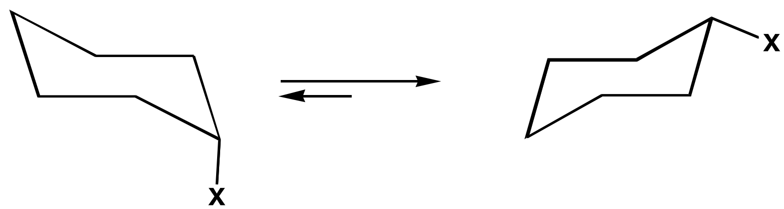
Energy differences Between Axial and Equatorial Conformations in Monosubstituted Cyclohexanes



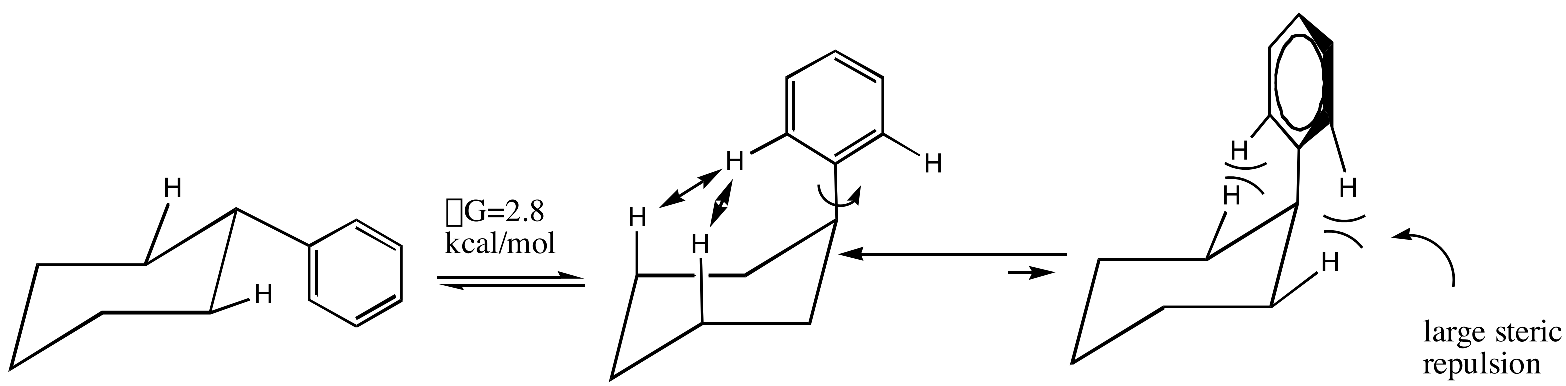
X	A value E(axial)-E(equatorial)
-F	0.2 kcal/mol (0.8 kJ/mol)
-CN	0.2 kcal/mol (0.8 kJ/mol)
-Cl	0.5 kcal/mol (2.1 kJ/mol)
-Br	0.6 kcal/mol (2.5 kJ/mol)
-OH	1.0 kcal/mol (4.1 kJ/mol)
-COOH	1.4 kcal/mol (5.9 kJ/mol)
$-CH_3$	1.7 kcal/mol (7.1 kJ/mol)
$-CH_2CH_3$	1.8 kcal/mol (7.5 kJ/mol)
$-CH(CH_3)_2$	2.1 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:

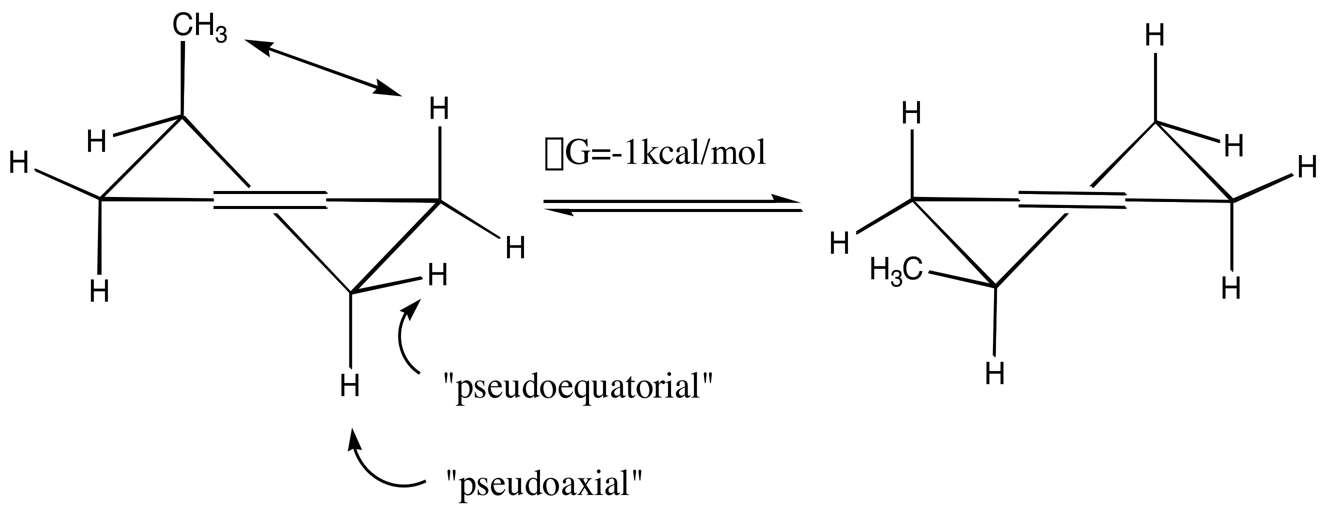
$$\Delta G^\circ = -RT\ln K_{eq}$$

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)

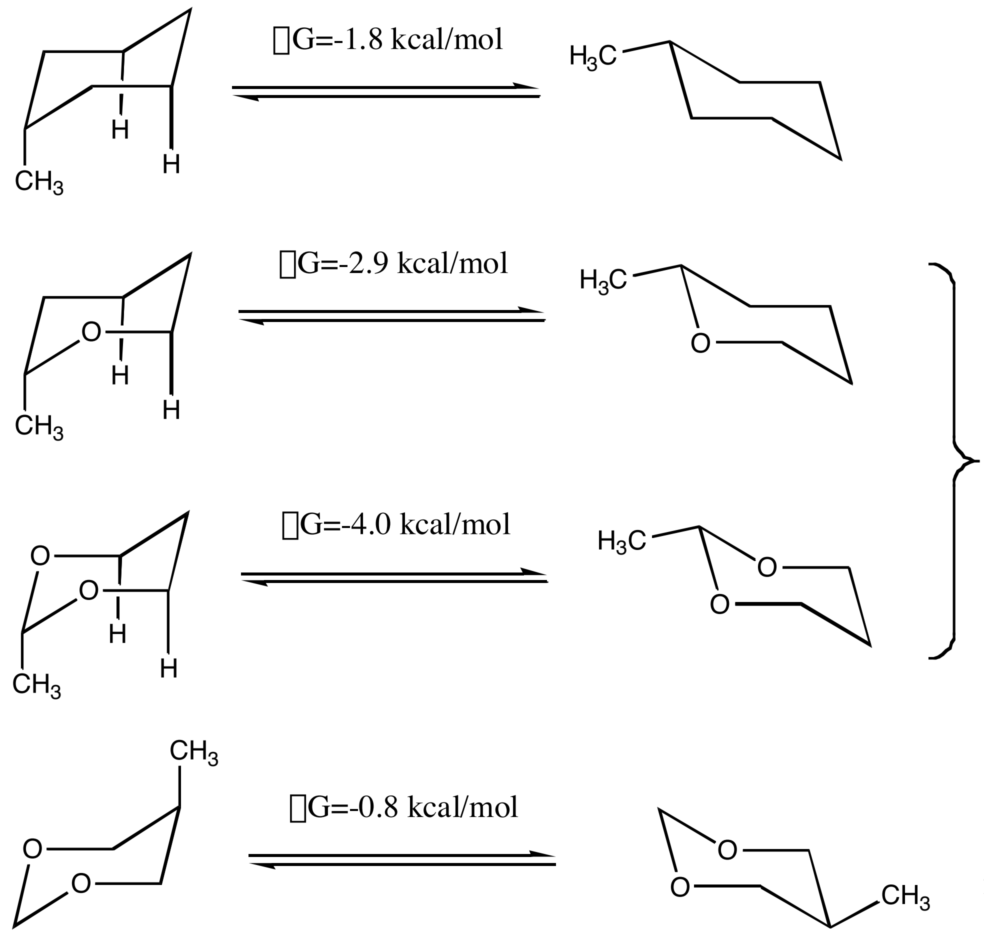
The plane of the phenyl subsitutent bisects the cyclohexane ring in the axial position, causing increased steric interaction with the axial H's



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



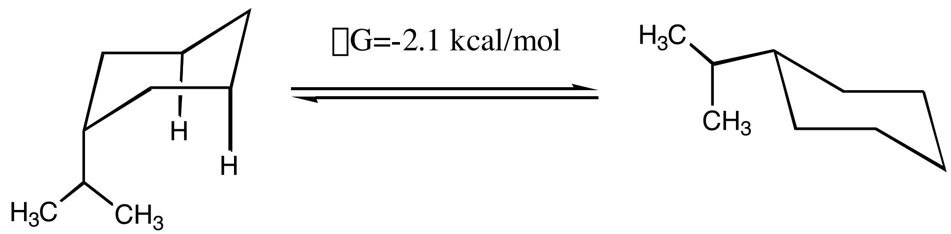
The effect of heteroatoms on conformational equilibria: C-O bond shorter than C-C bond

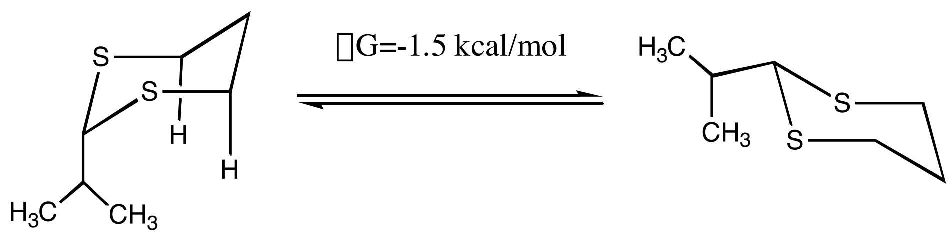


increased equatorial preference for substitutents in 2-position

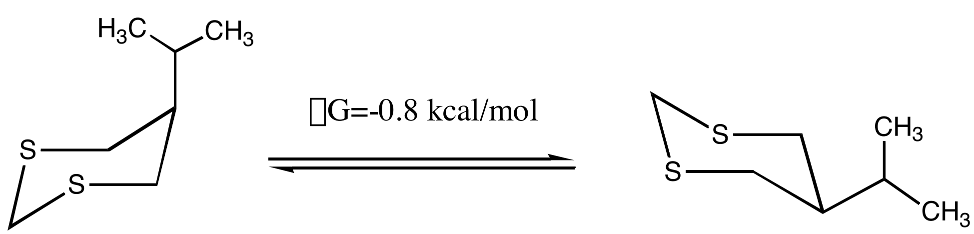
decreased equatorial preference for substitutents in 5-position

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



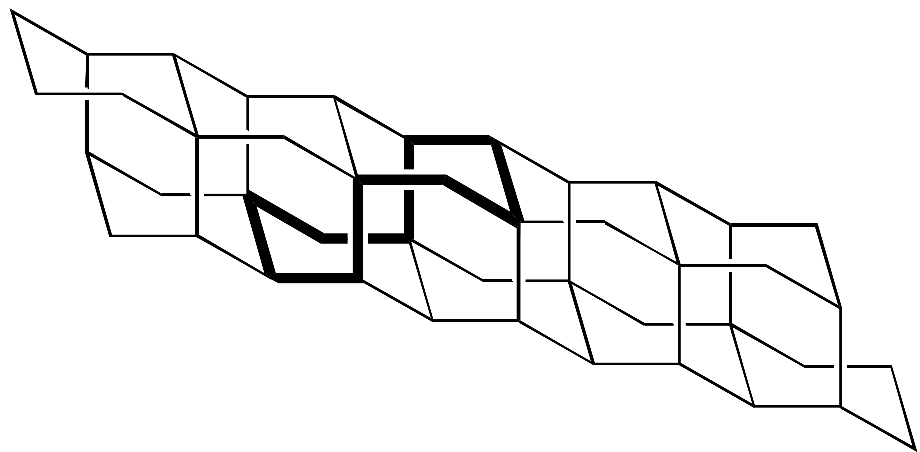


decreased equatorial preference for substitutents in 2-position

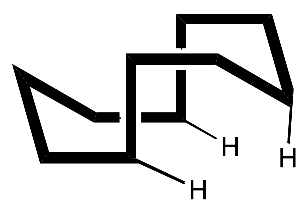


small equatorial preference for substitutents in 5-position

Diamond-Lattice section describing conformations for C_{10} through C_{24} cycloalkanes



Transannular Strain:

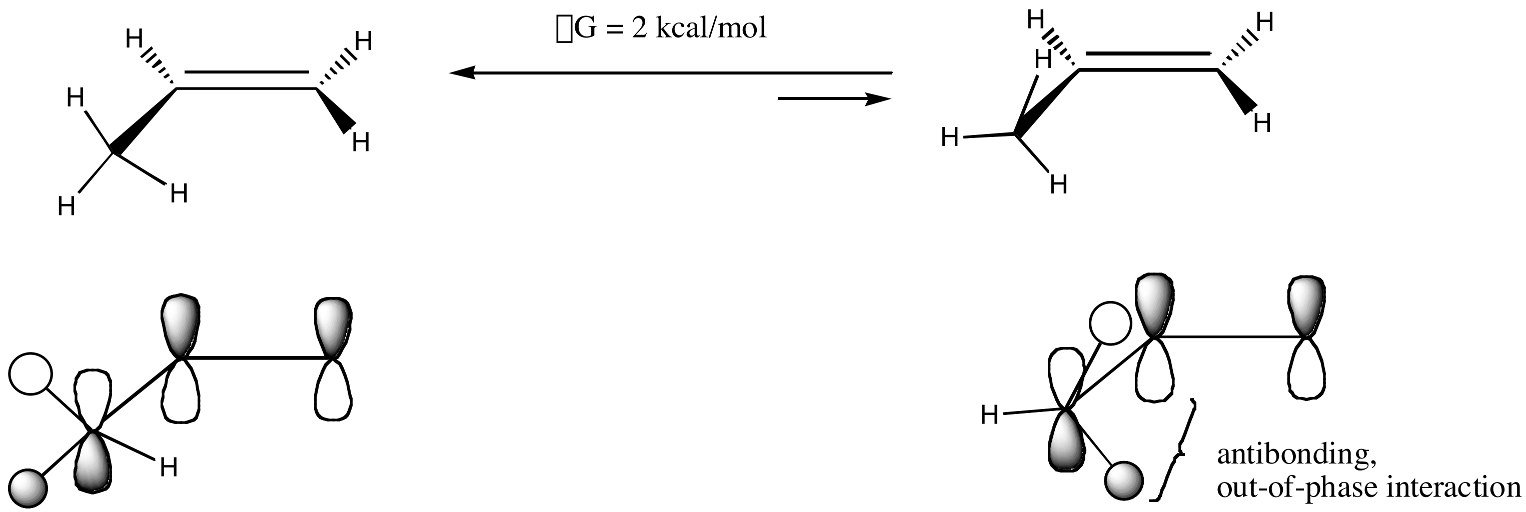


close van der Waals contact of transannular hydrogens

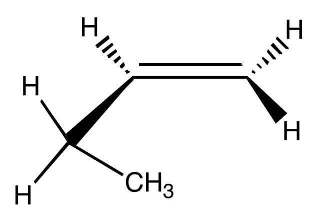
cyclodecane

boat-chair-boat conformation

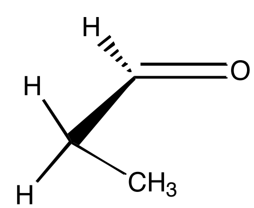
Eclipsed **Staggered**



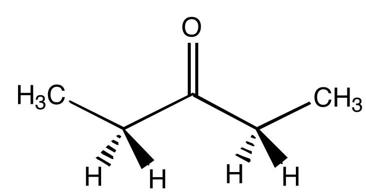
Preferred Conformers:



1-butene

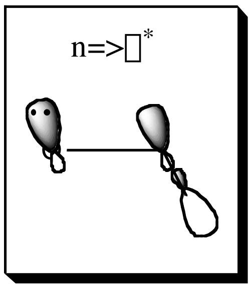


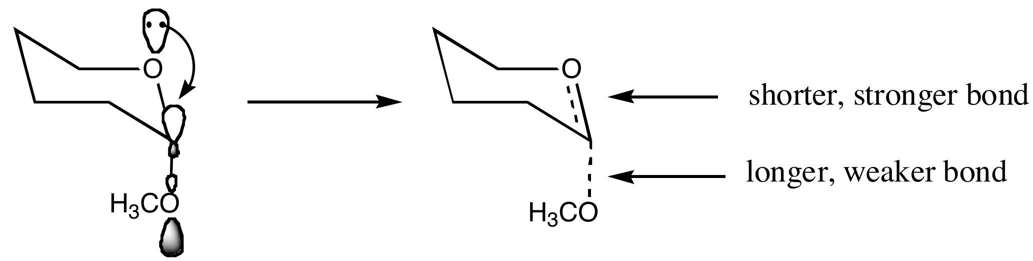
propionaldehyde

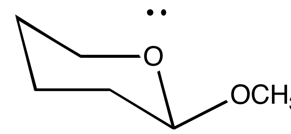


3-pentanone

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



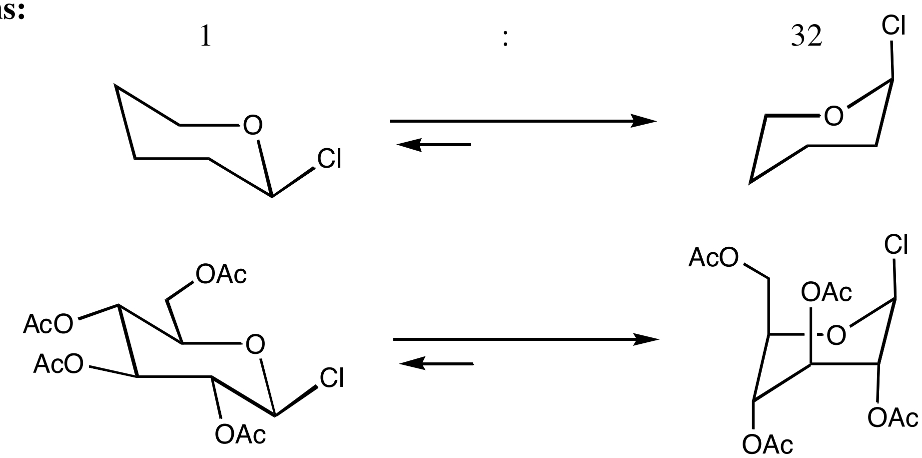


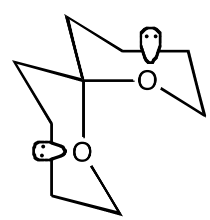


no effect

Preferred Conformations:

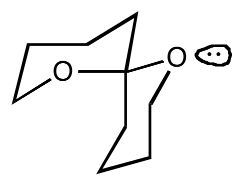
1 : 32





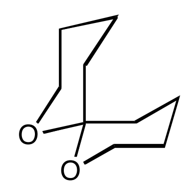
axial-axial (preferred)

double anomeric effect



axial-equatorial

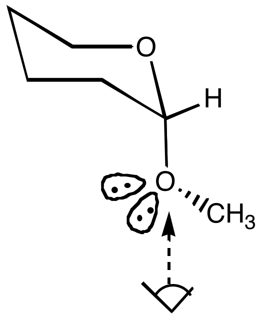
single anomeric effect

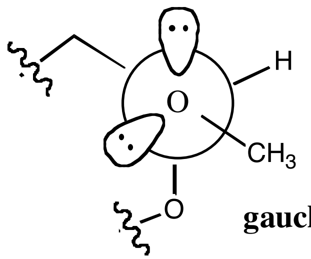


equatorial-equatorial

none

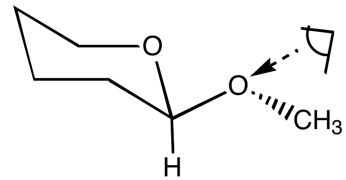
The Exo Anomeric Effect: a preference for a gauche conformation at the exo-glycosidic bond



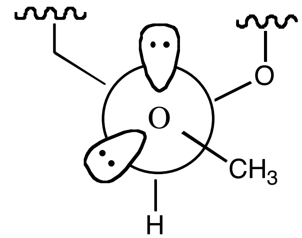


gauche

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



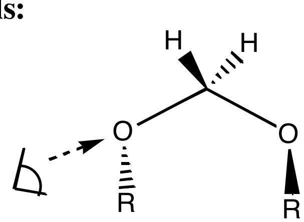
the CH_3 is gauche to the ring oxygen atom



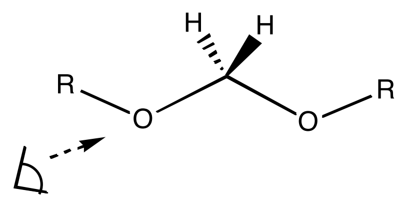
gauche

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

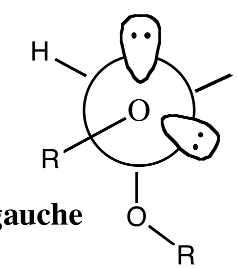
In Acyclic Acetals:



Favored

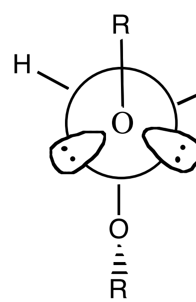


JOC, **1991**, *56*, 6412



gauche

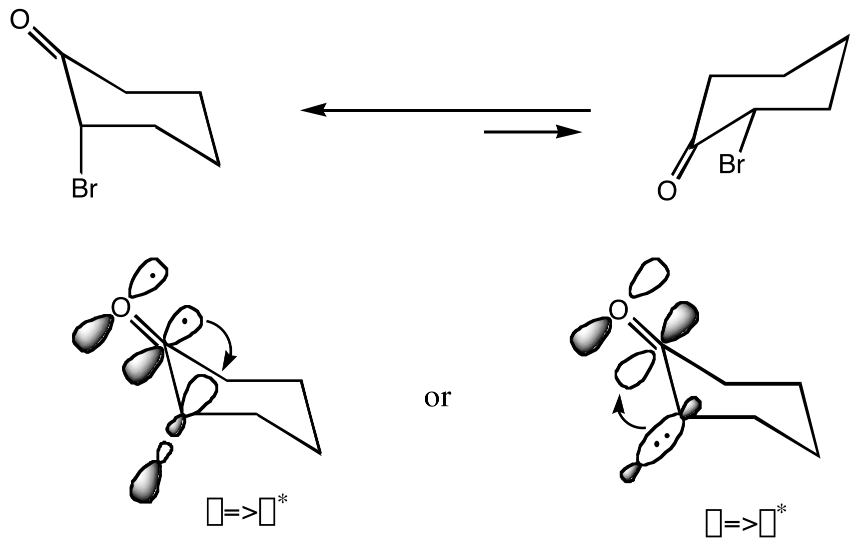
note:lone pair
and C-O bond
are *anti*.



no lone pair *anti*
to C-O bond

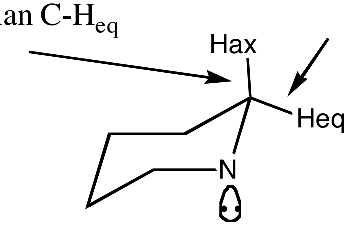
Stereoelectronic effects on conformation

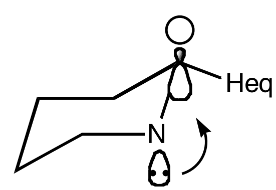
C-Br bond
is a good
acceptor and
also a good
donor



Trans, lone-pair effect

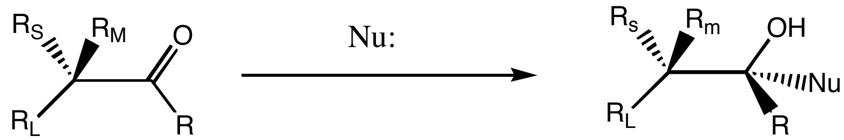
C-H_{ax} bond longer and weaker
than C-H_{eq}





donation into □□C-H
weakens C-H_{ax}, but shortens
and strengthens N-C bond

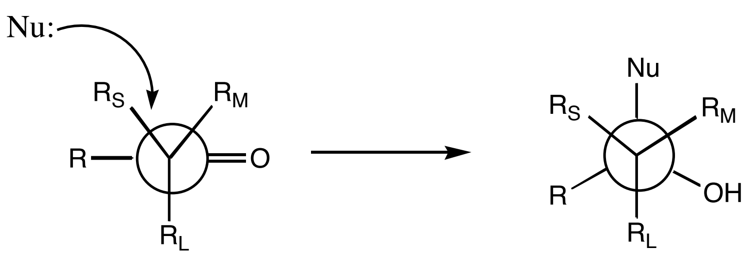
Conformational effects on Reactivity, I
Cram's Rule



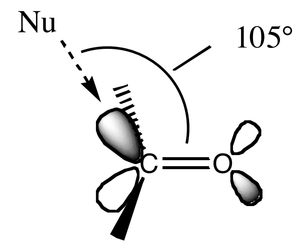
Nucleophile always approaches carbonyl from the R_S side

JACS, **1952**, *74*, 5828.

Steric Argument:



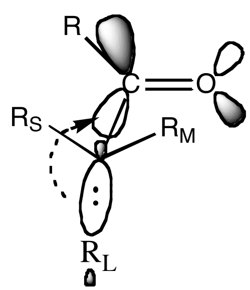
Trajectory of Nucleophile Approach:
Burgi-Dunitz Angle (105° to plane of carbonyl)



Nucleophile attacks □*

Tetrahedron, **1974**, *30*, 1563.

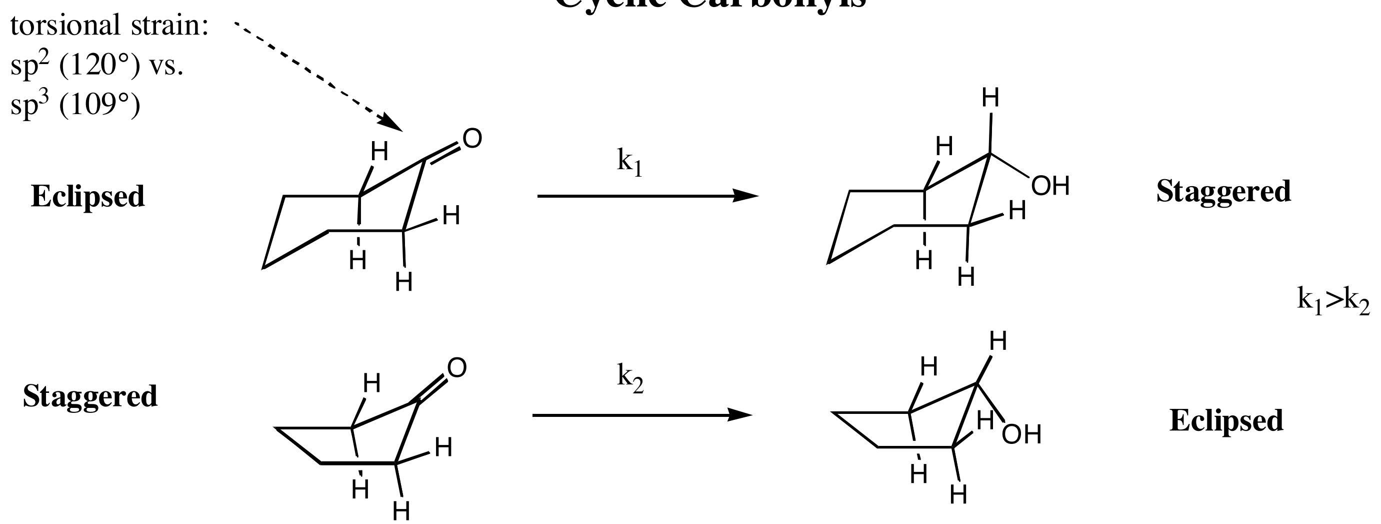
Felkin-Ahn Rationalization:



□□□□ interaction stabilizes LUMO, resulting in a stronger interaction with HOMO of nucleophile

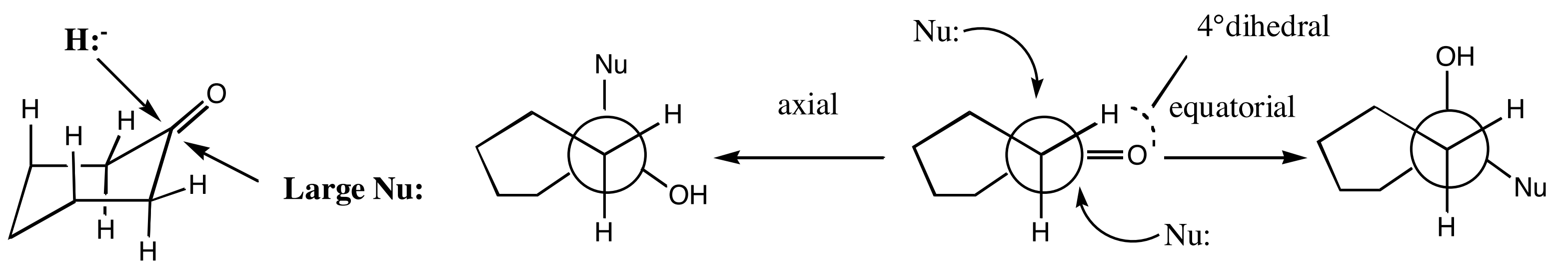
TL, **1976**, 155, 159.

Conformational effects on Reactivity, II
Cyclic Carbonyls



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

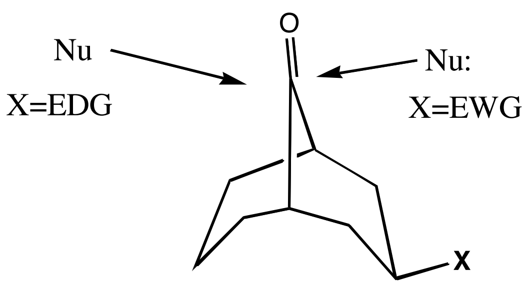
Addition of small nucleophiles to cyclohexanone occurs from axial direction, despite potential interaction with 1,3-H's

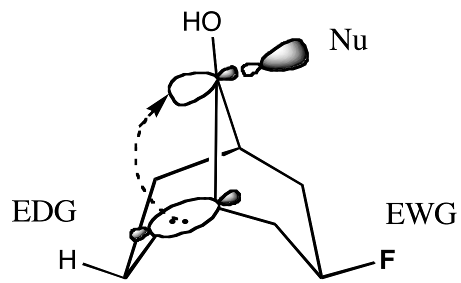


Equatorial Approach of the Nucleophile causes the carbonyl oxygen to go through fully eclipsed form; axial attack avoids eclipsing interaction!

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



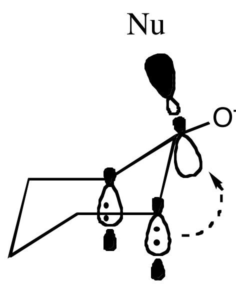


σ=>σ* interaction

EWG's decrease donor abilities of σ-bond nearby

Donor groups:more polarizable bonds better!

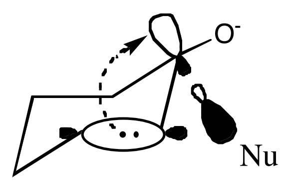
C–H > N-H > O-H > F-H
C–Cl > C–C > C-H > C-F
C-I > C-Br > C-Cl > C-F
C-S > C-C > C-N > C-O



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*

JACS, **1980**, *103*, 4540

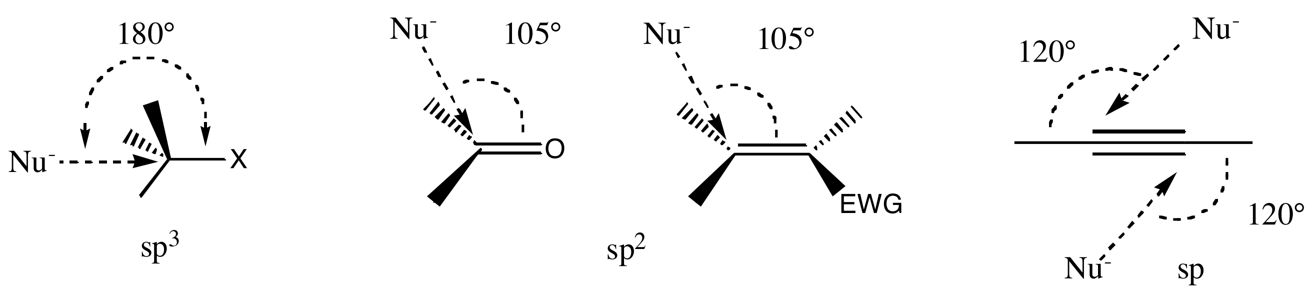
Baldwin's Rules for Ring Closure

Ring Size	Exo dig(sp)	Exo trig(sp^2)	Exo tet(sp^3)	Endo dig(sp)	Endo trig(sp^2)	Endo tet (sp^3)
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 sp^3, sp^2, and sp carbons



Baldwin's Rules: Examples