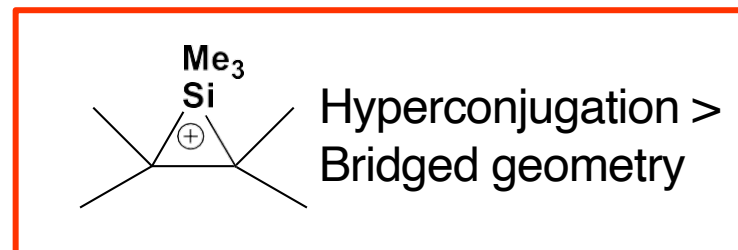
Stabilization by β - Si and Sn Groups



Carbon-silicon bonds are good donors for the formation of hyperconjugation and have a stabilizing effect of 38 kcal/mol compared to carbon-carbon bonds.

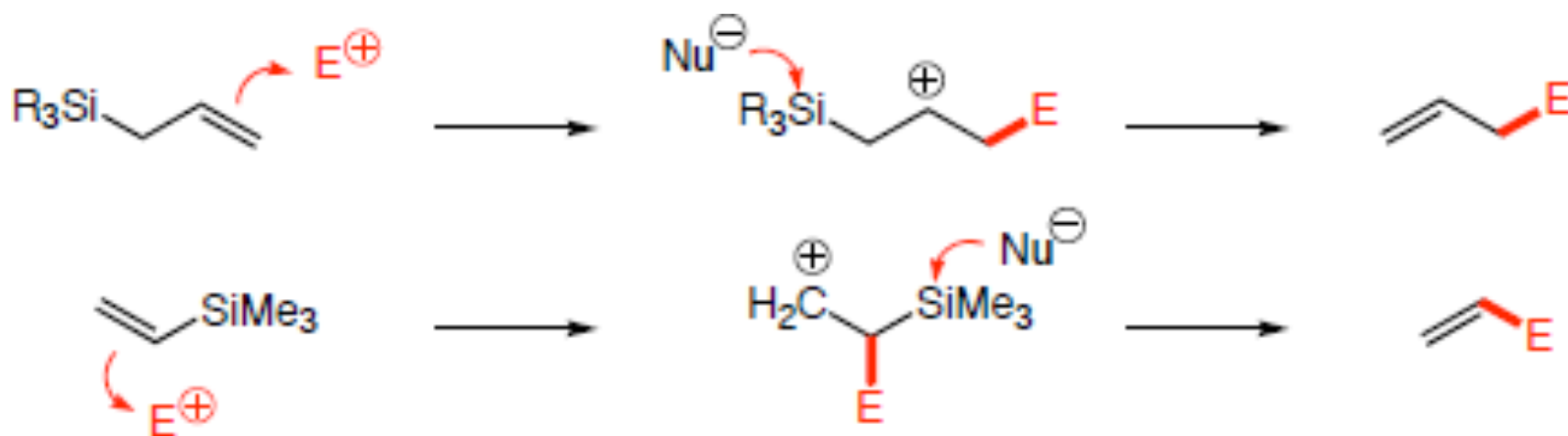


Calculation: A more stable than B by 38 kcal/mol.

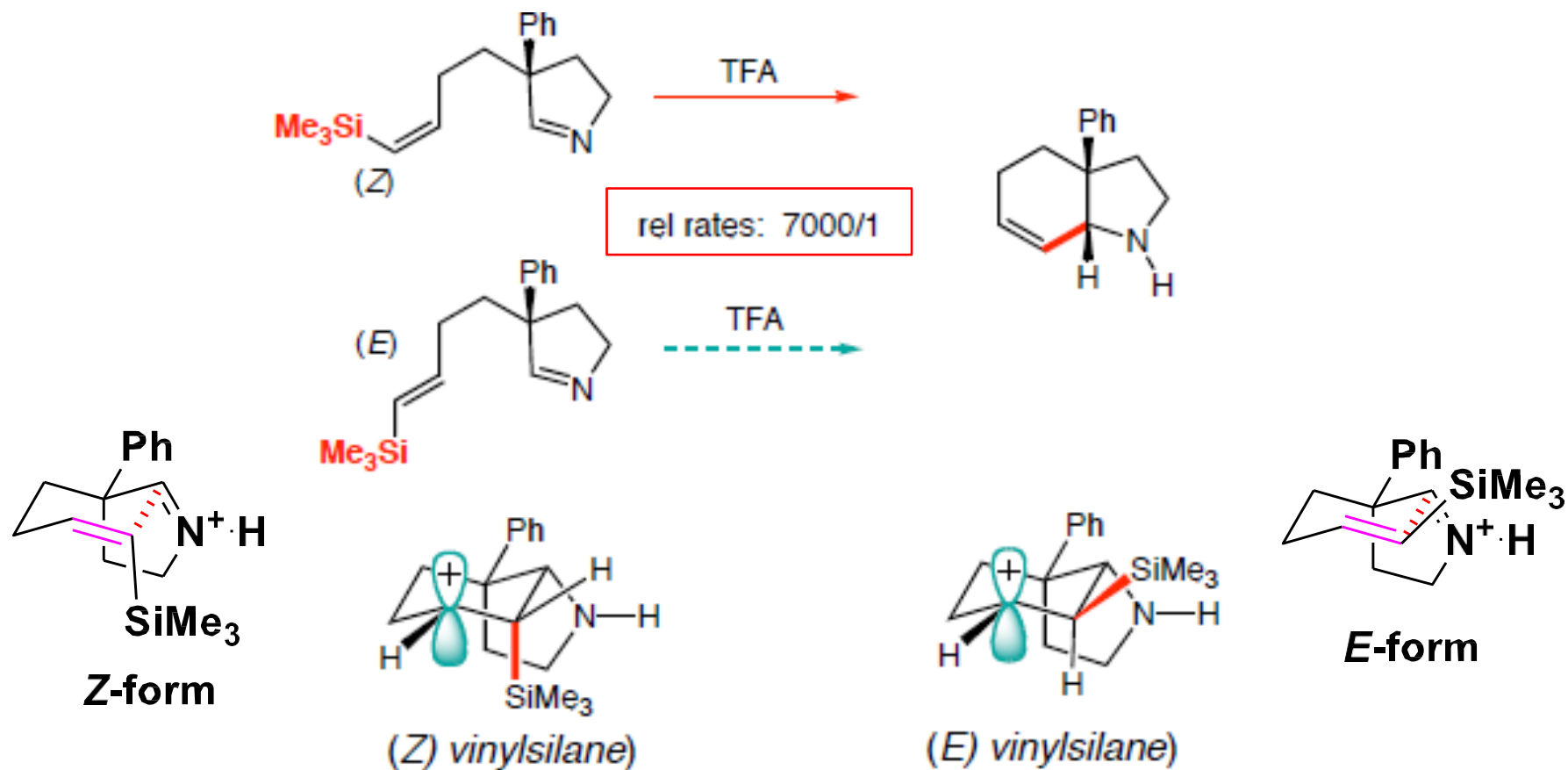


Because of the stabilizing effect of silicon groups on β -position carbocations, allylsilane and alkenylsilane have become important nucleophiles in organic synthesis.

Reaction mechanism of allylsilane and alkenylsilane with electrophiles



β -Silicon Effect is the major driving force of regioselectivity in the reaction of allylsilane and alkenylsilane with electrophiles!



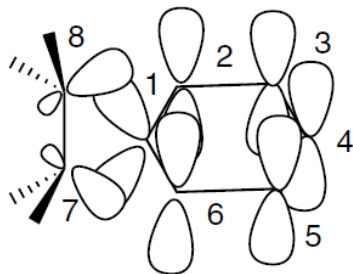
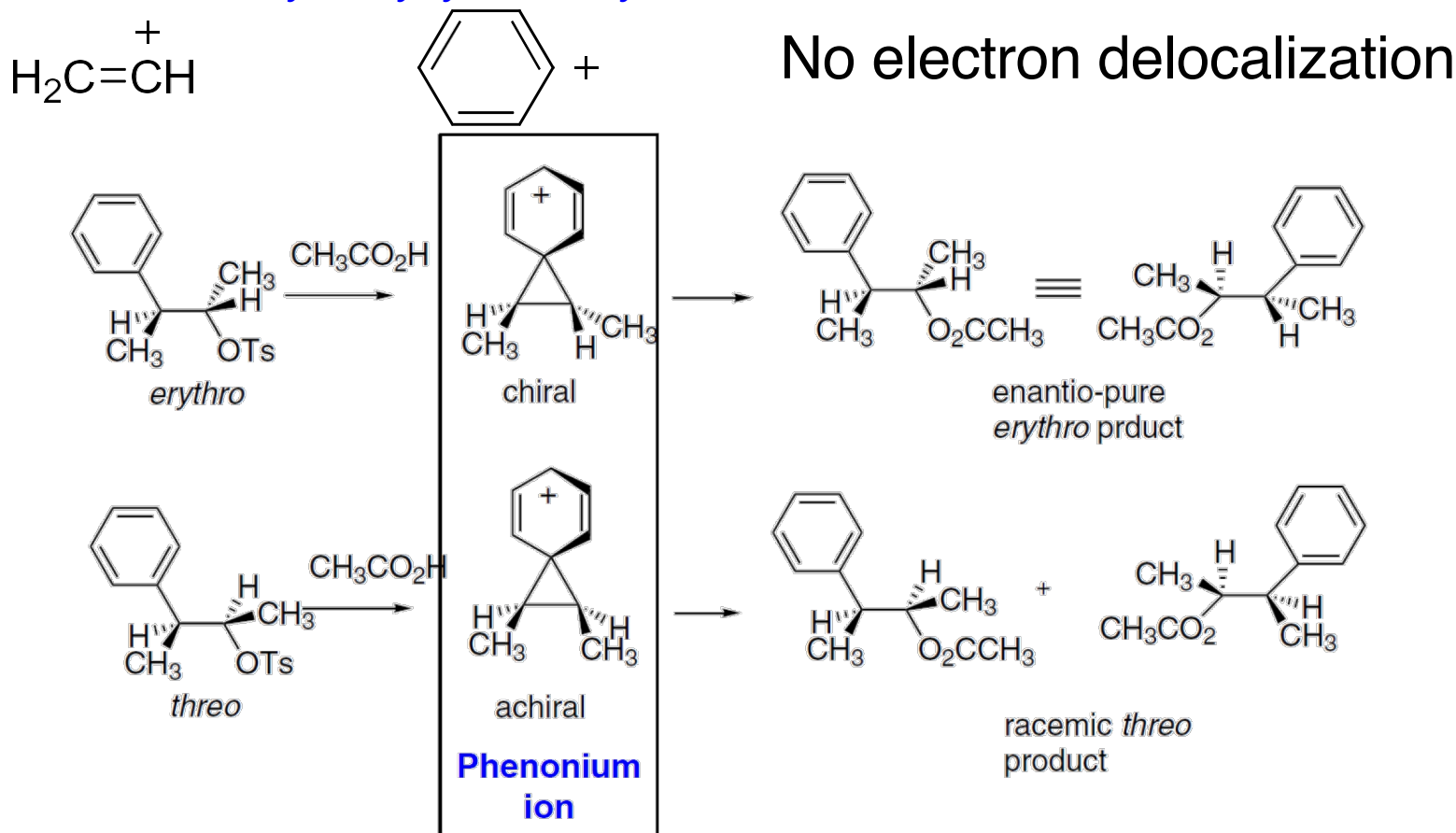
When Z-alkenylsilane reacts, the newly generated p orbital is trans-coplanar with C-Si and has the greatest degree of hyperconjugation.

Therefore, the reaction rates of E- and Z-configured substrates are very different!

Overman, *Tetrahedron Lett.* **1984**, 25, 5739.

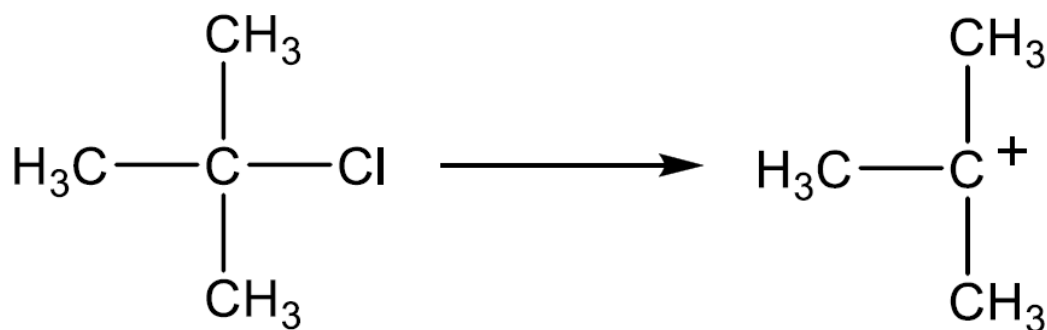
Aromatic Carbocations

Note: Alkenyl, alkynyl, and aryl carbocations are unstable!

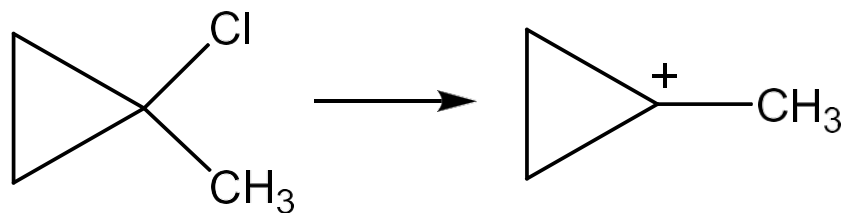


A computed structure of phenonium ion. The distance to C1 from C7 and C8 is 1.625 Å, while C7 and C8 bond length is 1.426 Å.

In tert-butane chloride, tension occurs because the size of the chlorine atom brings the three methyl groups close to each other.

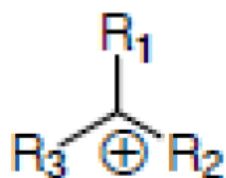


When a carbocation intermediate is generated, the tension of the intermediate is reduced so the reaction speed is fast.



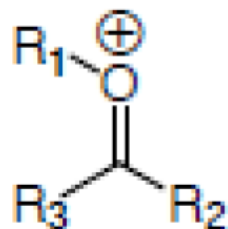
The tension of the intermediate increases so the reaction speed is slow.

Carbon-substituted

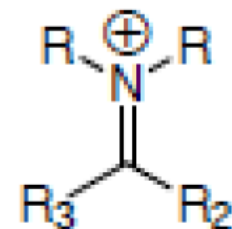


$R-R_3$ = alkyl or aryl

Heteroatom-stabilized



$R-R_3$ = alkyl or aryl



$R-R_3$ = alkyl or aryl

The following discussion will focus on carbocations unsubstituted with heteroatoms

Classical vs nonclassical carbonium ions



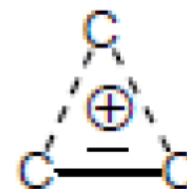
open
trivalent



hyperconjugation
no bridging



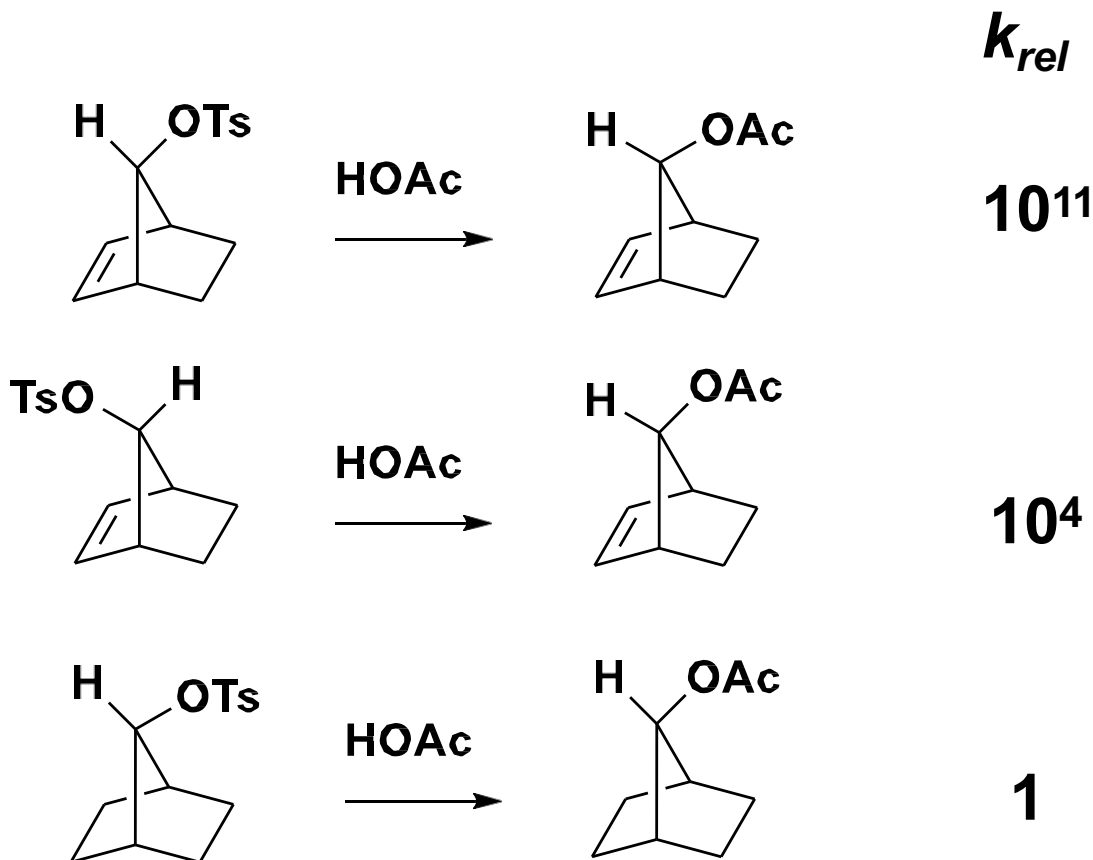
unsymmetrical
bridging



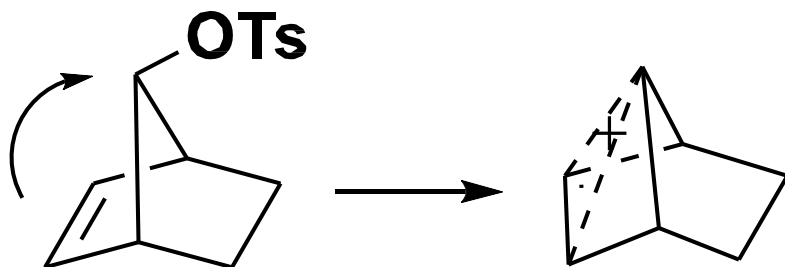
symmetrical
bridging

classical increasing nonclassical character → nonclassical

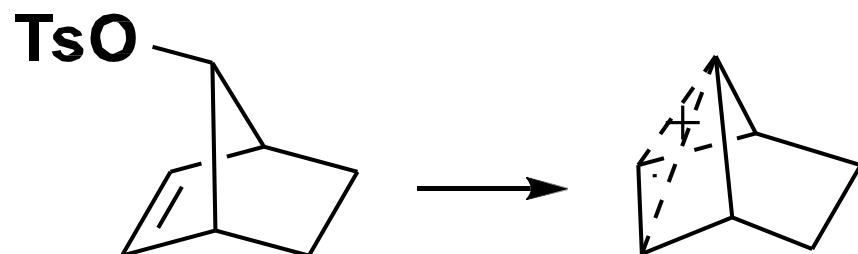
- Example: comparing the rates of acetylation



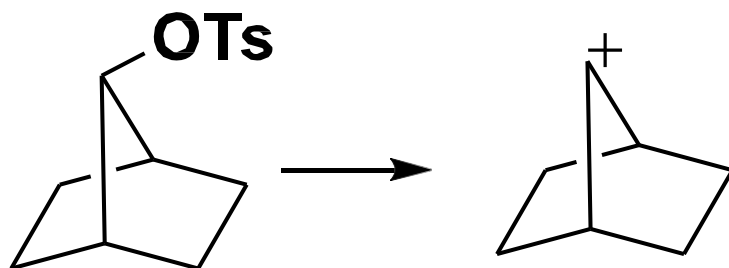
Group discussion: Why?



Quick S_N2
Reaction



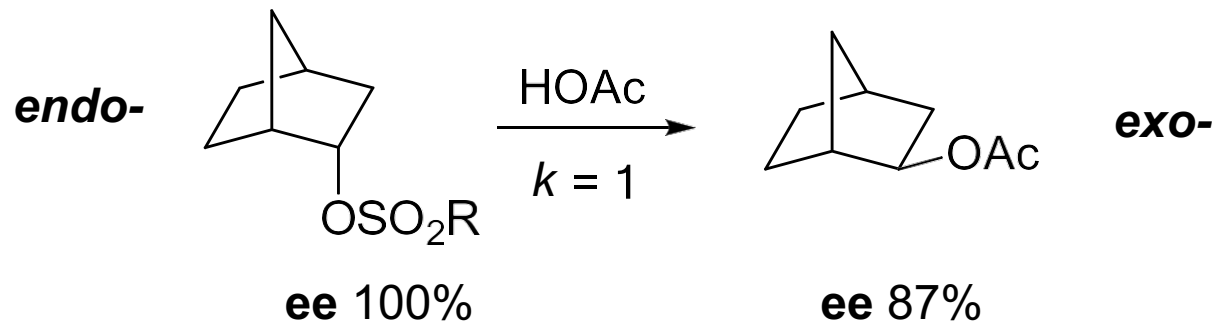
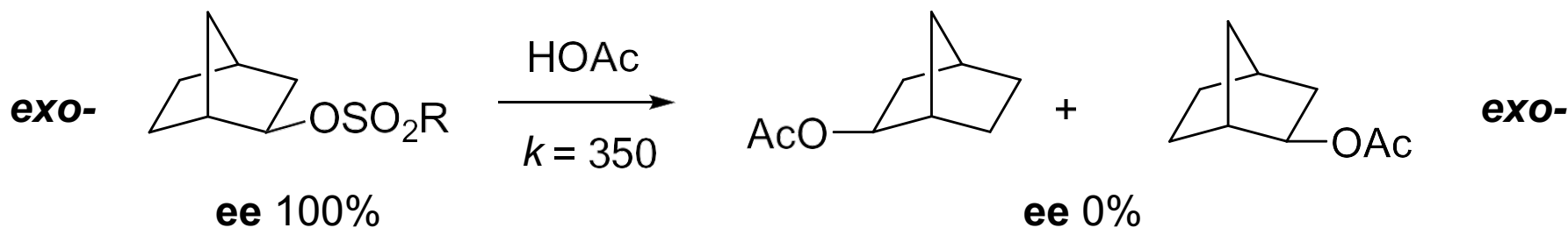
S_N1 Reaction
2e-3c carbocation
intermediate



S_N1 Reaction
normal carbocation
intermediate

Neighboring-Group Participation

- Solvolysis reaction of protobornyl ester



Result

1. *exo/endo* all produced *exo*
2. *exo* produced **ee 0%**
3. *endo* produced decreased **ee**

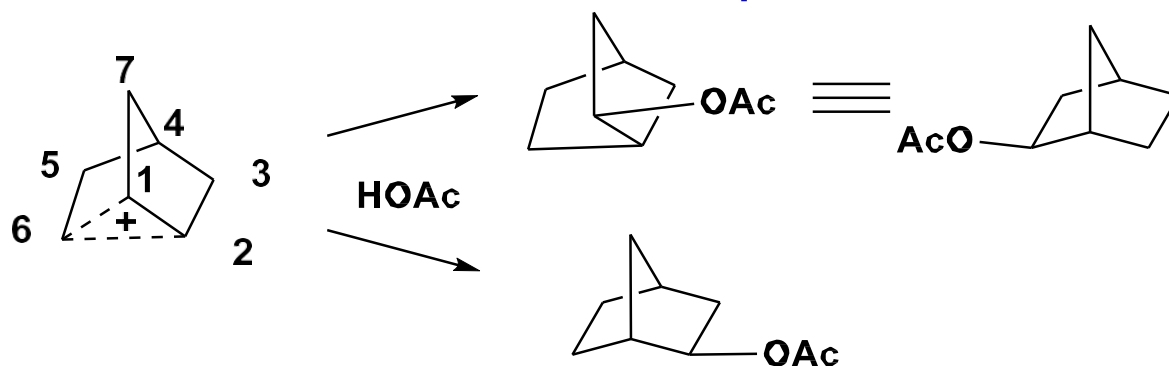
Group Discussion
Why?



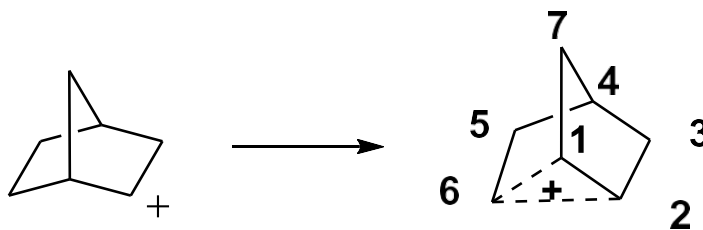
Saul Winstein

1,6- σ Rearrangement

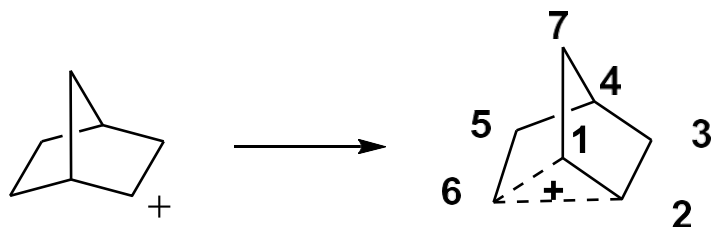
- The exo-isomer may participate in the leaving group through the 1,6- σ bond and form a non-classical positive ion intermediate.



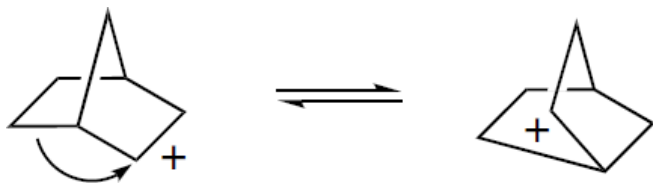
- Because the endo isomer initially forms a classical carbocation, the solvent can only attack C2 from the outside during the short period of time before it rearranges into a non-classical cation to obtain an exo product of one configuration. The weaker the nucleophilicity of the solvent, the greater the proportion of racemization. Since the attack of nucleophiles is slow, the number of racemates generated by rearranged non-classical positive ions will increase.



S. Winstein hypothesized that there are non-classical carbocation intermediates

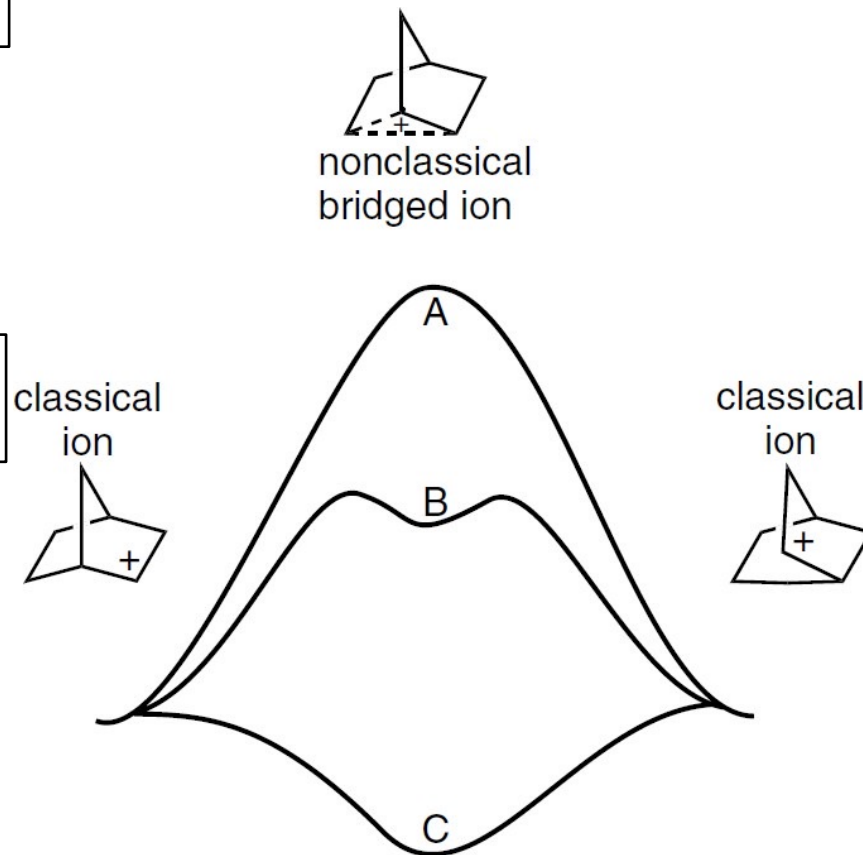


H. C. Brown hypothesized it is equilibrium. Non-classical carbocation is a transition state



"That man is nothing but a shyster lawyer."

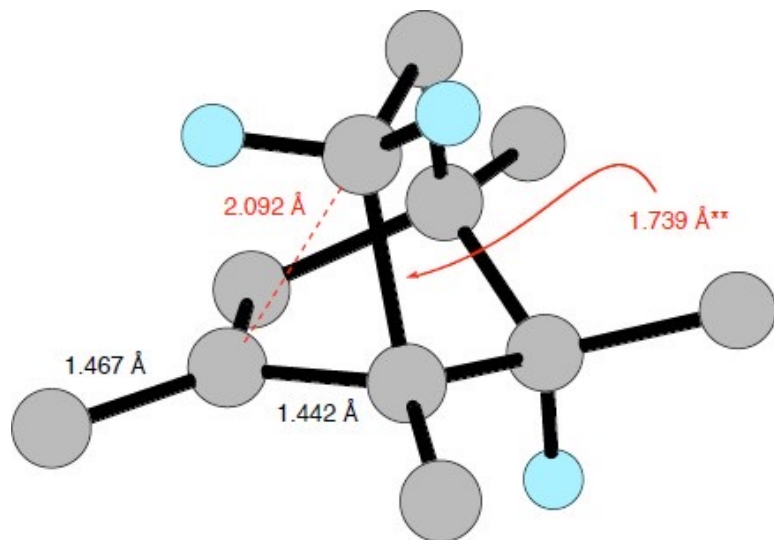
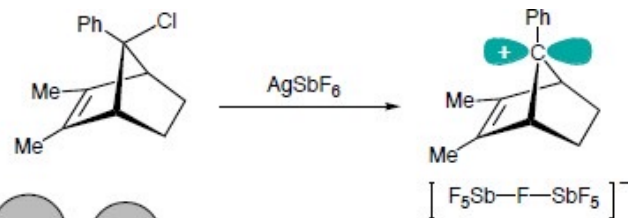
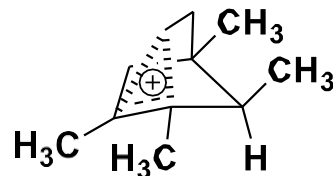
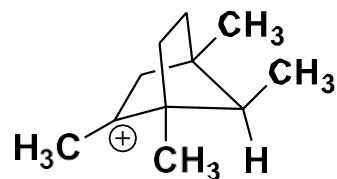
Saul Winstein in reference to H. C. Brown
September, 1969



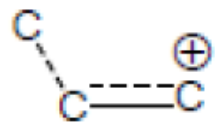
A: Transition State

B: Metastable Intermediate

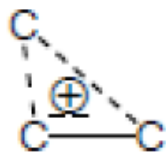
C: Stable Intermediate



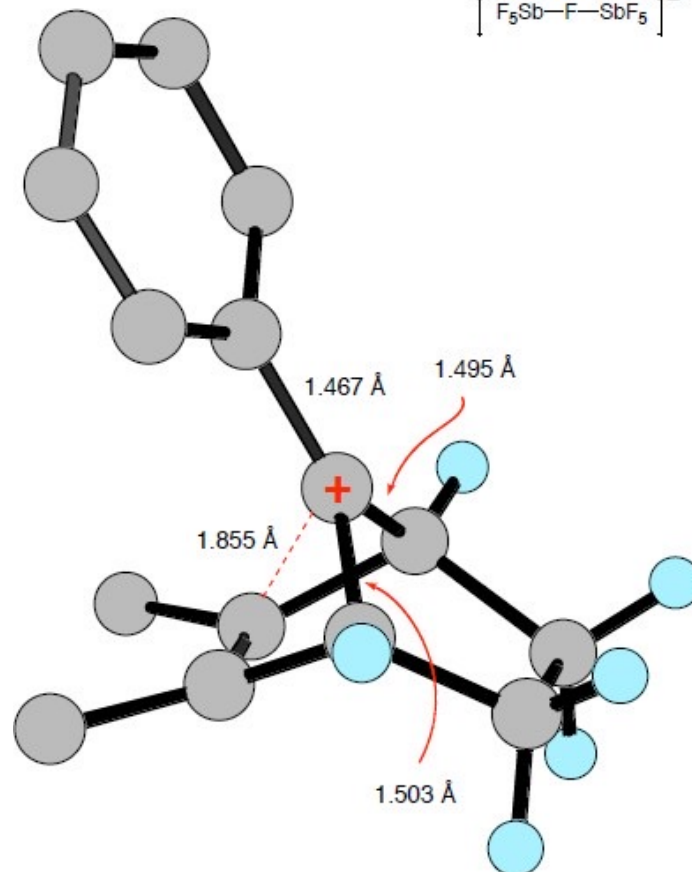
**One of the longest documented C-C bond lengths.



hyperconjugation
no bridging

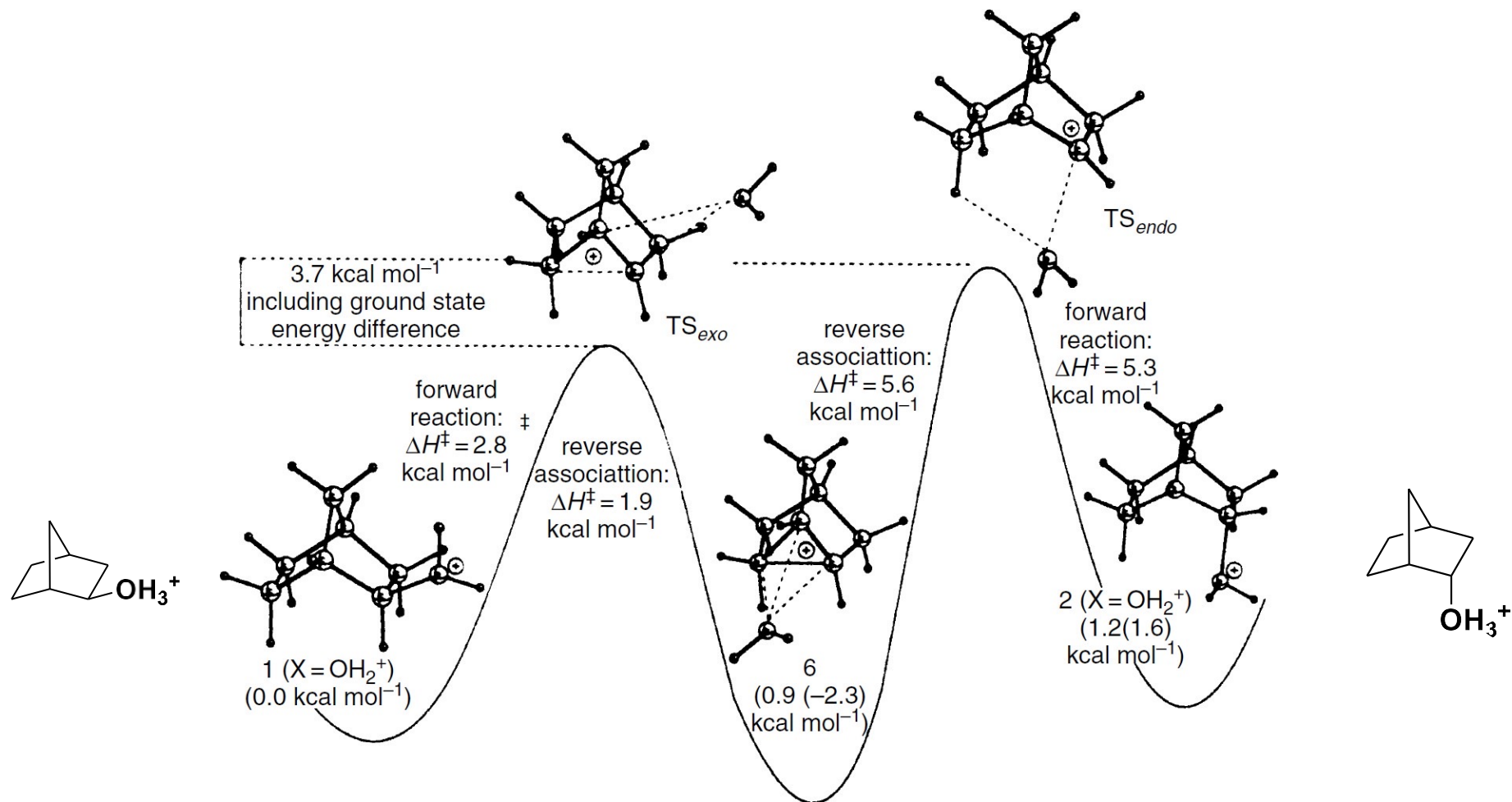


unsymmetrical
bridging

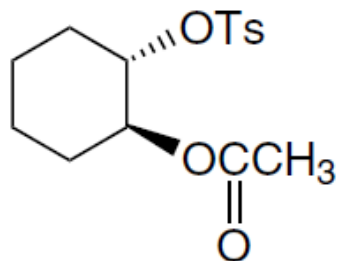


Energy Landscape of 2-Norbornanol

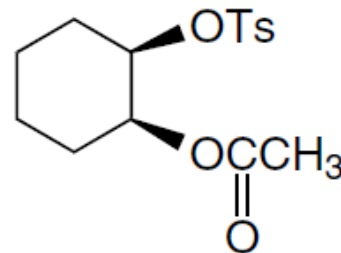
Computational energy diagram for intermediates and transition states in ionization and rearrangement of protonated 2-norbornanol



Reaction Kinetics

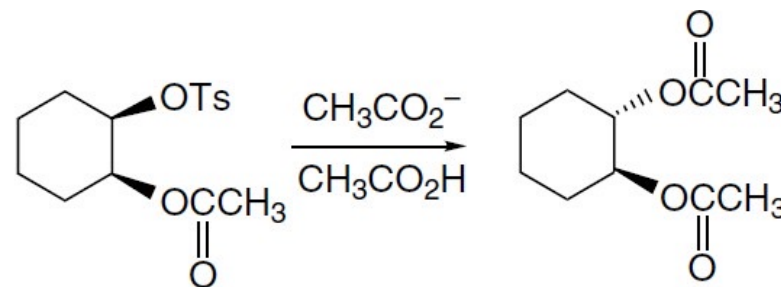
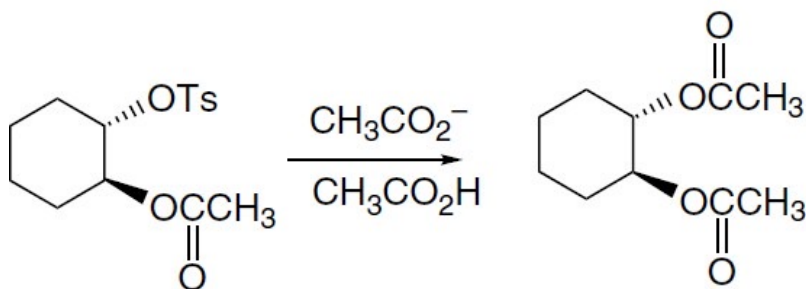


$$k = 1.9 \times 10^{-4} \text{ s}^{-1} (100^\circ \text{ C})$$

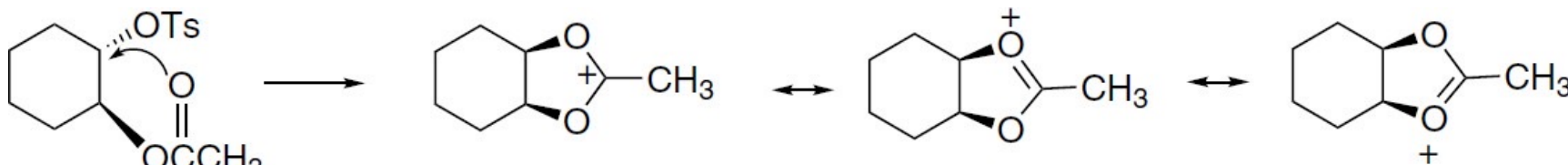


$$k = 2.9 \times 10^{-7} \text{ s}^{-1} (100^\circ \text{ C})$$

Stereoselective Product



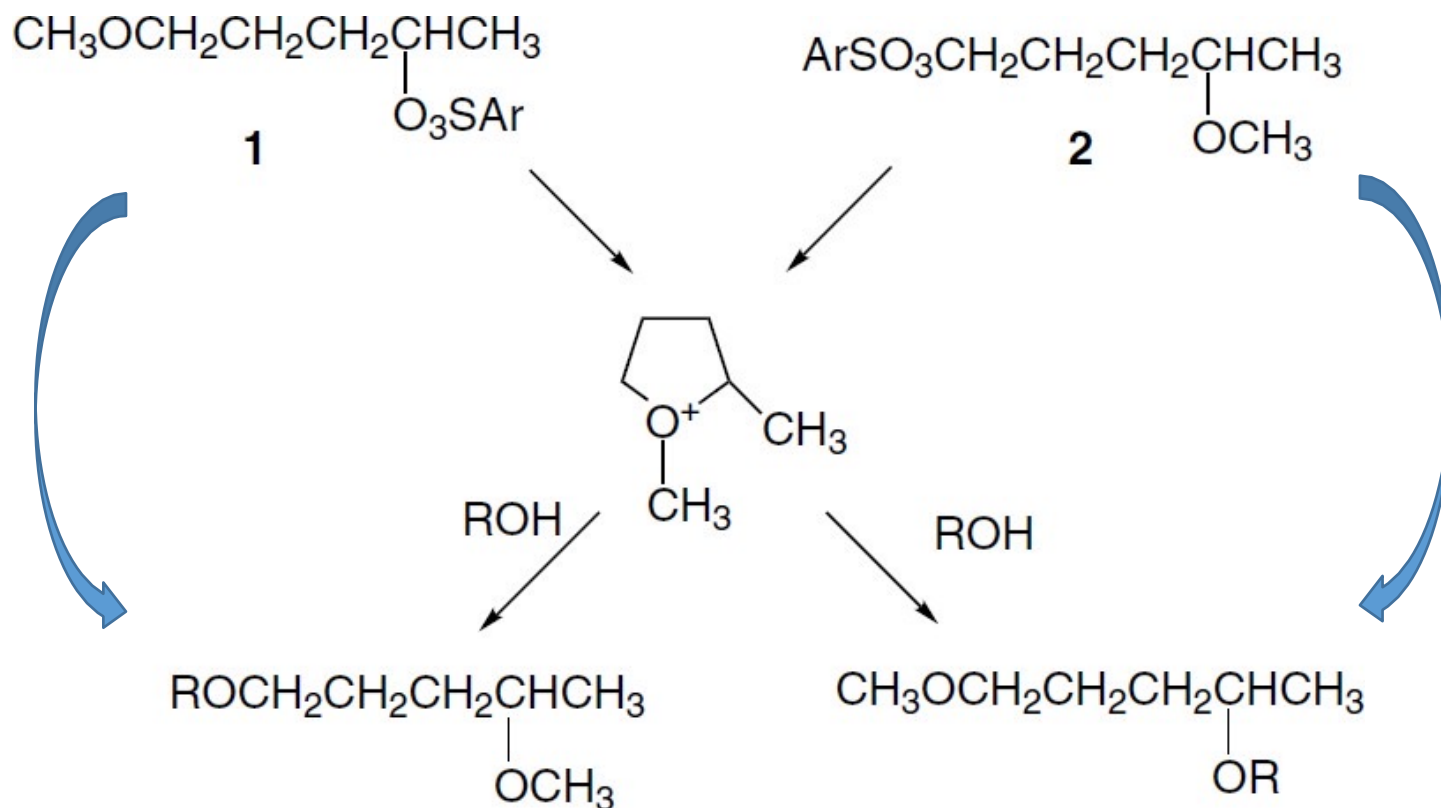
Mechanism? Group Discussion



Winstein, *J. Am. Chem. Soc.* **1948**, 70, 816.

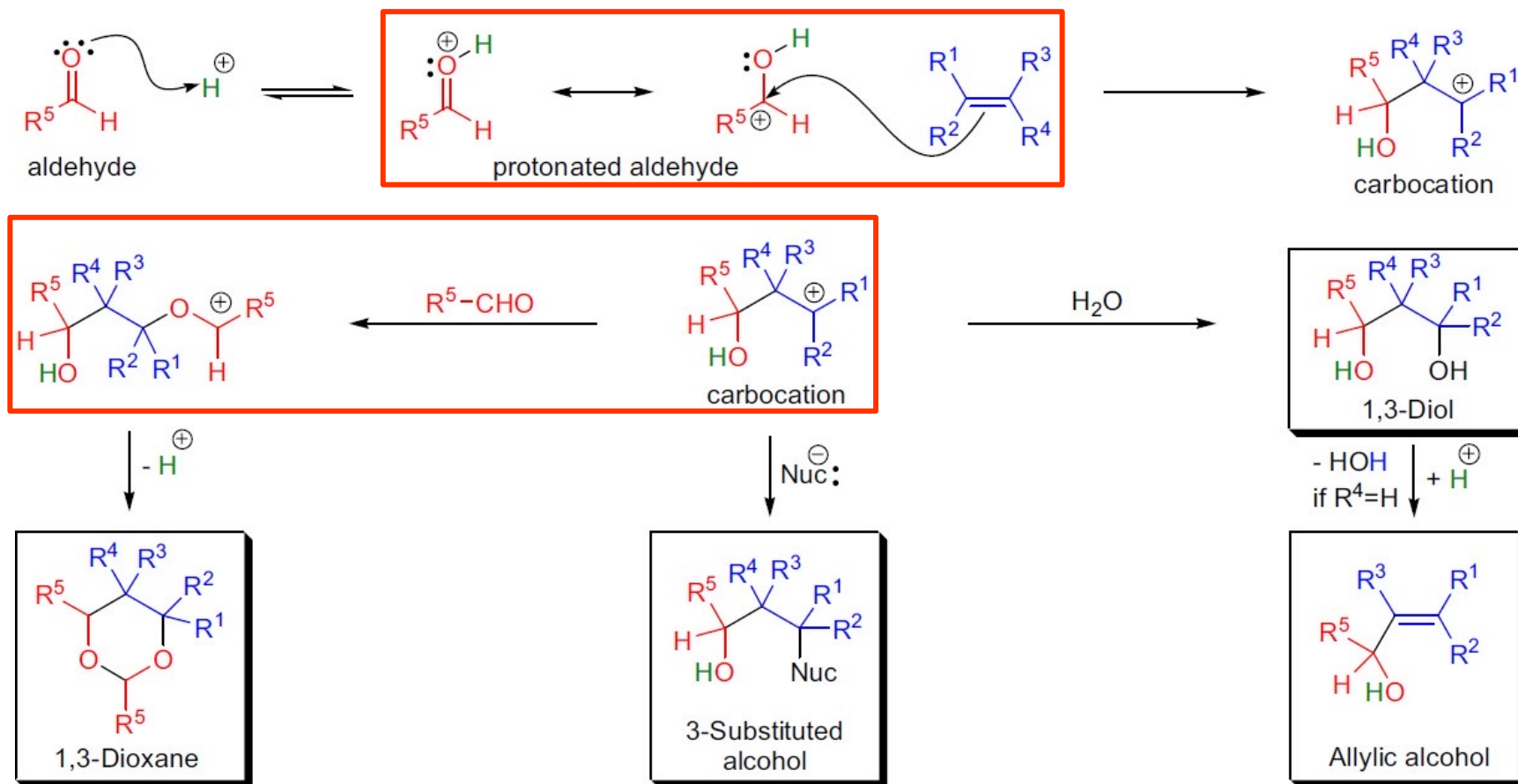
Distal Neighboring-Group

- Distal (alkoxy) group undergoes ortho group participation
- (Different reactants, same product; reaction accelerated)



Forming energetic favorable ring intermediate

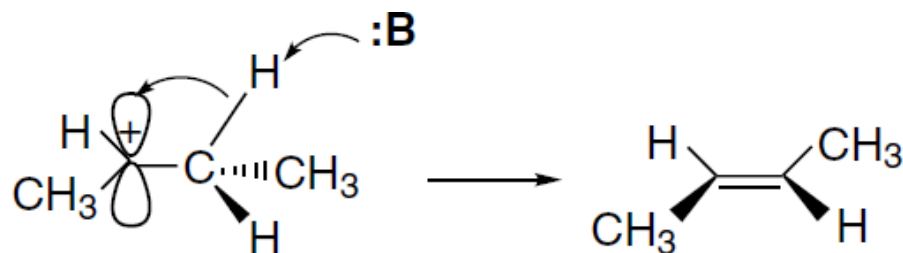
The Prins Reaction



Adams, Bhaynagar, *Synthesis* **1977**, 661.

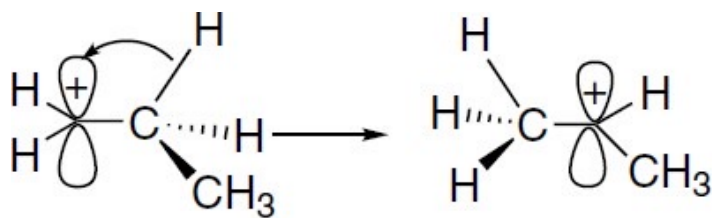
Kürti, Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, pp 364-365

Eliminate deprotonation (E1 reaction)

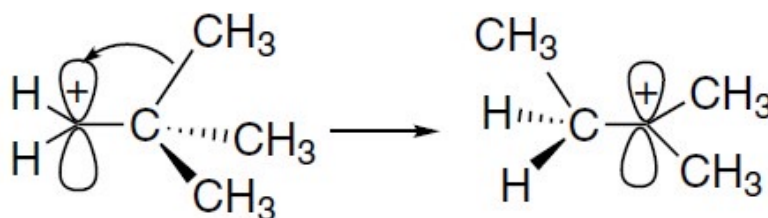


Proton removal leads to alkene formation

Rearrangement to more stable carbocations

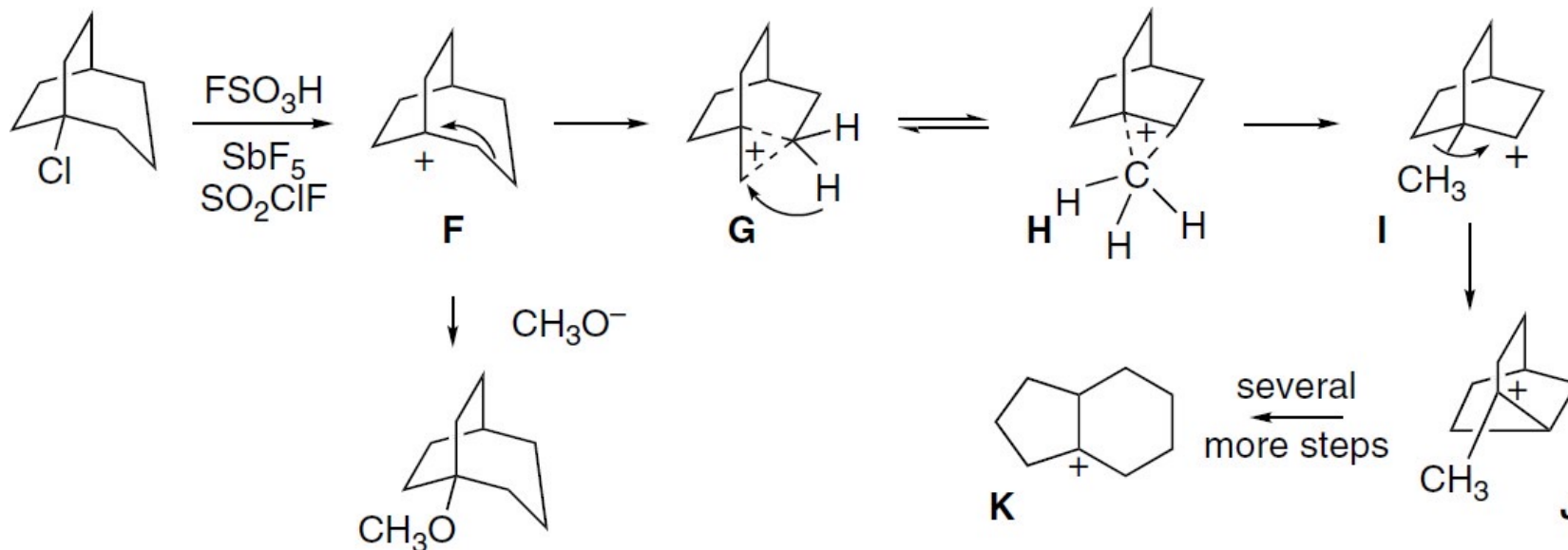
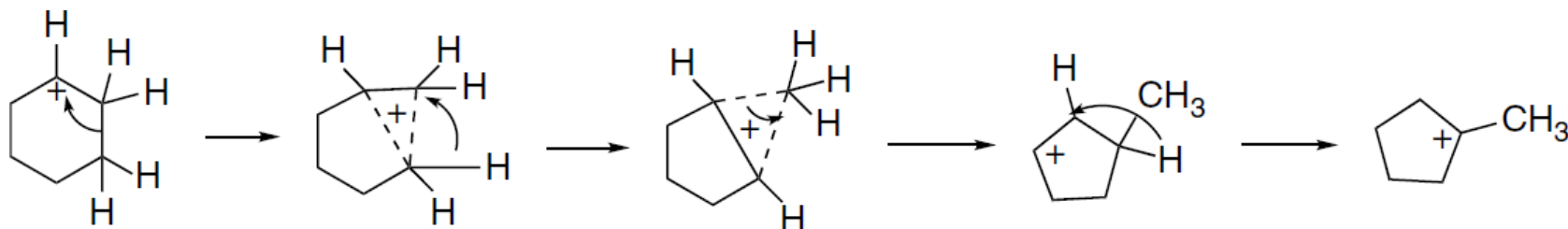


1-propyl cation rearranges to
2-propyl cation by hydride shift



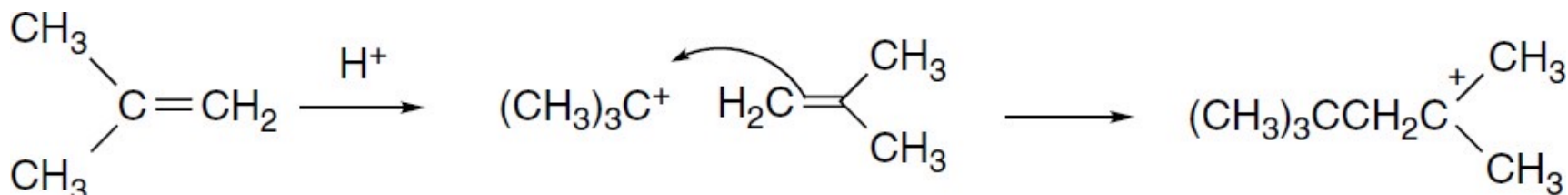
neopentyl cation rearranges to
t-pentyl cation by methyl shift

Rearrangement of Carboncations

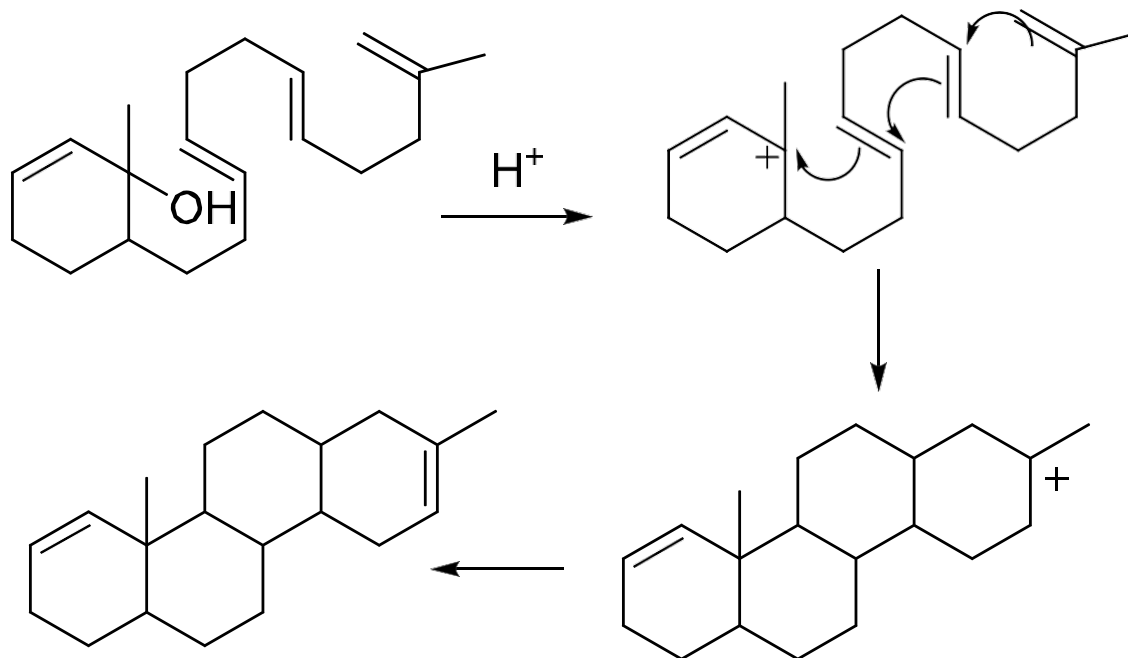


Thermodynamics: Rearrangement

Kinetics: S_N1 Substitution



Important reactions in petroleum catalytic reforming

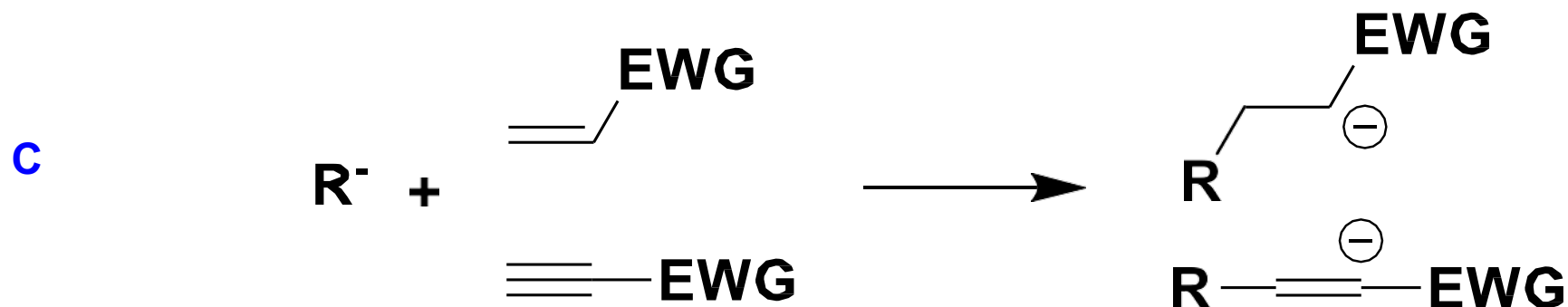


Biosynthesis and biomimetic synthesis

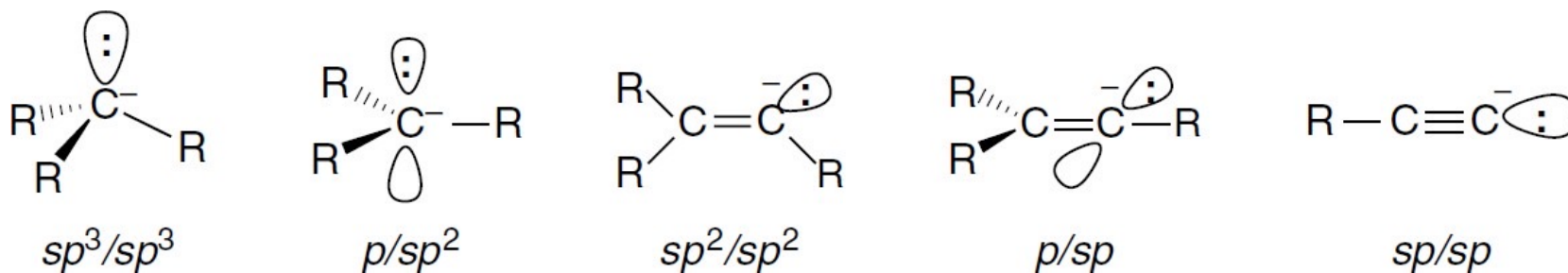
How to Get Carbanions?



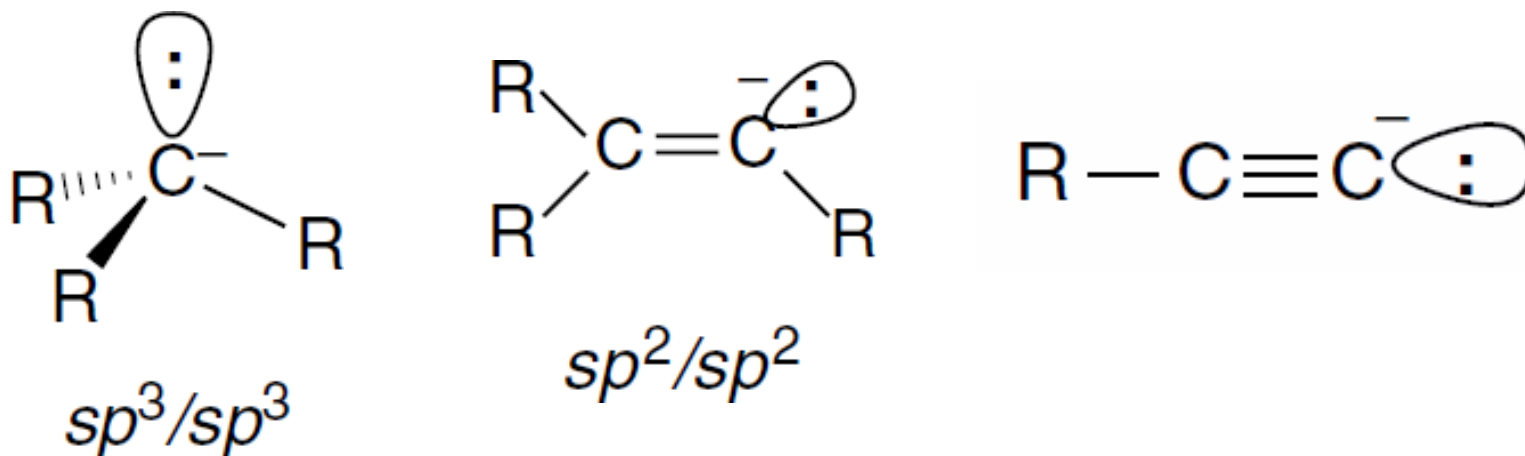
Metal = Li, Mg, etc



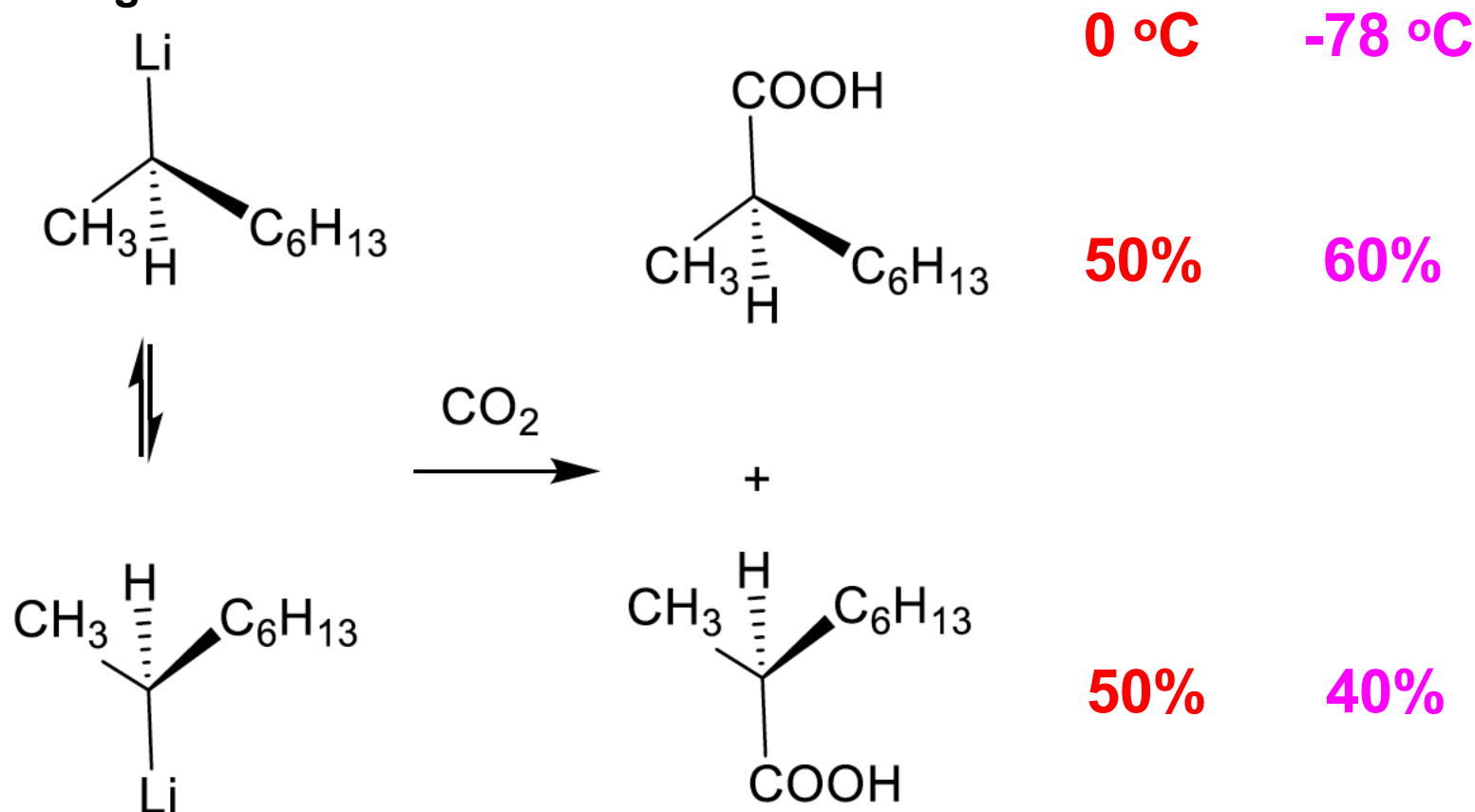
Five possible structures of carbanions:



Energetically favorable carbanions:

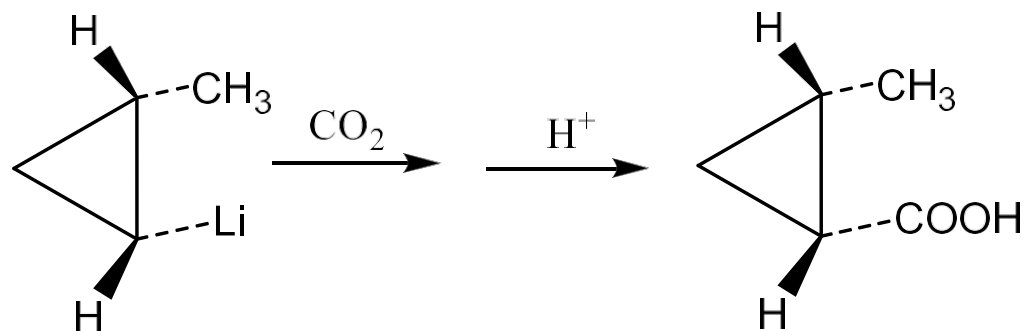


Starting material

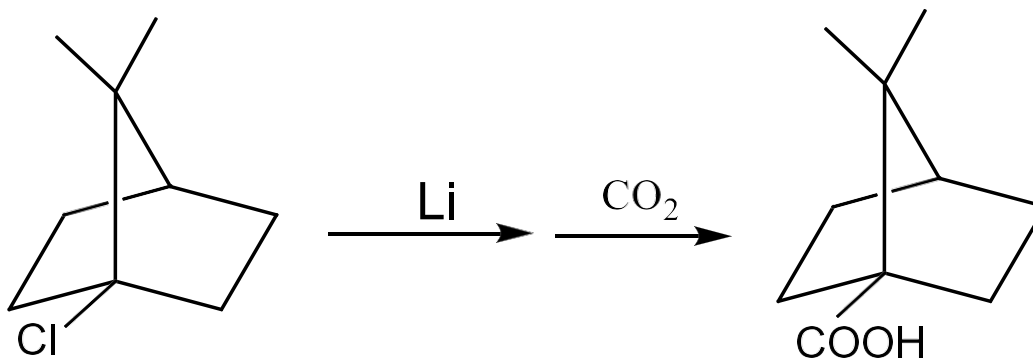


The reaction results can be explained by rapidly flipping pyramidal carbanion intermediates

Due to the increased flipping energy barrier of the three-membered ring carbanion, the configuration-maintained product is obtained.



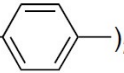
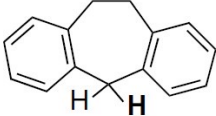
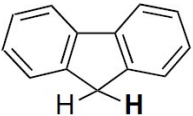
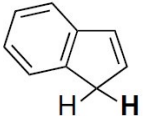
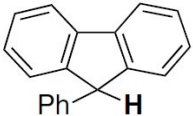
Unlike carbocations, bridgehead carbanions are easily formed



Stability of Carbanions

The stronger the acidity of the conjugate acid, the more stable the carbanion.

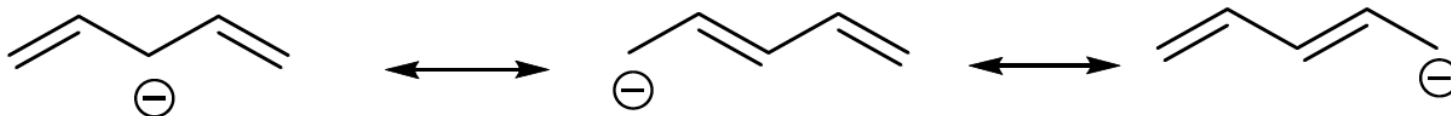
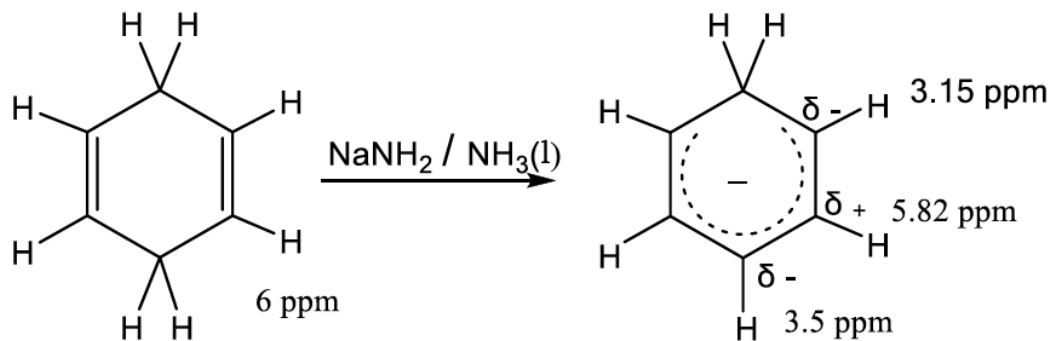
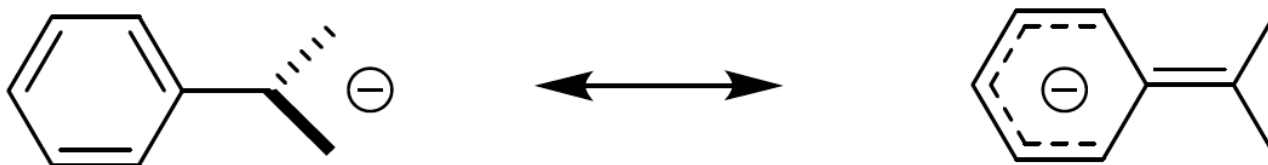
Conjugation
delocalization
effect
increases
carbanion
stability

Entry	Hydrocarbon	Cs ⁺ (CHA) ^a	Cs ⁺ (THF) ^b	K ⁺ (DMSO) ^c
1	PhCH ₂ —H	41.2	40.9	43
2	(CH ₃ —  —) ₂ CH—H	35.1	33.1	
3	(Ph) ₂ CH—H	33.4	33.3	32.3
4	(Ph) ₃ C—H	31.4	31.3	30.6
5		31.2		
6		22.7	22.9	22.6
7		19.9		20.1
8		18.5	18.2	17.9
9		16.6		18.1

Resonance of Benzyl

Influenced by
Aromaticity

- Carbanions connected to the π system can delocalize and stabilize negative charges.





Carbanions Stabilized by EWGs



Compound	p <i>K</i>
CH ₃ NO ₂	17.2
CH ₃ COPh	24.7
CH ₃ COCH ₃	26.5
CH ₃ SO ₂ Ph	29.0
CH ₃ CO ₂ C ₂ H ₅	30.5 ^b
CH ₃ SO ₂ CH ₃	31.1
CH ₃ CN	31.3
CH ₃ CON(C ₂ H ₅) ₂	34.5 ^b

NO₂ > COPh > COCH₃ > SO₂Ph > SO₂CH₃ > CN > CONEt₂

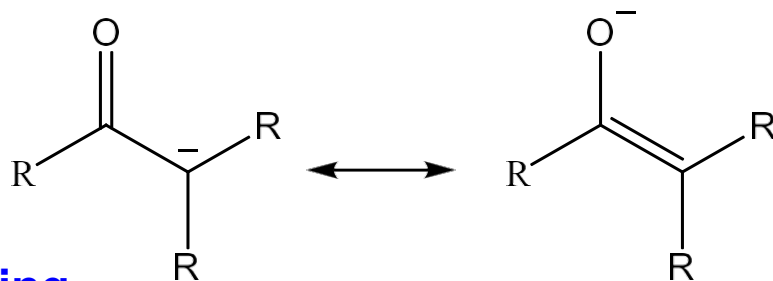


Carbanions Stabilized by EWGs



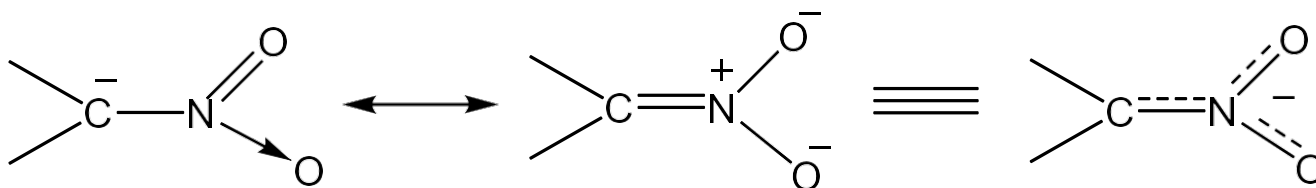
Ketones	pK	Esters	pK
	26.5	$\text{PhCH}_2\text{CO}_2\text{C}_2\text{H}_5$	22.6
	24.7	$\text{PhSCH}_2\text{CO}_2\text{C}_2\text{H}_5$	21.4
	19.9		25.2
	18.7	Ketoesters	
	25.8		14.2
	26.4	Diesters	
	16.95	$\text{CH}_2(\text{CO}_2\text{C}_2\text{H}_5)_2$	16.4
Diketones			7.3
	13.3	Nitroalkanes	
	13.35	CH_3NO_2	17.2
	11.2	PhCH_2NO_2	12.3
			16.0
			17.9

Stabilized by σ and π bonds



Both electron withdrawing

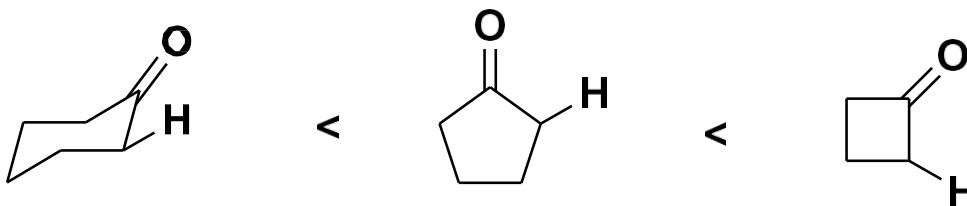
and π -conjugated



C-H acidity : $sp > sp^2 > sp^3$

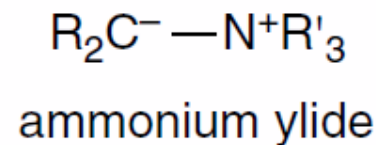
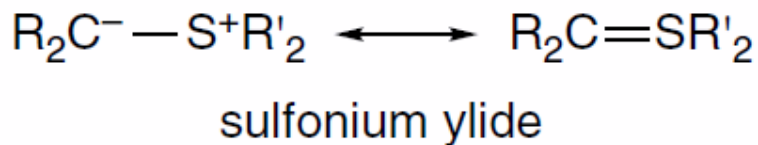
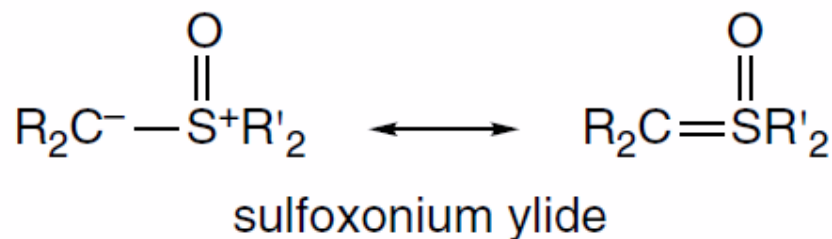
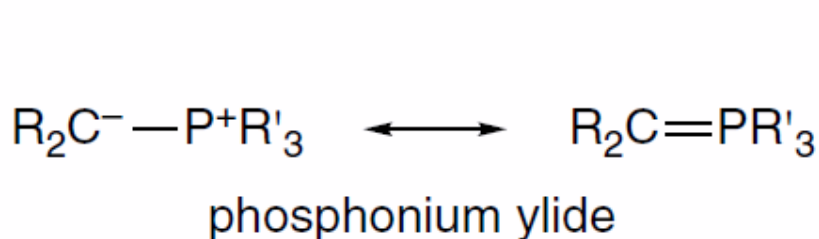
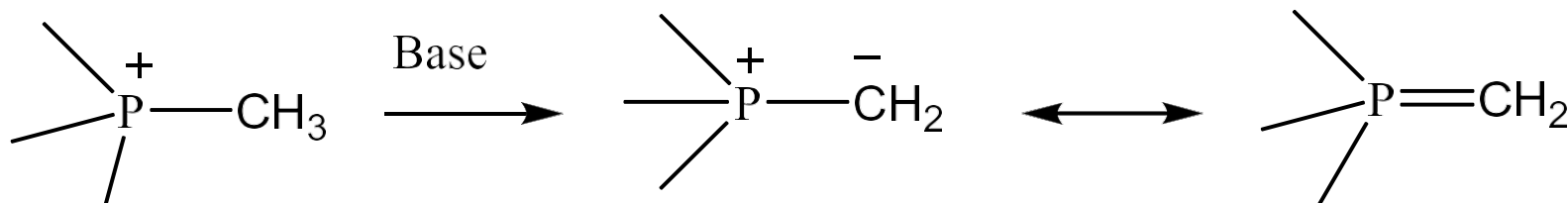
	ethane	ethene	ethyne
pK_a	55	36.5	25

α -H acidity



An ylide is a neutral dipolar molecule containing a formally negatively charged atom (usually a carbanion) directly attached to a heteroatom with a formal positive charge (usually nitrogen, phosphorus or sulfur), and in which both atoms have full octets of electrons.

The result can be viewed as a structure in which two adjacent atoms are connected by both a covalent and an ionic bond; normally written X^+-Y^- . Ylides are thus 1,2-dipolar compounds. They appear in organic chemistry as reagents or reactive intermediates.





Solvent Effect

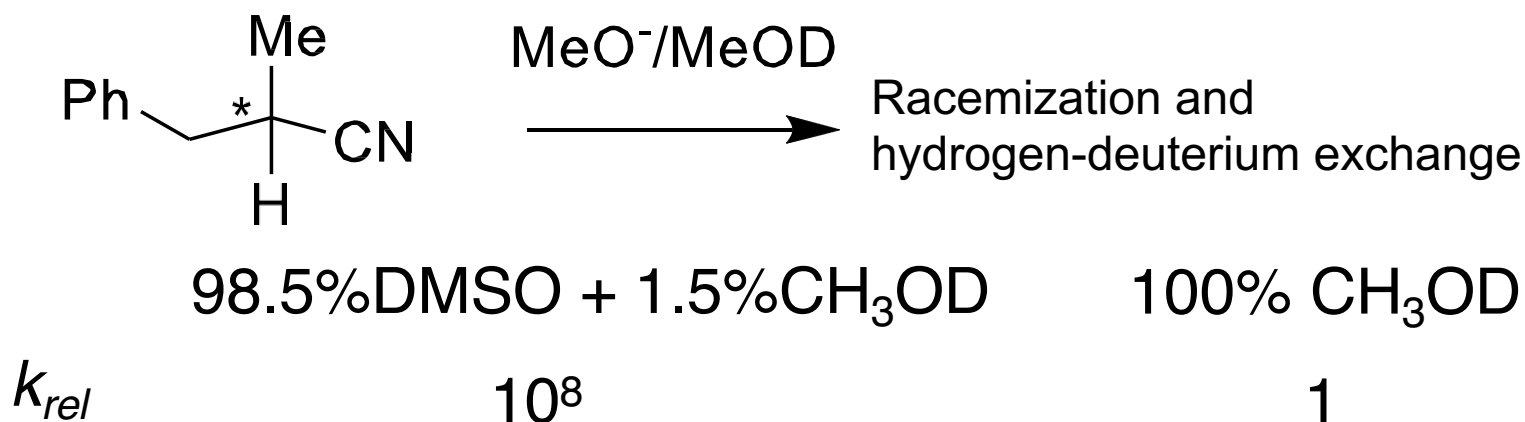


Acidity in gas phase $t\text{-BuOH} > i\text{-PrOH} > \text{EtOH} > \text{H}_2\text{O}$

Acidity in solution $t\text{-BuOH} < i\text{-PrOH} < \text{EtOH} < \text{H}_2\text{O}$

Polar protic solvents: solvate positive ions through the interaction between positive ions and unshared electron pairs, and solvate negative ions through hydrogen bonding.

Polar aprotic solvents can effectively stabilize positive ions but cannot solvate negative ions. **Carbanions are very active in polar aprotic solvents.**

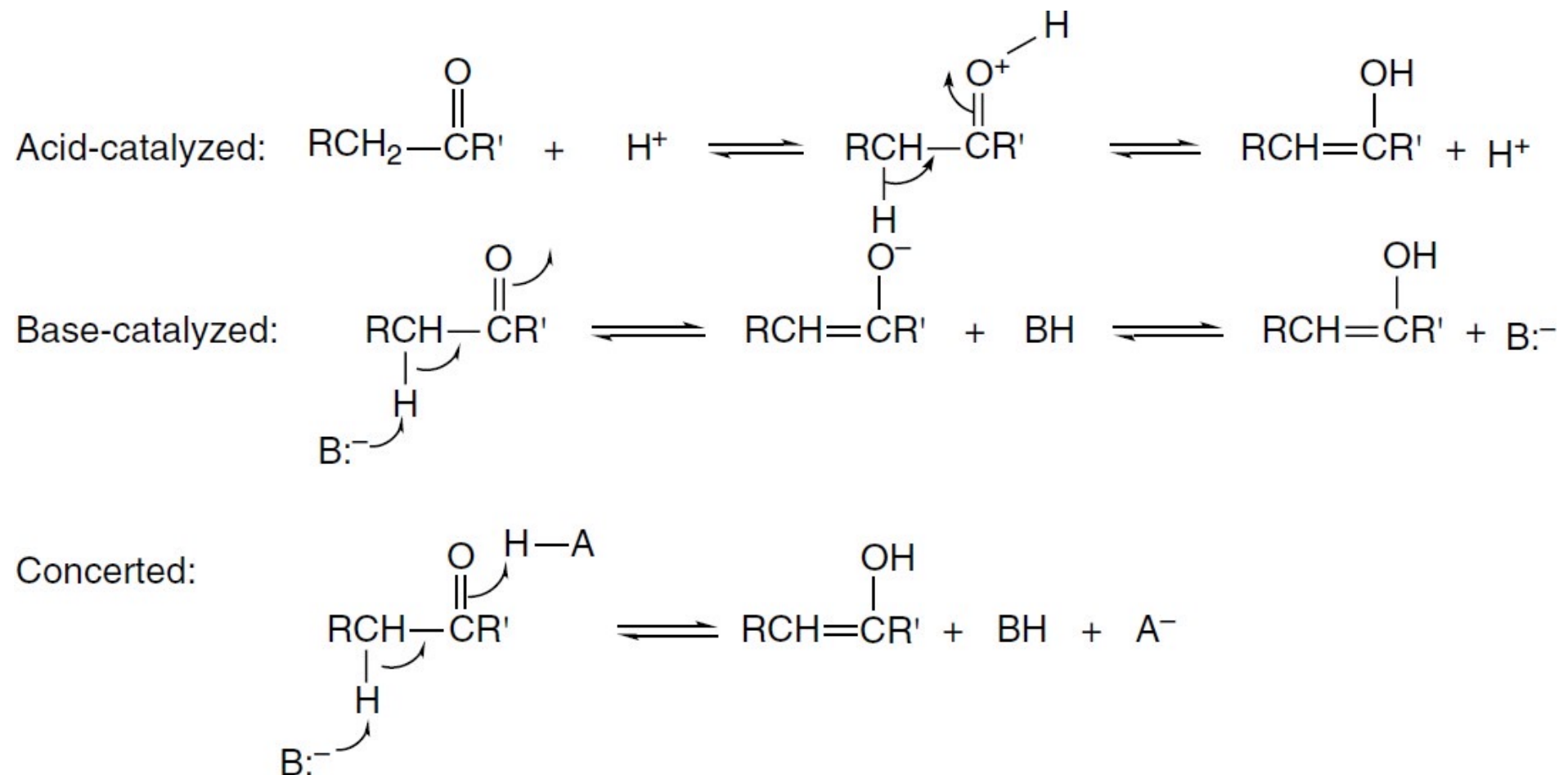




Carbanions for C–C Bond Formation

- Organic reactions using carbanions as intermediates are extremely common and can serve as **nucleophiles** in **substitution** and **addition** reactions.
- Organolithium reagents, Grignard reagents, copper-lithium reagents, etc. are typical carbon negative **nucleophiles** that undergo **substitution** and **addition** reactions.
- In addition to nucleophilic substitution reactions and addition reactions, carbanions with stable functional groups such as **enolates** also undergo **condensation** reactions such as **carbonyl α -position substitution**, **Michael addition**, **aldol condensation**, etc.
- The reactions of carbanions, especially the reactions of **enols** and **enolates**, and the reactions of **enamines** are the most important learning content of organic synthesis.

Keto-Enol Tautomerism



Keto-Enol Equilibrium

Relative rates of **acid**-catalyzed enolization of some ketones

Ketone	Relative rate
$\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{H}$	100
$\text{CH}_3\text{C}(=\text{O})\text{CH}(\text{H})\text{CH}_3$	220
$\text{H}-\text{CH}_2\text{C}(=\text{O})\text{CH}_2\text{CH}_3$	76
$\text{CH}_3\text{C}(=\text{O})\text{CH}(\text{H})\text{CH}_2\text{CH}_3$	171
$\text{CH}_3\text{C}(=\text{O})\text{C}(\text{H})(\text{CH}_3)_2$	195
$\text{H}-\text{CH}_2\text{C}(=\text{O})\text{CH}(\text{H})(\text{CH}_3)_2$	80
$\text{CH}_3\text{C}(=\text{O})\text{CH}(\text{H})\text{C}(\text{CH}_3)_3$	46
$\text{H}-\text{CH}_2\text{C}(=\text{O})\text{CH}_2\text{C}(\text{CH}_3)_3$	105

Prefer to have more substituted enol, by thermodynamically control

Relative rates of **base**-catalyzed enolization of some ketones

Ketone	Relative Rate ^a	E_a^b
$\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{H}$	100	11.9
$\text{CH}_3\text{C}(=\text{O})\text{CH}(\text{H})\text{CH}_3$	41.5	12.1
$\text{H}-\text{CH}_2\text{C}(=\text{O})\text{CH}_2\text{CH}_3$	45	
$\text{CH}_3\text{C}(=\text{O})\text{C}(\text{H})(\text{CH}_3)_2$	<0.1	
$\text{H}-\text{CH}_2\text{C}(=\text{O})\text{CH}(\text{H})(\text{CH}_3)_2$	45	12.3
$\text{CH}_3\text{C}(=\text{O})\text{CH}(\text{H})\text{C}(\text{CH}_3)_3$	0.45	
$\text{H}-\text{CH}_2\text{C}(=\text{O})\text{CH}_2\text{C}(\text{CH}_3)_3$	5.1	

Prefer to have less substituted enol, by kinetically control

Keto-Enol Equilibrium

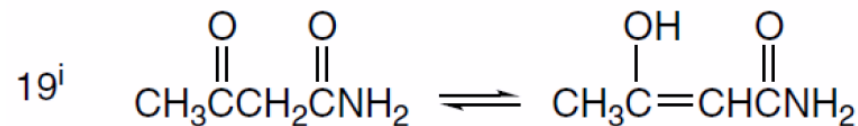
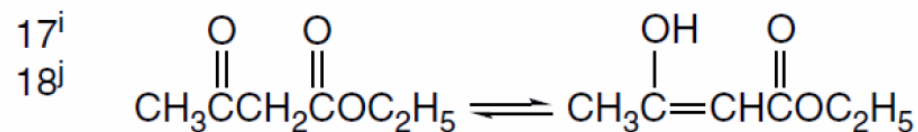
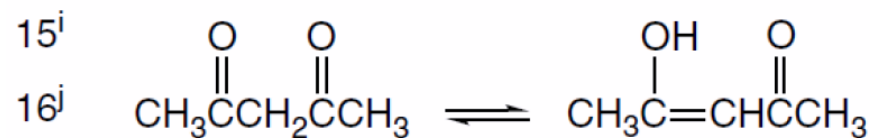
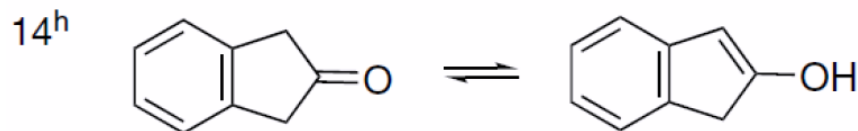
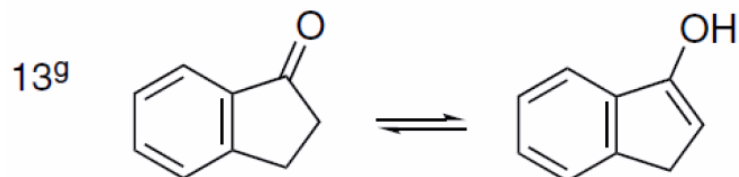
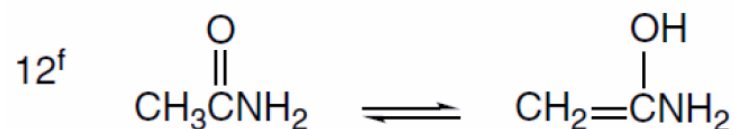
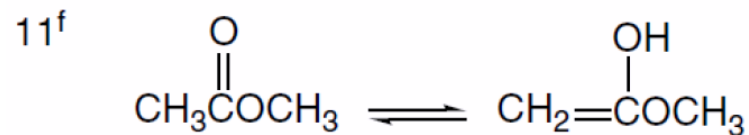
	Enolization equilibrium	$K_{\text{enol/keto}}$
1 ^b	$\text{CH}_3\text{CH}=\text{O} \rightleftharpoons \text{CH}_2=\text{CHOH}$	10^{-5}
2 ^c	$(\text{CH}_3)_2\text{CHCH}=\text{O} \rightleftharpoons (\text{CH}_3)_2\text{C}=\text{CHOH}$	1.4×10^{-4}
3 ^d	$\text{PhCH}_2\text{CH}=\text{O} \rightleftharpoons \text{PhCH}=\text{CHOH}$	8.5×10^{-4}
4 ^e	$\begin{array}{ccc} \text{O} & & \text{OH} \\ & & \\ \text{CH}_3\text{CCH}_3 & \rightleftharpoons & \text{CH}_2=\text{CCH}_3 \end{array}$	1.3×10^{-8}
5 ^e	$\begin{array}{ccc} \text{O} & & \text{OH} \\ & & \\ \text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_3 & \rightleftharpoons & \text{CH}_3\text{CH}=\text{CCH}_2\text{CH}_3 \end{array}$	3.7×10^{-8}
6 ^e	$\begin{array}{ccc} \text{O} & & \text{OH} \\ & & \\ (\text{CH}_3)_2\text{CHCCH}(\text{CH}_3)_2 & \rightleftharpoons & (\text{CH}_3)_2\text{C}=\text{CCH}(\text{CH}_3)_2 \end{array}$	3.0×10^{-8}
7 ^e	$\begin{array}{ccc} \text{O} & & \text{OH} \\ & & \\ \text{PhCCH}_3 & \rightleftharpoons & \text{PhC}=\text{CH}_2 \end{array}$	1.1×10^{-8}
8 ^e	$\begin{array}{ccc} \text{O} & & \text{OH} \\ & & \\ \text{PhCCH}(\text{CH}_3)_2 & \rightleftharpoons & \text{PhC}=\text{C}(\text{CH}_3)_2 \end{array}$	3.3×10^{-7}
9 ^e	$\begin{array}{ccc} \text{O} & & \text{OH} \\ & & \\ \text{Cyclopentanone} & \rightleftharpoons & \text{Cyclopentenol} \end{array}$	1.2×10^{-8}
10 ^e	$\begin{array}{ccc} \text{O} & & \text{OH} \\ & & \\ \text{Cyclohexanone} & \rightleftharpoons & \text{Cyclohexenol} \end{array}$	4.2×10^{-7}

Keto
is
all
preferable

Keto-Enol Equilibrium

$K_{\text{enol/keto}}$

$$3.2 \times 10^{-19}$$



$$2.3 \times 10^{-1} (\text{H}_2\text{O})$$

$$29 (\text{CCl}_4)$$

$$7 \times 10^{-2} (\text{H}_2\text{O})$$

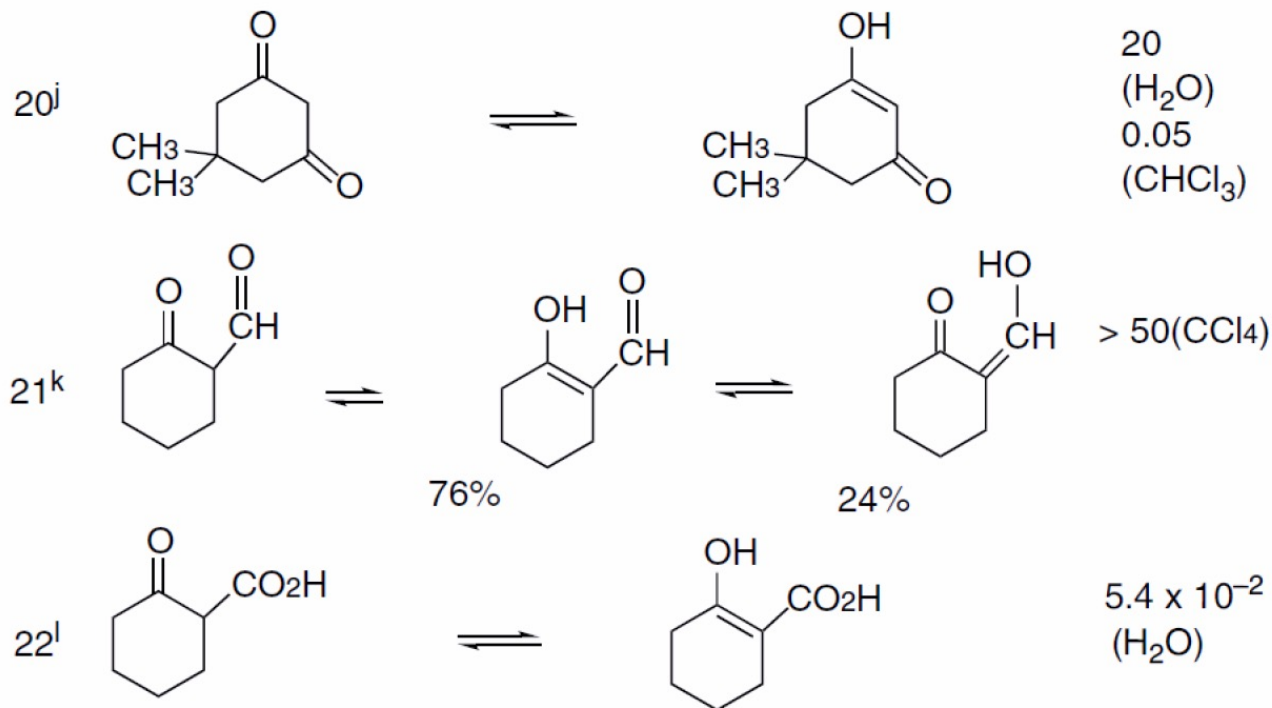
$$3 \times 10^{-1} (\text{CCl}_4)$$

$$1.3$$

$$(\text{H}_2\text{O})$$

Enol
is
preferable

Solvent
effect!

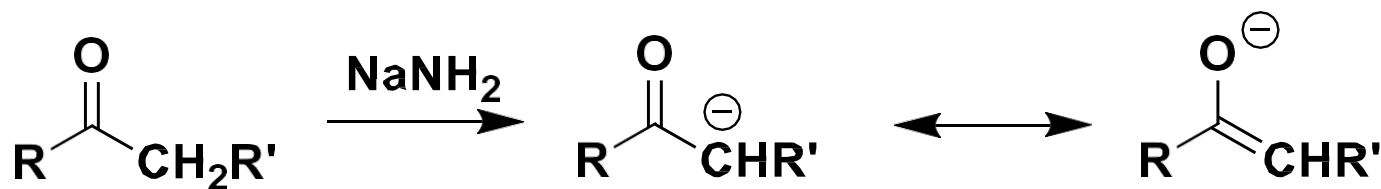


- In water unless otherwise noted.
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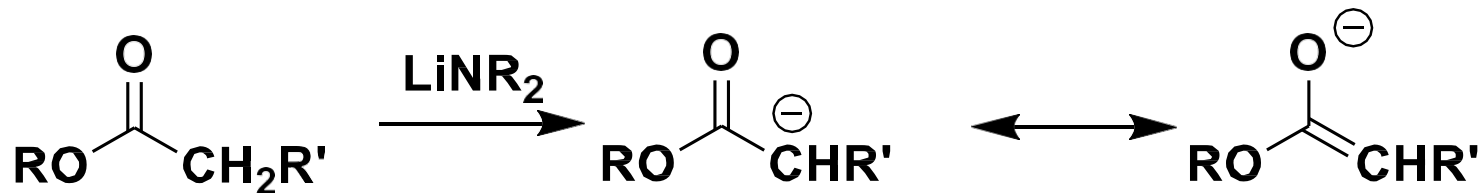
Enol
is
all
preferable

In the presence of a (strong) base, enol is converted into the **enolates** (enol anion). Compounds with different acidic properties require bases of different strengths.

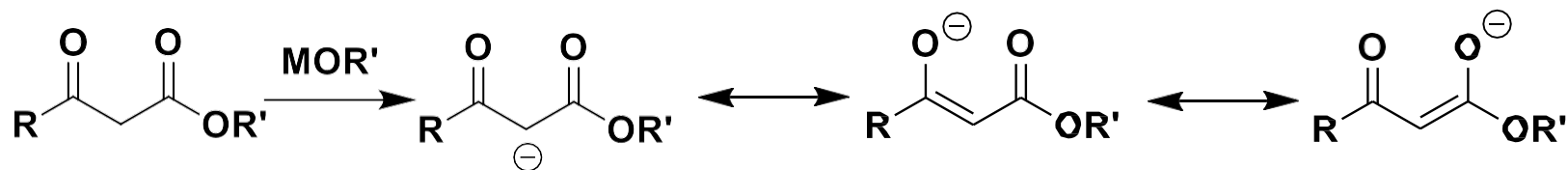
From Ketones



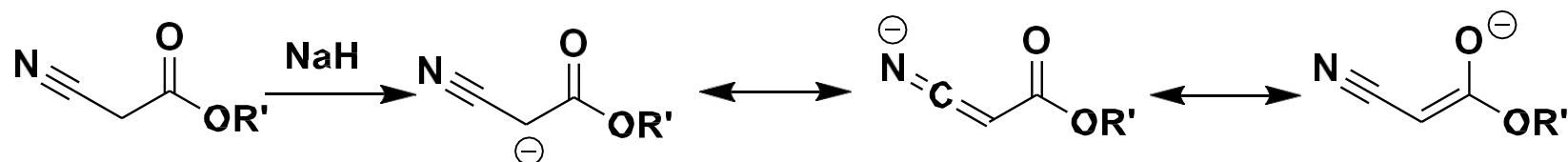
From Esters



From β -carbonyl ester



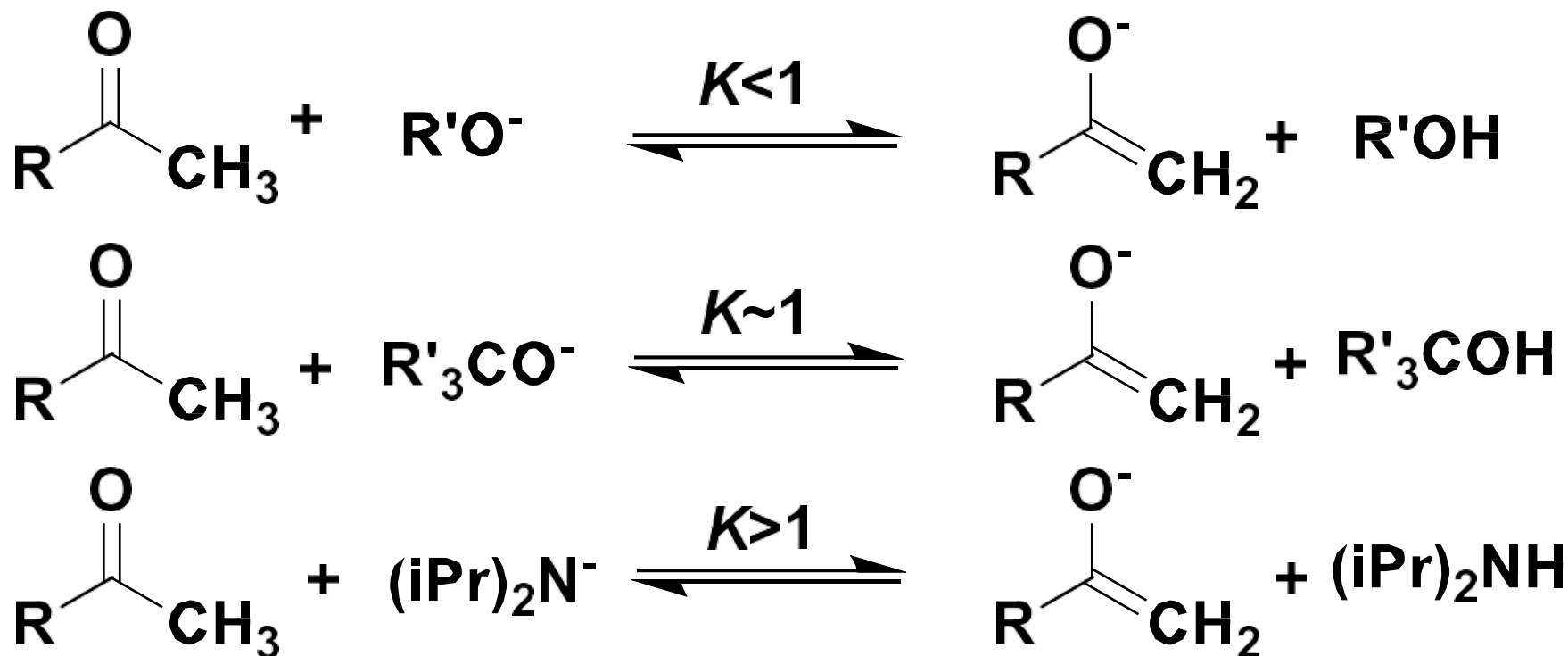
From α -cyanoester



From nitro-substituted compounds

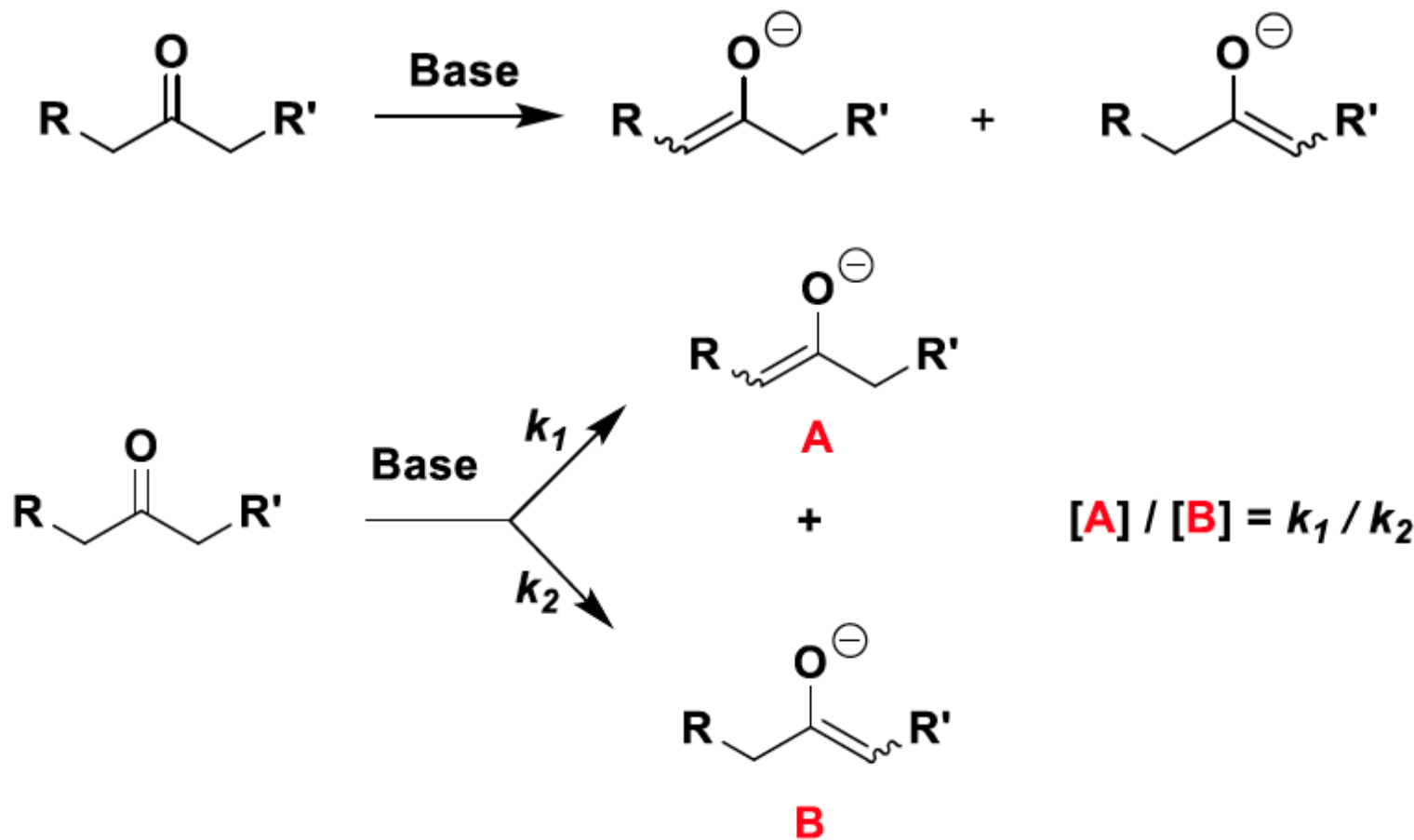


- The equilibrium of carbonyl compounds to form enolates is related to the strength of the base used



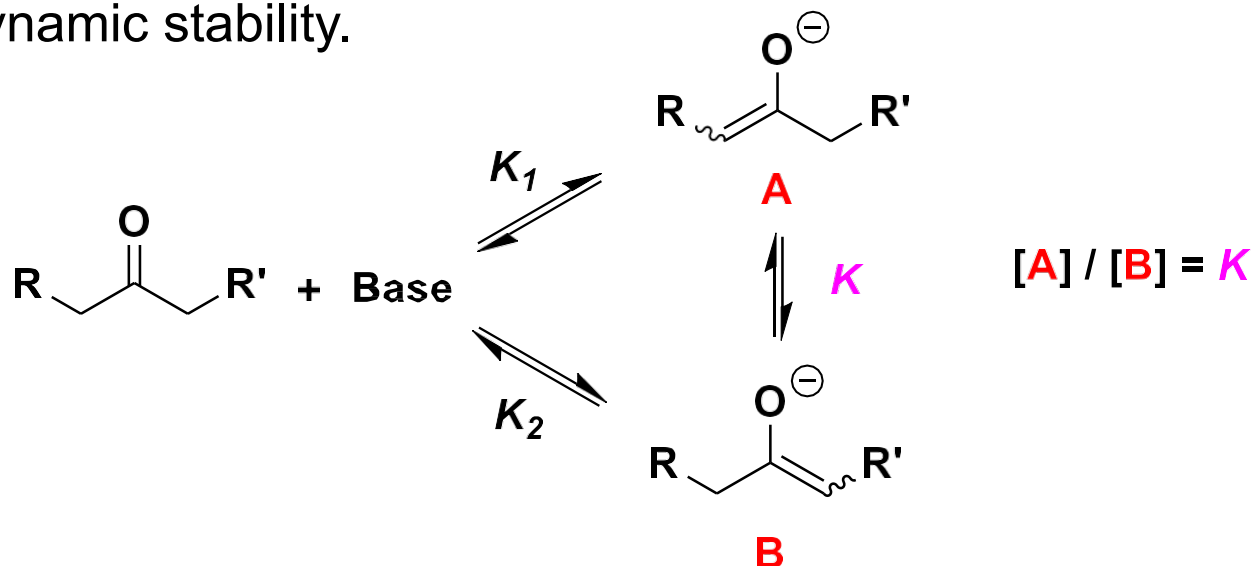
Basicity: $(\text{iPr})_2\text{N}^- > \text{R}'_3\text{CO}^- > \text{R}'\text{O}^-$

Regioselectivity of enol anions from asymmetric ketones



While the composition of the product is controlled by the rate of deprotonation, the ratio of enols of different structures is controlled by kinetics.

- If enol anions A and B can quickly transform into each other, the two will establish an equilibrium, and the ratio of enols is controlled by thermodynamic stability.



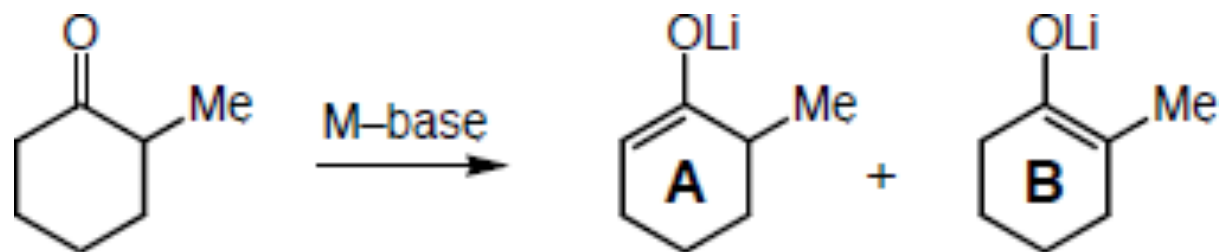
- For kinetic control: strong base, aprotic solvent, low temperature, no excess ketone
- For thermodynamic control: weak base, protic solvent, higher temperature, excess ketone

Example: The protic solvent converts the enolate into enol, making the reaction reversible and conducive to thermodynamical control.

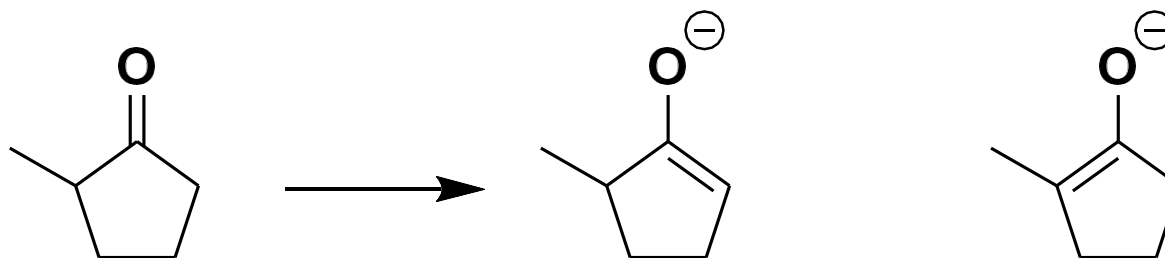
Use LDA or lithium bis(trimethylsilyl)amide $[(\text{CH}_3)_3\text{Si}]_2\text{NLi}$ in an aprotic solvent and without excess ketone is an ideal kinetic control condition.

Li^+ combines more strongly with oxygen anions than Na^+ and K^+ , which reduces the reversibility of the reaction and is conducive to kinetic control.

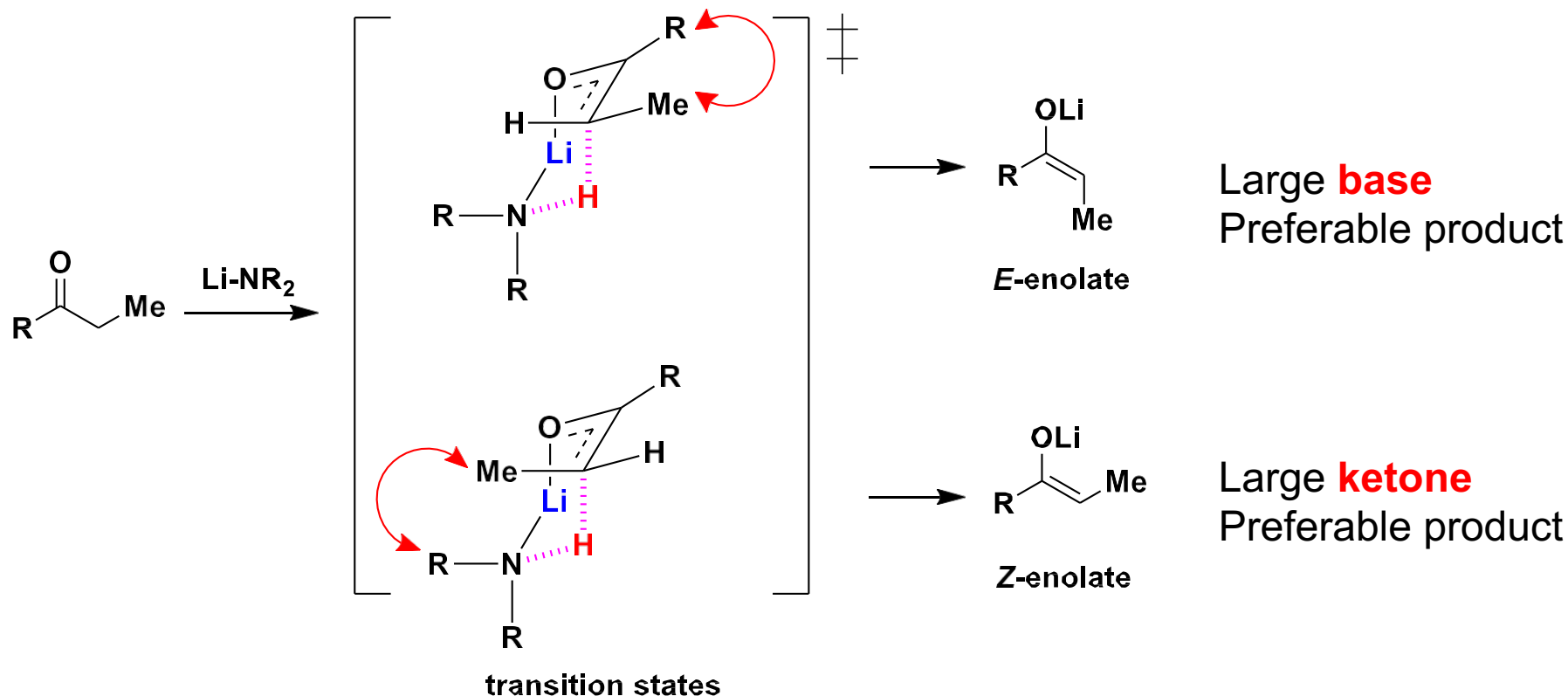
Kinetic vs Thermodynamic



Base	temp	control	Ratio (A:B)
$\text{LiN}(\text{i-Pr})_2$	-78°	kinetic	99:1
$\text{LiN}(\text{SiMe}_3)_2$	-78°	kinetic	95:5
$\text{Ph}_3\text{C-Li}$	-78°	kinetic	90:10
$\text{Ph}_3\text{C-Li}$	heat	thermo	10:90
Na-H	heat	thermo	26:74
K-H	heat	thermo	38:62

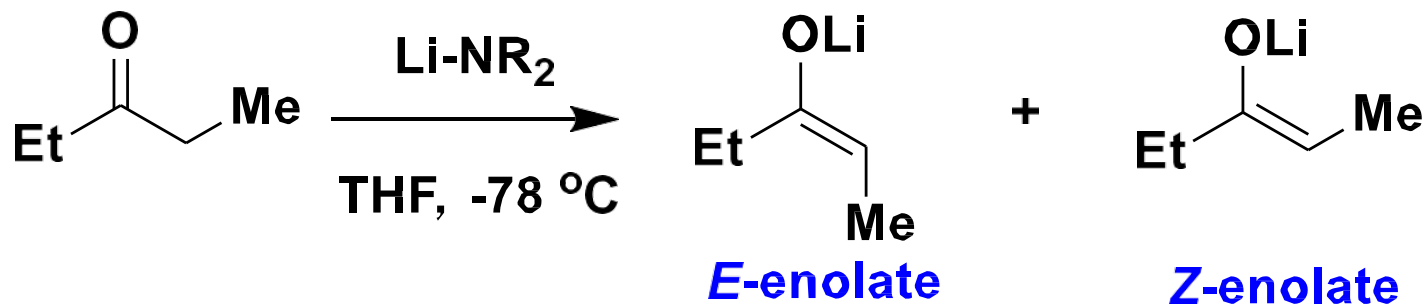


Stereoelectronic effects require removal of hydrogen parallel to the p orbital of the carbonyl group. Does cyclohexanone remove a-bond or e-bond hydrogen?

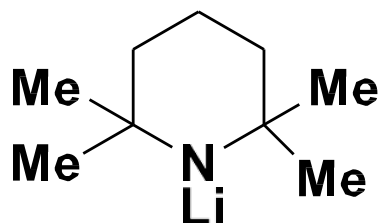


From the structure of the transition state, it should be possible to predict the effect of the R group in the **ketone** and the R group of the **base** on the production of *E*- and *Z*-enolate isomers!

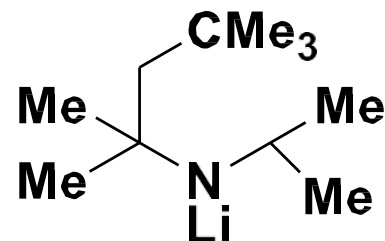
Stereoselectivity in Enolate Intermediate



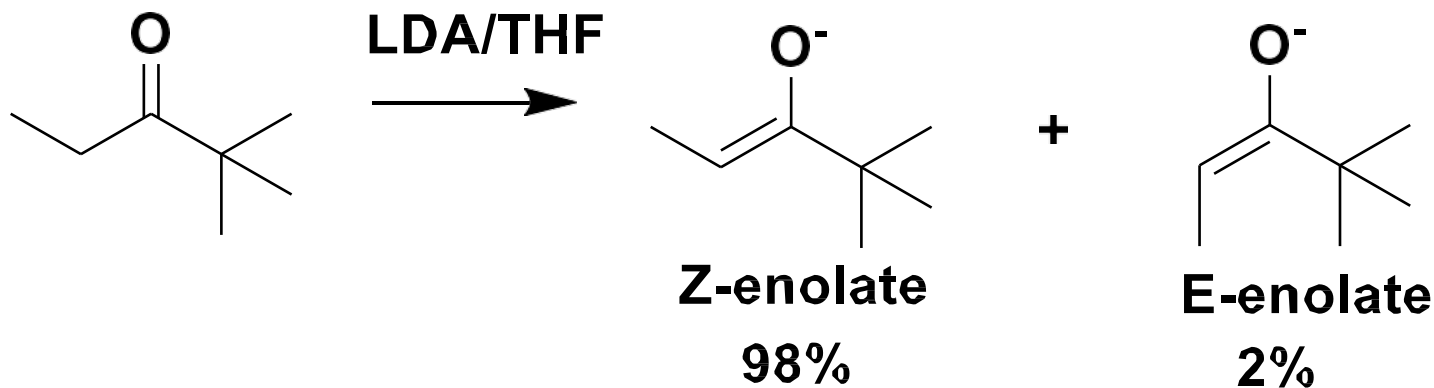
Li-N(i-Pr)₂
(LDA) 77:23



(LiTMP) 86:14

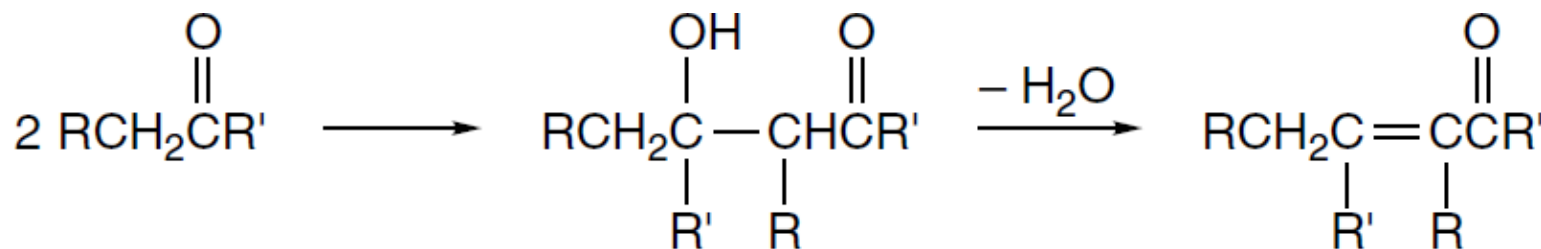


(LOBA) 98:2



Aldol addition

Aldol condensation



$\text{R}' = \text{H}, \text{ alkyl or aryl}$

- Aldol reaction can be **acid**-catalyzed or **base**-catalyzed.
- Under mild conditions such as low temperatures, **aldol adducts** can be obtained, while under severe conditions such as high temperatures, the reaction gives **α,β -unsaturated compounds**.
- The Aldol **addition** reaction is a reversible reaction, while the **condensation** reaction generates α,β -unsaturated compounds, and the stability of the product drives the completion of the reaction.

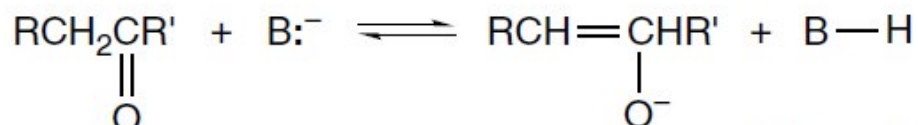


Aldol Reaction Mechanism in Base

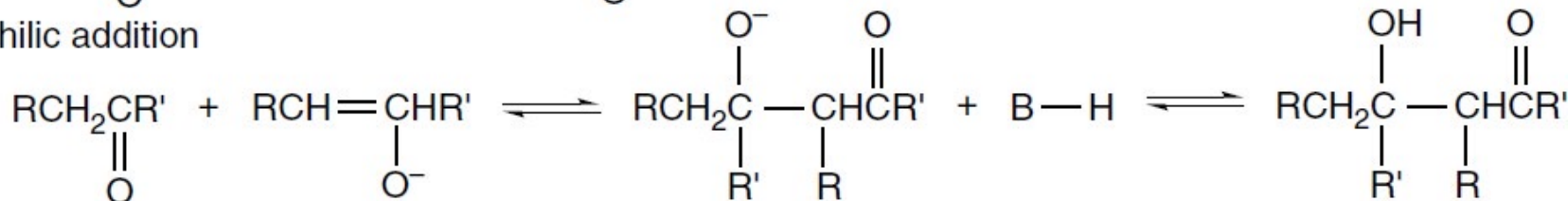


1. Addition phase

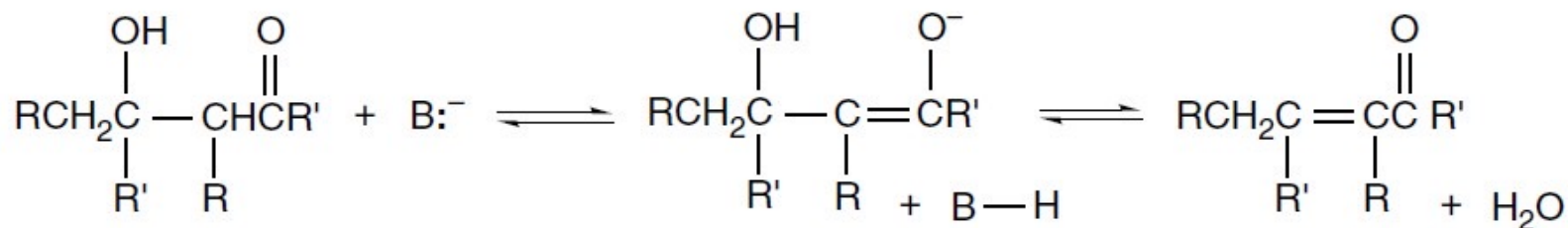
a. Enolate formation



b. Nucleophilic addition

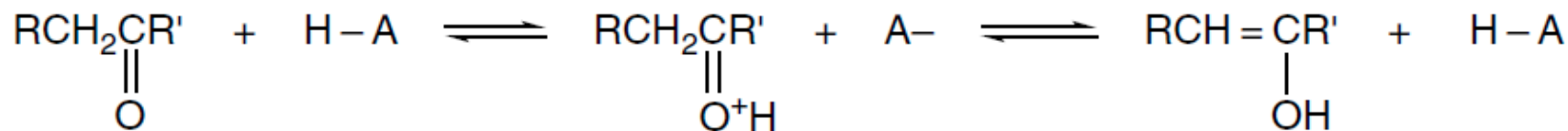


2. Dehydration phase

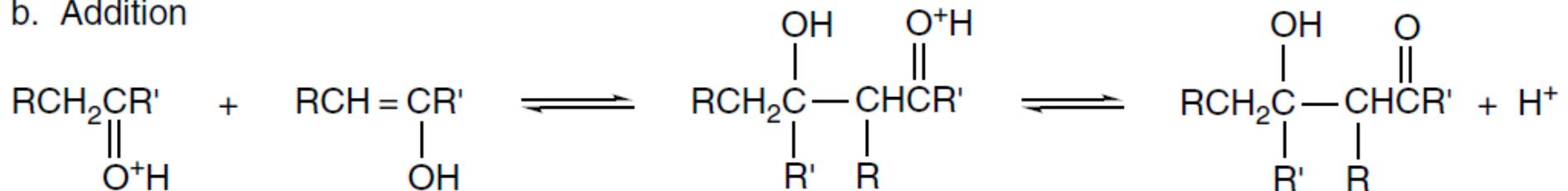


1. Addition phase

a. Enolization



b. Addition



2. Dehydration phase

