

## ❖ Isotope Effects

In the previous section of this chapter, we studied isotopic labeling as a tool to detect the reaction mechanism. There we assumed that the isotopic substitution has no effect on the chemical profile of the reaction whatsoever which is far from the truth because the isotopic substitution can change the rate of chemical reactions in a significant manner.

*The changes in the reaction rate when a particular atom in the reactant molecule is replaced by one of its isotopes are termed as isotopic effects.*

Formally, it is called as “kinetic isotope effect”, and it is calculated rate constants for the reactions with the lighter isotope ( $k_L$ ) by the rate constant for reaction with the heavier isotope ( $k_H$ ) i.e.

$$KIE = \frac{k_L}{k_H} \quad (20)$$

This variation in the rate of reaction because the heavier isotopologues have lower vibrational frequencies relative to their lighter isotopes, and can easily be rationalized quantum mechanically. In general, this means that greater energy is needed for heavier isotopologues to cross the transition state (or the dissociation limit in rare cases), and therefore, a lower reaction rate is observed. The kinetic isotopic effect can primarily be classified into two categories; primary and secondary isotope effects.

### ➤ *Primary Isotope Effects*

The primary kinetic isotope effect is observed if a bond to the isotopically-labeled atom is being broken or formed. Now depending on the nature of the route followed to study kinetic isotope effect (parallel measurement of rates vs intramolecular competition vs intermolecular competition), we can find if the bond-formation or bond-breaking has happened at the rate-determining step, or in the subsequent product-determining step. Furthermore, it is also worthy to note that many textbooks are propagating the misconception that a primary kinetic isotope effect must echo bond breaking or formation to the isotope at the rate-determining step always.

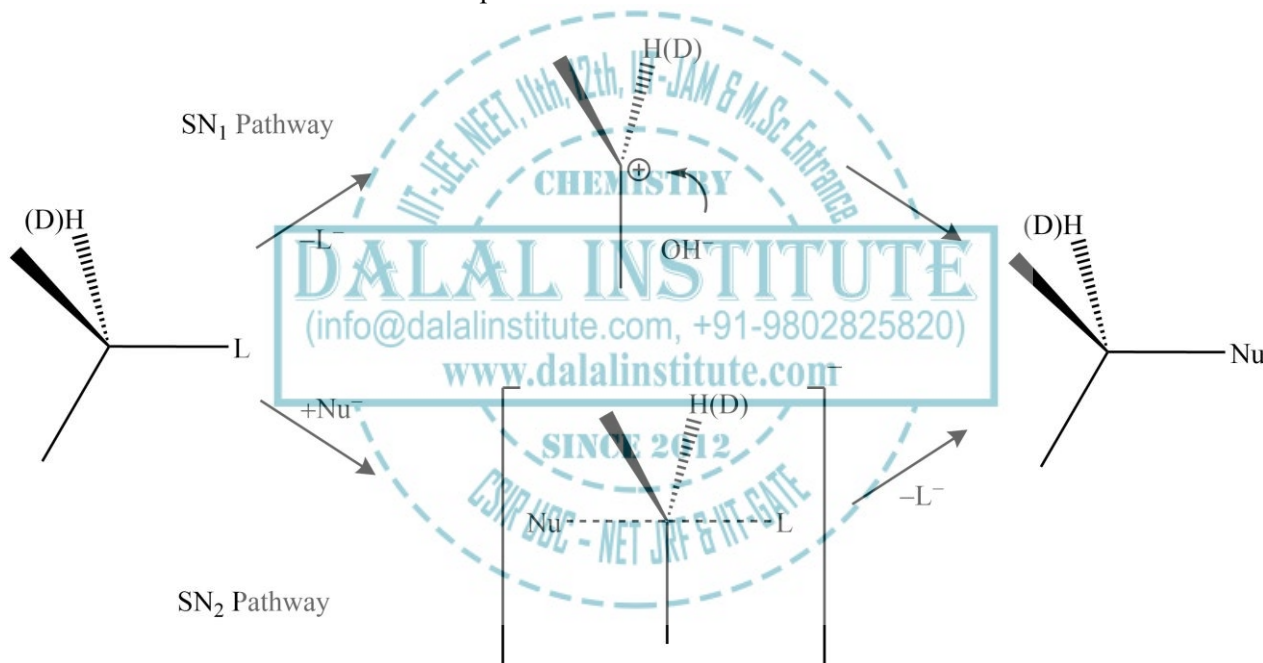
For nucleophilic substitutions mentioned earlier, the primary kinetic isotope effects have been studied for the attacking nucleophiles, leaving groups, and the  $\alpha$ -carbon at which the displacement occurs. The interpretation of the kinetic isotope effects as a function of the leaving group had been very complicated at first because of the significant contributions from temperature-independent factors. Though the primary kinetic isotope effect is less sensitive than the ideal, and the contribution from non-vibrational factors; the kinetic isotope effects at the  $\alpha$ -carbon are employed to advance the understanding of the transition state's symmetry of the  $S_N2$  pathway.

### ➤ *Secondary Isotope Effects*

We will get a secondary kinetic isotope effect if no bond formation or breaking happens to the isotopically-labeled atom in the reactant. Also, the secondary kinetic isotope effects are much smaller in magnitude than primary kinetic isotope effects; though the secondary isotope effects of deuterium can reach

up to 1.4 per atom. Furthermore, many experimental techniques have been invented and refined to measure heavy-element isotope effects with extremely good precision; and therefore, these kinds of effects are still very valuable for mechanisms-elucidating of many organic reactions.

In the case of many nucleophilic substitution reactions, secondary isotope effects of H at  $\alpha$ -carbon offer a direct route to differentiate between  $S_N2$  and  $S_N1$  type reactions. It is observed that  $S_N1$  reactions generally give rise to great secondary isotope effects (up to a theoretical maximum of 1.22); whereas  $S_N2$  reactions usually have primary isotope effects which are close to or less than one in most cases. Kinetic isotope effects having a value greater than unity are typically labeled as 'normal kinetic isotope effects', whereas isotope effects having a value less than unity are called as 'inverse kinetic isotope effects'. On the whole, transition states with smaller force constants are expected to have a normal kinetic isotope effect; and transition states with larger force constants are expected to have an inverse kinetic isotope effect when stretching vibrational contributions control the isotope effect.



The  $C\alpha-H(D)$  vibration at the  $\alpha$ -carbon dictates the magnitudes of these secondary isotope effects. Now because the carbon is converted into an  $sp^2$  hybridized carbocation during an  $S_N1$  reaction, the transition state for the rate-limiting step will have an increase in  $C\alpha-H(D)$  bond order; and therefore, an inverse kinetic isotope effect would be expected if only the stretching vibrations were the chief factors. On the other hand, large normal kinetic isotope effects are observed which are induced by significant out-of-plane bending vibrational contributions if we go from the reactants to the transition state of carbocation formation. In the case of  $S_N2$  reactions, bending vibrations will still play a vital role in the kinetic isotope effect, but stretching vibrational contributions are also of significant importance; and therefore, the resulting isotope effect may be inverse or normal depending upon the dominating factor.

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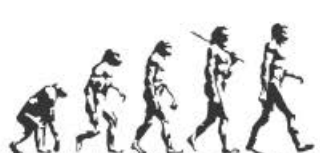
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# A TEXTBOOK OF ORGANIC CHEMISTRY

**Volume I**

**MANDEEP DALAL**



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# Table of Contents

|  |           |
|--|-----------|
| <b>CHAPTER 1</b> .....   | <b>11</b> |
| <b>Nature of Bonding in Organic Molecules</b> .....  | <b>11</b> |
| ❖ Delocalized Chemical Bonding .....   | 11        |
| ❖ Conjugation .....  | 14        |
| ❖ Cross Conjugation .....  | 16        |
| ❖ Resonance .....  | 18        |
| ❖ Hyperconjugation .....   | 27        |
| ❖ Tautomerism .....  | 31        |
| ❖ Aromaticity in Benzenoid and Nonbenzenoid Compounds .....  | 33        |
| ❖ Alternant and Non-Alternant Hydrocarbons .....   | 35        |
| ❖ Huckel's Rule: Energy Level of $\pi$ -Molecular Orbitals .....   | 37        |
| ❖ Annulenes .....  | 44        |
| ❖ Antiaromaticity .....  | 46        |
| ❖ Homoaromaticity .....  | 48        |
| ❖ PMO Approach .....   | 50        |
| ❖ Bonds Weaker Than Covalent .....   | 58        |
| ❖ Addition Compounds: Crown Ether Complexes and Cryptands, Inclusion Compounds, Cyclodextrins .....  | 65        |
| ❖ Catenanes and Rotaxanes .....  | 75        |
| ❖ Problems .....   | 79        |
| ❖ Bibliography .....   | 80        |
| <b>CHAPTER 2</b> .....   | <b>81</b> |
| <b>Stereochemistry</b> .....   | <b>81</b> |
| ❖ Chirality .....  | 81        |
| ❖ Elements of Symmetry .....   | 86        |
| ❖ Molecules with More Than One Chiral Centre: Diastereomerism .....  | 90        |
| ❖ Determination of Relative and Absolute Configuration (Octant Rule Excluded) with Special Reference to Lactic Acid, Alanine & Mandelic Acid ..... | 92        |
| ❖ Methods of Resolution .....  | 102       |
| ❖ Optical Purity .....   | 104       |
| ❖ Prochirality .....   | 105       |
| ❖ Enantiotopic and Diastereotopic Atoms, Groups and Faces .....  | 107       |
| ❖ Asymmetric Synthesis: Cram's Rule and Its Modifications, Prelog's Rule .....   | 113       |
| ❖ Conformational Analysis of Cycloalkanes (Upto Six Membered Rings) .....  | 116       |
| ❖ Decalins .....   | 122       |
| ❖ Conformations of Sugars .....  | 126       |
| ❖ Optical Activity in Absence of Chiral Carbon (Biphenyls, Allenes and Spiranes) .....   | 132       |
| ❖ Chirality Due to Helical Shape .....   | 137       |
| ❖ Geometrical Isomerism in Alkenes and Oximes .....  | 140       |
| ❖ Methods of Determining the Configuration .....   | 146       |

|   |            |
|---|------------|
| ❖ Problems.....   | 151        |
| ❖ Bibliography.....   | 152        |
| <b>CHAPTER 3.....</b>   | <b>153</b> |
| <b>Reaction Mechanism: Structure and Reactivity .....</b>   | <b>153</b> |
| ❖ Types of Mechanisms.....  | 153        |
| ❖ Types of Reactions .....  | 156        |
| ❖ Thermodynamic and Kinetic Requirements.....   | 159        |
| ❖ Kinetic and Thermodynamic Control .....   | 161        |
| ❖ Hammond's Postulate.....  | 163        |
| ❖ Curtin-Hammett Principle .....  | 164        |
| ❖ Potential Energy Diagrams: Transition States and Intermediates .....  | 166        |
| ❖ Methods of Determining Mechanisms.....  | 168        |
| ❖ Isotope Effects .....   | 172        |
| ❖ Hard and Soft Acids and Bases.....  | 174        |
| ❖ Generation, Structure, Stability and Reactivity of Carbocations, Carbanions, Free Radicals, Carbenes and Nitrenes.....                                  | 176        |
| ❖ Effect of Structure on Reactivity .....   | 200        |
| ❖ The Hammett Equation and Linear Free Energy Relationship.....   | 203        |
| ❖ Substituent and Reaction Constants.....   | 209        |
| ❖ Taft Equation.....  | 215        |
| ❖ Problems.....   | 219        |
| ❖ Bibliography.....   | 220        |
| <b>CHAPTER 4.....</b>   | <b>221</b> |
| <b>Carbohydrates .....</b>  | <b>221</b> |
| ❖ Types of Naturally Occurring Sugars .....   | 221        |
| ❖ Deoxy Sugars .....  | 227        |
| ❖ Amino Sugars.....   | 229        |
| ❖ Branch Chain Sugars .....   | 230        |
| ❖ General Methods of Determination of Structure and Ring Size of Sugars with Particular Reference to Maltose, Lactose, Sucrose, Starch and Cellulose..... | 231        |
| ❖ Problems.....   | 239        |
| ❖ Bibliography.....   | 240        |
| <b>CHAPTER 5.....</b>   | <b>241</b> |
| <b>Natural and Synthetic Dyes .....</b>   | <b>241</b> |
| ❖ Various Classes of Synthetic Dyes Including Heterocyclic Dyes .....   | 241        |
| ❖ Interaction Between Dyes and Fibers .....   | 245        |
| ❖ Structure Elucidation of Indigo and Alizarin .....  | 247        |
| ❖ Problems.....   | 252        |
| ❖ Bibliography.....   | 253        |
| <b>CHAPTER 6.....</b>   | <b>254</b> |
| <b>Aliphatic Nucleophilic Substitution .....</b>  | <b>254</b> |
| ❖ The $S_N2$ , $S_N1$ , Mixed $S_N1$ and $S_N2$ , $S_Ni$ , $S_N1'$ , $S_N2'$ , $S_Ni'$ and SET Mechanisms.....  | 254        |

|   |            |
|---|------------|
| ❖ The Neighbouring Group Mechanisms.....  | 263        |
| ❖ Neighbouring Group Participation by $\pi$ and $\sigma$ Bonds .....  | 265        |
| ❖ Anchimeric Assistance .....   | 269        |
| ❖ Classical and Nonclassical Carbocations .....   | 272        |
| ❖ Phenonium Ions .....  | 283        |
| ❖ Common Carbocation Rearrangements.....  | 284        |
| ❖ Applications of NMR Spectroscopy in the Detection of Carbocations .....                                     | 286        |
| ❖ Reactivity – Effects of Substrate Structure, Attacking Nucleophile, Leaving Group and Reaction Medium ..... | 288        |
| ❖ Ambident Nucleophiles and Regioselectivity .....  | 294        |
| ❖ Phase Transfer Catalysis.....   | 297        |
| ❖ Problems.....   | 300        |
| ❖ Bibliography .....  | 301        |
| <b>CHAPTER 7 .....</b>  | <b>302</b> |
| <b>Aliphatic Electrophilic Substitution .....</b>   | <b>302</b> |
| ❖ Bimolecular Mechanisms – $SE_2$ and $SE_i$ .....  | 302        |
| ❖ The $SE_1$ Mechanism .....  | 305        |
| ❖ Electrophilic Substitution Accompanied by Double Bond Shifts .....  | 307        |
| ❖ Effect of Substrates, Leaving Group and the Solvent Polarity on the Reactivity .....                        | 308        |
| ❖ Problems.....   | 310        |
| ❖ Bibliography .....  | 311        |
| <b>CHAPTER 8 .....</b>  | <b>312</b> |
| <b>Aromatic Electrophilic Substitution .....</b>  | <b>312</b> |
| ❖ The Arenium Ion Mechanism .....   | 312        |
| ❖ Orientation and Reactivity .....  | 314        |
| ❖ Energy Profile Diagrams .....   | 316        |
| ❖ The Ortho/Para Ratio.....   | 317        |
| ❖ <i>ipso</i> -Attack .....   | 319        |
| ❖ Orientation in Other Ring Systems .....   | 320        |
| ❖ Quantitative Treatment of Reactivity in Substrates and Electrophiles .....                                  | 321        |
| ❖ Diazonium Coupling.....   | 325        |
| ❖ Vilsmeier Reaction .....  | 326        |
| ❖ Gattermann-Koch Reaction .....  | 327        |
| ❖ Problems.....   | 329        |
| ❖ Bibliography .....  | 330        |
| <b>CHAPTER 9 .....</b>  | <b>331</b> |
| <b>Aromatic Nucleophilic Substitution .....</b>   | <b>331</b> |
| ❖ The $ArSN_1$ , $ArSN_2$ , Benzyne and $S_RN_1$ Mechanisms.....  | 331        |
| ❖ Reactivity – Effect of Substrate Structure, Leaving Group and Attacking Nucleophile.....                    | 336        |
| ❖ The von Richter, Sommelet-Hauser, and Smiles Rearrangements .....   | 339        |
| ❖ Problems.....   | 343        |
| ❖ Bibliography .....  | 344        |



|  |            |
|--|------------|
| <b>CHAPTER 10</b> .....  | <b>345</b> |
| <b>Elimination Reactions</b> .....   | 345        |
| ❖ The E <sub>2</sub> , E <sub>1</sub> and E <sub>1</sub> CB Mechanisms .....   | 345        |
| ❖ Orientation of the Double Bond.....  | 348        |
| ❖ Reactivity – Effects of Substrate Structures, Attacking Base, the Leaving Group and The Medium .....                                     | 352        |
| ❖ Mechanism and Orientation in Pyrolytic Elimination.....  | 355        |
| ❖ Problems.....  | 358        |
| ❖ Bibliography.....  | 359        |
| <b>CHAPTER 11</b> .....  | <b>360</b> |
| <b>Addition to Carbon-Carbon Multiple Bonds</b> .....  | 360        |
| ❖ Mechanistic and Stereochemical Aspects of Addition Reactions Involving Electrophiles, Nucleophiles and Free Radicals.....                | 360        |
| ❖ Regio- and Chemoselectivity: Orientation and Reactivity .....  | 370        |
| ❖ Addition to Cyclopropane Ring .....  | 374        |
| ❖ Hydrogenation of Double and Triple Bonds .....   | 375        |
| ❖ Hydrogenation of Aromatic Rings.....   | 377        |
| ❖ Hydroboration .....  | 378        |
| ❖ Michael Reaction.....  | 379        |
| ❖ Sharpless Asymmetric Epoxidation .....   | 380        |
| ❖ Problems.....  | 382        |
| ❖ Bibliography .....   | 383        |
| <b>CHAPTER 12</b> .....  | <b>384</b> |
| <b>Addition to Carbon-Hetero Multiple Bonds</b> .....  | 384        |
| ❖ Mechanism of Metal Hydride Reduction of Saturated and Unsaturated Carbonyl Compounds, Acids, Esters and Nitriles .....                   | 384        |
| ❖ Addition of Grignard Reagents, Organozinc and Organolithium Reagents to Carbonyl and Unsaturated Carbonyl Compounds.....                 | 400        |
| ❖ Wittig Reaction.....   | 406        |
| ❖ Mechanism of Condensation Reactions Involving Enolates: Aldol, Knoevenagel, Claisen, Mannich, Benzoin, Perkin and Stobbe Reactions ..... | 411        |
| ❖ Hydrolysis of Esters and Amides.....   | 433        |
| ❖ Ammonolysis of Esters.....   | 437        |
| ❖ Problems.....  | 439        |
| ❖ Bibliography.....  | 440        |
| <b>INDEX</b> .....   | <b>441</b> |



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