Chapter 17. Benzene and Aromaticity.

1. Naming Benzenoid Compounds (briefly). “Arenes”.
   a) One small substituent.
      i) Nitro, bromo, propyl, isopropyl, etc.
      ii) Trivial names. toluene, phenol, aniline. benzaldehyde, benzoic acid, benzonitrile.
   c) Two substituents. ortho, meta, para.
   d) Two or more substituents. Numbering.

2. Structure of benzene. Fact: All bonds equivalent.
   a) Resonance description. Toilet bowl description.
   b) Molecular orbital description. Six AOs, therefore six MOs.
      i) butadiene — acyclic — 0, 1, 2, 3 nodes. Hexadiene — acyclic — 0 to 5 nodes.
      ii) benzene — cyclic — can’t have one, three, or five nodes. Two possibilities for two nodes or
          four nodes, one for none or six. Thus six energy levels, of which two pairs are degenerate.
          Frost mnemonic.

   a) Only substitution, not addition. Hard to hydrogenate. Unusually unreactive.
   b) Hückel rule: Odd number of electron pairs in continuously overlapping cyclic array of p orbitals
      is unusually stable (aromatic). Even number of electron pairs in continuously overlapping cyclic
      array of p orbitals is unusually unstable (antiaromatic).
   c) Examples of aromatic compounds.
      i) benzene, pyridine, pyrimidine, pyrazine.
      ii) furan, pyrrole, thiophene, imidazole (like in histidine).
      iii) cyclopentadienyl anion. cycloheptatrienyl cation, tropolone.
      iv) not cyclopentadiene itself. not hexatriene.
      v) naphthalene, anthracene. indole (like in tryptophan).
      vi) purine, DNA bases

   d) Examples of antiaromatic compounds.
      i) cyclobutadiene. Elongates the bonds. Not isolable.
      ii) cyclopentadienyl cation.
      iii) cyclopentadienone.
      iv) cyclooctatetraene. Folds to avoid overlap.
   e) Energy of aromaticity.

ii) Cyclopentadiene 20 orders of magnitude more acidic than pentadiene.

iii) Can buy cycloheptatrienyl cation.

iv) Some more aromatic than others. Anthracene, furan do Diels-Alder reactions.


1. Reactivity of Benzene.
   a) Relatively unreactive!!!
   b) Substitution of electrophiles, not addition. Typical alkene reactions like hydrogenation, hydroboration, dihydroxylation are difficult or don’t go at all.
   c) Nucleophile!!!

2. Bromination and other halogenation reactions.
   a) \( \text{C}_6\text{H}_6 + \text{Br}_2 \rightarrow \text{NR} \), but \( \text{FeBr}_3 \) promotes reaction, gives \( \text{C}_6\text{H}_5\text{Br} \).
   b) Mechanism. Addition of electrophile gives cation. \( \text{Br}^- \) deprotonates cation to reestablish aromaticity. Doesn’t add!
   c) Polybromination can occur if \( \times \) \( \text{Br}_2 \) is used.
   d) \( \text{Cl}_2 + \text{FeCl}_3 \) reacts same way. \( \text{I}_2 + \text{CuCl}_2 \) reacts same way.
   e) Use: Makes C atom electrophilic by attachment of leaving group. Can’t do \( \text{S}_\text{N}1 \) or \( \text{S}_\text{N}2 \) substitution on aryl–X, but we have other methods to do substitution reactions — will cover soon.

3. Nitration.
   a) \( \text{C}_6\text{H}_6 + \text{HNO}_3 \rightarrow \) gives \( \text{C}_6\text{H}_5\text{NO}_2 \).
   b) Mechanism. Active species is \( \text{NO}_2^+ \) via \( \text{O}_2\text{NONO}_2 \).
   c) Not reversible. Second nitration is a lot harder. Why?

4. Friedel-Crafts alkylation.
   a) \( \text{C}_6\text{H}_6 + \text{RX} \rightarrow \) gives \( \text{C}_6\text{H}_5\text{R} \). Requires catalytic amount of strong Lewis acid \( \text{AlCl}_3 \) to make reaction go.
   b) Mechanism. Active species is \( \text{R}^+ \).
   c) Limitations.
   i) Second alkylation is easier. Why? To control, use excess of arene, esp. as solvent. Sterics sometimes prevents second alkylation. (E.g., anisole + \( t\)-\text{BuCl} gives mostly one product.)
   ii) Works only with \( \text{C}(\text{sp}^3)–\text{X} \). Aryl and vinyl halides don’t work.
   iii) Works best with \( 3^\circ \) halides, doesn’t work well for \( 1^\circ \) halides. \( \text{n-PrCl} \rightarrow \) \text{cumene}, \( \text{n-BuCl} \rightarrow \) \( s\)-\text{BuC}_6\text{H}_5 \) (65%) + \( n\)-\text{BuC}_6\text{H}_5 \) (35%), neopentyl chloride \( \rightarrow \) 1,1-dimethylpropylbenzene only.
   d) Useful to make C–C bonds!
5. Friedel-Crafts acylation.
   a) \( \text{C}_6\text{H}_6 + \text{RCOX} \rightarrow \text{C}_6\text{H}_5\text{COR} \). Requires at least two equivalents of strong Lewis acid \( \text{AlCl}_3 \) to make reaction go.
   b) Mechanism. When using acyl halide, active species is not \( \text{RCO}^+ \) like the book says, but \( \text{RC(Cl)}=\bar{\text{O}}-\text{AlCl}_3 \). When using acyl anhydride, mechanism can be same as acyl halide or go through \( \text{RC}=\text{O}^+ \).
   c) Acylation always stops after occurring once.
   d) Useful to make \( \text{C}–\text{C} \) bonds!
   e) Can be reduced with \( \text{Zn/H}_2 \) or \( \text{N}_2\text{H}_4 \), then \( \text{KOH} \) and \( \Delta \) to give \( 1^\circ \) alkylbenzenes.

6. Regiochemistry and reactivity of electrophilic aromatic substitution.
   a) \( o,p \)-directing, activating groups: \( \text{MeO}, \text{R}_2\text{N}, \text{alkyl} \).
   b) \( m \)-directing, deactivating groups: \( \text{COX}, \text{SO}_3\text{H}, \text{CN}, \text{NO}_2, \text{NR}_3 \).
   c) \( o,p \)-directing, deactivating groups: \( \text{Hal} \).
   d) Strongly acidic conditions of F–C reactions turns \( \text{NH}_2 \) \( (o,p\)-director) into \( \text{NH}_3^+ \) \( (m\)-director); do \( p \)-substitution by acetylation of N first with \( \text{Ac}_2\text{O} \), remove the Ac group with aq. \( \text{NaOH} \).

7. Electrophilic aromatic substitution of heteroaromatics.
   a) Pyridine reacts at \( \text{C}(3) \), “meta” to the N atom.
   b) Furan and pyrrole react at \( \text{C}(2) \), next to the heteroatom.
   c) All can be explained by looking at the relative stability of the different carbocationic intermediates and their resonance structures.

8. Further transformations of aromatic substituents.
   a) Diazonium ions.
      i) \( \text{C}_6\text{H}_5\text{NO}_2 + \text{H}_2, \text{Pd/C} \rightarrow \text{C}_6\text{H}_5\text{NH}_2 + \text{NaNO}_2, \text{HCl} \rightarrow \text{C}_6\text{H}_5\text{N}_2^+ \)
      ii) \( \text{C}_6\text{H}_5\text{N}_2^+ + \text{CuCl} \rightarrow \text{C}_6\text{H}_5\text{Cl} \)
      iii) \( \text{C}_6\text{H}_5\text{N}_2^+ + \text{CuBr} \rightarrow \text{C}_6\text{H}_5\text{Br} \)
      iv) \( \text{C}_6\text{H}_5\text{N}_2^+ + \text{KI} \rightarrow \text{C}_6\text{H}_5\text{I} \)
      v) \( \text{C}_6\text{H}_5\text{N}_2^+ + \text{H}_3\text{PO}_2 \rightarrow \text{C}_6\text{H}_6 \)
      vi) \( \text{C}_6\text{H}_5\text{N}_2^+ + \text{CuCN} \rightarrow \text{C}_6\text{H}_5\text{CN} \) (Useful to make \( \text{C}–\text{C} \) bonds!)
         a) \( \text{CN} \) can be converted to \( \text{CO}_2\text{H} \) with aq. \( \text{NaOH} \)
      vii) \( \text{C}_6\text{H}_5\text{N}_2^+ + \text{H}_2\text{O}, \text{CuO} \rightarrow \text{C}_6\text{H}_5\text{OH} \)
      viii) \( \text{C}_6\text{H}_5\text{N}_2^+ + \text{HBF}_4 \rightarrow \text{C}_6\text{H}_5\text{F} \)
   b) Metal-catalyzed couplings.
      i) \( \text{C}–\text{C} \) bond-forming reactions
         a) \( \text{ArCl} + \text{RMgCl} + \text{cat. (Ph}_3\text{P})_2\text{NiCl}_2 \rightarrow \text{ArR} \) (Kumada coupling)
         b) \( \text{ArX} + \text{RM} + \text{cat. Pd}(0) + \text{phosphine ligand} \rightarrow \text{ArR} \) (M = \( \text{SnBu}_3 \) or \( \text{SnMe}_3 \), \( \text{B(OH)}_2 \), \( \text{ZnCl} \) (Stille, Suzuki, Negishi couplings)
         c) \( \text{ArX} + \text{CO} + \text{MeOH} + \text{base} + \text{cat. Pd}(0) + \text{phosphine ligand} \rightarrow \text{ArCO}_2\text{Me} \)
d) \[ \text{ArX} + \text{RC}≡\text{CH} + \text{base} + \text{cat. CuI} + \text{cat. Pd(0)} + \text{phosphine ligand} \rightarrow \text{ArC≡CR} \] 
(Sonogashira coupling)

e) use C(sp^2) with B(OH)_2, C(sp^2) or C(sp^3) with Sn or Zn. C(sp^2) can be primary, secondary, or tertiary — no rearrangements, unlike F–C chemistry!

f) most widely used methods these days for attaching C(sp^3) and C(sp^2) to aromatic rings

g) Disconnection: Ar–R \Rightarrow Ar–Br + R–M.

(1) If R is C≡C, M = H is best.
(2) If R is C=C, M = B(OH)_2 is best.
(3) If R is C–C, M = ZnCl or SnMe_3 is best. F–C alkylation is also an option (watch for rearrangements when working forward!).
(4) If in doubt, M = SnMe_3, which works with all kinds of C.
(5) If R is C=O, use F–C acylation!

ii) C–N and C–O bond-forming reactions (Buchwald–Hartwig couplings)

a) \[ \text{ArX} + \text{ROH} + \text{base} + \text{cat. Pd(0)} + \text{phosphine ligand} \rightarrow \text{ArOR} \]

b) \[ \text{ArX} + \text{R}_2\text{NNH} + \text{base} + \text{cat. Pd(0)} + \text{phosphine ligand} \rightarrow \text{ArNR}_2 \]

c) Cannot do these reactions by S_N2 or S_N1!

c) Comparison of diazonium ions vs, cross-couplings.

i) Diazonium ion chemistry starts with \( \text{H} \rightarrow \text{NO}_2 \rightarrow \text{NH}_2 \rightarrow \text{N}_2^+ \), whereas metal-catalyzed reactions start with \( \text{H} \rightarrow \text{halogen} \). Diazonium chemistry has a meta director intervene before ortho–para director: can be useful for synthesis. (E.g., \( m \)-bromotoluene.)

ii) Metal-catalyzed route is much shorter; can often buy aryl halides.

iii) Metal-catalyzed reaction is much more versatile for making C–C bonds. Very mild conditions. Nonaqueous, so more compatible with organic reagents.

iv) Diazonium chemistry can introduce F or OH; neither easy to do with metal-catalyzed couplings.

v) Two methods can complement one another: e.g., 1,3,5-triethylbenzene.


a) Can’t be S_N2 because backside attack can’t occur. Can’t be S_N1 because aryl cations are way unstable. Can’t be electrophilic substitution because HO^- is a nucleophile.

b) The nitro groups make benzene \( \pi \) bonds electrophilic. Negative charge upon attack of HO^- is stabilized by NO_2 groups. What other electrophilic \( \pi \) bonds do we know about?

c) For aromatic ring to be electrophilic enough to react at room temperature, need at least one, preferably two NO_2 groups or other strong electron-withdrawing groups.

10. Aromatic side chain oxidation.

a) KMnO_4 converts alkyl chains attached to benzene rings into CO_2H groups.

b) All alkyl side chains that contain benzylic H atoms are oxidized.

a) Li, liquid NH$_3$ converts benzene into 1,4-cyclohexadiene.

b) Alkyl and alkoxy groups prefer to end up on the C(sp$^2$) of the cyclohexadiene product.

c) CO$_2$H group prefers to end up on the C(sp$^3$) of the cyclohexadiene product.

d) OH

\[ \text{NHCH}_3 \] is reduced to \[ \text{NHCH}_3 \] under the same conditions.

12. Note: Several ways to make ArCO$_2$H.

a) ArH $\rightarrow$ ArNO$_2$ $\rightarrow$ ArNH$_2$ $\rightarrow$ ArN$_2^+$ $+$ CuCN $\rightarrow$ ArCN $+$ aq. NaOH, $\Delta$, long time $\rightarrow$ ArCO$_2$H.

b) ArH $+$ X$_2$ $+$ FeX$_3$ $\rightarrow$ ArX $+$ CO, MeOH, cat. Pd(0), phosphine, base $\rightarrow$ ArCO$_2$Me $+$ aq. NaOH $\rightarrow$ ArCO$_2$H.

c) ArH $+$ CH$_3$Cl $+$ AlCl$_3$ $\rightarrow$ ArCH$_3$ $+$ KMnO$_4$ $\rightarrow$ ArCO$_2$H.