

Week 5

Aromaticity

5.1 Aromaticity 1

- 2/8:
- Office hours: Tuesday and Friday at 4:00 PM.
 - PSet 3 is due 2/17.
 - Aromatic compounds are called such because they're often fragrant. They're heavily associated with biological systems.
 - History of aromatic compounds.
 - 1825: Michael Faraday isolated a compound from his oil lamp having a C : H ratio of 1 : 1.
 - 1834: Benzoic acid plus heat makes $(\text{CH})_n + \text{CO}_2$.
 - Even hex-1,3,5-triene still has more hydrogens than carbons.
 - Benzene.
 - There are about 60 possible structures for C_6H_6 .
 - **Dewar benzene** is two fused 4-member rings with alkenes on opposing sides.
 - But benzene is highly unreactive in alkene reactions...
 - 1865: Kekulé proposed a “cyclohexatriene” structure.

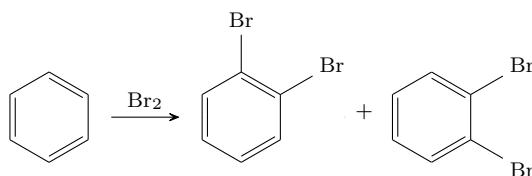


Figure 5.1: Bromination of cyclohexatriene.

- Evidence: You would expect bromination of cyclohexatriene to produce two products, but it only produces one (the two molecules must be rapidly interconverting, i.e., via resonance).
- Chemists began looking for more similar compounds.
- 1911: Cyclooctatriene was made.
 - It can be hydrogenated, so not consistent with the low reactivity of benzene.
- Cyclobutadiene was impossible to isolate due to a self-Diels-Alder reaction at any temperature greater than -260°C .
- Enthalpies of hydrogenation.

- Hydrogenation of cyclohexene has $\Delta H = -28.6$ kcal/mol.
- Hydrogenation of cyclohex-1,4-diene has $\Delta H = -57.2$ kcal/mol.
- Hydrogenation of cyclohex-1,3-diene has $\Delta H = -55.4$ kcal/mol.
 - The 1.8 kcal/mol difference between the previous two comes from conjugation as predicted by resonance.
- Hydrogenation of benzene has $\Delta H = -49.3$ kcal/mol.
 - That is a huge stabilization effect.
- The bond lengths in benzene are all equally 1.39 Å.
- MO theory: We need a method to draw the MOs for flat, cyclic conjugated compounds. We will use the **Frost method**.
- For hexa-1,3,5-triene, six p -orbitals combine to make six MOs.

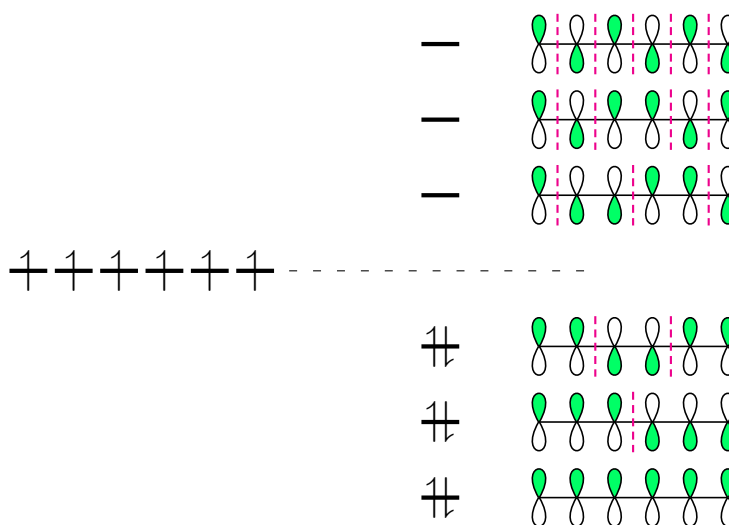


Figure 5.2: Hexa-1,3,5-triene MO diagram.

- Three are bonding; three are antibonding. We can guess at what the SALCs look like with a nodal analysis.
- For benzene, six p -orbitals combine to make six different MOs.
 - See Figures III.1 and III.2 in Labalme [1].
 - For conjugated cyclic systems with an even number of atoms, there will always be a single high and single low MO energy level.
- **Frost method:** The following procedure for drawing MOs for flat cyclic conjugated compounds.
 1. Draw a polygon of the molecule without double bonds and with a vertex at the bottom.
 2. Draw a line halfway through the structure.
 3. Put an MO at each vertex.
- For example, if we want to find the MOs of butadiene, we do the following.

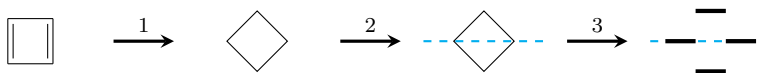


Figure 5.3: Frost method: Butadiene.

- We can even apply this to cyclotetradecaheptaene.

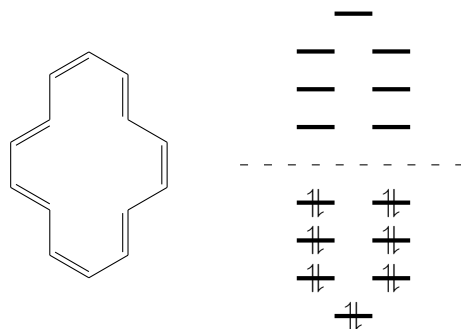


Figure 5.4: Frost method: Cyclotetradecaheptaene.

- **$(4n + 2)$ rule:** If a system has $4n + 2$ π -electrons for $n \in \mathbb{N}_0$, then it is aromatic.
 - Alternatively, if all bonding orbitals are filled and there are no electrons in non-bonding or anti-bonding orbitals, then the compound is aromatic.
- **Anti-aromatic** (molecule): A flat cyclic conjugated molecule with an uninterrupted flow of p -orbitals that does not satisfy the $(4n + 2)$ rule.
 - Alternatively, the molecule must have electrons in non-bonding or antibonding orbitals and six or fewer atoms in the cycle.
- **Non-aromatic** (molecule): A molecule with electrons in non-bonding or antibonding orbitals and seven or more atoms in the cycle.
- Unpaired electrons in nonbonding orbitals can be very destabilizing.
 - But since cyclooctatetraene is not flat (it's tub-shaped), it avoids the MO overlap that leads to anti-aromaticity.

5.2 Aromaticity 2

2/10:

- Note that the bond lengths of benzene are equal because the two resonance structures each contribute equally, and we can measure the bond length via x-ray crystallography.
- A magnetic field induces the π -electrons of aromatic compounds to circulate. This motion reinforces the magnetic field, leading to a substantial deshielding effect in NMR experiments.
 - Indeed, NMR is one of our key tools for identifying aromatic compounds.
- People in the 1820s thought that a compound had to smell to be aromatic. Of course, we now know that smell has nothing to do with chemical aromaticity.
- **Hückel's rules:** A set of rules that determines whether or not a compound is aromatic; a shortcut to the Frost diagram method.
 - To apply Hückel's rule, the molecule in question must be flat, cyclic, and have a p -orbital on each atom.
 - If one of these conditions does not apply, the molecule is simply non-aromatic.
 - If the conditions do apply, $4n + 2$ π electrons implies aromaticity and $4n$ ($n \in \mathbb{N}$) electrons implies anti-aromaticity (the number of atoms is less than 6) or non-aromaticity (the number of atoms is greater than 6).

- Note that if we chose the bottom vertex of cyclotetradecaheptaene to be any other vertex than the one shown in Figure 5.4 (or the one directly opposite it), we would end up with multiple lowest energy MOs (which would be incorrect).
- Anti-aromatic molecules react in any way they can to avoid existing in such a state.
 - Think of cyclobutadiene doing a self-Diels-Alder reaction to avoid being anti-aromatic.
 - Cyclooctatetraene is sufficiently big such that it need not react; it can just bend.
- Tougher Frost diagrams:
 - 5-membered ring: 3 bonding orbitals and 2 anti-bonding orbitals.
 - 7-membered ring: 3 bonding orbitals and 4 anti-bonding orbitals.
- Based on first principles, a structure with a ring system and a number of electrons that makes reasonable sense for aromaticity is aromatic.
 - However, in nature, 18 π -electrons tends to be the upper limit for aromaticity.
 - Chemists have gone up to 34 π -electrons and you can go even higher.
 - As long as the molecule is still flat, if everything else works, it is aromatic.
- Today, we will discuss three new classes of molecules that have aromaticity.
- Class 1: Anions/cations.
 - Treating cyclopentadiene with an appropriate base yields the cyclopentadienyl anion, which is aromatic.
 - The cyclopentadienyl anion has five equivalent resonance structures.
 - The Frost diagram analysis supports this claim, since the three bonding orbitals are completely filled and the two antibonding orbitals are empty.
 - Treating cycloheptatriene with the trityl cation abstracts a hydride leaving the tropylium ion, which is aromatic.

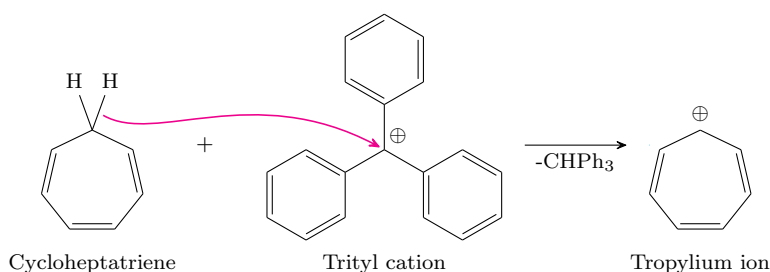


Figure 5.5: Aromaticity in the tropylium ion.

- When we have substituted compounds, we only care about the π -electrons in the ring system.
 - For example, in tropone, we only count seven π -electrons.

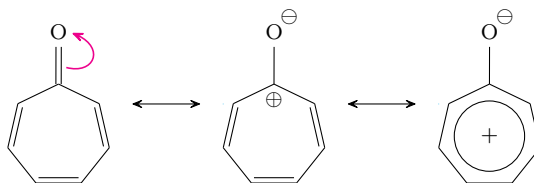


Figure 5.6: Aromaticity in tropone.

- However, if a molecule can become aromatic, it will. Thus, the actual structure of tropone is the right resonance structures above.
- We can indeed have 2π -electron aromatic systems [2].

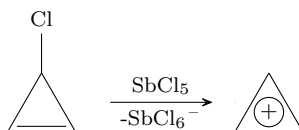


Figure 5.7: Aromaticity in the cyclopropenyl ion.

- This was the crowning achievement of a push in the 1950s-60s by organic chemists to push the bounds of aromatic compounds. It was done by Ron Breslow of Columbia in 1967.
- Joined rings can also rearrange à la tropone (Figure 5.6) into an aromatic system.

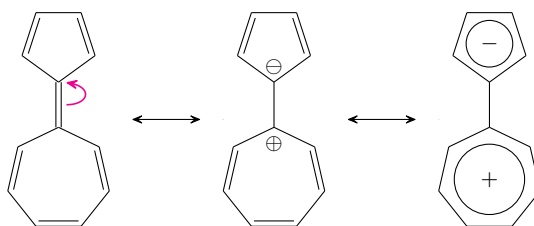


Figure 5.8: Aromaticity in sesquifulvalene.

- Although we can call this molecule aromatic overall, it would be better to say each ring is separately aromatic.
- In problems like this, get an initial electron count first (five for the top ring and seven for the bottom ring). This will then provide information about where you need to push electrons to create aromaticity. For example, seven is one too high and five is one too low, so we give one electron from the seven ring to the five ring to create two rings with six electrons.
- Not all such systems do, however: Fulvalene^[1], for instance would have to rearrange into an aromatic ring *and* an anti-aromatic ring, so it foregoes any rearrangement and is actually non-aromatic.
- Take-away: If one ring becomes aromatic and one remains non-aromatic, that's fine. If both rings become aromatic, that's great. If one ring would have to become anti-aromatic for the other to become aromatic, that will not happen.
- **Heterocyclic compound:** A cyclic compound containing atoms other than carbon and hydrogen. *Also known as heterocycle.*
- **Heteroatom:** Any atom that is not carbon or hydrogen.
 - Commonly oxygen, sulfur, or nitrogen.
- Class 2: Heterocyclic compounds.

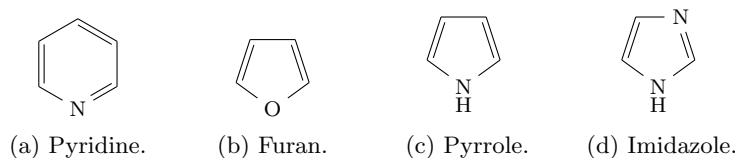


Figure 5.9: Common heterocyclic compounds.

¹Fulvalene looks exactly like sesquifulvalene, except that both rings have only five carbons.

- An analysis of pyridine.

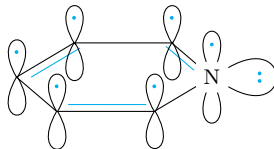


Figure 5.10: The structure of pyridine.

- The three double bonds in pyridine contribute the six π -electrons necessary for it to be aromatic.
- Importantly, this means that the lone pair of nitrogen is *not* needed for aromaticity, so it sits outside the compound in an sp^2 orbital.
- The fact that this lone pair is free implies that pyridine is an excellent base.
- An analysis of pyrrole.
 - The two double bonds *plus* the lone pair of the nitrogen constitute the six π -electrons necessary for it to be aromatic.
 - Although VSEPR theory suggests that the nitrogen would be sp^3 hybridized so as to get all electron pairs as far away as possible, the increase in energy by rehybridizing to sp^2 is more than compensated for by the aromatic stabilization energy.
 - For this reason, pyrrole is *not* a good base.
 - Indeed, if the nitrogen picks up another hydrogen, you lose aromaticity and introduce a +1 formal charge on the nitrogen. Thus, since the hydrogen adduct is so unstable, it is a strong acid on the order of HCl ($pK_a = 0.9$).
- An analysis of furan.
 - The two double bonds plus one of the lone pairs of the oxygen constitute the six π -electrons necessary for it to be aromatic.
 - However, there is still a lone pair left over on the oxygen, so furan can still act like a base.
- Adenine is a heterocyclic aromatic compound with 10 π -electrons. Some of its nitrogens contribute their lone pair electrons to the π -system, and others have them free to act as bases.
- Heterocycles can be anti-aromatic as well.

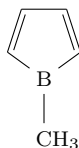


Figure 5.11: An anti-aromatic heterocycle.

- Boron is happy with three bonds, so it has an empty p -orbital.
- Thus, this is a flat cyclic molecule with an uninterrupted chain of p orbitals and $4n$ ($n = 1$) π -electrons. But this implies that it is anti-aromatic.
- Degrees of aromaticity.
 - Benzene is “the most” aromatic compound.

- All molecules with heteroatoms will have slightly different bond lengths and thus a lesser stabilization energy.
- Indeed, under forcing enough conditions, we can make some of the heteroaromatics actually do reactions.
 - For example, we can make furan do a Diels-Alder reaction at very high temperatures; this is never something we would see with benzene.
- Class 3: Polycyclic aromatic hydrocarbons (PAHs).

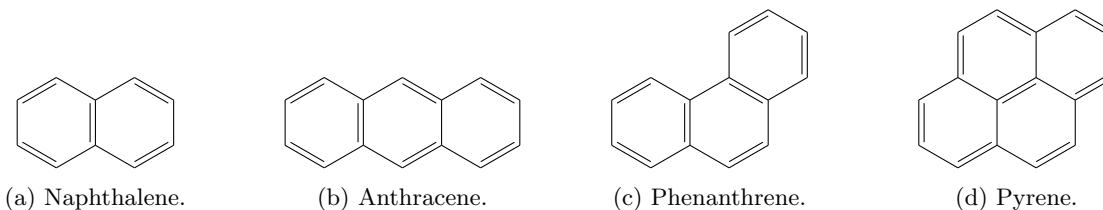


Figure 5.12: Common PAHs.

- Naphthalene is used in mothballs.
- These names won't be tested, but they're useful to know.
- An analysis of naphthalene.

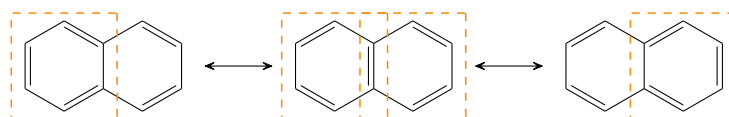


Figure 5.13: The structure of naphthalene.

- Although Figure 5.12a shows that naphthalene is a 10 π -electron system, it can be useful to think of it as two separate benzene rings.
- Doing so and drawing all resonance structures reveals that each ring only appears as benzene (as opposed to a diene) 2/3 of the time.
 - Every occurrence of a ring as benzene is boxed in Figure 5.13. Notice how each ring is boxed twice and not boxed once (across the three resonance structures).
- Thus, the aromatic stabilization of naphthalene is not twice benzene's -36.5 kcal/mol but rather $\frac{2}{3} \cdot 2 \approx 1.33$ times benzene's -36.5 kcal/mol.
 - If we assign benzene an aromaticity value of 1, we would assign naphthalene 1.33.
- The bonds in naphthalene alternate between 1.36 \AA and 1.42 \AA , a 0.03 \AA perturbation from the bond lengths in benzene.
- **Rocks of Gibraltar:** The molecules benzene, naphthalene, and pyrene, which in general will not undergo further chemical reactions due to the extent of their aromatic stabilization.
- An analysis of pyrene.

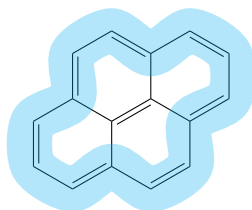


Figure 5.14: The structure of pyrene.

- Pyrene is aromatic, but it appears to have $16 = 4n$ π -electrons.
- However, since one of the criteria for aromaticity is a *cyclic* chain of π -orbitals, it is actually only the $14 = 4n + 2$ π -electrons around the periphery that constitute the aromatic system. The π -bond in the center of the molecule is just a lone alkene with no aromatic stabilization.
- You can hydrogenate the central double bond at very high pressures, but essentially for all intents and purposes, pyrene is a nonreactive molecule.
- Diels-Alder reactivity of anthracene.

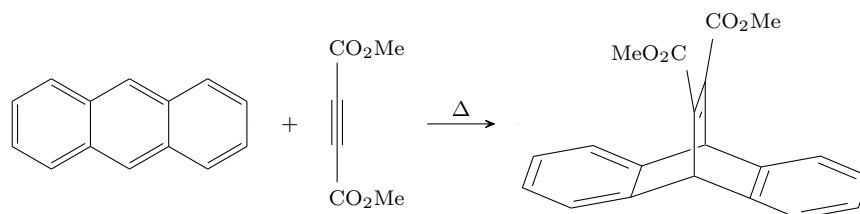


Figure 5.15: Diels-Alder reactivity of anthracene.

- Anthracene is finally destabilized enough to react in a Diels-Alder reaction.
- When we look to predict products, we want to maximize the amount of aromaticity left over after the reaction (because this will be the most stable product).
- If we perform the Diels-Alder reaction with the central diene, the product will have two benzene rings.
- The char marks on grilled meat contain a number of PAHs, notably benzopyrene.
 - Benzopyrene is one ring too far to be stable.
 - Since it is flat, it can intercalate in our DNA and cause a lot of issues, notably with regulating the cell cycle.
 - Thus, our bodies want to get rid of it, so it sends enzymes to epoxidize the benzene hanging off the pyrene.
 - Now that the molecule is polar, it can be excreted, but this is a risky strategy because epoxides are highly reactive and can damage other things.
- Vioxx vs. Celebrex.
 - It is possible that the reason that Vioxx is harmful and Celebrex is not is that Vioxx has a ring that is not aromatic whereas all of Celebrex's rings are aromatic.
- Special considerations.

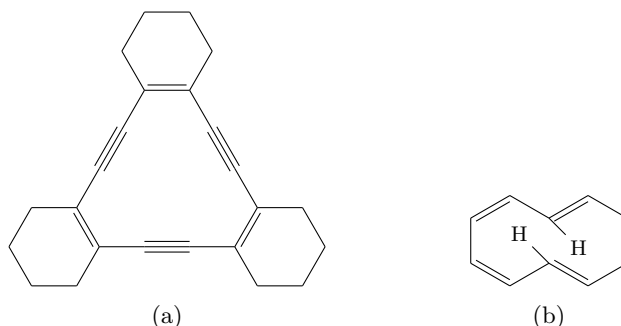


Figure 5.16: Special considerations for determining aromaticity.

- Triple bonds: A triple bond in the π -system still only contributes two electrons. This is because its other two π electrons are perpendicular to the π -system in question.
 - The compound in Figure 5.16a has 12 π -electrons but is still non-aromatic because the number of atoms is greater than six (it can bend).
- Sterics: If sterics prevent a molecule from being flat, it cannot be aromatic.
 - The compound in Figure 5.16b cannot lie flat due to the steric clashing of the two indicated hydrogens. Note that this clashing is unavoidable due to the conformation and the lack of freedom of rotation about the double bonds.
- Next week is all about the reactions of benzene.

5.3 Chapter 14: Aromatic Compounds

From Solomons et al. [3].

- 2/16:
- Nomenclature.
 - “In many simple compounds, *benzene* is the parent name and the substituent is simply indicated by a prefix” [3, p 619].
 - Examples: Fluorobenzene, chlorobenzene, nitrobenzene.
 - Other simple compounds have commonly accepted parent names.
 - Examples: Methylbenzene \rightarrow toluene, hydroxybenzene \rightarrow phenol, aminobenzene \rightarrow aniline.
 - Other compounds to be aware of: Benzenesulfonic acid ($\text{C}_6\text{H}_5\text{SO}_3\text{H}$), benzoic acid ($\text{C}_6\text{H}_5\text{COOH}$), acetophenone ($\text{C}_6\text{H}_5\text{COCH}_3$), and anisole ($\text{C}_6\text{H}_5\text{OCH}_3$).
 - Covers ortho, meta, para naming.
 - “When a substituent is one that together with the benzene ring gives a new base name, that substituent is assumed to be in position 1 and the new parent name is used” [3, p 620].
 - This means that molecules such as m-nitrobenzoic acid are named 3-nitrobenzoic acid.
 - Dimethylbenzenes are often known as xylenes.
 - Phenylmethyl becomes benzyl.
 - The only alkene chemistry in which benzene participates is hydrogenation (in the presence of finely divided nickel, under high temperatures and pressures).
 - **Benzene substitution:** The substitution of one of the hydrogens of benzene for a bromine, as initiated by the presence of a Lewis acid catalyst such as ferric bromide (FeBr_3).
 - Explanation: All hydrogens are equivalent and replacing any one of them with bromine results in the same product.
 - Possible explanation: Only one of benzene’s hydrogens is reactive.
 - Wrong, though — ruled out by the structure of benzene but plausible when we didn’t know its structure.
 - The Kekulé structure for benzene (cyclohexatriene) satisfied the requirements but failed for the reason of Figure 5.1.
 - Kekulé proposed a rapid equilibrium between the structures (resonance), but today we prefer the explanation of delocalization.
 - A new meaning of aromaticity: Aromatic compounds are highly unsaturated compounds that prefer substitution chemistry to addition chemistry.
 - Richard Willstätter first synthesized cyclooctatetraene in 1911.

- **Resonance energy:** The difference between the amount of heat actually released and that calculated on the basis of the Kekulé structure.
- “Resonance contributors, we emphasize again, are not in equilibrium. They are not structures of real molecules. They are the closest we can get if we are bound by simple rules of valence, but they are very useful in helping us visualize the actual molecule as a hybrid” [3, p 625].
- It was recently discovered that “crystalline benzene involves perpendicular interactions between benzene rings, so that the relatively positive periphery of one molecule associates with the relatively negative faces of the benzene molecules aligned above and below it” [3, p 627].
- In 1931, Erich Hückel carried out a series of quantum mechanical calculations that concluded that planar monocyclic rings containing $4n + 2$ π -electrons have **closed shells** of delocalized electrons (like benzene) and therefore have substantial resonance energies.
- **Closed shell:** A set of molecular orbitals that are all either completely occupied or completely empty (i.e., no MO in the set contains only one electron).
 - Molecules that lack closed shells have unpaired electrons (radicals) and are usually not stable.
- The **polygon-and-circle method** was developed by C. A. Coulson of Oxford university as a simple method of deriving the same energy levels that the quantum mechanical calculations of Hückel would furnish.
- **Polygon-and-circle method:** The following procedure.
 1. We start by drawing a polygon corresponding to the number of carbons in the ring, placing a corner of the polygon at the bottom.
 2. Next, we surround the polygon with a circle that touches each corner of the polygon (the circum-circle).
 3. At the points where the polygon touches the circle, we draw short horizontal lines outside the circle. The height of each line represents the relative energy of each π molecular orbital.
 4. Next, we draw a dashed horizontal line across and halfway up the circle. The energies of bonding π molecular orbitals are below this line. The energies of antibonding π molecular orbitals are above, and those for nonbonding orbitals are at the level of the dashed line.
 5. Based on the number of π electrons in the ring, we then place electron arrows on the lines corresponding to the respective orbitals, beginning at the lowest energy level and working upward. In doing so, we fill degenerate orbitals each with one electron first, then add to each unpaired electron another with opposite spin if it is available.
- **Annulene:** A monocyclic compound that can be represented by a structure having alternating single and double bonds.
 - The ring size of an annulene is indicated by a number in brackets.
 - For example, benzene is [6]annulene and cyclooctatetraene is [8]annulene.
- Hückel’s rule predicts that annulenes are aromatic iff they have $4n + 2$ π -electrons.
 - This prediction was verified in the 1960s (largely by F. Sondheimer) as numerous new annulenes became available for testing.
 - Annulenes 14-24 satisfy Hückel’s prediction.
 - Annulenes 10-12 are too strained to be planar, regardless of double bond placement (see Figure 5.16b).
- The ^1H NMR spectrum of benzene supports both equivalent hydrogens (only a singlet appears) and the cyclic nature of the π -system (the high chemical shift is indicative of a ring current).

- [18]annulene has six hydrogens within its ring and twelve hydrogens at the periphery. Because of the shape of the ring current, the internal hydrogens are highly shielded ($\delta = 3.0$) and the external hydrogens are highly deshielded ($\delta = 9.3$).
 - NMR spectroscopy provides direct physical evidence of whether or not the π -electrons are delocalized.
- Cycloheptatriene is also commonly known as tropyliene.
- To evaluate the stabilization (or lack thereof) of a cyclic compound with delocalized π electrons, we compare it to a conjugated linear model and consider what would happen (theoretically or experimentally) if we removed a hydrogen from each end of the linear compound to form a ring.
 - Such calculations/experiments are beyond the scope of Solomons et al. [3].
- **Benzenoid polycyclic aromatic hydrocarbon:** A molecule having two or more benzene rings fused together.
- **Nonbenzenoid aromatic compound:** A compound that is either the cyclopentadienyl anion, the cycloheptatrienyl cation, *trans*-15,16-dimethyldihydropyrene, or an aromatic annulene (except [6]annulene).
- Solomons et al. [3] briefly discusses fullerenes, such as buckyballs.
- Solomons et al. [3] discusses applications of aromatic compounds to biochemistry. In particular, it discusses NADH and NAD^+ .
- Discusses the infrared absorptions of aromatic compounds (not covered in class, but potentially relevant?).