Effect of nucleophile on reaction

- Nucleophile not involved in RDS of $S_N1$ so does not effect the reaction (well obviously it controls the formula of the product!)
- Nucleophile has a big effect on $S_N2$
- Large nucleophiles are poor in $S_N2$ reactions due to steric hindrance

Large nucleophile ($t$-BuOH) suffers steric interactions

Small nucleophile (MeOH) can easily approach
Nucleophile strength

- The **stronger** the nucleophile the **faster / more efficient** the $S_N2$ reaction
- Nucleophilic strength (nucleophilicity) relates to how easily a compound can donate an electron pair
- The **more electronegative** an atom the **less nucleophilic** as the electrons are held closer

Anion more nucleophilic than its neutral analogue

| nucleophilic strength (basicity) | $\text{R}_3\text{C}\Theta$ | $\text{R}_2\text{N}\Theta$ | $\text{RO}\Theta$ | $\text{F}\Theta$
|---|---|---|---|---|
| electronegativity | $\text{C}$ | $\text{N}$ | $\text{O}$ | $\text{F}$
| nucleophilic strength (basicity) | $\text{R}--\text{NH}_2$ | $\text{R}--\text{OH}$ | $\text{R}--\text{F}$

As we move along a row the electronegativity increases and nucleophilicity decreases

<table>
<thead>
<tr>
<th>nucleophilic strength (basicity)</th>
<th>$\text{H}_2\text{S}\Theta$</th>
<th>$\text{H}_2\text{O}\Theta$</th>
</tr>
</thead>
</table>
| $\text{I}\Theta$ | $\text{Br}\Theta$ | $\text{Cl}\Theta$ | $\text{F}\Theta$

As we go down a group both anions and neutral atoms get more nucleophilic - electrons not held as tightly as size increases
Solvent effects

$S_{N1}$
- Intermediate - the **carbocation** - is stabilised by **polar** solvents
- **Leaving group** stabilised by **protic** solvents (encourages dissociation)
- Water, alcohols & carboxylic acids good solvents for $S_{N1}$

$S_{N2}$
- Prefer less polar, aprotic solvents
- Less charge separation in $TS^+$ so less need for polar solvent
- Need aprotic solvent so that nucleophile is not solvated

\[ \text{CH}_3\text{Br} \rightarrow \text{H}_2\text{O} \]
Leaving group

- **Leaving group** (X) is involved in RDS of both reactions - very important
- Better leaving group - faster both reactions are
- Bond strength - **stronger** the bond **worse** the leaving group
- Stability of X⊖ - neutral or stable anions (more electronegative) make good leaving groups

![Leaving group diagram]

<table>
<thead>
<tr>
<th>Leaving group ability</th>
<th>H₂O⊖</th>
<th>Br⊖</th>
<th>HO⊖</th>
<th>F⊖</th>
</tr>
</thead>
<tbody>
<tr>
<td>weak base</td>
<td>&gt;</td>
<td>&gt;</td>
<td>&gt;</td>
<td>&gt;</td>
</tr>
<tr>
<td>strong base</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Alcohols as leaving groups

- Poor leaving group as they react directly with nucleophiles
- Observe deprotonation

But they are readily converted to good leaving groups!
- We can protonate them

\[ \text{SN}_1 \quad \text{SN}_2 \]
Alcohols as leaving groups II

Alcohols can be converted to good leaving groups with oxophilic reagents like $\text{SOCl}_2$, $\text{PCl}_5$, $\text{P(O)Cl}_3$, and $\text{PBr}_3$.

Addition of an electron-withdrawing group can make alcohols good leaving groups:

- $\text{R-Br} \xrightarrow{\text{Nu}^-} \text{R-Nu}$
- $\text{R-OH} \xrightarrow{\text{TsCl, pyr}} \text{R-OTs} \xrightarrow{\text{Nu}^-} \text{R-Nu}$

$\text{Ts} = \text{tosyl} = \text{toluenesulfonyl}$

good leaving group due to delocalisation
Ethers as leaving groups

- Normally ethers are stable under most conditions
- They are commonly used as solvents
- But with strong protic acids or Lewis acids they can be cleaved

\[
\text{MeO} \quad \text{HI} \quad \text{S}_2\text{N}_2 \quad \text{MeOH} + \text{MeI}
\]

\[
\text{B} = \text{group 3 so empty p orbital}
\]

\[
\text{Br} \quad \text{Br} \quad \text{Br}
\]

\[
\text{H}_2\text{O} \quad \text{BBr}_2
\]

\[
\text{B} \quad \Theta\text{Br}
\]
Epoxides as leaving groups

- Epoxides are excellent electrophiles
- Reason - O & 2 x C are sp³ so bond angles should be 109° but are forced to be closer to 60°
- The ring is under a lot of strain (ring strain)
- This can be released if the epoxide reacts and we get ring opening

Why do you think this isomer is formed?
Amines as nucleophiles

- Amines are good nucleophiles, readily attacking electrophiles.
- But we have a problem (as always)...

In reality we tend to produce a mixture!
The solution...

- Fortunately there are ways around this problem
- Use "masked" amine - a functional group that is readily converted to an amine
- Azide is very good as it is small and will attack most electrophiles

\[
R-X + \text{Na}^+ \stackrel{\text{N≡N≡N}}{\longrightarrow} R-N≡N≡N \quad \xrightarrow{\text{LiAlH}_4 \text{ reducing agent}} \quad R-NH_2
\]

Or...

\[
R-X + \text{K}^+ \stackrel{\text{N-\text{K}^+}}{\longrightarrow} R-N-\text{K}^+ \quad \xrightarrow{\text{NH}_2\text{NH}_2 \text{ hydrolysis}} \quad R-NH_2
\]