3D Visualization of Conformations of Disubstituted Cyclohexanes and Stereochemical Representations of Steroids

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Chapter 1

Introduction to Jmol

Jmol is a free, open-source programme for interactive molecular visualisation. Jmol is ideal for displaying and analysing molecular models in biochemistry, molecular biology, organic and inorganic chemistry, crystallography, and materials science. You can download the Jmol application from Jmol download, and also find the initial installation steps from Jmol installation In this project, I've utilised Jmol (14.6.4 2016.11.02) in Ubuntu 21.10 OS to discuss the stereochemistry of di-substituted cyclohexane, their reactions, and the stereochemistry of steroids. Let's look at some of initial steps to understand some of Jmol's fundamental features before diving into the topic.

- *Open Jmol application and open model kit*
- *Firstly draw the 3D structure of cyclohexane by making a main 6 membered cyclic chain. Now remove the extra hydrogens by right clicking on the Jmol window → select delete atom.*
- *Now fix the hydrogens and minimize the structure by right clicking on the Jmol window → . . . → fix hydrogens and minimize.*
- *Exit the model kit*
- *To label the atoms go to Display → Label → Number. All the atoms will be given numbers.*
- *To measure the bond lengths and angles right click on the Jmol panel → measurements → click for distance measurements/click for angle measurement. Now in the structure click on any two carbon atoms or a carbon and a hydrogen atom to measure the distance or the angle between them.*
- *Now adjust the cyclohexane to chair form by adjusting it with the mouse.*
- *To change the color of the axial and the equatorial bonds go to the console and type the script: set bondmode OR; select atomno= axial atoms no/ equatorial atoms no; colour bonds yellow (for axial)/ cyan (for equatorial).*
- *Save the structure by right clicking on the Jmol panel → File → Save file with script → Choose directory to save → Filename.mol*
- *You can also hide the equatorial or axial bonds accordingly using the script in the console: Hide atomno=axial atoms no/ equatorial atoms no.*

- *You can respectively save the .mol files representing the axial atoms and equatorial atoms by right clicking on the Jmol panel → File → Save file with script → Choose directory to save → Filename.mol*
- *To represent the structure in wireframe right click on the Jmol panel → Style → Scheme → wireframe.*
- *Save the structure Save the structure by right clicking on the Jmol panel → File → Save file with script → Choose directory to save → Filename.mol*
- *To export the structures in .png/.jpeg/.jpg right click on the Jmol panel → File → Export → Export image → Choose directory to save → Filename..png/.jpeg/.jpg. You can view the structure using any image viewer application.*

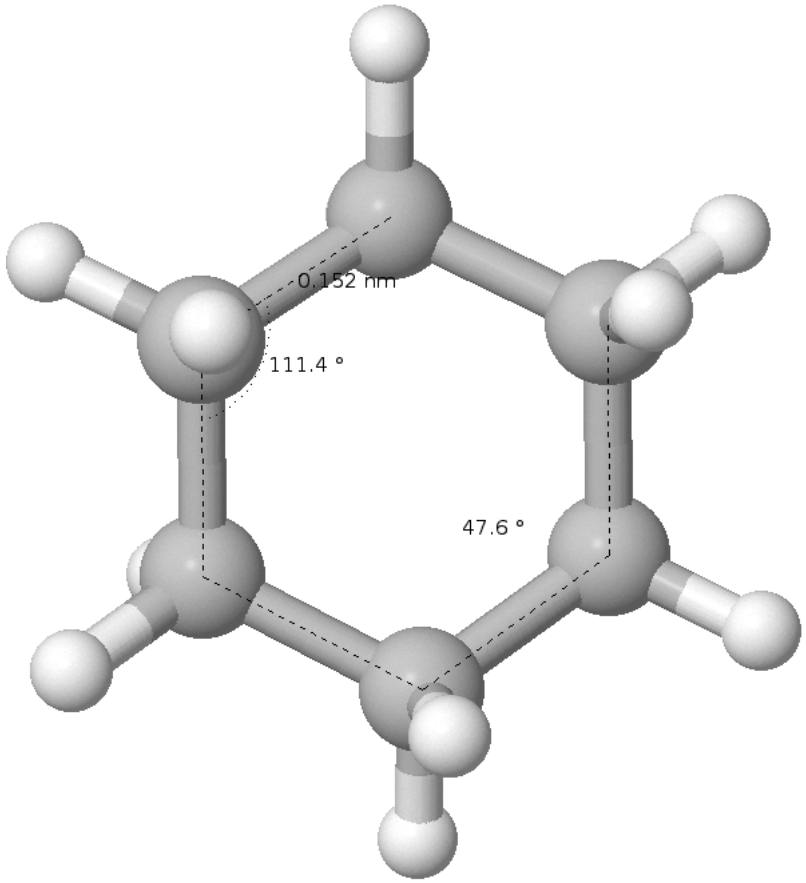

Figure 1.1: Cyclohexane

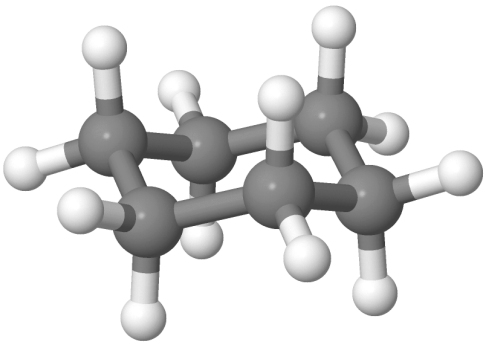

Figure 1.2: Cyclohexane in Chair conformer

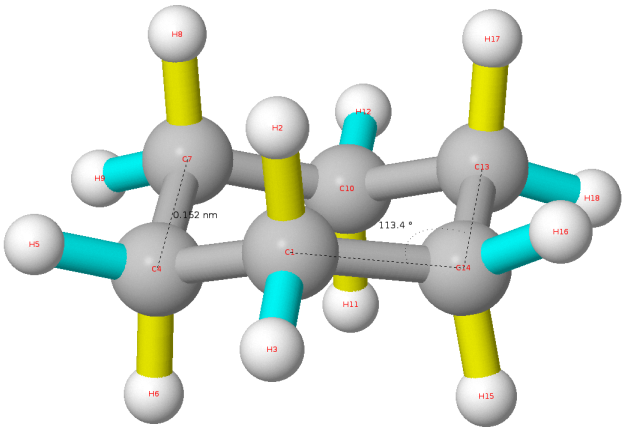

Figure 1.3: Representation of axial (yellow) and equatorial bonds (cyan) with measurements of cyclohexane in chair conformer

Chapter 2

Conformational analysis of di-substituted cyclohexanes

2.1 *Di-substituted cyclohexane*

Cyclohexane with 1,2, 1,3, and 1,4 disubstituted has cis and trans isomers. The cis-1,2 and cis-1,3 isomers are discovered to be meso forms when both substituents are identical, whereas the trans isomer is chiral. Regardless of the substituents, the (cis- and trans-) isomers of 1,4-disubstituted cyclohexane are both achiral. Due to the varying stereochemistry of the groups in the molecules, these compound's chemical reactivity also differs; which makes one isomer is chosen over the other. Here we have a detailed discussion on the stereochemistry of 1,2-, 1,3-, 1,4- dimethylcyclohexanes.

2.1.1 *1,2 di-methylcyclohexane*

The cis isomer of 1,2 dimethylcyclohexane has one methyl substituent in the equatorial position and other methyl substituent in the axial position (a,e). The axial methyl groups produces 1,3 diaxial steric interactions that makes the conformer unstable. A meso form is produced by the fast interconversion of two cis isomers forms (a,e and e,a). Thus, cis-1,2-dimethylcyclohexane is achiral. The trans isomer has both the methyl substituents on axial position (a,a)or equatorial position (e,e). The conformer with both the methyl substituents on the equatorial position (e,e) is most stable. Both the conformers (a,a and e,e) of trans isomer are chiral. The each axial methyl substituents in the trans a,a conformer contributes about 1.74 kcal/mol towards steric energy of the molecule, making the energy of the trans a,a conformer about 3.48 kcal/mol. Due to the two methyl groups are gauche to each other in the trans e,e conformer, the steric energy therefore will be that of gauche butane, 0.74 kcal/mol. Therefore The trans e,e conformer has (3.48-0.74 = 2.74) 2.74 kcal/mol less steric energy than a,a isomer.

2.1.2 *1,3 di-methylcyclohexane*

The conformers of 1,3-di-methylcyclohexane exists as a single in single conformations. The two possible conformations (a,e and e,a) of the trans isomer are superposable with one methyl substituent in the axial position while the other on the equatorial position. The cis isomer has two possible conformers with both the methyl substituents on axial position (a,a) and the other has both methyl substituents on equatorial position (e,e). The a,a conformer of cis isomer is

extremely unstable due to the presence of two synaxial methyl substituents, therefore, it exists in the achiral e,e conformation. A chiral trans isomer exists.

2.1.3 *1,4 di-methylcyclohexane*

The cis and trans isomers of 1,4-dimethyl cyclohexane are both achiral. The cis isomer has one methyl substituent on the axial and other is equatorial (a,e). The cis isomer exists as equimolar mixture of two indistinguishable and superposable conformers. The trans isomer has both the methyl substituents in axial (a,a) or equatorial position (e,e). The e,e conformer of the trans isomer is more prevalent (99.7%) than the a,a conformer (0.3%). The energy level of the a,a isomer is approximately 3.48 kcal/mol higher than the e,e conformer because each axial methyl group contributes 1.74 kcal/mol to the steric energy of the molecule.

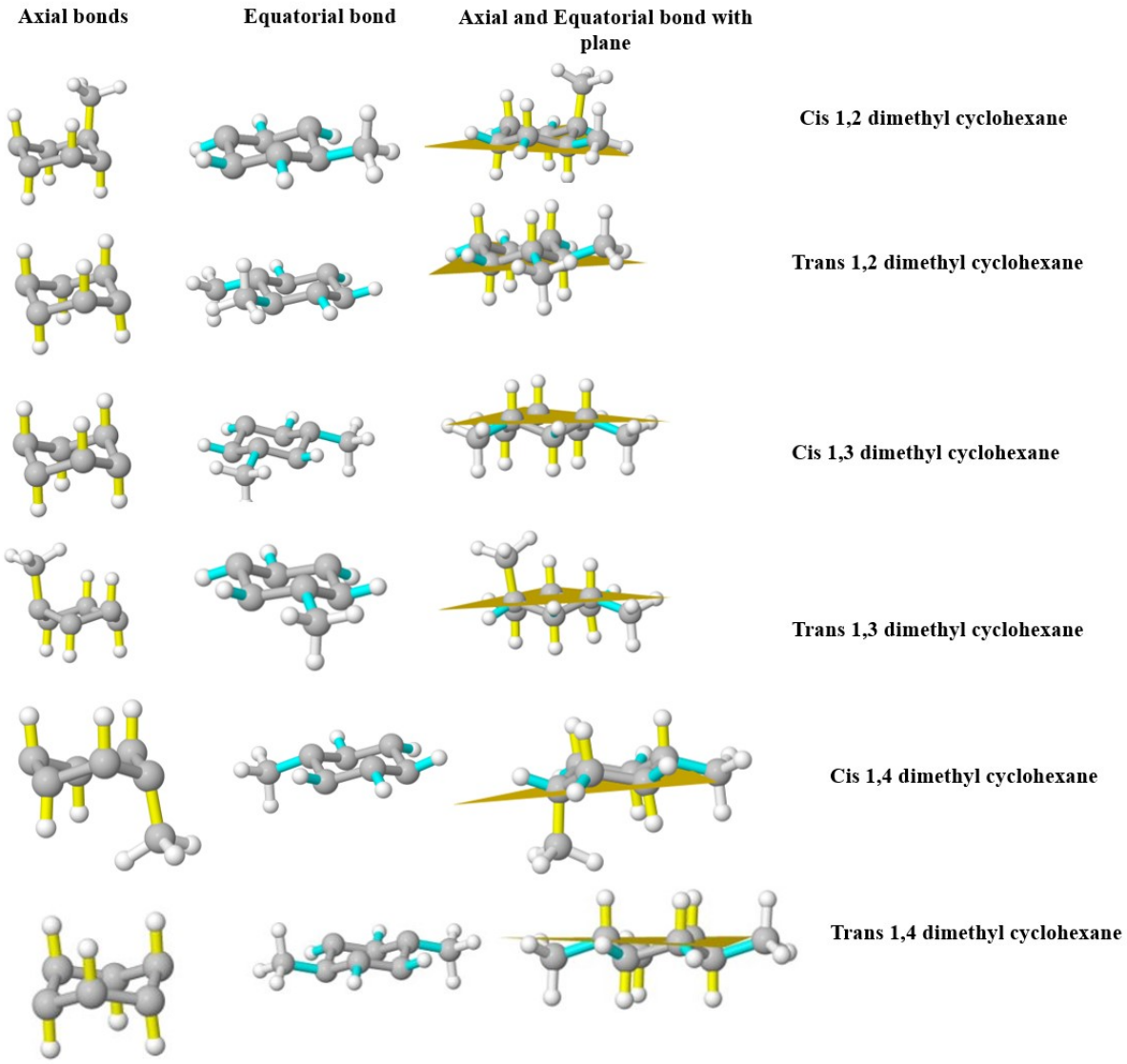

Figure 2.1: Representation of all axial, equatorial bonds and plane (300) of all Di-substituted cyclohexane

Isomer	Major Conformation
cis-1,2	e,a
trans-1,2	e,e
cis-1,3	e,e
trans-1,3	e,a
cis-1,4	e,a
trans-1,4	e,e

Table 2.1: Major conformers of Dimethylcyclohexanes

2.2 *Commands*

All the .mol files of the structures in the Fig:2.1 can be acessed from: MOL files.

2.2.1 *Cis 1,2 dimethylcyclohexane*

- **To colour the axial bonds:**
  set bondmode OR; select atomno=1, atomno=19,atomno=21,atomno=16,atomno=15,atomno=5; colour bonds yellow
- **To colour the equatorial bonds:**
  set bondmode OR; select atomno=10, atomno= 14,atomno=17,atomno=18,atomno=20,atomno=3; colour bonds cyan
- **To recolour the changed hydrogens in methyl to rasmol colours:**
  select atomno=11,atomno=12,atomno=13,atomno=22,atomno=23,atomno=24; colour bonds white
- **To add planes:**
  draw plane1 300 (atomno=9)(atomno=7)(atomno=4)
- **Hide equatorial atoms:**
  Hide atomno=10, atomno= 14,atomno=17,atomno=18,atomno=20,atomno=3, atomno=22, atomno=23,atomno=24
- **Hide axial atoms:**
  Hide atomno=1, atomno=19,atomno=21,atomno=16,atomno=15,atomno=5,atomno=11, atomno=12,atomno=13
- **Inversion:**
  invertSelected atom {C2};invertSelected atom {C4};invertSelected atom {C6};invertSelected atom {C7};invertSelected atom {C8};invertSelected atom {C9}

2.2.2 *Trans 1,2 dimethylcyclohexane*

- **To colour the axial bonds:**
  set bondmode OR; select atomno=13, atomno=17,atomno=20,atomno=14,atomno=12,atomno=18; colour bonds yellow

- **To colour the equatorial bonds:**
  set bondmode OR; select atomno=1, atomno= 8,atomno=15,atomno=16,atomno=19,atomno=21; colour bonds cyan
- **To recolour the changed hydrogens in methyl to rasmol colours:**
  select atomno=9,atomno=10,atomno=11,atomno=22,atomno=23,atomno=24; colour bonds white
- **To add planes:**
  draw plane1 300 (atomno=4)(atomno=2)(atomno=6)
- **Hide equatorial atoms:**
  Hide atomno=1, atomno= 8,atomno=15,atomno=16,atomno=19,atomno=21, atomno= 9,atomno=10,atomno=11,atomno=22,atomno=23,atomno=24
- **Hide axial atoms:**
  Hide atomno=13, atomno=17,atomno=20,atomno=14,atomno=12,atomno=18
- **Inversion:**
  invertSelected atom {C2};invertSelected atom {C3};invertSelected atom {C4};invertSelected atom {C5};invertSelected atom {C6};invertSelected atom {C7}

2.2.3 *Cis 1,3 dimethylcyclohexane*

- **To colour the axial bonds:**
  set bondmode OR; select atomno=3, atomno=19,atomno=6,atomno=21,atomno=16,atomno=14; colour bonds yellow
- **To colour the equatorial bonds:**
  set bondmode OR; select atomno=1, atomno= 10,atomno=20,atomno=18,atomno=17,atomno=15; colour bonds cyan
- **To recolour the changed hydrogens in methyl to rasmol colours:**
  select atomno=11,atomno=12,atomno=13,atomno=22,atomno=23,atomno=24; colour bonds white
- **To add planes:**
  draw plane1 300 (atomno=8)(atomno=5)(atomno=2)
- **Hide equatorial atoms:**
  Hide atomno=1, atomno= 10,atomno=20,atomno=18,atomno=17,atomno=15, atomno=11, atomno=12,atomno=13,atomno=22,atomno=23,atomno=24
- **Hide axial atoms:**
  Hide atomno=3, atomno=19,atomno=6,atomno=21,atomno=16,atomno=14
- **Inversion:**
  invertSelected atom {C2};invertSelected atom {C4};invertSelected atom {C5};invertSelected atom {C7};invertSelected atom {C8};invertSelected atom {C9}

2.2.4 *Trans 1,3 dimethylcyclohexane*

- **To colour the axial bonds:**
  set bondmode OR; select atomno=10, atomno=3,atomno=19,atomno=21,atomno=16,atomno=14; colour bonds yellow
- **To colour the equatorial bonds:**
  set bondmode OR; select atomno=1, atomno= 15,atomno=6,atomno=17,atomno=18,atomno=20; colour bonds cyan
- **To recolour the changed hydrogens in methyl to rasmol colours:**
  select atomno=11,atomno=12,atomno=13,atomno=22,atomno=23,atomno=24; colour bonds white
- **To add planes:**
  draw plane1 300 (atomno=5)(atomno=2)(atomno=8)
- **Hide equatorial atoms:**
  Hide atomno=1, atomno= 15,atomno=6,atomno=17,atomno=18,atomno=20,atomno=22, atomno=23,atomno=24
- **Hide axial atoms:**
  Hide atomno=10, atomno=3,atomno=19,atomno=21,atomno=16,atomno=14, atomno=22, atomno=23,atomno=24
- **Inversion:**
  invertSelected atom {C2};invertSelected atom {C4};invertSelected atom {C5};invertSelected atom {C7};invertSelected atom {C8};invertSelected atom {C9}

2.2.5 *Cis 1,4 dimethycyclohexane*

- **To colour the axial bonds:**
  set bondmode OR; select atomno=3, atomno=17,atomno=21,atomno=14,atomno=10,atomno=19; colour bonds yellow
- **To colour the equatorial bonds:**
  set bondmode OR; select atomno=2, atomno= 20,atomno=15,atomno=16,atomno=18,atomno=7; colour bonds cyan
- **To recolour the changed hydrogens in methyl to rasmol colours:**
  select atomno=11,atomno=12,atomno=13,atomno=22,atomno=23,atomno=24; colour bonds white
- **To add planes:**
  draw plane1 300 (atomno=9)(atomno=4)(atomno=6)
- **Hide equatorial atoms:**
  Hide atomno=2, atomno= 20,atomno=15,atomno=16,atomno=18,atomno=7, atomno=11, atomno=12,atomno=13

- **Hide axial atoms:**
  Hide select atomno=3, atomno=17,atomno=21,atomno=14,atomno=10,atomno=19, atomno=22, atomno=23,atomno=24

- **Inversion:**
  invertSelected atom {C2};invertSelected atom {C4};invertSelected atom {C5};invertSelected atom {C6};invertSelected atom {C8};invertSelected atom {C9}

2.2.6 *Trans 1,4 dimethycyclohexane*

- **To colour the axial bonds:**
  set bondmode OR; select atomno=19, atomno=17,atomno=3,atomno=7,atomno=21,atomno=14; colour bonds yellow

- **To colour the equatorial bonds:**
  set bondmode OR; select atomno=1, atomno= 10,atomno=15,atomno=16,atomno=18,atomno=20; colour bonds cyan

- **To recolour the changed hydrogens in methyl to rasmol colours:**
  select atomno=11,atomno=12,atomno=13,atomno=22,atomno=23,atomno=24; colour bonds white

- **To add planes:**
  draw plane1 300 (atomno=8)(atomno=2)(atomno=5)

- **Hide equatorial atoms:**
  Hide atomno=1, atomno= 10,atomno=15,atomno=16,atomno=18,atomno=20 atomno=11, atomno=12,atomno=13,atomno=22,atomno=23,atomno=24

- **Hide axial atoms:**
  Hide select atomno=19, atomno=17,atomno=3,atomno=7,atomno=21,atomno=14

- **Inversion:**
  invertSelected atom {C2};invertSelected atom {C4};invertSelected atom {C5};invertSelected atom {C6};invertSelected atom {C8};invertSelected atom {C9}

Chapter 3

Elimination and Nucleophilic Substitution reaction of substituted cyclohexane

3.1 *Elimination reactions*

3.1.1 *2-methyl-1-chlorocyclohexane*

The cis and trans isomers of the chemical compound 2-methyl-1-chlorocyclohexane react with alcoholic KOH at various rates to produce different products. The methyl substituent is located in the axial position on the cis-isomer, whereas the chlorine substituent is in the equatorial position. The E2 elimination occurs. The cis 2-methyl-1-chlorocyclohexane adopts a chair conformation, putting the chlorine substituent in an axial orientation and the methyl substituent in an equatorial orientation, lowering the energy of the cis isomer and allowing two adjacent axial hydrogens to be eliminated. According to the Zaitsev's rule, 1-methylcyclohexene is the primary byproduct of the E2 elimination of the cis isomer, while 3-methylcyclohexene is the minor byproduct.

The chlorine and methyl substituents are both in the equatorial position in the trans isomer, the isomer adopts a chair conformation for the E2 elimination, putting the chlorine substituent in the axial position needed for the elimination of the E2 molecule and the methyl substituent as well. This trans-chair isomer's conformer is substantially less stable since both substituents are in the axial position, and there is an energy barrier that needs to be crossed before an E2 reaction can take place. As a result, the E2 elimination of the trans isomer proceeds more slowly than that of the cis isomer. One neighbouring axial hydrogen for removal is all that the obtained chair conformer offers. Thus, only one product, 3-methyl cyclohexene, is produced.

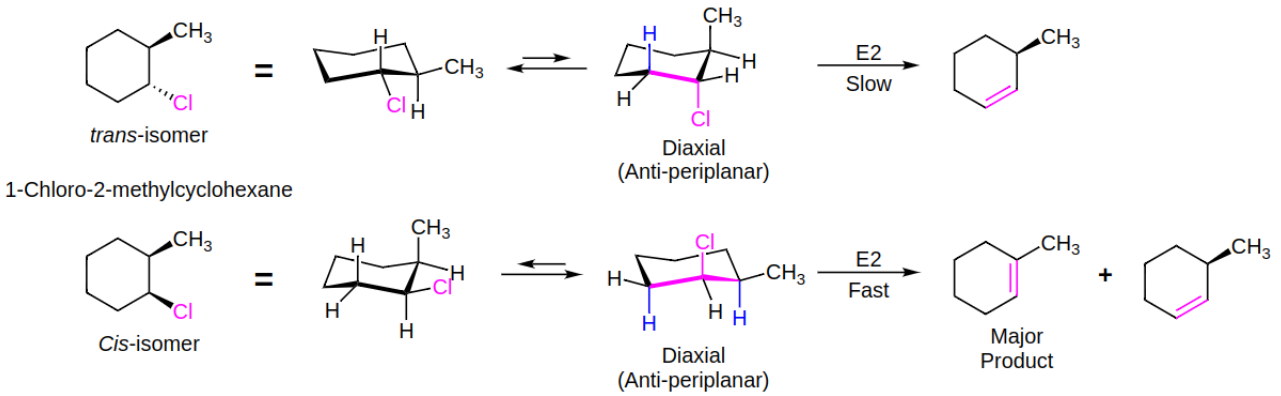

Figure 3.1: Elimination (E2) reactions of 2-methyl-1-chlorocyclohexane [5]

3.1.2 *1-bromo-4-tert-butylcyclohexane*

In both the cis and trans isomers of 1-bromo-4-tert-butylcyclohexane, the tert-butyl group is always in the equatorial position, while the bromine group is in the axial position in the cis isomer and the equatorial position in the trans isomer. The bromine substituent is in the axial position for the E2 elimination and there are two axial hydrogens in the cis isomer. The symmetry causes the two axial neighbouring hydrogens in the cis-isomer to react with base in an equal manner, causing fast elimination to produce 4-t-butyl cyclohex-1-ene.

Since the trans isomer contains both the bromine and the t-butyl substituent in the equatorial position, it must endure severe crowding distortions during E2 elimination. Additionally, in order to achieve this chair conformation with the bromine in the axial position, the t-butyl must be moved into the axial position, which causes steric distortions. As a result , the trans isomer favours nucleophilic substitution of the hydroxide ion over the elimination reaction.

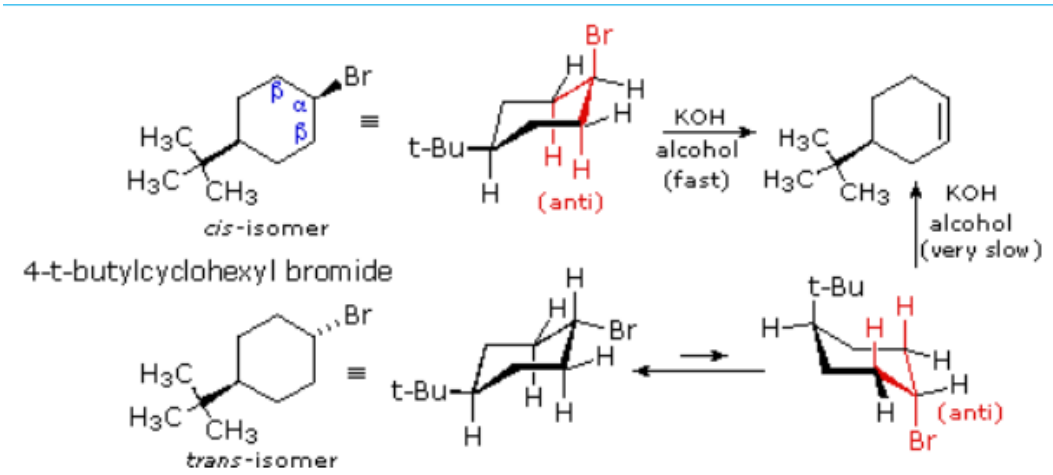

Figure 3.2: Elimination (E2) reactions of 1-bromo-4-tert-butylcyclohexane [4]

3.2 *Nucleophilic substitution reaction of di-substituted 1-bromo 4-methylcyclohexane*

The substitution of an axial substituent proceeds faster than the substitution of an equatorial substituent. The nucleophile attacks the σ^* of the leaving group, that is, directly behind the C–X bond. In case of the equatorial substituent the line of attack is blocked by the axial hydrogen as it passes directly through the region of space they occupy, while for an axial leaving group, the direction of attack is parallel with the axial hydrogens antiperiplanar to the leaving group, and approach is much less hindered.

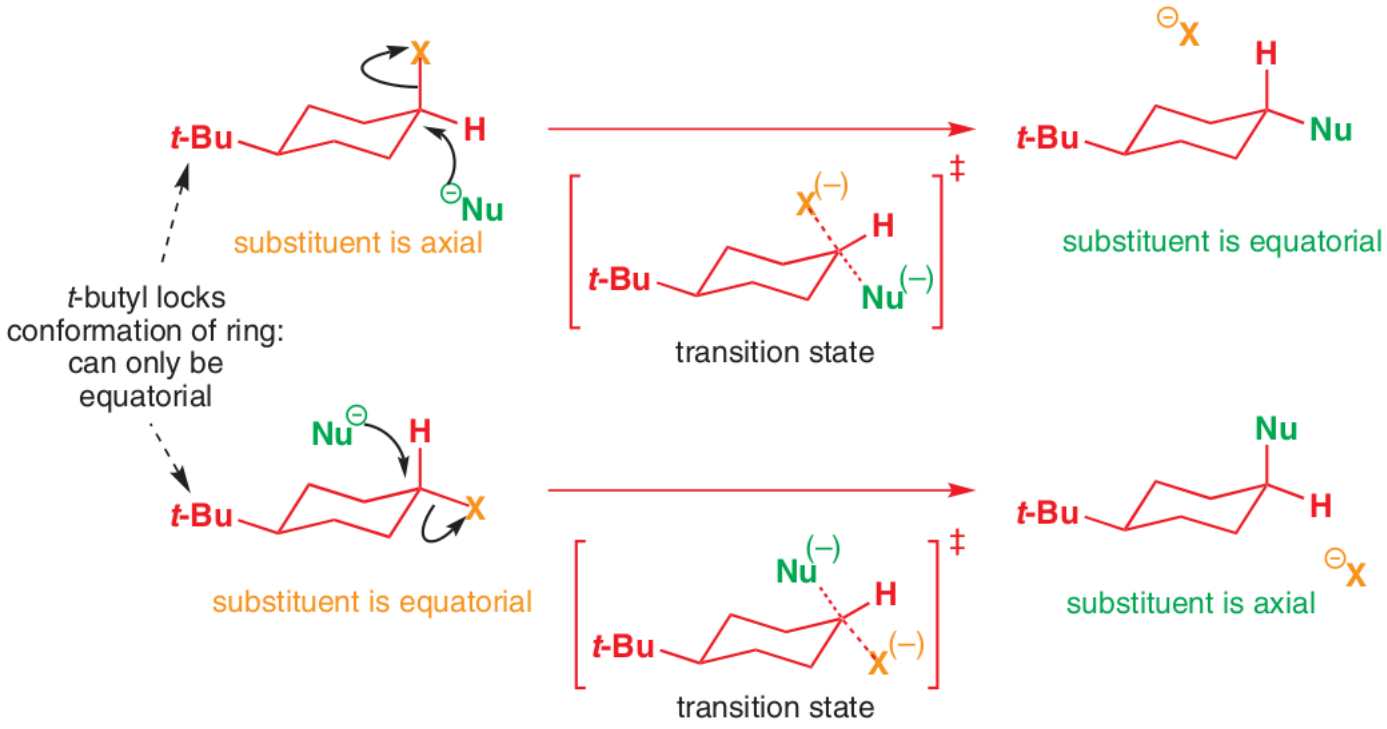

Figure 3.3: Reaction mechanism of nucleophlic substitution of di-substituted cyclohexane [3]

3.3 *Commands*

All the animations of the reactions along with the .mol files can be acessed from: Reactions

3.3.1 *Elimination reactions of 2-methyl-1-chlorocyclohexane*

- **Major Product (Cis):**

  capture"/home/forscher/Documents/FOSSEE 2022/majorcis.gif" loop 60; moveto / time, axisAngle */ 1.0 0 0 1 0 /* zoom, translation */ 132.25 0.0 0.0 /* center, rotationRadius */ -0.262895 -0.0151849985 0.110885024 4.8691683 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; delay 4; invertSelected atomC2; invertSelected atom C4; delay 2; set bondmode OR; select atomno=3, atomno=10; colour bonds yellow; delay 2; connect @2 @4 partial 2.2 radius 0.1; delay 2; delay 2; delete atomno=3, atomno=10; moveto /* time, axisAngle */ 1.0 955 -87 -283 69.08 /* zoom, translation */ 132.25 0.0 0.0 /* center, rotationRadius */ -0.262895*

-0.0151849985 0.110885024 4.8691683 / navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; delay 2; connect @2 @4 double; delay 2*

- **Minor Product (Cis):**

  capture"/home/forscher/Documents/FOSSEE 2022/minorcis.gif" loop 60; moveto / time, axisAngle */ 1.0 64 -998 14 35.32 /* zoom, translation */ 152.09 0.0 0.0 /* center, rotationRadius */ -0.262895 -0.0151849985 0.110885024 4.8691683 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; delay 4; invertSelected atomC2; invertSelected atom C4; delay 2; set bondmode OR; select atomno=12, atomno=10; colour bonds yellow; delay 2; connect @6 @4 partial 2.2 radius 0.1; delay 2; delay 2; delete atomno=12, atomno=10; moveto /* time, axisAngle */ 1.0 955 -87 -283 69.08 /* zoom, translation */ 132.25 0.0 0.0 /* center, rotationRadius */ -0.262895 -0.0151849985 0.110885024 4.8691683 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; delay 2; connect @6 @4 double; delay 2*

- **Major Product (Trans):**

  capture"/home/forscher/Documents/FOSSEE 2022/majortrans.gif" loop 60; moveto / time, axisAngle */ 1.0 -489 -872 -2 10.31 /* zoom, translation */ 132.25 0.0 0.0 /* center, rotationRadius */ -0.19443 0.40350997 -0.44415998 4.790324 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0;invertSelected atomC2; invertSelected atom C4; delay 2; set bondmode OR; select atomno=17,atomno=1; colour bonds yellow ; delay 2; connect @9 @2 partial 2.2 radius 0.1; delay 2; delay 2; delete atomno=17, atomno=1; moveto /* time, axisAngle */ 1.0 917 -306 -257 68.92 /* zoom, translation */ 132.25 0.0 0.0 /* center, rotationRadius */ -0.19443 0.40350997 -0.44415998 4.790324 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; connect @9 @2 double; delay 2*

3.3.2 *Elimination reactions of 1-bromo-4-tert-butylcyclohexane*

- **Cis Product**

  capture"/home/forscher/Documents/FOSSEE 2022/cis.gif" loop 60; moveto / time, axisAngle */ 1.0 -45 877 -479 6.37 /* zoom, translation */ 152.09 0.0 0.0 /* center, rotationRadius */ -0.81812 -0.76837003 -0.09341502 5.7648077 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; delay 2; set bondmode OR; select atomno=27, atomno=13; colour bonds yellow; delay 2; connect @9 @11 partial 2.2 radius 0.1; delay 2; delay 2; delete atomno=27, atomno=13; moveto /* time, axisAngle */ 1.0 951 294 97 64.54 /* zoom, translation */ 132.25 0.0 0.0 /* center, rotationRadius */ -0.81812 -0.76837003 -0.09341502 5.7648077 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0;connect @9 @11 double; delay 2*

- **Trans Product**

  capture"/home/forscher/Documents/FOSSEE 2022/trans.gif" loop 60; moveto / time, axisAngle */ 1.0 -313 -947 -78 13.95 /* zoom, translation */ 132.25 0.0 0.0 /* center, rotationRadius */ -1.1682701 -0.19222498 0.46774006 6.3398294 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0*

0.0; invertSelected atomC5; invertSelected atom C9; delay 2; set bondmode OR; select atomno=26, atomno=13; colour bonds yellow; delay 2; connect @9 @8 partial 2.2 radius 0.1; delay 2; delay 2; delete atomno=26, atomno=13; moveto / time, axisAngle */ 1.0 960 275 53 68.47 /* zoom, translation */ 132.25 0.0 0.0 /* center, rotationRadius */ -1.1682701 -0.19222498 0.46774006 6.3398294 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; connect @9 @8 double; delay 2*

3.3.3 *Nucleophilic reaction of 1-bromo 4-methylcyclohexane*

- **When substituent is in axial position:**

  capture "/home/forscher/Documents/FOSSEE 2022/Reactions/axial.gif"loop60; draw off; label off; delay 2;select @2; select @26; delay 2; connect @2 @26 partial radius 0.1; delay 3; select @2; select @24; connect @2 @24 partial radius 0.1; delay 2; delete @43; delete @26; delay 1; connect @2 @24 single; delay 2; invertSelected atom C2; minimize; minimize;minimize;minimize

- **When substituent is in equatorial position:**

  capture "equatorial.gif"loop 60; draw off; label off; dealy 1;select @2; select @1; delay 1;connect @2 @1 partial radius 0.1;dealy 2; select @2; select @24; connect @2 @24 partial radius 0.1; delay 3; delete @1; delete @43; delay 2; connect @2 @24 single; minimize; delay 3; invertSelected atom C2; delay 2; minimize; minimize;

Chapter 4

Reactions of 2-bromo-4-phenylcyclohexanols with base and silver oxide

The antiperiplanar groups participates in ring creation, rearrangement, surrounding group participation, and fragmentation. Ring contraction occurs when any element in the ring is antiperiplanar to the equatorial leaving group, which involves the diaxial disposition. The illustration of reactions of 2-bromo-4-phenyl cyclohexanol with base and silver oxide illustrates the effects of stereochemistry of groups. The conformational equilibria of the various stereoisomers are influenced by the phenyl group (-ΔG^{o}_{confo} = 2.9 kcal/mol). Fig 4.2 represents the different cases of the reactions of 2-bromo-4-phenylcyclohexanols with base and silver oxide. The enter-

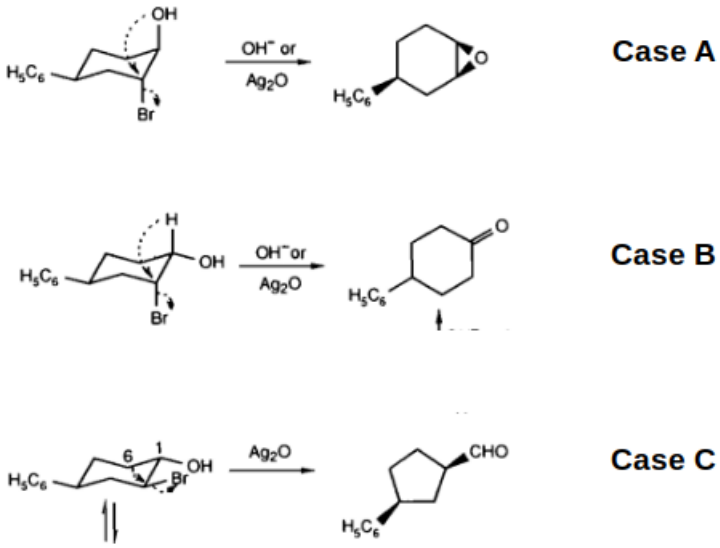

Figure 4.1: Reactions of 2-bromo-4-phenylcyclohexanols with base and silver oxide [2]

ing (OH or O-) and departing (Br) groups in case A are antiperiplanar (a,a) examples of how epoxide rings develops. Case B serves as an example of ketone creation via enolate formation (HBr elimination) or hydride shift: Since the departing bromine is antiperiplanar to the involving hydrogen. In case C, the ring bond antiperiplanar to the outgoing equatorial bromine [C(l)/C(6)] migrates as a result of the equatorial bromine's departure when Ag_2O is present, causing a ring contraction to cis-3-phenylcyclopentanecarboxyaldehyde.

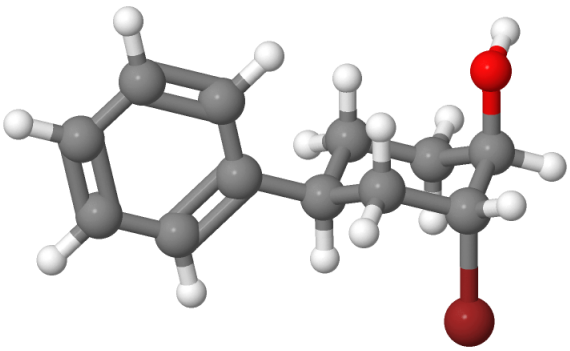

Figure 4.2: Initial structure of 2-bromo-4-phenylcyclohexanol viewed in Jmol window

4.1 *Commands*

The initial mol file can be acessed from :2-bromo-4-phenylcyclohexanol. The 3-D animation can be viewed from respectively: Case A, Case B, Case C . The below Jmol scripts were used to make the animations.

- **Case A:** *capture "anim1.gif"loop 60; moveto /* time, axisAngle */ 1.0 -219 179 -959 21.84 /* zoom, translation */ 115.0 0.0 0.0 /* center, rotationRadius */ -1.4429998 0.60660005 -0.19974995 6.3105116 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; connect @14 @2 partial radius 0.1; delay 1; connect @14 @3 partial radius 0.1; delay 1; delete @29; delete @16; delete @15; delete @1; delay 1; connect @14 @2 single; connect @3 @14 single; moveto /* time, axisAngle */ 1.0 807 589 35 73.09 /* zoom, translation */ 115.0 0.0 0.0 /* center, rotationRadius */ -1.4429998 0.60660005 -0.19974995 6.3105116 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; delay 2; minimize; minimize*

- **Case B:** *capture "anim2.gif"loop 60; moveto /* time, axisAngle */ 1.0 -219 179 -959 21.84 /* zoom, translation */ 115.0 0.0 0.0 /* center, rotationRadius */ -1.4429998 0.60660005 -0.19974995 6.3105116 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; invertSelected atom C3; delay 2; connect @3 @14 partial 2.2 radius 0.1; delay 2; delete @29; delete @15; delete @16; delete @1; connect @3 @14 double; delay 2; moveto /* time, axisAngle */ 1.0 807 589 35 73.09 /* zoom, translation */ 115.0 0.0 0.0 /* center, rotationRadius */ -1.4429998 0.60660005 -0.19974995 6.3105116 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; delay 2; minimize;*

- **Case C:** *capture "anim3.gif"loop 60; moveto /* time, axisAngle */ 1.0 -219 179 -959*

21.84 / zoom, translation */ 115.0 0.0 0.0 /* center, rotationRadius */ -1.4429998 0.60660005 -0.19974995 6.3105116 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; invertSelected atom C3; invertSelected atom C2; connect @3 @14 partial 2.2 radius 0.1; delay 1; delete @29; delete @1; delete @17; delete @18; delete @4;connect @5 @3 single;connect @3 @14 double; delay 2; moveto /* time, axisAngle */ 1.0 807 589 35 73.09 /* zoom, translation */ 115.0 0.0 0.0 /* center, rotationRadius */ -1.4429998 0.60660005 -0.19974995 6.3105116 /* navigation center, translation, depth */ 0 0 0 0 0 0 /* cameraDepth, cameraX, cameraY */ 3.0 0.0 0.0; delay 2; minimize; minimize; minimize;*

Chapter 5

Stereochemistry of Steroids

5.1 *Introduction*

The creation and design of medications depend heavily on stereochemistry. According to the data, nearly 56 percent of medications and 90 percent of them are sold as racemates, which are a blend of two enantiomers in equimolar amounts. Due to differences in how they interact with chiral bodily surroundings including enzymes, proteins, receptors, etc., the enantiomers display diverse biological functions. Using a three-point interaction model, Easson and Stedman explained the difference in the biological activities of the enantiomers through a three-point interaction model as in

In accordance with the hypothetical interaction model proposed by Easson and Stedman, one enantiomer is biologically active while the other is not. An alignment of Aa, Bb, and Cc between the active enantiomer, designated A, B, and C, and the receptor's binding sites, labelled a, b, and c, results in a biological effect. However, the inactive isomer does not bind with the receptor, and even when there is rotation, it does not exhibit an active response. Enantiomers can only bind to complementary-shaped receptor sites, which is similar to how hands fit into gloves. Due to chiral discrimination via diastereomeric formations with a chiral environment, the enantiomers also exhibit distinct chemical activity.

5.2 *Pharmacology*

Racemic drugs are divided into three categories based on their activity. The first class is based on the differences between two enantiomeric drug forms in terms of their pharmacological activity; Lehmann and Ariens assigned the term "eutomer" to the preferred, or active, stereoisomer, and the term "distomer" to the less desirable, or inactive stereoisomer. Drugs in the second group have pharmacodynamics and activity that are identical for the two enantiomers ,and the distomer that can be converted into a bioactive antipode by chiral inversion.

- *Racemic drugs with one major bioactive enantiomer:* All cardiovascular medications used to treat hypertension, heart failure, and arrhythmias fall under this group. Examples include calcium channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, and -adrenergic blocking medications.
- *Racemic drugs with equally bioactive enantiomers:* There exists very few drugs in this category; cyclophosphamide, flecainide, and fluoxetine are a few examples.

- *Racemic drugs with chiral inversion:* Unidirectional and bidirectional inversions are the two methods of chiral inversion. Nonsteroidal anti-inflammatory medicines (2-arylpropionate) can be used to explain the unidirectional inversion (NSAID). Since these medications' S-enantiomers have analgesic and anti-inflammatory effects, only the R-enantiomer goes through chiral inversion into the active S-enantiomer and not the vice versa.

  The 3-hydroxybenzodiazepines, which have both R and S enantiomers, are used to demonstrate the bidirectional chiral inversion. The amounts of R- and S-oxazepam in the treated rabbit serum varied, according to the researchers' study of the chiral inversion in a rabbit. The inversion was explained by the tautomerization of oxazepam, which is not possible in vivo due to the differing affinities with which each enantiomer is carried by albumin, a protein. The enantiomers' affinity for albumin may prevent the attack of hydroxyl ions (water), which would delay in vivo racemization and epimerization. As a result, the serum of these treated rabbits contains varied quantities of R- and S-oxazepam.

Let's discuss the effect of stereochemistry on clinically available β-blockers.

5.3 β-blockers

β-blockers are a class that blocks norepinephrine and epinephrine from binding the receptors. The pharmacological relevance of β-blockers depends on their selective vs non-selective nature, and existence or nonexistence of inherent sympathomimetic activity (ISA). β-blockers are used for lowering the risk of migraine headaches and are used to treat hypertension, angina pectoris, cardiac arrhythmias, glaucoma, and supraventricular and ventricular arrhythmias. β-blockers inhibit a wide range of smooth muscles in addition to stimulating cardiac muscles and blocking adrenergic receptors.β-blockers are known for lowering the risk of migraine headaches and are used to treat hypertension, angina pectoris, cardiac arrhythmias, glaucoma, and supraventricular and ventricular arrhythmias. Stereochemistry primarily impacts the pharmaceutical business because the majority of -blockers on the market are recognised as racemates and just a few medications are offered as single enantiomers.

5.4 Classification of β-blockers

- *Cardioselective β- adrenolytic without ISA:* The β1- receptors are are effectively inhibited by this class of beta-blockers, mostly in cardiac tissue. Furthermore, higher doses inhibit the β2-receptor. Atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol are a few examples.

- *Cardioselective β- adrenolytic with ISA:* The vasodilation impact and -blocking activity are demonstrated in this class. Acebutolol and celiprolol are two examples.

- *Nonselective β- adrenolytic without ISA:* This class inhibits both β1 type and β2 type receptors. Nadolol and propranolol are two examples.

- *Nonselective β- adrenolytic with ISA:* This class operates as a partial agonist as well as blocking the -receptors. ISA slightly lowers bradycardia and cardiac output. Pindol and bopindol are two examples.

- *Simultaneous blocking of α- and β-receptors:* This class acts on α-receptors along with β-receptors. Carvedilol and labetalol are two examples.
- *Lipophilic β-adrenolytics:* This type of β-blocker is highly soluble in solvents and quickly metabolizes in the liver. Labetalol and propranolol are two examples.
- *Hydrophilic β-adrenolytics:* This kind of β-blocker is renally eliminated and exhibits excellent affinity to plasma proteins. Sotalol, nadolol, and atenolol are few examples.

5.5 *Structural analysis of β-blockers*

β-blockers contains an aromatic ring , amino acid, and a hydroxyl group. Additionally, by addition of an oxymethylene bridge between the aromatic moiety and aminoethanol side chain, the β-blocking activity can be enhanced. According to reports, substitution at the ortho and meta positions of the aromatic ring boosts activity, whereas substitution at the para position causes the balance to change in favour of a stronger inhibition of cardioselective receptors. Some examples are :

- Metoprolol exhibits a stronger therapeutic effect since it possesses methoxy ethoxy group at the p-position.
- Toliprolol is a meta substituted derivative which has high β-blocking activity.
- Esmol possesses an ester moiety that makes it easier for it to be hydrolyzed in the blood, improving its therapeutic impact.

5.6 *Stereochemistry of β-blockers*

The spatial orientation of the -OH, -NH_2 group, and aromatic moiety, which are explicitly required for binding to the adrenergic receptors, differs between the enantiomers of β-blockers.According to the Easson and Stedman hypothetical interaction model, the active enantiomer has three strong binds with the receptor, whereas the inactive enantiomer exhibits fewer or no interactions with the receptor. This stereochemical orientation is the cause of this binding difference. The pharmacokinetics of β-blockers can be referred from [8].

5.7 *β-blockers in Market*

All the structures (.mol) of the listed β-blockers can be found here: β-blockers

1. *Atenolol:* This is marketed as a racemate and is a member of the β1-adrenergic blocker class. Atenolol's (S)-enantiomer's activity is more advantageous for its ability to inhibit β-adrenergic receptors. Atenolol's pharmacokinetic qualities have been studied in both rats and humans.
2. *Acebutolol:* This is marketed as a racemate for the treatment of hypertension and cardiac arrhythmias and belongs to a family of second-generation β-adrenergic agonists. While the (R)-enantiomer of acebutolol has a membrane-stabilizing action, the (S)-enantiomer has stronger β-adrenoceptor blocking activity.

3. *Betaxolol:* This is marketed as a racemate, whose (S)-enantiomer is 50-500 times more effective than the (R)-enantiomer. The (S)-enantiomer is used to diminish intraocular pressure. It primarily undergoes inactive metabolite metabolism before being excreted in the urine.

4. *Carvedilol:* It is a racemate-based nonselective β-adrenergic blocker with α1-blocking activity and antioxidant properties. It is employed to treat congestive heart failure. The (S)-carvedilol blocks both α- and β-adrenergic receptors, while the (R)- carvedilol is a purely α1-antagonist.

5. *Celiprolol:* It is a member of a group of third-generation β-blockers that can be found as a racemate. It exhibits innate vasodilator activity that is based on activating β2-adrenoreceptors. Celiprolol's (S)-enantiomer has significantly more anti-isoprenaline action than both its racemate and (R)-enantiomer.

6. *Esmolol:* It is a racemate that is clinically available as a β1-selective antagonist and utilised to treat ventricular and supraventricular arrhythmias as well as sudden cardiac death. While the (R) enantiomer is determined to be inactive, the (S) enantiomer exhibits β-blocking activity. Esmolol's quick hydrolysis in the blood, which results in both its immediate secondary effect and quick beginning of the therapeutic effect, is caused by the ester moiety in the drug's structure.

7. *Metoprolol:* The activity of enantiomers is influenced by the metabolic route. It passes through three different metabolic processes: the first involves benzyl part oxidation and -hydroxylation, which is stereospecific for (S)-enantiomer; the second involves O-demethylation and oxidation to -COOH, which is stereospecific for (R)-enantiomer; and the third involves N-dealkylation.

8. *Nebivolol:* This is a type of third-generation β-blocker that can be found as a racemate. Nebivolol has a different structure than other -blockers since the aromatic moiety is not connected to the aminopropanol group by ethereal oxygen, creating four chiral centres and sixteen stereoisomeric forms. However, because of the structure's symmetry, only 10 stereoisomers are feasible. While (R,S,S,S)-configuration exhibits the effectiveness of a vasodilator, (S,R,R,R)-configuration exhibits β1-adrenoceptor activity. The cytochrome P4502D6 enzyme complex performs first-pass metabolism on the (+)-enantiomer selective -blockage, and predominant binding to albumin.

9. *Penbutolol:* It is the first known β-blocker that is only used as the (S)-enantiomer. The ISA and antiarrhythmic effects of the (S)-enantiomer are maintained by the blockade of -adrenergic receptors.

10. *Propranolol:* This is a nonselective -adrenoceptor agonist, which blocks both β1- and β2-receptors. It is offered as a racemate with an identical molar ratio of both the (R) and (S) enantiomers. While the (S)-enantiomer exhibits cardiac β-blocking activity, the (R)-enantiomer has no pharmacological value.

11. *Sotalol:* Available as a racemate, which is used to treat cardiac arrhythmia, angina pectoris, and hypertension. The (R)-enantiomer, which is 30 to 60 times more potent than its (S)-counterparts, is responsible for the β-blocking activity. The antidysrhythmic effect of sotalol toward K channel blockage is the same in both of its enantiomers. Due to increased carcinogenicity in patients, it is not recommended to use (S)-enantiomers in patients with ventricular dysfunction and dietary limitation.

Drug Name	IUPAC Name	Marketed As & Relative activity	Elimination
Atenolol	2-[4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl] acetamide	Racemate & S-(-) > R-(+)	Renal
Acebutolol	N-3-acetyl-4-[(2-hydroxy-3-(isopropylamine)propoxy]phenyl butanamide	Racemate & S-(-) > R-(+)	Hepatic
Betaxolol	1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(propan-2-ylamino)propan 2-ol)	Racemate & S-(-) > R-(+)	Hepatic
Carvedilol	1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol	Racemate & S-(-) > R-(+)	Hepatic
Celiprolol	4-[3-(2-methyl propane-2-ylamino)-2-hydroxypropoxy] phenyl}-1,1' diethylurea	Racemate & S	Renal
Esmolol	3-[4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl]propanoate	Racemate & S-(-) > R-(+)	Renal
Metaprolol	1-[4-(2-methoxyethyl) phenoxy]-3-(propan-2-ylamino)propan-2-ol	Racemate & S-(-) > R-(+)	Hepatic
Nebivolol	1-(6-fluoro-3,4-dihydro-2H-chromen-2-yl)-2-[[2-(6-fluoro-3,4-dihydro-2H-chromen-2-yl)-2-hydroxyethyl]amino]ethanol	Racemate & SRRR	Hepatic
Penbutolol	1-(tert-butylamino)-3-(2-cyclopentylphenoxy)propan-2-ol	Single & S	Renal
Propranolol	1-(1-methylethylamino)-3-(1-naphthyloxy)propan-2-ol	Racemate & S-(-) > R-(+)	Hepatic
Sotalol	4-[1-hydroxy-2-(isopropylamine)ethyl]-methanesulfonanilide	Racemate & S-(-) > R-(+)	Renal

Table 5.1: Overview of β-blockers

Chapter 6

Stereospecificity in interaction of β-blockers and β- adrenergic receptor

6.1 *Introduction*

In this section, by using the contact command in Jmol I have tried to show the difference in the interaction sites of acebutolol drug, used to treat high blood pressure, irregular heartbeat, due to its stereochemistry. The interaction of the drug acebutolol was studied by docking it with human β- adrenergic receptor. The β-adrenergic receptors are crucial for controlling cardiac function. They belong to the family of G-protein coupled receptors. The receptors have three intracellular and extracellular loops, one extracellular N-terminal domain, and one intracellular C-terminal tail in addition to seven membrane spanning domains.

6.2 *Materials and methods*

6.2.1 *Ligands*

PubChem repository (https://pubchem.ncbi.nlm.nih.gov/) was used to obtain the 3-D structures of R-acebutolol, S-acebutolol.

6.2.2 *Homology modelling of protein*

The protein sequence of β- adrenergic receptor was retrived from ncbi database (GenBank: CAA02051.1). The structure of β- adrenergic receptor is generated by homology modelling using Swiss-model server (https://swissmodel.expasy.org/) with 7XJH template. The sequence identity of β- adrenergic receptor with the template 7XJH was found to be 87.57%. The Ramachandran plot and the ERRAT score were used to validate the protein structure using UCLA-DOE-LAB server (https://saves.mbi.ucla.edu/).

6.2.3 *Molecular Docking*

The pockets and cavities of the protein was determined CASTp server. The larger pocket was chosen for docking study. The AutoDock Vina v1.2.3 was used to carry out molecular docking study. The protein and ligands were optimized by removal of water, hetero atoms , addition of polar hydrogens and charges (Kollman). A grid box 54x62x40 was used for largest

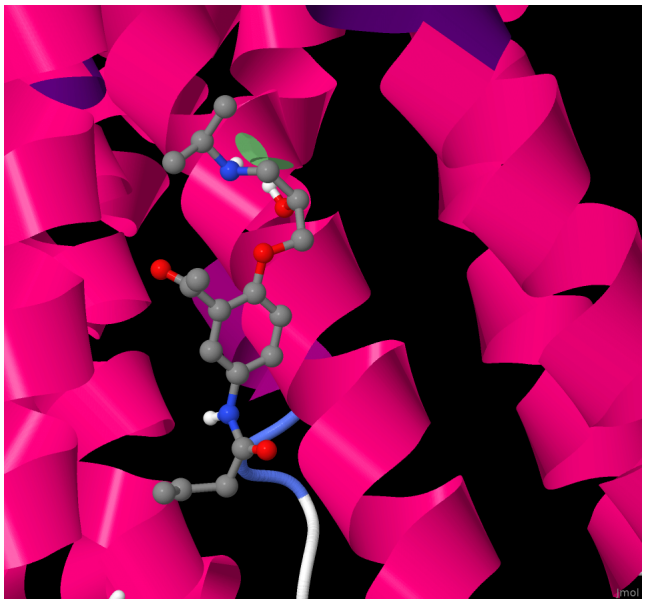

Figure 6.3: Hydrogen bond interaction of S-acebutolol

pocket determined using CASTp server. The autodock vina generated 10 conformations for each ligands. The analysis of the complex was done using Jmol.

6.3 *Results and analysis*

The best complex with the highest binding affinity was examined using Jmol's contact command. The S-acebutolol (B.E (Kcal/mol)=-5.601) had thirteen contacts with one hydrogen bond interaction with GLU126, compared to the R-four acebutolol's connections without a hydrogen bond (B.E (Kcal/mol)=-5.134).

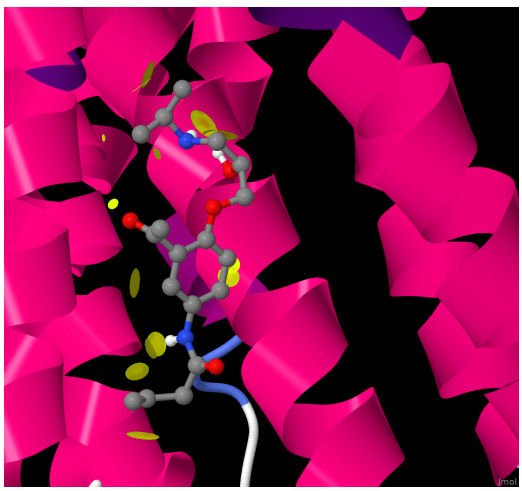

Figure 6.1: All interactions of S-acebutolol

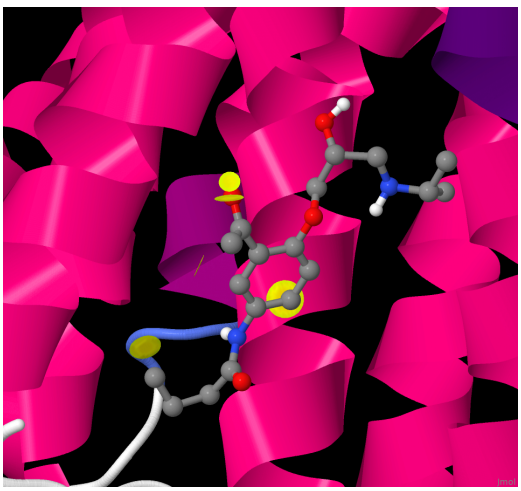

Figure 6.2: All interactions of R-acebutolol

6.4 *Commands*

All the files can be accessed from: interaction of β-blockers

- All the interactions can be addressed by the command *contact ligand*.
- The hydrogen bonding can be addressed by the command *contact ligand hBond*.

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