12.37 What product(s) would you expect from the reaction of 1-methylcyclohexene with NBS?

\[
\text{NBS} \quad \text{OCl}_4
\]

First step is to form an allylic radical; however, you have two different allylic protons that can be abstracted. Once you form those, bromination at those positions gives products 1 and 2. Each of those allylic radicals can also undergo resonance stabilization to delocalize the radical. Bromination at the other side of the double bond then gives products 3 and 4.

12.38 Which compound in each of the following pairs will react faster in an SN₂ reaction with OH⁻?

(a) CH₃Br or CH₃I
(b) CH₃CH₂I in ethanol or in dimethyl sulfoxide
(c) (CH₃)₂CCl or CH₂Cl
(d) H₂C=CHBr or H₂C=CHCH₂Br

(a) CH₃I. Alkyl iodides are more reactive than alkyl bromides because of the decreased strength of the carbon-iodide bond.
(b) The reaction in dimethyl sulfoxide. Protic solvents like ethanol will solvate OH⁻ and reduce its ability to act as a good nucleophile.
(c) CH₃Cl. Tertiary halides are very inert to SN₂ reactions because they have too much steric bulk for efficient backside attack.
(d) H₂C=CHCH₂Br. Allylic bromides react via SN₂ reactions. Vinylvic ones do not as the sp²-hybridized carbon they are attached to cannot undergo backside attack efficiently.

12.40 What effect would you expect the following changes to have on the rate of the reaction of ethanol with 2-iodo-2-methylbutane?
(a) The concentration of the halide is tripled.

(b) The concentration of the ethanol is halved by adding diethyl ether as the inert solvent.

First step is to figure out what reaction is occurring here. The starting material is a tertiary halide that is reacting with ethanol, presumably to generate the substitution product.

\[
\begin{align*}
\text{H}_3\text{C} \quad \text{I} & \quad \text{EtOH} \quad \text{H}_3\text{C} \quad \text{OEt} \\
\text{H}_3\text{C} & \quad \text{H}_3\text{C}
\end{align*}
\]

This has to be an SN1 mechanism because the halide is tertiary. The rate of SN1 reactions is directly proportional to the concentration of alkyl halide, so increasing halide concentration will increase the reaction rate (answer to part a). SN1 reactions are much faster in polar solvents, so adding 50% of diethyl ether, which decreases the solvent polarity, will slow down the reaction rate (answer to part b).

12.41 How might you prepare each of the following molecules using a nucleophilic substitution reaction at some step?

(a) \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CN}\) (b) \(\text{H}_3\text{C-CH}_2\text{ CN}\) (c) \(\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2\)

First step is to draw the structures, and then identify where the nucleophilic component could have been introduced. I am using retrosynthetic arrows to show how these structures could have been made retrosynthetically.

a. \(\begin{array}{c}
\text{CN} \\
\text{Br} + \text{CN}^{-}
\end{array}\) SN2 reaction

b. \(\begin{array}{c}
\text{H}_3\text{C-CH}_2\text{O} \\
\text{H}_3\text{C-CH}_2\text{OH} + \text{Cl}^{-}
\end{array}\) this will be SN1

\(\begin{array}{c}
\text{H}_3\text{C-CH}_2\text{O} \\
\text{H}_3\text{C-CH}_2\text{OH} + \text{Cl}^{-}
\end{array}\) this will be SN1

\(\begin{array}{c}
\text{H}_3\text{C-CH}_2\text{O} \\
\text{H}_3\text{C-CH}_2\text{OH} + \text{Cl}^{-}
\end{array}\) this will be SN1

(c. \(\begin{array}{c}
\text{NH}_2 \\
\text{Br} + \text{NaN}_3
\end{array}\) SN2 reaction

(a) This is pretty straightforward. \(\text{CN}^{-}\) is a nucleophile that could be introduced via an SN2 substitution reaction on a primary halide.

(b) The nucleophilic component here is the oxygen. You can disconnect theoretically on either side of the oxygen to generate a nucleophile, but since the substitution is different on each side, the first way will be an SN2 reaction pathway and the second will be via an SN1 reaction on a tertiary halide.

(c) This one is a little more complicated because \(\text{NH}_2\) itself is not a competent nucleophile. Probably this was made from the azide via reduction. The azide could be made from an SN2 reaction with sodium azide.

12.43 What products would you expect from the reaction of 1-bromopropane with each of the following?

(a) \(\text{NaNH}_2\) (b) \(\text{KOC(CH}_3)_3\) (c) \(\text{NaI}\) (d) \(\text{NaCN}\) (e) \(\text{Mg, then H}_2\text{O}\)
12.46 Propose structures for compounds that fit the following descriptions:

(a) An alkyl halide that gives a mixture of three alkenes on E2 reaction

(b) An organic halide that will not undergo nucleophilic substitution

(c) An alkyl halide that gives the non-Zaitsev product on E2 reaction

(d) An alcohol that reacts rapidly with HCl at 0°C

(a) Neopentyl bromide is too hindered to undergo an SN2 reaction. However, because it is still a primary halide, it is not going to undergo an SN1 reaction either. The structure of neopentyl bromide is shown below, together with a space-filling model:

(c) Zaitsev’s rule says that elimination gives the more substituted alkene. A reaction that gives the non-Zaitsev product is shown below:
(d) Tertiary alcohols react extremely rapidly with HCl:

\[ \text{H}_3\text{C} - \text{OH} + \text{HCl} \rightarrow \text{H}_3\text{C} - \text{Cl} \]

12.47 The following reactions are unlikely to occur as written. Tell what is wrong with each, and predict the actual product.

a. \[ \text{H}_3\text{C} - \text{Br} - \text{CH}_3 \xrightarrow{\text{KORBu} / \text{tBuOH}} \text{H}_3\text{C} - \text{CH}_2 - \text{CH}_3 \]
   a. Potassium tert-butoxide is a base and will cause elimination in a secondary halide to generate predominantly the more substituted alkene.

b. \[ \text{cyclohexeneF} \xrightarrow{\text{NaOH}} \text{cyclohexeneOH} \]
   b. The C-F bond is too strong to be substituted. No reaction will take place here.

c. \[ \text{cyclohexeneOH} \xrightarrow{\text{SOCl}_2 \text{pyridine (a base)}} \text{cyclohexeneCH}_3 \]
   c. Pyridine is going to cause elimination to occur faster than substitution.

12.50 Predict the product and give the stereochemistry resulting from reaction of each of the following nucleophiles with (R)-2-bromooctane:

(a) CN⁻ (b) CH₃CO₂⁻ (c) CH₃S⁻

All of these undergo stereochemical inversion at the secondary halide to yield the products shown below:
12.53 The SN2 reaction can occur intramolecularly (within the same molecule). What product would you expect from treatment of 4-bromo-butan-1-ol with base?

The base deprotonates the alcohol to generate a good nucleophile, which attacks the primary halide intramolecularly. The product is tetrahydrofuran (THF), shown below:

12.55 Predict the major alkene product of the following E1 reaction:

12.58 Arenes such as ethylbenzene react with NBS to give products in which bromine substitution has occurred at the benzylic position. Explain the result and propose a mechanism.

You form a benzylic radical. This radical is highly stabilized via resonance throughout the aromatic ring, which is why it is formed preferentially to any other radical. The radical is brominated to give the new alkyl halide product.

12.63 Internal alkynes can be made from terminal alkynes by converting the terminal alkyne to an acetylide anion and then treating the anion with a primary alkyl halide. Propose a mechanism for the alkylation:
The NaH$_2$ deprotonates the alkyne proton to generate an alkynyl anion, which acts as a nucleophile to kick off the bromide and form the new C-C bond.

12.71 When a primary alcohol is treated with p-toluenesulfonyl chloride at room temperature in the presence of an organic base such as pyridine, a tosylate is formed. When the same reaction is carried out at higher temperature, an alkyl halide is often formed. Explain.

\[
\begin{align*}
\text{CH}_3\text{OH} & \quad \xrightarrow{\text{Tos-Cl, pyridine, 60 °C}} \quad \text{CH}_3\text{Cl} \\
\end{align*}
\]

Chloride is not a great nucleophile, but when heated up to 60 °C it acts as a nucleophile to displace the hydroxyl group and form the product that is seen.

12.72 SN2 reactions take place with inversion of configuration, and SN1 reactions take place with racemization. The following substitution reaction, however, occurs with complete retention of configuration. Propose a mechanism.

\[
\begin{align*}
\text{BrCH}_2\text{COOH} & \quad \xrightarrow{1. 1\% \text{NaOH, H}_2\text{O}} \quad \xrightarrow{2. \text{H}_3\text{O}^+} \quad \text{HOCH}_2\text{COOH} \\
\end{align*}
\]

A complete retention of configuration almost always means that the reaction occurred in two SN2 steps, each of which took place with inversion of configuration. In this case, you can have participation from the carbonyl oxygen to generate an intermediate three membered ring that is broken apart by attack of a nucleophilic oxygen.

12.75 Amines are converted into alkenes by a two-step process called the Hoffmann elimination. Reaction of the amine with excess CH$_3$I in the first step yields an intermediate that undergoes E2 reaction when treated with basic silver oxide. Pentyamine, for example, yields pent-1-ene. Propose a structure for the intermediate, and explain why it undergoes ready elimination.

\[
\begin{align*}
\text{CH}_3\text{NH}_2 & \quad \xrightarrow{\text{base}} \quad \text{CH}_3\text{C}≡\text{N}^+ \quad \xrightarrow{\text{H}} \quad \text{CH}_3\text{C}≡\text{N}(\text{CH}_3)_3 \\
\end{align*}
\]

The primary amine group acts as a nucleophile to get methylated three times – until it gives an ammonium cation. A base then kicks off a neutral molecule – methylamine – which is why the elimination is so rapid.