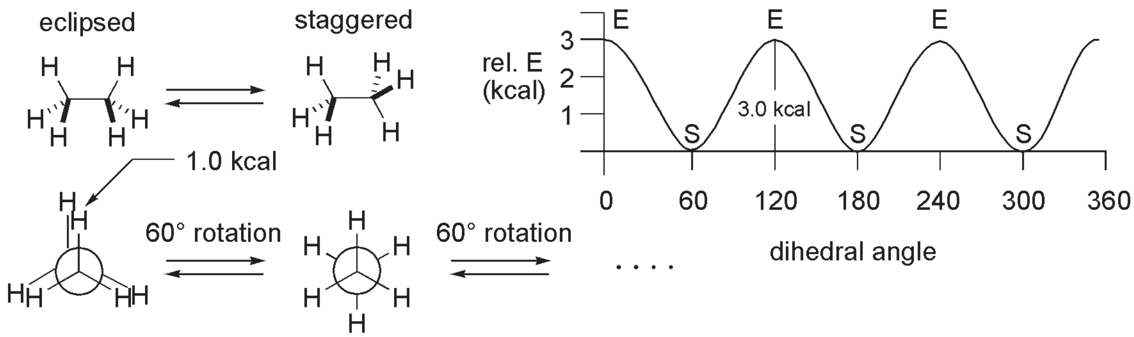
I. Conformational Analysis

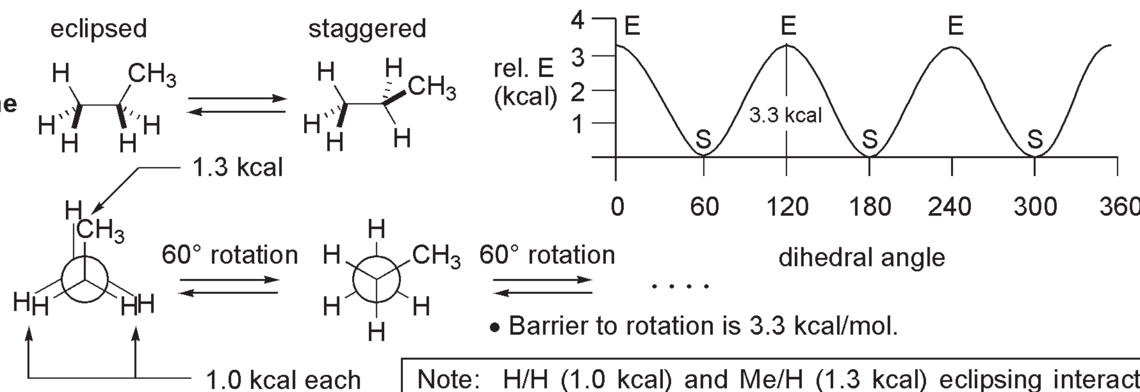
A. Acyclic sp^3–sp^3 Systems: Ethane, Propane, Butane

1. Ethane



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

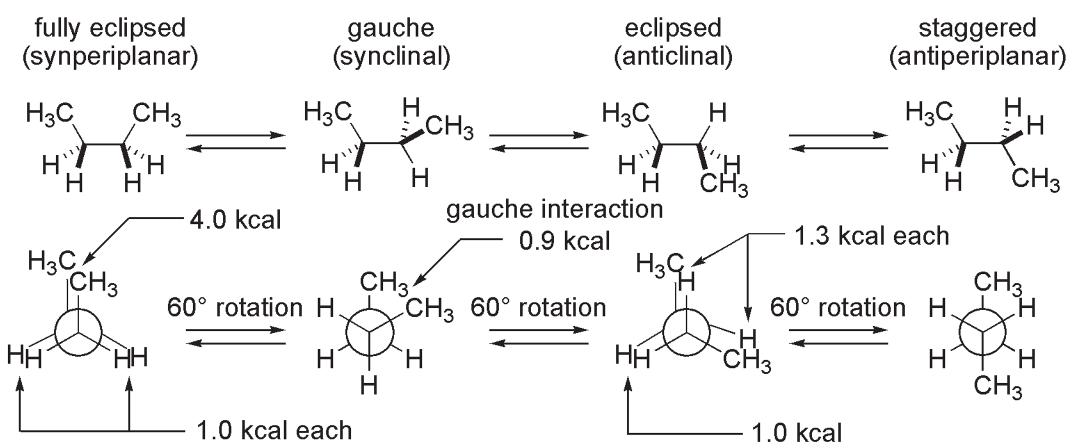
2. Propane

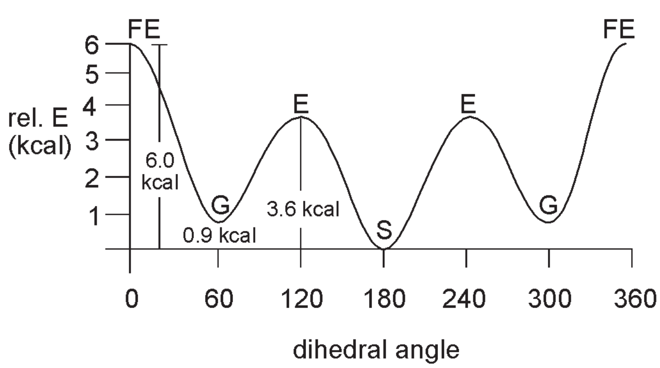


• Barrier to rotation is 3.3 kcal/mol.

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.

3. Butane

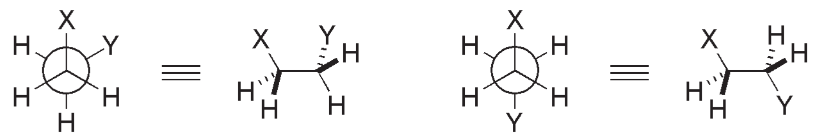




Note: the gauche butane interaction and its magnitude (0.9 kcal) are very important and we will discuss it frequently.

4. Substituted Ethanes

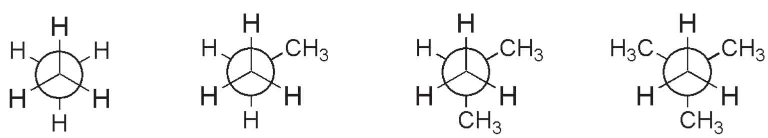
- There are exceptions to the lowest energy conformation. Sometimes, a gauche conformation is preferred over staggered if X,Y are electronegative substituents. cf: Kingsbury *J. Chem. Ed.* **1979**, *56*, 431.



gauche   staggered

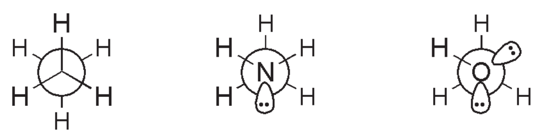
$E_{gauche} < E_{staggered}$ if X = OH, OAc and Y = Cl, F

5. Rotational Barriers



2.88 kcal/mol	3.40 kcal/mol	3.90 kcal/mol	4.70 kcal/mol	- Experimental
(3.0 kcal/mol	3.3 kcal/mol	3.6 kcal/mol	3.9 kcal/mol)	- Simple prediction

• The rotational barrier increases with the number of CH_3/H eclipsing interactions.

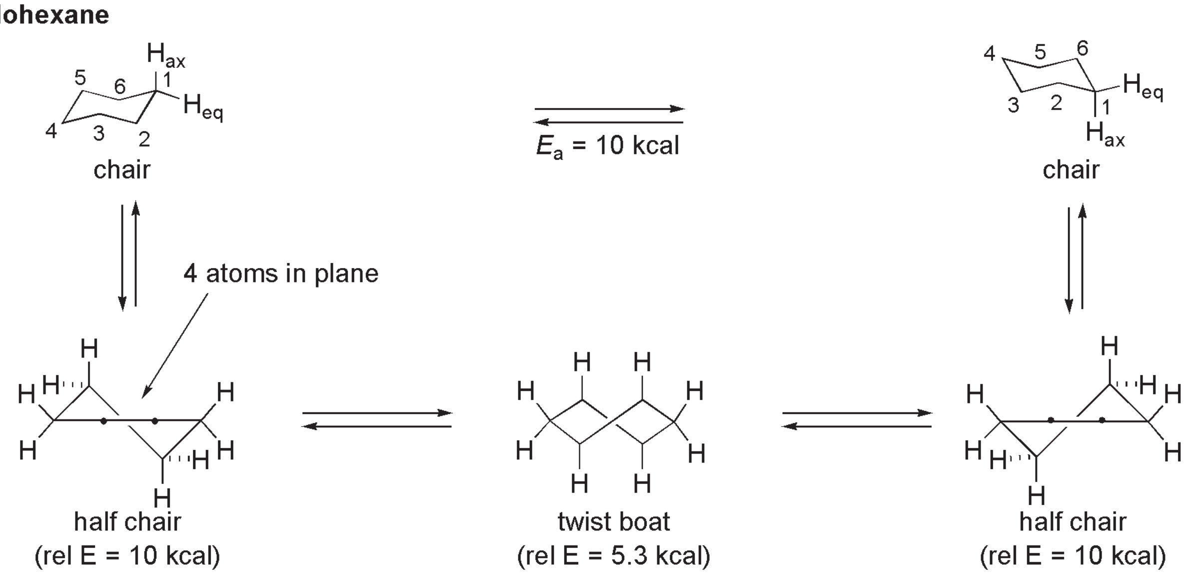


2.88 kcal/mol	1.98 kcal/mol	1.07 kcal/mol	- Experimental
(3.0 kcal/mol	2.0 kcal/mol	1.0 kcal/mol)	- Simple prediction

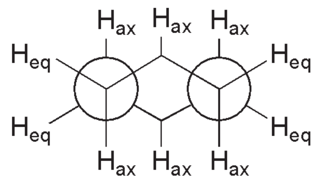
• The rotational barrier increases with the number of H/H eclipsing interactions.

B. Cyclohexane and Substituted Cyclohexanes, A Values ($\Delta G°$)

1. Cyclohexane

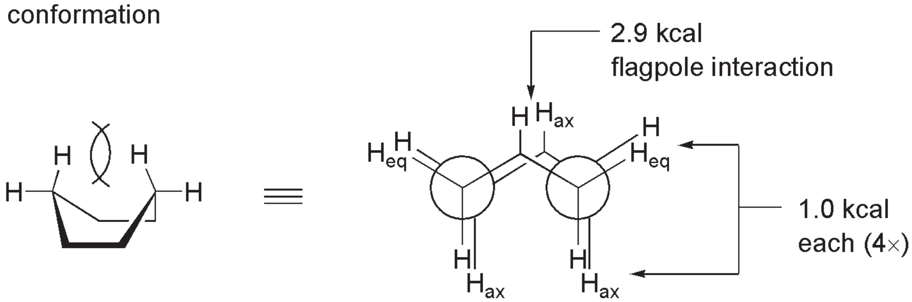


- Chair conformation (all bonds staggered)



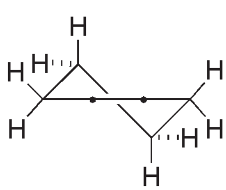
- Rapid interconversion at 25 °C (E_a = 10 kcal/mol, 20 kcal/mol available at 25 °C).
- H_{ax} and H_{eq} are indistinguishable by ^{1}H NMR at 25 °C.
- At temperatures < –70 °C, H_{eq} and H_{ax} become distinct in ^{1}H NMR.

- Boat conformation

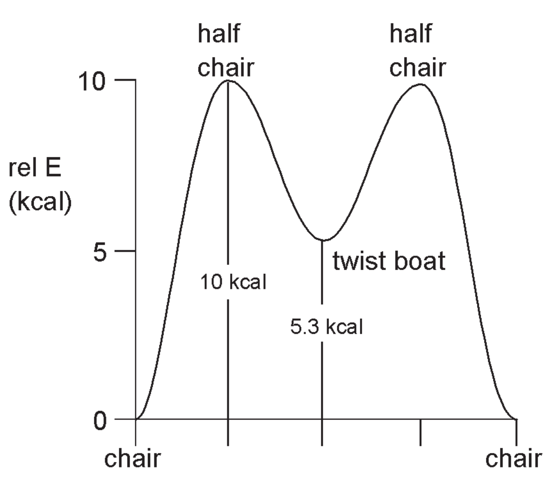


- Rel E = 6.9 kcal, not local minimum on energy surface.
- More stable boat can be obtained by twisting (relieves flagpole interaction).
- Twist boat conformation (rel E = 5.3 kcal) does represent an energy minimum.
- The boat conformation becomes realistic if flagpole interactions are removed, i.e.

- Half chair conformation



- Energy maximum (rel E = 10.0 kcal)

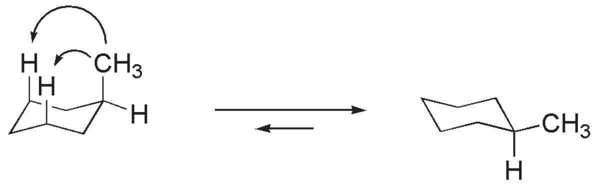


D.H.R. Barton received the 1969 Nobel Prize in Chemistry for his contributions to conformational analysis, especially as it relates to steroids and six-membered rings. Barton *Experientia* **1950**, *6*, 316.

Linus Pauling received the 1954 Nobel Prize in Chemistry for his pioneering work on the nature of the chemical bond. He received a second Nobel Prize, this time for peace, in 1962 for his peace activist efforts including his petition for nuclear disarmament ultimately signed by more than 13,000 scientists and presented to the United Nations. Pauling was among the first scientists to popularize the use of molecular models which he began building in the 1920's. The early models were constructed out of folded paper and progressed to metal shapes machined in Caltech's machine shop.

2. Substituted Cyclohexanes

- Methylcyclohexane



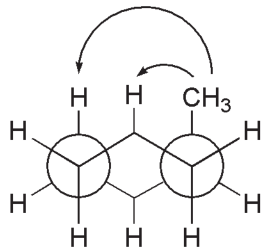
1.8 kcal more stable

$\Delta G° = -RT(\ln K)$

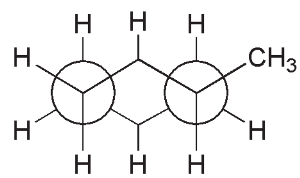
$\frac{-1.8 \times 1000}{1.99 \times 298} = -\ln K$

K = 21

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



2 gauche butane interactions
2 × 0.9 kcal = 1.8 kcal
(experimental 1.8 kcal)



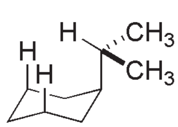
0 gauche butane interactions

- A Value ($-\Delta G°$) = Free energy difference between equatorial and axial cyclohexane substituent.

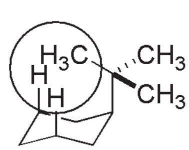
Typical A Values

R	A Value (kcal/mol)		R	A Value (kcal/mol)	
F	0.25		CHO	0.6–0.8	
Cl	0.52	ca. 0.5 kcal	$COCH_3$	1.2	
Br	0.5–0.6	ca. 0.5 kcal	CN	0.2	Small, linear groups
I	0.46	ca. 0.5 kcal	C≡CH	0.41	Small, linear groups
OH	0.7 (0.9)	ca. 0.7 kcal (2nd atom effect very small)	NO_2	1.1	
OCH_3	0.75	ca. 0.7 kcal (2nd atom effect very small)	$CH{=}CH_2$	1.7	
$OCOCH_3$	0.71	ca. 0.7 kcal (2nd atom effect very small)	CH_3	1.8	2nd atom effect very small
NH_2	1.8 (1.4)		CH_2CH_3	1.9 (1.8)	2nd atom effect very small
NR_2	2.1		${}^nC_3H_7$	2.1	2nd atom effect very small
CO_2H	1.2 (1.4)		${}^nC_4H_9$	2.1	2nd atom effect very small
CO_2Na	2.3		$CH(CH_3)_2$	2.1	2nd atom effect very small
CO_2Et	1.1		$C(CH_3)_3$	>4.5 (ca. 5.4)	
SO_2Ph	2.5		C_6H_5	3.1 (2.9)	

- Note on difference between ^{i}Pr and ^{t}Bu A values

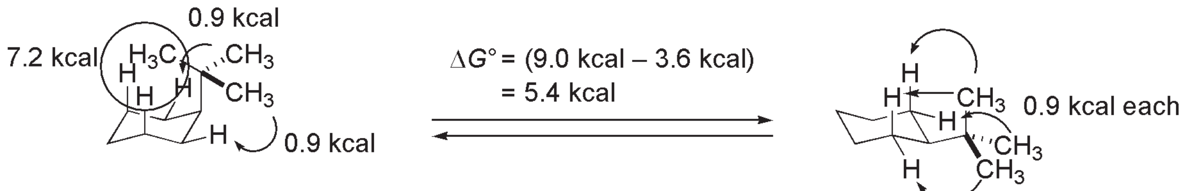


^{i}Pr group can position H toward "inside,"



but ^{t}Bu group cannot.
Very serious interaction, 7.2 kcal.

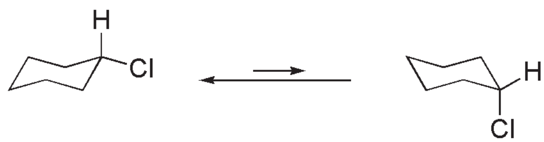
- Determination of A value for ^{t}Bu group



7.2 kcal + (2 × 0.9 kcal) = 9.0 kcal

4 × 0.9 kcal = 3.6 kcal

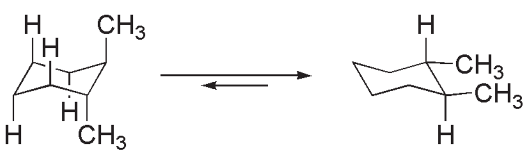
- Note on interconversion between axial and equatorial positions



$t_{1/2}$ = 22 years at –160 °C

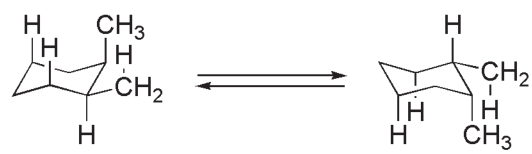
Even though Cl has a small A value (i.e., small $\Delta G°$ between equatorial and axial Cl), the E_a (energy of activation) is high (it must go through half chair conformation).

trans-1,2-dimethylcyclohexane

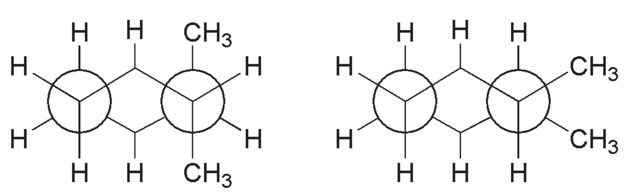


2.7 kcal/mol more stable

cis-1,2-dimethylcyclohexane

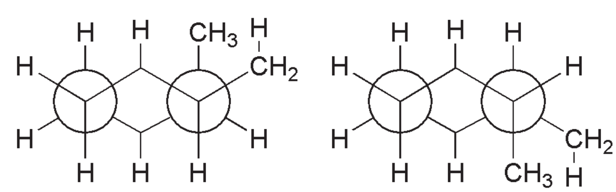


ΔE = 0 kcal/mol



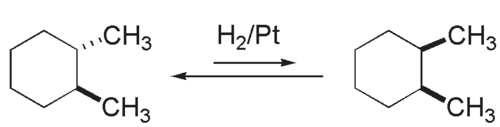
4 × (gauche interaction)
4 × (0.9 kcal) = 3.6 kcal

1 × (gauche interaction)
1 × (0.9 kcal) = 0.9 kcal



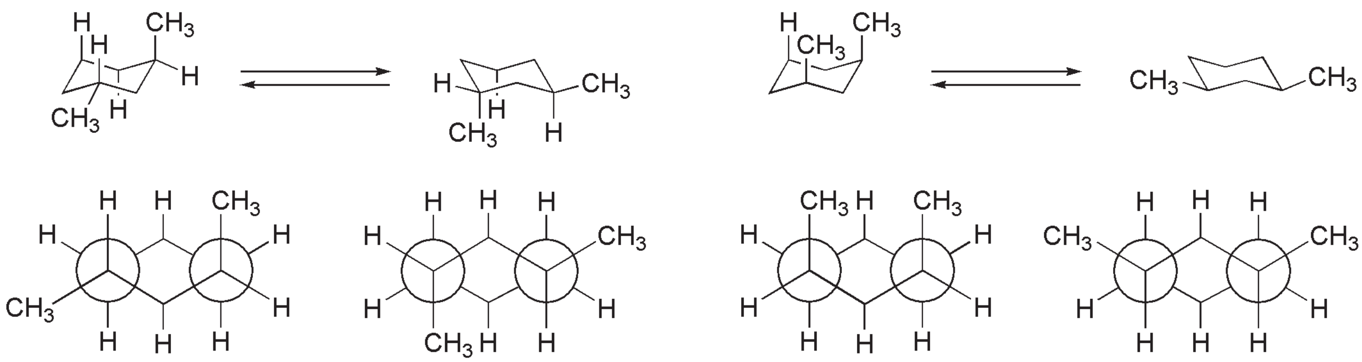
3 × (gauche interaction)
3 × (0.9 kcal) = 2.7 kcal

3 × (gauche interaction)
3 × (0.9 kcal) = 2.7 kcal



ΔG = 1.87 kcal/mol (exp)
ΔG = 1.80 kcal/mol (calcd)

trans-1,3-dimethylcyclohexane | *cis*-1,3-dimethylcyclohexane

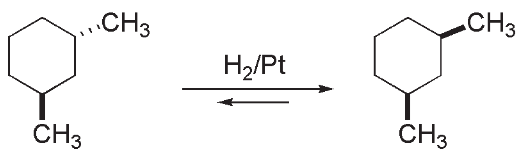


2 × (gauche interaction)
2 × (0.9 kcal) = 1.8 kcal

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

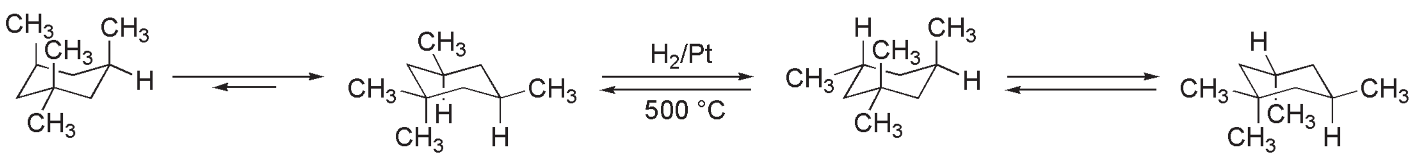
2 × (gauche interaction) +
1 × (Me–Me 1,3 diaxial int) =
2 × (0.9 kcal) + 3.7 kcal
= 5.5 kcal

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



ΔG = 1.80 kcal/mol (exp and calcd)

- Determination of ΔG 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) + ?

ΔG = 3.7 kcal/mol (exp)
So, Me–Me 1,3-diaxial interaction = 3.7 kcal/mol.

1,3-diaxial interactions

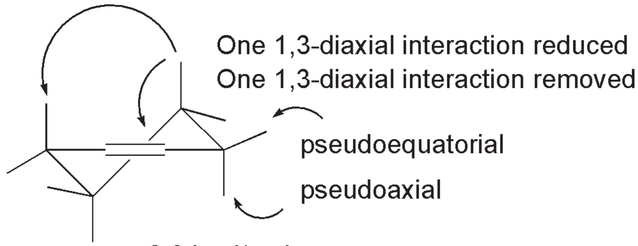
R/R	$\Delta G°$
OH/OH	1.9 kcal
OAc/OAc	2.0 kcal
OH/CH_3	2.4 (1.6) kcal
CH_3/CH_3	3.7 kcal

$\Delta G°$ 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

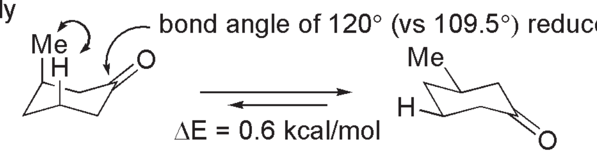


- half-chair
- E_a for ring interconversion = 5.3 kcal/mol
- The preference for equatorial orientation of methyl group in cyclohexene is less than in cyclohexane because of the ring distortion and the removal of one 1,3-diaxial interaction (1 kcal/mol).

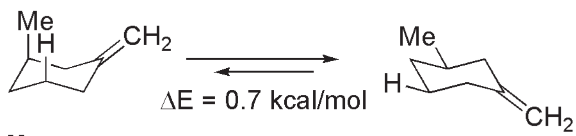
- Similarly

0.6 kcal/mol

bond angle of 120° (vs 109.5°) reduces remaining 1,3-diaxial interaction



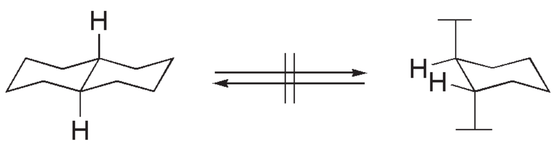
- One 1,3-diaxial interaction removed
- Remaining 1,3-diaxial interaction reduced



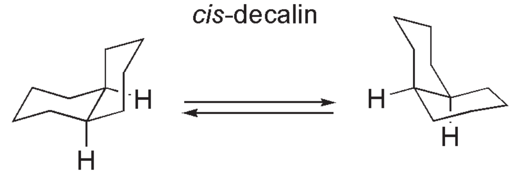
- One 1,3-diaxial interaction removed
- Remaining 1,3-diaxial interaction reduced

D. Decalins

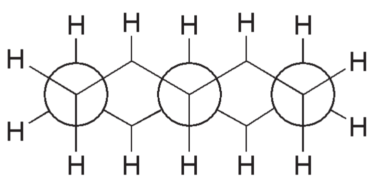
trans-decalin



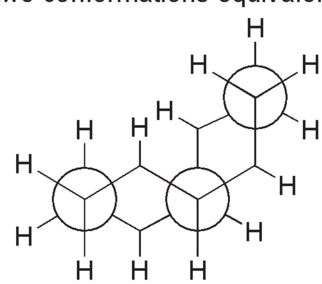
cis-decalin



two conformations equivalent



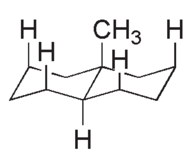
0.0 kcal



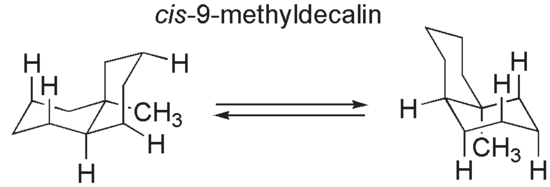
3 gauche interactions
3×0.9 kcal = 2.7 kcal

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

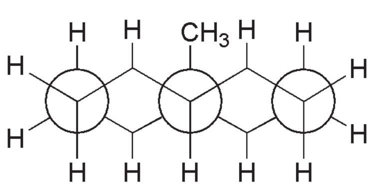
trans-9-methyldecalin



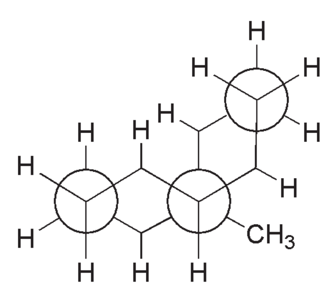
cis-9-methyldecalin



two conformations equivalent



4 gauche interactions
4×0.9 = 3.6 kcal



5 gauche interactions
5×0.9 = 4.5 kcal

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

E. Acyclic sp^3–sp^2 Systems

- Key references

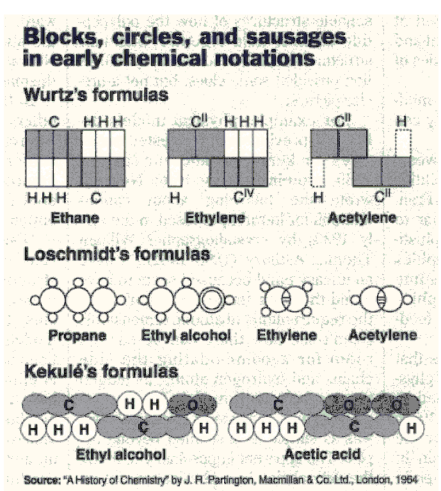
  - Origin of destabilization for eclipsed conformations:

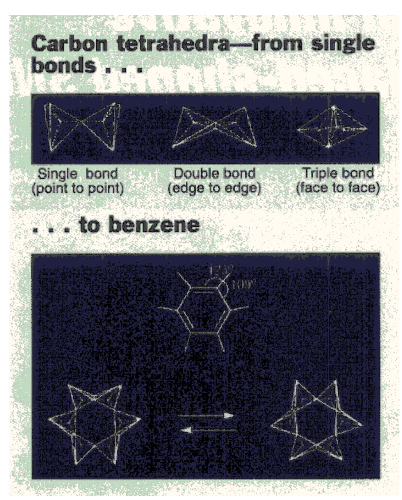
	Lowe	*Prog. Phys. Org. Chem.* **1968**, *6*, 1.
	Oosterhoff	*Pure Appl. Chem.* **1971**, *25*, 563.
	Wyn-Jones, Pethrick	*Top. Stereochem.* **1970**, *5*, 205.
		Quat. Rev., Chem. Soc. **1969**, *23*, 301.
	Brier	*J. Mol. Struct.* **1970**, *6*, 23.
	Lowe	*Science* **1973**, *179*, 527.

  - Molecular orbital calculations: Repulsion of overlapping filled orbitals:

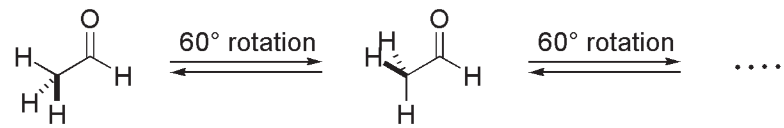
	Pitzer	*Acc. Chem. Res.* **1983**, *16*, 207.
- Propionaldehyde:	Butcher, Wilson	*J. Chem. Phys.* **1964**, *40*, 1671.
	Allinger, Hickey	*J. Mol. Struct.* **1973**, *17*, 233.
	Allinger	*J. Am. Chem. Soc.* **1969**, *91*, 337.
- Propene:	Allinger	*J. Am. Chem. Soc.* **1968**, *90*, 5773.
	Herschbach	*J. Chem. Phys.* **1958**, *28*, 728.
- 1-Butene:	Geise	*J. Am. Chem. Soc.* **1980**, *102*, 2189.
- Allylic 1,3-strain:	Houk, Hoffmann	*J. Am. Chem. Soc.* **1991**, *113*, 5006.
	Hoffmann	*Chem. Rev.* **1989**, *89*, 1841.

Jacobus van't Hoff studied with both Kekule and Wurtz and 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. Independently and two months later, Joseph A. Le Bel, who also studied with Kekule at the same time as van't Hoff, described a similar theory to the Paris Chem. Soc. Kekule himself had tetrahedral models in the lab and historians concur that they must have influenced van't Hoff and Le Bel. Interestingly, these proposals which serve as the very basis of stereochemistry today were met with bitter criticism.

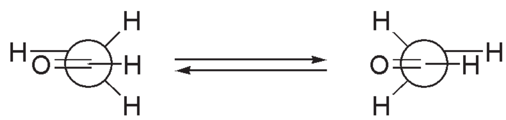


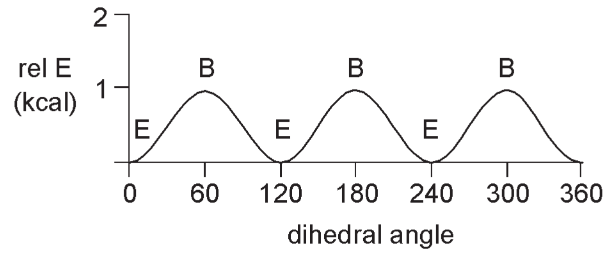


1. Acetaldehyde



eclipsed — bisected



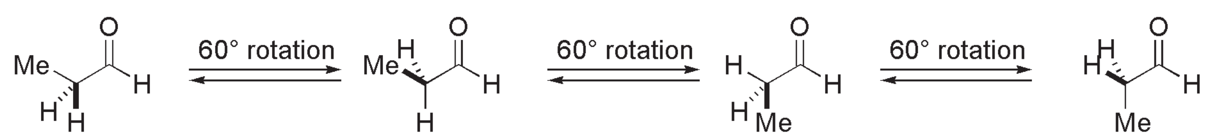


relative energies (kcal)

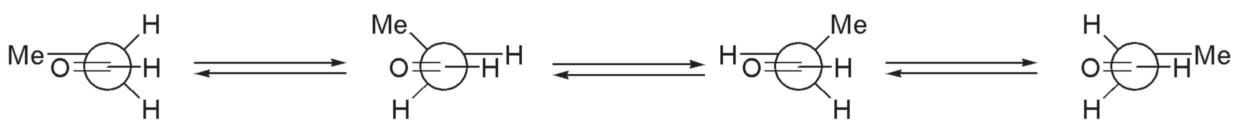
Exp	0.0	1.0
MM2	0.0	1.1–1.2

- Two extreme conformations
- Barrier to rotation is 1.0 kcal/mol
- H-eclipsed conformation more stable

2. Propionaldehyde

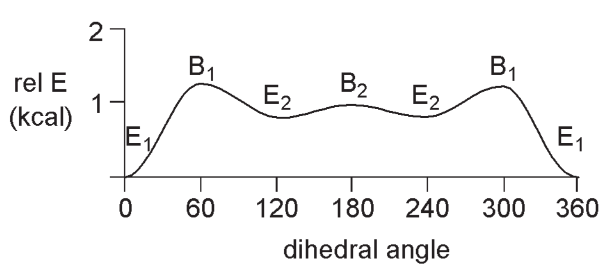


eclipsed — bisected — eclipsed — bisected

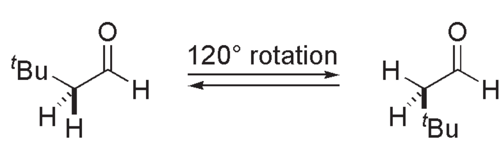


relative energies (kcal)

Exp	0.0	1.25, 2.28	0.8, 0.9, 1.0	unknown
MM2	0.0	2.1	0.8, 0.9	1.0, 2.3–1.7, 1.5
Ab initio	0.0	1.7	0.4	0.7



- *J. Chem. Phys.* **1964**, *40*, 1671.
- *J. Mol. Struct.* **1973**, *17*, 233.
- *J. Am. Chem. Soc.* **1969**, *91*, 337.



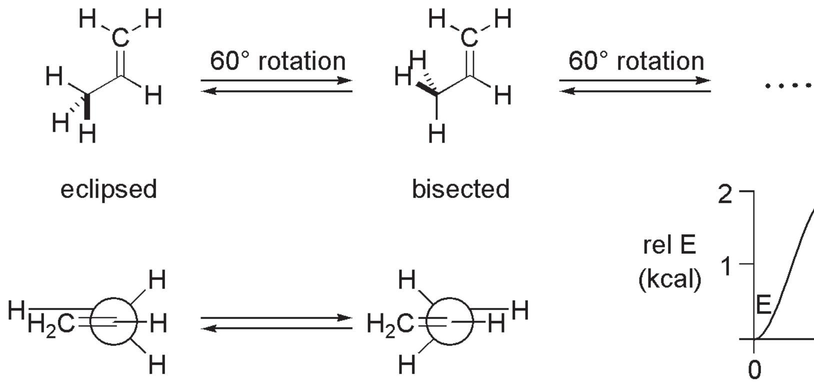
alkyl eclipsed — H-eclipsed

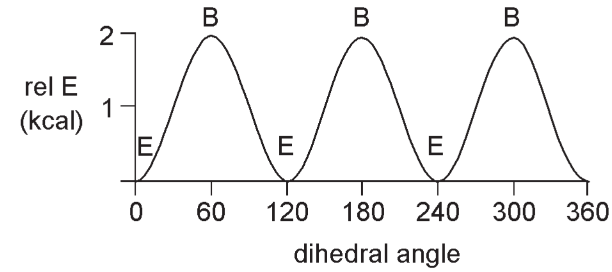
relative energies (kcal)

Exp	0.25	0.0

- Alkyl eclipsed conformation more stable than H-eclipsed and exceptions occur only if alkyl group is very bulky (i.e., ^{t}Bu).
- Because E differences are quite small, it is difficult to relate ground state conformation to experimental results. All will be populated at room temperature.

3. Propene





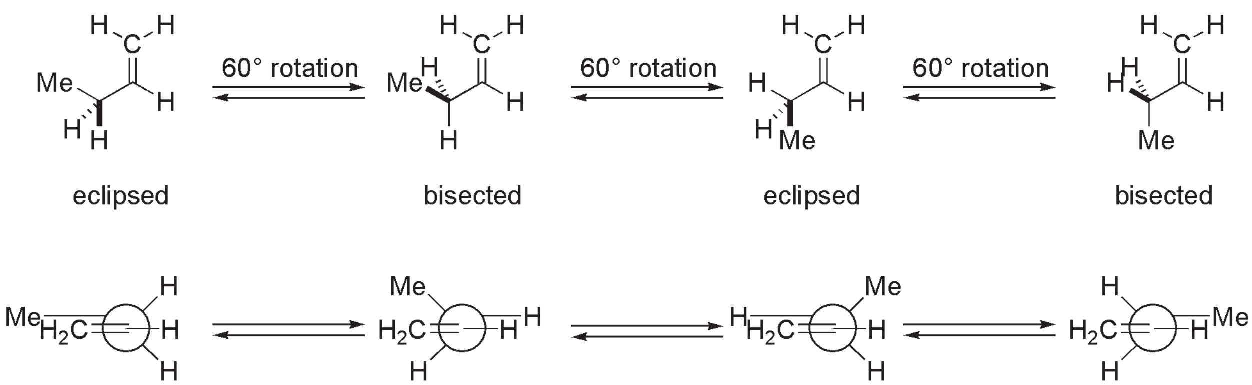
relative energies (kcal)

Exp	0.0	2.0
MM2	0.0	2.1–2.2

- Two extreme conformations
- Barrier to rotation is 2.0 kcal/mol

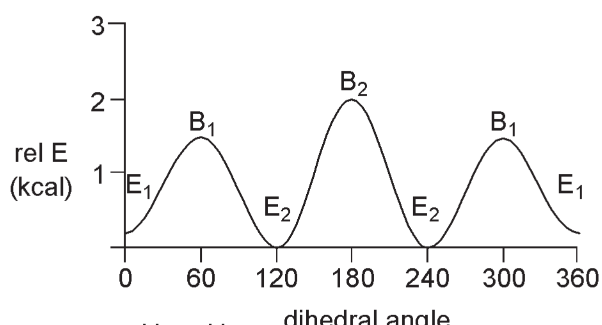
Note:

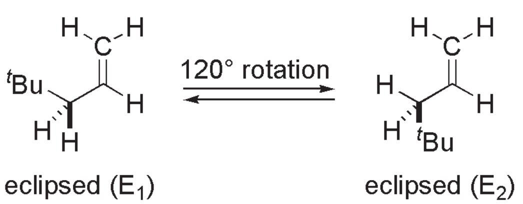
4. 1-Butene



relative energies (kcal)

Exp	0.0, 0.2, 0.4, 0.5	–	0.0	–
MM2	0.5, 0.7	1.4–1.7 (2.6)	0.0	1.4–1.8 (2.6)
Ab initio	0.6	–	0.0	2.0



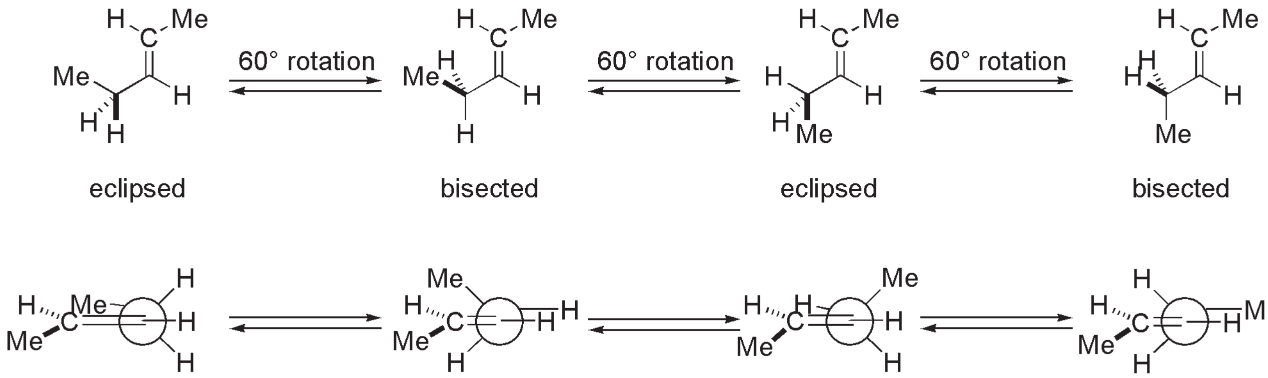


relative energies (kcal)

Exp	B_1, B_2 > E_1 > E_2

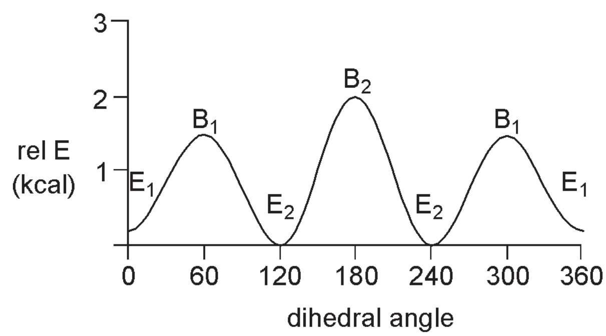
- There is an additional destabilization to placing the alkyl group eclipsed with C=C. This is due to the larger steric size of olefinic CH compared to carbonyl C=O.
- The eclipsed conformations (even with an α-^{t}Bu) are both more stable than bisected conformations.

5. *E*-2-Pentene



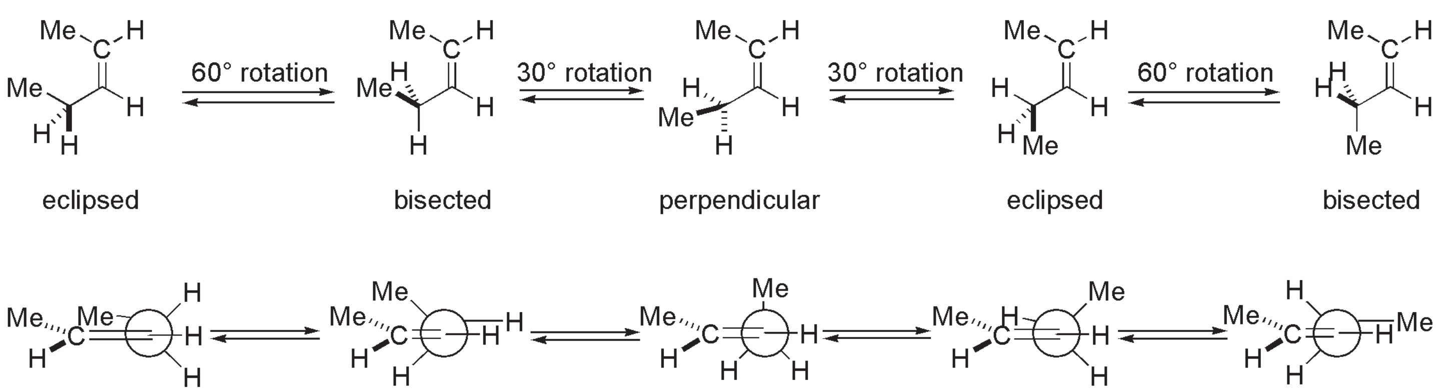
relative energies (kcal)

Exp	0.0 (0.0–0.4)	–	0.0	–
MM2	0.6	1.4–1.7 (2.6)	0.0	1.5–1.8 (2.6)



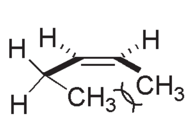
• Analogous to 1-butene

6. *Z*-2-Pentene

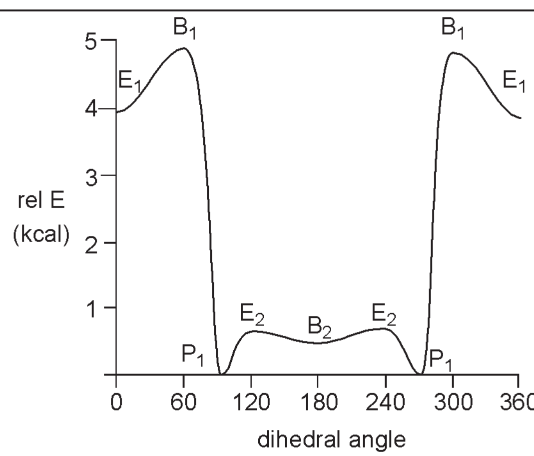


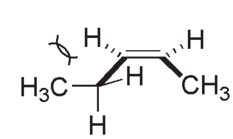
relative energies (kcal)

MM2	3.9	4.9	0.0	0.6	0.5



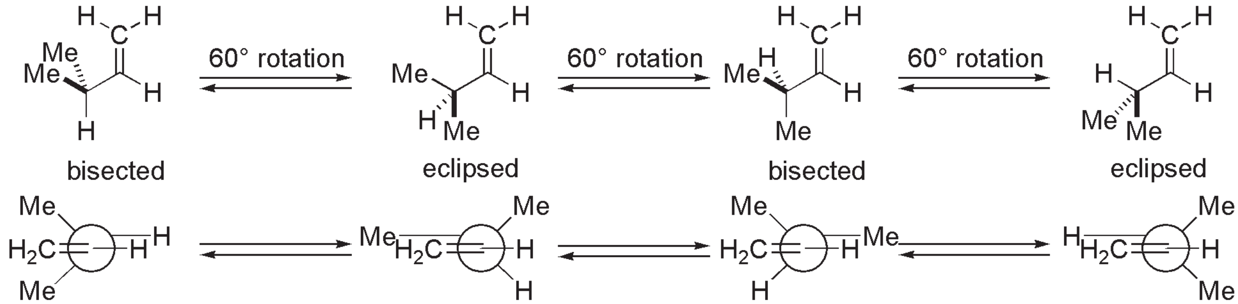
• Serious destabilizing interaction, referred to as allylic 1,3-strain (A 1,3-strain).





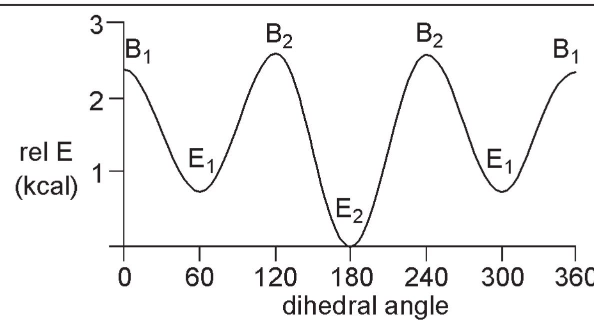
• The H/CH_3 eclipsing interaction in the bisected conformation is referred to as allylic 1,2-strain (A 1,2-strain).

7. 3-Methyl-1-butene



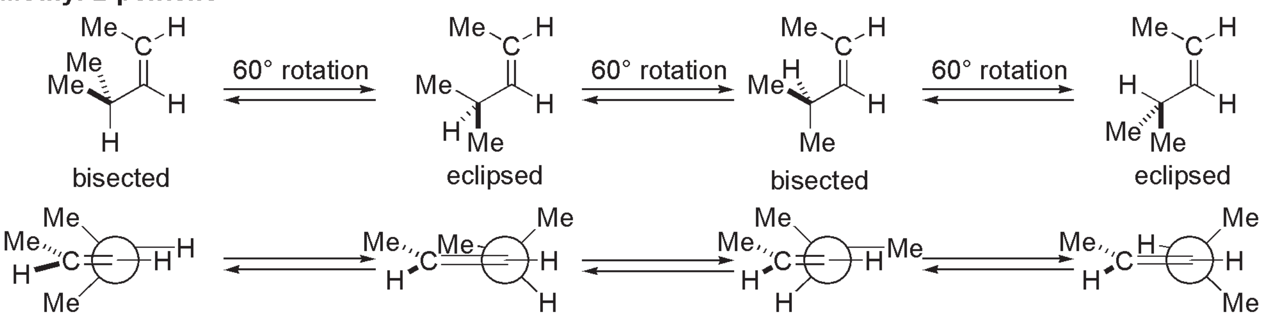
relative energies (kcal)

Ab initio	2.4–3.0	0.73–1.19	2.60–2.94	0.0



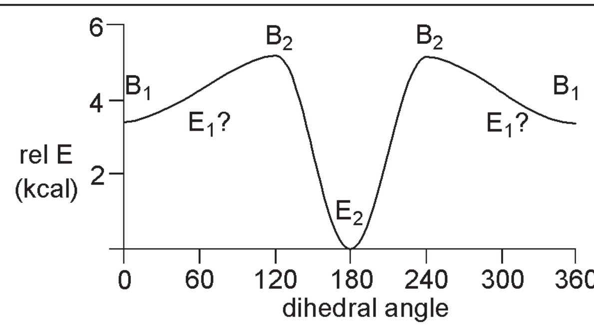
- *J. Am. Chem. Soc.* **1991**, *113*, 5006.
- *Chem. Rev.* **1989**, *89*, 1841.

8. 4-Methyl-2-pentene



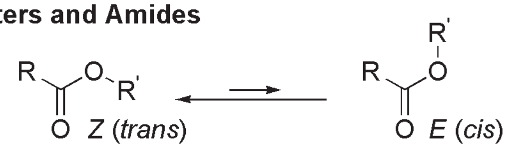
relative energies (kcal)

Ab initio	3.4–4.3	–	4.9–5.9	0.0

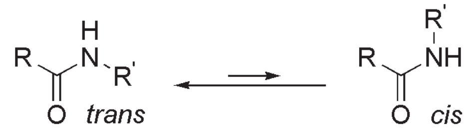


- Only H-eclipsed conformation is reasonable.

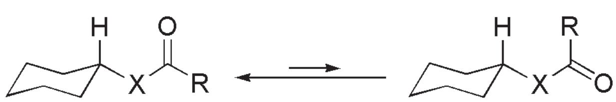
9. Esters and Amides

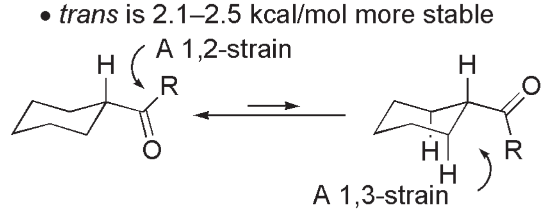


- *trans* is 4.75 kcal/mol more stable



- barrier to rotation = 18–22 kcal/mol
- *trans* is 2.1–2.5 kcal/mol more stable

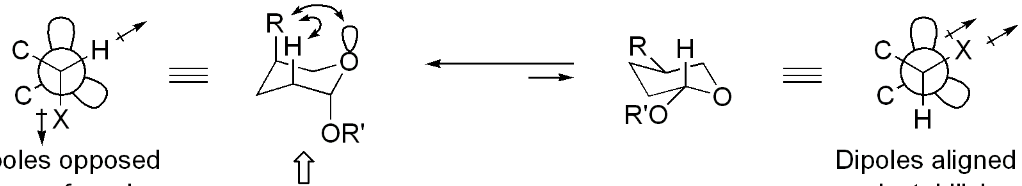




- H-eclipsed carbonyl conformation is 4–5 kcal/mol (X = O) or 2–2.5 kcal/mol (X = NH) more stable.

F. Anomeric Effect

1. Tetrahydropyrans (e.g., Carbohydrates)



X = OR'

Dipoles opposed
→ preferred

Dipoles aligned
→ destabilizing

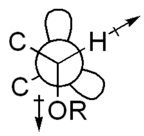
R = H, preferred conformation: $\Delta G°$ = 0.85 kcal/mol
- generally 0–2 kcal/mol, depends on C2/C3 substituents
- effect is greater in non-polar solvent

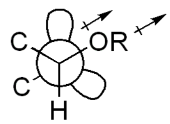
  Comprehensive Org. Chem. Vol. 5, 693.
  Comprehensive Het. Chem. Vol. 3, 629.
  Review: *Tetrahedron* **1992**, *48*, 5019.

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. ⇒ Reverse Anomeric Effect

- Explanations advanced:
  1. Dipole stabilization

opposing dipoles, stabilizing

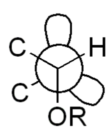


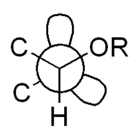


dipoles aligned, destabilizing

  2. Electrostatic repulsion

minimizes electrostatic repulsion between lone pairs and the electronegative substituent

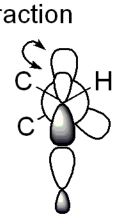


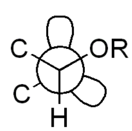


maximizes destabilizing electrostatic interaction between electronegative centers (charge repulsion)

  3. Electronic stabilization
     n–σ* orbital stabilizing interaction

n electron delocalization into σ* orbital

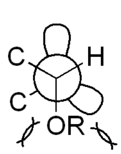


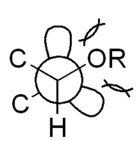


no stabilization possible

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

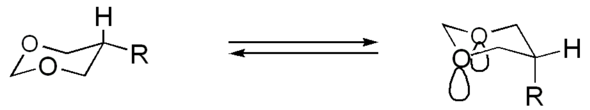
1 lone pair / OR gauche interaction + 1 C/OR gauche interaction (0.35 kcal/mol)





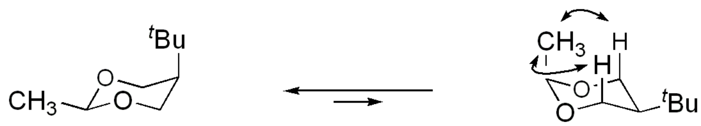
2 lone pair / OR gauche interactions, but would require that they be ~1.2 kcal/mol (unrealistic)

2. Anomeric Effect and 1,3-Dioxanes



lone pair / R interaction

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.
   ∴ $\Delta G°$ is much lower, lower preference between axial and equatorial C5 substituent.
3. Polar electropositive C2 substituents prefer equatorial position.
   C5 Axial position may be preferred for F, NO_2, $SOCH_3$, $^{+}NMe_3$.



preferred conformation

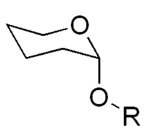
Eliel *J. Am. Chem. Soc.* **1968**, *90*, 3444.

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

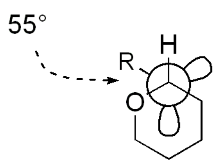
Group	Cyclohexane	Tetrahydropyran C2	1,3-Dioxane C2	1,3-Dioxane C5
CH_3	1.8	2.9	4.0	0.8
Et	1.8		4.0	0.7
^{i}Pr	2.1		4.2	1.0
^{t}Bu	>4.5			1.4

3. Exo Anomeric Effect

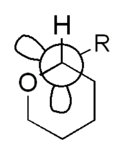
preferred orientation



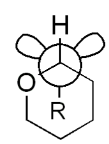
α-axial-glycosides



1 R/OR gauche

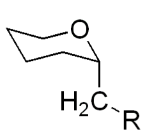


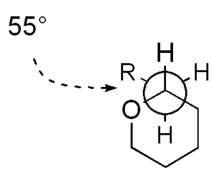
1 R/R gauche

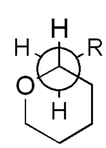


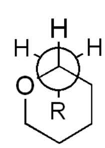
1 R/OR gauche
1 R/R gauche

Rel. E = 0.35 kcal/mol | 0.9 kcal/mol | 1.25 kcal/mol









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

G. 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	largely strain free
strain free	6	157.4	13	157.7	largely strain free
	7	158.3	14	157.4	largely strain free
	8	158.6	15	157.5	largely strain free
	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.

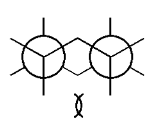
To form a small ring in synthetic sequences, must overcome the energy barrier implicated in forming a strained high energy product.

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):

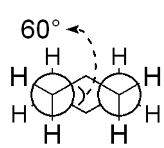
   a. Large angle strain
   - Bond angles enlarged from ideal 109.5° to 115–120°.
   - Bond angles enlarged to reduce transannular interactions.

   b. Steric (transannular) interactions
   - Analogous to 1,3-diaxial interactions in cyclohexanes, but can be 1,3-, 1,4-, or 1,5- ...



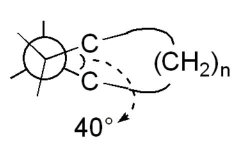
   c. Torsional strain (Pitzer strain)

in cyclohexanes



just like gauche butane

in medium rings
deviation from ideal ϕ of 60° and approach an eclipsing interaction

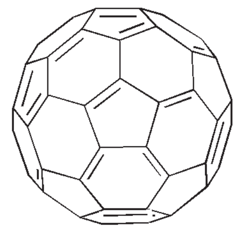


4. Large rings (12-membered and up):
   - Little or no strain.

5. Some highly strained molecules:

Buckminsterfullerene (C_{60}) has a strain energy of 480 kcal/mol and is one of the highest strain energies ever computed. However, since there are 60 atoms, this averages to ca. 8 kcal/mol per carbon atom - not particularly unusual.

First isolated in 1990:
Kroto, Heath, O'Brian, Curl, and Smalley
Nature **1985**, *318*, 162.

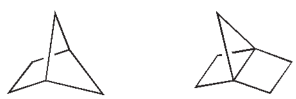


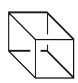
Robert Curl, Harold Kroto, and Richard Smalley shared the 1996 Nobel Prize in Chemistry for the discovery of fullerenes.

[1.1.1] propellane  Wiberg *J. Am. Chem. Soc.* **1982**, *104*, 5239.

strain energy = 98 kcal/mol

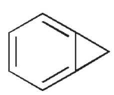
Note: The higher homologs are not stable at 25 °C.

 Wiberg *J. Am. Chem. Soc.* **1983**, *105*, 1227.

cubane  Eaton *J. Am. Chem. Soc.* **1964**, *86*, 3157.

strain energy = 155 kcal/mol

Note: Kinetically very stable, and may be prepared in kg quantities.

cyclopropabenzene  Vogel *Tetrahedron Lett.* **1965**, 3625.

strain energy = 68 kcal/mol

Note: Even traces of this substance provides an intolerable smell and efforts to establish its properties had to be cancelled at the Univ. of Heidelberg.