

Subject	Chemistry
Paper No. & Title	1 and Organic Chemistry-I (Nature of bonding and Stereochemistry)
Module No. & Title	33: Qualitative correlation between conformation and reactivity
Module Tag	CHE_P1_M33

Principal Investigator		Co- Principal Investigator and Technical Coordinator
Prof. A.K.Bakhshi Sir Shankar Lal Professor, Department of Chemistry University of Delhi		Dr. Vimal Rarh Deputy Director, Centre for e-Learning and Assistant Professor, Department of Chemistry, SGTB Khalsa College, University of Delhi <i>Specialised in : e-Learning and Educational Technologies</i>
Paper Coordinator	Content Writer	Reviewer
Prof. J. M. Khurana Professor, Department of Chemistry, University of Delhi	Dr. Ram Singh Department of Applied Chemistry, Delhi Technological University Dr. Geetanjali Asst. Professor, Department of Chemistry, Kirori Mal College, University of Delhi	Dr. Varun Kumar Sharma Asst. Professor, Department of Chemistry, Hindu College, University of Delhi
Anchor Institute : SGTB Khalsa College, University of Delhi		

CHEMISTRY	PAPER 1: Organic Chemistry-I (Nature of bonding and Stereochemistry)
	MODULE 33: Qualitative correlation between conformation and reactivity

TABLE OF CONTENT

1. Learning Outcomes
2. Introduction
3. Conformational studies of substrates
4. Curtin-Hammett principle
5. Various conditions of Curtin-Hammett principle
6. Applications of Curtin-Hammett principle
7. Winstein-Eliel rate equation
8. Summary

CHEMISTRY**PAPER 1: Organic Chemistry-I (Nature of bonding and Stereochemistry)****MODULE 33: Qualitative correlation between conformation and reactivity**

1. Learning Outcomes

After studying this module, you shall be able to:

- Understand the correlation between conformations and reactivity.
- Explain the stability of the product with respect to the conformation of reactants.
- Analyse Curtin-Hammett principle, various conditions of Curtin-Hammett principle and its applications along with Winstein-Eliel rate equation.

2. Introduction

The conformation-reactivity relationship is very important in understating the stereochemical aspects of product formation. Dynamic stereochemistry concerns with stereochemical studies of any rate process involving bond-making and bond breaking or interconversion of conformers. This depends upon the stability of the conformers. The relationship correlates the stereochemistry of starting material and products in terms of transition state. Conformations of starting materials plays important role in the reactivity. Barton in 1950 first time established the relation between conformation and stability and reactivity of alicyclic compounds. Conformational studies of important substrates are discussed in the following sections.

3. Conformational studies of substrates

(i) **Conformationally rigid diastereomers:** There are cyclic molecules whose reacting groups are locked into two different orientations. The axial and equatorial proportions provide a direct relationship between conformation and reactivity. Compounds with two or more cyclohexane

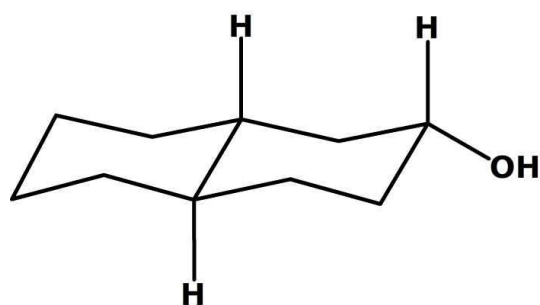
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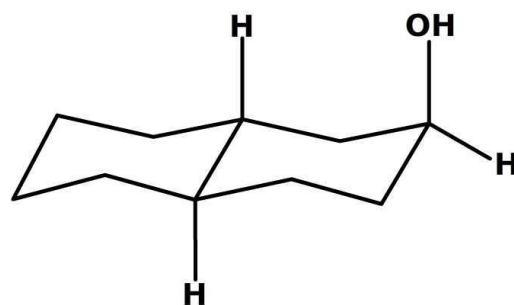
MODULE 33: Qualitative correlation between conformation and reactivity

rings linked through *trans* ring junctions and does not undergo ring inversion are rigid towards reactivity.

For example: In *trans*-2 α -decalol (I), -OH group is present at equatorial position while in *trans*-2 β -decalol (II), -OH group is present at axial position. When these two conformers are subjected to acetylation *trans*-2 α -decalol (I) reacts faster than *trans*-2 β -decalol (II).



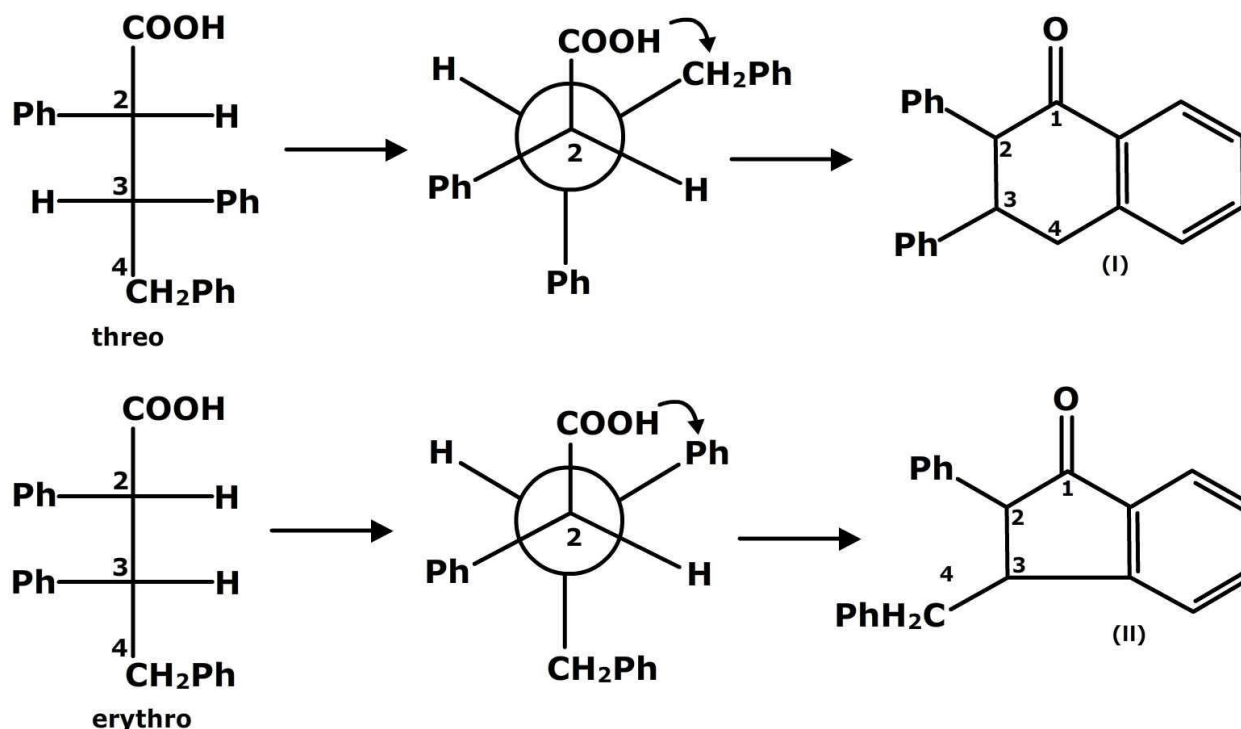
trans-2 α -decanol(I)



trans-2 β -decanol(II)

(ii) **Conformationally mobile diastereomers:** Those molecules which exist in erythro and threo isomeric forms come under this category. In this case, the relative specific reaction rates of the two diastereomers depend on the corresponding rates and their populations in the equilibrium mixture of each diastereomer.

For example, 2,3,4-triphenylbutyric acid exists in two diastereomers, threo and erythro respectively. Threo is the preferred conformation having the -COOH group very close to the -CH₂Ph group at C-4 carbon atom. It cyclizes with anhydrous HF mainly to tetralone (I), while erythro having the -COOH group very close to the -Ph group at C-3 carbon atom cyclizes with anhydrous HF mainly to indanone (II).



(iii) **Single substrate with two or more conformers:** The overall specific reaction rate (k) of a substrate in mobile equilibrium depends both on the ground state population of conformer and on their specific reaction rate as given in the equation:

$$K = \sum n_i k_i$$

where, n_i = mole fraction of i^{th} conformer

k_i = Specific reaction rate

K = Overall specific reaction rate

Quantitative correlation between conformation and reactivity has been explained by two principles, these are: (1) Curtin-Hammett principle and (2) Winstein-Eliel rate equation. At one time, these equations were extensively used to determine the conformational free energies.

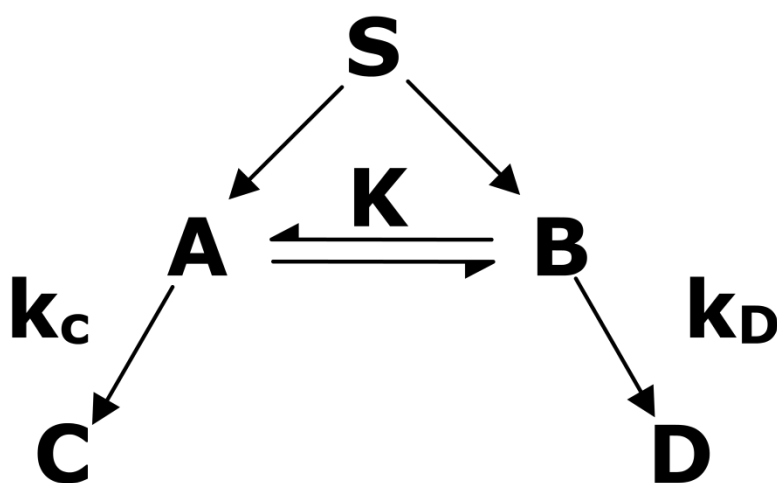
Together, the Curtin-Hammett principle and Winstein-Eliel rate equation gives a quantitative analysis of the conformation-reactivity relationship.

4. Curtin-Hammett principle

Curtin-Hammett principle applies to systems in which different products are formed from a substrate which exists in two different forms which are in equilibrium with one another. The rapidly interconverting reactants can be enantiomers, diastereomers, or constitutional isomers. But product formation must be irreversible and different products formed must be unable to interconvert or they must be in non-equilibrium.

Curtin-Hammett principle states that, “In a chemical reaction, if a product is formed from one conformational isomer and another product is formed from another conformational isomer which are rapidly interconvertible then the product composition is not solely dependent on the relative proportions of the conformational isomers in the substrate. The product ratio is controlled by the difference in standard Gibbs energies of the respective transition states. The reaction may proceed through a minor conformation if it is the one which provides access to the low-energy transition state and is completely independent of the difference in ground state stabilities of the conformers.”

For example, let **A** and **B** are two different conformers of a substrate (*S*), which are in rapid equilibrium with each other. Conformer **A** irreversibly converts into **C**, while the conformer **B** irreversibly converts into **D**, but products **C** and **D** are unable to interconvert, as shown below:

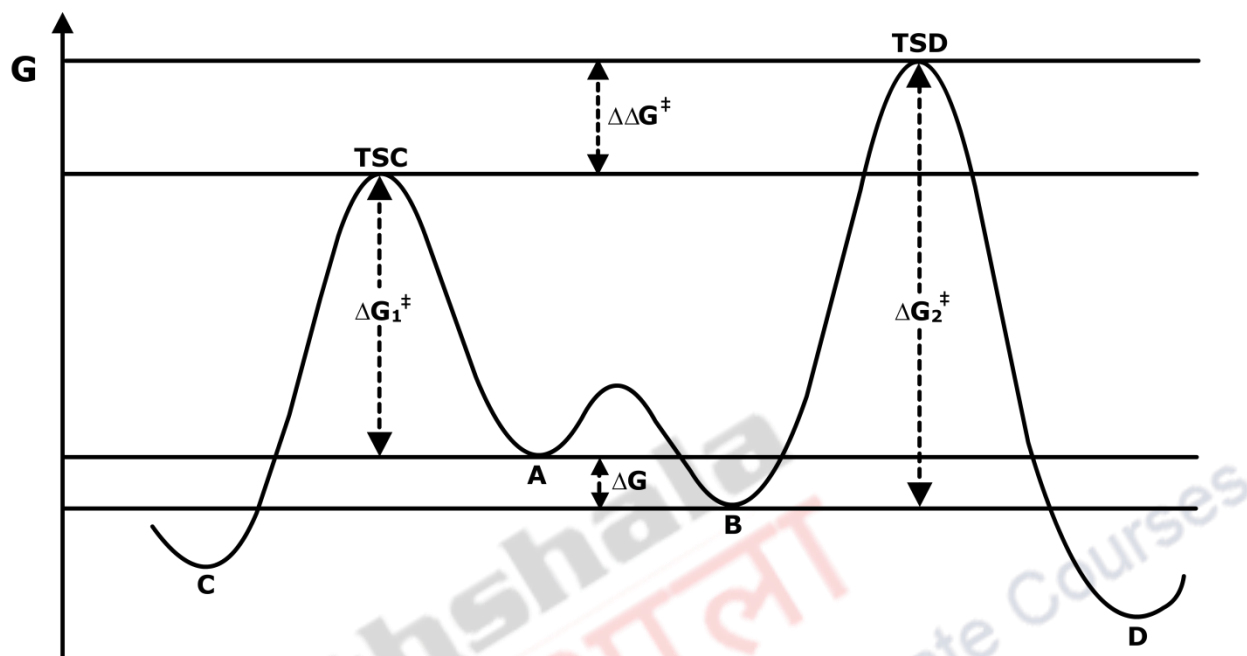


Here, K is the equilibrium constant between conformers **A** and **B**, and k_C and k_D are the rate constants for the formation of products **C** and **D** respectively. When K is larger than either k_C or k_D , then according to the Curtin-Hammett principle, the C:D product ratio is not equal to the A:B reactant ratio, but is instead determined by the relative energy of the transition states.

- K is larger than either k_C or k_D means the rate of inter-conversion between the reactants **A** and **B** is much faster than the rate of formation of products **C** or **D**.

If both the reactants **A** and **B** are at identical energy, then the reaction will depend only on the energy of the transition states leading to products **C** and **D**. However, if the two reactants **A** and **B** are at different energy levels (having low energy barrier for their inter-conversion) then the product distribution depends both on the relative quantity of **A** and **B** and on the relative barriers to products **C** and **D**.

The reaction coordinate free energy profile can be represented by the following scheme:



The ratio of products depends on the free energy (ΔG^\ddagger). Here C will be the major product, having lower (ΔG^\ddagger) for TS C, while product D has higher (ΔG^\ddagger) for TS D, so formed in less amount. From this we conclude that the product distribution depends on the relative free energies of substrates A and B.

5. Various conditions of Curtin- Hammett principle

Case I

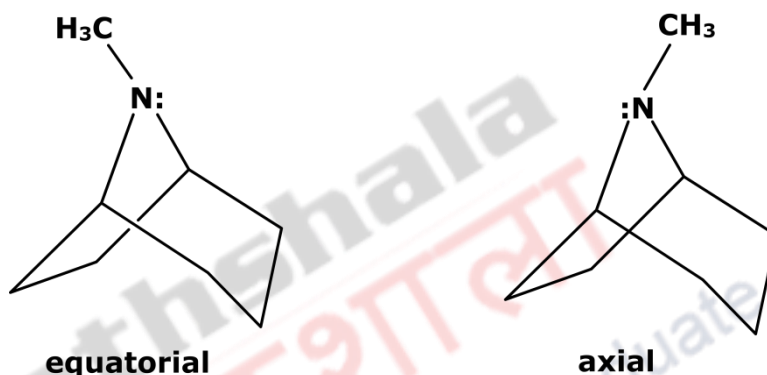
Less stable conformer leads to the major product or less stable conformer reacts more quickly than the more stable conformer: Less stable conformer is at high energy and thus it is present in less concentration at room temperature. On the other hand, more stable conformer is at low energy and thus it is present in high concentration at room temperature. Here, the less stable conformer reacts faster and form the product due to the low free energy (ΔG^\ddagger) of the transition state.

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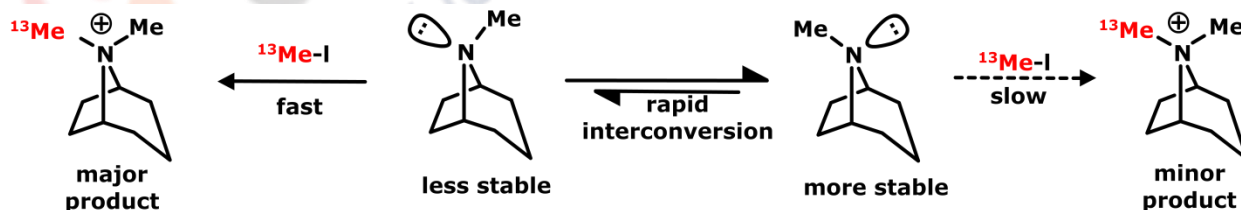
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MODULE 33: Qualitative correlation between conformation and reactivity

For example: Tropane is a [3.2.1]bicyclic nitrogen containing organic compound. This is a bicyclic amine having pyrrolidine ring on one side and a piperidine ring on the other side. This molecule exists in the two conformational forms. Conformation having methyl at the equatorial position is more stable than the conformation having methyl at the axial position due to steric hindrance. They are more sterically hindered on the side of the piperidine ring than on the side of the pyrrolidine ring.



Tropane on alkylation with methyl iodide forms major product from a less stable conformation. Here, the less stable conformer reacts via a more stable transition state to form the major product. Therefore, the ground state conformational distribution does not reflect the product distribution.

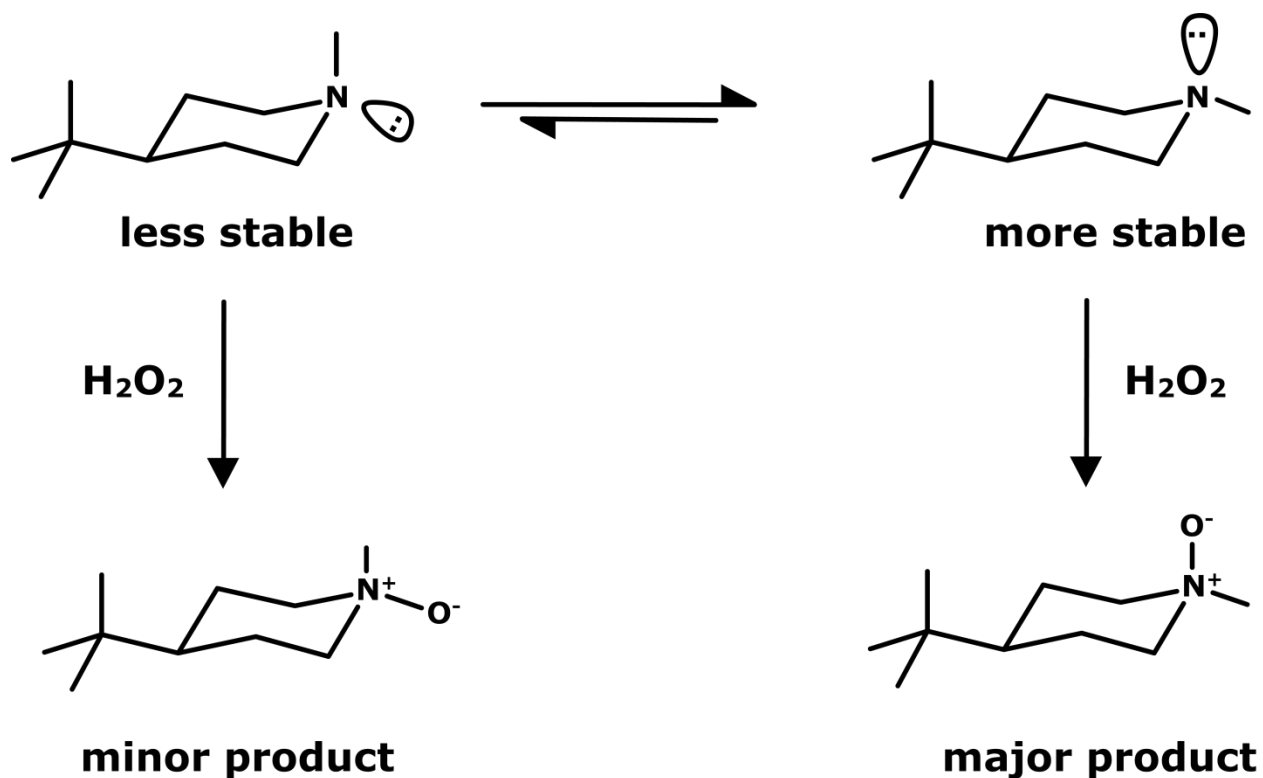


Case II

More stable conformer leads to the major product or more stable conformer reacts more quickly: More stable conformer is at low energy and it reacts faster to form the product via the

low free energy (ΔG^\ddagger) transition state. Here also the product distribution does not reflect the equilibrium conformer distribution.

For example: Diastereomeric conformer of 4-*tert*-butyl-1-methyl-piperidine in which both the methyl and *tert*-butyl substituents are at the equatorial position is 3.16 kcal/mol more stable than the conformer in which methyl is at the axial position and *tert*-butyl substituent is at the equatorial position. Here, more stable conformer of 4-*tert*-butyl-1-methyl-piperidine leads to the major product with the product ratio of 95:5.



Product Ratio: 5:95

Case III

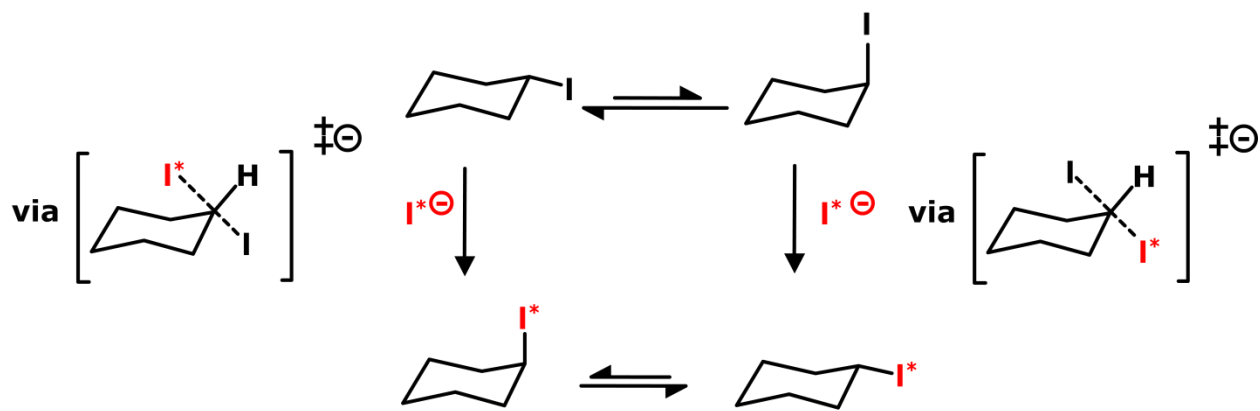
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PAPER 1: Organic Chemistry-I (Nature of bonding and Stereochemistry)

MODULE 33: Qualitative correlation between conformation and reactivity

Both conformers react at the same rate: Two different conformers in equilibrium react at the same rate through transition states having same energies. In this case, the selectivity of product formation depends only on the distribution of ground-state conformers.

For example: Cyclohexyl iodide reacts with radiolabeled iodide (I^*) and forms both axial substituted and equatorial substituted product through the same transition state. Hypothetically both the products should form in 1:1 ratio, but this is not the case.

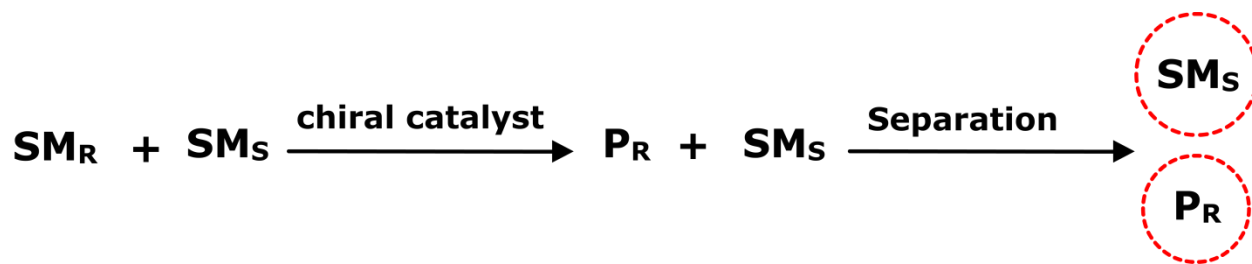


Hypothetical product ratio: 1:1
However, product equilibration precludes observation

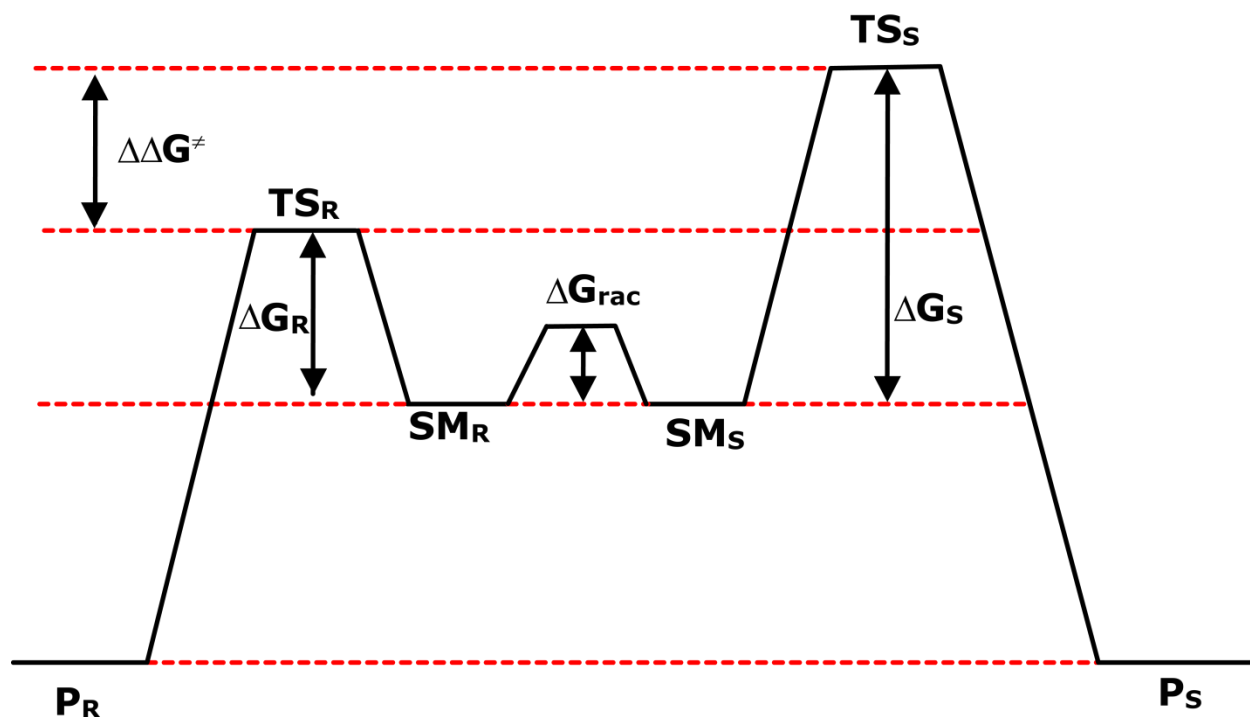
6. Application of Curtin-Hammett equation

(i) **Application to dynamic kinetic resolution:** Kinetic resolution is used to differentiate between two enantiomers in a racemic mixture.

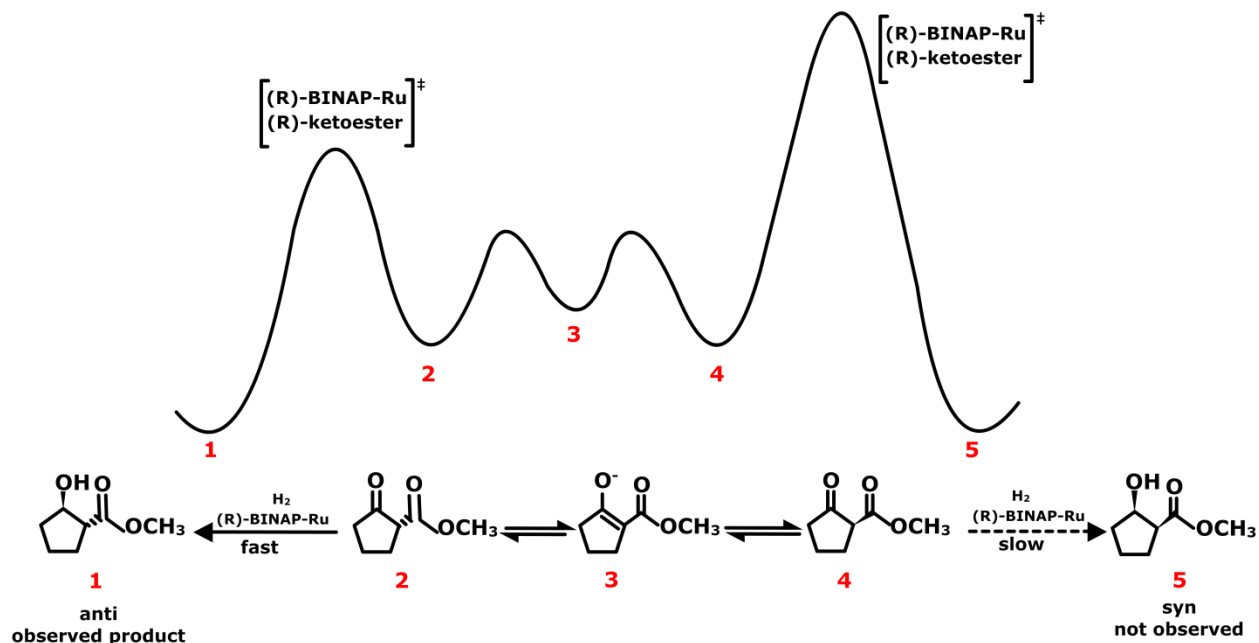
For example, if two enantiomers (S_R and S_S) are allowed to react with a chiral catalyst or reagent in a chemical reaction, then they react at a different reaction rate and results in the formation of an enantio-enriched sample of the less reactive enantiomer. The less reactive enantiomer is further separated from the products. It is shown below:



This enantiomeric excess (*ee*) of the unreacted starting material continuously rises as more product is formed, reaching 100% just before full completion of the reaction. But Dynamic Kinetic Resolution (DKR) is a kinetic resolution where 100% of a racemic mixture can be converted to one enantiomer. DKR is an example of a Curtin-Hammett system in which the composition of products is controlled by the free energies of the transition states and not the composition of the starting materials. It is applied in asymmetric synthesis. DKR uses a center of a particular molecule that can be easily epimerized so that the (*R*) and (*S*) enantiomers can interconvert throughout the reaction process. At this point, the catalyst can selectively lower energy of the transition state of a single enantiomer, leading to almost 100% yield of one reaction pathway over the other. Let us take a racemic mixture having both *R* (SM_R) and *S* (SM_S) enantiomers. When this racemic mixture is subjected to a reaction using a catalyst, then it selectively lower transition energy of (TR_R) of *R* enantiomer (*R*) leading to almost 100% yield of only one enantiomer *R* as product (P_R) over the other as shown below:

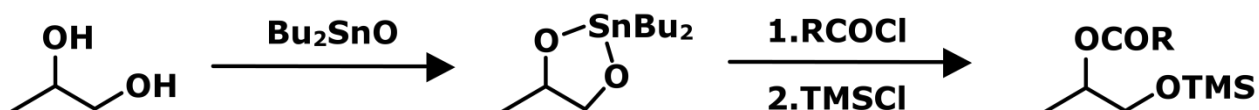


DKR is applied in Noyori's asymmetric hydrogenation. It is a chemical reaction in which ketones, aldehydes and imines are hydrogenated enantioselectively using chiral BINAP-Ru catalyst. The (*R*)-BINAP-Ru catalyze the synthesis the (*R*)-product, and the (*S*)-BINAP Ru catalyze the synthesis the (*S*)-product with high *ee*. Rapid equilibration between the enantiomeric conformers and irreversible hydrogenation place the reaction under Curtin-Hammett control. The use of a chiral catalyst results in a higher-energy and a lower-energy transition state for hydrogenation of the two enantiomers. The transformation occurs *via* the lower-energy transition state to form the product as a single enantiomer. Consistent with the Curtin-Hammett principle, the ratio of products depends on the absolute energetic barrier of the irreversible step of the reaction, and does not reflect the equilibrium distribution of substrate conformers. The relative free energy profile of one example of the Noyori asymmetric hydrogenation is shown below:

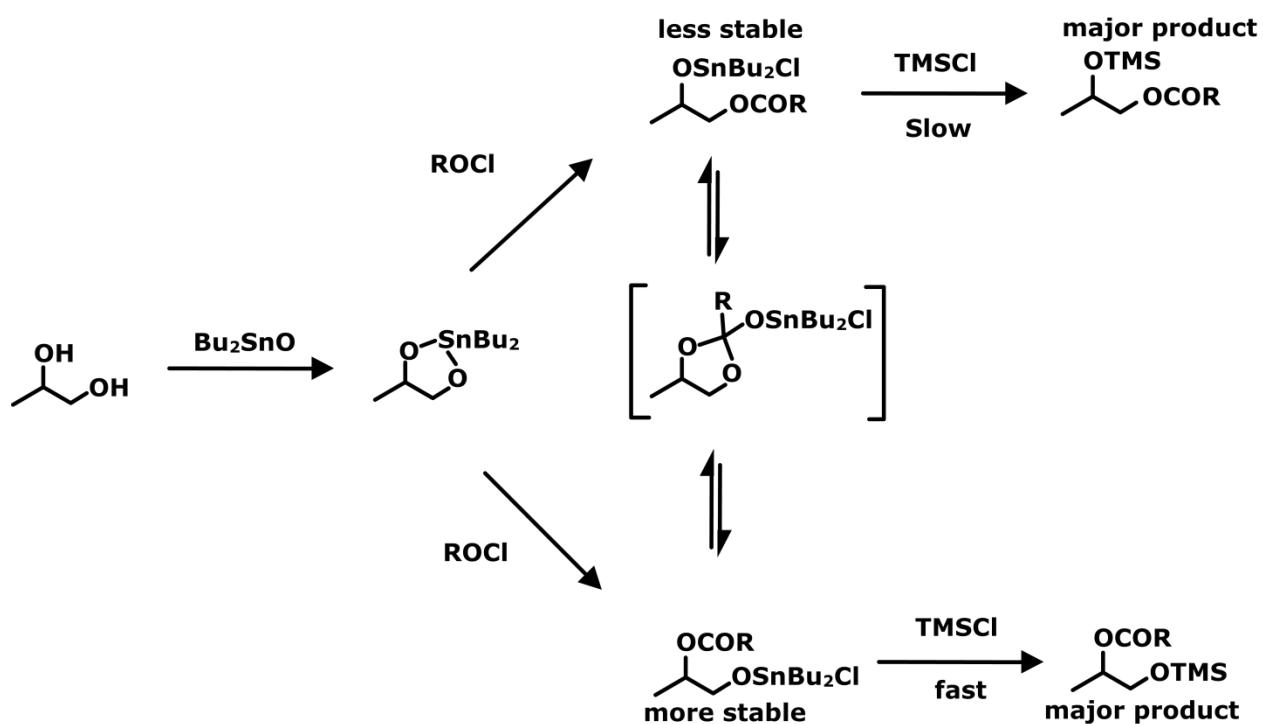


In the above example, β -keto-ester (3) exists in two conformers (2 and 4), which are in equilibrium with each other. The chiral catalyst (*R*)-BINAP-Ru lowers the energy of the (2) conformer in comparison to the (3) conformer. Thus, conformer (2) reacts faster and exclusively forms the 100% product (1) rather than (5).

(2) **Application to regioselective acylation:** Curtin-Hammett principle is used to explain regioselectivity in the acylation of 1,2-diols. Usually, the least-hindered site of an asymmetric 1,2-diol undergo esterification faster due to least steric hindrance between the diol and the acylating reagent. But Curtin-Hammett principle is used to explain selective esterification of the most substituted hydroxyl group in the synthesis of carbohydrates and other polyhydroxylated compounds using stannylene acetals as shown below:

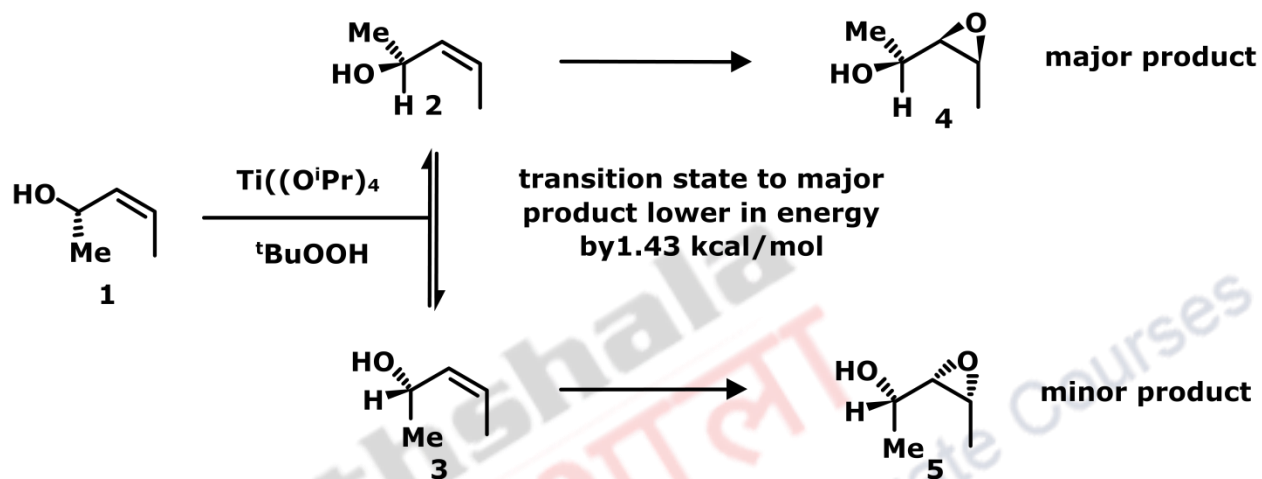


The asymmetric diol is first treated with a tin reagent (like Bu_2SnO) to produce the dibutylstannylene acetal. This compound is then treated with one equivalent of acyl chloride to produce the stannyl monoester. Two isomers of the stannyl ester are accessible, and can undergo rapid interconversion through a tetrahedral intermediate. Initially, the less stable isomer predominates, as it is formed more quickly from the stannyl acetal. However, allowing the two isomers to equilibrate results in an excess of the more stable primary alkoxy-stannane in solution. The reaction is then quenched irreversibly, with the less hindered primary alkoxy-stannane reacting more rapidly. This results in selective production of the more-substituted monoester. This is in accordance with Curtin-Hammett principle in which the more stable isomer reacts more rapidly.



(3) Application to asymmetric epoxidation: Pent-3-en-2-ol (1) is a chiral allylic alcohol, which exists in two conformations (2) or (3). It undergoes diastereoselective epoxidation by titanium peroxy complex to form major product (4) and minor product (5) via the transition states (2)

and (3) having 1.43 kcal/mol difference in transition state energies between the two conformers. The observed product ratio was 91:9.



7. Winstein-Eilel equation rate

It correlates the overall specific reaction rate (K) of a substrate with Specific reaction rate (k) of individual conformer irrespective of whether the products are equilibrating or non-equilibrating. For example, *trans*-4-*t*-butylcyclohexyl tosylate does not undergo E_2 elimination, since the equatorial conformer cannot have the tosyl group antiperiplanar with an adjacent hydrogen atom. On the other hand, *cis*-4-*t*-butylcyclohexyl tosylate undergoes E_2 elimination with a specific rate $7.1 \times 10^{-3} \text{ Lmol}^{-1}\text{sec}^{-1}$.

8. Summary

- The conformation-reactivity relationship is very important in understating the stereochemical aspects of product formation.
- Curtin-Hammett principle applies to systems in which different products are formed from a substrate which exists in two different forms which are in equilibrium with one another. The rapidly interconverting reactants can be enantiomers, diastereomers, or constitutional isomers.
- Curtin-Hammett principle is used in the dynamic kinetic resolution. Kinetic resolution is used to differentiate between two enantiomers in a racemic mixture.
- Curtin-Hammett principle is also applied in the asymmetric epoxidation.
- Curtin-Hammett principle is used to explain regioselectivity in the acylation.
- Noyori's asymmetric hydrogenation is also dependent upon the Curtin-Hammett principle.
- Winstein-Eliel rate equation correlates the overall specific reaction rate (K) of a substrate with Specific reaction rate (k) of individual conformer irrespective of whether the products are equilibrating or non-equilibrating.