CYCLIC STEREOCHEMISTRY

SEM-5, CC-12
PART-10, PPT-10

Part-10: Conformation and Reactivity in Cyclohexane-III

CONTENTS

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Cyclic Stereochemistry (PART-10, PPT-10)

Conformation and Reactivity in Cyclohexane-I

S_Ni Reaction in Cyclohexanes

Anancomeric trans- and *cis*-isomers of 4-*t*-butylcyclohexylamine behave differently towards nitrous acid. When *trans*-4-*t*-butylcyclohexylamine (A; Figure 1) is treated with nitrous acid then *retention of configuration* occurs to give almost exclusively the *equatorial* alcohol (C) via a fleeting diazonium salt intermediate. On the other hand, the corresponding *cis*-isomer gives an alkene (D) under the similar reaction condition.

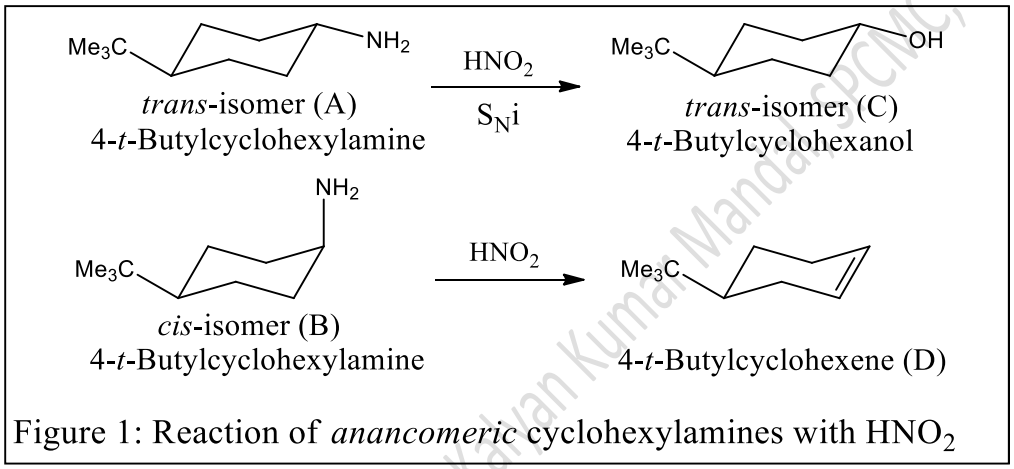


Figure 1: Reaction of *anancomeric* cyclohexylamines with HNO_2

In case of *trans*-isomer, the product formation can be explained on the basis of S_Ni reaction involving the formation of a short-lived solvated ion-pair (A') or through a cyclic intermediate (A''), which collapses rapidly to give the more stable *trans*-4-*t*-butylcyclohexanol with *equatorial*-alcohol (Mechanism is shown in Figure 2). The cyclohexyl diazoniun salt (A') is unsuitable to undergo S_N2 and E2 reactions.

In case of *cis*-isomer with *axial*-NH_2 group, diazotization leads to an intermediate (B') where the diazonium group is in *axial* position, and it is well disposed toward *trans diaxial* elimination. It undergoes E2 elimination easily because of favourable stereoelectronic effect in cyclohexyl system, and the predominant reaction product is olefin (D).

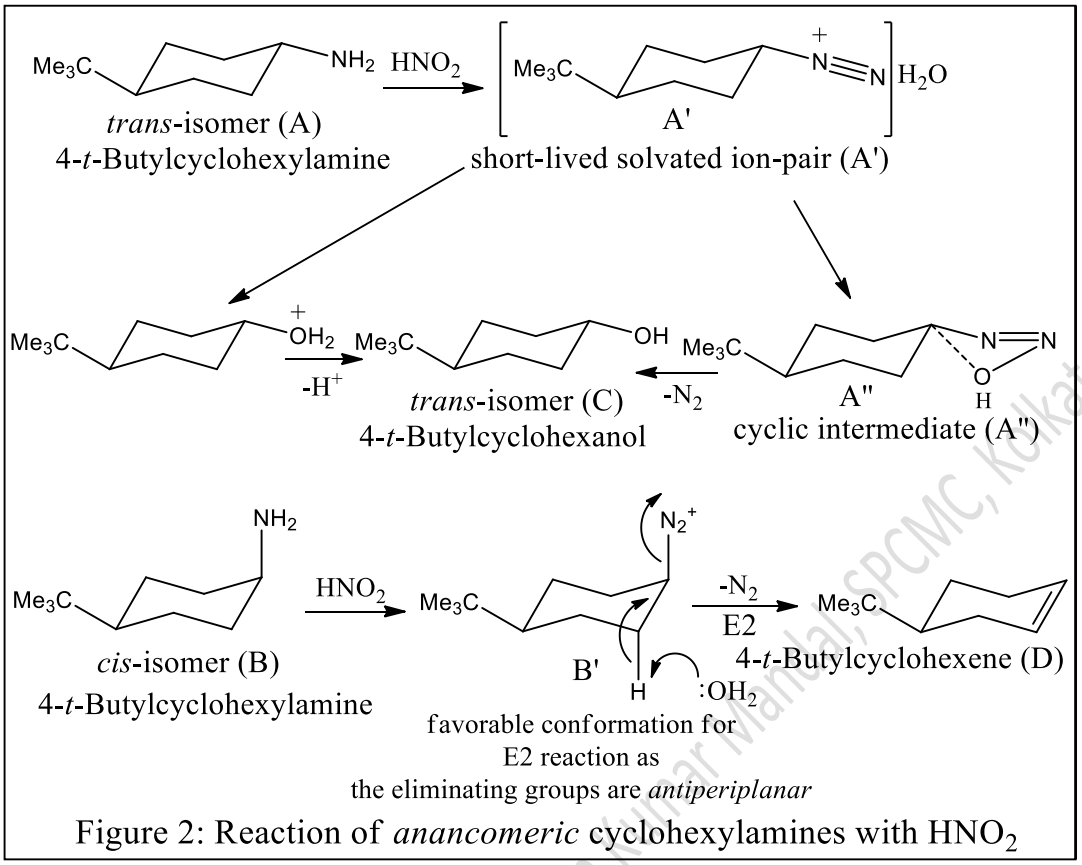


Figure 2: Reaction of *anancomeric* cyclohexylamines with HNO_2

Merged Substitution and Elimination Reactions

Anancomeric trans- and *cis*-isomers of 4-*t*-butylcyclohexyl tosylate behave differently towards bromide ion (NaBr or KBr) or thiophenolate (PhSNa). When *trans*-4-*t*-butylcyclohexyl tosylate (A; Figure 3) is treated with bromide ion or thiophenolate, an alkene (C) is formed exclusively. On the other hand, the corresponding *cis*-isomer undergoes bimolecular nucleophilic substitution to give *trans*-4-*t*-butylcyclohexyl bromide with inversion of configuration.

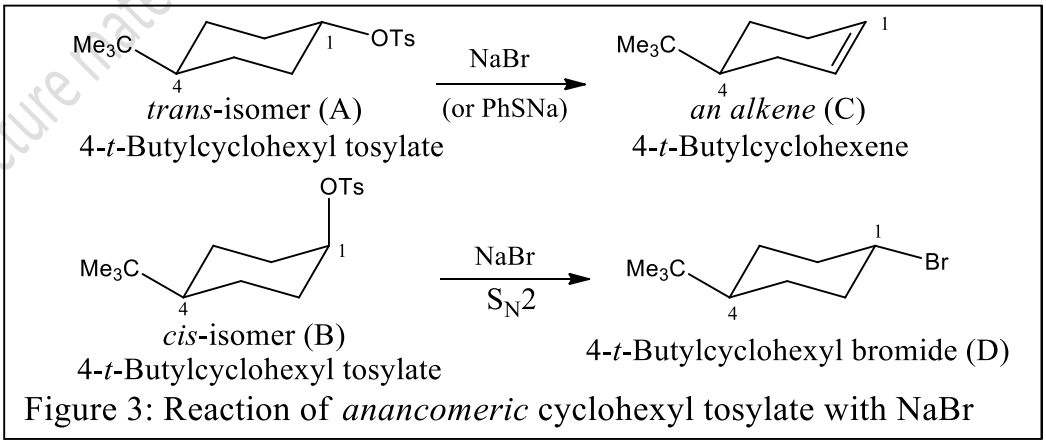


Figure 3: Reaction of *anancomeric* cyclohexyl tosylate with NaBr

The *trans*-isomer of *anancomeric* 4-*t*-butylcyclohexyl tosylate undergoes S_N2 reaction first in presence bromide ion. Here, the highly nuclophilic bromide or thiophenolate ions (although

not by the less nucleophilic and more basic ethoxide ion) approaches from the *axial* direction for the *equatorial* leaving group to give an intermediate *cis*-4-*t*-butylcyclohexyl bromide (C'). This bromide then readily undergoes E2 reaction under the condition of the reaction leading to the formation of an alkene, 4-*t*-butylcyclohexene (C) (Mechanism is shown in Figure 4). This process has been called 'merged substitution and elimination".

In case of *cis*-isomer with *axial*-OTs group is under suitable condition for SN_2 reaction where nucleophile approaches from the sterically favourable *equatorial* direction to give a stable product *trans* 4-*t*-butylcyclohexyl bromide with inversion of configuration.

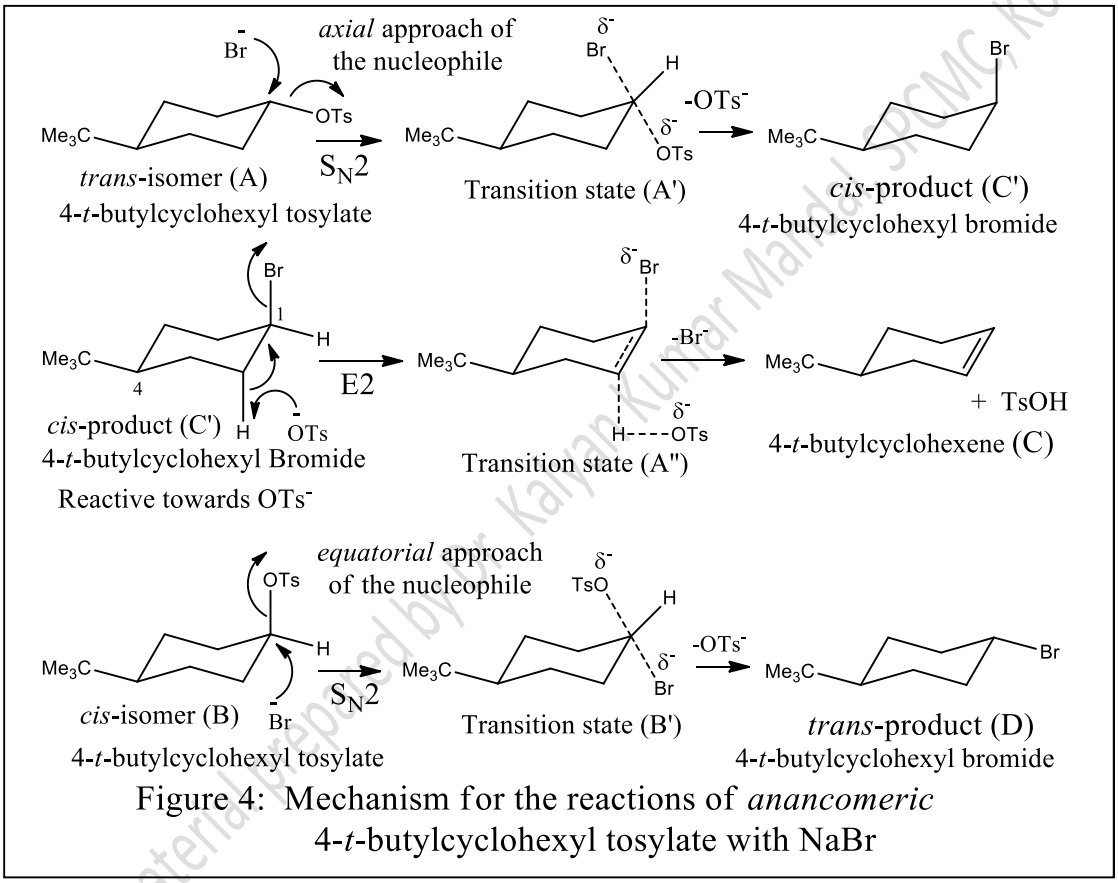


Figure 4: Mechanism for the reactions of *anancomeric* 4-*t*-butylcyclohexyl tosylate with NaBr

Comparison of *Diaxial* and *Axial-Equatorial* Elimination in Cyclohexanes

A comparison of *diaxial* and *axial-equatorial* elimination in cyclohexyl system is displayed in Figure 5. The reaction of *cis*- and *trans*-l,2-dibromocyclohexanes with potassium iodide in methanol at 80°C to give a common product, cyclohexene. The *trans*-dibromide reacts only 11.5 times as fast as the *cis*-dibromide, even though the *trans*-isomer can undergo *diaxial* elimination and the *cis*-isomer cannot.

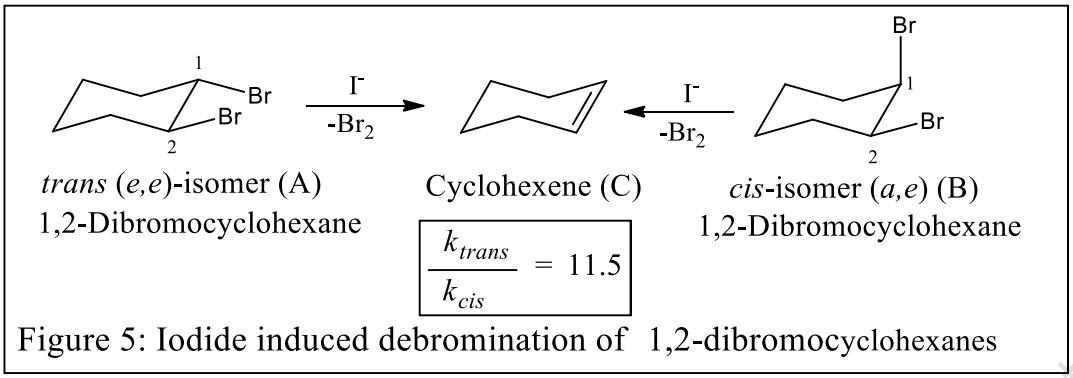


Figure 5: Iodide induced debromination of 1,2-dibromocyclohexanes

This fact is neither an indication of relatively rapid *cis* (*e*,*a*) elimination, nor does it mean that the *trans*-dibromide exists mainly in the *diequatorial* conformation, which is not favourably disposed toward elimination. The explanation based on kinetic study, is that in the *cis*-dibromide the *axial* bromine atom quite readily undergoes bimolecular substitution by iodide (rate-determining) to give the *trans* iodobromide, which may then flip over into the *diaxial* conformation and undergo rapid *diaxial* elimination. In case of *cis*-isomer, the reaction is a case of merged substitution and elimination. Figure 6 illustrates the mechanism of the reaction.

The *trans*-isomer, on the other hand, undergoes direct *diaxial* elimination via the flipping isomer (*a*,*a*) . The *e*,*e*-form though more populated in the conformational equilibrium with *a*,*a*-form, it suffers from strong dipole-dipole repulsion. Therefore, the *a*,*a*-form though disfavours sterically, but it is substantially populated in the equilibrium. In the *a*,*a*-form, the eliminating groups are suitably disposed for *trans-diaxial* elimination and is more reactive than the *e*,*e*-form towards iodide ion. Figure 6 illustrates the mechanism of the reaction. The rate factor of 11.5 thus reflects the somewhat higher rate of *diaxial* elimination over substitution.

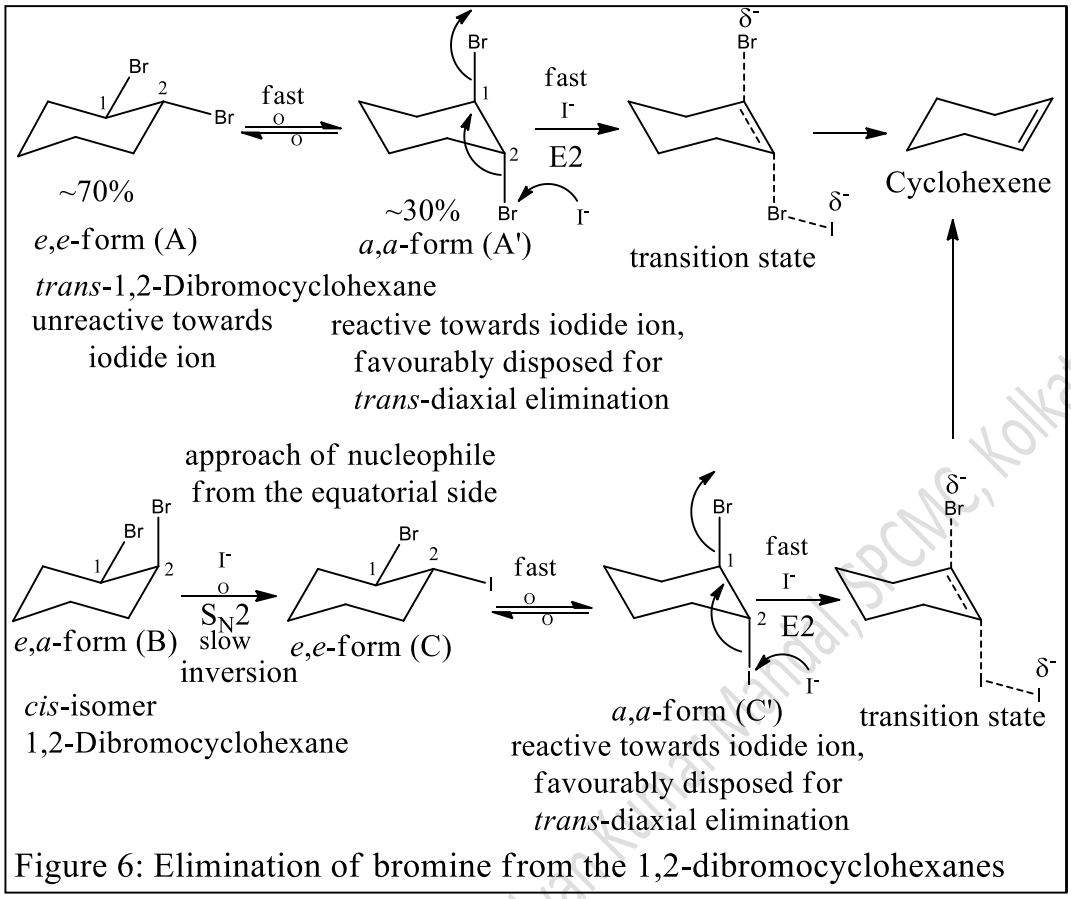


Figure 6: Elimination of bromine from the 1,2-dibromocyclohexanes

Antiperiplanar Arrangement in Cyclohexanes

Ring formation, rearrangement, neighbouring group participation, and fragmentation reactions constitute an interrelated set of reactions with the stereoelectronic requirement that the groups involved must be *antiperiplanar*. Normally, this involves *diaxial* disposition; however, since an element of the ring may be *antiperiplanar* to an *equatorial* leaving group, ring contractions can involve *equatorial* substituents. This situation applies also to fragmentation reactions.

The reactions of bromohydrins with base and with silver ions illustrate these principles. These reactions are explained for the four diastereomeric 2-bromo-4-phenylcyclohexanols. The phenyl group, $-\Delta G°_{confo}$ = 2.9 kcal mol^{-1} serves to bias the conformational equilibria of the various stereoisomers.

Reactions of 1,2-Bromohydrins with Base

Case A exemplifies epoxide ring formation. The entering (OH or O$^-$) and leaving (Br) groups are *antiperiplanar* (*a*,*a*).

Case B exemplifies ketone formation by either hydride shift or enolate formation (HBr elimination). The hydrogen involved is *antiperiplanar* to the leaving bromine.

In **Case C**, where the proper stereoelectronic situation is not attained in the most stable starting conformation, the molecule apparently reacts in the alternate conformation, even though this involves *syn-axial* phenyl and bromine interaction.

The fourth diastereomer **(Case D)** reacts differently with Ag_2O and base. With Ag_2O, departure of the *equatorial* bromine is induced. With base, epoxide ring formation takes place via the inverted chair.

Reactions involving Neighbouring Group

Case A exemplifies epoxide ring formation. The entering (OH or O^-) and leaving (Br) groups are *antiperiplanar* (*a*,*a*). S_N2 type displacement leads to the formation of epoxide as the main product.

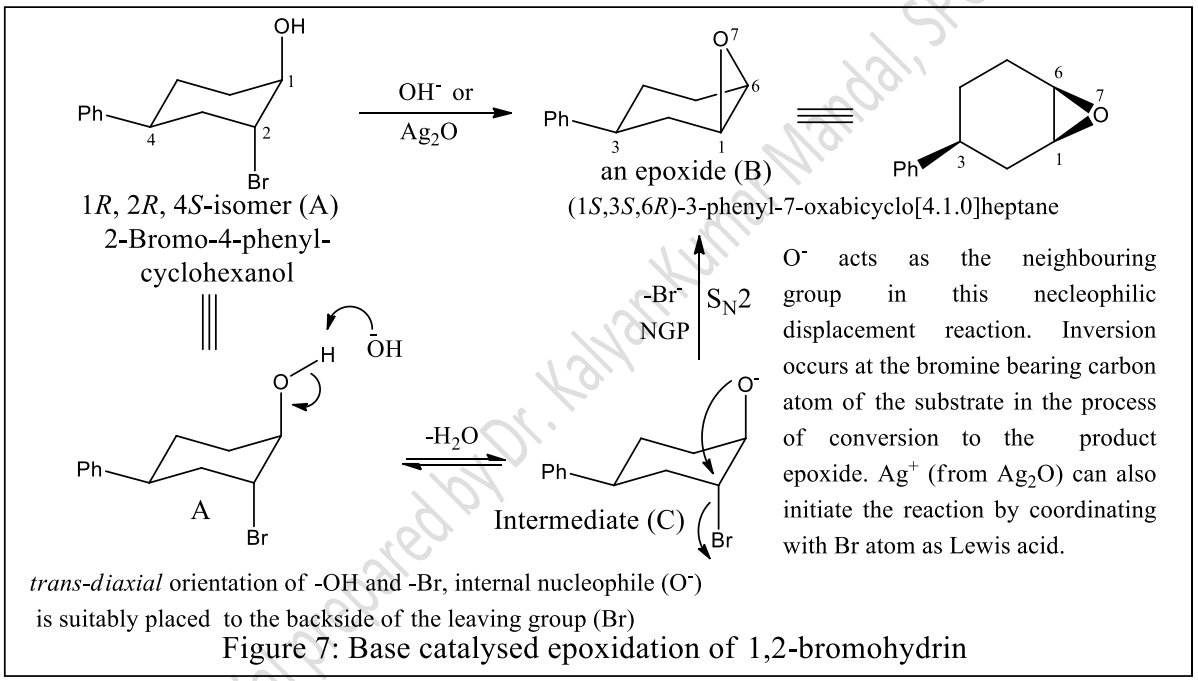
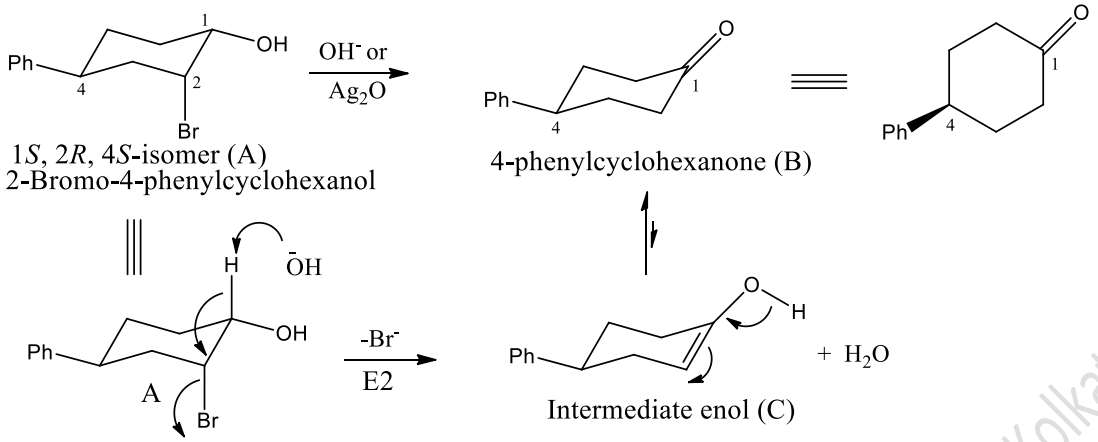


Figure 7: Base catalysed epoxidation of 1,2-bromohydrin

Reactions of 1,2-Bromohydrins with Base

Case B (Figure 8) exemplifies ketone formation by either hydride shift or enolate formation (HBr elimination). The hydrogen involved is *antiperiplanar* to the leaving bromine.



H and Br are *antiperiplanar* and E2 reaction is stereoelectronically favourable. *Base catalysed trans-diaxial* elimination of HBr gives an enol as an intermediate, which readily tautomerises to the more stable cyclohexanone derivative. Ag^+ (from Ag_2O) can also initiate the reaction by coordinating with Br atom as Lewis acid catalyst (electrophilic catalysis).

Figure 8: Reactions of 2-bromo-4-phenylcyclohexanols with base and Ag_2O

In Case C, where the proper stereoelectronic situation is not attained in the most stable starting conformation (A; Figure 9), the molecule apparently reacts in the alternate conformation, even though this involves *syn-axial* phenyl and bromine interaction.

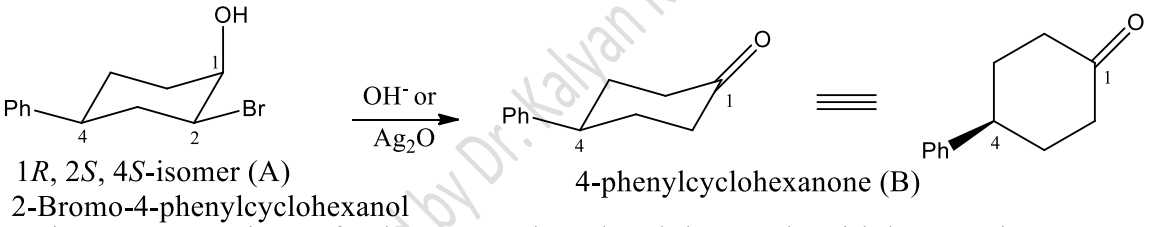


Figure 9: Reactions of 2-bromo-4-phenylcyclohexanols with base and Ag_2O

A ketone is formed in this reaction by either hydride shift or enolate formation (HBr elimination). The hydrogen involved is *antiperiplanar* to the leaving bromine. Figure 10 illustrates the mechanism of the reaction. H and Br are antiperiplanar and E2 reaction is stereoelectronically favourable in the less populated form (A') but the rate is slow than when the reaction occurs through the more populated form (A).

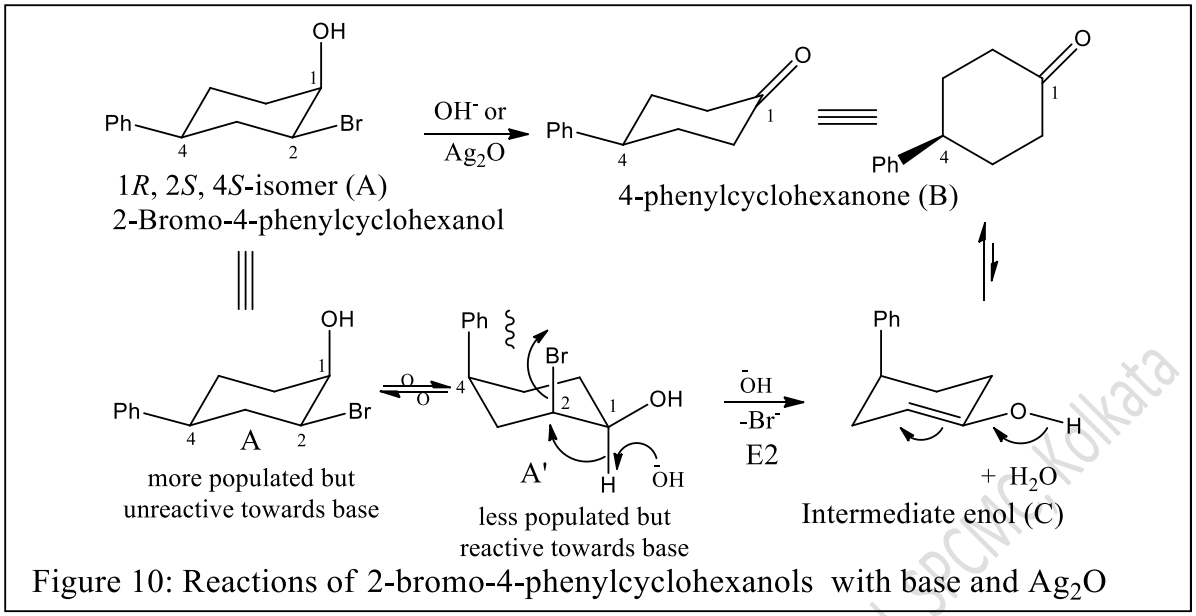


Figure 10: Reactions of 2-bromo-4-phenylcyclohexanols with base and Ag_2O

The fourth diastereomer (Case D; Figure 11) reacts differently with Ag_2O and base. With Ag_2O, departure of the *equatorial* bromine from A is induced and the ring bond *antiperiplanar* to the departing *equatorial* bromine [Cl-C6] migrates to produce a ring contraction to *cis*-3-phenylcyclopentanecarboxyaldehyde (B). Here, Ag^+ acts as the Lewis acid catalyst.

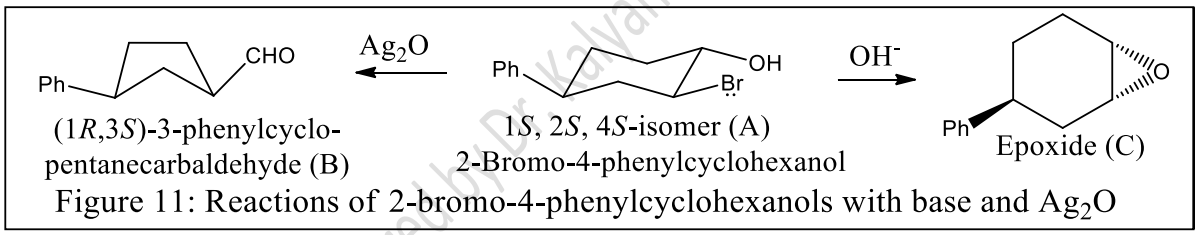


Figure 11: Reactions of 2-bromo-4-phenylcyclohexanols with base and Ag_2O

With base (hydroxide) the driving force for ring contraction in the secondary halide is insufficient and the molecule reacts in the alternate *inverted chair* conformation, even though this involves *syn-axial* phenyl and bromine, to produce an epoxide (C; Figure 12).

Reactions involving Neighbouring Group

S_N2 type displacement involving the participation of the oxide ion as the internal nucleophile leads to the formation of epoxide.

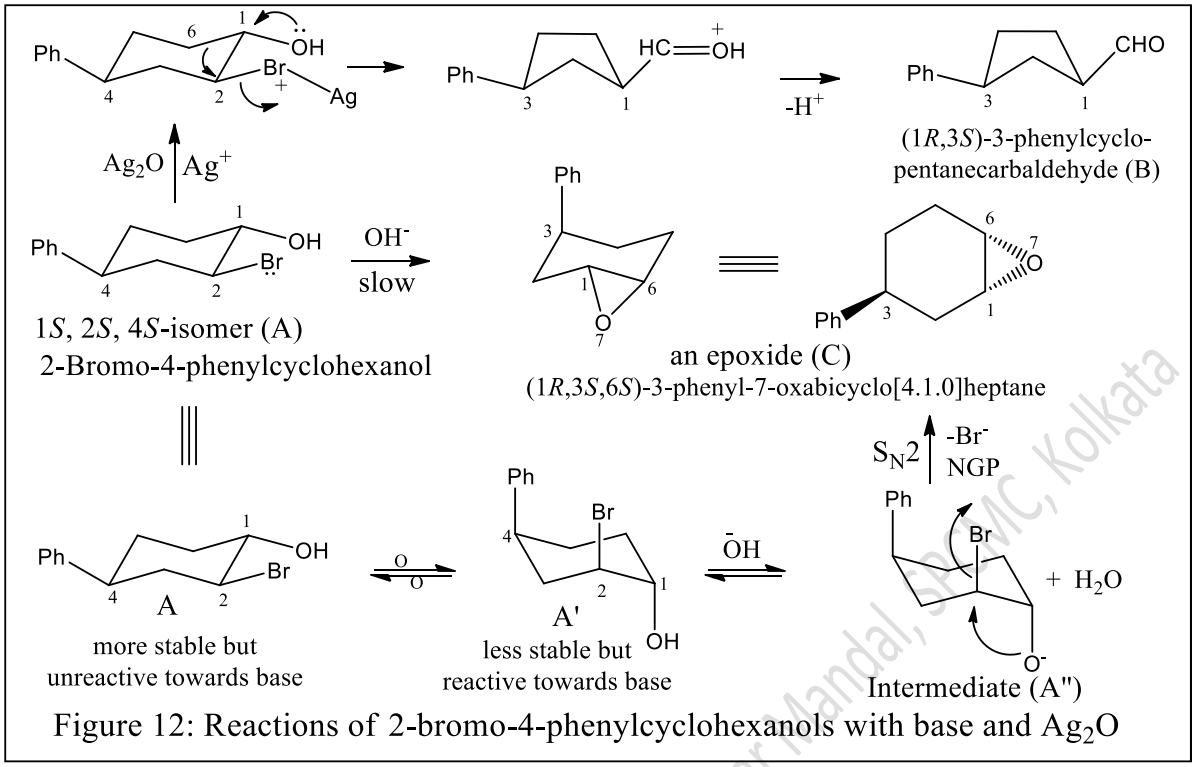


Figure 12: Reactions of 2-bromo-4-phenylcyclohexanols with base and Ag_2O

Acetolysis of 2-Acetoxycyclohexyl Tosylates

A classical example of neighbouring group participation in a cyclic system is the acetolysis of 2-acetoxycyclohexyl tosylate, both the *trans* (A; Figure 13) and the *cis* (B) isomers of which give *trans*-1,2-acetoxycyclohexane (C), the former through neighbouring group participation and the latter by direct S_N2 reactions.

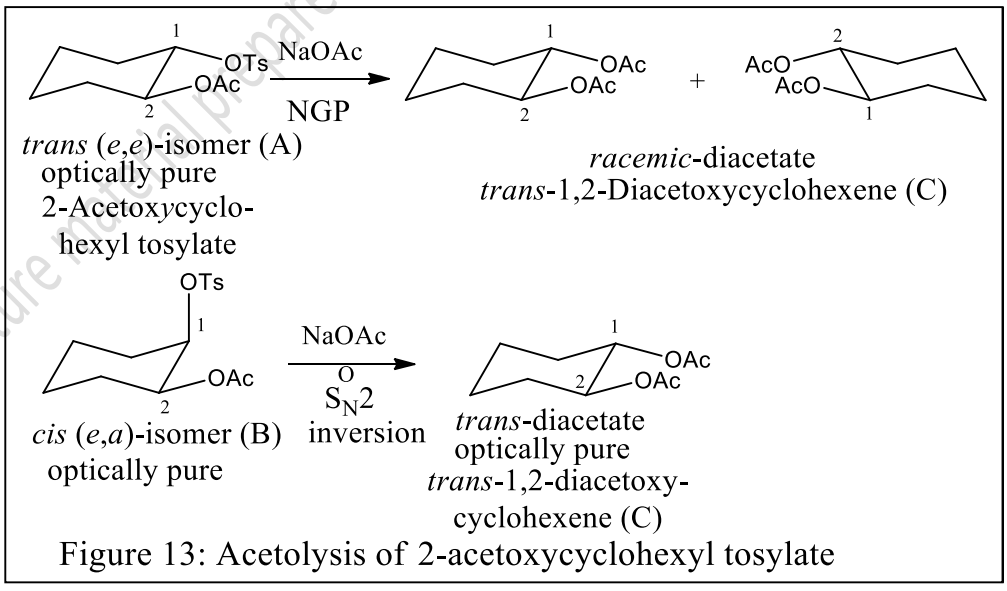


Figure 13: Acetolysis of 2-acetoxycyclohexyl tosylate

In the *diaxial* conformer (A'; Figure 14) of the *trans*-isomer, the acetoxy group is suitably disposed to remove the tosyl group by an intramolecular S_N2 reaction to give an intermediate acetoxinium ion (intermediate I) with *cis* fused 6,5-rings. This exists as a rapidly

interconvertible enantiomeric pair and a nucleophilic attack by acetate ion at either ring junction gives the *trans*-diacetate (C). Thus, if an optically active *trans* isomer (A) is used, a *racemic* mixture of the diacetate (C) is formed. The reactivity of the *trans*-isomer is almost 700 times greater than that of the *cis*-isomer despite the very low concentration of the reactive conformer of the former.

The *cis*-isomer reacts by normal S_N2 with the inversion of configuration at the stereogenic centre. The nuclophile, $^-$OAc, approaches from the sterically favourable *equatorial* side to give the *trans*-diacetate (C).

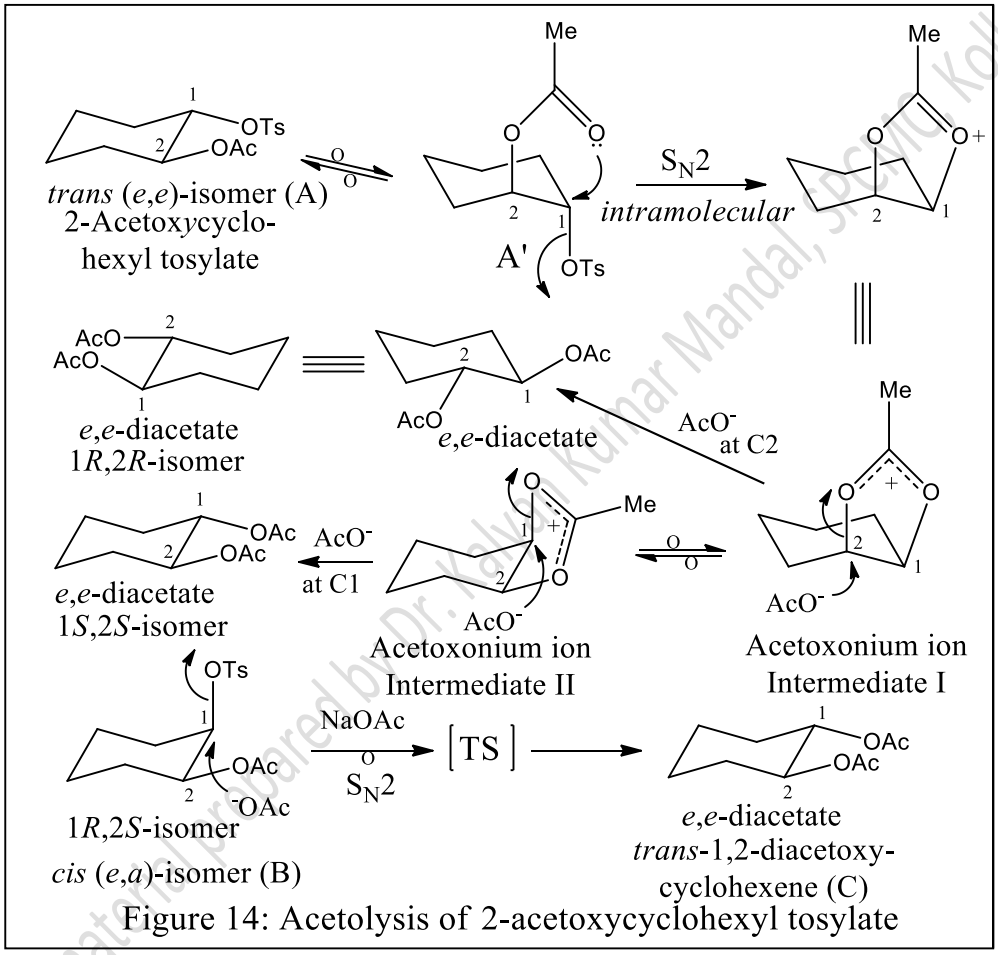


Figure 14: Acetolysis of 2-acetoxycyclohexyl tosylate

1,4-Participation Across a Six-Membered Ring

1,4-Participation across a six-membered ring (in the *boat* form) is seen in the acetolysis of *trans*-4-methoxy-1-tritiocyclohexyl *p*-toluenesulphonate. The *equatorial trans* isomer (A; Figure 15) acetolyses about twice as fast as the partly *axial cis*-isomer (B), and when the starting material is labeled with tritium in the 1 position, the *trans*-4-methoxycyclohexyl acetate product has the label nearly equally divided between the 1 and 4 positions.

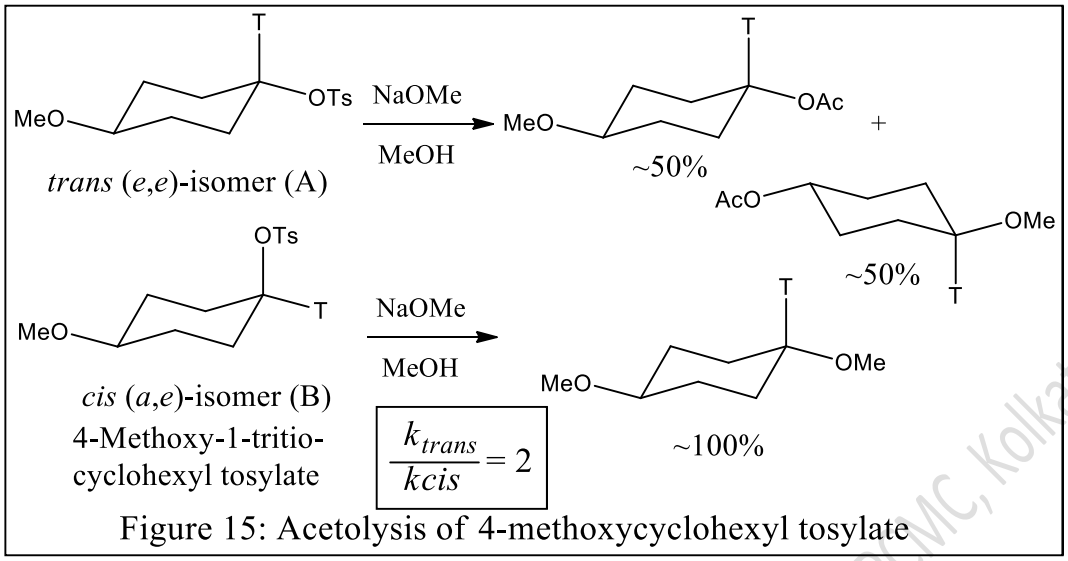


Figure 15: Acetolysis of 4-methoxycyclohexyl tosylate

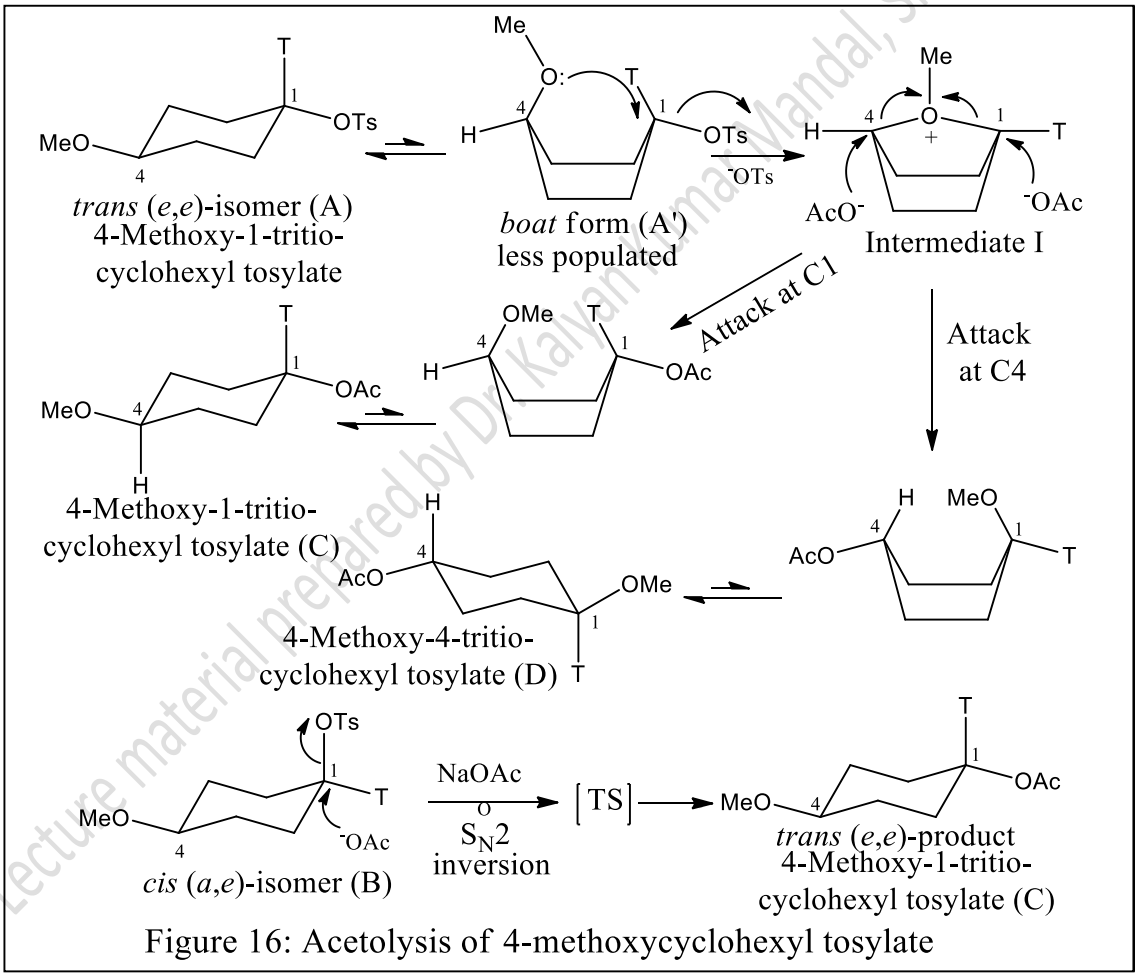


Figure 16: Acetolysis of 4-methoxycyclohexyl tosylate