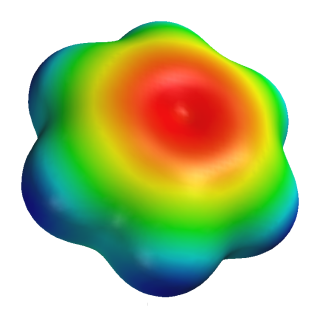
1. Benzene  orbitals: http://en.wikipedia.org/wiki/File:Benzene-3D-potential.png
   1. accessible electron density above and below carbon ring
   2. Shields from attach by nucleophiles
   3. Attracts electrophiles

1.  and -complexes
   1. Methylbenzene and HCl for 1:1 complex at – 78 C
   2. DCl does not exchange with H on ring (at this temperature)
   3. Sliver ion and dihalogens form -complexes

* 1. Stronger acid will form -complexes (Wheland intermediates): HCl and AlCl3
  2. Aromaticity is lost in the -complex
     1. -bond is formed
     2. Pentadienyl  system is formed
  3. Substitutions via -complex is at least 2 steps
     1. addition and dissociation
     2. arenium ion mechanism: arenium ions observed by NMR in superacid solutions
     3. -complex precedes most if not all formation of -complexes



1. Nitration???
   1. Sufuric acid activates Nitric acid to form nitronium ion

* 1. reaction is zero order in aromatic compound if more reactive than benzene
  2. formation of nitronium ion is rate determining ( slow step)
  3. Rate = k[Ar-H][NO2+] for less reactive aromatic compounds
  4. Three mechanisms for electrophilic aromatic substitution of H
     1. Difference in how electrophile attacks ring
     2. There are Concerted, first step RDS, second step RDS
     3. Observation: replace nitrobenzene with nitrobenzene-d5, kH/kD < 2
     4. Concerted and (b) rate determining are inconsistent (CH is broken in RDS)





1. Transition state structures – Hammond Postulate
   1. occasionally intermediates or analogs can be observed
   2. transition state has no finite lifetime – no barrier
   3. infer transition state structure from intermediates
   4. “**Hammond Postulate**: *If* ***two*** *states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structures. G. S. Hammond, JACS 77 (1955) 334.*”



1. Halogenation
   1. I2 < Br2 < Cl2 (order of reactivity) occurs directly only with more reactive aromatics!!!
   2. Benzene and unreactive aromatic require Lewis acid catalyst, e.g. AlCl3, FeX3
   3. F2 – explosive
   4. Rate = k[X2][arene][catalyst]



* 1. Normally No primary kinetic isotope effect – RDS is ?
  2. Other halogenation reagents: HOCl, HOBr, HOI, ICl, CH3CO2Cl, CF3CO2Br
  3. Note that rate laws are often complex

1. Sulfonation
   1. Sulfur trioxide is active agent
   2. formed in concentrated or fuming sulfuric acid
   3. Reversible, protonation can occur before CH bond breaks (protonate water)





1. Freidel Crafts alkylation
   1. Normally requires Lewis acid catalyst: AlCl3 >FeCl3 > BF3 > TiCl3> ZnCl2> SnCl4 (SbF5)
   2. Rate = k[RX][arene][catalyst] or k[RX][catalyst]
   3. Free alkyl cations form if stable, mechanism applies specifically to primary halide



* 1. Rearrangements can occur with more reactive catalyst



* 1. Exchange of halide indicates potential for rearrangement before addition to aromatic



* 1. Alkyl rearrangement also occur after product formation



* 1. Lewis acid also can cause dealkylation



* 1. Alkyl migration



Hcombustion(para) = -4542 kJ/mol, , Hcombustion(meta) = -4549 kJ/mol, meta is 7 kJ/mol less stable

* 1. Multiple alkylation biggest problem in synthesis – product more reactive

1. Freidel Crafts Acylation
   1. Rate = k[RCOCl][arene][catalyst] or k[RCOCl][catalyst]
   2. F-C acylation is more selective than alkylation
      1. indicating less reactive than alkyl toward arene
      2. either goes by acylium or complexed acid halide
      3. acylium not detected in non-polar solvents



* 1. benzoylchloride and benzoylbromide reaction with toluene in polar solvent
     1. diferent rates but same product distribution: 1% meta, 9% ortho, 90% para
     2. suggests same species attacks (PhC=O+)
     3. RDS is loss of halide
  2. In other conditions, ortho product is much lower, consistent with complex with AlX3.
  3. More than one mole of Lewis acid required (unlike FC alkylation)
     1. Ketone product a better donor than acid chloride
     2. catalyst deactivated by binding to ketone



* 1. multiple acylation not a problem
     1. Acylated arene is deactivated
     2. Catalyst bound to acylated arene even more deactivated
     3. Reduction of acyl arenes is best method to make alkyl arene
  2. Rearrangement not a problem unless acylium can decompose to more stable ion
  3. Other reagents
     1. Anhydrides and esters can form acyliums or activated complexes

, 

* + 1. Protic acids: HF, H2SO4

1. Ipso substitution
   1. Substitutions other than hydrogen: Br, I, SiR3, SnR3, SO3H, R
   2. Groups that attract addition (often electron rich  donors)
   3. Desulfurization: dilute hot acid, water adds to SO3 drives reaction to completion



* 1. Silanes and stannanes (SiR3 and SnR3): Protodesilylation remove H





* 1. Protodealkylation (section 7.7 ) especially stable alkyl cations
  2. ipso attack - five possible fates: electrophile migration, ipso group migration, ipso group loss, electrophile loss, nucleophile addition



1. Electrophilic addition to substituted benzene: directing groups
   1. Ortho, para versus meta
   2. Activating groups favor ortho and para,  effects are greater than  effects, why?



* 1. Activating (faster) or deactivating (slower) groups (relative to H, i.e. benzene)
  2. Directing groups: meta or ortho/para, normally all three isomers form



* 1. Deactivating groups, electron withdrawing, partial or positive charge



* 1. Deactivating groups slow down attack at all positions, more at ortho and para
  2.  for bromination (includes *o*, *m*, and *p*)
  3. Most deactivating groups are meta directors (slower than benzene)
     1. Avoids direct interaction with high charge at ortho and para positions







* 1. Activation by electron donating. Partial of full negative charge
  2. Favor direct interaction with high + charge at ortho and para positions







* + 1. o/p groups with lone pairs inherently form more stable cations: a fourth resonance form
    2.  for chlorination (includes *o*, *m*, and *p*)
  1. Relative rates (repeat of 10.2)



* 1. Why is OR group activating?
  2. Why is amide (or ester) slower then amine (or alcohol)
  3. OMe so active mono and dibromo product reacts too fast to isolate



* 1. Anilines are deactivating in acid solution, why?
     1. anilides PhNHCOR not easily protonated
     2. substitute anilide and then remove acyl group
  2. Halogens: Cl, Br, and I deactivate but are ortho and para directors
     1. o/p stabilized by -donation so faster than meta
     2.  withdrawing effect stronger than -donation so slower than benzene
     3.  for nitration (includes *o*, *m*, and *p*)

* 1. The dipoles for bromobenzene and methoxybenzene are revealing



1. Direction of Multiple groups
   1. strongest activating group controls position of substitution
   2. position between meta groups disfavored



1. Partial rate factors – rate relative to single benzene position
   1. 
   2. 
   3. 
   4. for example: if nitration of trichloromethylbenzene were 15 times slower than benzene and 29% of product is para then 
   5. partial rate factors depend on reaction and substituent



* + 1. does not mean that nitration < chlorination < bromination
    2. doesn’t mean nitration slower than chlorination
    3. nitration of benzene is faster than chlorination, and nitration of toluene is not that much faster: nitration is not as selective as chlorination
  1. steric effect on partial rate factors: reduces ortho substitution

1. other ring systems
   1. sulfonation of naphthalene





* 1. pyridine – more deactivated than nitrobenzene, electrophilic substitution not practical
     1. : heteroatom donates only single electron to aromatic ring, N attack



1. pyrrole
   1. heteroatom donates a pair of electrons to aromatic ring: more reactive than benzene and directs  (2) substitution (pyrrole)





* 1. dipoles indicate how different the two heterocyles are

1. Aromatic Nucleophilic Substitution
   1. Hydride is normally not a good leaving group
   2. nucleophilic substitution at hetero atom (ipso substitution)
   3. needs to be a potential leaving group
   4. Ortho/para electron withdrawing groups activate ipson substitution



* 1. first step is usually rate determining: rate shows little dependence on leaving group ability
     1. leaving group (X) dissociation is faster than loss of nucleophiles
     2. rate = k[ArX][Nu] for amines and good nucleophiles
     3. replacement of halogens: F > Cl > Br > I





* + 1. first step is rate determining, F activates attack best (most electronegative- attracts nucleophies) loss of X faster than CH3O-
    2. o/p withdrawing groups that can accept charge stabilize negative ipso intermediate



* 1. Loss of X (second step) is RDS with weaker nucleophiles like methylaniline



* + 1. The first step become slower with the poorer nuclephile, stil faster with F
    2. reverse is also faster, better leaving group, lower barrier
    3. From the intermediate: reverse barrier is now lower than forward barrier
    4. Overall rate: F < Cl < Br < I because loss of X is faster for better leaving group
    5. Rates for unactivatived halides increase by 109 in aprotic polar solvent



* 1. 2- or 4-halopyridines not 3- readily substitute by nucleophilic substitution, what is the mechanism?



1. Aryne mechanism
   1. Not a simple substitution



* 1. NH2- is known to exchange H and D.



* 1. Reaction is base elimination followed by addition. Orientation of products
  2. first or second step is rate determing depending on leaving group
     1. proton loss is rate determining for Br and I
     2. leaving group loss is rate determining for F and Cl
     3. formation of most stable carbanion intermediate determines position of nucleophile attack



* 1. Evidence for benzyne: dimer formation during reaction and trapping





Diaozocarboxylate?