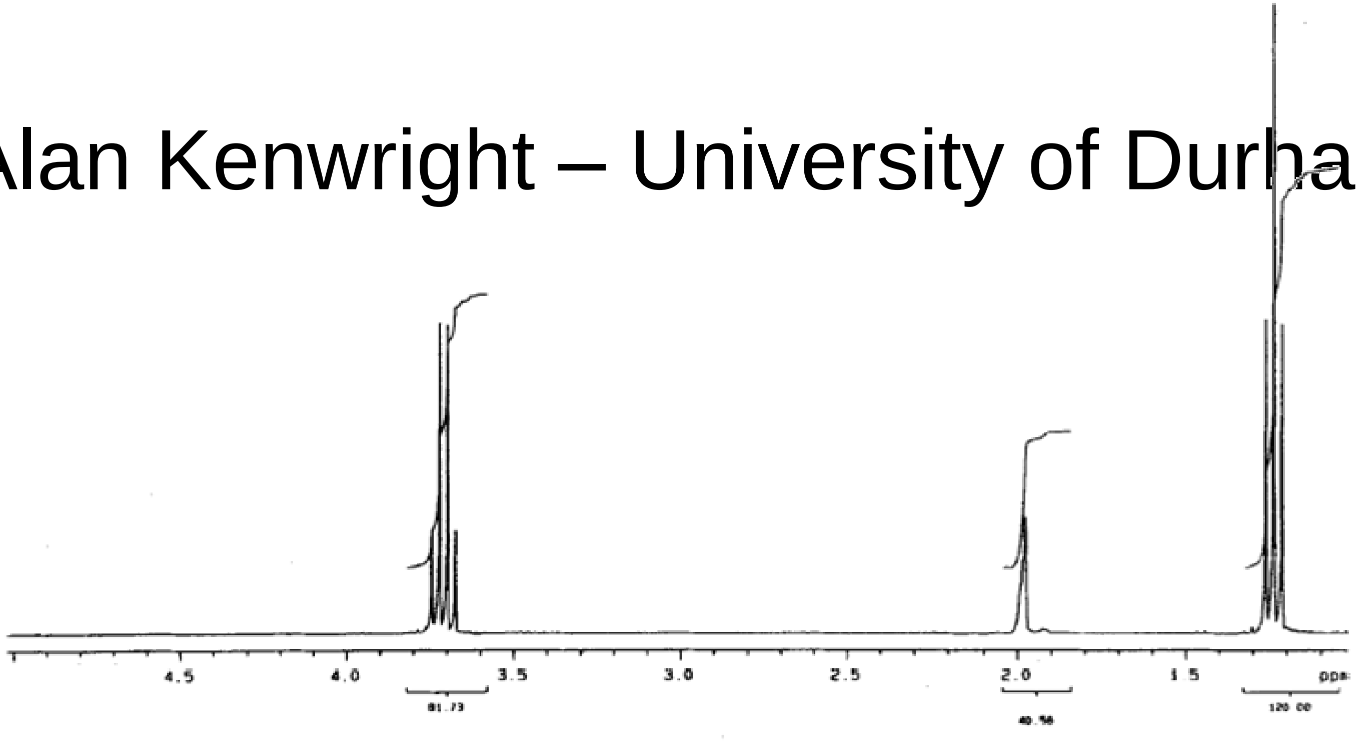
UKMRM – Manchester – 24/06/2015

Teaching NMR – what makes a good example?

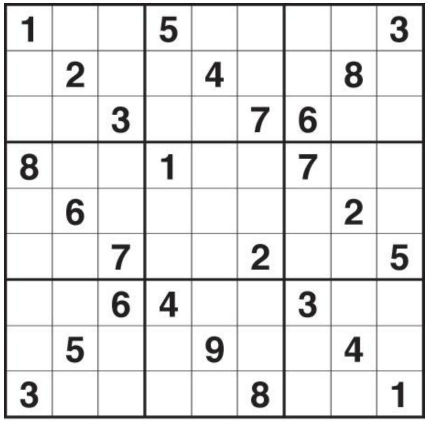
Alan Kenwright – University of Durham



Teaching NMR – what makes a good example?

Teaching NMR interpretation to practising chemists who are not NMR specialists.

Complex & Fuzzy



1			5					3
	2			4			8	
		3			7	6		
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	6						2	
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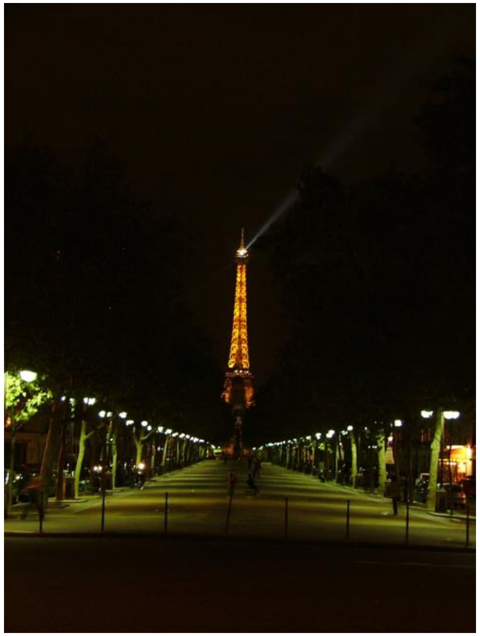
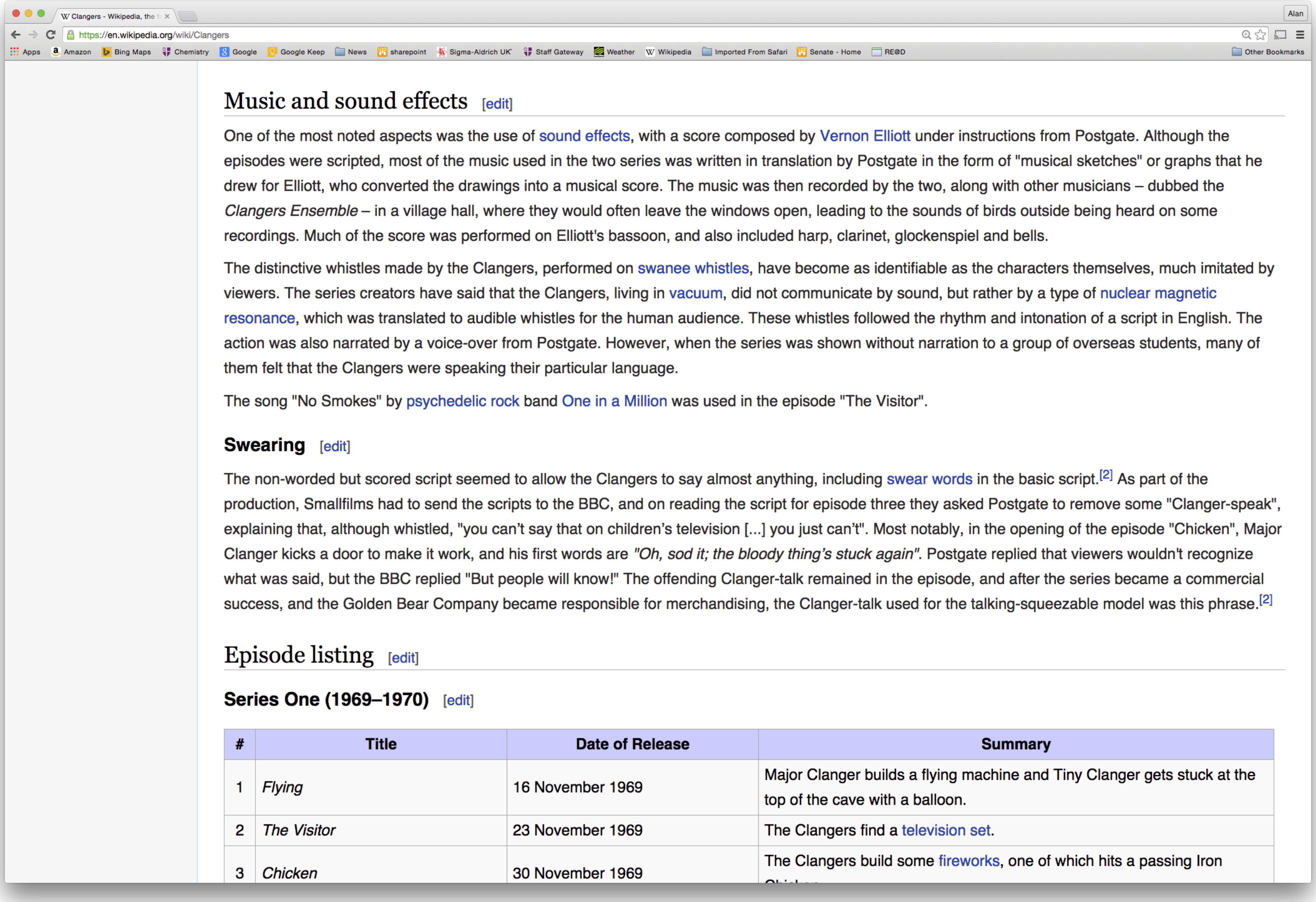
		6	4			3		
	5			9			4	
3					8			1





Music and sound effects [edit]

One of the most noted aspects was the use of sound effects, with a score composed by Vernon Elliott under instructions from Postgate. Although the episodes were scripted, most of the music used in the two series was written in translation by Postgate in the form of "musical sketches" or graphs that he drew for Elliott, who converted the drawings into a musical score. The music was then recorded by the two, along with other musicians – dubbed the *Clangers Ensemble* – in a village hall, where they would often leave the windows open, leading to the sounds of birds outside being heard on some recordings. Much of the score was performed on Elliott's bassoon, and also included harp, clarinet, glockenspiel and bells.

The distinctive whistles made by the Clangers, performed on swanee whistles, have become as identifiable as the characters themselves, much imitated by viewers. The series creators have said that the Clangers, living in vacuum, did not communicate by sound, but rather by a type of nuclear magnetic resonance, which was translated to audible whistles for the human audience. These whistles followed the rhythm and intonation of a script in English. The action was also narrated by a voice-over from Postgate. However, when the series was shown without narration to a group of overseas students, many of them felt that the Clangers were speaking their particular language.

The song "No Smokes" by psychedelic rock band One in a Million was used in the episode "The Visitor".

Swearing [edit]

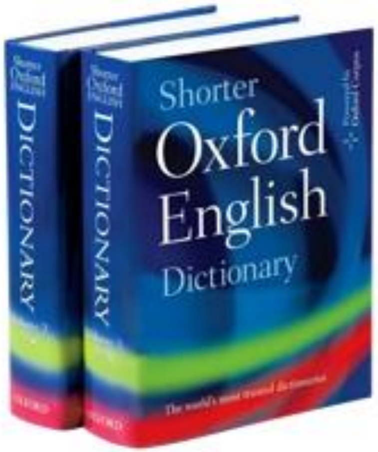
The non-worded but scored script seemed to allow the Clangers to say almost anything, including swear words in the basic script.[2] As part of the production, Smallfilms had to send the scripts to the BBC, and on reading the script for episode three they asked Postgate to remove some "Clanger-speak", explaining that, although whistled, "you can't say that on children's television [...] you just can't". Most notably, in the opening of the episode "Chicken", Major Clanger kicks a door to make it work, and his first words are *"Oh, sod it; the bloody thing's stuck again"*. Postgate replied that viewers wouldn't recognize what was said, but the BBC replied "But people will know!" The offending Clanger-talk remained in the episode, and after the series became a commercial success, and the Golden Bear Company became responsible for merchandising, the Clanger-talk used for the talking-squeezable model was this phrase.[2]

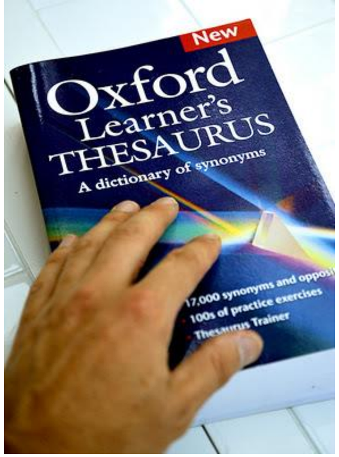
Episode listing [edit]

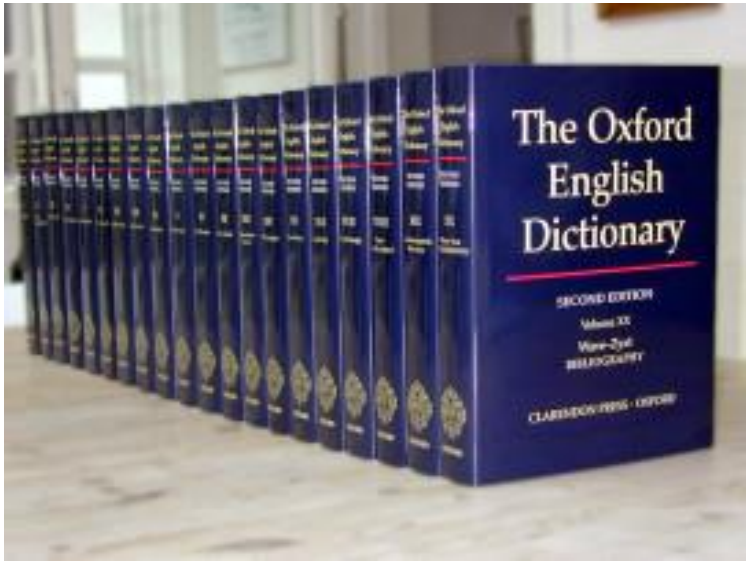
Series One (1969–1970) [edit]

#	Title	Date of Release	Summary
1	*Flying*	16 November 1969	Major Clanger builds a flying machine and Tiny Clanger gets stuck at the top of the cave with a balloon.
2	*The Visitor*	23 November 1969	The Clangers find a television set.
3	*Chicken*	30 November 1969	The Clangers build some fireworks, one of which hits a passing Iron

Sources of information







Context

Does your “possible” answer make sense in this particular (chemical) context?

Millions read this novel (4,5) **HARD TI(M)ES*** (M+READ THIS)* &lit

Honestly? No, otherwise (2,3,3) **ON THE SLY*** (HONESTLY)
Man United playing away later rued foul (9) **ADULTERER** (LATER RUED)*

Stupid cow needed my ring for this (7,8) **WEDDING CEREMONY** (COW NEEDED MY RING)*

The obvious?

- Sherlock Holmes and Dr. Watson went on a camping trip.
- After a good meal and a bottle of wine they bunked down for the night and went to sleep. Some hours later, Holmes awoke and nudged his friend. “Watson, look up at the sky and tell me what you see.”
- Watson replied, “I see millions upon millions of stars.”
- “So what does that tell you?” asked Sherlock.
- Watson pondered for a minute. “Astronomically, it tells me that there are millions of galaxies and potentially billions of planets. Astrologically, I observe that Saturn is in Leo. Horologically, I deduce that the time is approximately a quarter past three. Theologically, I can see that God is all powerful and that we are small and insignificant. Meteorologically, I suspect that we will have a beautiful day tomorrow. What does it tell you?”
- Holmes was silent for a minute and then spoke. “It tells me someone has stolen our tent!”

Level Zero – Five Finger Exercises

- Each of the following compounds exhibits a single ^{1}H NMR peak. Approximately where would you expect the peak for each compound (to the nearest 0.5 ppm)? If you are not sure of the structure of the compound look it up on the web (Wikipedia or the Aldrich catalogue are good, free sources)
  - Cyclohexane
  - Acetone (propanone)
  - Benzene
  - Glyoxal (ethanedial)
  - Dichloromethane
  - Trimethylamine
  - PETN (the well-known explosive!)

Level Zero – Five finger Exercises

- How could you distinguish between the following pairs of compounds (constitutional isomers) from their ^{1}H NMR spectra? Note – you are not provided with the spectra, so you need to “predict” the spectrum in each case in sufficient detail to allow you to make a distinction.
  - 1-bromopropane and 2-bromopropane
  - propanal and propanone
  - 1-butyne and 2-butyne
  - ethyl acetate ($MeCO_2Et$) and methyl propanoate ($EtCO_2Me$)

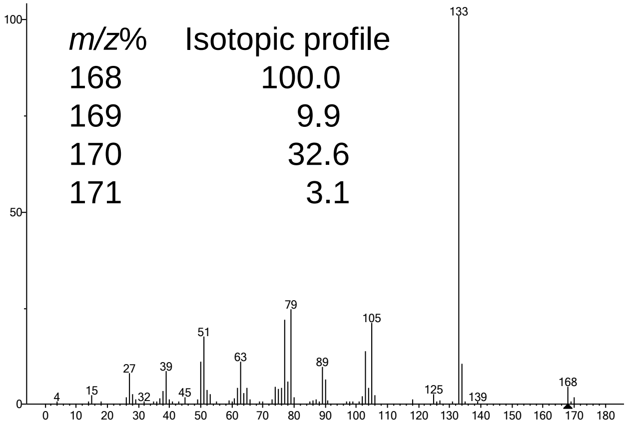
What’s to like?

The idea that approximate knowledge of chemical shift ranges is useful, but an accuracy of +/- 0.5 ppm (proton) is often sufficient

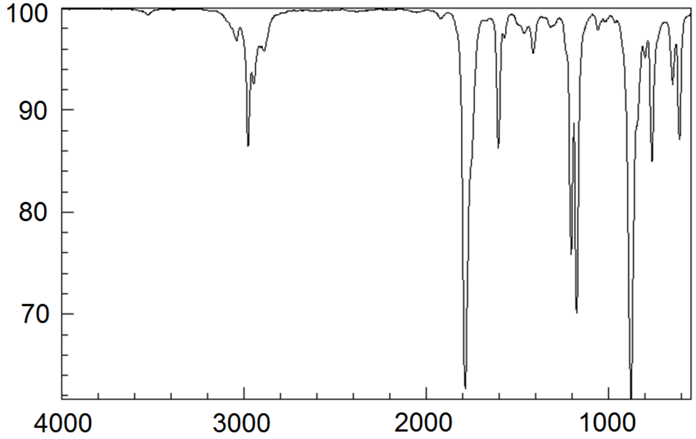
The idea that the ability to make a rough prediction of the spectral features expected (# signals, multiplicity, integrals, approximate chemical shifts) is very useful (vital?)

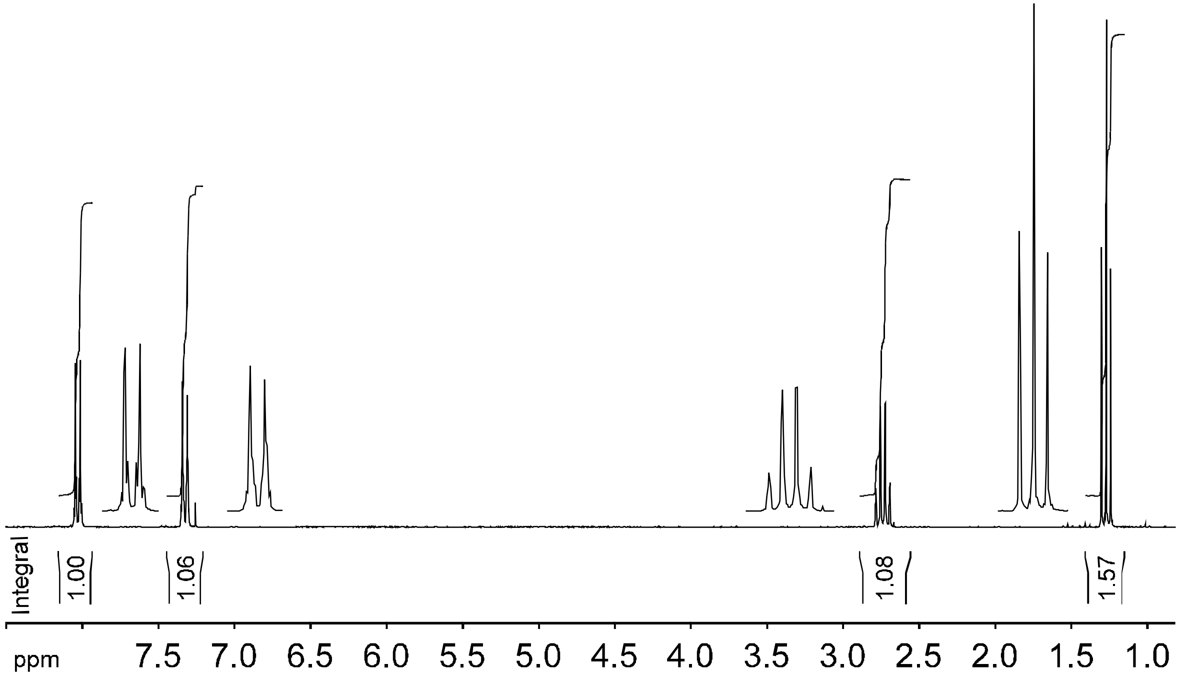
Level One – Simple, first order 1D

Identify the molecule of interest from the A) mass spectrum, B) ^{1}H NMR and C) IR.
There are **two** molecules which could reasonably fit the data above.
What are they, and can you decide if either is more likely?



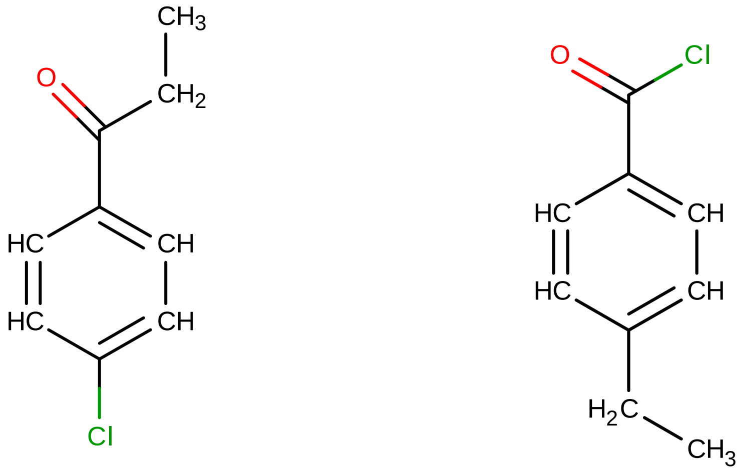
m/z%	Isotopic profile
168	100.0
169	9.9
170	32.6
171	3.1





Isotope pattern on the Mass Spec gives presence of Cl
IR gives presence of carbonyl (No OH)
NMR gives presence of ethyl group and presence of a symmetrical aromatic.

So the two possibilities are:



Proton NMR is not much help in distinguishing!
(Correct structure is the acid chloride - Corroborating evidence from other techniques).

How to confirm your answer? Just add some water!

What’s to like?

Aromatic substitution pattern

Complementarity of techniques (take the easy info from whatever is available!)

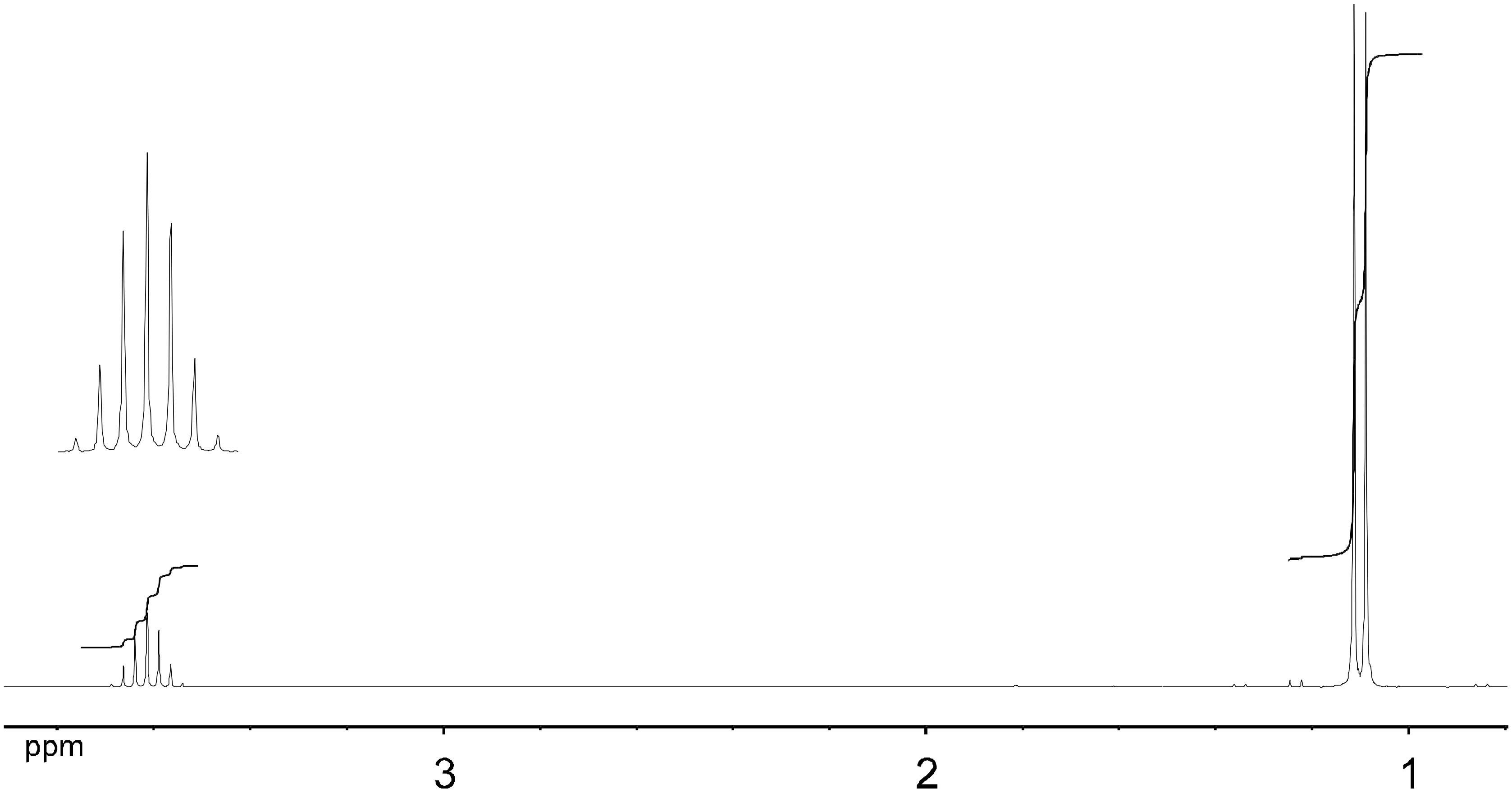
The necessity to distinguish between possible isomers.

The fact that proton NMR does not give easy distinction. Horses for courses.

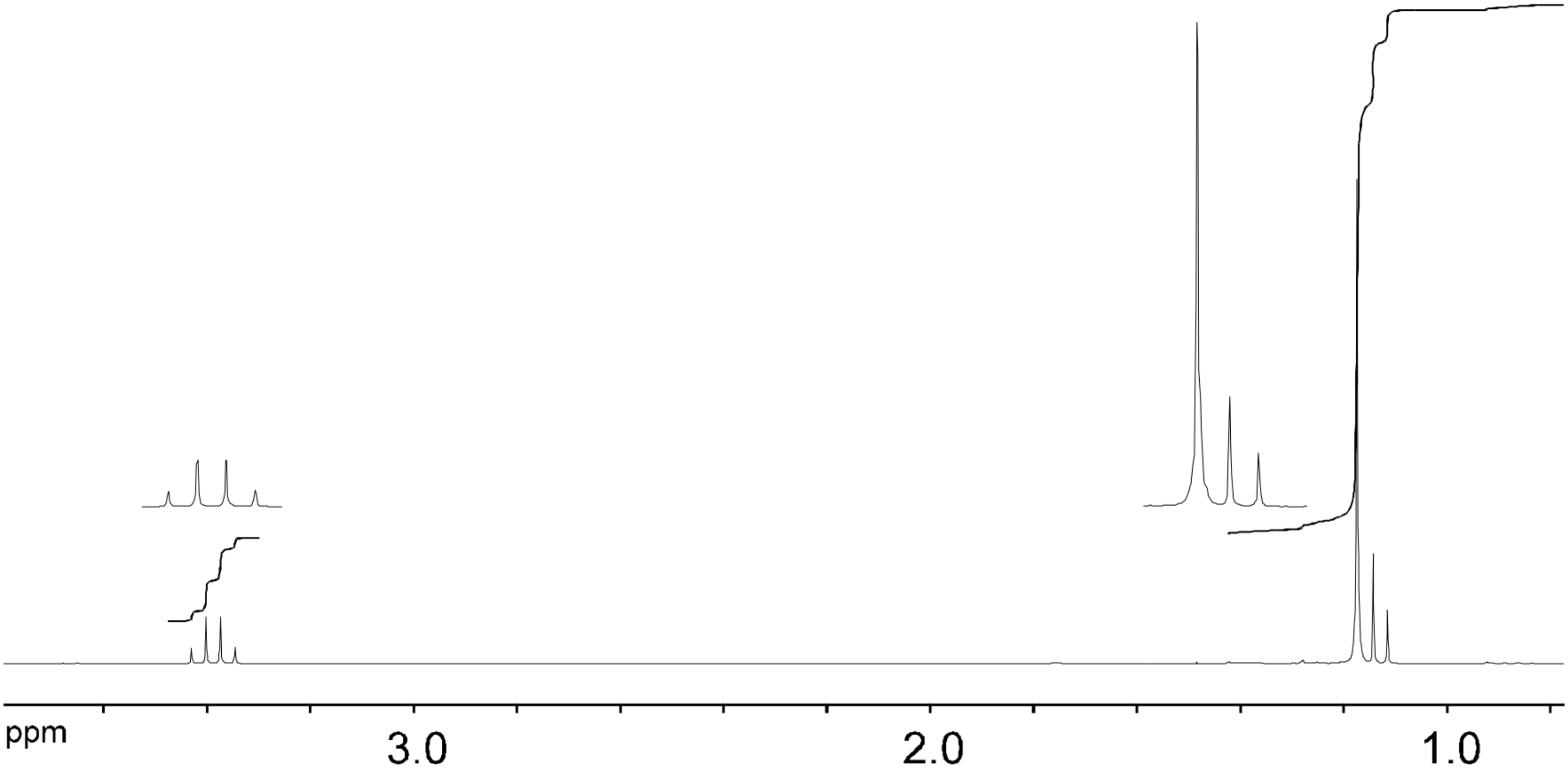
The requirement to think of “what else?”

Two compounds containing C, H and ? are isomers. ^{1}H NMR spectra are given for both compound 1 and compound 2. M/z = 102. Identify both.

Compound 1



Compound 2.



What’s to like?

Symmetry – if it looks as though you don’t have enough peaks in your NMR to account for the mass – think symmetry

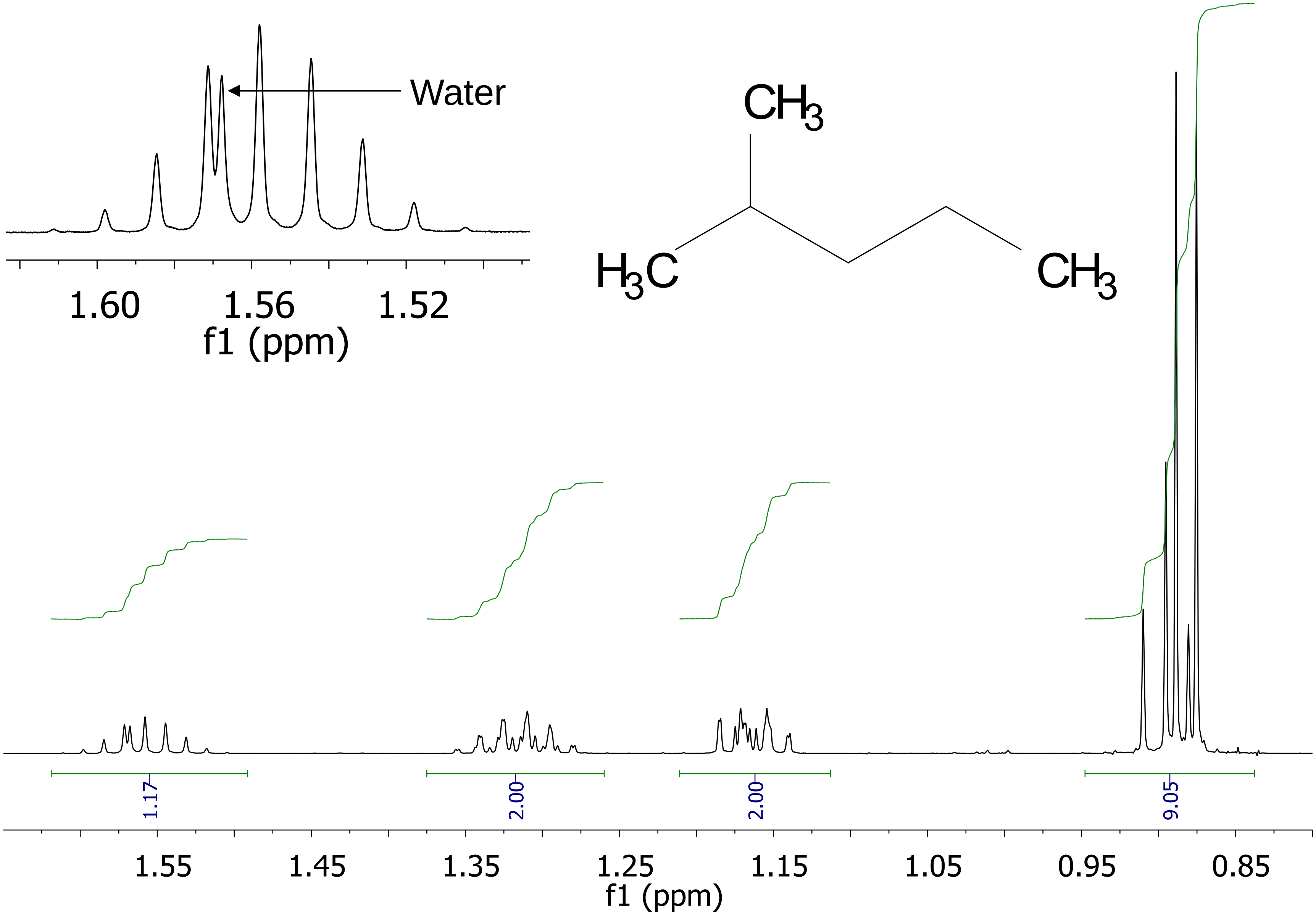
Peak overlap, Accidental degeneracy, Sod’s law

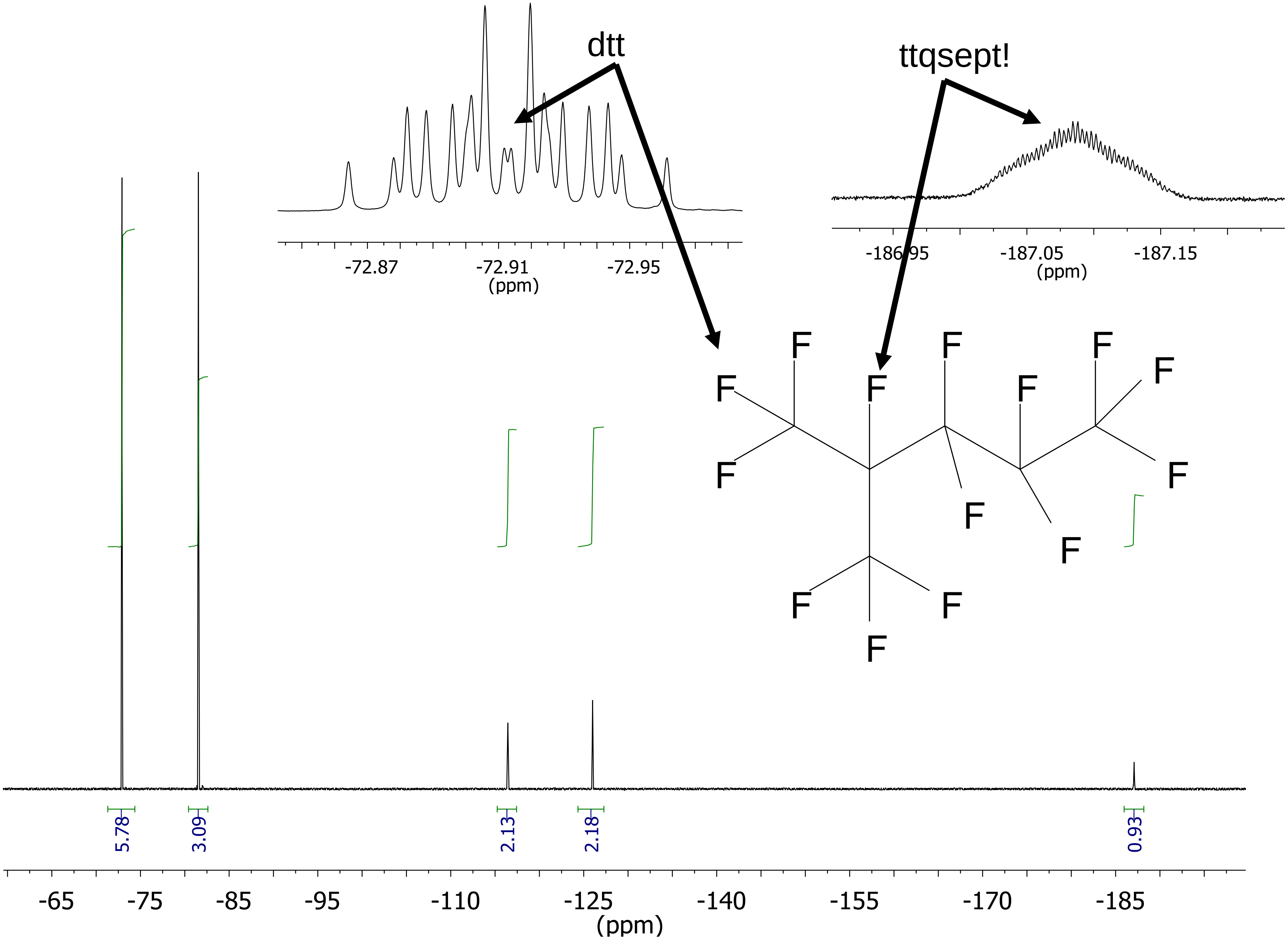
Again, isomers (NMR, good; MS, bad)

When considering other nuclei, be careful to separate “spin physics” from “heuristics”.

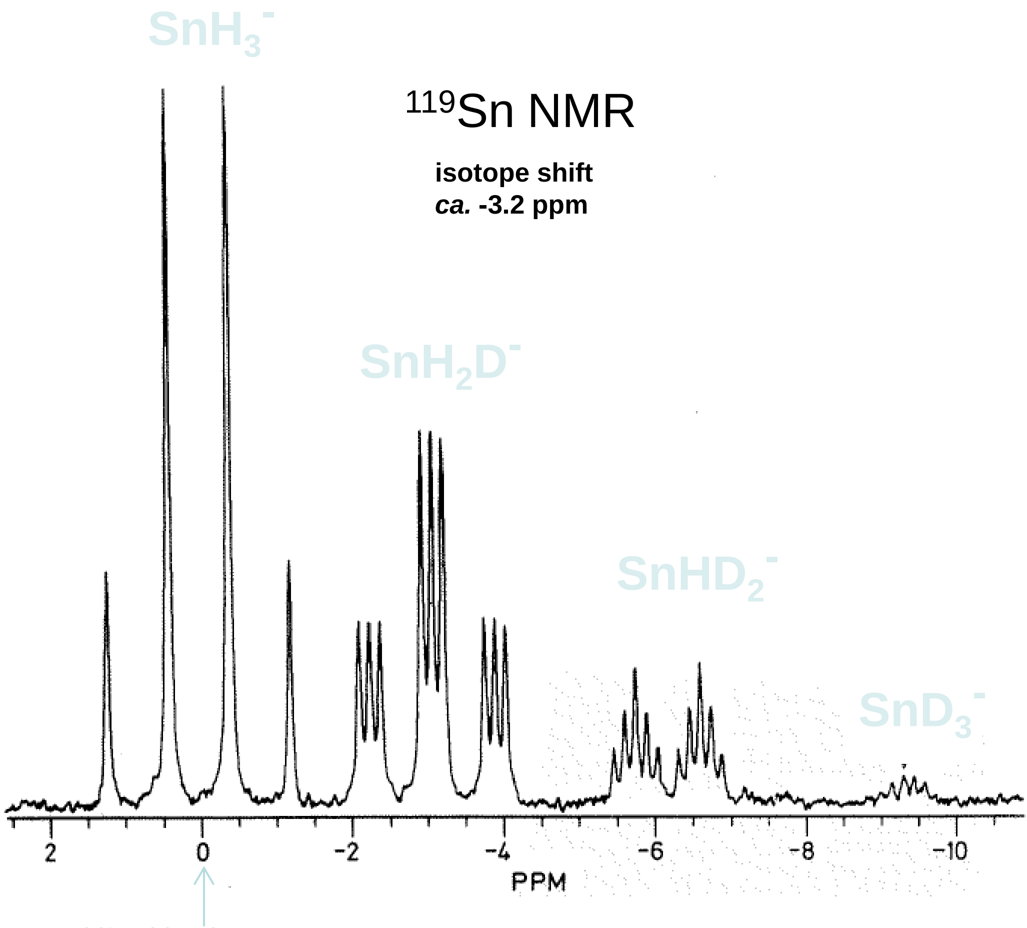
All 100% abundant spin-1/2 nuclei (^{1}H, ^{19}F, ^{31}P) behave exactly the same in terms of “spin physics” – but that does not mean that we can simply interpret their spectra as though they were protons.

We need to be aware of the assumptions (rules of thumb – “heuristics”) we bring to the task of assigning a spectrum.


Water
1.60
1.56
1.52
f1 (ppm)
CH3
H3C
CH3
1.17
2.00
2.00
9.05
1.55
1.45
1.35
1.25
1.15
1.05
0.95
0.85
f1 (ppm)


dtt
ttqsept!
-72.87
-72.91
(ppm)
-72.95
-186.95
-187.05
(ppm)
-187.15
5.78
3.09
2.13
2.18
0.93
-65
-75
-85
-95
-110
-125
-140
-155
-170
-185
(ppm)

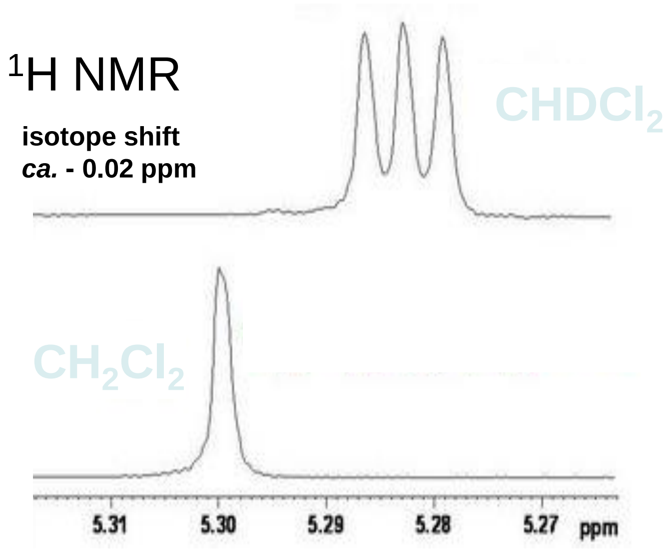
Deuterium Isotope Shifts in a ^{119}Sn and a ^{1}H NMR Spectrum



^{119}Sn NMR

isotope shift
***ca.* -3.2 ppm**

N.B. shift arbitrarily set to 0 ppm



^{1}H NMR

isotope shift
***ca.* - 0.02 ppm**

Isotope shifts are only observable for $^{1}H \rightarrow {}^{2}H$ in ^{1}H spectra; shifts for other isotopes are not resolved, hence ^{13}C or ^{29}Si satellites appear symmetrically distributed around main peak, for instance.

http://u-of-o-nmr-facility.blogspot.co.uk/2008/06/spin-spin-coupling-between-equivalent.html

R. E. Wasylishen, N.Burford, **Can. J. Chem.** 65(12):2707-2712 (1987). DOI:10.1139/v87-449

Level Two – Second order 1D
Diastereotopism
Magnetic vs Chemical equivalence

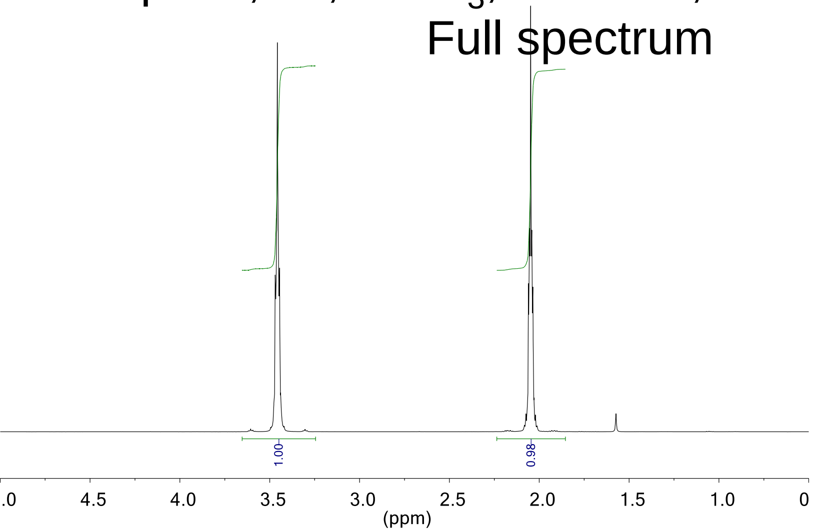
Prof. Boffin is one of the world’s experts on constitutional isomers. In fact he has an extensive collection of them. Over the Christmas vacation disaster struck when the cold weather caused the pipes to burst and Prof Boffin’s lab got flooded.

The samples in the lab were stored in small plastic trays, each of which held a set of bottles containing various isomers of the same molecular formula. The plastic trays were marked in permanent marker so their labels survived the flood, but the bottles just had paper labels which got soaked off. So now Prof Boffin has a problem. He has sets of samples which he knows to be isomers, and he knows what they are isomers of, but he doesn’t know which isomer is which.

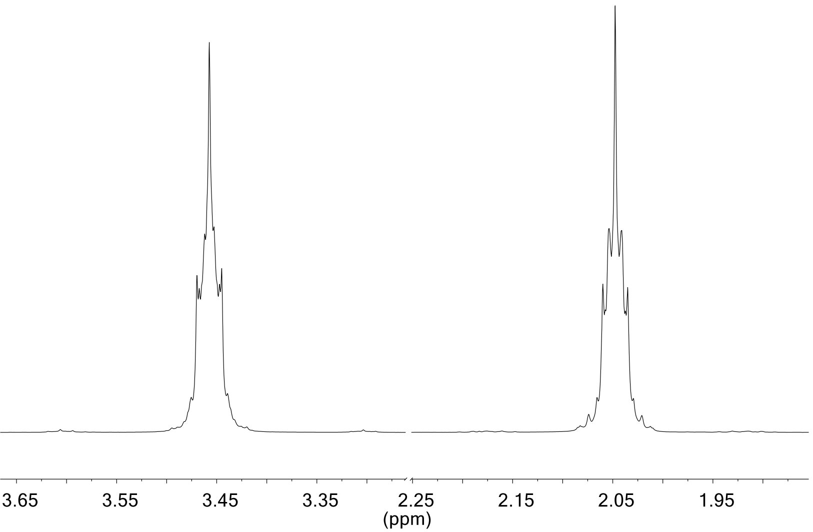
In particular, he is stuck with 5 isomers of $C_4H_8Br_2$ that he needs to sort out, so he asks you to help. Draw the possible structural isomers of $C_4H_8Br_2$. Now use the spectroscopic data provided to identify the four samples (arbitrarily labelled A, B, C, D, and E). As you would expect, IR and Mass Spec are of very little use in distinguishing between isomers, so you are provided with ^{1}H, and ^{13}C spectra for each sample.

Prof Boffin is something of a hard man to convince, so you will need to not only say which sample you think corresponds to which isomer, but justify your conclusions by explaining the relevant spectral features.

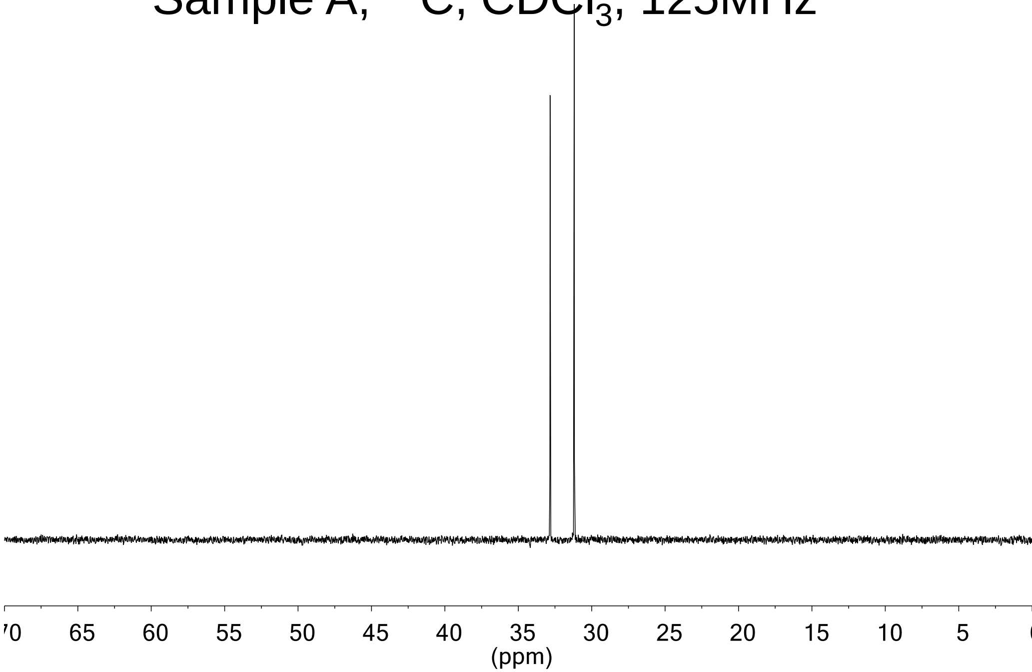
Sample A; ^{1}H, CDCl$_3$, 500MHz; Full spectrum



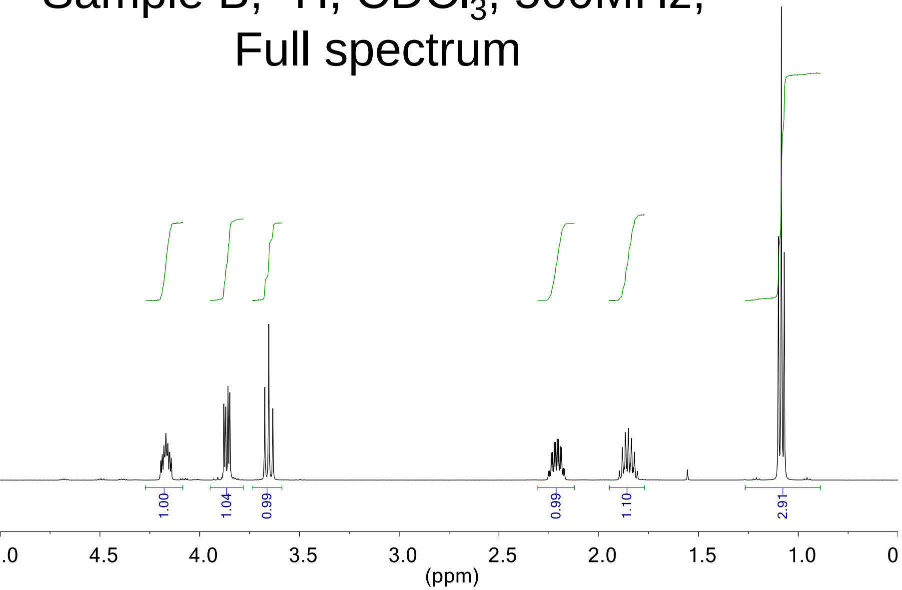
Sample A; ^{1}H, CDCl$_3$, 500MHz; Signal expansion



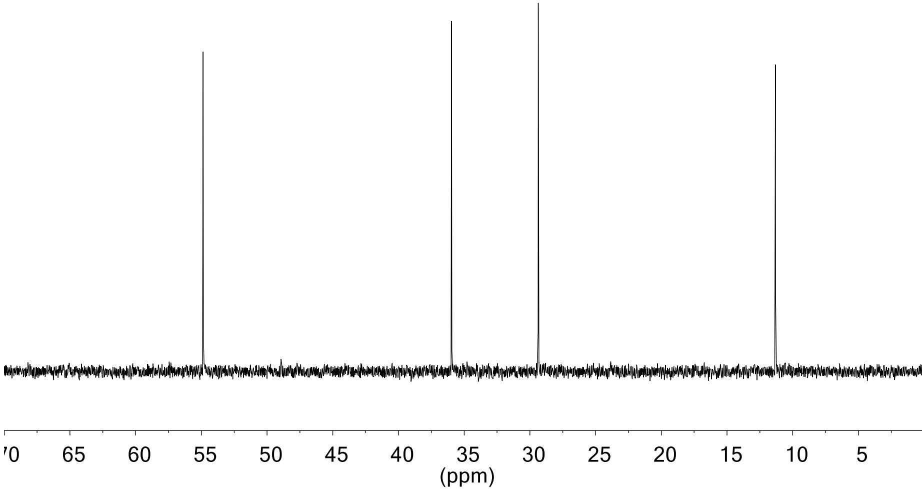
Sample A; ^{13}C, CDCl$_3$, 125MHz



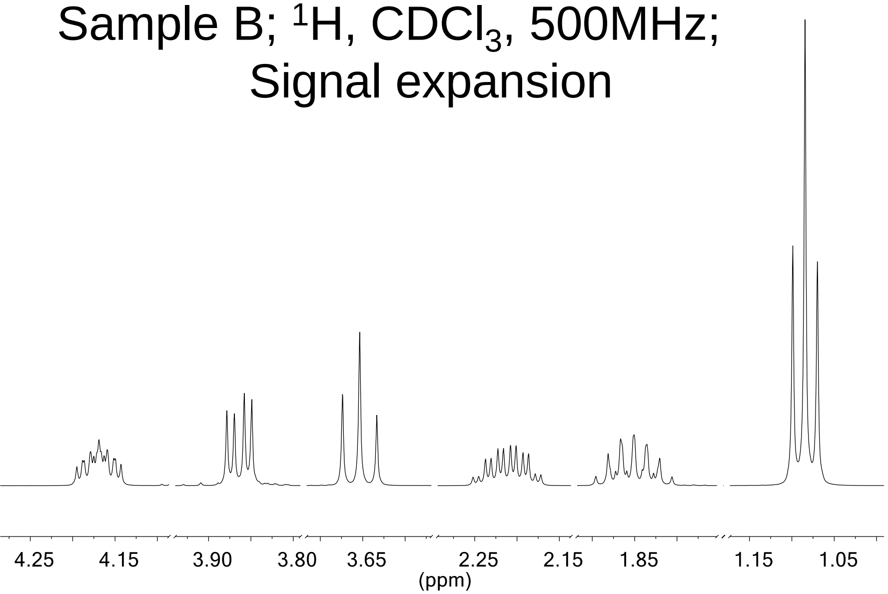
Sample B; ^{1}H, CDCl$_3$, 500MHz; Full spectrum



Sample B; ^{13}C, CDCl$_3$, 125MHz



Sample B; ^{1}H, CDCl$_3$, 500MHz; Signal expansion



What’s to like?

Chemical context – not particularly realistic, but that doesn’t matter.

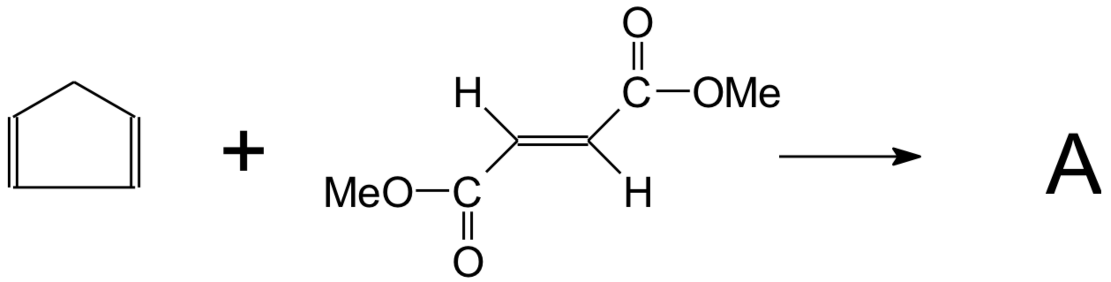
Need to think of a range of possible structures (isomers). Beware of “confirmation bias”.

Diastereotopism, symmetry, chemical vs magnetic equivalence, 2nd order spectra. You don’t need complex molecules to get complex spectra.

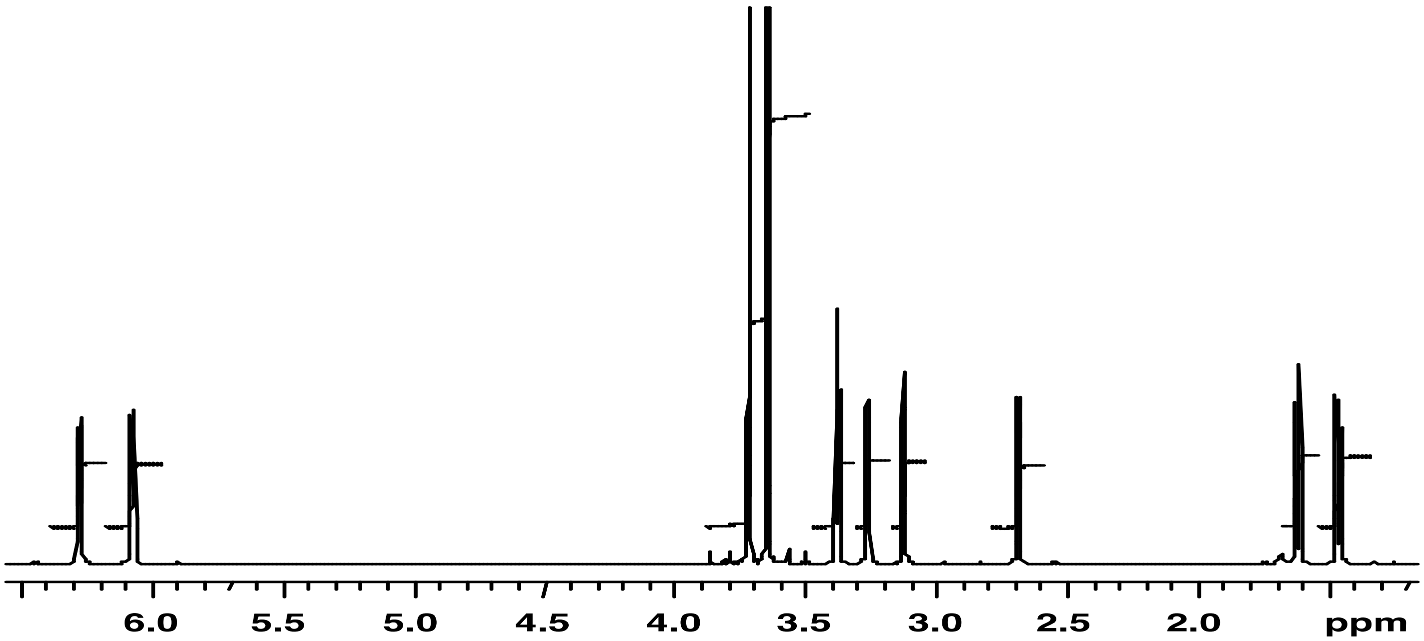
Need to “justify” conclusions.

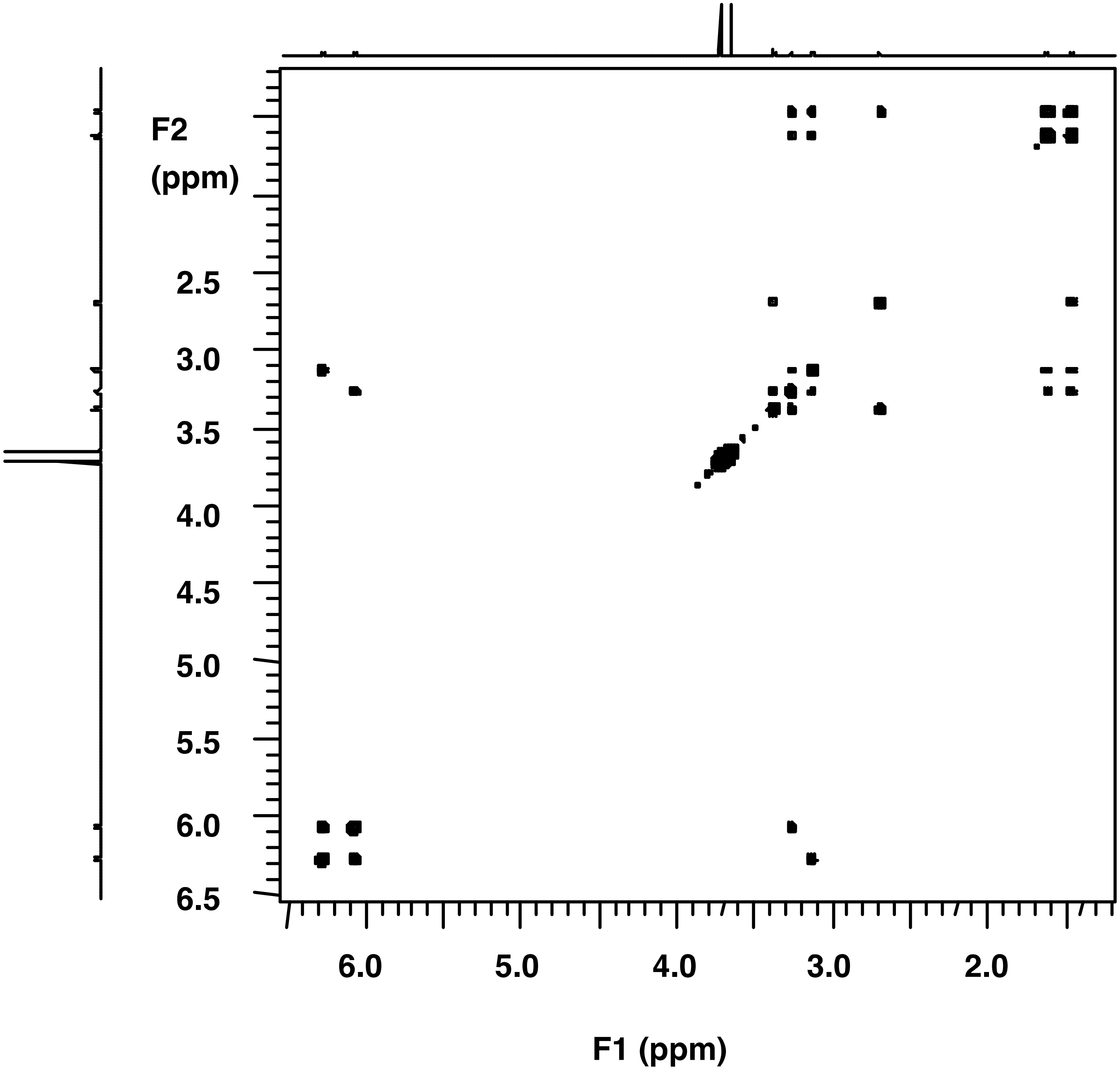
Level Three – Individual two-dimensional techniques

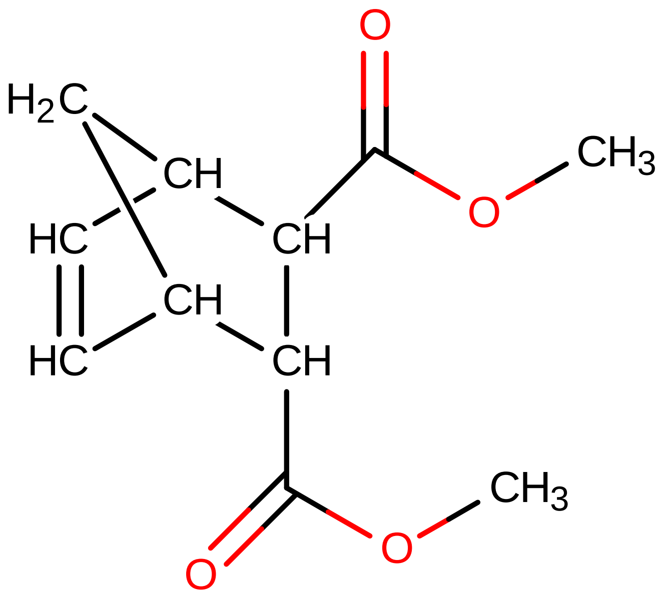
The Diels-Alder reaction of cyclopentadiene with dimethyl fumarate (*trans*-1,2-ethylenedicarboxylic acid dimethyl ester) gives the product A.



You are provided with the ^{1}H NMR spectrum and ^{1}H-^{1}H COSY (500 MHz; $CDCl_3$). Identify the product, A, and account for the features of the spectra as fully as possible. (A simple 3D model of your postulated structure would help with the assignments).




F2
(ppm)
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
6.0
5.0
4.0
3.0
2.0
F1 (ppm)


O
H2C
CH
CH3
HC
CH
O
CH
HC
CH
CH3
O
O

What’s to like?

Chemical context – simple reaction (Diels-Alder) leads to postulated structure (N/X).

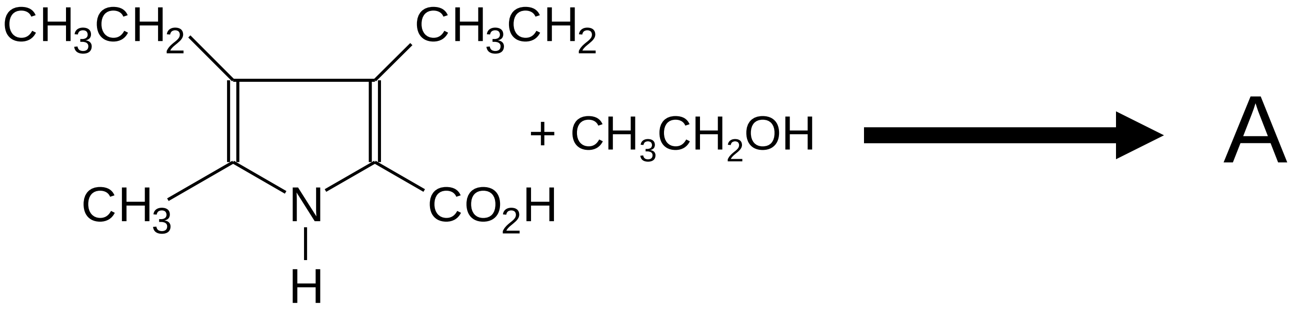
Easy identification of a starting point for assignment (double bond).

Every peak can be assigned (except methoxy), but need to make use of Karplus and 4-bond “W” coupling.

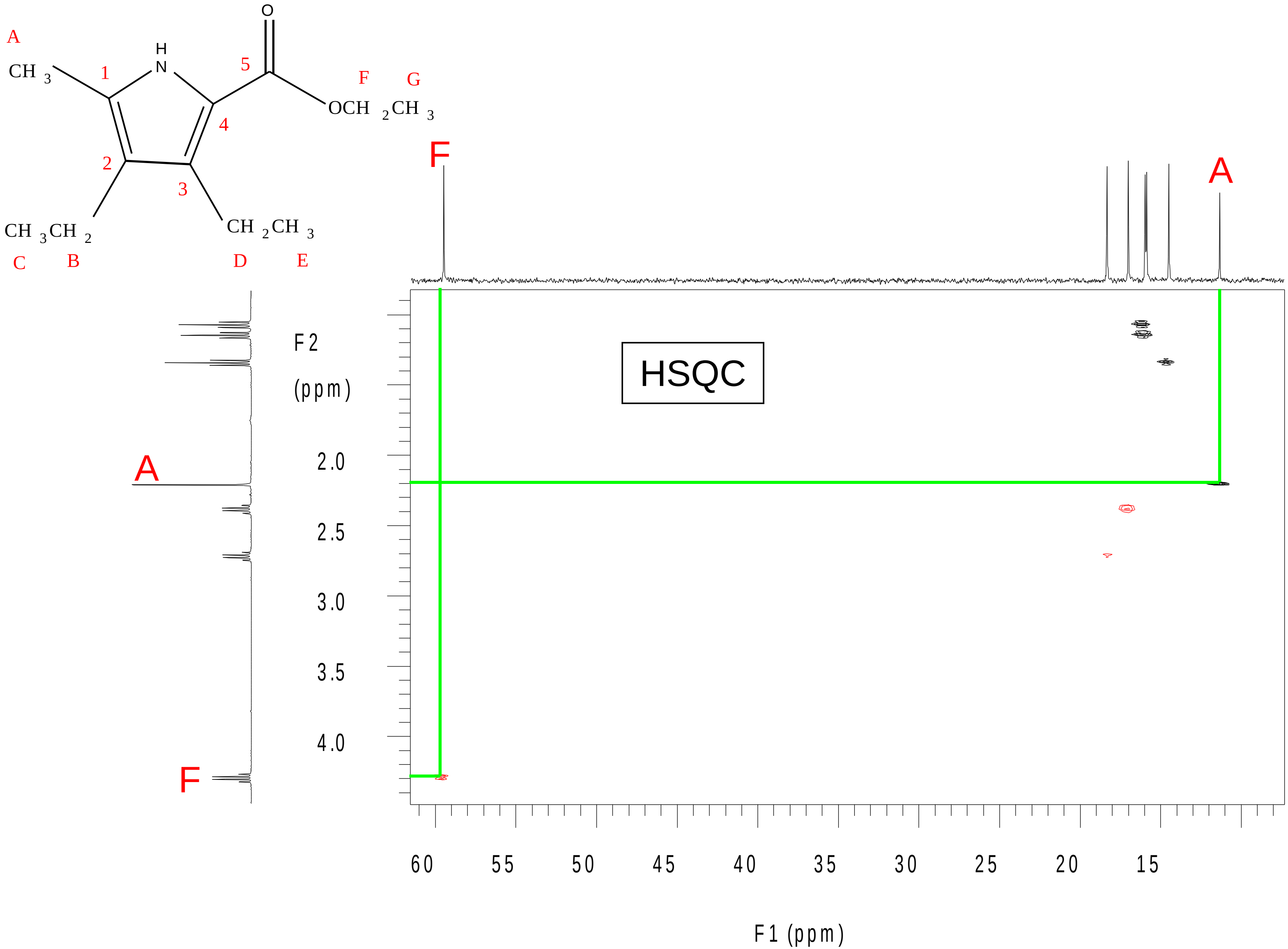
2D is not a replacement for 1D!.

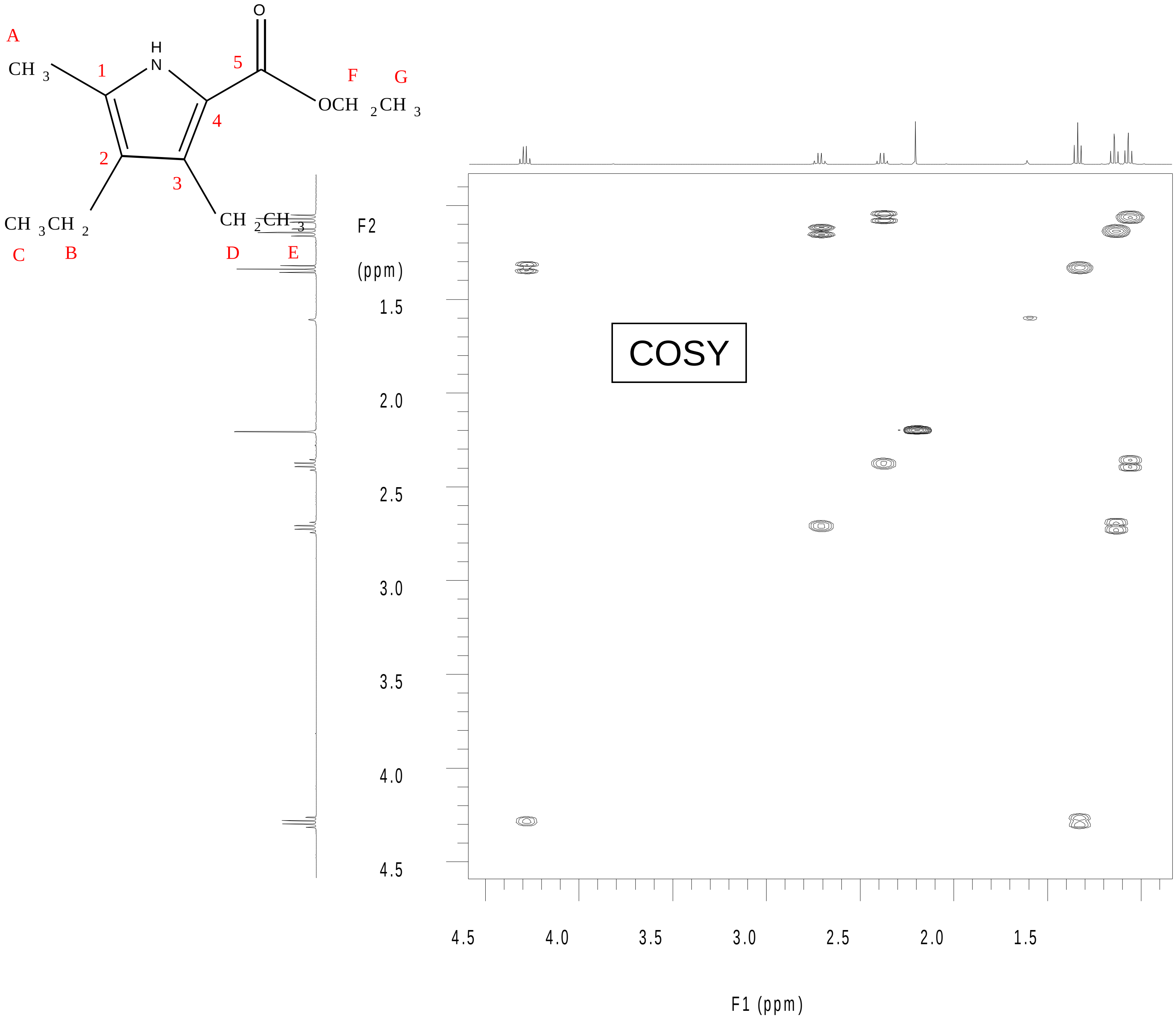
Level Four – Combined two-dimensional techniques

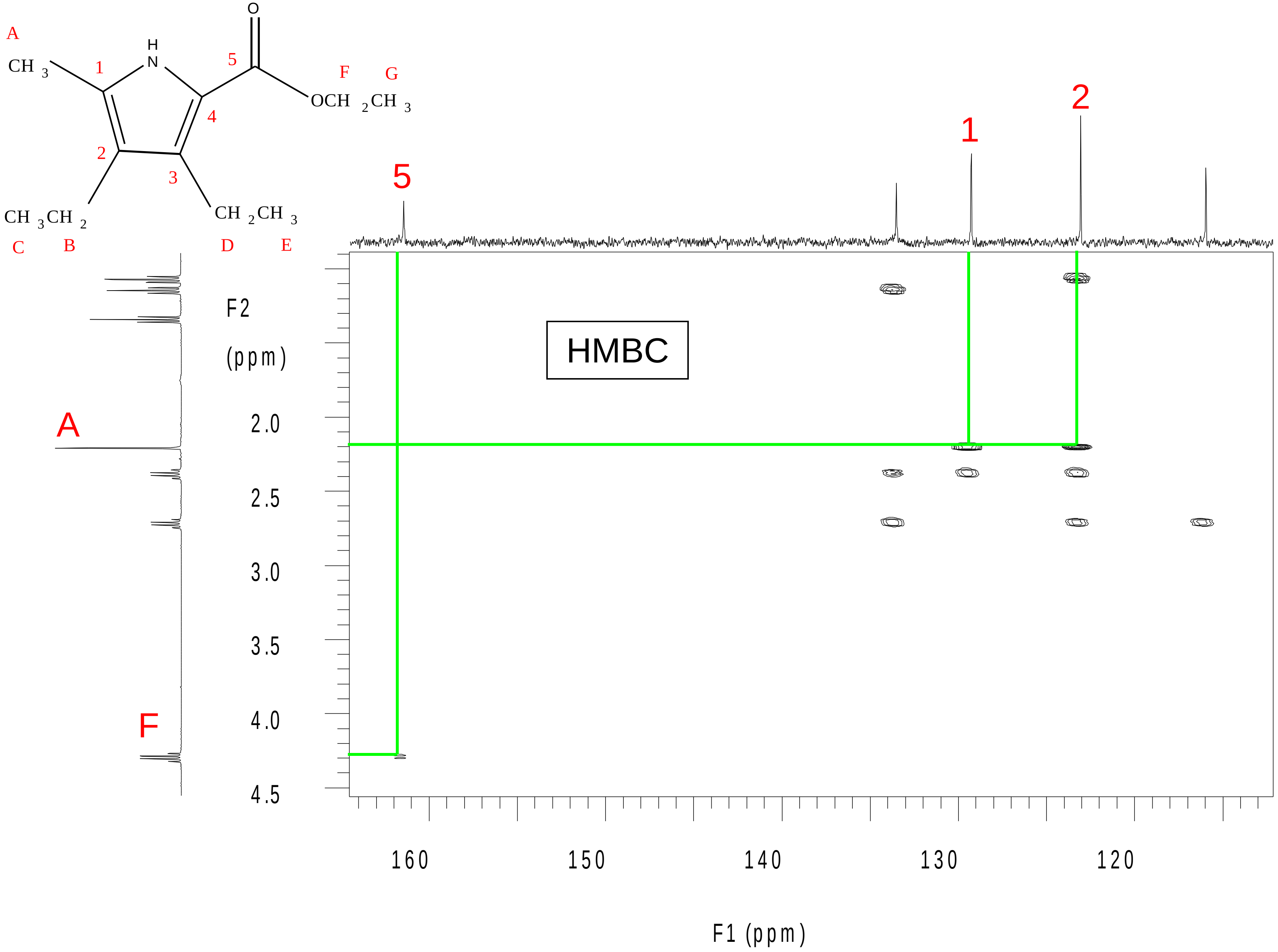
3,4,-diethyl-5-methyl-2-pyrrolecarboxyllic acid **(I)** was reacted with ethanol and the product **A** was isolated. Mass spectrometry shows the molecular ion to be 18 Daltons less than the sum of the two reagents. You are provided with ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, HSQC (one-bond correlation) and the relevant region of the HMBC (two- and/or three-bond correlation) spectra (400 MHz, $CDCl_3$). Identify the product **A** and assign the ^{1}H and ^{13}C NMR spectra.

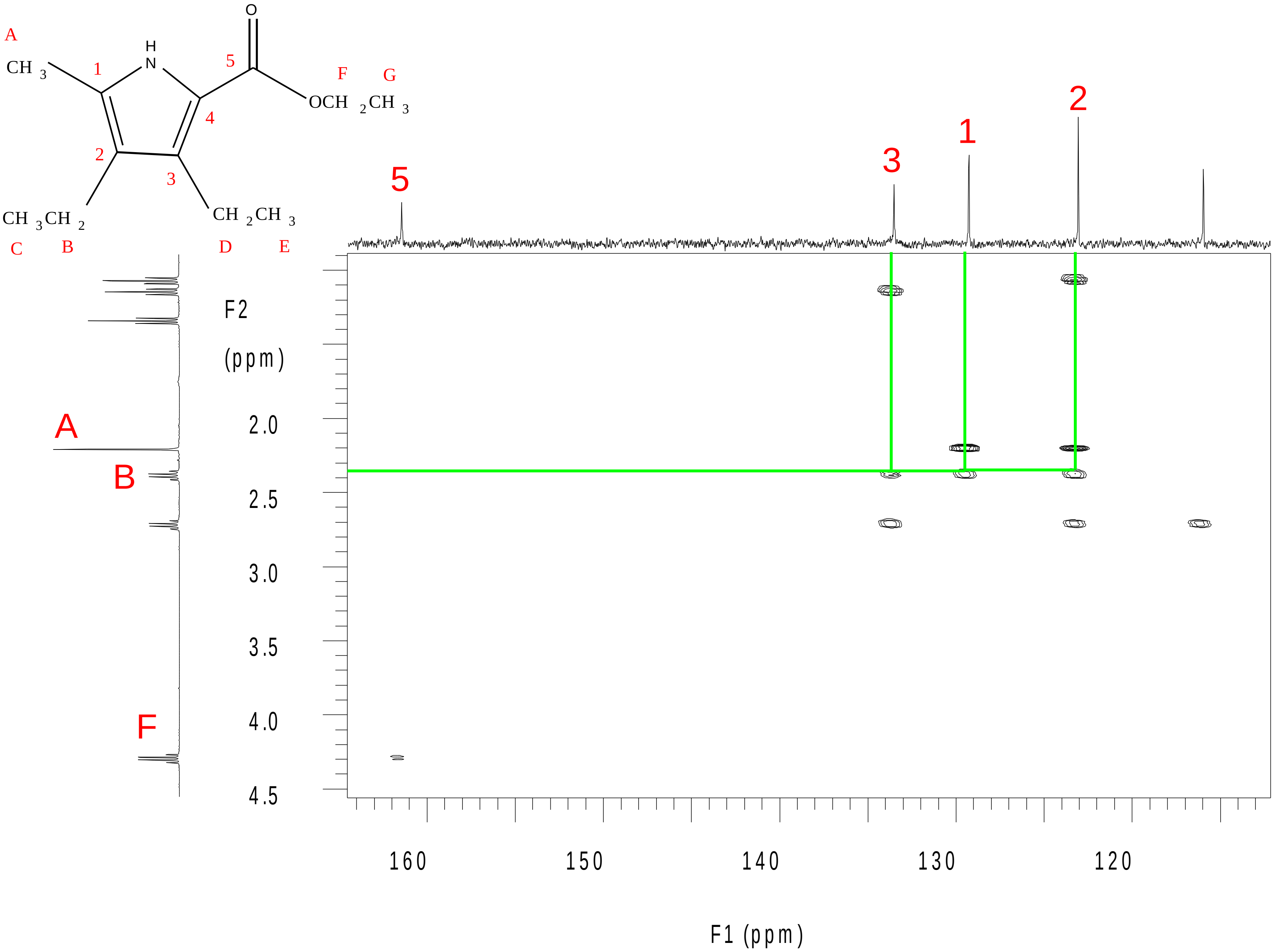


(I)


A
CH3
1
H
N
5
O
F
G
OCH2CH3
4
2
3
CH3CH2
CH2CH3
C
B
D
E
F
A
HSQC
F2 (ppm)
2.0
2.5
3.0
3.5
4.0
A
F
60
55
50
45
40
35
30
25
20
15
F1 (ppm)


A
CH 3
1
H
N
5
O
F
G
OCH 2CH 3
4
2
3
CH 3CH 2
CH 2CH 3
C
B
D
E
F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
COSY
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F1 (ppm)


A
CH3
1
H
N
5
O
F
G
OCH2CH3
4
2
3
CH3CH2
CH2CH3
C
B
D
E
5
1
2
HMBC
F2
(ppm)
A
2.0
2.5
3.0
3.5
F
4.0
4.5
160
150
140
130
120
F1 (ppm)


A
CH3
1
H
N
5
O
F
G
OCH2CH3
4
2
3
CH3CH2
CH2CH3
C
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3
1
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F2
(ppm)
A
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160
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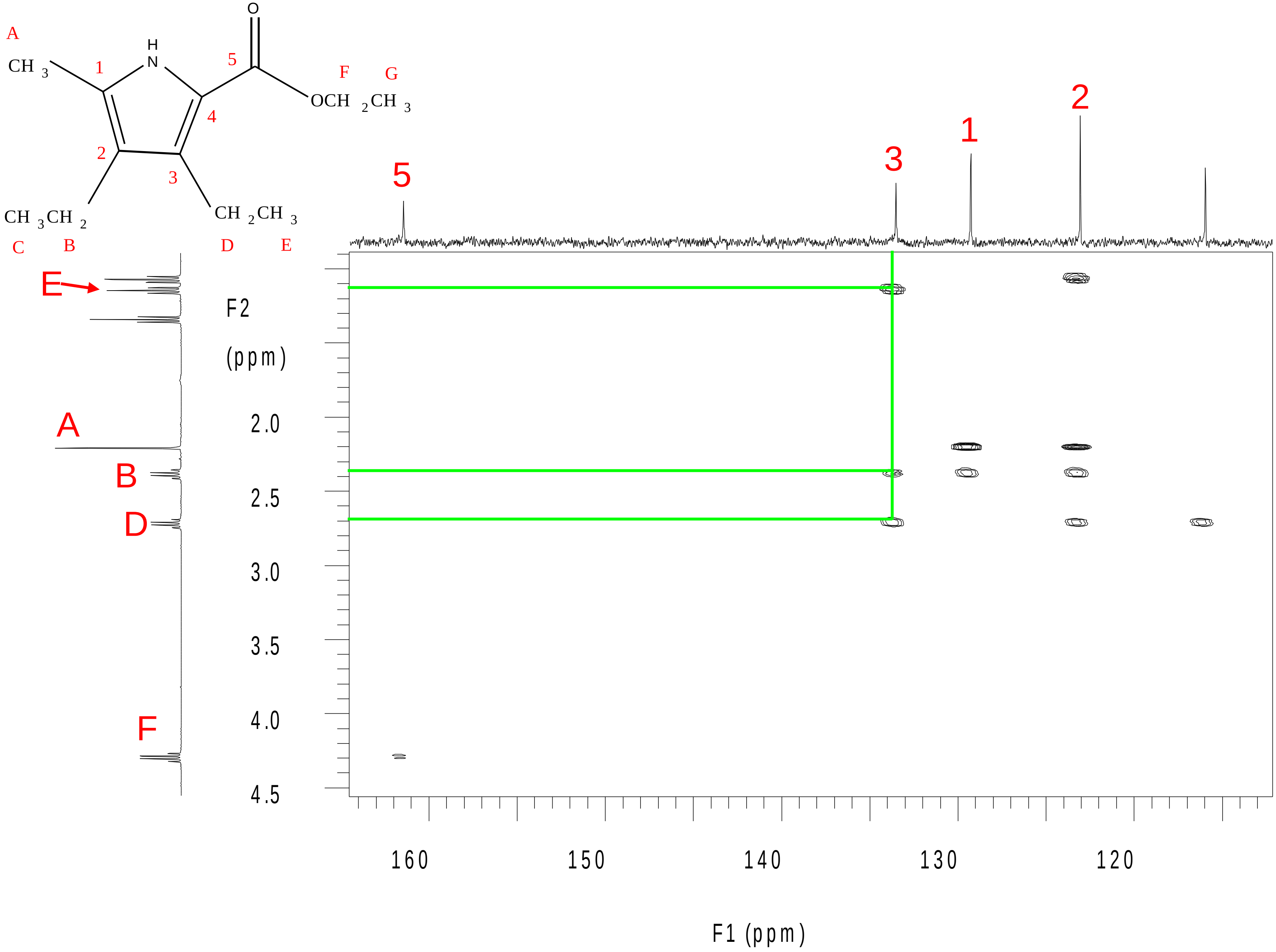
120
F1 (ppm)



A
CH3
1
H
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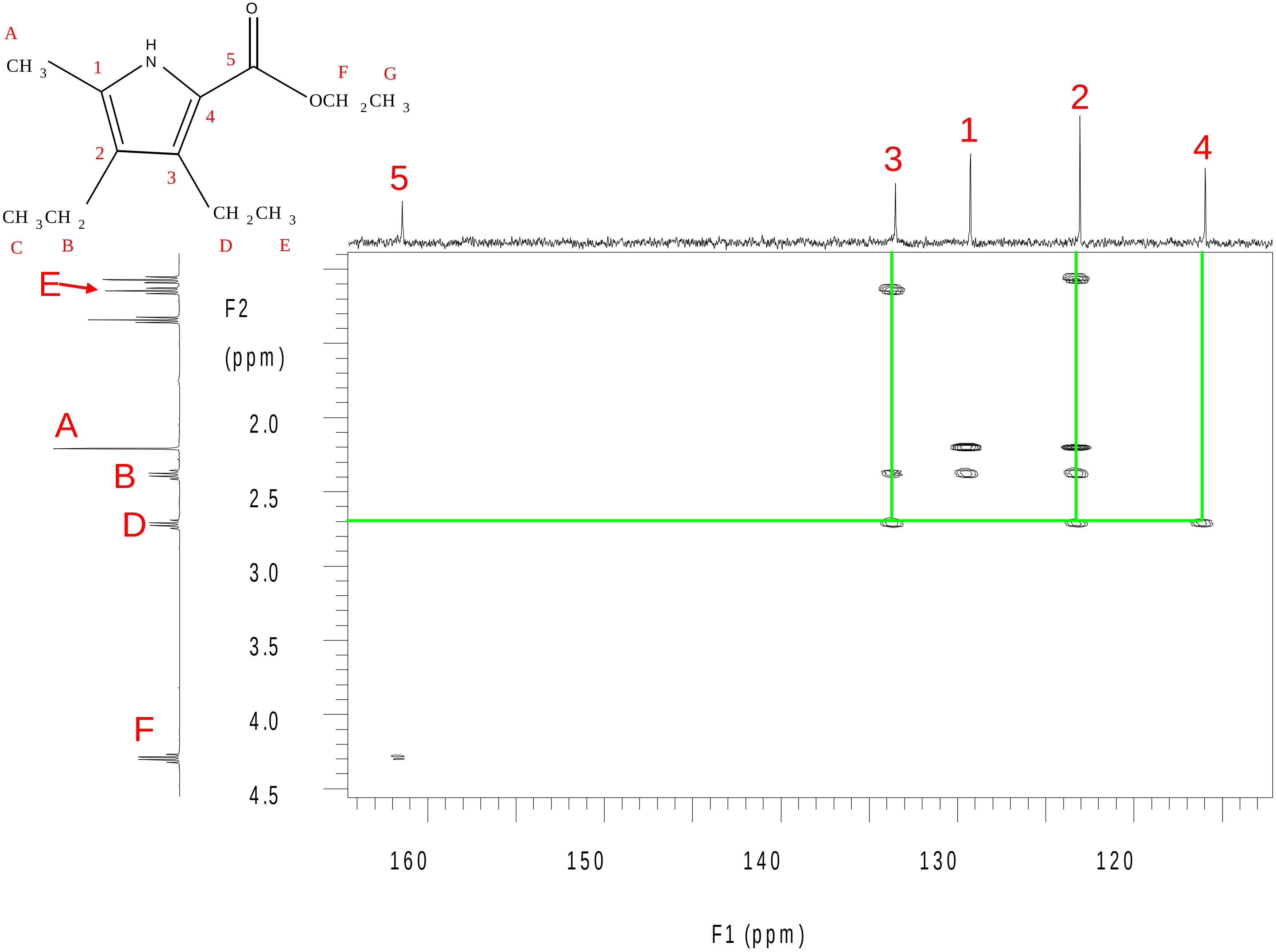
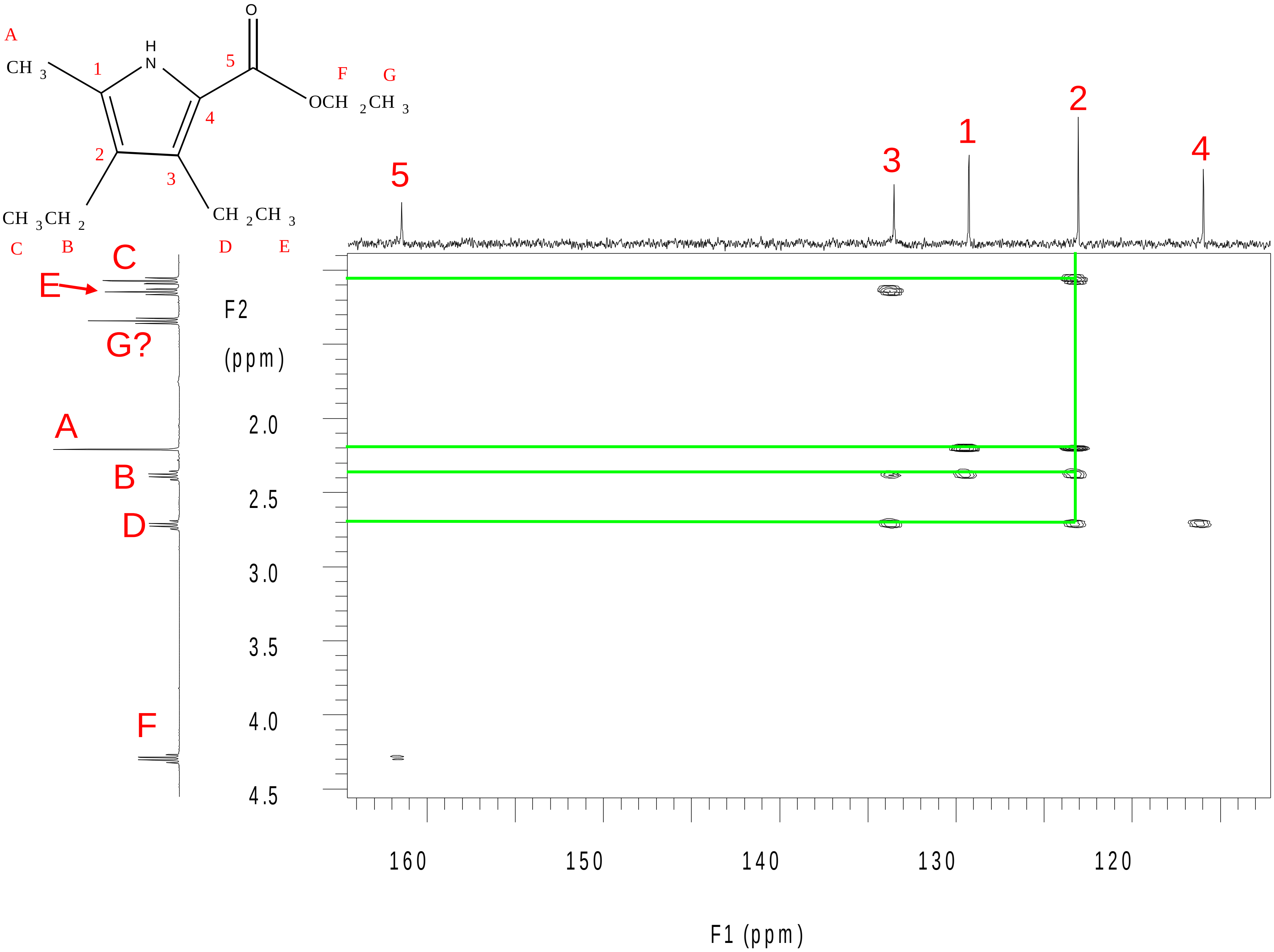
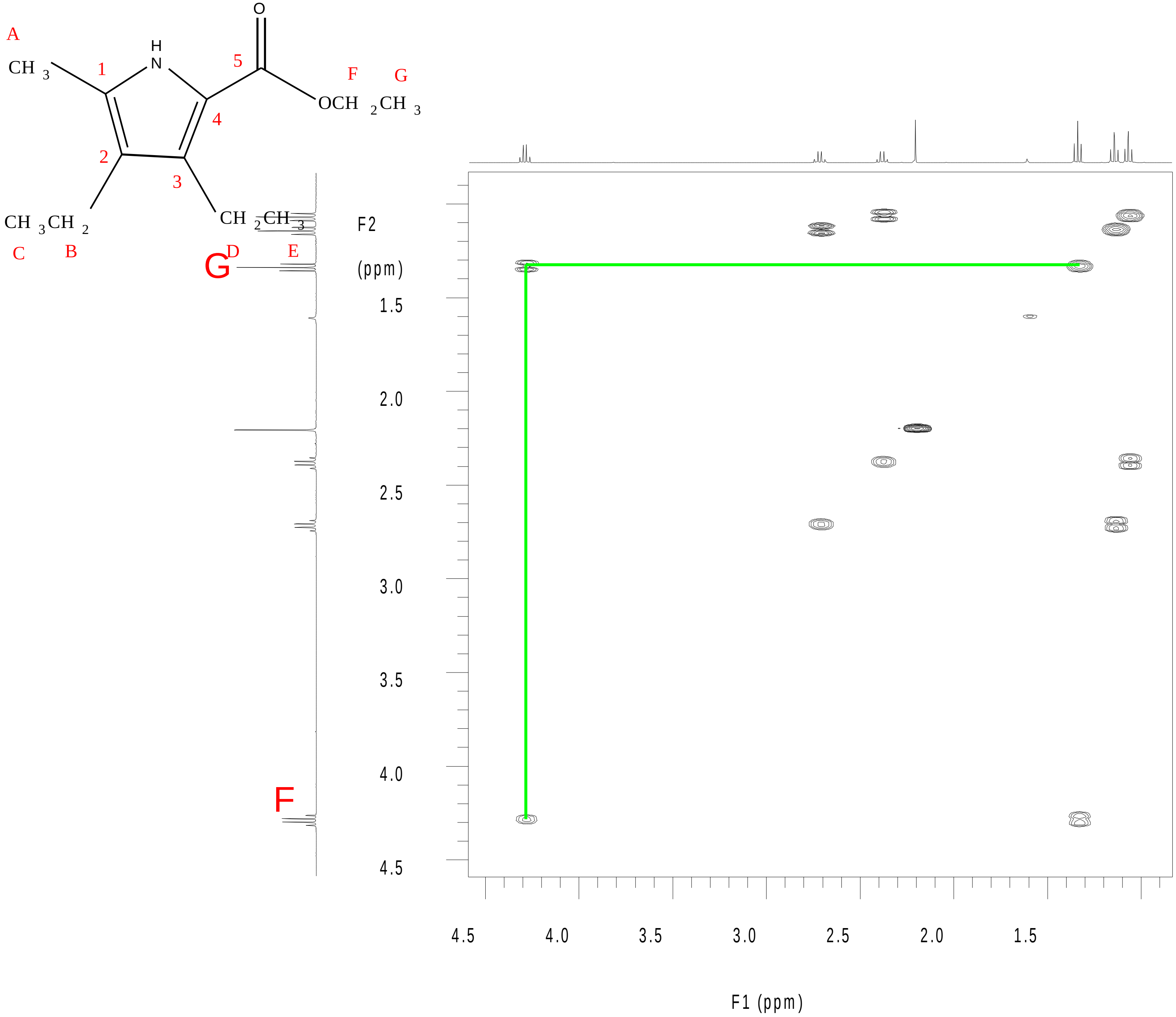
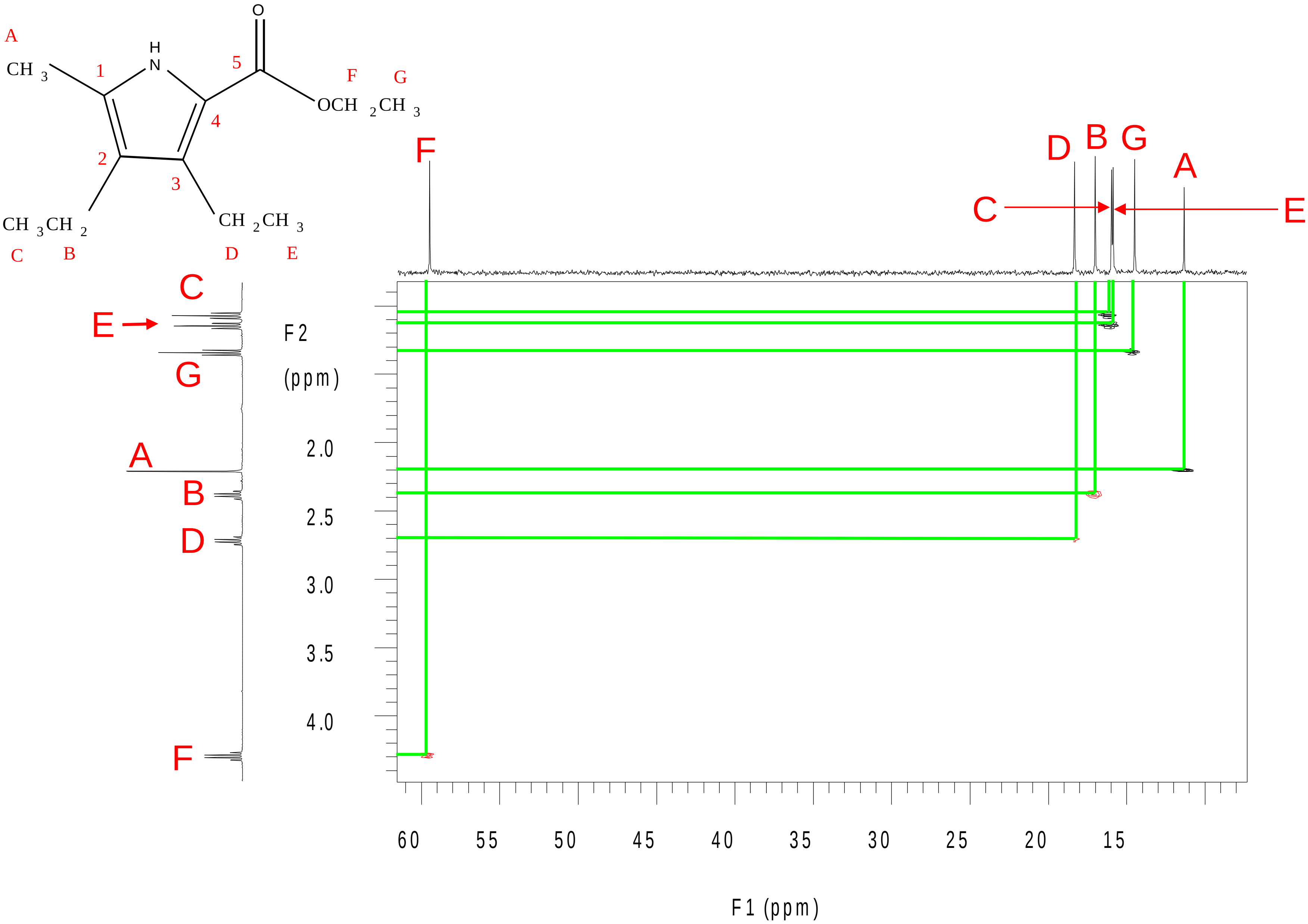
5
O
F
G
OCH2CH3
4
2
3
CH3CH2
CH2CH3
C
B
D
E
5
3
1
2
E
F2
(ppm)
A
B
D
F
2.0
2.5
3.0
3.5
4.0
4.5
160
150
140
130
120
F1 (ppm)


A
CH3
1
H
N
5
O
F
G
OCH2CH3
4
2
3
CH3CH2
CH2CH3
C
B
D
E
5
3
1
2
4
E
F2
(ppm)
A
2.0
B
2.5
D
3.0
3.5
F
4.0
4.5
160
150
140
130
120
F1 (ppm)



A
CH3
1
H
N
5
O
F
G
OCH2CH3
4
2
3
CH3CH2
CH2CH3
C
B
D
E
5
3
1
2
4
C
E
G?
A
B
D
F
F2
(ppm)
2.0
2.5
3.0
3.5
4.0
4.5
160
150
140
130
120
F1 (ppm)


A
CH3
1
H
N
5
O
F
G
OCH2CH3
4
2
3
CH3CH2
CH2CH3
C
B
D
E
G
F
F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F1 (ppm)


A
CH 3
1
H
N
5
O
F
G
OCH 2CH 3
4
2
3
CH 3CH 2
C
B
CH 2CH 3
D
E
F
D
B
G
A
C
E
C
E
G
A
B
D
F
F2
(ppm)
2.0
2.5
3.0
3.5
4.0
60
55
50
45
40
35
30
25
20
15
F1 (ppm)

What’s to like?

Chemical context – simple reaction (esterification) leads to postulated structure .

Need to use multiple techniques to get full assignment

HMBC beautifully illustrates the power of redundant information.

Illustrates how 2D allows definite assignments for near degenerate peaks (eg in carbon).

A researcher has developed an artificial enzyme that apparently couples glucose molecules together. From the product mixture, a single component has been isolated in pure form. Mass spectrometry gives a mass that is correct for two glucose molecules coupled together with the loss of H_2O. The component has been per-acetylated (to make it soluble in organic solvents and to improve the peak dispersion in the NMR spectra) to yield a sample **A**. You are provided with the following NMR data for **A**: 1-dimensional ^{1}H spectrum, 1-dimensional ^{13}C spectrum, COSY spectrum, NOESY spectrum, HSQC spectrum. The spectra provided only cover the range appropriate to the sugar moieties, so the acetyl peaks are not visible and no –OH signals are expected. The only certain piece of relevant spectroscopic data that you can find in the literature is that anomeric carbons in glucose type sugars come between 85 and 105 ppm in the ^{13}C spectrum.

Confirm that the spectra provided are consistent with the structure being a condensation product from 2 molecules of glucose with loss of water.

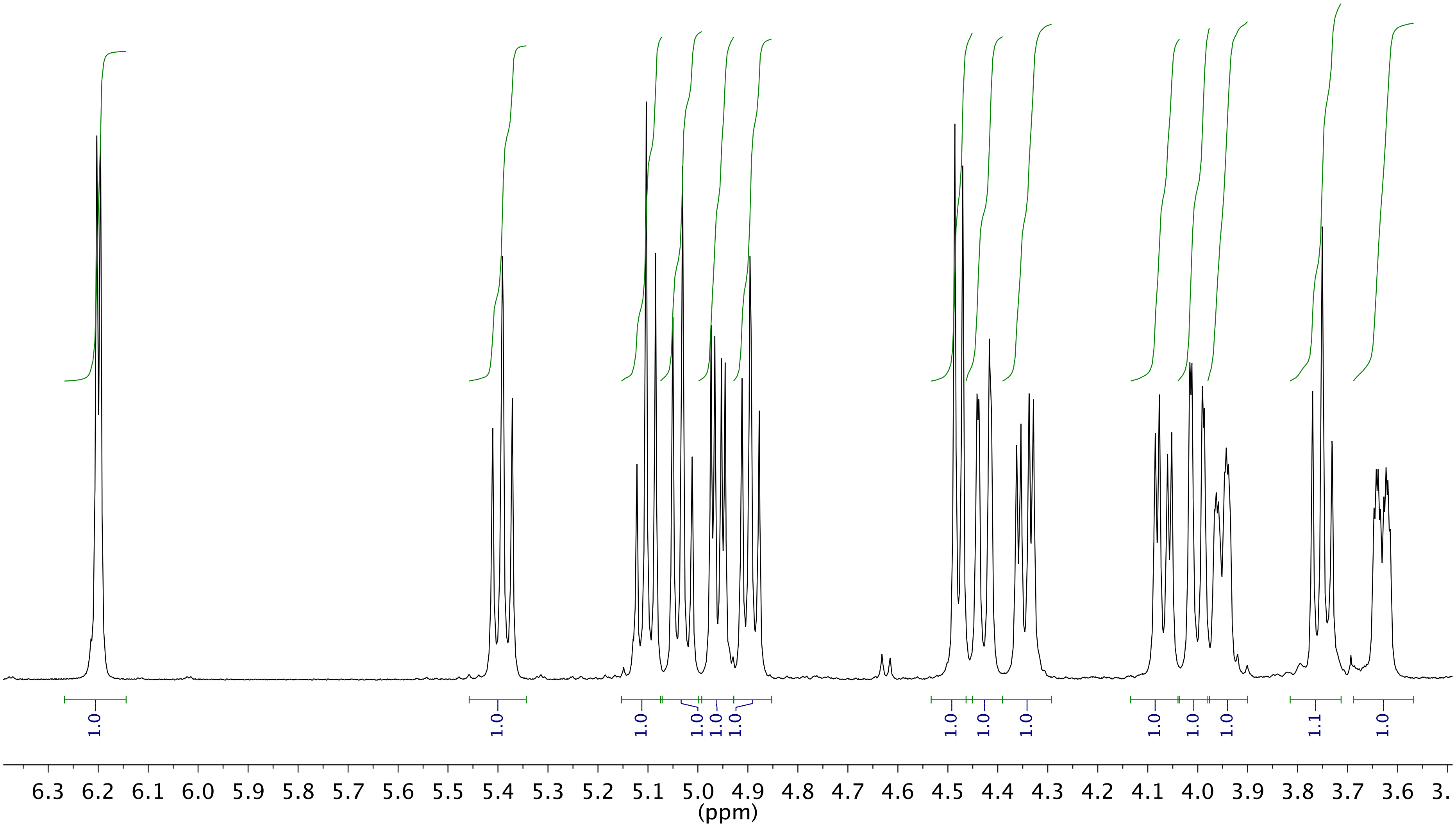
Use the two-dimensional NMR data provided to identify the site of coupling between the two rings.

Draw a clearly labelled diagram of your proposed structure. All acetyl groups can be represented as Ac.

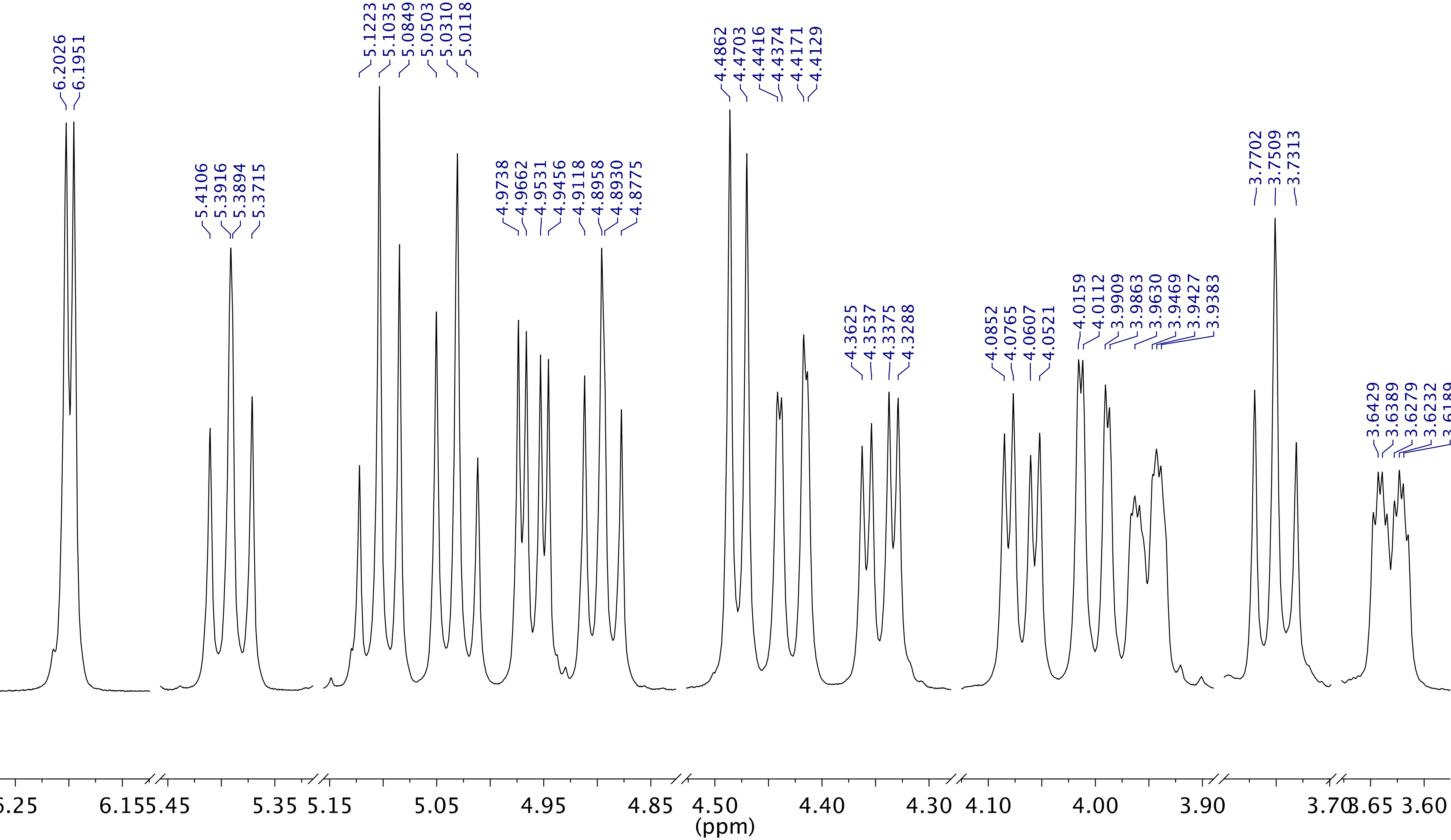
Use the two-dimensional NMR data provided to identify the stereochemistry at the site of coupling, and whether there have been any changes in stereochemistry elsewhere in the molecule.

Report the assignments of the one-dimensional ^{1}H and ^{13}C spectra in a format suitable for inclusion in a journal article.

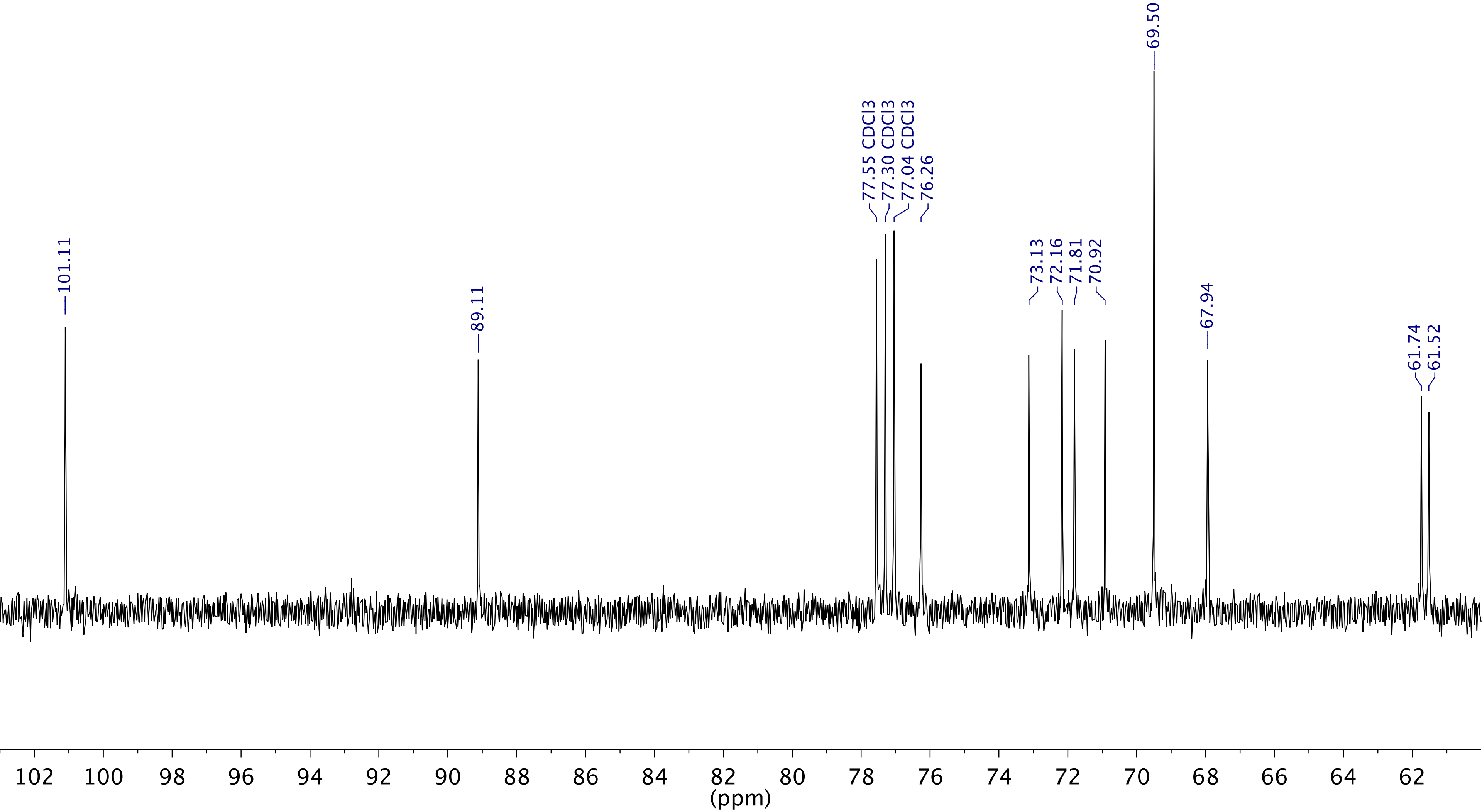
^{1}H, 500 MHz, CDCl$_3$ - full spectrum

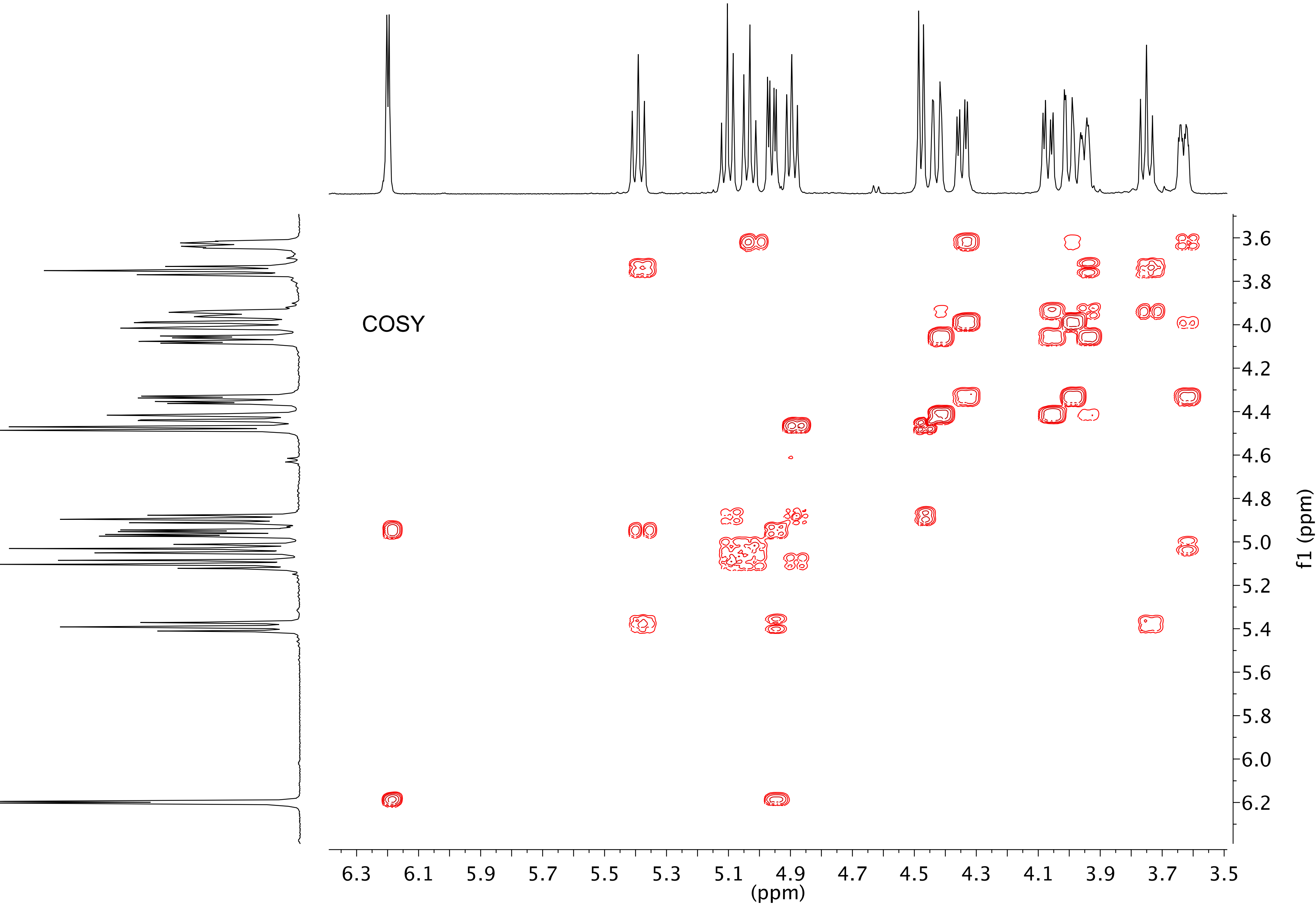


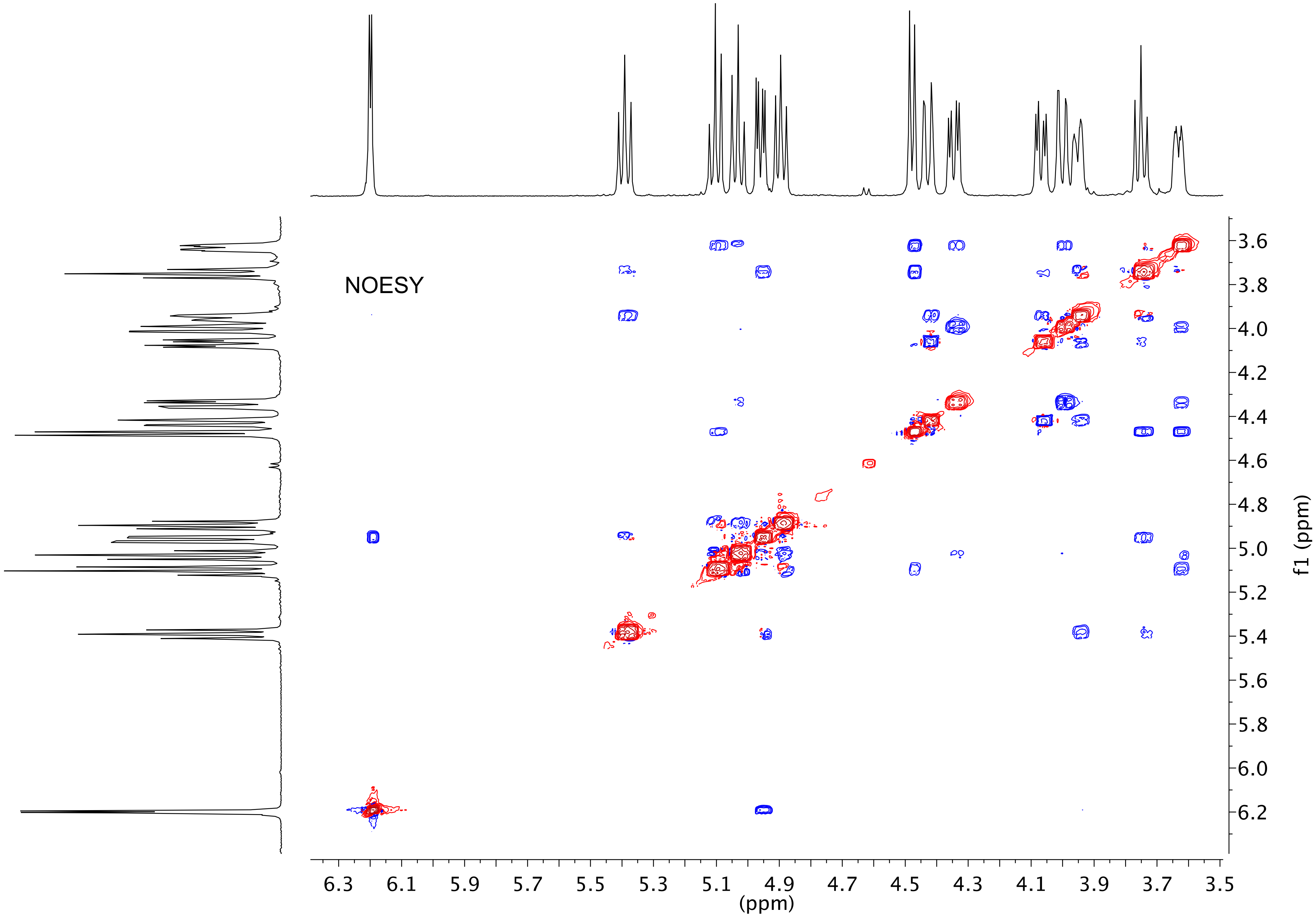
^1H, 500 MHz, $CDCl_3$ - expansions with peak positions

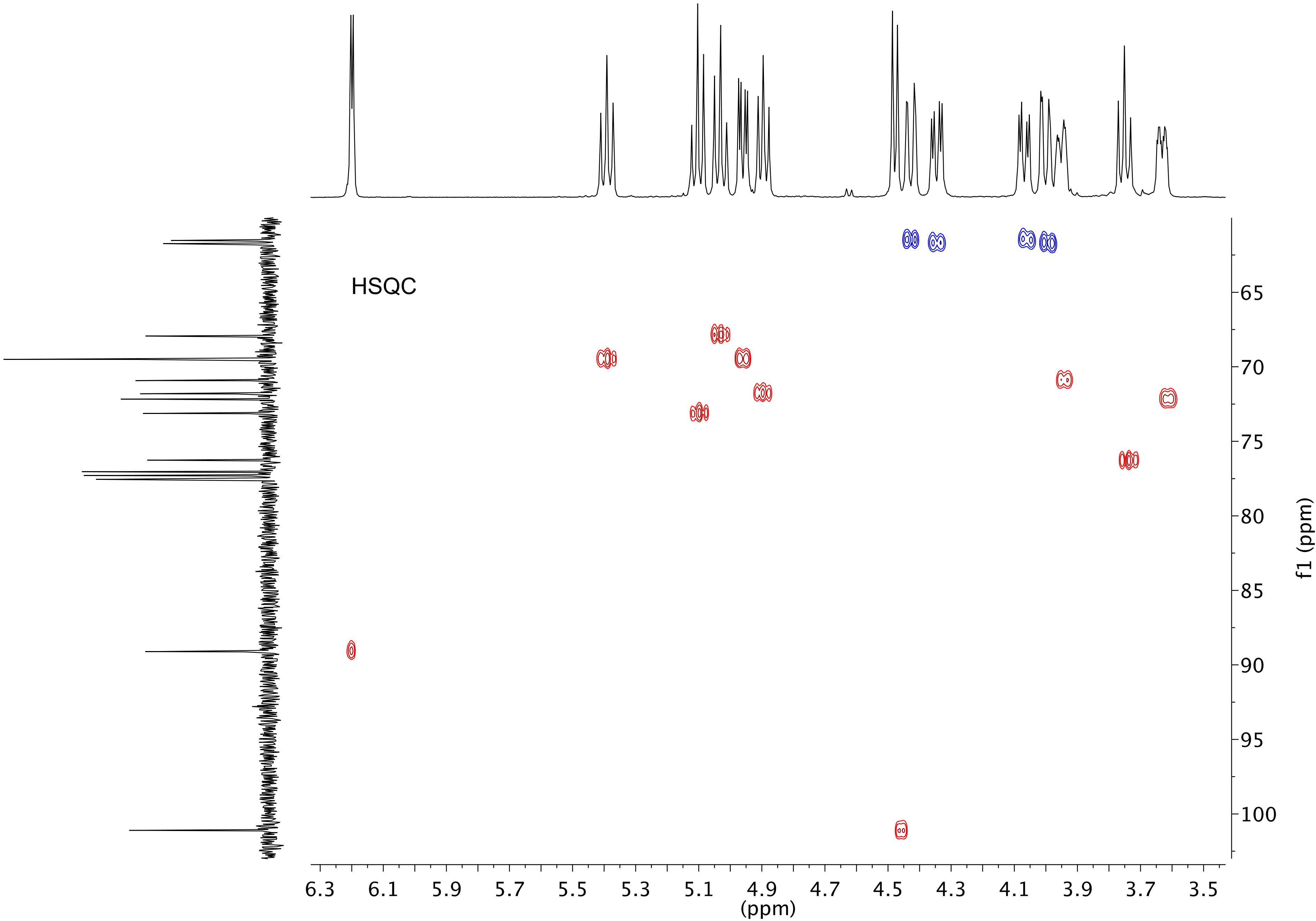


^{13}C, 125 MHz, $CDCl_3$ - full spectrum




COSY
6.3
6.1
5.9
5.7
5.5
5.3
5.1
4.9
4.7
4.5
4.3
4.1
3.9
3.7
3.5
(ppm)
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.6
5.8
6.0
6.2
f1 (ppm)


NOESY
6.3
6.1
5.9
5.7
5.5
5.3
5.1
4.9
4.7
4.5
4.3
4.1
3.9
3.7
3.5
(ppm)
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.6
5.8
6.0
6.2
f1 (ppm)


HSQC
6.3
6.1
5.9
5.7
5.5
5.3
5.1
4.9
4.7
4.5
4.3
4.1
3.9
3.7
3.5
(ppm)
65
70
75
80
85
90
95
100
f1 (ppm)

What’s to like?

Chemical context – range of possible, well-defined structures.

Need to use multiple techniques to get full assignment

Complementarity of COSY and NOESY – use of NOE in assigning stereochemistry.

Information (integrals and coupling constants) from 1D proton spectrum still useful (Karplus).

Nutshell

Problems and examples in a context students can relate to work best. (“Identify the unknown white powder” is poor because it requires an unrealistic approach)

Problems that require the student to (work out how to?) distinguish between alternative possibilities are good.

You don’t need complicated molecules to get complex spectra.

Assignment is not enough – you need to be able to justify your assignment.

A couple of potentially useful links if you are looking for example problems:

http://www.chem.uci.edu/~jsnowick/organicspectroscopy/index.html

http://nmrwiki.org/wiki/index.php?title=Materials_for_teaching_NMR

I am also happy to share teaching materials / problems with colleagues.
Email me at a.m.kenwright@durham.ac.uk