SUBSTITUATION & ELIMINATION REACTIONS

I Definitions

- Nucleophiles
  - "Nucleus loving"
  - Attack positive centers
  - Electron rich species with an unshared electron pair
  - For related nucleophiles (e.g. H_2O and OH^-), the more basic compound is a more reactive nucleophile.

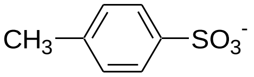
  Examples:

  H_2O, OH^-, CH_3OH, CH_3O^-, ROH, RO^-, NH_3, NH_2^-, CH_3SH, CH_3S^-, RSH, RS^-, I^-, Cl^-, Br^-, CN^-, N_3^-

- Leaving Groups
  - Weak bases
  - Typically the conjugate base of a strong acid
  - Relatively stable anions or neutral species

  Examples:

  I^-, Br^-, Cl^-, H_2O, ROH, $CH_3SO_3^-$ (Mesylate, or OMs),



(Tosylate, or OTs)

- Electrophiles
  - "Electron loving"
  - Electron deficient species, usually with a full or partial positive charge
- Solvent classifications:
  - Protic = can hydrogen bond (H bonded to F, O or N)
  - Aprotic = cannot hydrogen bond (no H bonded to F, O, or N)
- Carbocation intermediates
  - sp^2 hybridized, planar, empty p-orbital perpendicular to the molecular plane
  - Allow for the possibility of rearrangements (1,2-hydride and 1,2-alkyl shifts) to form more stable carbocations

II Nucleophilic Substitution Reactions

- ❖ S_N2
  - Single step reaction, no intermediate (concerted)
  - Bimolecular rate determining step, 2nd order kinetics
  - Inversion of configuration at carbon center (backside attack)
  - 5-membered transition state
  - Rate = k [nucleophile] [substrate]
    - ✧ Leaving groups
      - Better leaving group, faster reaction
      - NO reaction with weak leaving group
        - OH, OR, NR_2, F, CN, N_3 most common weak leaving groups
    - ✧ Electrophiles
      - CH_3>1°>2°>>3°
        - Tertiary substrate can NOT undergo S_N2 reaction
        - Why? Steric hindrance :
          - ▪ At reacting carbon:
            - More large (alkyl) groups, slower reaction
          - ▪ Beta-branching
            - If carbons NEXT to carbon center have bulky groups, then approach to carbon is hindered, and leads to a slower reaction
    - ✧ Nucleophiles
      - Better nucleophile, faster reaction
      - Weak nucleophiles (such as H_2O and ROH) do NOT undergo S_N2 reactions
      - Bulkier nucleophile, slower reaction (steric hindrance)
    - ✧ Solvent Effects
      - Polar, aprotic solvent increases rate of reaction
- ❖ S_N1
  - Multistep reaction, carbocation intermediate, 1st order kinetics
  - Unimolecular rate determining step, involves carbocation formation
  - Racemization at carbon center

- Rate = k [substrate]
  - ✧ Leaving groups
    - Better leaving group, faster reaction
    - NO reaction with moderate or weak leaving group
  - ✧ Electrophiles
    - 3°>2°>>1°
      - NO reaction with 1° R
    - Why? Carbocation stability
      - Stabilized by alkyl groups (through hyperconjugation and inductive effects)
        - ▪ More alkyl groups → more stable carbocation
      - Stabilized by conjugation
        - ▪ More resonance structures → more stable carbocation
  - ✧ Nucleophile does NOT affect the reaction rate
  - ✧ Solvent Effects
    - More polar solvent, faster reaction
    - NO reaction with aprotic solvent

III Elimination Reactions

- ❖ E2
  - Single step reaction, no intermediate (concerted)
  - Bimolecular rate determining step, 2nd order kinetics
  - Leaving group must be “anti” to the proton that is being abstracted by the base (H_β)
  - Major product follows Zaitsev’s Rule – most stable (substituted) alkene is the major product.
  - Rate = k [substrate] [base]
    - ✧ Leaving groups
      - Better leaving group, faster reaction
      - NO reaction with weak leaving group
    - ✧ Electrophiles

        - All OK, but must have H_β (anti to leaving group)
    - ✧ Bases
        - Better base, faster reaction
        - ONLY strong bases (OH^-, RO^-, NH_2^-) undergo E2 reactions
        - Large bases:
            - Do NOT affect the reaction rate
            - Do affect the product distribution (less Zaitsev products)
    - ✧ Solvent Effects
        - Polar, aprotic solvent increases rate of reaction

- ❖ E1
    - Multistep reaction, carbocation intermediate, 1st order kinetics
    - Unimolecular rate determining step, involves carbocation formation
    - Rate = k [substrate]
    - ✧ Leaving group
        - Better leaving group, faster reaction
        - NO reaction with moderate or weak leaving group
    - ✧ Electrophiles
        - 3°>2°>>1°
            - NO reaction with 1° R
        - Why? Carbocation stability
            - Stabilized by alkyl groups (through hyperconjugation and inductive effects)
                - ▪ More alkyl groups → more stable carbocation
            - Stabilized by conjugation
                - ▪ More resonance structures → more stable carbocation
    - ✧ Bases
        - Do NOT affect the reaction rate
        - Large bases do affect the product distribution (less Zaitsev products)
    - ✧ Solvent Effects
        - More polar solvent, faster reaction
        - NO reaction with aprotic solvent

IV Substitution vs. Elimination Reactions

- Generally:
  - Overall, elimination is favored over substitution
  - 1° substrate favors S_N2 reactions
  - 3° substrate favors E2 reactions
  - To favor elimination over substitution, use a good base that's a bad nucleophile. The bases that are preferred are bulky bases such as *t*-butoxide.
  - To favor substitution over elimination, use a good nucleophile that's a bad base, such as the halides (Cl^-, Br^-, I^-).
  - Increasing the temperature favors elimination
- Electrophile:
  - 1° S_N2, E2 reactions ONLY
  - 2° S_N1, S_N2, E2 reactions ONLY
  - 3° S_N1, E1, E2 reactions ONLY
  - Bulky beta-branching inhibits S_N2 reaction
- Leaving group
  - ✧ Need good or very good leaving group for S_N1, E1 reactions
  - ✧ Weak leaving groups do NOT react
- Nucleophile/base
  - Steric hindrance decreases nucleophilicity of base (prevents base from approaching carbon center)
  - Good base, bad nucleophile promotes elimination reactions
  - Bad base, good nucleophile promotes substitution reactions
  - Weak nucleophile/base, then ONLY S_N1, E1 reactions possible
- Solvent
  - Protic solvents stabilize ions, promote S_N1, E1 reactions
  - Aprotic solvents destabilize ions, ONLY S_N2, E2 reactions

V Table of Reactivities (In approximate *decreasing* order)

			Solvent Ionizing Power	
Nucleophilicity	Basicity	Leaving Group Ability	Protic	Aprotic
RS^-, HS^-	NH_2^-	I	H_2O	CH_3SOCH_3 (DMSO)
I^-	RO^-	OTs, OMs (OSO_2R)	HCO_2H	$(CH_3)_2NCHO$ (DMF)
🟦 CN^-, NCS^-	HO^-	🟦 Br, H_2O^+	CH_3OH	$(Me_2N)_3PO$ (HMPA)
🟦 $:NR_3$, $:NHR_2$	🟦 PhO^-, $R_3N:$	🟦 Cl, HOR^+	CH_3CH_2OH	CH_3CN
🟦 RO^-, HO^-	🟦 $:NH_3$, CN^-	🟥 NR_3^+	CH_3CO_2H	CH_3COCH_3
🟦 Br^-	🟥 $CH_3CO_2^-$ (AcO^-)	🟥 CH_3CO_2 (AcO)		
🟦 PhO^-, N_3^-	🟥 H_2O	🟩 OH, OR, NH_2, CN, N_3, F		
🟥 $:NH_3$, NO_2^-	🟥 ROH			
🟥 RSH	🟥 RCO_2H			
🟥 Cl^-	🟥 F^-			
🟥 $CH_3CO_2^-$ (AcO^-)	🟩 Cl^-			
🟥 $PhCO_2^-$	🟩 Br^-			
🟥 SO_4^{2-}	🟩 $HOSO_3^-$			
🟥 F^-	🟩 I^-			
🟥 NO_3^-				
🟩 HSO_4^-				
🟩 ROH				
🟩 H_2O				
🟩 RCO_2H				

Fill Code:
Very Strong
🟦 Strong
🟥 Moderate
🟩 Weak