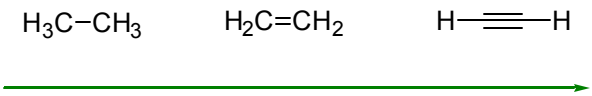
Paul Bracher
Chem 30 – Fall 2004 Exam I

Exam I Review Solution Set

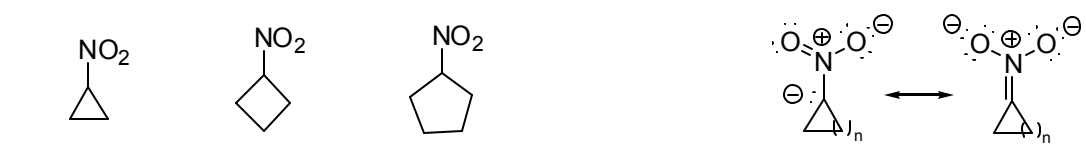
Problem 1 (refer to the Evans pK_a table and *Solvents and Solvent Effects in Organic Chemistry* by C. Reichardt). Explain the trend in relative acidity for each of the following series of compounds.

a)



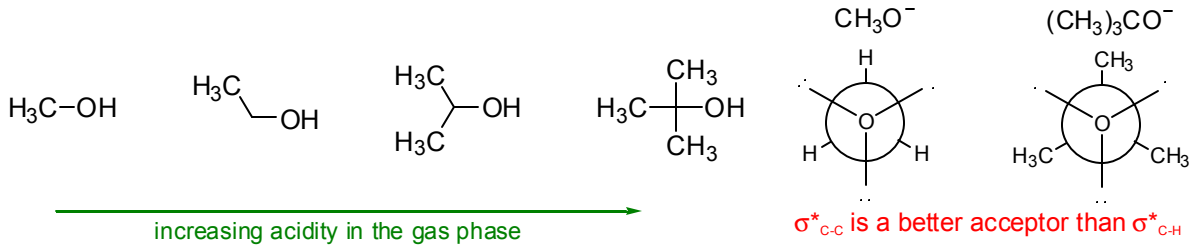
Acidity is typically evaluated at equilibrium, so we analyze the thermodynamic aspects of the system by looking at the relative energy of the ground states. (Kinetic aspects are evaluated by analyzing the stability of transition states). This is most commonly done by analyzing the stability of the conjugate bases. In this example, the hydrocarbons' acidities increase as the orbital bearing the carbanion has increasing s-character. For the same principle quantum number, s orbitals are more penetrating than p orbitals. Thus, the extra negative charge density will reside increasingly closer to the positively-charged nucleus, where it is more stabilized.

b)



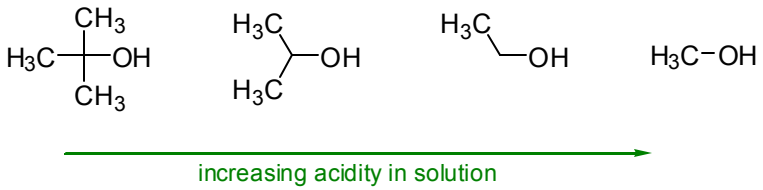
Again we base our analysis on the relative stability of the conjugate bases. These hydrocarbons' most acidic hydrogens are α to the nitro group due to the resonance stabilization of the carbanion (see above). The stereoelectronic requirement for this delocalization is that the α carbon adopt an sp^2 hybridization, with optimal bond angles of 120°. The optimal bond angle for cyclopropane is 60°, cyclobutane is 90°, etc. Therefore, acidity decreases as the ring size decreases due to the strain of having an sp^2 carbon in a progressively smaller ring.

c)



In the gas phase, all effects are based on intramolecular interactions—all intermolecular phenomena are inactive. Again we can make our analysis based on the stability of the conjugate bases (here: alkoxides). In the case of methyl alcohol, the lone pairs on oxygen can be stabilized by aligning with the σ^*_{C-H} bonds (refer to the Newman projections above). As the alcohols become more substituted, the σ^*_{C-H} orbitals are replaced with σ^*_{C-C} orbitals. σ^*_{C-C} are better electron acceptors, explaining the increase in stability of the conjugate base as the substitution increases.

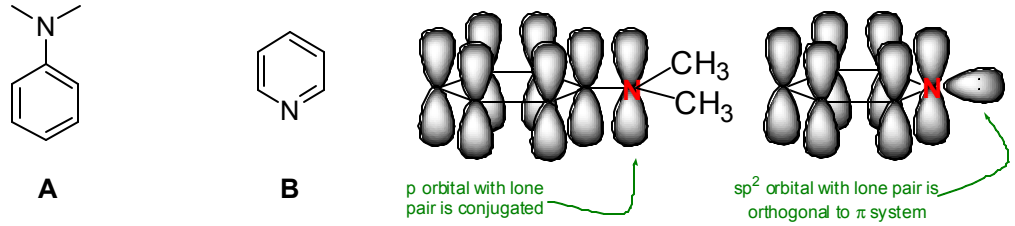
d)



The order has reversed for the same compounds in the gas phase. The reason *must* be due to a solvation effect. Why would a *t*-butoxide anion be less stable than a methoxide anion in solution? Because the large hydrophobic substituent hinders the ability of solvent molecules to access and solvate the negative charge. As the hydrocarbon substituent gets progressively smaller, solvent molecules are better able to organize around the anion to stabilize the high-energy species with intermolecular interactions (ion-dipole, dipole-dipole, dipole-induced dipole, etc.)

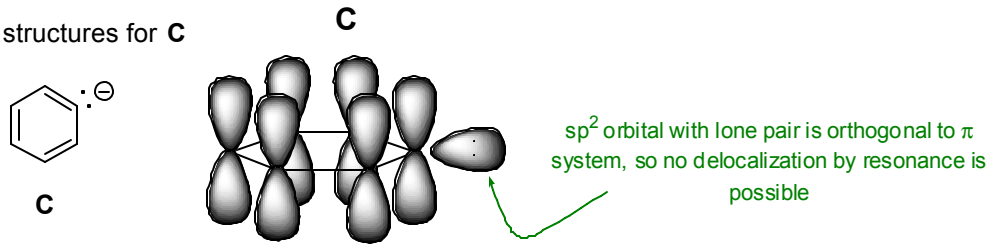
Problem 2 Answer the following set of ostensibly unrelated questions.

a) Compounds **A** and **B** both contain sp^2 hybridized nitrogens. Which compound do you expect to be more basic? Explain.



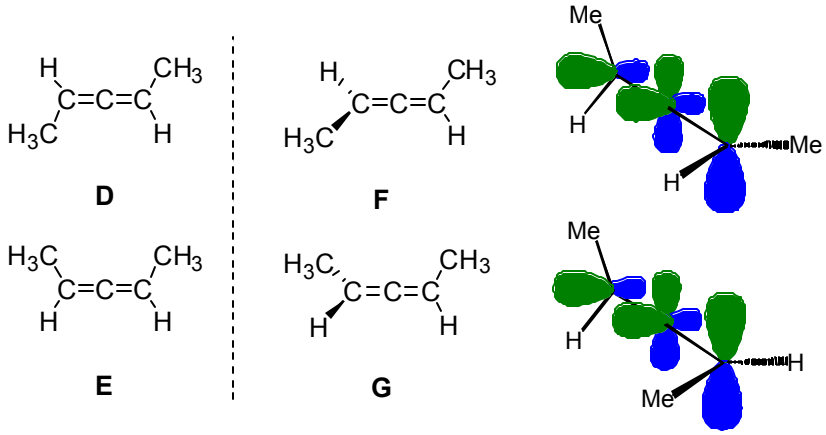
Pyridine (**B**) is significantly more acidic than N,N-dimethylaniline (**A**). This is clearly understood when the orbitals bearing the nonbonding electrons on nitrogen are drawn. In **A**, the lone pair is in a p orbital conjugated with the π system of the aromatic ring. This delocalization makes the lone pair less available to serve as a Lewis base. In **B**, the nonbonding pair is held in an sp^2 orbital that is orthogonal to the p orbitals in the ring. There is no delocalization of this electron density, rendering it more available to act as a Lewis base (by donating electron density into an empty orbital).

b) Draw all resonance structures for **C**



This is a trick question. The lone pair is held in an sp^2 orbital that is orthogonal the π system of the aromatic ring. Although you can push electrons on paper (to make a variety of peculiar and unstable Lewis structures), there will be no delocalization of charge unless your electron pushing corresponds to real orbital overlap. The fact that **C** has no resonance forms should not come as a surprise to you—when was the last time you saw benzene act as a proton donor?

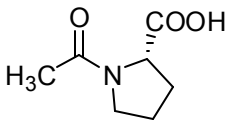
c) Which compound below is more reactive/less stable? Do you expect their difference in energy to be greater or less than that of *E*- vs. *Z*- 2-butene?



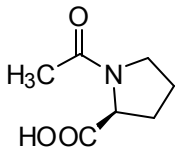
This is another trick question designed to make you think about bonding, orbitals, and how some seemingly reasonable Lewis structures are actually nonsense. In allenes, the middle carbon is sp hybridized and the two π bonds are formed with orthogonal sets of unhybridized p orbitals. As a result, the compound is not planar and Lewis structures **D** and **E** are incorrect 3D representations—*cis*/*trans* isomerization is impossible. The structures **F** and **G** are correct 3D structures; they are enantiomers. Remember: enantiomers do not have different physical properties, so they are equally reactive.

Problem 3 (based on K.R. Williams. *J. Chem. Educ.* **2002**, *79*, 372). The study of conformational analysis is especially important in protein chemistry.

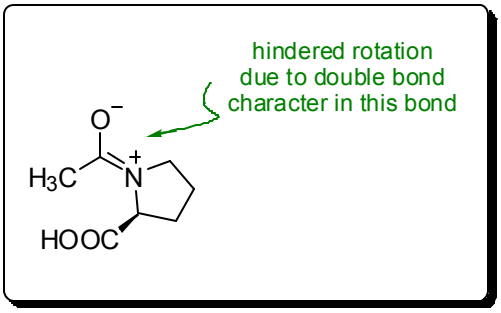
a) N-acetyl-L-proline exists as two stereoisomers that interconvert at room temperature and can be distinguished by NMR. Explain how a *cis-trans* relationship can exist about a single bond:



trans



cis



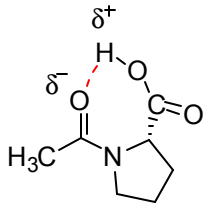
This is directly analogous to the situation discussed for N,N-dimethylformamide (DMF) in Chem 20. The resonance form above shows that the bond in question has significant double bond character, rationalizing how we could observe the presence of two stereoisomers. The double bond character in the C–N bond hinders rotation along the bond axis.

b) The equilibrium constant, K, for *cis*-to-*trans* interconversion can be determined by NMR. In a deuterated benzene-methylene chloride (C_6D_6–$CDCl_2$) solvent system, K = 8.7 (favoring the *trans* isomer). In heavy water (D_2O) buffered at pH = 7, K = 0.81. Explain why the *trans* stereoisomer is favored in organic solvent and why this predominance is reversed in the latter case.

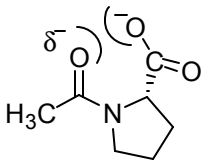
In an organic medium, the carboxylic acid is protonated and the polar functional groups are not well-solvated. In the *trans* isomer, the carboxylic acid can participate in a stabilizing intramolecular hydrogen bonding interaction with the oxygen atom of the amide functionality. This interaction is not possible in the *cis* isomer.

The effect is less pronounced in water because when the solvent molecules are polar, they interact with the polar functional groups, interfering with the intramolecular interaction. At pH = 7, the carboxylic acid group is deprotonated and will experience unfavorable e^-/e^- repulsion when it is in close proximity to the δ^- amide oxygen. This repulsion is not present in the *cis* isomer, explaining its predominance in alkaline water.

trans isomer

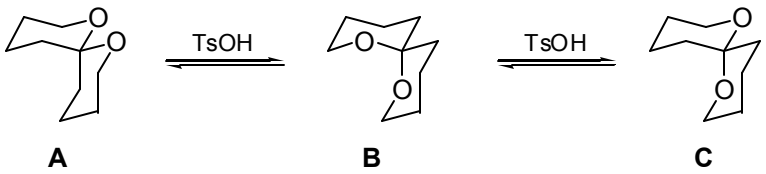


favorable interaction
in organic media



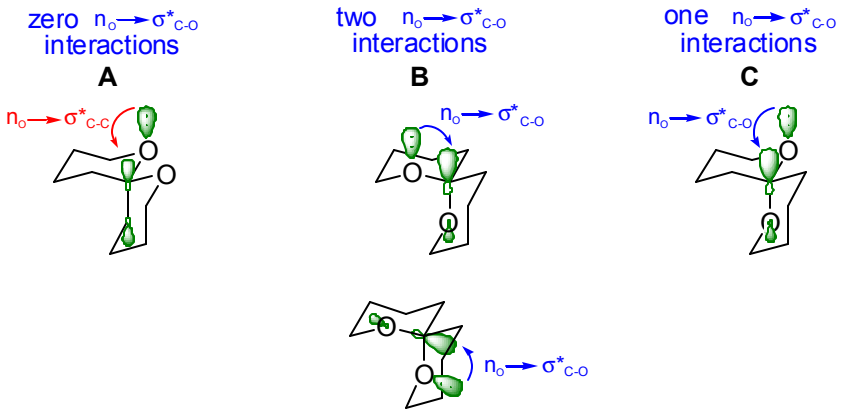
repulsive interaction
in basic solution

Problem 4 (taken from Chem 30, Exam I, Fall 2000). The spiroketal compound below isomerizes in the presence of acid. Of the three isomers shown (**A**–**C**), which structure would you expect to be the most stable? Which structure would you expect to be the least stable? Explain your selections.



This is a classic example of the "anomeric effect." By now, you should have recognized this at first glance. Don't worry about the mechanism of this reaction—we will cover it soon. We don't need a mechanism to evaluate the equilibrium mixture. The equilibrium is based on the thermodynamics of the system—we need only evaluate the relative stabilities of the three isomers.

Stabilizing interactions in molecules occur between high-lying occupied MOs and low-lying unoccupied MOs. In the compounds above, the highest lying electrons are in the nonbonding orbitals on oxygen. The LUMOs are the σ* orbitals of C–O bonds. A stabilizing interactions can exist only when the n and σ* orbitals are properly aligned. Drawing accurate 3D structures of these isomers will help you indentify these interactions. I always draw the lone pairs on the oxygens (by filling them in as pseudo axial/equatorial) then seeing if they can align anti to a C–O bond.



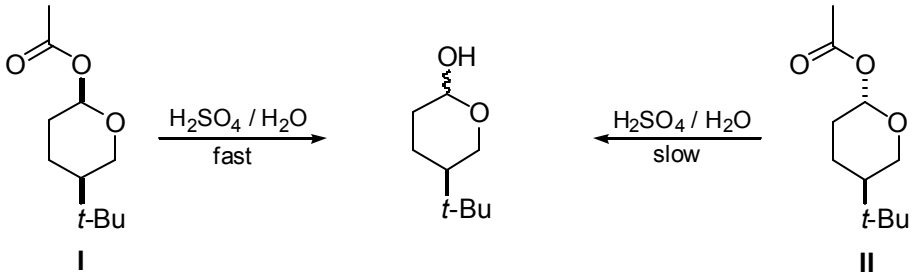
List of the principle stabilizing interactions:

A	zero	$n \rightarrow \sigma^*_{C-O}$ interactions
B	two	$n \rightarrow \sigma^*_{C-O}$ interactions
C	one	$n \rightarrow \sigma^*_{C-O}$ interaction

In **A** and **C**, one or more of the $n \rightarrow \sigma^*_{C-O}$ interactions is replaced by an $n \rightarrow \sigma^*_{C-C}$ interaction. These are not as stabilizing, for two reasons. First, the higher electronegativity of O vs. C means that the σ^*_{C-O} LUMO lies lower-in-energy (more stable) than σ^*_{C-C}. Second, the polarization of the antibonding orbital is such that the lobe behind carbon (into which the lone pair orbital donates electron density) is bigger for σ^*_{C-O} (shown in picture above). This leads better orbital overlap, maximizing the stabilizing interaction.

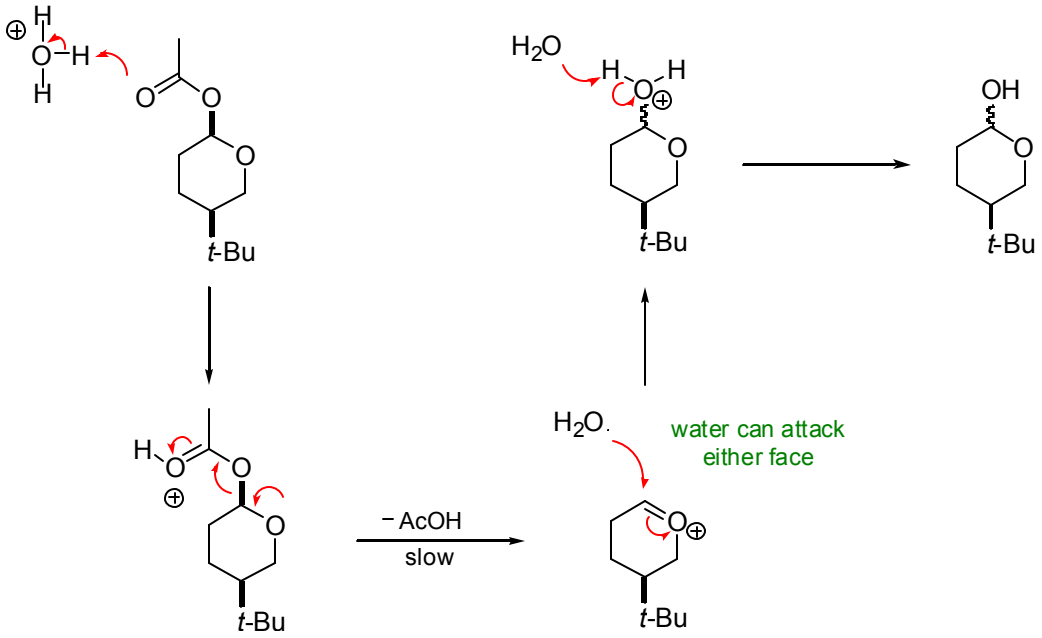
Thus, we expect that **B** is the most stable, **C** is next, and **A** is the least stable of the isomers shown.

Problem 5 (taken from Chem 30, Exam I, Fall 2000). The rate of hydrolysis of acetals **I** and **II** is observed to depend on the concentration of acid in solution.



I **II**

a) Using either isomer, propose an arrow formalism mechanism for this transformation that is consistent with the observation that the rate depends on $[H^+]$.



Analogous to the dehydration of alcohols in acid to form alkenes, we expect the loss of acetic acid to be the rate determining step for this reaction. The rate for this step will depend on $[H^+]$ because the rate of formation of the protonated intermediate also depends on $[H^+]$.

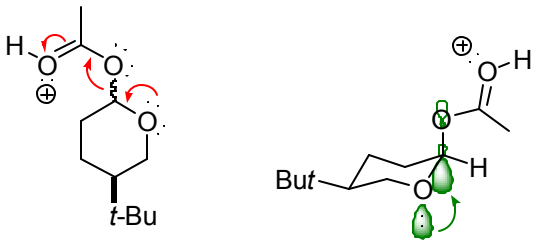
- To get full credit in your mechanism problems, be sure to draw all intermediates and show stepwise processes as distinct steps. Taking shortcuts in your answers can have the consequence of miscommunication, e.g., giving the reader the impression that a stepwise process is concerted.

- In acidic water: H_3O^+ is your source of acid, H_2O is your base/nucleophile
  basic water: H_2O is your source of acid, OH^- is your base/nucleophile

b) Explain why isomer **I** hydrolyzes faster than isomer **II**

The rate determining step in this process is the loss of acetate to generate a carbocation intermediate (analogous to the S_N1 reaction—but not exactly). So the question we must ask is what speeds the rate determining step?

By now, you are experts in the anomeric effect and all related stereoelectronic effects. The very bulky *t*-butyl substituent "locks the ring" because any conformational inversion of the ring would place it an axial position, where it experiences unfavorable steric interactions. In isomer **I**, the acetate substituent is held in an axial position.

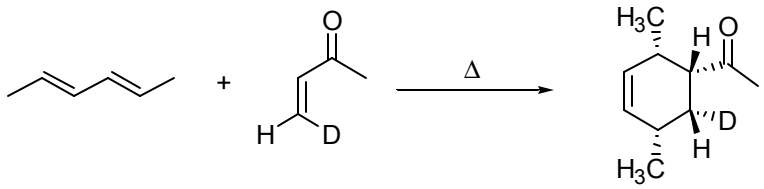


donation into σ*
weakens the C-O bond

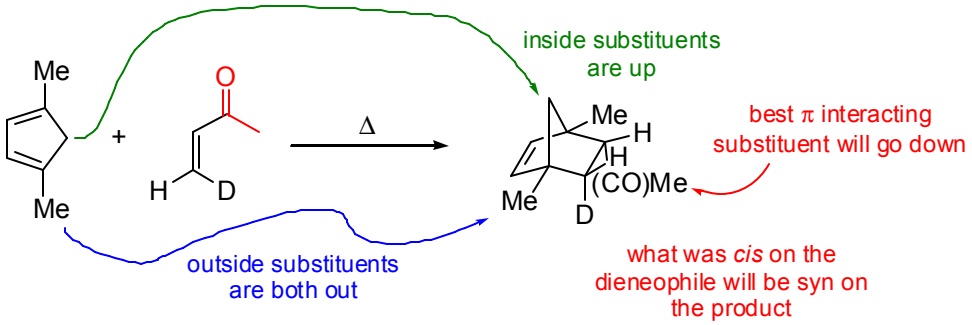
In this conformation, a lone pair on oxygen is aligned to donate electron density into the σ^*_{C-O} orbital (as shown above). Filling the antibonding orbital reduces the bond order and weakens the C–O bond, allowing it to break more easily in the rate determining step. This effect is not observed in the other stereoisomer.

Problem 6. Answer the following questions about the reaction below.

a) Predict the major product of this reaction. Indicate the relative stereochemistry of the substituents.



Remember the endo rule and the cyclopentadiene trick (see below). If you memorize this reaction and product, you can draw an analogy with any other endo Diels-Alder reaction to derive the correct stereochemistry:



b) Build all of the π molecular orbitals for the diene and dieneophile. Classify the reaction as [m+n].

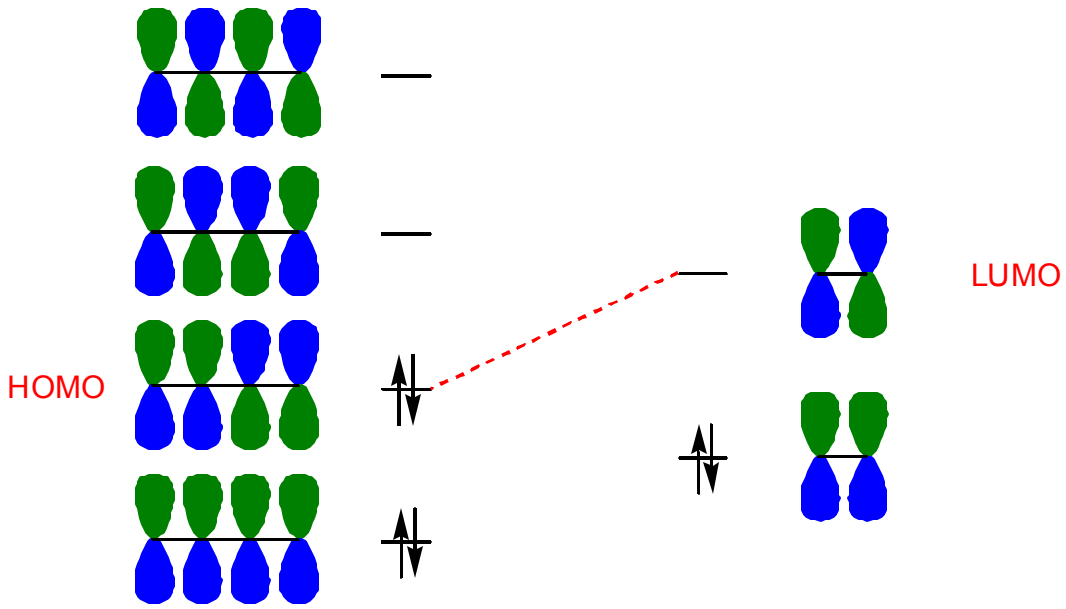
This is a [4+2] cycloaddition—a Diels-Alder reaction. Remember to count the number of p orbitals involved on each reactant—not the number of electrons or atoms.

(1E,4E)-1,4-Dimethyl-1,3-Butadiene

(4 conjugated 2p orbitals / 4 π electrons)

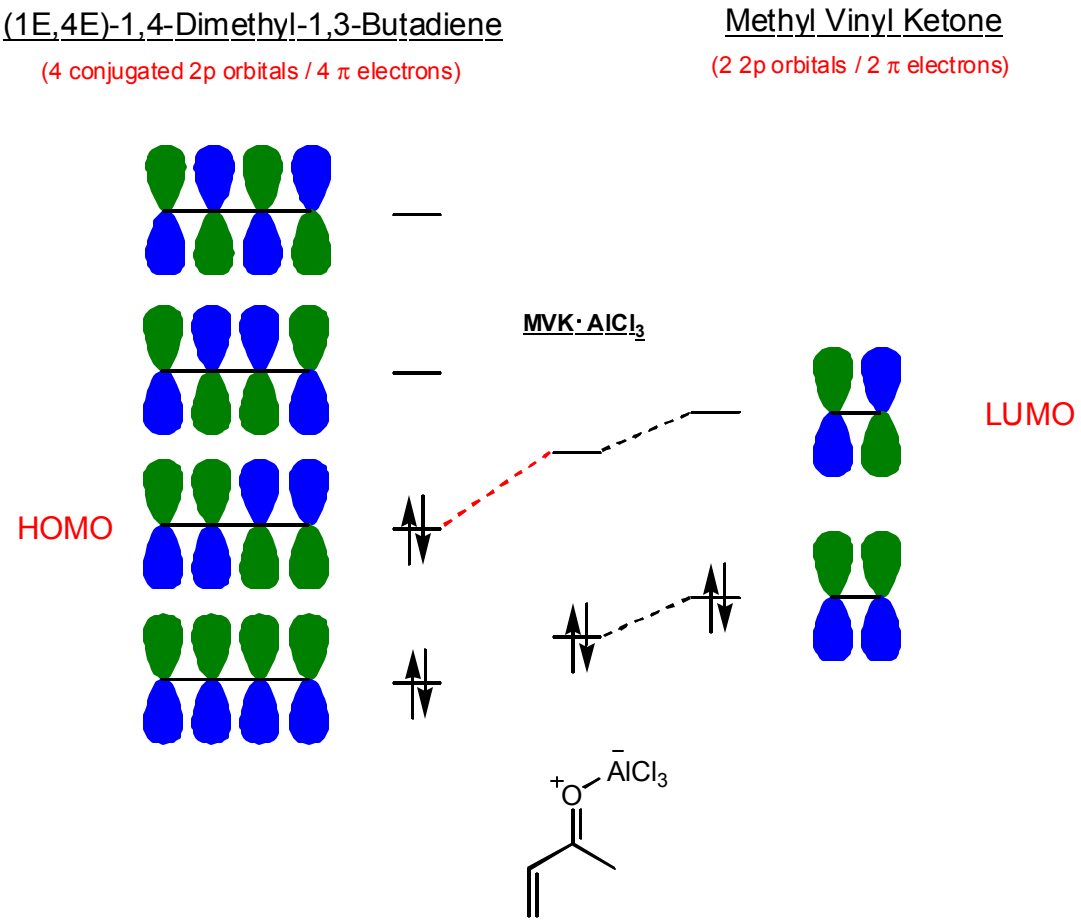
Methyl Vinyl Ketone

(2 2p orbitals / 2 π electrons)

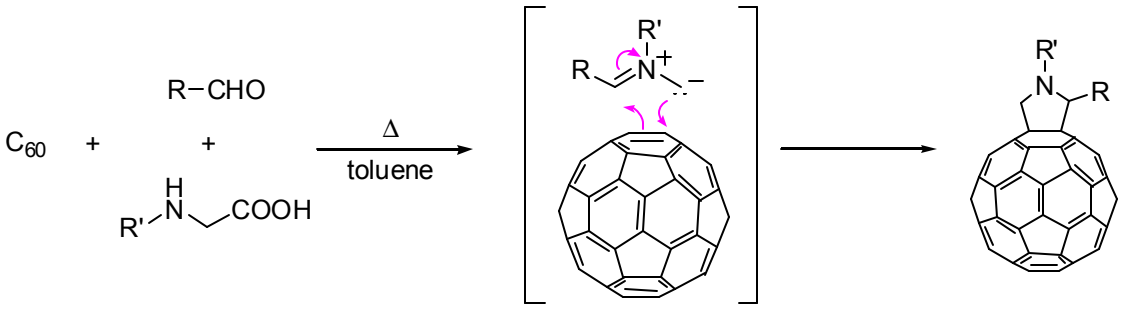


c) The reaction is accelerated when $AlCl_3$ is added. Provide an explanation that accounts for this result.

The $AlCl_3$ is a strong Lewis acid that catalyzes this Diels-Alder reaction. When bound to the oxygen of the α,β-unsaturated carbonyl group, it withdraws negative charge density from the dieneophile. This lowers the energy of the LUMO, bringing it closer-in-energy to that of the HOMO on the diene, thus increasing the rate of reaction.



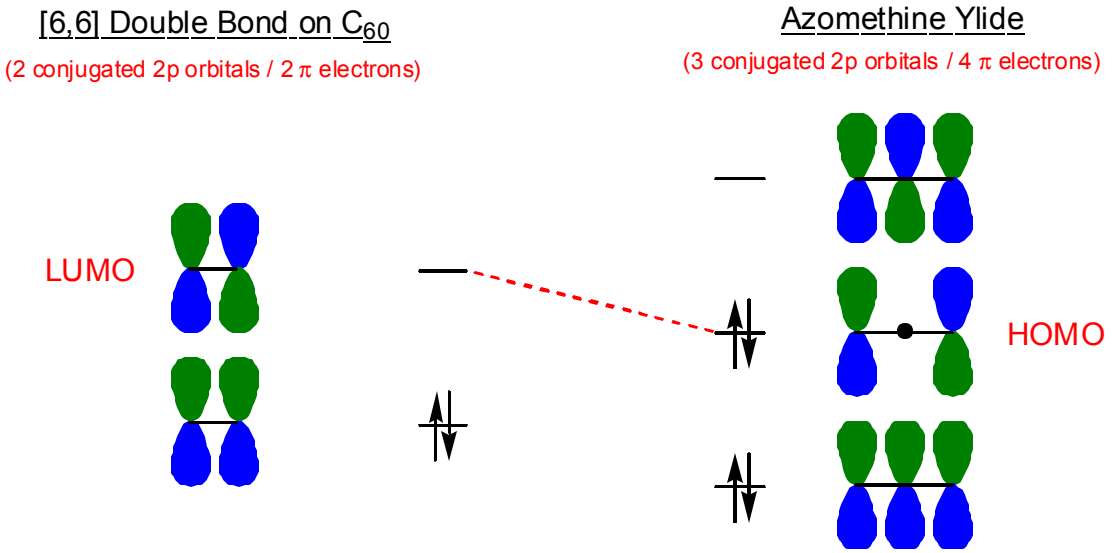
Problem 7 (taken from Chem 30, Problem Set 9, 2003). The [6,6] double bonds in C_{60} show similar reactivity to electron deficient olefins. The addition of azomethine ylides to C_{60} is known to fullerene chemists as the Prato Reaction. It is the most popular method to functionalize "buckyballs," allotropes of carbon with cage-like structures.



a) Classify the cycloaddition in the last step shown above as [m+n]

This is a [3+2] cycloaddition. Remember to count the number of p orbitals involved on each reactant—not the number of electrons or atoms.

b) Build all of the π molecular orbitals for both the ylide and the olefin.



The reaction proceeds in a concerted fashion because the wavesigns of the termini are matched.

c) Assign the HOMO–LUMO interaction for this reaction. Explain why it is allowed to proceed as a concerted process with heat.

Generally, you expect the reactant with the most electron donating groups to provide the HOMO and the reactant with the most electron withdrawing groups to supply the LUMO. BUT…in the prompt to this problem, you are told that fullerenes react as electron deficient olefins. Therefore, we expect that the LUMO is the reactive orbital on the C_{60} in this reaction. Always remember to READ THE PROBLEM for any clues and to answer every question posed to you in the prompt so that you don't lose cheap points.