Chemistry 125 First Semester
December 18, 2006 Final Examination

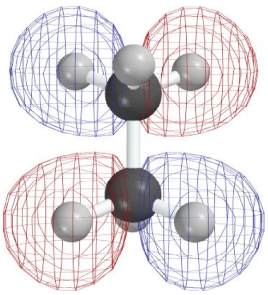
Statistics

	Final Exam	Semester Total
Average	229.5	463.1
Thirds	247 – 223	500 – 449

Grade Borders
A (510) A- (470) B+ (440) B (390) B- (360) C+

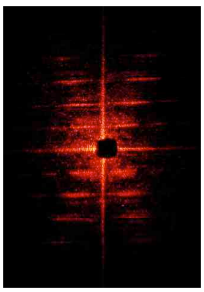
1. (56 minutes). On pages 1 and 2 are 18 diagrams, models, formulas, or other illustrations (labeled **A-R**).
In a blue book describe very briefly the **principal point** that each of **14** (**FOURTEEN ONLY**) of them was designed to show:
You should **omit 4** of the examples. Only the first 14 answers will be graded.

(A) This image from slide 30 of the lecture of 10/11/06 shows the HOMO of ethane. The point it made is that, from the united-atom perspective, molecular orbitals look like the orbitals of 1-electron atoms. This one looks like a $3d_{xy}$ atomic orbital.
[Note that although there are two nodal planes, the orbital is occupied. It is made from *1s* orbitals of 4 H atoms overlapping favorably with *2p* orbitals of the carbons. The vertical node is of the C atomic orbitals; the horizonal node is antibonding between the carbons. This is the least favorable combination of four CH σ bonds and thus the HOMO.]

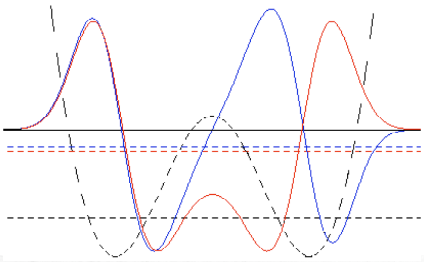


(B) This image from slide 16 of the lecture of 11/27/06 shows van't Hoff's model of maleic acid. These cardboard models illustrated the stereochemical implications of the tetrahedral carbon. In this case the shared edge forbids rotation about the double bond and allows two achiral isomers (cis,trans or Z,E), maleic and fumaric acids.
(Note that this is an alkene, ***not*** an allene, which, unlike this alkene, is chiral.)

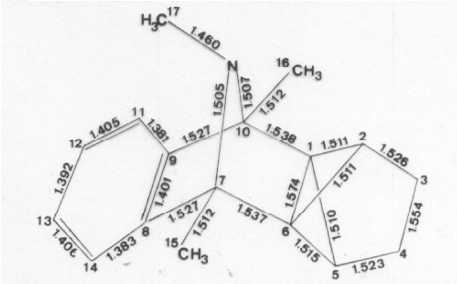
(C) This image from slides 55-56 of the lecture of 9/18/06 shows the diffraction pattern from a lightbulb filament irradiated by a red laser. It shows what is expected from a **single** helix – an "X" pattern with intensity decreasing smoothly from the center out. The angle of the X shows the pitch of the helix and the spacing of the spots shows the distance between successive rounds relative ot the light wavelength. It served as an introduction to the DNA double helix.



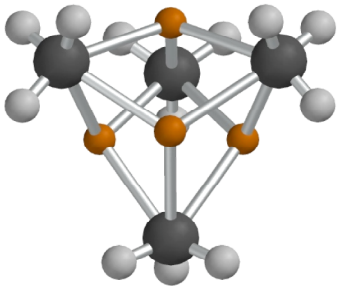
(D) This image from slide 18 of the lecture of 10/20/06 shows how the two closely spaced IR peaks for NH_3 were interpreted in terms of a pyramidal double-minimum potential with a planar barrier between the minima. A single minimum would give more or less evenly spaced energy levels, but the double-minimum-with-a-low-barrier gives closely spaced levels with tunneling splitting. [interpretation as "orbitals" got some credit (but not coulombic!), esp. if tunneling was mentioned.]



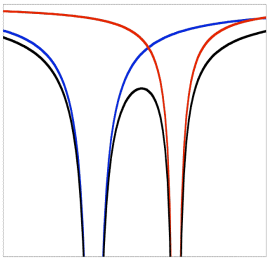
(E) This image from slide 21 of the lecture of 9/22/06 introduced a molecule with "pathological" bonding revealed by X-ray difference maps. Bonds in the 3-membered rings were bent (or missing altogether for 1.574) because of weird overlap. This is why Dunitz studied it carefully. [It reappeared secondarily in slide 15 of the lecture of 9/27/06 in a discussing precision and vibrational ampliltude – partial credit]



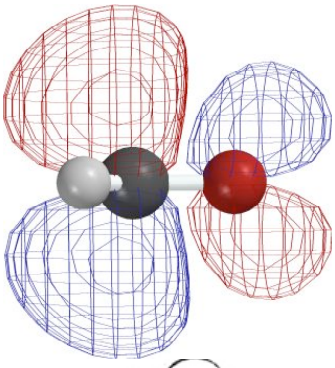
(F) This image from slide 18 of the lecture of 10/30/06 shows the CH_3Li tetramer, $(CH_3Li)_4$. The main point was that it forms the cubic tetramer because of the possibility of forming 4-center 2-electron bonds with Lithium atoms, which have numerous vacant valence-shell orbitals.



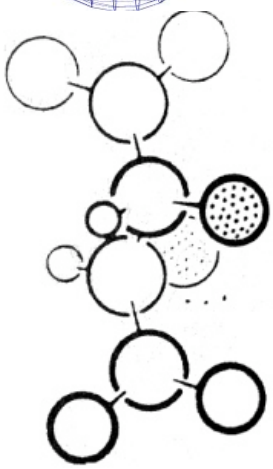
(G) This image from slide 34 of the lecture of 9/6/06 and slide 32 of 9/8/06 shows the addition of two coulombic (inverse square) potentials to give the composite double-minimum potential. The point was that such adding of inverse forces cannot give a single minimum. A chain of atoms governed by such a force law cannot cohere [and when a Morse-Law chain is stretched to the point that it enters the inverse-force law region, the chain will pop]. Similarly, an electron between two nuclei cannot classically be stable.



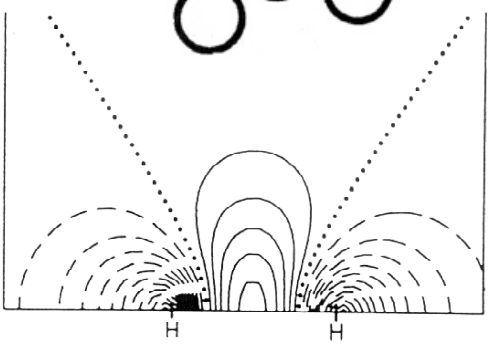
(H) This image from slide 7 of the lecture of 10/30/06 shows the π^* orbital of the C=O bond of formaldehyde. The point was to analyze the preferred direction of approach of a high HOMO attacking this low LUMO. To maximize overlap the attacking orbital should approach from the top left as far as possible from the two nodes. It is true that the orbital is large on C because its π bonding "mate" is large on the O with its high nuclear charge, and that its overall shape is analogous to an atomic d-orbital, but these were not the main point of showing this orbital.



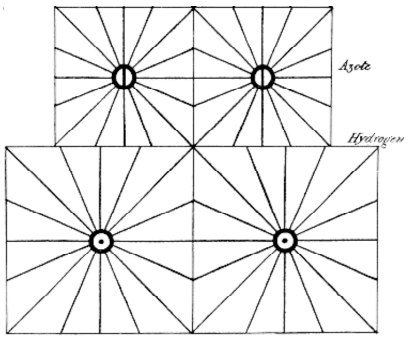
(I) This image slide 6 of the lecture of 12/1/06 shows the absolute configuration of *d*-tartaric acid as determined by Bijvoet in 1949 using x-ray anomalous dispersion from its sodium rubidium salt. This result confirmed Fischer guess of the configuration of D-glyceraldehyde. It is true that this illustration is an example of several ways of showing 3D structures on 2D paper, but this was a decidedly secondary point.



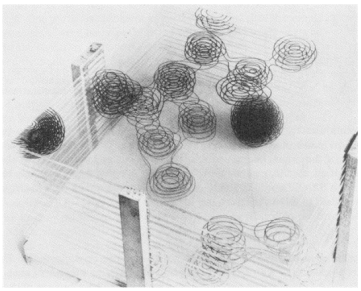
(J) This image from from slide 5 of the lecture of 10/13/06 is a ***difference*** density map between the simplest LCAO electron density of H_2 and undistorted atomic electron densities. The solid contours show density increase due to bonding and the dashed contours show where this density came from. While more sophisticated models based on hybrid orbitals, SCF, *etc*. are more realistic, this simplest approximation already accounts for about 50% of the bonding energy.



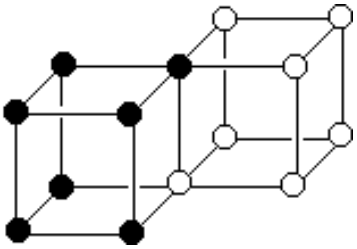
(K) This image from slide 16 of the lecture of 11/3/06 shows Dalton's explanation of the failure of atmospheric gases to stratify on the basis of their densities. He supposed that each gaseous atom [denoted by the alchemy-based symbol in the center] is surrounded by a "heat envelope", and that when the lines of the envelope matched between atoms of the same type, they repelled one another. Atoms of different types would thus not repel one another. Thus failure to segregate depended on "homorepulsion", not "heteroattraction" as had been suggested by others.



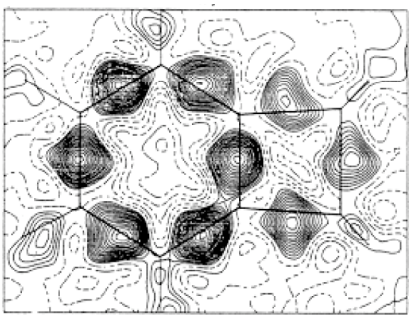
(L) This image from slide 7 of the lecture of 9/22/06 shows a 4-dimensional electron density map model for the potassium salt of penicillin [by Dorothy Hodgkin in the late 1940s]. The most notable feature was that the molecule appears as a set of spherical atoms with no dramatic indication of bonding. The potassium ion stands out by the number of density contours corresponding to its high atomic number.



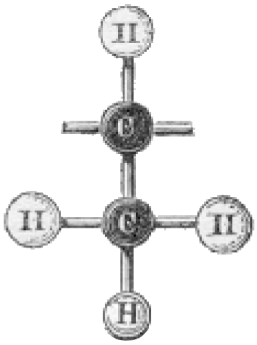
(M) This image from slide 8 of the lecture of 9/22/06 shows Lewis's explanation of valence in terms of electron count. Halogen atoms with seven valence electrons can complete their "cubic octets" by sharing an edge to form a shared-pair single bond. [Note the difference from van't Hoff tetrahedral models, where a shared edge denoted a double bond.]



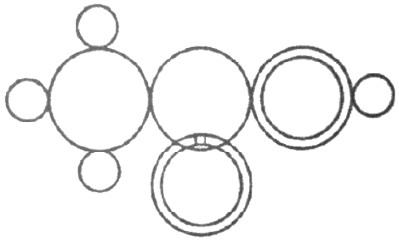
(N) This image from slide 19 of the lecture of 11/15/06 is an electron difference density map of a molecule that was designed to test whether distorting the length of one bond in a benzene ring could led to alternation in length between single and double bonds, or whether the aromatic "resonant" bond lengths would persist. The intermediate lengths did persist, as did the rough equivalence of bonding density around the six-membered ring. [The bonds of the four-membered ring are bent, but this had been demonstrated previously.]



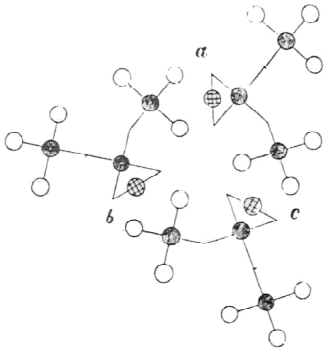
(O) This image is from slide 10 of the lecture of 11/13/06 shows the model used by Hoffman in 1865 to explain the high reactivity of the "olefiant gas", or ethylene in terms of "unsaturated valences" in the molecule which could unite with chlorine. [Of course he erred in showing the molecular constitution, which should have shown a double bond between two CH2 groups.]



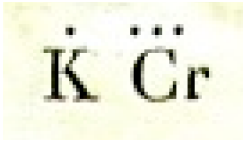
(P) This image from slide 45 of the lecture of 11/10/06 is Lohschmidt's constitutional diagram for acetic acid. Atoms of various elements were shown by different circles (small for H, large for C, double for O). Single bonds were shown by tangency; double by overlap (with two short lines)



(Q) This image from slide 16 of the lecture of 11/13/06 shows Kekulé's diagram (based on Dewar-type models) of the trimerization of acetone to mesitylene with the loss of three molecules of water to generate double bonds at a, b, and c. The principal point was that this mechanistic speculation allowed Kekulé to conclude that the methyl groups of mesitylene are occupy alternant positions (1,3,5) of the benzene ring.



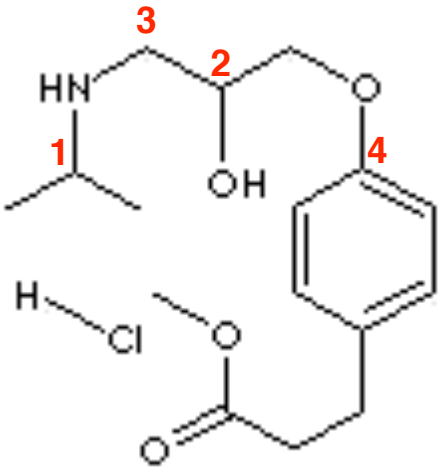
(R) This image from slide 6 of the lecture of 11/6/06 is Berzelius's formula for potassium chromate [actually K_2CrO_4]. He formulated it as an oxide of potassium with a trioxide chromium. He introduced the idea of using the first letter(s) of an element's name as its symbol, with dots above to indicate associated oxygen atoms.



2. "Brevibloc" or "Esmolol Hydrochloride" (formula at the right from a pharmaceutical website) is a "beta-blocker" that may be administered intravenously as an aqueous solution to a patient during surgery to slow abnormally rapid beating of the heart.

The website also gives a more systematic name for the drug:

(±)-4-(2-Hydroxy-3-((1-methylethyl)amino)propoxy)phenylpropionic acid, methyl ester.



A. (2 min) **Label specific atoms** in the structure 1, 2, 3, and 4 corresponding to the numbers used in the systematic name.

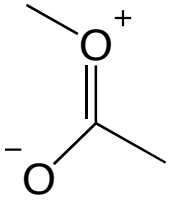
B. (1 min) Give the **trivial name for 1-methylethyl**: _____iso-propyl_____

C. (2.5 min) List the **names of five functional groups** in Esmolol (neglecting the HCl)

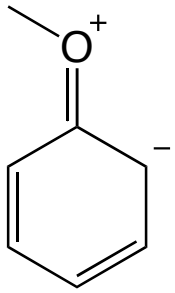
(secondary) Amine, Alcohol, Ether, Aromatic Ring, Ester

D. (4 min) **Explain** briefly **in HOMO/LUMO terms** which of these functional groups involve (or be involved in) "resonance".

Within the ester a high unshared pair of the "ether" oxygen mixes with the low π* LUMO of C=O :



A high unshared pair of the ether oxygen mixes with the π* LUMO of the aromatic ring :



E. (4 min) Generic versions of Esmolol are on the market. Suppose a manufacturer proposed a "**chiral switch**", and you were an officer of the U.S. Food and Drug Administration in charge of supervising **clinical trials**. Would you suggest comparing equal **concentrations of the old and new forms** (1:1), or twice as much of the old form (2:1), or twice as much of the new form (1:2)? **Give a reason** for your recommendation.

Since the hypothesis underlying a chiral switch is that one of the enantiomers is much more effective than the other, it would be sensible to test the recommended dose (by mass) of the original racemate [Note the (±) racemate designation in the systematic name of Esmolol] against half the mass of the single enantiomer. (*i.e.* 2:1) Equal effectiveness would mean that only this enantiomer is active in the desired way. There is a chance that there would be fewer side effects because of the absence of the "wrong" enantiomer. One might also increase the dose of the single enantiomer a bit in case the "wrong" enantiomer had some reduced effectiveness. [One would probably not use twice the weight of the single enantiomer (1:2), as was done with esomeprazole, unless one was testing the hypothesis that one could increase the dose because the "wrong" enantiomer is deleterious.]

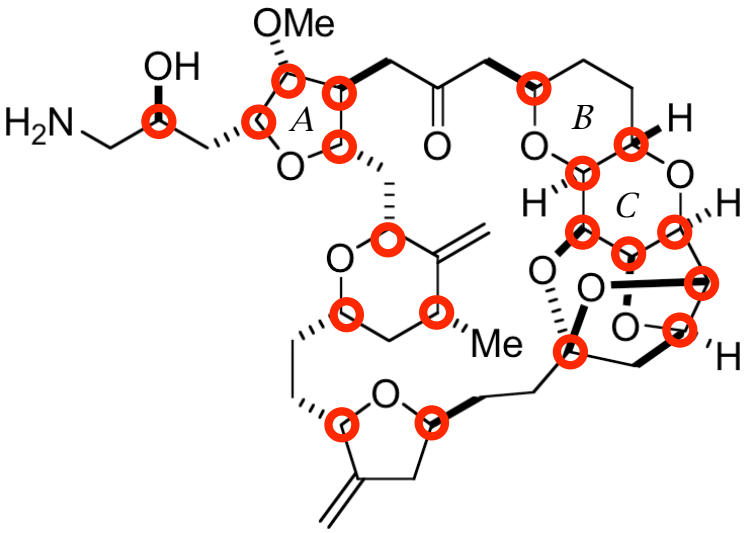
F. (4 min) Explain how *d*-tartaric acid might be useful in preparing material for research relevant to this chiral switch.

Since the drug is an amine (actually an ammonium salt), it would be possible to prepare the salt of the racemic amine drug with the *d*-tartaric (instead of hydrochloric) acid. This salt would consist of diastereomeric forms with different solubility. Careful crystallization would allow separation of the diastereomers, and thus of the enantiomers of the amine. Treating with base would allow recovering the resolved amines, which could be treated with HCl to yield the desired hydrochloride salts for testing.

G. (3.5 min) Directions for intravenous administration of the drug caution "BREVIBLOC SHOULD NOT BE ADMIXED WITH SODIUM BICARBONATE". Given that bicarbonate is a weak base and not normally harmful during injection, why do you think the admixture might be dangerous? (Hint: the structure showing HCl is erroneous. Bad idea to inject raw HCl.)

Esmolol is an amine, and is thus basic. It reacts with HCl to form an ammonium chloride salt, which is soluble in water. If it were mixed with the stronger base sodium bicarbonate that would remove the HCl, the insoluble amine would be formed and precipitate from the aqueous solution. It is important to inject a solution into the bloodstream, since a solid might block a blood vessel.

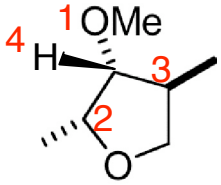
3. The synthetic cancer drug candidate E7389 (right) is remarkable because it possesses so many chiral centers.



A. (3 min) Draw a **small circles around each chiral center** in the formula.

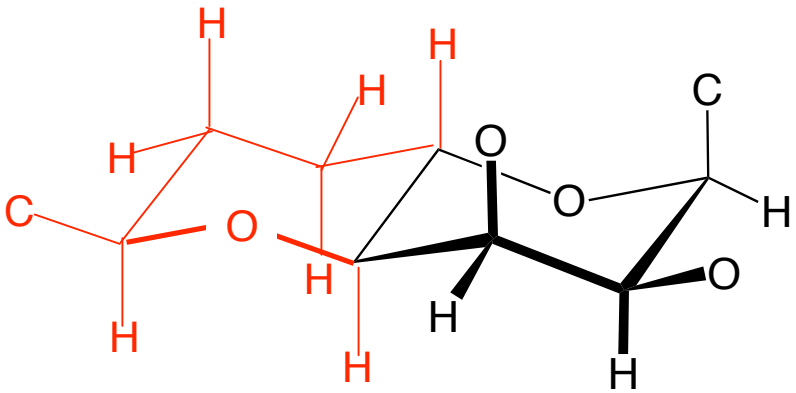
B. (4 min) Redraw below enough of the **chiral center that is uppermost** in the formula so that you can **label priorities**, and then **give it a systematic CIP name**.

1) O
2) C(OCH)
3) C(CCH)
4) H



R

C. (8 min) The fused 6-membered rings labeled "*B*" and "*C*" in E7389 have a conformation similar to that of "trans-decalin". The partial structure below shows **Ring C** with most of the atoms attached directly to it. **Complete this structure to include Ring *B* and all the atoms attached directly to it**. Don't worry about shading the bonds realistically, but do be careful to **draw lines at the correct angles**.



D. (2 min) Is it possible that the formula of E7389 represents a ***meso*** configuration?

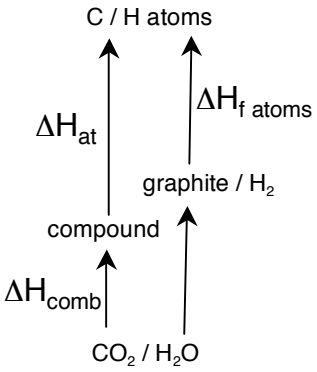
No. It has no constitutional symmetry and thus cannot possibly be its own mirror image.

E. (6 min) What are the **likely sources of significant strain** involving the **5-membered ring** "***A***" near the top left of the formula for E7389? **Explain whether** you expect this ring to be **planar**.

Baeyer would have thought the 5-membered ring to be unstrained, because the 108° angles of a regular pentagon are so close to the natural 109.5° tetrahedral angles of the carbon atom (the bonds at O are also nearly tetrahedral). However, if the ring were flat, there would be severe strain from eclipsed torsional angles around the ring, and there would also be severe 1,4-van der Waals repulsions from *cis* substituents. As in cyclopentane, the compromise would involve puckering the ring at the expense of bond angle strain in order to reduce eclipsing strain and 1,4-van der Waals repulsion.

4. (8 min) Why was it important to measure the heat of formation of carbon atoms in order to be able to use constitutional formulas to estimate molecular energy? (Try to mention two other "kinds" of heat in your answer. A diagram may help.)

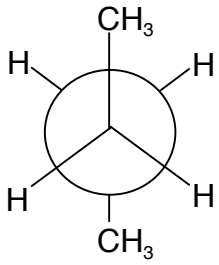
Constitutional formulas involve bonds, so using them to estimate molecular energies involves a model in which one sums bond energies to estimate heat of atomization (ΔH_{at}). To calibrate such a model, one needs to measure heats of atomization of typical compounds. The experiment involved for most compounds is measuring heat of combustion (ΔH_{comb}) with a combustion calorimeter. To go from such a heat of combustion to the heat of atomization one needs the heats of combustion of the elements in their standard states (H_2 gas, graphite, *etc.*), and one needs the elemental heats of atomization; for carbon this is the heat of formation of the carbon atom from graphite.



5. (10 min) Use the circles to draw **Newman projections** for the *anti, anticlinal-eclipsed*, and *gauche* conformations of butane. Give **numerical** values for their relative **energies** (defining anti as 0). Use these numbers to **estimate one equilibrium** constant **and one rate** constant.

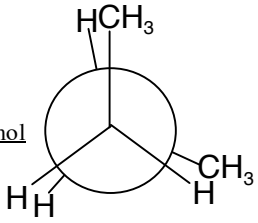
anti

Energy = 0



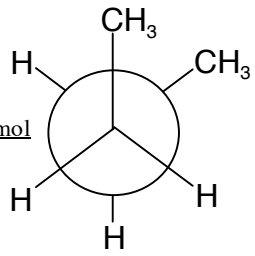
anticlinal-eclipsed

Energy = **3.4** kcal/mol



Gauche

Energy = **0.9** kcal/mol



Rate Constant k

anti → *gauche* = $10^{13} \times 10^{-3/4 \times 3.4}$ / sec

= $10^{13-2.6}$ / sec = $10^{-10.4}$ / sec

Equilibrium Constant K

gauche/anti = $10^{-3/4 \times 0.9} = 10^{-0.67}$

[≈ 1/5 (~2/5 if you count both gauches)]

6. (4 min) Explain a way in which "correlation energy" and "strain energy" might be considered to be **analogous** concepts.

Each measures an error – the difference between the prediction of a simplistic model and an actual experimental quantity (or a much ore precise theoretical one). In the case of correlation energy the difference it between a true molecular energy and a prediction based on self-consistent field theory. In the case of strain energy it is the difference between true molecular energy and a model based on bond (or group) additivity.

7. (4 min) Write a **mathematical** formula for a $2p_x$ orbital.

(don't worry about constants). $2p_x = x\, e^{-\rho/2}$ [or a more complicated equivalent]

8. (15 min) Identify the "intramolecular HOMO-LUMO mixing" within the **amide** functional group, and **explain how it affects** each of the listed molecular properties:

Identify HOMO/LUMO mixing:

HOMO: unshared pair of nitrogen (n_N) LUMO: π^* of carbonyl (π^*_{CO})

heat of formation:

Because of the HOMO/LUMO mixing (resonance). An amide is more stable that expected from bond additivity. Thus is has a more negative heat of formation from the elements.

bond distances:

Partial occupancy of the antibonding π^*_{CO} lengthens the C=O bond. New bonding between N and C, shortens the C—N bond.

bond angles at N:

"Dehybridization" of the N atom to change the unshared pair orbital of N from an sp^X hybrid to pure p gives better overlap with the neighboring π^*_{CO}. Furthermore partial loss of the unshared pair from N makes it less advantageous to use 2s orbital character in the lone pair orbital. Thus the three σ-bonding orbitals of N become sp^2, and the angles at N are ~120°. N is normally pyramidal in simple amines and planar in amides.

ease of rotation about the C-N bond:

It is more difficult to rotate about the CN bond of an amide than about the CN bond of an amine, because this destroys the overlap between the unshared pair orbital and π^*_{CO}.in the amide ("inhibits resonance").

reactivity as an acid:

HOMO/LUMO mixing results in a lower HOMO and a higher LUMO. In this sense an amide is less acidic than a normal carbonyl compound (which is acidic because of the low π^*_{CO}). [If one considers the ease with which a proton is lost from the N-H group as the measure of acidity, the amide is more acidic than an amine, because it is easier for the N to acquire a negative charge when its unshared pair of electrons has been shifted toward the C=O group, giving N a partial positive charge in the unionized form. Another way of saying the same thing is that there is more effective HOMO/LUMO mixing when the unshared pair on N is raised in energy by its acquisition of a negative charge.]

reactivity as a base:

HOMO/LUMO mixing results in a lower HOMO and a higher LUMO. The lowered HOMO makes an amide a weaker base than an amine.

9. (9 min) Choose **any reaction process that involves several steps** and draw a mechanism using curved arrows to show every electron (pair) shift involved (*e.g.* alkene + Cl_2 → dichloroalkane; **or** alkane + Cl_2 → alkyl chloride + HCl; **or** NH_3 + Cl_2 → NH_2Cl + NH_4Cl; **or whatever**). No discussion of HOMOs and LUMOs required, but draw the arrows carefully.

Obviously there are an unlimited number of possibilities for correct answers, such as the following, or others mentioned above that were discussed in the lectures of 11/08/06 slide 37 and 10/27/06 slide 15. It is important to start curved arrows where an electron pair begins (in a bond or as an unshared pair), and to place the arrow's tip where the pair ends (between two atoms or on an atom). Note that chlorination of an alkane by substitution of Cl for H involves "odd" electrons (free radicals) and uses single-barbed arrows.