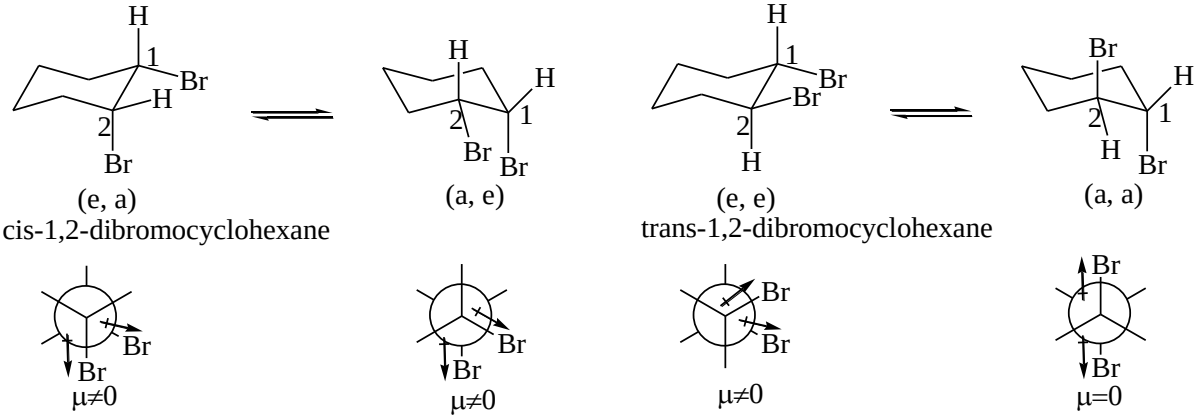
1. Compare the dipole moment of 1,2-dibromocyclohexane.

Let us see the structure of cis and trans isomer of 1,2-dibromocyclohexane.

In case of cis isomer the dihedral angle between two C-Br bond is 60° for both the conformer. So the observed dipole moment (μ_{obs}=3.12D) and calculated dipole moment (μ_{cal}= 3.09D) are very close.



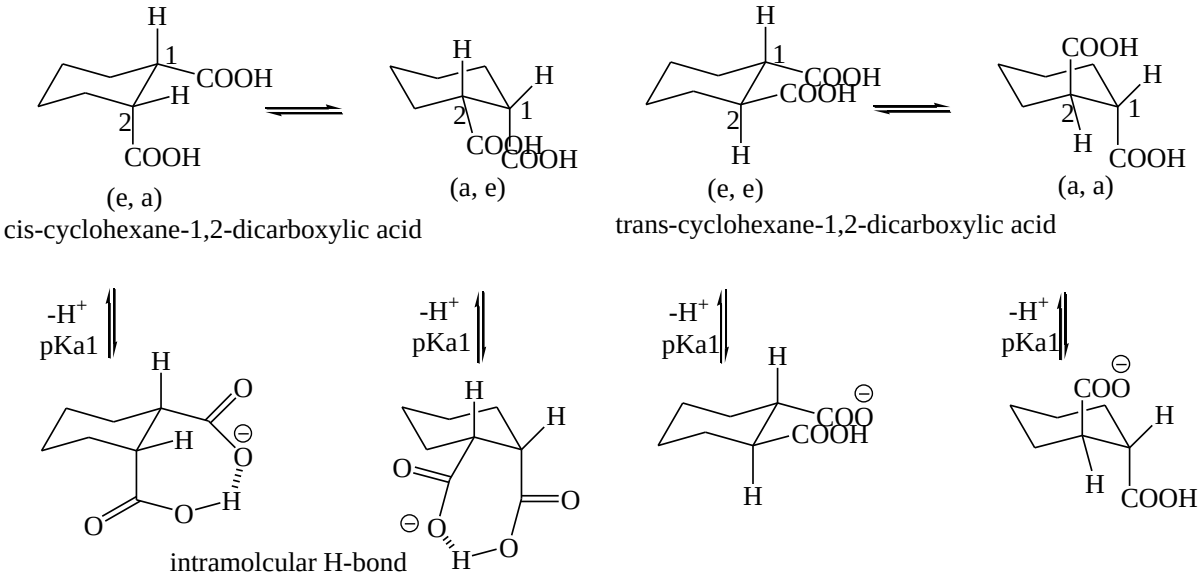
But in case of trans isomer, in one conformation the dihedral angle between two C-Br bond is 60° but for other conformer it is 180°. So the μ_{obs} will be the average of the corresponding population % of the conformers and which is 2.11D. In the case of e,e conformer μ_{cal} is 3.09D but for a,a conformer it is zero. But the observed μ is greater than the mean value of the two conformer and this indicate that the % population of e,e conformr is much more than a,a conformer.

2. Compare the acid strength of cis and trans isomer of cyclohexane-1,2-dicarboxylic acid.

   (Explain the fact that the differences between two pKa of cyclohexane-1,2-dicarboxylic acid is greater for cis isomer than the trans isomer.)

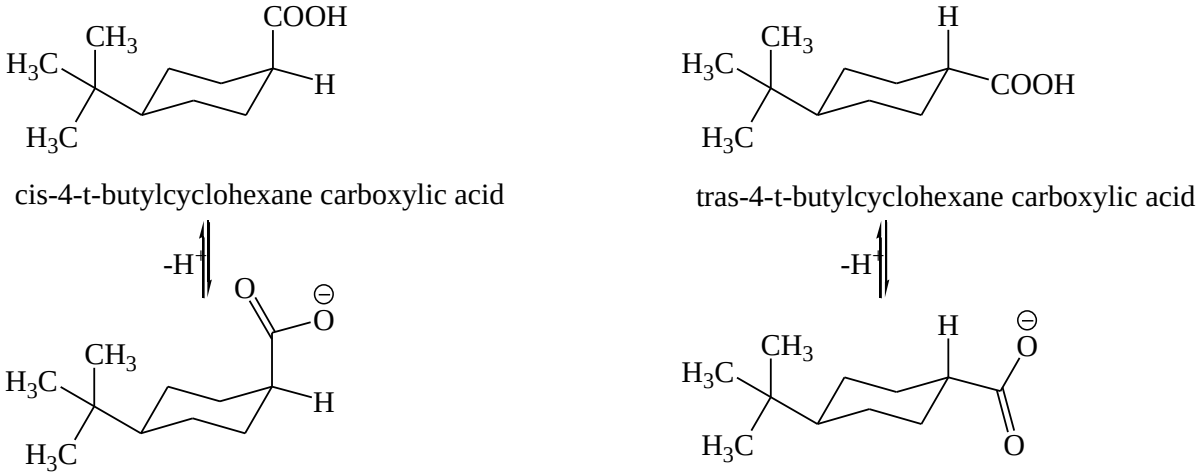
In case of cis-cyclohexane-1,2-dicarboxylic acid the first ionisation will be very fast as the corresponding conjugate bases will be highly stable due to formation of intramolecular H-bonding. Hence the pKa1 will be of low value and it will be same for the both conformer as the possibility of intramolecular hydrogen bond formation is equal in both conformer. Due to same reason, i.e, intramolecular H-bonding, the second ionization (pKa2) will be slow and hence pKa2 will be high. As a consequence the difference between pKa2 and pKa1 will be high.

In trans isomer although pKa1 is same for the both conformer but the value of pKa1 is high as there is no possibility of intramolecular H-bond formation after first ionization. Similarly the pKa2 will be low as second ionization will be easy. So the difference between pKa2 and pKa1 will be less.



3. Compare the acidity of cis and trans isomer of 4-t-butylcyclohexane carboxylic acid.

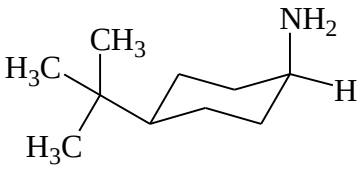
Due to the presence of tertiary butyl group at 4 position the conformation of the above compound will be locked and the t-butyl group will be at equatorial position. Here the conjugate base of the trans isomer will be more stable as the carboxylate anion at equatorial position will be more solvated and hence will be more stable compared to axial carboxylate group (cis isomer). For better solvation the water molecules can easily acess the less hindered equatorial position. So trans-4-t- butylcyclohexane carboxylic acid is more acidic compared to the cis isomer.



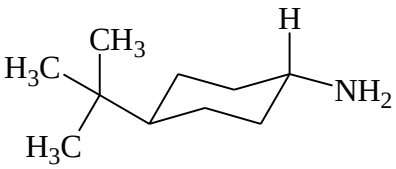
4. Compare the basicity of cis and trans isomer of 4-t-butylcyclohexyl amine.

Due to the presence of tertiary butyl group at 4 position the conformation of the above compound will be locked and the t-butyl group will be at equatorial position. Here the conjugate acide of the trans isomer will be more stable as the protonated amine at equatorial position will be more solvated and hence will be more stable compared to axial counterpart (cis isomer). For better solvation the water molecules can easily acess the less hindered

equatorial position. So trans-4-t- butylcyclohexyl amine is more basic compared to the cis isomer.



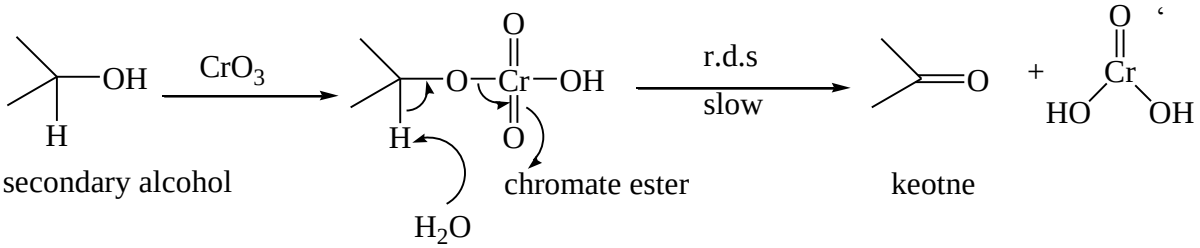
cis-4-t-butylcyclohexyl amine



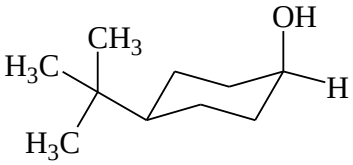
tras-4-t-butylcyclohexyl amine

5. Compare the rate of chromic acid oxidation of cis and trans 4-t-butylcyclohexanol.

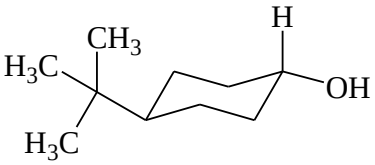
Let us have a close look on chromic acid oxidation of a secondary alcohol-



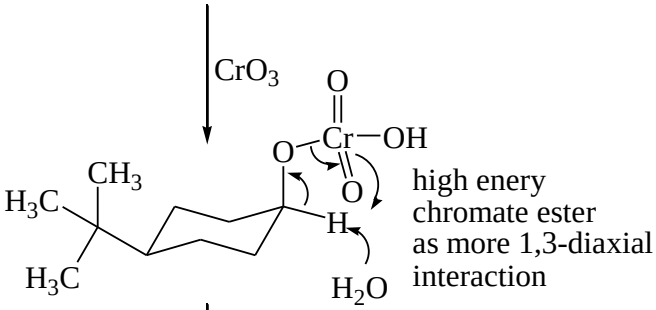
secondary alcohol chromate ester keotne



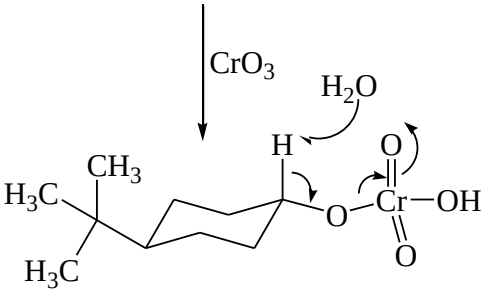
cis-4-t-butylcyclohexanol

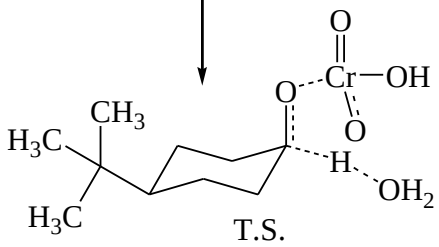


tras-4-t-butylcyclohexanol

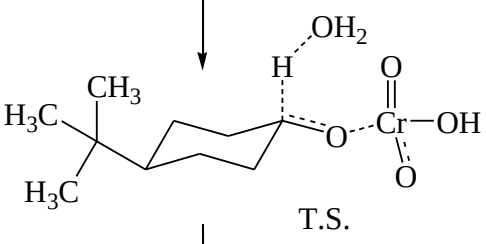


high enery chromate ester as more 1,3-diaxial interaction

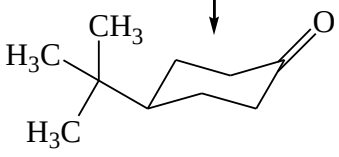




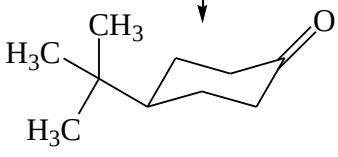
T.S. stabilised T..S. as more strain released



T.S.

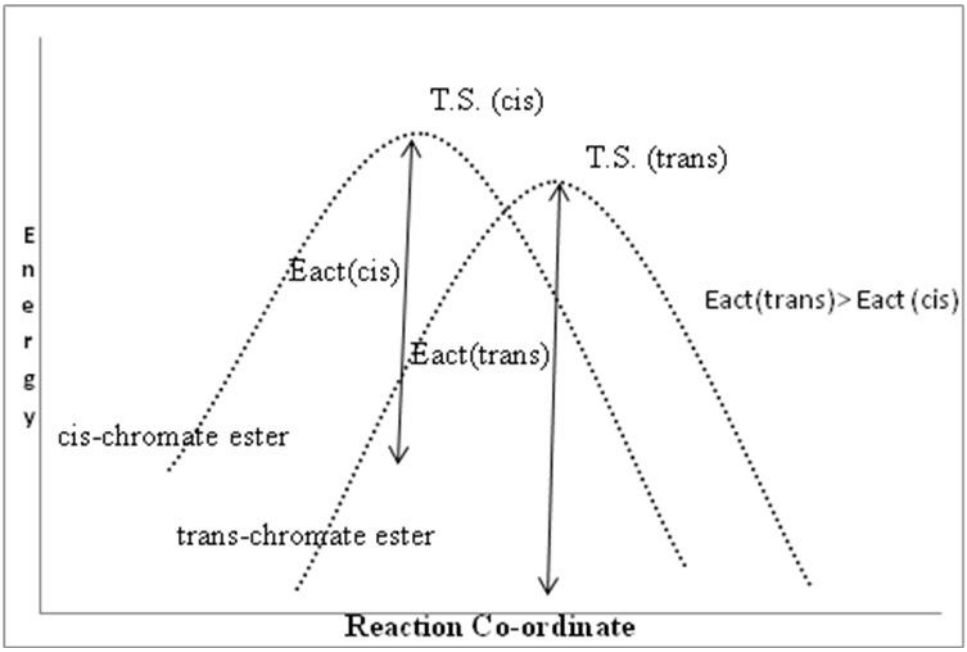


4-t-butylcyclohexanone



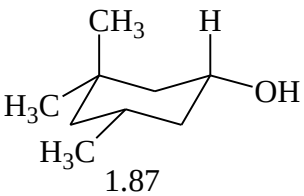
4-t-butylcyclohexanone

The reactive species in the chromic acid oxidation is Cr(VI) oxidewhich form a chromate ester at first step. Water molecule at second step abstract the proton and gives the oxidised product ketone. The second step is the slowest step and rate determining step. In this step a bulky chromate ester is converted to a simple ketone and hence steric strain is released in this step.

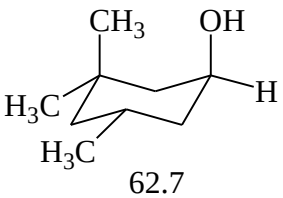


If we compare the oxidation of cis and trans isomer of 4-t-butylcyclohexanol, in each case the starin will be released at r.d.s.. But the extend of strain release will be more in cis isomer (axial chromate ester) as the T.S. will be more stabilised compared to trans isomer. If we see the realative energy profile diagram of this step, the chromate ester (reactant) of the cis isomer have much more energy compared to the trans ismer as the bulky chromate ester group experience much more diaxial interaction at axial position. At T.S. where the chromate ester bond breaking happening, the strain release will be much more for cis isomer and hence the T.S. of the cis isomer will be much more stable compared to the trans isomer. Hence the activation energy (Eact) which is the difference between reactant and T.S. will be less for cis isomer and so the oxidation rate is faster for cis isomer.

6. Compare the chrmic acid oxidation rate of this two alcohol.



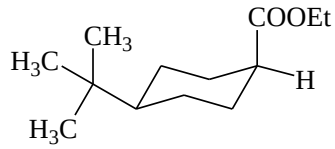
1.87



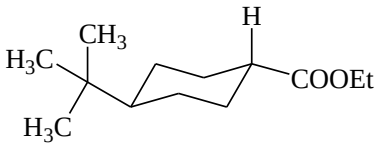
62.7

7. Compare the rate of hydrolysis of cis and trans isomer of ethyl 4-t-butylcyclohexane carboxylate.

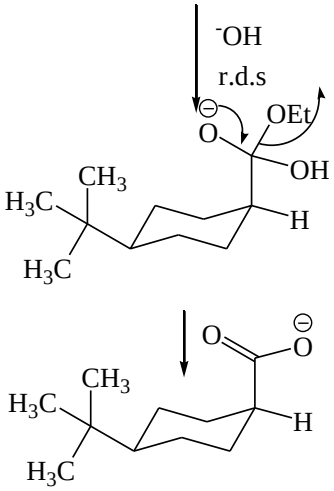
In case of base catalysed ester hydrolysis, the attack of base ($^-$OH) on the carbonyl group of ester is the r.d.s. Here steric crowding is increasing during the attack of the base as the sp^2 carbonyl is being converted to sp^3 tetrahedral centre. So, the T.S. of the r.d.s. will be of high energy as the steric crowding increases. Now the energy of the T.S. of cis isomer (axial ester) will increase much more compare to the trans isomer (equatorial ester). So eventually the Eact for cis isomer will be much higher compared to the trans isomer and hence cis isomer will react slowly in base catalysed ester hydrolysis.

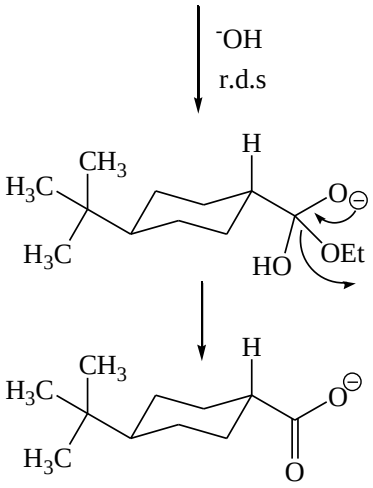


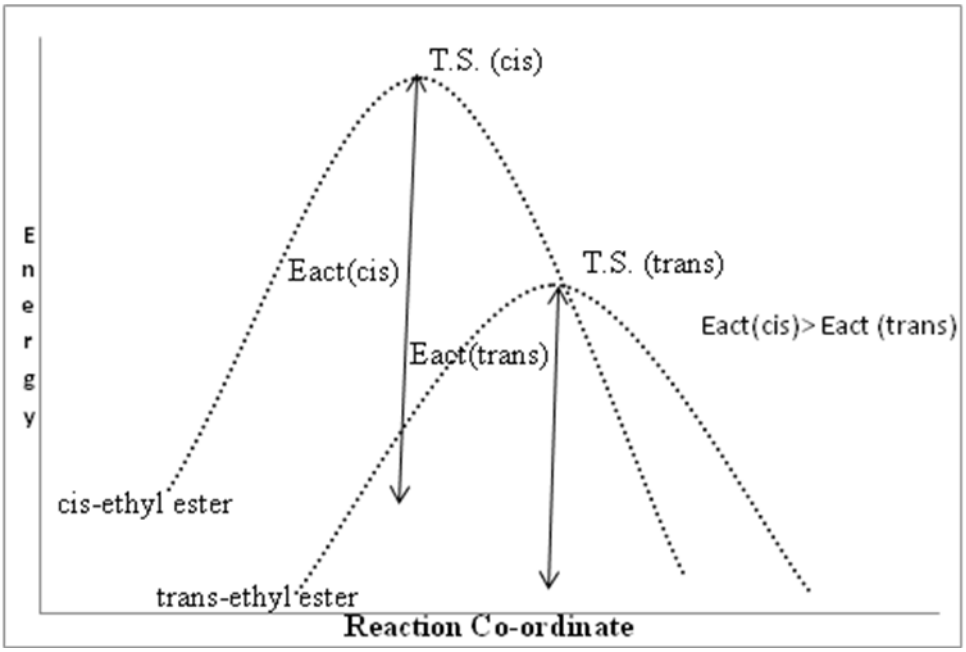
Ethyl (cis-4-t-butylcyclohexane) carboxylate



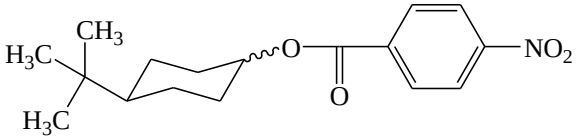
Ethyl (trans-4-t-butylcyclohexane) carboxylate



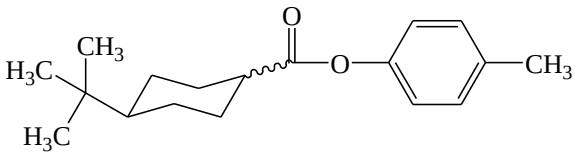




8. Explain this ratio of base catalysed ester hydrolysis between cis and trans isomer of two different compound.



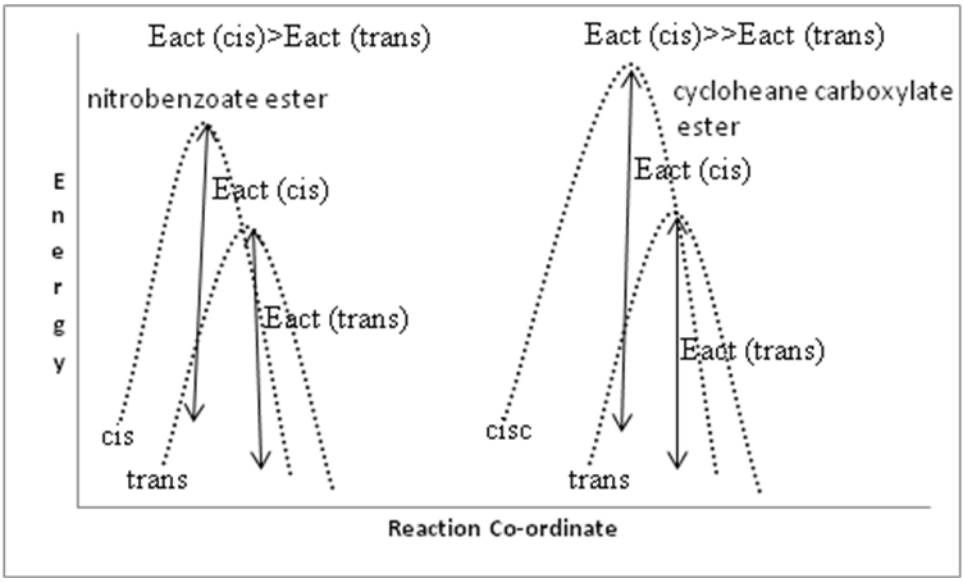
Rate of hydrolysis (k_{trans}/k_{cis})=2.25



Rate of hydrolysis (k_{trans}/k_{cis})=20

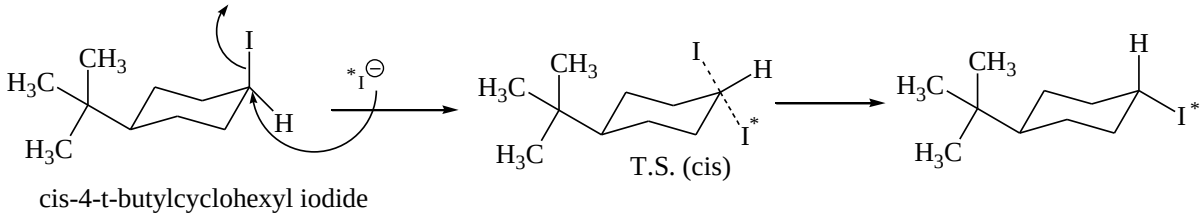
In first example the substrate ester is formed by acid of *para*-nitrobenzoic acid and substituted cyclohexanol. This implies that the carbonyl centre is apart from the cyclohexane system by a oxygen atom. So during base catalysed hydrolysis the more crowded tetrahedral T.S. formed is located somehow apart by an oxygen atom from cyclohexane system and hence relative diaxial interaction which will be experienced by axial ester isomer will be not that much effective to increase the activation energy. This phenonomenon explain only 2.25 times increased ester hydrolysis rate for the trans isomer over cis.

On the other hand in second compound the ester is being formed by substituted cyclohexane carboxylic acid and para cresol and hence the carbonyl carbon is directly attached to cyclohexane ring. So during base catalysed hydrolysis the more crowded tetrahedral type T.S. formed is very close to the cyclohexane ring and as a consequence for axial (cis) isomer during hydrolysis the energy of T.S. increases tremendously. Thus the reaction rate slows a lot and hence reaction rate ration of trans isomer increases dramtically over cis isomer.

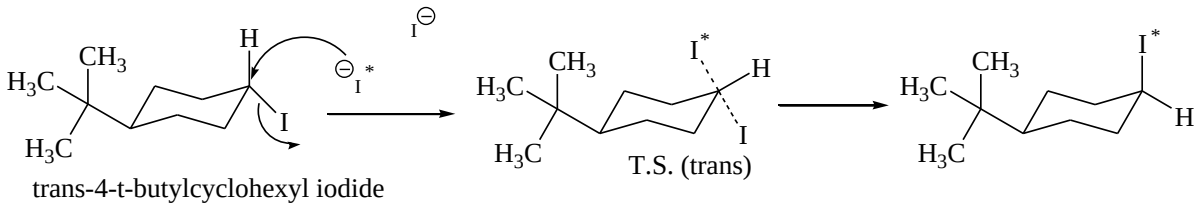


9. Compare the rate of substitution reaction by $^{125}I^-$ with cis and trans isomer of 4-t-butylcyclohexyl iodide.

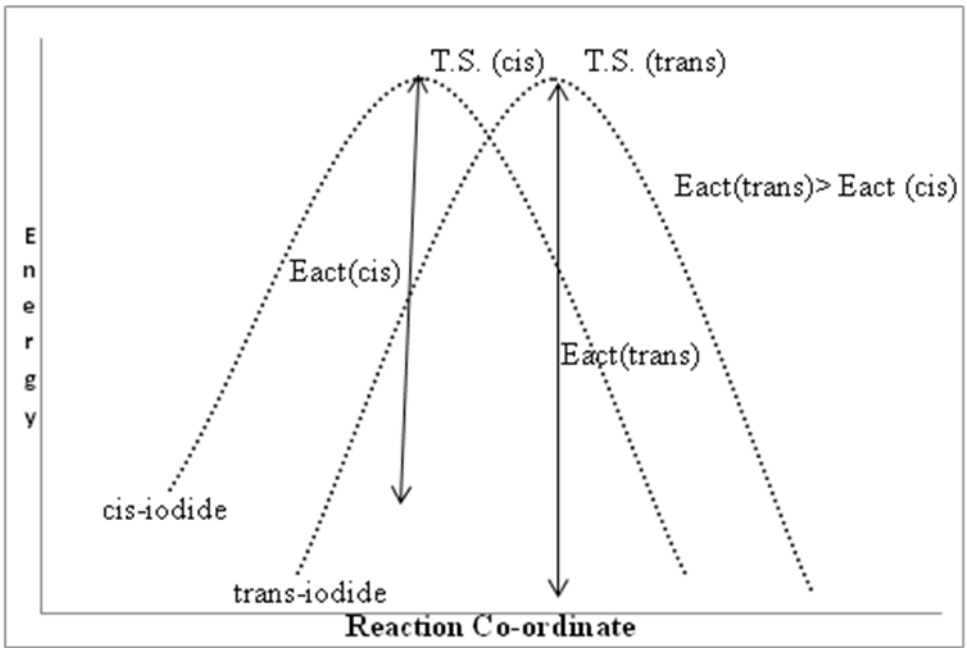
In this case the nucleophile and the leaving group is same and hence the T.S. will be identical for both cis and trans isomer which indicate that the energy of the T.S. is same for both isomer. Actually in a typical S_N2 reaction in a cyclohexane system when the leaving group is at equatorial position, nucleophile attacks from axial side and vive versa. Here the energy of the cis isomer where large iodide group is at axial position is high compared to the trans isomer due to 1,3 di-axial interaction. So the effective activation energy for cis isomer will be less than the trans isomer and hence cis isomer will react at faster rate compared to the trans isomer.



cis-4-t-butylcyclohexyl iodide



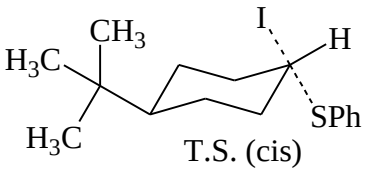
trans-4-t-butylcyclohexyl iodide



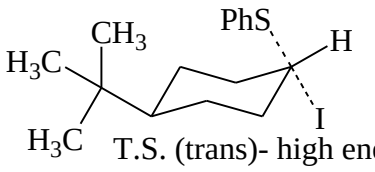
10. Compare the rate of substitution reaction of cis and trans isomer of 4-t-butylcyclohexyl bromide with sodium thiophenoxide.

In this case the size of the nucleophile ($^-$SPh) is greater than the leaving group (Br^-). So during substitution reaction the axial approach of the nucleophile will be of higher activation

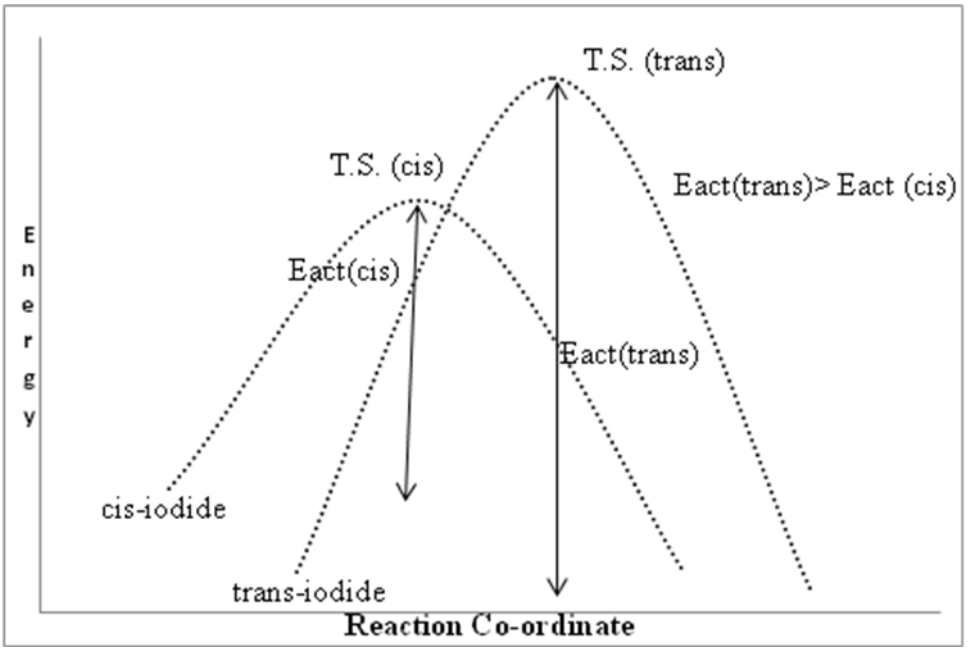
energy as larger nucleophile will experience much 1,3-di-axial interaction. This happen for a trans isomer where leaving group is at equatorial position. Now if we compare the energy of reactant, obviously the energy of cis isomer will be larger than the trans isomer. All these phenomenon tells that the effective activation energy for cis isomer is less compared to the trans isomer and hence the reaction rate is much more.



T.S. (cis)

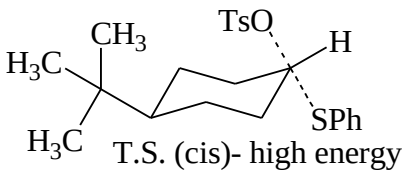


T.S. (trans)- high energy

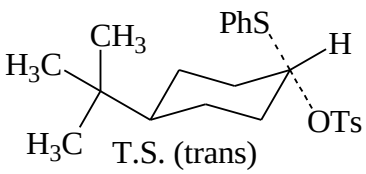


11. Compare the rate of substitution reaction of 4-t-butylcyclohexyl tosylate with sodium thiophenoxide.

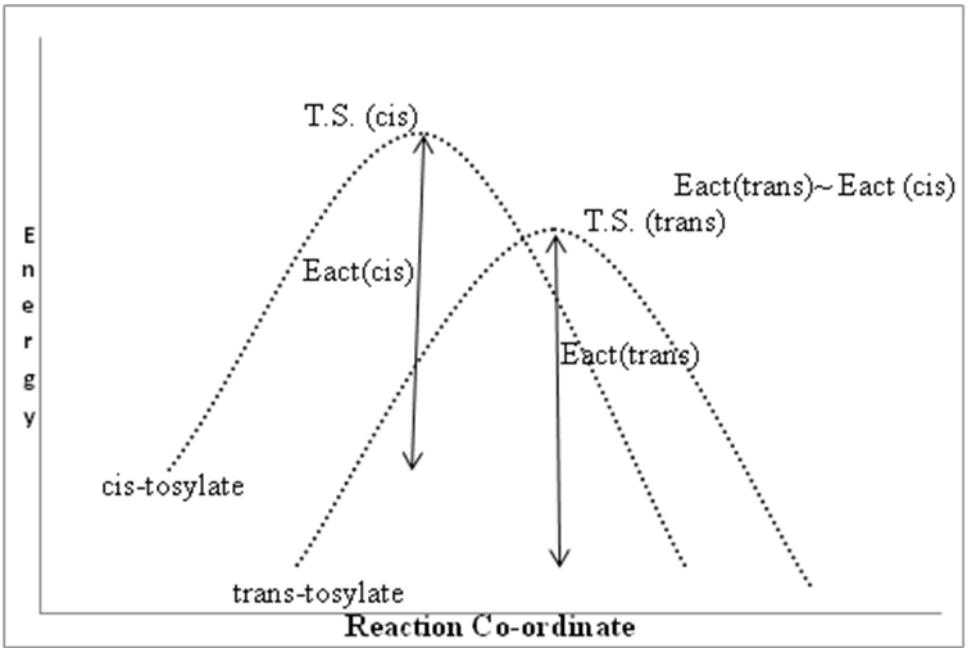
In this case the size of nucleophile ($^{-}$SPh) is smaller than the leaving group ($^{-}$OTs). So during substitution reaction the equatorial approach of the nucleophile will be of higher activation energy as larger leaving group will experience much 1,3-di-axial interaction. This happens for a cis isomer where leaving group is at axial position. Now if we compare the energy of reactant, obviously the energy of cis isomer will be larger than the trans isomer. These entire phenomenon tells that the effective activation energy for cis and trans isomer is comparable and hence the reaction rate is comparable.



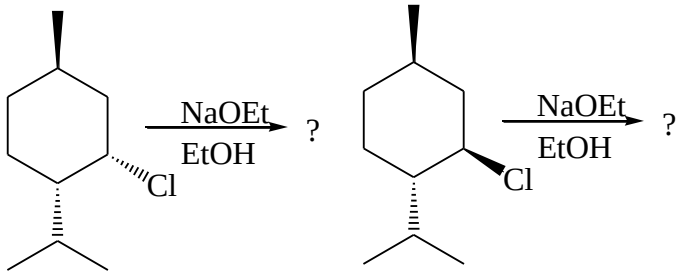
T.S. (cis)- high energy



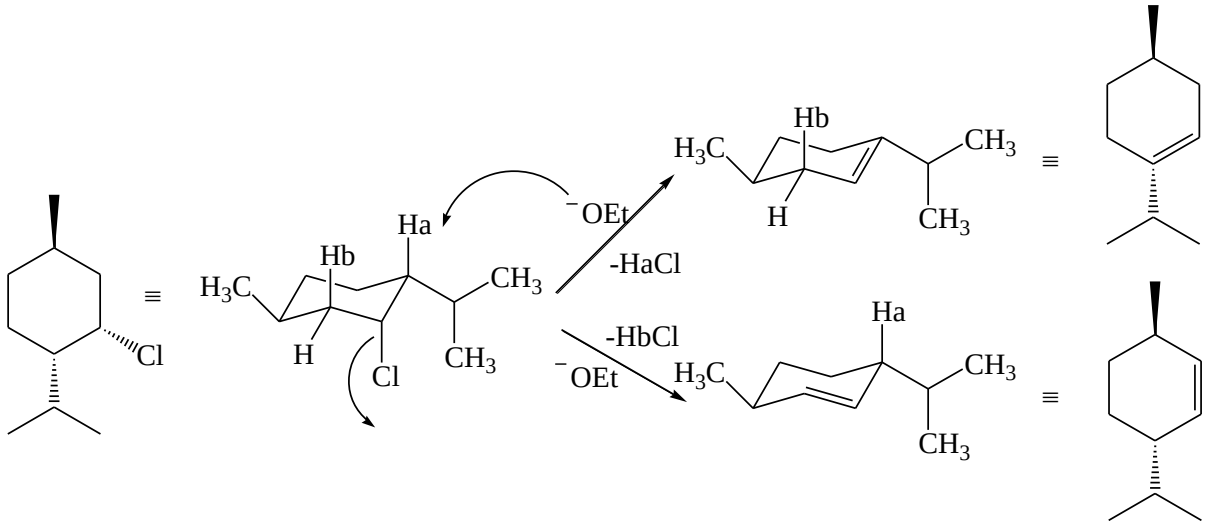
T.S. (trans)



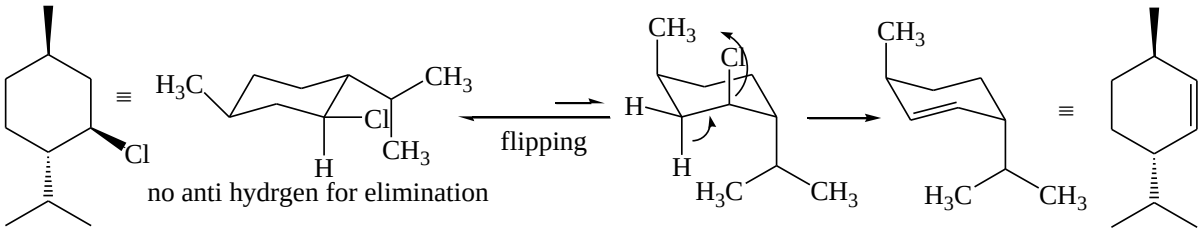
12. Predict the product of the following reaction-



This reaction is an example of 1,2-elimination reaction where abstracting hydrogen and the leaving group must be anti-periplaner to fulfil the condition of a typical E_2 reaction.



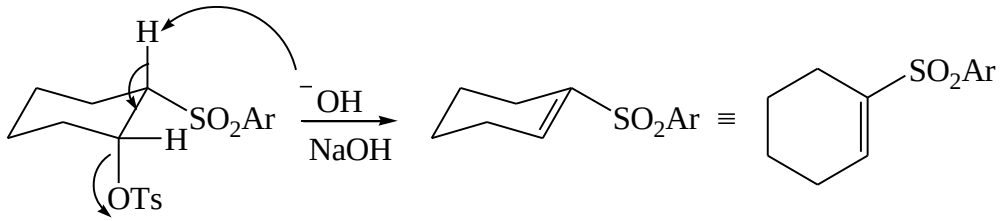
For this isomer there is two anti hydrogen present corresponding to the leaving group chlorine, so reaction can follow either route to give two different product.



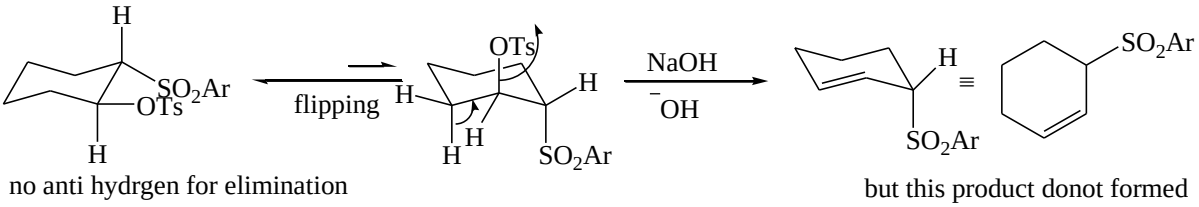
Whereas in this isomer there is no anti hydrogen for elimination but after flipping there is only one anti hydrogen for elimination and hence we get only one product. Point to note that although the fliiped conformer is very higher energy and hence % population is very less but once the reaction starts, equilibrium drives towards the product.

13. Explain what will happen when p-toluenesulphonates of cis and trans 2-p-toluenesulphonylcyclohexanol is reacted with NaOH?

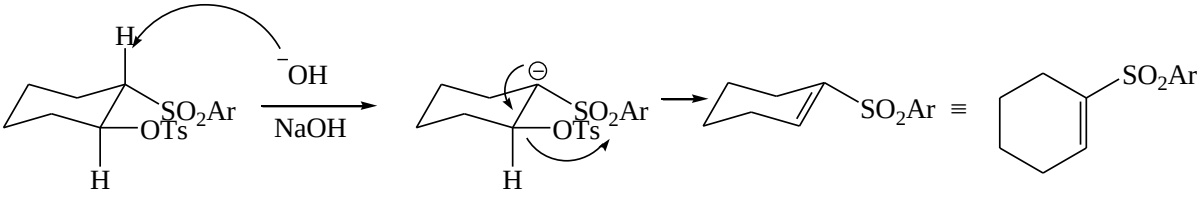
In cis isomer the leaving group tosyl and hydrogen atom is perfectly anti position for a E2 elimination and we got the desire product.



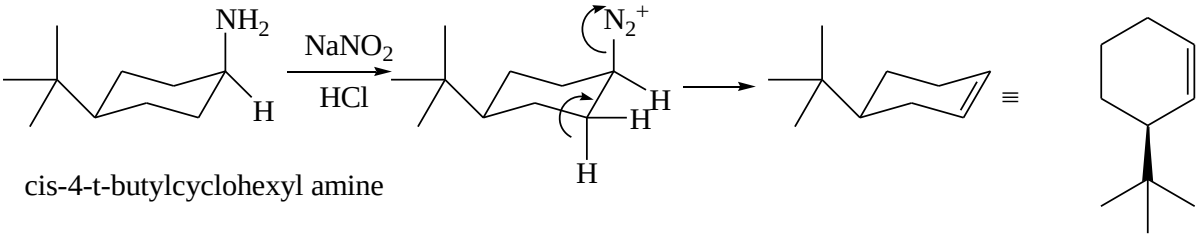
In trans isomer, there is no anti hydrogen for elimination but after flipping the flipped conformer have one anti hydrogen and we should expect this product which is different from previous product.



However in reality we do not get this product rather we get a similar product as obtained from cis isomer. Actually for the trans isomer the flipping does not happen as two bulky group cant be at axial position and hence the reaction follow a different mechanistic pathway. Due to presence of a strong electron withdrawing group $–SO_2Ar$, the reaction follows E_1CB mechanism.

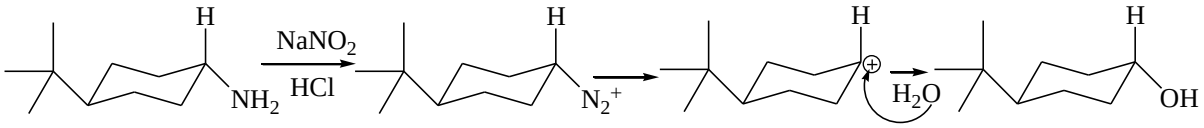


14. What will happen when cis and trans isomer of 4-t-butylcyclohexyl amine is treated with $NaNO_2$/HCl?



cis-4-t-butylcyclohexyl amine

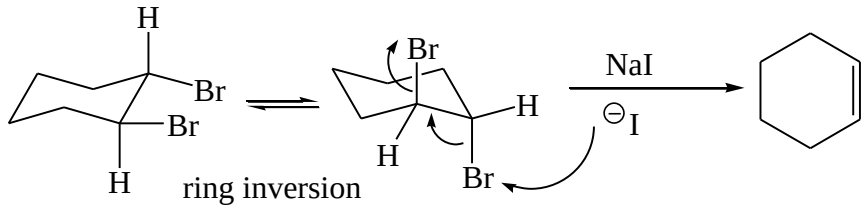
In this reaction the primary amine will react with sodium nitrite in presence of HCl to give $-N_2^+$ which is highly unstable. In case f cis isomer, the N_2^+ have a anti H to elimate and ultimately we got a alkene.



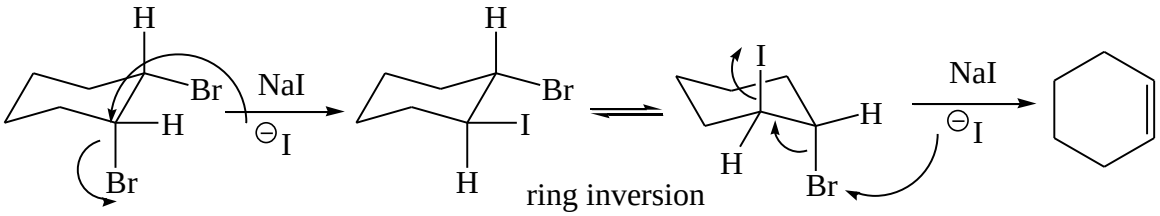
trans-4-t-butylcyclohexyl amine

But the trans isomer don't have any anti H corresponding to $-N_2^+$ group and hence we got a substitution product alcohol.

15. Compare the rate of reaction of cis and trans isomer of 1,2-dibromocyclohexane with NaI.



trans isomer



cis isomer

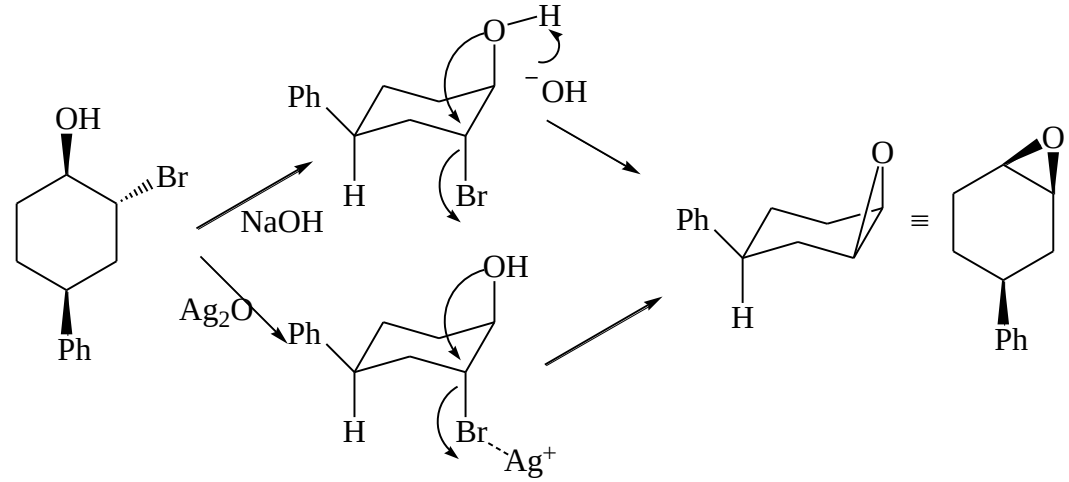
In both cases the product is same cyclohexene but the cis isomer react much more faster rate compared to trans isomer. In cis isomer first the nucleophile iodide replace axial bromide and

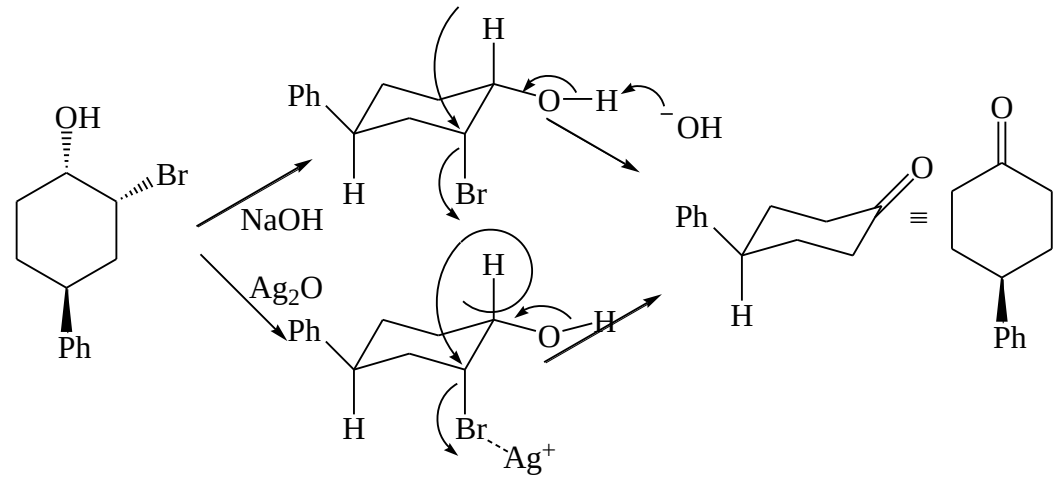
then a ring inversion followed by elimination gives cyclohexene. This is nucleophilic catalysis and hence reaction rate is high for a low activation energy.

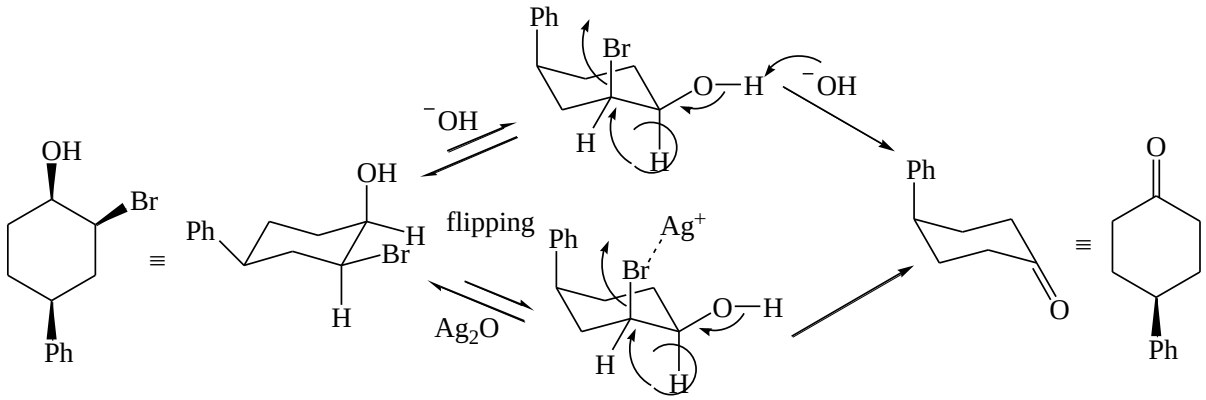
The diequatorial trans conformer after flipping take part in direct elimination reaction to form cyclohexene.

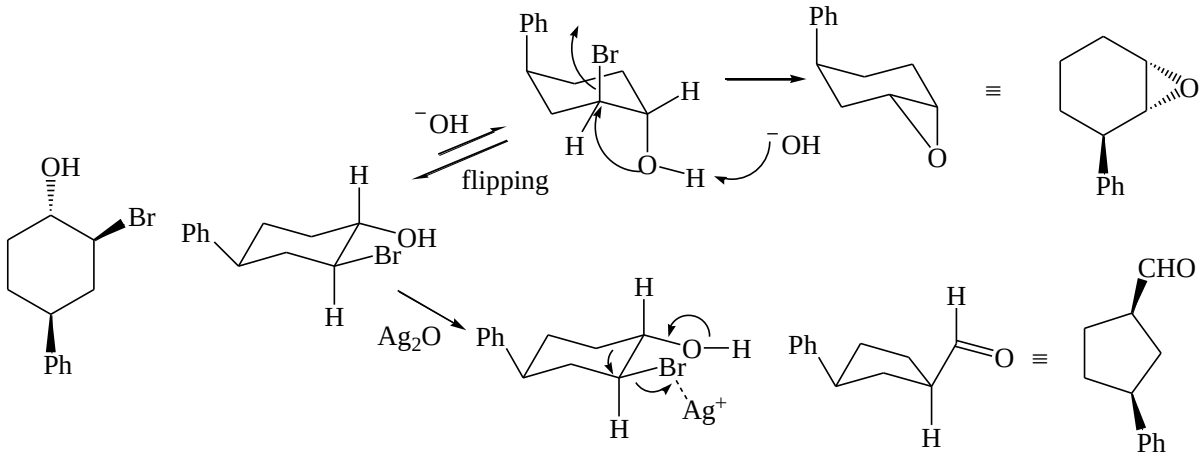
16. Explain the reaction of 2-bromo-4-phenylcyclohexanol with either NaOH or Ag_2O.

Let us see how different stereoisomer of the above compound behaves with either base or silver oxide.



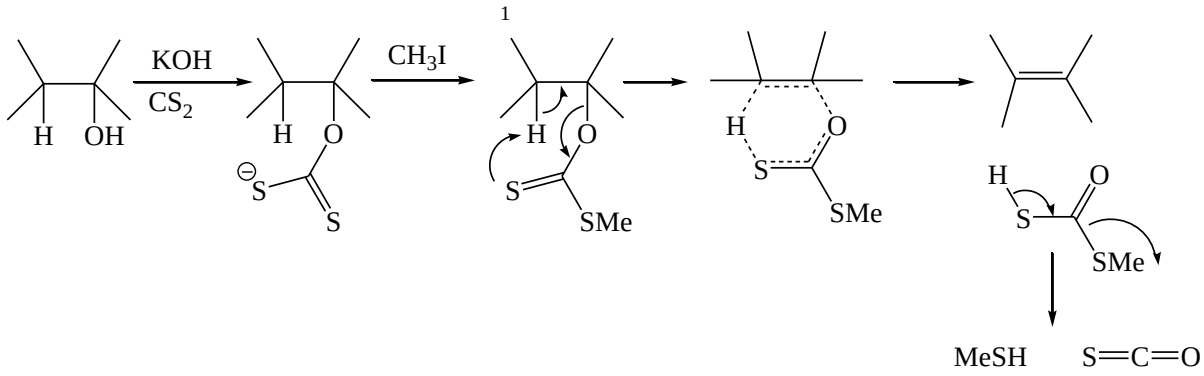


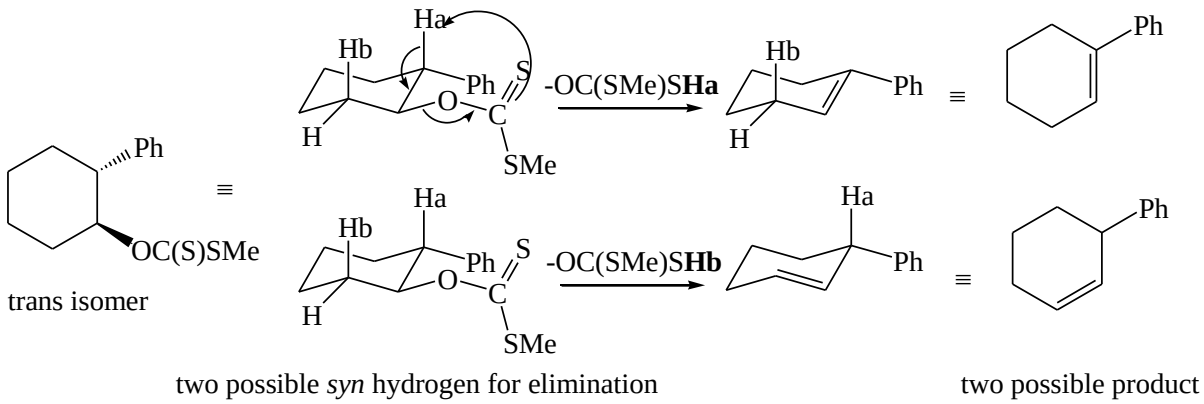




17. Explain the reaction with product-

These two compounds are in xanthate class and hence upon heating they will follow pyrolytic elimination to give alkene. This reaction is a syn elimination where a syn hydrogen at beta position with respect to the xanthate group is necessary to fulfil the mechanism of the reaction. A general mechanism is as –

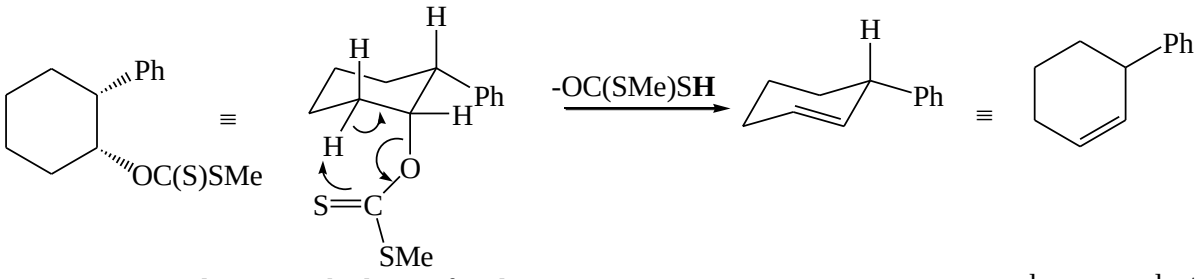




two possible *syn* hydrogen for elimination

two possible product

In case of trans isomer (e,e conformer), there is two possible syn hydrogen present with respect to the xanthate group and hence elimination could take part with either hydrogen to give rise two different product.

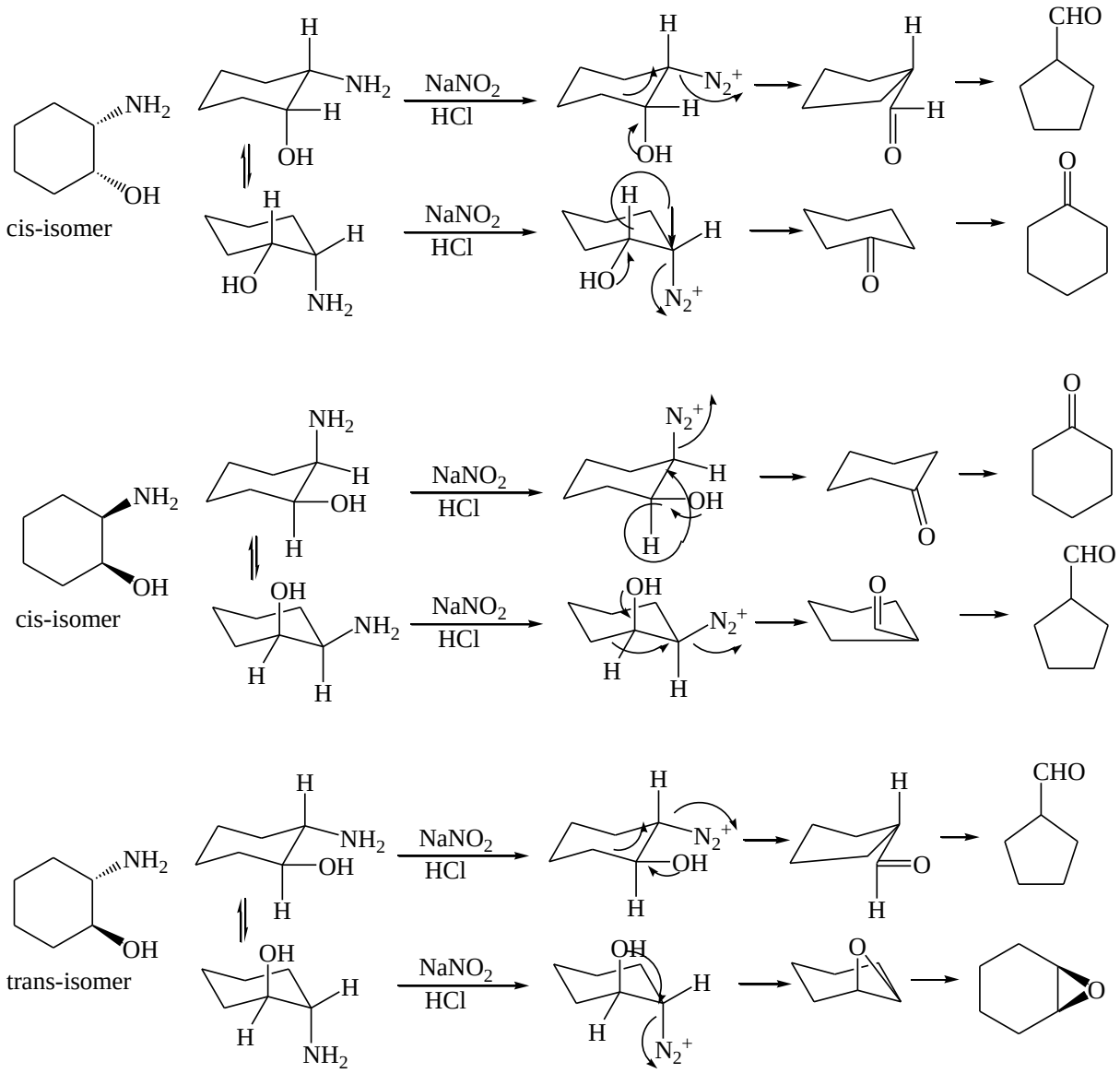


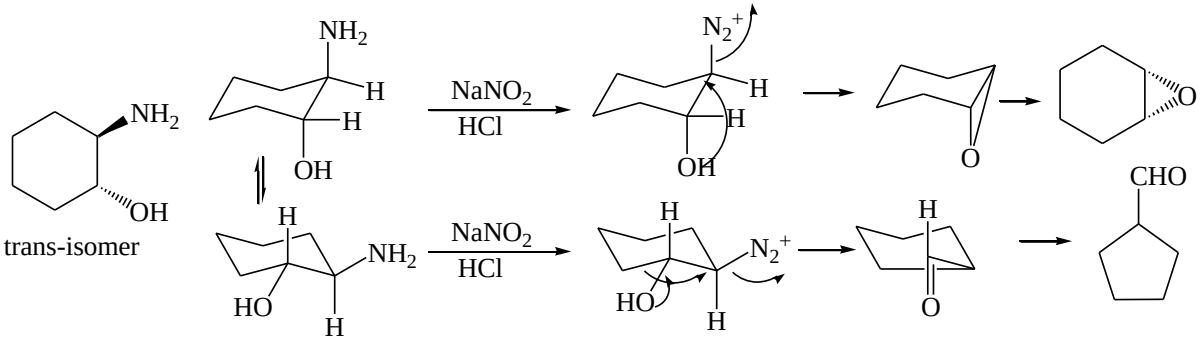
only one *syn* hydrogen for elimination

only one product

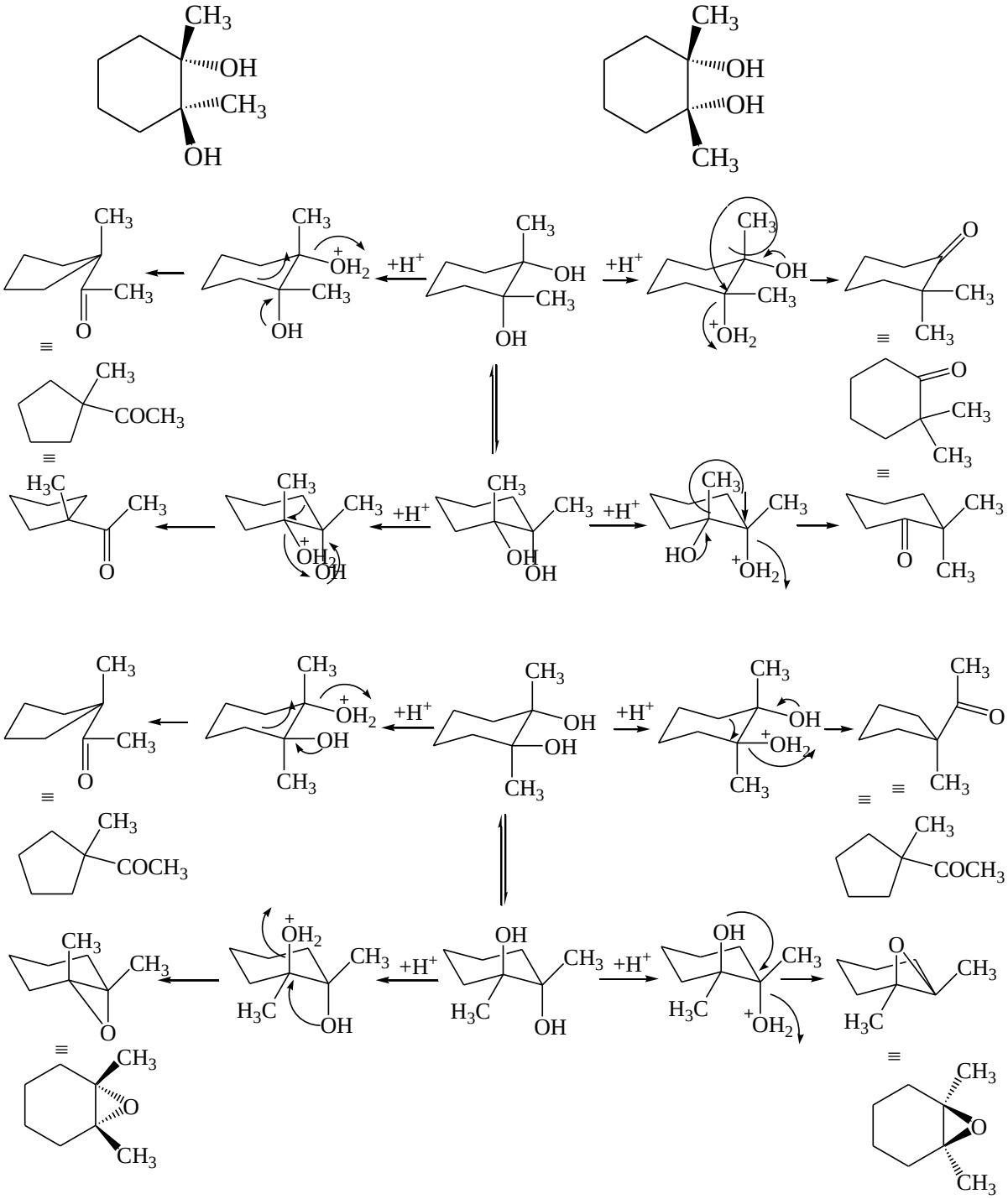
Whereas in cis isomer there is only one syn hydrogen with respect to the xanthate group and hence only one product we got by elimination.

18. Predict the products that will be formed when different isomers of 2-aminocyclohexanol will react with $NaNO_2$ and HCl?

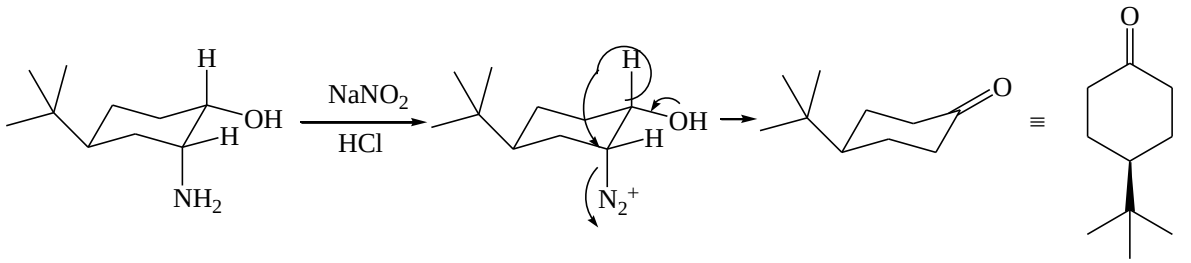


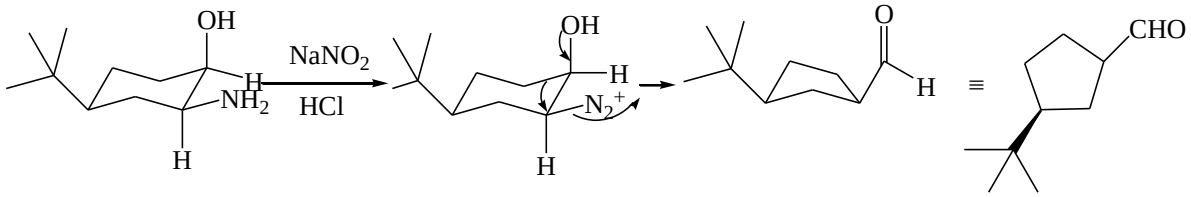


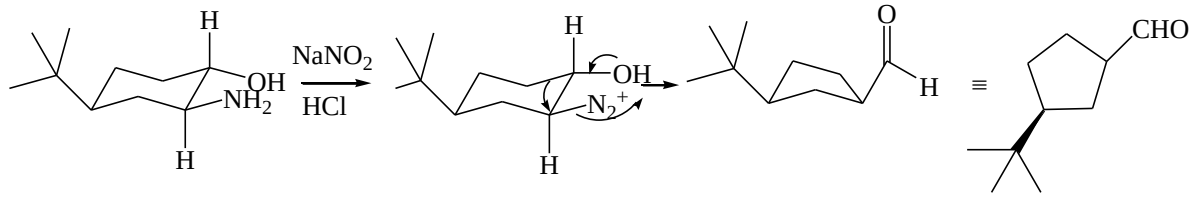
19. Predict the products when different isomers of 1,2-dimethylcyclohexane-1,2-diol reacted with 60% H_2SO_4?

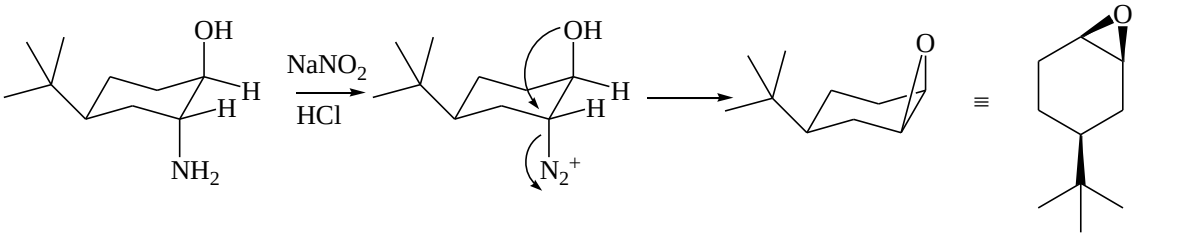


20. Predict the product of the following reaction-

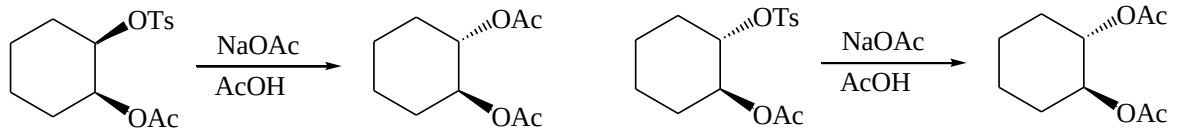






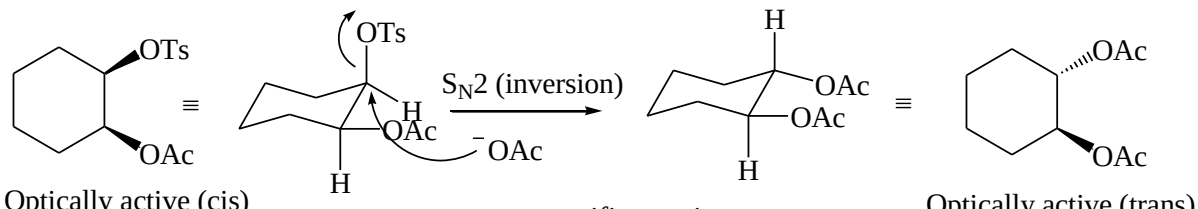


21. Explain the observation of these reaction-



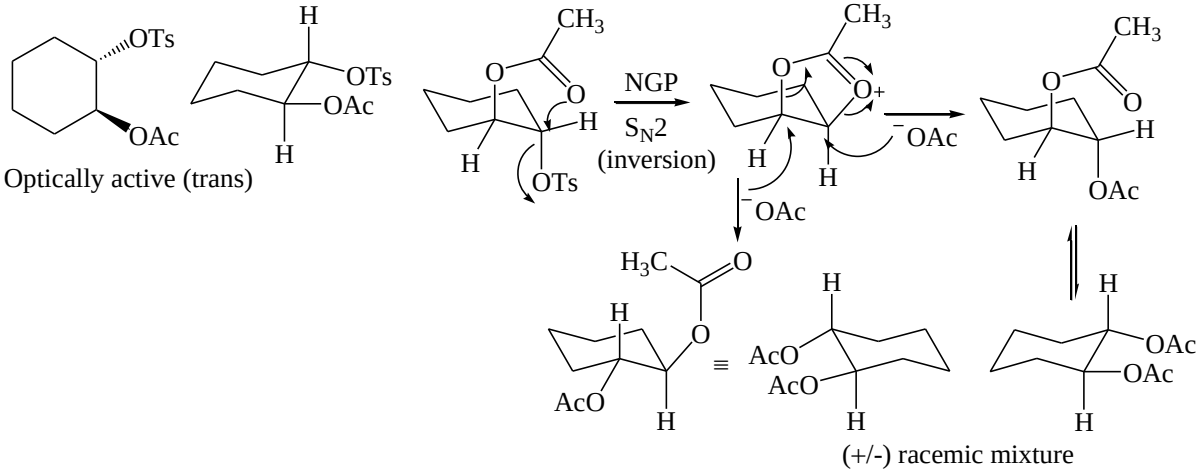
Optically active (cis) Optically active (trans) Optically active (trans) (+/-) racemic mixture

This reaction is a example of substitution reaction where in first example (cis isomer) a direct SN2 reaction happen by $^{-}$OAc nucleophile and tsylate acts as a leaving group. A direct inversion of an optically active compound leads to an optically active product (stereospecific reaction).

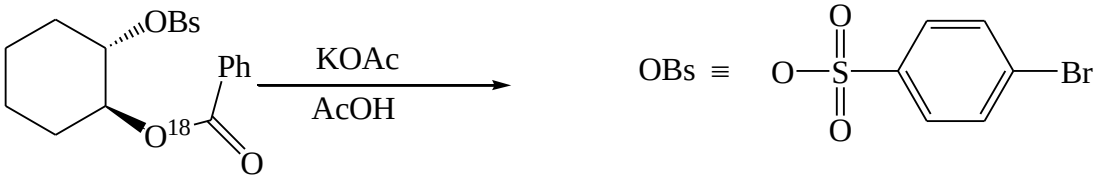


Optically active (cis) stereospecific reaction Optically active (trans)

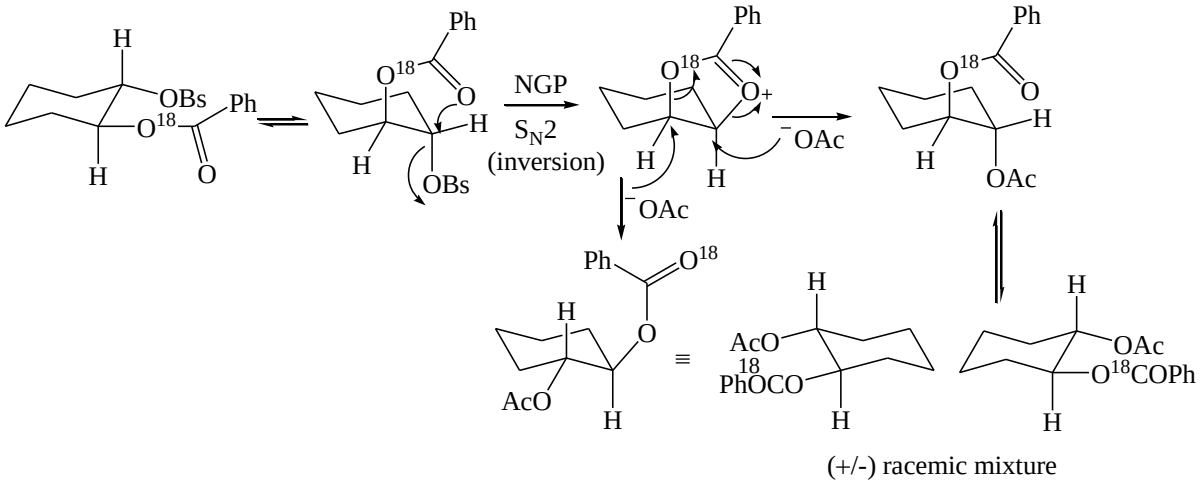
In case of the trans isomer, the ee conformer flipped to aa conformer and geometrically acetyl group is perfectly aligned to take part in a SN2 reaction from back side of tosyl group which is known as neighbouring group participation. In second step outside nucleophile $^{-}$OAc can attack on any carbon in a SN2 manner to give a racemic mixture.



22. Predict the product f the following reaction?

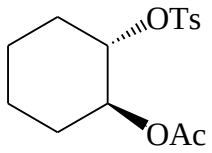


This is a substitution where brosylate group will be replaced by acetyl group. Here NGP will also take place followed by attack by acetate group. Here as one oxygen is lebbeled, final distribution of the lebelled oxygen will be like this. Obviously we will get a racemic mixture but scrambling lebelled oxygen will take place. This is an evendence in favour of NGP.



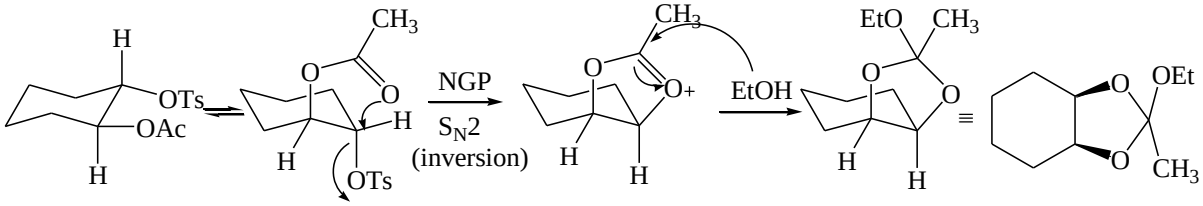
23. What is the proof of NGP?

Let us take a trans isomer like this and perform acetolysis in presence of ethanol and we got this product which clearly indicates the NGP mechanism.

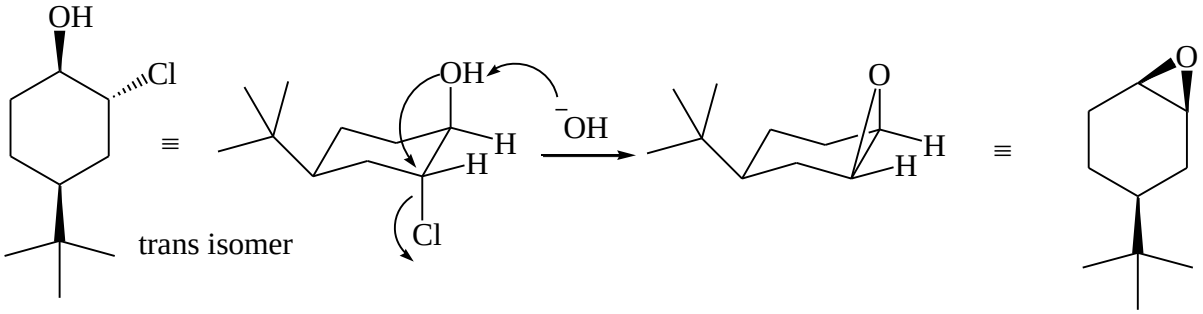


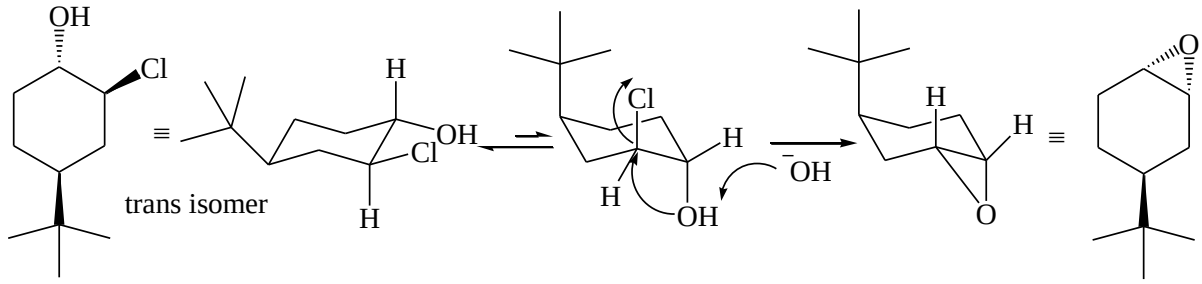
Optically active (trans)

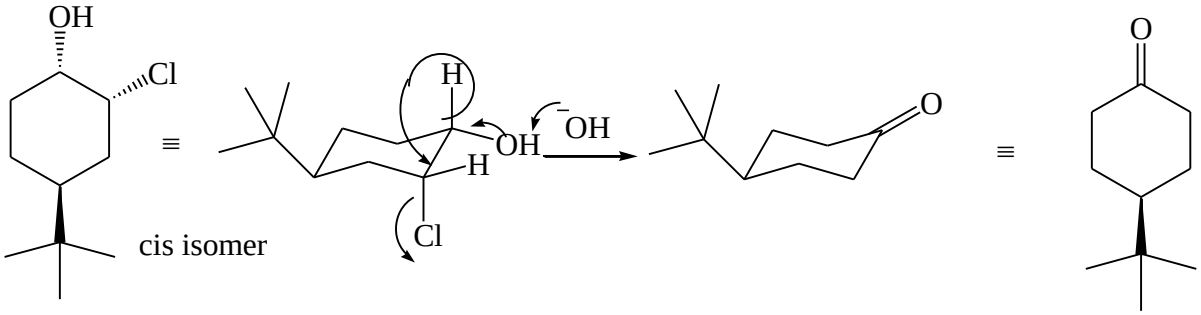
Optically active (trans)



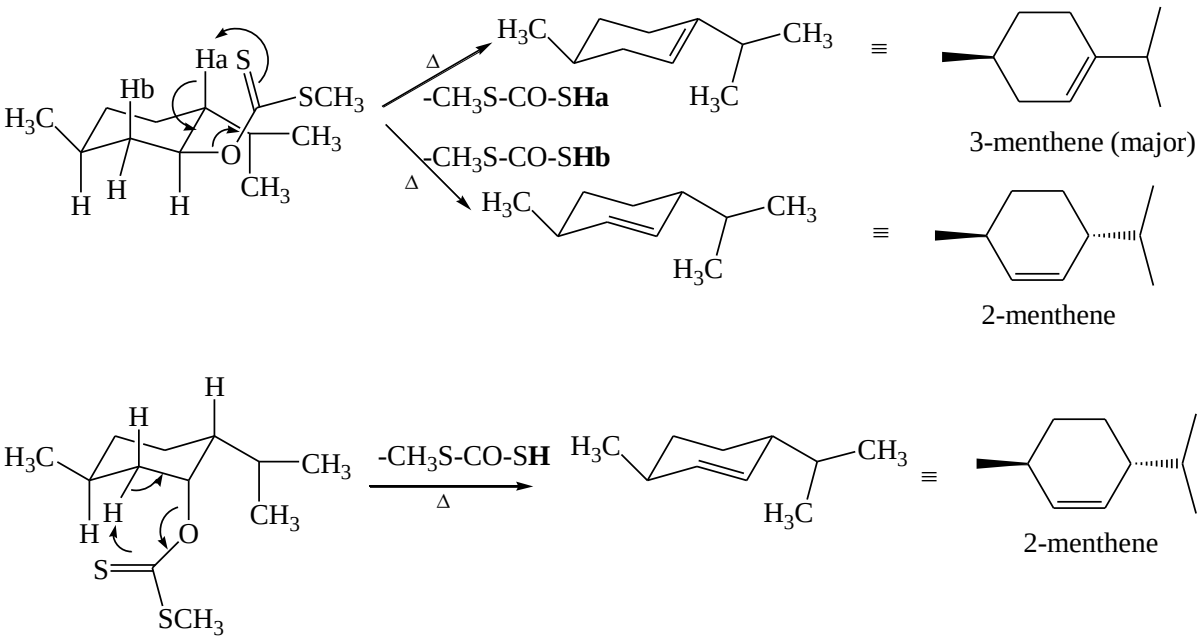
24. Predict the product of the following reaction-







25. Predict the product of the following reaction-



26. Predict the product of the following reaction-