4.3 Ambident Nucleophiles

Nucleophiles which have two sites at which an electrophile may attack are called ambident.

- hard electrophiles reacting at the harder nucleophilic site
- soft electrophiles reacting at the softer site

4.3.1 Thiocyanate ion, Cyanide ion and Nitrite ion (and the Nitronium Cation)

isomerization

<table>
<thead>
<tr>
<th>kinetic</th>
<th>isomerization</th>
<th>thermodynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^+$ fast</td>
<td>$-$</td>
<td>$R^+$ slow</td>
</tr>
<tr>
<td>$R-N=C=S$</td>
<td>4.40</td>
<td></td>
</tr>
<tr>
<td>$R^+$</td>
<td>$C=N$</td>
<td>$R^+$</td>
</tr>
<tr>
<td>$R-C=N$</td>
<td>4.42</td>
<td></td>
</tr>
<tr>
<td>$R^+$</td>
<td>$O-N=O$</td>
<td>$R^+$</td>
</tr>
<tr>
<td>$R^+$</td>
<td>$O$</td>
<td></td>
</tr>
</tbody>
</table>

Reaction is so fast that the selectivity is not controlled.
4.3.2 Enolate Ions

Why does an enolate ion react with some electrophiles at carbon and with others at oxygen?

![Chemical structures and orbital energies](image)

4.3.3 Allyl Anions

4.3.3.1 X-substituted Allyl Anions

![Chemical structures](image)

The harder the leaving group, the lower the proportion of C-alkylation
The softer the leaving group, the lower will be the energy of the LUMO.
**Fig. 4.3** Estimating the coefficients of the HOMO of an X-substituted allyl anion

Li vs Zn

C-Substituted Allyl Anions - Pentadienyl Anions

Both α attack and γ attack

**Fig. 4.4** Electron distribution in the cyclohexadienyl system

(a) Calculated total π-electron populations  
(b) Calculated values for c for the HOMO  
(c) Spin densities obtained from ESR and converted to c values using the McConnell equation
Z-Substituted Allyl Anions - Dienolate Ions

α attack

\[
\begin{align*}
\text{Si}_2\text{B} &\rightarrow \text{R} \quad \text{Me} \rightarrow \text{Si}_2\text{B} \\
4.70 &\quad 4.71 \\
\text{Me}_2\text{SO}_4 &\rightarrow \text{mes} \rightarrow \text{Si}_2\text{B} \\
\text{O} &\rightarrow \text{Si}_2\text{B} \\
\text{Li} &\rightarrow \text{Li} \\
\text{Ph} &\rightarrow \text{Me} \\
\text{4.72} &\rightarrow \text{4.73} \\
\end{align*}
\]

α_γ attack 72:28  α_γ 34:66

\[
\begin{align*}
\text{BH} &= \text{Si}_2\text{B} \\
\text{BH} &= \text{sec-isoamyl}
\end{align*}
\]

Dienol ether

\[
\begin{align*}
\text{Me}_2\text{SiO} &\rightarrow \text{Br} \quad \text{ZnBr}_2 \text{cat.} \\
\text{O} &\rightarrow \text{O} \\
\text{4.76} &\rightarrow \text{4.77} \\
\end{align*}
\]

γ carbon is more nucleophilic site towards soft electrophile

\[
\begin{align*}
\text{γ} &\rightarrow \text{α} \quad \text{OMe} \\
\text{1.053} &\rightarrow \text{1.071} \\
\text{4.77} &\rightarrow \text{4.78} \\
\end{align*}
\]

Fig. 4.5 Crude estimate of the coefficients of the π orbitals of a 1-Z-substituted allyl anion

Fig. 4.6 Crude estimate of the coefficients of the π orbitals of a 1-X-substituted diene

\[
\begin{align*}
\text{NC} &\rightarrow \text{Li} \quad \text{Me} \\
\text{4.79} &\rightarrow \text{NC} \\
\text{NMe}_2 &\rightarrow \text{NMe}_2 \\
\text{50:50}
\end{align*}
\]
4.3.4 Aromatic Electrophilic Substitution

4.3.4.1 Molecular orbitals of the Intermediates in Electrophilic Attack on Monosubstituted Benzenes

Origin of \( \sigma-p \)-regioselectivity

Wheland intermediate

Curly arrows illustrate the electron distribution in the frontier orbital, and for reaction kinetics it is the frontier orbital that is most important.

But, for the thermodynamic argument, we need to know the energy of all of the filled orbitals, and not just one of them.

\[ \psi_3 \text{ in 4.87 does not lower the energy level} \text{ because there are no } \pi \text{-bonding interactions between any of the adjacent atoms-it is a nonbonding molecular orbital.} \]

1.4.3 Longer Conjugated System

Fig. 4.7 Coefficients and energies of the \( \pi \) molecular orbitals of the intermediates in the electrophilic substitution of the benzyl anion at the ortho, para, and meta positions

Fig. 1.42 The energies and coefficients of the \( \pi \) molecular orbitals of the smaller conjugated systems
Model for an $Z$-substituted Benzene Ring

$m$-regioselectivity

\[
\begin{align*}
4.88 & \quad \overset{E^+}{\longrightarrow} \quad 4.89 + 4.90 + 4.91 \\
(\psi_1 + \psi_2) & \text{of 4.91 is greater than those of 4.89 and 4.96.}
\end{align*}
\]

4.3.4.2 The Frontier Orbitals of Monosubstituted Benzenes

The endothermicity of $1.28\beta$ on the right is not much greater than that for benzene ($1.27\beta$); however, the presence of two positive charges in the intermediate on the right has not been allowed for, and this will obviously raise the energy of this intermediate.

Fig. 4.8 Relative rates of aromatic substitutions based on product-like character in the transition structure

Benzyl system

Fig. 4.9 The lower $\pi$ orbitals of the benzyl system
Rule of Orbital Coefficients Estimation

(1) Place a zero on the smaller number of alternate atoms: node

(2) the sum of the coefficients on all the unmarked atoms joined to any one of the marked atoms must be zero

\[ f = 2c_3^2 + c_2^2e^{-D\Delta\lambda} \]

Where \( C_3 \) and \( C_2 \) are the coefficients at that site in the two highest-energy \( \pi \) orbitals \( \psi_3 \) and \( \psi_2 \), respectively, with the one labelled \( \psi_3 \) having arbitrarily the higher energy, \( \Delta\lambda \) is the difference in energy between \( \psi_3 \) and \( \psi_2 \), and \( D \) is a constant (3 is used in fact) representing some kind of measure of the contribution of \( \psi_2 \) to the overall effect.


4.3.4.3 Halogenobenzenes

A mixture of the properties of the \( Z \)- and \( X \)-substituted benzenes

Slow reaction with \( o/p \) directing

The \( o/p \) orientation is mainly dependent on the coefficients and overall charges at each of the atoms, and the reduced rate could be largely determined by the energies of the higher occupied orbitals.
4.3.4.4 Frontier Orbitals of Polycyclic Aromatic Molecules.

Fig. 4.11 Frontier electron populations and the sites (arrowed) of nitrination

4.3.4.5 ortho/para Ratios

Table 4.5 $\alpha/2p$ ratios in aromatic nitration of PhX as a function of substituent R

<table>
<thead>
<tr>
<th>Type of substituent</th>
<th>R</th>
<th>$%\alpha$</th>
<th>$%\beta$</th>
<th>$%\delta$</th>
<th>$\alpha/2p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>OMe</td>
<td>17</td>
<td></td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>C</td>
<td>Ph</td>
<td>53</td>
<td>47</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>Z</td>
<td>CO$_2$Et</td>
<td>28</td>
<td>68</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>Z</td>
<td>NO$_2$</td>
<td>6</td>
<td>93</td>
<td>0.25</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Steric effect

3.50$\beta$

(3.05$\beta$)

(2.93$\beta$)

4.3.4.6 Pyrrole, Furan and Thiophen

More stable

Table 4.6 $\alpha/2p$ ratios in aromatic substitution as a function of the electrophile

<table>
<thead>
<tr>
<th>Electrophilic substitution</th>
<th>$\alpha/2p$ for toluene (Ph-X)</th>
<th>$\alpha/2p$ for biphenyl (Ph-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxylation</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>Chlorination with Cl$^+$</td>
<td>1.63</td>
<td></td>
</tr>
<tr>
<td>Bromination with Br$^+$</td>
<td>1.29</td>
<td>0.69</td>
</tr>
<tr>
<td>Protodehalogenation</td>
<td>1.06–0.3</td>
<td>1.0–0.19</td>
</tr>
<tr>
<td>Protodesilylation</td>
<td>0.84</td>
<td>2.14</td>
</tr>
<tr>
<td>Nitrination</td>
<td>0.72</td>
<td>1.68</td>
</tr>
<tr>
<td>Chlorination with Cl$_2$</td>
<td>0.97–0.25</td>
<td>0.32</td>
</tr>
<tr>
<td>Friedel-Crafts ethylation</td>
<td>0.47</td>
<td>0.41</td>
</tr>
<tr>
<td>Sulfoxide</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Mercuriation</td>
<td>0.25</td>
<td>0.01</td>
</tr>
<tr>
<td>Bromination with Br$_3$</td>
<td>0.25–0.11</td>
<td>0.03</td>
</tr>
<tr>
<td>Friedel-Crafts acetylation</td>
<td>0.0006</td>
<td>very small</td>
</tr>
</tbody>
</table>
4.3.4.7 Pyridine N-oxide

Estimation by the Salem-Klopman Equation

Hardest $SO_2$ : C3
$NO_3^-$ : C4
Softest $HgOAc^-$ : C2

4.4 Electrophilicity

Characterised by having a low-energy LUMO and electron deficiency, either as a full positive charge or as a polarised bond with a partial positive charge at one or more sites

4.4.1 Trigonal Electrophile

Carbonyl groups

acid chlorides > aldehydes > ketones > esters > amides > carboxylate

strong electrophilicity weak

Acid chlorides:

(i) the $\pi$ stabilisation is small, because chlorine is electronegative, and consequently the energy match is poor
(ii) the $\pi$ stabilisation is offset by strong inductive electron withdrawal along the C-Cl bond, raising the electrophilicity of the carbonyl group
(iii) anomeric stabilisation in the tetrahedral intermediate is greater—conjugation of the oxyanion with the C-Cl $\sigma^*$ orbital pulls down the energy of the transition structure.

Stabilisation in the intermediate plays a larger role in determining electrophilicity than the differences in the energy of the starting materials

electrophilicity in alkyl halides in $S_N1$, $S_N2$, E1 and E2 reactions

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

Opposite order in aromatic halides $(F^- > Cl^- > Br^- > I^-)$

$X = F$ vs $Cl$ (I)
$600 (3100)$ times faster

Anomeric effect

$X = I$
$X = Br$
$X = Cl$
$X = F$

Fig. 4.14 Relative energies of starting materials, transition structures and tetrahedral intermediates for nucleophilic attack on aryl halides
### 2.2.3.3 The Anomeric Effect

The Anomeric Effect

- ![Image of Anomeric Effect](image)

4.4.2 Tetrahedral Electrophiles

Electrophilicity of alkyl halides in S\(_{N2}\) reactions:
methyl > ethyl > isopropyl > tert-butyl.

Steric effect and hyperconjugation which lowers the energy of the LUMO of the C-Br bond in tert-butyl bromide more than that in methyl bromide also reduces the coefficient on, and at the same time lowers the overall energy of the starting material.

- ![Image of Steric Effect](image)

4.4.3 Hard and Soft Electrophiles

The hardest electrophiles are small, charged and have a relatively high-energy LUMO, and soft electrophiles are large, have little charge and have a conspicuously low-energy LUMO.

- ![Image of Hard and Soft Electrophiles](image)

Even within a group of very similar electrophiles, all soft like primary alkyl halides undergoing S\(_{N2}\) displacement, the scale of electrophilicity is not constant.

- ![Image of Hard and Soft Electrophiles Example](image)

4.5 Ambident Electrophile

Large LUMO Coefficient

- ![Image of Ambident Electrophile](image)

Fig. 4.15 LUMOs of some carbon electrophiles and the sites of nucleophilic attack upon them
4.5.1 Aromatic Electrophiles

Pyridinium Cation

Charge

thermodynamically stable

hard

Nu\(^{-}\)

products

soft

Nu\(^{-}\)

products

LUMO

4.5.1.2 ortho- and para-Halogenonitrobenzenes.

Linear-conjugated

faster

Cross-conjugated

4.131

4.132

Table 4.8 Effect of the nucleophile on the relative rates of attack on the fluoro and chlorodinitrobenzenes

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>(k_F/k_Cl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H(_2)N(_2))(_2)O=S=</td>
<td>0.11</td>
</tr>
<tr>
<td>PhS(^{-})</td>
<td>3.26</td>
</tr>
<tr>
<td>H(_2)N(^{-})</td>
<td>33</td>
</tr>
<tr>
<td>MeO(^{-})</td>
<td>460</td>
</tr>
<tr>
<td>Me(^{-})</td>
<td>890</td>
</tr>
<tr>
<td>F(^{-}) or Cl(^{-})</td>
<td>3160</td>
</tr>
</tbody>
</table>

Fig. 4.16 Relative reactivity of halogenonitrobenzenes
4.5.2 Aliphatic Electrophiles

4.5.2.1 α,β-Unsaturated Carbonyl Compounds

Thermodynamically stable

![Chemical equation and structures](image)

4.5.2.2 Allyl Halides

In polar solvent $S_n2$, $S_{n1}$, $S_{n1'}$

![Chemical reactions and structures](image)
4.5.2.3 Unsymmetrical Anhydrides

LiAlH₄: 100 : 0 (R = MeO)
88 : 12 (R = Me)

Elimination vs. Substitution

G. Biale, JACS 1971, 93, 4735

Singlet carbene

Triplet carbene

concerted

stepwise

Carbene

HOMO: high   LUMO: low   High Reactivity
Nucleophilic and electrophilic

Fig. 4.19   The filled and lowest unfilled molecular orbitals of methylene

4.202  4.203
Nucleophilic Carbenes

Electrophilic Carbenes

Cycloaddition, insertion into C-H

Aromatic Carbene

Fig. 4.20 Frontier orbital interactions for carbenes with electrophilic and nucleophilic reagents
The dipole of pyrrole points in the direction 4.120. The explanation usually offered is that the orbitals are polarised in the sense illustrated by the canonical structures 4.121 and 4.122. This cannot be the reason, because this is only one of the π orbitals, the HOMO. We can see on the drawing 4.104 that the total π charge, is higher on the nitrogen atom and lower on the carbon atoms. The same must be true in the σ framework. Why then is the dipole pointing in the other direction?