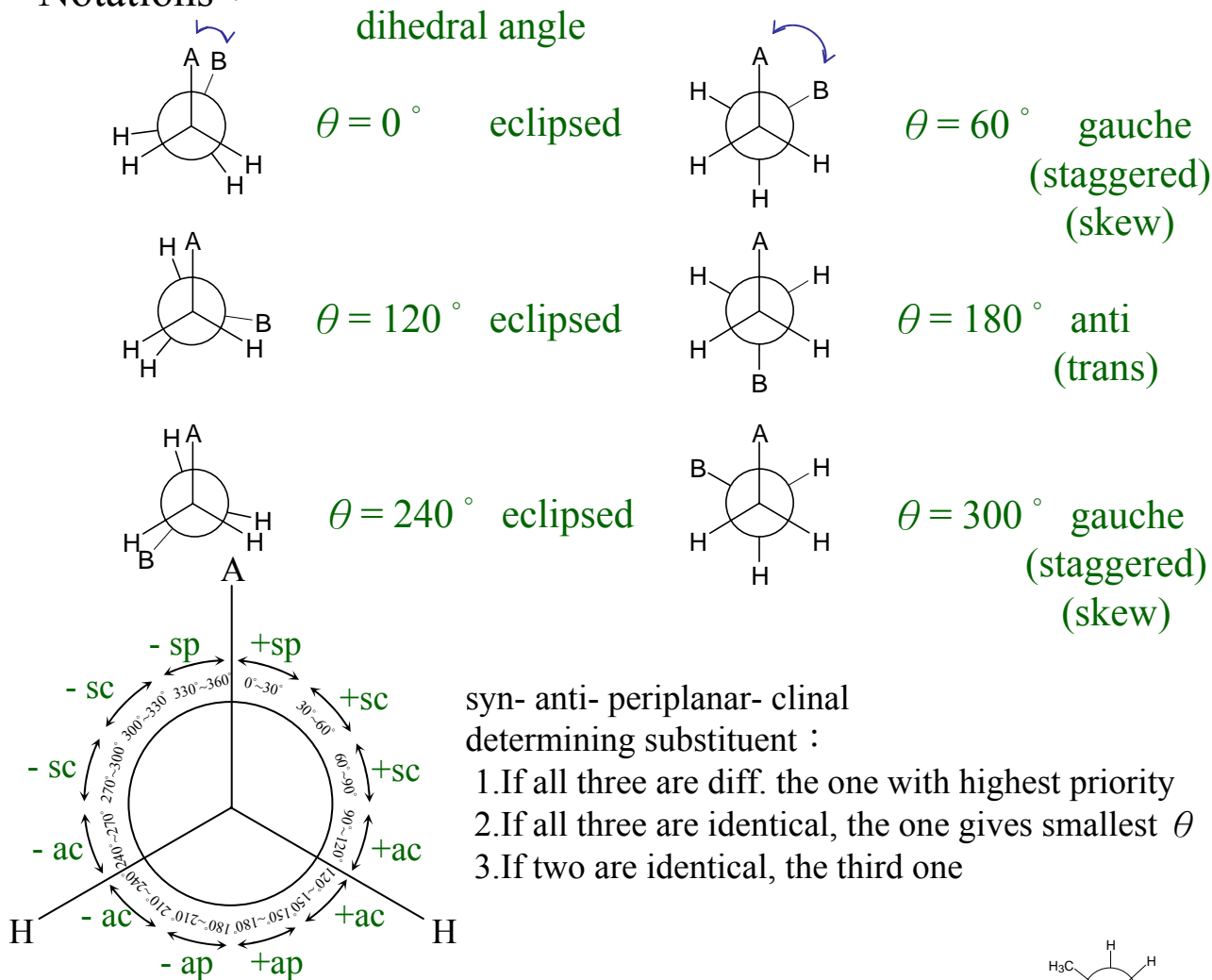


Chap. 3 Conformational Analysis and Molecular Mechanics

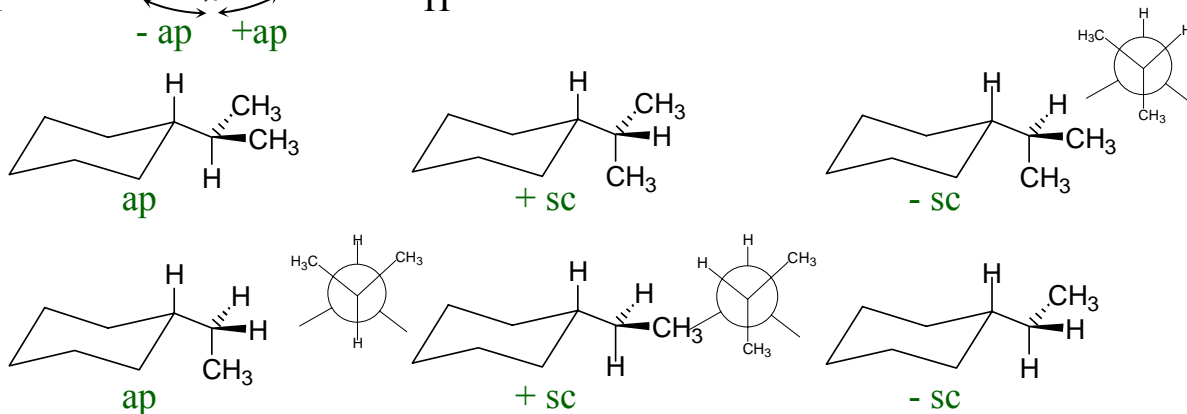
Conformation : One of several different spatial arrangements that a molecule can achieve by rotation about single bonds between atoms.

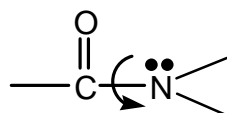
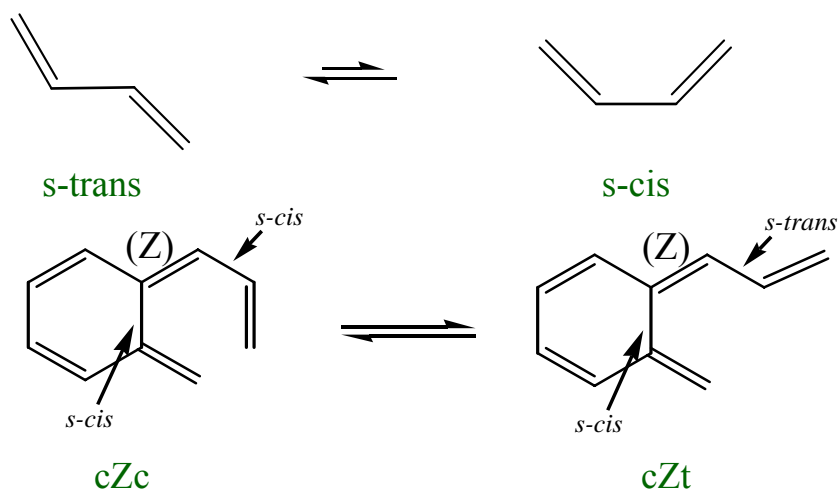
Notations :



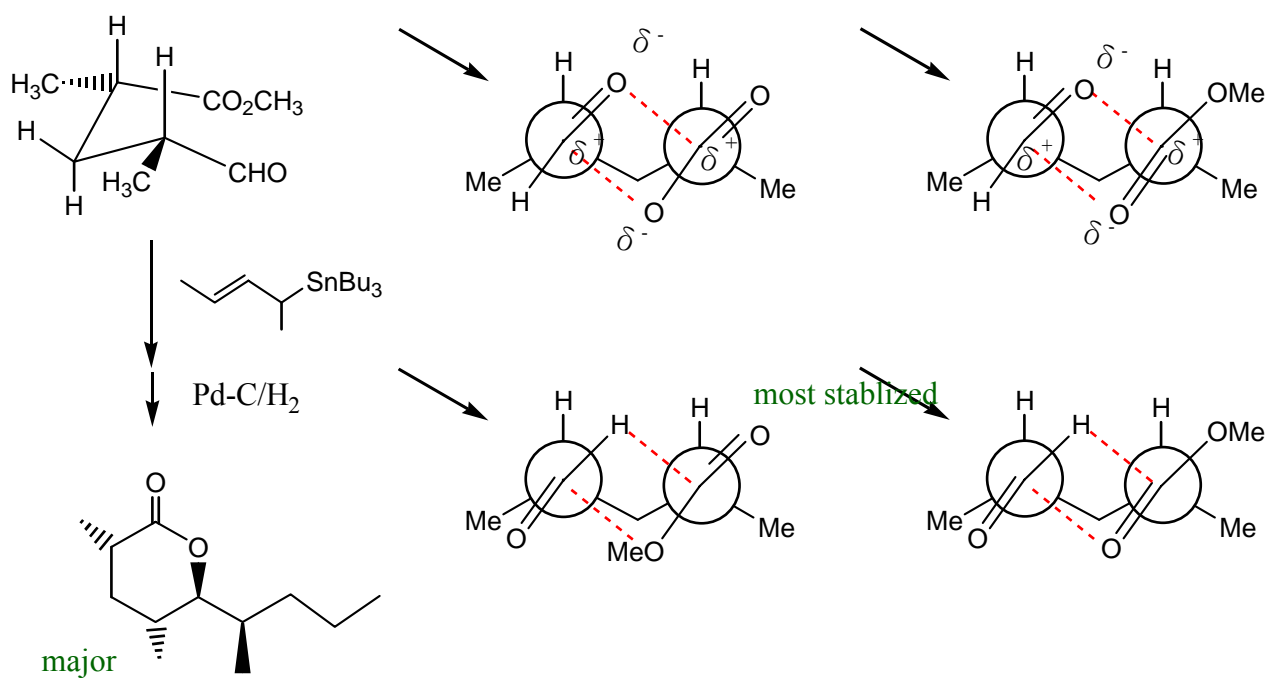
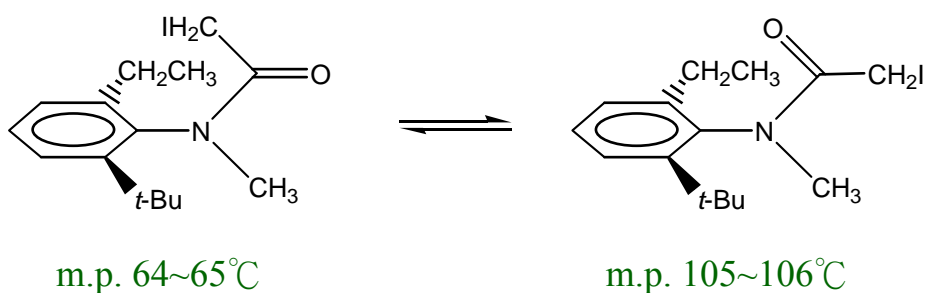
syn- anti- periplanar- clinal
determining substituent :

1. If all three are diff. the one with highest priority
2. If all three are identical, the one gives smallest θ
3. If two are identical, the third one

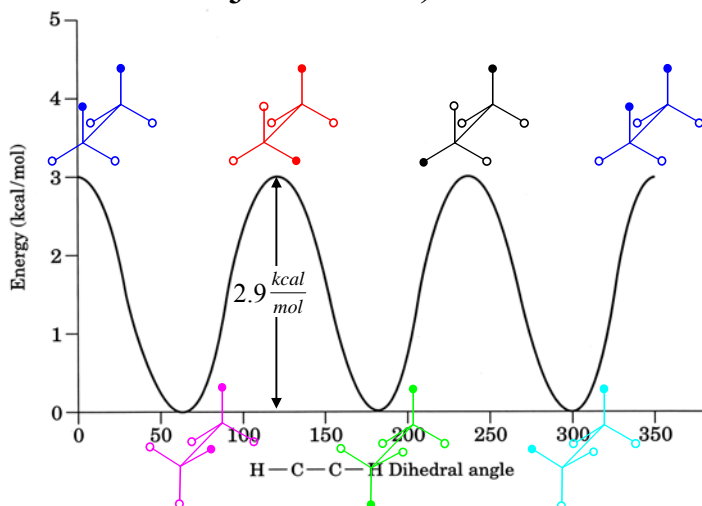




the C – N bond rotation is hindered and conformation isomer could be isolated.

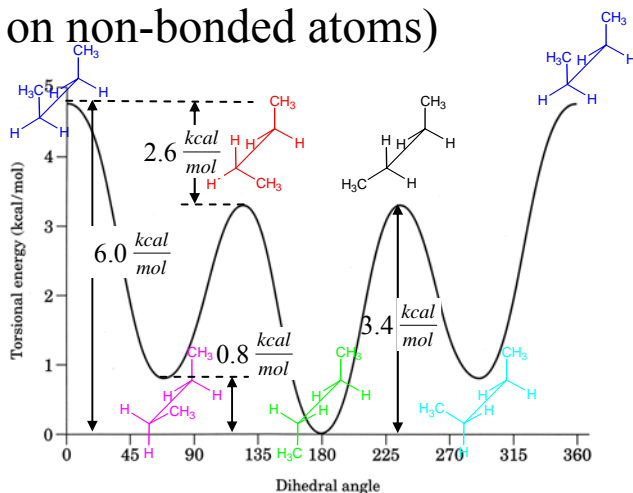


1. Torsional Strain (due to deviation from staggered bonds on adj. carbons)

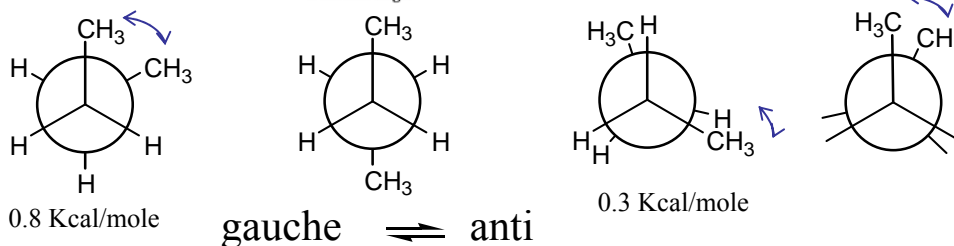


$$E(\varphi) = 0.5V(1 + \cos 3\varphi)$$

2. van der Waals strain (repulsion due to overlap of electron clouds on non-bonded atoms)



a superimposition of torsional strain of ethane and van der waals strain



$$\begin{aligned} \Delta G^\circ &= \Delta H^\circ - T \Delta S^\circ \\ &= -0.8 \text{ Kcal/mol} - (-0.00198 \times 298 \times \ln 2) = -0.8 + 0.41 \\ &= -0.39 \text{ Kcal/mol} \end{aligned}$$

$$\Delta G^\circ = -RT \ln K \quad K = \text{anti/gauche} = 1.9 \rightarrow 66\% \text{ anti}$$

Barrier foldedness

Ethane and butane have a three-fold rotational profile.

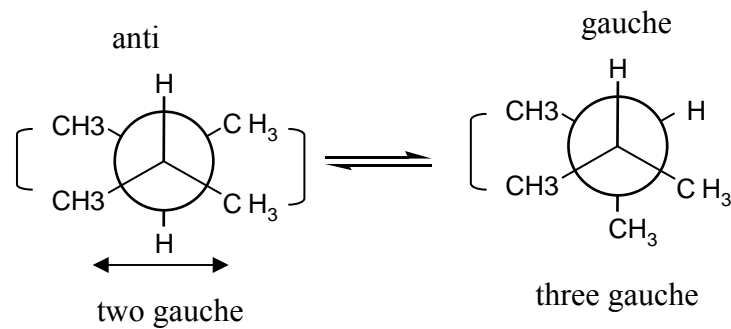
Rotation around CH₃-C₆H₅ has a six-fold profile.

An n-fold rotor and an m-fold rotor give a barrier with

$$F = (n \times m) / q$$

Where q is the number of eclipsing bond in the TS

Tetraalkylethane

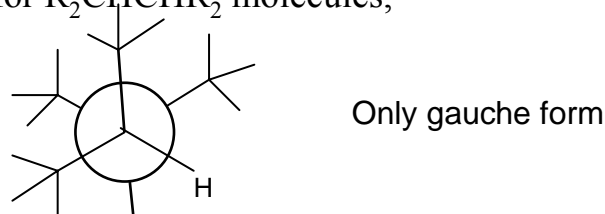


expected composition: 70:30 anti to gauche

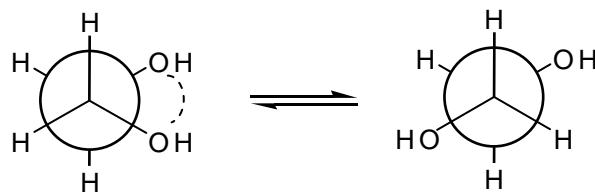
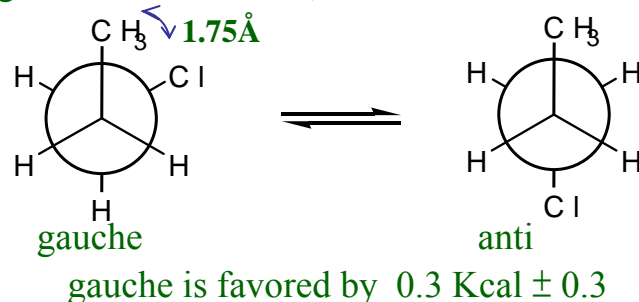
experimental composition: 1:2, $\Delta H = 0!$

geminal repulsion aggravate the vicinal repulsion in anti form and destabilize the anti form more than the gauche form

A general case for R₂CHCHR₂ molecules,

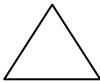


-stabilizing London interaction, distance \approx sum of van der Waals radii



3. Angle Strain (Bayer strain), (deviation from standard bond angle.)

Bayer's Theory based on planer geometry

		Angle Strain/CH ₂	total Angle Strain	expt'l Strain/CH ₂
	cyclopropane	24° 44'	74° 12'	9.2 kcal/mol
Angle Strain $= \frac{1}{2}(109.5^\circ - 60^\circ)$ $= 24.75^\circ$	cyclobutane	9° 44'	38° 56'	6.55
	cyclopentane	0° 44'	3° 40'	1.3
	cyclohexane	-5° 16'	-31° 36'	0
	cyclodecane	-17° 16'	-172° 42'	1.2

The discrepancy is due to non-planar geometry

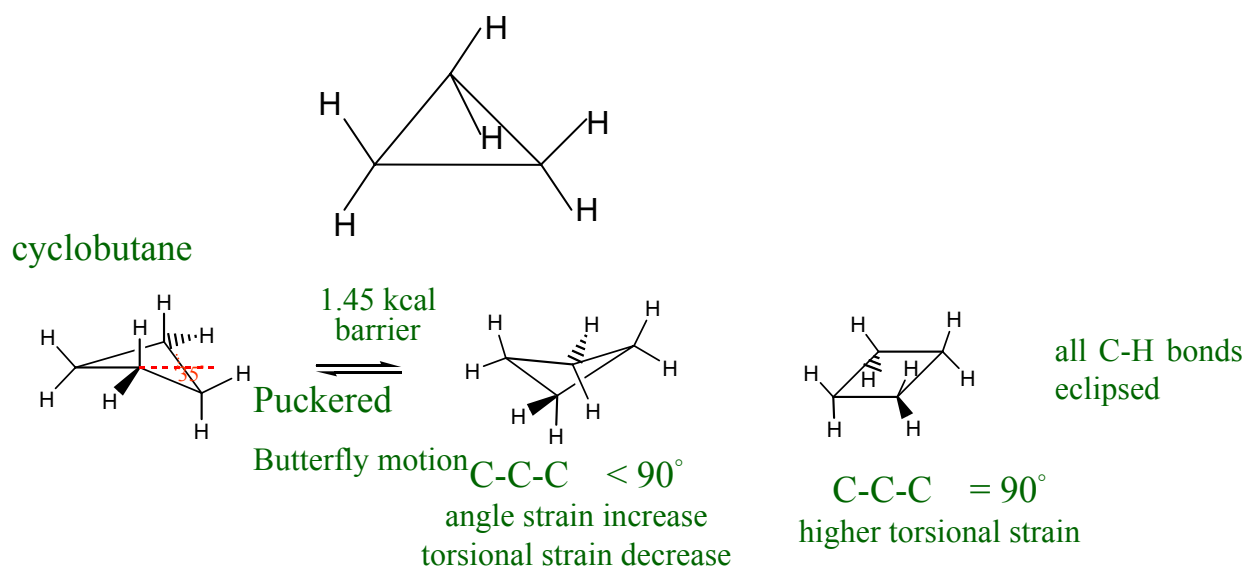
cyclopropane

Cyclopropane C-C bond are short (1.51Å) than normal C-C bond (1.54Å)
 H-C-H bond angle open up (115°) than the value for H-C-H (106°) in the CH₂ of propane.
 C-H of cyclopropane are more acidic than normal alkanes.

→rehybridization, smaller C-C-C bond angle, more p character is used.

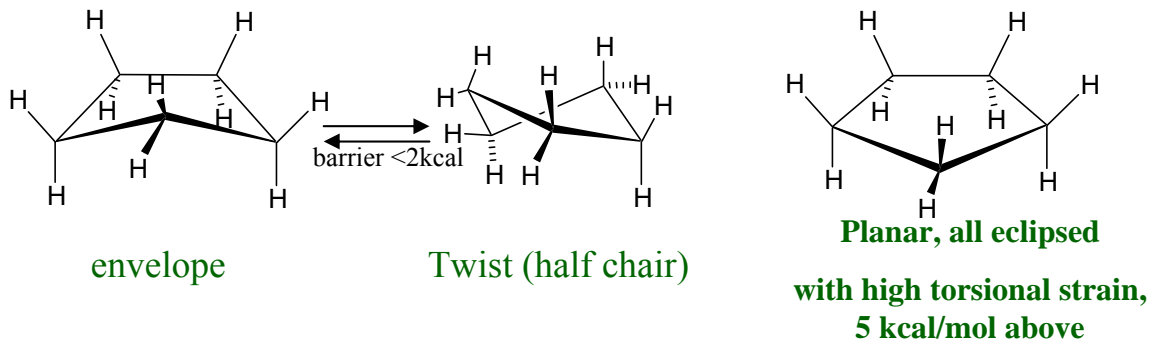
Then more s character for C-H bonds.

Strain energy of cyclopropane 27.5 kcal/mole, may come from angle strain and also the eclipsing C-H bonds (eclipsing effect, a torsional strain)



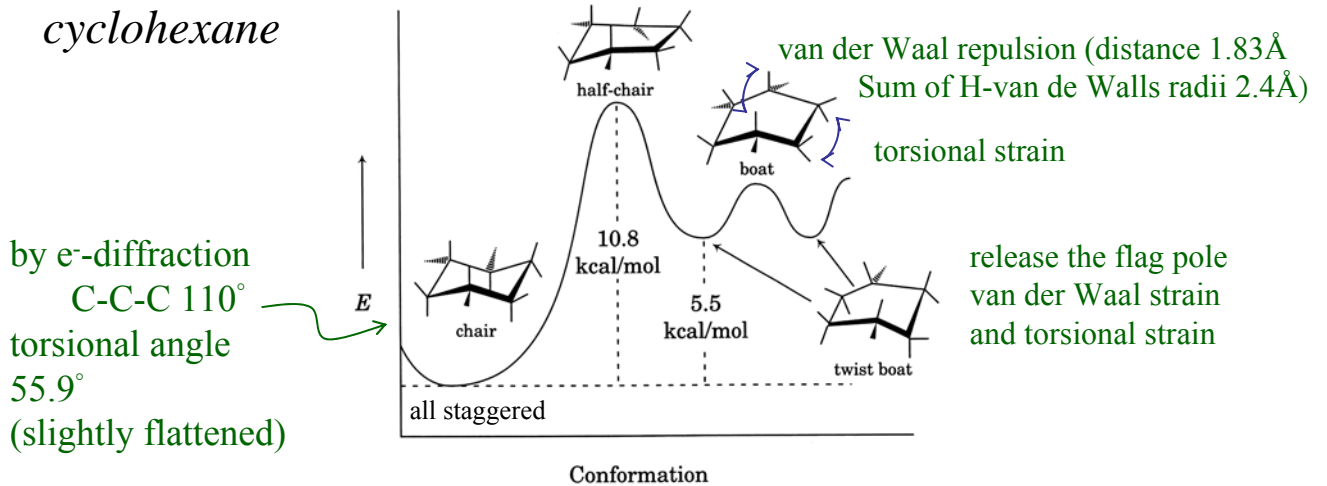
C-C bond length 1.55 Å, strain energy 26.5 kcal/mol

cyclopentane



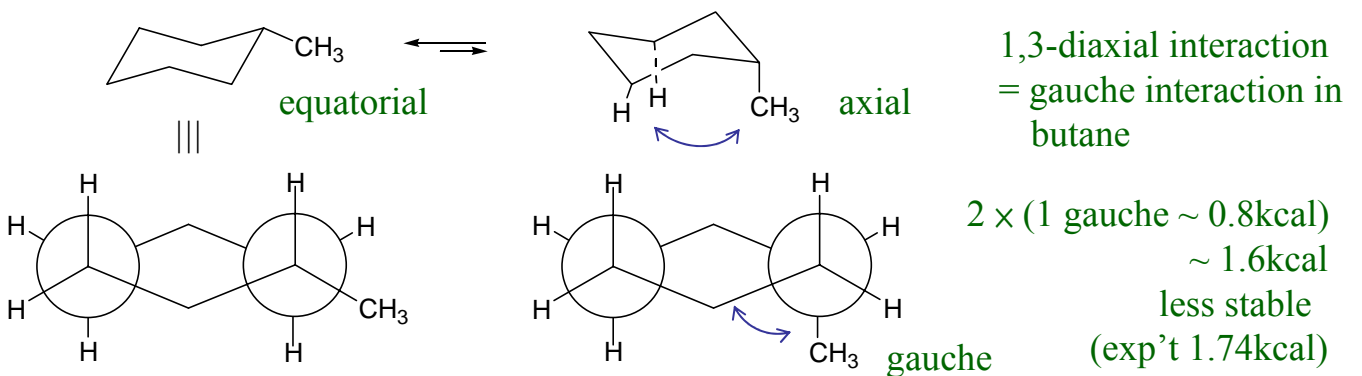
the conformation is constantly changing → pseudo rotation, strain energy 6.2 kcal/mol, mostly due to torsional, some angle strain

cyclohexane



the chair form and twist boat form are separated by a high energy barrier.

substituted cyclohexane



equatorial preference = 1.74 kcal/mol \rightarrow A-value conformational free energy

$$\Delta G^\circ = -RT \ln K \quad K = \frac{[eq]}{[ax]} = \frac{95}{5} = 19$$

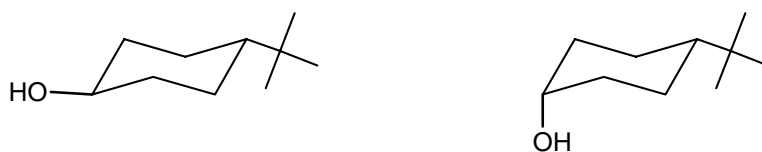
Table 3.2 Conformational preferences of monosubstituted cyclohexanes.

Substituent	Equatorial Preference (kcal/mol)				
-F	0.15				
-Cl	0.43				
-Br	0.38				
-I	0.43				
-CN	0.17	K	$-\Delta H(\text{kcal})$	$\Delta S(\text{eu})$	
-CH ₃	1.74 ⁶⁸	}	\rightarrow 19	1.75	-0.03
-CH ₂ CH ₃	1.79 ⁶⁸		\rightarrow 21	1.60	0.64
-CH(CH ₃) ₂	2.21 ⁶⁸		\rightarrow 42	1.52	2.31
-C(CH ₃) ₃	>5.4 ⁶⁹		\rightarrow 9432		
-C ₆ H ₁₁	2.15				entropy determines the trend
-C ₆ H ₅	3.0				
-COOH	1.35				
-COO ⁻	1.92				
-CO ₂ CH ₃	1.27				
-OH	0.52 (aprotic solvent)				
	0.87 (protic solvent)				
-OCH ₃	0.60				
-NH ₂	1.20 (aprotic solvent)				
	1.60 (protic solvent)				
-NH(CH ₃)	1.0 (aprotic solvent)				
-N(CH ₃) ₂	2.1 (protic solvent)				

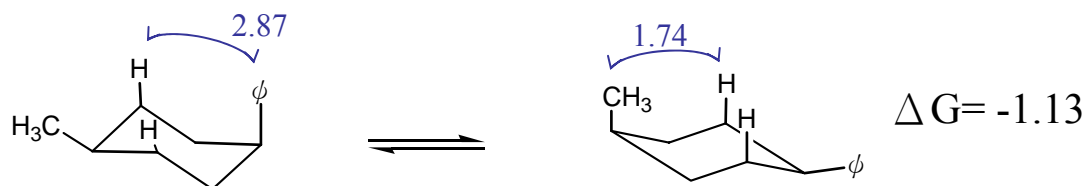
useful locking gp. \rightarrow

(Data from reference 70, except as noted.)

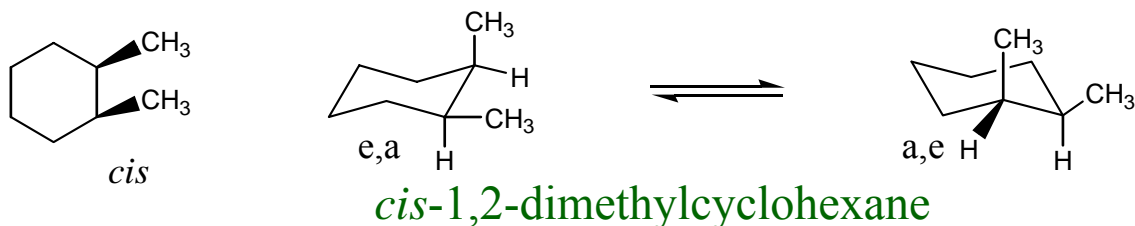
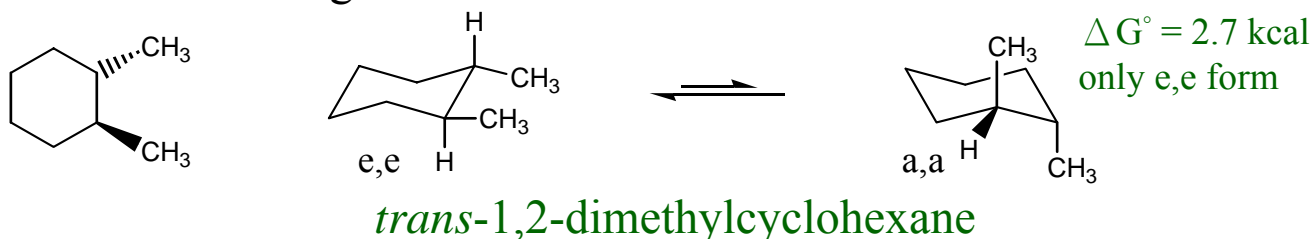
t-Butyl is a locking gp. so that it dictates the conformation.



if two substituents are non-interaction, the A-values are additive



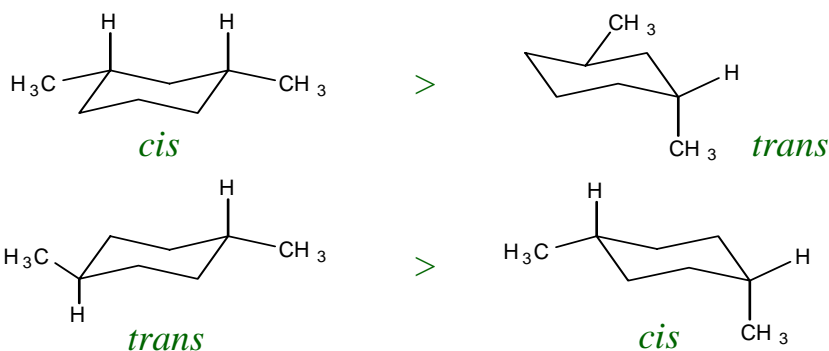
two interacting substituents



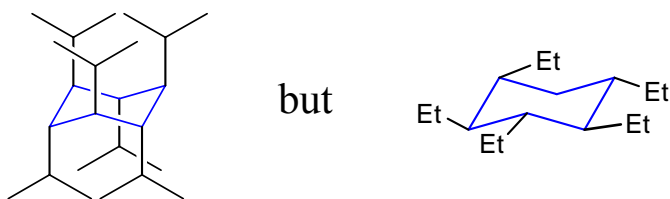
for *trans* the e,e form has one gauche interaction

for *cis* the e,a form = a,e form, has 2x1,3-diaxial + 1 gauche inter

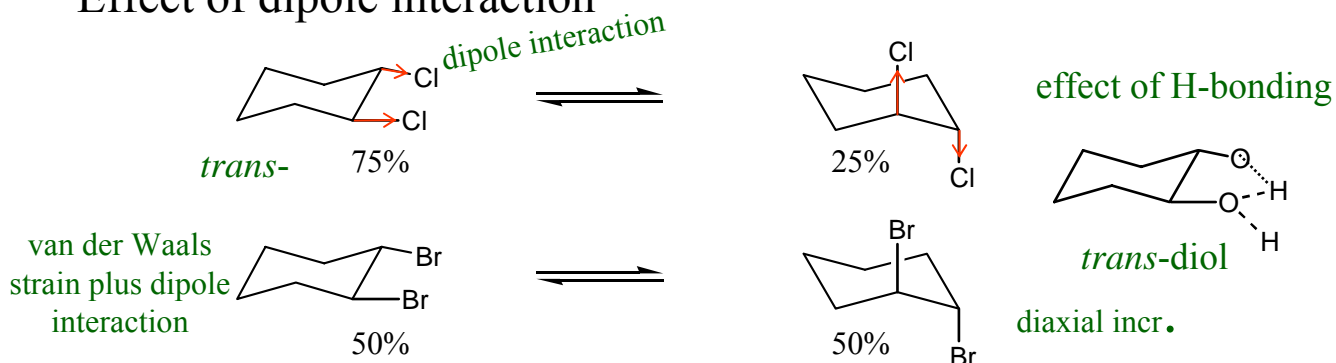
\therefore *trans* more stable by 2x1,3-diaxial $\sim 1.8 \text{ kcal}$ (expt'l 1.87)



Exception for favored equatorial preference may exist due to shape.

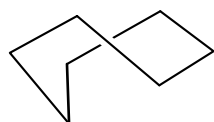


Effect of dipole interaction

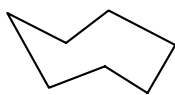


For larger rings, more conformations are possible due to the flexibility, but the strain may increase.

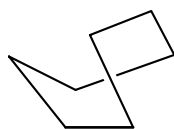
cycloheptane



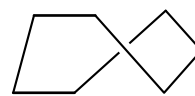
twist-chair
most stable



chair

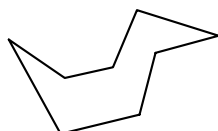


boat



twist-boat

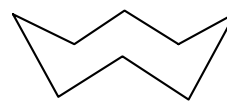
cyclooctane



boat-chair
most stable

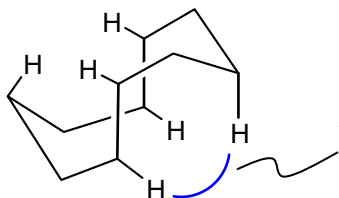


boat-boat



crown

cyclodecane




















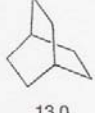
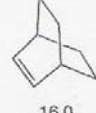

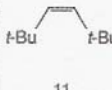
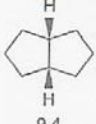
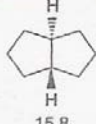
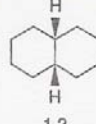
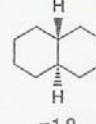
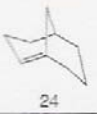
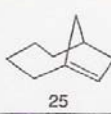
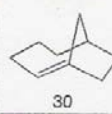
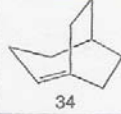

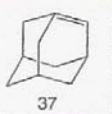

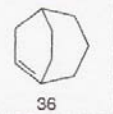
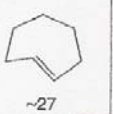




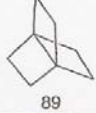






boat-chair-boat

van der Waals repulsion, release of this repulsion by twisting will introduce torsional strain.

Strain Energies and Group Increment Correction Factors for Cycloalkanes, $(CH_2)_n$ (in kcal/mol)

n	Strain energy	Group increment	n	Strain energy
3	27.5	27.6 angle & torsional	10	12.4
4	26.3		11	11.3
5	6.2	6.3 torsional strain	12	4.1
6	0.1		13	5.2
7	6.2	6.4 cross-ring vdw strain	14	1.9
8	9.7		15	1.9
9	12.6		16	2.0

 27.5	 54.5	 41	 26.3	 31-34	 29	 66.5	 65	 60-64
 57.3	 50.7	 6.2	 5.9	 5-6	 33.9	 41.2	 ~50	 17.0
 24-27	 13.0	 16.0	 12.1	 11	 9.4	 15.8	 1.2	 -1.9
 24	 25	 30	 34	 37	 37	 38	 36	 ~27
 16.7	 98	 104	 105	 89	 ~166	 ~140	 ~68	 31-33

For simple bicyclic system, the strain is close to the sum of individual rings.
 e.g. for bicyclo[3,1,0]heptane $6.2 + 27.5 = 33.7$ (expt'l 33.9)
 Exception for smaller rings due to extra strain by fusion.

Cycloalkene

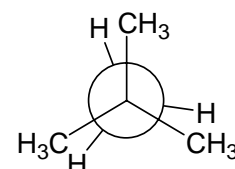
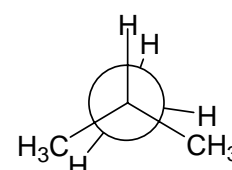
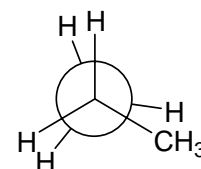
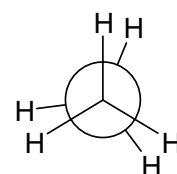
The *trans*-double bond introduces strain in a cyclic system. The smaller the ring is, the higher the strain is.

Bredt's rule: For bicyclo[a,b,c], the smallest number $S = a + b + c$ that can accommodate a bridgehead double bond.

The stability of bridgehead olefins follow the stability pattern of *trans* cyclic olefins.

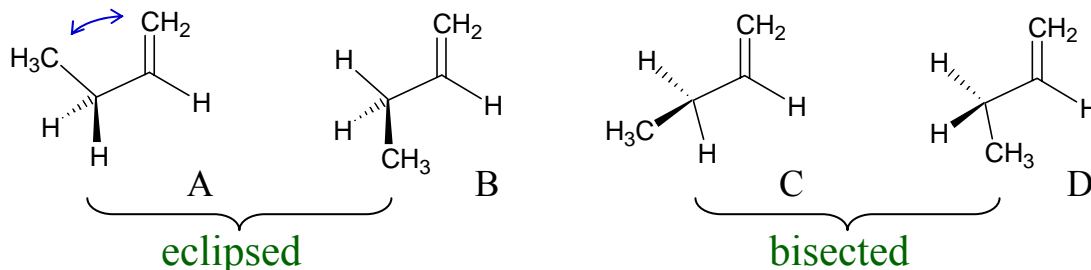
Table 3.3 Rotational Energy Barriers of Compounds of the Type CH₃-X

Compound		Barrier height (kcal/mol)
Alkanes		
1. CH ₃ -CH ₃	C-C 1.54Å	2.88
2. CH ₃ -CH ₂ CH ₃		3.4) 0.5
3. CH ₃ -CH(CH ₃) ₂		3.9) 0.5
4. CH ₃ -C(CH ₃) ₃		4.7) 0.8
5. CH ₃ -SiH ₃	Si-C	1.7
Haloethanes		
6. CH ₃ -CH ₂ F	1.87Å	3.3
7. CH ₃ -CH ₂ Cl	vdw inc.	3.7
8. CH ₃ -CH ₂ Br	↓ bond length inc.	3.7
9. CH ₃ -CH ₂ I		3.2
Heteroatom substitution		
10. CH ₃ -NH ₂	no. of eclipsed bonds	1.98
11. CH ₃ -NHCH ₃		3.62) 1.6, more sensitive
12. CH ₃ -OH		1.07
13. CH ₃ -OCH ₃		2.7) 1.6, due to shorter bond



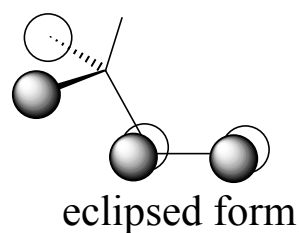
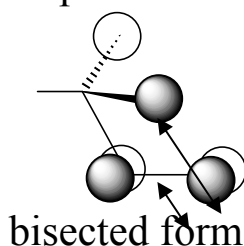
Ethane 2.88

1-Alkene



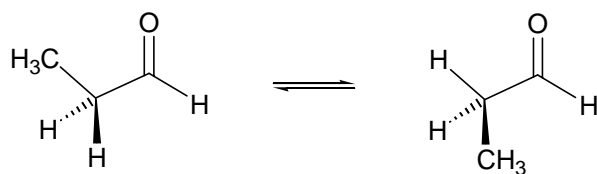
more stable, and B is slightly more stable than A (by 0.15kcal)
 increase the size of group at C-3
 increase the preference for B

by M.O. interpretation



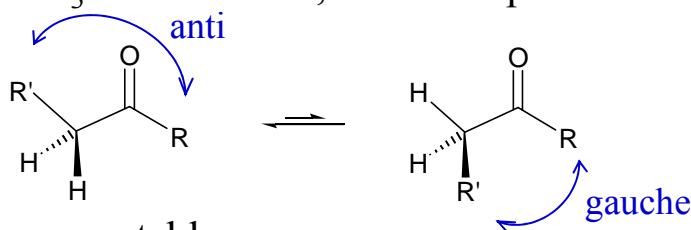
Major repulsive interaction between filled methyl and filled π

For carbonyl cpds.

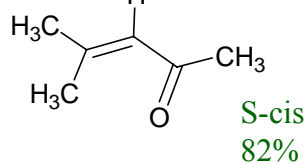
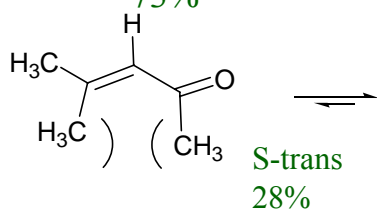
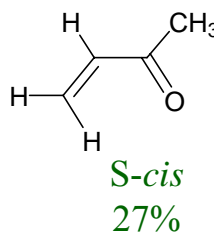
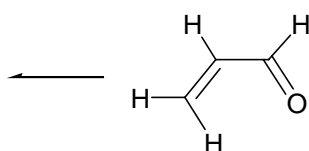
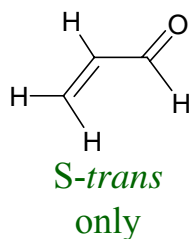
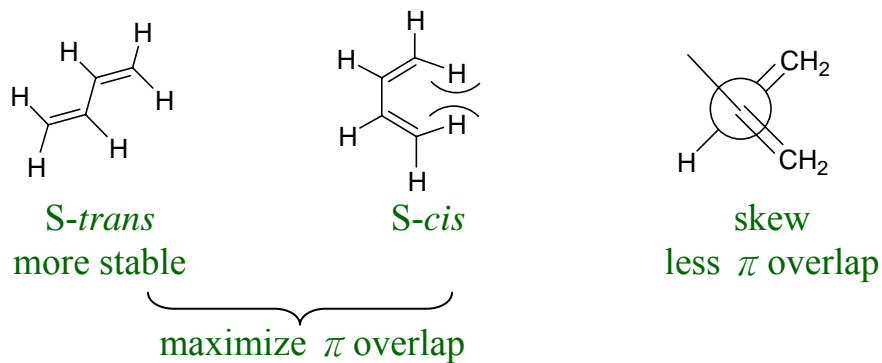


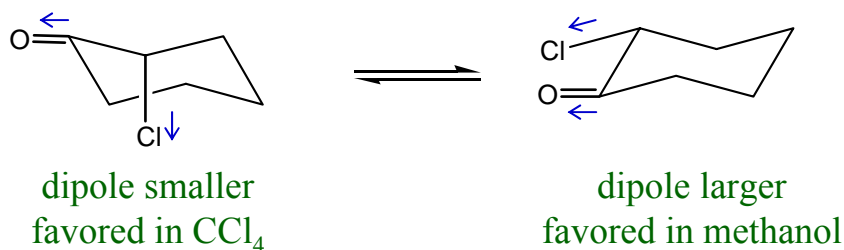
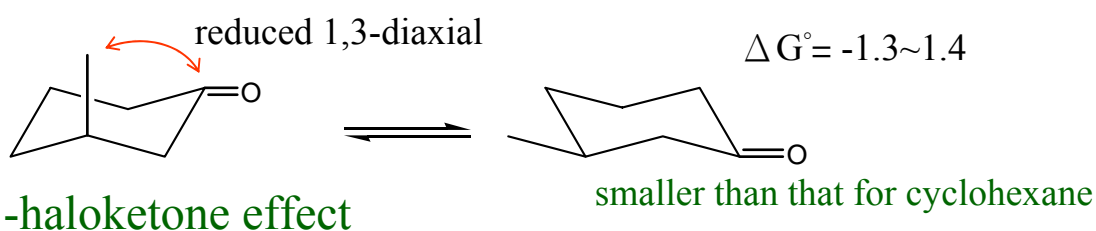
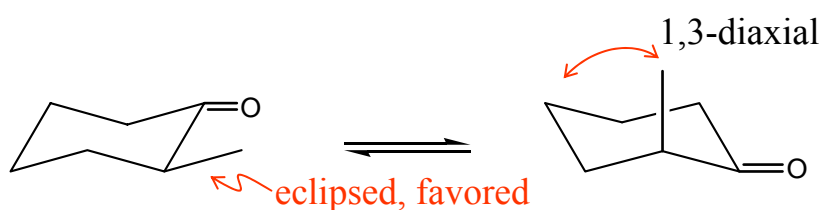
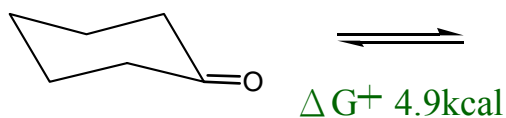
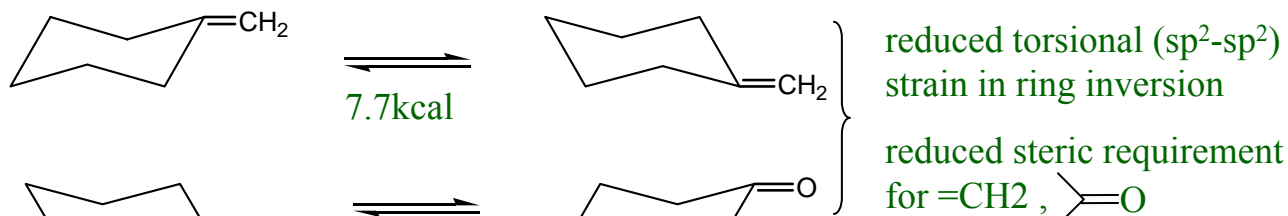
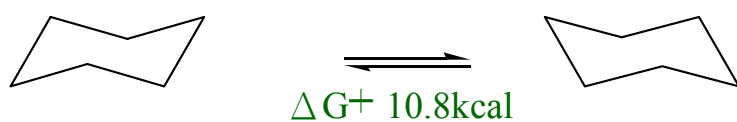
more stable by 0.9 kcal, (may due to non-bonded interaction between the C-H of the methyl and oxygen. C...H...O hydrogen bonding)

if CH₃ become *t*-Bu, the H-eclipsed becomes favored

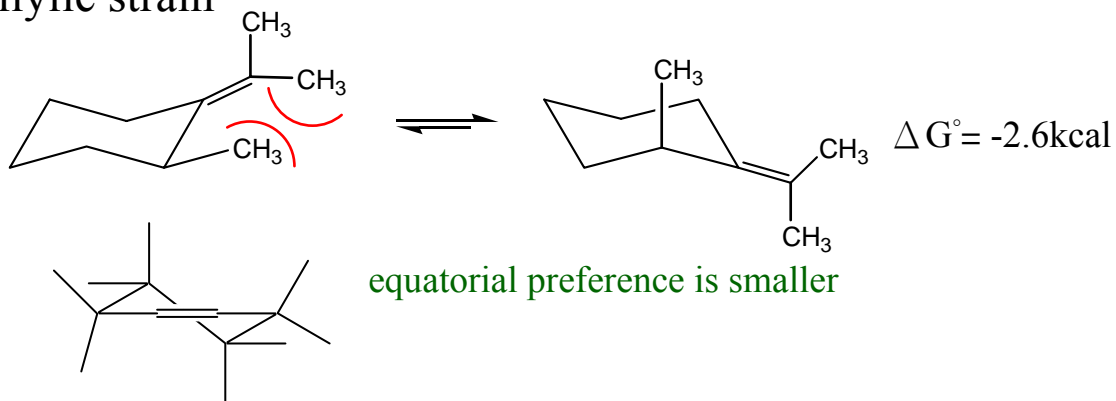


diene even more stable

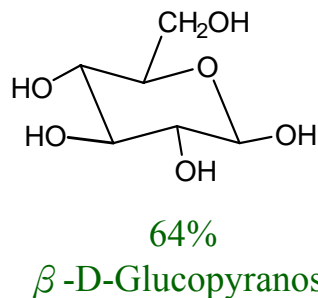
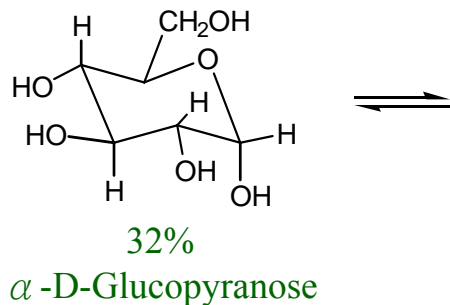




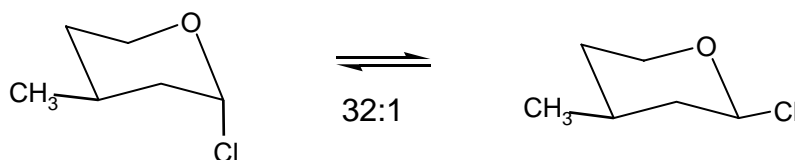
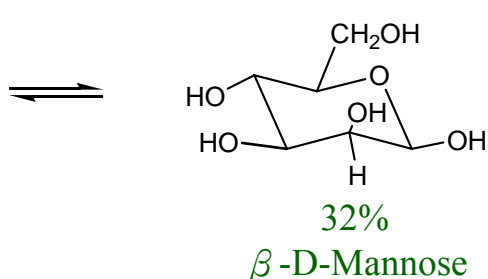
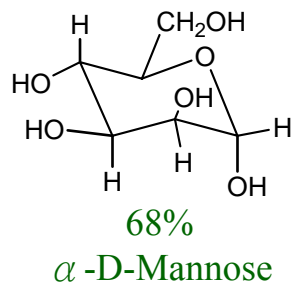
4. allylic strain



Anomeric Effects

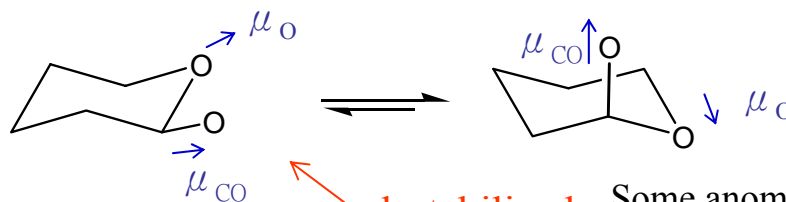


(By A of 0.87
90% exp'ted)



Suggested interpretations

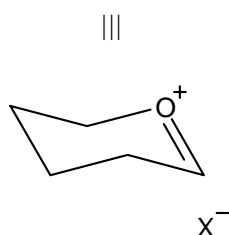
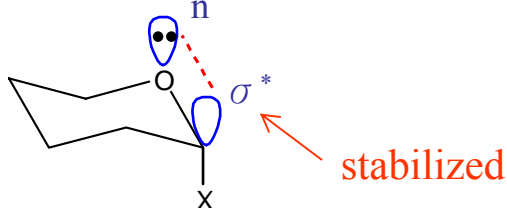
1. dipolar interaction



destabilized

Some anomeric effect are solvent dependent

2. Molecular orbital interaction

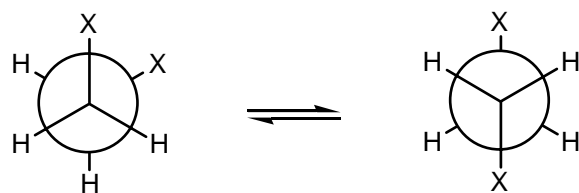


longer C-X bond

shorter O-C bond

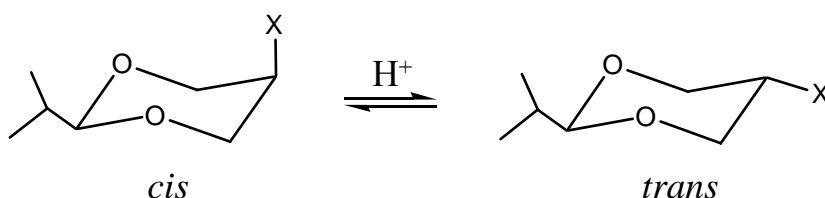
X-ray data agrees

Special Conformations



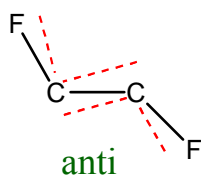
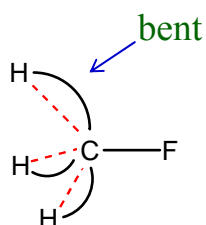
X	ΔE_{t-g}	
F	-0.6	gauche
Cl	1.2	} anti favored
Br	1.7	
I	2.6	

the gauche form increases with more electronegative atoms

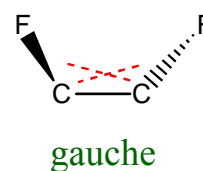


X	ΔE_{t-g}	
F	0.3	} gauche incr. for electronegative atoms
Cl	1.1	
Br	1.25	
OMe	0.63	

bent-bond interpretation : With more electronegative atom X
Small H-C-X angle expected



C-C bond length
longer by 0.01Å
(By *ab initio* calc.)



better overlap
bond length shorter

§ Molecular Mechanics

use classical mechanics, atoms and bonds are treated as mass and springs, to calculate the total energy of a conformation.

MM1, MM2, MM3, UFF,
N.L. Allinger

MM2 Total steric energy $E_{\text{steric}} = E(r) + E(\theta) + E(\Phi) + E(d)$

$E(r)$: the energy of stretching or compressing an individual bond

$E(\theta)$: energy of distorting a bond angle from ideal value

$E(\Phi)$: torsional strain (due to non-staggered bonds)

$E(d)$: non-bonded interaction, van der Waals force

$$E(r) = 0.5k_r \times (\Delta r)^2 \times (1 + CS \times \Delta r)$$

k_r : force constant

Δr : deformation of bond length

CS : cubic stretching constant

$$E(\theta) = 0.5k_\theta \times (\Delta \theta)^2 \times (1 + SF \times \Delta \theta^4)$$

stretching-bending E_{SB} strain energy may be added.

$$E(\Phi) = 0.5V_0 \times (1 + \cos 3\Phi)$$

more General term

$$E(\Phi) = 0.5V_1 \times (1 + \cos \Phi) + 0.5V_2 \times (1 - \cos 2\Phi) \\ + 0.5V_3 \times (1 + \cos 3\Phi)$$

$E(d)$ depends on extent and pattern of substitution. The interaction is attractive as the distance decreases, then repulsive at small distance.

Other terms include electrostatic interactions, hydrogen bonding...

Input File

```
gauche BUTANE
  1  2  3  4  0  0  0  0  0  0  0  0  0  0  0  0
  1  5  1  6  1  7  2  8  2  9  3 10  3 11  4 12
  4 13  4 14
-0.99450  0.36461  1.25785  1  -0.19237 -0.79026  0.64416  1
  0.16751 -0.57567 -0.83551  1  1.02035  0.67436 -1.08807  1
-1.22001  0.14650  2.32252  5  -0.40988  1.30620  1.19903  5
-1.94901  0.49837  0.70753  5  -0.76482 -1.73514  0.75297  5
  0.73596 -0.94743  1.23223  5  0.70118 -1.46973 -1.22046  5
-0.76285 -0.51485 -1.43806  5  1.24327  0.76931 -2.17124  5
  0.47470  1.58046 -0.75181  5  1.97614  0.60119 -0.52865  5
```

The molecular mechanics program reads the input file and uses the atom coordinates and bonding information to compute the steric energy of the initial conformation of the structure.¹¹⁷

Initial Calculation of Coordinates and Energy

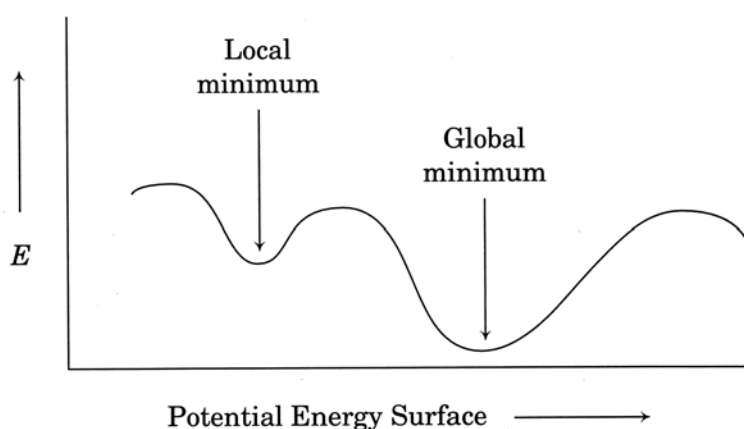
```
gauche BUTANE
GEOMETRY AND STERIC ENERGY OF INITIAL CONFORMATION.
CONNECTED ATOMS
  1- 2- 3- 4-
ATTACHED ATOMS
  1- 5, 1- 6, 1- 7, 2- 8, 2- 9, 3-10, 3-11, 4-12,
  4-13, 4-14,
INITIAL ATOMIC COORDINATES
ATOM      X      Y      Z      TYPE
C( 1)    -.99450  .36461  1.25785  ( 1)
C( 2)    -.19237  -.79026  .64416  ( 1)
C( 3)     .16751  -.57567  -.83551  ( 1)
C( 4)     1.02035  .67436  -1.08807  ( 1)
H( 5)    -1.22001  .14650  2.32252  ( 5)
H( 6)    -.40988  1.30620  1.19903  ( 5)
H( 7)    -1.94901  .49837  .70753  ( 5)
H( 8)    -.76482  -1.73514  .75297  ( 5)
H( 9)     .73596  -.94743  1.23223  ( 5)
H(10)     .70118  -1.46973  -1.22046  ( 5)
H(11)    -.76285  -.51485  -1.43806  ( 5)
H(12)     1.24327  .76931  -2.17124  ( 5)
H(13)     .47470  1.58046  -.75181  ( 5)
H(14)     1.97614  .60119  -.52865  ( 5)

INITIAL STERIC ENERGY IS 3.6711 KCAL.
  COMPRESSION      .1756
  BENDING          .6224
  STRETCH-BEND     .0670
  VANDERWAALS
    1,4 ENERGY    2.2947
    OTHER          .1294
  TORSIONAL       .3820
```

¹¹⁷For clarity, some parts of the output file not discussed here have been omitted from the listing.

To calculate the strain, an initial conformation is assigned and iterative minimization of total strain energy is carried out.

- a minimum in total energy may contain components that is not the lowest among all conformers
- the calculation approaches local minimum, which may not be a global minimum, so that initial assignment of conformation is important.



Cyclohexane case

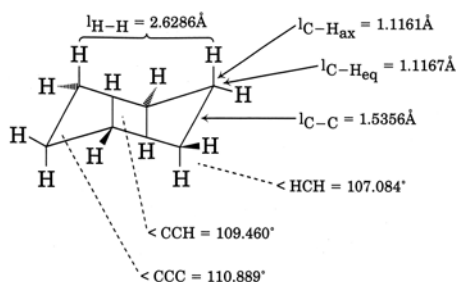
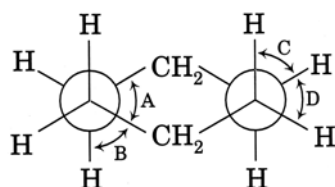


Table 3.6 Selected van der Waals interactions from an MM2 calculation.

Atom Pair	R (Å)	Σ vdW radii (Å)	Energy (kcal/mol)
C1 - C4	2.959	3.800	0.312
C1 - H11	2.810	3.340	0.102
C1 - H12	3.499	3.340	-0.053
C1 - H13	3.971	3.340	-0.035
C1 - H14	3.376	3.340	-0.054
C1 - H15	2.769	3.340	0.102
C1 - H16	3.499	3.340	-0.053

Table 3.7 Calculated contributions to steric energy of cyclohexane in the chair conformation.

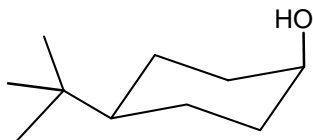
Parameter	E (kcal/mol)
Compression	0.3376
Bending	0.3652
Stretch-bend	0.0826
van der Waals	
1,4-interaction	4.6733
other	-1.0633
Torsional	2.1556
Total	6.5510



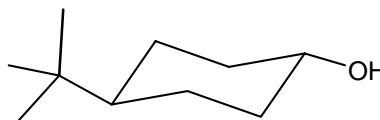
A = 56.33° B = 64.51°
C = 57.26° D = 60.10°

Conformational effects on reactivity

cis-



trans-



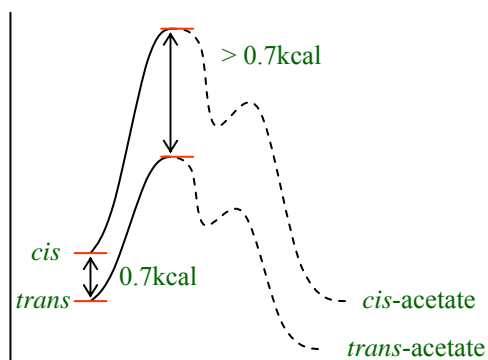
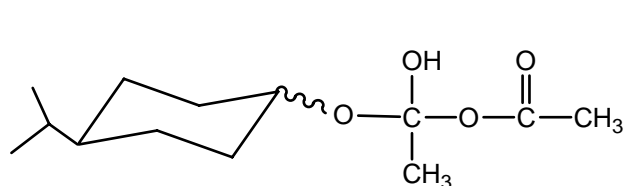
Rel. rate of oxidation

3.23 : 1

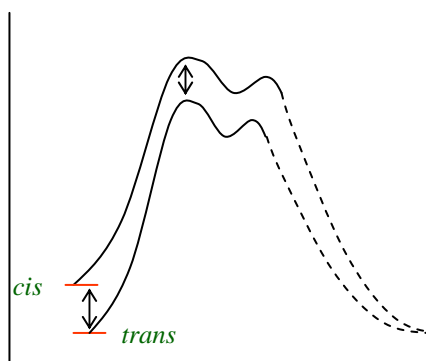
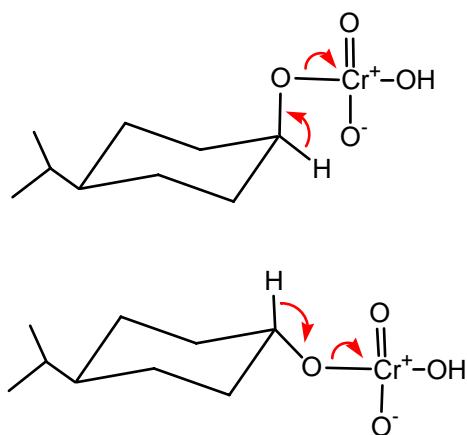
Rel. rate of acetylation

1 : 3.7

the rate is determined by the transition state energy



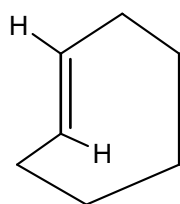
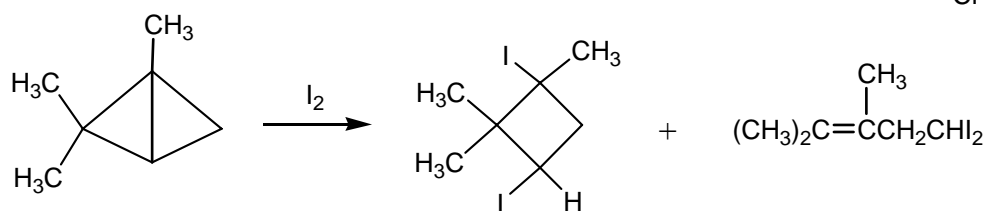
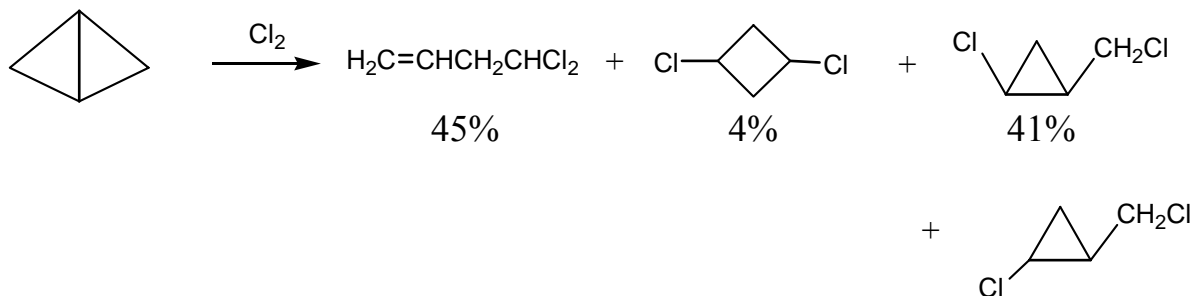
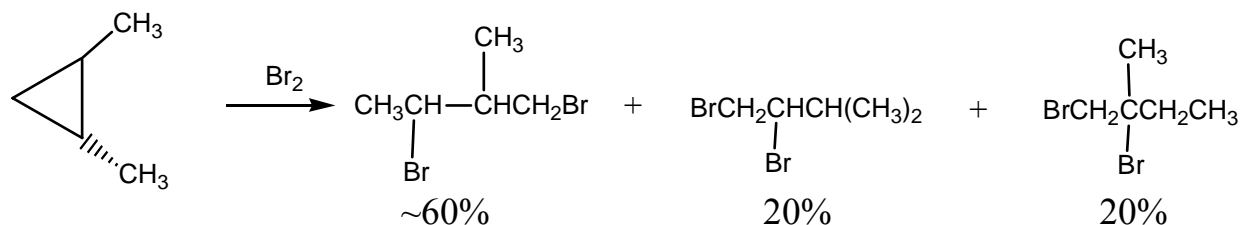
energy difference in T.S. increases due to larger gp.



In transition state, the diaxial interaction is released by going from $sp^3 \rightarrow sp^2$

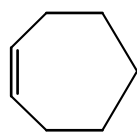
Effect of angle strain on reactivity

Smaller rings are more strained and more reactive.



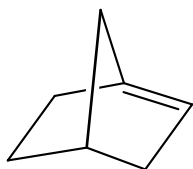
Coplanarity of double bond substituents can only exist transiently.

trans-cyloalkene,



with ring size ≥ 11 , the trans-isomers become more stable

Bridge head double bond



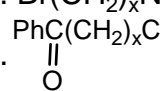
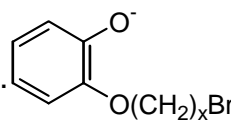
Bred't rule : the existence of C=C or C=N bonds (1924) at a bridgehead position in a polycyclic system is not possible, unless for large rings.

Effect of Ring Size and Ring Closure facility

Roughly the rate of ring closure for a particular rxn

$$5 > 6 > 3 > 7 > 4 > 8 \sim 10$$

Scheme 3.4 Relative Rates of Ring Closure as a Function of Ring Size

Reaction	Ring size =	Relative rate					
		3	4	5	6	7	8
1. $\text{Br}(\text{CH}_2)_x\text{CO}_2^- \rightarrow$ lactone		8.3×10^{-4}	0.31	90	1	$\frac{0.005}{2}$	6×10^{-5}
2. $\text{Br}(\text{CH}_2)_x\text{NH}_2 \rightarrow$ cyclic amine		0.07	0.001	100	1	0.002	—
3.  \rightarrow nucleophilic participation in solvolysis		—	0.37	36	1	0.13	—
4.  \rightarrow cyclic ether formation		—	—	—	1	0.01	4×10^{-4}
5. $\text{ArSO}_2\text{N}(\text{CH}_2)_x\text{Cl} \rightarrow$ cyclization		17	33	—	1	—	—

Small ring disfavored by enthalpy

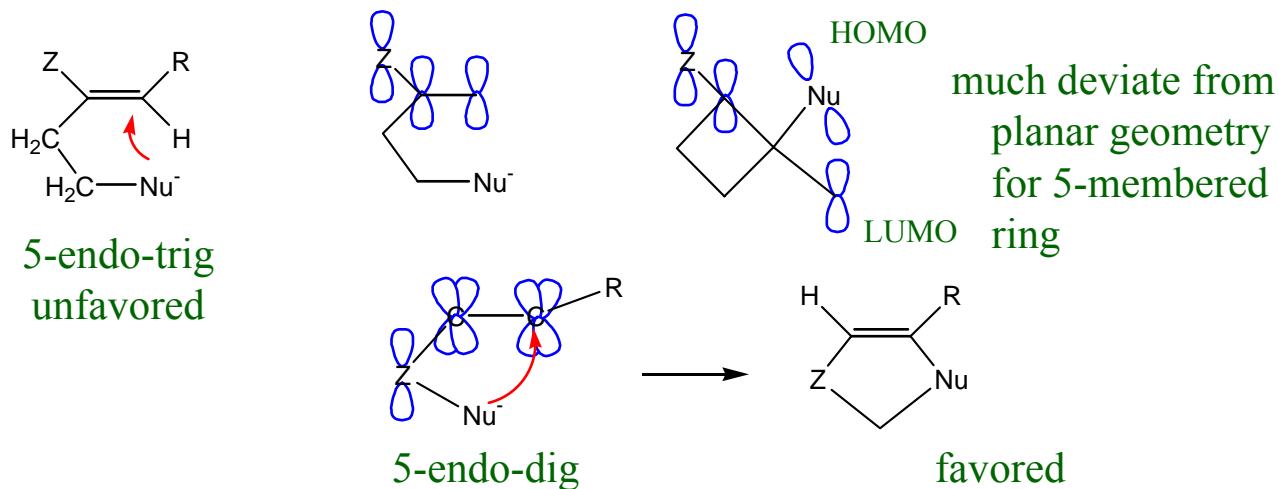
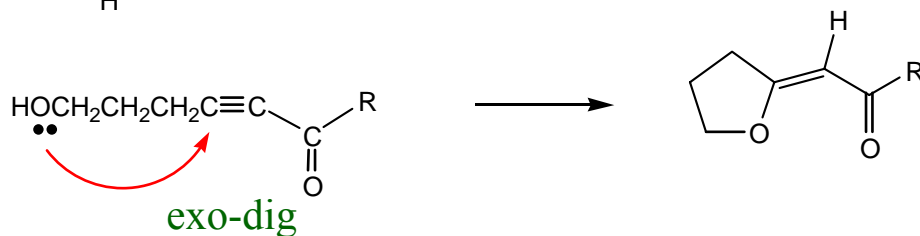
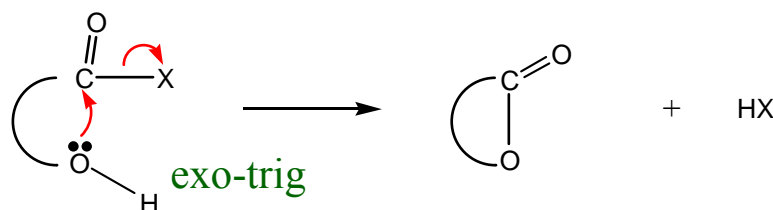
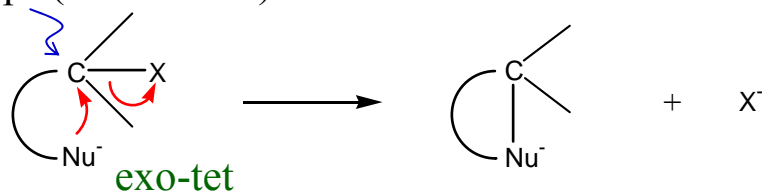
Large ring disfavored by entropy

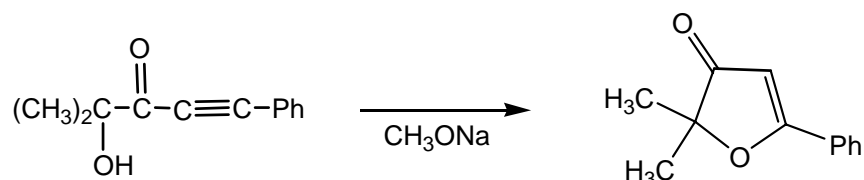
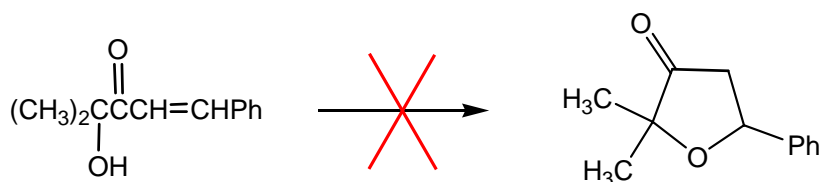
Baldwin's Rule

Table 3.11 Classification of Ring-Closure Types

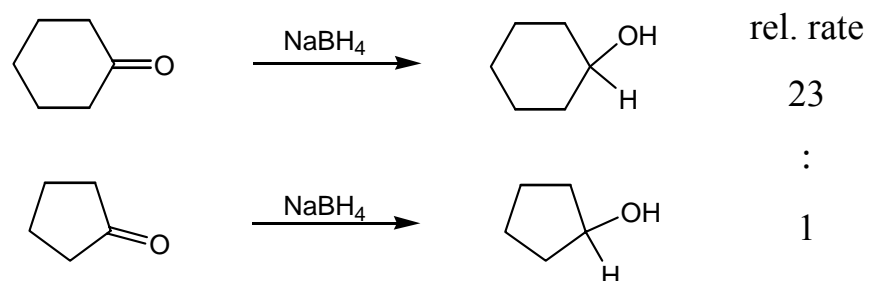
Ring size	Exocyclic bonds			Endocyclic bonds	
	sp (dig)	sp ² (trig)	sp ³ (tet)	sp (dig)	sp ² (trig)
3	unfav	fav	fav	fav	fav
4	unfav	fav	fav	fav	unfav
5	fav	fav	fav	fav	unfav
6	fav	fav	fav	fav	fav
7	fav	fav	fav	fav	fav

sp³ (tetrahedral)



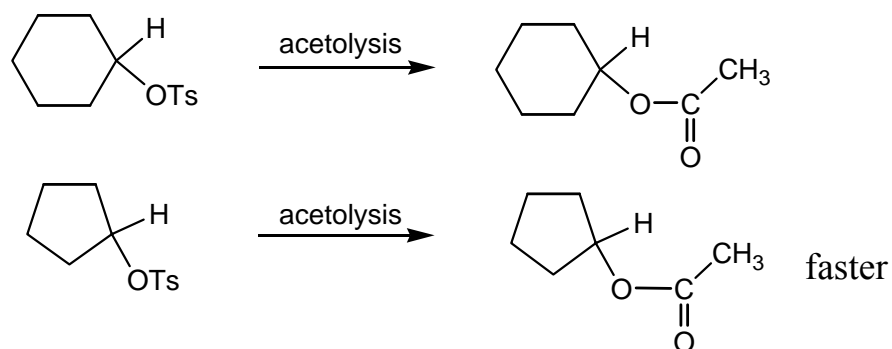


Effect of torsional strain

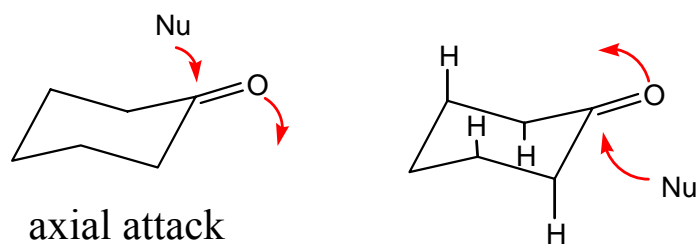


reactivity

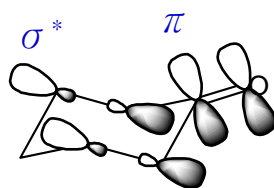
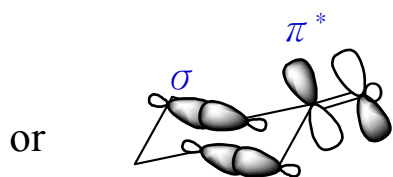
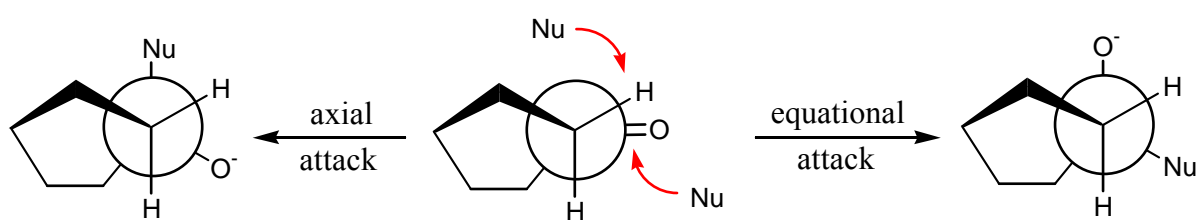
The rxn converts a sp^2 carbon to sp^3 carbon
 in 6-membered ring, all staggered bonds
 in 5-membered ring, eclipsing interaction increases



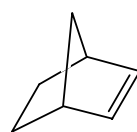
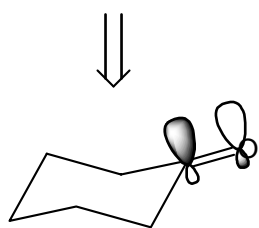
In transition state, a sp^3 is converted to sp^2 ,
 eclipsing effect in 5-membered ring released.



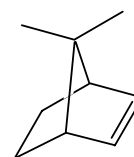
Bulky reagents attack from the equatorial direction (steric control)
 Smaller nucleophiles attack from axial direction



Stereo electronic effect



exo : endo



exo : endo

B_2H_6
 Hydroboration
 RCO_3H
 Epoxidation
 H_2, Pd
 hydrogenation

99.5 0.5
 99.5 0.5
 90 10

22 78
 12 88
 10 90