CHE 2060 Module 6: Nucleophilic substitution lecture summary

6. Nucleophilic substitution reactions

6.1: Two mechanistic models for nucleophilic substitution

- Hydrolysis (breaking bonds with water) can be done via SN1 or SN2
- SN reaction only occur at sp3-hybridized carbons

6.1A: The SN2 mechanism

- One-step, concerted, 5-bond C intermediate, biomolecular first step
- Attack from the back, chiral inversion

6.1B: The SN1 mechanism

- Two-step: (1) LG leaves creating carbocation [slow]; (2) attack of Nu:-; (3) H+ polishing
- Unimolecular first step
- No chiral inversion; may create racemic mixture

6.2: Nucleophiles

6.2A: What is a nucleophile?

- Bases move only a proton; Nu: are weaker bases and do more than moving a proton.
- Commonly: N, O, S, X (halides), azide (N3-1), carboanions

6.2B: Protonation state

- (-) > neutral >> (+)

6.2C: Periodic trends in nucleophilicity

- Nu: strength: (What makes an atom want to donate or share its e: ?)
  - ↓ across rows; more protons, less willing to donate :
  - in protic solvents ↑ down columns as bases weaken
  - in aprotic solvents ↓ down columns (Nu: strength ~ base strength)
  - SH > OH

6.2D: Resonance effects on nucleophilicity

- Resonance stabilization weakens Nu:

6.2E: Steric effects on nucleophilicity

- Steric hinderance (bulk) weakens Nu:

6.3: Electrophiles

6.3A: Steric hindrance at the electrophile

- Steric hinderance (bulk) weakens E+ (bulky ↓ SN2, not SN1)

6.3B: Carbocation stability

- Generally carbocation stability ↑ by delocalization, resonance, e- donating (distance)
  - ↓ by e- withdrawing groups not in resonance
- SN1: 3° > 2° (> 1°)
- SN2: methyl > 1° > 2° > 3°

6.4: Leaving groups

- Weak bases best (use pKa); larger halogens better; p-toluenesulfonic acid
- Stabilization of (-) on LG makes it easier for LG to leave

6.5: Regiospecificity of SN1 reactions with allylic electrophile

- Chemical rxns can produce many products; enzymatic rxns are more regiospecific

6.6: SN1 or SN2? Predicting the mechanism

- See diagnostic table below

6.7: Biological nucleophilic substitution reactions

6.7A: A biochemical SN2 reaction

- SAM; thioethers are excellent leaving groups / weak bases (size: S<O)

6.7B: A biochemical SN1 reaction

6.7C: A biochemical SN1/SN2 hybrid reaction

- Adding an isoprenoid tail to allow a protein to associate with cell membrane

6.8: Nucleophilic substitution in the lab

6.8A: The Williamson ether synthesis

- 1°OH -- SN2 → ROR using methyl bromide to carry the methyl group
- (2° or 3° OH are just covered to 1°OH)

6.8B: Turning a poor leaving group into a good one: tosylates

- OH is a poor LG. In lab, convert it to an organic tosylate for better LG

factor	SN1	SN2
number of steps	3	1 (concerted)
E+ (substrate)	sterically hindered	unhindered
E+ stability	3°, 2° or stabilized	1°, 2°°
Nu:	weak Nu:	strong Nu:(-)
LG	good	good
TS	carbocation	5-bond trigonal planar
solvent	protic	polar aprotic
If chiral products?	enantiomers	chiral inversion