8.S: Nucleophilic Substitution Reactions (Summary)

Before you move on to the next chapter, you should be comfortable with the following concepts and skills:

Nucleophilic substitution basics

- Illustrate the transition state for an S_N2 reaction
- Draw a complete mechanism for an S_N1 reaction, in particular a hydrolysis or other solvolysis S_N1 reaction.
- Illustrate all transition states that are part of an S_N1 reaction.
- Understand that non-enzymatic S_N1 reactions result in both inversion and retention of configuration (racemization) at the electrophilic carbon. Enzymatic S_N1 reactions are stereospecific, usually resulting in inversion at the electrophilic carbon.

Nucleophiles

- Be able to recognize the nucleophile, electrophile, and leaving group in an SN1 or SN2 reaction.
- Understand that – with the exception of the vertical periodic trend in protic solvents – in most cases anything that makes something a stronger base also makes it a more powerful nucleophile:
  - The vertical periodic trend in nucleophilicity for reactions in polar aprotic solvents: chloride ion is a better nucleophile than bromide ion in acetone solvent.
- Inductive effect: electron-withdrawing groups decrease nucleophilicity
- Resonance effects:
  - Delocalization of negative charge/electron density decreases nucleophilicity. For example, methoxide ion (CH3O-) is a stronger nucleophile than acetate ion.
- In addition:
  - The vertical periodic trend in protic solvent (water or alcohol) is opposite the trend in basicity: for example, thiols are more nucleophilic than alcohols.
- Electrophiles
  - Less hindered electrophiles will react faster in SN2 reactions: for example chloromethane is a better electrophile than a primary alkyl chloride.

Leaving groups

- Common laboratory leaving groups are halides and para-toluenesulfonate (abbreviated tosyl, or OTs).
- Common biochemical leaving groups are phosphates and sulfide.

Carbocation stability

- More substituted carbocations are more stable: for example, a tertiary carbocation is more stable than a secondary carbocation.
- The presence of electron-withdrawing groups (by inductive or resonance effects) decreases carbocation stability.
- The presence of a heteroatom can stabilize a nearby carbocation by the resonance-based electron donating effect. Otherwise, heteroatoms act as weakly electron withdrawing carbocation-destabilizing groups by inductive effects.

General concepts and skills

- Be able to predict whether a given substitution reaction is likely to proceed by S_N2 or S_N1 mechanisms, based on the identity of the nucleophile, the electrophile, and the solvent.
  - S_N1 reactions involve weaker nucleophiles relatively stable carbocations, and are accelerated by protic solvents.
- Be able to 'think backwards' to show the starting compounds in a substitution reaction, given a product or products.
- Understand how S-adenosylmethionine (SAM) acts as a methyl group donor in biochemical S_N2 reactions.
- Be able to select appropriate alkyl halide and alcohol starting compounds to synthesize a given ether product, using the Williamson ether synthesis procedure.

Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)