CYCLIC STEREOCHEMISTRY

SEM-5, CC-12
PART-8, PPT-8

Part-8: Conformation and Reactivity in Cyclohexane-I

CONTENTS

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Cyclic Stereochemistry (PART-8, PPT-8)

Conformation and Reactivity in Cyclohexane-I

It is usually observed that the *equatorially* substituted cyclohexanes are more stable than the *axially* substituted cyclohexanes. Conformational analysis (Barton, 1950) concerns the effects of conformation on chemical reactivity. In simple cyclohexane derivatives most of the reactions may be assumed to involve a single *chair* conformation, provided the inversion of one *chair* form to another is restricted by introducing sufficiently bulky substituent like *t*-butyl group in suitable position.

It is convenient to divide these effects into two kinds, steric and stereoelectronic effects (even though it is realized that all chemical effects ultimately relate mainly to bonding and nonbonding electrons. The main contributors to steric, or van der Waals, effects are the electron clouds of nonbonding atoms).

By "steric effects" is meant the effects due to close approach of two groups in a molecule (or between molecules) such that appreciable van der Waals forces (either attractive, at relative long distances, or repulsive, at short distances) are called into play. Such effects may occur in the *ground state* of a molecule, or in the *transition state* for a given reaction, or both.

The van der Waals interactions can be attractive but its effect is quite small and depends largely on the separating distance between the interacting groups. The van der Waals repulsive interactions, however, can become quite large if the nonbonded distances are sufficiently short. The attractive potential is always quite small, whereas the repulsive potential can become quite large if the nonbonded distances are sufficiently short.

Steric effects can accelerate or retarded reaction rates. When the rate of a reaction is slowed down due to steric effects then it is called *steric hindrance*. In this case, repulsion effect is enhanced more in *transition state (or intermediate)* than the *ground state*. The free energy of activation in this situation is increased because the energy level of the *transition state* is more elevated than that of the *ground state* compared to the reference case. Consequently, the rate of the reaction is slowed down.

In many other cases, steric effects can accelerate the reaction rate. In this situation, the energy level of the *ground state* is elevated more than that of the *transition state* compared to the reference case. The Phenomenon is termed *steric assistance*. These two kinds of situations, *steric hindrance* and *steric assistance*, are depicted in Figure 1.

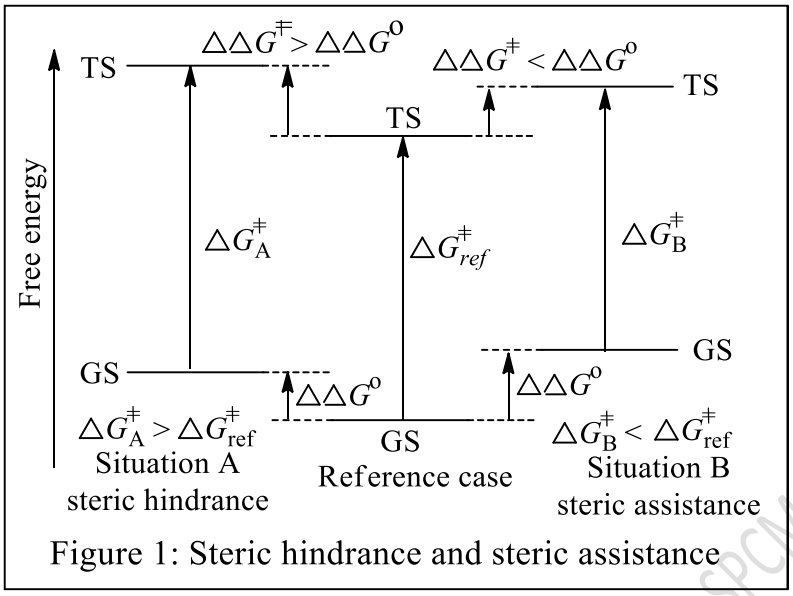

Figure 1: Steric hindrance and steric assistance

In the first, more familiar situation A, the repulsion is substantial in the *transition state* (TS) and small or absent in the *ground state* (GS). Compared to a reference case, the activation energy in this situation is increased ($\Delta G^{\neq}_A > \Delta G^{\neq}_{ref}$), because the energy level of the *transition state* is elevated more than that of the *ground state*. Consequently, the reaction that follows the situation A in the energy diagram (Figure 1) is slowed down relative to the reference case. This situation is termed one of "steric hindrance." This is very familiar situation in many reactions including reactions in cyclohexanes.

In the other situation B, the steric repulsion is more important in the *ground state* than in the *transition state*. As a result, the energy level of the *ground state* is elevated more than that of the *transition state*; thus, the activation energy for the reaction is decreased ($\Delta G^{\neq}_B < \Delta G^{\neq}_{ref}$) and the reaction is accelerated relative to the reference case. This situation is called one of "steric assistance". *Other factors, such as, torsional strain, electrostatic interactions, H-bonding, etc., also depend very much on the steric disposition of atoms and groups concerned and may be considered along with the steric factor.*

Stereoelectronic Effects

Deslongchamps (1983) defines stereoelectronic effects as effects on reactivity of the spatial disposition of particular electron pairs, bonded or nonbonded. In many cases, these are electron pairs in bonds that are formed, broken, or otherwise dislocated in the reaction under investigation. In other cases, they are unshared electrons on exocyclic or endocyclic hetero atoms.

The stereoelectronic effects manifest themselves in the form of certain stereoelectronic requirements which must be fulfilled before the reaction can take place. The stereoelectronic effects, like steric effects, also operate in the *ground state* affecting the thermodynamic stability of the products. These effects are very much pronounced in S_N2 (Substitution

Nucleophilic Bimolecular) displacement reactions and E2 (Elimination Bimolecular) reactions.

Saponification of *Anancomeric* Ethyl 4-*t*-butylclohexanecarboxylates

The Saponification rate of the *anancomeric cis*- ethyl 4-*tert*-butylcyclohexanecarboxylate (*axial*-CO_2Et; A) is about 20 times less than that of the *trans*- (*equatorial*-CO_2Et; B) isomer. The saponification rate for the unsubstituted, conformationally heterogeneous compound C is intermediate (Figure 2).

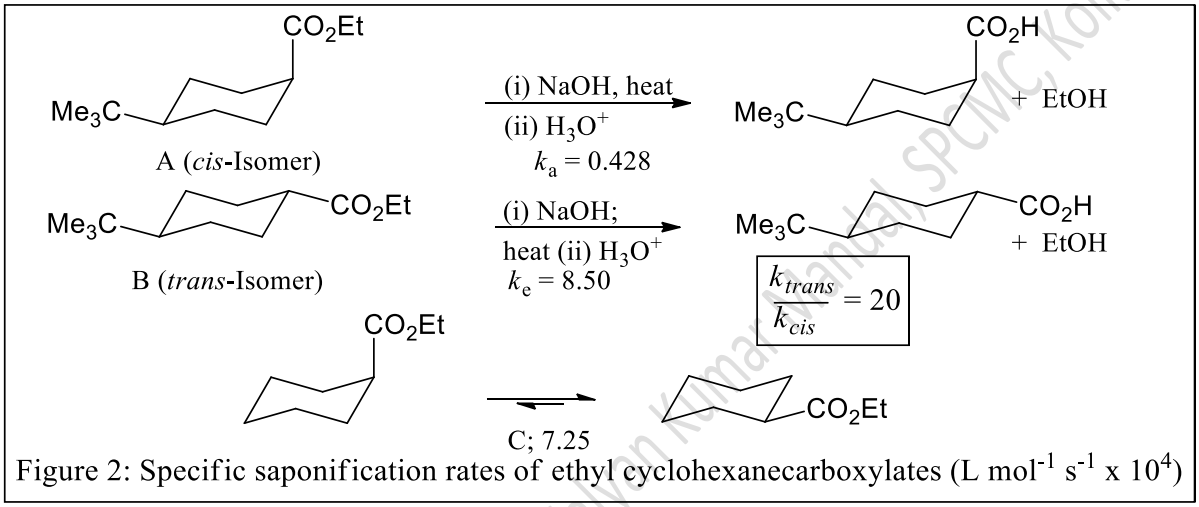

Figure 2: Specific saponification rates of ethyl cyclohexanecarboxylates (L mol^{-1} s^{-1} x 10^4)

Saponification of *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylates (Figure 3) illustrates steric hindrance/steric retardation. This reaction involves the formation of a tetrahedral intermediate. The carbonyl group in the ground state is sp^2 hybridized and the *rate-determining transition state*, in which an HO^- moiety becomes attached to the CO_2Et group, is sp^3 hybridized. Conformational energies of sp^3 hybridised groups are generally larger than those of sp^2 hybridized ones. The latter (in contrast to the former) can escape crowding by turning their flat sides to the ring. In the present case there is an additional factor that the *ground state* is neutral but the *transition state* is negatively charged, and therefore more solvated.

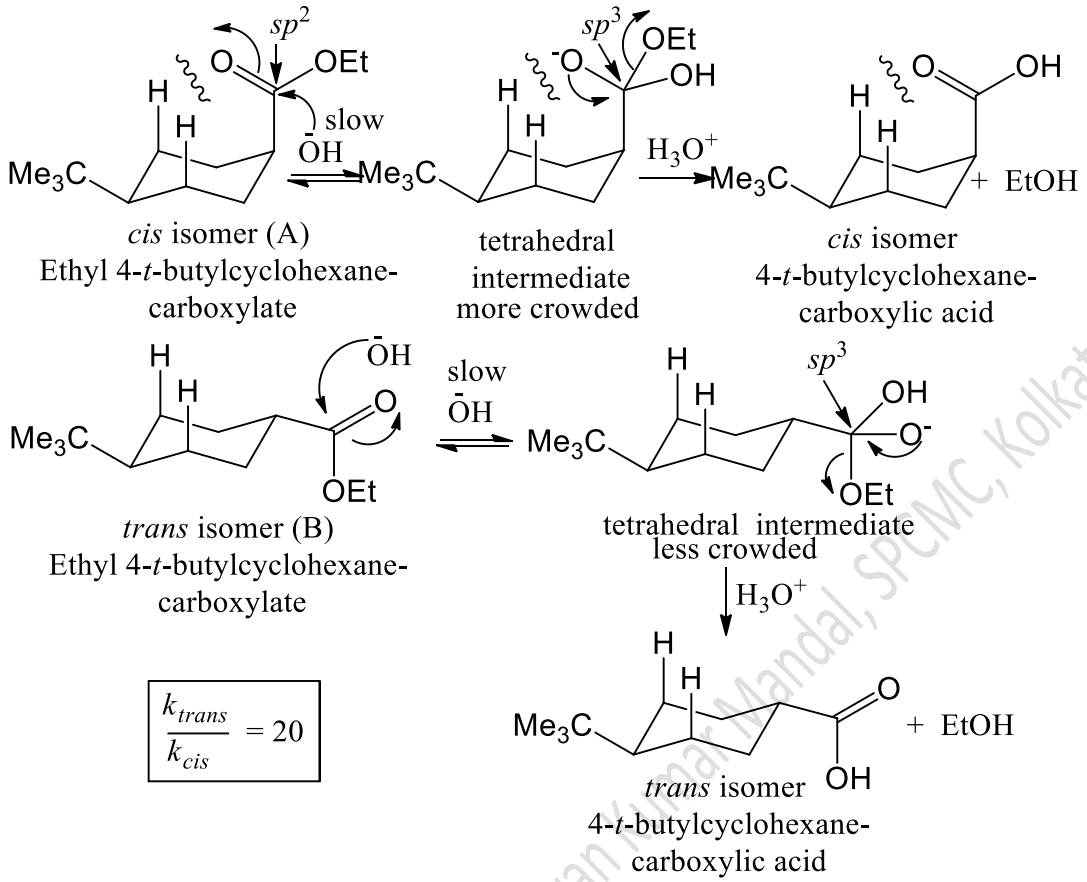

Figure 3: $B_{Ac}2$ mechanism for saponification of an ester

The conformational energies (in kcal mol^{-1}) of CO_2H, CO_2^- and CO_2Et groups are 1.4, 2.0 and 1.2, respectively. Solvation, therefore, leads to an additional bias against the *axial* position. In the *cis*-isomer, -CO_2Et group is *axial*, and suffers unfavourable *gauche-butane* interaction. Therefore, the energy levels of both the *ground state* and the *transition state* are elevated more than that of the *trans*-isomer as in the latter -CO_2Et group is *equatorial*.

Again, in case of the *cis*-compound, elevation of the energy level of the *transition state* is even more than that of the *trans*-compound as the intermediates contain bulkier groups (sp^3 hybridised groups) which is *axial* in the *cis*-compound. The group, -C(OH)(OEt)O-, is more solvated than the neutral -CO_2Et and consequently steric hindrance (*gauche-butane* as well as *syn-diaxial* interactions) is further enhanced in the *cis*-isomer (A) than that in the *trans*-isomer (B).

Therefore, the activation energy for the reaction of *cis*-compound is higher than that of the *trans*-compound. Consequently, the saponification rate of the *anancomeric cis*-4-*tert*-butyl (*axial*-CO_2Et, A) isomer is slower and is about 20 times less than that of the *trans* (*equatorial*-CO_2Et, B) isomer. The effect on rate is less pronounced when the carboxyl substituent is in the alcohol part of the ester than when it is in the acid part. This is due to the fact that the site of crowding (carboxyl carbon of -CO_2R) is closer to the ring in the latter than in the former.

Saponification of *Anancomeric* 4-*t*-butylcyclohexyl Alkanoates

The difference in the rates of a reaction for an *axial* and an *equatorial* isomer is diminished as the site of crowding moves away from the ring. Thus, k_{trans}/k_{cis} for the saponification (Figure 4) of 4-*t*-butylcyclohexyl acetates in aqueous dioxane is 6.7 (in this case, C=O is one atom removed from C-1).

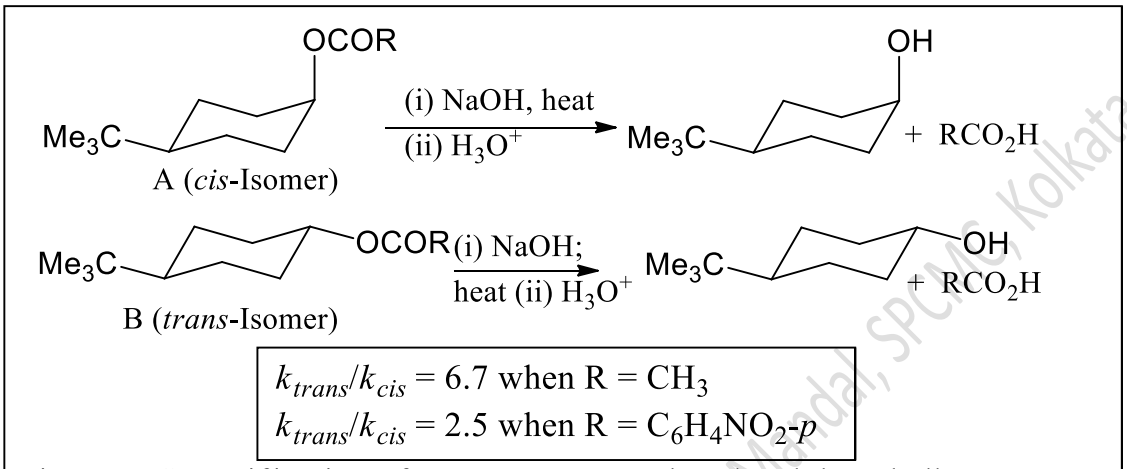

Figure 4: Saponification of *anancomeric* 4-*t*-butylcyclohexyl alkanoates

Saponification of *anancomeric cis*- and *trans* 4-(*tert*-butyl)cyclohexyl alkanoates (Figure 5), also, illustrates steric hindrance/steric retardation. In this case the ratio of the rates of hydrolysis (k_{trans}/k_{cis}) is found to be much less than the similar hydrolysis of 4-*t*-butylcyclohexanecarboxylates (k_{trans}/k_{cis} = 20). This is due to the fact that these are esters of cyclohexanols where the ester carbonyl is one bond further removed from the cyclohexane ring and steric hindrance has less effect on the reactivity. As the site of crowding (carboxyl carbon of -OCOR) is away from the ring, unfavourable repulsive interactions, such as, *gauche-butane*, *syn-diaxial* interactions are reduced.

Faster rate of hydrolysis of 4-(*tert*-butyl)cyclohexyl 4-nitrobenzoate than that of 4-(*tert*-butyl)cyclohexyl acetate is due to the fact that the former contains a better leaving group than the latter.

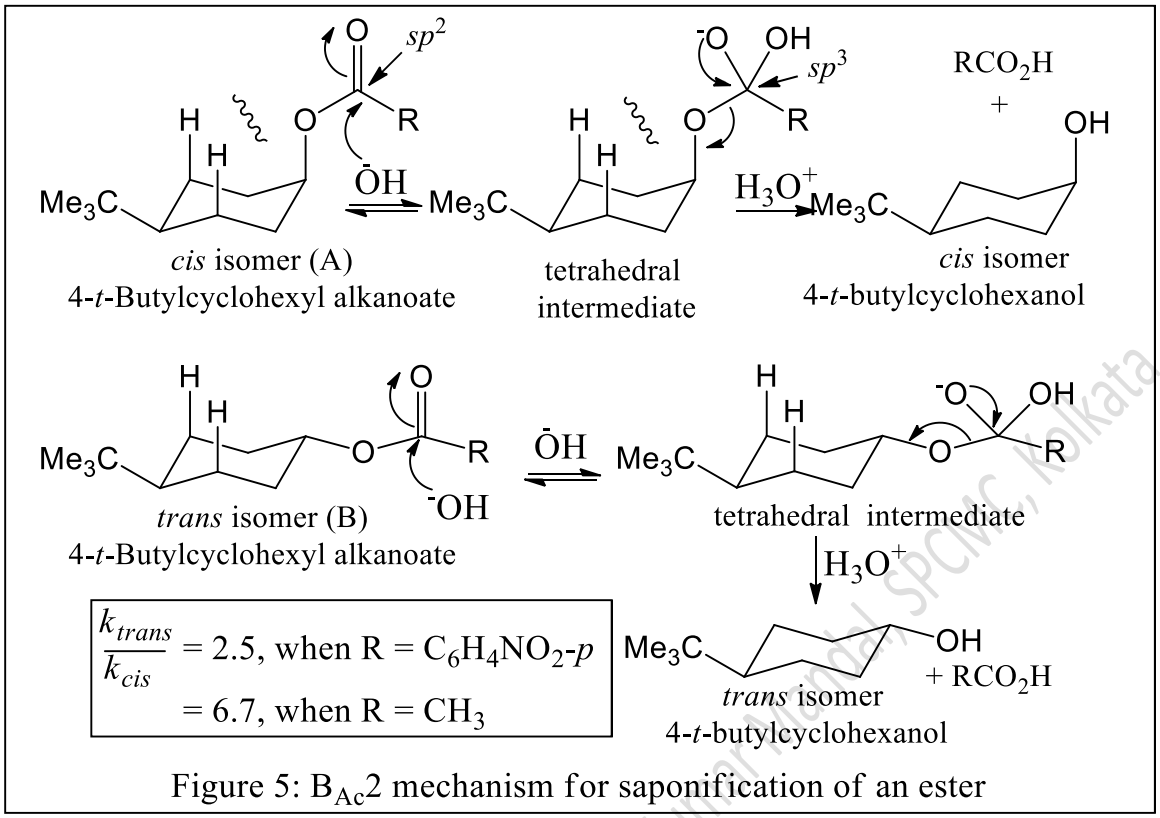

Figure 5: $B_{Ac}2$ mechanism for saponification of an ester

Esterification Reaction of Cyclohexane Carboxylic Acids

Esterification reaction is just the reverse process of ester hydrolysis. Therefore, the rates of esterification of *anancomeric axial* and *equatorial* cyclohexane carboxylic acids and cyclohexanols will exhibit the same differences as in the case of hydrolysis of esters. Thus, *trans*-4-*t*-butylcyclohexanecarboxylic acid will undergo esterification reaction at a much faster rate than *cis*-4-*t*-butylcyclohexanecarboxylic acid.

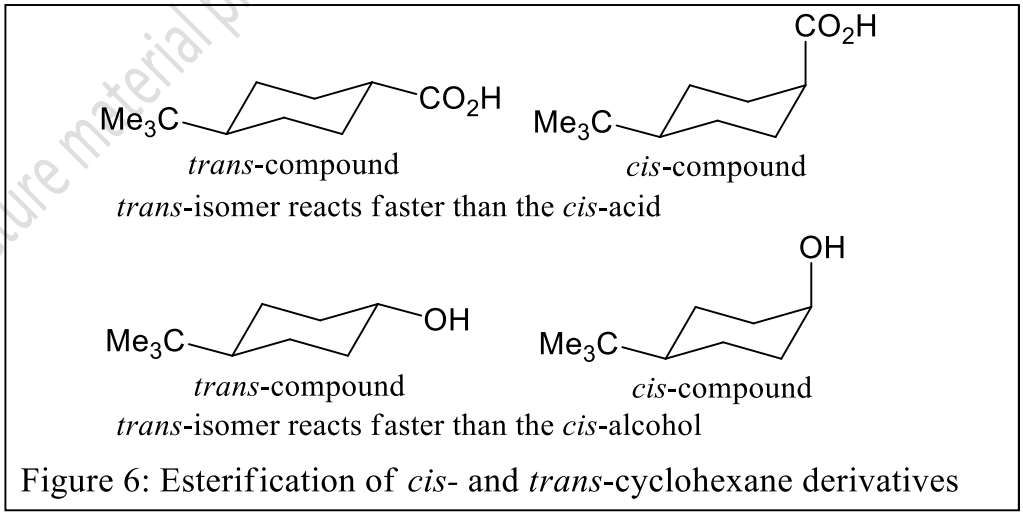

Figure 6: Esterification of *cis*- and *trans*-cyclohexane derivatives

Oxidation of *Anancomeric* Cyclohexanols

A case of *steric assistance/steric acceleration* involves rates of the oxidation of *anancomeric* cyclohexanols (shown in Figure 7). The rates of the oxidations parallel the degree of crowding of the hydroxyl group, or, more concisely, the degree of relief of strain that occurs when the sp^3 hybridized alcohol (or the corresponding chromate, which is an intermediate in the oxidation) is converted, in the *rate-determining step*, to the sp^2 hybridized ketone, with resulting relief of *syn-axial* strain.

The compound A (*cis*-4-*t*-butylcyclohexanol) reacts faster than B (*trans*-4-*t*-butylcyclohexanol) (relief of two *syn-axial* OH/H interactions); C also reacts faster than B (relief of a *syn-axial* CH_3/H interaction), and D reacts much faster than any of the others (relief of a severe CH_3/OH *syn-axial* interaction).

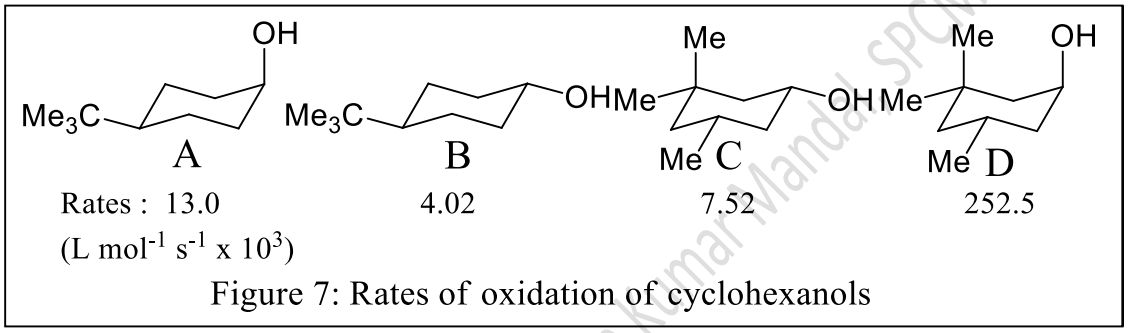

Figure 7: Rates of oxidation of cyclohexanols

The *cis*-4-*t*-butylcyclohexanol (A; *axial* hydroxyl group) is oxidized at 25°C more rapidly (3- to 4-times) than the *trans*-isomer (B) having *equatorial* hydroxyl group (Figure 8). This is a case of steric acceleration (mechanism shown in Figure 9).

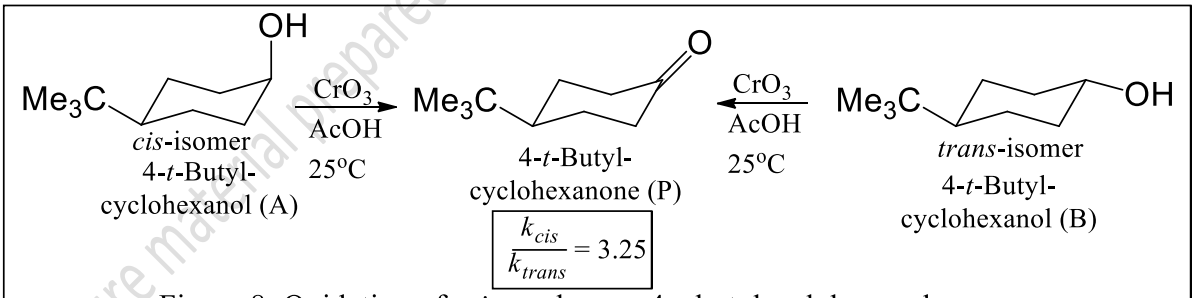

Figure 8: Oxidation of *cis*- and *trans*-4-*t*-butylcyclohexanols

Oxidation of *Anancomeric* 4-*t*-butylcyclohexanols

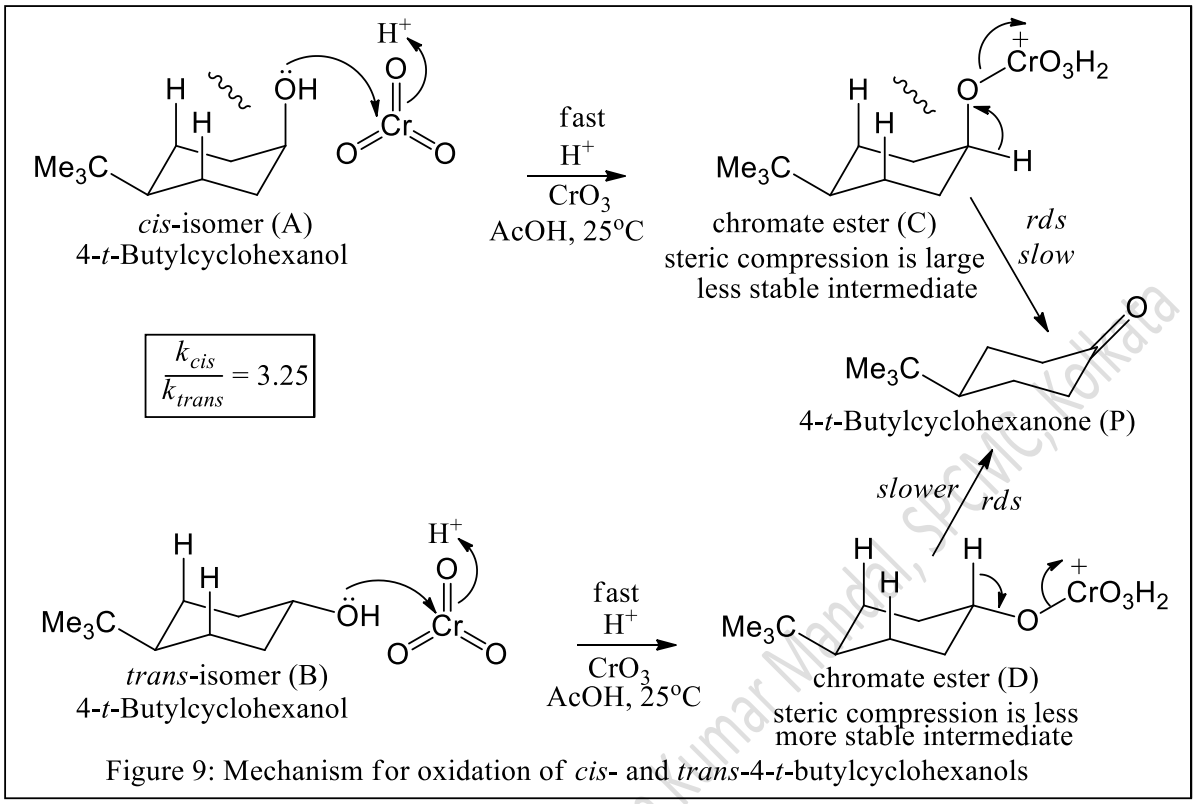

Figure 9: Mechanism for oxidation of *cis*- and *trans*-4-*t*-butylcyclohexanols

The *rate determining step* of the oxidation of cyclohexanols is the loss of H^+ from the rapidly formed chromate ester (C and D; Figure 9). The faster rate of oxidation of *axial* alcohol is due to the relief of steric strain in the *transition state* in the process of conversion of chromate ester to the product 4-*t*-butylcyclohexanone (P).

The difference of free energies between the *axial* and *equatorial* chromate esters in the *ground state* exceeds that between the respective *transition states* due to the more product-like (ketone) structure. The *transition states* involved in the conversion of chromate esters to the common product 4-*t*-butylcyclohexanone may be assumed to have approximately similar energies. As a result, the activation energy for the reaction is decreased ($\Delta G^{\neq}_c < \Delta G_t$) for the *cis-isomer* compared to that of the *trans-isomer* and the reaction is, therefore, accelerated for the *cis-isomer* relative to the *trans-isomer*. This is thus a case of "steric assistance". The energy diagram is shown in Figure 10.

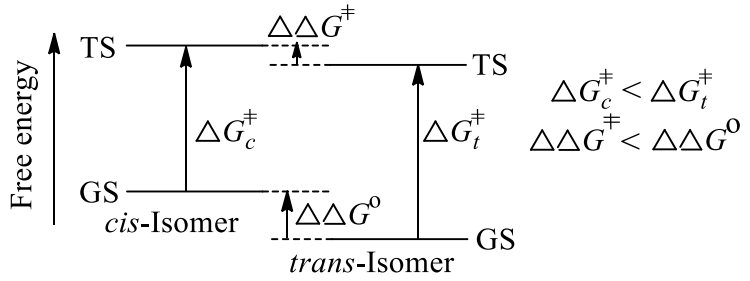

Figure 10: Free energy changes in oxidation of alcohols