

## Reactions of Alkyl Halides: Alkyl Halides, Nucleophiles and Leaving Groups

### Nucleophilic Substitution

The carbon-halogen bond is polarized (electronegativity) and relatively weak. Compare C-C (356 kJ/mol) C-Cl (350 kJ/mol) C-Br (293 kJ/mol) C-I (239 kJ/mol)

Negatively charged nucleophiles attack the positive carbon atom that carries the halide.

The alkyl halide is called the **substrate**. The halide is the **leaving group**, and leaves with its bonding electron pair. The new bonding pair of electrons comes from the attacking nucleophile.

Q. What is the sequence of events (the mechanism) of the nucleophilic substitution?

Concerted

Stepwise

A. Both are possible. Which one happens depends on the structure of the substrate

## Leaving Groups

Halide is the leaving group in the examples above. In general, a good leaving group is a stable, weakly basic molecule or anion.

Nucleophiles can be anionic or neutral. Either way, the charges must balance on the reactant and product sides of the reaction, and the charge on the leaving group will tell you what charge to put on the product.

## Order of Reaction

Review the kinetics part of your General Chemistry class!

For the simple reaction of a strong nucleophile ( $\text{OH}^-$ ) with an unhindered substrate ( $\text{CH}_3\text{Cl}$ , chloromethane) the reaction can be experimentally shown to be **second order overall**.

The reaction is bimolecular. This class of reactions is called  **$\text{S}_{\text{N}}2$** . Substitution, Nucleophilic, Second order.

## Mechanism of the S<sub>N</sub>2 Reaction

The incoming electron pair of the nucleophile interacts with the antibonding molecular orbital on the opposite face of the tetrahedral center from the leaving group. This is called **back side attack**.

The mechanism for S<sub>N</sub>2 reactions is **concerted**. As the nucleophile-substrate bond begins to form, the substrate-leaving group bond weakens. The “half way” stage is a high energy **transition state**.

This mechanism predicts that the configuration of the product will be inverted. This was first observed by Paul Walden in 1896, and the process bears his name – the **Walden inversion**.

**The S<sub>N</sub>2 reaction always goes with inversion of configuration.**

**Important!** You can't trap, capture, or otherwise isolate a transition state experimentally. However, they can be observed, and Ahmed Zewail was awarded the 1998 Nobel Prize in chemistry for doing exactly that.

The reaction of hydroxide ion with chloromethane is exergonic. It has a negative free energy. It is also exothermic. At 333 K,  $\Delta G^\circ = -100 \text{ kJ/mol}$ ,  $\Delta H^\circ = -75 \text{ kJ/mol}$ . What does this say about the entropy?

So we can construct a free energy diagram to illustrate the course of the reaction.

What about the activation energy?

## Reactions of Alkyl Halides: First Order Nucleophilic Substitution, $S_N1$

When chloromethane reacts with hydroxide ion the reaction is second order

When t-butyl chloride reacts with hydroxide ion the reaction depends only on the concentration of t-butyl chloride, and is independent of  $[OH^-]$ . The reaction is first order in t-butyl chloride and first order overall.

From this we can conclude that hydroxide ion is not involved in the transition state of the rate-determining (slowest) step.

The slowest step of the reaction involves only molecules of t-butyl chloride. This reaction is Substitution, Nucleophilic, First order or  $S_N1$ .

# The S<sub>N</sub>1 Reaction: A Multistep Mechanism

Review the kinetics part of your General Chemistry class!

In a multistep reaction, one step likely goes slower than the others

$k = A\exp(-\Delta G^\ddagger/RT)$  tells us that this is the step with the highest activation energy,  $\Delta G^\ddagger$

First step rate-determining

Intermediate step rate-determining

Last step rate-determining

The first step is rate-determining for the  $S_N1$  reaction of t-butyl chloride with hydroxide ion. The subsequent steps are fast. The concentrations of intermediates are vanishingly small.

Step 1

Step 2

Step 3

The solvent  $H_2O$  is the other reactant. The  $OH^-$  drives the reaction forward by mopping up the  $H_3O^+$  produced. This is an example of **solvolysis** (cleavage by solvent).

## Structure and Stability of Carbocations

The carbocation is  $sp^2$  hybridized. The carbocation has a trigonal planar structure, and the positive charge is “in” the vacant p-orbital.

Carbocation stability can be explained by inductive or resonance effects

## S<sub>N</sub>1 Reactions and Stereochemistry

The nucleophile can attack the planar carbocation from either side. Which enantiomer dominates depends on the structure of the carbocation, the structure of the nucleophile, and the reaction conditions.

In many cases, the chances of attack are the same at both sides, so an enantiomeric substrate undergoes S<sub>N</sub>1 reaction to give a **racemic mixture** of enantiomers. The reaction proceeds with **racemization**.

Racemization occurs whenever a reaction proceeds through an achiral intermediate. But don't expect an equal mixture of enantiomers every time!

## Reactions of Alkyl Halides: Factors Affecting the Rates of S<sub>N</sub>1 and S<sub>N</sub>2 Reactions

### 1. The structure of the substrate

substrate	relative rate (S <sub>N</sub> 2)
CH <sub>3</sub> Cl	1
CH <sub>3</sub> CH <sub>2</sub> Cl	3 × 10 <sup>-2</sup>
(CH <sub>3</sub> ) <sub>2</sub> CHCl	1 × 10 <sup>-3</sup>
(CH <sub>3</sub> ) <sub>3</sub> CCl	~0

There's a clear trend here. The more blocked the back side is, the slower the second order reaction. This slowing of reactions by blockage is called **steric hindrance**. The reactivity trend isn't necessarily 1° > 2° > 3° (which might imply inductive effects). We can confirm that the effect is steric (not electronic) because the primary alkyl halide neopentyl chloride is more than a million times less reactive than chloromethane.

If you have any doubts about steric effects, build a molecular model!

For  $S_N1$  reactions, the rate is governed by the stability of the carbocation. A stable carbocation is around for longer, so there's more chance of it reacting with a nucleophile. Unstable carbocations rapidly recombine with their leaving groups, and there is no net reaction.

Factors that stabilize the intermediate carbocation will also lower the energy of the transition state of the rate-determining step (so the reaction will go faster). For primary alkyl halides there is little or no stabilization, so the energy of the transition state is very high, and the reaction is slow. For an unhindered substrate the  $S_N2$  reaction will be much faster.

Carbocations are stabilized by electronic effects. Electron donating groups can stabilize the positive charge on the carbocation. Resonance can delocalize the positive charge (remember, the more delocalization, the more stable the molecule).

Some stable carbocations

## 2. Concentration and reactivity of the nucleophile ( $S_N2$ )

Nucleophilicity and basicity: Nucleophilicity is measured by **rate of reaction** with a substrate bearing a leaving group. Basicity is often used as an indicator of nucleophilicity, but basicity (pKa) is an **equilibrium**, not a kinetic phenomenon. For example  $\text{OH}^-$  (pKa  $\text{H}_2\text{O} \sim 16$ ) is a stronger base than  $\text{CN}^-$  (pKa  $\text{HCN} \sim 10$ ), but cyanide is a stronger nucleophile than hydroxide.

A negatively charged nucleophile is always more reactive than its conjugate acid.

For the same nucleophilic atom, nucleophilicity parallels basicity

And obviously a higher concentration of nucleophile will increase the rate of an  $S_N2$  reaction.

### 3. The nature of the solvent: solvent effects on S<sub>N</sub>2 reactions

Better solvation by **protic solvents** (solvents with a dissociable proton, eg H<sub>2</sub>O) decreases nucleophilicity by dispersing the negative charge on the nucleophile through H-bonds.

Within a group, larger nucleophiles are stronger. They are more poorly solvated, and they are more polarizable (negative charge can be “bunched up”, increasing the effective charge density).

Poor solvation of anions by **polar, aprotic solvents** (eg DMF, DMSO) means that nucleophilicity follows basicity.

The rates of S<sub>N</sub>2 reactions increase in polar, aprotic solvents compared to protic solvents.

## Solvent effects on S<sub>N</sub>1 reactions

Polar, protic solvents stabilize both the carbocation and the leaving group anion.

Solvents with high dielectric constants can screen the anion from the cation more effectively than solvents with low dielectric constants. Better screening means longer lived separation, and greater chance of reaction.

solvent	dielectric constant
water	80
formic acid	59
DMSO	49
DMF	37
acetonitrile	36
methanol	33
ethanol	24
acetone	21

#### 4. The nature of the leaving group

Weak bases are good leaving groups (strong conjugate acids, don't want to associate with protons or +ve charge as much as strong bases).

Strongly basic ions rarely act as leaving groups. But  $\text{-OH}$  (strongly basic leaving group) can be converted into an excellent leaving group using a strong Brønsted acid.

## Reactions of Alkyl Halides: Elimination Reactions of Alkyl Halides: E1 Reactions

Consider the reaction between methoxide ion (a strong base and a powerful nucleophile) with ethyl bromide (a primary halide) in ethanol (a protic solvent). Unhindered substrate, strong nucleophile, weak base as leaving group and polar solvent all favor an  $S_N2$  reaction. The only factor we could improve is the solvent, which would favor  $S_N2$  even more if it was aprotic.

90% of the expected product is formed in this reaction. What about the other ten percent?

10% might not seem much, but look what happens as the substrate gets more hindered:

These are elimination reactions, and they have the general form:

OK, so we don't expect  $S_N2$  reactions with hindered substrates, but we do expect  $S_N1$  reactions. Why do we get elimination instead?

To answer that, we need to consider the mechanism. Elimination and  $S_N1$  can both involve the same carbocation intermediate (although there's another elimination mechanism that doesn't have a carbocation intermediate – more of that later).

Here's what happens in the  $S_N1$  case:

However, if the solvent can act as a base it can abstract a proton from a carbon atom adjacent to the carbocation and the H-C bonding electron pair will relocate to form a double bond and neutralize the positive charge on the carbocation:

Just like the  $S_N1$  reaction, the rate of this elimination reaction depends only on the substrate concentration. The carbocation reacts with solvent, so the concentration of the nucleophile doesn't matter. This is a first order elimination reaction, **E1**.

E1 reactions almost always accompany  $S_N1$  reactions. There isn't a good way to favor one over the other, so chemists wanting to do elimination reactions usually change the reaction conditions so that another mechanism operates.

## Elimination Reactions of Alkyl Halides: E2 Reactions

The slow step in both  $S_N1$  and E1 reactions is the formation of the carbocation. If a carbocation forms, even a weak base can abstract a  $\beta$ -proton and give the E1 product. It is likely that such a base can also add as a nucleophile in an  $S_N1$  reaction.

This can be resolved by using a strong base in high concentration. Although this doesn't stop the first order formation of a carbocation, it does provide a much faster competing reaction path. The products of the faster path always dominate the reaction.

The mechanism of the competing reaction involves direct reaction of the base with the substrate:

The rate of this reaction is first order in substrate and first order in base. It is second order overall, and is thus called an **E2** elimination.

## Bases used in Elimination Reactions

Sodium or potassium hydroxide, sodium ethoxide, or sodium hydride are often used as bases in elimination reactions.

### Favoring E2 over S<sub>N</sub>2

Just as steric crowding in the substrate can slow down S<sub>N</sub>2 reactions, steric crowding in the base can slow down S<sub>N</sub>2 reactions without affecting the elimination reaction. In an elimination reaction, no bonds are formed between the substrate and the base.

The t-butoxide ion is often used in elimination reactions.

Strongly polarizable, weak bases favor substitution. Weakly polarizable, strong bases favor elimination.

High temperature favors elimination because (a) the activation energy is higher than that for S<sub>N</sub>2 and (b) the reaction has a favorable entropy so a larger TΔS term helps.

Summary: Table 6.7 and Review Tools on p279