1. There are 8 isomeric alcohols with the formula $C_5H_{12}O$. Draw these and name them. Determine if they are $1^o$, $2^o$ or $3^o$.

\[
\begin{align*}
\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-OH} & \quad \text{OH} & \quad \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3 \\
1^o & \quad 2^o & \quad 2^o \\
\text{CH}_3\text{-CH}_2\text{-CH}-\text{CH}_2\text{-OH} & \quad \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_3 & \quad \text{CH}_3\text{OH} \\
1^o & \quad 3^o & \quad 2^o \\
\text{CH}_3\text{CH}_2\text{CHCH}_3 & \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \\
1^o & \quad 1^o \\
\end{align*}
\]

2. Each of the following is an example of a substitution reaction. Label the leaving group (in the substrate) and the nucleophile.

(a) \[
\begin{align*}
\text{ClCH}_2\text{COC(CH}_3\text{)_3} & \quad \text{NaN}_3 & \quad \text{N}_3\text{CH}_2\text{COC(CH}_3\text{)_3} \\
nucleophile & \quad \text{leaving group} & \quad \text{nucleophile} \\
\end{align*}
\]

(b) \[
\begin{align*}
\text{NC}\text{-CH}_2\text{Cl} & \quad \text{OH} & \quad \text{NC}\text{-CH}_2\text{OH} \\
\text{leaving group} & \quad \text{nucleophile} & \quad \text{nucleophile} \\
\end{align*}
\]
3. Show how to synthesize the following from 1-bromopropane by a substitution reaction.

(a) \( \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \ + \ \text{NaN}_3 \rightarrow \ \text{CH}_3\text{CH}_2\text{CH}_2\text{N}_3 \)

(b) \( \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \ + \ \text{CH}_3\text{CH}_2\text{ONa} \rightarrow \ \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3 \)

(c) \( \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \ + \ \text{CH}_3\text{CO}_2\text{K} \rightarrow \ \text{CH}_3\text{C}==\text{O}==\text{CH}_2==\text{CH}_2==\text{CH}_3 \)

4. Predict the products of these following substitution reactions.

(a) \( \text{BrCH}_2\text{C}==\text{OCH}_2\text{CH}_3 \rightarrow \text{NaI} \rightarrow \text{ICH}_2\text{C}==\text{OCH}_2\text{CH}_3 \)

(b) \( \text{O}_2\text{N}==\text{CH}_2\text{Cl} \rightarrow \text{CH}_3\text{CO}_2\text{Na} \rightarrow \text{O}_2\text{N}==\text{CH}_2\text{O}_2\text{CCH}_3 \)

(c) \( \text{CH}_2\text{SNa} \ + \ \text{CH}_3\text{CH}_2\text{Br} \rightarrow \text{CH}_2\text{SCH}_2\text{CH}_3 \)

(d) \( \text{HC}==\text{CNa} \ + \ \text{CH}_3\text{CH}_2\text{Br} \rightarrow \text{HC}==\text{C}==\text{CH}_3 \)
5. Which of the following substrates (if any) in each pair below would you expect to react more rapidly by $S_N2$? Why?

(a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$ or $\text{(CH}_3\text{)}_2\text{CHBr}$

$1^\circ$ reacts faster than $2^\circ$ by $S_N2$.

(b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$ or $\text{CH}_3\text{CH}_2\text{CH}_2\text{I}$

I$^-$ is a better leaving group than Cl$^-$. 

(c) $\text{(CH}_3\text{CH}_2\text{)}_2\text{CHOTf} + \text{EtOH}$ or $\text{(CH}_3\text{CH}_2\text{)}_2\text{CHOTf} + \text{NaOEt}$

The salt produces EtO$^-$, which is a better nucleophile than EtOH.

(d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{OTs} + \text{NaI}$

SN2 goes better in polar aprotic solvents.

6. Show the mechanisms and products of your choices in Problem 6 (c) and (d).

(c) $\text{(CH}_3\text{CH}_2\text{)}_2\text{CH-OTf} + \text{EtO}^- \rightarrow (\text{CH}_3\text{CH}_2\text{)}_2\text{CH-OEt}$

(d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{-OTs} + \text{I}^- \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{-I}$
7. Show the products and their stereochemistry in the following $S_N2$ reactions.

![Diagram](image)

The stereochemistry of $S_N2$ results in inversion of configuration at the reaction center, due to back-side attack by the nucleophile.
8. Write an equation, clearly showing the stereochemistry of the starting material and the product, for the reaction of (S)-1-bromo-2-methylbutane with sodium iodide in acetone. What is the configuration (R or S) of the product?

\[
\text{CH}_3 \quad \text{BrCH}_2 - \text{CH} - \text{CH}_2 \text{CH}_3
\]

\[
\xrightarrow{2} \text{CH}_2 \text{CH}_3
\]

\[
\xrightarrow{1} \text{CH}_3 \quad \text{CH}_2 \text{Br} \quad \text{I}^- \quad \text{CH}_3 \quad \text{CH}_2 \text{I}
\]

Notice, reaction did not occur at the chiral center, therefore the stereochemistry of the chiral center was uncompromised. Inversion at the reaction center did occur; however, since that carbon is achiral, stereochemistry is unimportant.

9. Which of the following substrates (if any) in each pair below would you expect to react more rapidly by S_N1? Why?

(a) (CH_3)_3CBr or (CH_3)_3COTs

Tosylate is a better leaving group.

(b) (CH_3)_3CBr or (CH_3)_2CHBr

\[\text{3}^\circ \text{ reacts faster than } \text{2}^\circ \text{ by S}_N1.\]

(c) (CH_3)_3CBr + NaOCH_3 or (CH_3)_3CBr + NaOH

Neither. The nucleophile does not participate in the rate-limiting step. Therefore, it does not affect the rate of reaction.

(d) (CH_3)_2CHBr + NaN_3 or (CH_3)_2CHBr + NaN_3

EtOH or CH_3CN

Polar protic solvents favor S_N1.
10. Show the products and their stereochemistry for the following SN1 reactions.

(a) 

\[
\text{CH}_3\text{OTf} + \text{CH}_3\text{CO}_2\text{Na} \rightarrow \text{CH}_3\text{O}_2\text{CCH}_3\text{CH}_3 + \text{CH}_3\text{CH}_3\text{CO}_2\text{H}
\]

retention inversion

The stereochemistry of SN1 results in racemization about the reaction center. The reaction goes through an achiral carbocation intermediate.

(b) 

\[
\text{(CH}_3)_3\text{C} + \text{I}^- \rightarrow \text{(CH}_3)_3\text{C} + \text{(CH}_3)_3\text{C}
\]

The stereochemistry of SN1 results in racemization about the reaction center. The reaction goes through an achiral carbocation intermediate.
11. Show the mechanism that explains how the following reactions could occur.

(a)
~CH₂ refers to a 1,2-methylene shift. That is, carbon 3 (a CH₂ or methylene) shifts the electrons is uses to bond to carbon 2 over to carbon 1. Since carbon 2 loses the electrons, it ends up with the positive charge.

12. Arrange the isomers of molecular formula C₄H₉Cl in order of decreasing rate of reaction with sodium iodide in acetone (hint: Would NaI in acetone favor Sₙ₁ or Sₙ₂ mechanism?).

NaI in acetone favors Sₙ₂ because this mechanism operates better in polar aprotic solvent, such as acetone. Therefore, we expect the alkyl halides to react 1° > 2° > 3°.

\[
\begin{align*}
CH₃CH₂CH₂CH₂Cl & > CH₃CHCH₂CH₂Cl & > CH₃CH₂CH₂CH₃ & > CH₃CCH₃Cl \\
1° RX & 1° RX & 2° RX & 3° RX
\end{align*}
\]

Of the two primary alkyl halides, we would expect 1-chlorobutane to react a bit faster because it is less sterically hindered than with 1-chloro-2-methylpropane.
13. Secondary alkyl halides can undergo $S_N1$ or $S_N2$ reactions. Solvent is one factor that may exert an influence. (a) For each of the reactions below, suggest which mechanism is more likely. Justify your answer. (b) Suggest two experimental methods by which you might verify your predictions. Explain what you expect to observe.

Reaction 1 is expected to occur by $S_N1$. EtOH is a polar protic solvent which will assist in pulling the leaving group from the alkyl halide, forming a carbocation.

Reaction 2 is expected to occur by $S_N2$. DMF (dimethylformamide) is a polar aprotic solvent.

There are two experiments that can be performed to test the proposals above.

(1) **Kinetics.** Check the order of reaction with respect to NaN$_3$. If the first reaction does go by $S_N1$, then the kinetics will be independent of the concentration of NaN$_3$. If the second reaction occurs by $S_N2$, then the kinetics will be affected by the concentration of NaN$_3$.

(2) **Stereochemistry of reaction.** Start with chiral reactant. If the first reaction occurs by $S_N1$, we expect racemization in the product. If the second reaction occurs by $S_N2$, then we expect inversion of configuration.

14. Identify the products of the following reactions.

The solvent favors a $S_N2$ reaction, so the nucleophile will prefer to attach the less substituted, $1^\circ$ carbon.
15. Show the mechanism and products of reaction for the following. Label the rate-limiting step.

(a) This reaction occurs by SN1.

\[
\begin{align*}
\text{CH}_3\text{OH} + \text{HCl} \quad &\xrightarrow{30 \degree \text{C}} \quad \text{CH}_3\text{Cl} \\
\end{align*}
\]
(b) \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \xrightarrow{\text{NaBr, H}_2\text{SO}_4, 95 \degree \text{C}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \)

This reaction occurs by S\(_\text{n2}\). The mixture of NaBr and H\(_2\)SO\(_4\) is a means of making HBr.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} + & \quad \text{H-Br} \quad \xleftrightarrow{} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}_2^+ + \quad \text{Br}^- \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}_2^+ + & \quad \text{Br}^- \quad \xrightarrow{} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \quad \text{H}_2\text{O} \quad \text{(RDS)}
\end{align*}
\]

16. The reaction of 2,2-dimethyl-1-propanol with HBr is very slow and gives 2-bromo-2-methylbutane as the major product.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \quad + \quad \text{HBr} \quad \xrightarrow{} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}
\end{align*}
\]

Give a mechanistic explanation for these observations.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + & \quad \text{H-Br} \quad \leftrightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH}_2^+ + \quad \text{Br}^- \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}_2^+ \quad + \quad & \quad \text{Br}^- \quad \leftrightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \quad \text{H}_2\text{O} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}_2^+ \quad + \quad & \quad \text{H}_2\text{O} \quad \xrightarrow{1,2\text{-methyl shift}} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \quad + \quad & \quad \text{Br}^- \quad \xrightarrow{} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \quad \text{H}_2\text{O} \\
\end{align*}
\]
17. Show two methods by which each of the following reactions could be achieved. Explain which would be the best method and why.

(a) \[
\begin{align*}
\text{CH}_3\text{-CH-CH-CH}_3 + \text{CH}_3\text{OH} &\rightarrow \text{CH}_3\text{-CH-CH-CH}_3 + \text{CH}_3\text{Br} \\
\text{CH}_3\text{-CH-CH-CH}_3 &\rightarrow \text{CH}_3\text{-CH-CH-CH}_3
\end{align*}
\]

(1) \[
\begin{align*}
\text{CH}_3\text{-CH-CH-CH}_3 + \text{PBr}_3 &\rightarrow \text{CH}_3\text{-CH-CH-CH}_3 + \text{CH}_3\text{Br} \\
\text{CH}_3\text{-CH-CH-CH}_3 &\rightarrow \text{CH}_3\text{-CH-CH-CH}_3
\end{align*}
\]

(2) \[
\begin{align*}
\text{CH}_3\text{-CH-CH-CH}_3 + \text{HBr} &\rightarrow \text{CH}_3\text{-CH-CH-CH}_3 + \text{CH}_3\text{Br} \\
\text{CH}_3\text{-CH-CH-CH}_3 &\rightarrow \text{CH}_3\text{-CH-CH-CH}_3
\end{align*}
\]

Rearrangement does not occur with PBr\(_3\). With HBr, there is always the chance of rearrangement. If the alcohol is tertiary, then rearrangement is unlikely, as a tertiary carbocation intermediate will be produced. If the alcohol is 1\(^o\) or 2\(^o\), rearrangement is always a possibility, however slight. As a result, reaction route (1) above is the preferred one, because the alcohol is secondary and we want to avoid the possibility of rearrangement.

(b) \[
\begin{align*}
\text{CH}_2\text{CH}_3\text{OH} &\rightarrow \text{CH}_2\text{CH}_3\text{Cl} \\
\text{CH}_2\text{CH}_3\text{OH} &\rightarrow \text{CH}_2\text{CH}_3\text{OH}
\end{align*}
\]

(1) \[
\begin{align*}
\text{CH}_2\text{CH}_3\text{OH} + \text{SOCl}_2 &\rightarrow \text{CH}_2\text{CH}_3\text{Cl} \\
\text{CH}_2\text{CH}_3\text{OH} &\rightarrow \text{CH}_2\text{CH}_3\text{Cl}
\end{align*}
\]

(2) \[
\begin{align*}
\text{CH}_2\text{CH}_3\text{OH} + \text{HCl} &\rightarrow \text{CH}_2\text{CH}_3\text{Cl} \\
\text{CH}_2\text{CH}_3\text{OH} &\rightarrow \text{CH}_2\text{CH}_3\text{Cl}
\end{align*}
\]

In this case, the second method, using HCl, would be best. The alcohol is 3\(^o\). It is already stable and rearrangement is not likely occur.
In this case, the alcohol is 1°. Reaction should go by S_N2. However, rearrangement from 1° all the way to 3° is sufficiently favorable that S_N1 will occur to accommodate the rearrangement. This means conversion using thionyl chloride would be best.

18. Outline an efficient synthesis of each of the following compounds from the indicated starting material and any necessary organic or inorganic reagents.

(a) cyanocyclopentane from cyclopentane

When starting with an alkane, there is no good leaving group. C-H bonds are not easily broken. First, we need to add a leaving group. The only reaction we know for breaking C-H bonds is free radical halogenation. Once the halogen is added (Br2 could have been used as well), we can then substitute it with the desired nucleophile.
19. Something is wrong with each of the following reactions. Identify the error and suggest a better route to achieve the same result.

(a) \[
\begin{align*}
\text{CH}_3 & \quad \text{CH} & \quad \text{OH} \quad \text{NaI} \quad \text{acetone} \quad \text{CH}_3 & \quad \text{CH} & \quad \text{I} \\
\text{CH}_3 & \quad & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

When an alcohol is the starting material, the reaction must be run in acidic solution. OH is a terrible leaving group, and will not be replaced by I, a relatively weak nucleophile. Two better methods to achieve the desired results are:
In this reaction, we need a neutral or negatively charged nucleophile to replace Br\(^-\). The mixture of water and acid produce H\(_3\)O\(^+\), which is not a nucleophile. The better way to achieve this reaction is: