Nucleophilic Substitution Reactions

Introduction

In our discussion of acid-base chemistry we alluded to the similarities between the reactions of \(\text{HCl}+\text{NaOH}\) on the one hand and \(\text{CH}_3\text{Cl} + \text{NaOH}\) on the other. Scheme 1 compares the two.

![Scheme 1: One and the Same](image)

The reaction of \(\text{HCl}+\text{NaOH}\) is a specific example of a more general type of reaction known as a nucleophilic substitution. The reaction of \(\text{CH}_3\text{Cl} + \text{NaOH}\) exemplifies a type of nucleophilic substitution called nucleophilic aliphatic substitution, where the word aliphatic indicates that the substitution occurs at an sp\(^3\) hybridized carbon atom. The study of nucleophilic aliphatic substitution reactions has provided chemists with detailed insights into the nature of chemical reactivity. Scheme 2 presents a generalized description of nucleophilic aliphatic substitution reactions.

![Scheme 2: Nucleophilic Aliphatic Substitution](image)

Before we begin our discussion of the details of Scheme 2, let’s clarify some terms.

Definitions

- **Nucleophile**: A nucleophile is a Lewis base, i.e. an electron pair donor. Any reagent that contains an atom with at least one lone pair of electrons is a potential nucleophile. Common examples include halide ions such as \(\text{I}^-\) and \(\text{Br}^-\), hydroxide ion, \(\text{OH}^-\), water, \(\text{H}_2\text{O}\), and ammonia, \(\text{NH}_3\). Note that X may represent a single atom or a polyatomic group. Note, too, that the central atom of a nucleophile may have a formal charge of 0 or -1.
• **Electrophile:** An electrophile is a Lewis acid, i.e. an electron pair acceptor. Any reagent that contains an atom which has a formal or a partial positive charge is a potential electrophile.

• **Leaving group:** A leaving group is any atom or polyatomic group that is replaced by a nucleophile during a nucleophilic aliphatic substitution reaction. Leaving groups are generally conjugate bases of strong acids. Common examples include halide ions such as \(\text{I}^-\) and \(\text{Br}^-\), water, \(\text{H}_2\text{O}\), and carboxylate ions such as trifluoroacetate, \(\text{CF}_3\text{CO}_2^-\). The central atom of the leaving group is always an electronegative atom, most commonly halogen or oxygen.

• **Substituent:** A substituent is any atom or polyatomic group attached to the electrophilic center of the substrate.

There are two features of Scheme 2 that merit further comment.

First, notice that the reaction is depicted as an equilibrium process. In most nucleophilic aliphatic substitution reactions, the value of the equilibrium constant is very large, i.e. the reaction is essentially irreversible. The rules that we developed for assessing the equilibrium constant of any acid-base reaction will serve as a useful guide in estimating the equilibrium constant for nucleophilic aliphatic substitution reactions as well.

Second, since the reaction is an equilibrium process, there is no fundamental difference between a nucleophile and a leaving group. It all depends on your perspective; the reagent that acts as a nucleophile in the forward direction assumes the role of a leaving group in the reverse direction.

**Exercise 1** Calculate the value of \(K_{eq}\) for each of the following nucleophilic aliphatic substitution reactions. Enter an exponential value such as \(10^{-2}\) as 10e-2.

\[
\text{\begin{tikzpicture}
\node (A) at (0,0) {$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}^-$};
\node (B) at (1,0) {$\text{Br}^-\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$};
\node (C) at (2,0) {$\text{H}_2\text{O}$};
\node (D) at (3,0) {$\text{CH}_3\text{CH}_2\text{CH}_2\text{I}^-$};
\node (E) at (4,0) {$\text{Br}^-\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$};
\node (F) at (5,0) {$\text{H}_2\text{O}$};
\node (G) at (6,0) {$\text{CH}_3\text{CH}_2\text{CH}_2\text{I}^-$};
\node (H) at (7,0) {$\text{Br}^-\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$};
\end{tikzpicture}}
\]

**Exercise 2** Given the value of \(K_{eq}\) for the first reaction above, which ion is more accurately described as the nucleophile?  
○ iodide ion  ○ bromide ion

Having seen the features of nucleophilic aliphatic substitution reactions in broad outline, we will now examine the process in more detail. Specifically, we will look at the effect of each of the following parameters on the rates of nucleophilic aliphatic substitution reactions:

• the substituent(s) connected to the substrate
• the leaving group
• the nucleophile
• the solvent
Before we examine each of these variables however, we first need to develop a basic understanding of one of the most useful experimental methods there is for gaining insight into the nature of chemical reactions, chemical kinetics.

Contributors

- Otis Rothenberger (Illinois State University) and Thomas Newton University of Southern Maine)