Chapter 8

Nucleophilic Substitution Reaction

Content

S_N1 vs S_N2 reaction

Mechanism and competitions

8.1 Nucleophilic substitution Reaction

8.2 Reaction Mechanism

⇒ shows how the nuclei and the electrons move and how the bonds change as the rxn proceeds.

Three possible mechanism
(1) R---L broken, then Nu-R bond formation (S_N1)
(2) Nu-R-L bond formation, then Nu–R--- L bond broken
(3) Nu---L broken and Nu-R bond formation happens simultaneously (S_N2)

(2) is impossible because there are five bonds to carbon.
***(1) and (3) are possible*.**

8.3 Bimolecular nucleophilic substitution (S_N2)

If the the bond to the leaving group is broken and the bond to the nucleophile is formed simultaneous, then rxn rate is proportional to <u>both reactants</u>!
(c) mechanism in the previous page.

$\Delta G^o < 0$; exergonic (spontaneous rxn)

$\Delta G^o > 0$; endorgonic (non spontaneous rxn)
ΔH; exothermic and endothermic

8.4 Stereochemistry of the S_N2 Rxn

Possible stereochemical outcomes

Transition state

S_N2 always occurs with inversion of configuration

8.5 Effect of substituents on the rate of S_N2

1. Steric effect see Fig. 8.4 and 8.5

2. Resonance effect; Resonance-stabilized transition state of Allyl, benzyl, etc, which as a pi bonds adjacent to the reactive side

8.6 Unimolecular nucleophilic substitution (S_N1)

Experimental results show that the rxn rate only depends on the concentration of *t*-butly chloride;

S_N1 reaction mechanism

Why ?
According to the theory made by Hammond.

How ?

The structures of both transition states are closer to the carbocation not the reactant and the product.

8.7 Effect of substituents on the rate of the S_N1 reaction

1. Methyl and primary alkyl chloride do not react by S_N1.
2. 3^o alkyl chloride > 2^o alkyl chloride.
3. Allyl and phenyl groups increase the rxn rate.
$\Rightarrow$ The stability of the carbocation determines the rxn rate

Why?

1. Hyperconjugation between sigma MO and *p* AO

2. Resonance stabilization

8.8 Stereochemistry of the S_N1 reaction

$\Rightarrow$Racemization (50% inversion +50% retention)

Some S_NI shows more inversion than retention.

Why?
Ion pair can be involved in the reaction.

When?
The life time of carbocation is short (=carbocation is unstable)

Therefore when the carbocation has a long lifetime, a racemic product is obtained

The life time depends on the nucleophile and the solvent

See next page or page 277 Fig 8.9

8.9 Effect of leaving group on S_N1 and S_N2

In both S_N1 and S_N2 reactions, the bond to the leaving groups is broken during the RDS. ***(see slide 6 & 12)***

Therefore the structures of the leaving groups affect the reaction rate.

General rule; the more stable the leaving group is as a free species, the faster the rxn is.

The more stable it is, the weaker base it is.

$\therefore$ Good leaving group = weak base

Ex) –OH is a bad leaving group, -Cl is a good leaving group.
–H, –NH2, and –OR do not act as leaving groups.

Cl^- < Br^- < I^- $\Rightarrow$ I^- is weakest base (most stable) and Cl^- is least stable (–F; very poor leaving group)

$\Rightarrow$ acidity; HCl < HBr < HI

mesylate and tosylate are very weak base and excellent leaving group because of the resonance stabilization

How alcohols are used in the substitution reactions

⇒ -OH is very poor leaving group

1. Reactions in an acidic condition

$-OH_2^+$ is a good leaving group because H_2O is a weak base

2. Using mesylate or tosylate

Methanesulfonyl chloride

Toluenesulfonyl chloride

8.10 Nucleophiles

-Nucleophilicity is only important in S_N2. In S_N1 nucleophiles are not involved in in RDS.

-Nucleophilicity ↑ as basicity ↑, but not always.

General Rules

The smaller (the higher basicity), the stroner the H-bonding with H_2O or alcohol

8.11 Effect of solvent

The roles of Solvents

- dissolves the reactants; they can contact each other
- no reaction with the reactants, intermediates, and product + no decomposition of them
- be chosen considering polarity; affect the stability or reactivity of the polar molecules

Polar solvents can stabilize ions.

If the transition state is more polar than the reactants, polar solvents will stabilize the transition state and increase the reaction rate.

If the reactants is more polar than the transition state, polar solvents will decrease the reaction rate.

Effect of polarity on S_N1

Polar solvents can stabilize ions the transition states including the carbocation.

Effect polarity on S_N2 reaction

Polar solvents decrease the rxn rate because the transition state is less polar (charges are dispersed).

Polar solvents increase the rxn rate because the transition state is more polar.

Protic solvents and aprotic solvents

Protic solvent; has an ability to form H-bonds to the nucleophile
⇒ makes nucleophile less reactive

Aprotic solvent; no H-bonding

Million times faster in dimethylformamide(DMF) than in methanol

In DMF (aprotic solvent), nucleophilicity; Cl^- > Br^- > I^-

In alcohol (protic solvent), nucleophilicity; Cl^- < Br^- < I^-

📖288 Table 8.4; **common solvents for substitution rxn**

8.12 Competition between S_N1 and S_N2

- S_N1 pathway is favored when
  1. carbocation is stabilized; 3° >2°, 1° carbocation is not formed
  2. only poor nucleophiles are present.
  3. the solvent is polar

- S_N2 favored when
  1. electrophilic carbon is not sterically hindered;

     methyl > 1°> 2°
  2. strong nucleophiles are present
  3. the solvent is aprotic (to make the nucleophile more reactive)

8.13 Intramolecular Substitution Rxn

- intermolecular vs intramolecular

4- membered rings are not easily formed.
3-, 5-, 6- membered rings can be formed.
Larger rings are less easily formed.

8.14 Competing Reactions

Elimination(chap. 9 & 10) and S_N2 (S_N1) are competing when the nucleophile is basic.

S_N1 is also possible because the electrophile is 2º alkyl halide.

Competition between S_N1 and elimination rxn

Carbocation Rearrangements

hydride shift

alkyl shift

Allylic
rearrangement

Reactions involving carbocation rearrangements