Topic 20: Phosphorus Chemistry

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>C</th>
<th>N</th>
<th>O</th>
<th>F</th>
</tr>
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<tbody>
<tr>
<td>Al</td>
<td>1.6</td>
<td></td>
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<tr>
<td>Si</td>
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<tr>
<td>P</td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cl</td>
<td>3.0</td>
<td></td>
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</tbody>
</table>

References:
Literature cited
Phosphorus Functional Groups

Here’s how to name phosphorus functional groups:

- **Phosphine**: \( R \cdot P \cdot R \)
- **Phosphinite**: \( R \cdot P \cdot OR \)
- **Phosphonite**: \( R \cdot P \cdot OR \)
- **Phosphine oxide**: \( R \cdot O \cdot P \cdot R \)
- **Phosphinate**: \( R \cdot O \cdot P \cdot OR \)
- **Phosphonate**: \( R \cdot O \cdot P \cdot OR \)
- **Phosphite (ester)**: \( R \cdot O \cdot PO \cdot OR \)
- **Phosphate (ester)**: \( R \cdot O \cdot PO \cdot OR \)

Few of these functional groups are common.

- **Glyphosate**
- **Sarin**
Phosphorus Functional Groups

- $pK_a$s reveal the difference in basicity between trialkylphosphines and triarylphosphines


- Trialkylphosphines are way more nucleophilic than triarylphosphines
POCl₃ is a Very Reactive Electrophile

- Old conditions for elimination of OH groups. Contrast the outcomes.

- Phosphates don’t substitute very quickly, but Cl₃P=O is special

- Vilsmeier-Haack Reaction - amides attack Cl₃P=O

Mechanism for formation of the Vilsmeier reagent:
**Phosphates as Leaving Groups and/or Electrophiles**

- Phosphates are good leaving groups. In biology, magnesium-diphosphophate is the most common leaving group.

  ![Diagrams showing leaving groups and reactions](image)

- In acid-hydrolysis of trimethyl phosphate, C-O bond cleavage competes with P-O bond cleavage because phosphates are good leaving groups and it is difficult to attack a phosphate.
Hydrolysis of Phosphites and Phosphates

- Phosphites hydrolyze much faster than phosphates.

\[
\begin{align*}
\text{phosphate} & \quad \text{phosphite} \\
\begin{array}{c}
\text{RO-PO-OR} \\
\text{RO-PO-OR}
\end{array} & \quad \begin{array}{c}
\text{..} \\
\text{..}
\end{array}
\end{align*}
\]

<table>
<thead>
<tr>
<th></th>
<th>Phosphite</th>
<th>Phosphate</th>
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</thead>
<tbody>
<tr>
<td>( \text{HO}^- )</td>
<td>1,000</td>
<td>1</td>
</tr>
<tr>
<td>( \text{H}_3\text{O}^+ )</td>
<td>1,000,000,000,000</td>
<td>1</td>
</tr>
</tbody>
</table>

- If you want to synthesize P-O bonds use phosphites, not phosphates because you can always oxidize a phosphite up to a phosphate later. Modern DNA synthesis is based on the chemistry of phosphites + acid.

\[
\text{DMTO} \quad \text{NHBz} \quad \text{acid} \quad \text{OH} \quad \text{DNA} \quad \text{pKa 4.9} \quad 1 \text{ minute} \quad \text{DMTO} \quad \text{NHBz} \quad \text{DNA} \quad \text{HN} \quad \text{DNA} \quad \text{HN}
\]

F. Westheimer  
*JACS* **1988**, **181**  
*Chem. Ber.* **1960**, **1220**

Mechanism: Fast Acid-Catalyzed Exchange at Phosphites

- Recall dehydrobromination from sophomore organic chemistry.

\[
\begin{align*}
3 \text{ OH} & \quad \text{(cat HA)} \\
\text{Br} & \quad \text{OH} \\
\text{P} & \quad \text{Br} \\
\text{Br} & \quad \text{OH} \\
\end{align*}
\]

- The mechanism involves protonation of the phosphite.
P=O Bond Formation Drives Many Reactions

■ Mechanism for oxidation by I₂/H₂O in DNA synthesis

\[ \begin{align*}
R\cdot P\cdot R & \quad \xrightarrow{H₂O:} \quad R\cdot P\cdot R \quad \xrightarrow{B:} \quad R\cdot P\cdot R \quad \xrightarrow{B:} \quad R\cdot P\cdot R \quad \rightarrow \quad R\cdot P\cdot R
\end{align*} \]

■ Phosphines oxidize easily

\[ \begin{align*}
\text{Bu}_3\text{P} & \quad \text{fast, very air sensitive} \\
\text{Ph}_3\text{P} & \quad \text{slower}
\end{align*} \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Energy (kcal/mol)</th>
</tr>
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<tbody>
<tr>
<td>C-O</td>
<td>89</td>
</tr>
<tr>
<td>Ph₃P=O</td>
<td>137</td>
</tr>
<tr>
<td>Bu₃P=O</td>
<td>128</td>
</tr>
</tbody>
</table>

Clayden, et al. *JCS* 1960, 3284

■ Convention: **Draw P=O**, but all the reactivity is best explained by **+P—O⁻**

D. G. Gilheany “Structure and bonding in tertiary phosphine chalcogenides”

*Chemistry of Organophosphorus Compounds* p. 1-52
Phosphites act as nucleophiles in the Michaelis-Arbuzov reaction; a phosphate acts as a leaving group.

Kosolapoff, G. M. Org. React. 1951, 6, 276.
Ph₃P=O as a Leaving Group

- **Appel reaction.** Note attack at halogen in a Br-C bond and the ability of haloform anions to act as leaving groups.

- Note the stability of haloform anions and the ability to act as a leaving group.

<table>
<thead>
<tr>
<th>cpd</th>
<th>estimated pKₐ (MeOH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₃C-H</td>
<td>30.5</td>
</tr>
<tr>
<td>Cl₃C-H</td>
<td>24.4</td>
</tr>
<tr>
<td>Br₃C-H</td>
<td>22.7</td>
</tr>
<tr>
<td>I₃C-H</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Streitweiser, A.; et al. JACS 1976, 5229
Ph$_3$P=O as a Leaving Group

- The **Mitsunobu reaction** for "inversion" of alcohols

\[
\text{HO} - \xrightarrow{\text{Ph$_3$P:}} - \text{O} \\
\text{OH} \quad \text{Ar} \\
\text{HO} - \xrightarrow{\text{Ph$_3$P:}} - \text{O} \\
\text{OH} \quad \text{Ar}
\]

Mechanism depends on order of addition  
The Staudinger Reaction of Azides

- Recall the stereoelectronics for *anti* addition to $\pi^*$.

- The Staudinger mechanism is easily understood if you draw the right resonance structure for $N_3$.
The Staudinger Reaction of Azides

The Staudinger ligation takes place under physiological conditions

The Wittig Reaction - Review

- Makes C=C bonds from C=O

- **Concerted [2+2]**, but the C-C bond forms slightly before the P-O bond.


- **P=O elimination**: above -20 °C if R = alkyl, below -20 °C if R = EWG

- Making phosphonium ylides

\[
\begin{align*}
\text{Ph} & \quad \text{P} & \quad \text{Ph} & \quad \text{Ph} \\
\text{Br} & \quad \text{CH}_3 & \quad \text{Br} & \quad \text{CH}_3 \\
\text{C}_6\text{H}_6 & \quad \text{rt, 2 days} & \quad n\text{-BuLi} & \quad \text{ether, rt}
\end{align*}
\]

\[
\begin{align*}
pK_a & \quad 18
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{P} & \quad \text{Ph} & \quad \text{Ph} \\
\text{CH}_2 & \quad \text{CH}_2 & \quad \text{Ph} & \quad \text{P} & \quad \text{Ph} & \quad \text{Ph}
\end{align*}
\]

*this res. struct. not very useful*