Chemistry 125 First Semester Final Examination **December 18, 2009**

Answer Key

1. (20 minutes) Give a brief **definition** for **one** member from each the following 8 pairs of terms used in the Chem 125 this semester. In some cases it might help to give an example. **Circle the One Member from each Pair that you are defining.**

a) Correlation energy / SCF

Correlation energy is the difference between energy calculated by a full SCF quantum mechanical procedure and the true energy of a molecule. The discrepancy arises because the SCF procedure does not allow correlated motion of electrons to reduce their repulsion.

Self-Consistent Field describes a molecular orbital calculation in which the potential energy function for calculating the orbital for one electron includes repulsion from the other electrons approximated as a fixed cloud. Cycling from electron to electron until self-consistency is reached gives a much better approximation to reality than ignoring electron-electron repulsion or using "effective" nuclear charges, but the energy is inevitably overestimated because of neglecting electron correlation.

b) Stereogenic / Epimer

Stereogenic carbon atoms are those which four different substituents, the arrangement of which can be right- or left-handed. Other atoms can also be stereogenic, such as the sulfur in an unsymmetrically substituted sulfoxide group (omeprazole).

Epimers are diastereomers that differ in configuration at only one of several stereogenic centers.

c) Conglomerate / Racemate

A **conglomerate** is a mixture of enantiomeric crystals each of which contains molecules of only one configuration, such as Pasteur's sodium ammonium tartrate.

A **racemate** is a 50:50 mixture of enantiomers. A solid racemate is crystal in which the repeating unit cell contains both enantiomers.

d) Synclinal / Enantiotopic

Synclinal describes torsional angles between 30° and 90° (or -30° and -90°).

Enantiotopic describes the relationship between groups (or atoms) whose surroundings are non-superposable mirror images.

e) Orbital / LCAO

An **Orbital** is a one-electron wavefunction.

A **Linear Combination of Atomic Orbitals** (LCAO) is a molecular orbital approximated by a weighted sum of atomic orbitals.

f) Earnshaw's Theorem / Cubic Octet

Earnshaw's Theorem states that there can be no potential energy minimum (or maximum) in a system governed by inverse-square force laws. With respect to the nuclei and electrons of chemical molecules this means that Coulomb's law alone (or together with magnetism and gravity) cannot explain structure. [The secret is to use Schrödinger's kinetic energy.]

G. N. Lewis proposed a nested **Cubic Octet** structure for electrons in an atom to rationalize Mendeleef's periodicity of the elements. He then applied the theory to explain valence in terms of shared edges and faces for single and double bonds. [He sidestepped Earnshaw's Theorem by assuming, incorrectly, that Coulomb's Law breaks down at very short distance.]

g) Difference Density Map / 3-Center-2-Electron Bond

An electron **Difference Density Map** plots the difference between the observed electron density (from x-ray diffraction or reliable quantum calculation) and the superposition of the molecule's undistorted atoms. It shows the shift in electron density that arises from bonding (~1/20 of a "Lewis"), and is thus a way to visualize bonding.

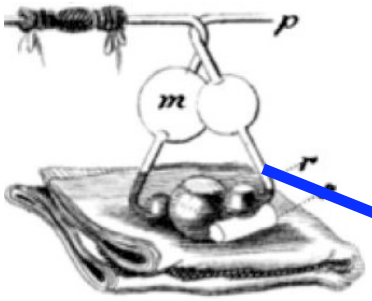
A **3-Center-2-Electron Bond** occurs when a low vacant orbital (e.g. the 2p orbital of BH_3) overlaps with and stabilizes a pair of bonding electrons between two other atoms (e.g. the high-energy electrons in a B-H bond). All three atoms are then bonded together by the electron pair.

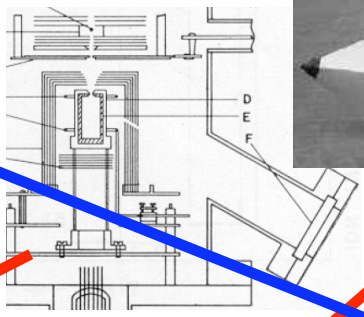
h) Zero-Point Energy / Tunneling

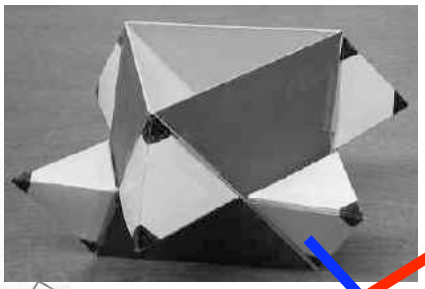
Zero-Point Energy is the minimum energy for a system that is allowed by quantum mechanics. It is particularly relevant for the vibrational energy of a pair of bonded atoms. It arises because of the kinetic energy that Schrödinger's equation imposes through the shape of the wavefunction.

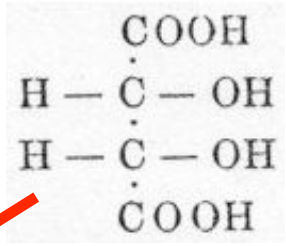
Tunneling is the ability of a particle to exist in, or pass through, a region where its potential energy exceeds its total energy. The classical analogue would be to "tunnel" into a potential energy barrier, but this is a misleading analogy, because in fact in the region the potential energy is normal, but the kinetic energy is negative. Every wavefunction for a bound system has regions where its curvature is away from the baseline so that its kinetic energy is negative.

2. (6 min) **Draw unambiguous lines** to connect each device, model, formula, or notation with its inventor.
[Note: 12 items – 11 people]



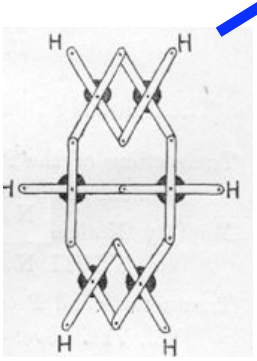


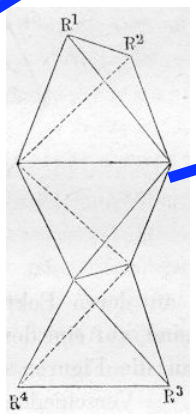


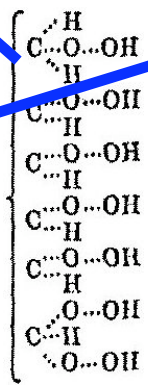


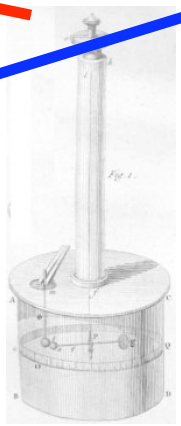
(D)-glyceraldehyde

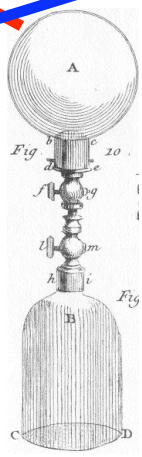
Chupka Coulomb Couper Dewar Fischer Kekulé Lavoisier Liebig Paternó Sachse van't Hoff

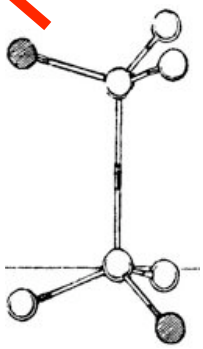




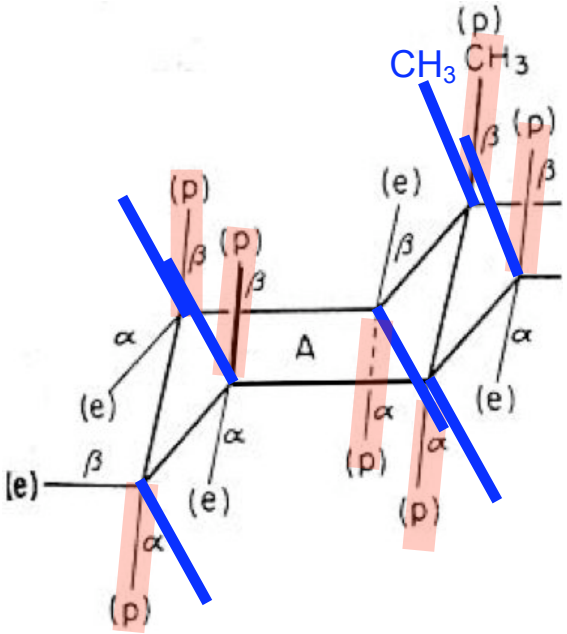








3. (5 min) Correct this picture of ring "A" of a steroid from a 1950 paper, and interpret each of the labels:



(e) "Equatorial" (large component in the mean plane of the 6 ring carbon atoms)

(p) "Polar" (parallel to the 3-fold symmetry axis of the 6 ring carbon atoms [now called "axial" to avoid confusion with electrical polarity])

(α) Pointing away from the viewer
(when the steroid rings are drawn in the conventional orientation)

(β) Pointing toward from the viewer
(when the steroid rings are drawn in the conventional orientation)

4. (12 min) Tell briefly how **tartaric acid** played an important role in developing the theory or practice of organic chemistry in each of **4 (FOUR ONLY)** of the following 6 years: **1769, 1830, 1848, 1874, 1949, 1980**.

1769 Scheele isolates pure tartaric acid. His isolation of numerous pure organic acids (mostly as heavy-metal salts) gave organic chemistry subjects that would reward investigation much more richly that intractable mixtures would do.

1830 Berzelius finds that racemic acid (John's Acid from the Vosges) has the same constitutional formula as tartaric acid and coins the word "isomer" to describe the relationship between pairs of compounds with the same constitution and different properties.

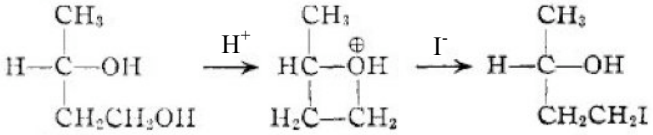
1848 Pasteur separates the mirror-image crystals of sodium ammonium tartrate starting from racemic acid, showing that racemic acid is a 50:50 mixture of enantiomers. He inferred that the atoms in such a substance must have arranged in a chiral structure.

1874 van't Hoff explains the puzzling handedness of a dozen or so organic compounds by noting that each such substance has a carbon atom with four different substituents. He proposes that the bonds from a carbon atom point toward the vertices (or faces) of a regular tetrahedron. He explains that the isomerism of tartaric acid in terms of its having two such carbons with identical substituents so as to give meso- as well as right- and left-handed forms.

1949 Bijvoet uses "anomalous dispersion" in x-ray diffraction to determine for the first time the absolute configuration of a chiral substance, sodium rubidium tartrate.

1980 Katsuki and Sharpless develop titanium diethyl tartrate as a general catalyst for oxidizing allylic alcohols to yield a single enantiomer of the epoxide. This is a pioneering example of stereospecific catalysis, which is now widely used to make single-enantiomer drugs.

5. (6 minutes) Explain how the likely formation of a 4-membered ring intermediate by alternative "make as you break" processes rendered the stereochemical course of Levene's conversion of (–)-1,3-butanediol to (–)-4-iodo-2-butanol problematic.



Acid protonates one OH group which then leaves as H_2O as the other OH group forms a four-membered ring by attacking the carbon involved from the opposite side (the small lobe of the carbon's sp^3 hybrid orbital). Since the new oxygen is on the opposite face of the carbon attacked, this process inverts the configuration of the carbon attacked.

The question is which carbon is attacked. If it is the number 1 carbon, the inversion makes no difference since that carbon is not stereogenic and the subsequent attack by iodide returns and alcohol with the initial configuration of the number 3 carbon.

If, on the other hand, the number 3 carbon is attacked by the OH on carbon 1, and then iodide attacks the number 1 carbon to give the product, the configuration at the number 3 carbon in the product iodoalcohol will be opposite to that in the starting diol.

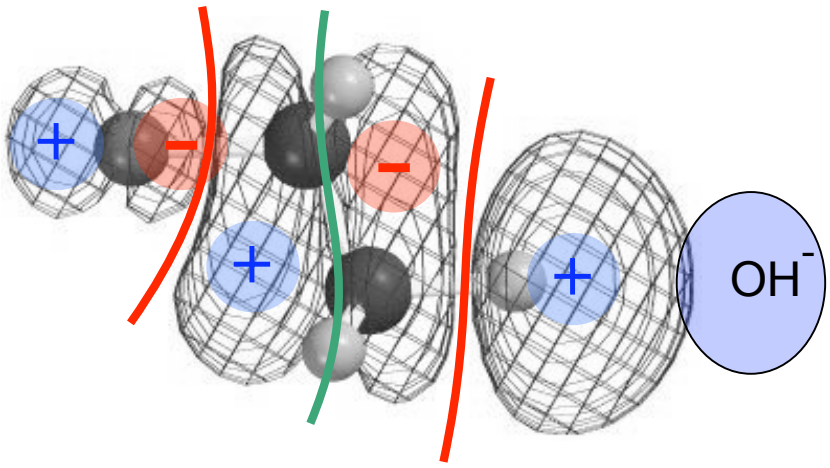
The possibility of the second pathway rendered Levene's structural correlation problematic, though Wiberg confirmed that the first pathway must have dominated by preparing its product in an unambiguous way.

6. (5 min) Where does "overlap" crop up in a quantum mechanical calculation? [Show a mathematical formula.]

Squaring an orbital formulated as the sum of two simpler orbitals (to find the probability density for its electrons) generates not only the probability density of the two components, but also the red "cross-term" from their product, which is large in the "overlap" region where both components have a significant value. Adding this term to the density of the individual components increases (for a bonding interaction) or decreases (for an antibonding interaction) the electron density in the region between the two components.

$$(A + B)^2 = A^2 + B^2 + 2\,AB$$

7. (6 min) Explain how the LUMO of ethyl fluoride would function during an "E2" elimination reaction with hydroxide.



When hydroxide approaches from the right, its HOMO mixes with this LUMO creating sigma bonding between the rightmost H and OH. Partial occupancy of this LUMO weakens the bonds across the red antibonding nodes (breaking off H^+ on the right and F^- on the left) but strengthening the central C-C bond by forming a second (π) bond with the green atomic orbital node. The products are thus F^-, $CH_2{=}CH_2$, and HOH.

8. (3 min) Rationalize briefly why, even at high temperature, the most likely energy for a molecular "degree of freedom" is zero.

With a limited total amount of energy (an amount given by the temperature, which measures the average energy), the more energy one assigns to a given degree of freedom, the less there is to be assigned to all the other degrees of freedom in the system.

To maximize the number of permutations of energy among the other groups of freedom, and thus to maximize the total probability of having a particular amount of energy in "our" degree of freedom (when all permutations are equally likely), the amount of energy in our degree of freedom should be zero.

This is the underlying rationale for the Boltzmann distribution.

9. (3 min) Explain in a few sentences why compounds that inhibit crystal nucleation help treat malaria.

In red blood cells the malarial parasite grows by metabolizing the protein portion of hemoglobin. The residual iron-containing heme molecule is poisonous to the parasite, which protects itself by catalyzing crystallization of heme into the very slightly soluble crystalline solid called hemozoin. Stopping this crystallization would force the parasite to poison itself. This is most efficiently and safely done when the crystals are very small (during nucleation) so that very little of the inhibiting agent is required.

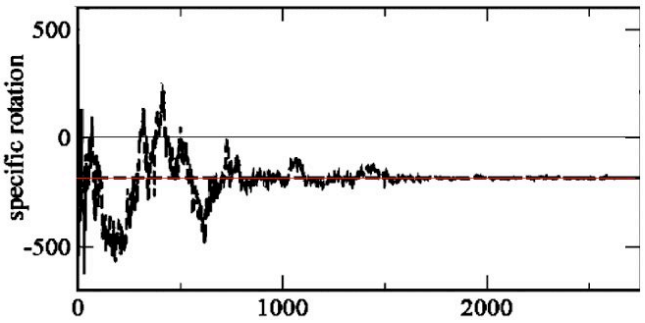
10. (4 min) Explain why there was reason to suppose that a chiral switch might not work for the sulfoxide omeprazole (Prilosec). [Words alone will do; you need not draw molecular structures.]

Omeprazole is a pro-drug that is converted by acid to its active form. Although Prilosec is a chiral racemate, the active drug is achiral (its sulfur atom is no longer trivalent). Making omeprazole as a single enantiomer would thus have no influence on the reactivity of the active form, and even the process of converting the pro-drug to the active form would be insensitive to its chirality, since acid with which it reacts in this process is achiral (no enzyme required).

[Of course it is possible that the ability of the pro-drug to get to the stomach's "parietal" cells, where the drug needs to be generated, would be influenced by its handedness. So only clinical trials could establish the efficacy of the chiral switch.]

11. (3 min) Explain this graph and what it says about calculating the optical rotation of an organic compound.

This graph [sketched by Prof. Wiberg in his guest lecture and presented in frame 9 of Lecture 29] shows the wild oscillation in calculated optical rotatory strength of a compound (2,3-pentadiene) based on including contributions from increasing numbers of electronically excited states. That so many states are seriously involved makes it clear that finding simple ways to predict a compound's rotatory strength is not going to be easy. [This is because individual contributions depend on fortuitous coincidence of electrical and magnetic factors, rather than on either one of them being particularly large, which might be qualitatively predictable.]



12. (6 min) Explain in terms of the factors influencing hybridization whether H_3O^+ should be planar or pyramidal.

H_3O^+ is very closely analogous to the structure of NH_3, because these molecules are "isoelectronic", the only difference being that the oxygen nucleus contains an additional proton (and an irrelevant neutron).

From the point of view of forming the three strongest bonds, the oxygen would want to use sp^2 hybridization (120° angles, planar).

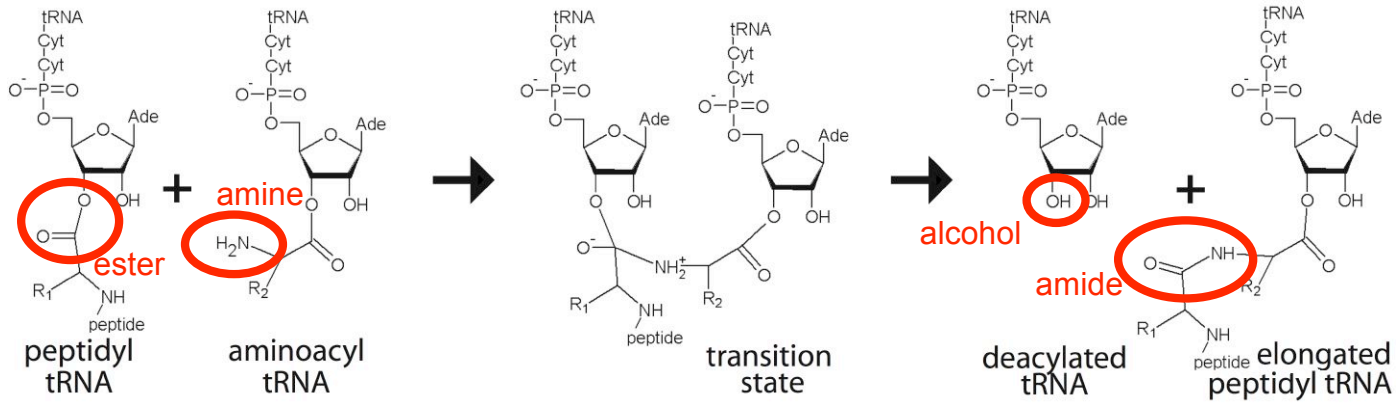
From the point of view of stabilizing the atomic electrons, oxygen would want to maximize the s-orbital content of its unshared-pair orbital, leaving pure p-orbitals for the bonds (90° angles, sharply pyramidal)

The molecule reaches a pyramidal compromise between these extremes.

[The HOH angle is 113.6° *vs.* 107.3° for HNH, suggesting that the increased nuclear charge favors unshared pair stabilization over bond strength.]

12. Big news in the Chemistry and MB&B Departments at Yale this semester was the Nobel Prize awarded to Prof. Steitz for his X-ray studies of the ribosome (together with Profs. Moore and Strobel and their coworkers). The remainder of the exam consists of questions on this theme.

The crucial steps in the programmed biosynthesis of proteins catalyzed by the ribosome are shown in this figure from a 2005 Steitz-Strobel paper:



A. (3 min) In **the starting materials and products** of the scheme above (**neglecting the "transition state") CIRCLE** and **NAME** the **four functional groups** whose bonding changes or has changed during the process.

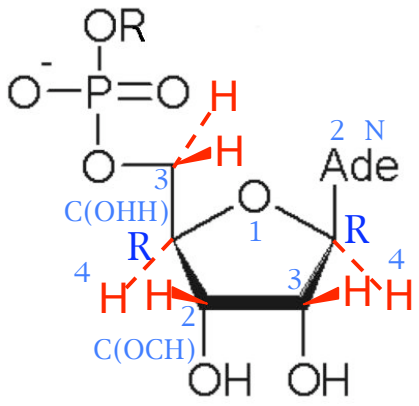
B. (7 min) Many of the names in this scheme include the **suffix "yl".** Tell how this suffix was first used in a publication in 1832, what it was used to name, and how it related to the general theory of organic chemistry that was proposed in that paper.

"-yl" appeared first in "benzoyl" the name Liebig and Wöhler gave to the C_7H_5O radical that persisted through a series of chemical transformations beginning with the oil of bitter almonds (benzaldehyde). The suffix derived from the Greek "hyle" to mean "the matter of." The radical theory of organic chemistry assumed that such "indestructible" grouping of atoms played the same role in organic chemistry that "electropositive" (or "electronegative") elements played in inorganic chemistry, in which they were assumed to be held together by Coulombic attraction. Radicals allowed extending the concept of dualism from inorganic to organic chemistry.

Although organic dualism bit the dust, we still name radicals with the "–yl" suffix.

C. (5 min) Notice that all compounds in the scheme include this structure, where "Ade" stands for adenine, a group with a nitrogen atom that links to the 5-membered ring. **Add H atoms** to the C atoms where they have been omitted being careful to **show the configuration at each carbon unambiguously**.

Label the **two carbons bonded to the ring oxygen** with the proper **CIP** designator of their absolute configuration.



[Although the two stereogenic carbons are pseudo mirror images, they are both (R), because N has priority over C(OCH), but C(OCH) has priority over C(OHH).]

D. (8 min) **Explain whether or not you would expect the ring in Question C to be planar**.
In your explanation mention at least **3 molecular mechanics factors** that should influence the ring shape **and** mention the **analogy to another familiar five-atom ring**. (You might include a sketch to illustrate your thinking)

Since the 108° angles between sides of a planar pentagon are very near the 109.5° tetrahedral angle, a planar geometry would minimize bond angle strain.

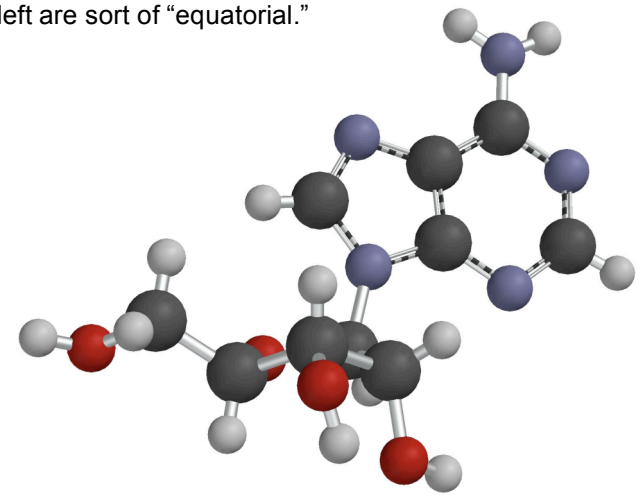
However substituents on the four ring carbons would be eclipsed with a planar ring. This would contribute torsional strain.

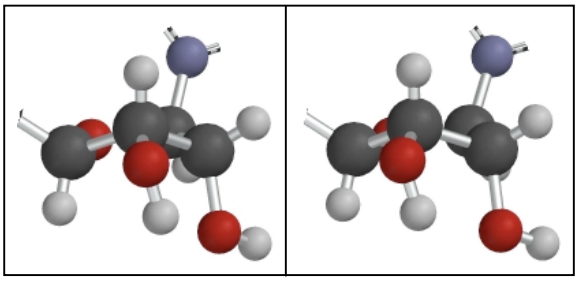
Furthermore the large substituents on the carbons flanking the ring oxygen would be close together, contributing non-1,4-van der Waals repulsion energy (which would probably overwhelm the non-1,4-van der Waals attraction from their more distant atoms).

Thus, as in cyclopentane, we would expect an envelope conformation in which one of the ring atoms is pulled out of the plane of the others, increasing bond angle strain, but decreasing torsional strain and van der Waals repulsion.

In the specific case of crystalline adenosine the molecular conformation determined by x-ray diffraction in 1972 is shown in the following figures (on the right is a stereo-pair of the 5-membered ring). The ring carbon nearest the viewer is above the approximate plane of the other ring atoms (the flap of the envelope).

Note that the adenine substituent in the back and the adjacent OH group on the right are sort of "axial" (a term which properly applies to chair cyclohexane), while the OH near the viewer and the CH_2OH group on the left are sort of "equatorial."





E. (3 min) Discuss briefly whether the force between the **OH groups** on the ring in Question C should be attractive or repulsive.

Although there could be some 1,4-van der Waals repulsion between these two OH groups, which are eclipsed in the planar ring and gauche in the puckered ring, the interaction might well be attractive because of H-bonding attraction between the positive H of one OH group and the negative O of the other.

In the x-ray conformation shown above the OH groups in front and on the bottom right are indeed oriented to suggest a weak H-bond.

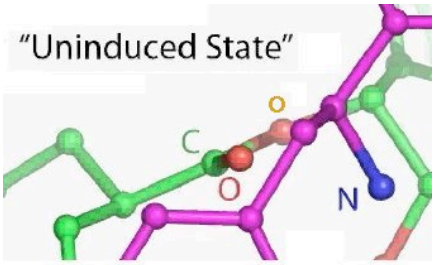
F. (4 min) Suppose the CH_2-OPO_2-OR group in the compound of Question C is similar in shape and size to **CH_2-CH_2-$C(CH_3)_3$**. Would you expect this group to have a larger or smaller **A-value** than the t-butyl group when it is a substituent on **cyclohexane**? Explain your thinking.

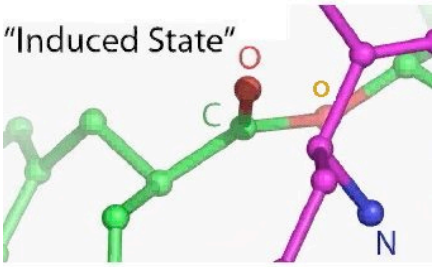
Remember the big jump in A-value (preference for axial over equatorial location) on going from iso-propyl to t-butyl that arises because the t-butyl group cannot rotate to get its methyl group out of the way. By the same token the CH_2-CH_2-$C(CH_3)_3$ group (or the CH_2-OPO_2-OR group), although larger than t-butyl, would have enough rotational flexibility to get out of the way of other ring substituents and should have a smaller A value than t-butyl.

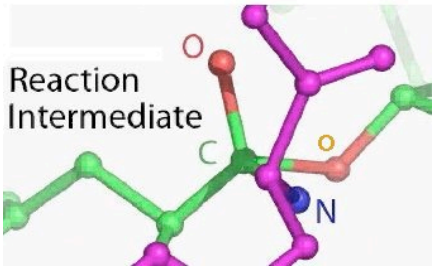
[From this point of view, it is remarkable that the apparently larger adenine group in the structure shown above is pseudo-axial, while the smaller CH_2OH group is pseudo-equatorial.]

In his Nobel address ten days ago Prof. Steitz showed a movie illustrating how the ribosome changes shape when the appropriate aminoacyl-t-RNA comes along, pushing around the reagents and thus facilitating the reaction shown in the scheme on page 6.

The movie was based on his **x-ray studies of a number of complexes** of different relevant molecules with the ribosome. Three key x-ray structures are summarized in these figures, where important atoms of the reacting groups are labeled as N, C, O. [H atoms are omitted.] The "Uninduced State" has an erroneous aminoacyl-t-RNA; the "Induced State" has the correct t-RNA; and the "Reaction Intermediate" corresponds to what they labeled "transition state" in the scheme above.

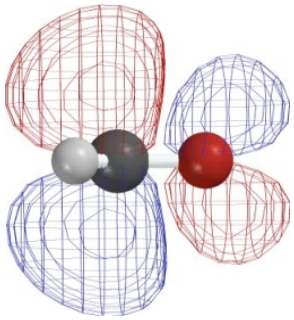






G. (5 min) **Name** the molecular orbital that makes the CO group reactive in this process. Also **draw it, explaining** the **size** and **sign** of its atomic orbital components.

$\pi^*_{C=O}$



The LUMO is the antibonding combination of *2p* atomic orbitals on C and O (hence the vertical node). It is larger on C because the lower energy bonding MO (π) used up most of the *2p* orbital of oxygen.

(The video animation of the structures shown during the exam is available on the course website.)

H. (4 min) Explain how you would expect the adjacent oxygen atom to influence the reactivity of the CO orbital you drew in Question G.

An unshared pair of electrons on the adjacent oxygen within the ester group will mix with $\pi^*_{C=O}$. This mixing lowers the energy of the molecule by lowering the energy of the former lone pair, but more importantly for reactivity it raises the LUMO, making it less reactive.

I. (4 min) Explain in terms of **overlap** why the "Induced State" structure is so much more favorable for reaction than the "Uninduced State".

In the "Uninduced State" the N atom lies more or less along the C-O axis, not only far from the C atom that needs to be attacked, but also in the nodal plane of the $\pi^*_{C=O}$ orbital. In the "Induced State" the N atom moves closer to the C atom, and the CO group rotates so that the N unshared pair can begin to overlap with the $2p_C$ AO within the $\pi^*_{C=O}$ MO.

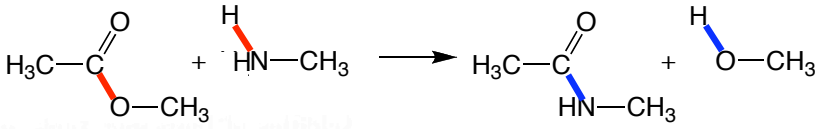
J. (8 min) In the 2005 paper describing this work Steitz wrote, "Small-molecule studies[15] show that that the optimal angle for nucleophilic attack is about 105° from the plane…" His reference 15 is to work by Swiss chemists in 1973. Explain how those workers (with initials B and D) determined this angle, and how their work with small-molecule was analogous to this work with the enormous ribosome.

Bürgi and Dunitz defined a trajectory for addition of an amine to a carbonyl group by arranging the results of X-ray diffraction studies of numerous crystals containing these groups as if they were frames in a motion picture of the process. They found that N approaches the C atom of the C=O group along a straight line that makes an angle of 110° with the C=O bond. [Incidentally, some of the discrepancies in the value of the "Bürgi-Dunitz" angle results from different values they published as the work progressed. The value in ref. 15 was 107°.]

As in the Bürgi-Dunitz approach, the ribosome reaction trajectory movie of Steitz resulted from combining a number of static X-ray images, in each of which reaction was arrested by other packing constraints in the crystal.

K. (5 min) Here is a simplistic model for the chemical transfomation catalyzed by the ribosome:

Show how to use the following table of average bond energies (naively - appropriate or not) to estimate the change in energy for this reaction.



Average Bond Energies, kcal mole^{-1}

H	C	N	O	F	Si	S	Cl	Br	I	
104	99	93	111	135	76	83	103	87	71	H
	83[a]	73[b]	86[c]	116	72	65	81	68	52	C

[a] C=C 146, C≡C 200.

[b] C=N 147, C≡N 213.

[c] C=O 176 (aldehydes), 179 (ketones).

Bonds Lost : 86 + 93 = 179

Bonds Formed : 73 + 111 = 184

Net Stabilization : 5 kcal/mole

L. (4 min) Actual data for the compounds in Question K (from http://webbook.nist.gov/chemistry/) suggest that the transformation is favorable by 14 kcal/mole. **What values would you look for** on such a website in order to calculate the energy change? Use this value to **estimate an approximate equilibrium constant** at room temperature,

Look for Heats of Formation (or Heats of Combustion, but ΔH_f is more often tabulated).

$$K \sim 10^{-(3/4)\Delta H} = 10^{-(3/4)(-14)} = 10^{10.5} \sim 3 \times 10^{10}$$

M. (5 min) Propose an explanation for the discrepancy between the actual value of the energy change given in Question L and your estimate from Question K.

The products are more stable that the starting materials by 14 kcal/mole, when we calculated only 5 kcal/mole from adding bond energies. What is the source of the extra 9 kcal/mole stabilization?

The most likely source is resonance stabilization of the amide caused by mixing the unshared pair of nitrogen with the adjacent $\pi^*_{C=O}$ LUMO. In Lecture 17 we saw that this stabilization in an amide group is worth about 16 kcal/mole.

Only 9 kcal/mole of extra stabilization of the product is required. This reduction comes because in the starting ester there is also some resonance stabilization from mixing an unshared pair of oxygen with the adjacent $\pi^*_{C=O}$ LUMO. This stabilization should be smaller because the higher nuclear charge of oxygen makes its unshared pairs lower in energy than the pair of nitrogen and thus less susceptible to such resonance stabilization. Lowering the reaction heat from 21 kcal/mole (5 kcal/mole bond energies corrected for 16 kcal/mole amide resonance) to 14 kcal/mole (observed) suggests that resonance stabilization in the ester is worth about 7 kcal/mole.

N. (6 min) The larger product molecule in Question K much more **strongly prefers to have a planar conformation** than does the larger starting material molecule. **Explain** how this preference relates to your answer to Question M **AND explain** a second way in which this preference should influence the free energy change for the reaction.

Since the resonance stabilization mentioned in Question M requires a planar conformation for the amide, it serves to hinder rotation about the N-to-carbonyl bond. Analogous rotation in the ester is much easier both because of lower resonance stabilization and because there is a second unshared pair on O that can become stabilized as the first pair rotates out of overlap.

The greater resistance to rotation of the amide means that its allowed energy levels should be more widely spaced than those of the ester (like the stiff chair *vs*. the floppy twist-boat of cyclohexane). Thus the amide should have lower entropy than the ester, which would counteract the equilibrium bias in favor of products in the (ester + amine) to (amide + alcohol) transformation.