

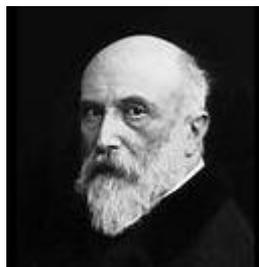
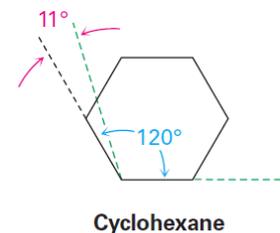
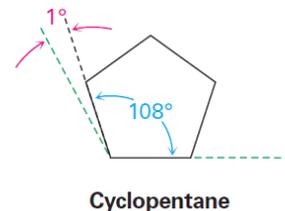
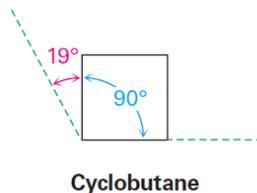
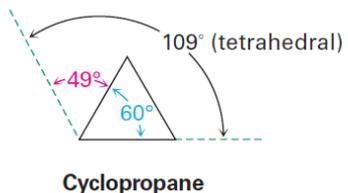
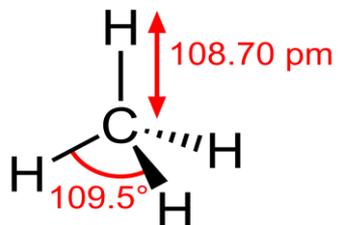
IQUSP

QFL-1221 Estrutura e reatividade de compostos orgânicos

Análise conformacional

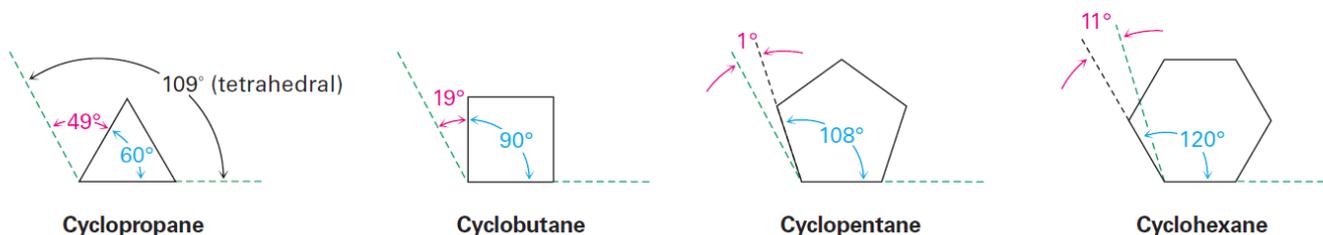
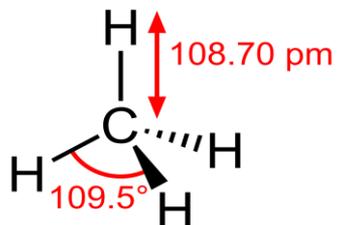
Parte 2 – Moléculas cíclicas

Estabilidade de cicloalcanos: Teoria das tensões de Baeyer



Adolf von Baeyer (PN 1905)

Estabilidade de cicloalcanos: Teoria das tensões de Baeyer



Number of atoms in ring	Internal angle in planar ring	109.5°— internal angle ^a
3	60°	49.5°
4	90°	19.5°
5	108°	1.5°
6	120°	-10.5°
7	128.5°	-19°
8	135°	-25.5°

^a A measure of strain per carbon atom.

Calores de combustão para alcanos lineares

Straight-chain alkane	$\text{CH}_3(\text{CH}_2)_n\text{CH}_3: n =$	$-\Delta H_{\text{combustion}}, \text{kJ mol}^{-1}$	Difference, kJ mol^{-1}
ethane	0	1560	660 657 659 658 659 658 660 658 658 661
propane	1	2220	
butane	2	2877	
pentane	3	3536	
hexane	4	4194	
heptane	5	4853	
octane	6	5511	
nonane	7	6171	
decane	8	6829	
undecane	9	7487	
dodecane	10	8148	

contribuição/ CH_2

Clayden, p. 455.

valor médio $658,7 \text{ kJ}\cdot\text{mol}^{-1}$

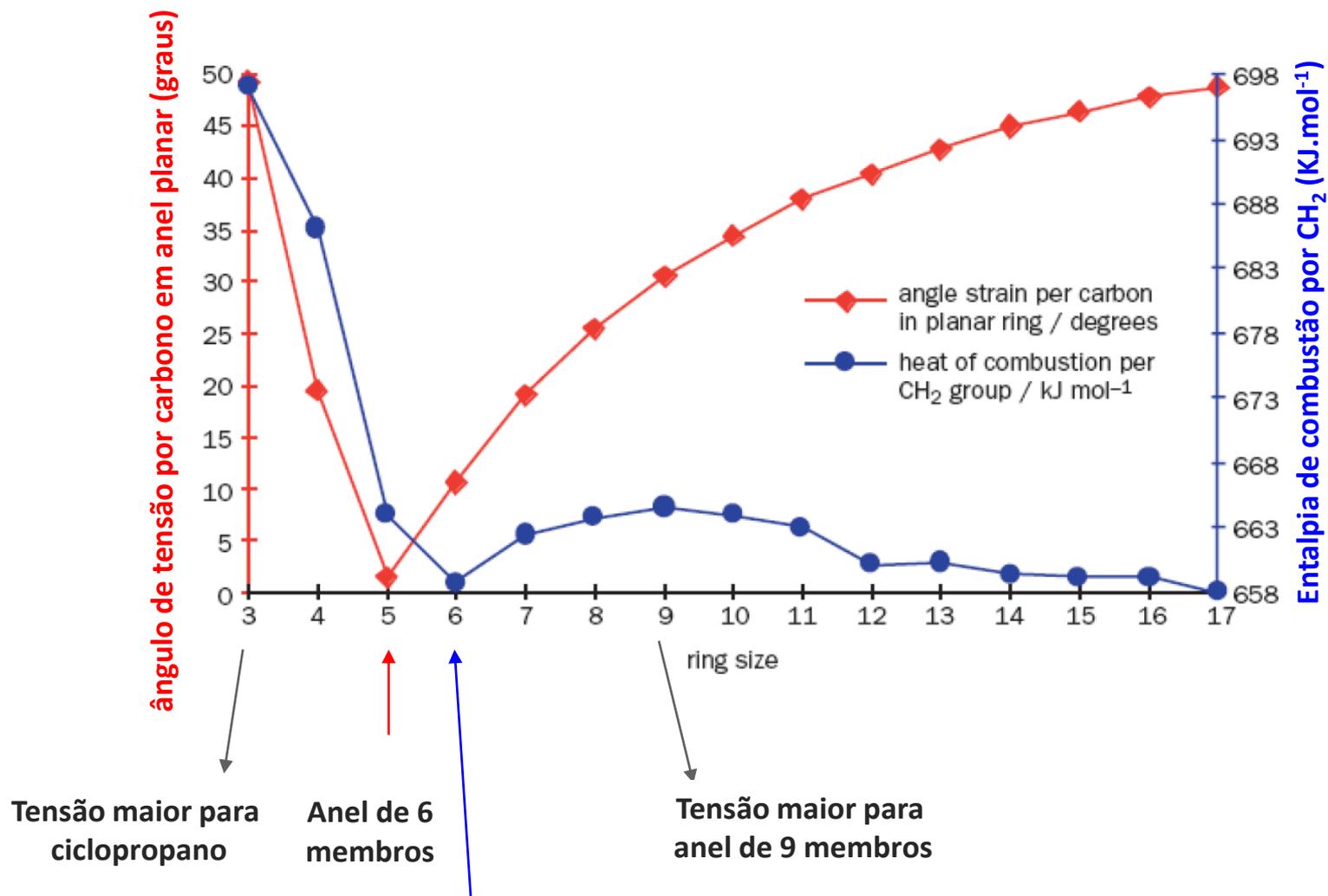
Calores de combustão teóricos e experimentais para cicloalcanos em Kcal.mol⁻¹ (KJ.mol⁻¹)

Ring size (C _n)	$\Delta H^\circ_{\text{comb}}$ (calculated)	$\Delta H^\circ_{\text{comb}}$ (experimental)	Total strain	Strain per CH ₂ group
3	-472.2 (1976)	-499.8 (2091)	27.6 (115)	9.2 (38)
4	-629.6 (2634)	-655.9 (2744)	26.3 (110)	6.6 (28)
5	-787.0 (3293)	-793.5 (3320)	6.5 (27)	1.3 (5.4)
6	-944.4 (3951)	-944.5 (3952)	0.1 (0.4)	0.0 (0.0)
7	-1101.8 (4610)	-1108.2 (4637)	6.4 (27)	0.9 (3.8)
8	-1259.2 (5268)	-1269.2 (5310)	10.0 (42)	1.3 (5.4)
9	-1416.6 (5927)	-1429.5 (5981)	12.9 (54)	1.4 (5.9)
10	-1574.0 (6586)	-1586.0 (6636)	14.0 (59)	1.4 (5.9)
11	-1731.4 (7244)	-1742.4 (7290)	11.0 (46)	1.1 (4.6)
12	-1888.8 (7903)	-1891.2 (7913)	2.4 (10)	0.2 (0.8)
14	-2203.6 (9220)	-2203.6 (9220)	0.0 (0.0)	0.0 (0.0)

Note: The calculated numbers are based on the value of -157.4 kcal mol⁻¹ (658.6 kJ mol⁻¹) for a CH₂ group.

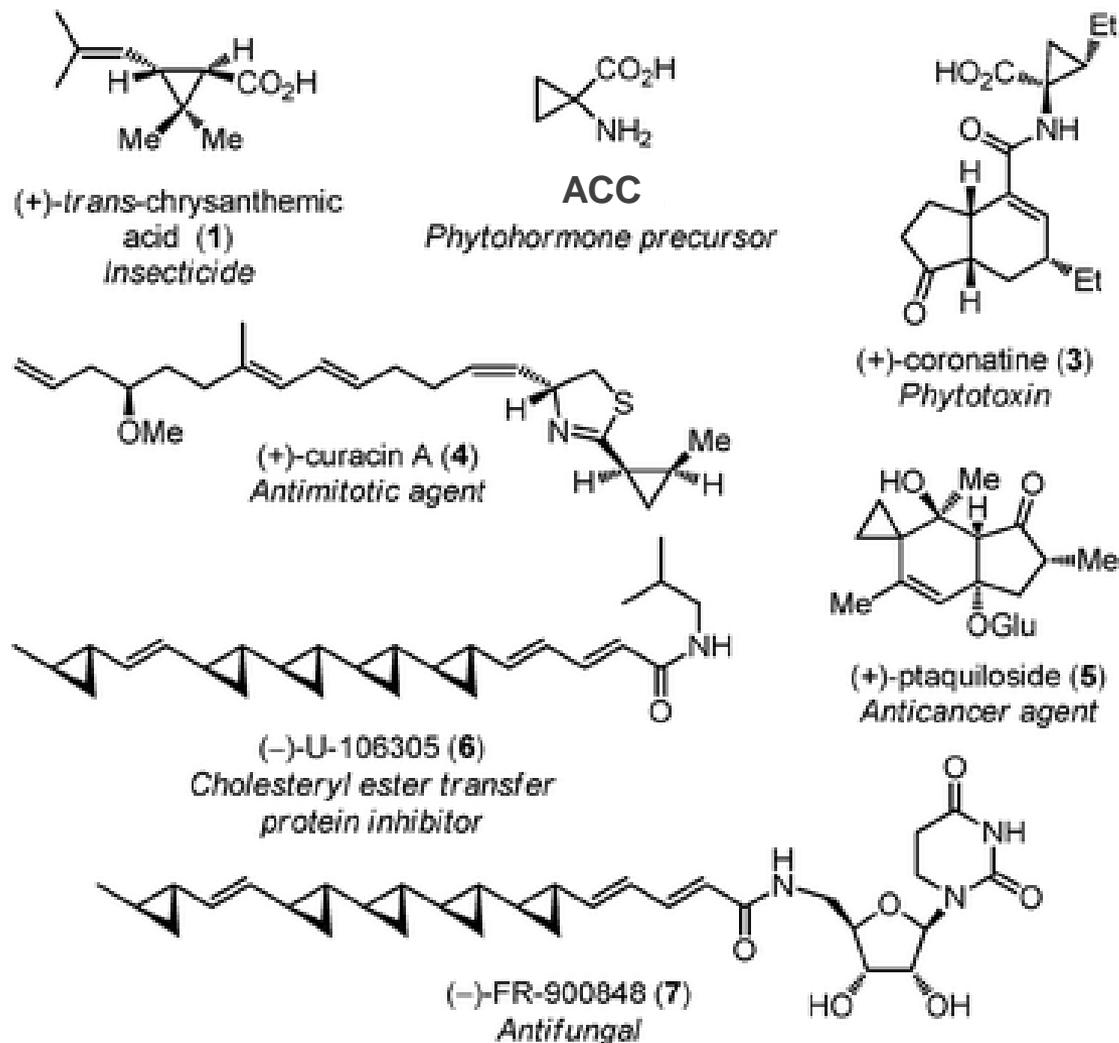
Vollhardt, p. 136.

Estabilidade de cicloalcanos

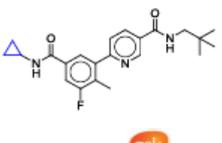
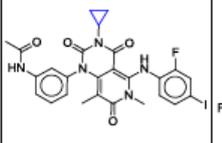
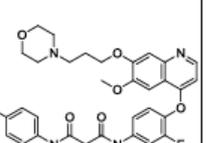
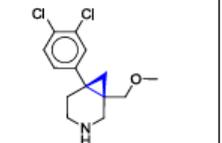
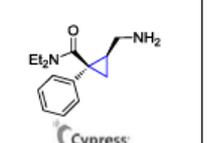
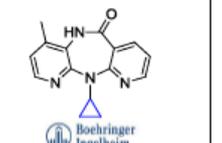
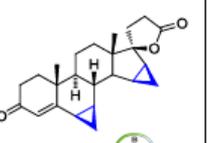
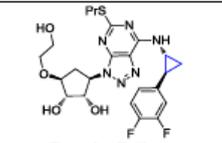
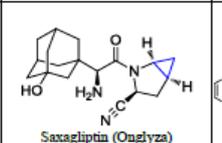
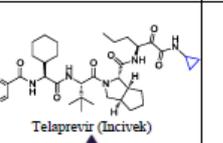
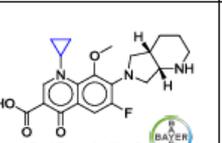
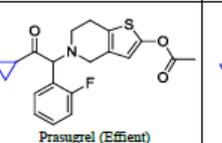
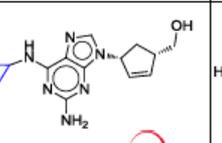
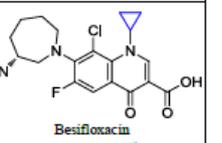
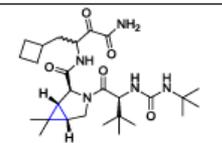
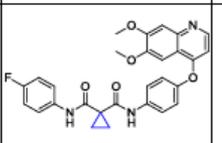
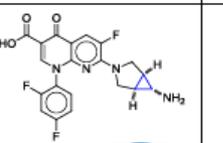
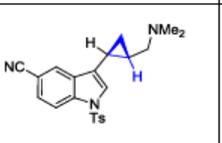
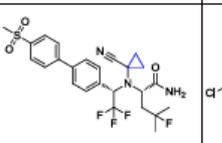
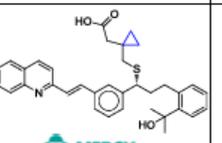
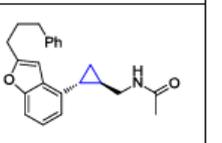
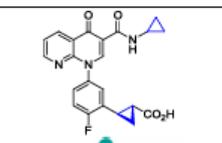
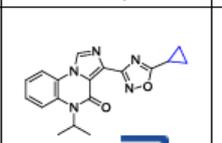
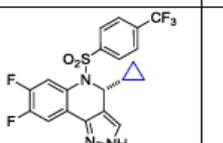
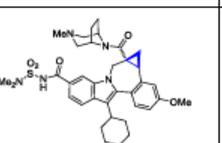
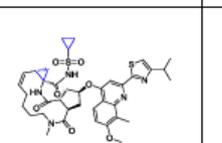
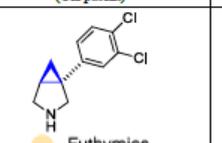
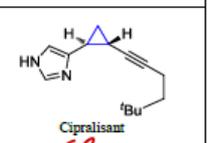
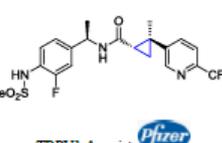
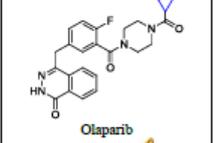
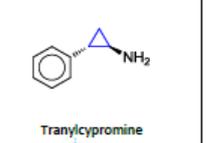
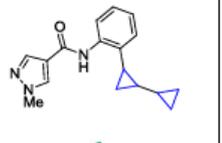
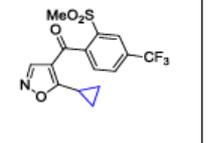
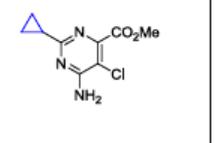


Anel de 6 e > 14 membros possuem calores de combustão ~658 KJ.mol⁻¹.

Ciclopropanos naturais

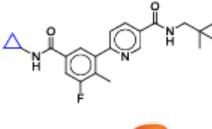
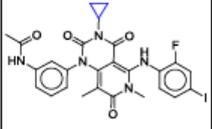
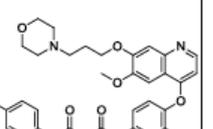
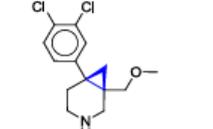
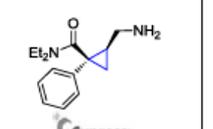
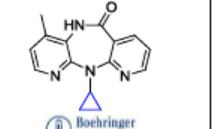
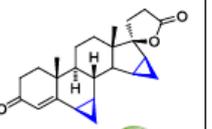
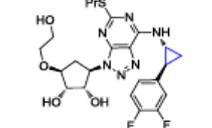
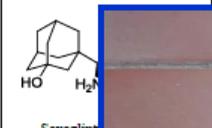
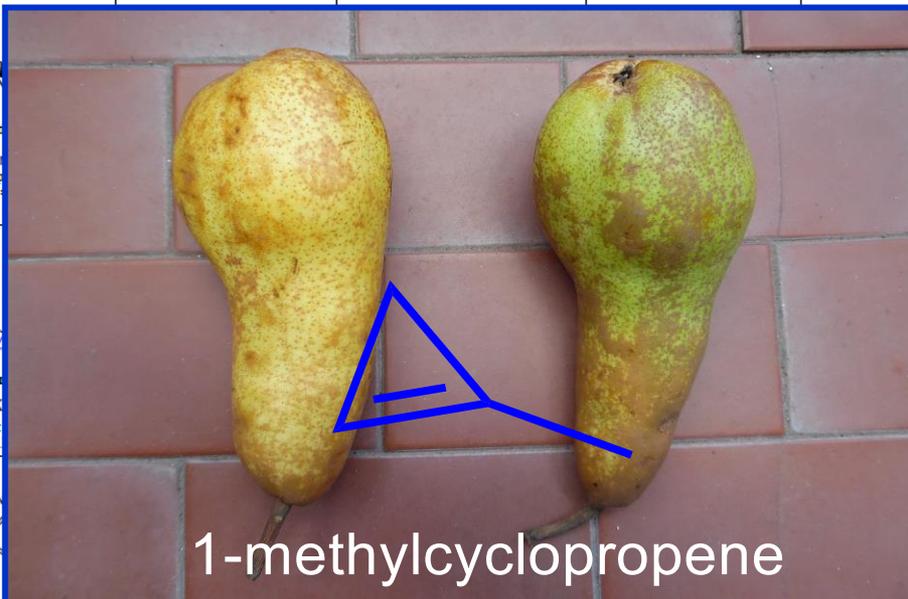
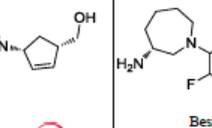
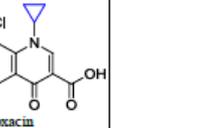
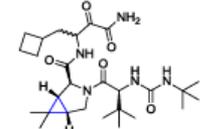
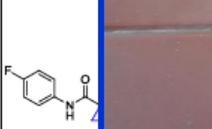
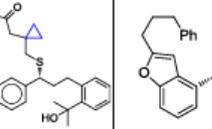
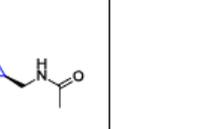
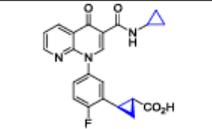
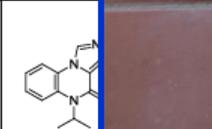
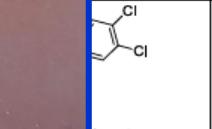
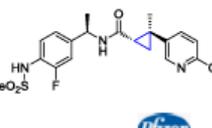
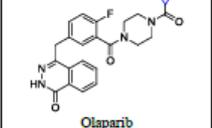
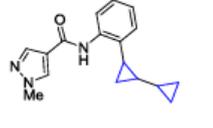
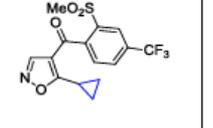
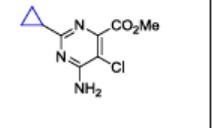


Drogas contendo anéis ciclopropânicos

 <p>Losmapimod p38 mitogen-activated protein kinases inhibitor Phase 2</p>	 <p>Trametinib (Mekinist) MEK inhibitor FDA Approved May 2013</p>	 <p>Foretinib c-Met Inhibitor, Phase 2</p>	 <p>GSK1360707F Triple re-uptake inhibitor</p>	 <p>Milnacipran (Savella) Approved for fibromyalgia 2012 Sales = \$105million</p>	 <p>Nevirapine (Viramune) Non-nucleoside reverse transcriptase inhibitor 2012 Sales = \$295million</p>	 <p>Drospirenone Synthetic birthcontrol hormone 2012 Sales = \$1344 million</p>
 <p>Ticagrelor (Brilinta) AstraZeneca Platelet aggregation inhibitor Est. sales 2018 = \$1.3 billion</p>	 <p>Saxagliptin (Onglyza) BMS/AstraZeneca Dipeptidyl peptidase-4 inhibitor 2012 Sales = \$545 million</p>	 <p>Telaprevir (Incivek) Vertex NS3 protease inhibitor 2012 Sales = \$1162 million</p>	 <p>Moxifloxacin (Avelox) Fluoroquinolone antibiotic 2010 Sales = \$1125 million Now off-patent</p>	 <p>Prasugrel (Effient) Lilly ADP receptor inhibitor 2012 Sales = \$457 million</p>	 <p>Abacavir (Ziagen) Nucleoside analogue RT inhibitor 2010 Sales = \$159 million</p>	 <p>Besifloxacin Bausch & Lomb Pro-inflammatory cytokine inhibitor 2012 Sales = \$33 million</p>
 <p>Boceprevir (Victrelis) Schering-Plough Hepatitis C protease inhibitor 2012 Sales = \$502 million</p>	 <p>Cabozantinib (Cometriq) Exelixis c-Met Inhibitor Est. sales 2013 = \$100 million</p>	 <p>Trovafloxacin Pfizer DNA gyrase inhibitor 1998 Sales = \$160 million (withdrawn)</p>	 <p>BMS-50130 Bristol-Myers Squibb Selective serotonin reuptake inhibitor</p>	 <p>Odanacatib Merck Inhibitor of cathepsin K Est. sales 2017 = \$1 billion</p>	 <p>Montelukast (Singulair) Merck Leukotriene receptor antagonist 2010 Sales = \$5 billion (Off patent)</p>	 <p>Bristol-Myers Squibb Oral melatonin receptor agonist</p>
 <p>MK-0952 Merck Selective PDE4 inhibitor Phase 2</p>	 <p>Panadipion Merck GABA_A receptor partial agonist</p>	 <p>ELND006 Elan γ-secretase inhibitor Phase 3 (abandoned 2011)</p>	 <p>BMS-791325 Bristol-Myers Squibb NS5B Polymerase Inhibitor Phase 2</p>	 <p>Simeprevir Medivir/Janssen Hep. C protease inhibitor</p>	 <p>Amitifadine Euthymics Bioscience Triple re-uptake inhibitor Phase 2b/3a</p>	 <p>Cipralisant Lilly Potent histamine H₁-antagonist</p>
 <p>TRPV1 Agonist Pfizer Phase 1</p>	 <p>Olaparib AstraZeneca PARP Inhibitor Phase 3</p>	 <p>Tranylcypromine Covis MAO inhibitor 2012 Sales = \$80 million</p>	 <p>Sedaxane Syngenta due for launch 2012</p>	 <p>Isoxafutole (Bayer) inhibitor of HPPD</p>	 <p>Aminocyclopyrachlor (DuPont) A new synthetic auxin</p>	 <p>1-MCP Syngenta Synthetic plant growth regulator st. Sales 2023 = \$500 million</p>

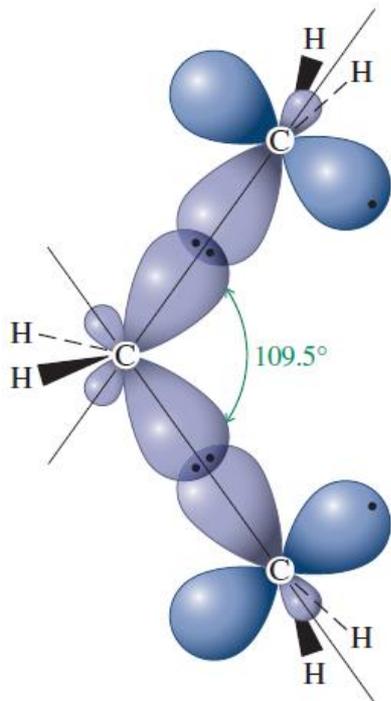
<https://brayresearch.files.wordpress.com/2013/07/cyclopropane-containing-drugs.pdf>

Drogas contendo anéis ciclopropânicos

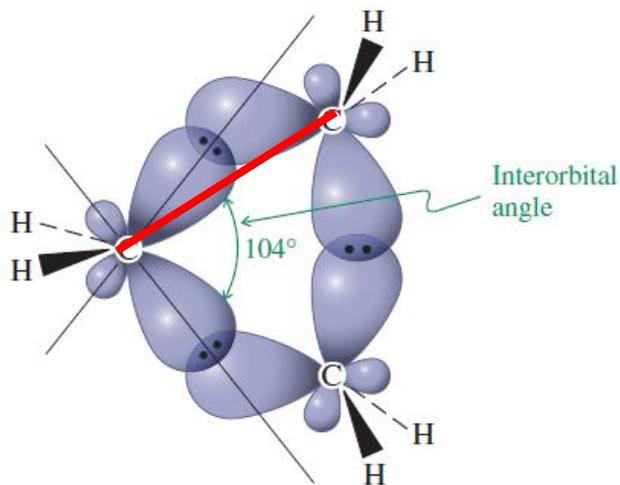
 <p>Losmapimod p38 mitogen-activated protein kinases inhibitor Phase 2</p>	 <p>Trametinib (Mekinist) MEK inhibitor FDA Approved May 2013</p>	 <p>Foretinib c-Met Inhibitor, Phase 2</p>	 <p>GSK1360707F Triple re-uptake inhibitor</p>	 <p>Milnacipran (Savella) Approved for fibromyalgia 2012 Sales = \$105million</p>	 <p>Nevirapine (Viramune) Non-nucleoside reverse transcriptase inhibitor 2012 Sales = \$295million</p>	 <p>Drospirenone Synthetic birthcontrol hormone 2012 Sales = \$1344 million</p>
 <p>Ticagrelor (Brilinta) AstraZeneca Platelet aggregation inhibitor Est. sales 2018 = \$1.3 billion</p>	 <p>Saxagliptin BMS/AstraZeneca Dipeptidyl peptidase-4 inhibitor 2012 Sales = \$1.1 billion</p>	 <p>1-methylcyclopropene</p>		 <p>Besifloxacin ViiV Healthcare Fluoroquinolone RT inhibitor 2012 Sales = \$159 million</p>	 <p>Besifloxacin Bausch + Lomb Pro-inflammatory cytokine inhibitor 2012 Sales = \$33 million</p>	
 <p>Boceprevir (Victrelis) Schering-Plough Hepatitis C protease inhibitor 2012 Sales = \$502 million</p>	 <p>Cabozantinib (Exemore) Schering-Plough c-Met Inhibitor Est. sales 2011 = \$1.1 billion</p>			 <p>Singlaur (Singlaur) Merck Melatonin receptor antagonist 2012 Sales = \$5 billion (patent)</p>	 <p>Ciproisant Bristol-Myers Squibb Oral melatonin receptor agonist</p>	
 <p>MK-0952 Merck Selective PDE4 inhibitor Phase 2</p>	 <p>Panadiplob GABA_A receptor partial agonist</p>	 <p>ELND006 elan γ-secretase inhibitor Phase 3 (abandoned 2011)</p>	 <p>N5SB Polymerase Inhibitor Bristol-Myers Squibb Phase 2</p>	 <p>Medivir Janssen Hep. C protease inhibitor</p>	 <p>Amiflutidine Pharmics Science Triple re-uptake inhibitor Phase 2b/3a</p>	
 <p>TRPV1 Agonist Pfizer Phase 1</p>	 <p>Olaparib AstraZeneca PARP Inhibitor Phase 3</p>	 <p>Tranylcypromine COVIS MAO inhibitor 2012 Sales = \$80 million</p>	 <p>Sedaxane Syngenta due for launch 2012</p>	 <p>Isoxaf lutole (Bayer) inhibitor of HPPD</p>	 <p>Aminocyclopyrachlor (DuPont) A new synthetic auxin</p>	
					 <p>1-MCP Syngenta Synthetic plant growth regulator st. Sales 2023 = \$500 million</p>	

<https://brayresearch.files.wordpress.com/2013/07/cyclopropane-containing-drugs.pdf>

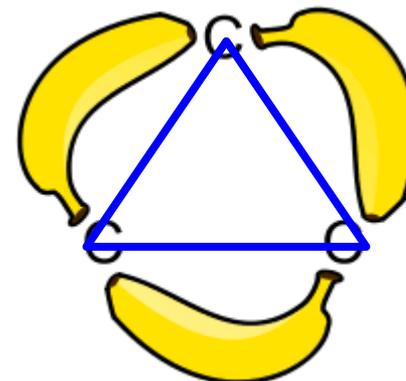
Conformações em ciclopropanos



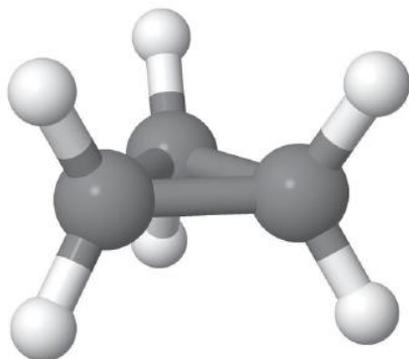
propano



ciclopropano
(calor de combustão
 $27,7 \text{ Kcal.mol}^{-1}$)

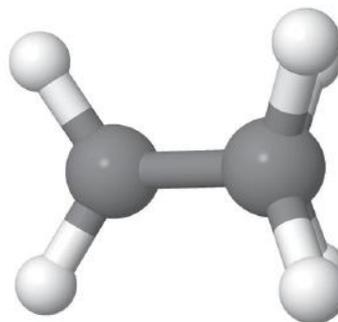


Conformações em ciclopropanos

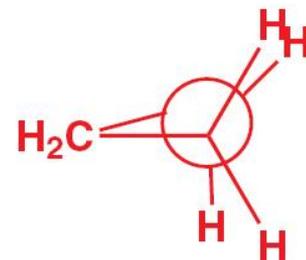


vista lateral
do ciclopropano

vista lateral ao longo
da ligação C-C

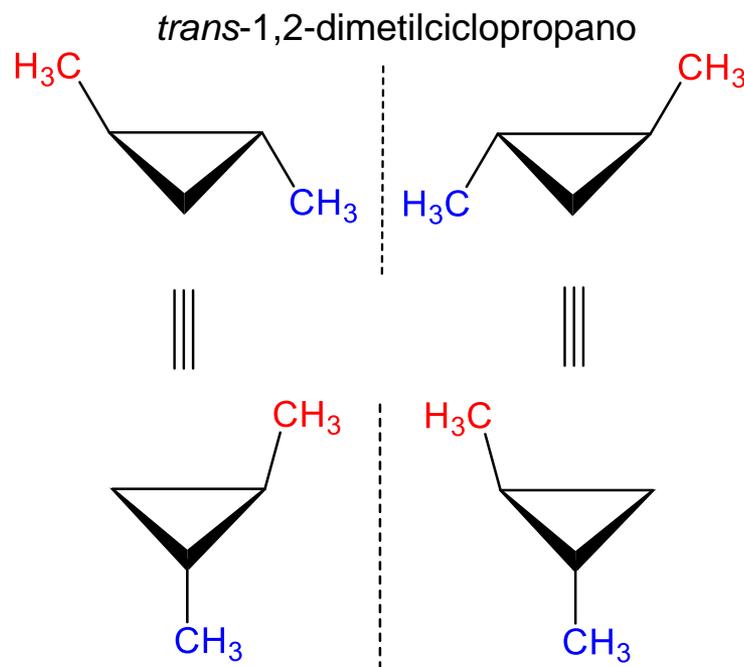
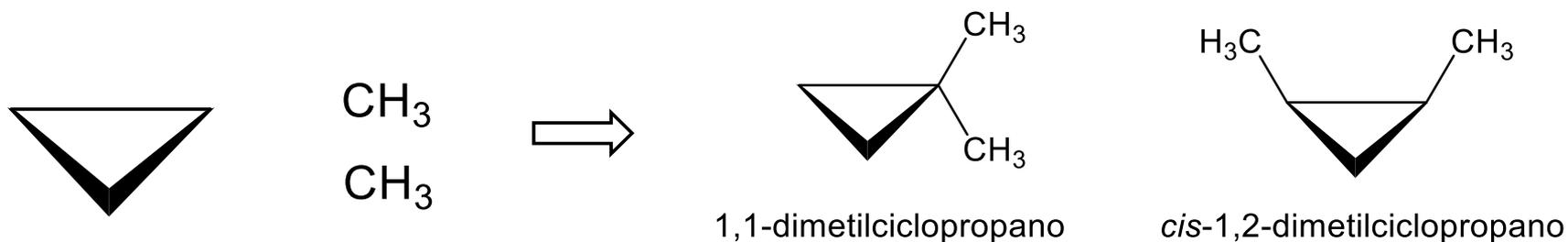


vista lateral ao longo da ligação C-C
mostrando como as ligações C-H
são eclipsadas



Isomerismo em ciclopropanos

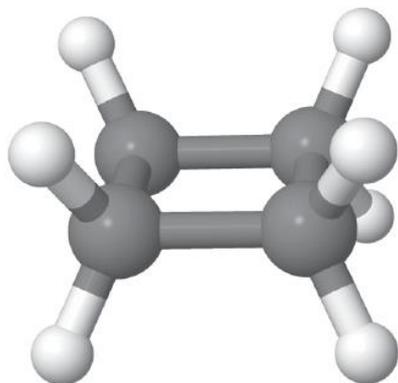
Quantos isômeros dimetilciclopropânicos existem?



4 isômeros
(3 constitucionais;
1 par de enantiômero)

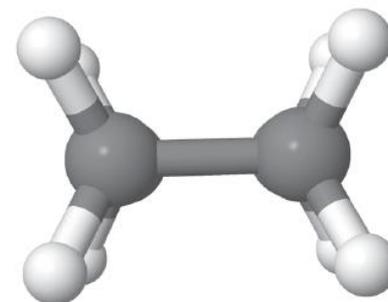
Conformações em ciclobutano

(calor de combustão 26,3 Kcal.mol⁻¹)

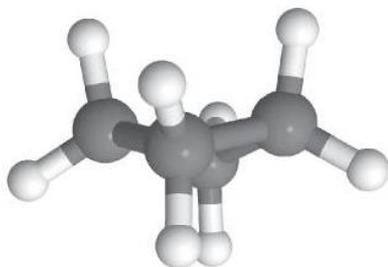


ciclobutano planar
(que não é a conformação real)

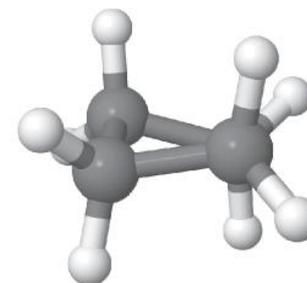
vista ao longo das
ligações C-C



vista lateral do ciclobutano
mostrando as ligações C-H eclipsadas



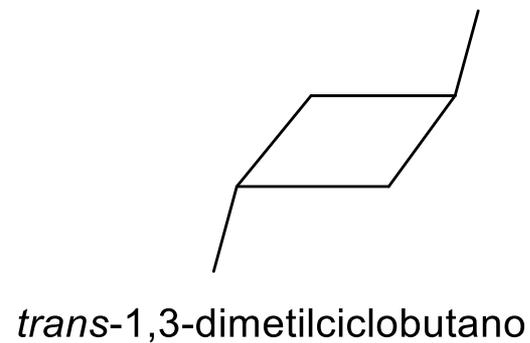
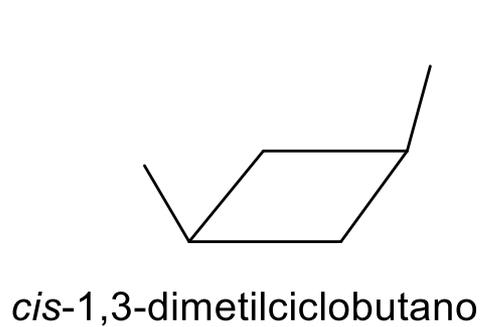
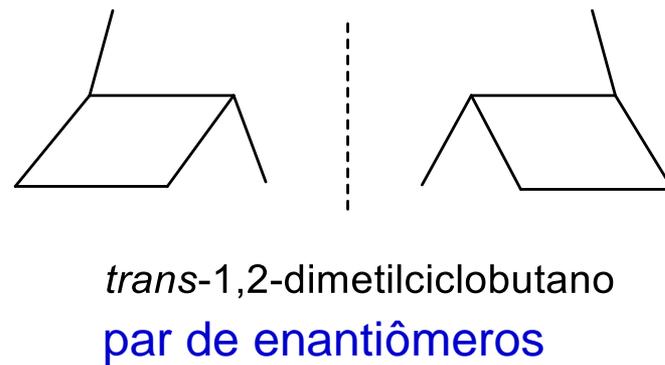
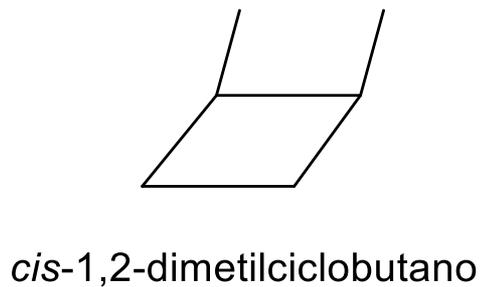
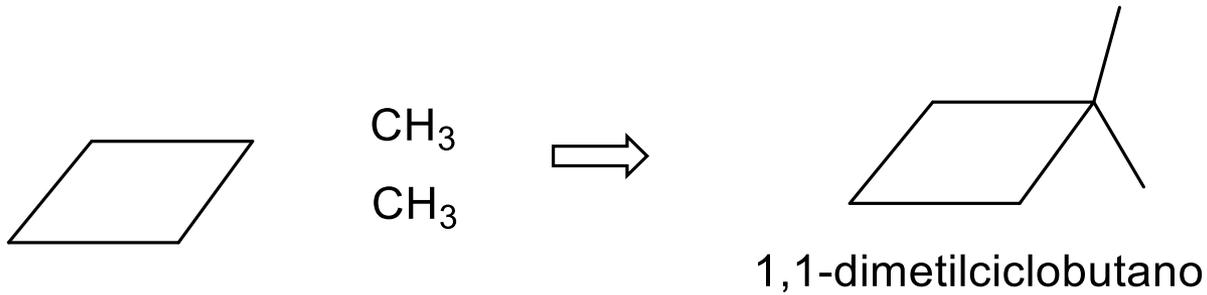
vista ao longo das
ligações C-C



conformação do ciclobutano
em “asa de borboleta”

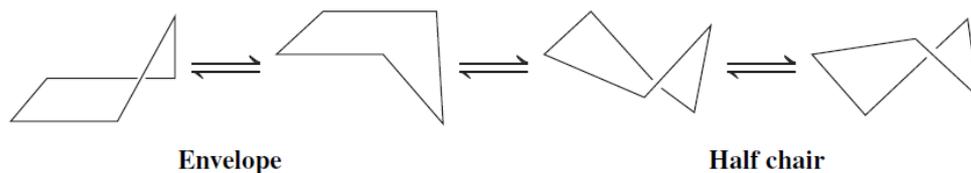
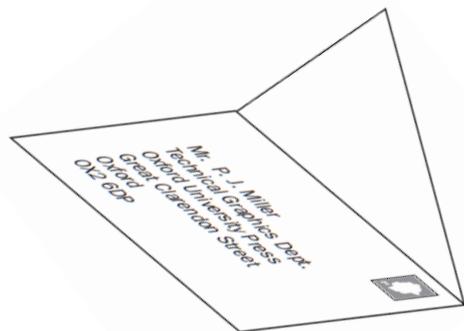
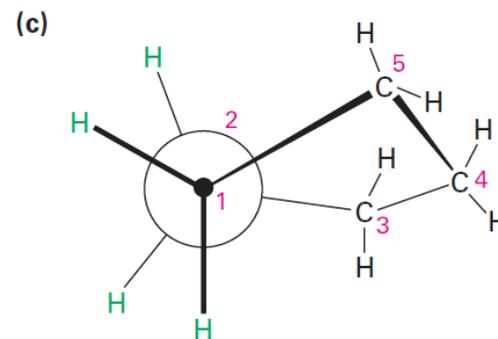
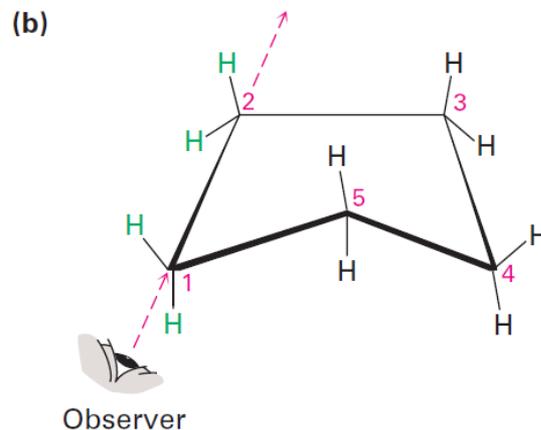
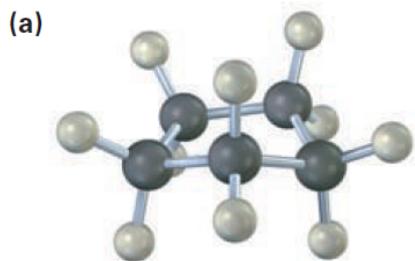
ligações C-H não são totalmente
eclipsadas

Quantos isômeros dimetilciclobutânicos existem?



Conformações em ciclopentano

(calor de combustão $6,5 \text{ Kcal.mol}^{-1}$)

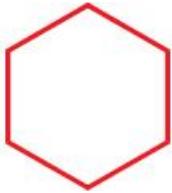


O ciclopentano possui menos tensão de anel do que o ciclopropano e ciclobutano.

Conformações no cicloexano

(calor de combustão $0,1 \text{ kcal.mol}^{-1}$)

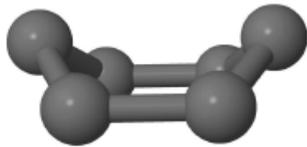
A



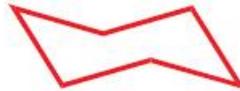
No plano

D

bote



B

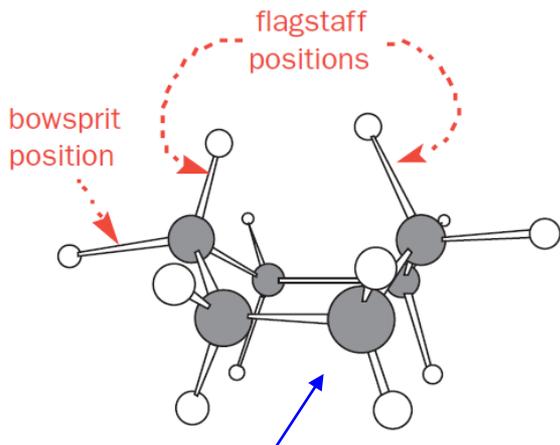


cadeira

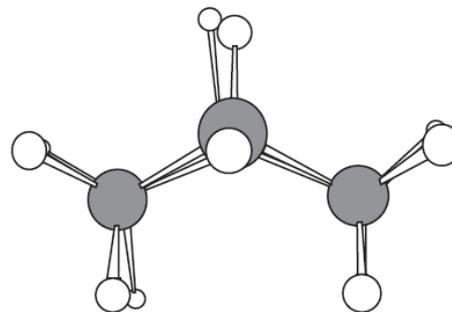
C



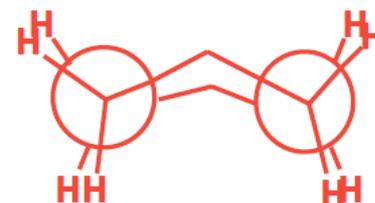
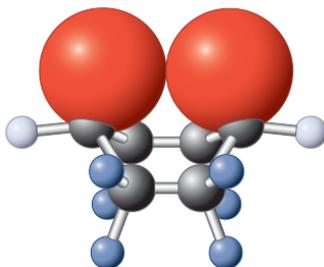
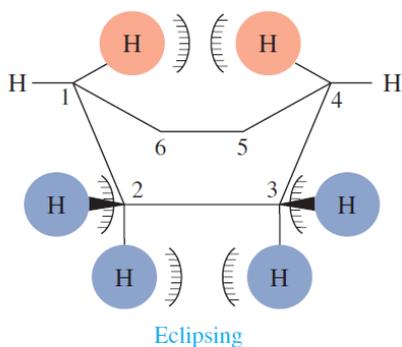
Conformação bote do ciclo-hexano



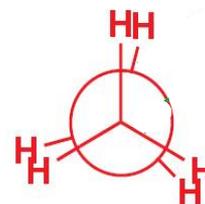
vista ao longo
de C-C



repulsões estéricas

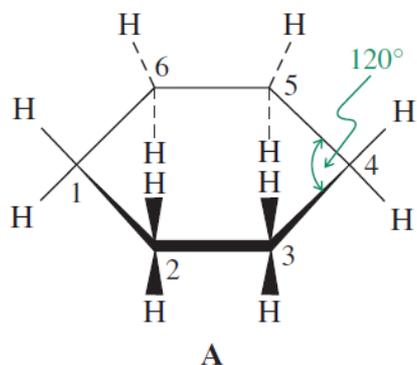


Projeção de Newman

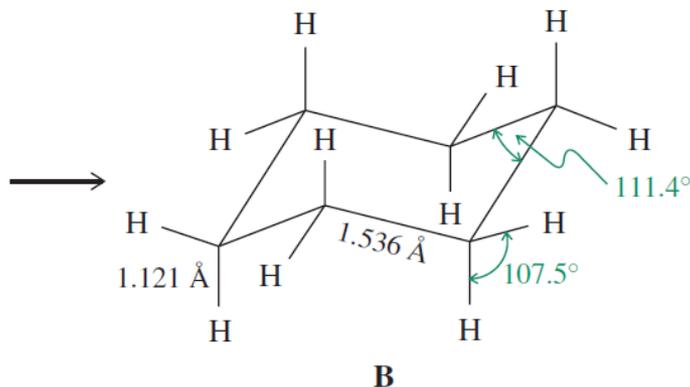


Projeção de Newman
eclipsada para o etano

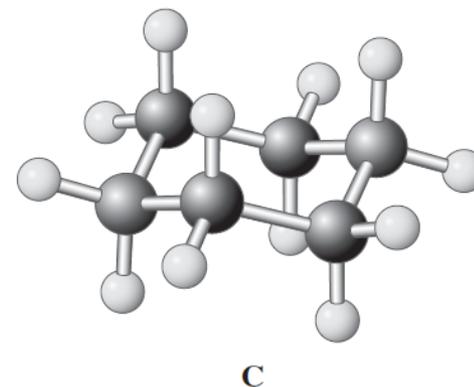
A conformação cadeira do ciclo-hexano (preferida)



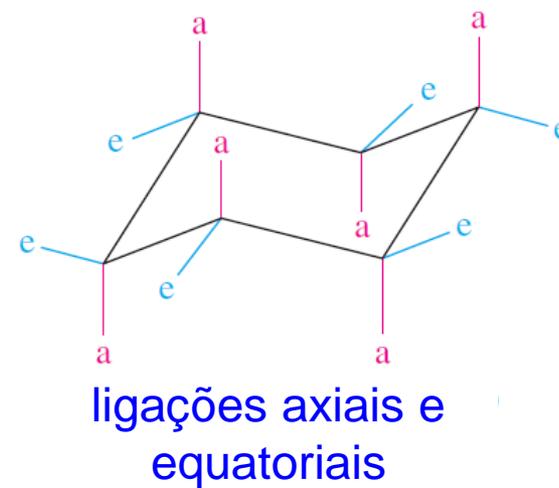
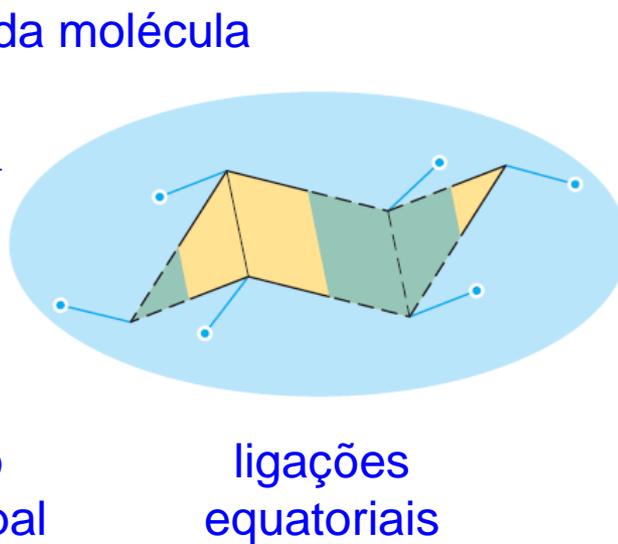
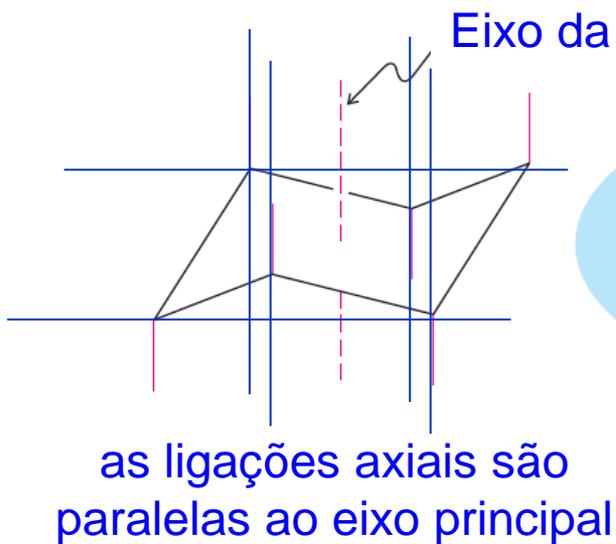
totalmente no plano
ângulos de 120°
e 12 hidrogênios
eclipsados



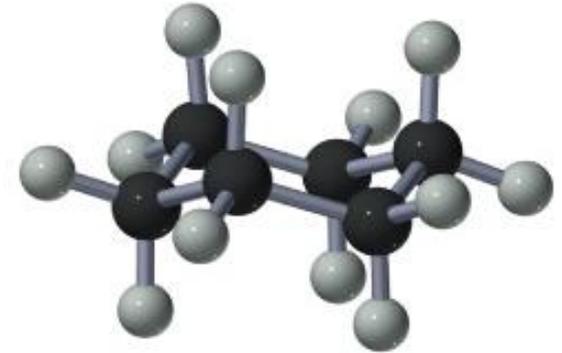
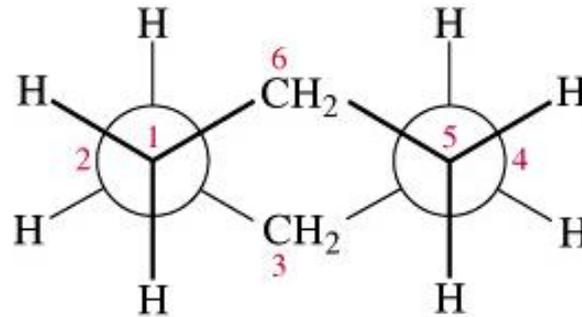
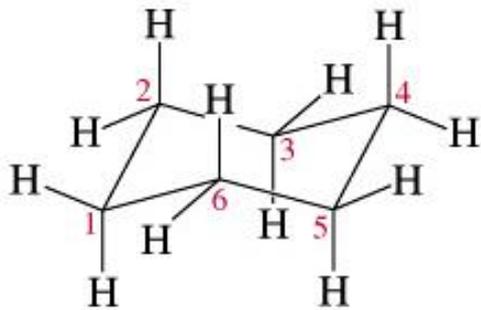
conformação em cadeira
ângulos como no carbono
tetraédrico
sem hidrogênios
eclipsados



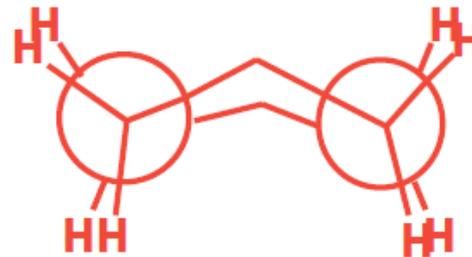
Como representar a conformação cadeira do ciclo-hexano



A conformação cadeira do ciclo-hexano

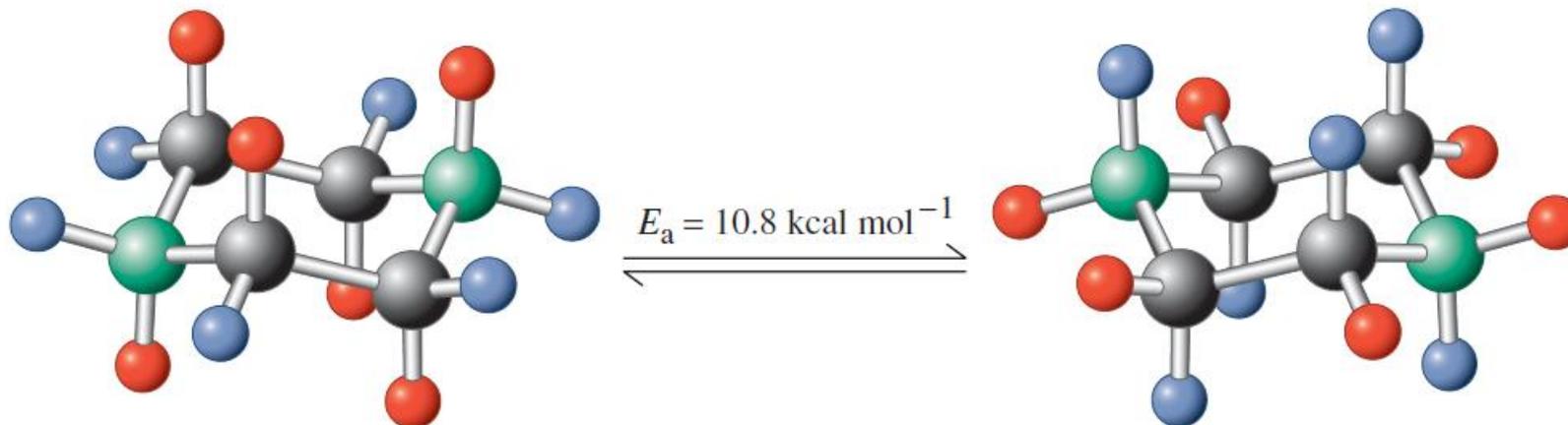


Projeção de Newman
para a conformação cadeira



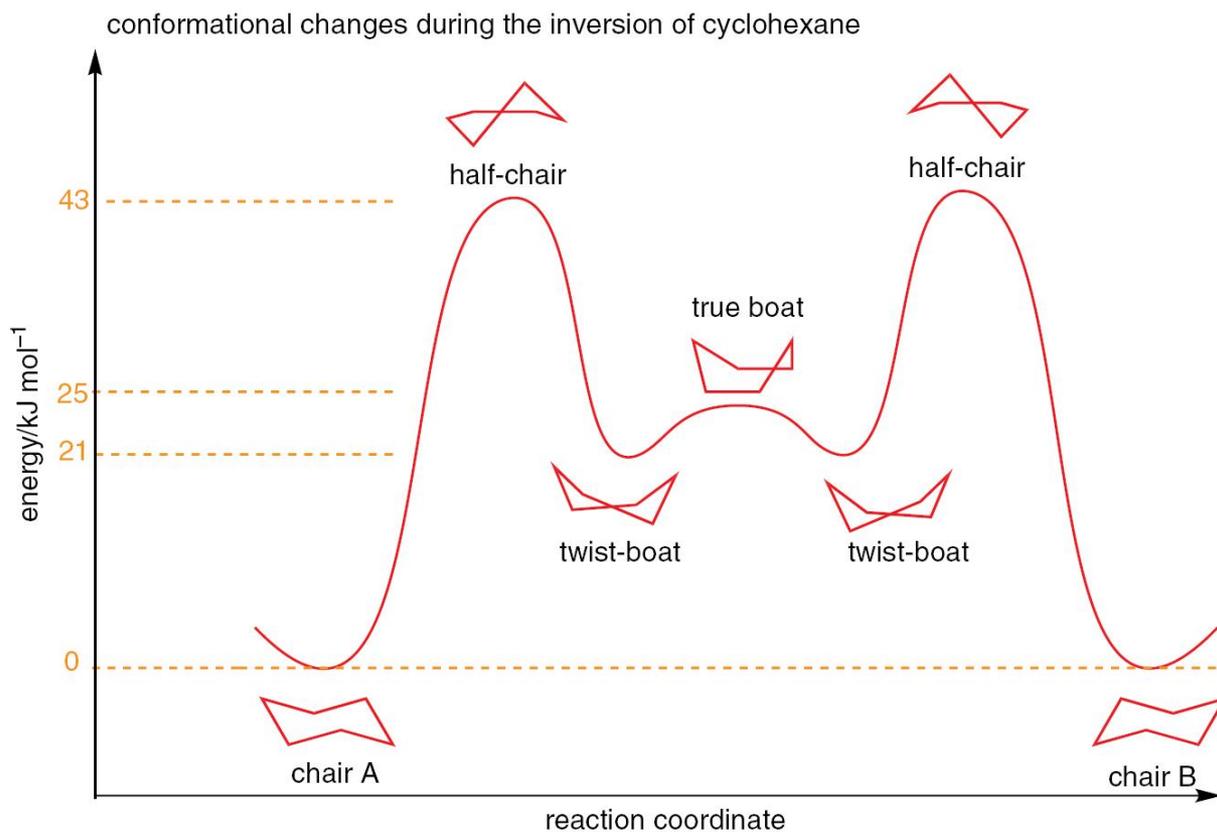
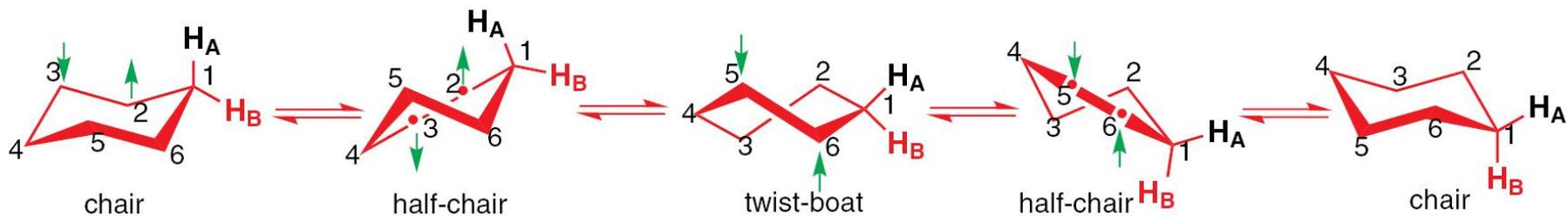
Projeção de Newman
para a conformação bote

Interconversão de conformações cadeira do ciclo-hexano

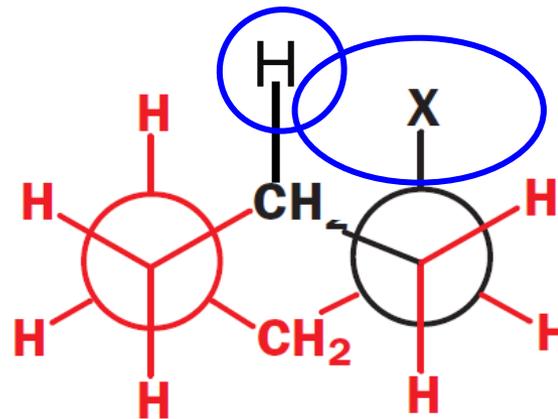
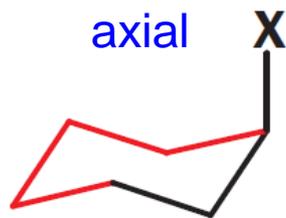
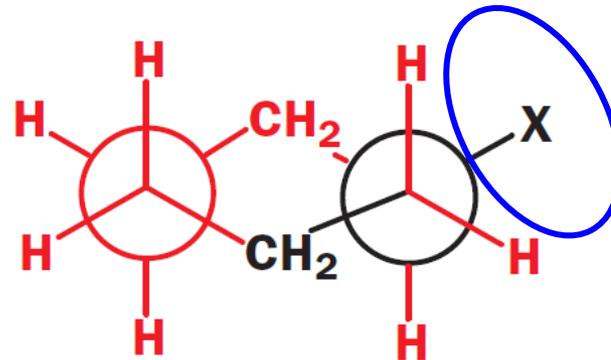
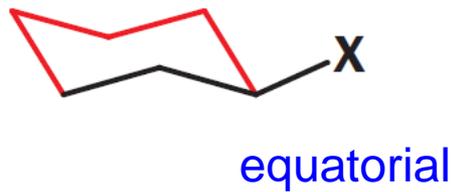


[http://paginas.grupoa.com.br/vollhardtquimi
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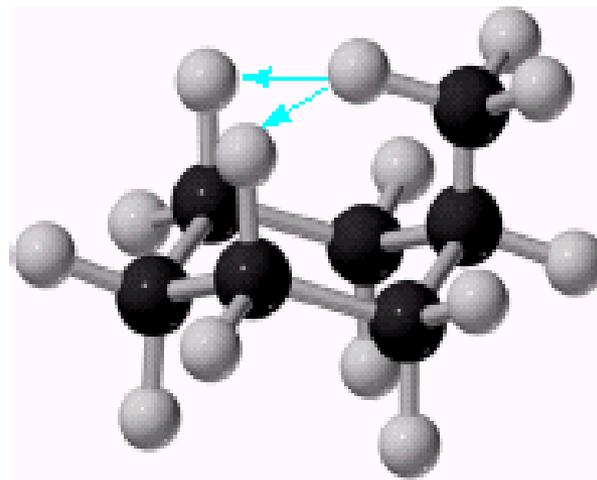
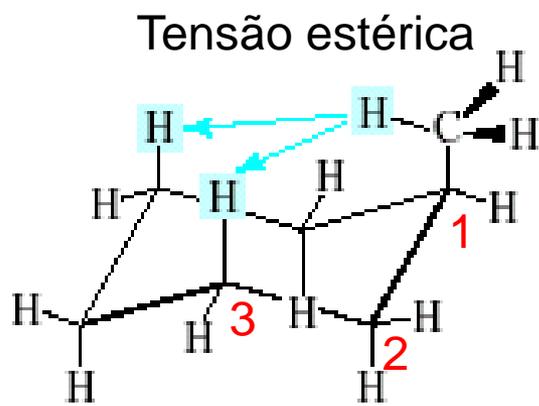
Interconversão de conformações cadeira do ciclo-hexano



Conformações de ciclo-hexanos monossubstituídos



Interação 1,3-diaxial no ciclo-hexano monosubstituído



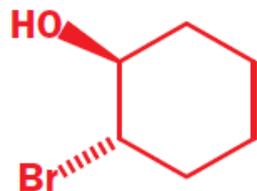
Conformações de ciclo-hexanos monossustituídos



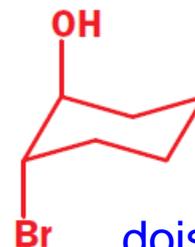
$$K = \frac{\text{concentration of equatorial conformer}}{\text{concentration of axial conformer}}$$

X	Equilibrium constant, K	Energy difference between axial and equatorial conformers, kJ mol^{-1}	% with substituent equatorial
H	1	0	50
Me	19	7.3	95
Et	20	7.5	95
<i>i</i> -Pr	42	9.3	98
<i>t</i> -Bu	>3000	>20	>99.9
OMe	2.7	2.5	73
Ph	110	11.7	99

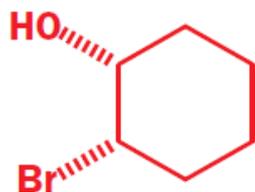
Análise conformacional dos isômeros *cis* e *trans* de ciclohexanos 1,2-dissubstituídos



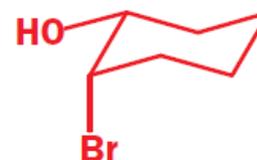
dois substituintes
em equatoriais



dois substituintes
em axiais

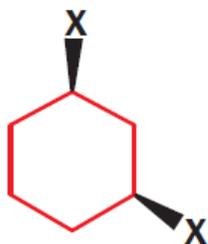


Br em equatorial
e OH axial

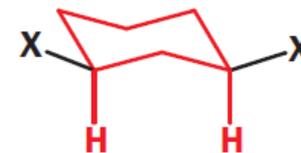
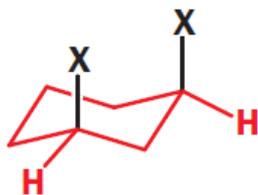


Br (substituinte maior)
em axial e OH em
equatorial

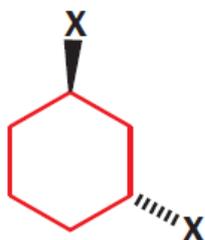
Análise conformacional dos isômeros *cis* e *trans* de ciclohexanos 1,3-dissubstituídos



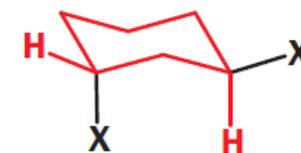
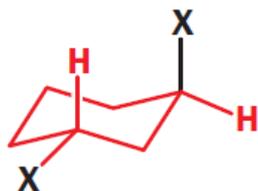
ciclohexanos
cis-1,3-dissubstituídos



em ambas conformações os substituídos estão para cima do plano

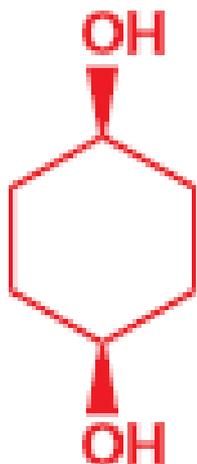


ciclohexanos
trans-1,3-dissubstituídos

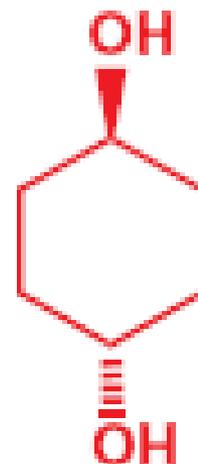


em ambas conformações os substituídos estão
uma para cima e outra para baixo do plano

Os isômeros *cis* e *trans* do 1,4-di-hidroxi-ciclo-hexanos possuem pontos de fusão distintos



m.p. 113–114 °C



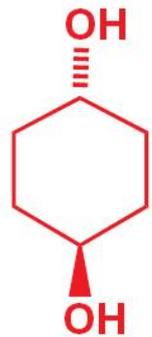
m.p. 143–144 °C

Análise conformacional dos isômeros *cis* e *trans* do 1,4-di-hidroxi-ciclo-hexanois



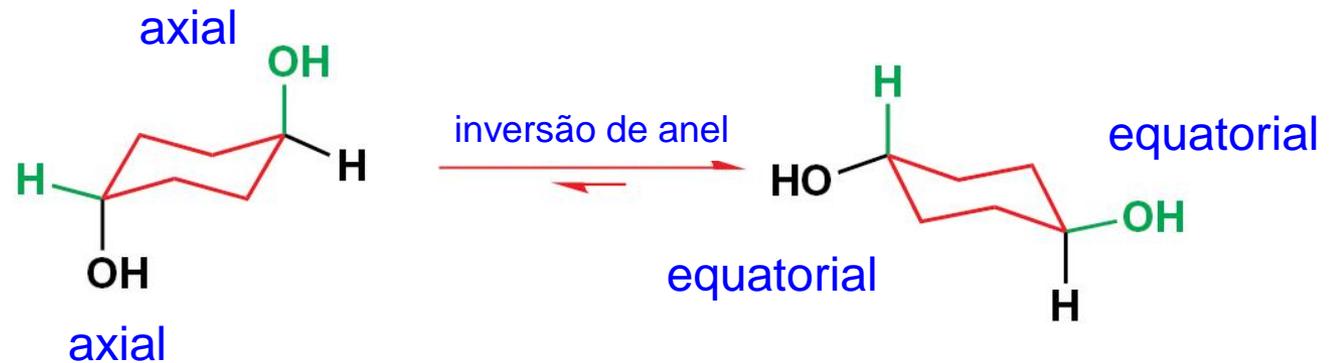
cis-1,4-ciclohexanodiol

m.p. 113–114 °C

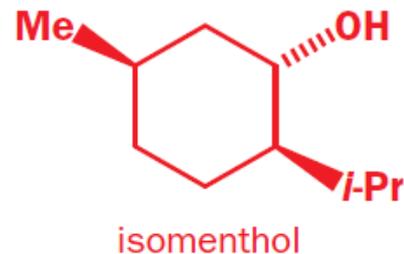
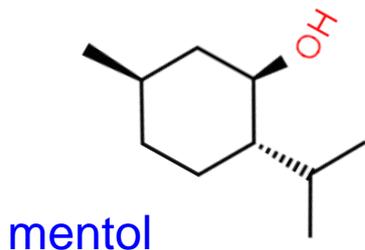


trans-1,4-ciclohexanodiol

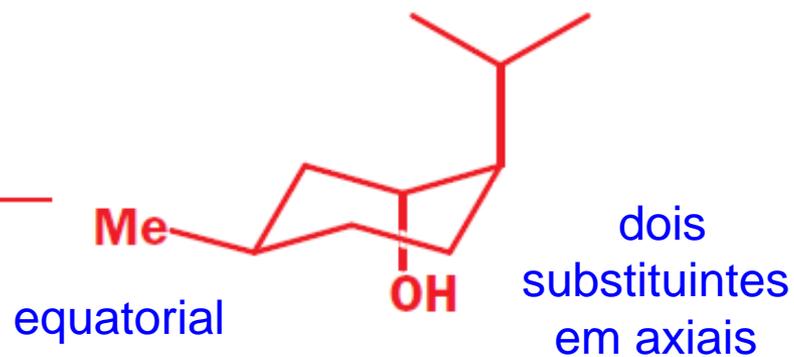
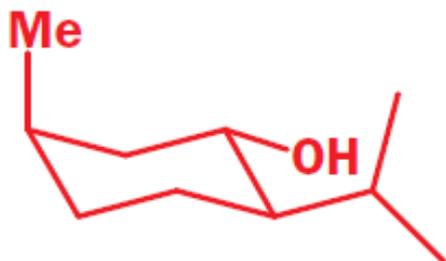
m.p. 143–144 °C



Análise conformacional de ciclohexanos 1,2,4-trissubstituídos (isomentol)



axial



Análise conformacional de ciclohexanos 1,4-dissubstituídos



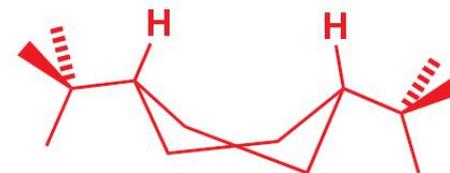
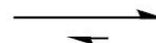
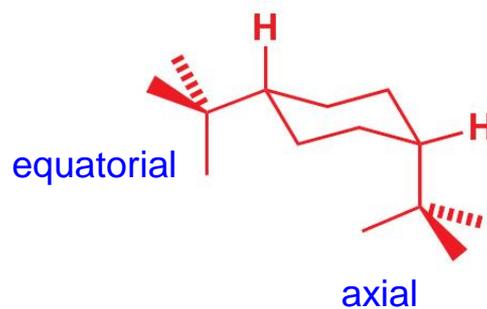
cis-4-terbutilciclohexanol



trans-4-terbutilciclohexanol

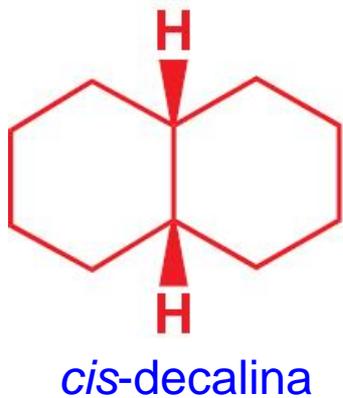


cis-1,4-di-*t*-butil-ciclohexano

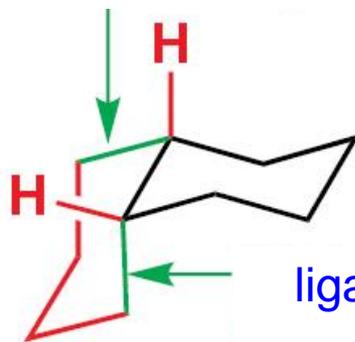


os grupos *t*-butilas
ficam em pseudoequatoriais
(conformação preferida)

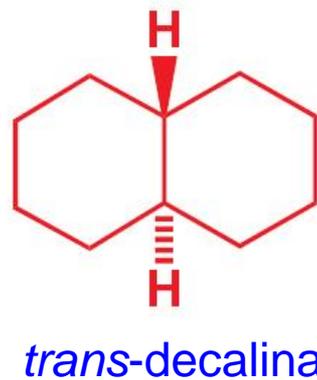
Análise conformacional decalinas *cis* e *trans*



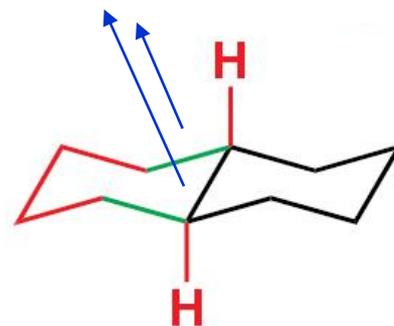
ligação equatorial



ligação em axial

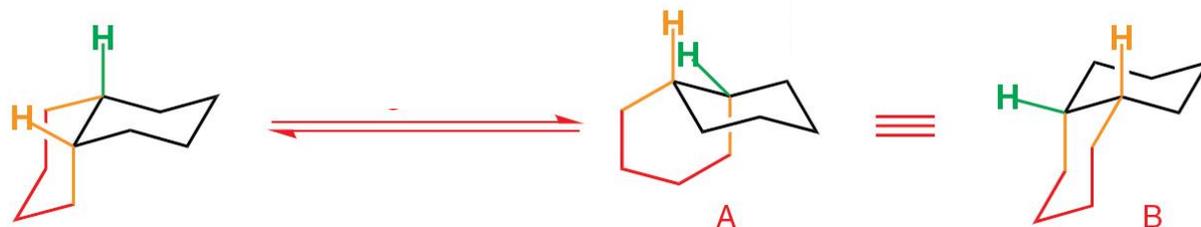


ligações em equatorial

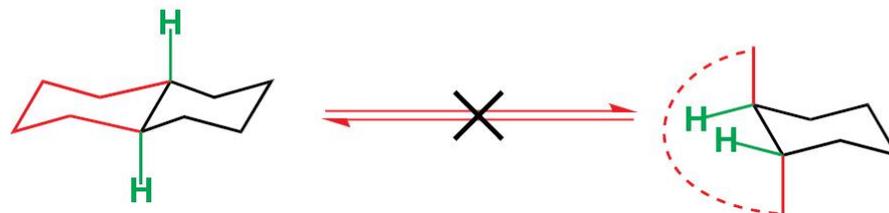


Análise conformacional decalinas *cis* e *trans*

inversão de anel na *cis*-decalina

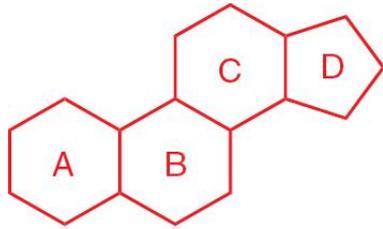


inversão de anel na *trans*-decalina
não é possível

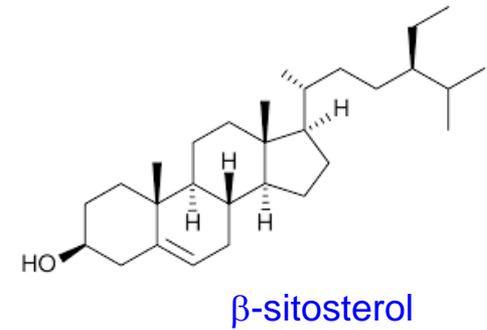
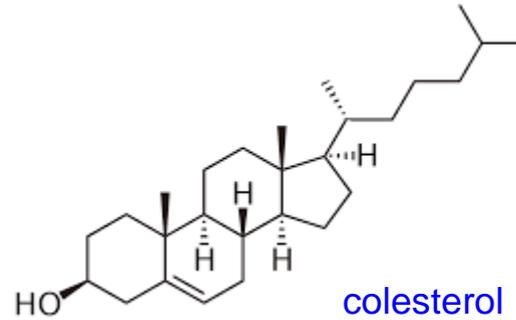


a *trans*-decalina é mais estável

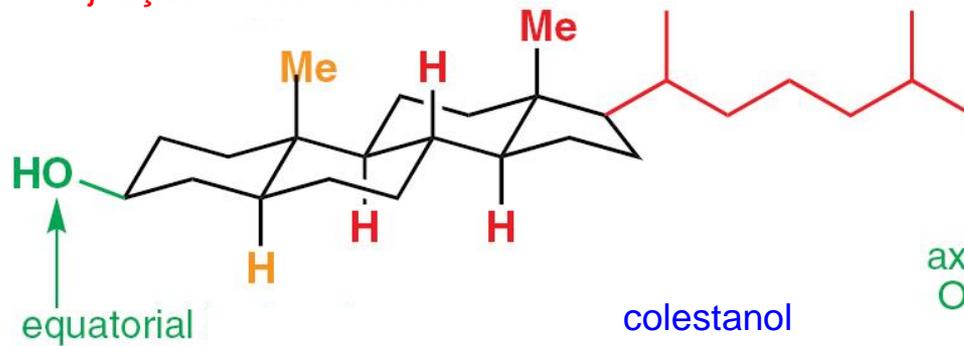
Estrutura de compostos policíclicos



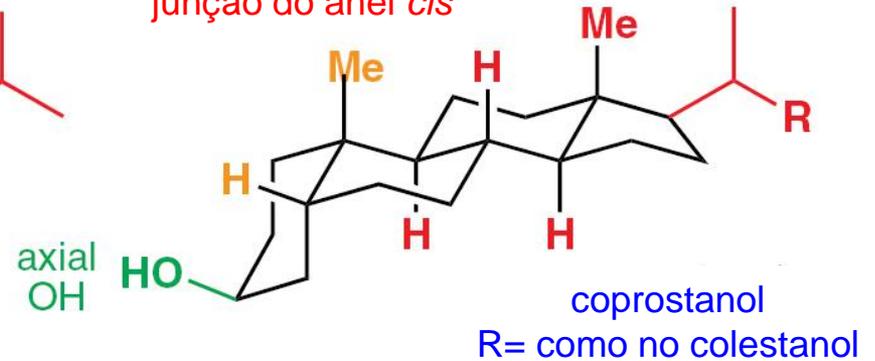
esqueleto de um esteroide



junção do anel *trans*



junção do anel *cis*



Consequencias das conformações

- Efeitos sobre propriedades físicas (pontos de fusão)
- Atividade catalítica de enzimas
- Estereoseletividade nas reações de eliminação bimolecular
- Estereoespecificidade em reações de substituição nucleofílica bimolecular

Literatura sugerida

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- 3) Vollhard e Schore, 6^a edição, Cap. 2, Rotação em torno de ligações simples, p. 79-86; Cap. 4, Cicloalcanos, p. 131-157.
- 4) McMurry, 5^a ed. Chapter 3, Cycloalkanes, p. 95-102; Chapter 4, Stereochemistry of alkanes and cycloalkanes, p. 111-141.
- 5) Clayden, Greeves, Warren and Wothers, 2001, Chapter 18, Conformational analysis, p. 448-475.