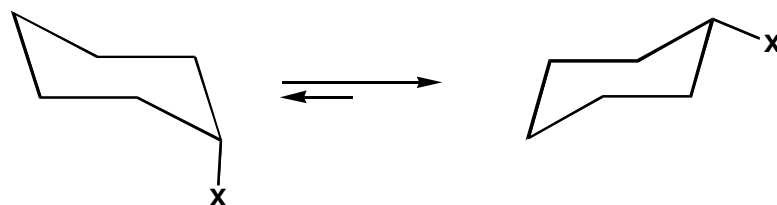


Energy differences Between Axial and Equatorial Conformations in Monosubstituted Cyclohexanes



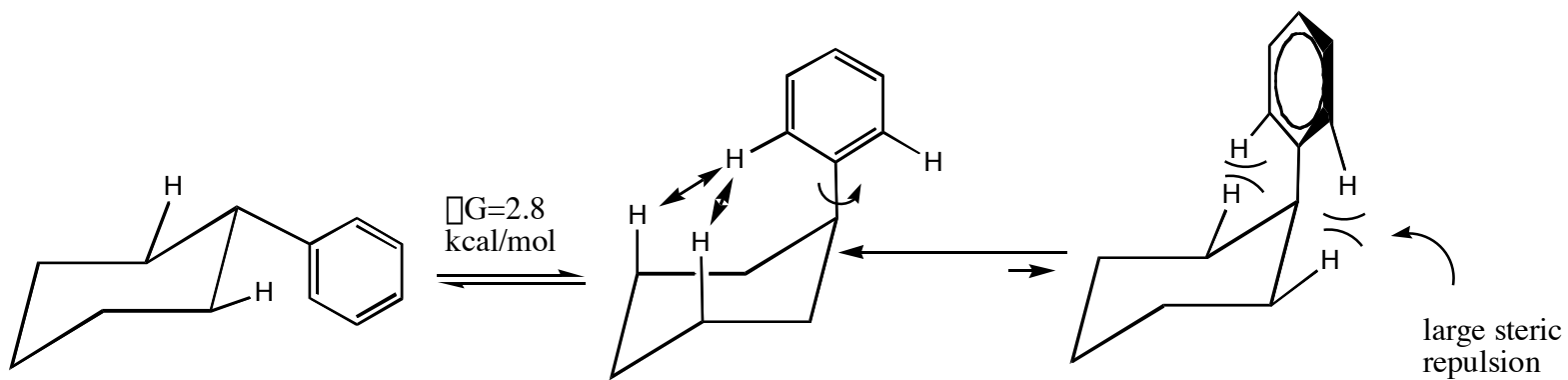
| X | A value E(axial)-E(equatorial) |
|------------------------------------|---|
| -F | 0.2 kcal/mol (0.8 kJ/mol) |
| -CN | 0.2 kcal/mol (0.8 kJ/mol) |
| -Cl | 0.5 kcal/mol (2.1 kJ/mol) |
| -Br | 0.6 kcal/mol (2.5 kJ/mol) |
| -OH | 1.0 kcal/mol (4.1 kJ/mol) |
| -COOH | 1.4 kcal/mol (5.9 kJ/mol) |
| -CH ₃ | 1.7 kcal/mol (7.1 kJ/mol) |
| -CH ₂ CH ₃ | 1.8 kcal/mol (7.5 kJ/mol) |
| -CH(CH ₃) ₂ | 2.1 kcal/mol (8.8 kJ/mol) |
| -C(CH ₃) ₃ | 4.9 kcal/mol (20 kJ/mol) |
| -Ph | 2.8 kcal/mol (12 kJ/mol) |

The relationship between stability and isomer percentages at equilibrium:

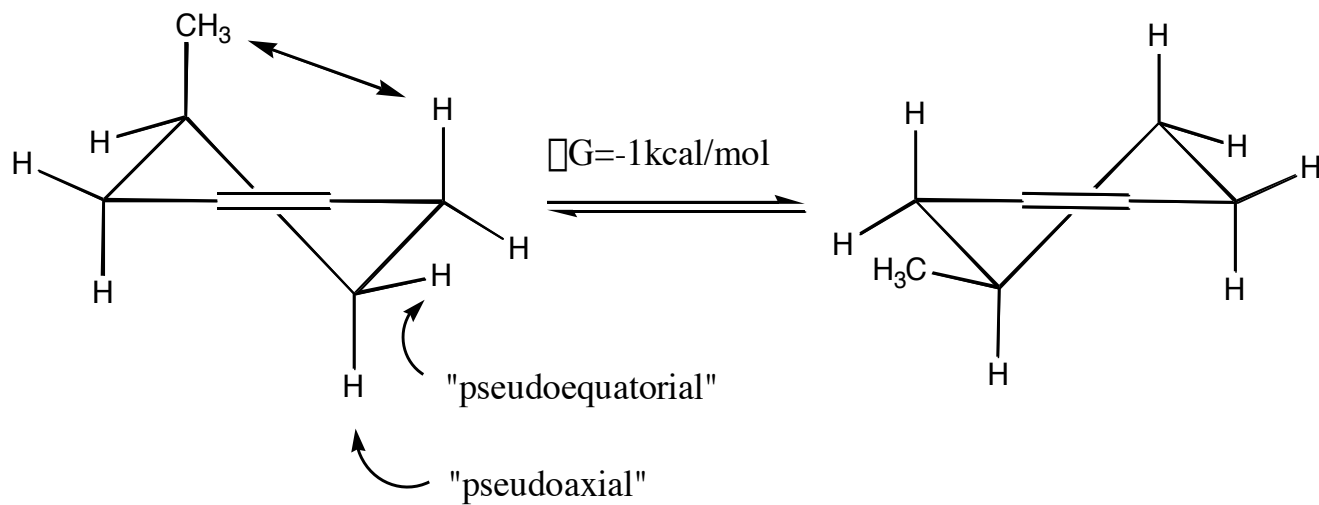
$$\Delta G^\circ = -RT \ln K_{eq}$$

| More stable isomer(%) | Less stable isomer (%) | Energy difference (ΔG°)at 25°C |
|------------------------------|-------------------------------|---|
| 50 | 50 | 0 kcal/mol (0 kJ/mol) |
| 75 | 25 | -0.651 kcal/mol (2.72 kJ/mol) |
| 90 | 10 | -1.302 kcal/mol (5.45 kJ/mol) |
| 95 | 5 | -1.744 kcal/mol (7.29 kJ/mol) |
| 99 | 1 | - 2.500 kcal/mol (11.38 kJ/mol) |
| 99.9 | 0.1 | -4.092 kcal/mol (17.11 kJ/mol) |

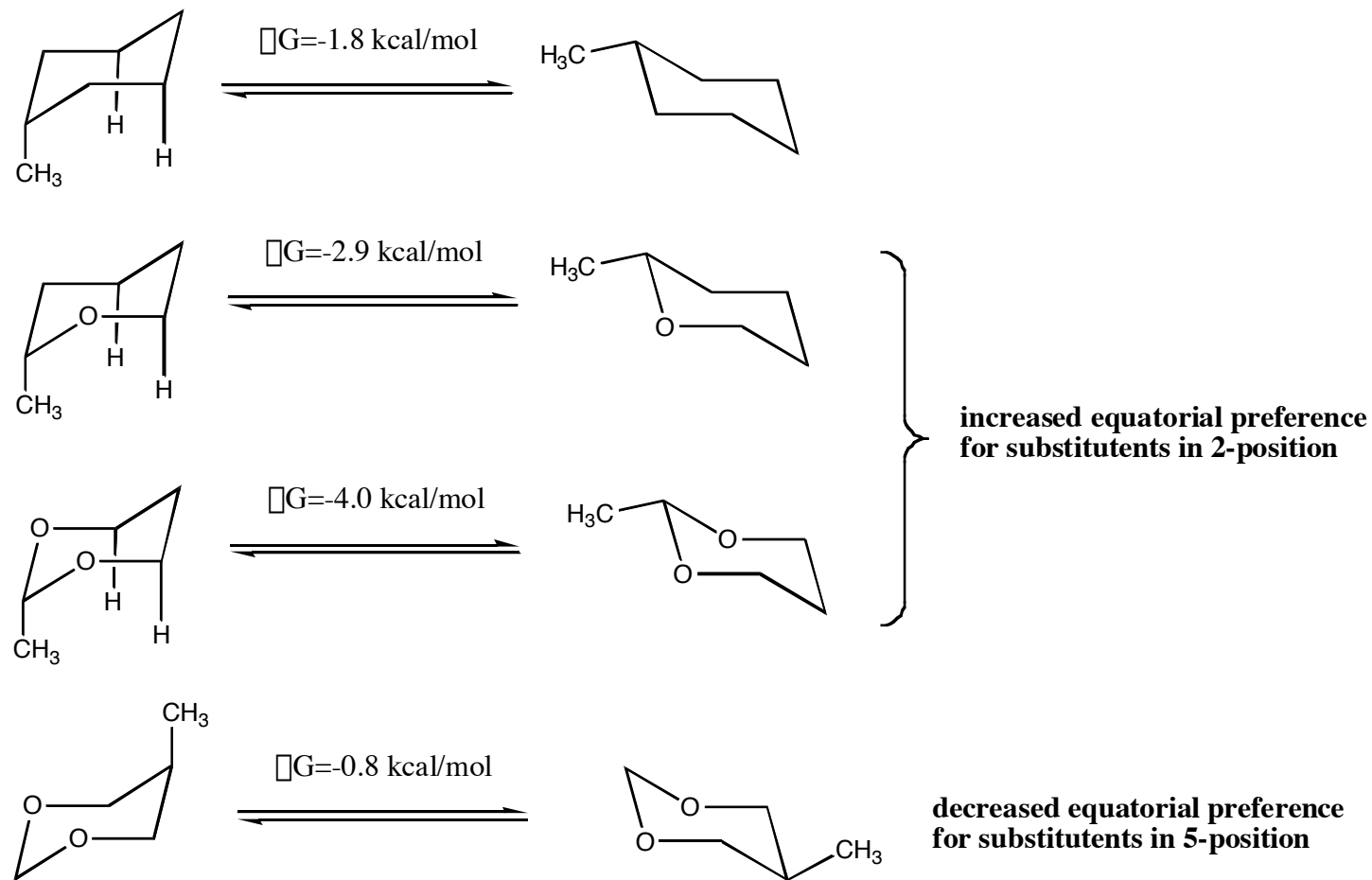
The plane of the phenyl substituent bisects the cyclohexane ring in the axial position, causing increased steric interaction with the axial H's



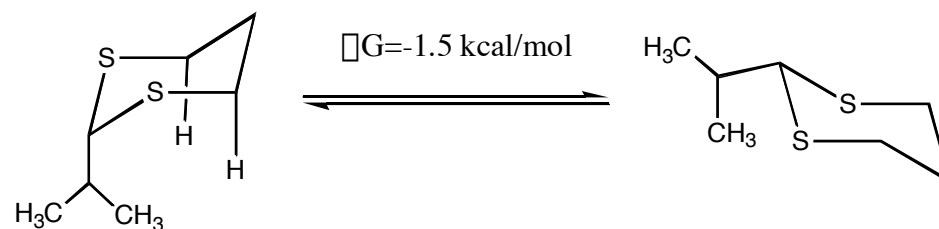
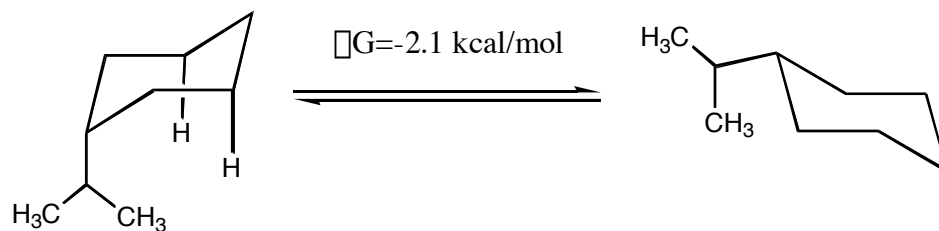
Cyclohexenes display a smaller axial-equatorial preference:
only one diaxial interaction possible:



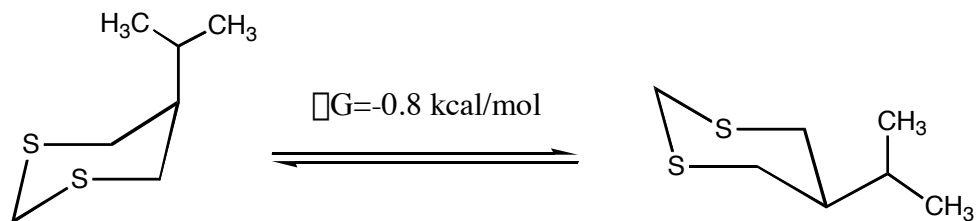
The effect of heteroatoms on conformational equilibria: C-O bond shorter than C-C bond



The effect of heteroatoms on conformational equilibria: C-S bond longer than C-C bond

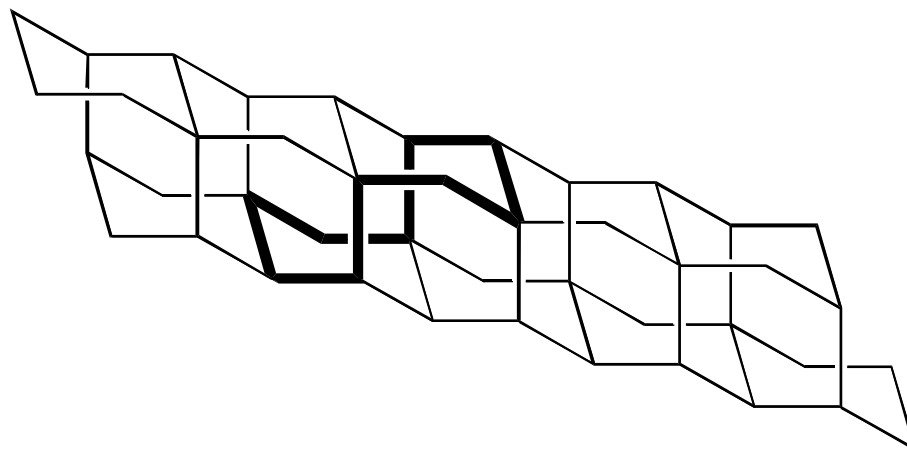


**decreased equatorial preference
for substituents in 2-position**

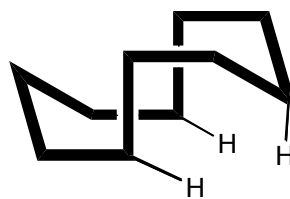


**small equatorial preference
for substituents in 5-position**

Diamond-Lattice section describing conformations for C₁₀ through C₂₄ cycloalkanes



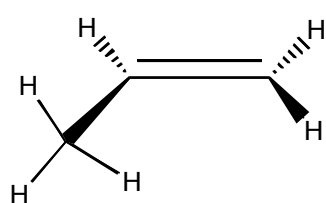
Transannular Strain:



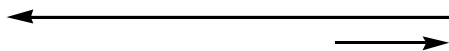
close van der Waals contact of
transannular hydrogens

cyclodecane
boat-chair-boat conformation

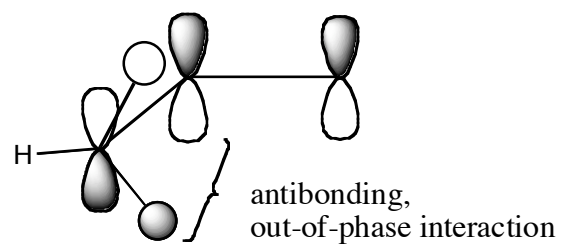
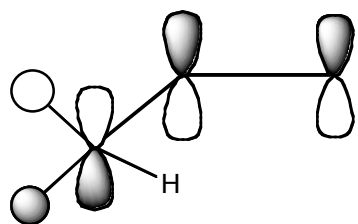
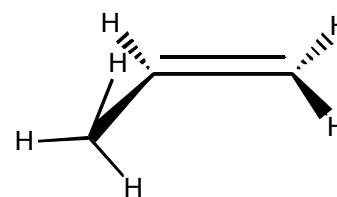
Eclipsed



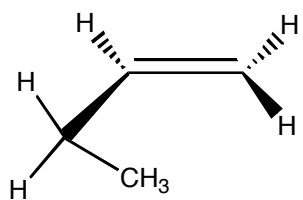
$\Delta G = 2 \text{ kcal/mol}$



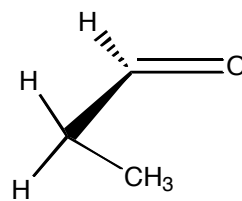
Staggered



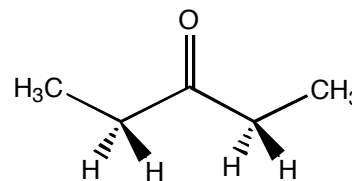
Preferred Conformers:



1-butene

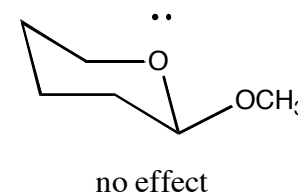
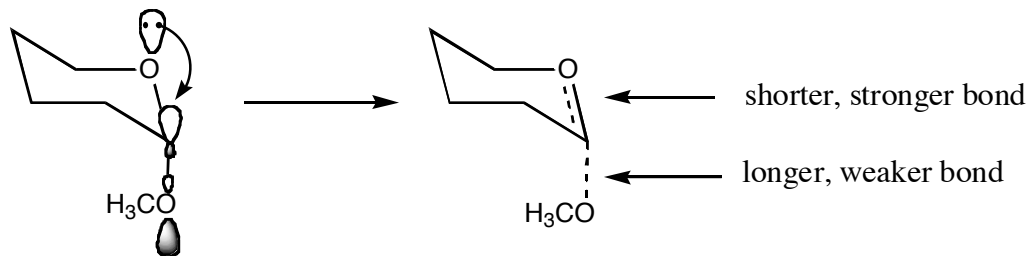
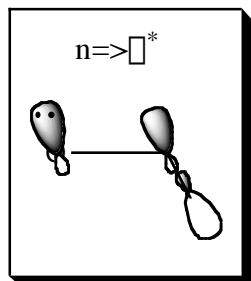


propionaldehyde

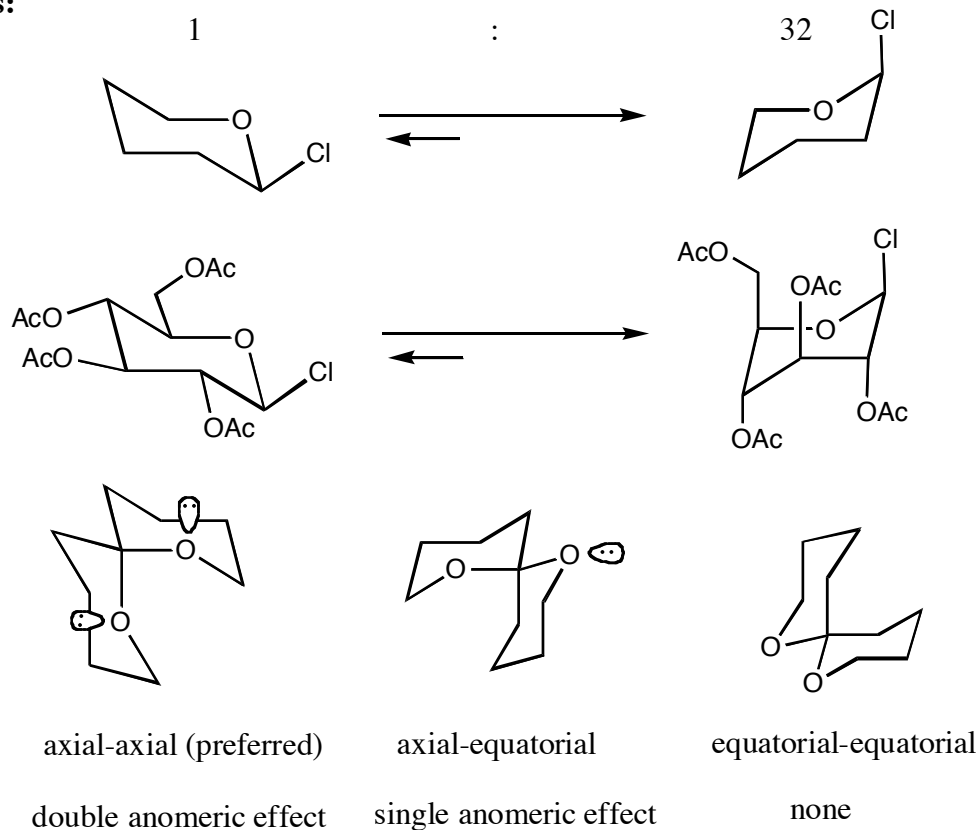


3-pentanone

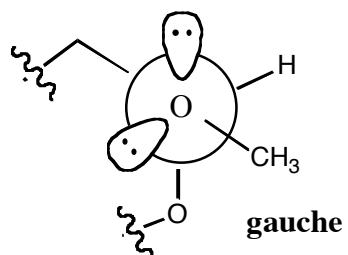
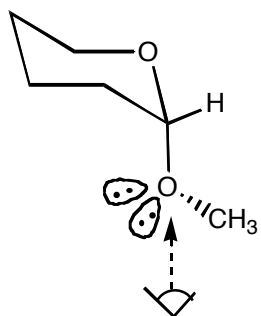
The Anomeric Effect: a donor orbital (lone pair > bonding pair) is placed *anti* to the C-X bond acting as an acceptor.



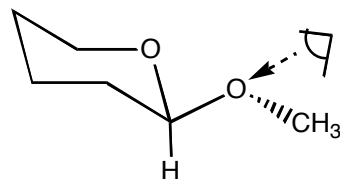
Preferred Conformations:



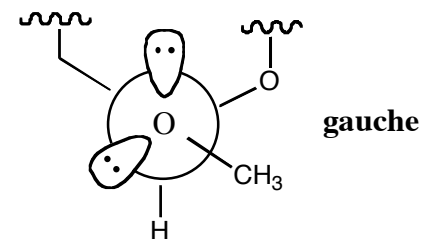
The Exo Anomeric Effect: a preference for a gauche conformation at the exo-glycosidic bond



note: lone pair and C-O bond are *anti*.

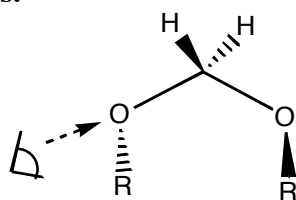


the CH₃ is gauche to the ring oxygen atom

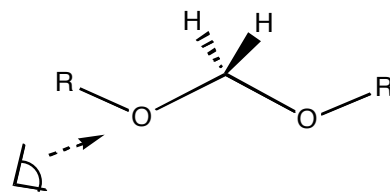
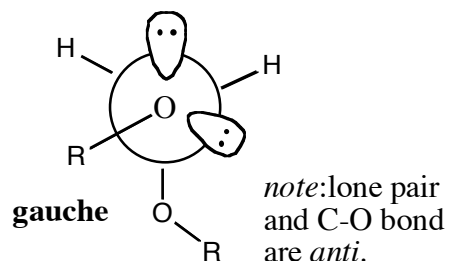


note: lone pair and C-O bond are *anti*.

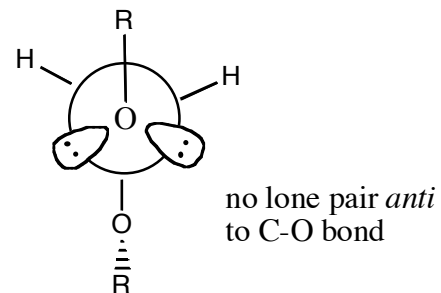
In Acyclic Acetals:



Favored

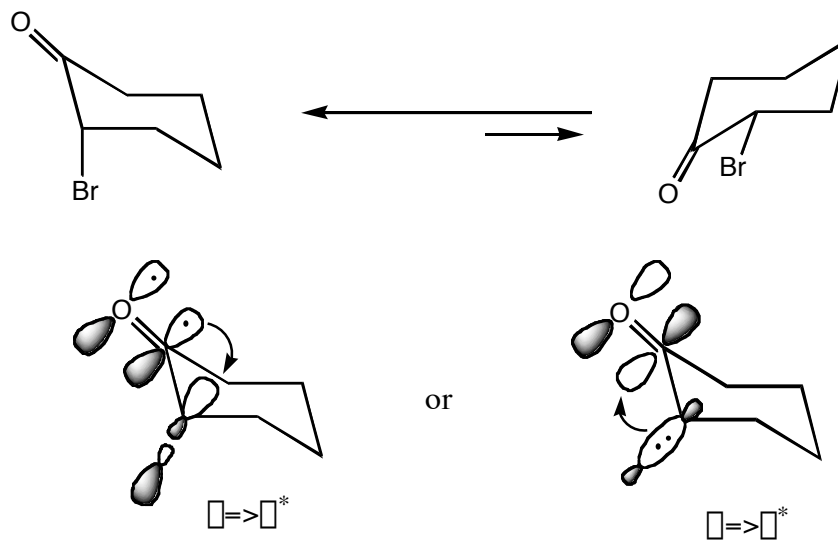


JOC, 1991, 56, 6412



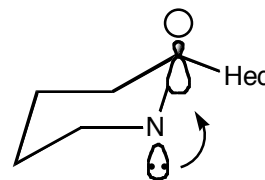
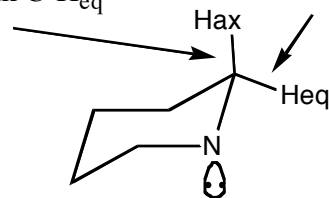
Stereoelectronic effects on conformation

C-Br bond
is a good
acceptor and
also a good
donor



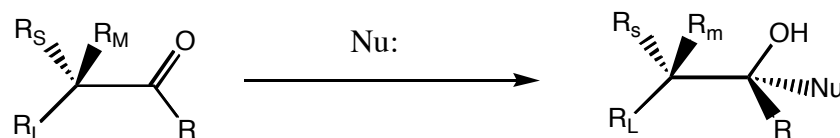
Trans, lone-pair effect

C-H_{ax} bond longer and weaker
than C-H_{eq}



donation into $\sigma^*_{\text{C-H}}$
weakens C-H_{ax}, but shortens
and strengthens N-C bond

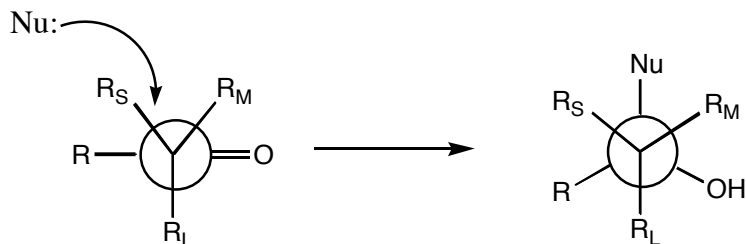
Conformational effects on Reactivity, I Cram's Rule



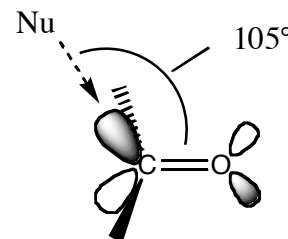
Nucleophile always approaches carbonyl from the R_S side

JACS, 1952, 74, 5828.

Steric Argument:



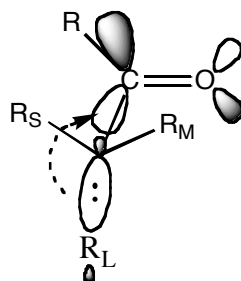
**Trajectory of Nucleophile Approach:
Burgi-Dunitz Angle (105° to plane of carbonyl)**



Nucleophile attacks \square^*

Tetrahedron, 1974, 30, 1563.

Felkin-Ahn Rationalization:



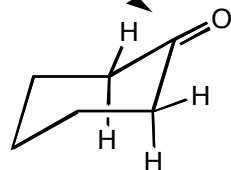
$\square\square\square$ interaction stabilizes LUMO, resulting in a stronger interaction with HOMO of nucleophile

TL, 1976, 155, 159.

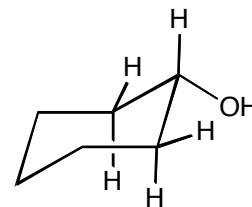
Conformational effects on Reactivity, II Cyclic Carbonyls

torsional strain:
sp² (120°) vs.
sp³ (109°)

Eclipsed



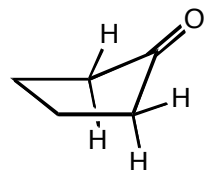
k_1



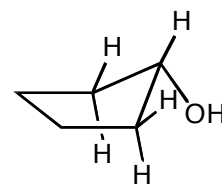
Staggered

$k_1 > k_2$

Staggered



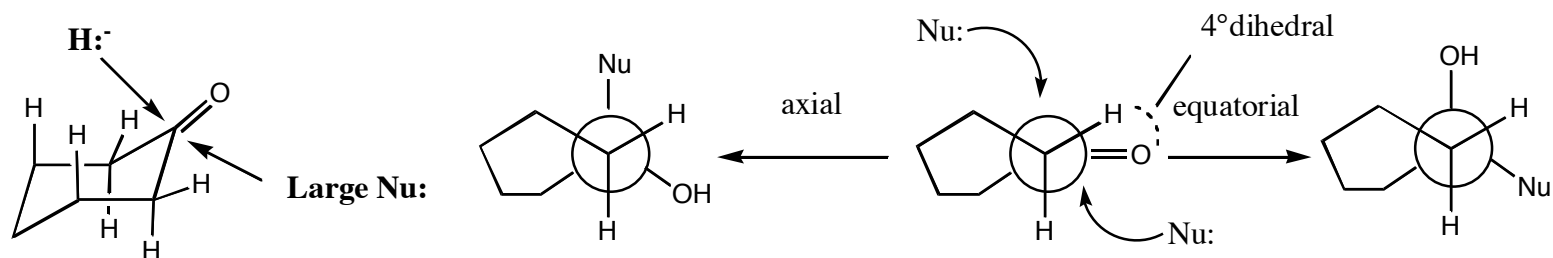
k_2



Eclipsed

reduction rate (k) for cyclohexanone/ acyclic ketone = 335

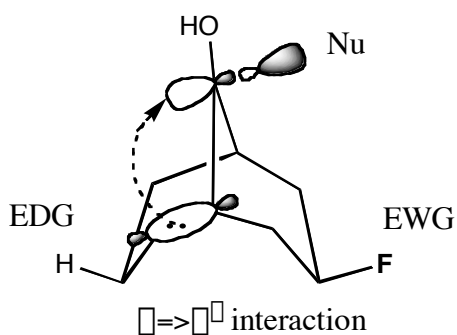
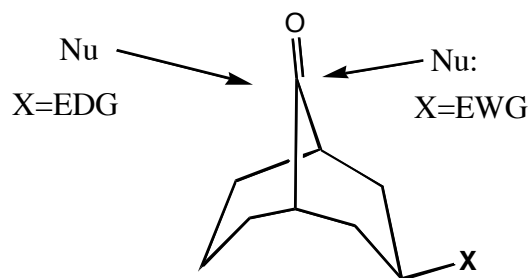
Addition of small nucleophiles to cyclohexanone occurs from axial direction, despite potential interaction with 1,3-H's



**Equatorial Approach of the Nucleophile causes the carbonyl oxygen to go through fully eclipsed form;
axial attack avoids eclipsing interaction!**

Conformational effects on Reactivity, III Addition to Carbonyls

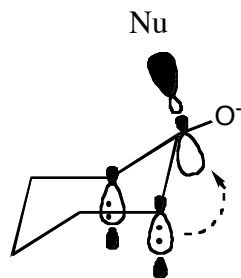
Cieplak Hypothesis: Nucleophiles add to carbonyl from the same side as electron withdrawing groups and from the opposite side as electron-donating groups



EWG's decrease donor
abilities of σ-bond nearby

Donor groups: more polarizable bonds better!

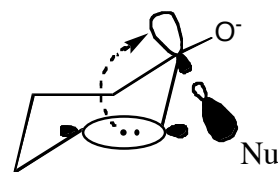
C-H > N-H > O-H > F-H
C-Cl > C-C > C-H > C-F
C-I > C-Br > C-Cl > C-F
C-S > C-C > C-N > C-O



C-H σ=>σ* interaction

C-H bond better
aligned for donation

Axial approach of nucleophile preferred



C-C σ=>σ* interaction

Alignment for donation
not as favorable for C-C
donation to developing σ*

Baldwin's Rules for Ring Closure

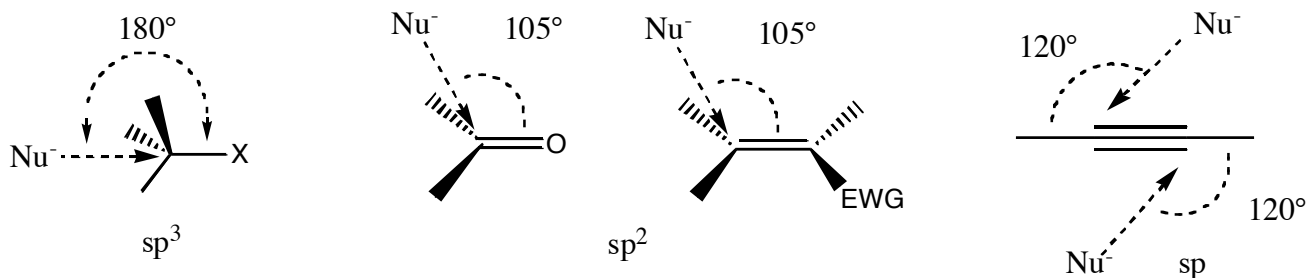
| Ring Size | <u>Exo</u> | <u>Exo</u> | <u>Exo</u> | <u>Endo</u> | <u>Endo</u> | <u>Endo</u> |
|-----------|----------------|-----------------------------|----------------------------|----------------|-----------------------------|----------------------------|
| | <u>dig(sp)</u> | <u>trig(sp²)</u> | <u>tet(sp³)</u> | <u>dig(sp)</u> | <u>trig(sp²)</u> | <u>tet(sp³)</u> |
| 3 | unfav | favorable | favorable | favorable | unfav | unfav |
| 4 | unfav | favorable | favorable | favorable | unfav | unfav |
| 5 | favorable | favorable | favorable | favorable | unfav | unfav |
| 6 | favorable | favorable | favorable | favorable | favorable | unfav |
| 7 | favorable | favorable | favorable | favorable | favorable | — |



"For intramolecular reactions, the favored pathways are those where the length and nature of the linking chain enables the terminal atoms to achieve the proper geometry for reaction"

J. Chem. Soc., Chem. Commun. **1974**, 734, 736.

Basis: trajectory for nucleophile attack on sp³, sp², and sp carbons



Baldwin's Rules: Examples

