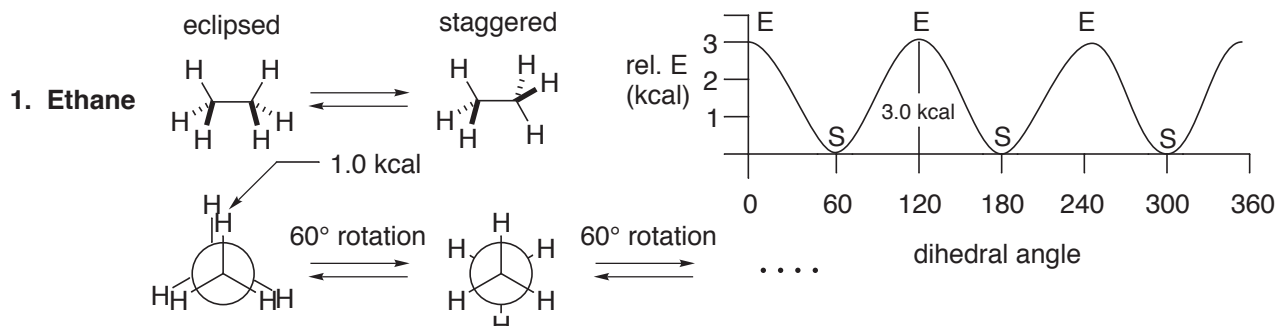
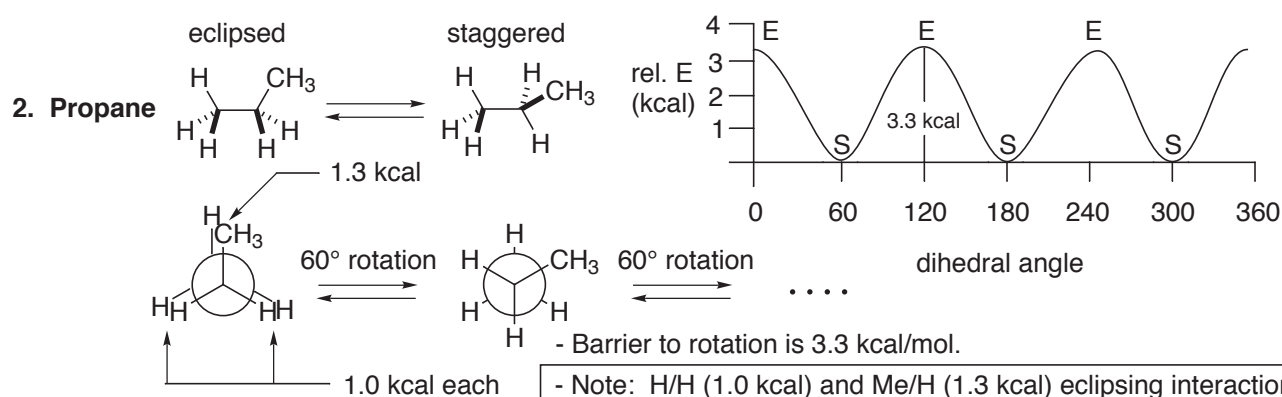


I. Conformational Analysis

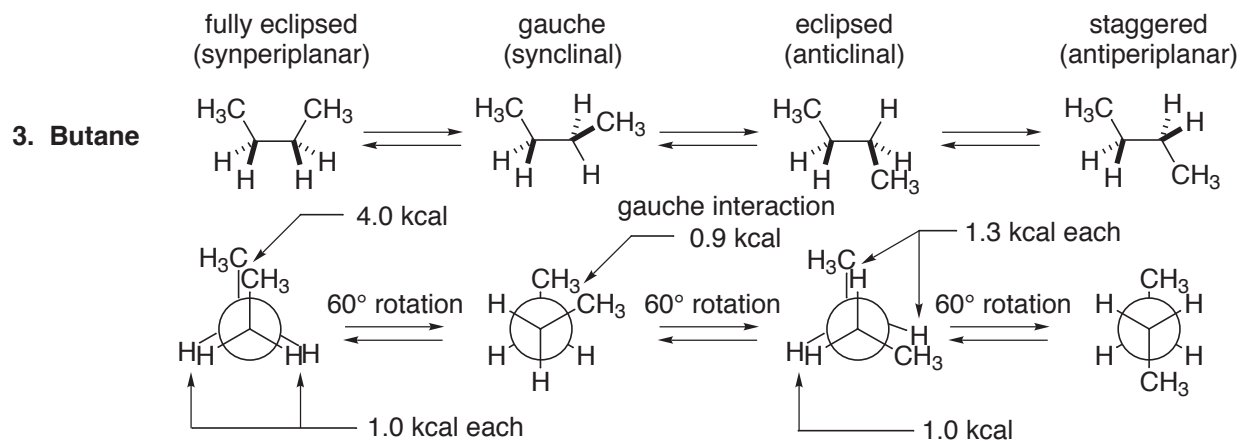
A. Acyclic sp^3 - sp^3 Systems: Ethane, Propane, Butane



- Two extreme conformations, barrier to rotation is 3.0 kcal/mol.



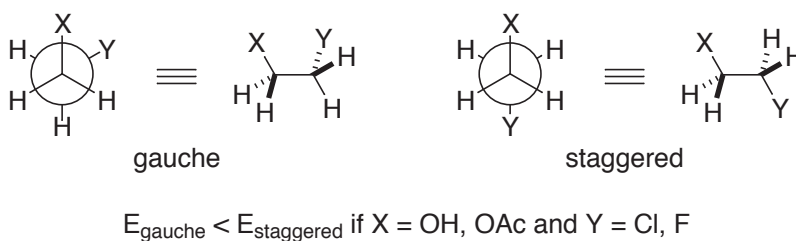
- Barrier to rotation is 3.3 kcal/mol.
- Note: H/H (1.0 kcal) and Me/H (1.3 kcal) eclipsing interactions are comparable and this is important in our discussions of torsional strain.



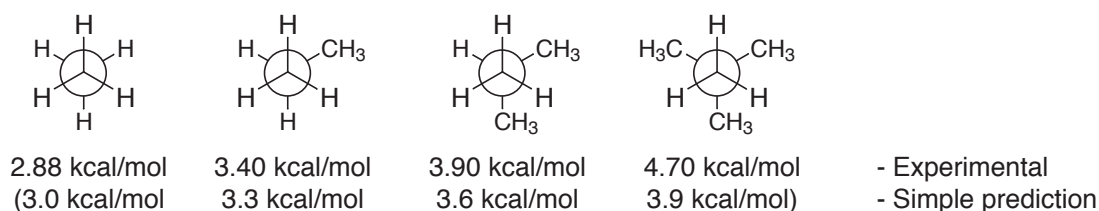
- Note: the gauche butane interaction and its magnitude (0.9 kcal) are very important and we will discuss it frequently.

4. Substituted Ethanes

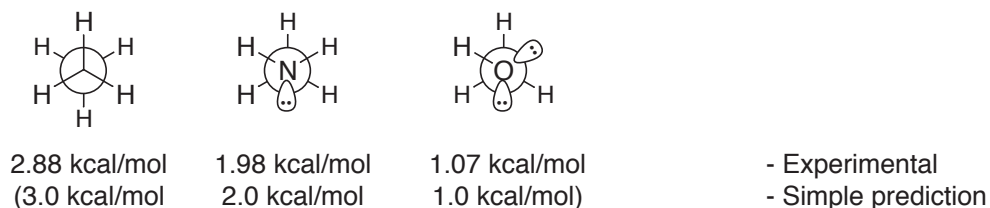
- There are some exceptions to the lowest energy conformation. Sometimes, a gauche conformation is preferred over staggered if X,Y are electronegative substituents.
cf: Kingsbury *J. Chem. Ed.* **1979**, 56, 431.



5. Rotational Barriers



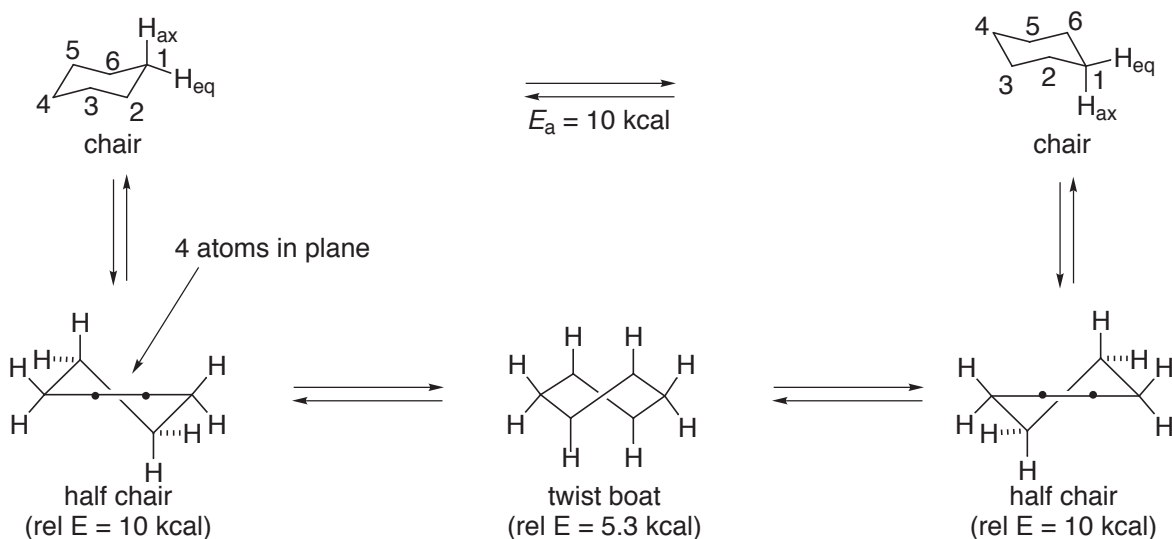
- The rotational barrier increases with the number of CH₃/H eclipsing interactions.



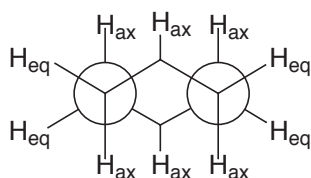
- The rotational barrier increases with the number of H/H eclipsing interactions.

B. Cyclohexane and Substituted Cyclohexanes, A Values (ΔG°)

1. Cyclohexane

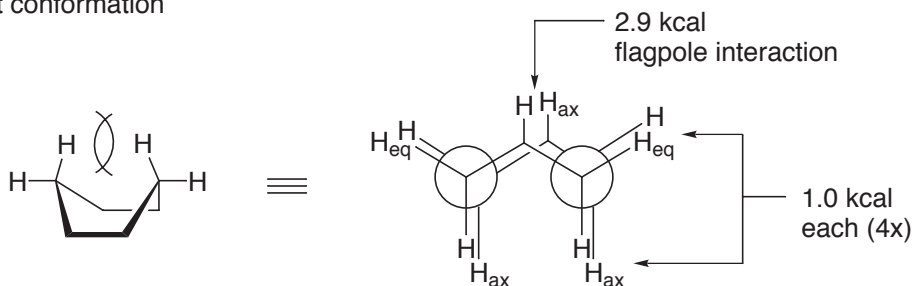


- Chair conformation (all bonds staggered)



- Rapid interconversion at 25 °C ($E_a = 10$ kcal/mol, 20 kcal/mol available at 25 °C).
- H_{ax} and H_{eq} are indistinguishable by 1H NMR at 25 °C.
- At temperatures < -70 °C, H_{eq} and H_{ax} become distinct in 1H NMR.

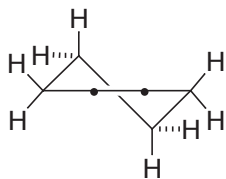
- Boat conformation



- Rel E = 6.9 kcal, not local minimum on energy surface.
- More stable boat can be obtained by twisting (relieves flagpole interaction somewhat).
- Twist boat conformation (rel E = 5.3 kcal) does represent an energy minimum.
- The boat conformation becomes realistic if flagpole interactions are removed, i.e.

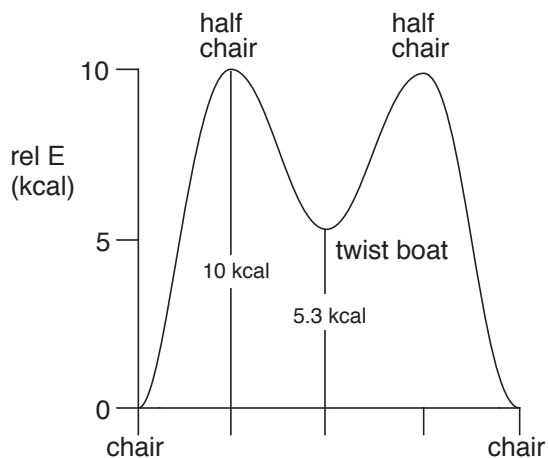


- Half chair conformation



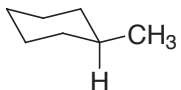
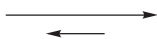
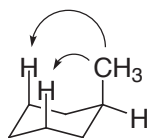
- Energy maximum (rel E = 10.0 kcal)

D.H.R. Barton received the 1969 Nobel Prize in Chemistry for his contributions to conformational analysis, especially as it relates to steroids and six-membered rings. Barton *Experientia* **1950**, 6, 316.



2. Substituted Cyclohexanes

- Methylcyclohexane



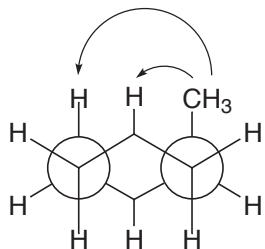
1.8 kcal more stable

$$\Delta G^\circ = -RT(\ln K)$$

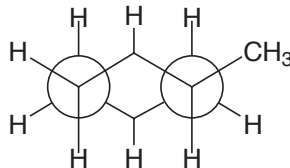
$$\frac{-1.8 \times 1000}{1.99 \times 298} = -\ln K$$

$$K = 21$$

- The gauche butane interaction is most often identifiable as 1,3-diaxial interactions.



2 gauche butane interactions
 $2 \times 0.9 \text{ kcal} = 1.8 \text{ kcal}$
(experimental 1.8 kcal)



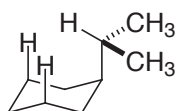
0 gauche butane interactions

- A Value ($-\Delta G^\circ$) = Free energy difference between equatorial and axial substituent on a cyclohexane ring.

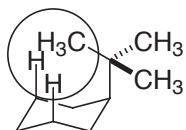
Typical A Values

R	A Value (kcal/mol)	R	A Value (kcal/mol)
F	0.25	CN	0.2
Cl	0.52	C≡CH	0.41
Br	0.5–0.6	NO ₂	1.1
I	0.46	CH=CH ₂	1.7
OH	0.7 (0.9)	CH ₃	1.8
OCH ₃	0.75	CH ₂ CH ₃	1.9 (1.8)
OCOCH ₃	0.71	ⁿ C ₃ H ₇	2.1
NH ₂	1.8 (1.4)	ⁿ C ₄ H ₉	2.1
NR ₂	2.1	CH(CH ₃) ₂	2.1
CO ₂ H	1.2 (1.4)	C(CH ₃) ₃	>4.5 (ca. 5.4)
CO ₂ Na	2.3	C ₆ H ₅	3.1 (2.9)
CO ₂ Et	1.1		
SO ₂ Ph	2.5		

- Note on difference between ⁱPr and ^tBu A values.

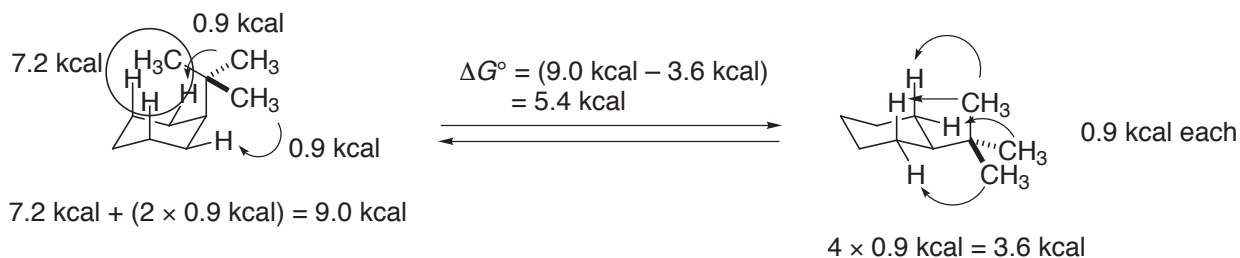


ⁱPr group can position
H toward "inside,"

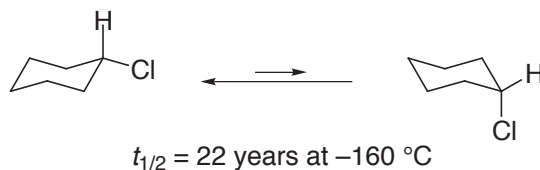


but ^tBu group cannot.
Very serious interaction, 7.2 kcal.

- Determination of A value for ^tBu group.

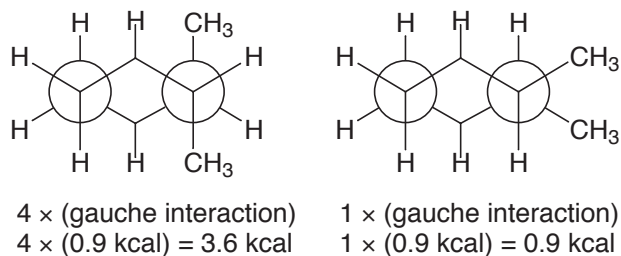
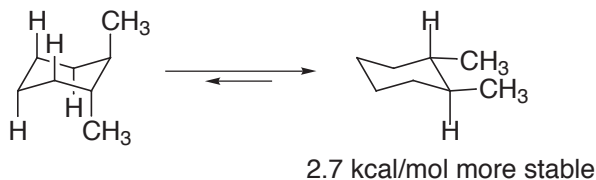


- Note on interconversion between axial and equatorial positions.

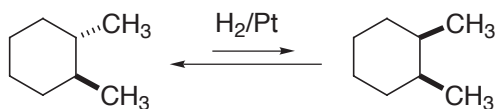
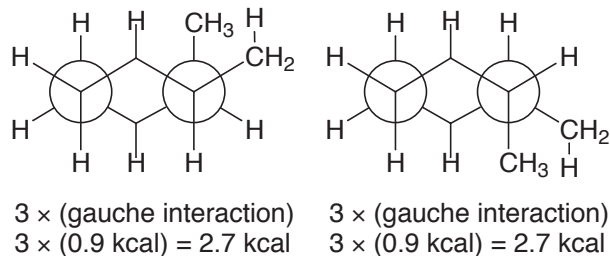
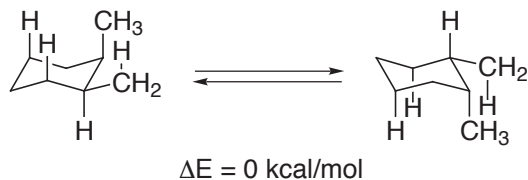


Even though Cl has a small A value (i.e., small ΔG° between rings with equatorial and axial Cl group), the E_a (energy of activation) is high (it must go through half chair conformation).

trans-1,2-dimethylcyclohexane



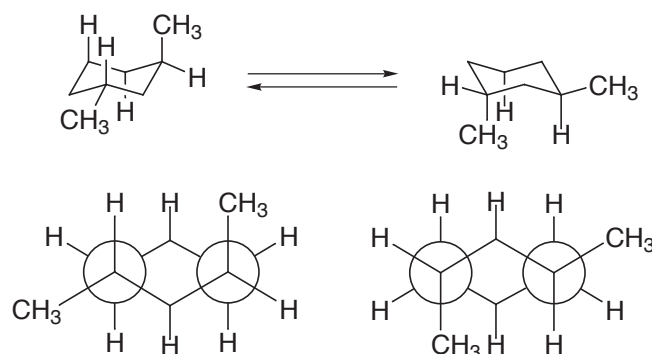
cis-1,2-dimethylcyclohexane



$\Delta G = 1.87 \text{ kcal/mol (exp)}$
 $\Delta G = 1.80 \text{ kcal/mol (calcd)}$

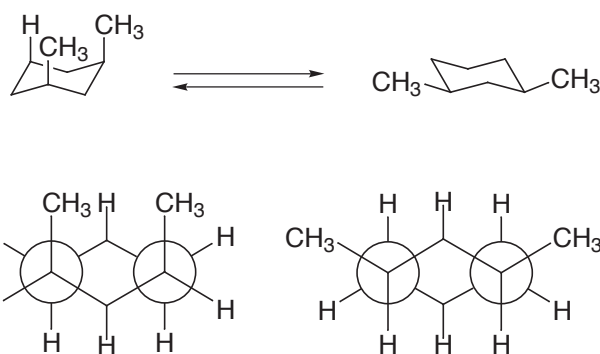
trans-1,3-dimethylcyclohexane

cis-1,3-dimethylcyclohexane



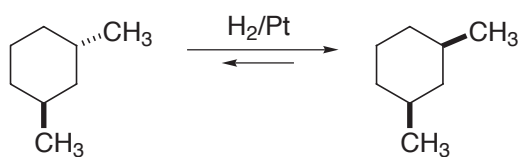
2 × (gauche interaction)
2 × (0.9 kcal) = 1.8 kcal

2 × (gauche interaction)
2 × (0.9 kcal) = 1.8 kcal



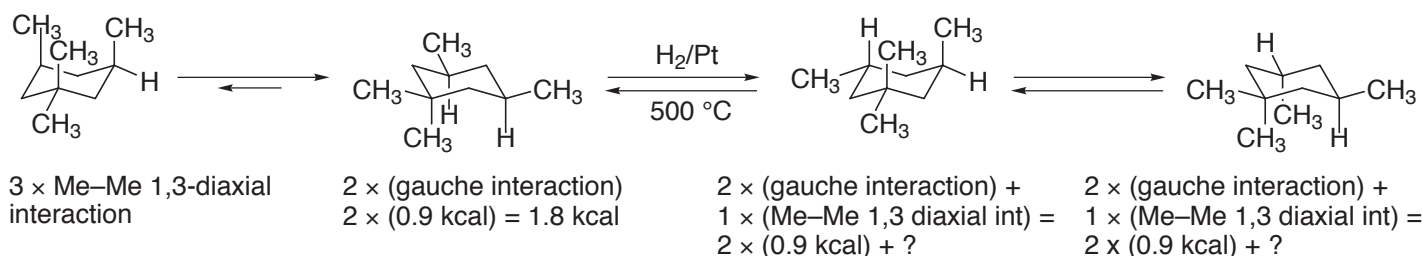
2 × (gauche interaction) +
1 × (Me–Me 1,3 diaxial int)
2 × (0.9 kcal) + 3.7 kcal
= 5.5 kcal

0 × (gauche interaction)
0 × (0.9 kcal) = 0 kcal



$\Delta G = 1.80$ kcal/mol (exp and calcd)

- Determination of energy value of Me–Me 1,3-diaxial interaction.



3 × Me–Me 1,3-diaxial
interaction

2 × (gauche interaction)
2 × (0.9 kcal) = 1.8 kcal

2 × (gauche interaction) +
1 × (Me–Me 1,3 diaxial int) =
2 × (0.9 kcal) + ?

2 × (gauche interaction) +
1 × (Me–Me 1,3 diaxial int) =
2 × (0.9 kcal) + ?

$\Delta G = 3.7$ kcal/mol (exp)
So, Me–Me 1,3-diaxial interaction = 3.7 kcal/mol.

1,3-diaxial interactions

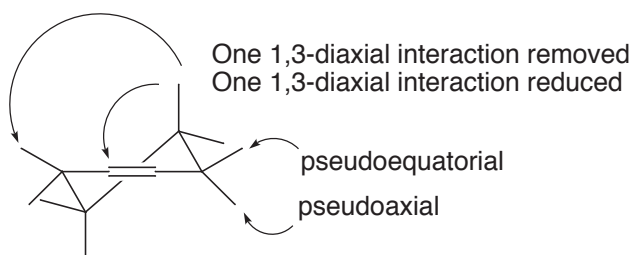
R/R	ΔG°
OH/OH	1.9 kcal
OAc/OAc	2.0 kcal
OH/CH ₃	2.4 (1.6) kcal
CH ₃ /CH ₃	3.7 kcal

ΔG° of common interactions

	ax OH	ax CH ₃	eq OH
ax H	0.45*	0.9	0.0
ax OH	1.9	1.6	0.35
eq OH	0.35	0.35	0.35
eq CH ₃	0.35	0.9	0.35

*1/2 of A value

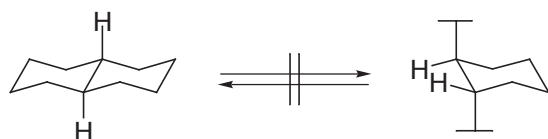
C. Cyclohexene



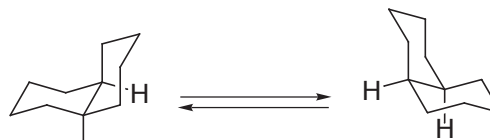
- half-chair
- E_a for ring interconversion = 5.3 kcal/mol
- the preference for equatorial orientation of a methyl group in cyclohexene is less than in cyclohexane because of the ring distortion and the removal of one 1,3-diaxial interaction (1 kcal/mol)

D. Decalins

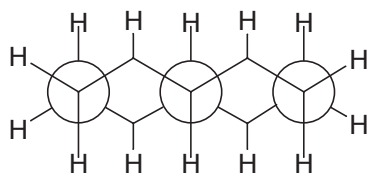
trans-decalin



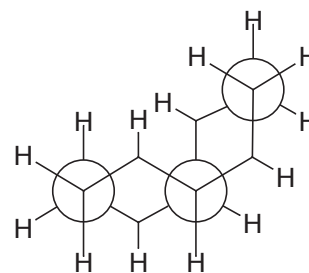
cis-decalin



two conformations equivalent



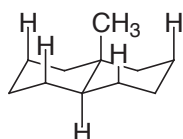
0.0 kcal



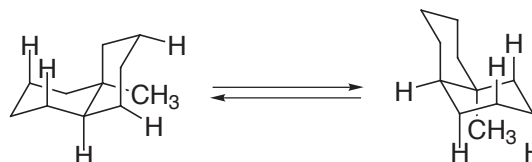
3 gauche interactions
 $3 \times 0.9 \text{ kcal} = 2.7 \text{ kcal}$

ΔE between *cis*- and *trans*-decalin = 2.7 kcal/mol

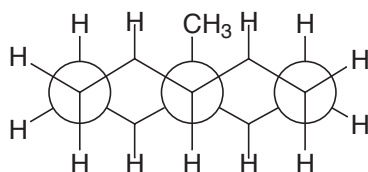
trans-9-methyldecalin



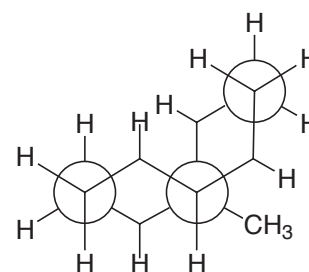
cis-9-methyldecalin



two conformations equivalent



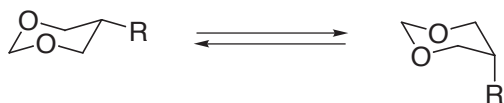
4 gauche interactions
 $4 \times 0.9 = 3.6 \text{ kcal}$



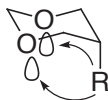
5 gauche interactions
 $5 \times 0.9 = 4.5 \text{ kcal}$

ΔE between *cis*- and *trans*-9-methyldecalin = 0.9 kcal/mol

E. 1,3-Dioxanes



- Less preference for R group to be equatorial because the lone pair has a smaller steric requirement than a C–H bond (ΔG° lower).
- In fact, some polar substituents (i.e. F, NO₂, SOCH₃, ⁺NMe₃, etc) prefer axial position.



F. Acyclic sp³–sp² Systems

- Key references

- Origin of destabilization for eclipsed conformations:

Lowe	<i>Prog. Phys. Org. Chem.</i> 1968 , 6, 1.
Oosterhoff	<i>Pure Appl. Chem.</i> 1971 , 25, 563.
Wyn-Jones, Pethrick	<i>Top. Stereochem.</i> 1970 , 5, 205.
	<i>Quat. Rev., Chem. Soc.</i> 1969 , 23, 301.
Brier	<i>J. Mol. Struct.</i> 1970 , 6, 23.
Lowe	<i>Science</i> 1973 , 179, 527.

- Molecular orbital calculations: Repulsion of overlapping filled orbitals:

Pitzer	<i>Acc. Chem. Res.</i> 1983 , 16, 207.
--------	-----------------------------------------------

- Propionaldehyde:

Butcher, Wilson	<i>J. Chem. Phys.</i> 1964 , 40, 1671.
Allinger, Hickey	<i>J. Mol. Struct.</i> 1973 , 17, 233.
Allinger	<i>J. Am. Chem. Soc.</i> 1969 , 91, 337.
- Propene:

Allinger	<i>J. Am. Chem. Soc.</i> 1968 , 90, 5773.
Herschbach	<i>J. Chem. Phys.</i> 1958 , 28, 728.
- 1-Butene:

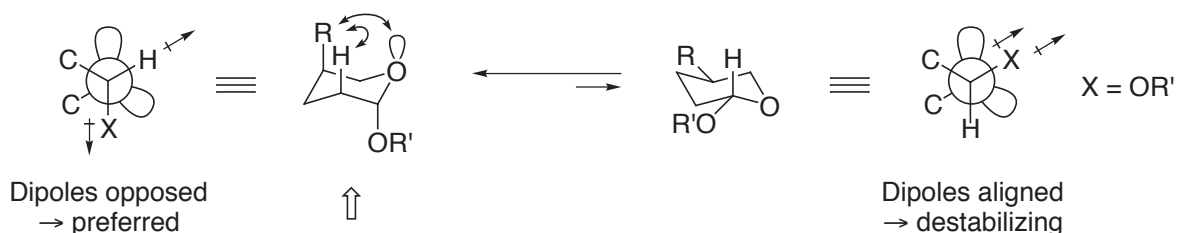
Geise	<i>J. Am. Chem. Soc.</i> 1980 , 102, 2189.
-------	---------------------------------------------------
- Allylic 1,3-strain:

Houk, Hoffmann	<i>J. Am. Chem. Soc.</i> 1991 , 113, 5006.
Hoffmann	<i>Chem. Rev.</i> 1989 , 89, 1841.

Jacobus van't Hoff received the first Nobel Prize in Chemistry (1901) in recognition of his discovery of the laws of chemical kinetics and the laws governing the osmotic pressure of solutions. More than any other person, he created the formal structure of physical chemistry and he developed chemical stereochemistry which led chemists to picture molecules as objects with three dimensional shapes. He published his revolutionary ideas about chemistry in three dimensions just after his 22nd birthday in 1874, before he completed his Ph.D, in a 15 page pamphlet which included the models of organic molecules with atoms surrounding a carbon atom situated at the apexes of a tetrahedron. Interestingly, these proposals which serve as the very basis of stereochemistry today were met with bitter criticism.

G. Anomeric Effect

1. Tetrahydropyrans (e.g., Carbohydrates)



$R = H$, preferred conformation. $\Delta G^\circ = 0.85$ kcal/mol

- generally 0–2 kcal/mol, depends on C2/C3 substituents
- effect greater in non-polar solvent

Comprehensive Org. Chem. Vol. 5, 693.

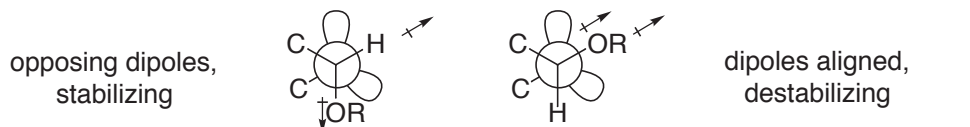
Comprehensive Het. Chem. Vol. 3, 629.

Review: *Tetrahedron* **1992**, 48, 5019.

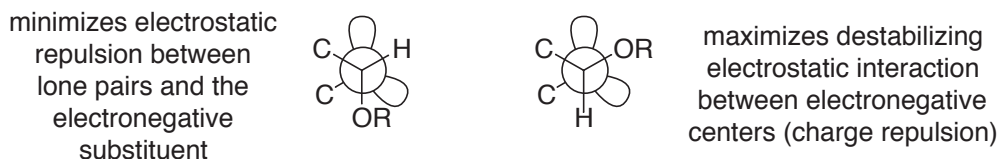
1. A value for R group will be smaller, less preference for equatorial vs axial C3 or C5 substituent since one 1,3-diaxial interaction is with a lone pair versus C–H bond.
2. Polar, electronegative group (e.g., OR and Cl) adjacent to oxygen prefers axial position.
3. Alkyl group adjacent to oxygen prefers equatorial position.
4. Electropositive group (such as $^+NR_3$, NO_2 , $SOCH_3$) adjacent to oxygen strongly prefers equatorial position. \Rightarrow Reverse Anomeric Effect

- Explanations Advanced:

1. Dipole stabilization

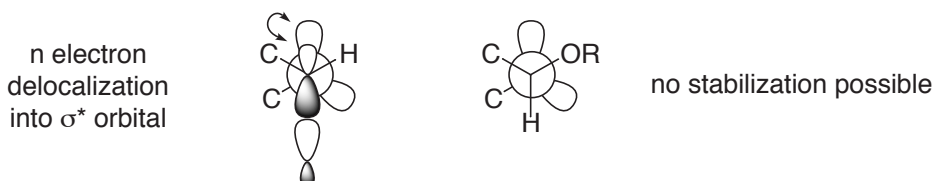


2. Electrostatic repulsion

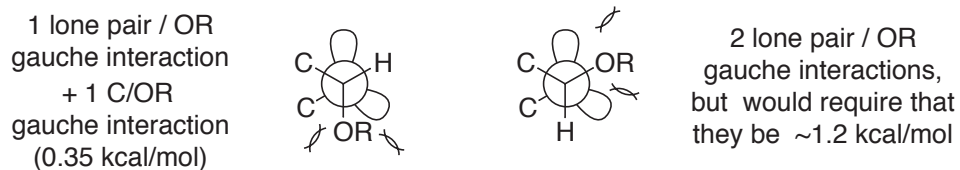


3. Electronic stabilization

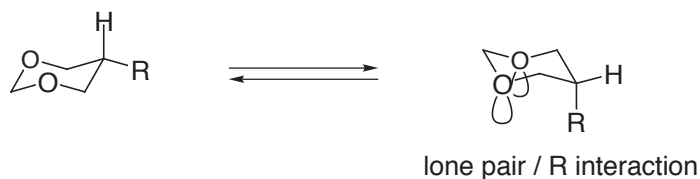
$n-\sigma^*$ orbital stabilizing interaction



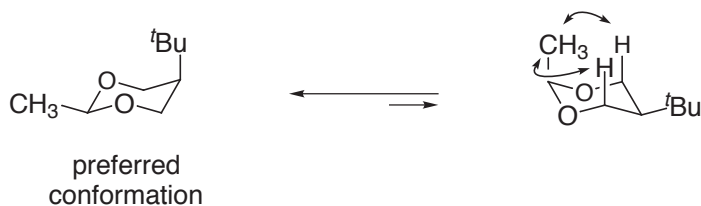
4. Gauche interaction involving lone pairs is large (i.e., steric)



2. Anomeric Effect and 1,3-Dioxanes



1. Polar, electronegative C2/C4 substituents prefer axial orientation.
2. The lone pair on oxygen has a smaller steric requirement than a C–H bond.
 ΔG° is much lower, lower preference between axial and equatorial C5 substituent
3. Polar electropositive groups C2 equatorial position preferred:
C5 axial position may be preferred for F, NO₂, SOCH₃, ⁺NMe₃.

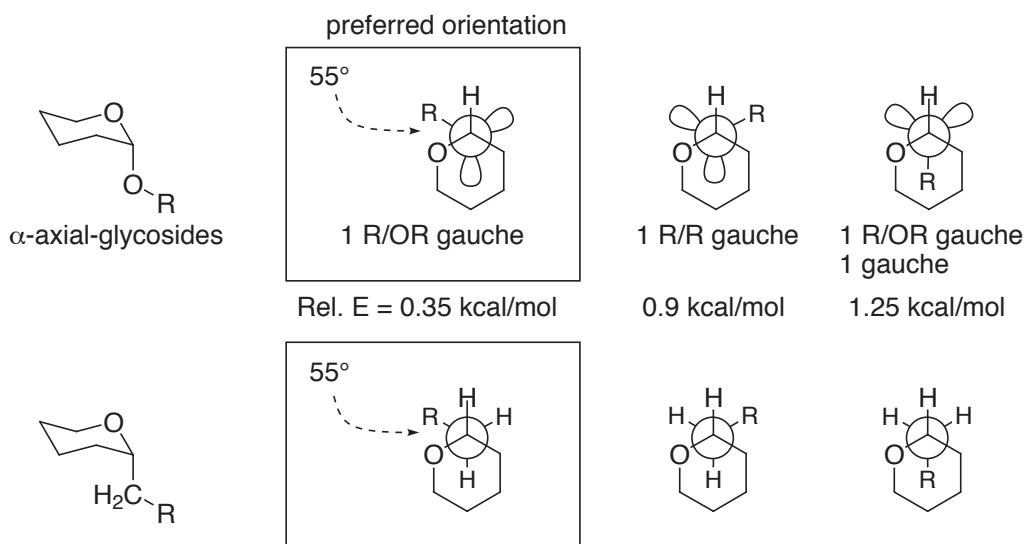


Eliel *J. Am. Chem. Soc.* **1968**, *90*, 3444.

A Value (kcal/mol) for Substituents on Tetrahydropyran and 1,3-Dioxane versus Cyclohexane

Group	Cyclohexane	Tetrahydropyran C2	1,3-Dioxane C2	1,3-Dioxane C5
CH ₃	1.8	2.9	4.0	0.8
Et	1.8		4.0	0.7
ⁱ Pr	2.1		4.2	1.0
^t Bu	>4.5			1.4

3. Exo Anomeric Effect



Kishi *J. Org. Chem.* **1991**, *56*, 6412.

H. Strain

Cyclic Hydrocarbon, Heats of Combustion/Methylene Group (gas phase)			
Ring Size	$-\Delta H_c$ (kcal/mol)	Ring Size	$-\Delta H_c$ (kcal/mol)
3	166.3	10	158.6
4	163.9	11	158.4
5	158.7	12	157.8
strain free 6	157.4	13	157.7
7	158.3	14	157.4
8	158.6	15	157.5
9	158.8	16	157.5

} largely strain free

1. Small rings (3- and 4-membered rings): small angle strain

▷ For cyclopropane, reduction of bond angle from ideal 109.5° to 60°
27.5 kcal/mol of strain energy.

▷ For cyclopropene, reduction of bond angle from ideal 120° to 60°
52.6 kcal/mol of strain energy.

To form a small ring in synthetic sequences, must overcome the energy barrier implicated in forming a strained high energy product.

2. Common rings (5-, 6-, and 7-membered rings):

- largely unstrained and the strain that is present is largely torsional strain (Pitzer strain).

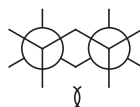
3. Medium rings (8- to 11-membered rings):

a. large angle strain

- bond angles enlarged from ideal 109.5° to $115\text{--}120^\circ$.
- bond angles enlarged to reduce transannular interactions.

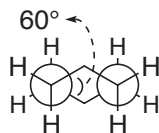
b. steric (transannular) interactions

- analogous to 1,3-diaxial interactions in cyclohexanes, but can be 1,3-, 1,4-, or 1,5- ...



c. torsional strain (Pitzer strain)

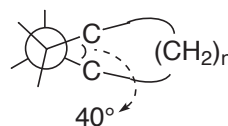
in cyclohexanes



just like gauche butane.

in medium rings

- deviation from ideal ϕ of 60° and approach an eclipsing interaction.



4. Large rings (12-membered and up):

- little or no strain.

I. pK_a of Common Organic Acids

Acid	pK_a	Acid	pK_a
cyclohexane	45	$(CH_3)_2CHOH$	18
ethane	42	CH_3CH_2OH	17
benzene	37	cyclic ketones	17
ethylene	36	e.g. cyclohexanone	17
Et_2NH	36	CH_3OH	16 (16–18)
NH_3 (ammonia)	35	$CH_3CONHCH_3$	16–17
toluene, propene	35	$PhCH_2COPh$	16
$(C_6H_5)_3CH$	28–33	H_2O	16
DMSO ($CH_3S(O)CH_3$)	31	cyclopentadiene	15
$C_6H_5NH_2$	27	$CH_2(CO_2Et)_2$	13
$HC\equiv CH$	25	$CH_2(CN)_2$	11
CH_3CN	25	$CH_3COCH_2CO_2Et$	11
CH_3CO_2Et	25	CH_3NO_2	10
$CH_3SO_2CH_3$	23–27	phenol	10
CH_3CONMe_2	25	$R_3NH^+Cl^-$	10
aliphatic ketones	20–23	HCN	9
$(CH_3)_3CCOCH(CH_3)_2$	23	$CH_3CH_2NO_2$	9
$(CH_3)_3CCOCH_3$	21	$CH_3COCH_2COCH_3$	9
CH_3COCH_3	20	$CH_2(CN)CO_2Et$	9
$CH_3COC_6H_5$	19	CH_3CO_2H	5
$(CH_3)_3COH$	19	$py\cdot HCl$	5
$C_6H_5C\equiv CH$	19	$C_6H_5NH_3^+Cl^-$	5



$$K_a = \frac{[H^+][X^-]}{[HX]}$$

$$pK_a = -\log K_a = -\log[H^+]$$

Increase in pK_a means decrease in $[H^+]$ and acidity

Decrease in pK_a means increase in $[H^+]$ and acidity

For more extensive lists, see:

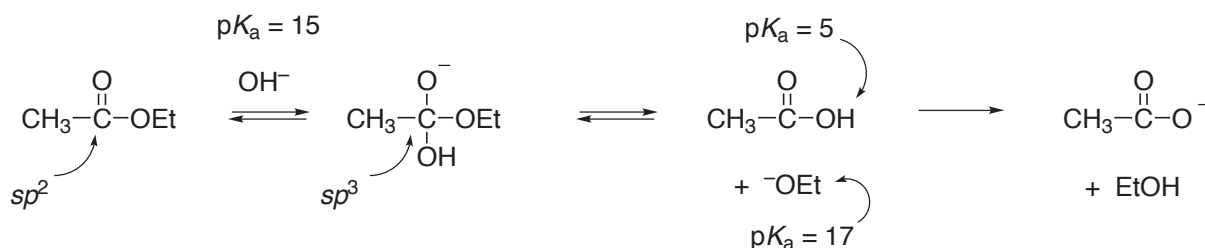
The Chemist's Companion, p 58–63.

Familiarity with these pK_a 's will allow prediction/estimation of acidities of other compounds. This is important, since many organic reactions have a pK_a basis (i.e., enolate alkylations).

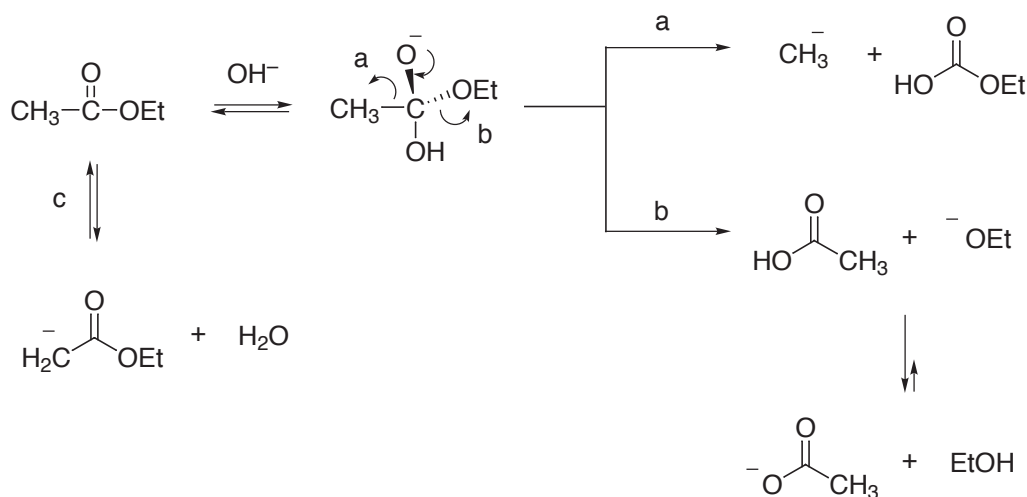
Alfred Werner, who received the 1913 Nobel Prize in Chemistry for his studies of stereochemistry and inorganic complexes, is also responsible for the redefinition of (acids and) bases as compounds that have varying degrees of ability to attack hydrogen ions in water resulting in an increase in hydroxide ion.

III. Reaction Mechanisms and Conformational Effects on Reactivity

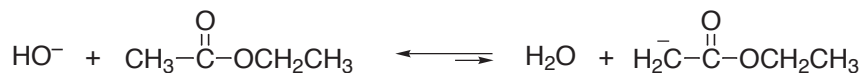
A. Ester Hydrolysis



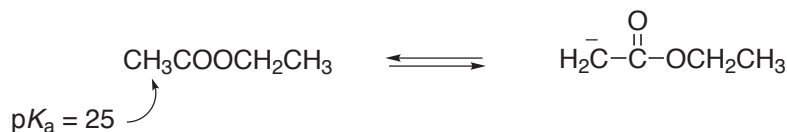
Reaction driven to completion by final, irreversible step (compare $pK_a = 17$ to $pK_a = 5$).



- So, possible competing reaction is α -H removal, but pK_a difference means equilibrium strongly favors ester and OH^- , i.e.;

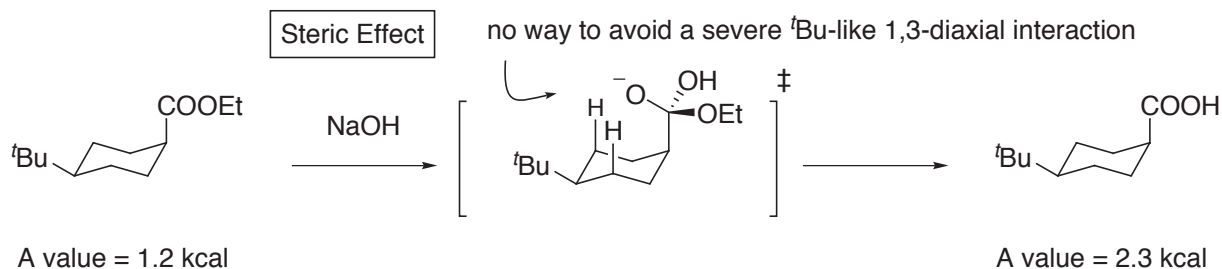
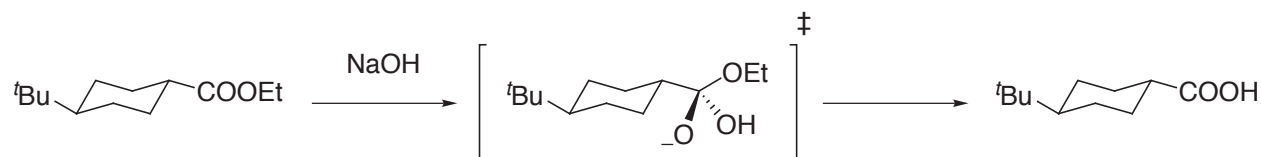


- To deprotonate an ester, must use a strong base which is non-nucleophilic, such as $^t\text{BuOK}$ or LDA.



1. $^t\text{BuOK}$ (pK_a of $^t\text{BuOH} = 19$) \rightarrow generates low concentration of anion, and a significant amount of ester always present
 \Rightarrow self (Claisen) condensation
2. LDA (pK_a of $^i\text{Pr}_2\text{NH} = 36$) \rightarrow generates a high concentration of enolate and thus is a good base to carry out stoichiometric alkylation of ester

1. Kinetics of Ester Hydrolysis (Stereochemistry and Rates of Reactions)



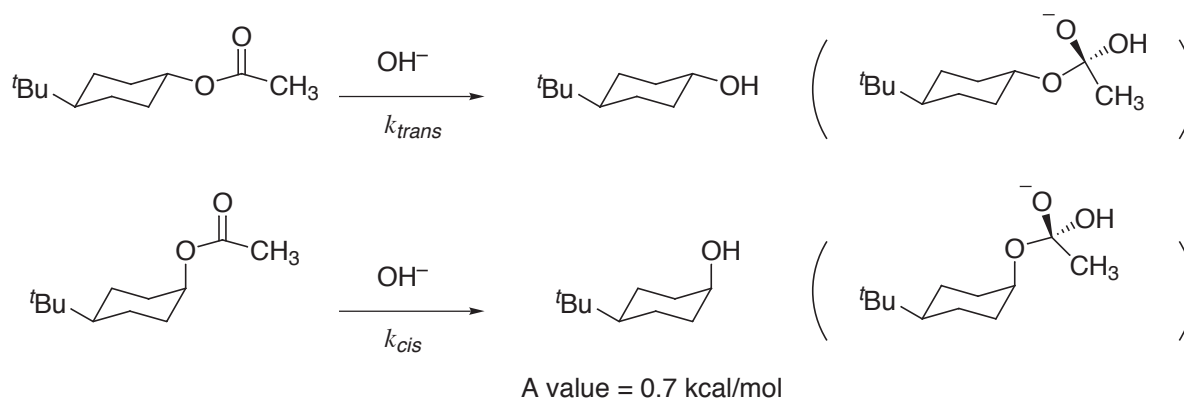
$$\frac{k_{trans}}{k_{cis}} = 19.8$$

The rate determining step for ester hydrolysis is the formation of tetrahedral intermediate and the ratio of $k_{trans}/k_{cis} \gg 1$.

Eliel *J. Am. Chem. Soc.* **1961**, *83*, 2351.

- Difference in rates much greater than expected if simply considering the difference in either the product or reactant A values.
- Reaction of axial ester decelerated due to more severe developing 1,3-diaxial interactions in transition state (i.e., an axial ^tBu-like group).

2. Same effect is observed, but to a lesser extent with acetate hydrolysis



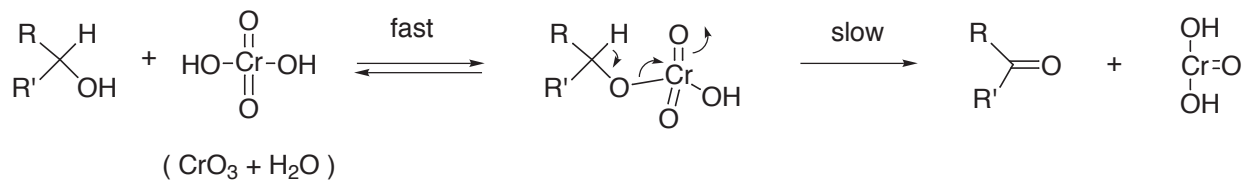
$$\frac{k_{trans}}{k_{cis}} = 6.65$$

effect is smaller because of the more remote distance of the steric interactions

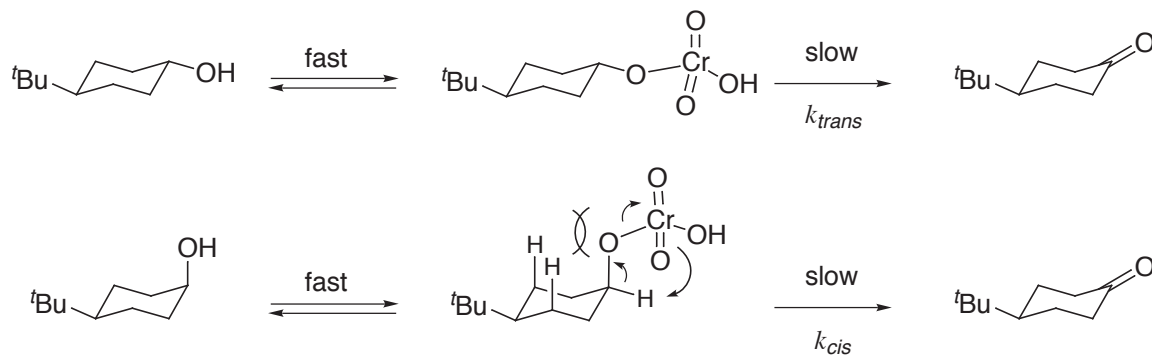
Similarly, the rates of acetylation are $k_{trans}/k_{cis} = 3.7$

Eliel *J. Am. Chem. Soc.* **1966**, *88*, 3334.

B. Alcohol Oxidations



Westheimer *J. Am. Chem. Soc.* **1951**, 73, 65.



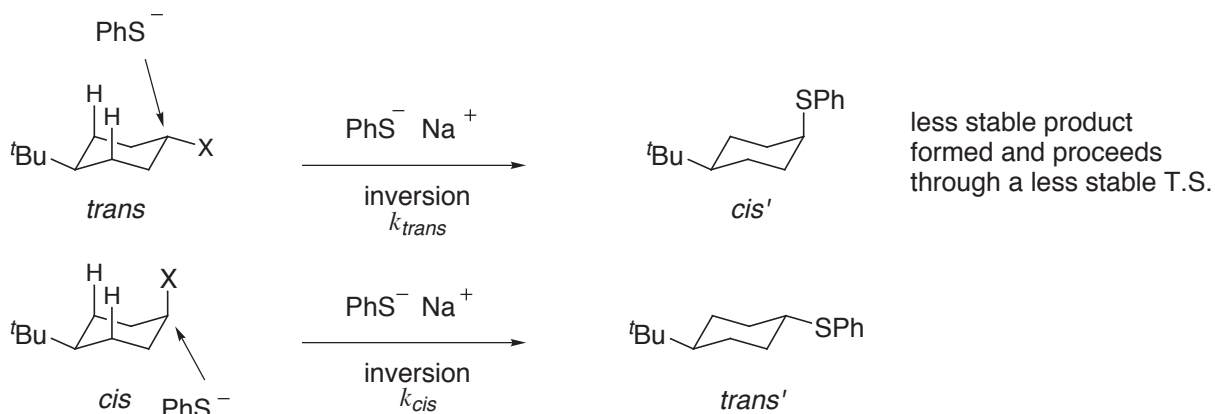
$$\frac{k_{cis}}{k_{trans}} = 4$$

The rate determining step for the alcohol oxidation is break down of the chromate ester with cleavage of C–H bond and O–Cr bond.

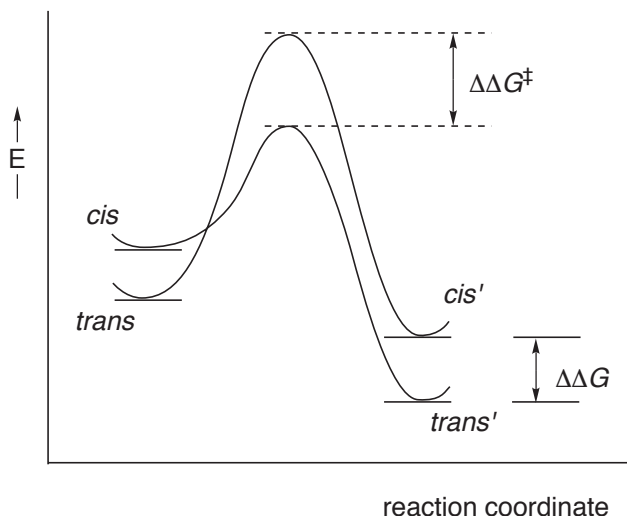
Destabilizing 1,3-diaxial interactions in *cis* chromate ester accelerate its breakdown to the ketone (would be slower if the slow step for the reaction were formation of chromate ester).

Eliel *J. Am. Chem. Soc.* **1966**, 88, 3327.

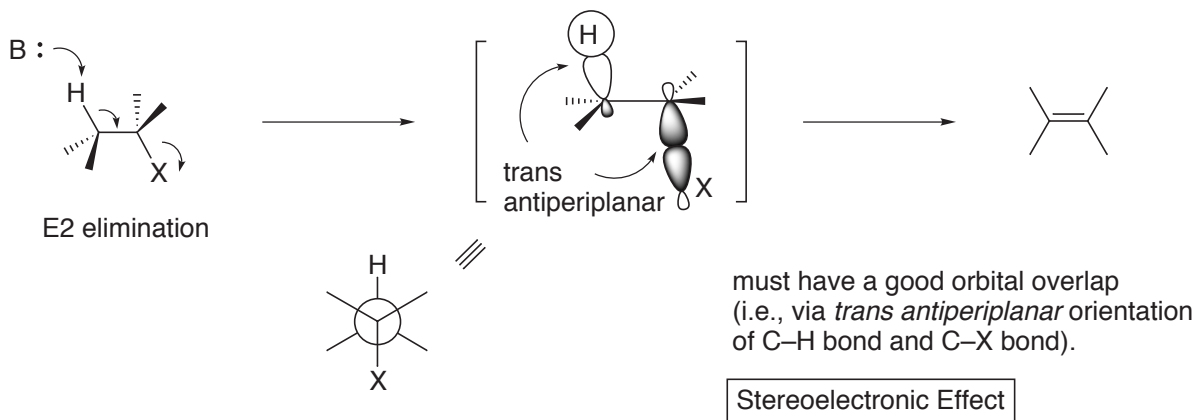
C. $\text{S}_{\text{N}}2$ Reactions



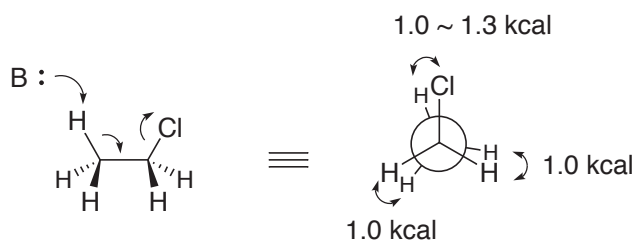
- The free energy of activation (E_a , or ΔG^\ddagger) for reaction of the *trans* isomer is higher due to steric interactions felt in the transition state (interactions of incoming nucleophile with axial H's).
- $\rightarrow k_{\text{cis}} > k_{\text{trans}}$
- $\Delta\Delta G^\ddagger$ greater than $\Delta\Delta G$ of products.
- The reaction of the *trans* isomer is kinetically slower and thermodynamically less favorable.



D. Elimination Reactions

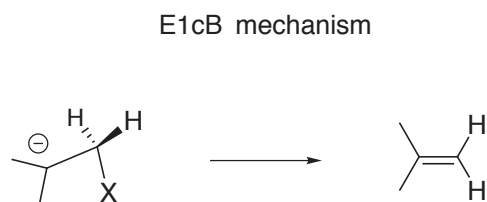
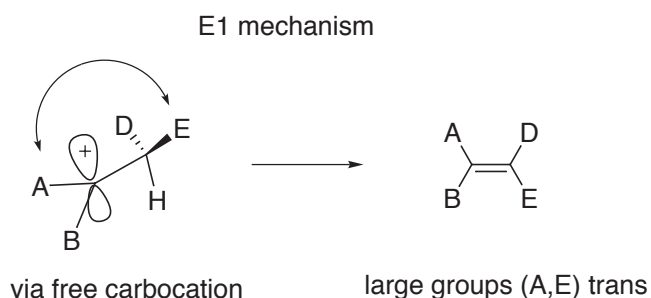


- Alternatively, if dihedral angle = 0° (i.e., eclipsed X and H), elimination can take place (orbital overlap good).



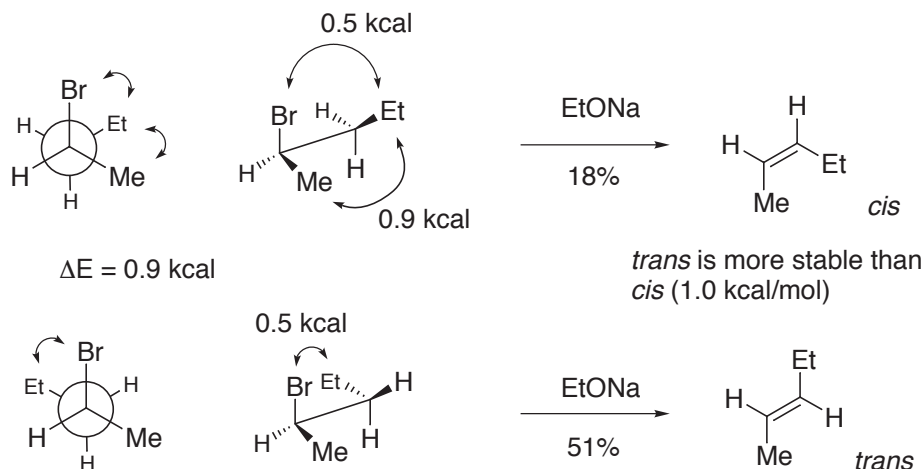
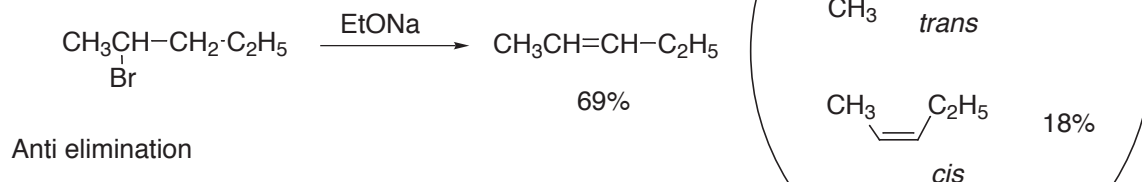
eclipsed conformation is 3.0–3.3 kcal/mol higher in E, so elimination takes place mainly through *trans antiperiplanar* arrangement.

- Alternate mechanisms also possible:



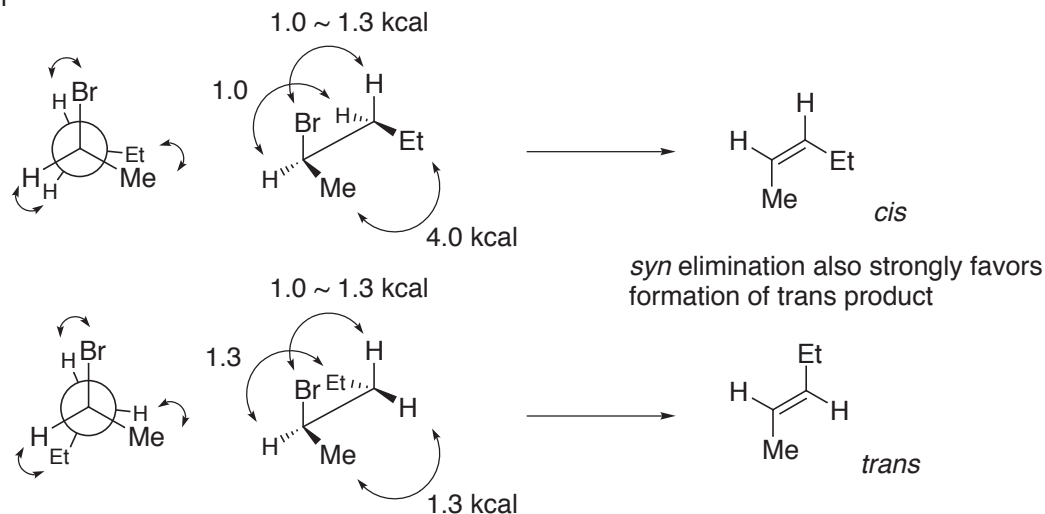
Acyclic Substrate

– Examples:



– For other possible mechanisms:

Syn elimination



Both are very much destabilized relative to *anti*-elimination T.S. / conformations. Neither contribute to ground state conformation of bromide at room temperature.

And, there is another product formed:

