5 - REACTIVITY OF SOME SUBSTITUTED AROMATIC COMPOUNDS

1. Aromatic Amines

a) Basicity ($SF/SFS$ 20.3 A)

- approx. $10^6$ times less basic than $R-NH_2$
- approx. $10^6$ times more acidic than $R-NH_3^+$

Reasons:
1. electron withdrawing effect of phenyl ring compared to alkyl group
2. delocalization of the unshared pair of electrons on the amino group. This means the electrons are less available for forming the bond with the $H^+$. 

The $pK_a$'s of various anilines can be readily influenced by the substituents on the ring. The parent, unsubstituted system ($X = H$) has a $pK_a$ of 4.60.
2. Diazonium Salts \((SF/SFS\ 20.6-20.8)\)

As seen above, diazonium compounds can be generated with \(\text{NaNO}_2\) and acid. The general procedure involves the addition of a cold aq. solution of the \(\text{NaNO}_2\) to the amine salt dissolved in mineral acid, while keeping the temperature at 0-5 °C. One can watch for excess \(\text{HNO}_2\) by using starch-KI paper. Primary alkylamines, \(\text{R-NH}_2\), also react with nitrous acid, but the alkanediazonium ions usually lose \(\text{N}_2\) (g) to give \(\text{R}^+\), even with primary alkyl groups, leading to the expected products. The \(\text{R}^+\) formed is sometimes referred to as a "hot" carbonium ion.

\[
\begin{align*}
\text{ROH, RCl or alkene} & \quad \uparrow \quad \text{react} \\
\text{R-NH}_2 + \text{HONO} + \text{H}^+ + \text{Cl}^- & \rightarrow [\text{R-N=N=N}] \rightarrow \text{R}^+ + \text{N}_2 \\
+ & \quad \text{rearrangement} \\
2\text{H}_2\text{O} + \text{Cl}^- & \rightarrow \text{R}^+ \leftarrow \text{ROH, RCl or alkene} \\
\end{align*}
\]

Aromatic diazonium salts are stable if kept cold (0-5 °C) and in solution, but they often decompose violently when isolated. Their stability (compared to alkanediazonium salts) is due in part to resonance stabilization of the diazonium ion and in part to the very high energy of the aryl cation that would result from the loss of \(\text{N}_2\) (g).
Ar+ is extremely unstable. The vacant sp² orbital cannot overlap with the 2p orbitals involved in the \( \pi \) bonding.

a) Mechanism of Formation

\[
\begin{align*}
\text{HO-N=O} + \text{H}^+ & \rightleftharpoons \text{H}_2\text{O}^-\text{N}=\text{O} & \rightleftharpoons \text{H}_2\text{O} + \text{N}^+\text{O} \\
\text{Ar-NH}_2 + \overset{\cdot}{\text{N}}\text{=O} & \rightleftharpoons \text{Ar-NH}_2\text{N}=\text{O} & \rightleftharpoons \text{Ar-NHN}=\text{O} & \rightleftharpoons \text{Ar-N=NH-}\overset{\cdot}{\text{O}}\text{H} \\
\text{Ar-N=N-OH} + \text{H}^+ & \rightleftharpoons \text{Ar-N=N-}\overset{\cdot}{\text{O}}\text{H}_2 & \rightleftharpoons \text{H}_2\text{O} + \text{Ar-N=NH-}\overset{\cdot}{\text{N}}
\end{align*}
\]

b) Reactions of Arenediazonium Salts

Many reactions of arenediazonium ions are those expected of the aryl cation, formed only because \( \text{N}_2 \) is such a good leaving group. In such reactions, the rate is first order in \([\text{ArN}_2^+]\) and is independent of the concentration of nucleophile.

\[
\text{Ar}^-\overset{\cdot}{\text{N}}\equiv\text{N} \xrightarrow{\Delta} \text{Ar}^+ + \text{N}_2
\]

Other reactions, particularly those catalyzed by Cu(I) salts, likely involve the radical \( \text{Ar}^- \) as an intermediate. In some cases an adduct of the diazonium ion and the nucleophile is first formed. This intermediate may then decompose to \( \text{Ar}^+ \) or \( \text{Ar}^- \) which reacts further.
\[ \text{Ar}^+\text{N}≡\text{N} + \text{Cu(I)X} \rightleftharpoons \text{Ar-}\text{N=N•} + \text{Cu(II)X}^+ \]

\[ \text{Ar-}\text{N=N•} \rightarrow \text{N}_2 + \text{Ar•} \quad \text{CuX or CuX}^+ \rightarrow \text{ArX} \]

i) Thermal Decomposition

\[ \text{Ar}^+\text{N}≡\text{N} \xrightarrow{\Delta} \text{Ar}^+ + \text{N}_2 \xrightarrow{X^-} \text{ArX} \]

In the presence of nucleophiles:

\[
\begin{align*}
\text{N}_2^+ & \xrightarrow{\Delta, \text{H}_2\text{O}} \text{OH}^- \\
\text{EtO-S-S-K}^+ & \xrightarrow{\Delta, \text{KI}} \text{I}^- \xrightarrow{\text{potassium ethyl xanthate}} \text{N}_2
\end{align*}
\]

(best with hydrosulfate diazonium salt to avoid ArCl formation)

\[
\begin{align*}
\text{S-SOEt} & \xrightarrow{^\cdot\text{OH}, \text{H}_2\text{O}} \text{SH}^- \\
\text{SH}^- & \xrightarrow{\text{benzenethiol}} \text{COS} + \text{EtOH}
\end{align*}
\]

(best with hydrosulfate diazonium salt to avoid ArCl formation)
ii) Sandmeyer Reaction

\[
\begin{align*}
&\text{NH}_2\text{CH}_3 + \text{NaNO}_2 \xrightarrow{\text{HBr, 0-5 °C}} \text{Br}^+\text{Br}^- \xrightarrow{\text{CuBr}} \text{Br}^+

&\text{NH}_2\text{CO}_2\text{H} + \text{NaNO}_2 \xrightarrow{\text{HCl, 0-5 °C}} \text{Cl}^-\text{CO}_2\text{H} \xrightarrow{\text{CuCl}} \text{Cl}^-\text{CO}_2\text{H}

&\text{NH}_2\text{CH}_3 + \text{NaNO}_2 \xrightarrow{\text{HCl, 0-5 °C}} \text{CN}^+\text{Cl}^- \xrightarrow{\text{CuCN}} \text{CN}^+
\end{align*}
\]

iii) Gatterman Reaction

\[
\begin{align*}
&\text{NH}_2\text{NO}_2 \xrightarrow{\text{NaNO}_2} \text{NO}_2^-\text{BF}_4^- \xrightarrow{\Delta, \text{Cu powder}} \text{NO}_2^-\text{BF}_4^- \xrightarrow{\text{aq. NaNO}_2} \text{NO}_2^-\text{BF}_4^- + \text{N}_2 + \text{BF}_3
\end{align*}
\]

(tetrafluoroborate salt (filter, wash make suspension in H_2O))
iv) Schiemann Reaction

\[
\begin{align*}
\text{NH}_2 & \quad \text{NaNO}_2 \quad \text{HBF}_4 \quad \Delta \quad \text{as dry salt or} \\
& \quad \text{ppt., filter} \\
& \quad \text{in an inert solvent} \\
& \quad \text{such as THF} \\
& \quad \text{N}_2 \quad \text{BF}_3 \\
\end{align*}
\]

an improved procedure:

\[
\begin{align*}
\text{NH}_2 & \quad \text{Br} \quad \text{NaNO}_2 \quad \text{HPF}_6 \quad \Delta \quad \text{as dry salt} \\
& \quad \text{ppt., filter} \\
& \quad \text{hexafluorophosphoric acid} \\
& \quad + \quad \text{N}_2 \quad + \quad \text{PF}_5 \\
\end{align*}
\]

v) Replacement by H

When ArN\textsubscript{2}\textsuperscript{+} is treated with H\textsubscript{3}PO\textsubscript{2} (hypophosphorous acid) or NaBH\textsubscript{4}, the nitrogen containing group is lost and a hydrogen takes its place. H\textsubscript{3}PO\textsubscript{2} comes as a 50% solution in water. H\textsubscript{3}PO\textsubscript{2} reductions are catalyzed by Cu\textsubscript{2}O. This reaction allows one to use the activating and directing properties of the amino group and later remove it. The H\textsubscript{3}PO\textsubscript{2} can be added to the diazonium salt or the amine can be added to a cold mixture of mineral acid, NaNO\textsubscript{2} and H\textsubscript{3}PO\textsubscript{2}. 

\[
\begin{align*}
\text{NH}_2 & \quad \text{Br} \quad \text{Br} \quad \text{Br} \quad \text{NaNO}_2 \quad \text{H}_2\text{SO}_4 \\
& \quad 0-5 \, ^\circ\text{C} \\
& \quad + \quad \text{H}_2\text{O} \\
& \quad \text{CO}_2\text{H} \\
& \quad \text{H}_3\text{PO}_2 \\
\end{align*}
\]

The current material is best presented in association with some CHEM*270 chemistry. It pertains to the introduction of groups onto phenyl rings by way of electrophilic aromatic substitution. You should recall from your previous course the various methods/reagents for introducing acyl, alkyl, nitro groups, halogens and sulfonic acids. Also, very consequential are the position-directing power and overall activating/deactivating influences of the various group that can be placed on an aromatic ring.

It is important to remember the usefulness of the sulfonic acid group, which can temporarily protect one of more aromatic sites from electrophilic aromatic substitution.

Also important is the reactivity of the amino substituent toward electrophilic aromatic substitution. Usually acetylation is required to diminish the high reactivity and electron rich character of the amino group. The result is a protected nitrogen which does not participate directly in the chemistry, but whose presence still strongly activates the aromatic ring toward electrophilic substitution at the ortho and para sites. Once the required ring transformations are achieved, the nitrogen can be deprotected through removal of the acetyl group. Only on certain occasions is the acetylation not required (See scheme in previous section).
Other valuable reactions which you already know or are new to you are demonstrated. In the following scheme, note the methods for reduction of NO$_2$ to NH$_2$ groups, both in the presence and the absence of a second NO$_2$ group.

The combination of electrophilic aromatic substitution and diazonium substitution methods provides the synthetic chemist with a complementary collection of reactions that provide access to a large number of polysubstituted aromatic systems.
4. **Aryl Halides** *(SF/SFS 21.11)*

You have already encountered two preparations of aryl halides. Those include the electrophilic halogenation of aromatics as was introduced in CHEM*270 and the other is the Sandmeyer reaction of diazonium salts as we have just studied.

Aryl halide do not undergo nucleophilic substitution by an S\(_{N}\)\(_1\) mechanism because the aryl cation, Ar\(^+\), is very high in energy. Substitution by an S\(_{N}\)\(_2\) mechanism is impossible because the backside of the carbon bearing the halogen is blocked and inversion cannot occur.

a) **Addition-Elimination Mechanism**

Aryl halides with at least one activating substituent (-R substituent such as -NO\(_2\), -CN, or carbonyl) \textit{ortho} or \textit{para} to the halogen undergo substitution by an addition-elimination pathway.

![Chemical diagram](image-url)
mechanism:

\[
\text{BrNO}_2 + \text{Nu}^- \rightleftharpoons \text{BrNu} \leftrightarrow \text{BrNu} \leftrightarrow \text{BrNu} \leftrightarrow \text{BrNu} \quad \text{most important}
\]

\[
\text{BrNu} \rightarrow \text{Nu}^- + \text{Br}^-
\]

analogy:

\[
\text{Nu}^- + \text{RCX} \rightleftharpoons \text{RNCX} \rightarrow \text{RCNu}^- + \text{X}^-
\]

acyl halide, anhydride, ester or amide

formation of ester, amide, etc. or hydrolysis

reactivity:

\[
\begin{align*}
\text{O}_2\text{N} & \quad > \quad \text{NO}_2 \\
\text{NO}_2 & \quad > \quad \text{NO}_2
\end{align*}
\]
Stable anionic adducts can be formed when there is a poor leaving group and the ring has several -R substituents.

2,4,6-trinitroanisole  \rightarrow \text{a Meisenheimer complex} \rightarrow 2,4,6-trinitrophenetole

usual reactivity:

Addition is fast for Ar-F and Ar-Cl and is slow for Ar-Br and Ar-I while elimination follows the opposite trend (in all cases Nu\(^-\) = \text{-OCH}_3\) or some other nucleophile that is a poorer leaving group than halide).
b) Elimination-Addition Mechanism (Benzyne Mechanism)

Non-activated halides plus very strong bases (usually $\text{NH}_2^-$ or $\text{RHN}^-$) undergo reaction via an elimination-addition mechanism.

\[
\begin{align*}
\text{CH}_3 \text{CH}_2 \text{Cl} & \xrightarrow{\text{NH}_2^-} \text{NH}_3 (\cdot) \quad \text{CH}_3 \text{C} = \text{NH}_2 + \text{CH}_3 \text{C} = \text{NH}_2 + \text{Cl}^- \\
\text{C} \text{H}_3 \text{Cl} & \xrightarrow{\text{NH}_2^-} \text{NH}_3 (\cdot) \quad \text{C} \text{H}_3 \text{C} = \text{NH}_2 + \text{C} \text{H}_3 \text{C} = \text{NH}_2 + \text{Cl}^- \\
\text{I}^+ & \xrightarrow{\text{NH}_2^-} \text{NH}_3 (\cdot) \quad \text{I}^+ \text{C} = \text{NH}_2 + \text{I}^+ \text{C} = \text{NH}_2 \quad \text{approx. 50%} \quad \text{approx. 50%}
\end{align*}
\]

proposed intermediate: benzyne

\[
\begin{align*}
\text{\textbullet} & \quad \text{or} \\
\text{\textbullet} \\
\text{\textbullet}
\end{align*}
\]
Benzyne is a bent alkyne

Benzyne is so reactive that it reacts at either end of the strained triple bond. Due to pKₐ's any acid-base equilibrium between ArH and NH₂⁻ would lie strongly on the reactant side.

\[
pK_a = ~43 \quad pK_a < 43 \quad pK_a = ~34
\]

Mechanism:

\[
\begin{align*}
\text{products} & \quad \text{fast} \quad \text{NH}_2^- \quad \text{or} \quad \text{NH}_3 \\
\text{X=F:} & \quad k_{-1} \gg k_2 \quad (\text{exchange of H more rapid than loss of X}^-) \\
\text{X=Br, I:} & \quad k_2 \gg k_{-1}
\end{align*}
\]
$k_1 : F > Cl > Br > I$ (decreasing electron withdrawing effect)

$\hat{k}_2 : I > Br > Cl > F$ (usual leaving group abilities)

Net result: reactivity with $\text{NH}_2^-$ in $\text{NH}_3()$:

<table>
<thead>
<tr>
<th>Proton abstraction</th>
<th>C-X bond cleavage</th>
</tr>
</thead>
<tbody>
<tr>
<td>rate determining</td>
<td>rate determining</td>
</tr>
</tbody>
</table>

Br $>$ I $>$ Cl $>>$ F

In substituted aryl halides the more acidic proton is lost:

Benzyne can also be formed by other methods. Grignard-like chemistry:
The decomposition of the diazonium salt of o-aminobenzoic acid (anthranilic acid) gives benzyne:

\[
\text{NH}_2\text{CO}_2\text{H} \overset{\text{C}_5\text{H}_{11}\text{ONO}}{\underset{\text{THF, H}^+}{\xrightarrow{\Delta}}} \text{CO}_2^+ \overset{\Delta}{\xrightarrow{\text{ClCH}_2\text{CH}_2\text{Cl}}} \text{benzyne}
\]

A current favourite:

\[
\text{NH}_2\text{Pb(OAc)}_4 \xrightarrow{\Delta} \text{benzyne} + 2\text{N}_2
\]
5. Phenols and Phenyl Ethers (SF/SFS 21.1-21.4)

a) Synthesis

i) Hydrolysis of Chlorobenzene (Dow Process)

\[
\text{Cl} + 10\% \text{NaOH(aq)} \xrightarrow{\text{high pressure} \atop 370 \degree C} \text{ONa} \xrightarrow{\text{HCl}} \text{OH} + \text{NaCl} + H_2O
\]

via benzyne mechanism

ii) From Cumene Hydroperoxide (industrial)

\[
\text{Me} \xrightarrow{\text{H}_3\text{PO}_4 \atop 250 \degree C \text{ pressure}} \text{Me} \xrightarrow{\text{O}_2 \text{ (air) \atop 95-135 \degree C}} \text{Me} \text{O-O-H}
\]

cumene

cumene hydroperoxide

then:

\[
\text{Me} \text{O-O-H} \xrightarrow{\text{H}_3\text{O}^+} \text{OH} + \text{O}
\]

The oxygenation step proceeds by a free radical mechanism (SF/SFS 21.4B). The final step can be explained by the mechanism on the next page.
iii) Alkali Fusion of Arenesulfonates

\[
\text{SO}_3^- \text{Na}^+ \text{ (or } \text{K}^+) \xrightarrow{\text{NaOH-KOH melt} \ 250-350 \ ^\circ \text{C}} \text{PhONO}_2^-
\]

<table>
<thead>
<tr>
<th>salt</th>
<th>m.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaOH</td>
<td>318 °</td>
</tr>
<tr>
<td>KOH</td>
<td>380 °</td>
</tr>
<tr>
<td>eutectic</td>
<td>180 °</td>
</tr>
</tbody>
</table>

This method has limited use since only alkyl and aryl substituents can withstand the conditions.
iv) Diazonium Salts (see previous)

v) Nucleophilic Substitution of Aryl Halides (see previous)

vi) Williamson Ether Synthesis (SF/SFS 21.6)

\[ \text{Ar}^- + \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \rightarrow \text{Ar}O\text{CH}_2\text{CH}_2\text{CH}_3 + \text{Br}^- \]

The reaction proceeds best with 1° halides or sulfonates and also Me₂SO₄.

b) Acidity of Phenols (SF/SFS 21.5)

\[ K_a \sim 10^{-10} \]

\[ pK_a = 10\]

The 10⁶ fold greater acidity of phenol over ethanol is a result of two factors: inductive (polar) effects (sp² vs. sp³ carbons) and resonance.
Acidity is increased by electron withdrawing (-I or -R) substituents. Because O\(^-\) is a strong +R substituent, -R substituents in the ortho and para have a particularly large effect ("through-resonance" or "direct resonance interaction").

\[
\begin{array}{cccc}
\text{OH} & \text{OH} & \text{OH} & \text{OH} \\
\text{O} & \text{NO}_2 & \text{NO}_2 & \text{NO}_2 \\
\end{array}
\]

\[
pK_a, H_2O \quad 10.0 \quad 8.39 \quad 7.15 \quad 0.25
\]

25 °C

c) Some Reactions of Phenols and Phenyl Ethers (SF/SFS 21.8)

The -O\(^-\) substituent of phenolate anions is both a +I and +R and has a tremendous activating effect for electrophilic attack. As a result, there are several electrophilic substitutions that are unique for phenolate ions.

i) Bromination

\[
\begin{array}{c}
\text{Br-Br} \quad \text{Br} \quad \text{Br} \\
\text{O} \quad \text{OH} \quad \text{H} \quad \text{Br} \\
\text{O} \quad \text{Br} \quad \text{Br} \\
\end{array}
\]

precipitates

\[
\begin{array}{c}
\text{NaHSO}_3 \\
\text{Br} \quad \text{Br} \quad \text{Br} \quad \text{Br} \\
\end{array}
\]
ii) Carboxylation (the Kolbe reaction)

\[
\begin{align*}
\text{Na}^+ & \quad \text{CO}_2 \quad \text{Na}^- & \quad \text{OH} \quad \text{CO}_2 \quad \text{Na}^- \\
\text{C}_6\text{H}_5\text{CO}^- & \quad \text{Na}^+ & \quad \text{OH} \quad \text{CO}_2 \quad \text{Na}^- \\
\end{align*}
\]

125-150 °C, CO\(_2\), pressure

\text{sodium salicylate}

\[
\begin{align*}
\text{Na}^+ & \quad \text{CO}_2 \quad \text{Na}^- & \quad \text{OH} \quad \text{CO}_2 \quad \text{Na}^- \\
\text{C}_6\text{H}_5\text{CO}^- & \quad \text{Na}^+ & \quad \text{OH} \quad \text{CO}_2 \quad \text{Na}^- \\
\end{align*}
\]

240 °C

\text{sodium \(\mu\)-hydroxybenzoate}