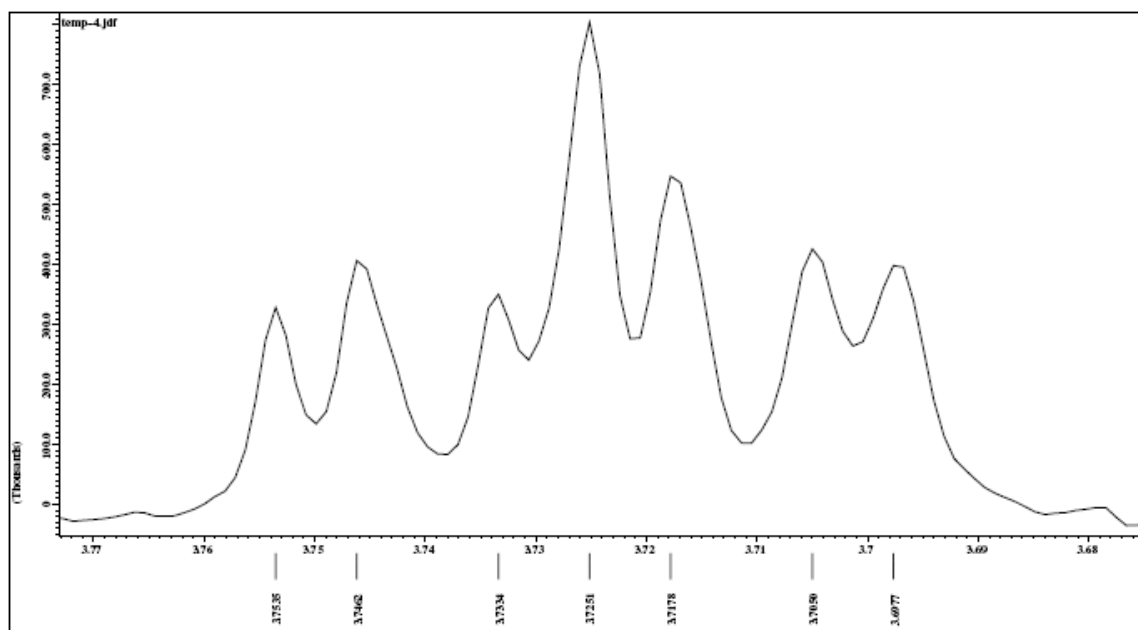
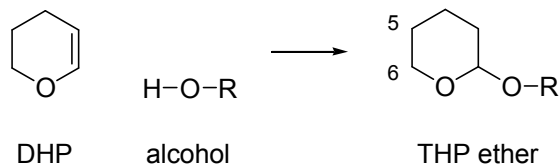


381 Homework Set
Due Monday, April 27, 2009

Name: _____

Write all your answers on a separate answer sheet. Clearly and fully label your answers.

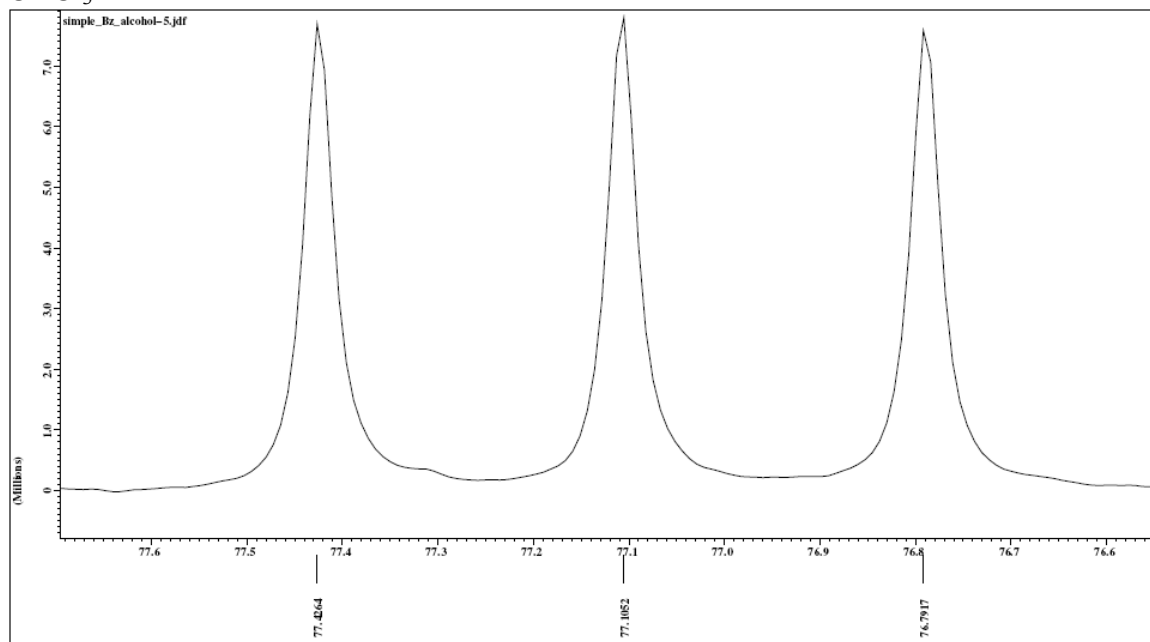
1. The THP group (THP = tetrahydropyranyl) is a common protecting group for alcohols. Such protected alcohols are called "THP ethers". The THP ethers are formed by reacting an alcohol with DHP (dihydropyran) in the presence of a catalytic amount of acid. THP ethers show very characteristic peaks in a ^1H NMR spectrum. One peak is shown below and corresponds to one of the hydrogens on C6 of the THP ring.



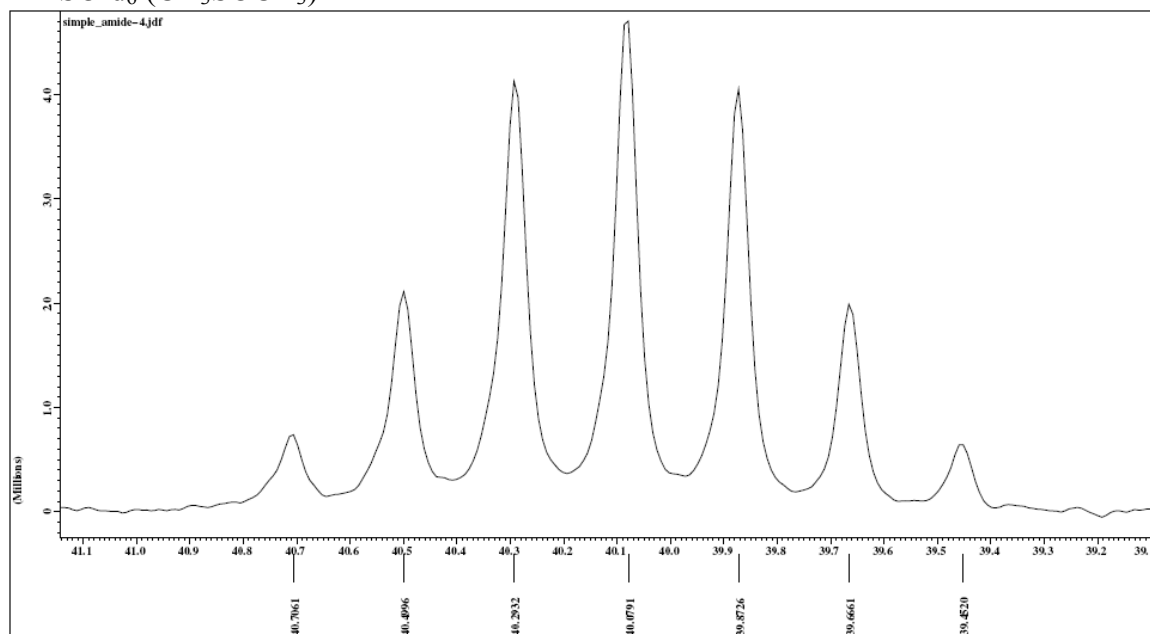
This peak shows complex splitting. One unfortunate feature of a THP group is that the two hydrogens on C6 are not identical. Because they are different, they split each other (called *geminal coupling*). Coupling constants for geminal protons are around 10-15 Hz. In total, each hydrogen on C6 has three coupling neighbors – two vicinal neighbors on C5, and a geminal neighbor on C6. With three neighbors, one would predict a splitting pattern of *ddd* (doublet of doublets of doublets). The pattern above is indeed a *ddd* with some overlapping. Determine the coupling constants for the various interactions. [The spectrum was recorded on a 400 MHz instrument.]

2. Hydrogen (^1H) has two possible spin values $+\frac{1}{2}$ and $-\frac{1}{2}$. Hydrogen (^1H) therefore splits a neighboring hydrogen into two lines of equal intensity. Deuterium (^2H) has a spin of +1 and therefore has three possible spin values $-1, 0, +1$. Deuterium (^2H) splits a neighbor into *three* lines of equal intensity. An example is the ^{13}C signal of CDCl_3 . The attached deuterium splits the carbon into a triplet – not a 1:2:1 triplet like we see in ^1H coupling, but a 1:1:1 triplet for ^2H coupling.

CDCl_3

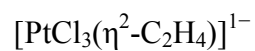
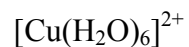
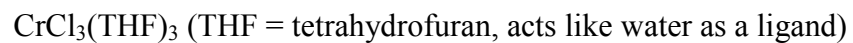
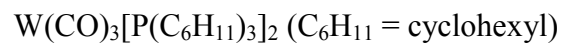


DMSO-d_6 (CD_3SOCD_3)

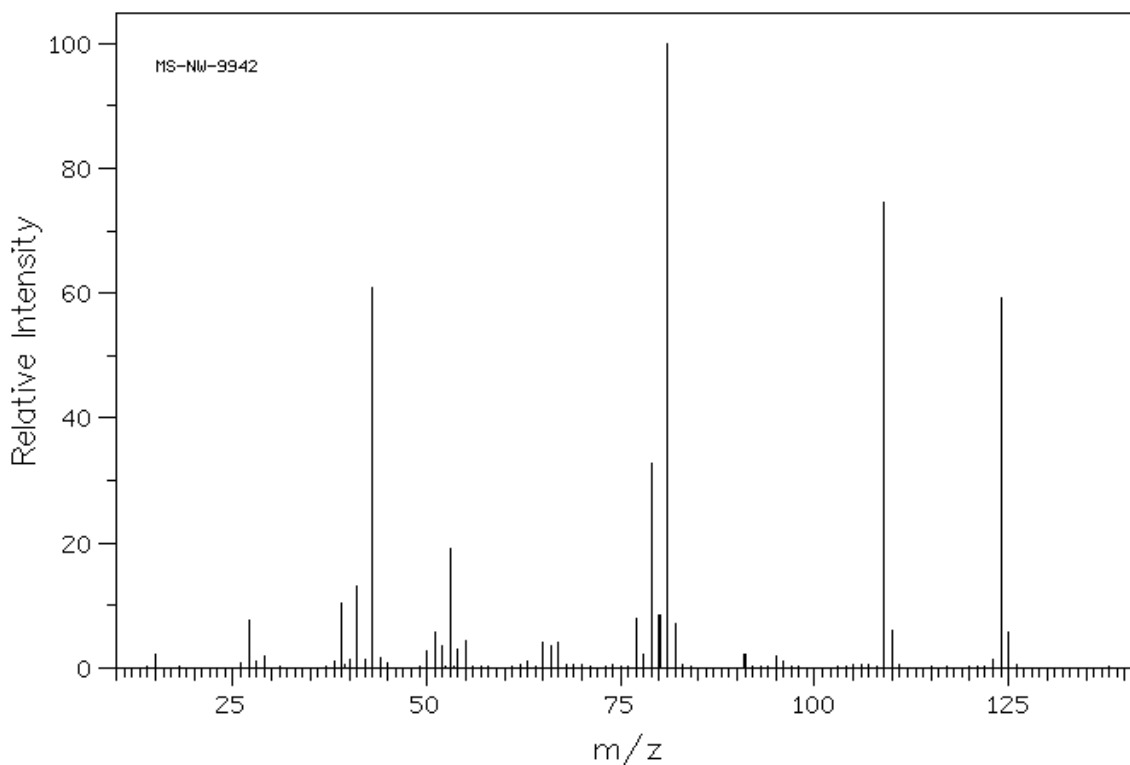


Based on the CDCl_3 spectrum, calculate the coupling constant between ^2H and ^{13}C . [The spectrum was recorded at 100 MHz.] DMSO-d_6 is much more complex. What would you predict for the splitting ratios for a CD_3 group in a ^{13}C spectrum. Show the splitting tree branching to justify your answer. Does the DMSO-d_6 spectrum fit your expectations?

3. Below are a number of transition metal complexes. Give a valence electron count for each of the complexes. For the octahedral complexes (those with six ligands), predict whether the complex is high or low field. Also, for the octahedral complexes draw out the *d*-orbitals and show the electronic configuration.



4. Acetylcyclohexene has the MS spectrum shown below. Show the structure of the parent ion (m/z 124), and provide a full mechanism (show all electron movement) to account for two of the fragments listed below. This molecule could go through a retro-Diels-Alder fragmentation. The retro-DA would give a fragment at m/z 96 ($M - 28$). Give a mechanism that accounts for this fragment. [Remember that almost *all* identifiable fragments arise from a single fragmentation. Do not propose mechanisms that involve the fragmentation of fragments. In other words, your fragmentation should occur in one step. Consult your notes and/or Wade.]

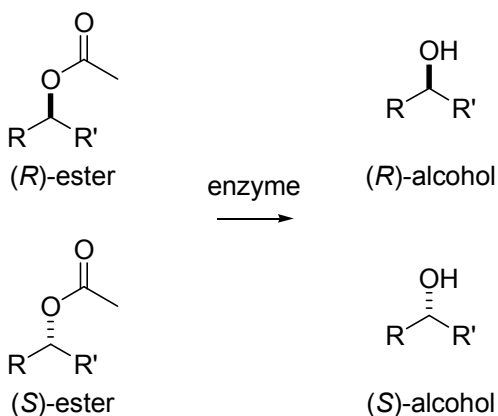


Peak data

m/z	rel. intensity
43	69
53	19
79	33
81	100
109	75
124	59

5. In a kinetic resolution, an enzyme preferentially reacts with one enantiomer over another. The result is a mixture of starting materials and products that are enantiomerically enriched. The enantiomeric excess (e.e.) of the starting materials and products depends on the selectivity of the enzyme (E value) and the degree of conversion of the reaction. A very crude way to determine the e.e. profile of a kinetic resolution is to artificially generate some data and plot the data with Excel. [A more proper way would be through calculus. What we are doing is like estimating the area under a curve as a series of rectangles – not perfect, but it can give some useful numbers.]

Our hypothetical reaction is shown below – hydrolysis of a racemic ester to an alcohol. The enzyme hydrolyzes the (R)-ester to the (R)-alcohol faster than the (S)-ester to the (S)-alcohol. The rate difference is the factor E . The rate of formation of the (S)-alcohol can be defined as the product of the rate constant of the enzyme for the (S)-ester (k_S) and the concentration of the (S)-ester ($[S]$) (Eq. 1). Multiplying both sides of Equation 1 gives the absolute change in $[S]$ ($\Delta[S]$) during over a time change of Δt (Equation 2). [This is an approximation. If we keep Δt very small, the error is not too bad.] The E value is the ratio of k_R to k_S (Eq. 3), so the change in $[R]$ can be expressed in terms of k_S (Eq. 4). This is all we need to generate our data.



$$\frac{d[S]}{dt} = k_S[S] = \text{rate of } [S] \text{ change} \quad (\text{Eq. 1})$$

$$\Delta[S] = k_S[S]\Delta t = \text{change in } [S] \quad (\text{Eq. 2})$$

$$E = k_R / k_S \quad (\text{Eq. 3})$$

$$\Delta[R] = k_R[R]\Delta t = k_S E[R]\Delta t = \text{change in } [R] \quad (\text{Eq. 4})$$

An Excel spreadsheet to the class contains a number of columns. The first is the E value of an enzyme (column A, value set as 2 for all cells). The next column is time (column B) and used to determine Δt between adjacent points. The percent conversion is next (column C). The starting concentrations of the (R)- and (S)-esters are both 0.5 (columns D and E). k_S is arbitrarily set at 0.01 (column G), so k_R is 0.02 ($E \times k_S$) (column F). Once the starting concentrations are known with relative rate constants, $\Delta[R]$ and $\Delta[S]$ over a Δt interval can be calculated (columns H and I). The amounts of product (R)- and (S)-alcohols are given in columns J and K. Columns L and M give the percent e.e. of the unreacted (S)-ester and formed (R)-alcohol.

Using the Chart Wizard, one can create a scatter plot with the e.e. (y-axis) of the starting material and product against percent conversion (x-axis). Each of these plots will have two

series (lines), one for the alcohol (y-data: column L, x-data: column C) and another for the ester (y-data: column M, x-data: column C). The two-line graphs will resemble the graphs we drew free-hand in class when talking about kinetic resolution. The data included in the spreadsheet are for an enzyme with $E = 2$. Any E value may be used by changing all the values in column A to the desired value.

Generate **three** full-page graphs showing the product and starting material e.e. for enzymes with E values of 5, 10, and 25. Format each data series (two per graph) such that no data point markers are shown and the points are connected with smoothed lines. As always, make sure that your graphs are properly labeled. Using these graphs, answer the questions below.

- A. For all three graphs, the lines intersect at a common position on the x-axis. What is this position? For any one of your graphs, show mathematically that all the material is accounted for. [This is a conservation of mass question. Assume you have a mole of racemic starting ester. At the point of intersection on the x-axis, what is the percent conversion and e.e. of the product? How much (in moles) of each enantiomer of the alcohol must you have? Therefore, how much (in moles) of each enantiomer of the ester must be left?] Show your math and elaborate it with comments.
- B. A kinetic resolution can provide compounds with varying degrees of optical purity. If a chemist must have the (*R*)-alcohol (product) with an e.e. of 90%, what is the maximum percent yield possible for each of the three enzymes?
- C. Sometimes in a kinetic resolution, the enantiomer that reacts slower is the desired compound. If a chemist must have the (*S*)-ester with an e.e. of 90%, what is the maximum percent yield possible for each of the three enzymes.