

PHPH 618 Receptor Pharmacology

Pharmacodynamically Important Chemical Bonds & Groups

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I. Physical-Chemical Bases of Ligand – Target Interactions

- A. This lecture is an antecedent to Dr. Dawson's introduction to the theoretical underpinnings and practical aspects of the interactions between a ligand and a receptive target
- B. Visualization of the process (**various figures**)
- C. What is really going on? Is it all vibration and translocation (movement)
- D. What about other possibilities (e.g. Abramson's papers)
- E. What then are the essential physical features to be considered?
- F. Chemicals bonds
- G. Electrostatic attraction-repulsion
- H. Isomerism – stereoisomers
- I. Spatial considerations – i.e. steric hindrance

II. Chemical Bonding

- A. Van der Waals attractions/London dispersion forces (**figure**)
 - 1. intermolecular attractions between nonpolar molecules with transient asymmetrical distribution (temporary dipole) of e^- density
 - 2. temporary dipole of 1 molecule induces opposite dipole in approaching molecule
 - 3. attraction referred to as induced dipole-induced dipole attraction
 - 4. weakest bond: $\sim 0.5-1.0$ kcal/mole / atom involved
 - 5. temperature dependent
 - 6. occurs over short distances so tight packing influential
 - 7. steric factors effect greatly e.g. branching
 - 8. important in hydrocarbon and aromatic systems
 - 9. of little import in H_2O
 - 10. hydrophobic interactions occur in aqueous environment when 2 nonpolar moieties closely approach causing otherwise ordered H_2O to become disordered to re-associate; increased entropy decreases free energy thus stabilizing D-R complex
- B. Dipole-Dipole bonding (hydrogen bonding) (**figures**)
 - 1. stronger than Van der Waals attractions
 - 2. energy of H bonding is 1-10 kcal/mole per interaction
 - 3. results from unequal sharing of a pair of electrons in a covalent bond
 - 4. occurs when two atoms making up bond differ significantly in their electronegativity
 - 5. electropositive H bonds to electronegative oxygen, sulfur, nitrogen
 - 6. H bonds – type of dipole-dipole interaction between proton in X-H, where X is electronegative and other electronegative atoms (Y) containing pair of unbonded electrons
 - 7. Charge-transfer complexes – another molecular dipole-dipole interaction when e donor (e.g. O, N, S; Tyr, Asp) contacts electron acceptor (Cys) & a charge transfer occurs
 - 8. Amino acids His, Trp, Asn act as both donors & acceptors

C. Ionic Attractions (**slides of examples**)

1. result from attraction of a negative atom for a positive one
2. 5 kcal/mole or more
3. least effected by temperature and distance
4. Ionic interactions – @ pH7.4 +: Arg, Lys, >> His; -: Asp, Glu

D. Ion-Dipole bonding (**slides of examples**)

1. very important
2. occur between an ion (cation or anion) and formal dipole (e.g. cation shows bonding to region of hi electron density as e.g. oxygen in water)
3. relatively insensitive to temp and distance
4. important in forming salts
5. Ion-Dipole & Dipole-Dipole interactions – C with electronegative atoms: O, N, S, Br, Cl, I that produce asymmetric electronic dipoles (weak)

III. Chemical Groups

A. Alkanes (C_nH_{2n+2})

1. Structures (**slides of examples**)
2. Physical-Chemical Properties
 - a. unable to undergo H bonding
 - b. ionic bonding or ion-dipole bonding
 - c. attracted to other groups via weak Van der Waals forces
 - d. bonding interactions between small alkanes (containing 1-4 C atoms) is weak and so exist as gases at room temperature
 - e. alkanes containing 5-20 C atoms are liquids at room temperature due to increased bonding
 - f. alkanes can not penetrate water lattice so are immiscible
 - g. in contrast very lipid soluble
 - h. tend to be very stable cmpds wrt to air, light, heat, aqueous acids and bases
 - i. alkanes w/ branching chains may contain chiral C atom and therefore display asymmetry – chiral molecule
 - j. stereoisomers, enantiomers (**slides of examples**)

B. Alkenes (C_nH_{2n})

1. Structures (**slides of examples**)
2. Physical Chemical Properties
 - a. similar to alkanes
 - b. 2-4 C atoms exist as gases at room temp
 - c. greater than 4 C's exist as liquids at room temp
 - d. weak interactions are of the induced dipole-induced dipole type
 - e. cannot hydrogen bond
 - f. exist as weak permanent dipole
 - g. can't dissolve in water but very lipid soluble
 - h. double bond in alkenes confers a reactive site that alkanes lack
 - i. prone to oxidation to peroxides that are unstable and can explode

C. Aromatic Hydrocarbons

1. Structures (**slides of examples**)
2. Physical Chemical properties
 - a. not just cyclic alkenes
 - b. aromatic ring structure promotes resonance stabilization of structure
 - c. electron clouds in aromatic systems exist above and below the plane of the ring
 - d. delocalized electrons are not readily available as in alkenes so not as chemically reactive
 - e. typical rxn involves an electrophile (electron-loving positively charged species attacks electron-dense cloud of aromatic ring)
 - f. in biological systems hydroxylation of aromatic systems via CYP450 is an important (essential) means of metabolizing (inactivating/removal)

D. Halogenated Hydrocarbons

1. Structures (**slides of examples**)
2. Physical Chemical properties
 - a. monohaloalanes act as permanent dipoles due to strong electronegative halide atom
 - b. however, being a permanent dipole does not insure dipole-dipole interactions will occur
 - c. halogens are rich in electron density so no region significantly deficient in electrons so intermolecular interactions are weak and most of the Van der Waals type
 - d. poor water solubility
 - e. tend to increase lipophilic nature of any cmpd they are associated with chemically unreactive

E. Alcohols

1. Structures (**slides of examples**)
2. Physical Chemical Properties
 - a. OH group participates in intermolecular H bonding
 - b. electronegativity of oxygen and electropositive proton permanent dipole exist
 - c. unequal sharing of electrons
 - d. water soluble via H bonding but depends on length of hydrocarbon chain and location in chain of hydroxyl radical with secondary more soluble than primary
 - e. added hydroxyl groups increase solubility in water
 - f. alcohol functional group relatively stable as a unit except in presence of oxidizing agents w/ primary alcohols converting to carboxylic acids via and aldehyde intermediate
 - g. secondary alcohols oxidize to ketones
 - h. tertiary alcohol is stable to mild oxidation

F. Phenols

1. Structures (**slides**)
 - a. carboxylic acid = phenol
2. Physical Chemical Properties
 - a. OH group important contributor to properties of phenols
 - b. strong electronegative group (oxygen) attached to electropositive H

- c. permanent dipole situation permits intermolecular hydrogen bonding > hi boiling point
- d. pretty high solubility on water
- e. as lipophilic nature of phenol increases solubility in water drops
- f. addition of CH₃ moiety = cresol or halogen significantly reduces water solubility
- g. addition of second hydroxyl group as in catechol increases water solubility
- h. solubility in water decreases as a function of the length of any attached hydrocarbon
- i. phenols are weak acids compared to carboxylic acids, e.g.
- j. acidity of phenols depends on ability of hydroxyl to give up proton
- k. is dependent on stability of phenolate ion (O⁻) which is stabilized by aromatic resonance (overlap of pair of electrons associated with oxygen with delocalized cloud of electrons above and below ring; unlike hydroxyl in alcohols – which are neutral not acidic- and lack resonance)
- l. phenols are able to hydrogen bond with water molecules and as acids (and ions to some degree) engage in stronger ion-dipole bonding with water
- m. acidity influenced by ring substituents with ortho- substitutions being unpredictable while meta and para- produce predictable effects related to acidity
- n. ring substitutions consisting of electron donors decreases acidity (greatest effect in para- position)
- o. addition of electron-withdrawing groups increases acidity (greatest effect in para- position)
 - i. .due to ability of substituents to stabilize the phenolate (ionized form of phenol)
- p. phenols (as acids) are chemically reactive – form salts with strong bases (not all will dissolve but most do)
- q. easily oxidized to quinones (yellowish color) by atmospheric oxygen
- r. store protected from oxygen (e.g. under water) in closed container protected from light

G. Ethers

- 1. Structures (**slides**)
- 2. Physical Chemical Properties
 - a. synthesized from combining 2 alcohols or alcohol and phenol
 - b. low boiling point w/ poor water solubility and chemically almost inert
 - c. weak Van der Waals attractions influence
 - d. lower-membered ethers can H bond to water and have partial solubility via electron rich oxygen
 - e. as hydrocarbon lengthens solubility drops
 - f. important in anesthesia
 - g. relatively unreactive
 - h. stable entities except if in contact with atmospheric oxygen resulting in peroxide formation (explosive)
 - i. Cu added can help prevent via soaking up oxygen

H. Aldehydes & Ketones

1. Structures (**slides**)
2. Physical Chemical properties
 - a. carbonyl group is polar
 - b. oxygen more electronegative than C so cloud electrons distorted toward oxygen
 - c. ketones > aldehydes exist an equilibrium with “enol” form (**figure**)
 - d. hi electron density around O allows aldehydes and ketones to H bond with water thus limited solubility (similar to ethers but stronger)
 - e. longer the hydrocarbon portion solubility drops
 - f. ketone functional group relatively nonreactive
 - g. aldehydes in contrast -1 oxidation state from stable carboxylic acid structure so most are rapidly oxidized in air
 - h. low molecular weight aldehydes can undergo polymerization to cyclic trimers (heat sensitive) or straight-chain polymers

I. Amines

1. Structures (**slides**)
2. Physical Chemical Properties
 - a. amino functional group the most common in medicinal agents
 - b. important for 2 reasons
 - c. role in solubilizing drug as the free base or as water soluble salt of the amine
 - d. is to act as a binding site holding drug to a specific site in body to produce biologic activity
 - e. polar compounds
 - f. may not show good water solubility
 - g. e.g. in tertiary AMINE no electropositive H connected to N atom
 - h. primary and secondary do have electropositive H connected to N atom but N not as electronegative as O atoms so dipole is weak and intermolecular H bonding minimal so low boiling points
 - i. re water solubility the amine has an unshared pair of electrons leading to high electron density around N atom promoting water solubility due to H bonding between H in water and electron dense N
 - j. similar to low MW ethers but occurs to a greater extent with basic amines
 - k. primary amines more soluble than secondary >> tertiary amine can solubilize up to six or 7 methylenes making them equivalent to an alcohol
 - l. extremely important property of amines is their basicity and ability to form salts
 - m. Bronsted definition of base is ability to accept proton from an acid
 - n. unshared pair of e's more readily a basic amine donates e's stronger the base
 - o. measure of amine basicity obtained by considering acidity of conjugate acid produced by protonating amine to give an ammonium ion (pKa)
 - p. strong amine base holds on to proton existing as ammonium with large pKa
 - q. factors affect basicity
 - r. electronic and steric
 - s. if electron-donating groups (e.g. alkyl) attached to basic N its electrons will be more readily available for donating and vice versa (e-withdrawing groups e.g. aryls or phenols)
 - t. steric effects particularly important for tertiary amines; for alkyl amines secondary amines more basic than tertiary > primary

- u. aromatic amines very different with ring acting as an electron sink (e withdrawing) leading to drops in basicity of 6 orders of magnitude)
- v. substitutions on the ring affect basicity of amines with meta and para (withdrawing group here decreasing basicity and vice versa)
- w. since amines are basic form salts with acids and if dissociable will promote water solubility (often HCl but also sulfuric, tartaric, succinic, citric
- x. meta substitution is predictable while ortho unpredictable re basicity
- y. adding a base to an amine salt liberates amine that can ppt
- z. some acids (pamoic and hydroxynaphtholic) form amine salts that are water-insoluble (good for drugs targeted to GI tract e.g.)

J. Carboxylic Acids

1. Structures (**slides**)
2. Physical Chemical Properties
3. Functional group consists of polar (H bond) carbonyl and hydroxyl groups
 - a. solubility a function of hydrocarbon length
 - b. bonds to water
 - c. carboxyl group can solubilize 5 C atoms
 - d. carboxls more soluble in EtOH-water due to Van der Waals and dipole-dipole bonding
 - e. acidic properties (dissociates easily)very impt