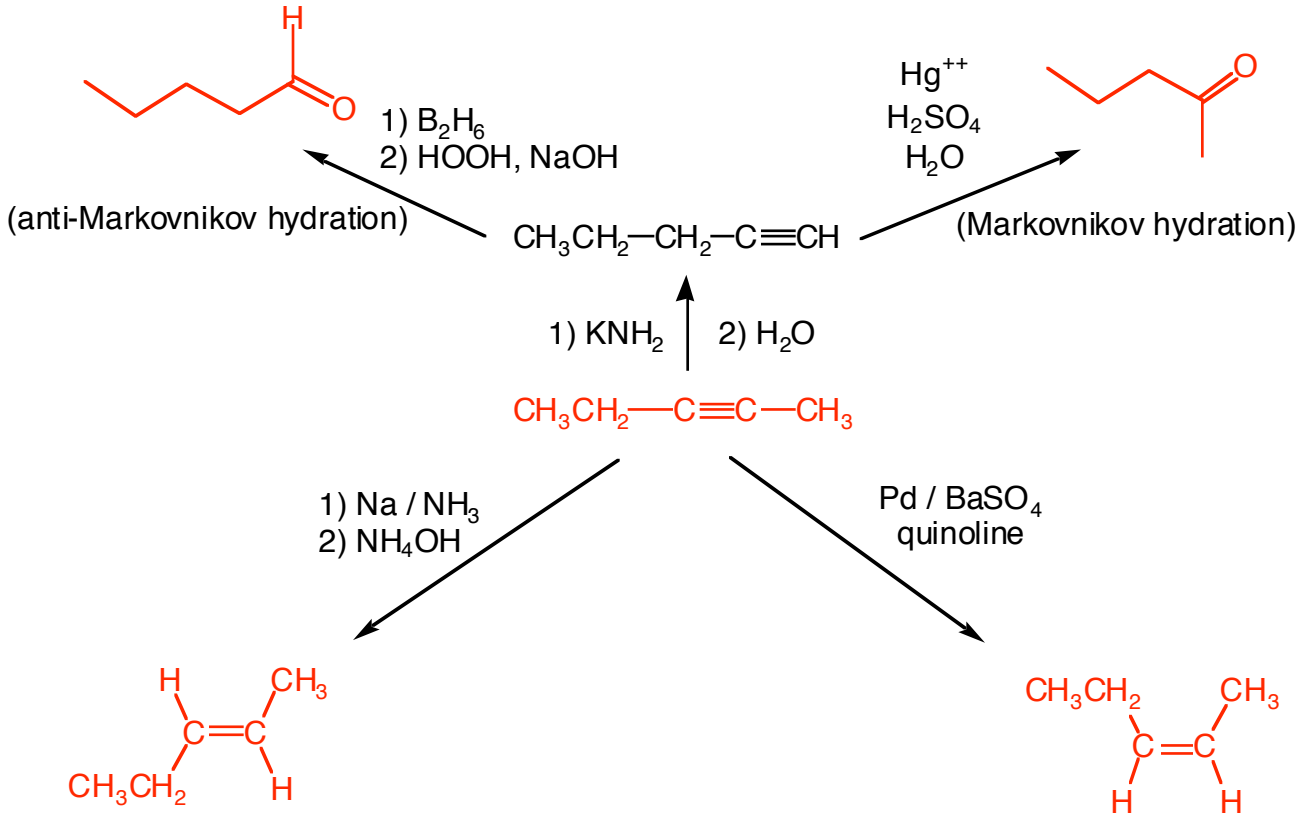
Chemistry 125 Sixth Examination Answer Key **March 3, 2003**

Average Score : 61.3 1/3 of scores greater than 70 ; 2/3 greater than 55

1. (8 min) Show how one may transform 2-pentyne in the center of the following diagram into each of the four molecules in the corners of the diagram in high yield. Just give reagents, not mechanisms, but if more than one reaction is necessary, show the structure of stable intermediate molecule(s).



Note that hydration of the 2-pentyne (whether Markovnikov or anti-Markovnikov) would give a regiochemical mixture of products, but if the alkyne is first isomerized to 1-pentyne (by use of very strong amide base, KAPA would be fine) then each type of hydration gives a single enol and a specific carbonyl compound.

Reduction must be stereospecific, either *anti* (via vinyl radical and anion) or *syn* (using a poisoned catalyst to avoid hydrogenation of the Z-alkene product).

If you did poorly on this question, you probably need more work on reaction/synthesis problems.

2. (3 min) Explain how you would use **BOTH PMR and CMR** spectroscopies to distinguish between the isomeric **alkenes** at the bottom of the diagram in Question 1. Don't explain the entire spectra, just mention one feature in each spectrum that allows reliable discrimination between the molecules.

PMR: Coupling between vinyl protons across the C=C double bond is larger when the protons are anti (about 14 Hz) than when they are cis (about 8 Hz). [In fact this difference may be difficult to determine because the chemical shifts of the vinyl protons will be very similar and there will also be splitting by other protons yielding very complex spectra. The chloroacrylonitriles of Figs. 13.34-35 in the text were carefully chosen to give atypically simple spectra.]

CMR: The steric gamma effect will make the crowded methyl group of the Z-isomer come at higher field (smaller chemical shift from TMS about 11 ppm) that the corresponding methyl carbon of the E-isomer

(about 17 ppm). [CMR will be preferable to PMR for making this distinction, because the proton-decoupled spectrum will be show sharp single peaks for the two different methyl groups.]

3. (3 min) Explain the role of oxygen in **BOLD** imaging.

BOLD stands for Blood Oxygen-Level Dependent Magnetic Resonance Imaging.

Because molecular oxygen is magnetic, it is able to interact with the nuclear spins of the protons in water to help maintain (or restore) Boltzmann equilibrium, that is, it can speed the relaxation of high-energy protons to the low-energy orientation when light absorption has begun to equalize the two populations. Thus when a region of the brain becomes active and is increasingly supplied by oxygen-rich blood, the water in this blood will have faster relaxation (and a stronger saturated signal) that water in typical blood.

By using an inhomegeneous magnetic field, and comparing the relaxation times of water at different precession frequencies before and during a certain brain activity, one can discover where that activity is localized.

4. (5 min) Explain why neither HCl nor HI can give the kind of anti-Markovnikov addition to alkenes that is sometimes observed for HBr.

Anti-Markovnikov addition proceeds by a free-radical chain reaction. The two propagation steps for this chain are:

1)Addition of halogen atom, X, to the double bond of the alkene giving a beta-halo alkyl radical, and

2)Abstraction of an hydrogen atom (not just a proton, an electron too) from HX by the alkyl radical to complete the addition of HX to the alkene and regenerate an halogen atom to begin step 1 again.

For the chani reaction to be important **both of these reactions must be fast.** If **either** of them is very slow, the radicals waiting to react will find one another and couple to terminate the radical chain. Under these conditions Markovnikov electrophilic addition will predominate.

For X = Br both reactions steps are exothermic and rapid. In the first step the new C-Br bond (68 kcal/mole) is stronger than the “second” C-C bond lost from the double bond of the alkene (63 kcal/mole), and in the second the new C-H bond (about 98 kcal/mole) is stronger than the H-Br bond lost (87 kcal/mole).

For X = Cl, the second step is endothermic and slow because of the necessity of breaking the strong H-Cl bond (103 kcall/mole).

For X = I, the first step is endothermic and slow because the new C-I bond (52 kcal/mole) is weaker that the “second” C-C bond being lost.

Thus only with H-Br are both steps rapid and the chain mechanism important.

5. (4 min) Explain mechanistically how adding CCl_4 during polymerization of vinyl chloride influences the structure of the polymer.

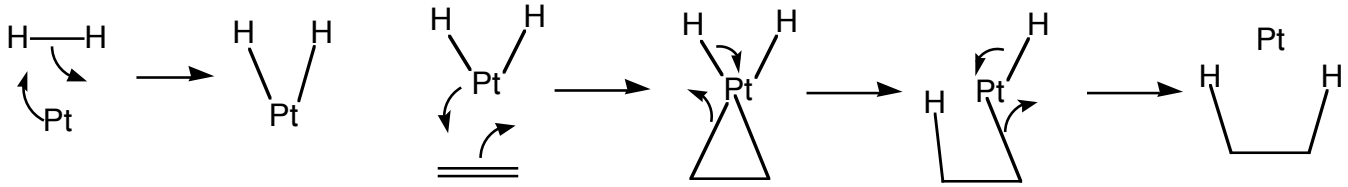
CCl_4, like $HCCl_3$, is a chain-transfer agent that shortens polymer molecules without terminating the free-radical chain process.

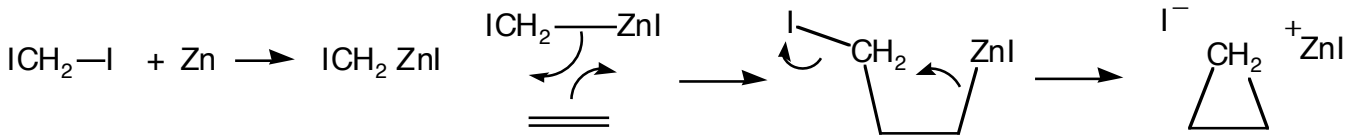
The radical carbon at the end of a growing R-CH_2-CHCl chain abstracts an atom, Cl from CCl_4, or H from $HCCl_3$ [notice these are atoms, not ions], to cap the molecular chain.

The resulting $\bullet CCl_3$ radical attacks the CH_2 group of a vinyl chloride molecule to sustain the chain reaction and begin a new molecular chain.

[A number of people mentioned the tacticity of the polymer chain, which is not relevant to the role of the chain transfer agent.]

6. (5 min) Draw the multistep mechanism for **ONE** of the following two processes:
Hydrogenation of an alkene with Pt catalysis **OR** Cyclopropanation of an alkene with CH_2I_2 and Zn(Cu)

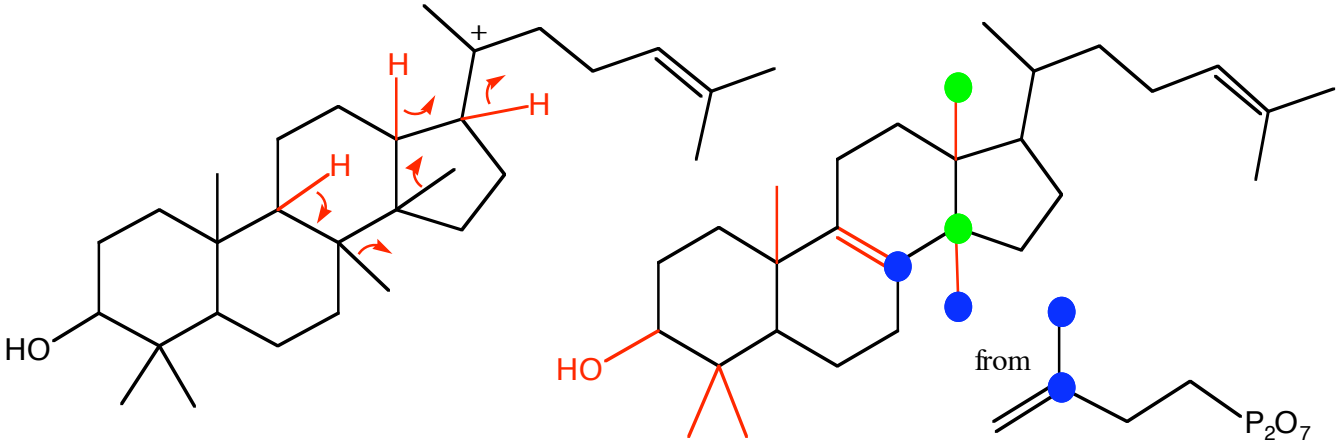




Curved arrows must make sense in terms of electron-pair motion resulting from HOMO/LUMO interaction.

[Both of these mechanisms are illustrated in the course web page on "Nucleophilic Participation During Electrophilic Addition to Alkenes" .]

7. (5 min) This cation below left is an intermediate in the synthesis of lanosterol from isopentenyl pyrophosphate. **Elaborate the diagram** (include **curved arrows**) to show the multistage rearrangement that happens next, **and complete the structure on the right** to show its **product**. Mention in a couple sentences experimental evidence consistent with your mechanism.

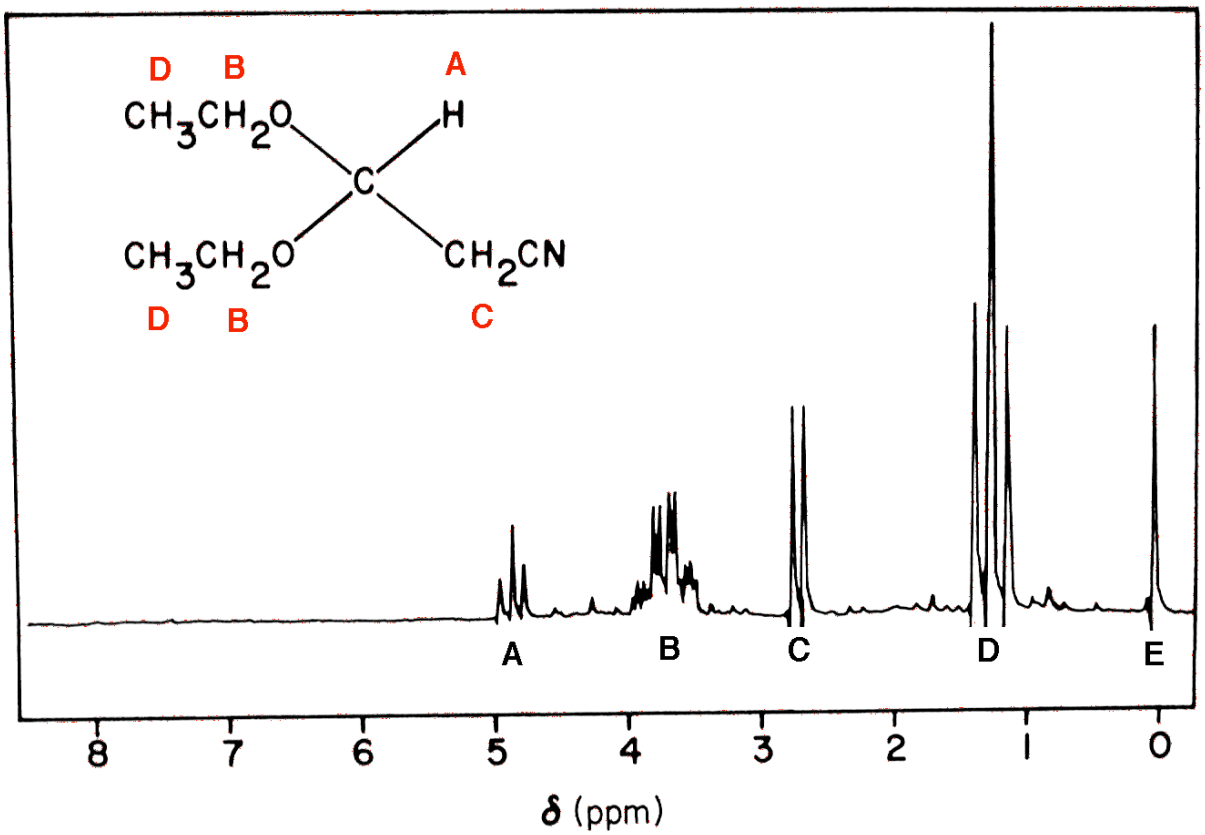


[Too many answers included random curved arrows that did not denote electrons moving from one bond to establish a new bond involving a site that formerly housed the low LUMO of a cation. Consider carefully where each curved arrow starts and ends in the above diagram. Note, for example, how the arrows denoting the initial hydride shifts differ from the one denoting the ultimate proton loss .]

Carrying out the biosynthesis beginning with a sample of **dilute double C-13 labeled** isopentenyl pyrophosphate shows which pairs of bonded carbons maintain their bond from starting material to product. The **double** label is so that the strong C-13 peaks will show doublet spin-spin splitting in the proton-decoupled CMR spectrum when initially labeled carbons remain bonded to one another. The labeled molecules are **dilute** so that C-13s will not likely be bonded to other C-13s if they did not come from the same individual molecule. The two methide shifts in the above mechanism predict, correctly, that the CMR signals for the rearranged methyl groups (and for the carbons from which they migrated) will appear as singlets in the

proton-decoupled spectrum of lanosterol. The blue dots in the above structure show a pair of C-13 that no longer split one another because they are no longer directly bonded. So do the green dots.

8. The following is one of the most embarrassing NMR spectra of all time. It was published in 1982 in a paper whose author list included a Chemistry Nobel Laureate (who may not have played a very big role in writing the paper). The spectrum was captioned "Figure 1. Proton magnetic resonance spectrum of 3,3-diethoxypropanenitrile showing the existence of the two conformers." The **paper contended** that unexpected doubling of some of the peaks in the spectrum showed that the molecule existed as a mixture of **two different conformational isomers**.



A) (8 min) Each significant signal in the spectrum is labeled with a letter. **Write the appropriate letter above each proton** (or group of protons) in the structural diagram.

In a few words explain the **size, position, and multiplicity** of each of these signals:

A Size: 1 H Position: shifted downfield by electron withdrawal of two oxygens on C

Multiplicity: 1:2:1 triplet split by two "C" protons on next adjacent carbon

B Size: 4 H Position: shifted downfield by electron withdrawal of one oxygens on C

Multiplicity: 1:3:3:1 quartet split by three "D" protons on next adjacent carbon (also "unexpected doubling", meaning that thepattern is more complex that a simple quartet, each line of which is at least doubled.)

C Size: 2 H Position: shifted downfield by electron withdrawal of cyano group (maybe by diamagnetic anisotropy of this group as well)

Multiplicity: 1:1 doublet split by the "A" proton on next adjacent carbon

D Size: 6 H Position: normal 1-2 ppm for methyl group of alkane

Multiplicity: 1:2:1 triplet split by two "B" protons on next adjacent carbon

E Size: from a separate molecule, TMS, added as reference for chemical shift, thus size of peak depends relative to those of the sample depends on how much TMS was used (not much)

Position: Reference of ppm scale – rather high field because Si on which methyls are attached is less electronegative than carbon.

Multiplicity: Singlet – all methyl protons equivalent

B) (1 min) Which of the five patterns has the **"unexpected doubling"** that suggested the existence of two conformers to the authors? **B** (see above)

C) (2 min) The spectrum was measured at room temperature with a 60 MHz spectrometer. What is the approximate magnitude of the "unexpected" doubling in Hz?

The scale at the bottom of the spectrum is in parts per million (ppm). One ppm of 60 MHz is 60 Hz. The unexplained doubling separates peaks by a small fraction (less than 1/10) of 60 Hz, perhaps 2 or 3 Hz.

Another point of comparison is the splitting of the methyl triplet, which is normally about 7 Hz. The doublet splitting in B is a little less than half of this value, so again about 2-3 Hz.

D) (4 min) If the authors were correct, what could one say about the **rate of interconversion** of the two proposed conformational isomers from having observed this doubling, and what would this say about the **barrier** (kcal/mole) to interconversion?

If there are two conformational isomers, each giving one of the quartets which overlap to give the doubling of the quartet, they must be interconverting slowly enough that the peaks for each conformer remain sharp.

Remember that broadening and coalescence occur when the frequency of interconversion is comparable to the frequency separation of the corresponding peaks in the spectrum. Since the separation of the peaks is a few Hz (see part C), that is a few per second, the frequency of interconversion must be much less than 1 per second if the peaks are to remain sharp rather than broadening and coalescing to a single average peak.

So the **rate constant, k, for the conformational isomerization must be less than 1/sec**.

How high a barrier would give a k of 1/sec?

Remember that k ~ 10^13 /sec * 10^-3/4 * barrier

If k ~ 1/sec, then 10^13 is about equal to 10^3/4 * barrier

Or barrier ~ 4/3 * 13 = 17 kcal / mole

Since the rate is slower than 1/sec, **the barrier must be greater than 17 kcal/mole**.

[This is what makes the claim of conformational isomerism so ludicrous. In such simple molecules barriers to conformational change (e.g. anti- to gauche-butane) are only 3 kcal/mole or so, 5 or 6 times smaller than what would be necessary to explain this doubling in terms of slow interconversion. Even the chair-chair flip of cyclohexane, which you will remember requires substantial bond angle deformation, has a barrier of only about 11 kcal/mole (measured by NMR).]

E) (2 min, Hard question for little credit) Suggest a more probable interpretation of the doubling based on **stereotopicity** relationship between the two protons within each of this compound's methylene groups.

The two hydrogens on the CH_2 group adjacent to CN (the ones labeled "C") are enantiotopic. One can imagine a mirror plane passing through H-C-C-CN on the right of the molecule, and each of these two protons lies in one of these mirror-image environments. Since these hydrogens are enenatiotopic, they have the same chemical shift and their magnetic interaction does not influence the spectrum observed ("they do not split one another"). The only splitting is by the lone proton ("A") which splits the "C" signal into a clean doublet.

By contrast, there is no mirror plane that would pass through the carbon and oxygen atoms of one ethoxy group (C-C-O-C), so the protons of its CH_2 group do not have mirror image environments, they are **diastereotopic**, just plain different in environment. (The same is true for the other CH_2 group.) One trick for seeing that they are diastereotopic is to name the configuration that would result by promoting the priority of

one (or the other) of the two hydrogens of the CH_2 group. Doing so would not only make the CH_2 carbon a chiral center**, it would also make the central carbon bearing two oxygens a chiral center** because the two ethyl groups would no longer be equivalent in priority. So diastereomers are involved. [Of course this is a subtle point – as the question warned.]

Since the ethoxy CH_2 protons are in different environments, they have slightly different chemical shifts – hence the "anomalous" doubling of the quartet "B". It is in fact **two quartets with slightly different chemical shifts.**