**Final Exam**
Answer Key

Final Exam Mean: 131
Final Exam Median: 126
Final Exam St. Dev.:   28

> The printout of Susie's COSY spectrum that was in your exam, somehow, didn't print correctly; the diagonal that was supposed to stretch across the spectrum was broken up, and there were a couple of crosspeaks that didn't show. My hard copy, and the PDF copy that is now posted to the web, were fine. Unfortunately, I didn't notice the problem until after the exam was over. Because the problem affected everyone equally, and it was still fairly easy to figure out without this information, I decided to grade the problem normally.

1. Before assigning chemical shifts to specific protons, I thought it was helpful to look at Susie's target molecule and identify distinct types of protons that would appear in specific regions of the ^{1}H NMR spectrum. Molecule **3** has:

   - Three acetyl methyl groups, which should appear as singlets around δ = 2.1 ppm;
   - Three alkyl methyl groups which should appear as doublets (because all three have one proton neighbor) around δ = 1 ppm;
   - Four protons adjacent to amide nitrogen, which will show up downfield of a typical amine nitrogen, maybe δ = 3-3.5;
   - Five protons adjacent to ester oxygen, which will be waay downfield, maybe δ = 4-5 ppm;
   - Two α-keto protons, maybe close to the three acetyl methyl groups;
   - And six inequivalent alkyl protons that are coupled to a lot of neighbors, and will probably look like a mess.

   Susie's NMR spectrum has all of these things, and we can use both chemical shift and coupling partners to identify most of them quickly. The 9 acetyl protons don't couple to anything, and appear at δ = 2.05, 2.06 and 2.08 ppm; the integral on the right side of this peak group makes it clear there's a 1H multiplet hiding underneath them, so we'll have to watch out for that. The three alkyl methyl doublets are at $\delta \approx$ 0.89 (x2) and 0.94 ppm (x1). Each of these has just one coupling partner, and the COSY spectrum makes it very clear which is coupled to which; the two upfield doublets are both coupled to a multiplet at δ = 1.81 ppm, and the one downfield doublet is coupled to the multiplet that's buried under the acetyl groups. (See closeup on the next page.) This can only happen if H(7) and H(8) are at both at δ = 0.89, and H(9) is at δ = 0.94. We can assign H(2) and H(6) to the coupling partners of these. So, so far we've got

| proton	δ (ppm)
H(2)	2.01-2.02
H(6)	1.81
H(7)	0.88
H(8)	0.89
H(9)	0.93
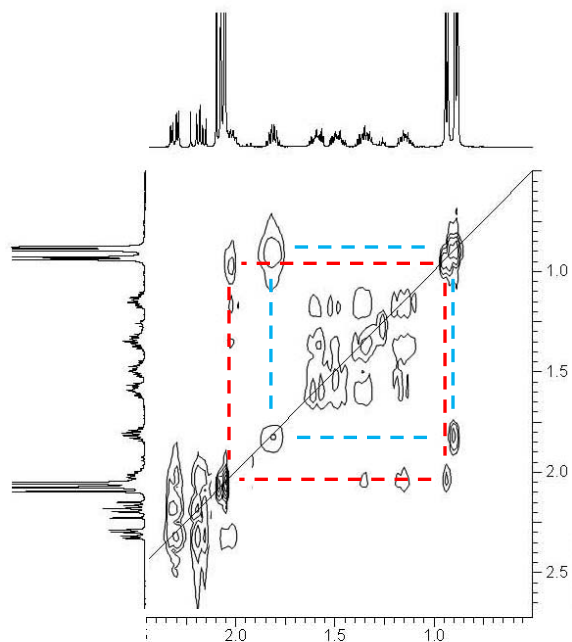
The multiplet at δ = 1.81 shows a COSY crosspeak to the multiplet at δ = 4.71, which should be H(5), the farthest-downfield of the three α-oxygen atoms. We can walk from there to the two multiplets at δ = 1.59 and 1.50, which must be the two H(4) protons. Those are coupled in the big brick of COSY crosspeaks to H(3) at δ = 1.35 and 1.14.

Only thing we're missing from the chart is the two H(1) protons. Some missing crosspeaks in the printout made these a little more difficult to find than they should have been, but the only protons with the right chemical shift and the right splitting pattern (doublet of doublet for each) are at δ = 2.31 and 2.17. And that completes our chart (next page).

Rubric: 4 points each box.

proton	δ (ppm)
H(1)	2.31
[x2]	2.17
H(2)	2.01-2.02
H(3)	1.35
[x2]	1.14
H(4)	1.59
[x2]	1.50
H(5)	4.71

④ each.
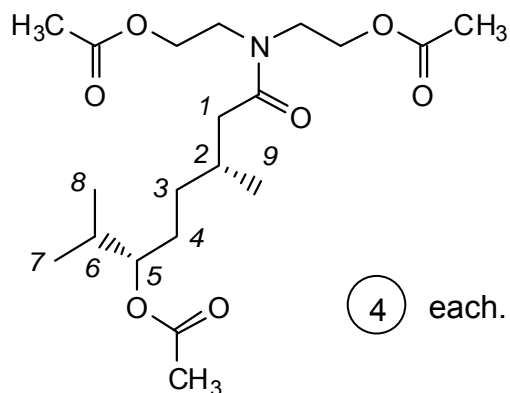
| H(6)	1.81
H(7)	0.88
H(8)	0.89
H(9)	0.93

2. Out of the two multiplets I assigned, resolution enhancement in the first one actually obscured information; there were small peaks on the left and right edges of the multiplet that actually disappeared when the multiplet was resolution enhanced. So we didn't grade the first multiplet—everyone got 16 points automatically for the first box.

The second multiplet was more straightforward.

coupling constants (Hz)
4.9
8.8
11.7
13.7

④ each.
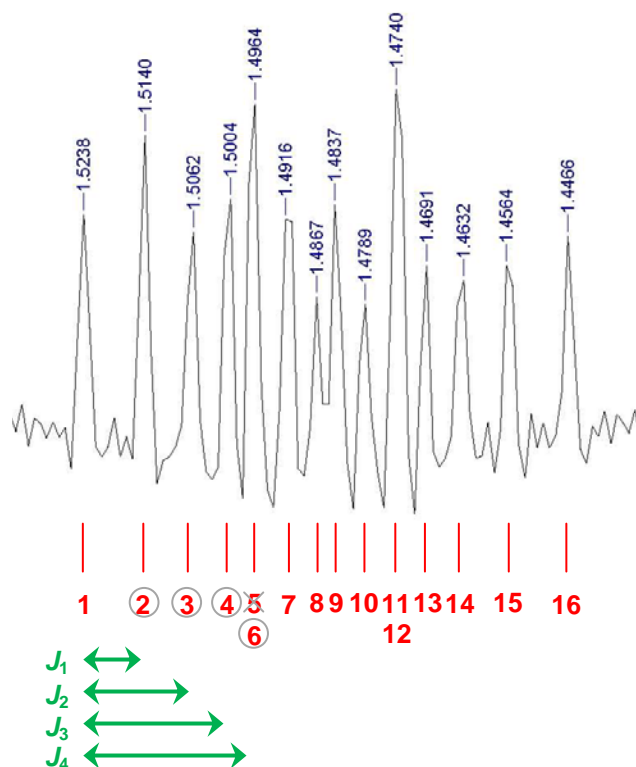
3. Susie took an IR spectrum of her product, shown below. What functional groups are responsible for each of the peaks labeled on the spectrum?
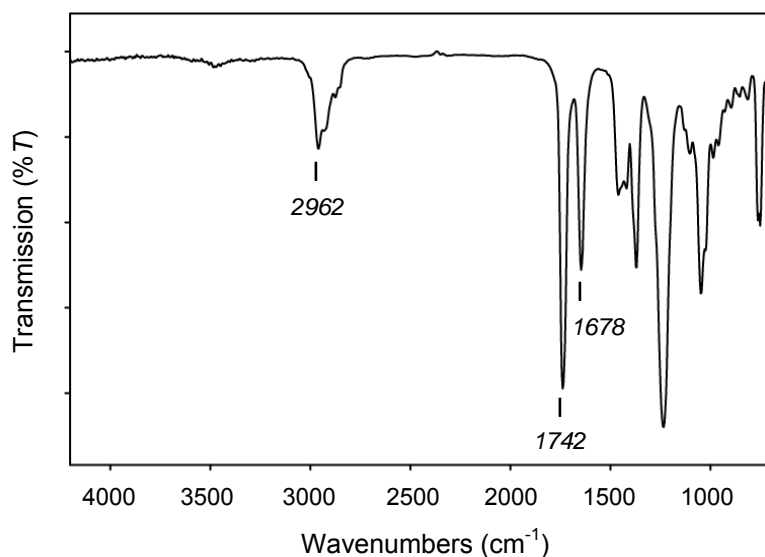
functional group

ν = 2962 cm^{-1}

sp^3 C-H   (3)

ν = 1742 cm^{-1}

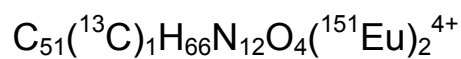ester C=O   (3)

ν = 1678 cm^{-1}

amide C=O   (3)

4. Susie attempted to do EI-MS using the Hoye lab GC/MS instrument, but she observed only fragments, and not the expected parent mass. Reducing the electron beam voltage did not solve this problem. What other MS technique might she use, on the same instrument, to better observe the parent mass? (Just name the technique, no need to describe it.)
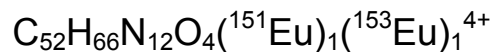
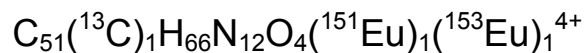chemical ionization (CI) MS   (4)

5.

m/z = 306.34: $C_{51}(^{13}C)_1H_{66}N_{12}O_4(^{151}Eu)_2^{4+}$ (3)

m/z = 306.59: $C_{52}H_{66}N_{12}O_4(^{151}Eu)_1(^{153}Eu)_1^{4+}$ (3)

m/z = 306.85: $C_{51}(^{13}C)_1H_{66}N_{12}O_4(^{151}Eu)_1(^{153}Eu)_1^{4+}$ (3)

6. If Prof. Lisowski had performed an ion mobility spectrometry experiment on his reaction mixture using a drift cell, would you expect the dimer to emerge from the collision cell

          earlier,   **later,** ③   *or*   **at the same time**   (*circle one*)

compared to the monomer starting material?

7. The product Eu complex was fluorescent. Would you expect the wavelength of maximum fluorescence intensity ($\lambda_{max,fl}$) to be

        greater than, ③   **less than,**   *or*   **equal to**   (*circle one*)

the wavelength of maximum absorbance ($\lambda_{max,abs}$)?

8. ^1H NMR, ^1H-^1H COSY, ^1H-^1H NOESY, and ^1H-^{13}C HMQC spectra of Dr. Lisowski's reaction product, dissolved in D_2O, are attached to the back of this exam. Many of the ^1H chemical shifts in the complex are far downfield of where you would expect them, based on functionality and chemical shift tables alone. Why?

> Dr. Lisowski's complex is very similar to the europium-based "chemical shift reagents" we discussed in class; europium is paramagnetic, and has strong shielding effects on nearby protons.

    Rubric: *6 points total.*
       3 points for mentioning europium.
       3 points for either stating that Eu is paramagnetic, or analogy to chemical shift reagents.

9. Clearly, a challenging problem. Here, you didn't have the advantage of using typical chemical shifts or coupling constants to assign protons; all you had here was 2D NMR. COSY shows direct ^1H-^1H coupling. What kind of ^1H-^1H coupling should we expect to see in Lisowski's complex? There are basically three coupled groups of NMR-active protons in the molecule:

- The 10 diaminocyclohexane protons, which should couple with each other a lot, and could look like a mess by COSY;
- The 3 aryl protons, which should form a simple coupled set B1-A-B2;
- The 2 imine protons C1 and C2, which are all alone. These shouldn't couple to anything.

Ordinarily, I would recommend looking at the COSY spectrum to try to identify obviously identifiable coupled partners—say, an alkane proton coupled to an alkene proton. But here, we don't know the correlation between functional group and chemical shift, so that approach won't work. Instead, I think the best approach was to start looking in the COSY for protons that had few or no coupling partners:
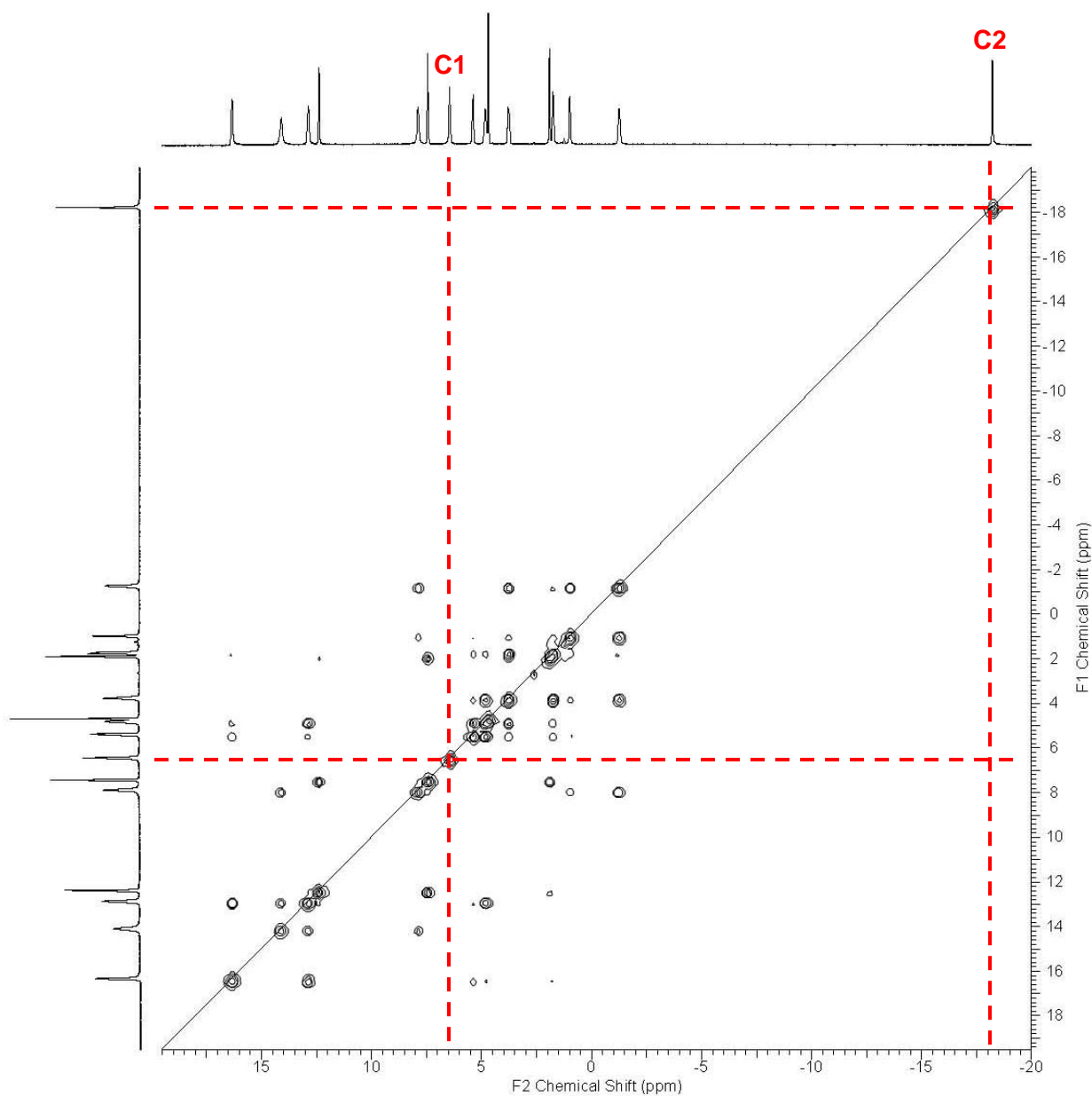
For example, the red lines illustrate peaks in the 1D spectrum that have no crosspeaks in the 2D spectrum. These must be H_{C1} and H_{C2}. In addition, because the problem said that a nearby Eu-OH shifts peaks upfield, we can deduce that H_{C2}, which sits on the Eu-OH axis, must be the resonance at δ = -18.15 ppm, and H_{C1} must be at δ = 6.50 ppm.

The set B1-A-B2 should be coupled to each other, but to no other protons. So, in the COSY, we should see a set of three coupled resonances that don't have any other partners. We can indeed see that in the COSY closeup:
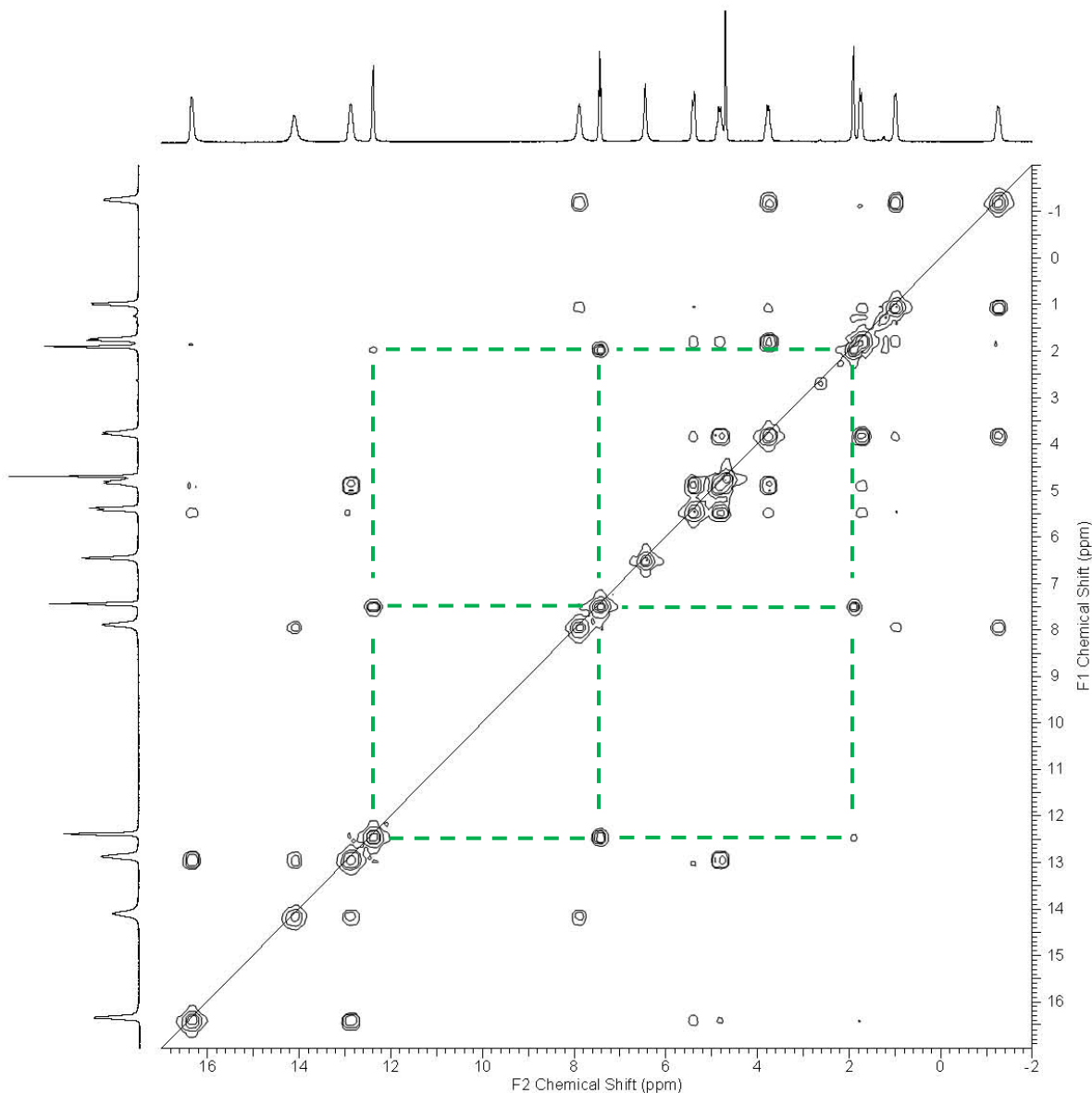
You can see this in green above. Ordinarily, you might imagine that H_{B1} and H_{B2} shouldn't show a COSY crosspeak, but large ^4J values (1-2 Hz) in aromatic systems are common, and the COSY peak is small. If you didn't find it in the COSY alone, another way to locate it was to see what was close to either H_{C1} or H_{C2} in the NOESY spectrum. Looking at the NOESY, H_{C2} shows NOE correlations with just three peaks, the most-upfield of which is H_{B2}.

In the COSY, lots of peaks in the upper right are coupled to one another, and lots of other peaks in the lower left are coupled to one another. Of the upper right peaks,

two show NOE correlations to the H$_{C2}$ that we've already identified: δ = -1.20, and δ = 1.04. In the structure of the complex, the protons that are closest in space are H$_{E2ax}$ and H$_{E2eq}$. (I think H$_{D2}$ is farther than either of these to H$_{C2}$.) So I tentatively assigned these to H$_{E2ax}$ and H$_{E2eq}$. In the COSY, one of these two protons has very strong correlations with other neighbors, and the other has weak correlations; I took this to mean that one was an axial E2 proton, with lots of 180° dihedral angles and large coupling constants with other protons, and the other was an equatorial E2 proton, with weaker correlations and smaller coupling constants.
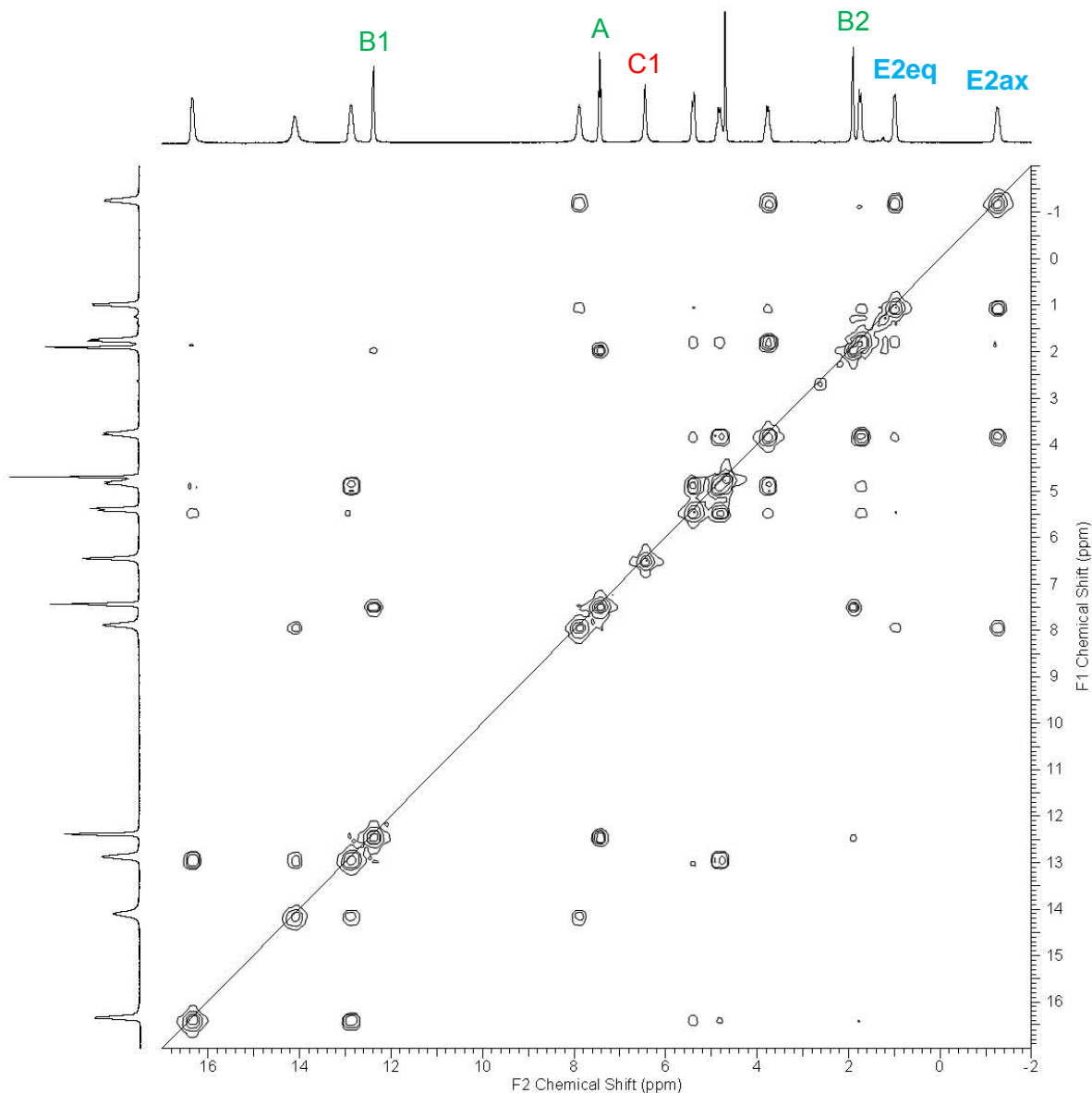

H$_{E2eq}$ and H$_{E2ax}$ are coupled to each other, and mutually coupled to two other protons. One of these two other protons is coupled to just one other partner, while the other is coupled to multiple other partners. The proton with just one other partner

should be H_{D2} (and its one other partner should be H_{D1}). The proton with multiple partners should be one of the H_{F2} protons.
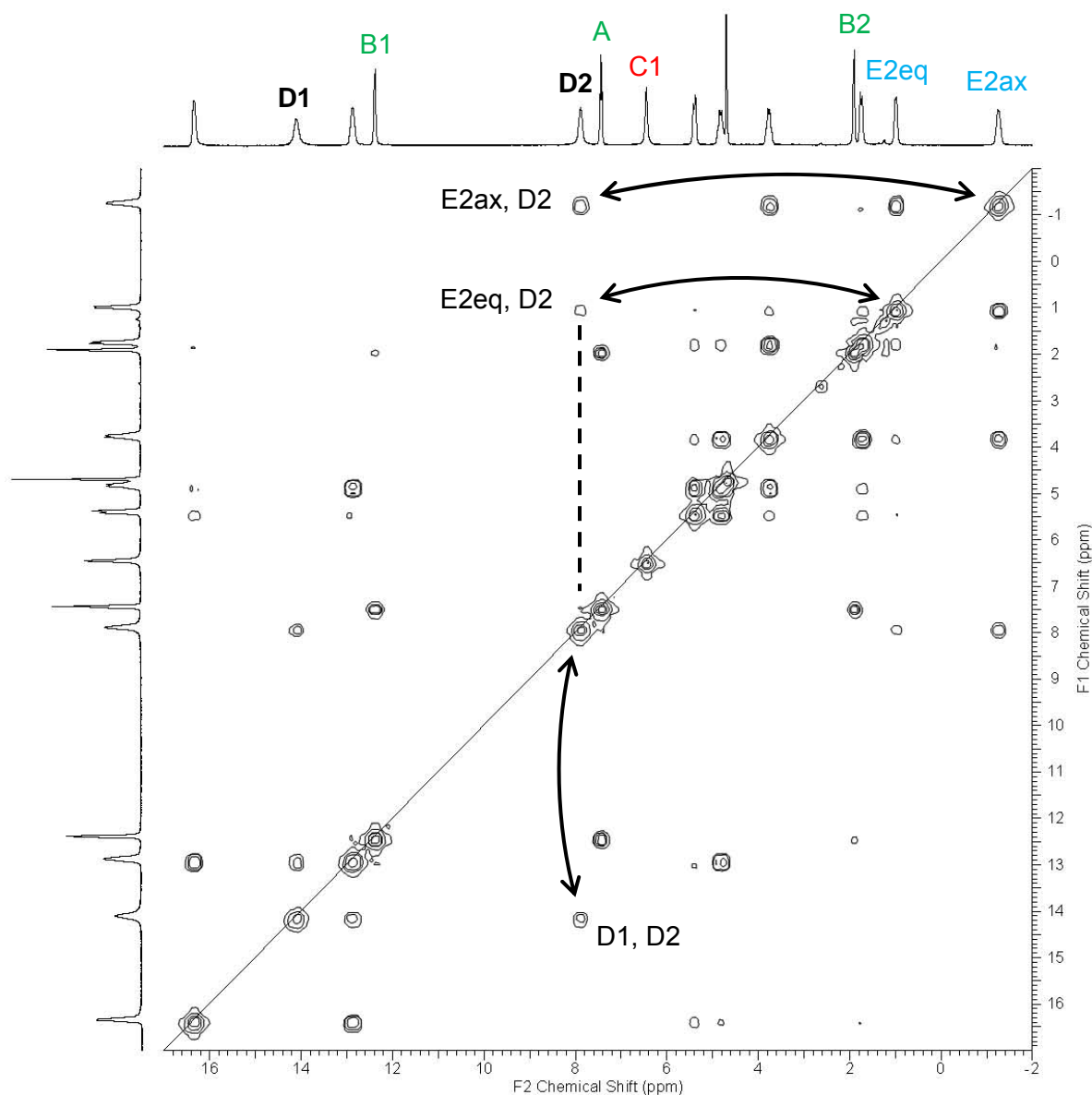

So far, all of these assignments are consistent with the HMQC spectrum; out of all of the protons we've assigned, the HMQC doesn't show any of them attached to the same carbon as another proton, except for the H_{E2eq}-H_{E2ax} pair. There is another HMQC pair that couples to H_{E2eq} and H_{E2ax} in the COSY, that must be neighbors to H_{E2eq} and H_{E2ax}, so these must be H_{F2eq} and H_{F2ax}.
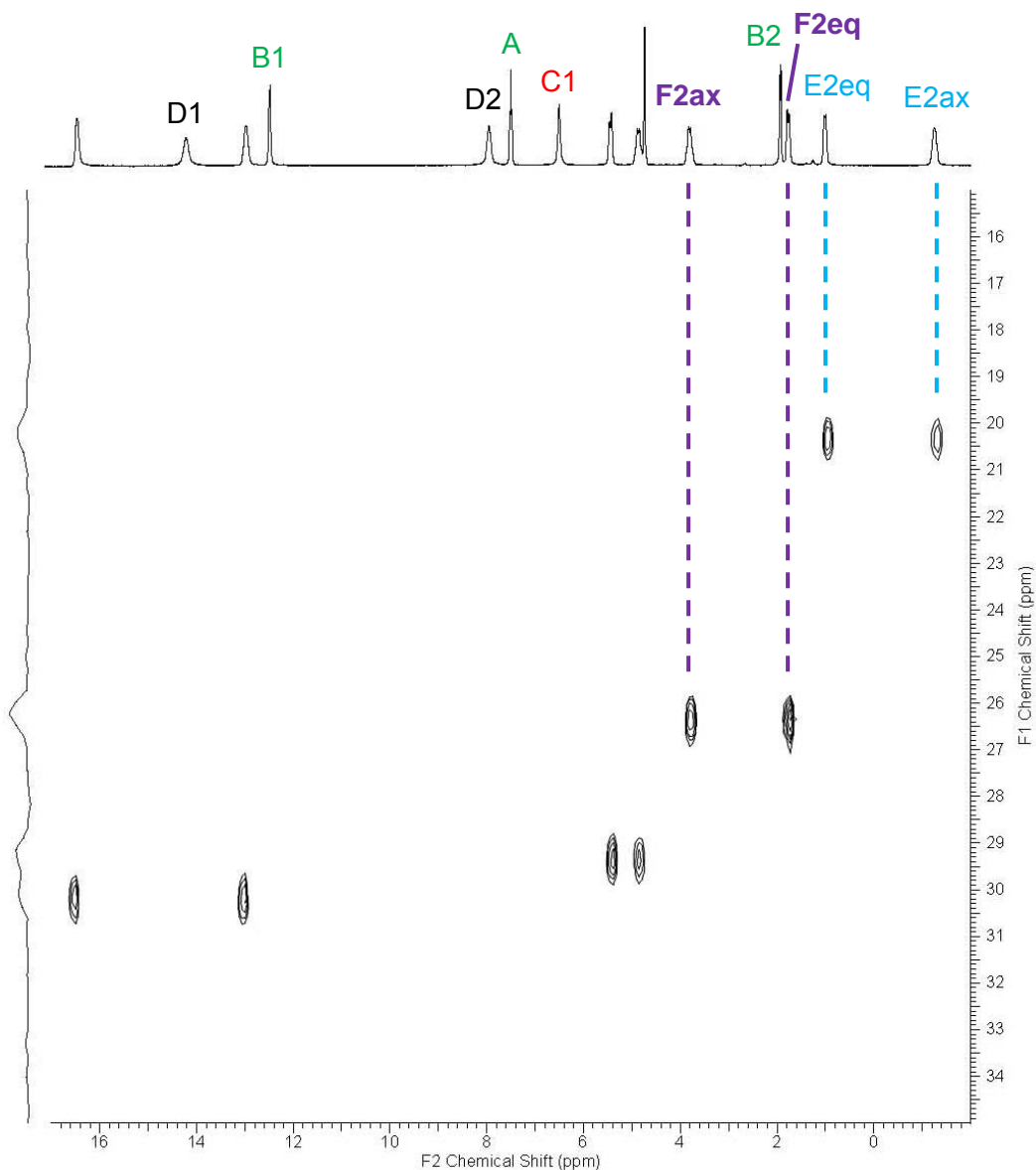
I've labeled the downfield F2 proton "F2ax" because it shows a strong crosspeak with H_{E2ax} (and has the optimal 180° dihedral angle for coupling), and the upfield proton "F2eq" because it shows weak coupling to H_{E2ax}.

That does it for the "2" series of protons, and all we're left with now are a bunch of downfield protons, which must correspond to the "1" series. H_{D1} couples to just one proton other than H_{D2} in the COSY spectrum, and we can assume that's H_{E1ax} (again with the 180° dihedral angle). The HMQC tells us where the other E1eq proton is. That leaves us with the two F1 protons to assign; H_{E1ax} will couple most strongly to H_{F1ax} in the COSY, and the weaker COSY crosspeaks belong to H_{F1eq}. So, putting that all together,
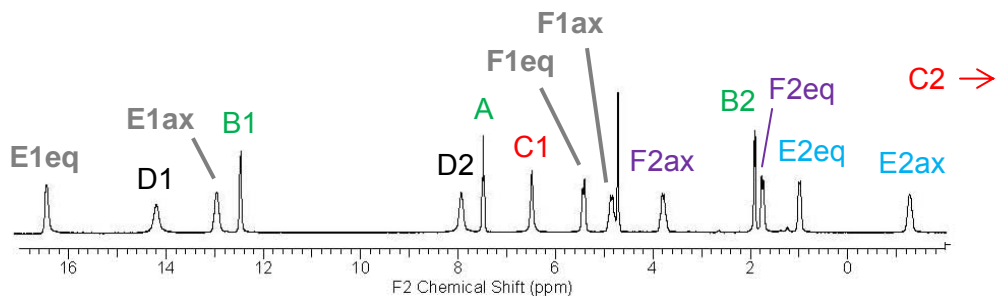
proton	δ (ppm)
H$_A$	7.50
H$_{B1}$	12.44
H$_{B2}$	1.96
H$_{C1}$	6.50
H$_{C2}$	-18.15

proton	δ (ppm)
H$_{D1}$	14.16
H$_{D2}$	7.94
H$_{E1eq}$	16.40
H$_{E1ax}$	12.93
H$_{E2eq}$	1.04

proton	δ (ppm)
H$_{E2ax}$	-1.20
H$_{F1eq}$	5.45
H$_{F1ax}$	4.88
H$_{F2eq}$	1.80
H$_{F2ax}$	3.82

(4) each.

Rubric: *60 points total.*
  4 points each box.
    2 points partial for each assignment to an incorrect ax/eq position, but otherwise correct.
   *2 points partial for each assignment to incorrect sets "1" or "2", but otherwise correct.*
    1 point partial, per box, for switching all "E" and "F" sets. Switch must be complete.
  Alternately, if all but 1 or 2 "1" and "2" assignment is switched,
  3 points each box.
    2 points partial for each assignment to an incorrect ax/eq position, but otherwise correct.

10. In the COSY, there are a few very tiny crosspeaks that aren't explained in the answer to problem 9:
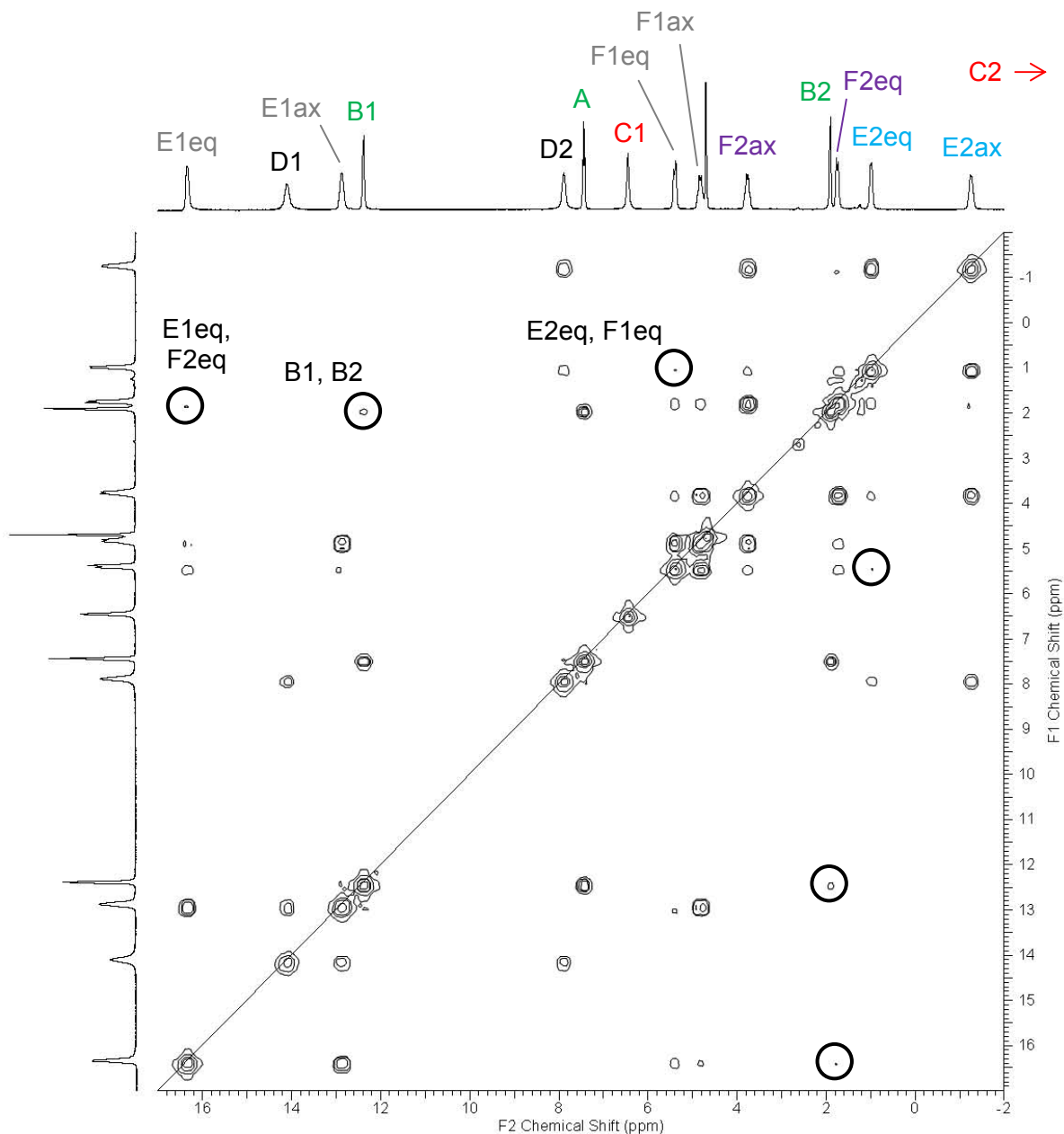
All three of these are 4-bond (^4J) couplings, and they are strong enough to be observed in the COSY because they have the characteristic, optimal "W" arrangement of atoms in the 4 bonds. (This is sometimes called "W-coupling" for this reason.)

Incorrect answers to problem 9 may have led you to incorrect answers to this problem. Because it was possible to judge whether the geometries in these answers

were good or not, we did not offer partial credit for answers that had non-"W" arrangements but were consistent with your answers to problem 9.
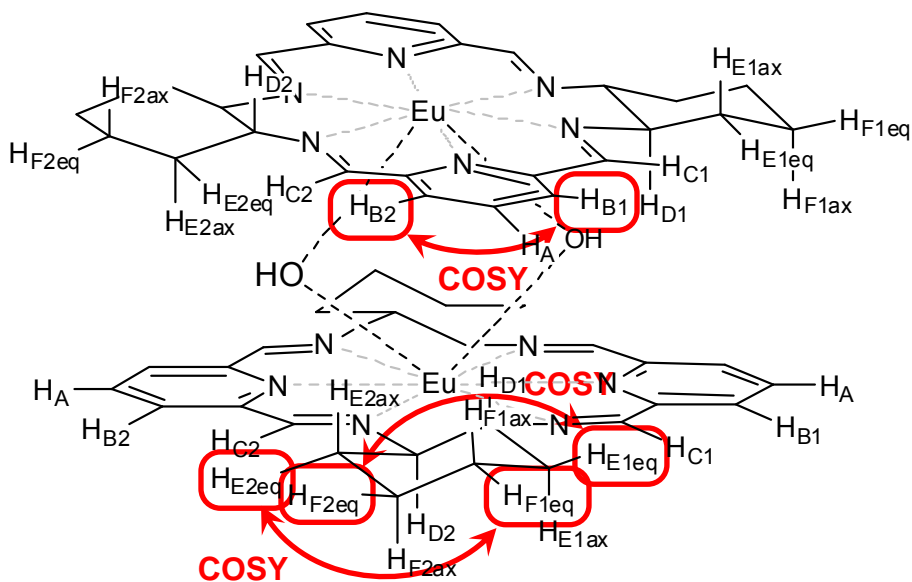
11. There are lots of crosspeaks in the NOESY spectrum that are identical to COSY corsspeaks—that simply confirm that protons are adjacent to one another. And then there are a few crosspeaks for H_{C1} and H_{C2} to protons that are nearby from the same ring (or at least that could be from the same ring). But there are a few crosspeaks—those to the aromatic protons H_A, H_{B1} and H_{B2}—that can't be to next neighbors.

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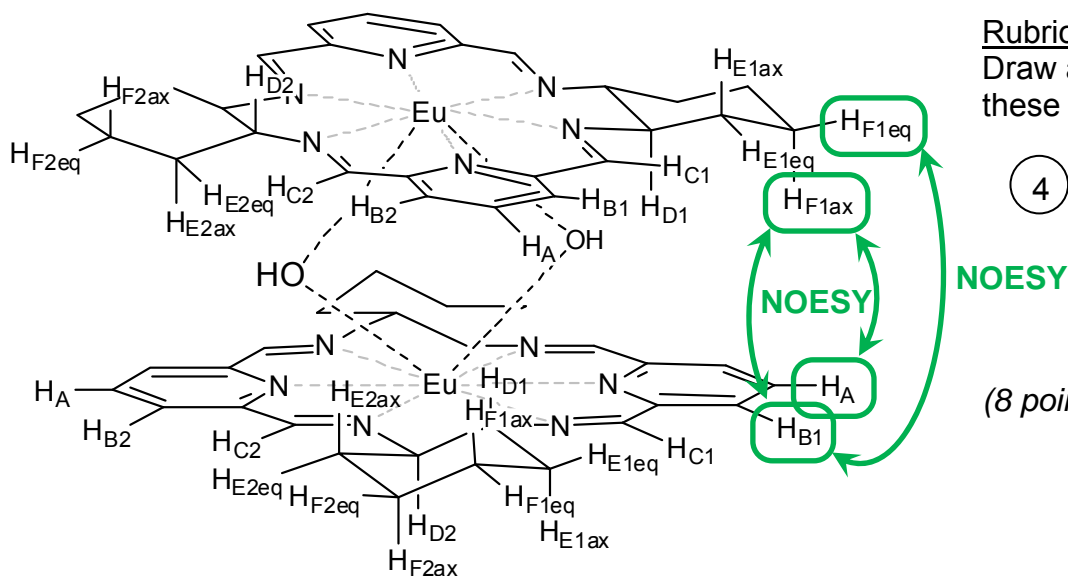
Once again, we didn't give credit for incorrect answers to problem 11 that were consistent with incorrect answers to problem 9, mainly because your incorrect answers should have led you to re-evaluate your answers to problem 9.

12. Dr. Lisowski hypothesized that this dimer might be in equilibrium with two monomers (as shown at right). Describe an NMR experiment that he might have performed, and the results he would need to see, to confirm his hypothesis.

$[Eu_2L_2(\mu\text{-}OH)_2(H_2O)_2]^{4+}$

$\updownarrow$ **?**

$2 [EuL(OH)(H_2O)]^{2+}$
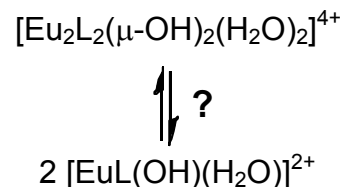
> If this equilibrium were occurring, Dr. Lisowski wouldn't be able to observe it by NMR if it occurred faster than the NMR timescale (if the forward and reverse reactions were both too fast). To resolve this, Lisowski could have performed a variable-temperature experiment, lowering the sample temperature below the "coalescence" temperature where both dimer and monomer could be observed independently. If that occurred, Lisowski would know he had an equilibrating mixture of monomers and dimers.

Rubric: *10 points total.*
- 4 points for mentioning changing sample temperature.
- 6 points for describing peaks separating into distinct contributions from dimer & monomer, or "coalescence". *(Actually, de-coalescence in this case, but either term is fine.)*