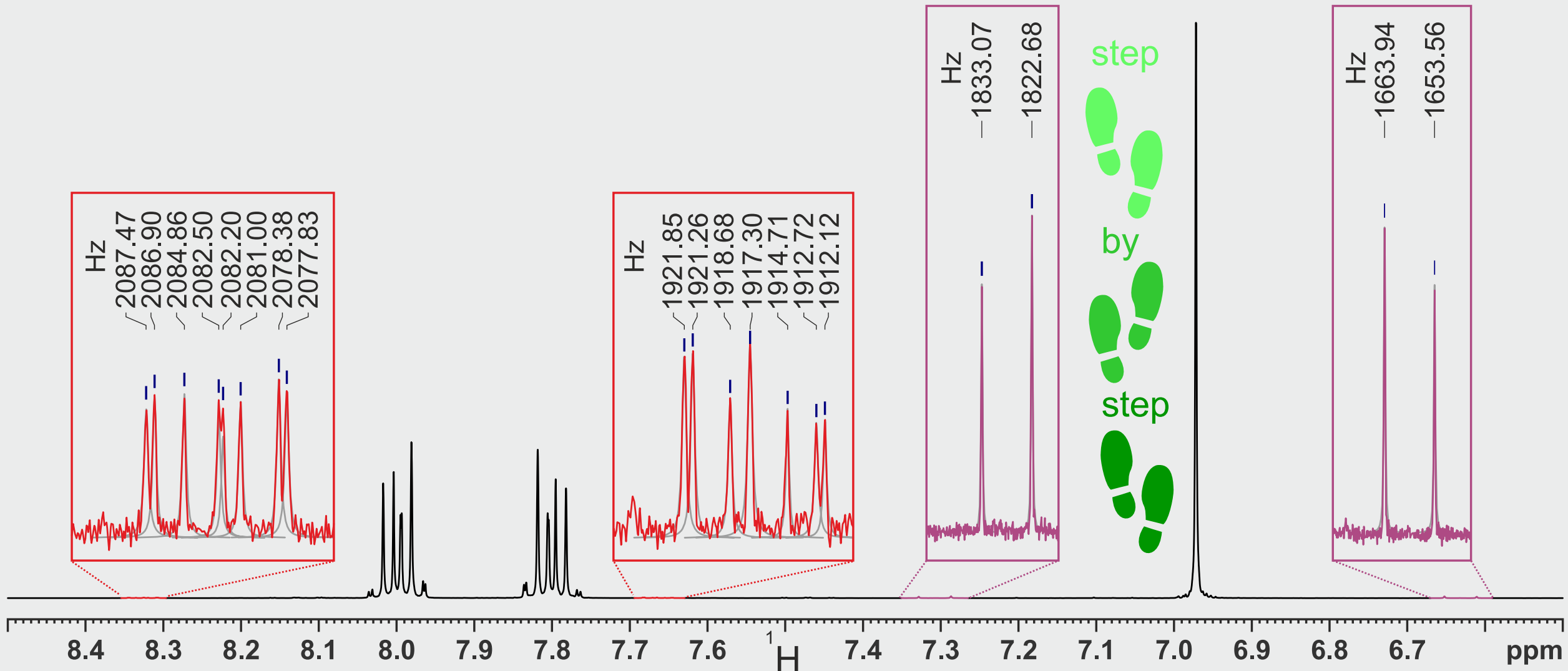


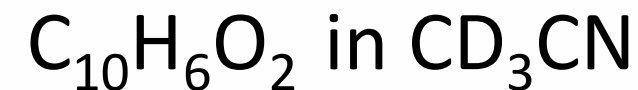
Exercise plus Solution – Quick PDF overview

It is recommended to use this PDF version only for a quick overview of the NMR challenge. All animations of the PowerPoint version are missing, under certain circumstances quality deficiencies may also occur. The higher quality PowerPoint files are freely available for download at any time.



Problem of the Month:

August 2021

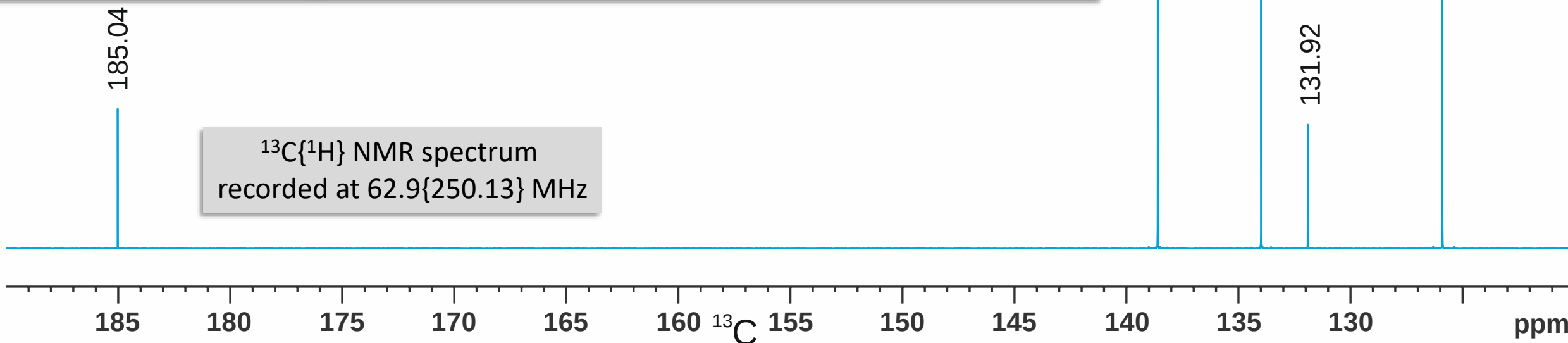


To get the structure of this compound, you do not even need a database. Entering the molecular formula into a search engine of your choice would be sufficient. In this case, the excellent signal-to-noise ratio of the carbon spectra opens up a rarely used opportunity to deduce the structure using carbon-carbon coupling constants.

Deduce the constitution and assign all nuclei.

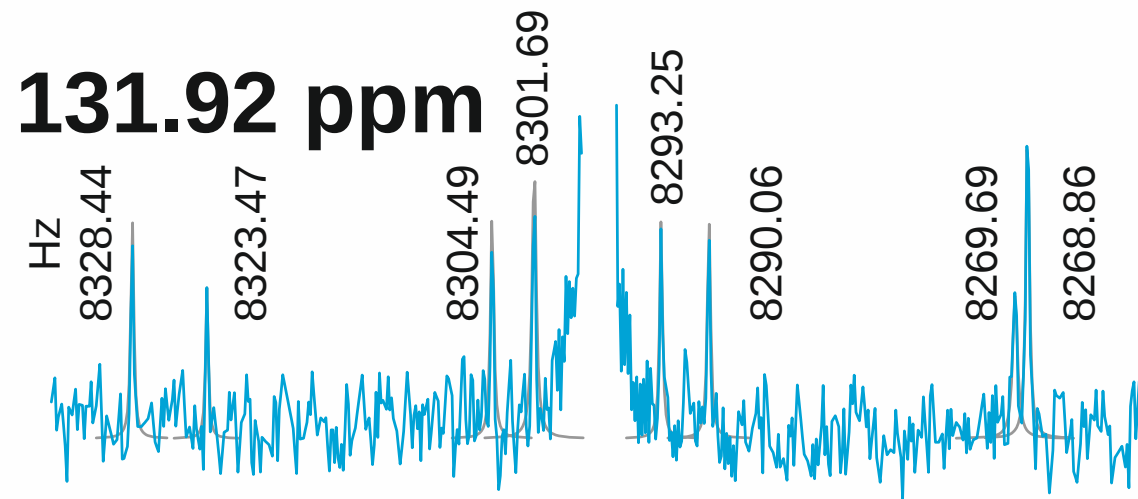
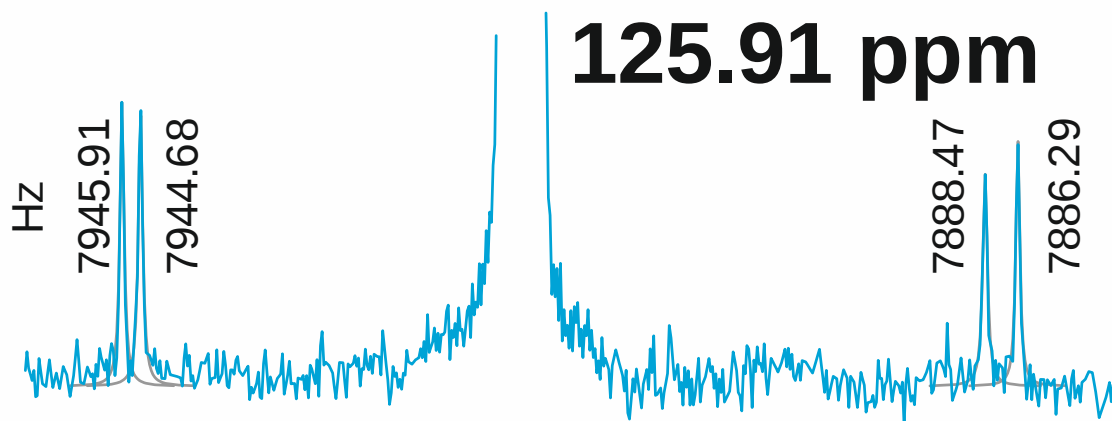
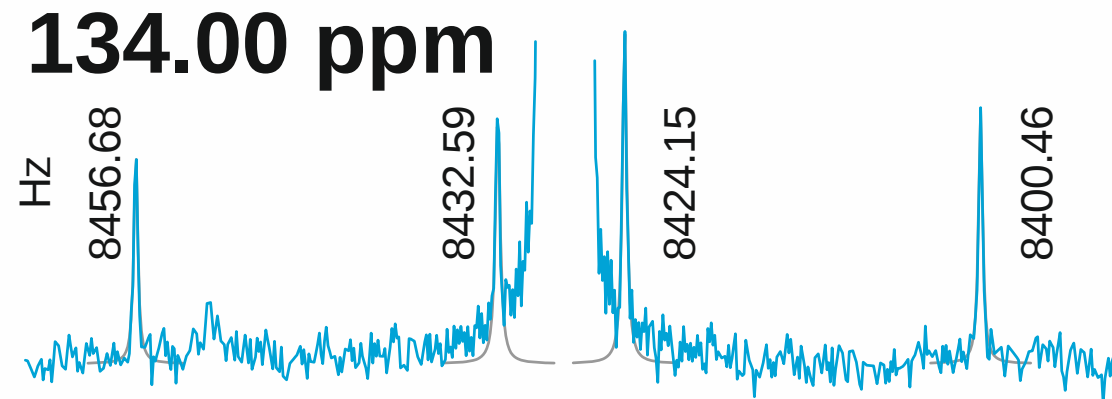
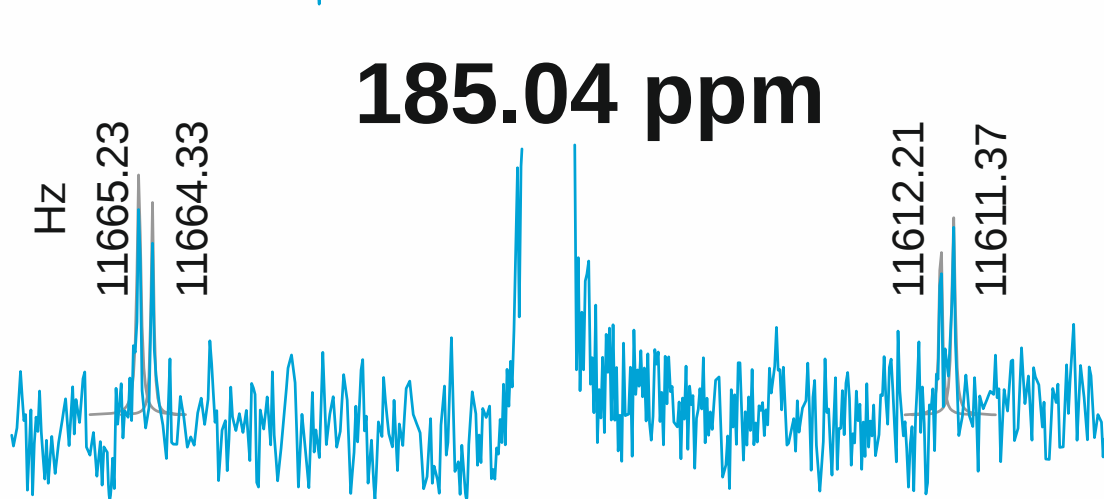
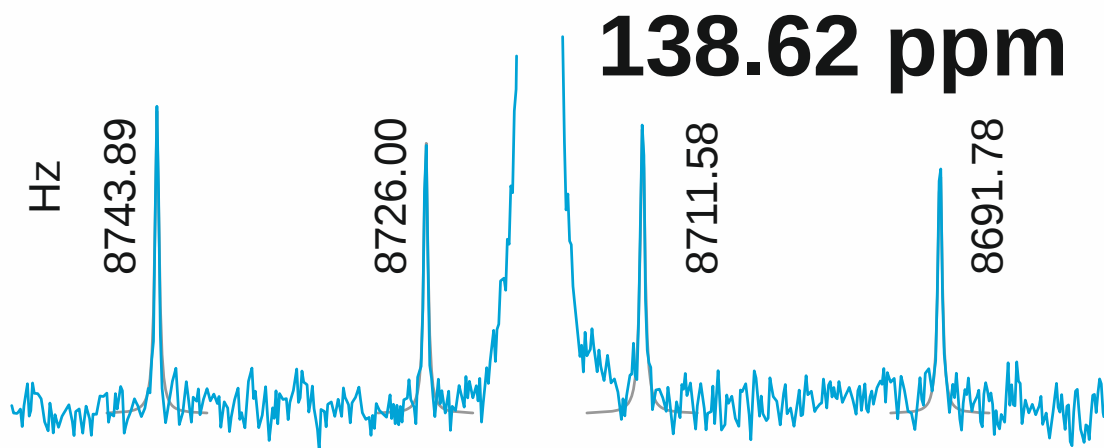
Measure as many homonuclear coupling constants as possible and assign them.

(don't forget, $J_{\text{C,C}}$ of course are also homonuclear coupling constants)



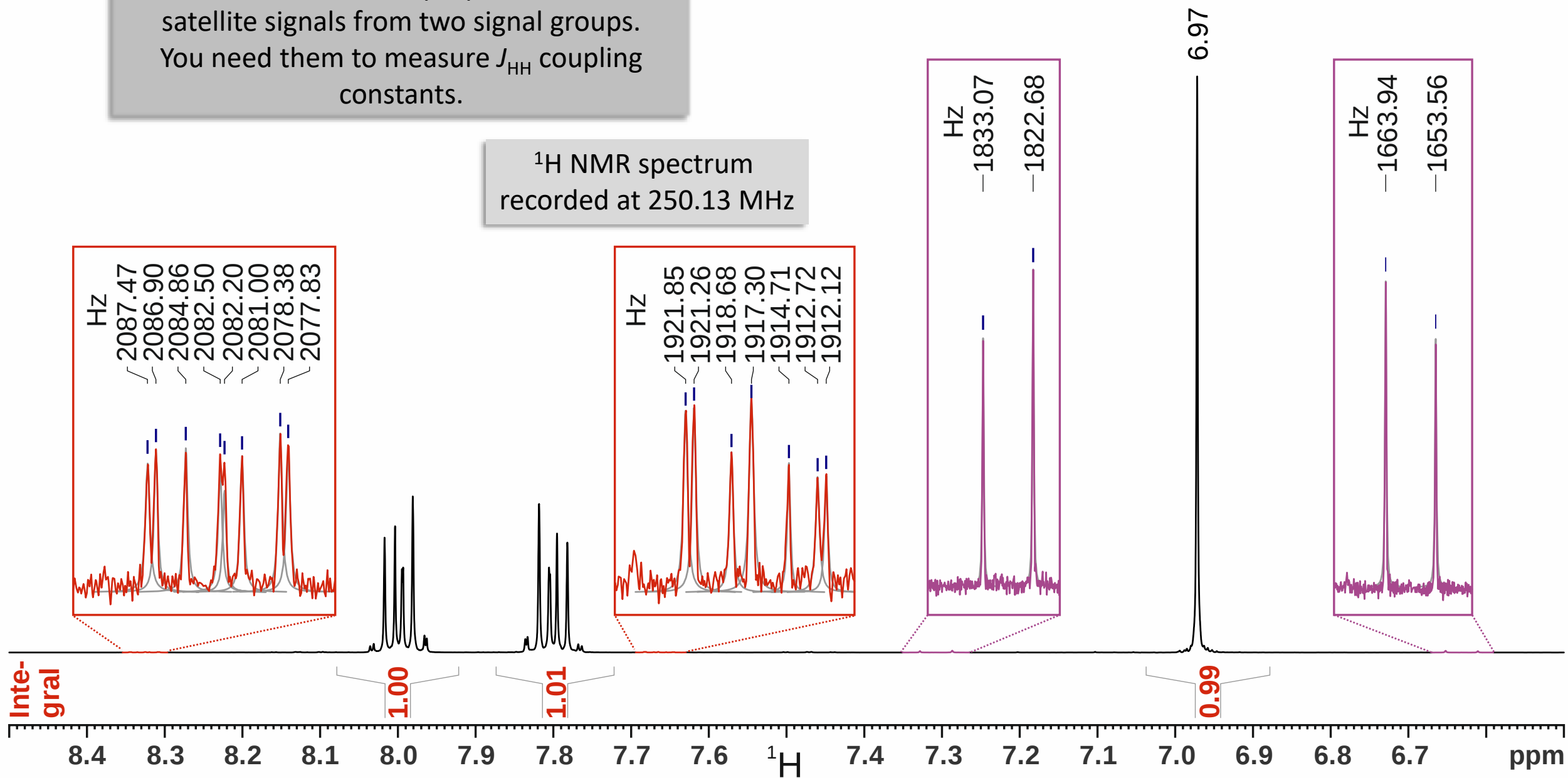
The five carbon signals at high magnification

$^{13}\text{C}\{^1\text{H}\}$ NMR spectrum
recorded at 62.9{250.13} MHz

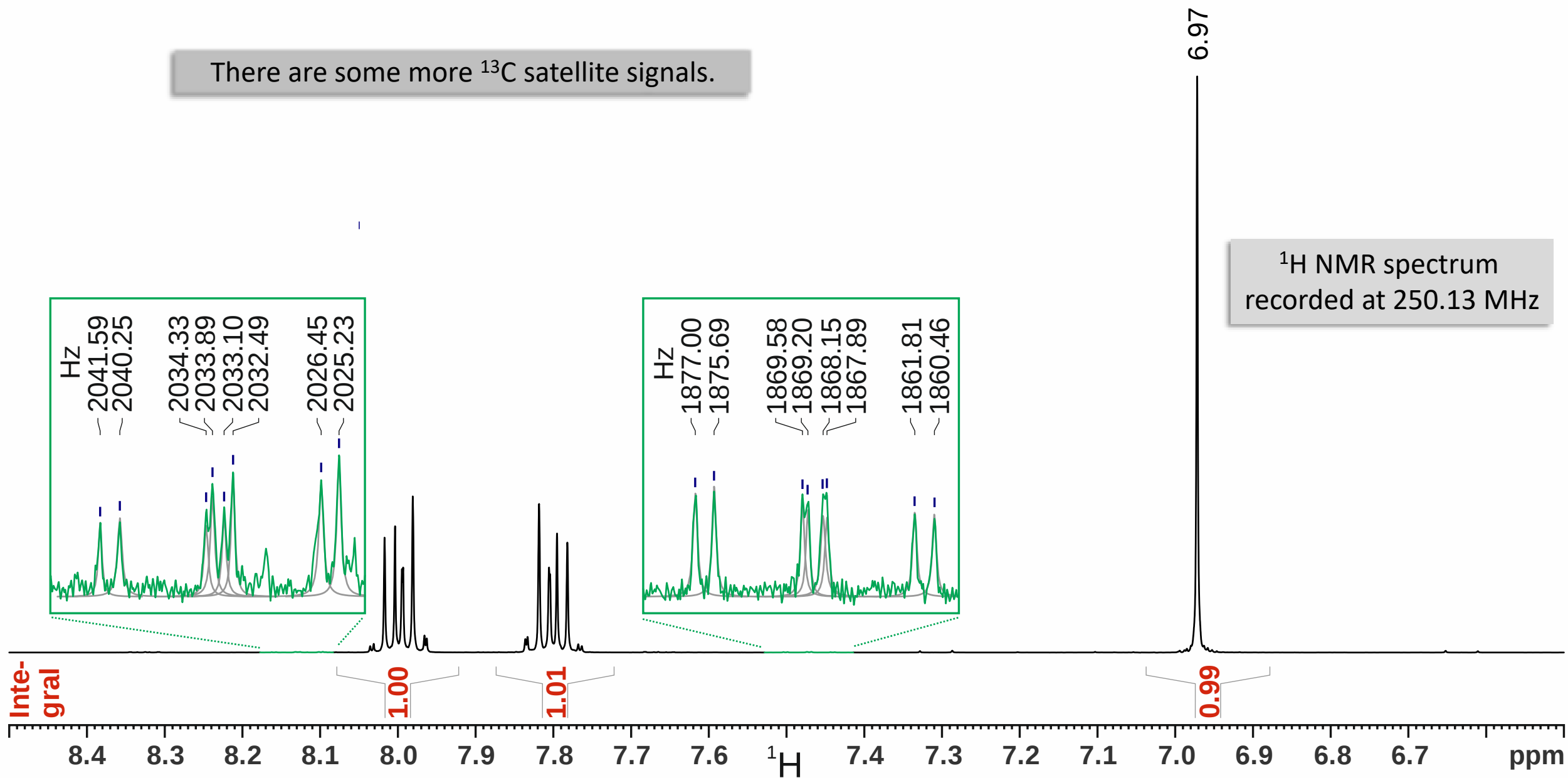


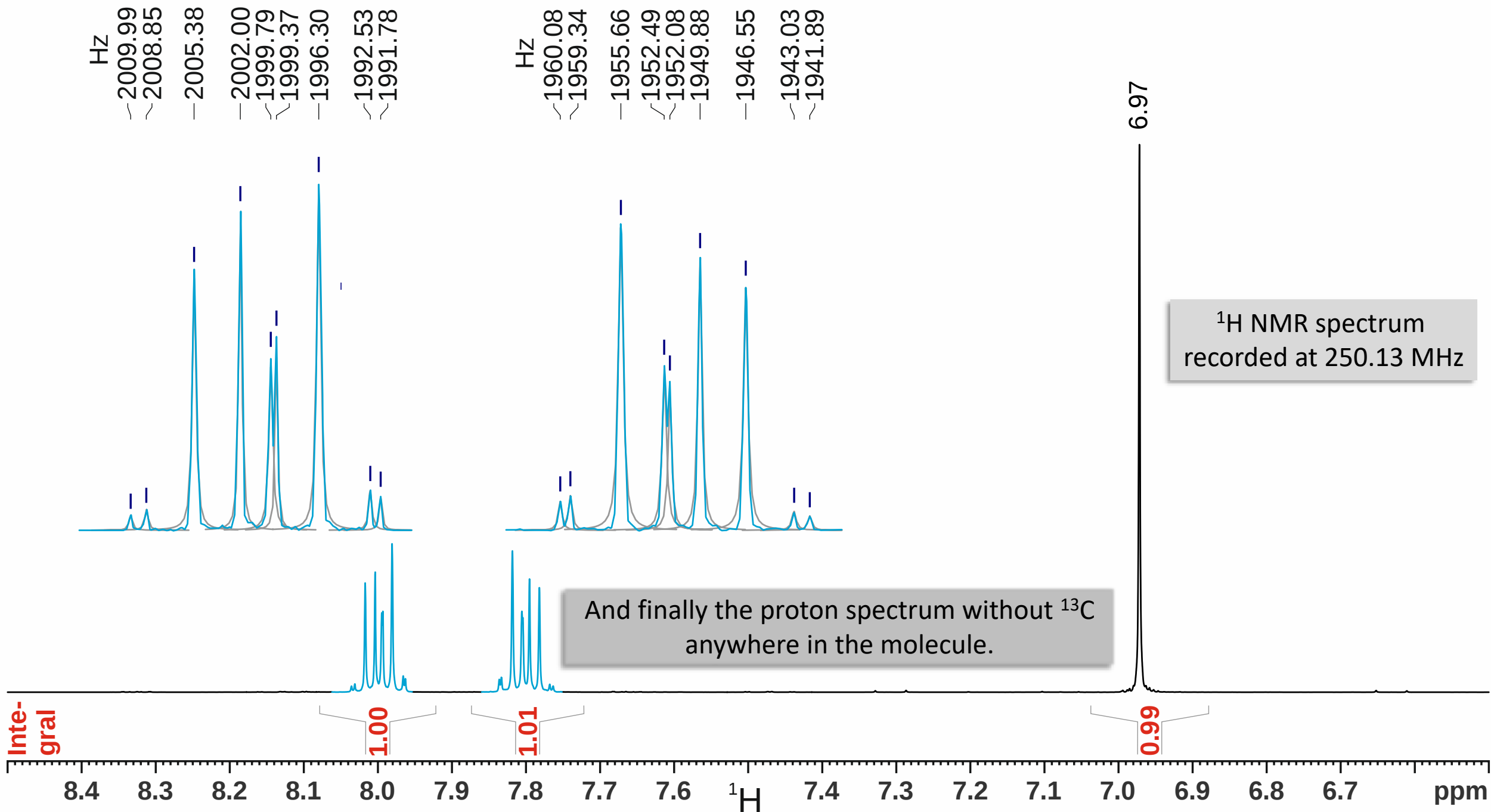
The insets in red and purple are the ^{13}C satellite signals from two signal groups. You need them to measure J_{HH} coupling constants.

^1H NMR spectrum
recorded at 250.13 MHz



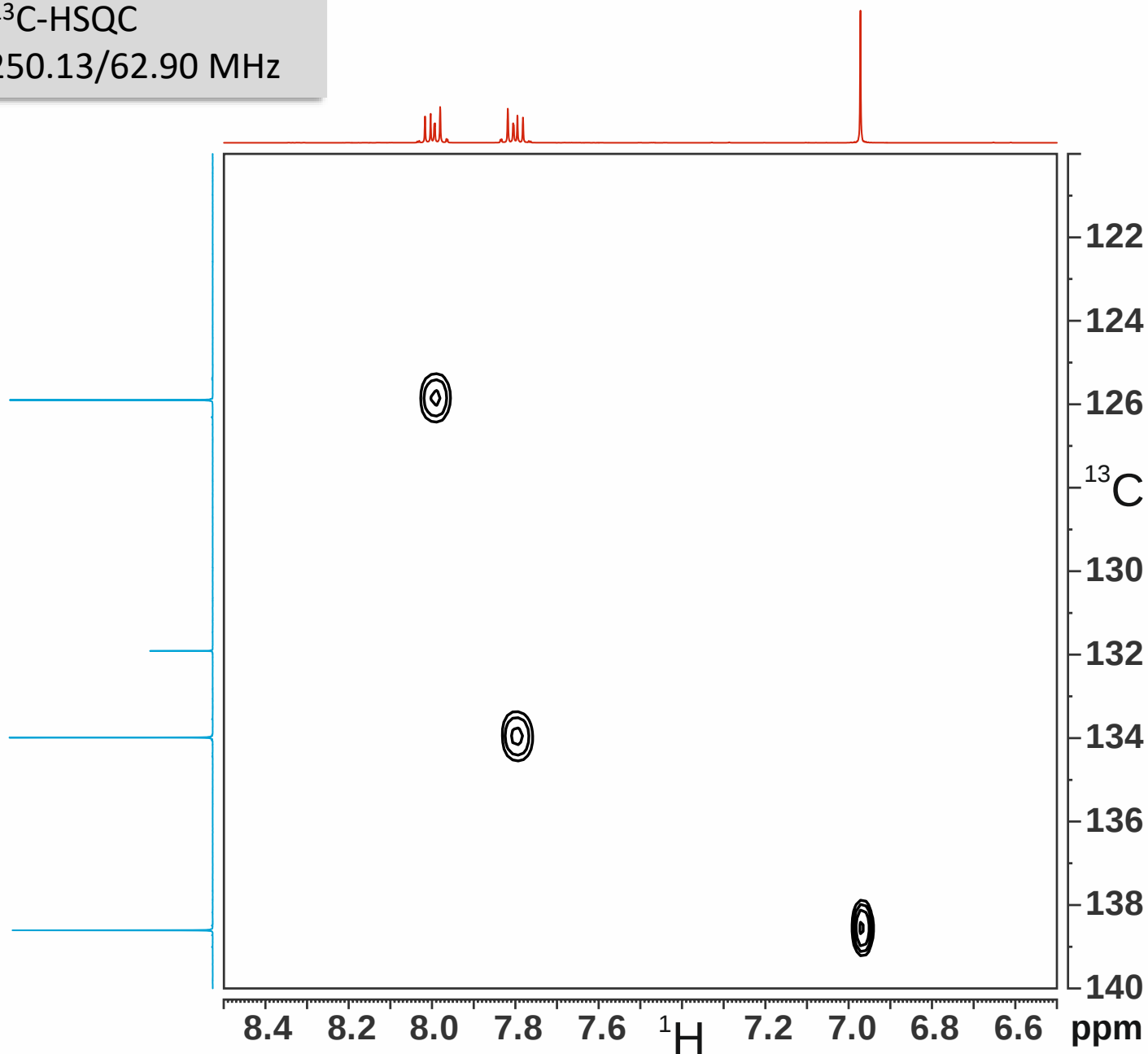
There are some more ^{13}C satellite signals.



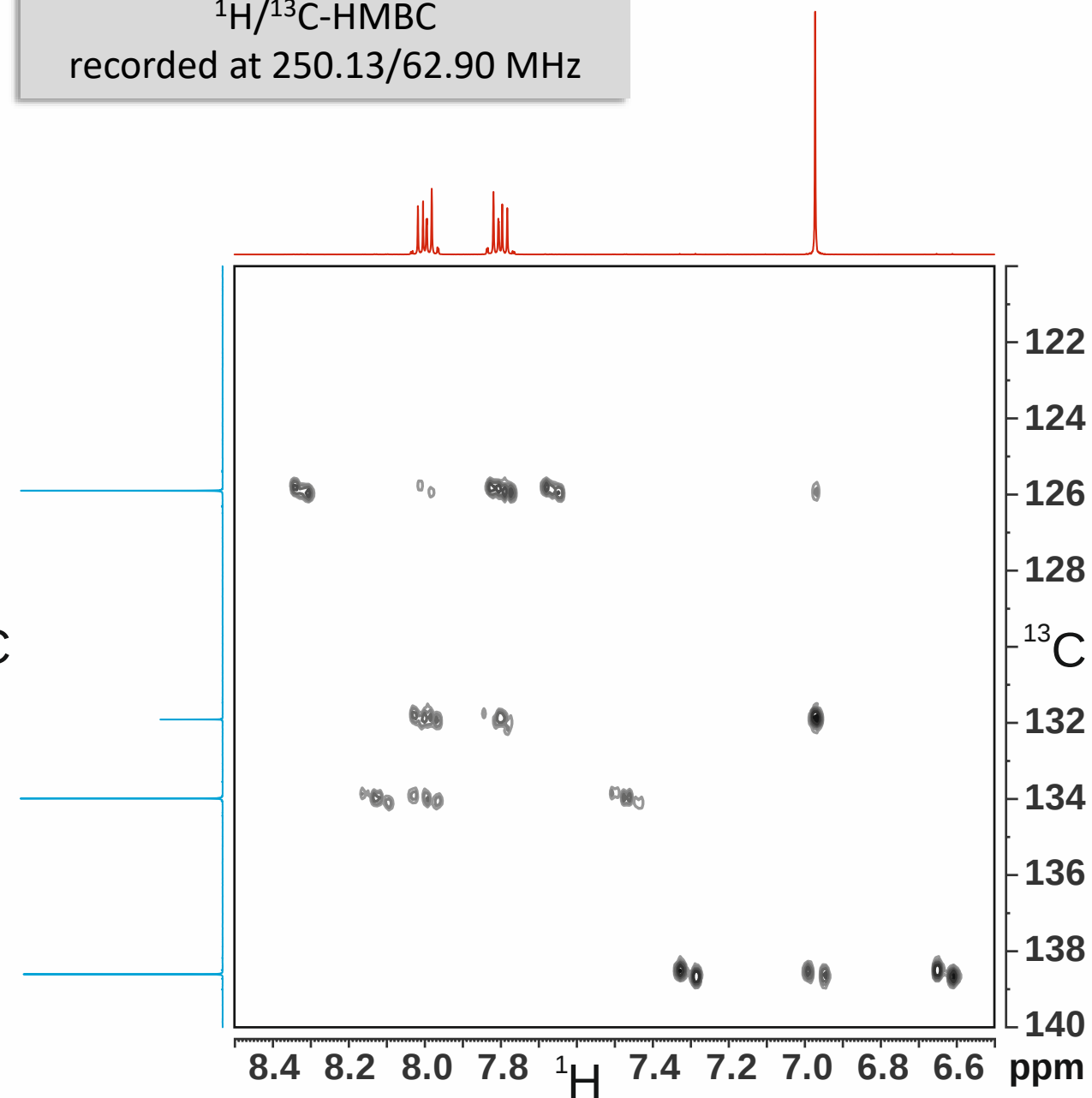
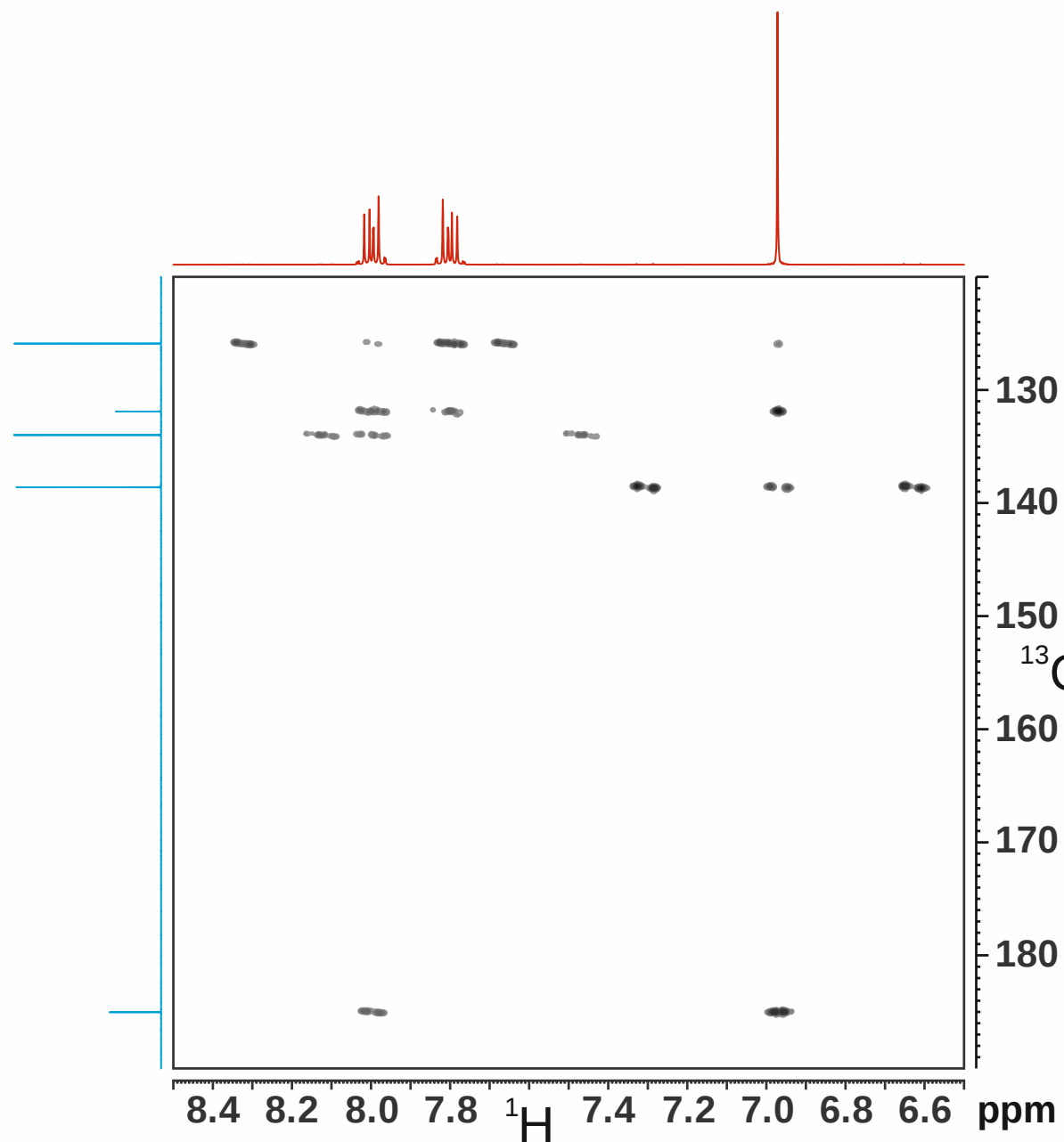


$^1\text{H}/^{13}\text{C}$ -HSQC
recorded at 250.13/62.90 MHz

The HMBC at the next page is not really necessary to solve this challenge. You might use it to check your solution using independent data.

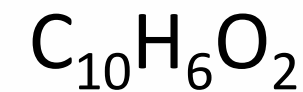


$^1\text{H}/^{13}\text{C}$ -HMBC
recorded at 250.13/62.90 MHz

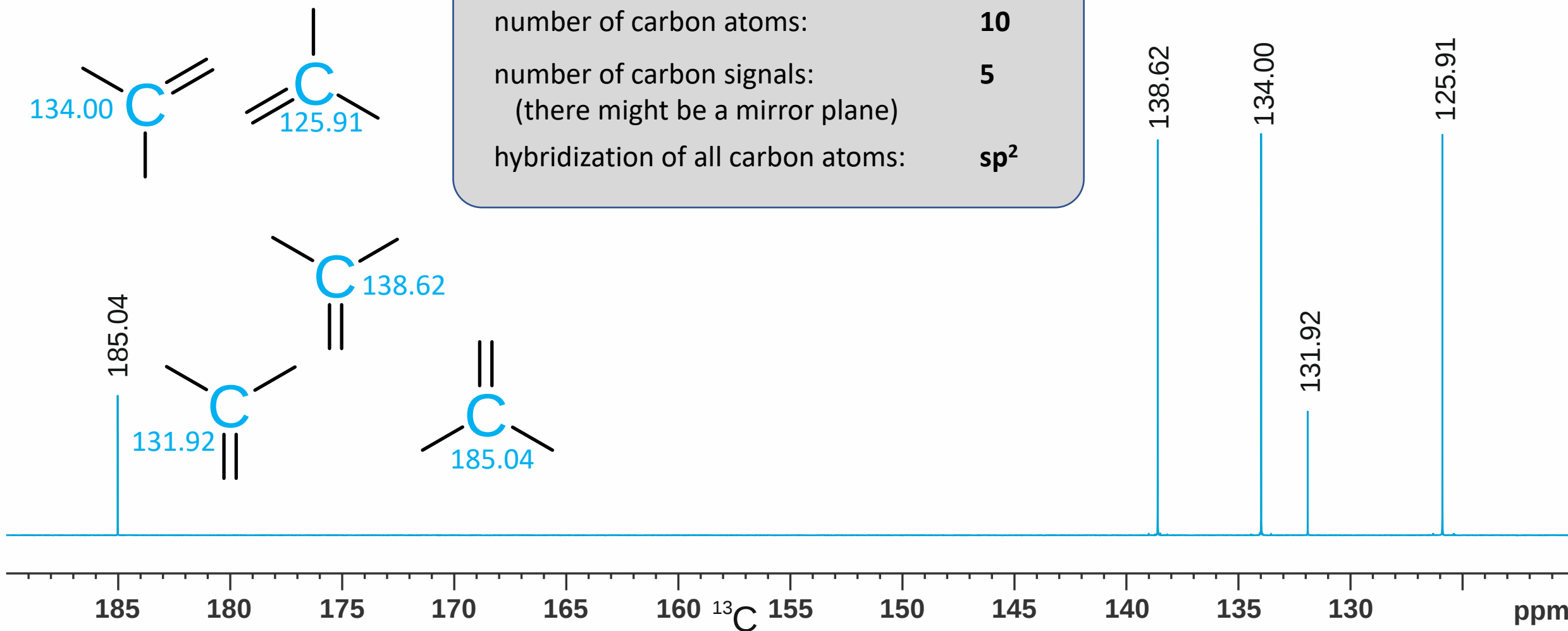


Basic considerations

Double bond equivalents,
symmetry

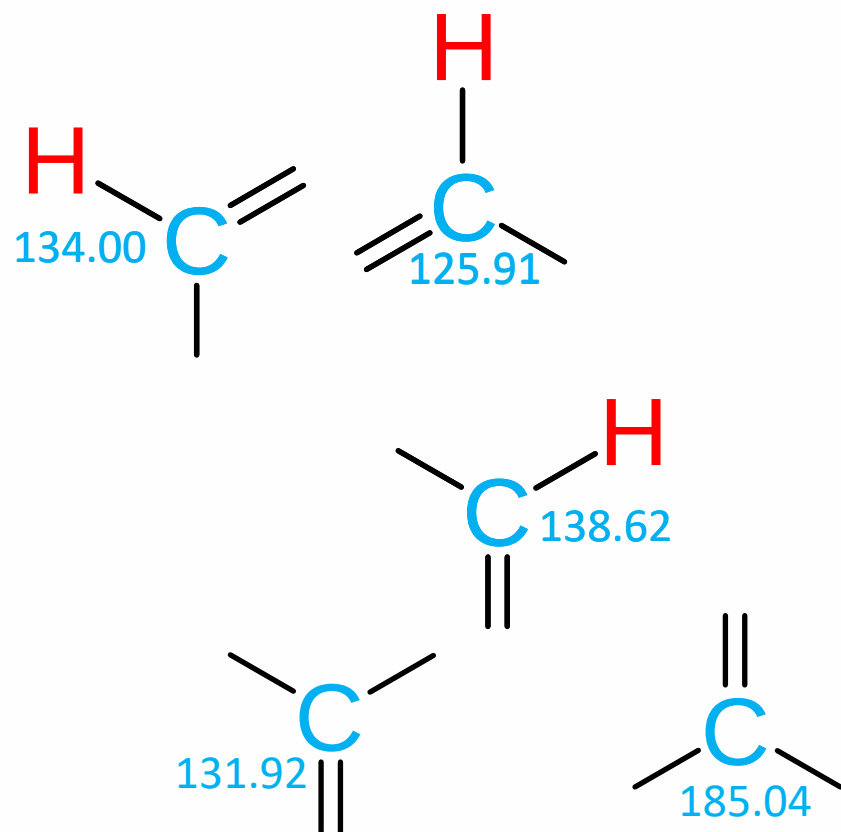


double bond equivalents:	8 (!)
number of carbon atoms:	10
number of carbon signals: (there might be a mirror plane)	5
hybridization of all carbon atoms:	sp²

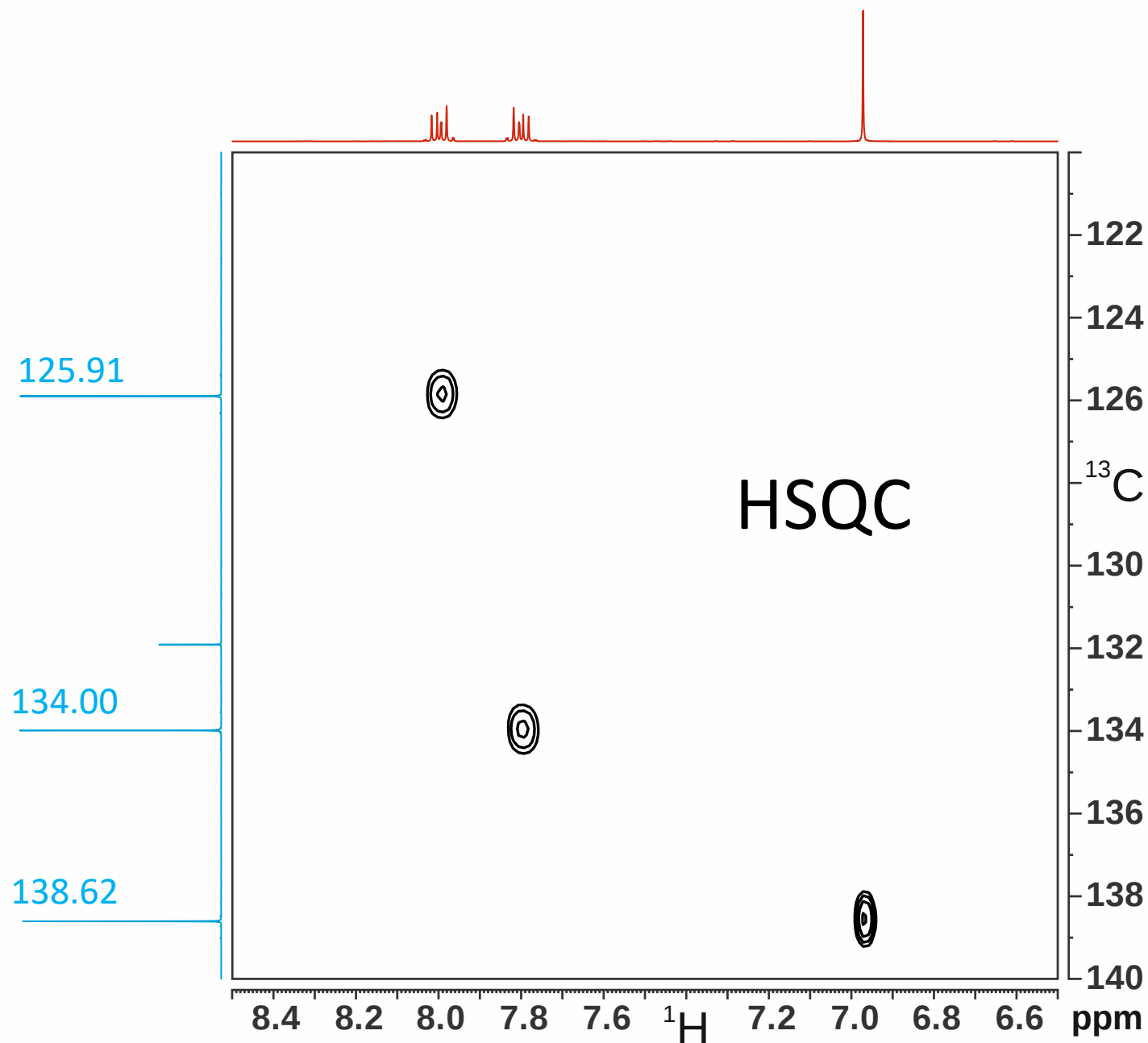


Some more details

Double bond equivalents,
symmetry

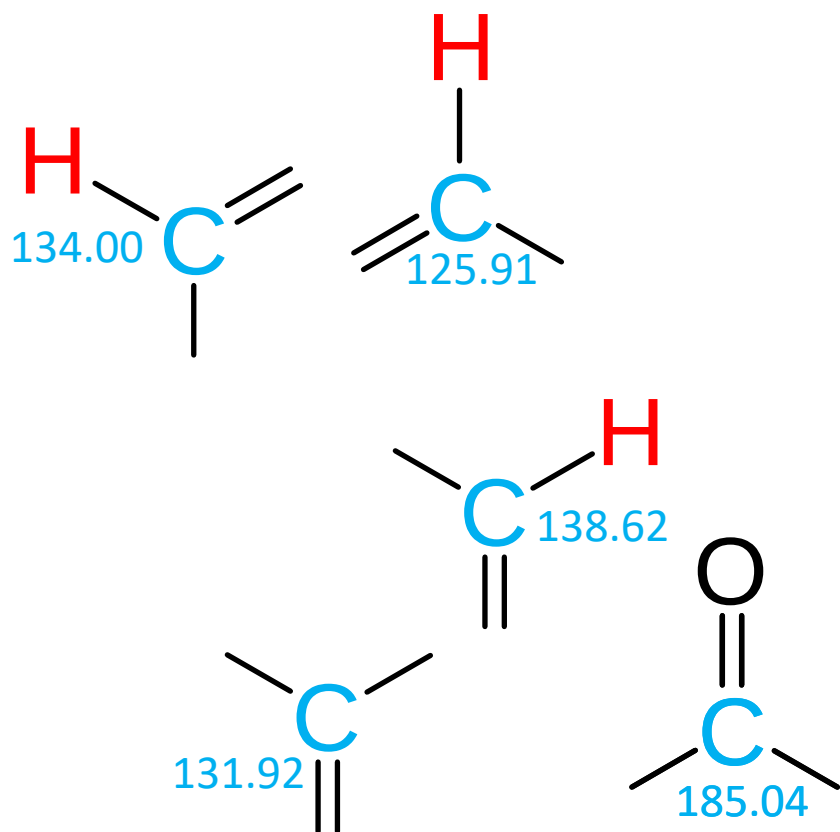


According to the HSQC three of the carbon atoms have to be $=\text{CH}_n$ groups. For the moment we don't deal with the number of attached protons.



Some more details

Double bond equivalents,
symmetry



With a very high amount of probability, we have $n = 1$, which means $=CH-$ and no $=CH_2$.

Why?

If we summarize all atoms found so far, we have exactly half the number of carbon atoms and protons (assuming $n = 1$) in the molecular formula. A mirror plane would double both the number of carbon atoms and protons.

But what about the carbon with the chemical shift of 185.04 ppm?

We have

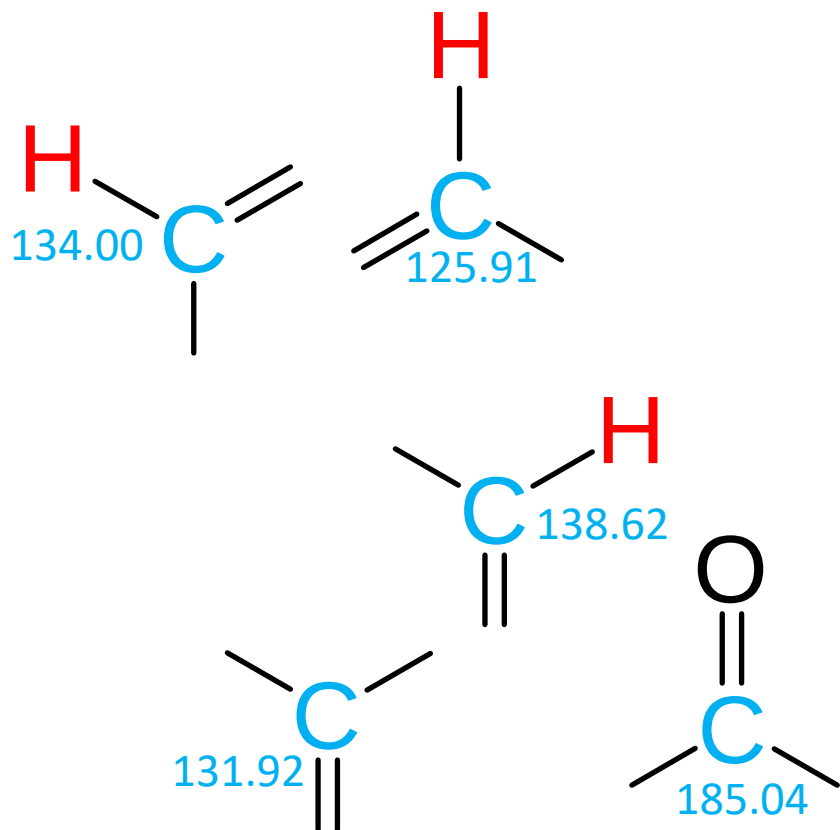
- the very low field chemical shift
- the high number of double bond equivalents and
- the oxygen from the molecular formula

and we can deduce a **carbonyl group**.

If we now count all of the atoms at the left side of this slide, we have exactly half of the molecular formula.

Carbon-carbon couplings

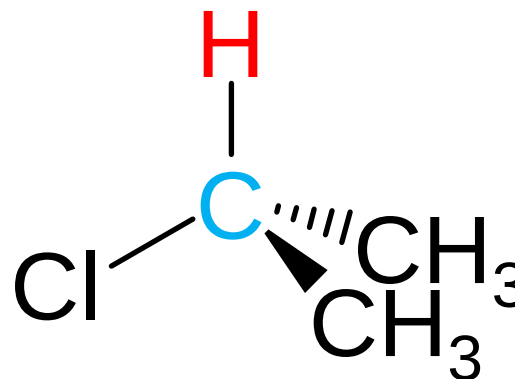
Probability and spectra



Because of the excellent signal-to-noise-ratio in the one dimensional carbon spectrum, we might think about using one bond carbon-carbon coupling constants to get the backbone of this molecule.

But first let us try to understand some basics.

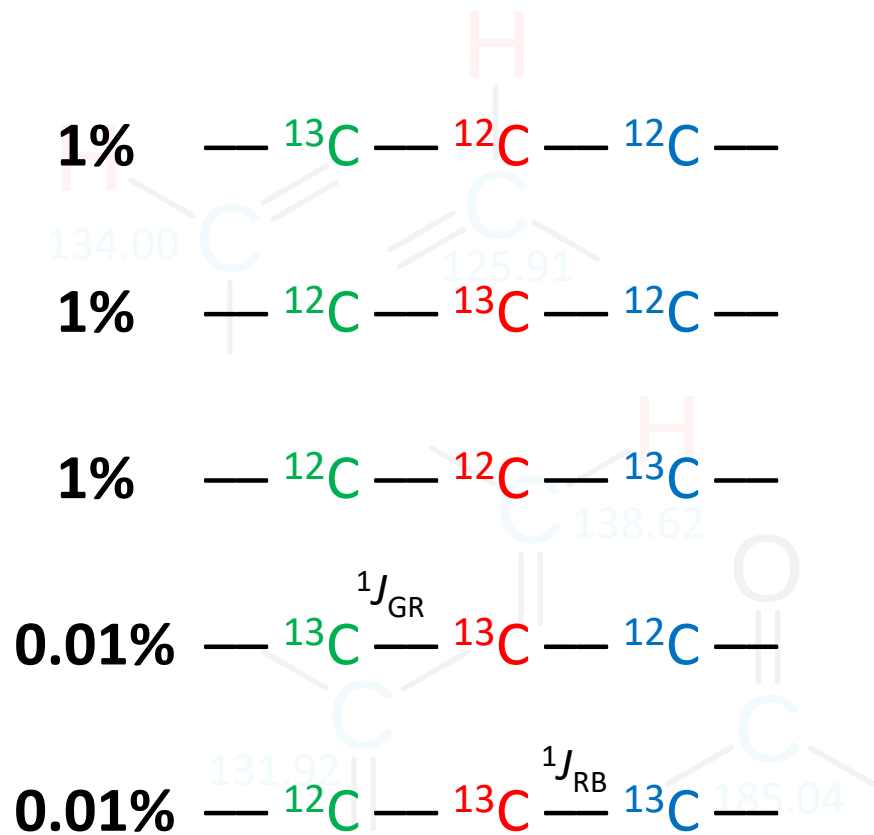
As you know, in 2-chloro-propane you see a septet for the **proton** attached to C-2. But what about the carbon-carbon coupling pattern for C-2? Is it a triplet due to the chemical equivalence of carbon atoms C-1 and C-3? (No! Why?)



Let us simulate some carbon spectra using a backbone similar to 2-chloro-propane.

Carbon-carbon couplings

Probability and spectra

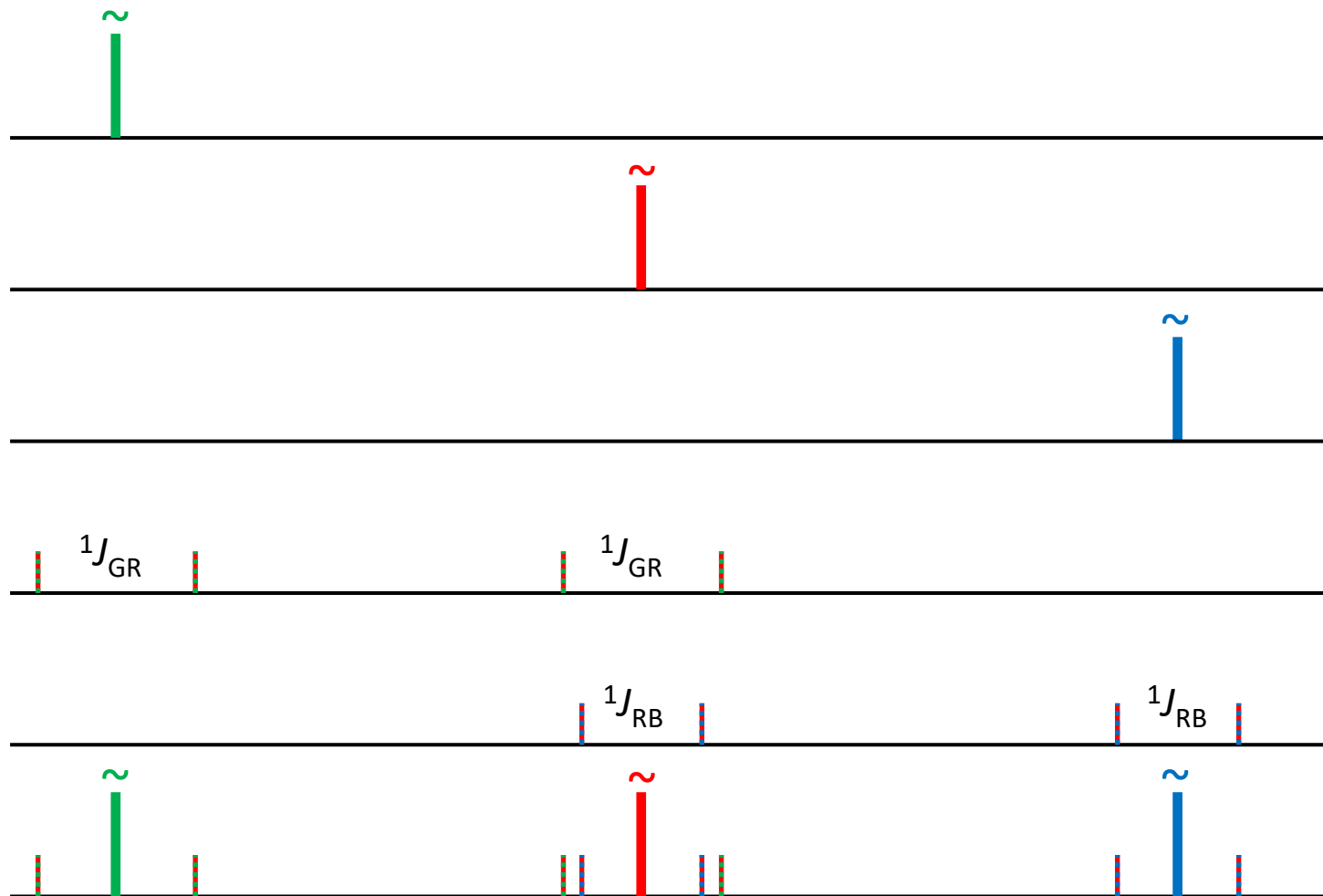


Sum of all components

(there is no signal at all from about 97% of all sample molecules)

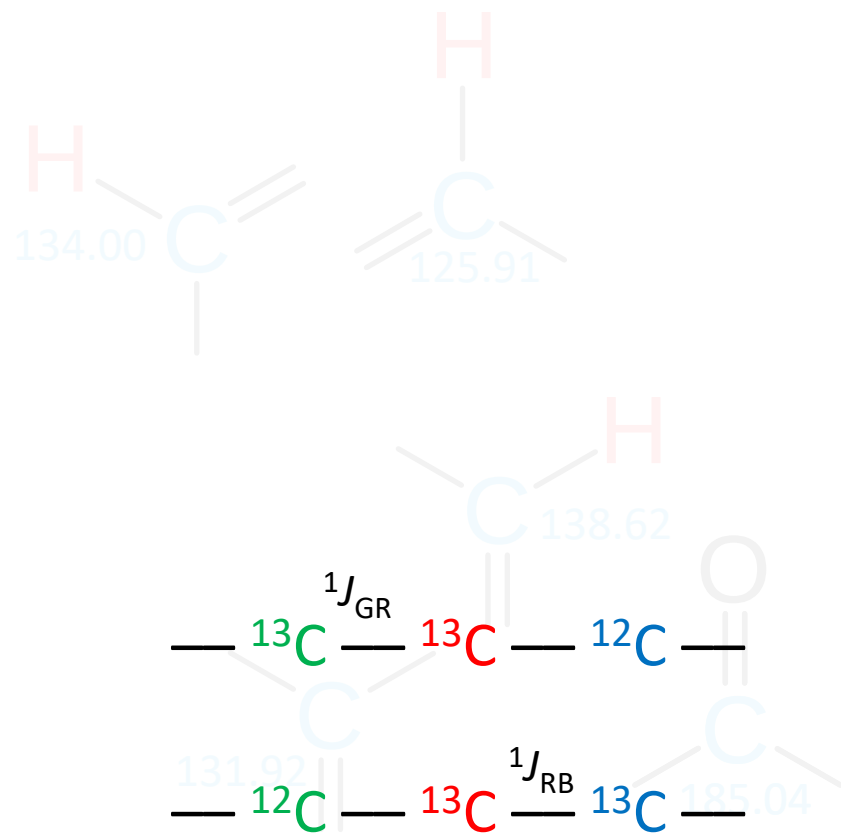
We should remember, that **every** NMR spectrum is **not** the result of **one molecule**, but of a huge ensemble of molecules.

Let's simulate the carbon spectrum of the single (asymmetric) model compound



Carbon-carbon couplings

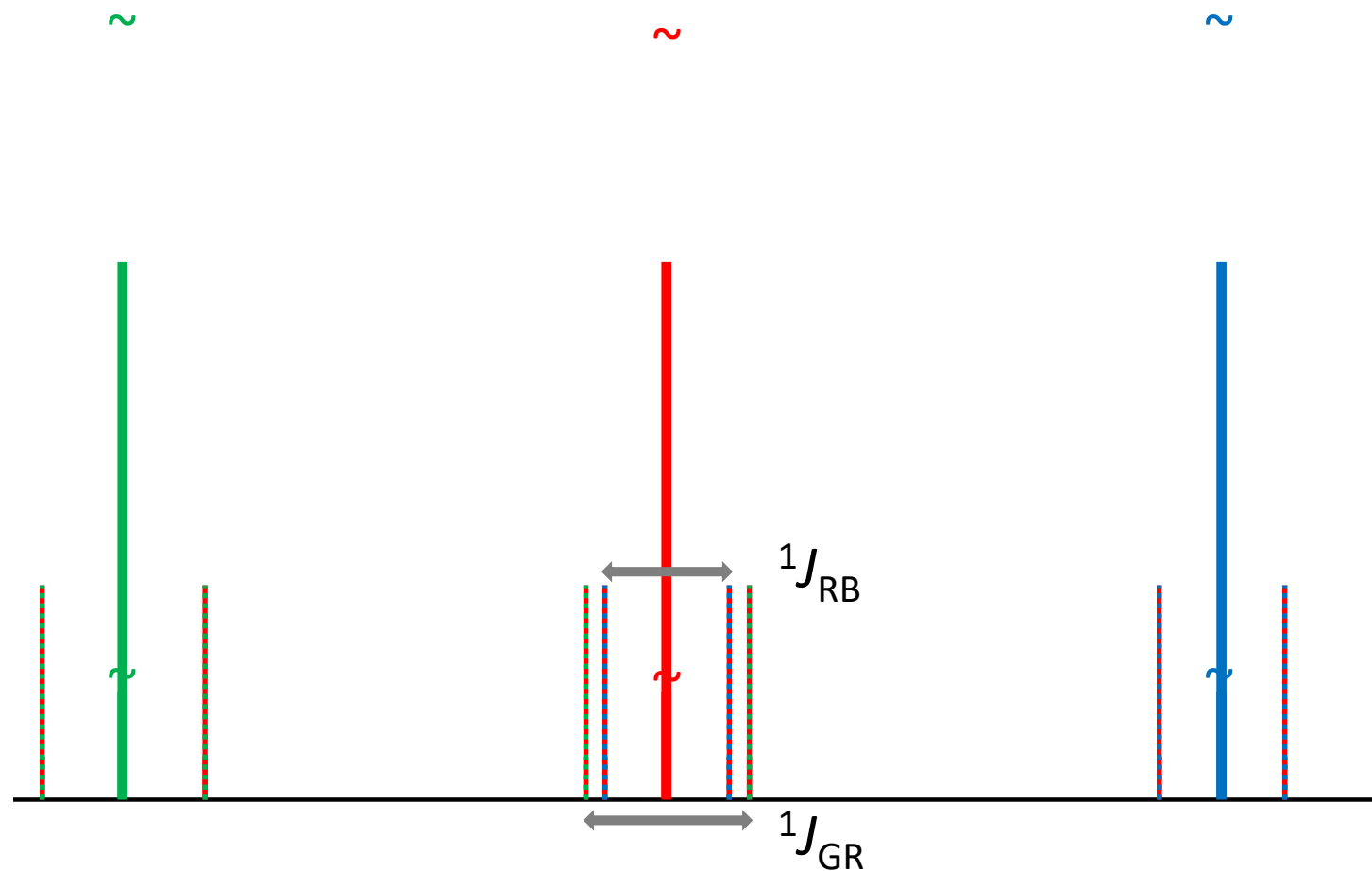
Probability and spectra



Let us inspect the final sum in some more detail with our focus to the carbon-carbon coupling pattern.

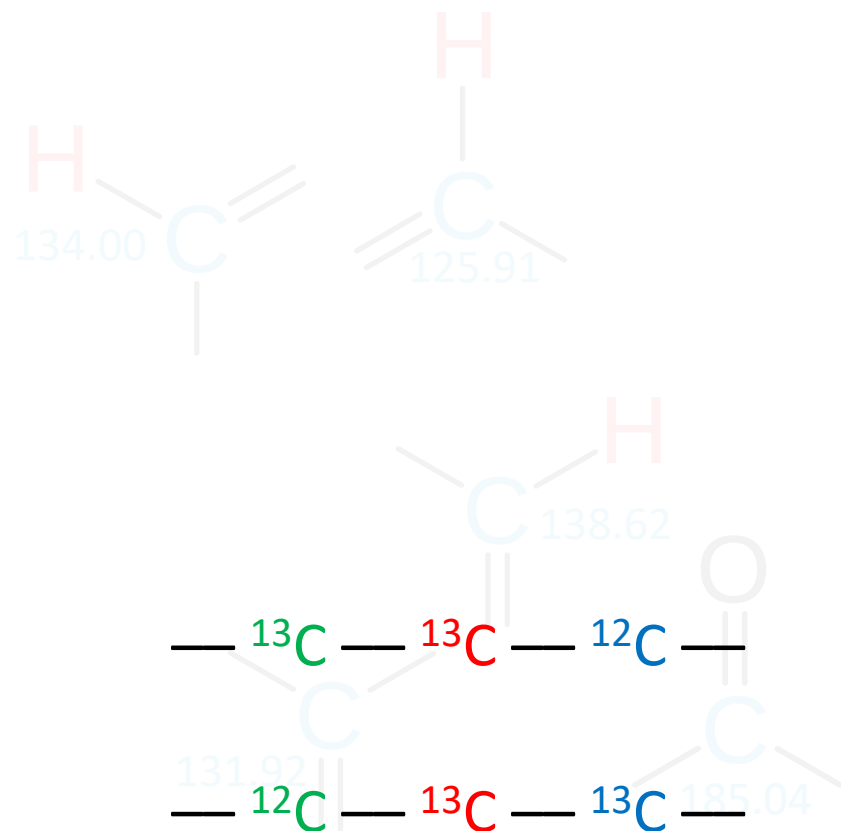
It seems to be trivial to measure both $^1J_{GR}$ and $^1J_{RB}$. (Green, Red, Blue)

But ...



Carbon-carbon couplings

Possible higher order spectra



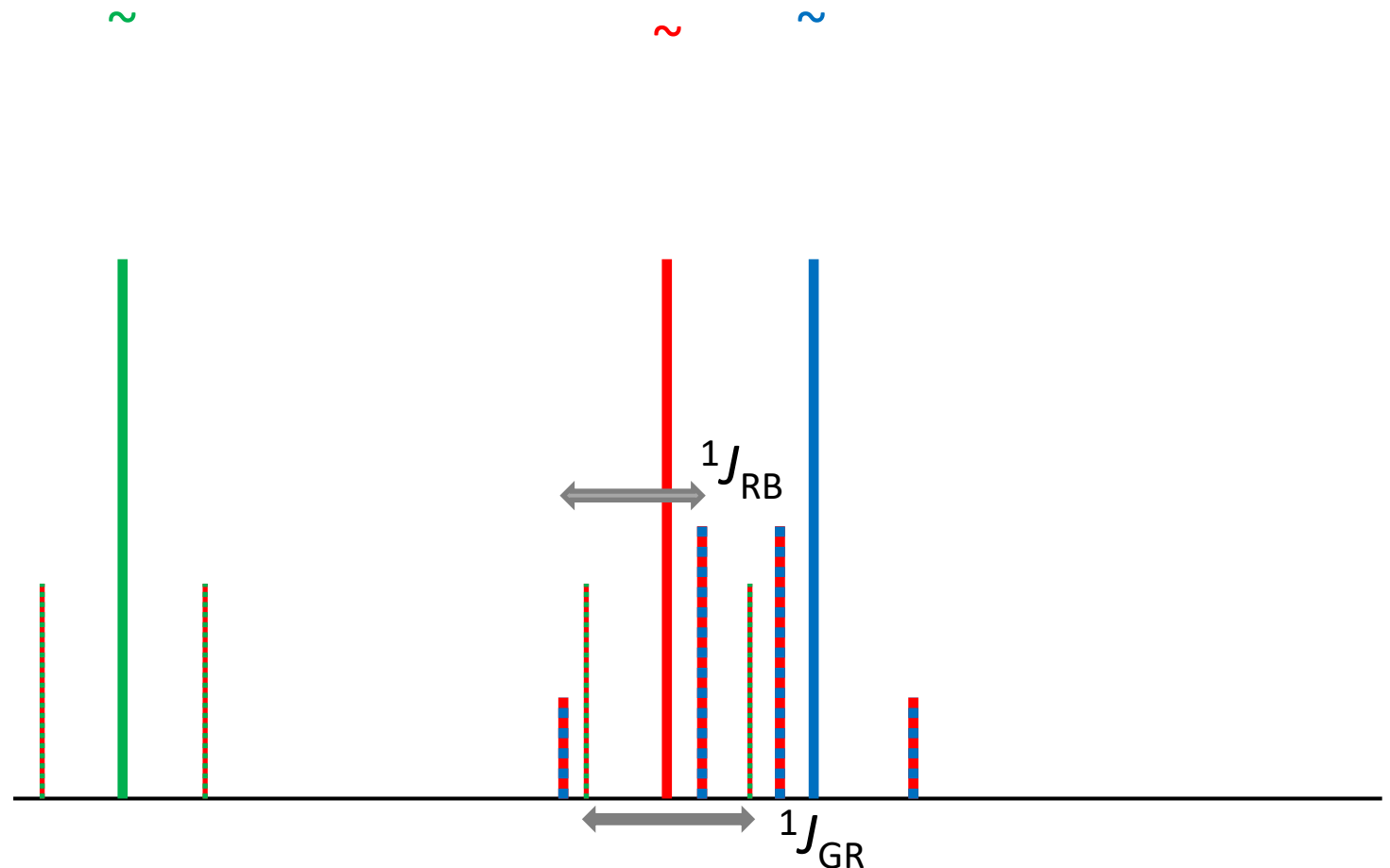
The chemical shift difference between two directly connected carbon atoms might be as low as 1 ppm, which is about 63 Hz at 5.9 Tesla magnetic field strength. A typical value for $^1J_{\text{CC}}$ is 50 Hz, which means we would have an **AB** system.



Possible higher order spectra

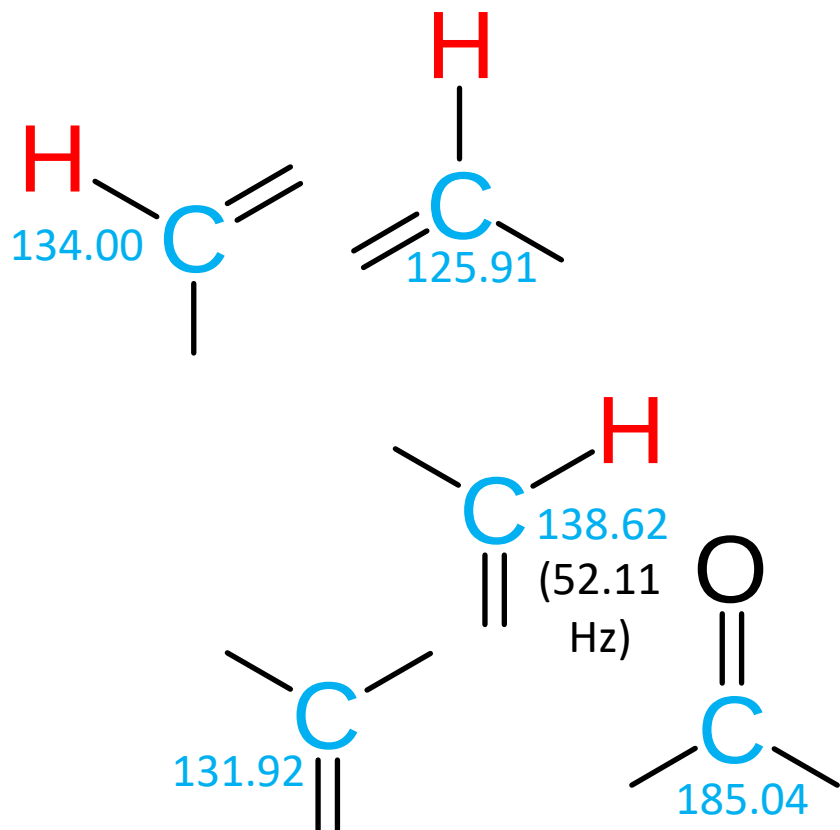
Chemical structure of 2,3,4-trimethylpentan-2-ol with ^{13}C NMR chemical shifts (ppm):

- CH₃ (left): 134.00
- CH₃ (top): 125.91
- CH₃ (right): 138.62
- CH₂ (left): 131.92
- CH₂ (right): 195.04



Carbon-carbon couplings

Detailed analysis

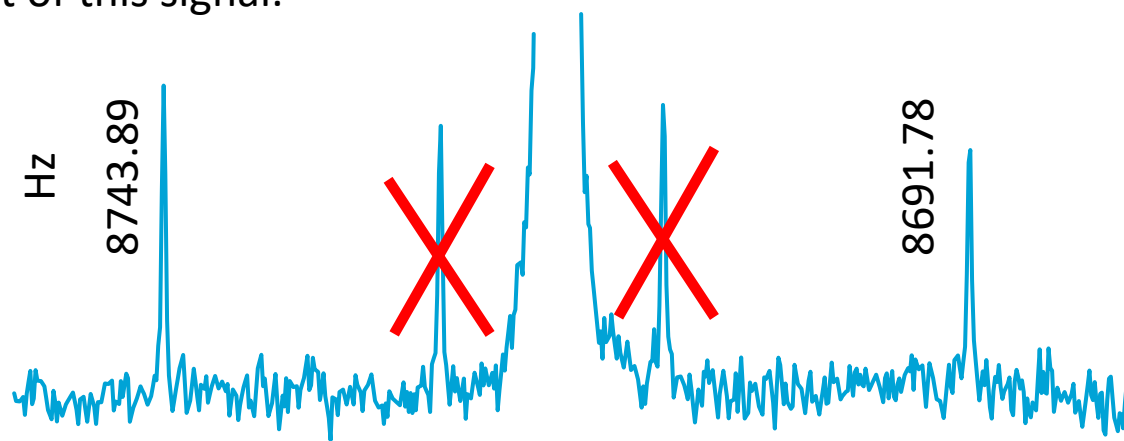


To start the detailed analysis let us select a carbon signal with a low number of satellites coming from carbon-carbon couplings.

The signal at 138.62 ppm appears to be well suited.

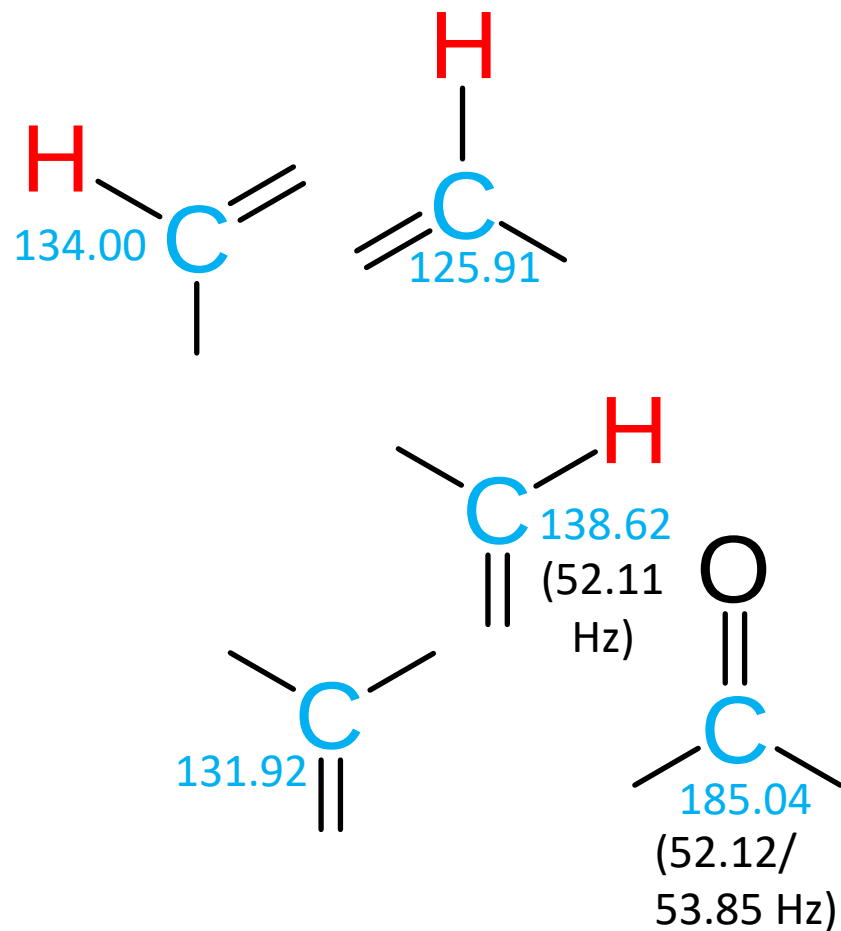
A typical value for $^1J_{\text{CC}}$ is between 40 and 60 Hz, which means that the two satellite signals marked with red crosses are due to carbon-carbon coupling over more than one bond.

If we use the two remaining satellite peaks we get a coupling constant of $^1J_{\text{CC}} = 52.11$ Hz. We note this value next to the carbon chemical shift of this signal.



Carbon-carbon couplings

Detailed analysis

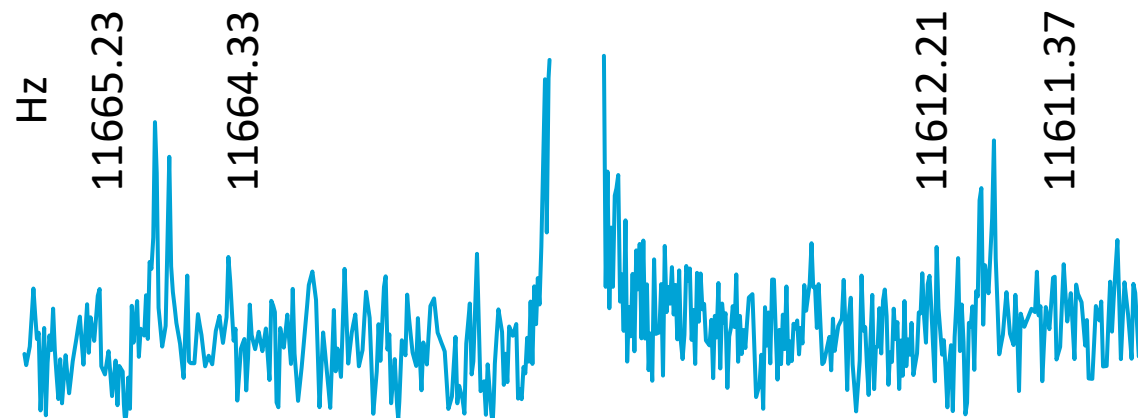


The coupling constant of 52.12 Hz must appear a second time in one of the four remaining carbon signals.

To shorten the search, here the result. We will see the coupling constant a second time in the coupling pattern of the satellite signals at 185.04 ppm.

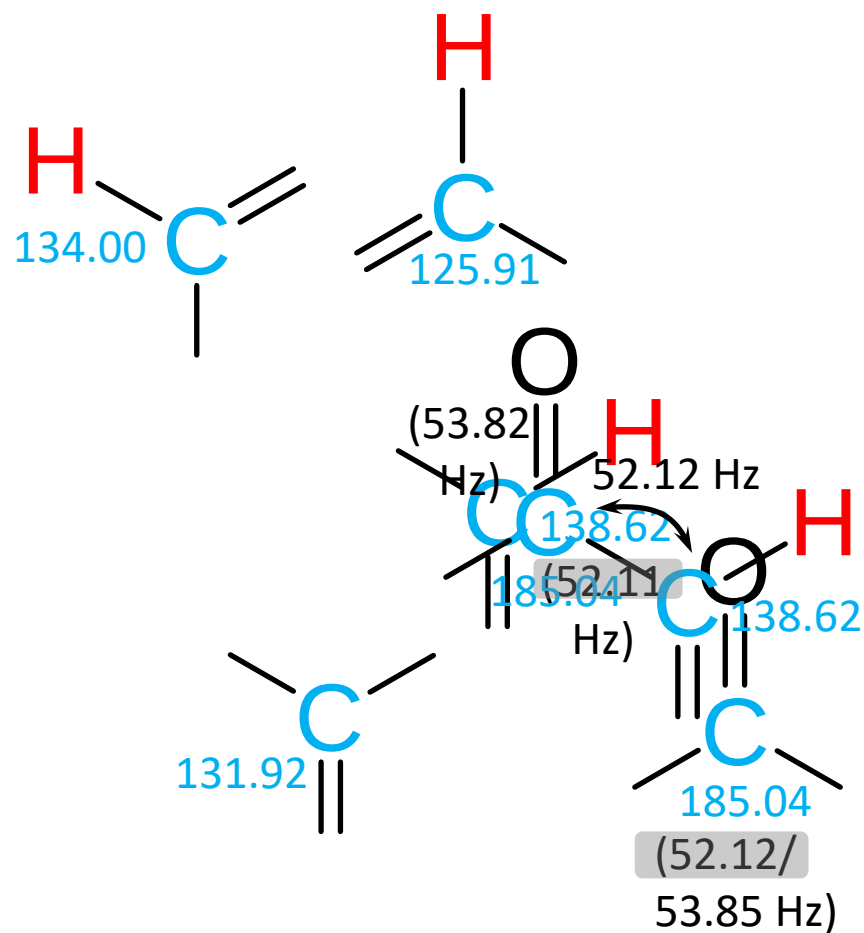
185.04 ppm is far away from all other carbon signals, we don't have to worry about **AB** effects, described earlier.

Our evaluation yields two carbon-carbon coupling constants of **52.12 Hz** (11664.33 – 11612.21) and **53.85 Hz**, respectively, which we will note next to the corresponding chemical shift.

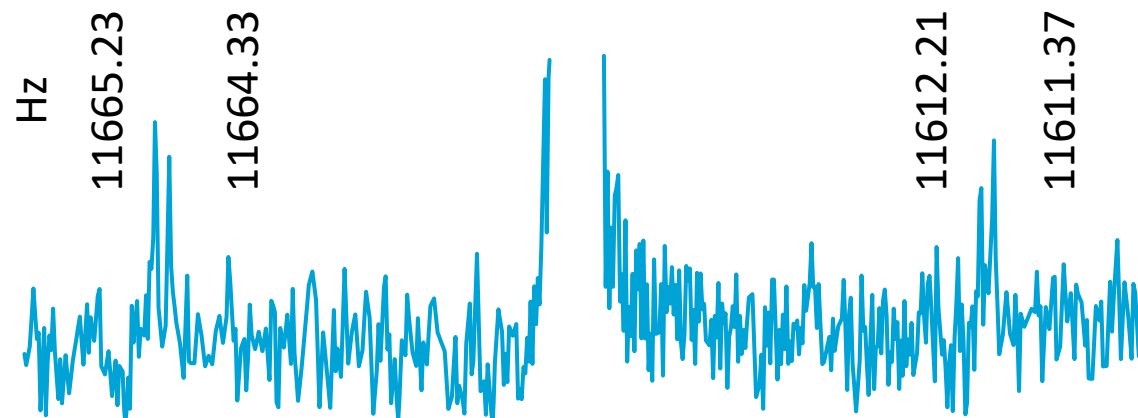


Carbon-carbon couplings

Detailed analysis

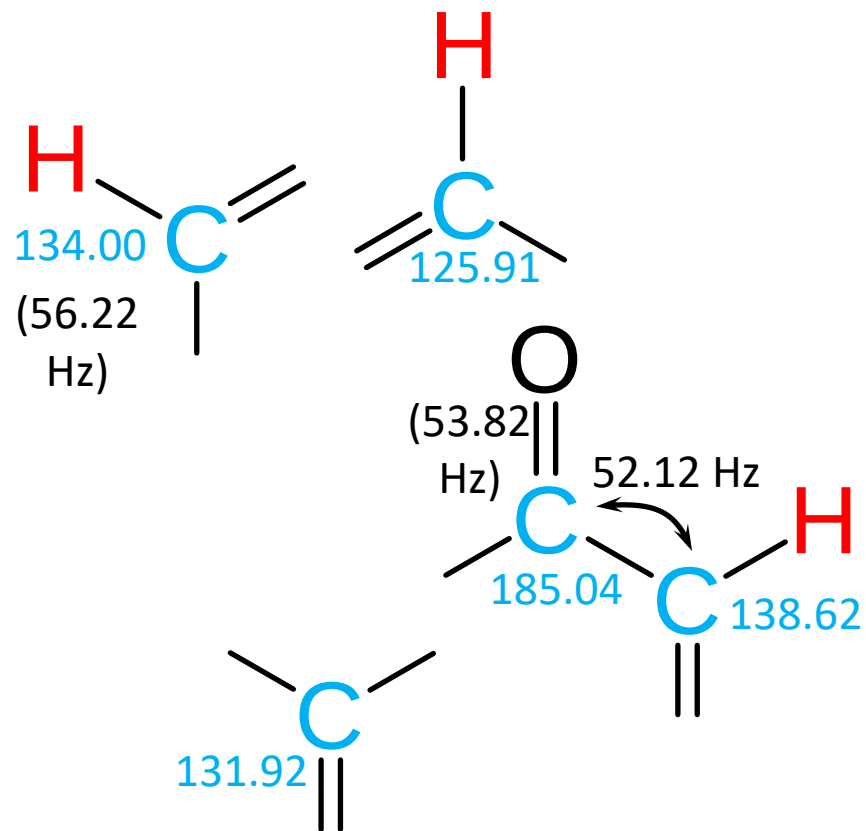


One $^1J_{CC}$ (52.11/52.12 Hz) exists twice. The corresponding carbon atoms have to be connected.



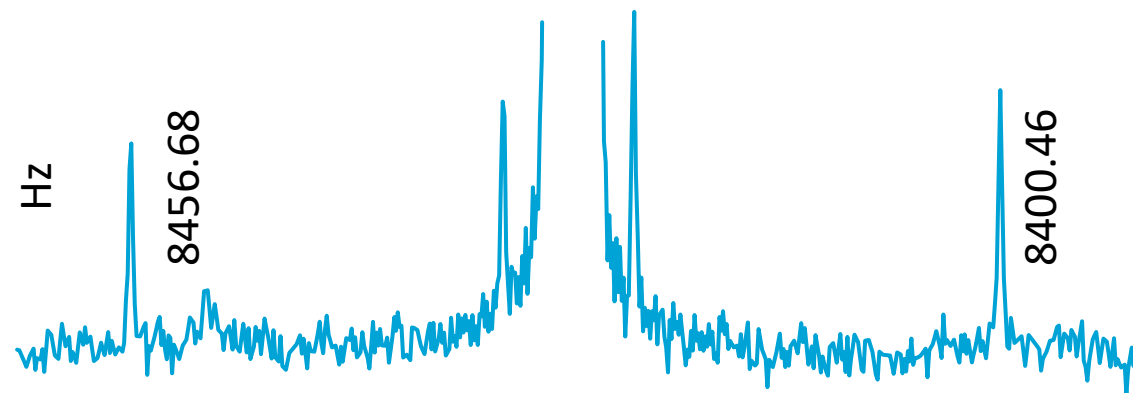
Carbon-carbon couplings

Detailed analysis



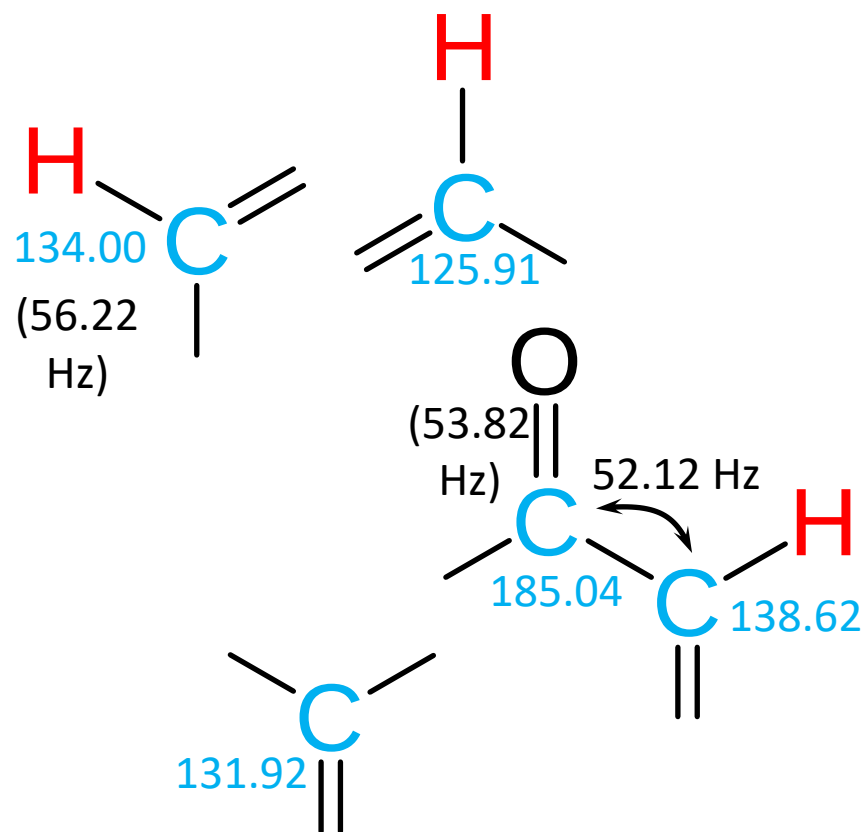
There is another carbon signal at 134.00 ppm from which only one $^1J_{CC}$ can be extracted.

As done before, we note the result of **56.22 Hz** next to the carbon chemical shift.



Carbon-carbon couplings

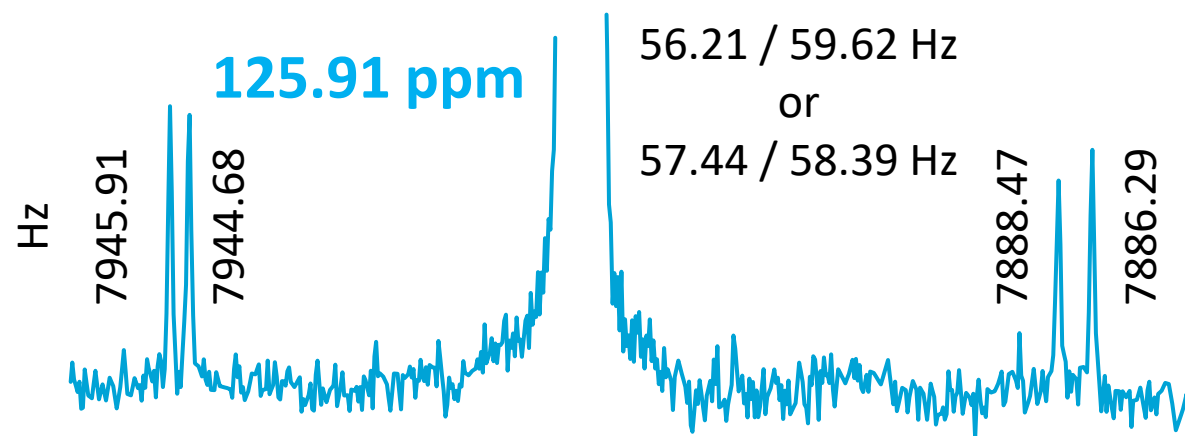
Detailed analysis



The coupling constant of **56.22 Hz** must appear a second time in the satellite signals of either the carbon atom at **125.91 ppm** or at **131.92 ppm**.

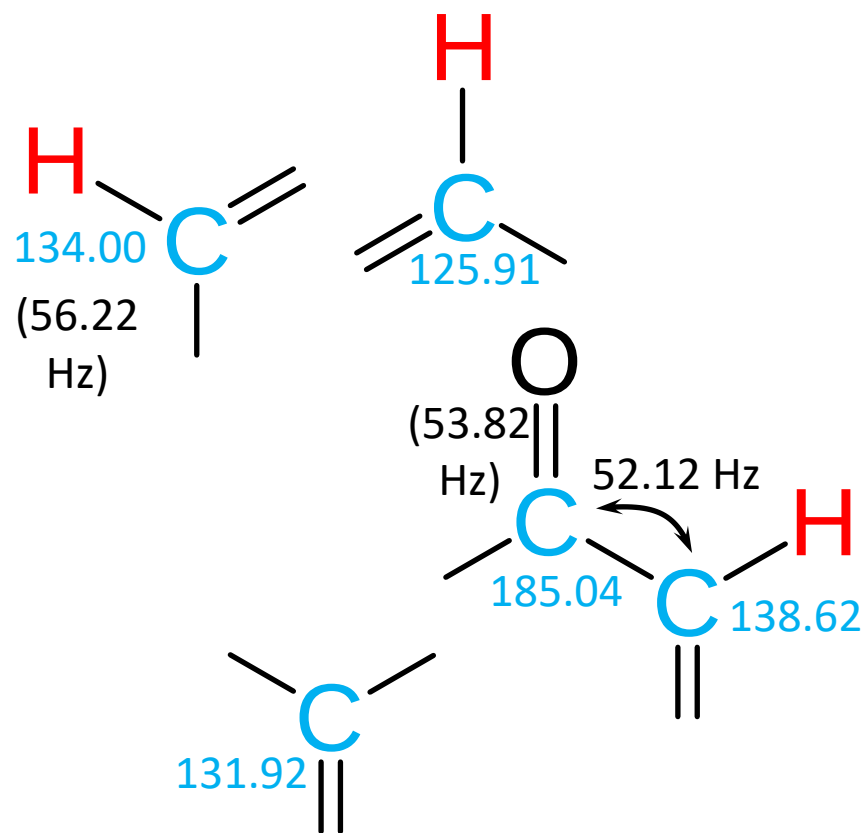
In both cases, however, the satellite signals are sometimes so close together that the **AB** case discussed above cannot be ruled out. We therefore have to determine four possible $^1J_{CC}$ on a trial basis.

Let us start with the analysis of the carbon signal at **125.91 ppm**. We get two possible combinations of two values for $^1J_{CC}$.

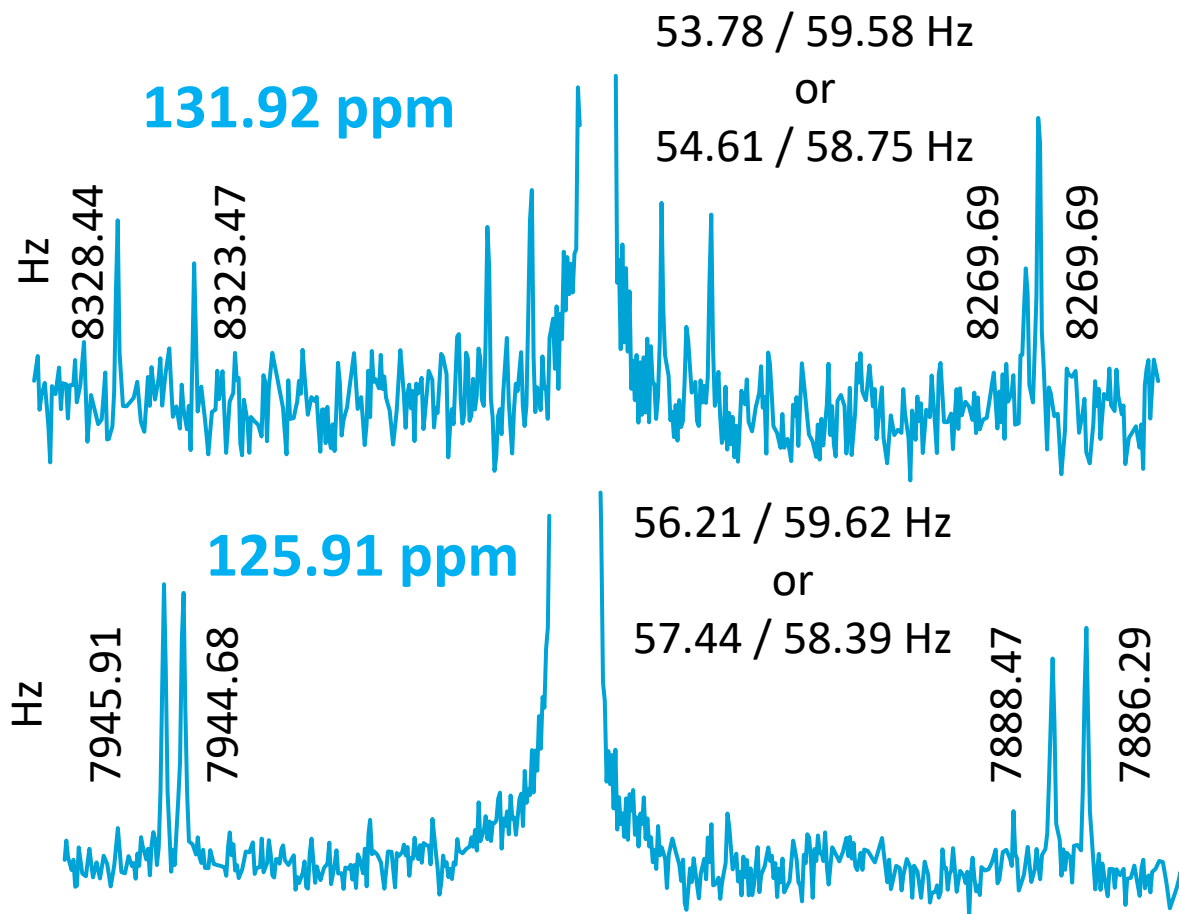


Carbon-carbon couplings

Detailed analysis

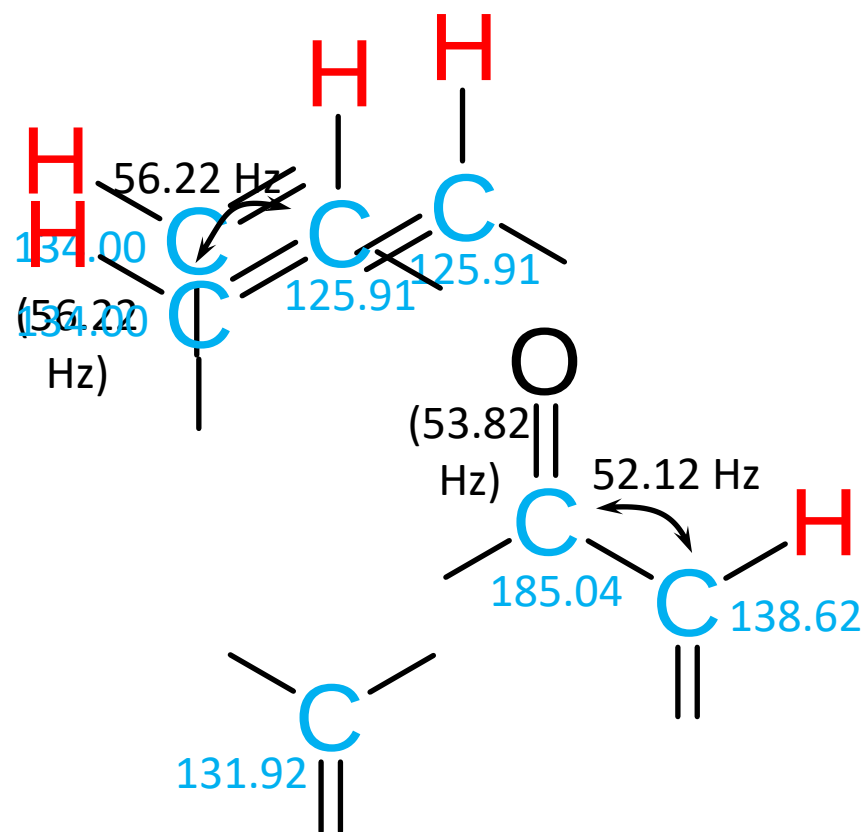


Doing the same calculation for the satellites of the carbon signal at **131.92 ppm** we get two further pairs of possible values for $^1J_{CC}$. Only one pair is the correct one, but for the moment we cannot decide which one.



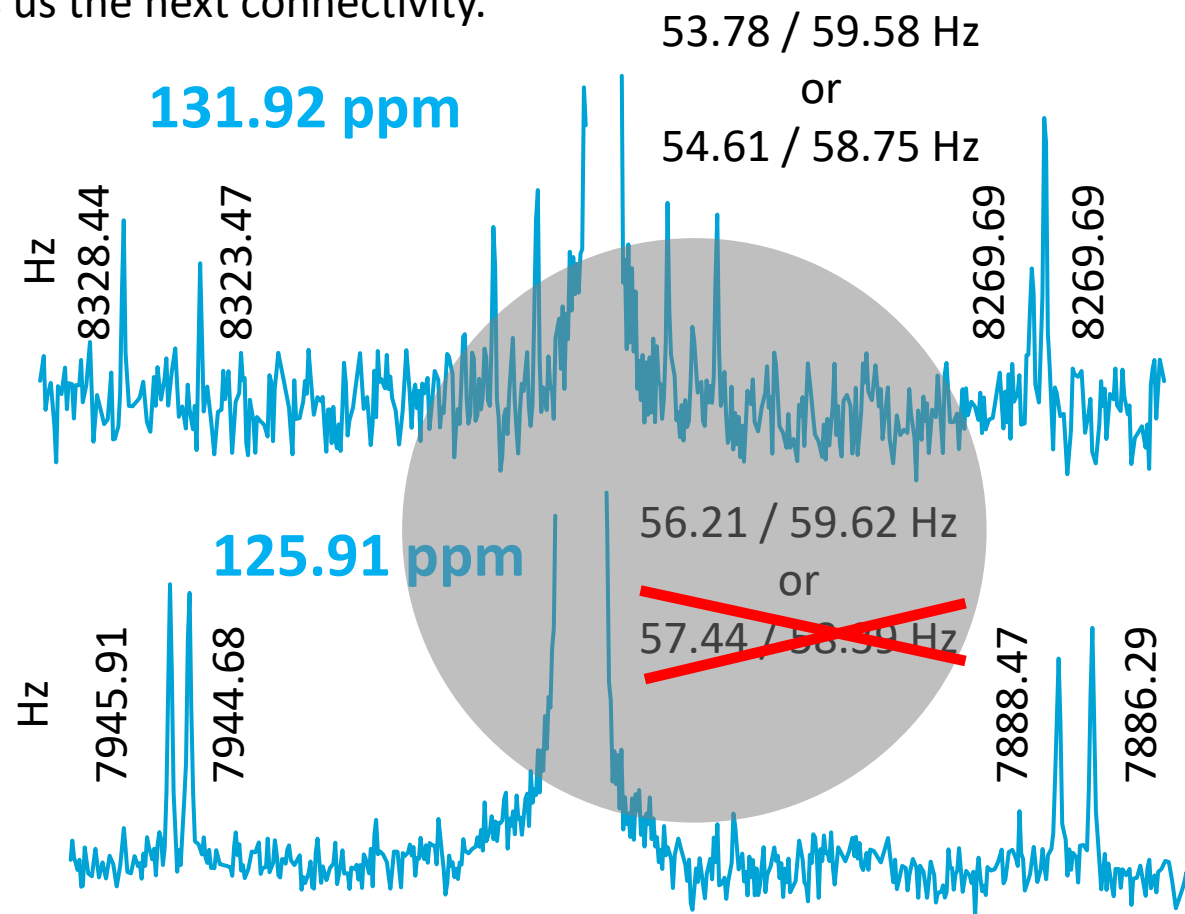
Carbon-carbon couplings

Detailed analysis



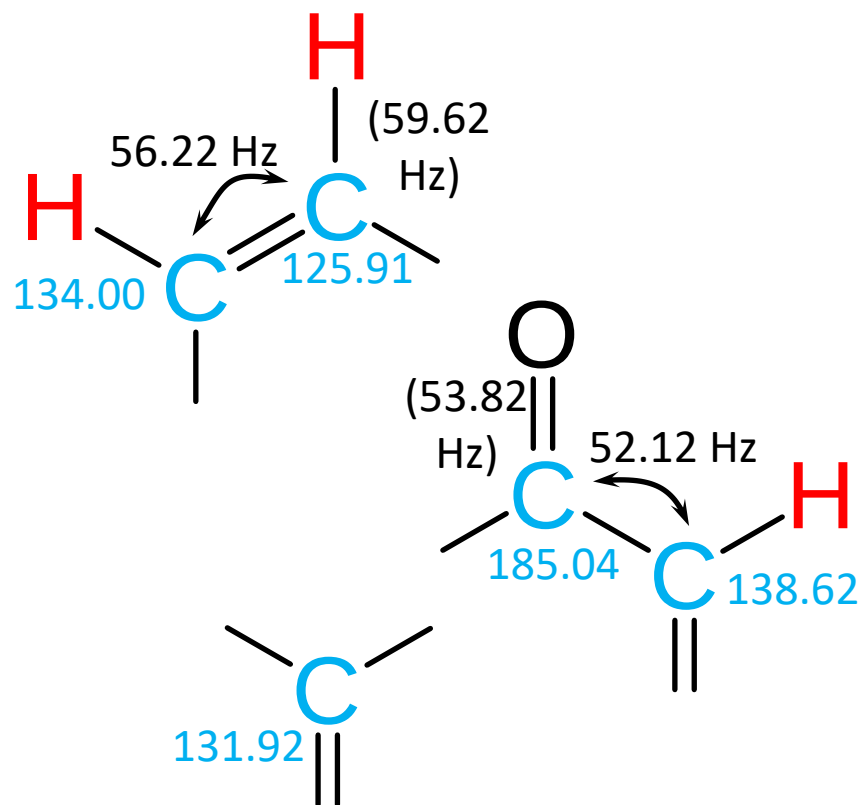
The carbon-carbon coupling constant of **56.22 Hz** appears the second time as part of the satellite pattern of the signal at **125.91 ppm**.

This rules out one pair of possible carbon carbon coupling constants and shows us the next connectivity.

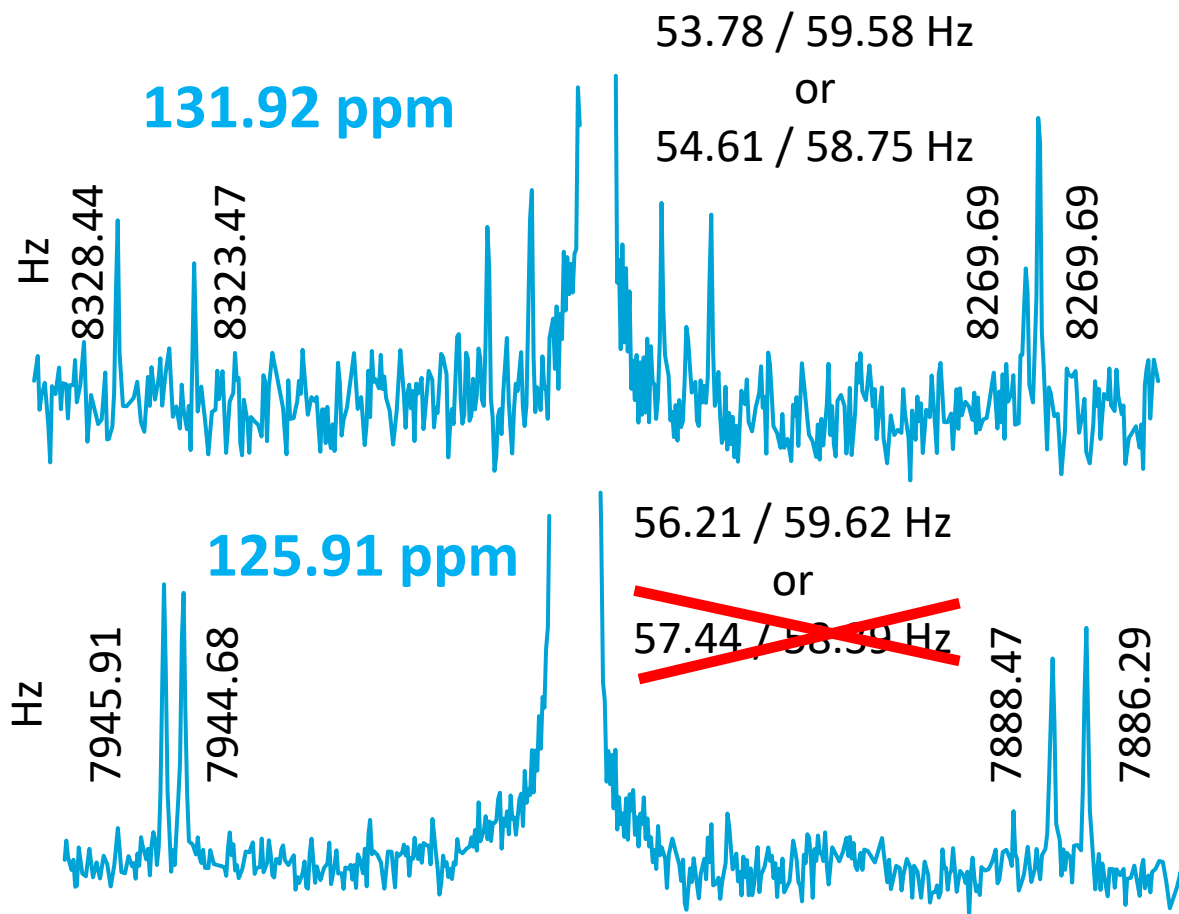


Carbon-carbon couplings

Detailed analysis



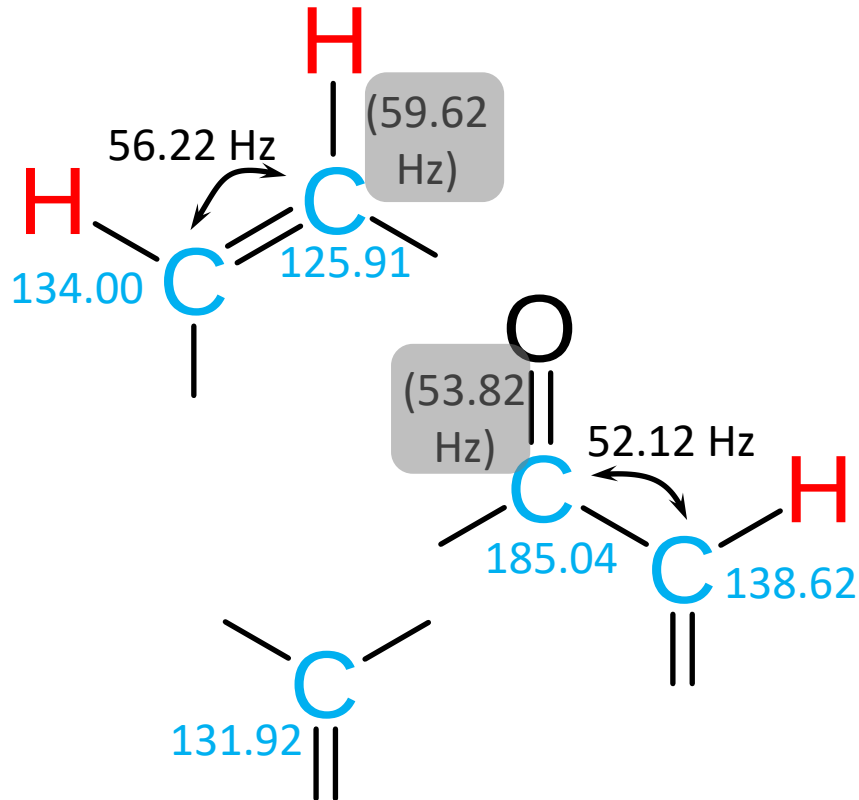
As second carbon-carbon coupling constant from the satellite pattern of the carbon signal at **125.91 ppm** we note the value of **59.62 Hz** next to the carbon signal for further use.



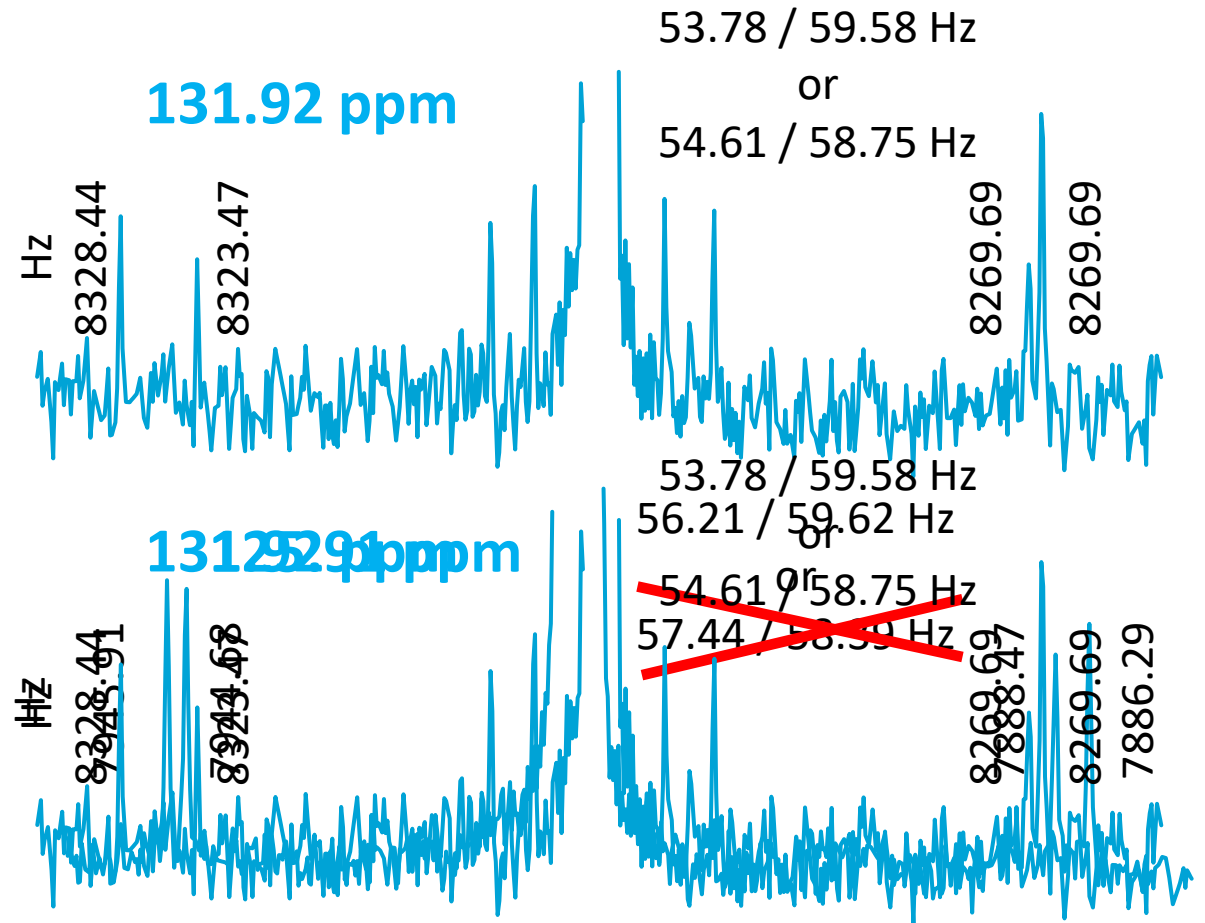
We no longer need the lower part of the carbon spectrum.

Carbon-carbon couplings

Detailed analysis



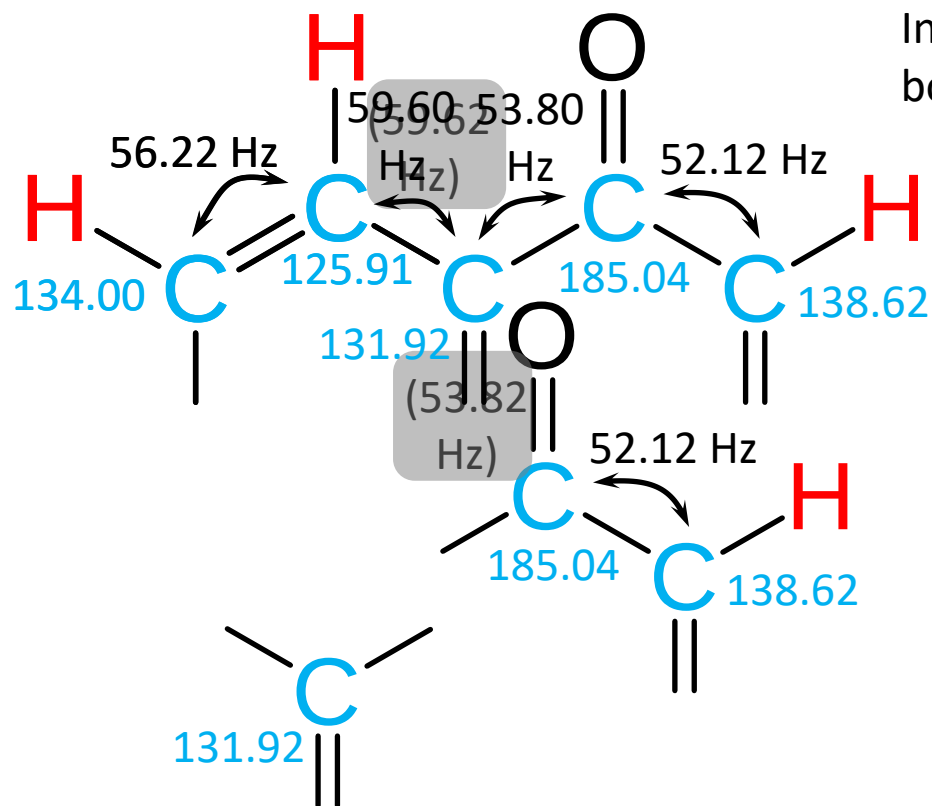
As second carbon-carbon coupling constant from the satellite pattern of the carbon signal at 125.91 ppm we note the value of 59.62 Hz next to the carbon signal for further use. There is no other remaining carbon atom.



We no longer need the lower part of the carbon spectrum.

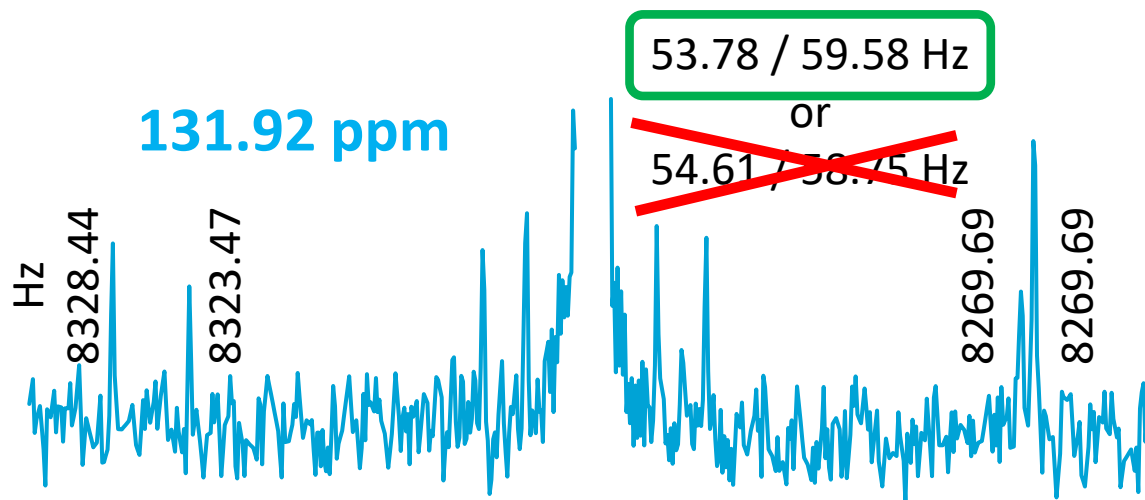
Carbon-carbon couplings

Detailed analysis



The two carbon-carbon coupling constants of **59.62 Hz** and **53.82 Hz** have to be hidden in the satellite pattern of the carbon signal at **131.92 ppm**. There is no other remaining carbon atom.

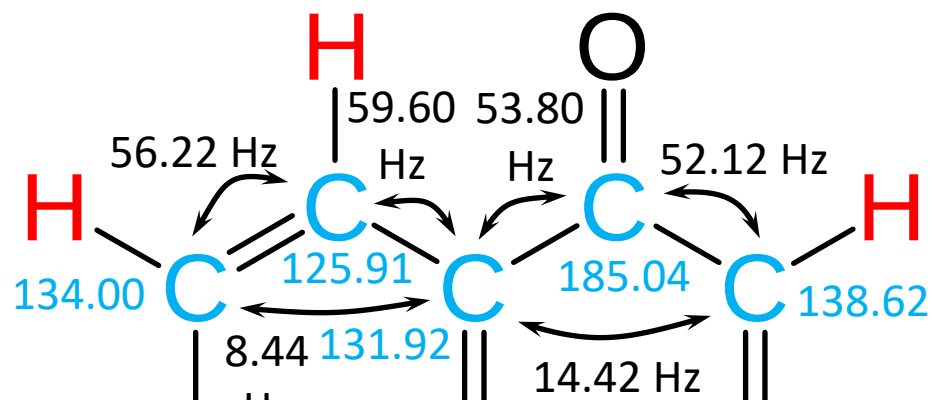
Indeed, one of the pair of coupling constants measured before contains both values with deviations in the range of some 0.01 Hz.



Now we are able to link all fragments.

Symmetry

Final structure



Mirroring the whole fragments gives our final structure. There will be no carbon-carbon coupling visible between equivalent carbon atoms.

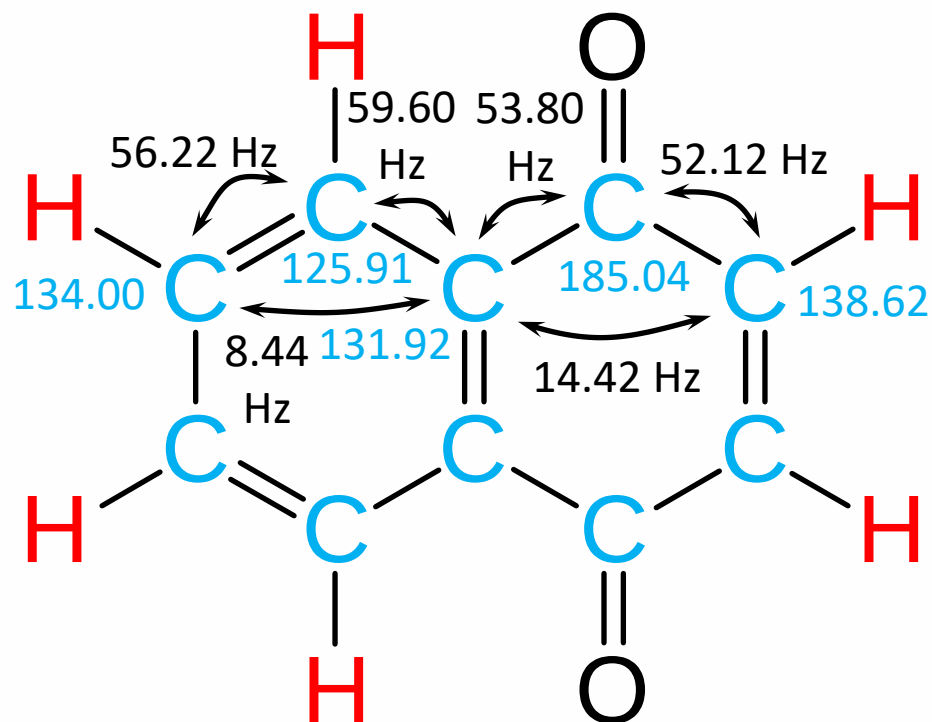
Inspecting the satellites of the carbon signals at 134.00, 131.92 and 138.62 ppm reveals two further carbon carbon coupling constants of 8.44 and 14.42 Hz.

Because structure and carbon assignment are already known, those have to be geminal coupling constants.

Of course there are more carbon carbon coupling constants, but they cannot be resolved using the spectra presented here.

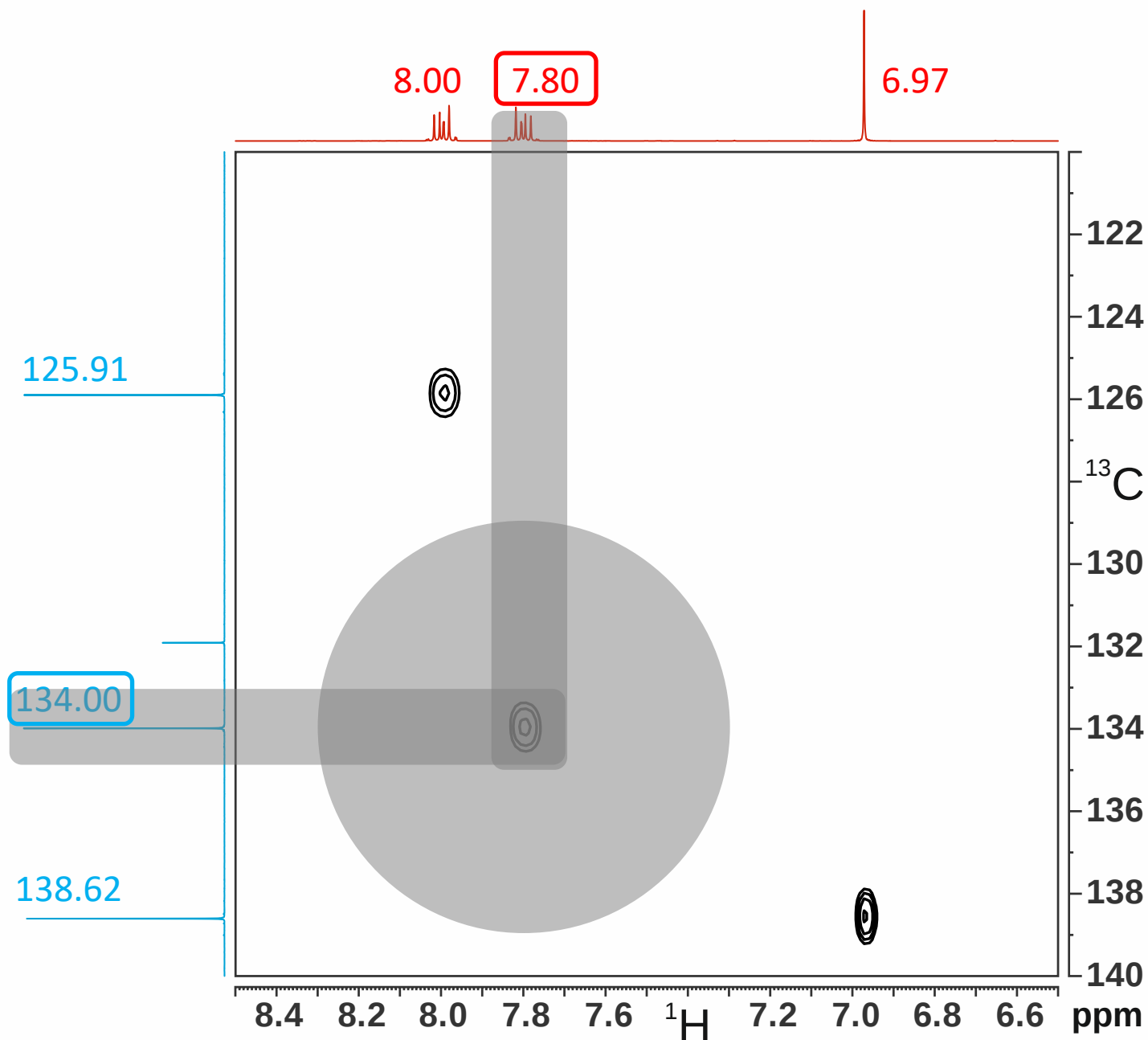
Proton assignment

The last step



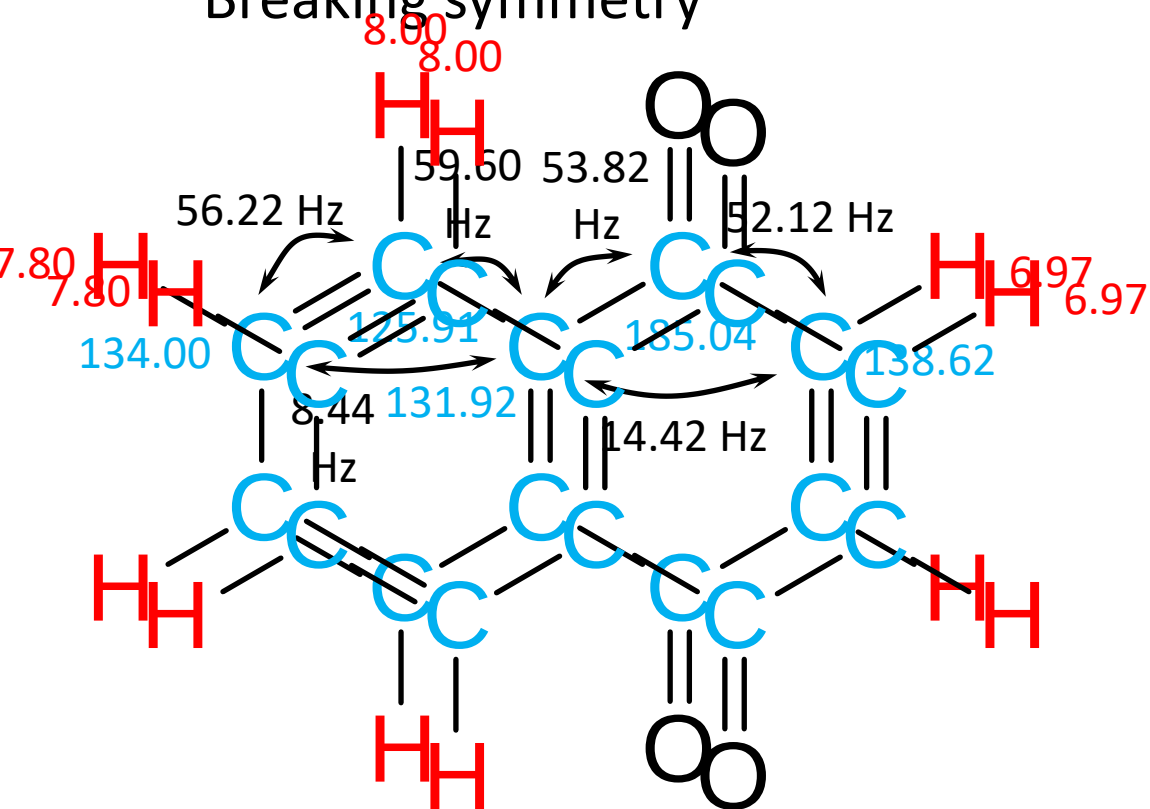
The proton assignment is possible using the HSQC.

Only one example is presented here.



Proton proton coupling constants

Breaking symmetry

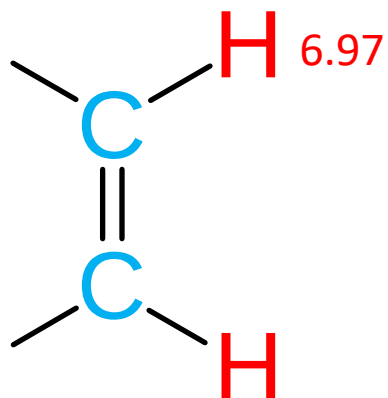
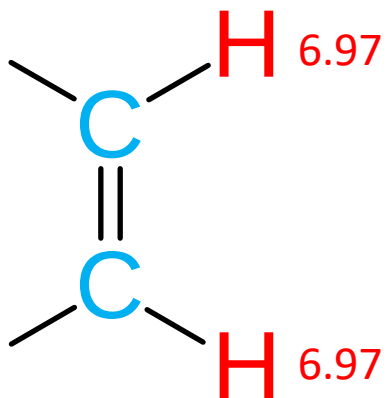


But how can we measure coupling constants
between protons with the same chemical shift?

Let us start with the protons with the chemical
shift of **6.97 ppm**. They are clearly separated
from the other protons. In the ^1H -NMR spectrum
the signal at **6.97 ppm** is a singlet. Let us neglect
the rest of the molecule for the sake of clarity.

Proton proton coupling constants

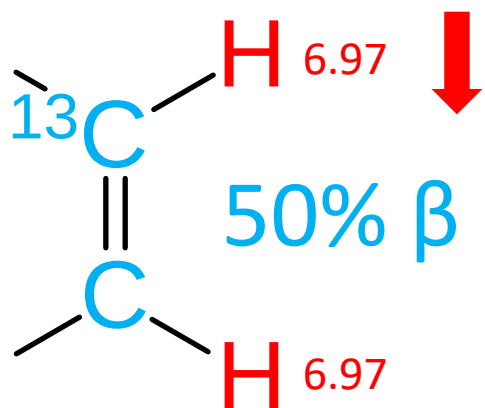
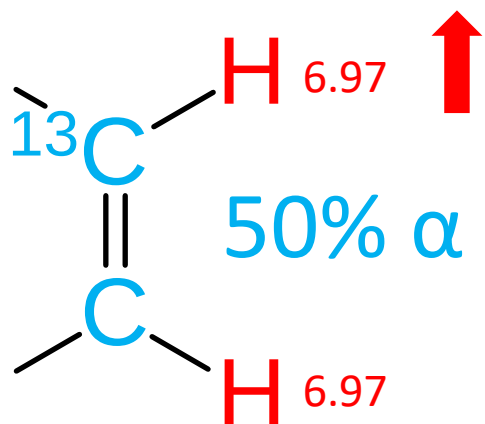
Breaking symmetry



With a probability of about 1% the carbon next to one of the protons is a ^{13}C isotope.

Proton proton coupling constants

Breaking symmetry



With a probability of about 1% the carbon next to one of the protons is a ^{13}C isotope.

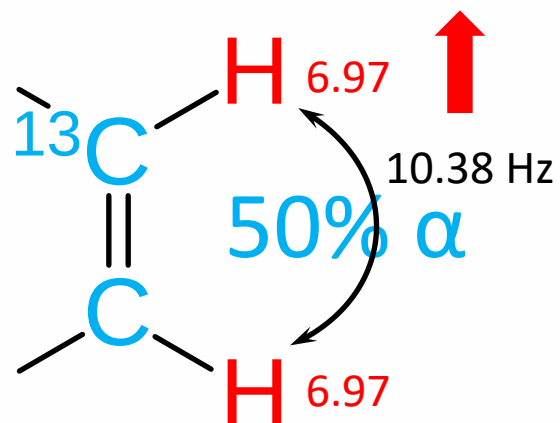
According to the Boltzmann statistics the orientation of the ^{13}C nucleus is with a nearly perfect 50% probability either α or β .

Due to the additional magnetic field coming from the ^{13}C nucleus, the signal of the proton attached to this carbon becomes shifted up- or downfield depending on the orientation of the ^{13}C nucleus.

The second proton becomes less influenced from the orientation of the ^{13}C nucleus. Finally we get two different chemical shifts for both protons and are able to measure the homonuclear coupling constant between them.

Proton proton coupling constants

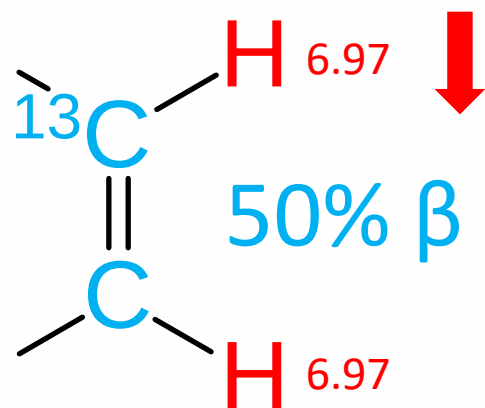
Breaking symmetry



Because of the low natural abundance of ^{13}C , the signals we are interested in appear as low-intensity satellites.

Now it is easy to get the coupling constant from one of the doublets.

We have the **correct result** now and might be happy.



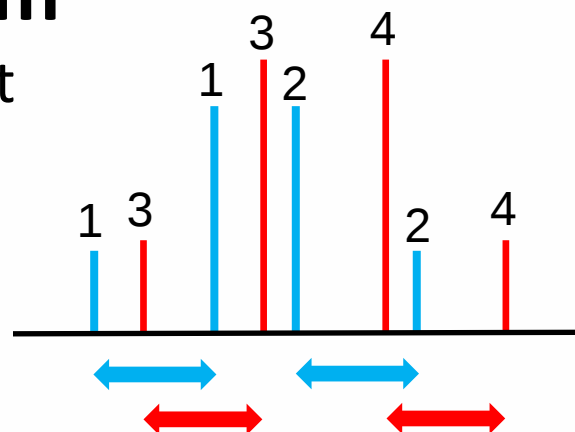
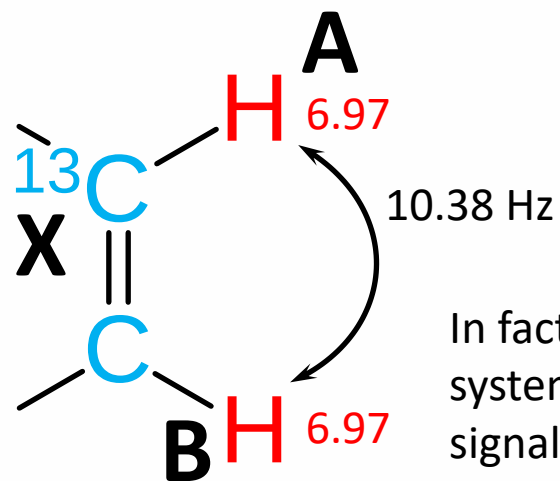
But...

In spite of the correct result the explanation is wrong.



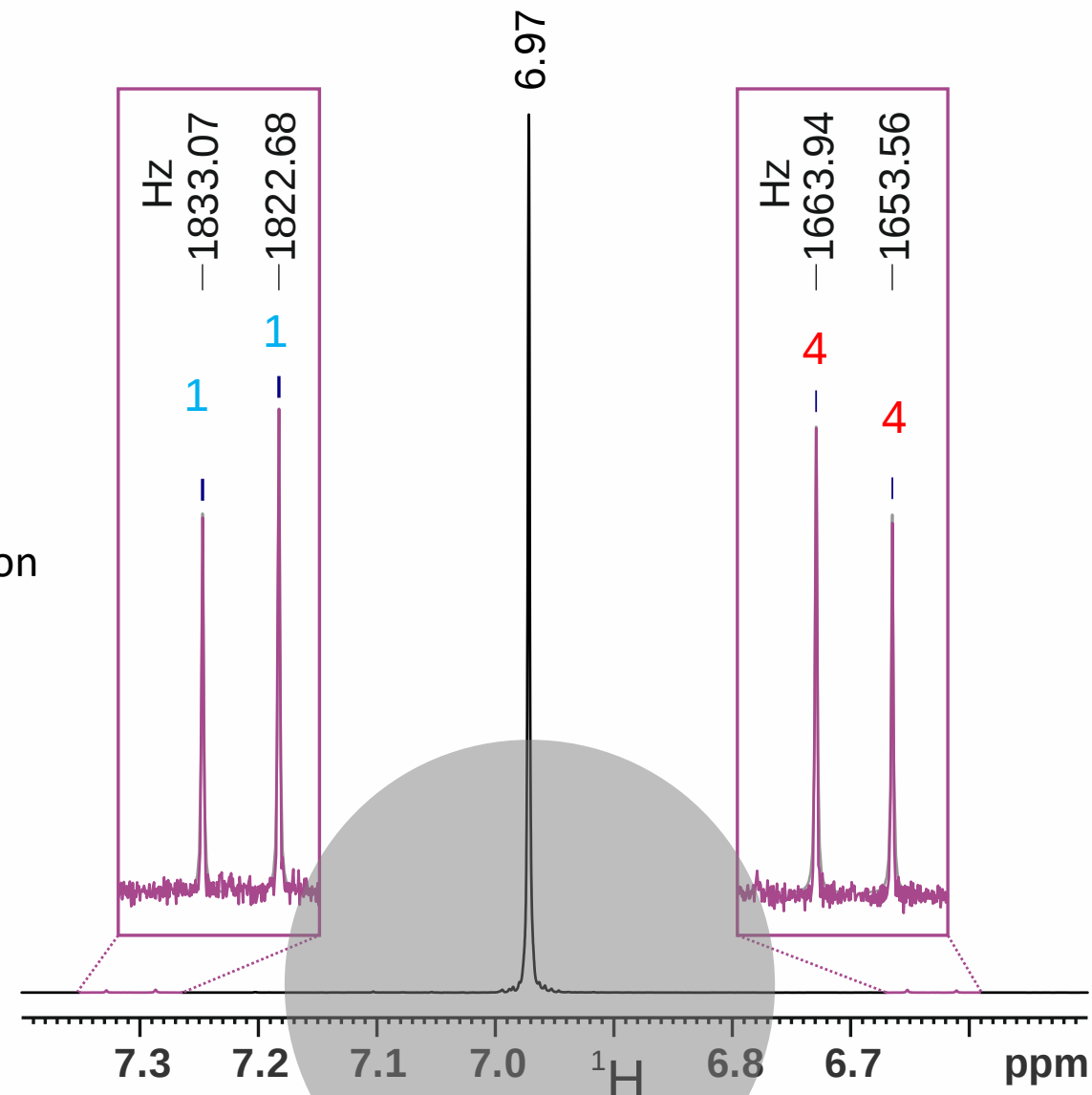
Some theory about the ABX spin system

Location of A and B part



In fact we have to deal with a three spin system. In the carbon satellites of the proton signal we are looking at the **AB** part of an **ABX** spin system.

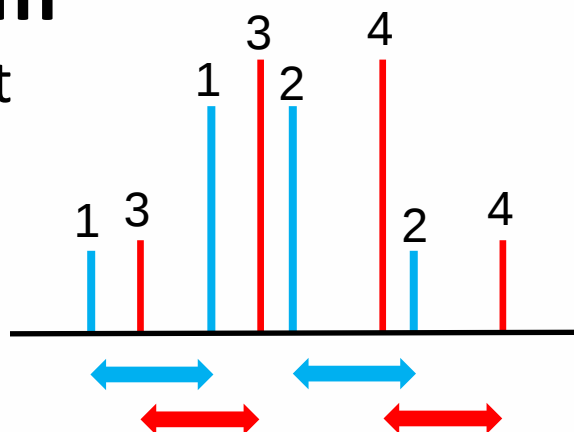
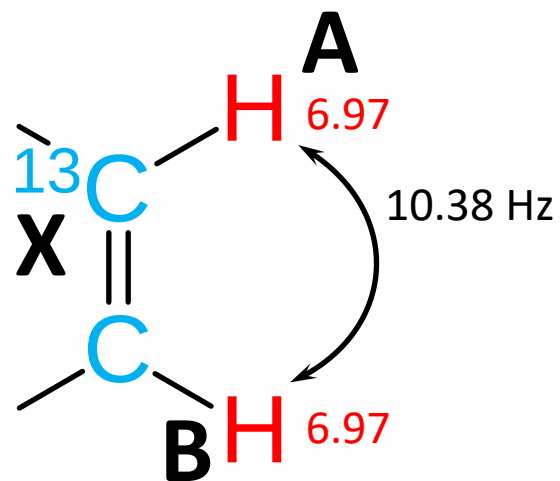
The **AB** part of an **ABX** spin system consists always of 8 lines. The coupling constant between the nuclei **A** and **B** appears four times. You get the value of J_{AB} as difference between the line pairs with the same number. In our spectrum we see only four of the eight lines. Which ones? Compare the numbering in the line spectrum and in the real spectrum. The coupling constant you are looking for can be determined from the four visible signals as shown before. But where are the lines labelled with **2** and **3**?



Let us investigate this part of the spectrum in some more detail.

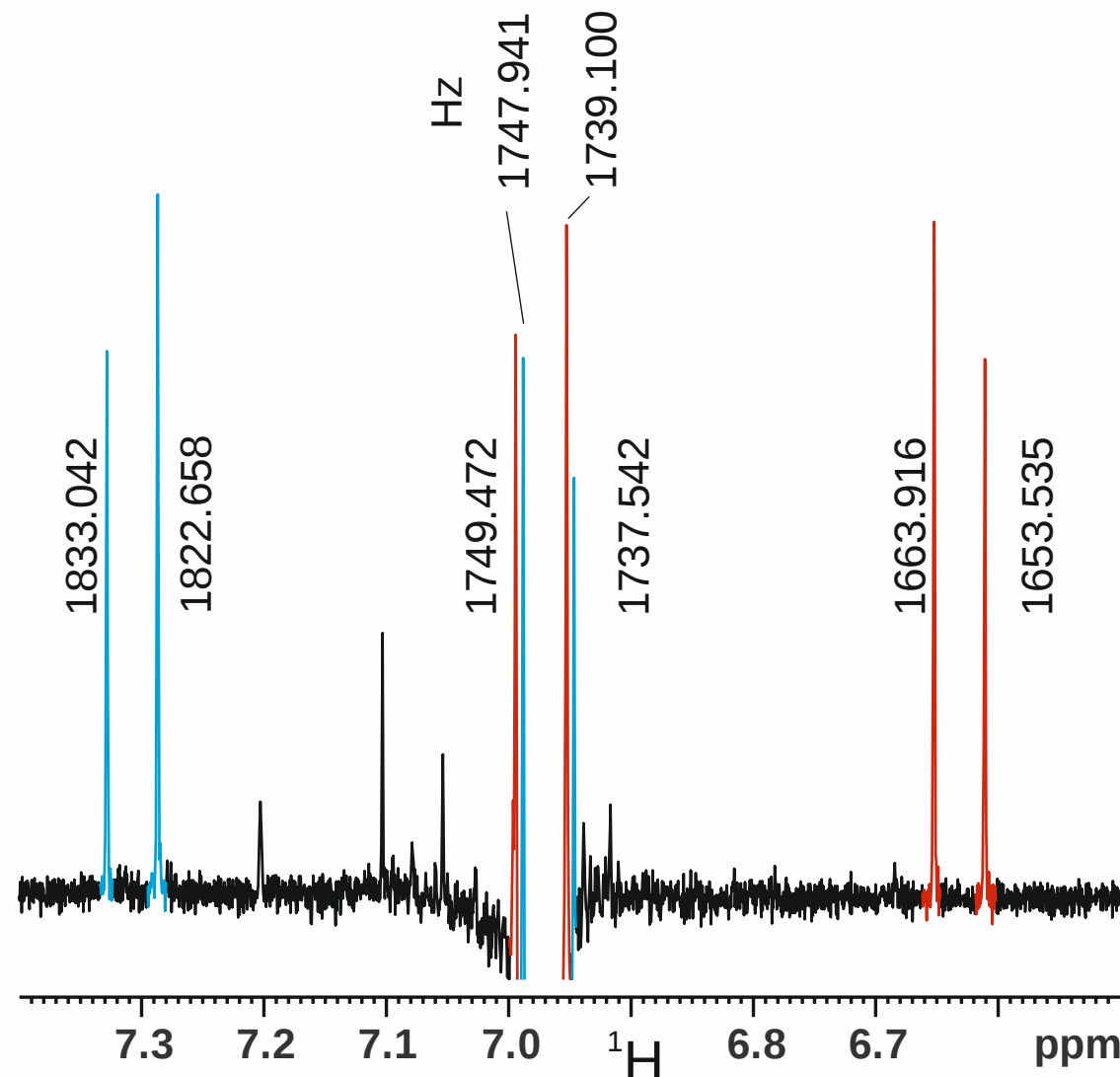
Some theory about the ABX spin system

Location of A and B part



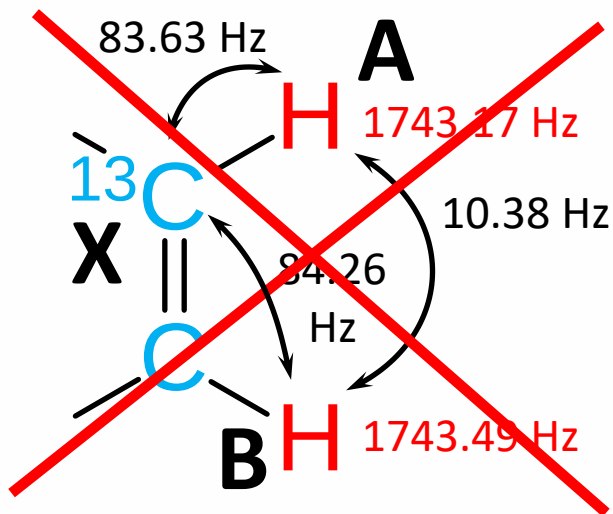
After some signal enhancement processing, removing the strong center line, removing four further satellite lines very close to the center line coming from coupling with $^{13}\text{C}=\text{O}$, we get our eight lines of the **AB** system.

We get our coupling constant of **10.38 Hz** four times with a deviation of ± 0.01 Hz. These lines were intentionally not part of the problem set to avoid confusion by a huge number of lines. They are not necessary to get the homonuclear coupling constant, but recognizing the **A** and the **B** part is far from being trivial, the coupling constant will help a little bit.



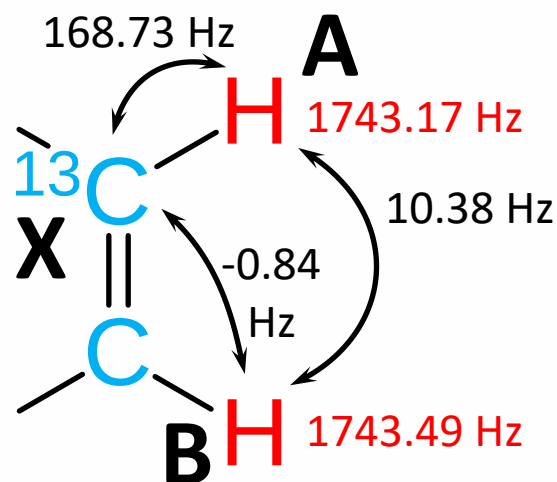
Some theory about the ABX spin system

Some mathematics

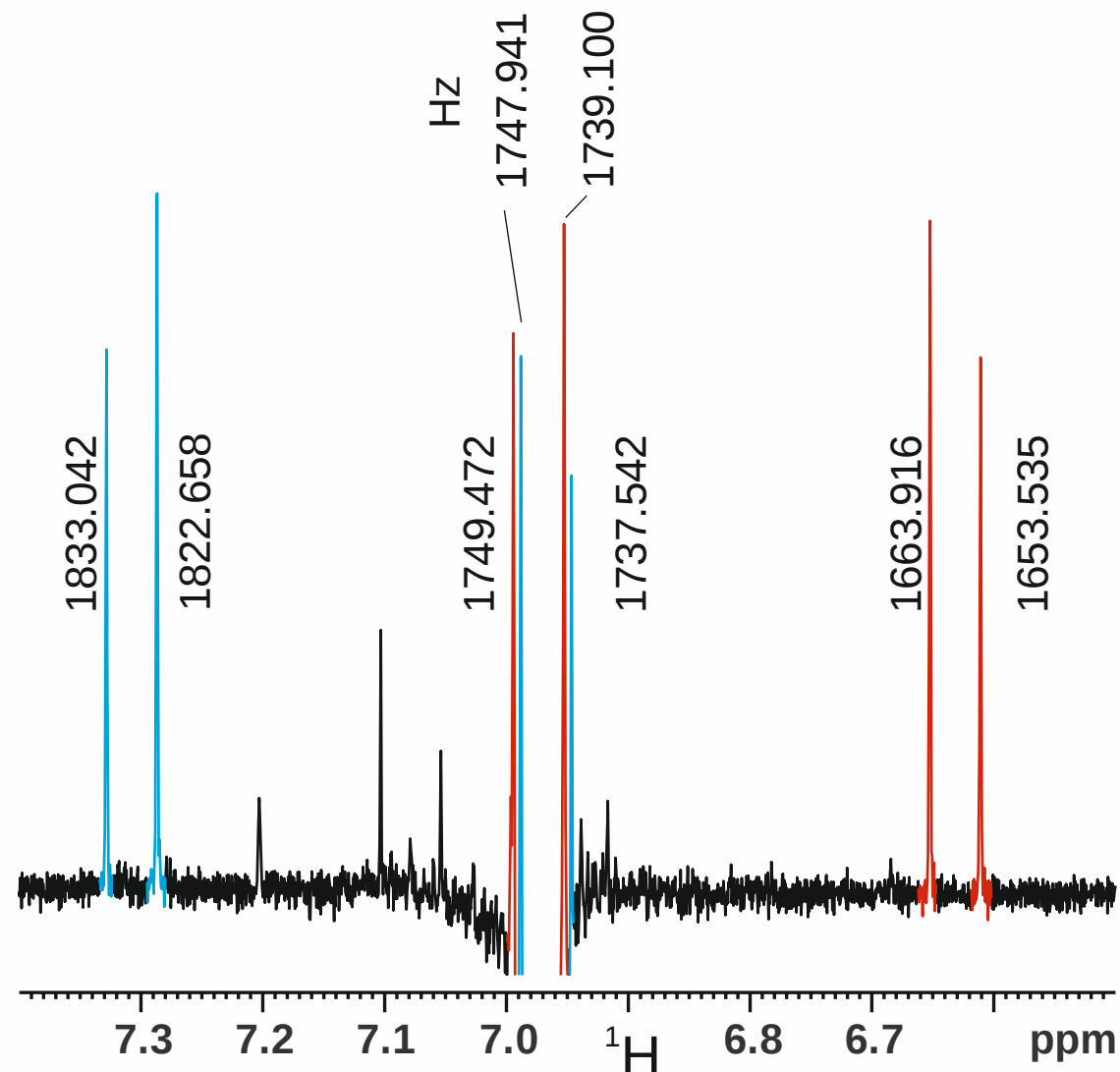


Solving the **AB** part of the **ABX** spin system (the full mathematics is available as an appendix) results in two possible solutions.

Even not being able to see the **X** part, we easily can exclude the first solution.



The reason for presenting chemical shifts on the Hz scale is the small difference between the two values, which is not visible in the ppm scale.



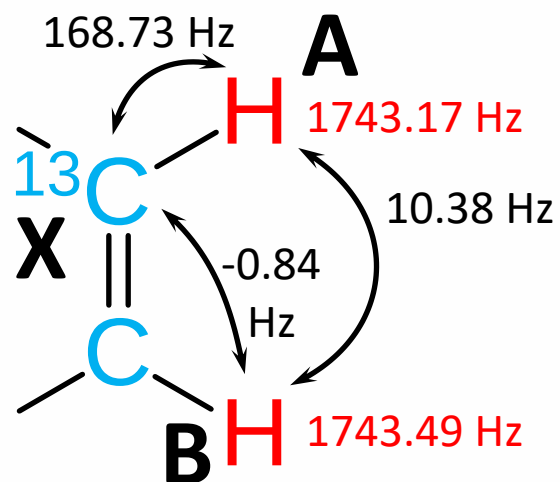
Some theory about the ABX spin system

A last question?

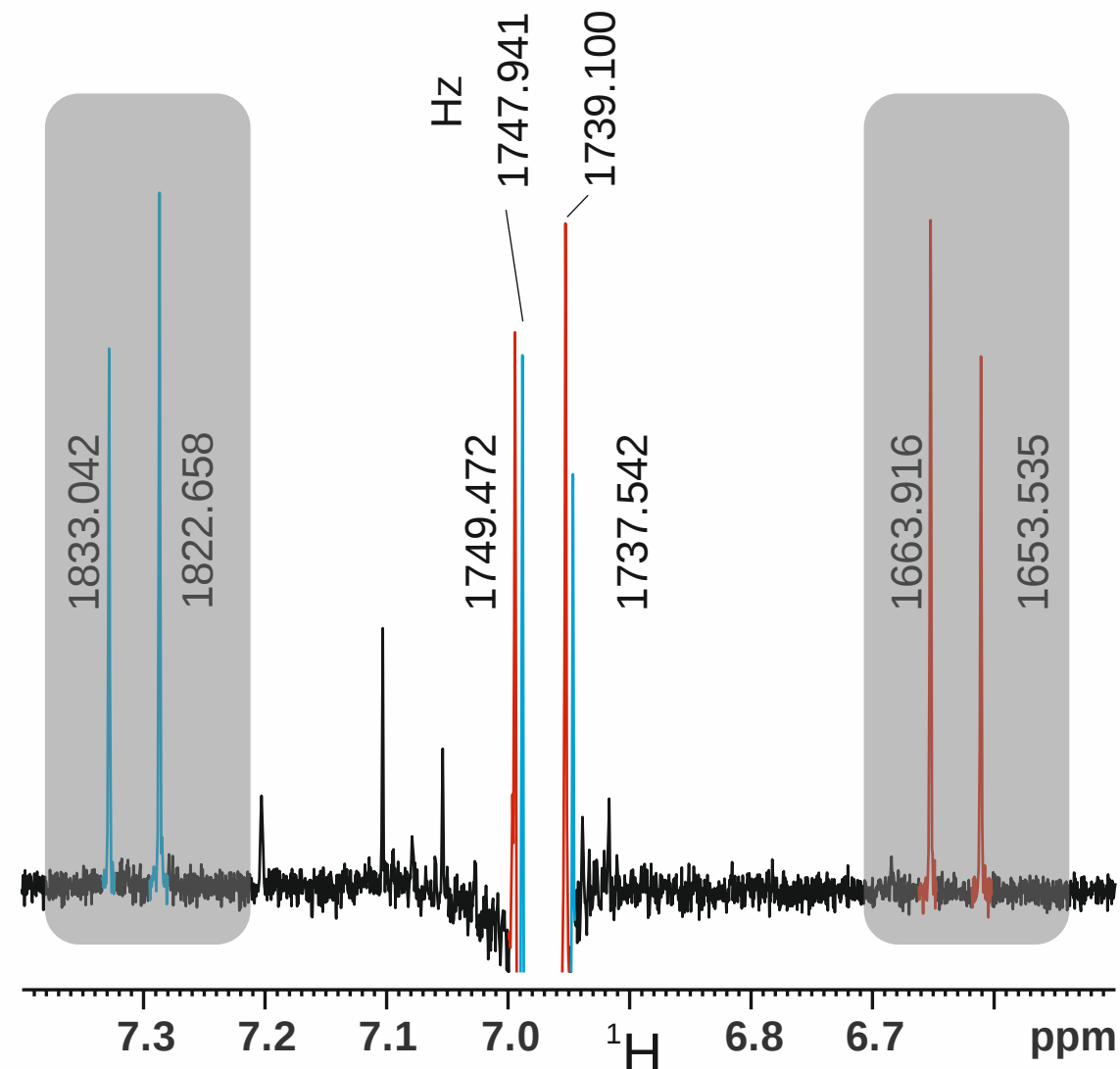
Are we able to simply extract $^1J_{AX}$ from these lines?

No!

Because it looks as though both J_{BX} and the chemical shift difference between **A** and **B** are very low in our case (we would end with $J = 168.81$ Hz), but each pair of lines corresponds to a different orientation of the **B** spin. The difference doesn't reveal the desired information directly.



(If it is still confusing, the last paragraph on page 1 of the first appendix may also be helpful for understanding.)

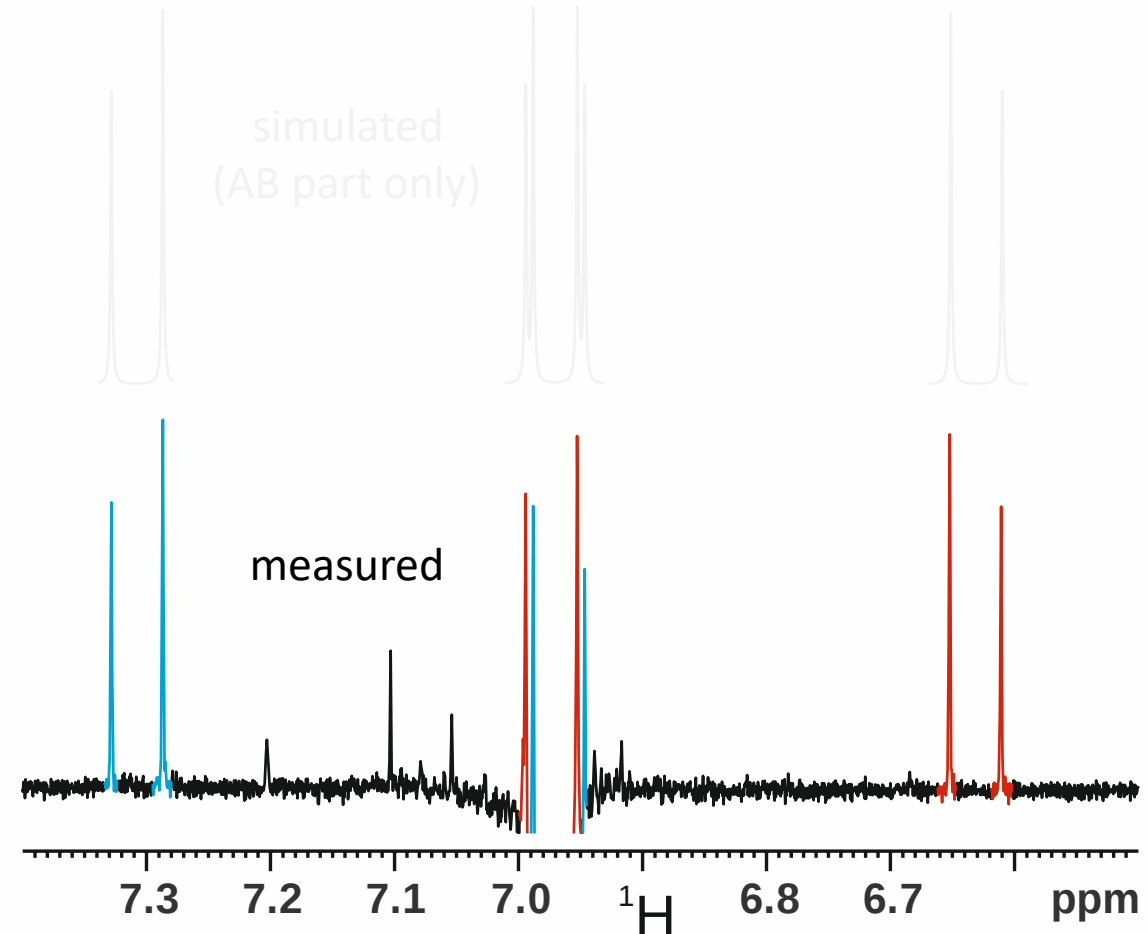
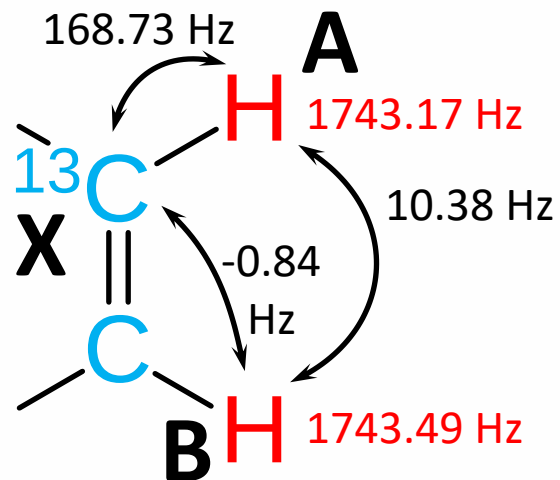


Some theory about the ABX spin system

Correct analysis?

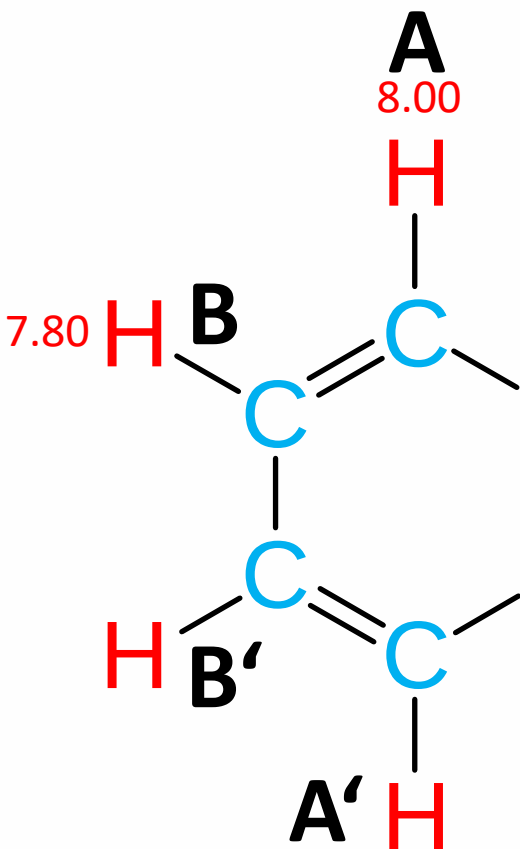
We cannot see the **X** part of the spin system. But to check our calculated coupling constants it is sufficient to assume the absolute frequency of the **X** nucleus at about 25% of the chemical shifts for the protons.

(Please don't calculate 25% from 1743 Hz ...
You still have to add the frequency of the reference signal, resulting in about 250.132 MHz)



Proton proton coupling constants

The second ring

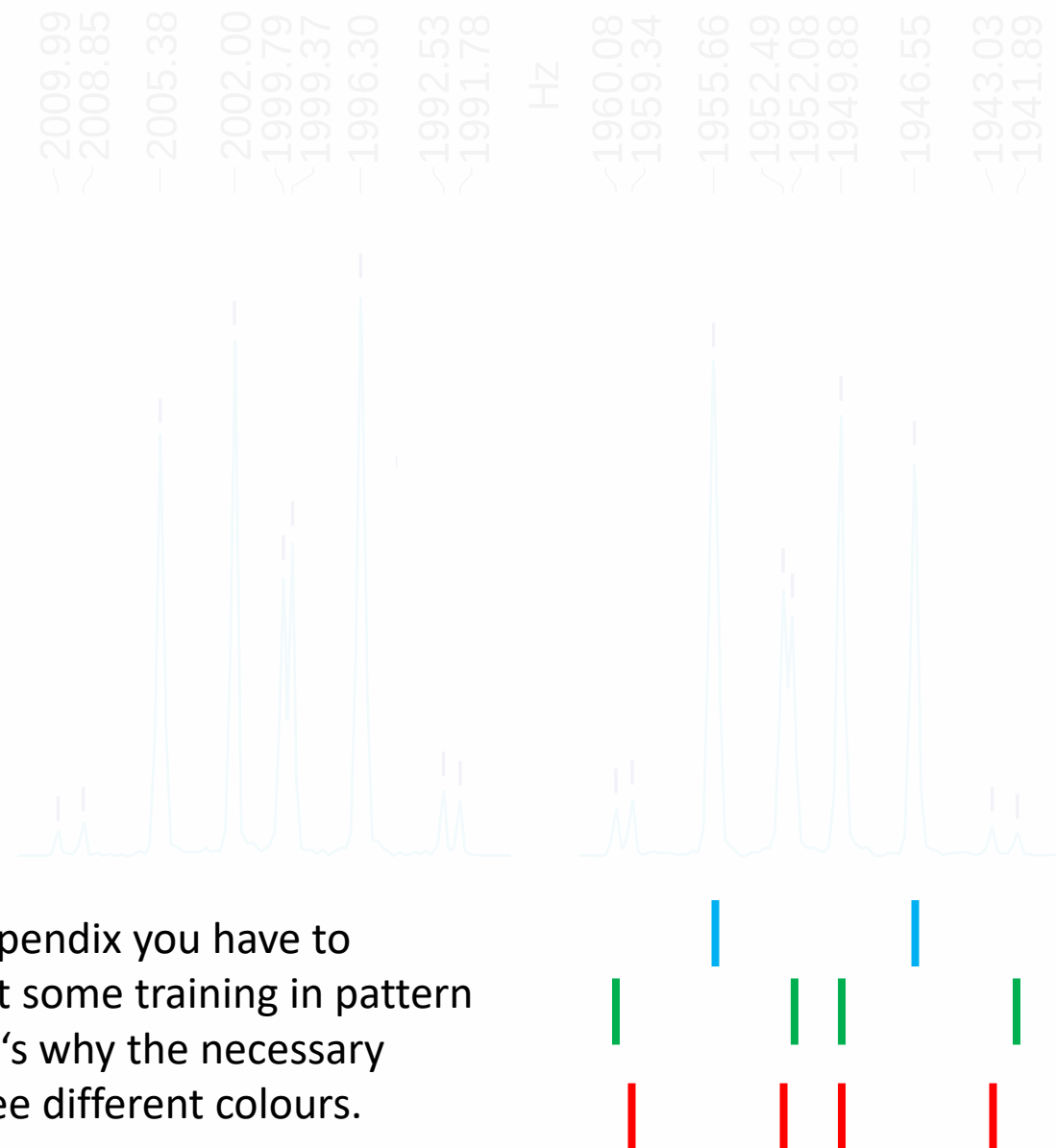


The spin system of the remaining four protons is of the type AA'BB'.

There is an analytical solution available for the AA'XX' type (see appendix).

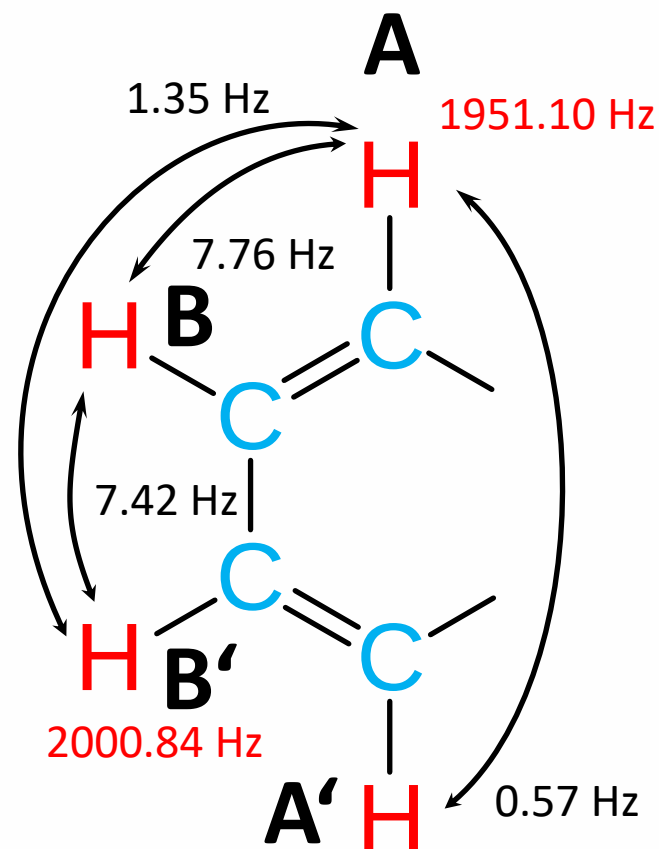
Let us try to use this solution for our spectrum. After extracting the values we may simulate our spectrum and maybe some fine tuning is sufficient to get the final parameters.

To do the calculations described in the appendix you have to recognize three groups of signals. Without some training in pattern recognition this is a little bit difficult. That's why the necessary signals groups are labelled here using three different colours.

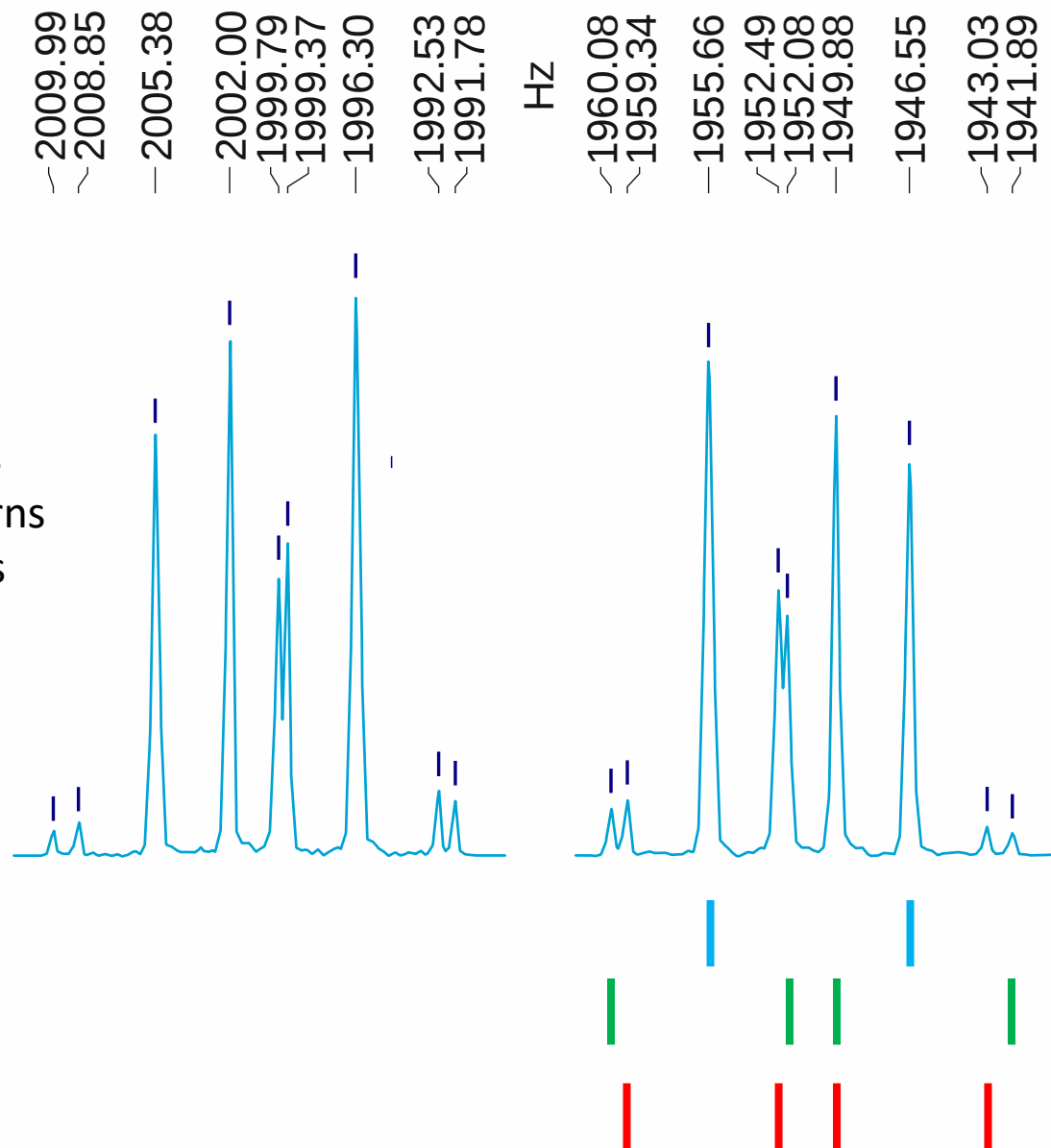


Proton proton coupling constants

The second ring

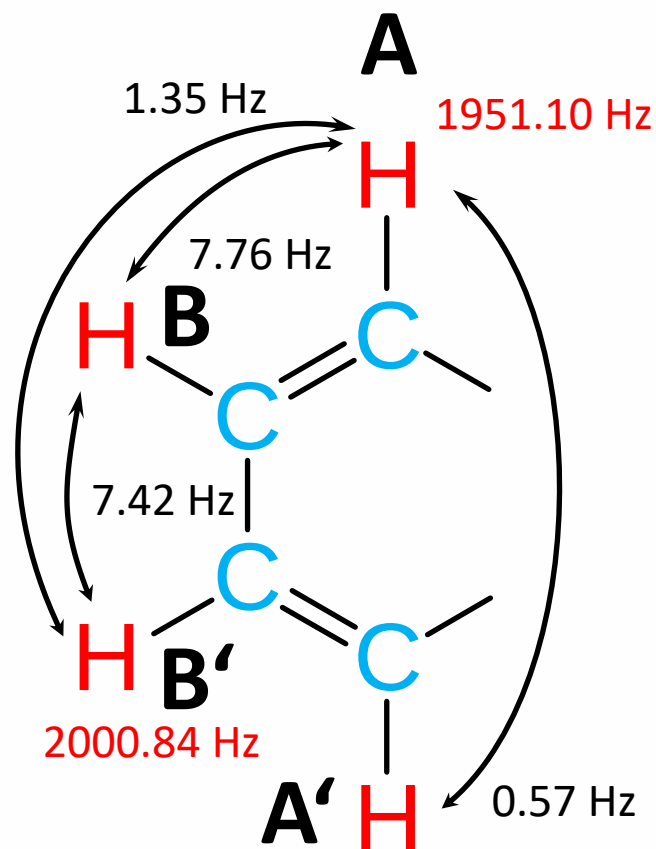


Using the formalism presented as appendix to analyze AA'XX' patterns we end in four coupling constants and two chemical shifts.

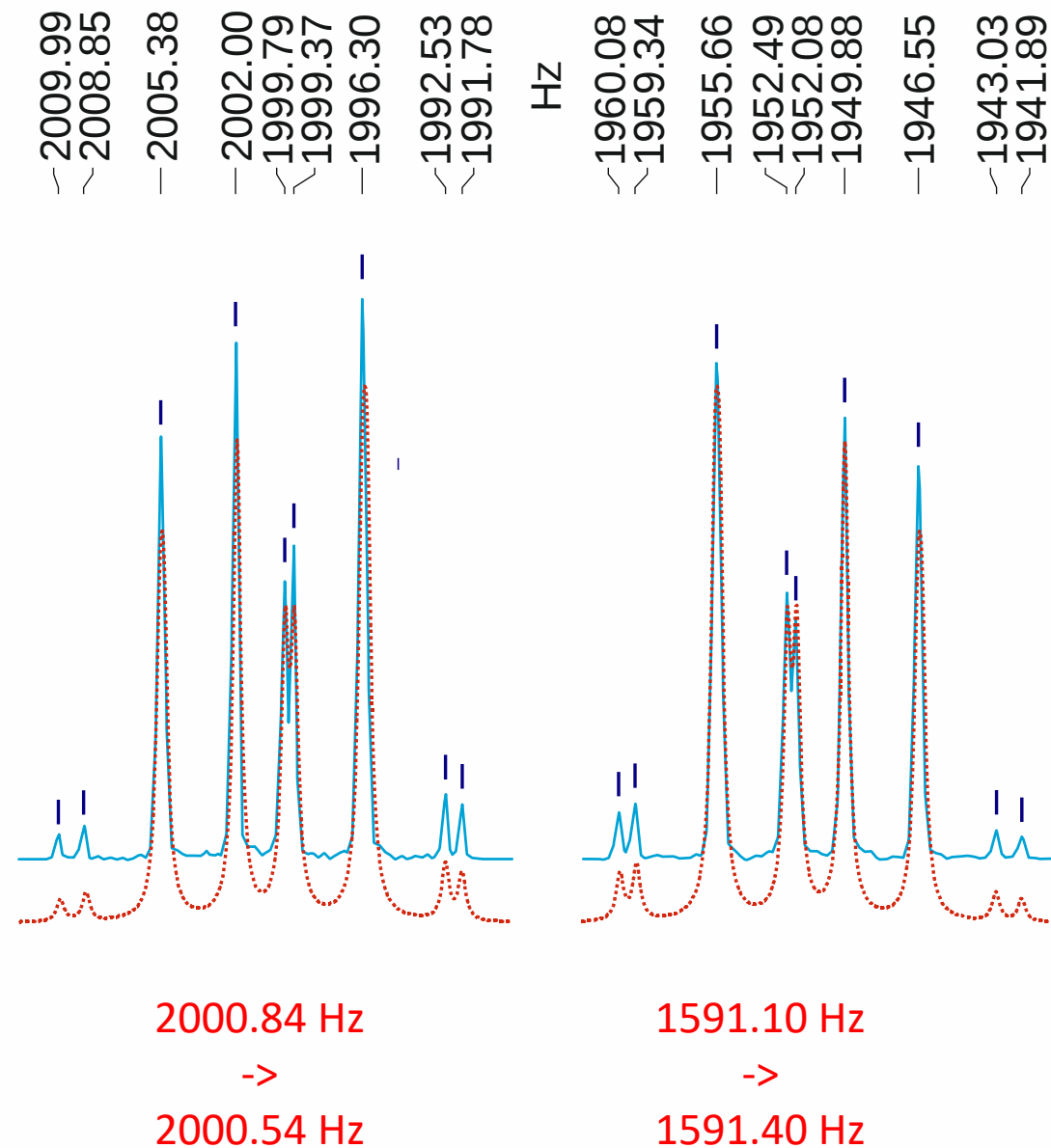


Proton proton coupling constants

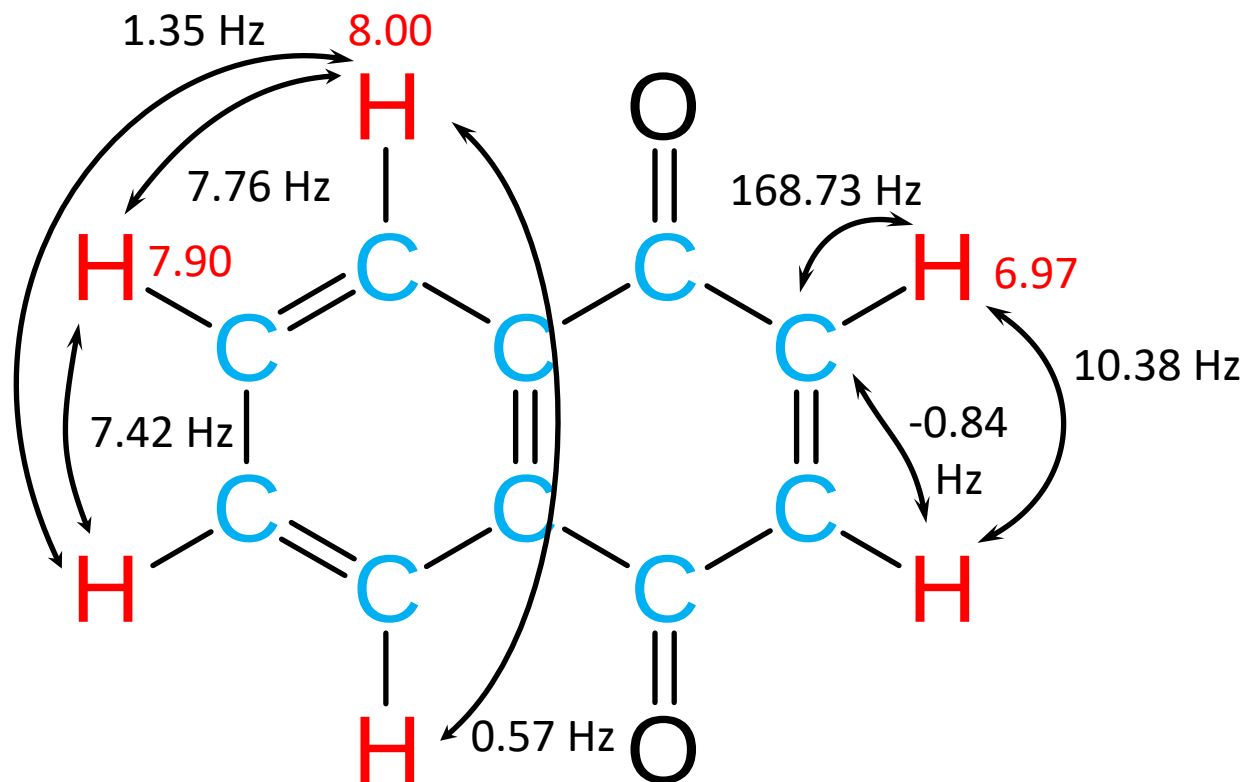
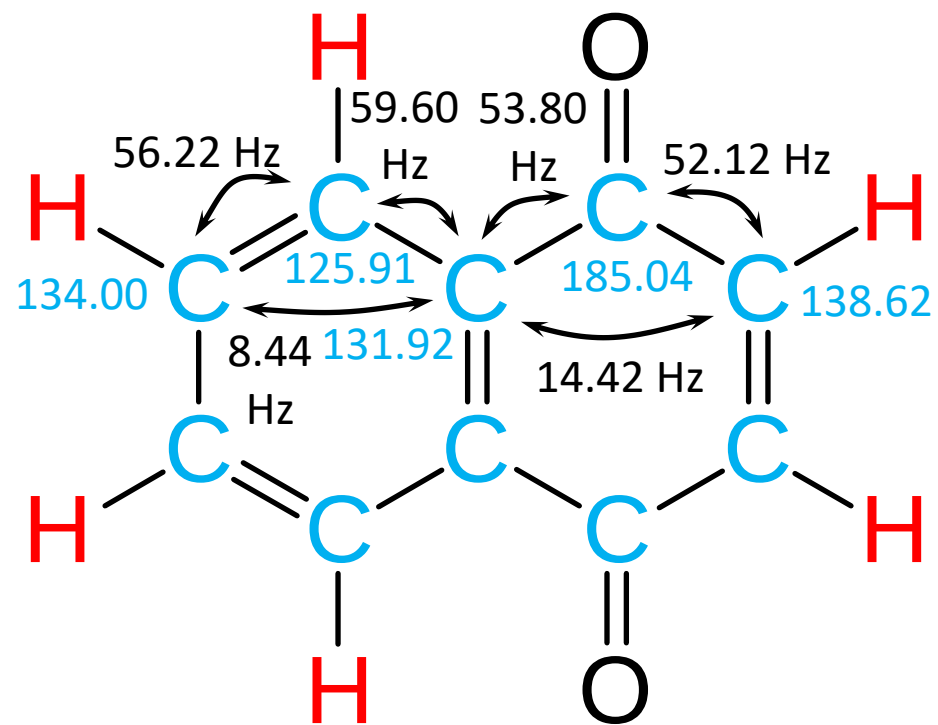
The second ring



And with only minor modification of both chemical shifts, the simulation of the spin system using those parameters is perfect.



Summary



Contributions

Spectrometer time

TU Munich

Measurements

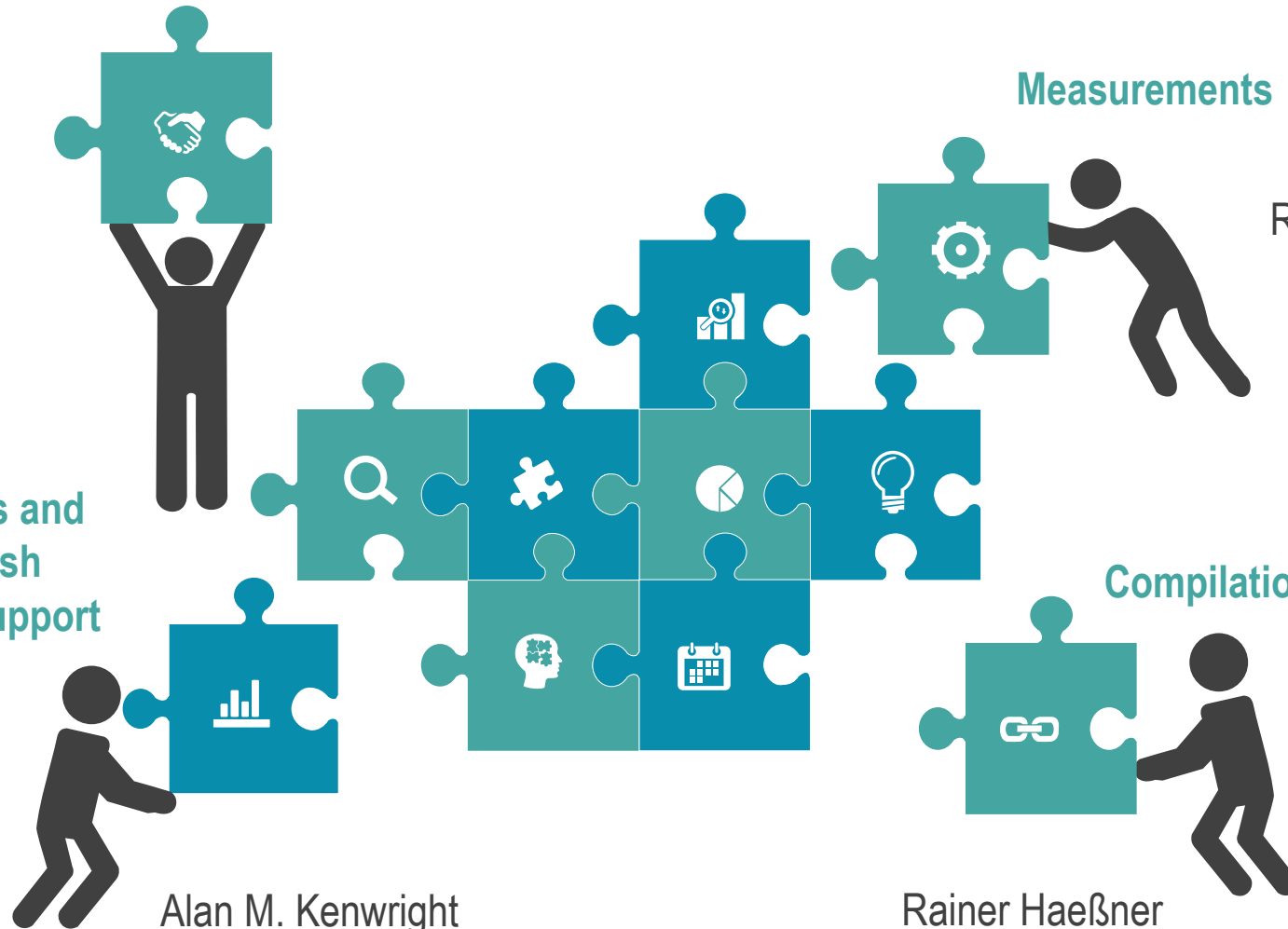
Rainer Haeßner

Discussions and
native English
language support

Compilation

Alan M. Kenwright

Rainer Haeßner

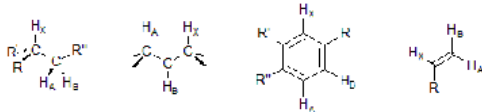


Appendix

ABX spin system

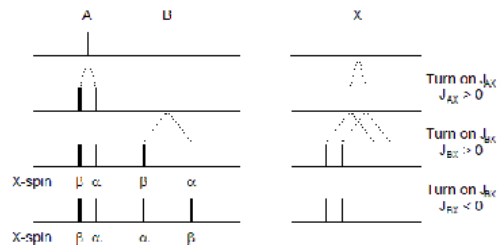
ABX Spectrum

AMX, ABX and ABC patterns, and various related spin systems are very common in organic molecules. Below some of the structural types which give these patterns.



It is worth examining ABX patterns in some detail because, in the progression from first-order NMR patterns to incomprehensible jungles of peaks, they represent the last stopping point where a complete analysis is still possible, and where insights into the problems that arise in the analysis of more complex systems can be achieved. Specifically, ABX patterns are the simplest systems which show the phenomenon sometimes referred to as "virtual coupling" and they are the simplest systems in which both the magnitude and the sign of J coupling constants is significant. Furthermore, there are several pathological forms of ABX patterns which are sufficiently nonintuitive that the unwary spectroscopist can misassign coupling constants and even structures.

Development of an ABX Pattern. Consider the stick diagram below which represents an ABX pattern in which we sequentially turn on first the A-X and then the B-X coupling:



One of the two lines in the A-pattern arises from those molecules with the spin of the X-nucleus aligned against the field (α) and the other from those which have the X-spin aligned with the field (β). Similarly for the B-pattern. Note, however, that the line assignments of the pattern with both J_{AX} and J_{BX} nonzero will be different depending on the relative sign of J_{AX} and J_{BX} , as illustrated in the Figure. Up to this point the line positions are identical.

The key to understanding ABX patterns is to realize that the nuclei with $X = a$ and those with $X = b$ are actually on different molecules, and cannot interact with each other. Thus, when we finally turn on J_{AB} , it will be the $X = a$ line of A and the $X = a$ line of B that will couple to form an AB-quartet, similarly the two $X=b$ lines will form a second AB-quartet.

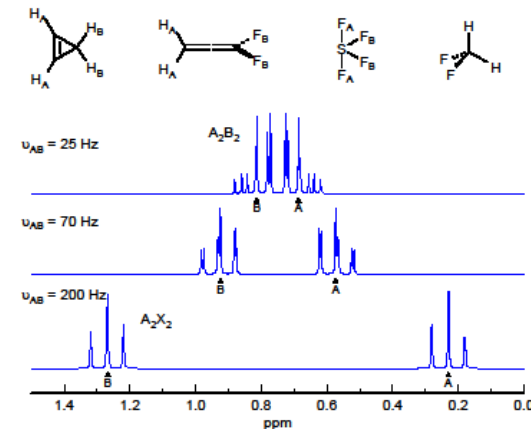
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AA'XX' spin system

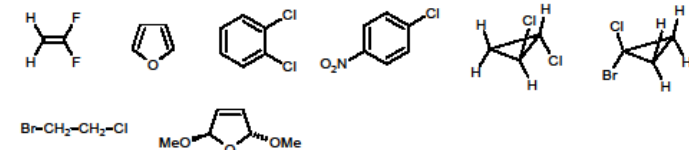
5.14 A_2X_2 , A_2B_2 , AA'XX' and AA'BB' Spectra

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In A_2X_2 and A_2B_2 patterns the two A nuclei and the two X (B) nuclei are magnetically equivalent: they have the same chemical shift by symmetry, and each A proton is coupled equally to the two X (or B) protons. True A_2X_2 patterns are quite rare. Both the A and X protons are identical triplets. More complicated patterns are seen when the chemical shift difference approaches or is smaller than the J_{AB} coupling. However, both A_2B_2 and $AA'BB'$ always give centrosymmetric patterns (A_2 part mirror image of the B_2 part).



AA'XX' and AA'BB' spectra are much more common. Here each A proton is coupled differently to the B and B' protons. Some molecules with such patterns are:



If the J_{AB} coupling is identical to the $J_{AB'}$ coupling by accident then the system becomes A_2B_2 or A_2X_2