Chapter 11

Organic Reaction Mechanisms, Part 2: Substitutions at Aliphatic Centers and Thermal Isomerizations/Rearrangements

Substitution $\alpha$ to a carbonyl center: Enol and enolate chemistry

The hydrogens on carbons adjacent to carbonyls, the $\alpha$-hydrogens, are relatively acidic (pKa = ~18-22) -> This acidity enables a broad class of substitution reactions.

11.1 Tautomerization

: involves the shift of a hydrogen atom across a $\pi$ system. eg) keto-enol tautomerization

11.1.1 Electron pushing for keto-enol tautomerizations

Scheme 11.1
Acid-catalyzed formation of an enol from acetone.
11.1.2 The thermodynamics of enol formation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Equilibrium constant</th>
<th>Compound</th>
<th>Equilibrium constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CH}_3-CO-\text{CH}_3 )</td>
<td>( 6.3 \times 10^{-8} )</td>
<td>( \text{CH}_3\text{CH}_2\text{COH} )</td>
<td>( 5.0 \times 10^{-6} )</td>
</tr>
<tr>
<td>( \text{CH}_3\text{CH}_2\text{COCH}_3 )</td>
<td>( 5.0 \times 10^{-9} )</td>
<td>( \text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3 )</td>
<td>( 1.2 \times 10^{-4} )</td>
</tr>
<tr>
<td>( \text{C}_5\text{H}_8\text{O} )</td>
<td>( 6.3 \times 10^{-8} )</td>
<td>( \text{C}_5\text{H}_8\text{OC} )</td>
<td>( 1.6 \times 10^{-3} )</td>
</tr>
<tr>
<td>( \text{C}_5\text{H}_8\text{O} )</td>
<td>( 2.0 \times 10^{-6} )</td>
<td>( \text{C}_5\text{H}_8\text{OC}\text{CH}_3 )</td>
<td>( 2.0 \times 10^{-7} )</td>
</tr>
<tr>
<td>( \text{C}_5\text{H}_8\text{O} )</td>
<td>( 1.1 \times 10^{-3} )</td>
<td>( \text{C}_5\text{H}_8\text{OC}\text{OR} )</td>
<td>( 0.09 )</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5\text{O} )</td>
<td>( 4 \times 10^{13} )</td>
<td>( \text{C}_6\text{H}_5\text{OH} )</td>
<td>( )</td>
</tr>
</tbody>
</table>

normal alkyl ketones and aldehydes; the enol form -> minor 
\( \beta \)-diketones; enol form -> major due to intramolecular HB 
phenol and other enols within aromatic rings; enol form -> predominantly
11.1.3 Catalysis of enolization

- **Base-catalyzed enolization** (general-base catalysis)
  - RDS
  - Pre-equilibrium

- **Acid-catalyzed enolization** (general-acid catalysis, but is commonly the combination of specific-acid and general-base catalysis)
  - RDS
11.1.4 Kinetic vs. thermodynamic control in enolate and enol formation

trapping agent for enolate

**thermodynamic control**

**kinetic control**

HMPA = hexamethylphosphoramide

more stable
-> predominant
Going Deeper

Enolate Aggregation

We noted above the tendency for enolates to aggregate. The aggregates are organized in large part by the counterion of the base, Li⁺ in the case of LDA or LTMP. To the side, prototypical dimers and tetramers are shown. In the absence of ligands such as HMPA, diamines, and THF, even larger aggregates exist.

11.2 $\alpha$-Halogenation

Mechanism

Rate = first order in [CO] and zero order in [X$_2$]
large primary KIE (6.1 for Br$_2$ of methyl cyclohexyl ketone in NaOMe/MeOH)
All the experimental observations support a rate-determining formation of the enolate or enol, followed by rapid trapping of the intermediate by the halogen.
Under acidic conditions, monohalogenated product is usually formed. Under basic conditions, multiply halogenated products are formed.

More acidic than unhalogenated CH

More substituted one
-> major because the reaction proceeds via the most stable enol.

Note: with base, the least substituted R group is preferentially halogenated, due to kinetic control.

Haloform reaction
11.3 $\alpha$-alkylations

Scheme 11.3
Electron pushing for enolate alkylation.

11.3.2 Stereochemistry: conformational effects

Cyclohexanone

A. kinetic control

B. chair-like conformation
boat-like conformation

Figure 11.1
A. The reaction of 4-$t$-butylcyclohexanone enolate with alkyl halides gives the trans product predominately.
B. Two different trajectories lead to chair- and boat-like transition states giving trans and cis products, respectively.
Exocyclic enolates

Note: Because these alkylations are exothermic, the transition states are early, and the stereochemistry is not very sensitive to the alkylating agent.

2-Substituted exocyclic enolates

Alkylation of the lower energy enolate gives the major product. However, as the Curtin-Hammett principle states, this is not always the case.
11.4 The aldol reaction

Scheme 11.4
The electron-pushing scheme for the aldol reaction.

11.3.2 Conformational effects on the aldol reaction

mixed aldol reaction
Figure 11.2
Analysis of conformational effects on aldol reactions. 

A. The equilibria and products from Z-enolates.

B. The equilibria and products from E-enolates.
Control of Stereochemistry in Enolate Reactions

Typically, the products of an aldol or other reactions of enolates are chiral molecules, and often the starting materials are not. Thus, another stereochemical issue arises—namely, the preferential formation of one enantiomeric product over the other. This again is a large research area, with many clever and effective solutions. One especially useful approach has been developed by Evans.

The Evans approach shown below makes use of enantiomerically pure oxazolidinones known as chiral auxiliaries. A chiral auxiliary is a fragment that is appended to a reactive species in order to influence the stereochemistry of subsequent reactions. After the desired effect is achieved, the auxiliary is removed and (hopefully) recycled for further use.

As shown in the scheme below, starting from the amino acid valine, reduction of the carboxylic acid with borane and reaction with diethyl carbonate produces the oxazolidinone with a bulky isopropyl group strategically positioned. The nitrogen is acylated, and then enolate formation with LDA produces a well-defined structure thanks to chelation of the lithium ion by the enolate oxygen and the carbonyl of the oxazolidinone. When an electrophile (E) approaches, the isopropyl group blocks the bottom face, and so attack occurs preferentially from the top face, producing excellent control of stereochemistry. Removal of the auxiliary produces an enantiomerically enriched product that formally arises from the reaction of an electrophile with the enolate of a propionic acid derivative. Many variations are possible, and a wide range of electrophiles is compatible with this useful reaction.

Substitution on aliphatic centers

11.5 Nucleophilic aliphatic substitution reactions

11.5.1 $S_N2$ and $S_N1$ electron-pushing examples

Concerted reactions: the bond breaking and bond formation steps all occur at the same time in one single elementary step.
Synchronous reactions: the breaking and forming of bonds has occurred to the same extent at the transition state
Asynchronous reactions: have one of these two parts of the reaction lagging behind the other at the transition state.
Most $S_N2$ reactions are mostly asynchronous, meaning that the extents of nucleophilic attack and leaving group departure at the transition state are unequal.

Scheme 11.5
$S_N2$ examples. A. Williamson ether synthesis, B. Alkylation of an amine, and C. Alkylation of an enolate.
$S_N1$ reactions: more complex substitution pathway.
$\rightarrow$ 1$^{\text{st}}$ step: the formation of a carbocation, 2$^{\text{nd}}$ step: nucleophilic attack.

Scheme 11.6

$S_N1'$ and $S_N2'$: less common aliphatic substitution pathways

Scheme 11.7
A. An $S_N2'$ reaction. B. An $S_N1'$ reaction.
11.5.4 Stereochemistry

Sₙ₂; backside attack -> inversion of stereochemistry

Sₙ₂; no reaction since the ring system completely blocks access of a Nu.

In reality, whereas full inversion of stereochemistry is always seen in Sₙ₂, full racemization of stereochemistry in Sₙ₁ is rare. Instead, partial inversion of stereochemistry is commonly found.
11.5.5 Orbital considerations

![Diagram of orbital considerations]

11.5.6 Solvent effects – 책 읽어 볼 것

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**Table 11.2**

Comparison of the Charge Distribution on Various Reactants and Transition States for a Series of A. S_N2 Reactions and B. S_N1 Reactions (LG = Leaving Group)

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Transition states</th>
<th>Effect of increasing the polarity of the solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. S_N2 reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuc^- + R-LG</td>
<td>Nuc^6----R----LG^6^-</td>
<td>Retards the reaction</td>
</tr>
<tr>
<td>Nuc + R-LG</td>
<td>Nuc^6----R----LG^6^-</td>
<td>Speeds the reaction</td>
</tr>
<tr>
<td>Nuc^- + R-LG^+</td>
<td>Nuc^6----R----LG^6^+</td>
<td>Retards the reaction</td>
</tr>
<tr>
<td>Nuc + R-LG^+</td>
<td>Nuc^6----R----LG^6^+</td>
<td>Retards the reaction</td>
</tr>
<tr>
<td>B. S_N1 reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-LG</td>
<td>R^6^+----LG^6^-</td>
<td>Speeds the reaction</td>
</tr>
<tr>
<td>R-LG^+</td>
<td>R^6^+----LG^6^+</td>
<td>Retards the reaction</td>
</tr>
</tbody>
</table>
Figure 11.3
A. A reaction coordinate diagram where the higher polarity solvent leads to better solvation of all species, but preferentially solvates the reactant. Entry 1 in Table 11.2 would fit this scenario. B. A reaction coordinate diagram where the higher polarity solvent leads to better solvation of all species, but preferentially solvates the activated complex. Entry 2 in Table 11.2 would fit this scenario.
Many highly polar solvents, such as DMF and DMSO are aprotic, and negative nucleophiles are very reactive in these solvents. Therefore, when changing from a polar protic solvent to a polar aprotic solvent, dramatic rate increases are observed for S\textsubscript{N}2 reactions that involve negatively charged nucleophiles, such as \textsuperscript{-}OH, \textsuperscript{-}N\textsubscript{3}, \textsuperscript{-}CN, etc.

One problem for this is poor solubility of nucleophiles. In this case, a crown ether is added.

\[
\text{Sol}^+ - \text{O}^- - \text{O-Sol}^+ \\
\text{Sol}^+ - \text{O}^- \\
\text{Sol}^+ \text{M}^+ - \text{O-Sol}^+ \\
\text{Sol}^+ - \text{N}_3
\]

Table 11.3
Relative Rate Constants (\(k_{rel}\))
for the Reaction of Chloride with Methyl Iodide*  

<table>
<thead>
<tr>
<th>Solvent</th>
<th>(k_{rel})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>0.9</td>
</tr>
<tr>
<td>Water</td>
<td>1.0</td>
</tr>
<tr>
<td>Formamide</td>
<td>14.1</td>
</tr>
<tr>
<td>Nitromethane</td>
<td>(1.41 \times 10^4)</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>(3.58 \times 10^3)</td>
</tr>
<tr>
<td>DMF</td>
<td>(7.08 \times 10^5)</td>
</tr>
<tr>
<td>Acetone</td>
<td>(1.41 \times 10^6)</td>
</tr>
</tbody>
</table>

The extent of solvation of the leaving group in both $S_N1$ and $S_N2$ reactions affects the rate, too. In both reactions, the charge on the leaving group is changing during rds. Polar protic solvent enhance the departure of leaving groups that are developing negative charge. The addition of electrophilic reactants can enhance the leaving group departure even further by prior coordination to the leaving group. The most common example of this is addition of a silver salt to an alkyl halide (R-X), where the metal enhances the departure of the halide and results in a precipitate of AgX.

11.5.8 An overall picture of $S_N2$ and $S_N1$ reactions

$S_N2$ reaction; relatively straightforward
$S_N1$; more complex
-> the separated ion, solvent-separated ion, or contact ion pair

Figure 11.4
A variety of pathways for $S_N2$ and $S_N1$ reactions.
11.5.9 Nucleophiles

1. Nu\(^-\) -> high solvation (eg. hard nucleophilies) -> lower the ground state energy -> increase in activation energy -> slower rate
2. Stronger bond between the nucleophilic atom and carbon -> lower activation energy -> increase rate
3. Nu\(^-\) -> bulky -> increase nonbonding repulsions -> increase activation energy -> slower rate
4. Nucleophilicity with high electronegative atom -> difficulty to donate electron to a reactant
   O < N < S
5. Polarizability; more polarizability -> increase rate due to easy donation of electron to a reactant

6. Same atoms; basicity와 nucleophilicity 일치
   MeO\(^-\) > PhO\(^-\) > AcO\(^-\) > NO\(_3^-\)
7. 같은 족일 때 아래로 갈수록 nucleophilicity 증가
   I\(^-\) > Br\(^-\) > Cl\(^-\) > F\(^-\)
   PhSe\(^-\) > PhS\(^-\) > PhO\(^-\)
   Why? Electronegativity, polarizability, solvation
11.5.10 Leaving groups

* Conjugate base of strong acid -> good leaving group

\[
\begin{array}{c}
\text{CF}_3\text{CO}_2^- & \text{CH}_3\text{CO}_2^- \\
k_{rel} \times 10^6 & 1
\end{array}
\]

\[
\begin{array}{c}
\text{4-NO}_2\text{PhSO}_3^- & \text{4-CH}_3\text{PhSO}_3^- \\
k_{rel} & 10 \quad 1
\end{array}
\]

I\(^-\) > Br\(^-\) > Cl\(^-\) >> F\(^-\)

\(\text{CF}_3\text{SO}_3^-(\text{triflate, trifluoromethanesulfonate}); \text{highly reactive}\)

* Silver salts are frequently used to accelerate substitution of unreactive halides

\[\text{R-Br} + \text{HO}^- \rightarrow \text{R-OH} + \text{Br}^-\]

\[\text{R--Br--Ag}\]

* Diazonium salts

\[
\begin{array}{c}
\text{R-NH}_2 + \text{NaNO}_2 \xrightarrow{\text{H}^+} \text{R-N=O} + \text{H}_2\text{O} \\
\xrightarrow{\text{H}^+} \text{R-N=N-OH} \xrightarrow{\text{H}^+} \text{R=N}_2^+ + \text{H}_2\text{O}
\end{array}
\]

\text{good leaving group}
11.5.11 Structure-function correlations with the R group

*Effect of R group structure on $S_N2$ reactions*

Table 11.5
Average Relative Rates of $S_N2$ Substitution Reactions on Various R–X Species

<table>
<thead>
<tr>
<th>R group</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>1</td>
</tr>
<tr>
<td>Ethyl</td>
<td>$3.3 \times 10^{-1}$</td>
</tr>
<tr>
<td>Propyl</td>
<td>$1.3 \times 10^{-2}$</td>
</tr>
<tr>
<td>Isopropyl</td>
<td>$8.3 \times 10^{-4}$</td>
</tr>
<tr>
<td>$t$-Butyl</td>
<td>$5.5 \times 10^{-5}$</td>
</tr>
<tr>
<td>Neopentyl</td>
<td>$3.3 \times 10^{-7}$</td>
</tr>
<tr>
<td>Allyl</td>
<td>1.3</td>
</tr>
<tr>
<td>Benzyl</td>
<td>4.0</td>
</tr>
</tbody>
</table>

"*Estimated from Cook, D., and Parker, A. J.
Electronic effect – less significant than steric effect. However, these effects can be important.
This orbital results from addition of the lone pair on the nucleophile to the antibonding R-X bond. It can mix with $\pi^*$ orbitals of the alkenyl or phenyl group.

Alternative explanation: inductive effect. -> Electron withdrawing nature of the sp$^2$ carbons of a vinyl or phenyl group makes the carbon more electrophilic, and therefore more reactive toward nucleophilic attack.

Other groups adjacent to the leaving group can also be expected to stabilize an S_N2 transition state by resonance, including cyano and carbonyl. However, the effect actually depends upon the nucleophile.
Effect of R group structure on $S_N1$ reactions

Alkyl groups

$$k_{CH_3}/k_{Ph} = 5.5 \times 10^4$$  
$$k_{Ph}/k_{CH_3} = 4.6 \times 10^3$$

alkyl group substitution: hyperconjugation 

Ph $\rightarrow$ resonance stabilization

Table 11.7
Hammett $\rho$ Values for $S_N1$ Solvolysis
Reactions of Various R–X Structures

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant†</th>
<th>$\rho$ Value</th>
<th>Experimental conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[X \text{PhCl} ]</td>
<td>$-2.68$</td>
<td>40% Ethanol/60% diethylether, 0 °C</td>
</tr>
<tr>
<td>2</td>
<td>[X \text{OpNB} ]</td>
<td>$-3.82$</td>
<td>80% Aqueous acetone, 25 °C</td>
</tr>
<tr>
<td>3</td>
<td>[X \text{HCl} ]</td>
<td>$-4.06$</td>
<td>2-Propanol, 25 °C</td>
</tr>
<tr>
<td>4</td>
<td>[X \text{CH}_3 \text{Cl} ]</td>
<td>$-4.54$</td>
<td>90% Aqueous acetone, 25 °C</td>
</tr>
<tr>
<td>5</td>
<td>[X \text{OpNB} ]</td>
<td>$-4.60$</td>
<td>80% Aqueous acetone, 25 °C</td>
</tr>
<tr>
<td>6</td>
<td>[X \text{OpNB} ]</td>
<td>$-5.15$</td>
<td>80% Aqueous acetone, 25 °C</td>
</tr>
</tbody>
</table>

by Hammon postulate, the transition state would be most reactant-like, thereby having the least cationic character. -> 치환기의 영향이 적다.
**CN or CO groups**

CN or CO; electron withdrawing via an inductive effect, but donate electrons via resonance

\[
\begin{align*}
  &\text{inductive effect} \\
  &\text{resonance}
\end{align*}
\]

Therefore, the electron withdrawing cyano and carbonyl groups actually impede SN1 reactions more when they are one carbon away from the carbenium ion.

**Resonance structures**

**Heteroatoms**

Stabilize a carbenium ions by resonance

\[-\text{thereby accelerate } S_N1 \text{ reactions.}\]

N: the best at stabilizing a carbenium ion

S: a variable effect in the resonance stabilization;

its orbitals are larger than those of C and hence the sizes are mismatched, but S is very polarizable.

**Resonance structures**
Carbenium ions are stabilized by double bond.

Figure 11.7
Solvolysis of cholesteryl tosylate enjoys an extra stabilization due to the geometry of the adjacent double bond.

Solvolysis is ca. 100 times faster than without the double bond.
11.5.12 Carbocation rearrangement
Whenever a carbocation is an intermediate in a mechanism, rearrangements are possible.
Stereochemical requirements for carbocation rearrangements

Carbocations are in general fluxional molecules (유동성 분자)

Rate of these degenerate shifts at -139 °C: $3.1 \times 10^7 /s$
(all five carbons become equivalent in $^{13}$C NMR)
Carbocation Rearrangements in Rings

We have presented carbocation rearrangements in the context of substitution reactions. Yet, rearrangements and issues that are relevant to carbocation structure are applicable to any reaction involving carbocations—namely, additions, eliminations, rearrangements, etc. One example is the acid-catalyzed ring opening of epoxides.

Unusual rearrangements occur in the acid-catalyzed ring opening of large-ring epoxides, and with other reactions that create carbocations within large rings. The acid-catalyzed ring opening of epoxy cyclooctene in 90% formic acid/10% water gives the products shown below, in addition to the expected trans-1,2-cyclooctanediol.

A hydrogen from across the ring has migrated to yield the products. This kind of a migration is referred to as a transannular shift. In Chapter 2 transannular strain (Figure 2.13) was discussed. It arises from steric repulsions between hydrogens across from each other in medium-sized rings. The hydrogens in position 5 from the cationic site shown below are in close proximity to the cationic carbon and they can shift across the ring.

The resulting 1,4-diol is exclusively cis, although the carbenium ion should lead to both cis and trans products. Therefore, the mechanism involves some extent of migration of the hydrogen during the ring opening, creating a bridged carbonium ion similar to those discussed with regards to non-classical carbocations (see Section 11.5.14). The hydrogen will migrate to the backside of the epoxide as it opens, and attack by water occurs from the top side, resulting in cis stereochemistry.

11.5.13 Anchimetric assistance (neighboring group participation) in $S_N1$ reactions

**Heteroatoms: O, N, S, X**

**Figure 11.8**

A. Anchimeric assistance in the solvolysis of a cyclohexyl tosylate.

B. The symmetrical intermediate proposed.

cis compound $\rightarrow$ slower solvolysis (no anchimetric assistance) $\rightarrow$ trans product
Table 11.9
Relative Rate Constants and Activation Parameters for the Acetolysis of 2-Substituted Cyclohexyl Broxylates

\[
\text{HOAc} \rightarrow \text{Ac}^+ \text{Y}^{-} \rightleftharpoons \text{AcOH} + \text{Y}^+ 
\]

<table>
<thead>
<tr>
<th>Y</th>
<th>(k_{rel})</th>
<th>(\Delta H^\dagger) (kcal/mol)</th>
<th>(\Delta S^\dagger) (eu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1</td>
<td>26</td>
<td>1.5</td>
</tr>
<tr>
<td>trans-OAc</td>
<td>0.24</td>
<td>26</td>
<td>-4.2</td>
</tr>
<tr>
<td>cis-OAc</td>
<td>3.8 \times 10^{-4}</td>
<td>31</td>
<td>-3.5</td>
</tr>
<tr>
<td>trans-Br</td>
<td>0.1</td>
<td>28</td>
<td>-0.8</td>
</tr>
<tr>
<td>trans-OMe</td>
<td>0.06</td>
<td>27</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

OAc; EWG -> slower than Y =H

trans; anchimetric assistance
cis; no

some anchimetric assistance because these are faster than cis-OAc

Anchimeric Assistance in War

Although chemistry has played a large role in improving human life, it can also be put to negative uses. In World War I, chemical weapons were commonly used, and mustard gas was the most prevalent. The solvolysis of mustard gas occurs with no kinetic dependence upon the nucleophile. The reason for the $S_N1$ behavior is anchimeric assistance by the neighboring sulfur, creating a cyclic sulfonium ion. This cyclic structure rapidly reacts with a variety of nucleophiles, including water, but also proteins and other biomolecules. These reactions create HCl, which severely burns and blisters the skin.

Conclusion: if no neighboring group participation
$\rightarrow$ retardation of rate due to inductive effect by an electronegative heteroatoms
Arenes

Retention of configuration

Figure 11.9
A. Pathway followed in the solvolysis of erythro-3-phenyl-2-butylltosylate.
B. Pathway followed in the solvolysis of threo-3-phenyl-2-butylltosylate.
**π-bonds**

\[
\begin{align*}
\text{anti} & : OTs \\
\text{syn} & : TsO \\
\text{AcOH acetolysis} & : 10^{11} \\
\end{align*}
\]

\[
\begin{align*}
\text{product} & : OAc \\
\text{allylic cation} & : AcO \\
\text{increase in strain energy} & : (\text{sp}^3 \rightarrow \text{sp}^2)
\end{align*}
\]
11.5.14 $S_N1$ reactions involving non-classical carbocations

**Norbornyl cation**

---

**Figure 11.10**
The accepted solvolysis pathway for 2-norbornyl systems.
Cyclopropylcarbinyl carbocation

Another one of the more extensively investigated carbocation system derives from $S_N1$ reactions on homoallyl, cyclobutyl or cyclopropylcarbinyl derivatives. Solvolyses of all three of these systems give very interesting product mixtures.

Solvolysis 
ca. $10^6$ times faster

Similar product ratios
-> there is likely a common intermediate in all three of these reactions
Considerable evidence exists in support of both the bicyclobutonium and cyclopropylcarbinyl carbenium ions as important contributors to $\text{C}_4\text{H}_7^+$. 
11.5.15 Summary of carbocation stabilization in various reactions

- allyl, benzyl, cyano, C=O

![Diagram](image)

**Figure 11.11**
Various ways to stabilize carbenium ions. All are similar in that filled orbitals aligned with the empty p orbital on the cation center will donate electrons toward that center.
11.5.16 The interplay between substitution and elimination

Figure 11.12
The interplay between nucleophilic substitution and elimination in 1°, 2°, and 3° systems. See the text for a discussion of certain exceptions and special cases. Adapted from a scheme presented in Kemp, D.S., and Vellaccio, F. (1980). Organic Chemistry, Worth Publishers, New York, pp. 227–228.
Isomerization and rearrangement

11.8. Migrations to electrophilic carbonds

11.8.1 Pinacol rearrangement

Scheme 11.12
The pinacol rearrangement of the compound pinacol.

Table 11.12
Relative Migratory Aptitudes in the Pinacol Rearrangement*

<table>
<thead>
<tr>
<th>R group</th>
<th>Migratory aptitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Methoxyphenyl</td>
<td>500</td>
</tr>
<tr>
<td>p-Tolyl</td>
<td>15.7</td>
</tr>
<tr>
<td>p-Biphenyl</td>
<td>11.5</td>
</tr>
<tr>
<td>m-Tolyl</td>
<td>1.95</td>
</tr>
<tr>
<td>m-Methoxyphenyl</td>
<td>1.6</td>
</tr>
<tr>
<td>Phenyl</td>
<td>1.0</td>
</tr>
<tr>
<td>p-Chlorophenyl</td>
<td>0.66</td>
</tr>
</tbody>
</table>


EDG (o, p) -> accelerate migration
EWG in all positions -> retard migration
11.8.4 Stereoelectronic and stereochemical considerations in the Pinacol rearrangement

The pinacol rearrangement can be initiated from either alcohol, which can complicate mechanistic analysis. Therefore, many studies have investigated a related reaction called the semi-pinacol rearrangement. Only groups that are antiperplanar to the LG can migrate.
11.8.5 Benzilic acid rearrangement

\[
\text{Benzil} \xrightarrow{1. \text{NaOH}} \xrightarrow{2. \text{Acid}} \text{Benzilic acid}
\]
11.9. Migrations to electrophilic heteroatoms

11.9.1 Beckmann rearrangement: transformation of oxime to an amide
Under conditions where E and Z forms cannot interconvert (acid can catalyze the isomerization), the group anti to the leaving group is one that migrates.

-> this supports a mechanism involving simultaneous migration.

Picric acid; good LG -> no need of acid -> no isomerization between E and Z

The reaction correlates well with Hammett $\sigma^+$ value.

-> Rearrangement step; rate determining step
11.9.2 Hofmann rearrangement: transformation of amides to amines by Br₂ in basic media

\[
\text{amides} \xrightarrow{\text{Br}_2, \text{NaOH}} R'\text{NH}_2 + \text{CO}_2
\]

[Reaction mechanism diagram]

N-bromoamide
11.9.3 Schmidt rearrangement: transformation of aldehyde or ketone to amides by \( \text{HN}_3 \)

To support this mechanism, a vinyl azide gives the same intermediate and product. The group anti to the LG migrates just like the Beckmann rearrangement.
11.9.4 Baeyer-Villiger oxidation: oxidation of aldehyde or ketone to ester by peracids

For most ketones and aldehydes, rds is the rearrangement, because significant substituent effects for the migrating group are found. (EDG -> migration)
11.9.5 Favorskii rearrangement and other carbanion rearrangements

Favorskii rearrangement

\[ \text{Bromo ketone} \xrightarrow{1. \text{OH}^-/H_2O} \xrightarrow{2. \text{Acid}} \text{Cyclic species} \]

\[ \text{Oxallyl species} \]

\[ \text{Product} \]

\[ \text{Acid Workup} \]
Other carbanion rearrangements