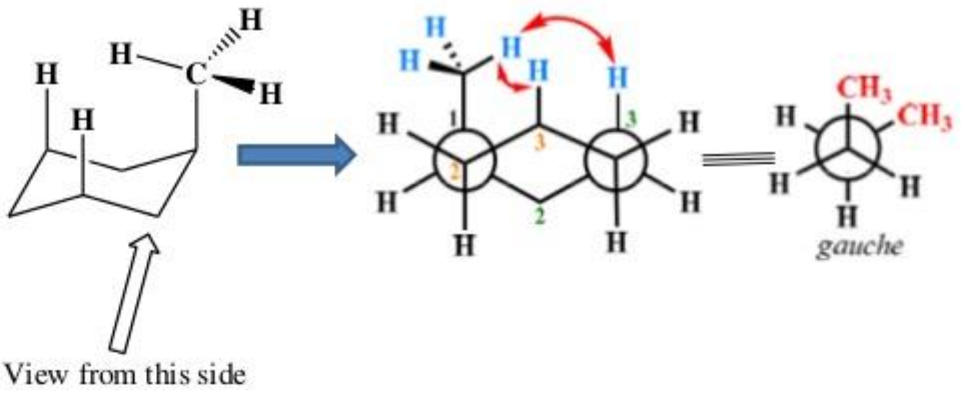
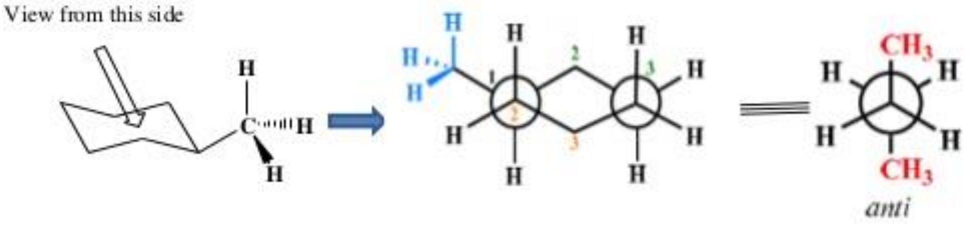
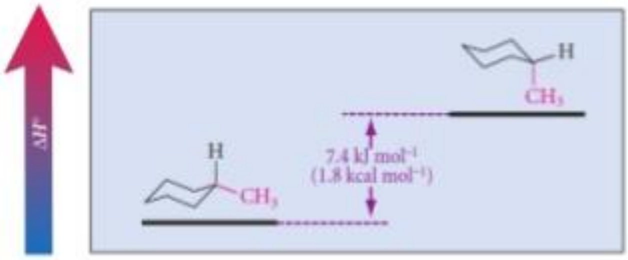




Due to difference in energy between placing a substituent in the axial vs equatorial position, the two chair conformers are no longer equal energy.

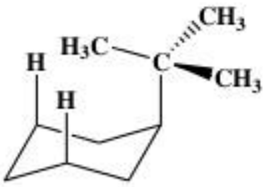


With methyl substituent a hydrogen a hydrogen is directed towards 1, 3 – hydrogens. As the substituent becomes larger, steric interaction with 1, 3-hydrogen increases.

With ethyl substituent, if the extra methyl is pointed towards 1, 3-hydrogens can rotate to move away. Has energy similar to methyl cyclohexane i.e. 1.8 Kcal/mol.

With isopropyl substituent, can still have a conformer with hydrogen pointed towards 1, 3-hydrogens. Has energy of about 2.1 Kcal/mol.

With tertiary butyl group must have methyl group towards 1, 3-hydrogens. Its energy is greater than 4.5 Kcal/mol.



The relative population of the two chair conformers can be calculated by the equation,

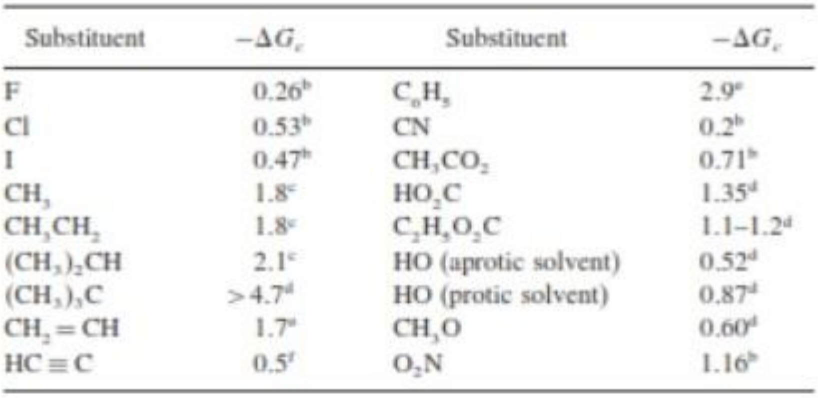
$$\Delta G = -RT \ln K_{eq}$$

The free-energy difference between conformers is referred to as the conformational free energy. For substituted cyclohexanes it is conventional to specify the value of -Gc for the equilibrium:

$$[\text{Equatorial}] \rightleftharpoons [\text{Axial}]$$

$$K_{eq} = \frac{[\text{Axial}]}{[\text{Equatorial}]}$$

As - G_c is negative when the equatorial conformation is more stable than the axial, the value of - G_c is positive for groups that favor the equatorial position. The larger the - G_c, the greater the preference for the equatorial position.



Substituent	$-\Delta G_c$	Substituent	$-\Delta G_c$
F	0.26^b	C_6H_5	2.9^e
Cl	0.53^b	CN	0.2^b
I	0.47^b	CH_3CO_2	0.71^b
CH_3	1.8^c	HO_2C	1.35^d
CH_3CH_2	1.8^c	$C_2H_5O_2C$	$1.1–1.2^d$
$(CH_3)_2CH$	2.1^c	HO (aprotic solvent)	0.52^d
$(CH_3)_3C$	$>4.7^d$	HO (protic solvent)	0.87^d
$CH_2=CH$	1.7^e	CH_3O	0.60^d
$HC\equiv C$	0.5^f	O_2N	1.16^b

The equatorial conformer of ethyl cyclohexane is 7.4 KJ/mol more stable than the axial conformer. Calculate the percentage of ethyl cyclohexane which is in equatorial at 25°C.

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

$$K_{eq} = e^{-\Delta G/RT}$$

$$= e^{-7.4 / 0.0083 \times 298}$$

$$= e^{-2.99}$$

$$K_{eq} = 0.0504$$

$$K_{eq} = \frac{[\text{Axial}]}{[\text{Equatorial}]} = 0.0504$$

$$100 = \text{Axial} + \text{Equatorial}$$

$$100 = 0.0504 \times \text{Equatorial} + \text{Equatorial}$$

$$100 = 1.0504 \times \text{Equatorial}$$

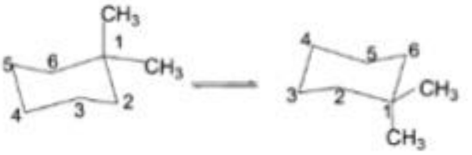
$$\text{Equatorial} = \frac{100}{1.0504} = 95.25\ \%$$

Disubstituted Cyclohexanes and Diastereoisomerism:

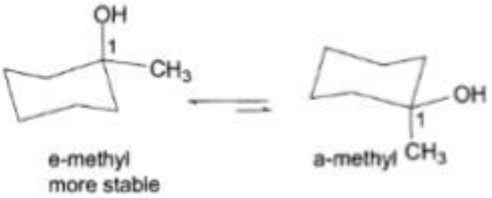
In a disubstituted cyclohexane, the most stable conformation is the one in which the largest number of substituents are in equatorial positions. If the number of equatorial and axial substituents of the same size in two conformations is the same, then the two conformations are equally stable.

1, 1 -Disubstituted cyclohexanes:

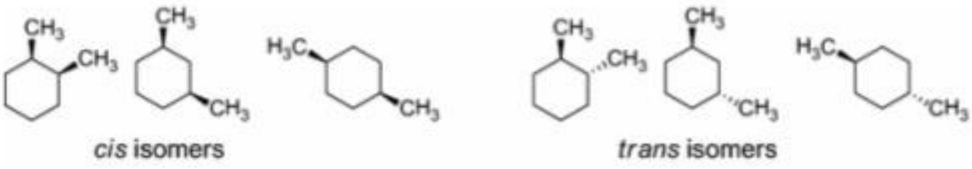
The two identical groups, like in 1, 1-dimethylcyclohexane, occupy an equatorial and an axial position in both conformations. Hence, both are equally stable and so identical.



When two different substituents are present, the bulkier one preferentially occupies the equatorial position. Example is 1-methyl-1-cyclohexanol. The conformation with the larger methyl group in the equatorial position is more stable, so the two conformers are present in unequal amounts. Because the substituents are present in different positions, the two conformations are diastereomers. However, since they interconvert very fast, they cannot be separated.



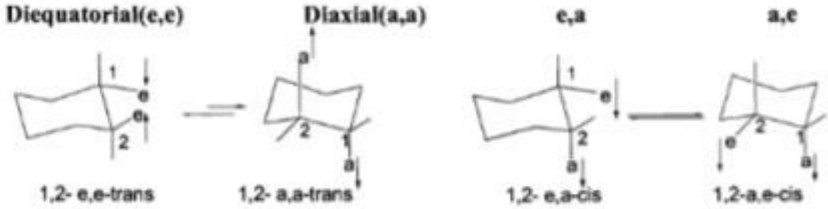
1,2-, 1,3- and 1,4-disubstituted cyclohexanes exhibit *cis–trans* isomerism. In a *cis* isomer, both substituents are on the same side of the ring, while in a *trans* isomer the two substituents are on the opposite sides. *Cis–trans* isomerism is a consequence of restricted rotation about carbon–carbon bonds in cyclic compounds. Note that in a *cis* isomer both substituents point "up" (or "down") and that in a *trans* isomer one substituent points "up" and the other one "down". The chair flip does not change the orientation of substituents. One that was pointing "up" still points "up" and the one that was pointing "down" still points "down".

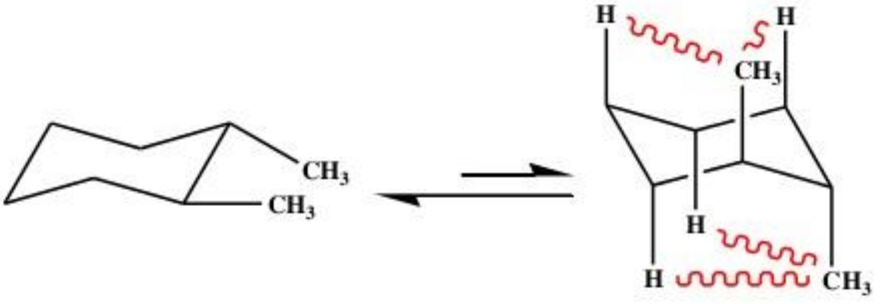


Substitution Pattern and Cis/Trans Isomerism

Substitution	Position	Isomer
1, 2- and 1, 4- disubstituted	e, e & a, a	trans
	e, a & a, e	cis
1, 3-disubstituted	e, e & a, a	cis
	e, a & a, e	trans

1, 2- disubstituted





(e, e)

E_{rel} = 0.9 Kcal/mol

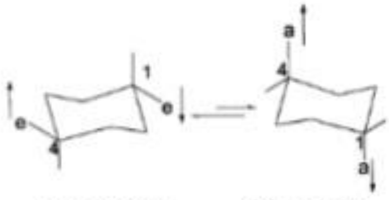
No axial methyl but one gauche butane interaction between to methyl groups

(a, a)

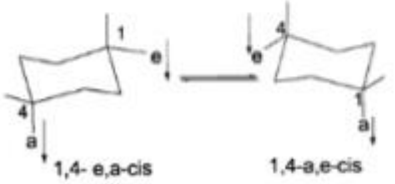
E_{rel} = 2 x 1.8 = 3.6 Kcal/mol

Two axial methyl i.e. two 1,3-diaxial interaction

1, 4- disubstituted

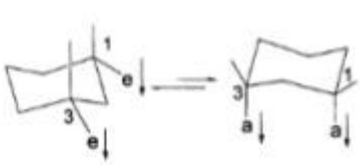


1,4- e,e-trans 1,4- a,a-trans

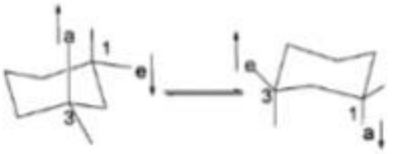


1,4- e,a-cis 1,4-a,e-cis

1, 3-disubstituted

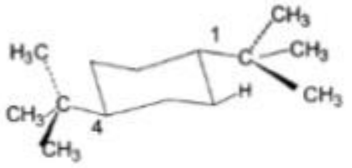


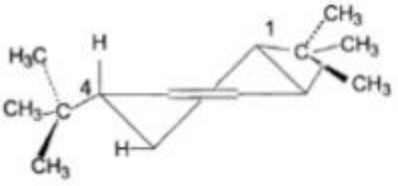
1,3- e,e-cis 1,3- a,a-cis



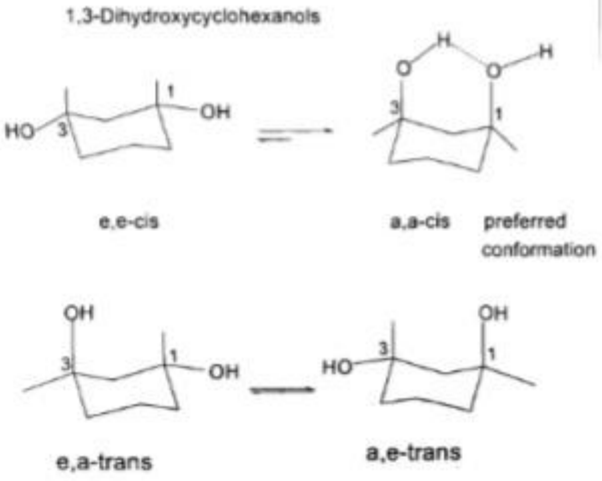
1,3- e,a-trans 1,3-a,e-trans

Two substitutions by bulky groups, ring distortion takes place. In the chair conformation of 1,4-di-t-butylcyclohexane the bulky t-butyl groups even in diequatorial positions cannot avoid steric interactions with the adjacent hydrogens. Hence, the molecule prefers to pucker into a twist boat form so that these groups are away from all the adjacent hydrogens. In the twist boat form, the groups are not exactly equatorial as in the chair conformation, but are directed away from the ring and are known as the pseudoequatorial positions.

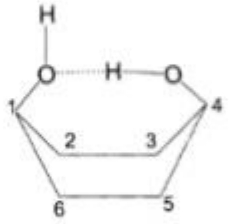




Another factor which predominates in deciding the stability of the conformations is the intramoleculer H-bonding e.g. in the 1, 3- and 1, 4- dihydroxy cyclohexanes. The diaxial chair contormation of cis-l, 3-dihydroxycyclohexane is preferred due to stabilization by intramolecular H-bonding, as the two hydroxy groups are closer, while this is not possible in the diequatorial form.



More interesting is the example of cis-l, 4-dihydroxycyclohexane where the unfavourable boat form is the preferred conformation due to intramolecular H-bonding and the molecule exists in only one form.

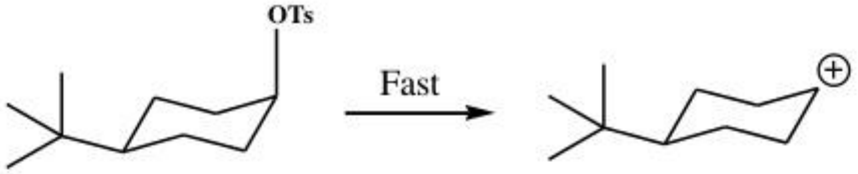


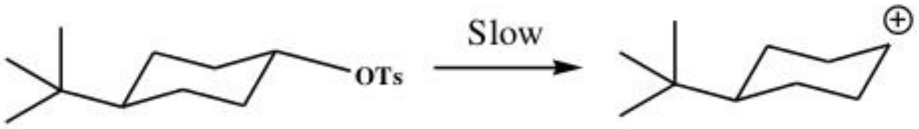
Conformational effect on reactivity:

In cyclic system to satisfy a particular mechanism a suitable conformation may be of higher energy is adopted.

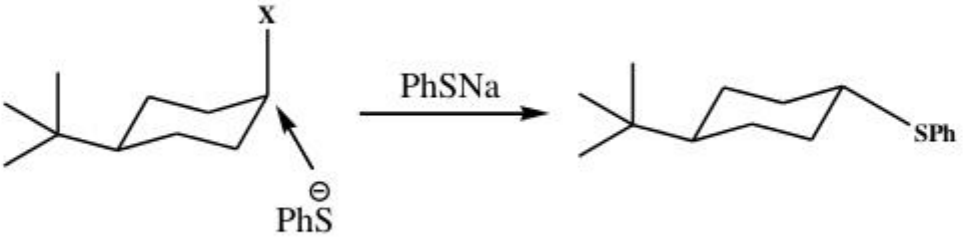
Substitution reactions:

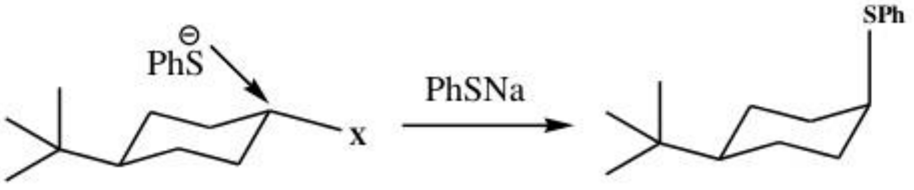
S_N1: Acetolysis of cis-4-t-butylcyclohexyltosylate. Axial conformer reacts faster due to relieve in the steric strain due to 1,3-diaxial interaction and forms carbocation very easily.





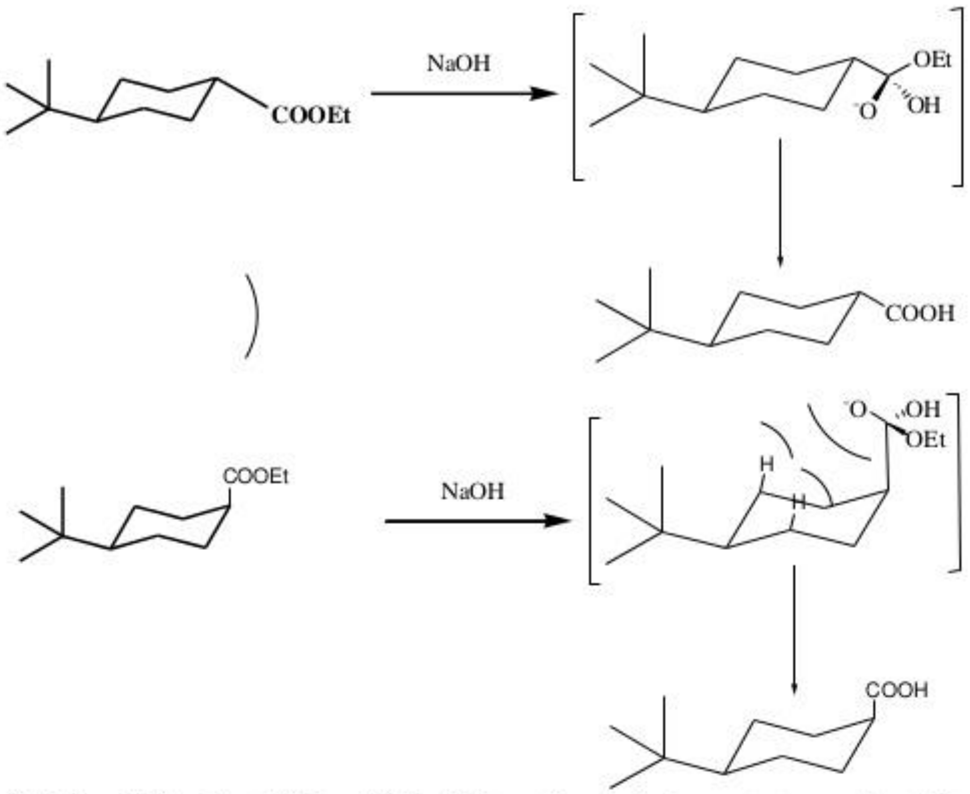
S$_N$2 reaction: Axial conformer reacts faster due to relieve in the steric strain due to 1,3-diaxial interaction and leads to more stable (e, e) conformation with two bulky in equatorial position. Displacement equatorial X group by PhS$^-$ leads to the formation of less stable (e, a) conformation.



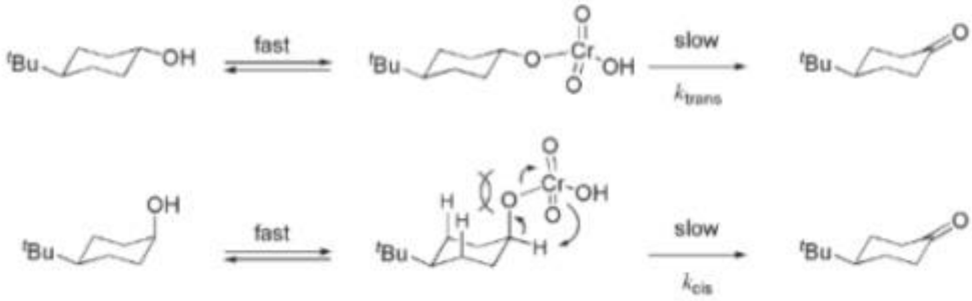


Less stable product

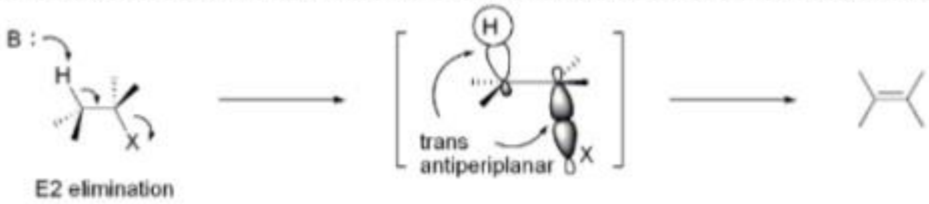
Saponification of an ester: If the ester is in the axial position or in a equatorial position what is the rate. The equatorial acetate will be hydrolysed faster as compared to the axial ester. Reaction of axial ester decelerated due to severe developing 1,3-diaxial interactions in transition state.



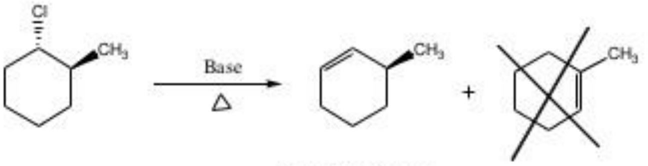
Alcohol oxidation: Destabilizing 1,3-diaxial interactions in cis chromate ester accelerated its break down to the ketone.



E_2 elimination reaction: occurs through anti periplanar transition state. In cyclic compounds, two leaving groups must be diaxial so as to assume anti periplanar arrangement.



1-Chloro-2methylcyclohexane undergoes elimination reaction in presence of base to give 3-methylcyclohexene and 2-methylcyclohexene is not all formed.



Only prodct formed

1-Chloro-2methylcyclohexane undergoes elimination reaction to give 3-methylcyclohexene through less stable conformer. Since less stable conformer has two groups in diaxial position i.e. one axial hydrogen and one axial chloro group and hence it assume anti periplanar arrangement must for elimination reaction.

2-methylcyclohexene is not formed at all because the hydrogen is in equatorial position and anti periplanar arrangement is not possible.