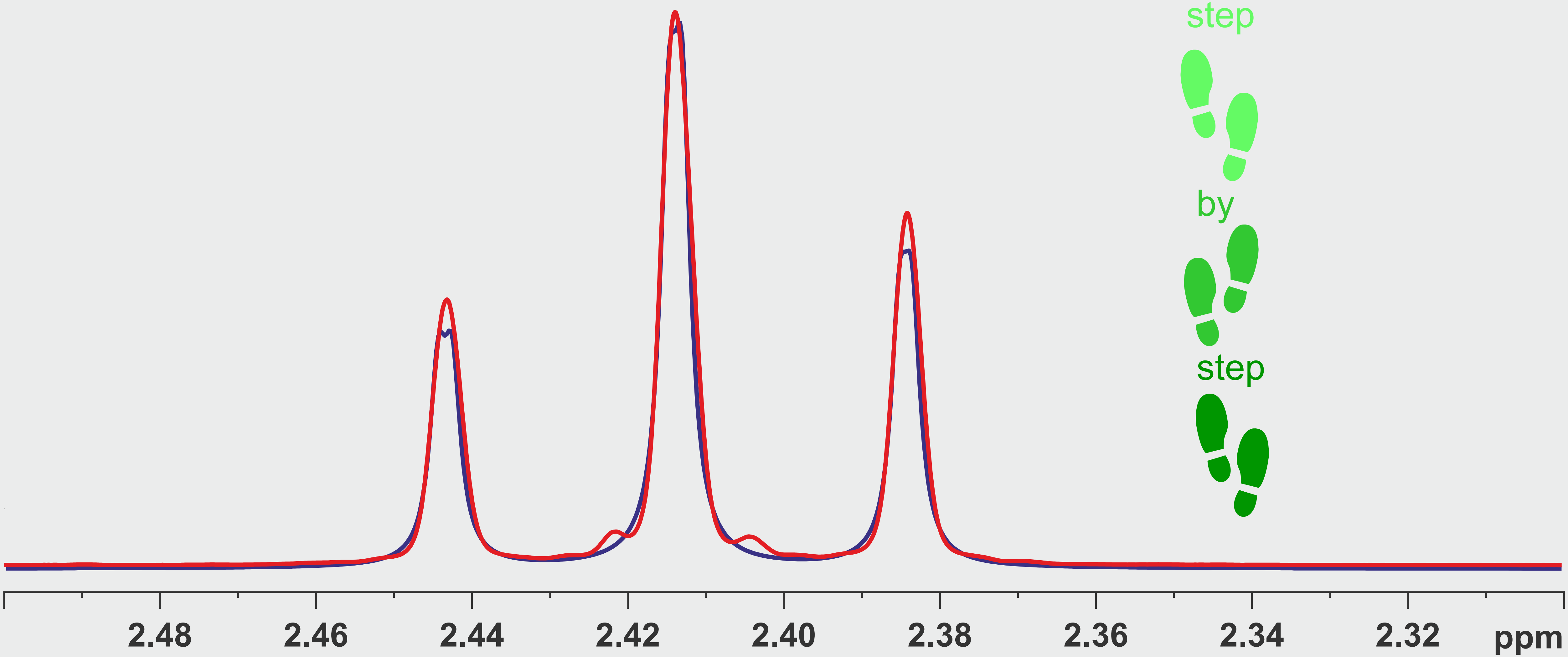
Exercise plus Solution – Quick overview

It is recommended to use this 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.



step

by

step

Problem of the Month:

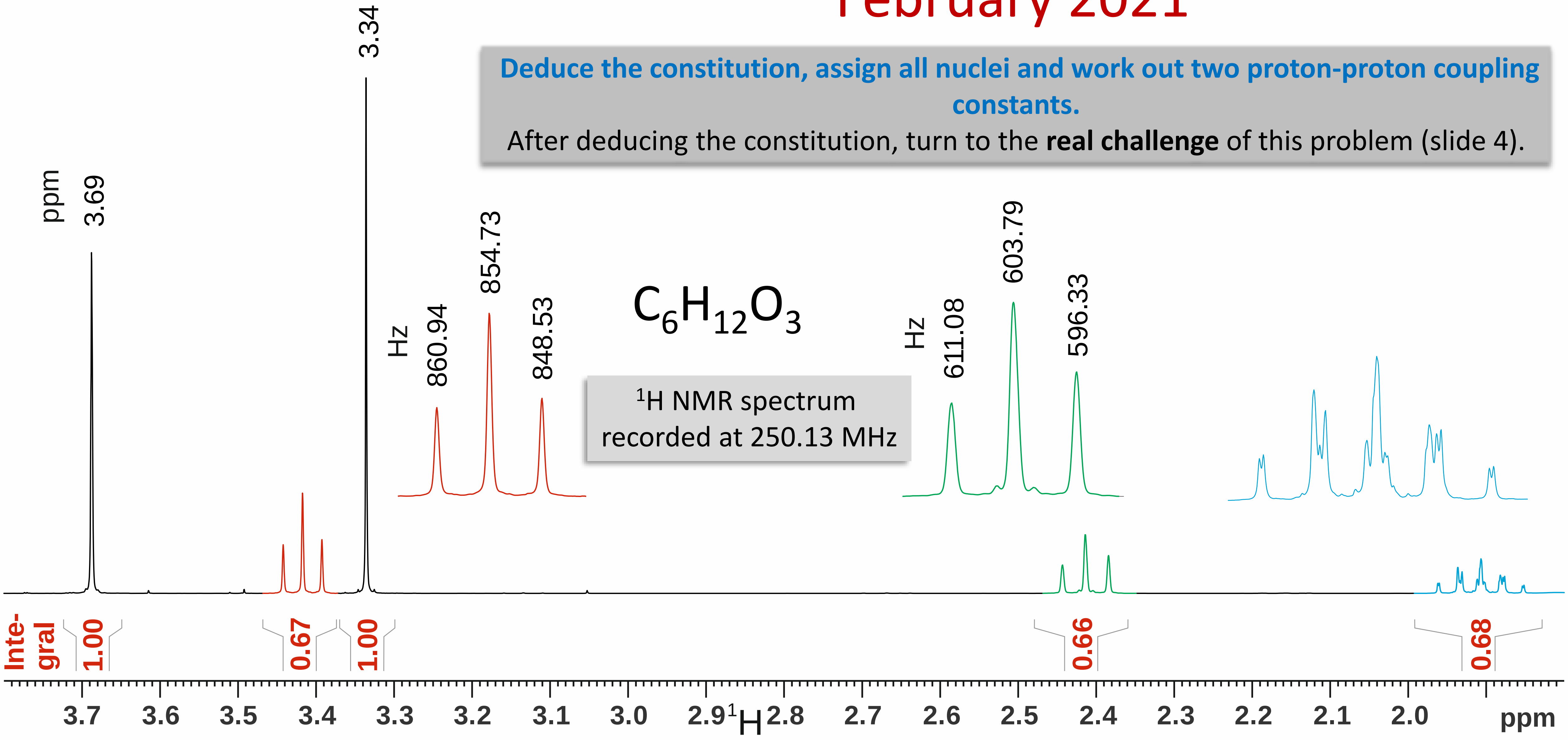
February 2021

Deduce the constitution, assign all nuclei and work out two proton-proton coupling constants.

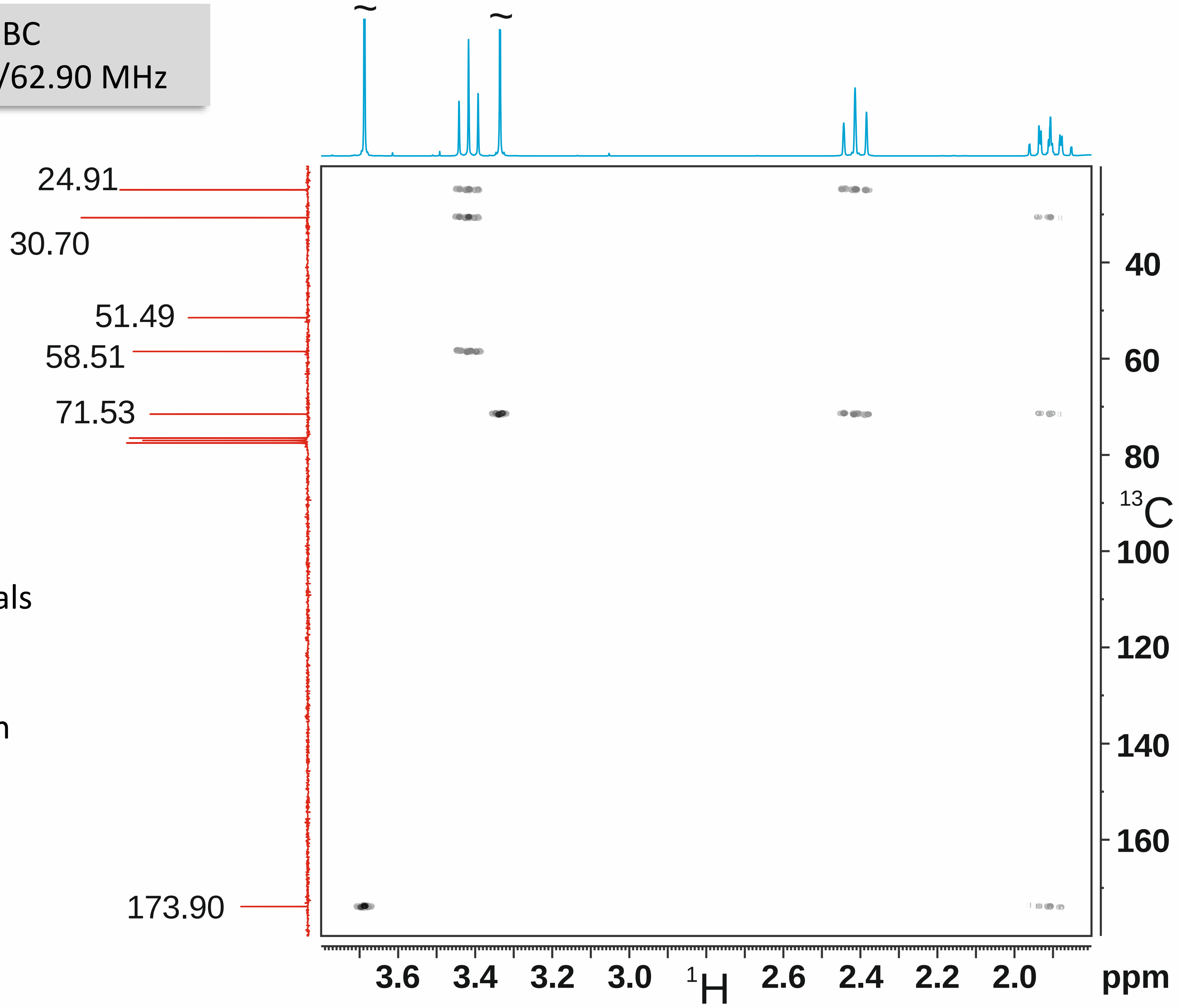
After deducing the constitution, turn to the **real challenge** of this problem (slide 4).

$C_6H_{12}O_3$

^{1}H NMR spectrum recorded at 250.13 MHz



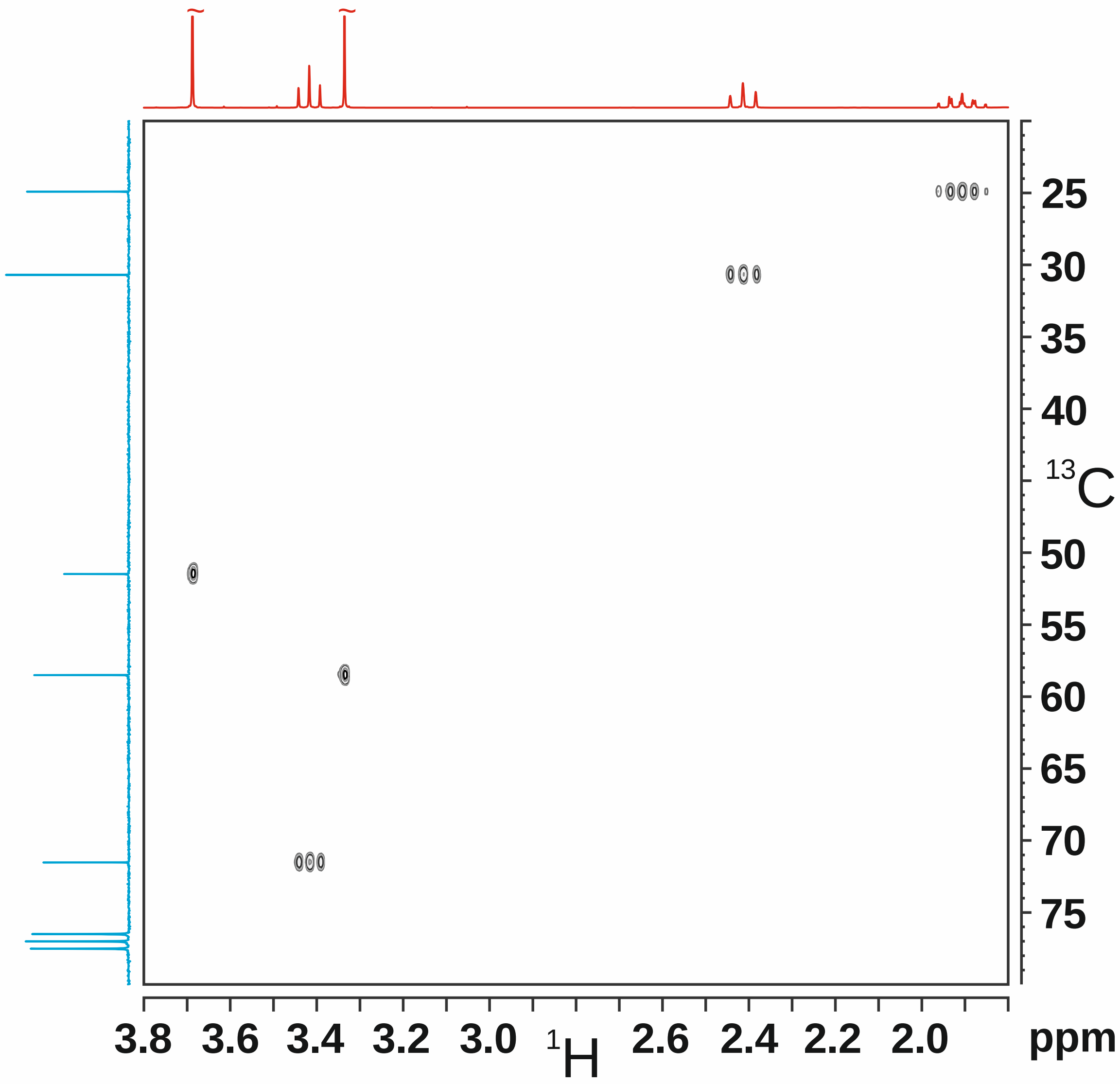
$^1H/^{13}C$-HMBC
recorded at 250.13/62.90 MHz



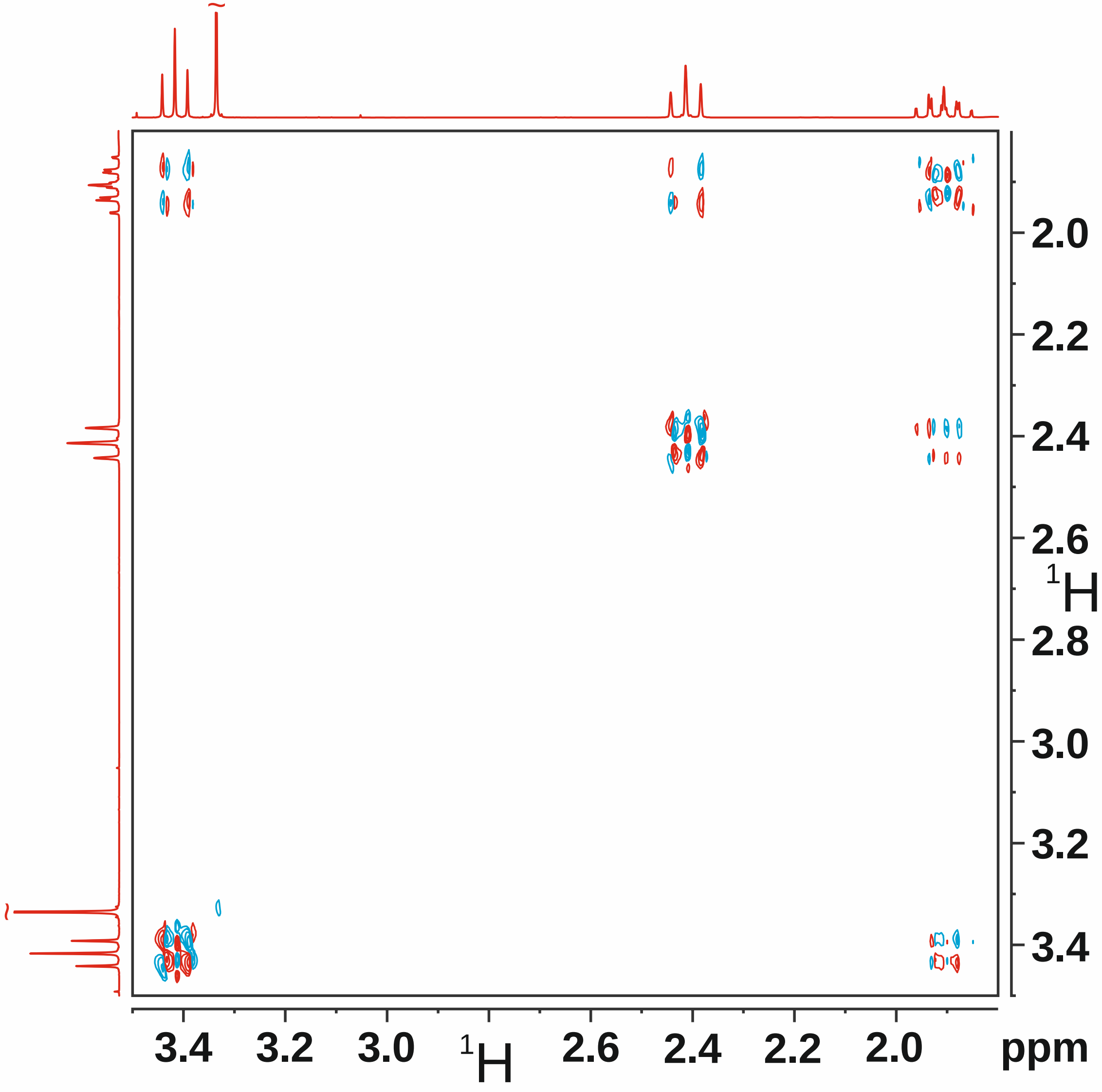
The f_1 projection contains all six carbon signals of the compound.

There is no separate one dimensional carbon spectrum given.

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



$^{1}H/^{1}H$-DQF-COSY
recorded at 250.13 MHz



And now the challenge

With three chemical shifts and two coupling constants, you can simulate the three multiplets in the proton spectrum. The simulation for the multiplet at about 3.4 ppm will provide an almost perfect result, but in the case of the other two multiplet there are small but significant deviations. The multiplet at about 1.9 ppm looks a bit more complex than expected, although there exists a clear base structure. But the mutiplet at about 2.4 ppm should be a pure triplet.

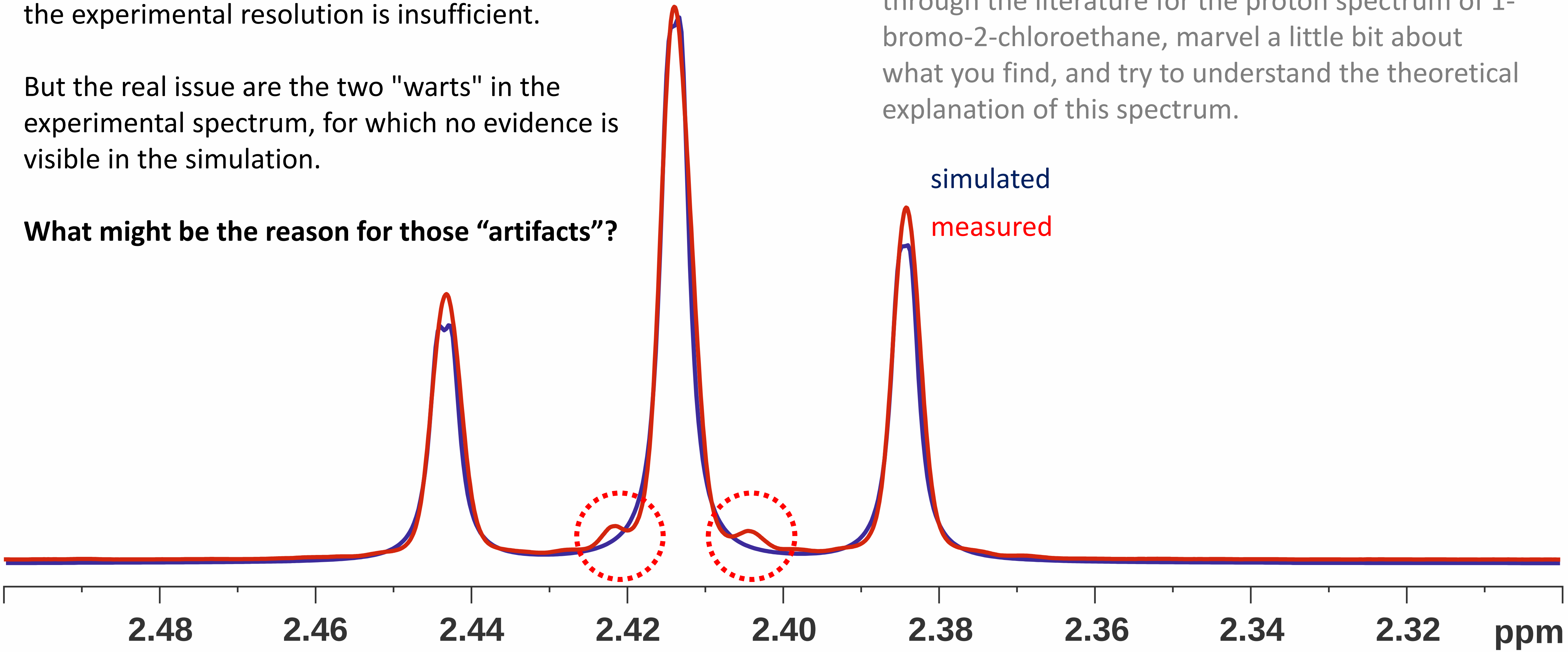
Because of the small difference in chemical shift between the multiplets at 1.9 ppm and 2.4 ppm, fine splitting is visible in the simulation for which the experimental resolution is insufficient.

But the real issue are the two "warts" in the experimental spectrum, for which no evidence is visible in the simulation.

What might be the reason for those “artifacts”?

Hint:

To answer this extremely difficult question, trawl through the literature for the proton spectrum of 1-bromo-2-chloroethane, marvel a little bit about what you find, and try to understand the theoretical explanation of this spectrum.

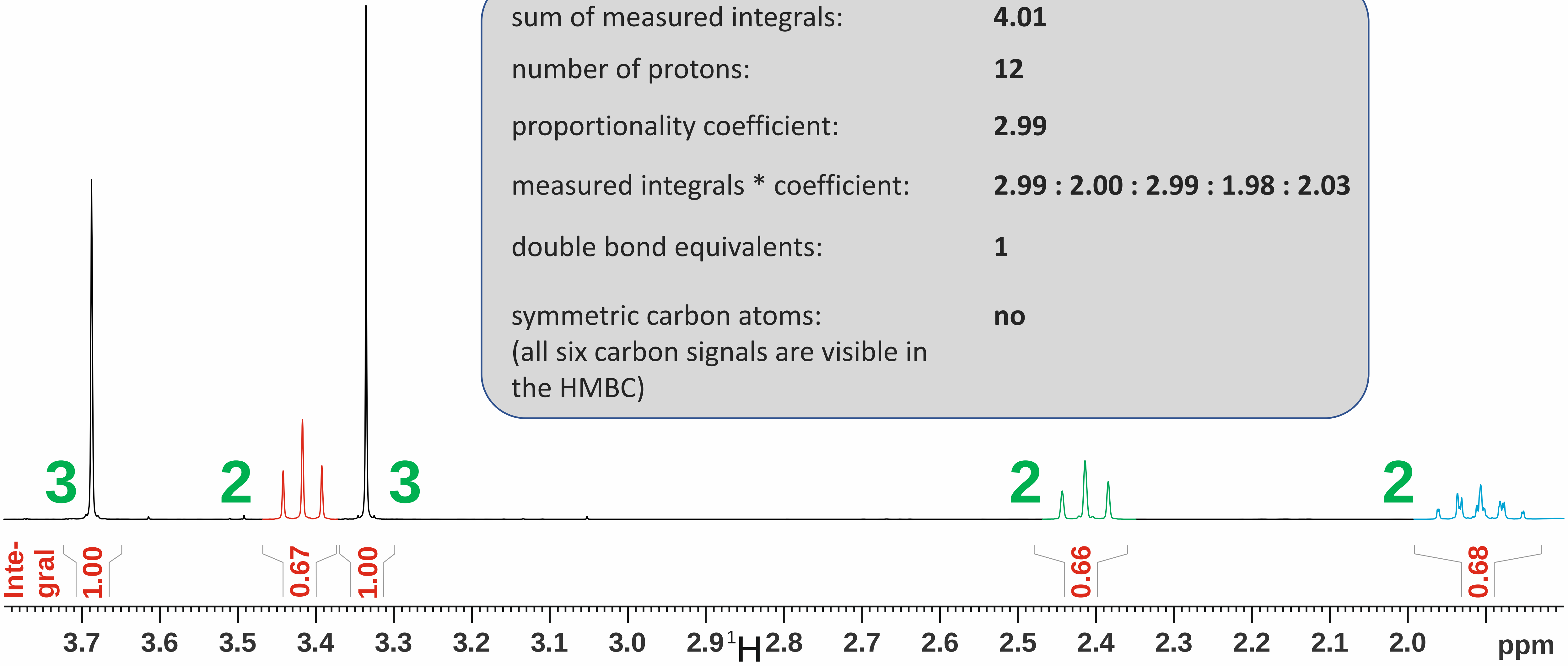


Basics

Integration,double bond equivalents, symmetry

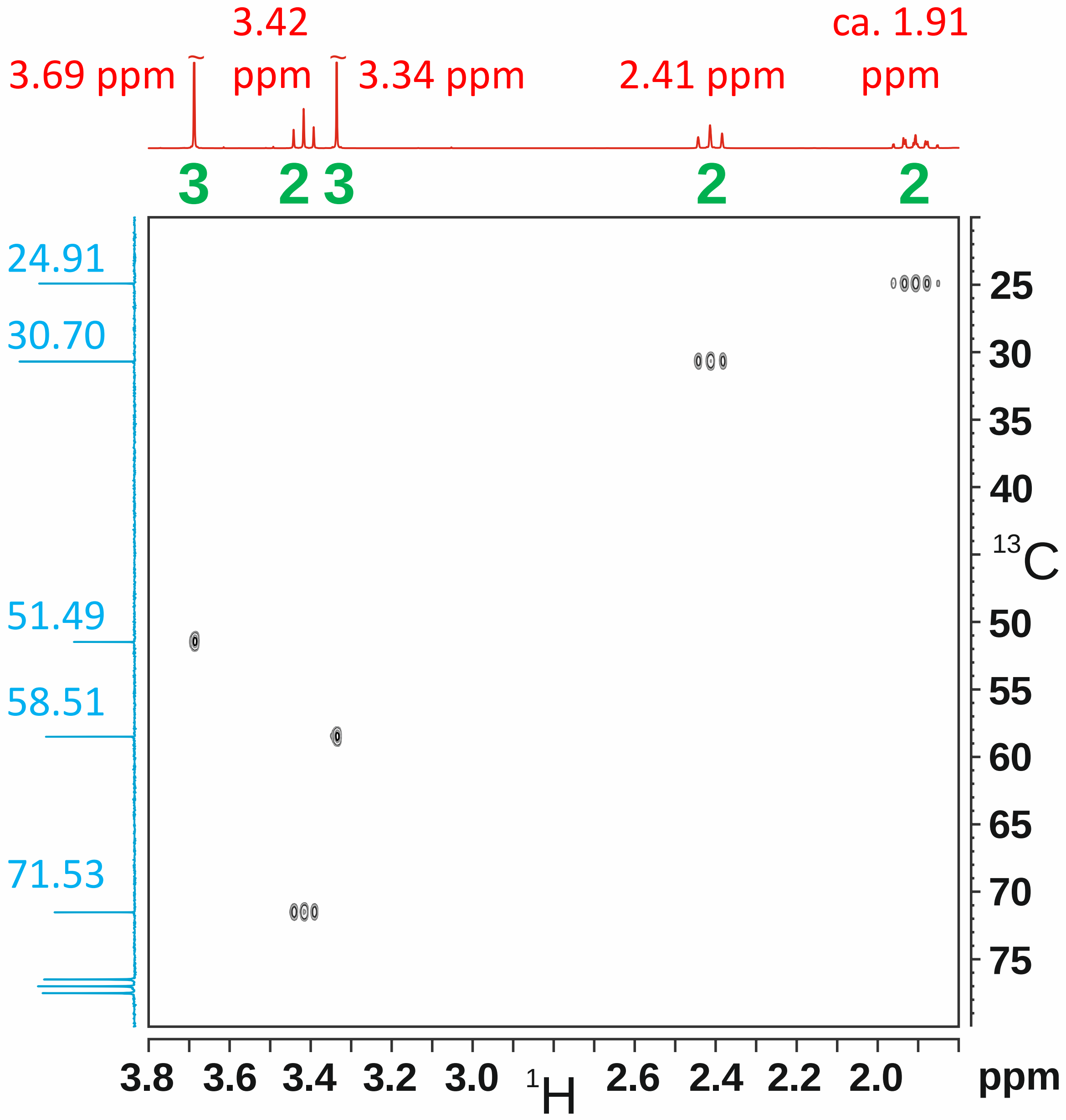
$C_6H_{12}O_3$

sum of measured integrals:	**4.01**
number of protons:	**12**
proportionality coefficient:	**2.99**
measured integrals * coefficient:	**2.99 : 2.00 : 2.99 : 1.98 : 2.03**
double bond equivalents:	**1**
symmetric carbon atoms: (all six carbon signals are visible in the HMBC)	**no**



Building blocks

CH_n-fragments



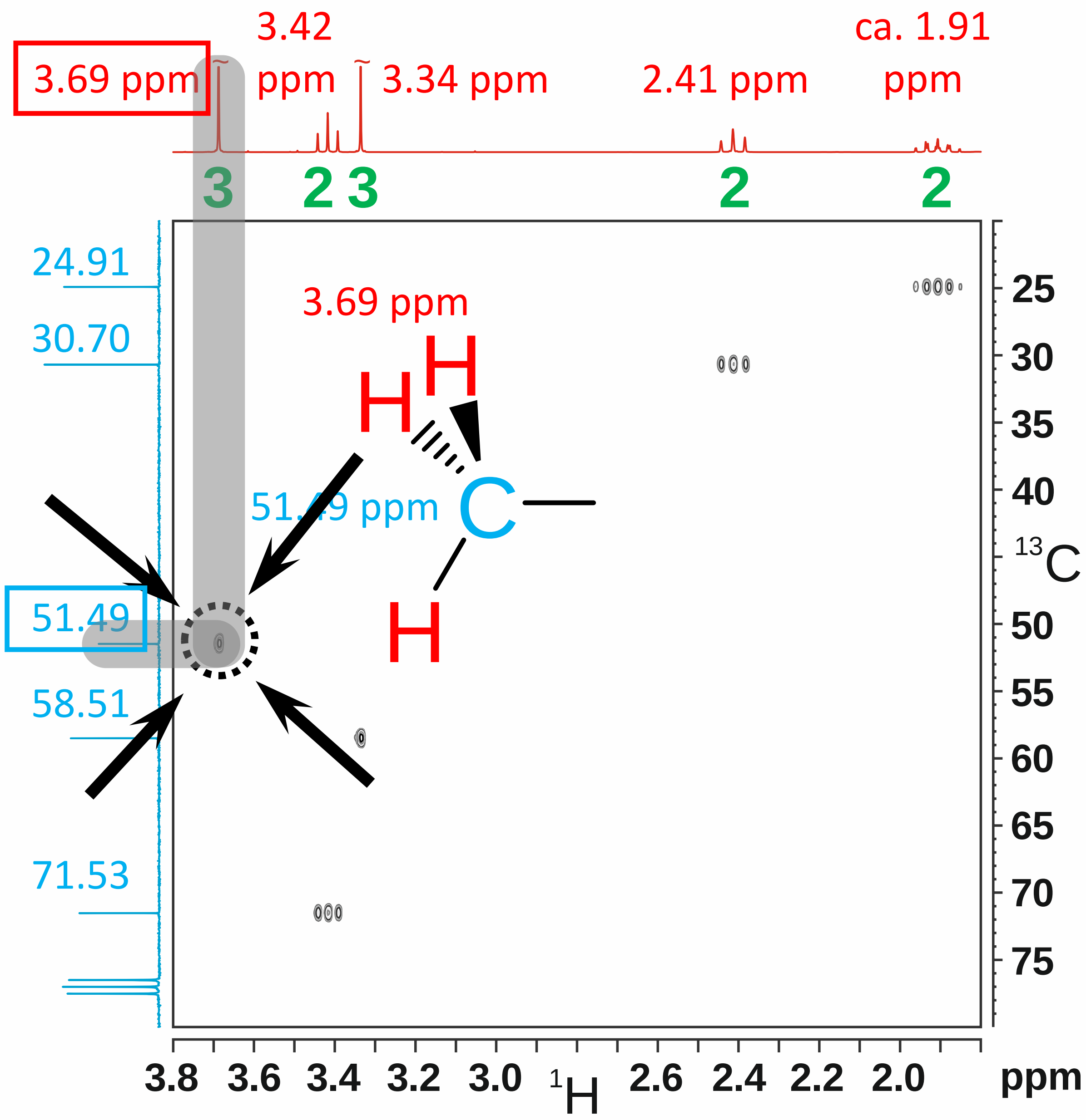
It is very easy to evaluate a HSQC. The sensitivity, of course, is less than the sensitivity of a one dimensional proton spectrum but much higher than a one dimensional carbon spectrum. Therefore, the measurement of a HSQC is always recommended, if possible.

We need some data for the projections, chemical shifts and integrals from the one dimensional proton spectrum and the carbon chemical shifts from the one dimensional carbon spectrum.

The one dimensional carbon spectrum is not explicitely given here but used as a pseudo projection for the HMBC. The chemical shifts can be picked there.

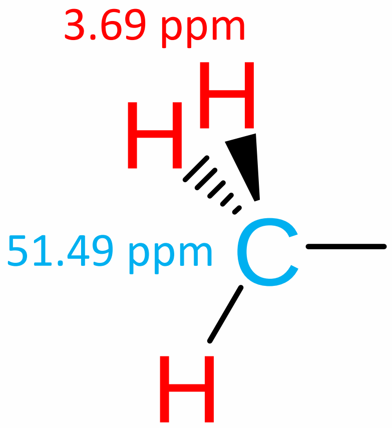
Building blocks

CH$_n$-fragments



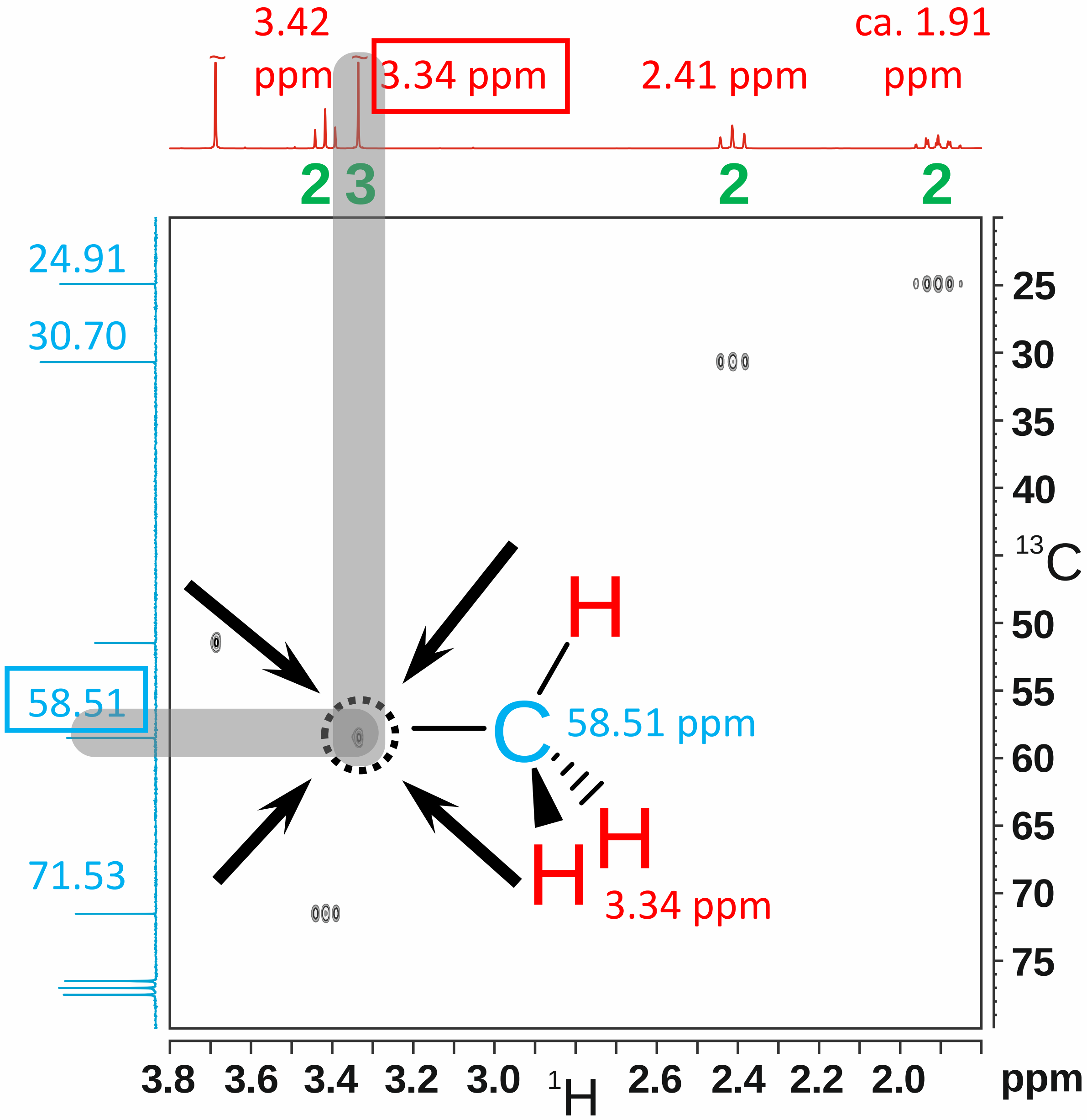
The proton signals at 3.69 ppm and 3.34 ppm could only belong to methyl groups according to their integral. The possibility of three symmetric CH-groups could be immediately excluded by our initial considerations (slide 1).

Please continue to the second methyl group …



Building blocks

CH$_n$-fragments



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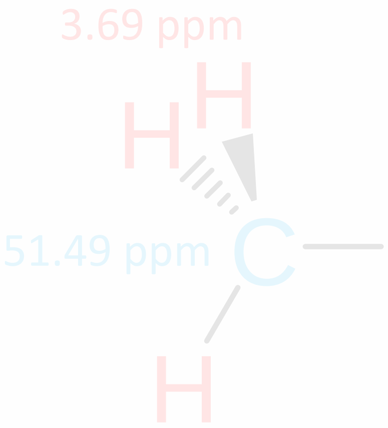
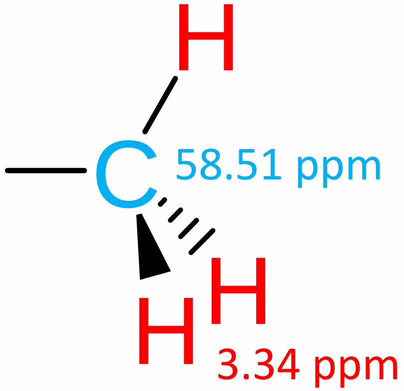
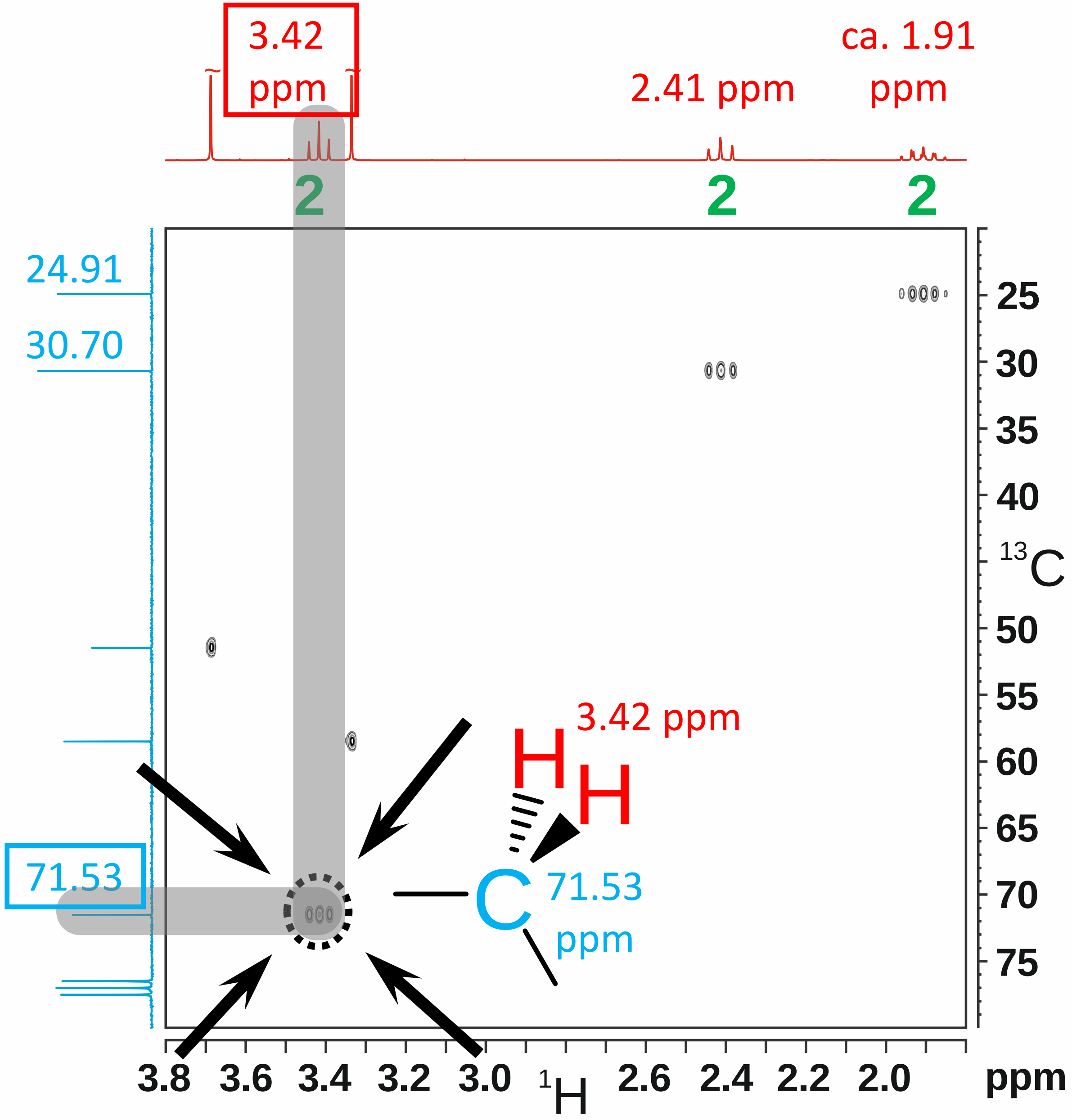


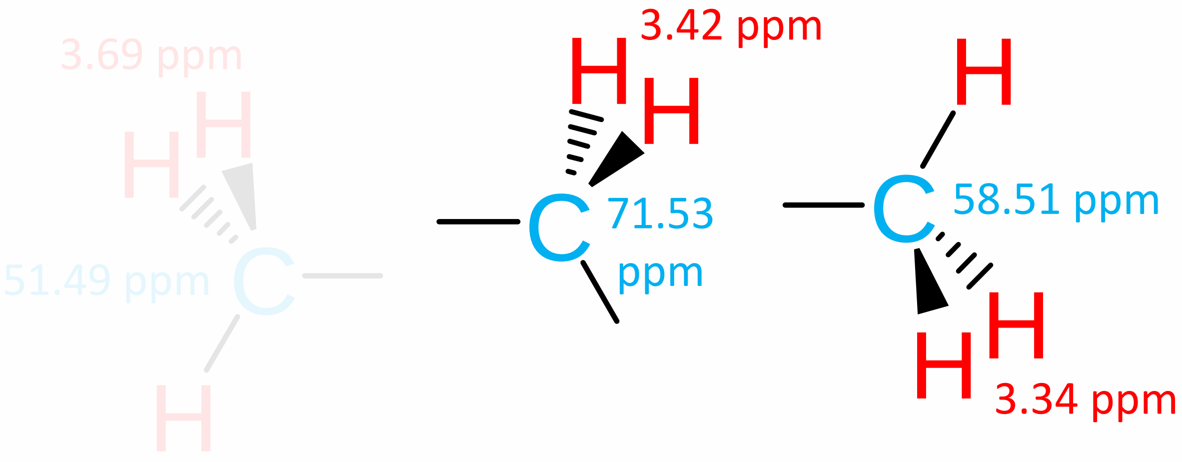


Building blocks

CH_n-fragments

The remaining cross peaks belong to methylene groups.
Let us extract them step by step.





Building blocks

CH_n-fragments

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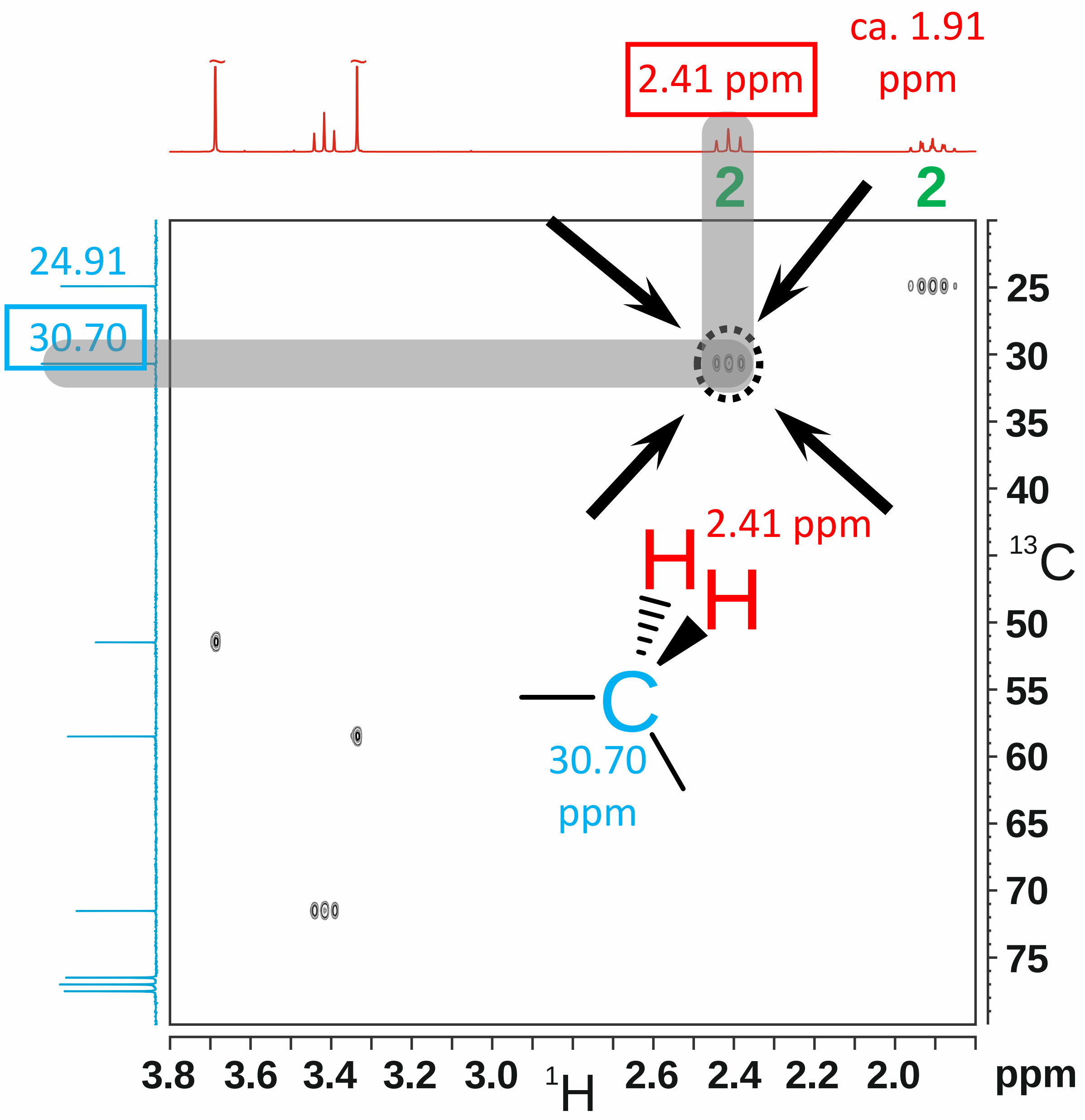

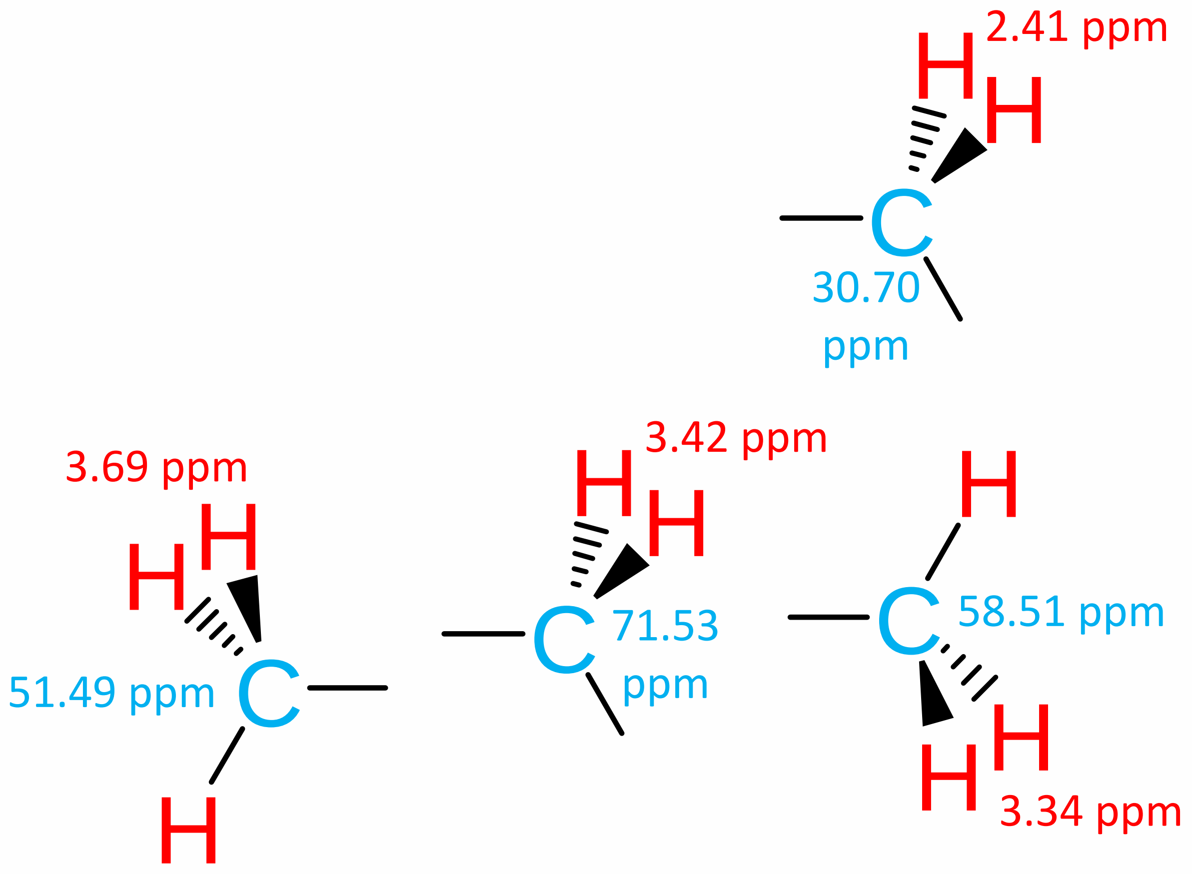

Building blocks

CH$_n$-fragments

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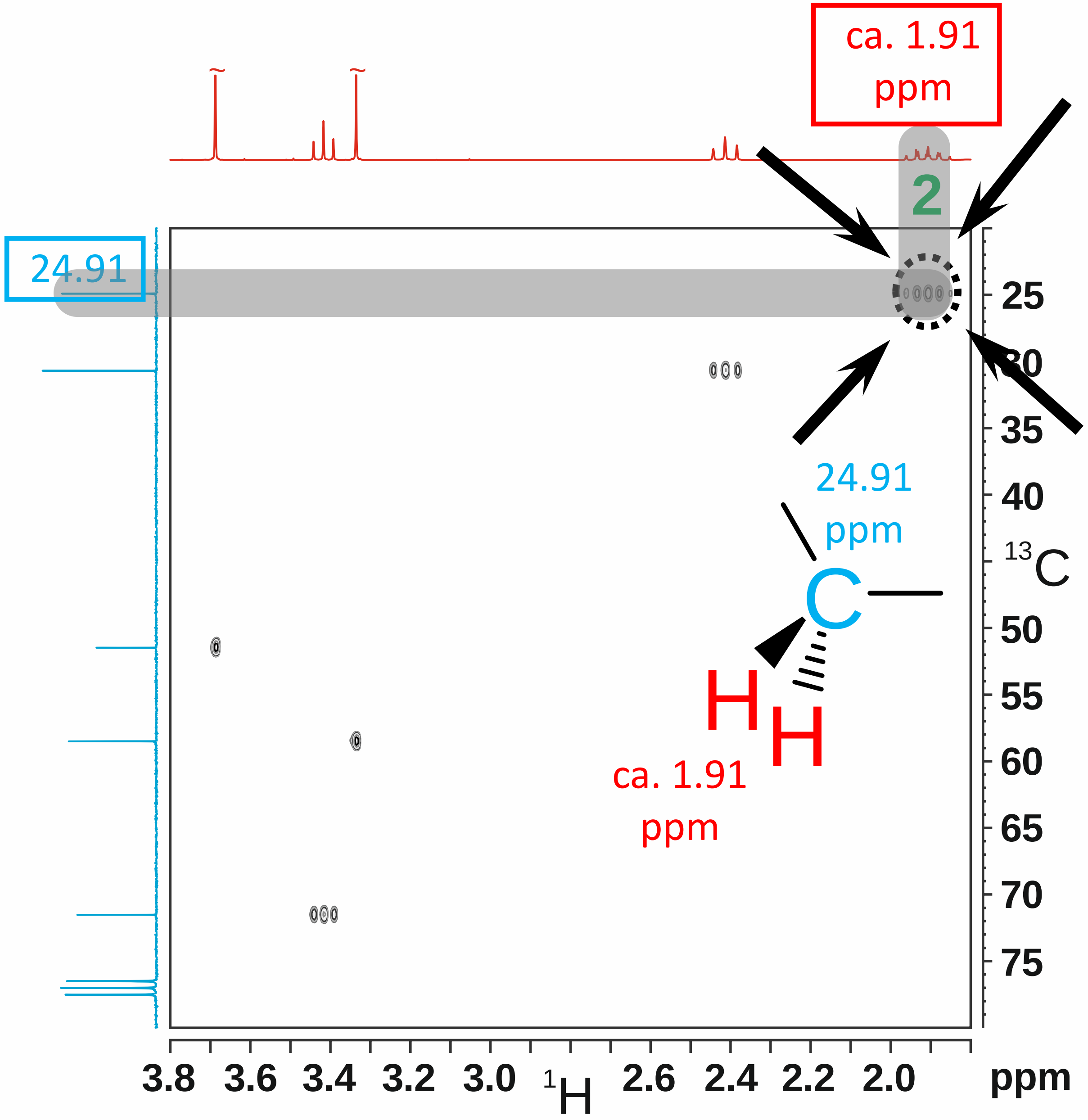
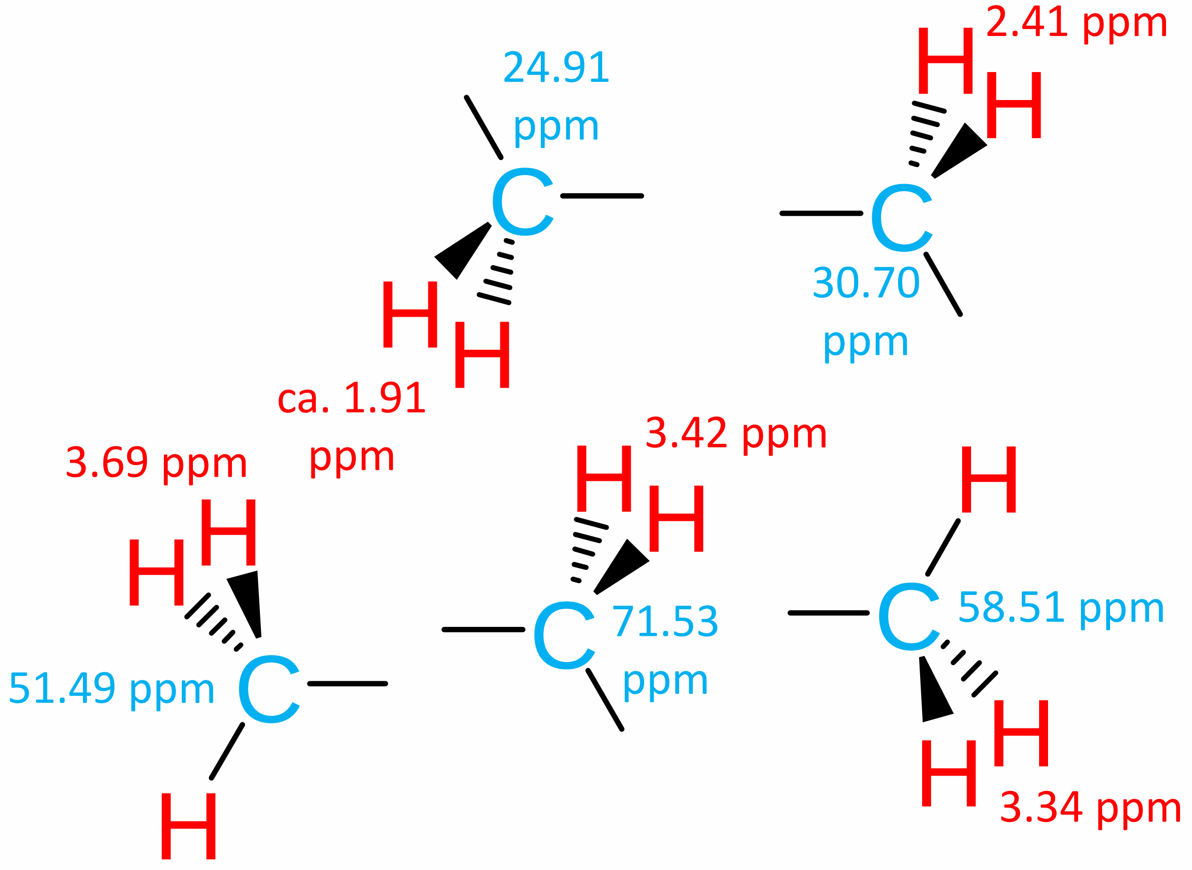
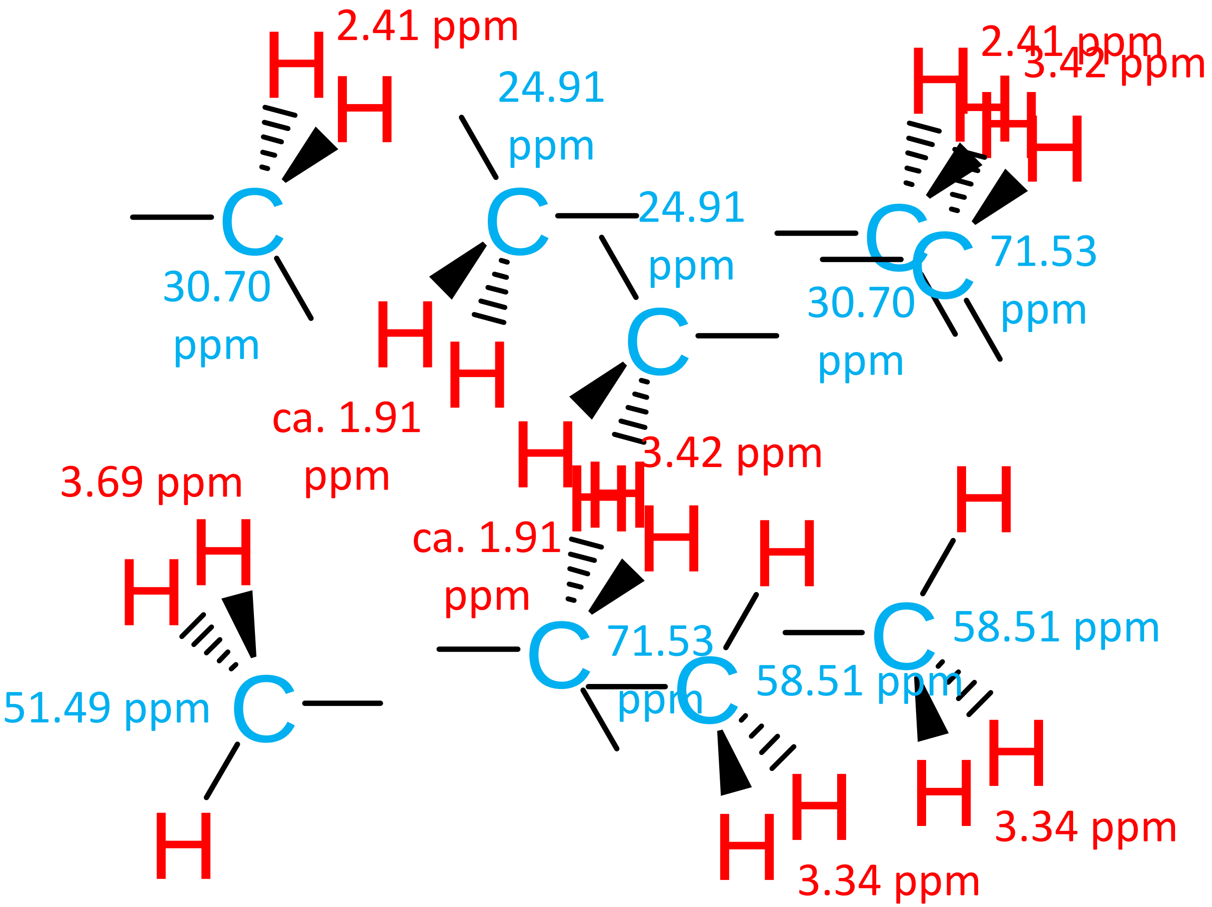




Linking the pieces

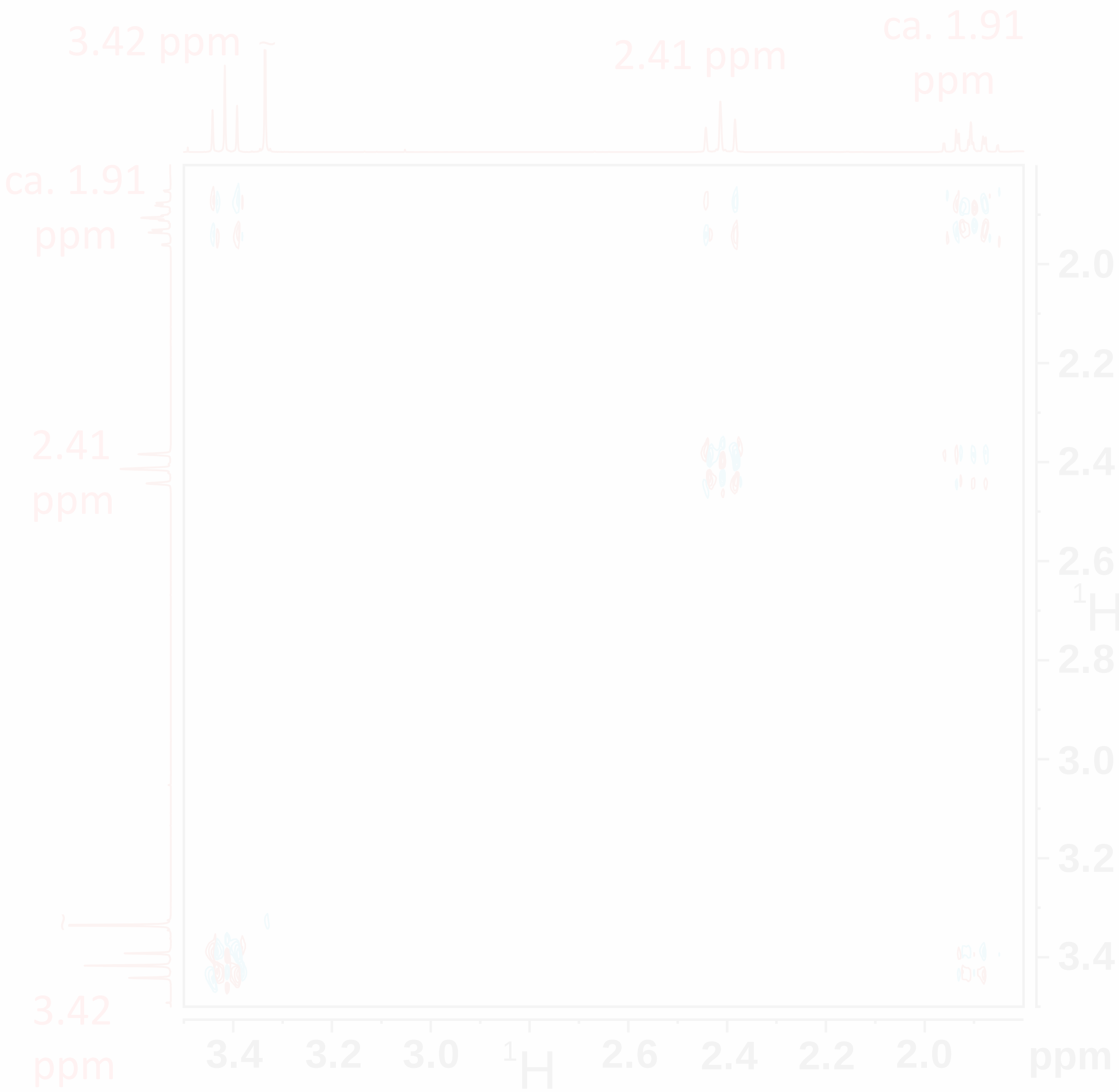
part 1 – alkyl chain

First let us reorder the fragments a little bit to make the next steps easier.

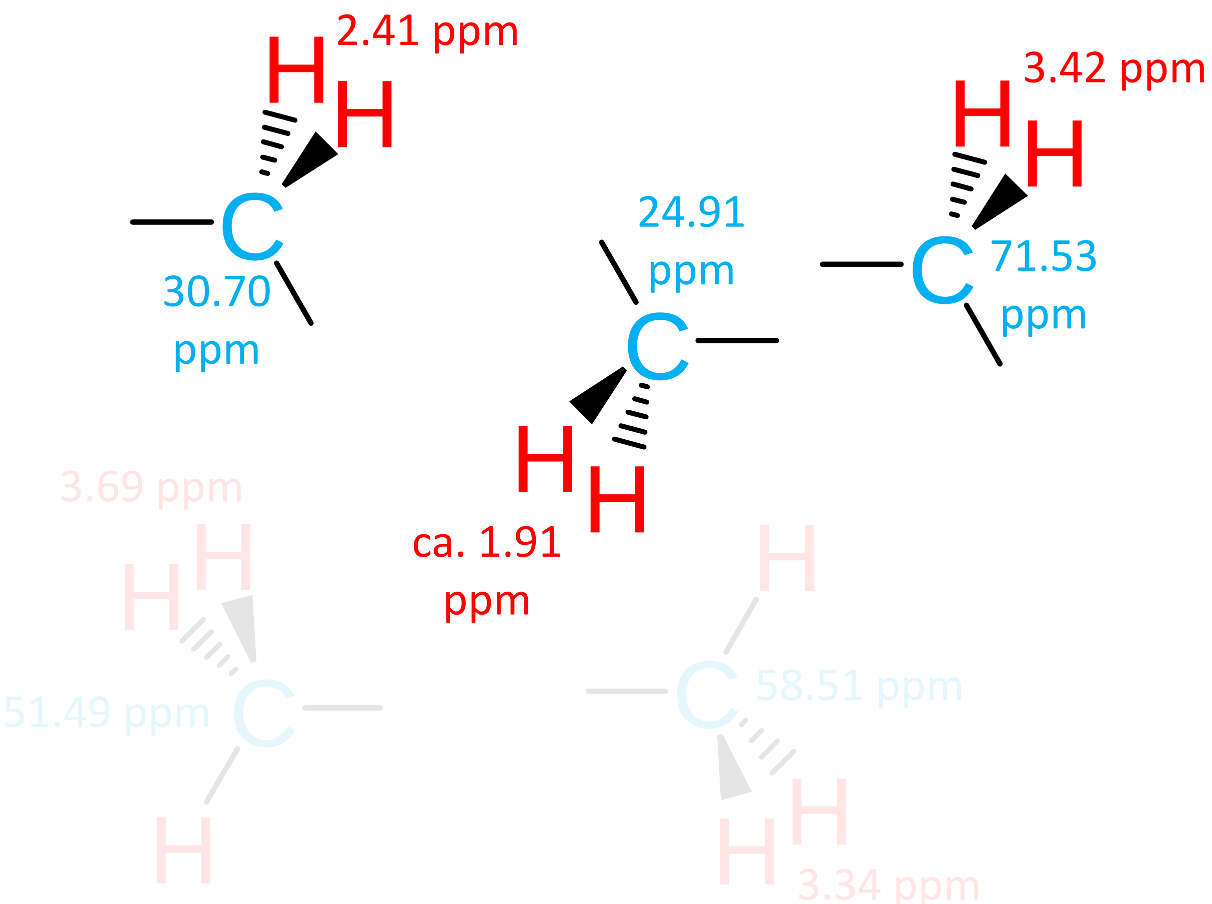


Linking the pieces

part 1 – alkyl chain

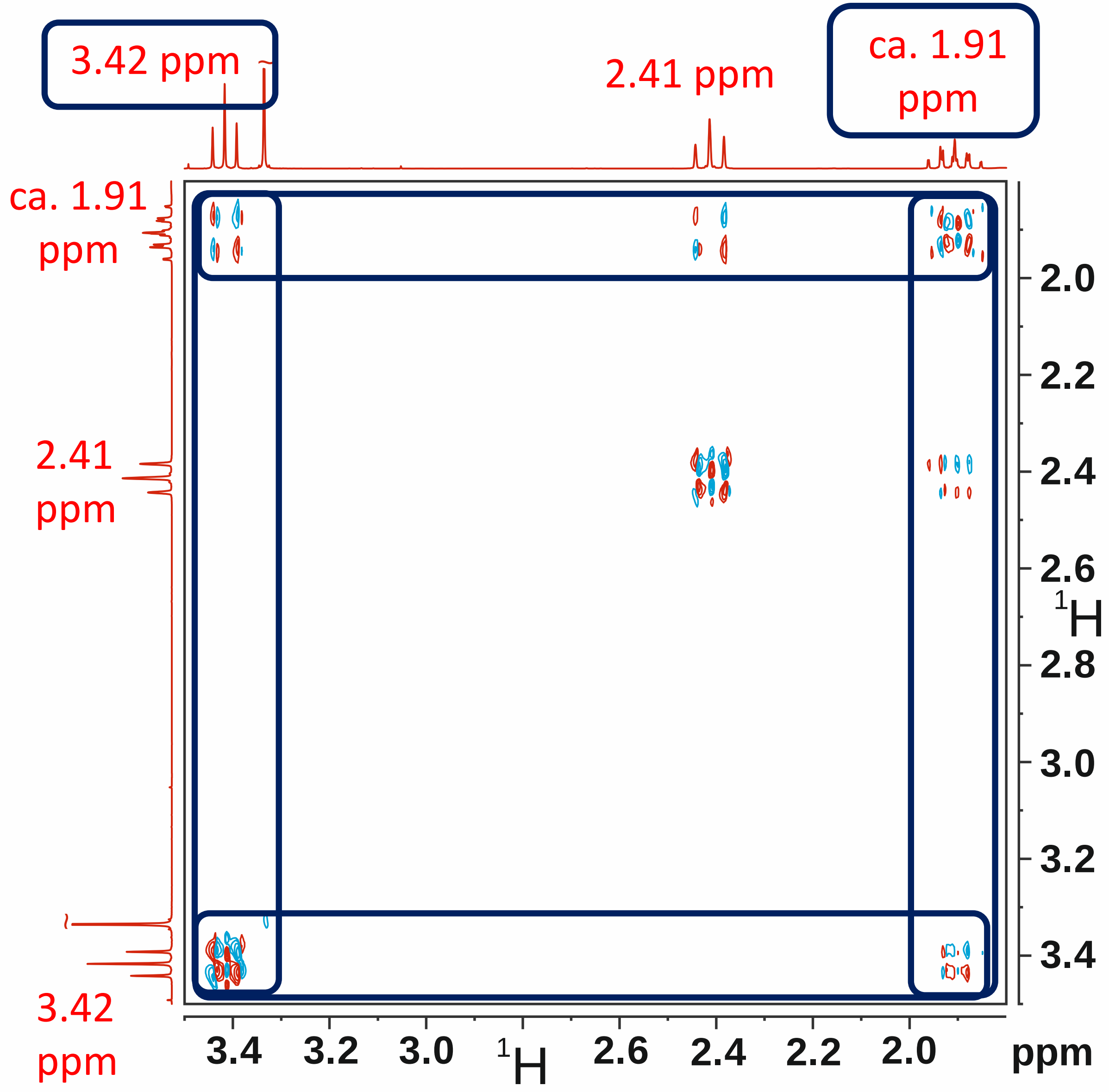


During our work with the COSY we have no use for the methyl groups.

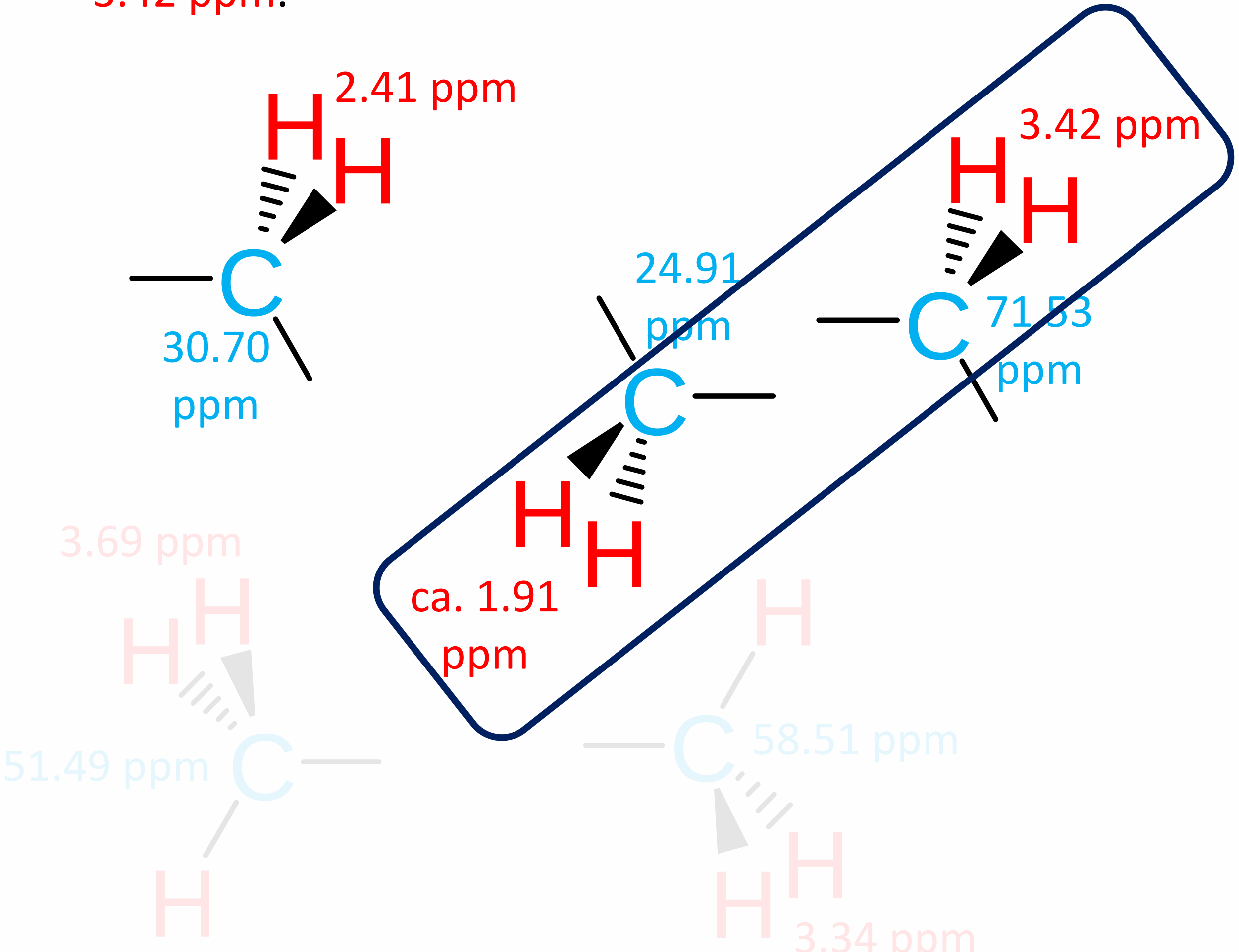


Linking the pieces

part 1 – alkyl chain



The first visible proximity in the COSY, is between the protons with the chemical shifts of ca. 1.91 ppm and 3.42 ppm.



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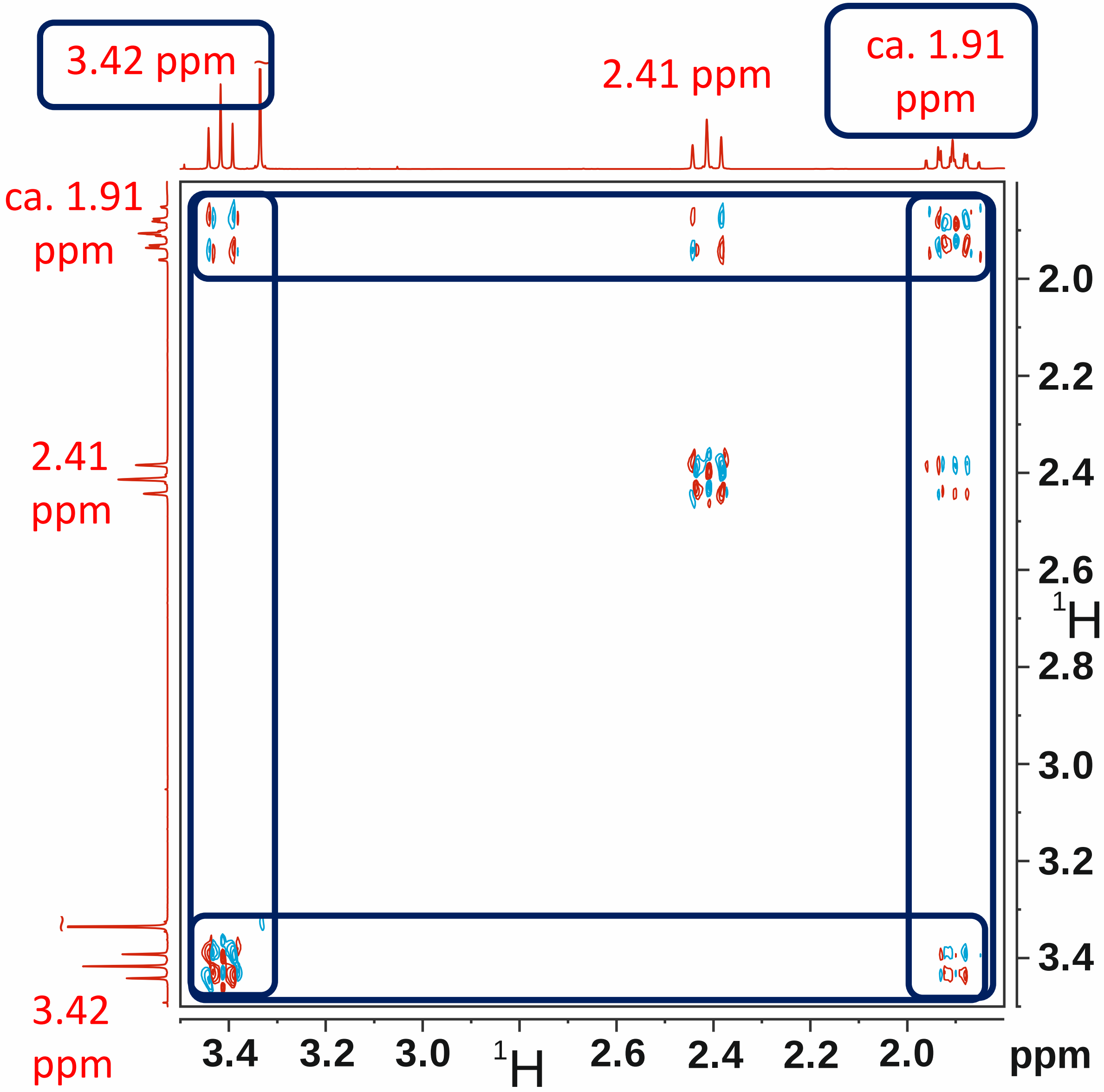
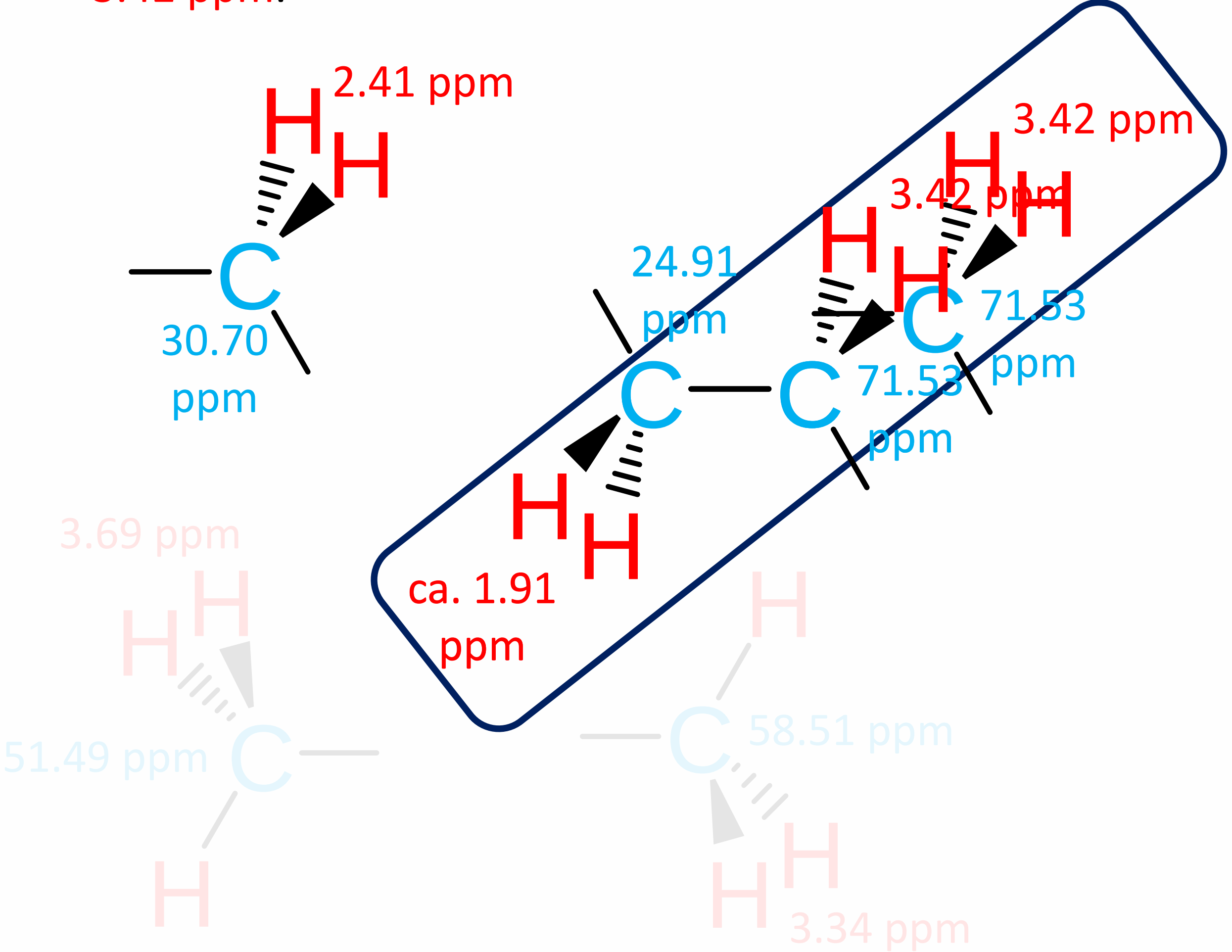
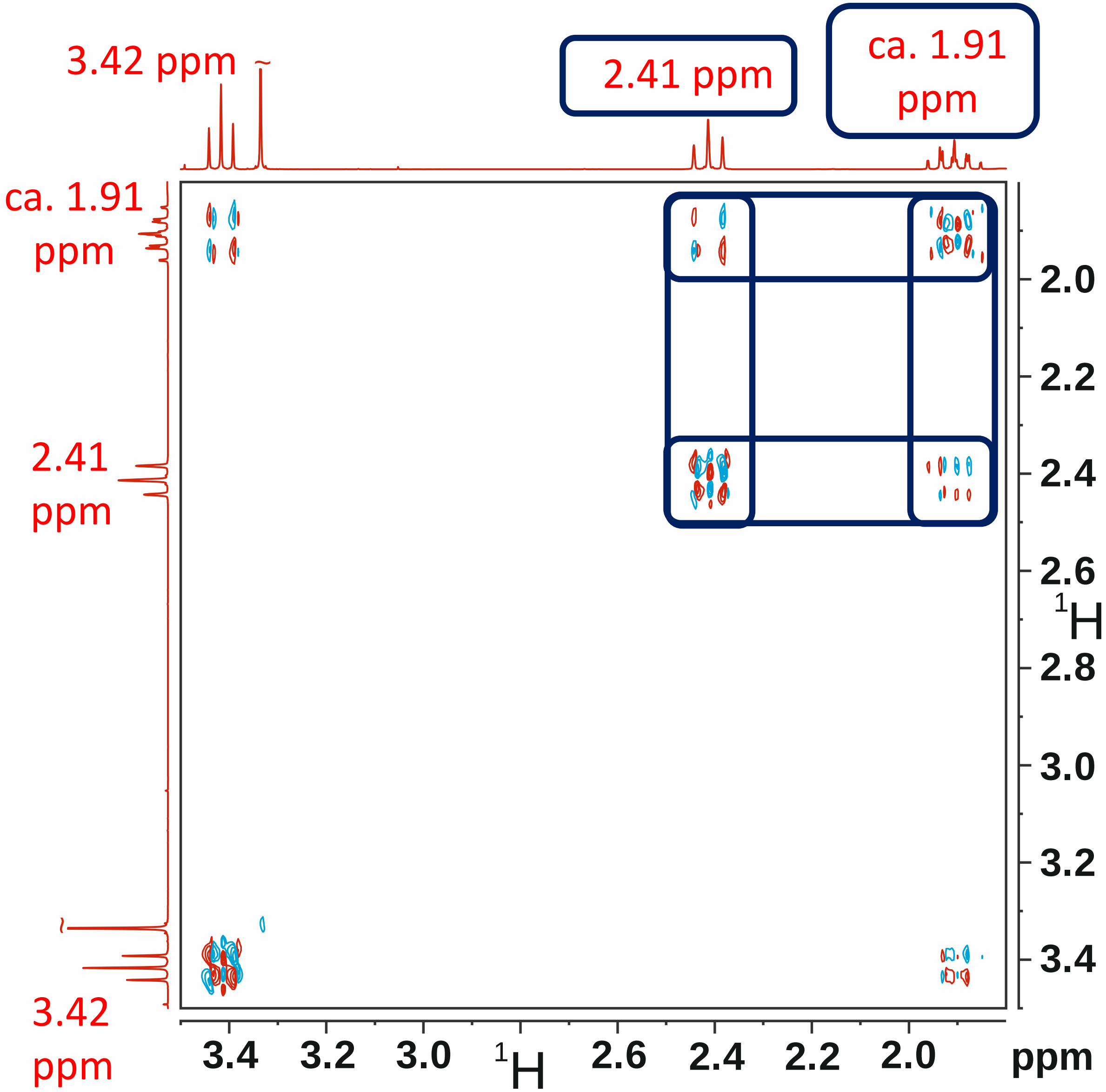


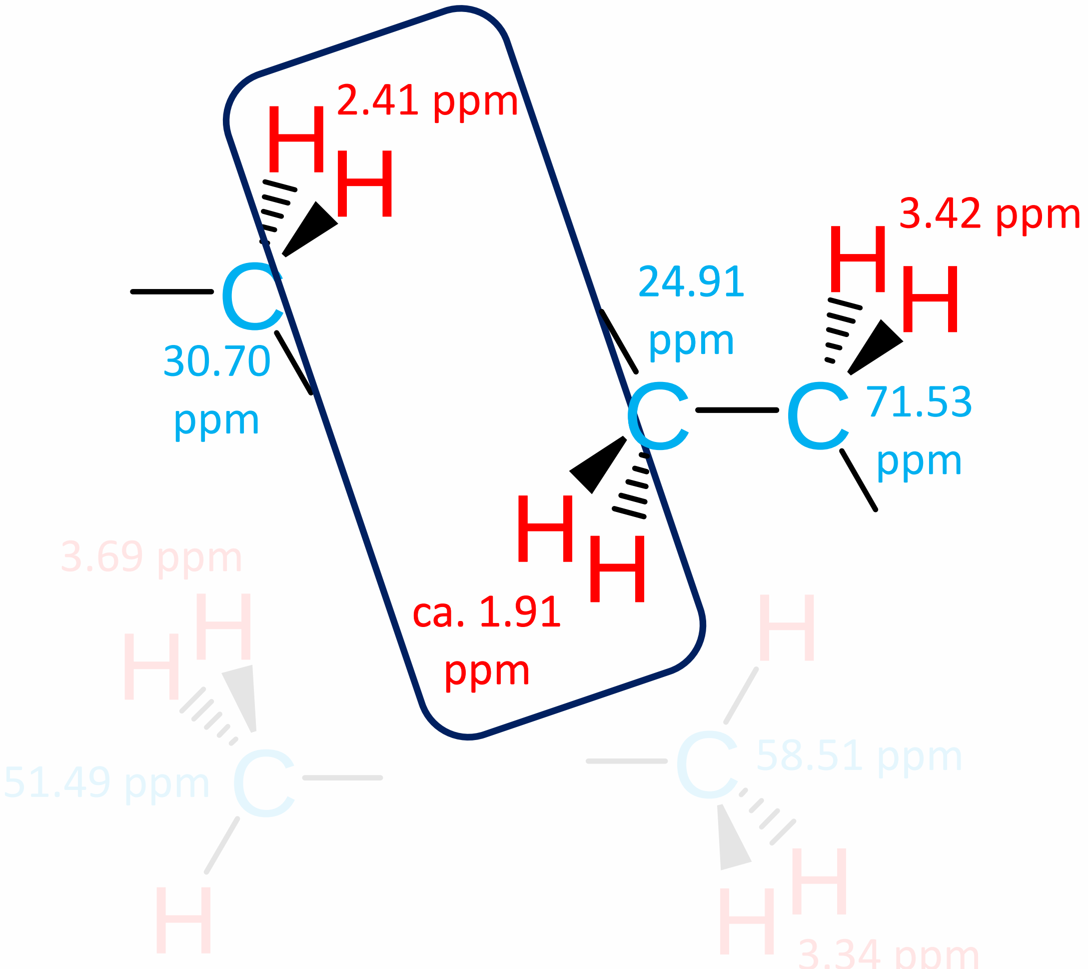


Linking the pieces

part 1 – alkyl chain

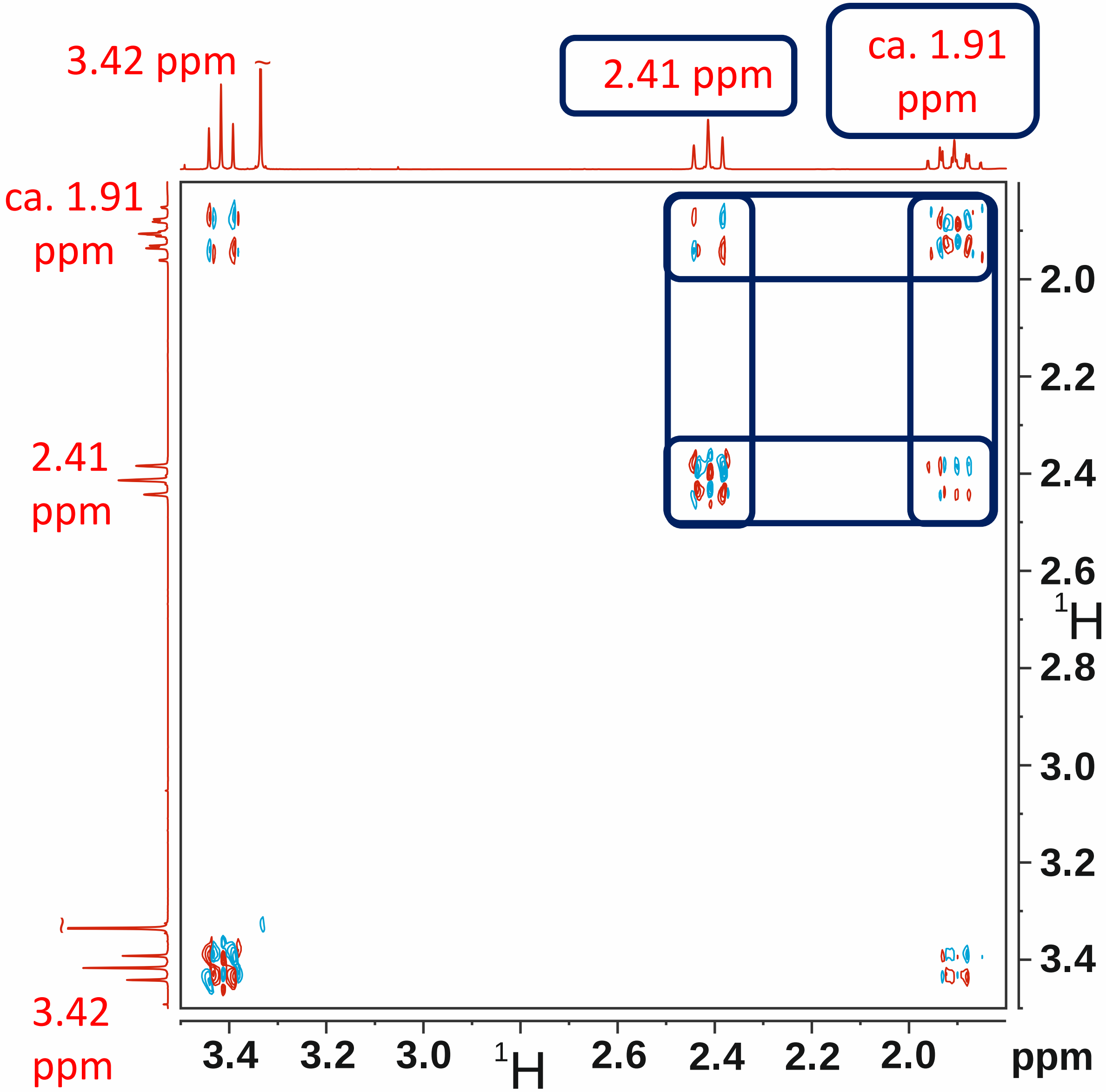
The second proximity, visible in the COSY, is between the protons with the chemical shifts of ca. 1.91 ppm and 2.41 ppm, which allows us to complete the alkyl fragment.





Linking the pieces

part 1 – alkyl chain



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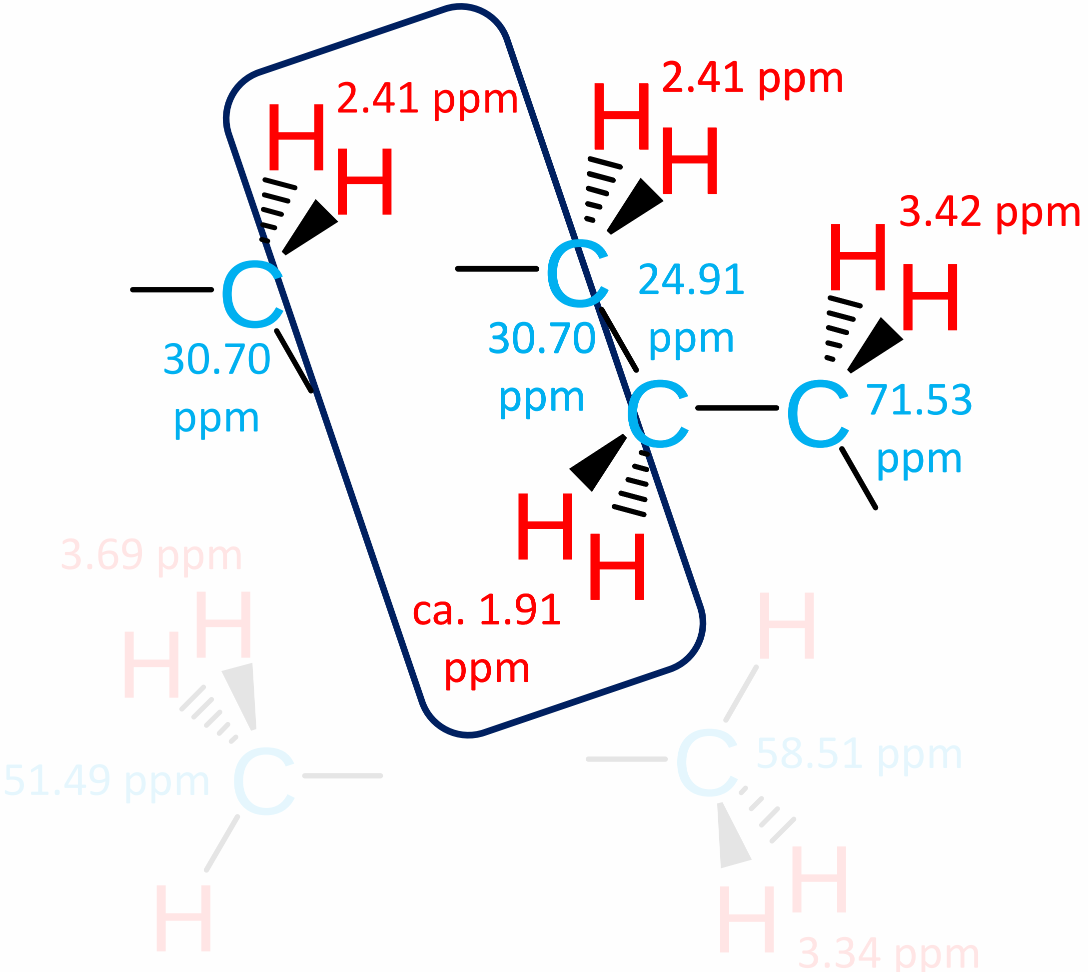
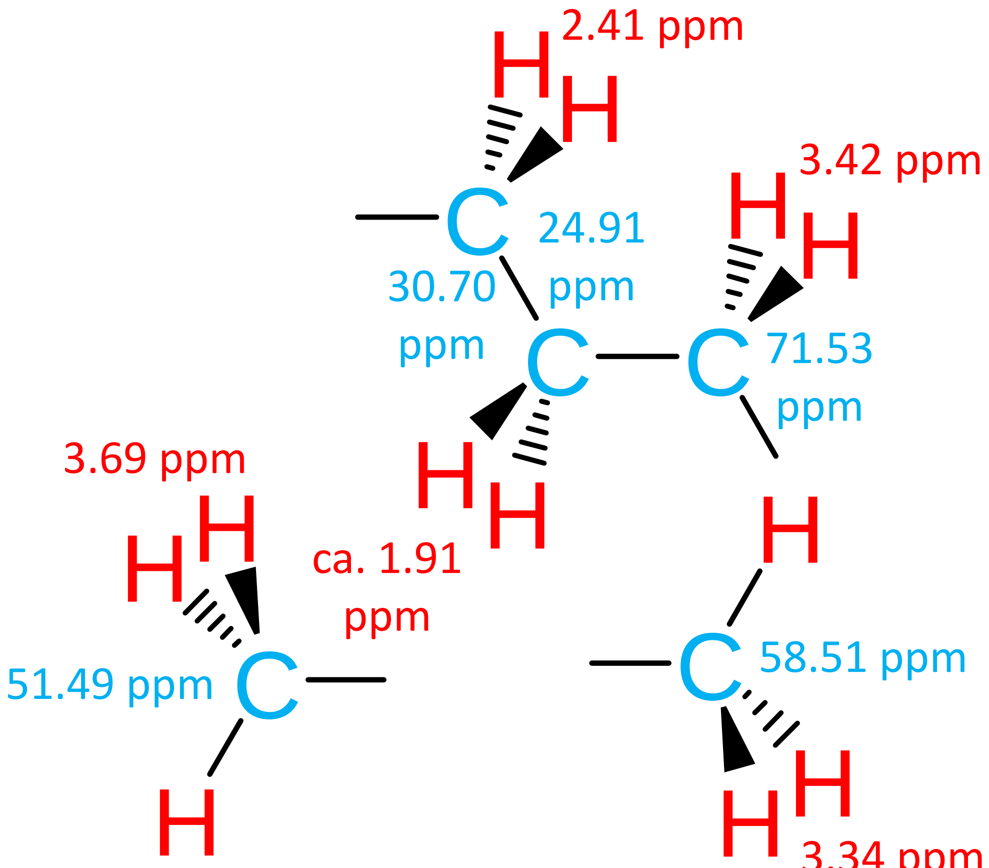


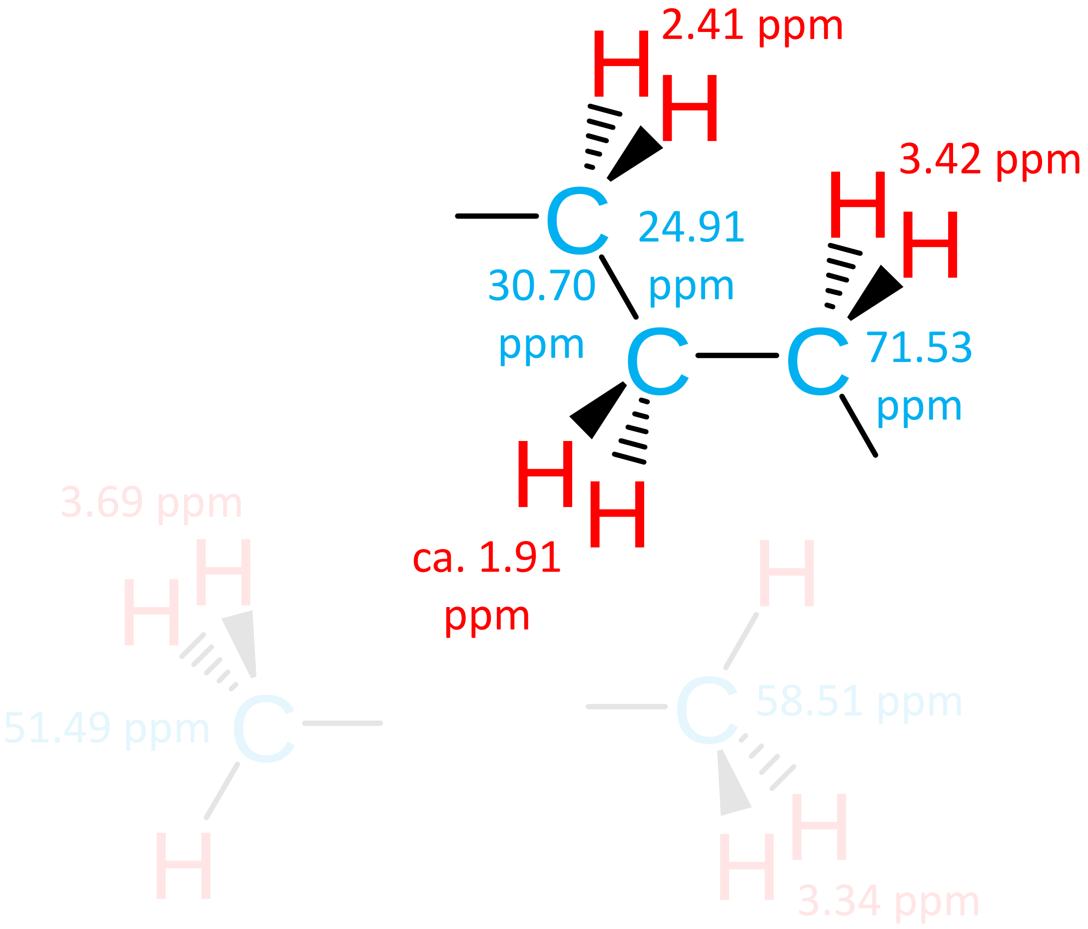
Something missing?

time for a short inventory

We no longer need the COSY.

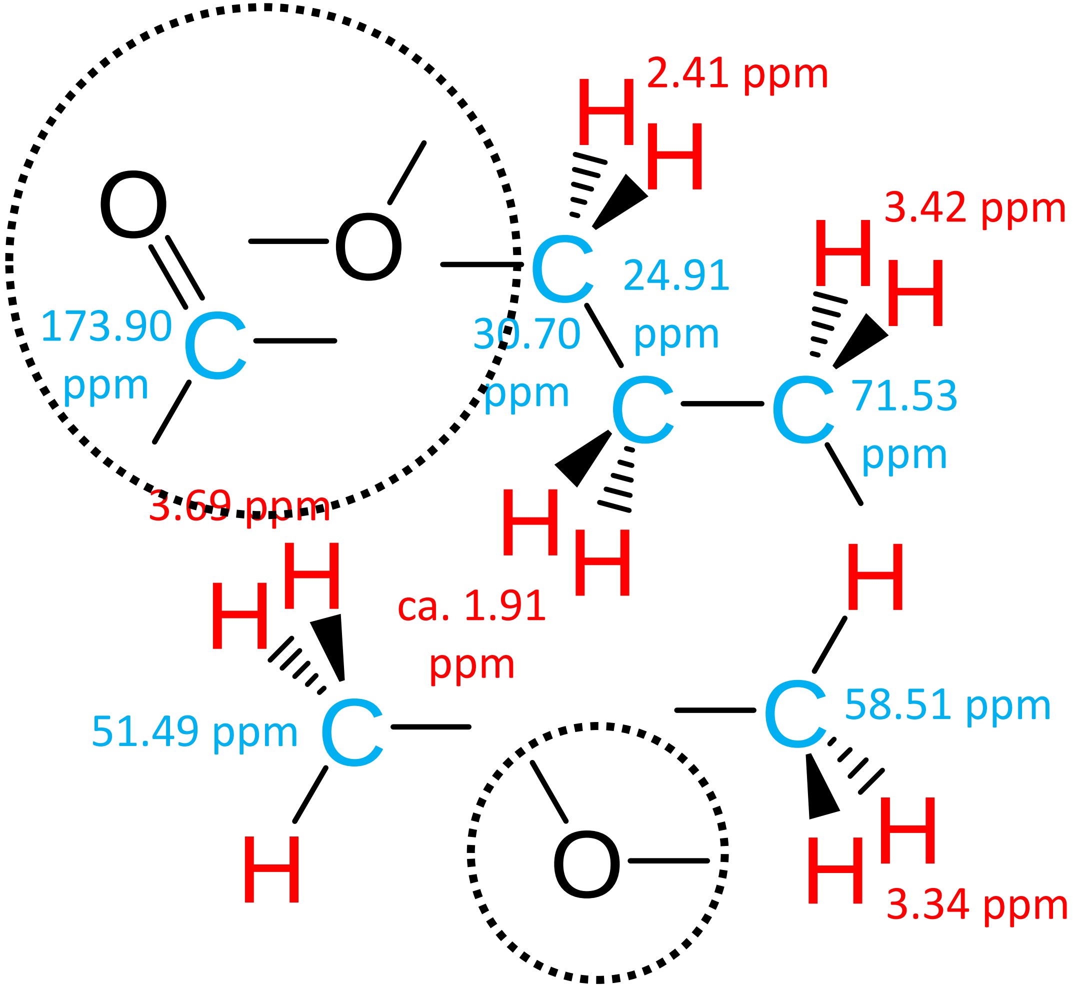
To continue let us recall the methyl groups and rearrange the fragments a little bit for further use.





Something missing?

time for a short inventory



molecular formula	$C_6H_{12}O_3$
known fragments	C_5H_{12}
unassigned carbon atom without attached hydrogen	173.9 ppm
missing	CO_3 one double bond equivalent

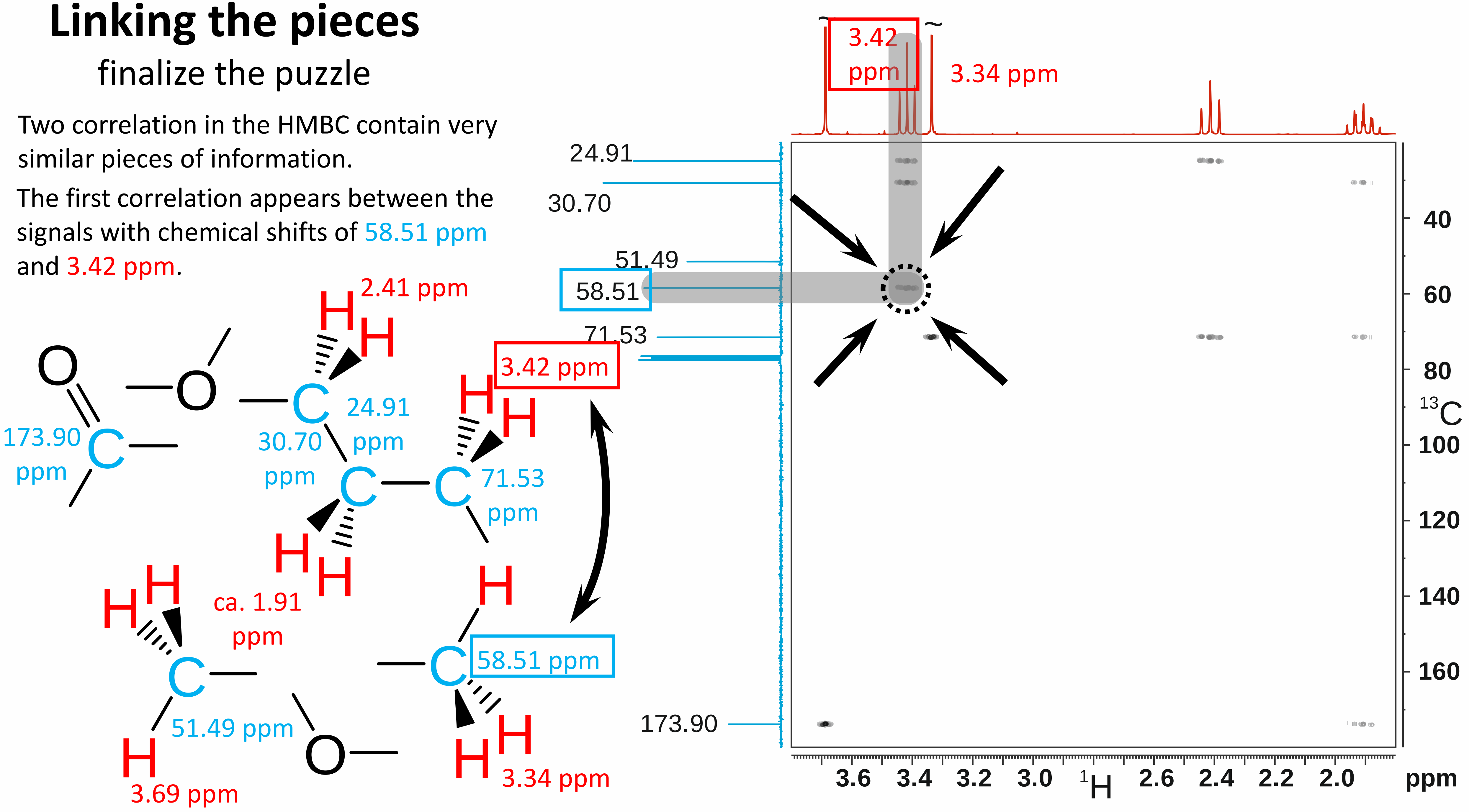
As a result let us increase our unordered pile of building blocks by three hydrogen free fragments.

Linking the pieces

finalize the puzzle

Two correlation in the HMBC contain very similar pieces of information.

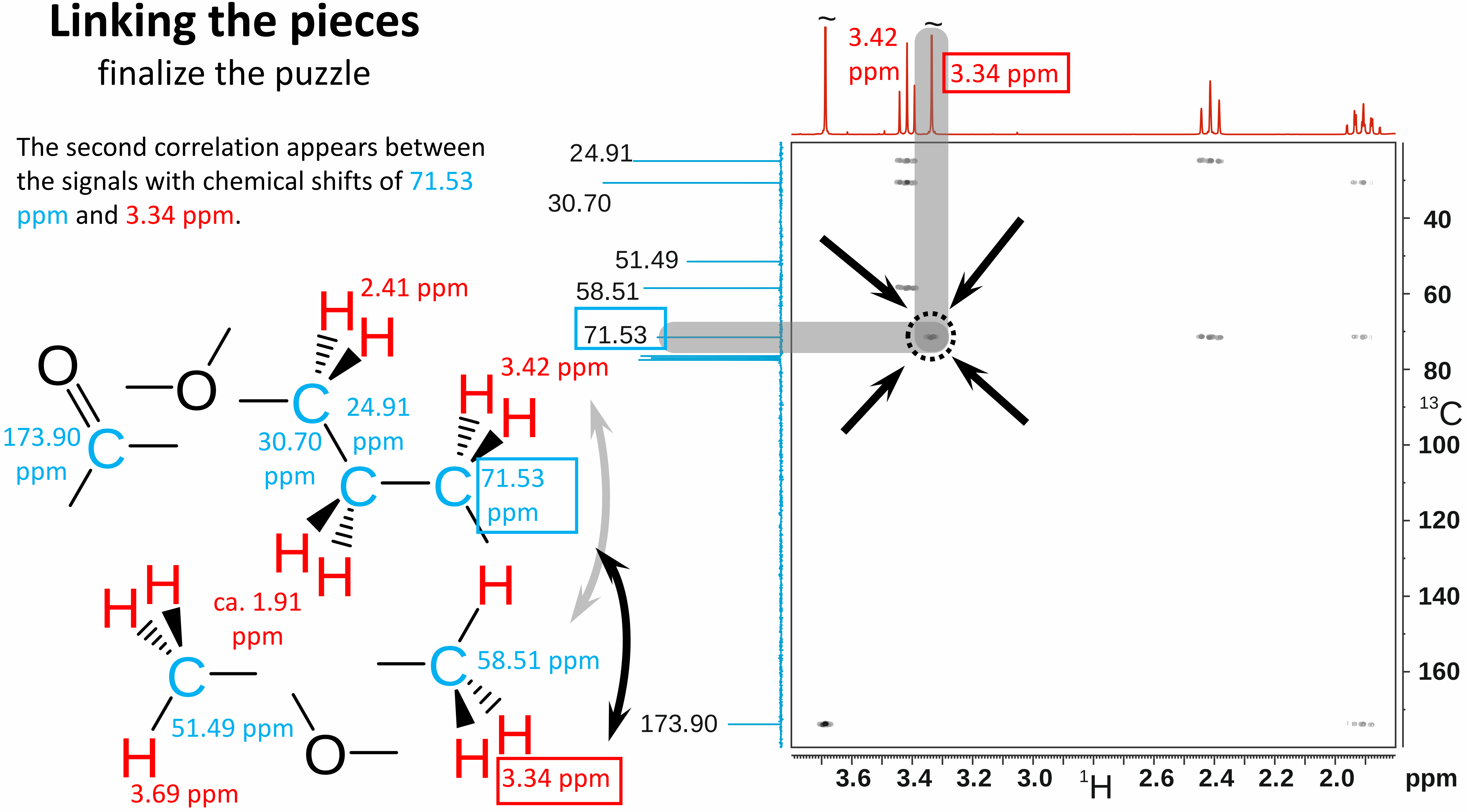
The first correlation appears between the signals with chemical shifts of 58.51 ppm and 3.42 ppm.



Linking the pieces

finalize the puzzle

The second correlation appears between the signals with chemical shifts of 71.53 ppm and 3.34 ppm.

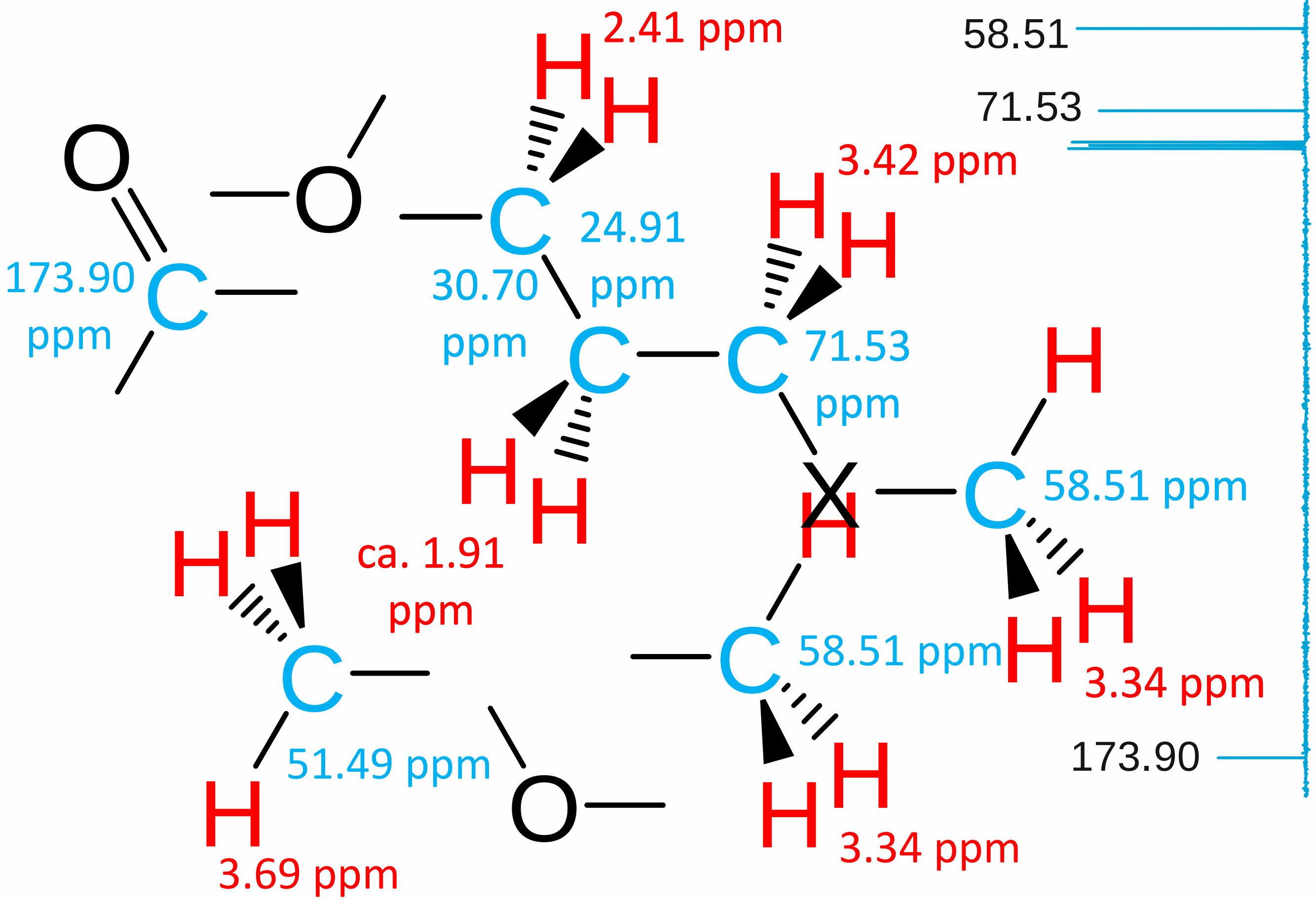


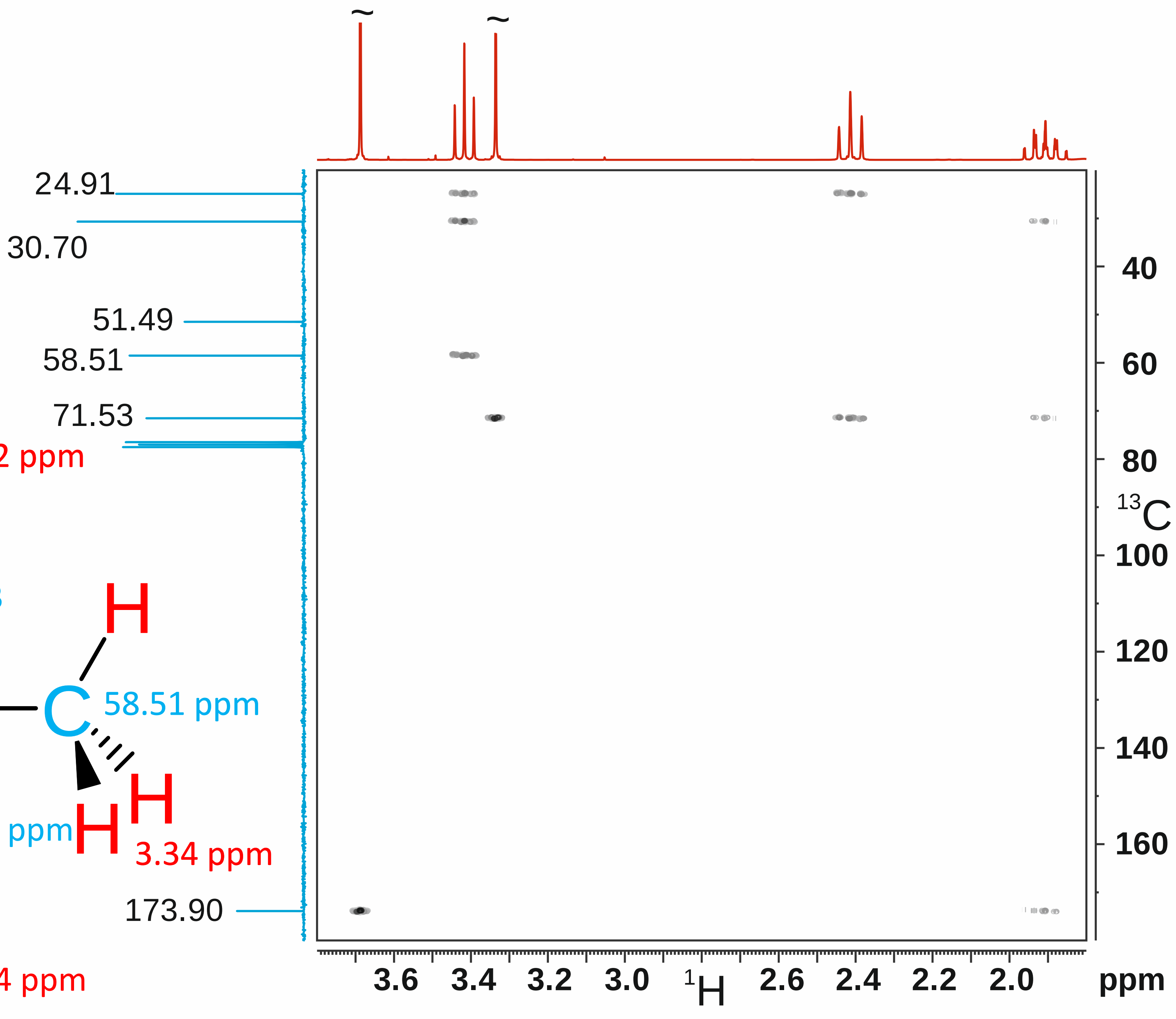
Linking the pieces

finalize the puzzle

There is one structural arrangement which explains both peaks.

X is either - O - or - CO -.



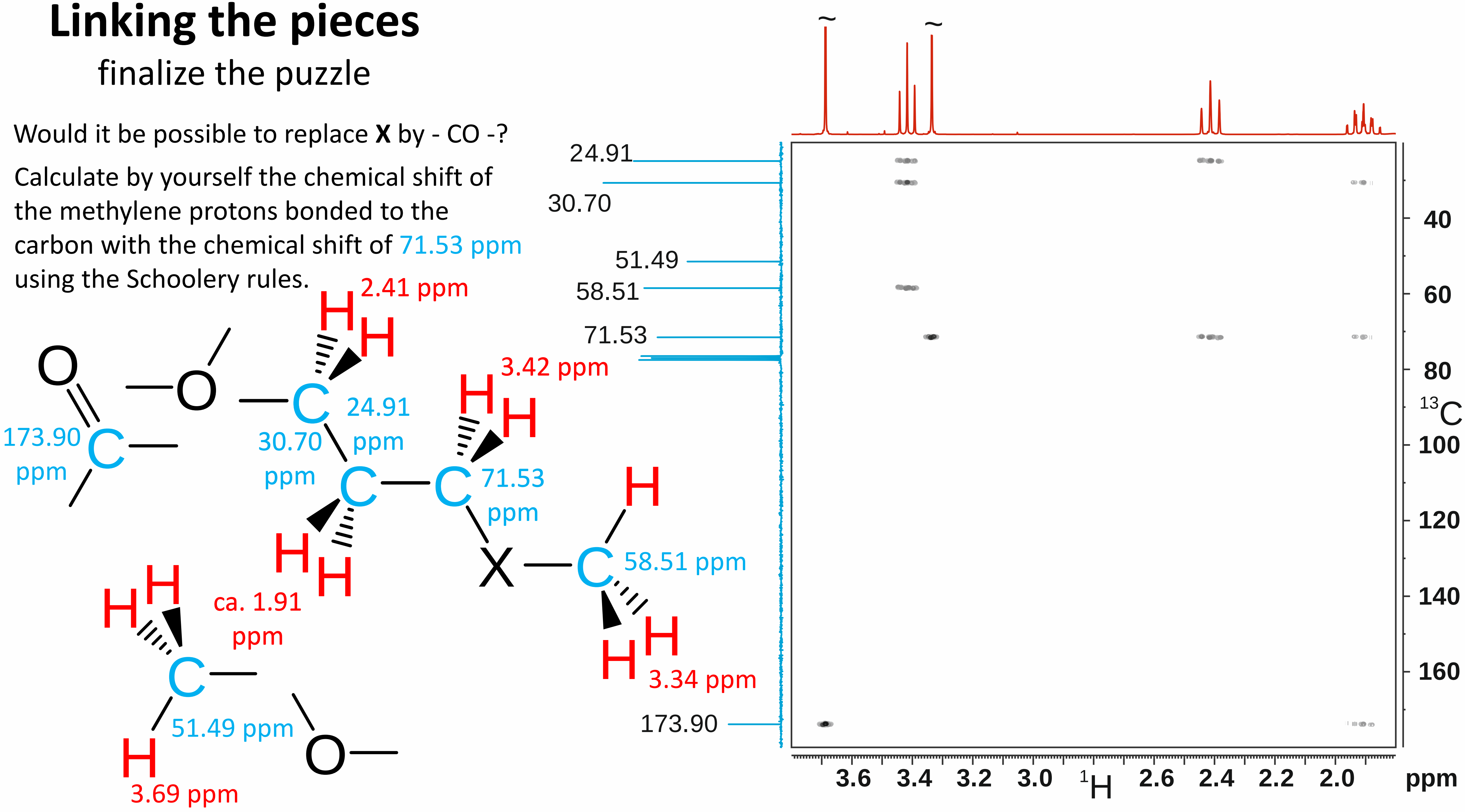


Linking the pieces

finalize the puzzle

Would it be possible to replace **X** by - CO -?

Calculate by yourself the chemical shift of the methylene protons bonded to the carbon with the chemical shift of 71.53 ppm using the Schoolery rules.

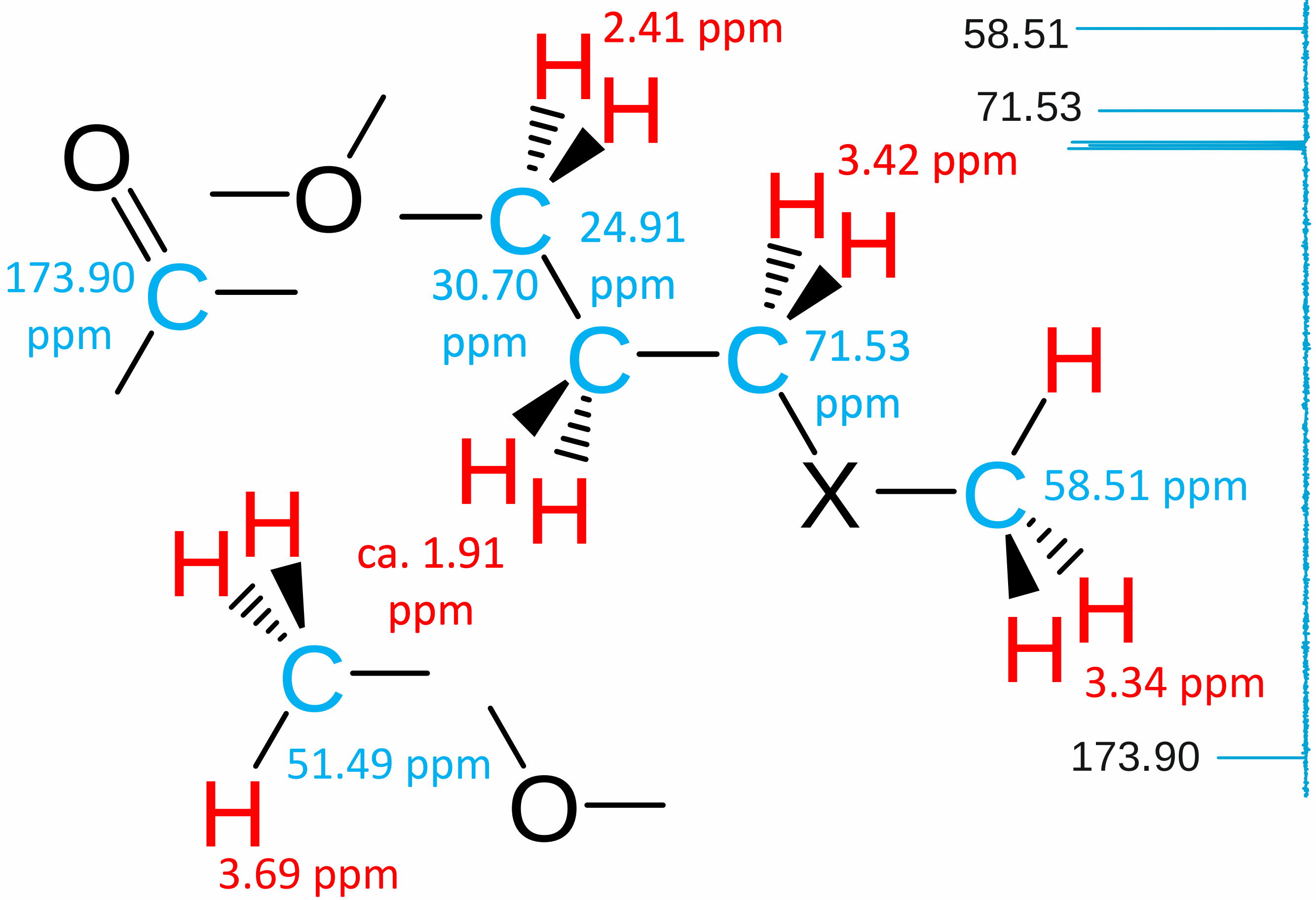


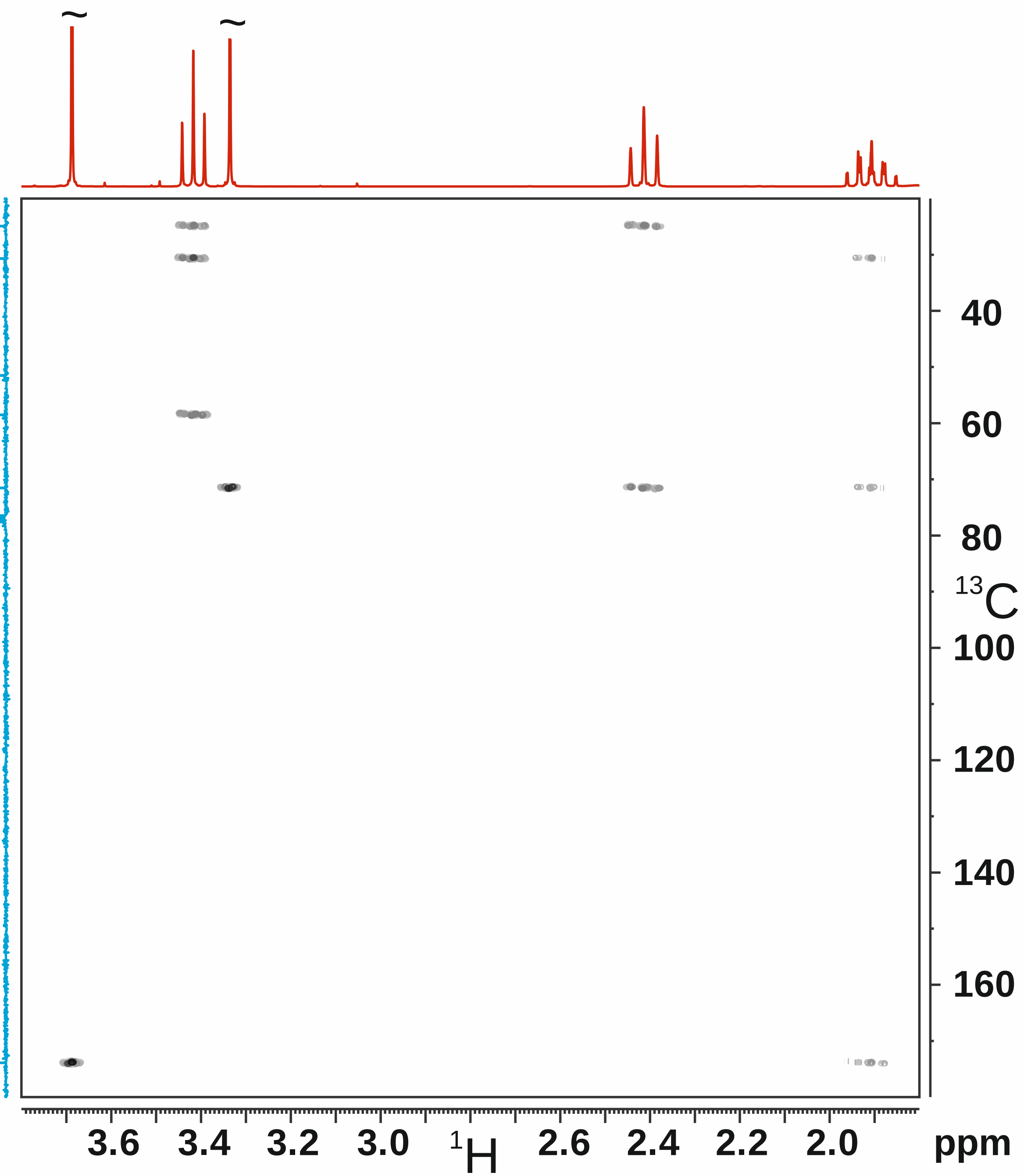
Linking the pieces

finalize the puzzle

You get

X = - O - 3.06 ppm
X = - CO - 2.40 ppm



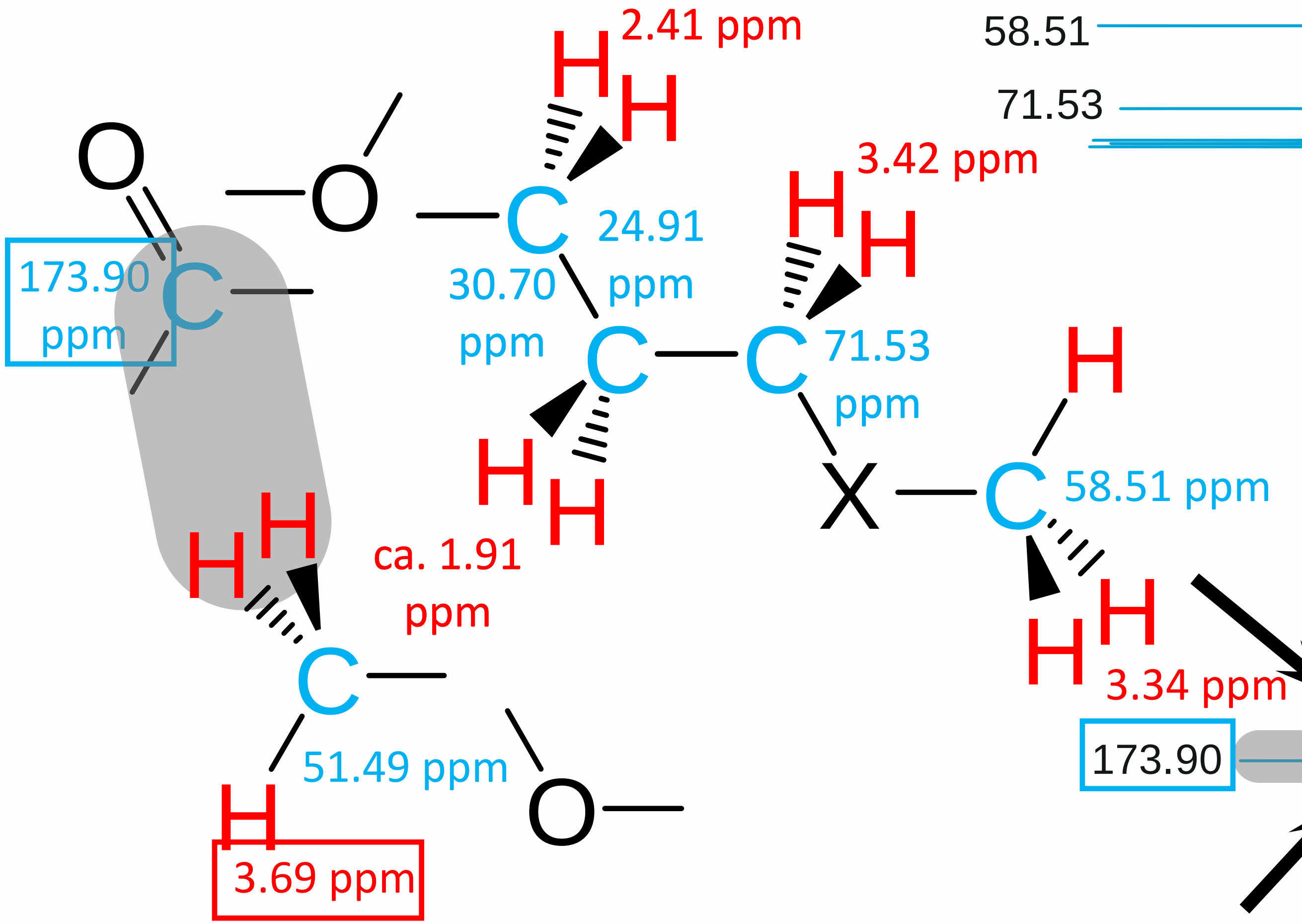


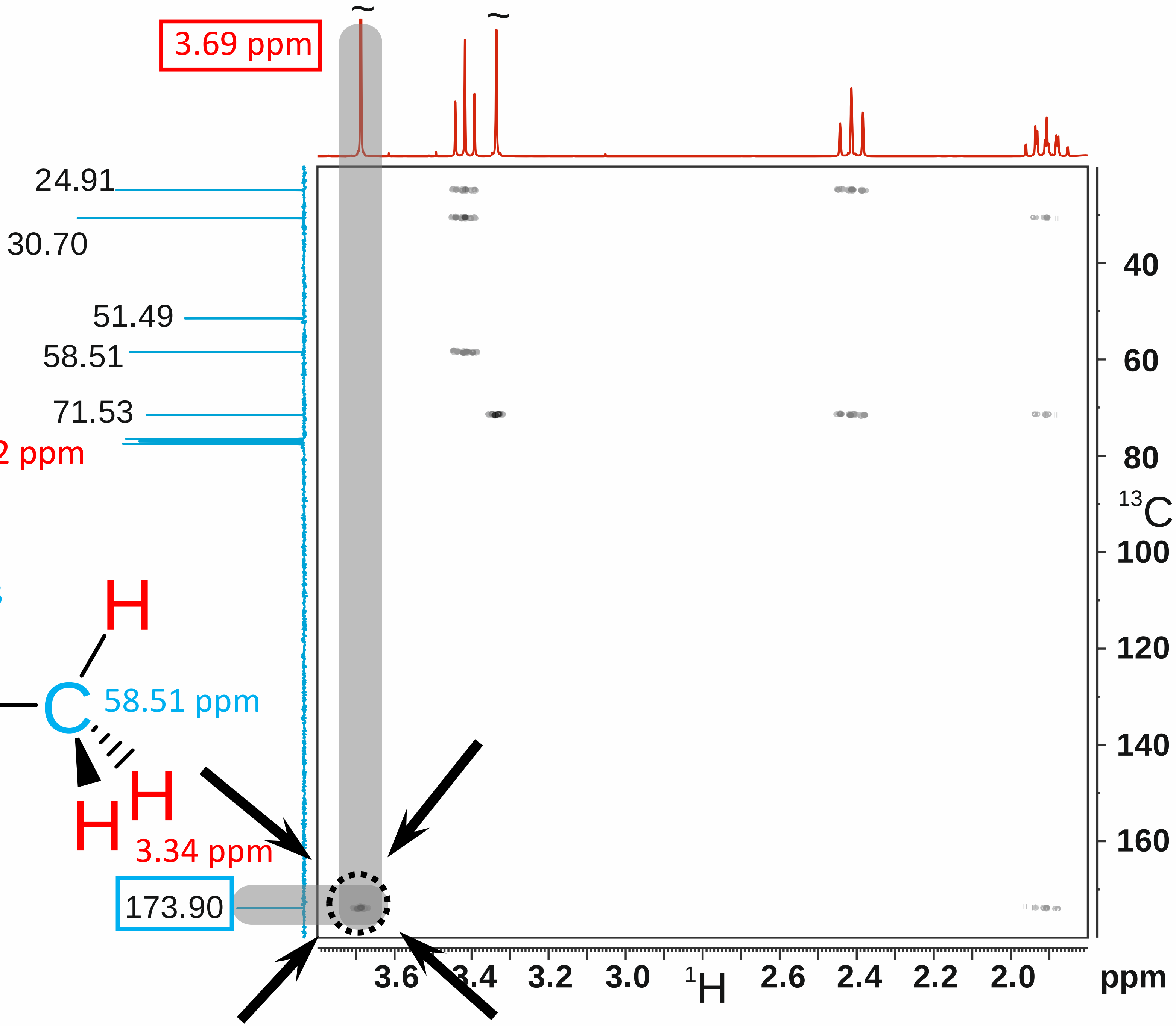
Linking the pieces

finalize the puzzle

There is one more possibility to exclude **X** = - CO -.

Have a look for this cross peak.

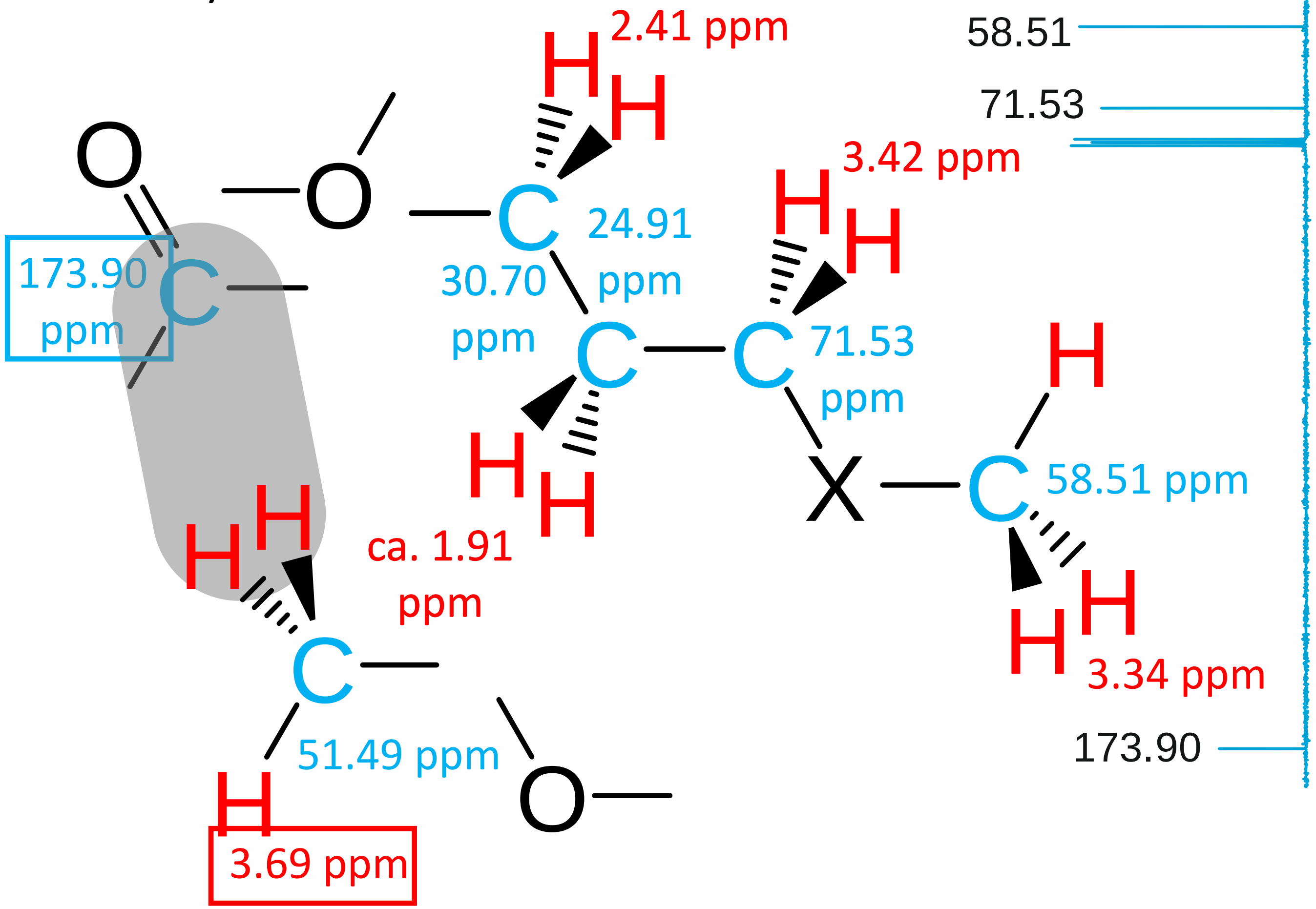


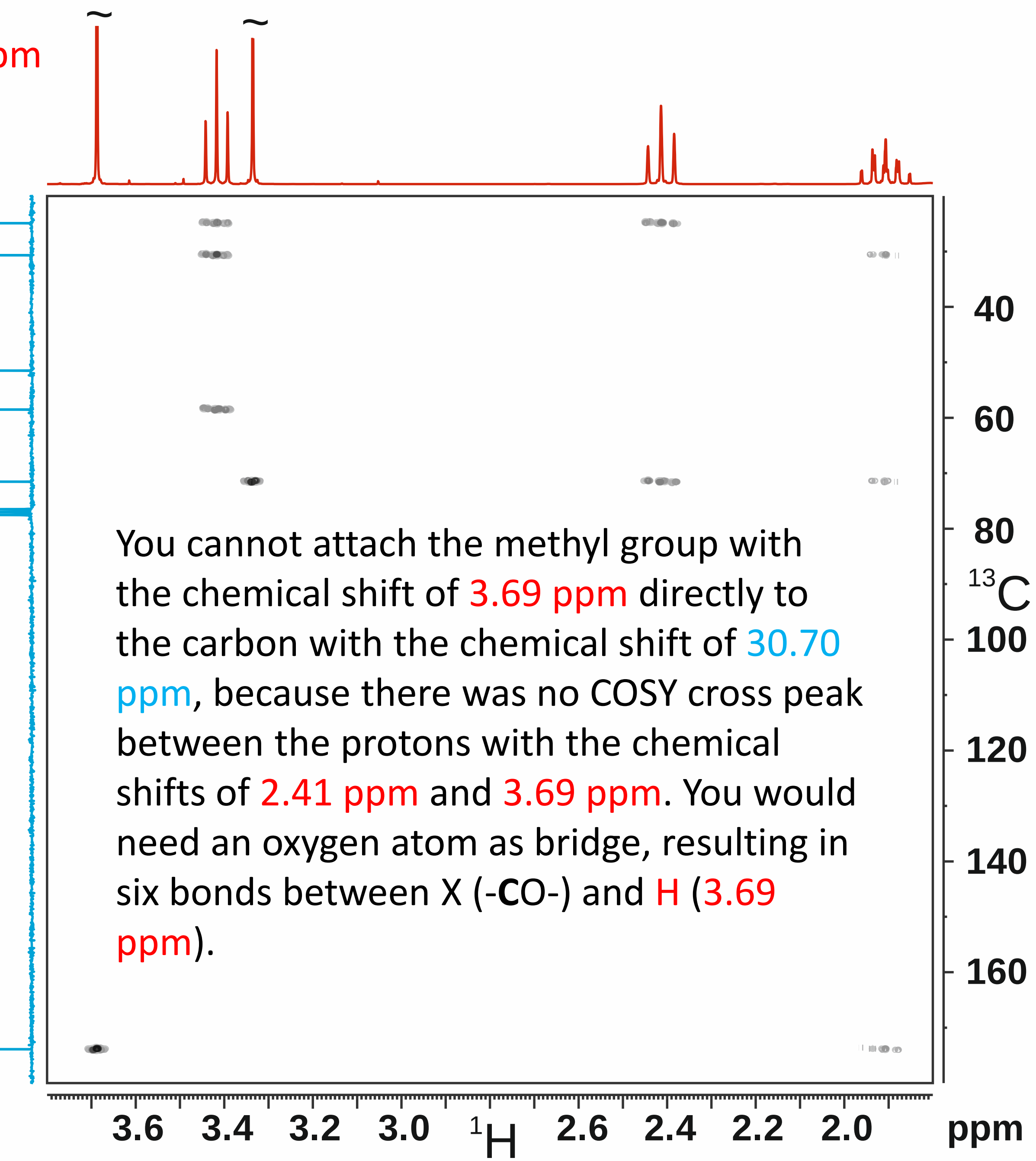


Linking the pieces

finalize the puzzle

If you insert **- CO -** instead of **X** and keep everything else in place the length of the coupling path to the protons with the chemical shift of 3.69 ppm is at least 6 bonds. Try it!



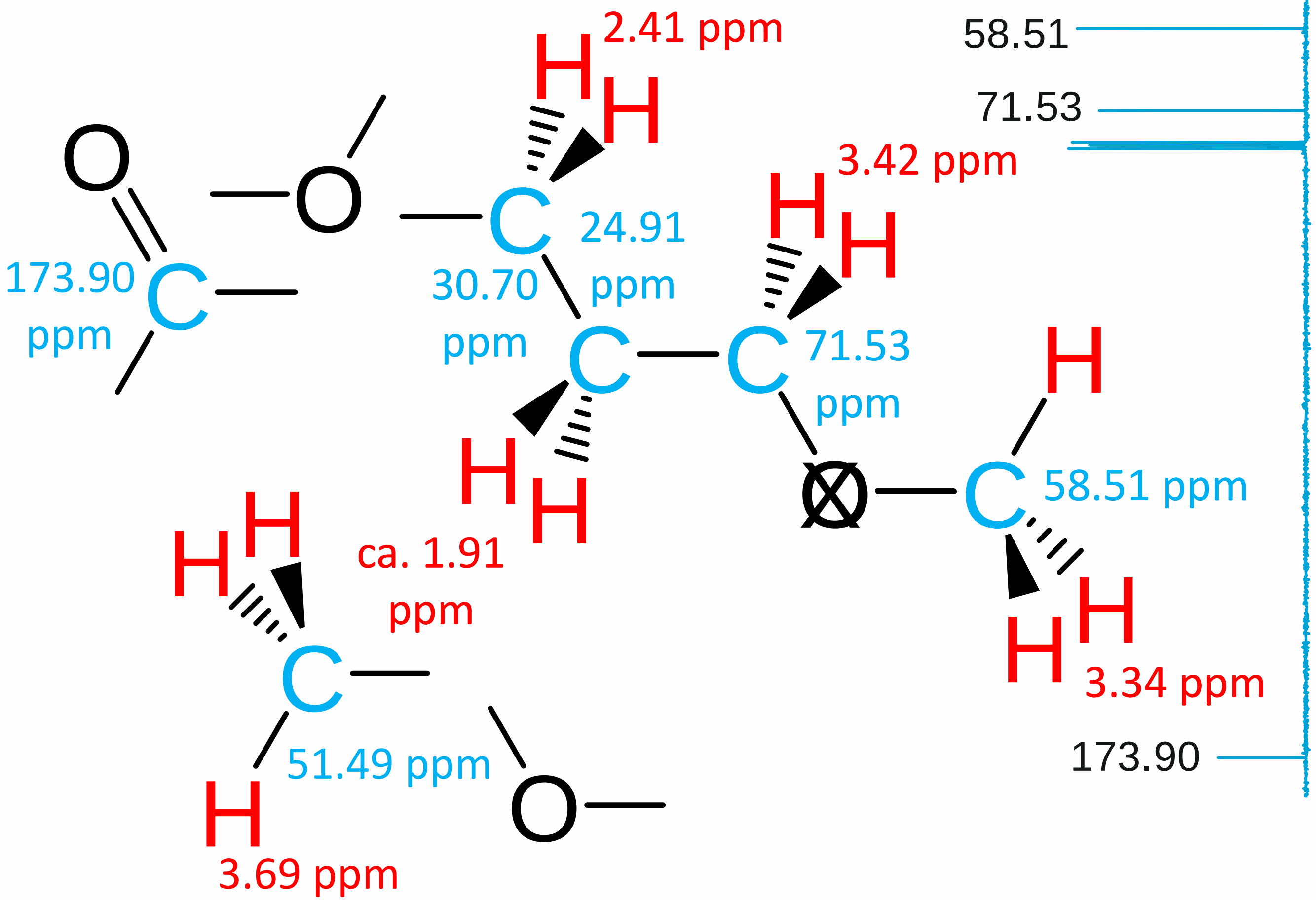


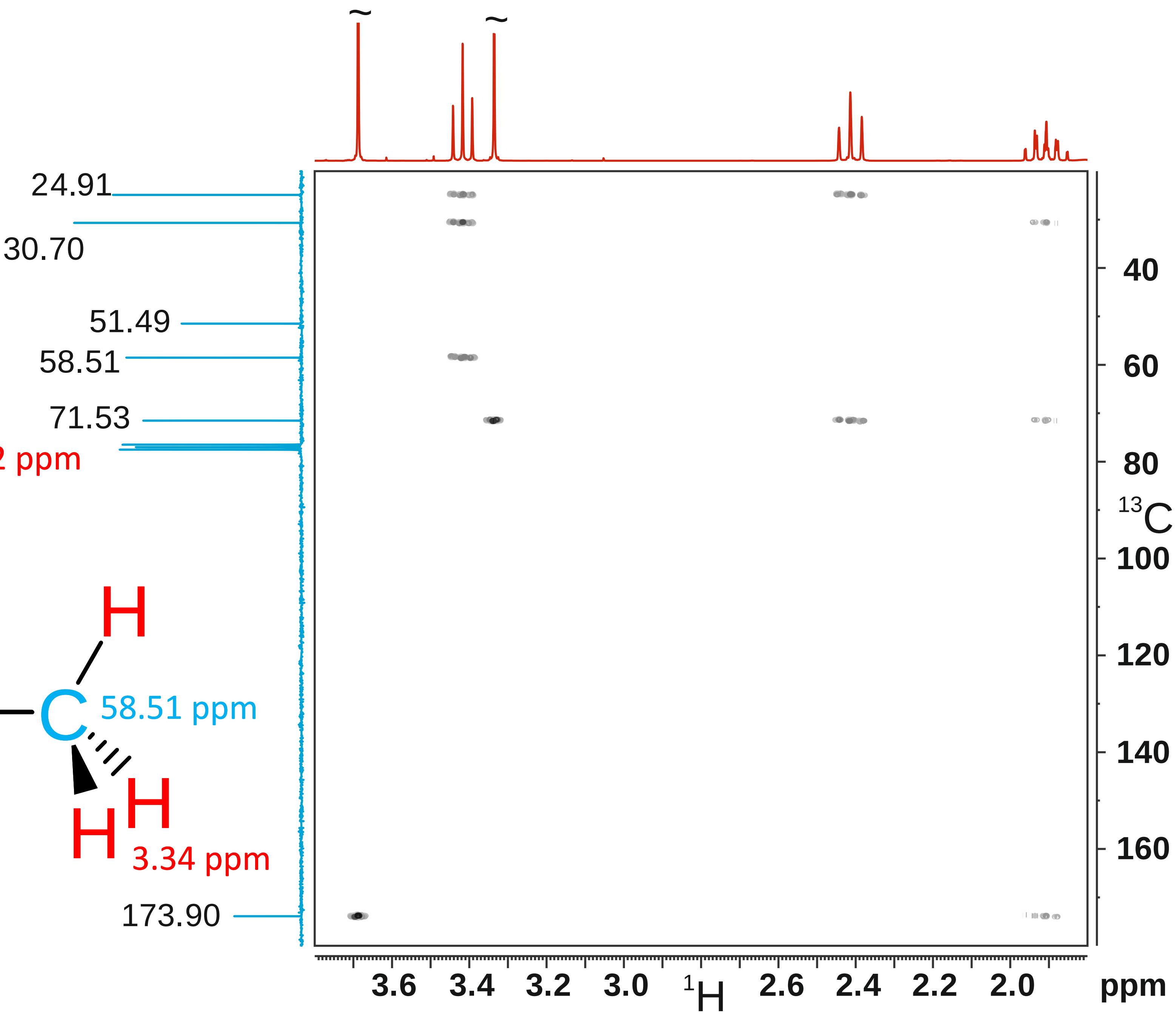
You cannot attach the methyl group with the chemical shift of 3.69 ppm directly to the carbon with the chemical shift of 30.70 ppm, because there was no COSY cross peak between the protons with the chemical shifts of 2.41 ppm and 3.69 ppm. You would need an oxygen atom as bridge, resulting in six bonds between X (-**C**O-) and H (3.69 ppm).

Linking the pieces

finalize the puzzle

After changing **X** to **O** there are only two possibilities to finalize the structure.

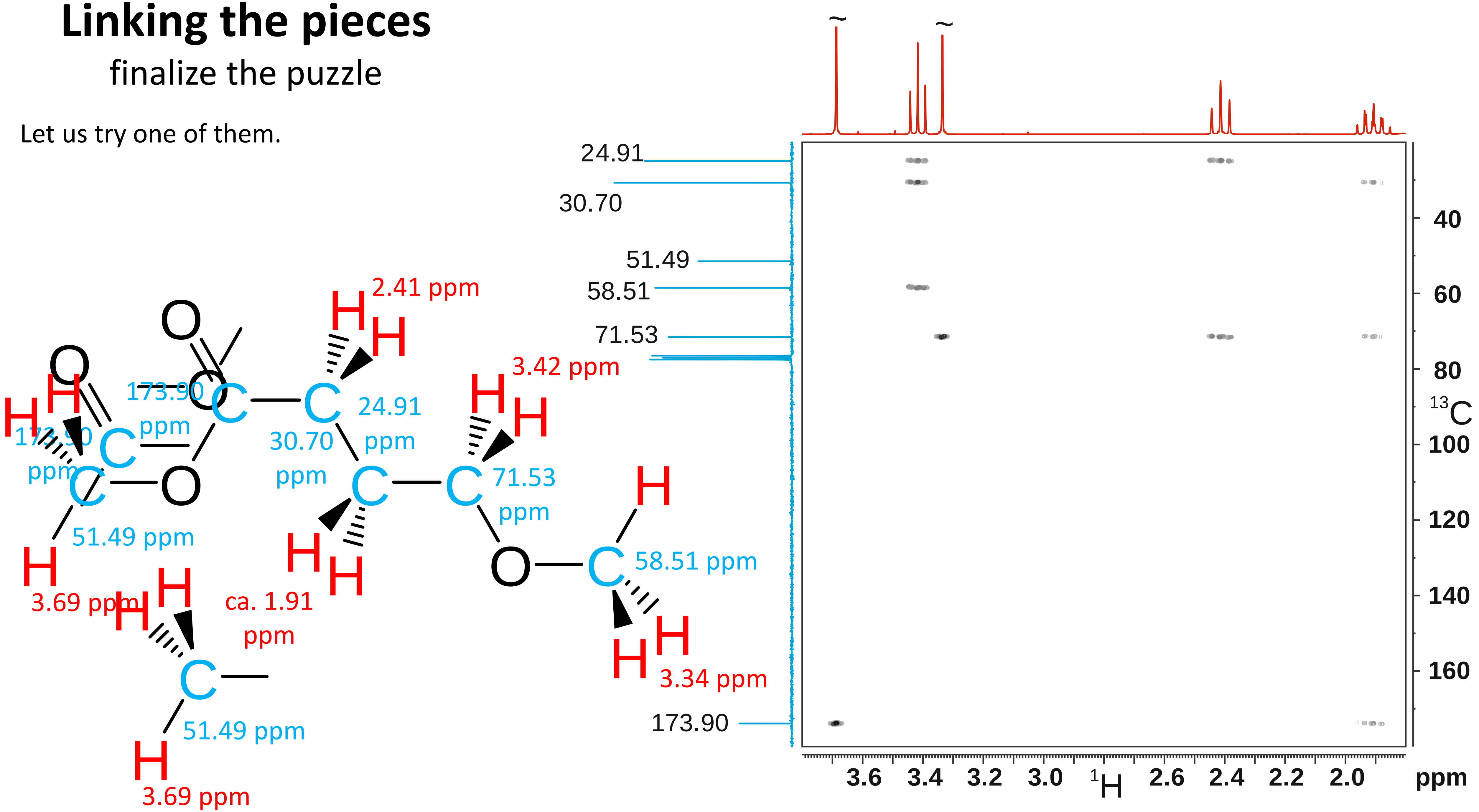




Linking the pieces

finalize the puzzle

Let us try one of them.

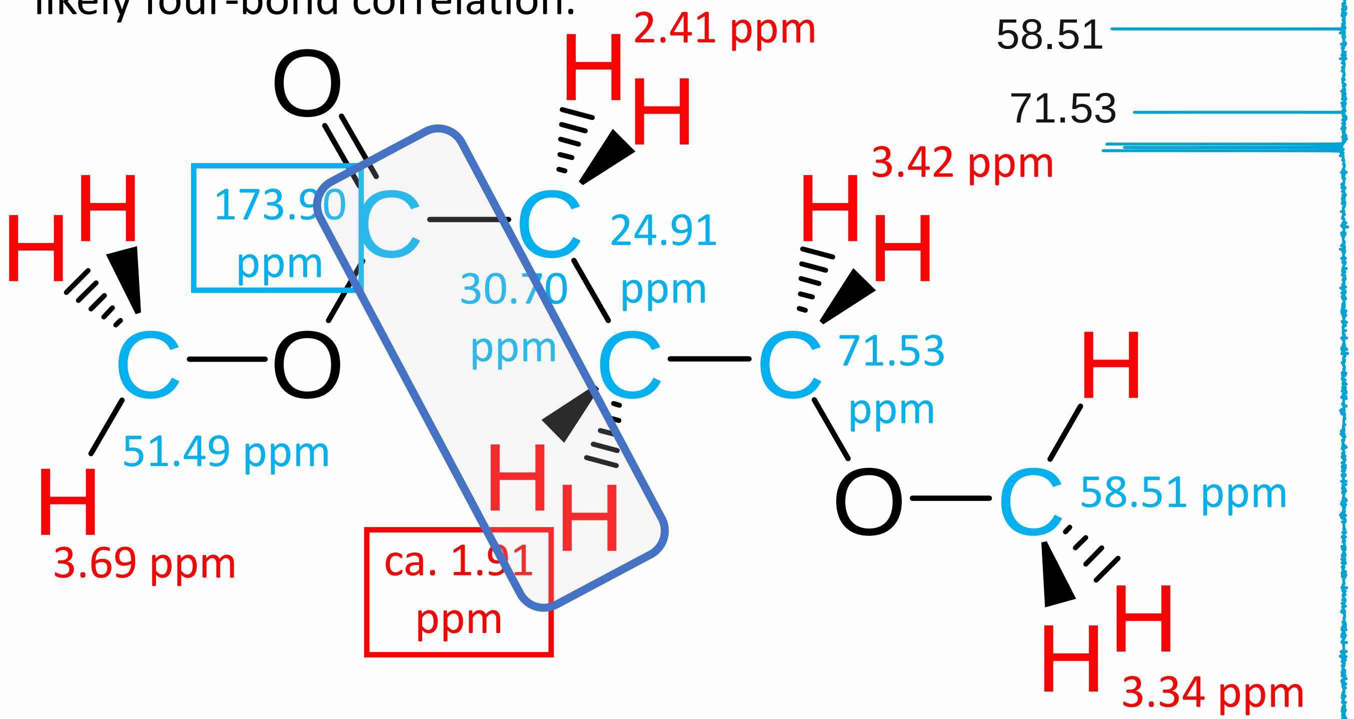


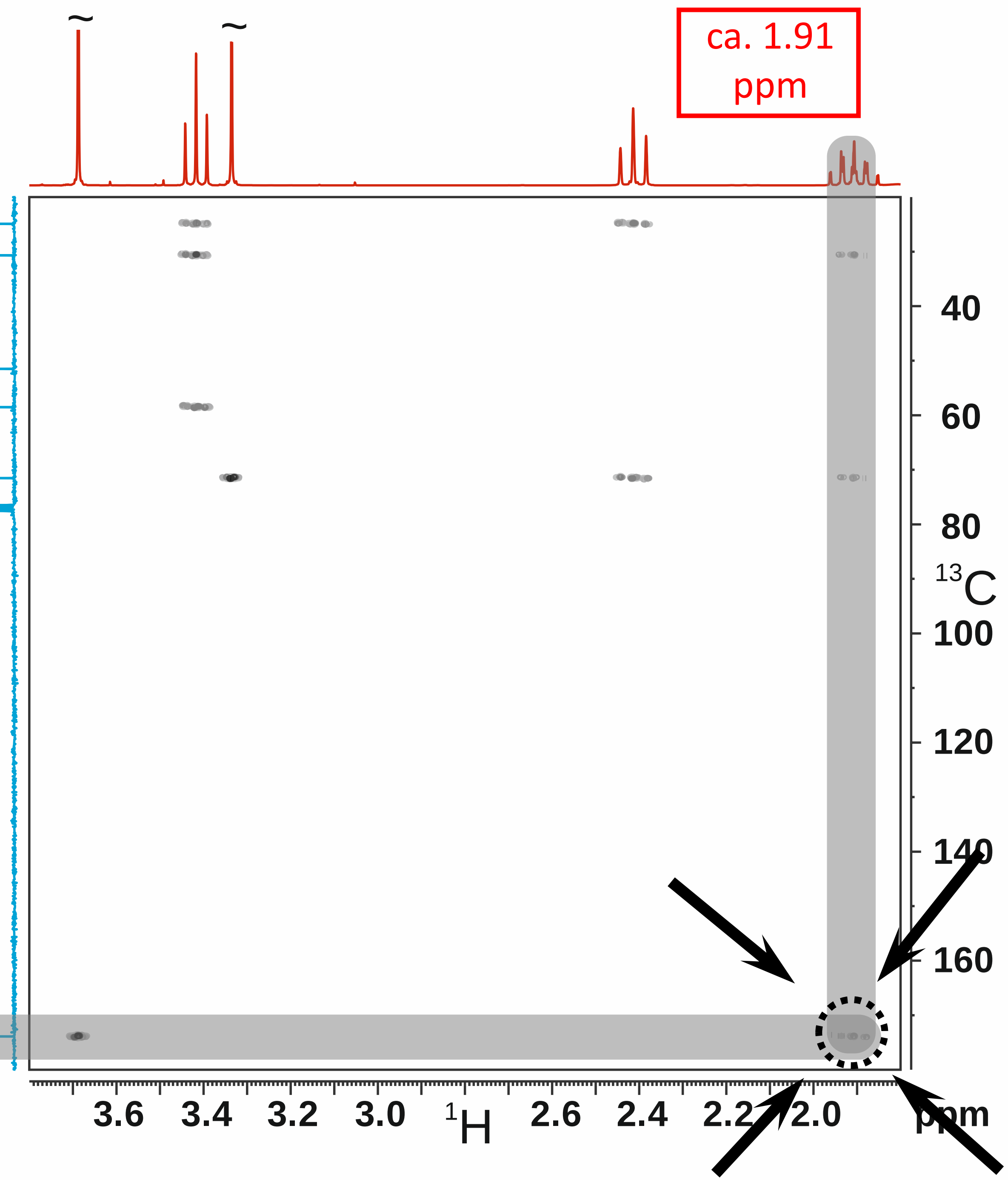
Linking the pieces

finalize the puzzle

Let us first inspect one HMBC cross peak.

This is a classical three bond correlation. In the case of the alternative arrangement of the -CO-O- group, this would be a much less likely four-bond correlation.

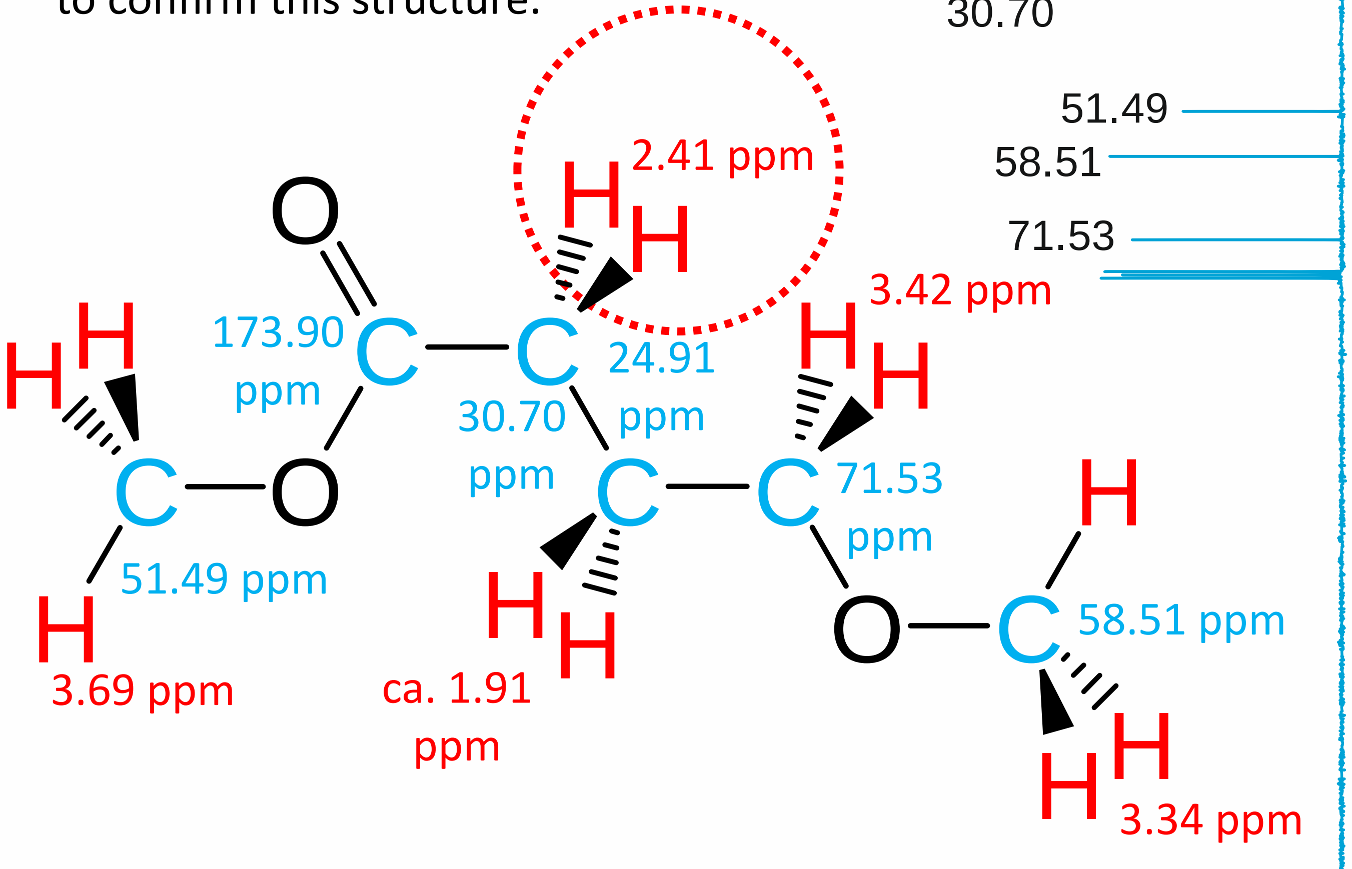


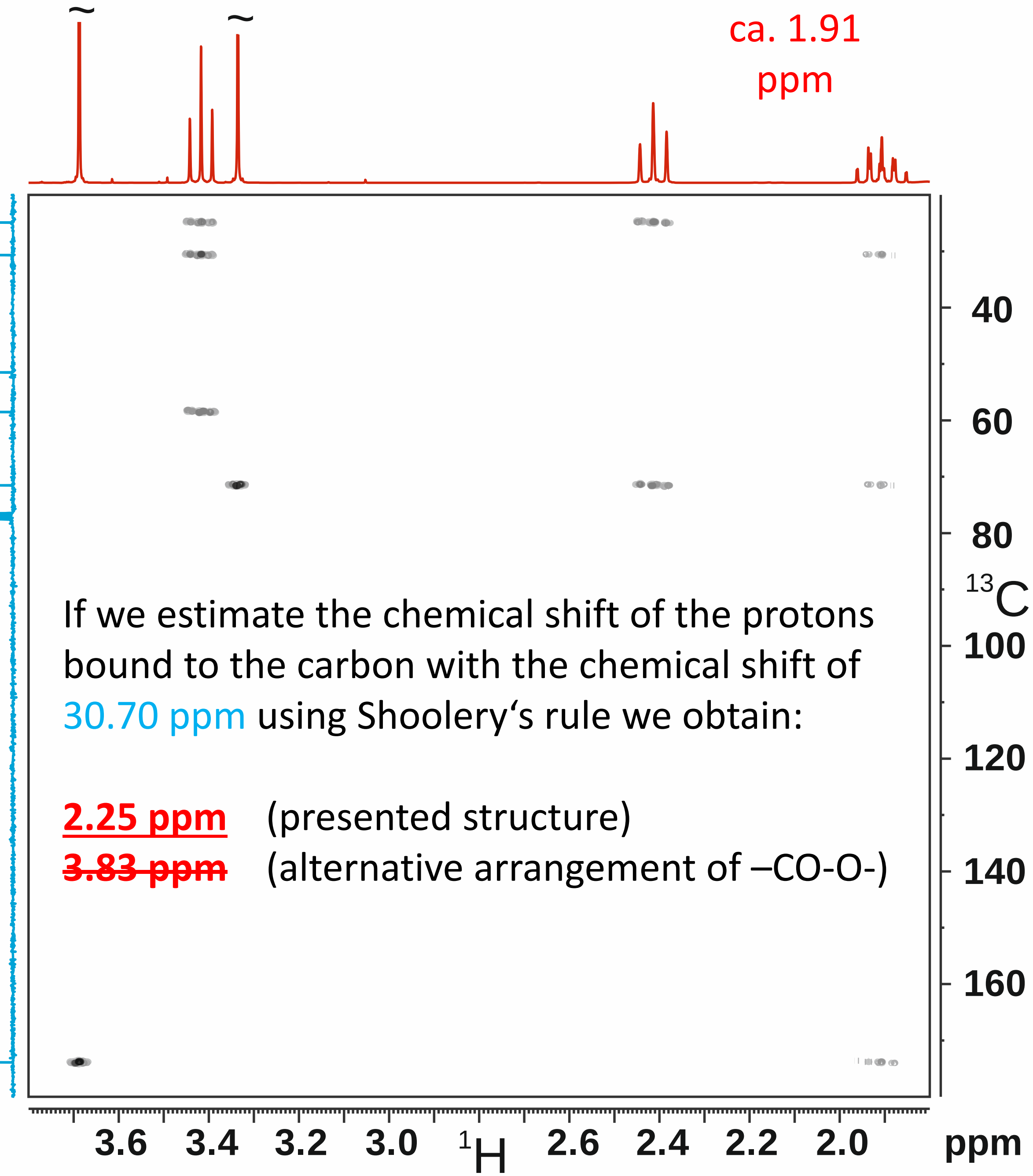


Linking the pieces

finalize the puzzle

Good old Shoolery's rule is another way to confirm this structure.





If we estimate the chemical shift of the protons bound to the carbon with the chemical shift of 30.70 ppm using Shoolery's rule we obtain:

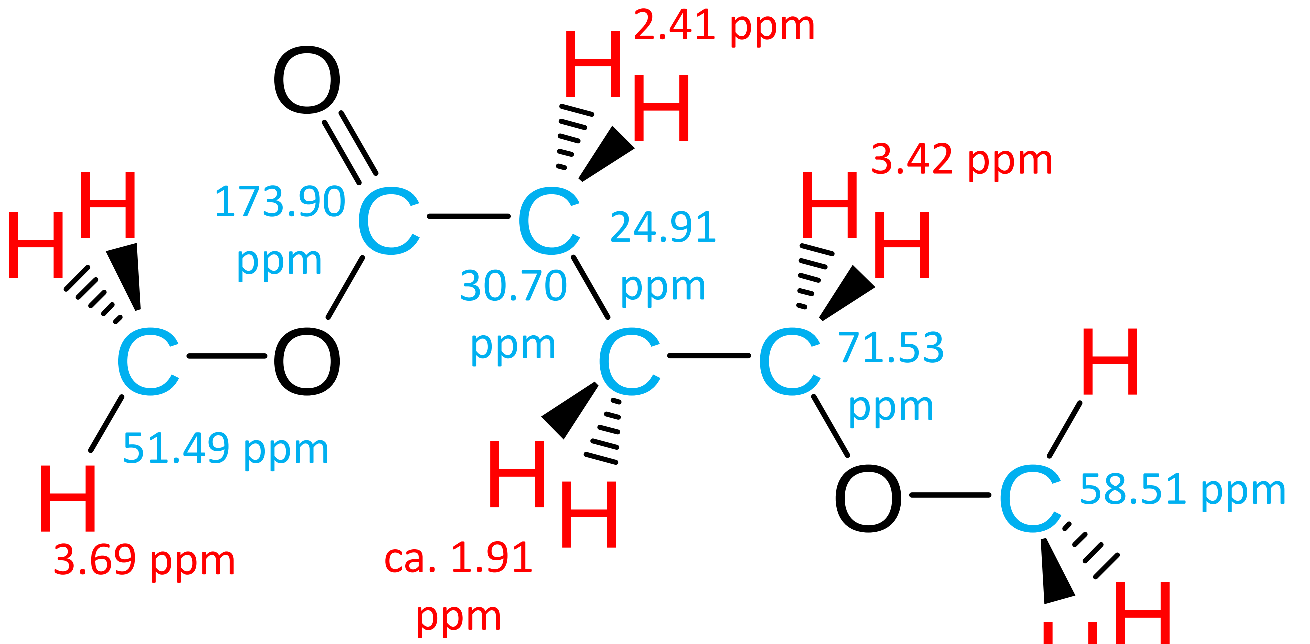
2.25 ppm (presented structure)

~~**3.83 ppm**~~ (alternative arrangement of –CO-O-)

Coupling constants

It looks simple, but it is not

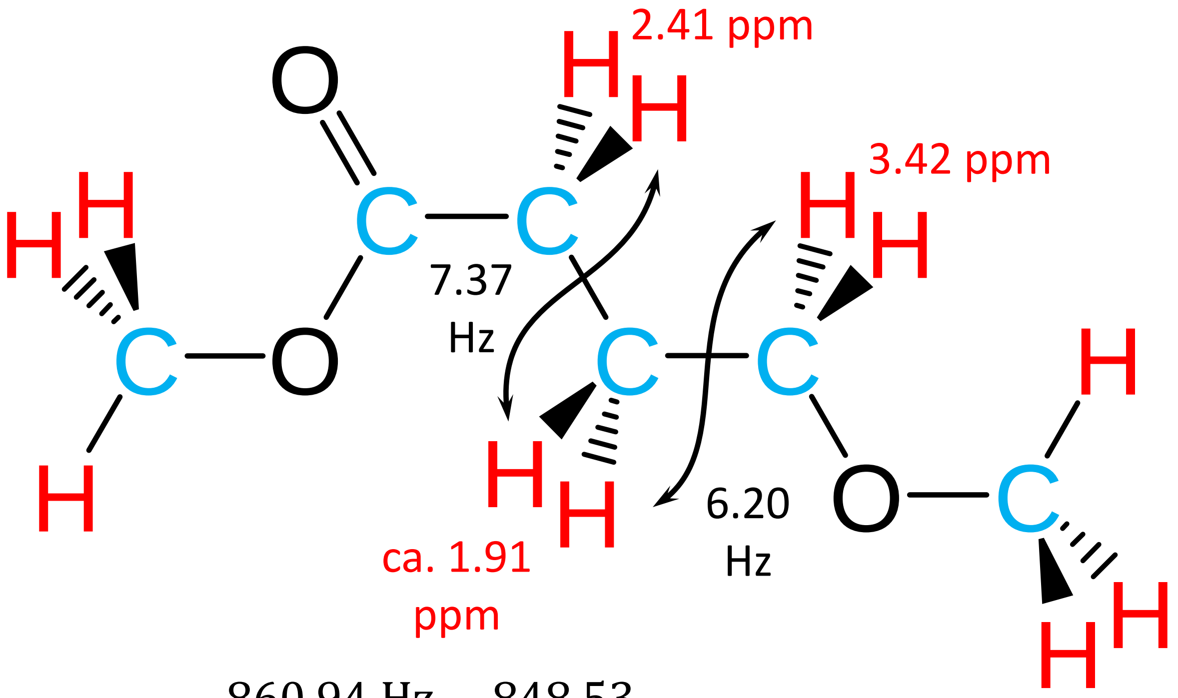
For the sake of clarity let us remove all carbon assignments and the proton assignments of both methyl groups. We don‘t need them anymore.



Coupling constants

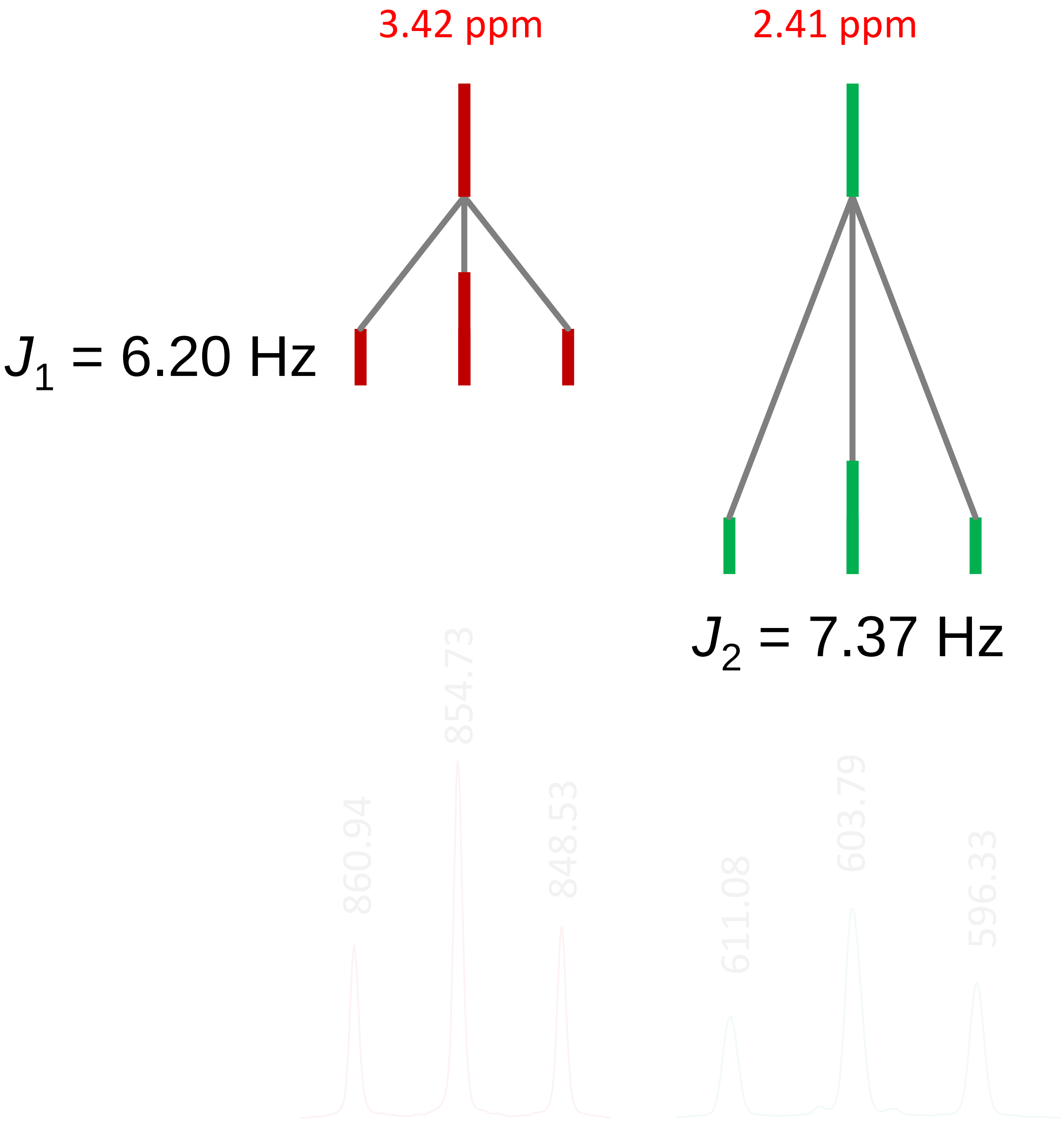
easy start

Both sets of chemically equivalent methylene protons at 2.41 ppm and 3.42 ppm have two chemically equivalent protons at about 1.91 ppm as the only vicinal coupling partners. We expect a triplet in both cases.



$$J_1 = \frac{860.94\text{ Hz} - 848.53}{2} = \mathbf{6.20\ Hz}$$

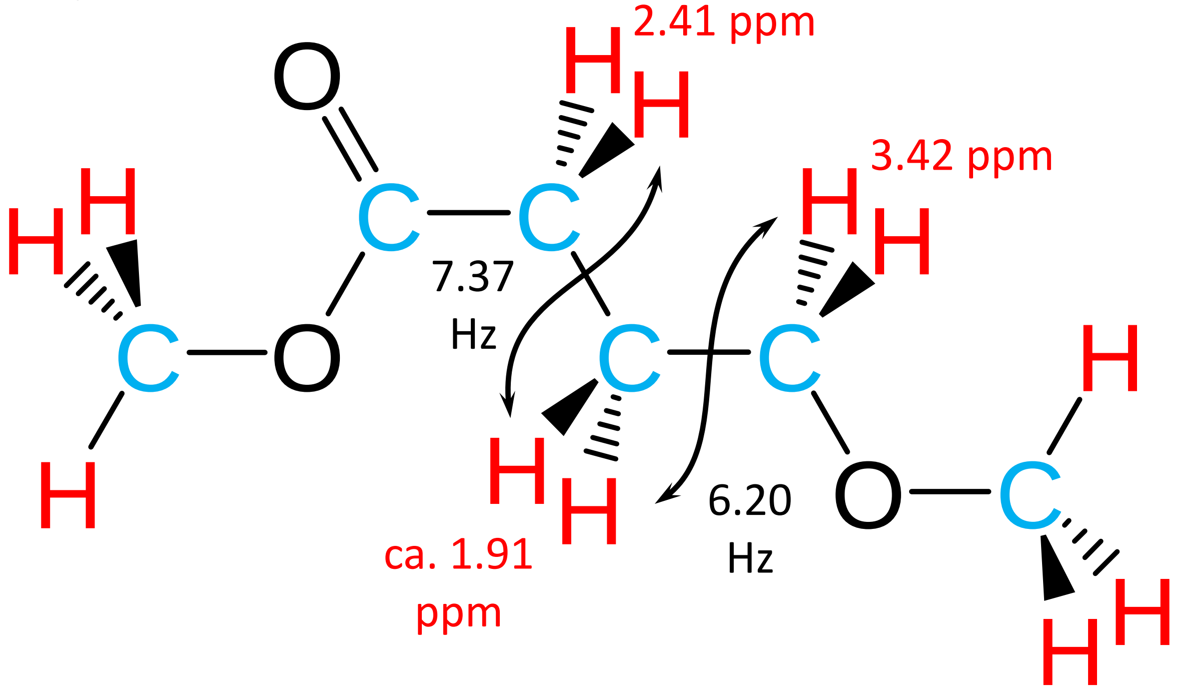
$$J_2 = \frac{611.08\text{ Hz} - 596.33}{2} = \mathbf{7.37\ Hz}$$



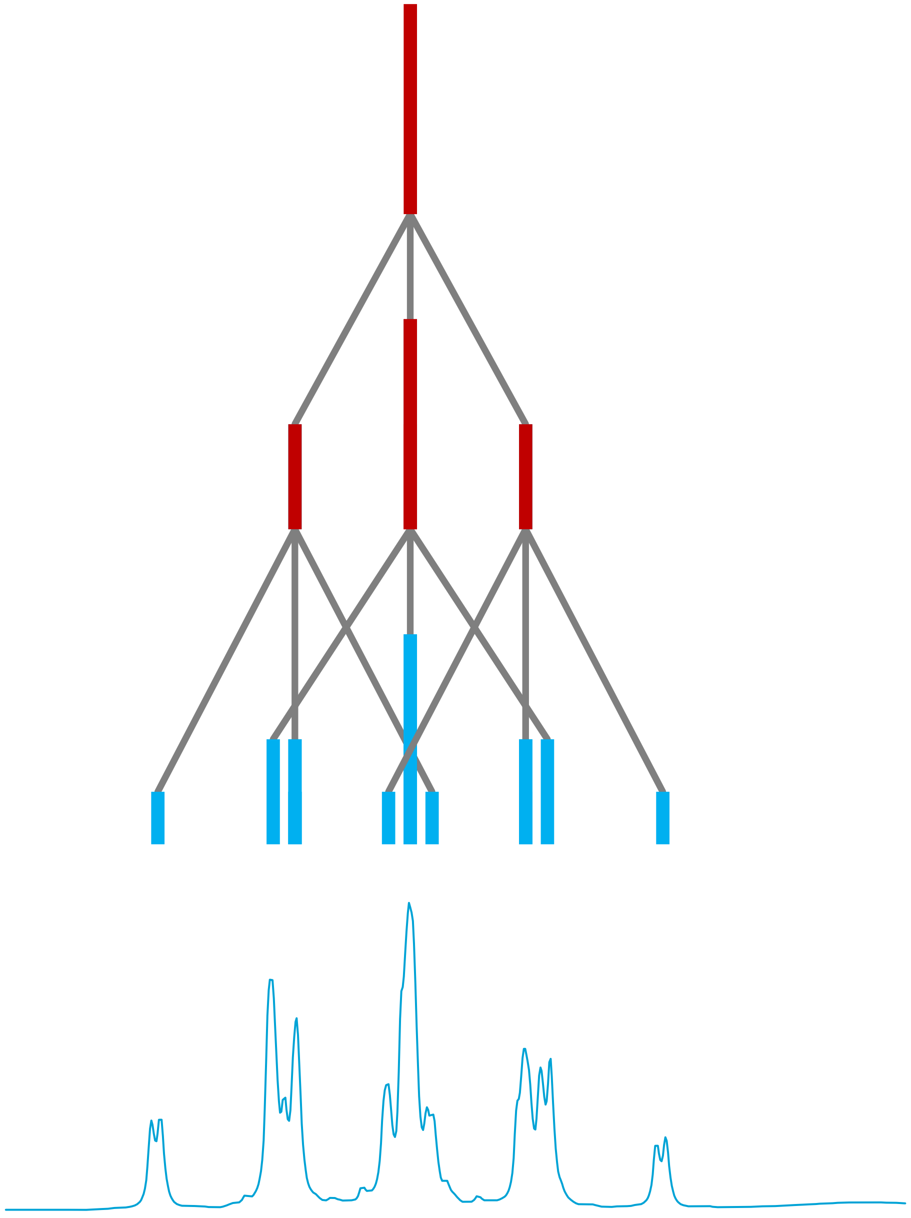
Coupling constants

done

For the methylene protons at 1.91 ppm we expect a triplet of triplets. Because 1.91 ppm and 2.41 ppm are relatively close in chemical shift, we expect very first signs of higher order (e.g slight „roofing“) but, in principle the triplet of triplets looks fine.



$$\frac{\Delta\delta}{J} = \frac{(2.41\ \text{ppm} - 1.91\text{ppm}) * 250.13\ \text{MHz}}{7.37\ \text{Hz}} = \mathbf{16.97}$$



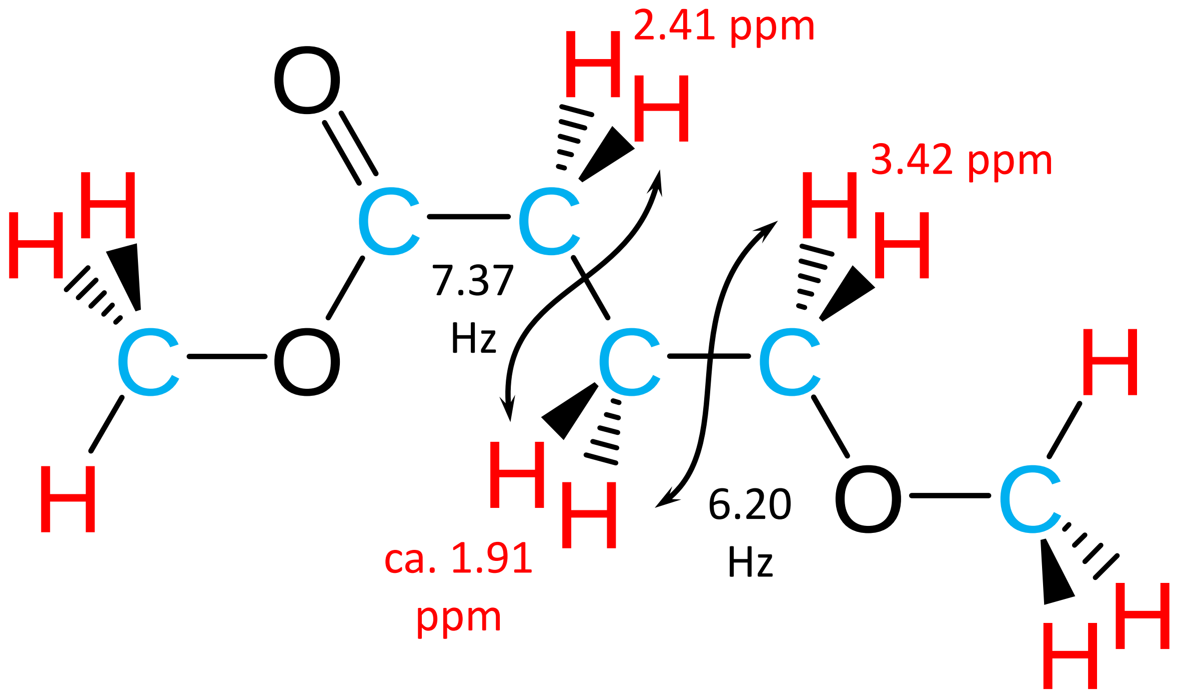
Coupling constants

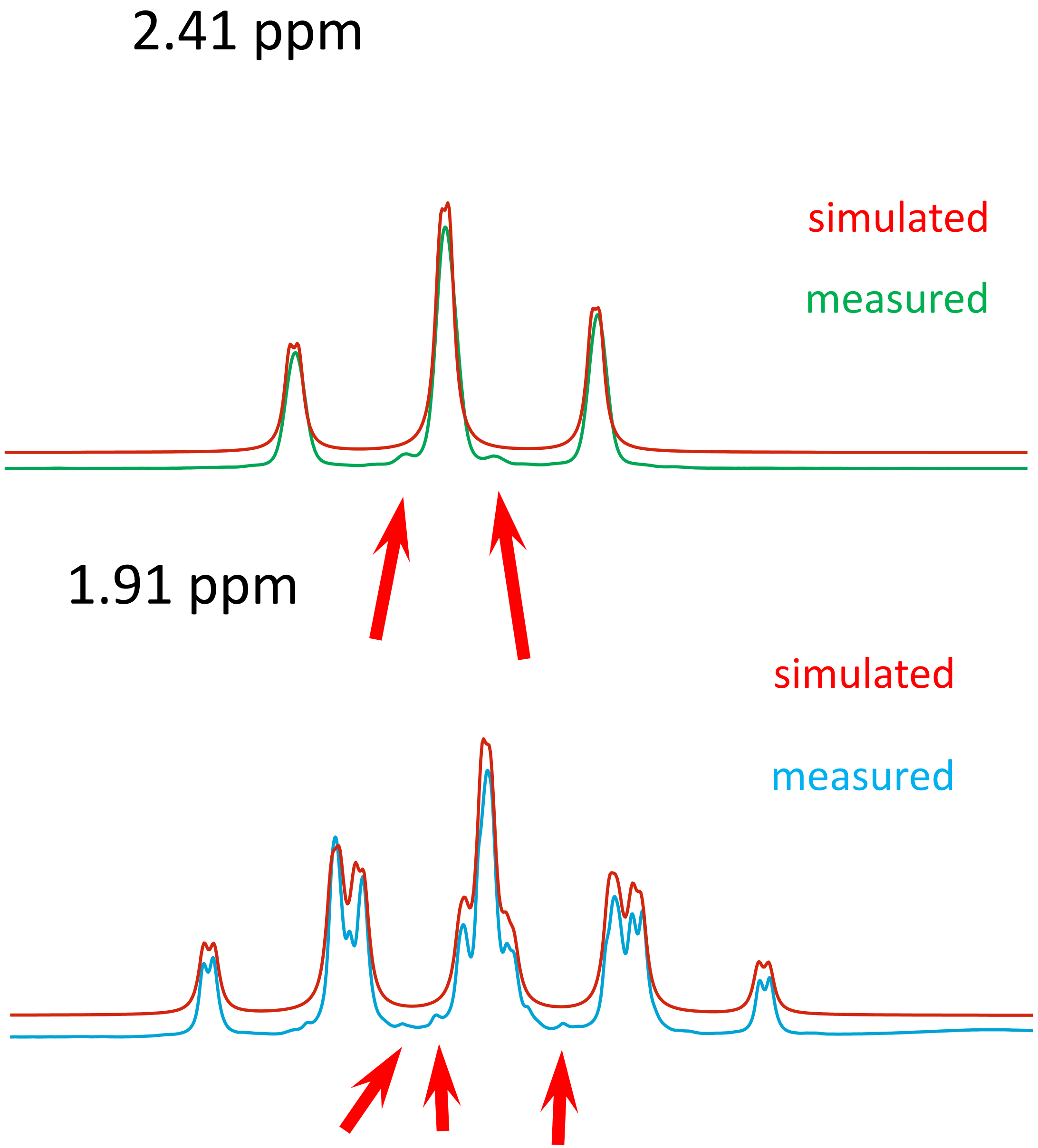
A last check

The simulation of two multiplets looks fine.

But … Have a closer look.

Some experimental details are missing in the simulation. Noise?

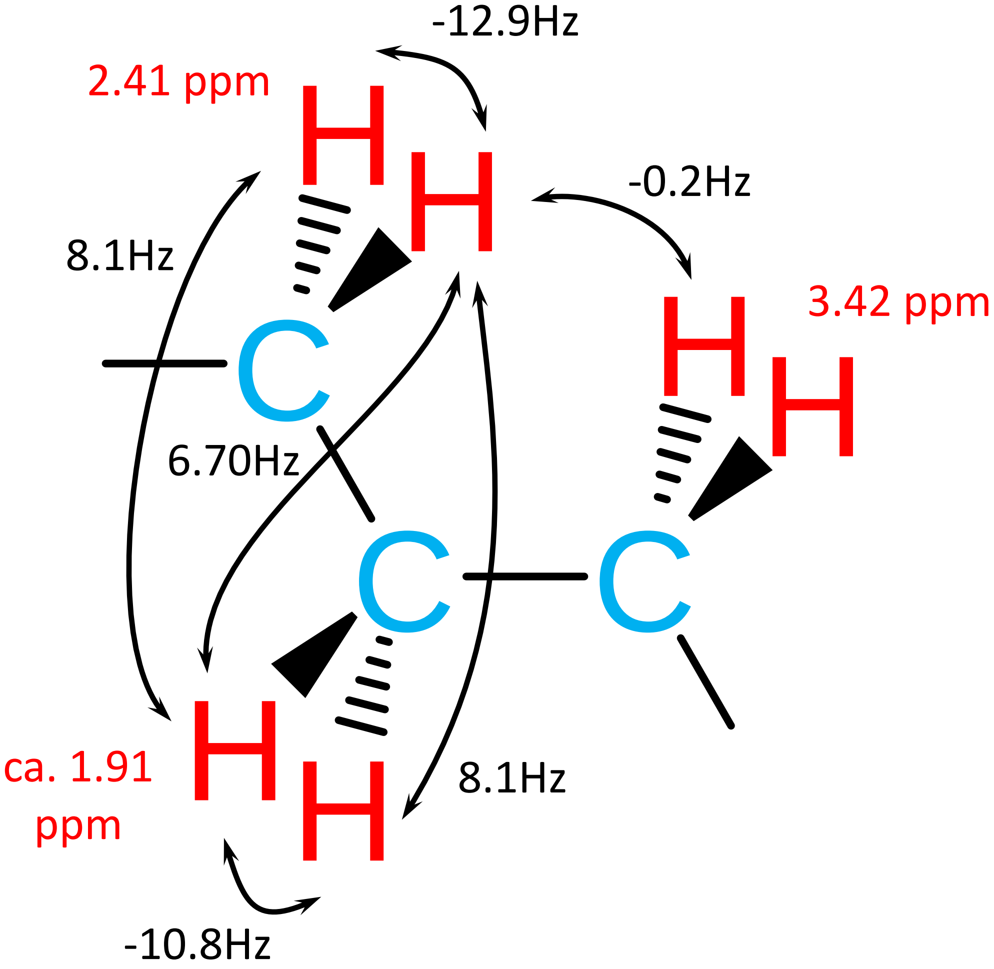




Coupling constants

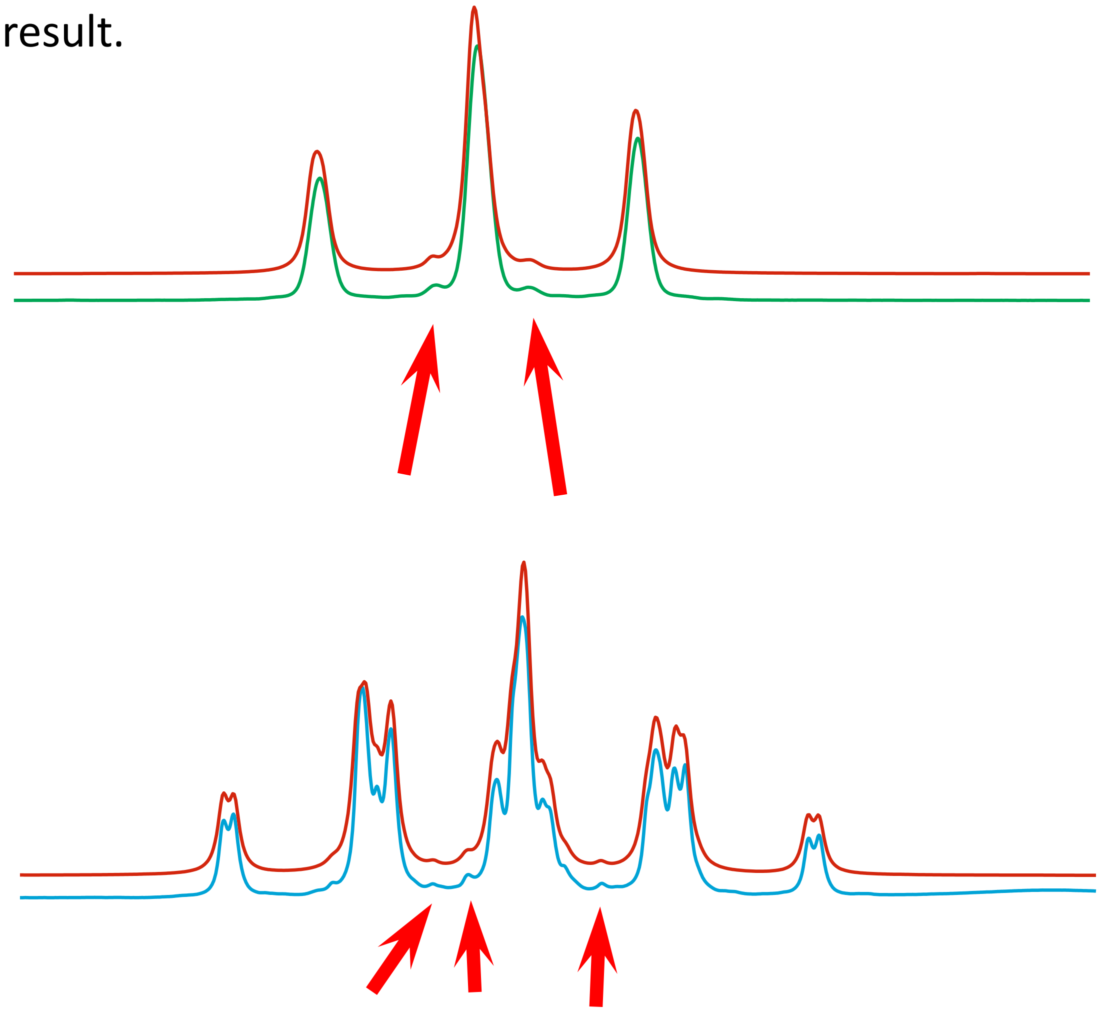
Some refinement

The second coupling pathway with a coupling constant of 6.70 Hz is not shown here for reason of clarity.



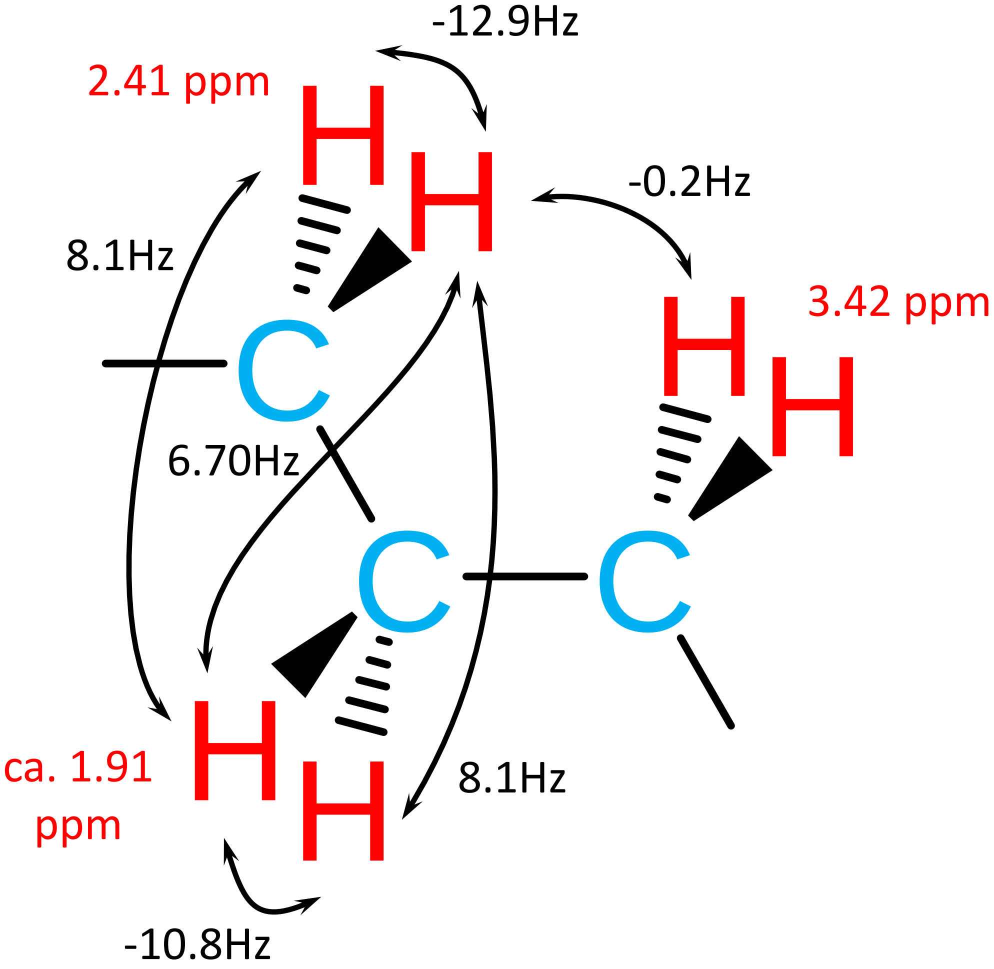
After changing some coupling constants and adding geminal coupling constants and a long rang coupling constant the „warts“ are simulated nearly perfectly.

It is not possible to measure these values directly from the spectra presented here, but you can repeat the simulation using the values given and see that they give the correct result.



Coupling constants

Some refinement

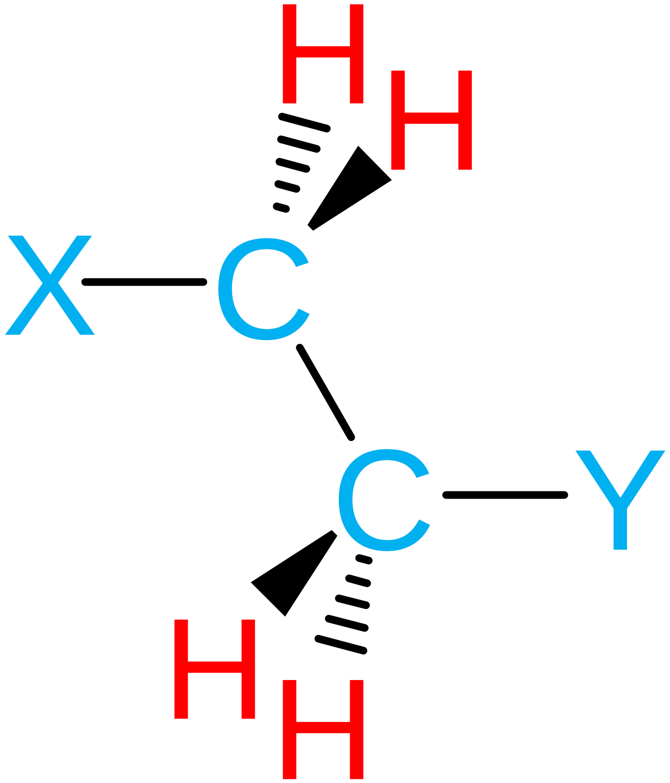


But …

Why should vicinal coupling constants between chemically equivalent protons have different values? There is the possibility of free rotation around the single bond between the carbon atoms. The vicinal coupling constants, of course, depend on the dihedral angle following the Karplus equation, but this effect should be averaged out by the fast rotation around all possible dihedral angles between 0 and 360 degrees.

Coupling constants

An explanation

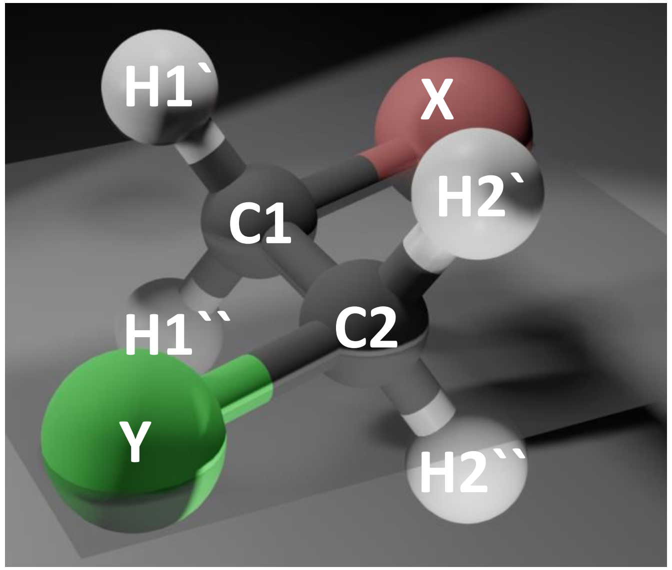


Let us reduce our molecule to a bisubstituted ethane derivative with two different substituents

X = -CO-O-CH_3

and

Y = -CH2-O-CH_3.



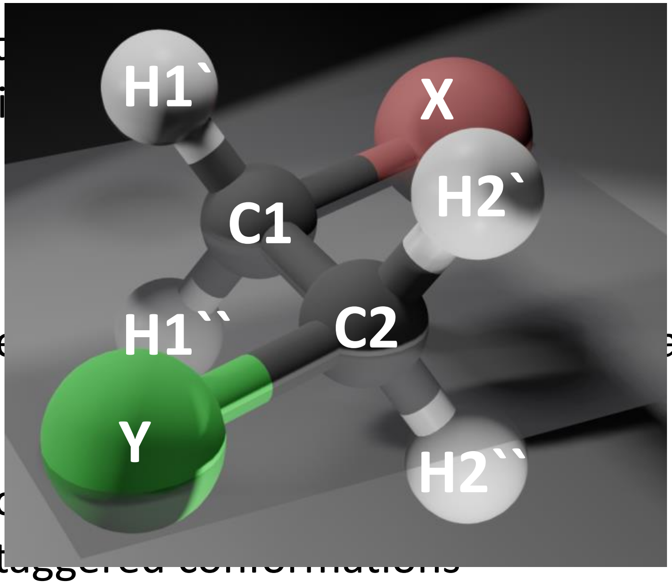
For the moment don‘t worry about the hydrogen atoms with four different labels shown here, although you expect that H1` and H1`` or H2`and H2`` should be equivalent.

Symmetry

Are H2`and H2`` chemically equivalent?

If you see the static structure of our unsymmetric ethane derivative there seems to be no question.

There is a symmetry plane inside the molecule, which makes both **H1`/H1``** and **H2`/H2``** chemically equivalent.

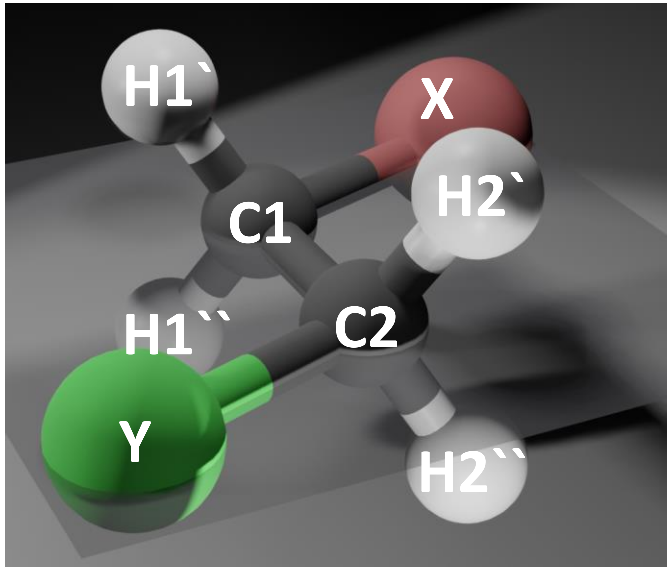


But there is free rotat [illegible] possible and the rotamer shown here i [illegible]

Let us introduce some [illegible] around the **C1-C2** bond.

- The first assumptic [illegible] steric hindrance will favour the three st [illegible]
- The second assumption is that bond rotation is so much faster than NMR dwell time and we are seeing the average of the three staggered rotamers.

These assumptions are only necessary to keep the mathematics simple.



Symmetry

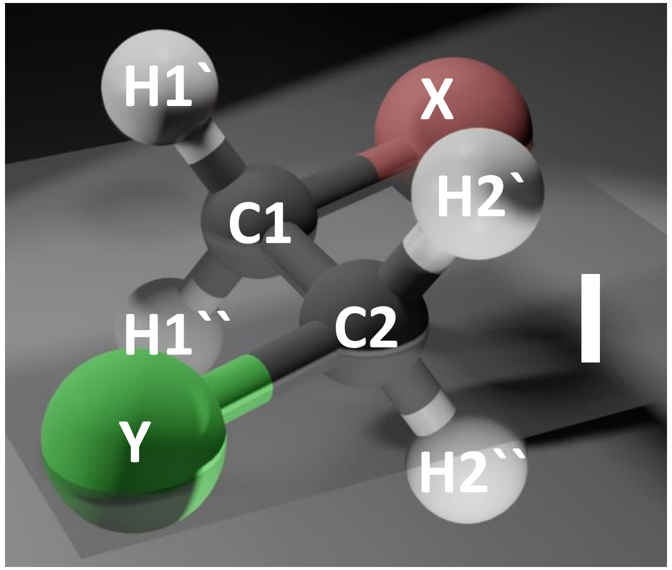
Are H2`and H2`` chemically equivalent?

First let us create the three rotamers (**I**, **II** and **III**)

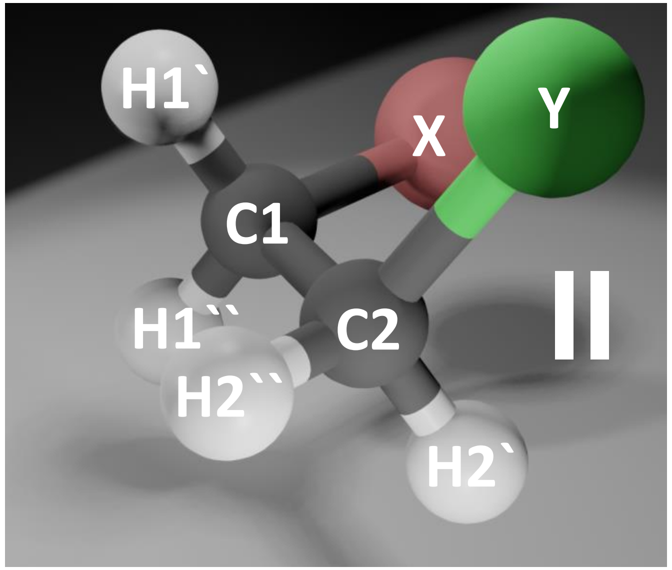
If we turn **C2** in rotamer **I** clockwise by 120 degree we get rotamer **II**.

Turning once more by 120 degree results in rotamer **III**.

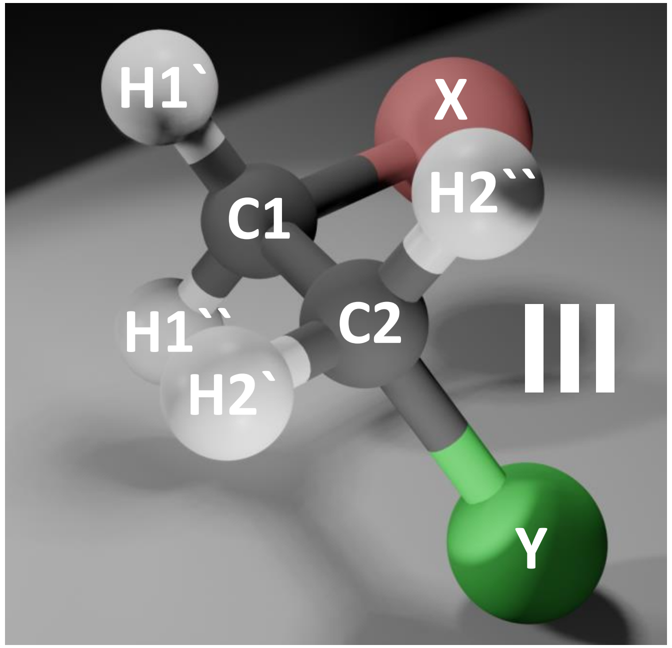
For rotamer **III** it is recommendable to change the viewpoint. Turn the whole molecule around the **C1**-**C2** bond by 180 degree and have a view to the molecule from the right side instead from the left side.



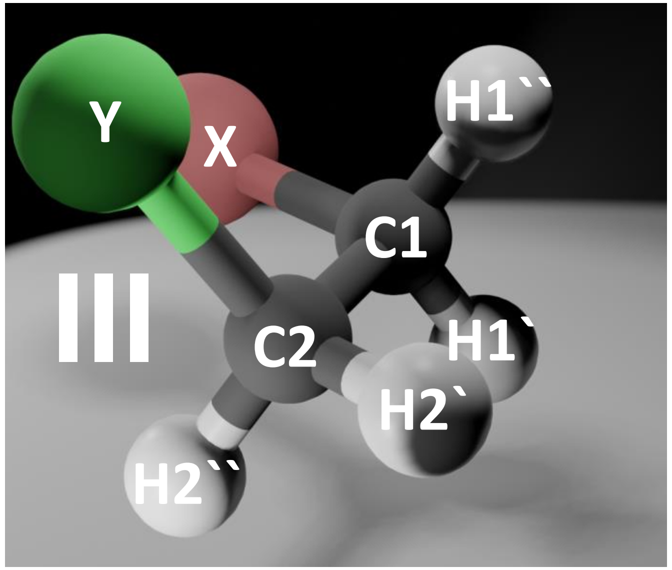
C2
120°



C2
120°

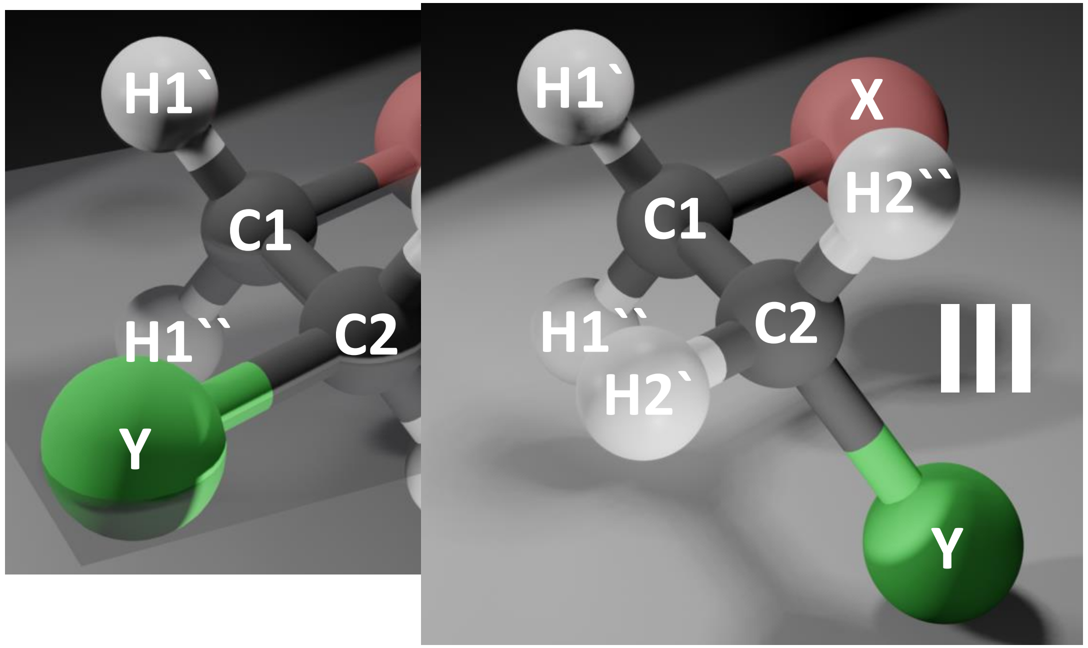


C1-C2 180°
change view
to right side



Symmetry

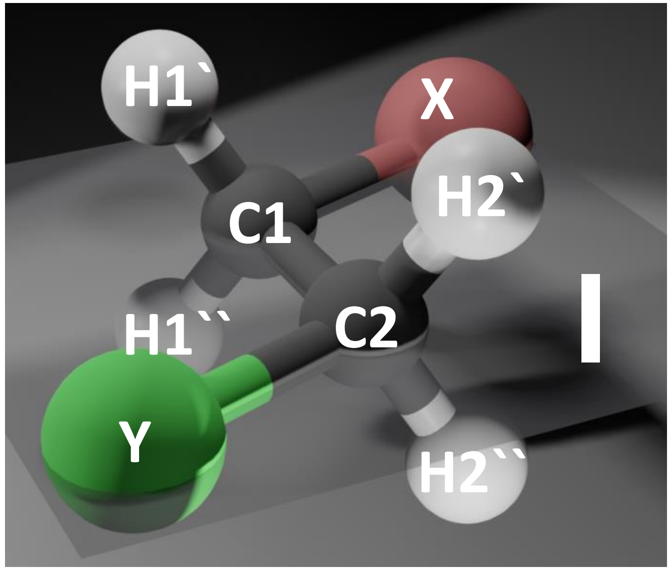
Are H2`and H2`` chemically equivalent?

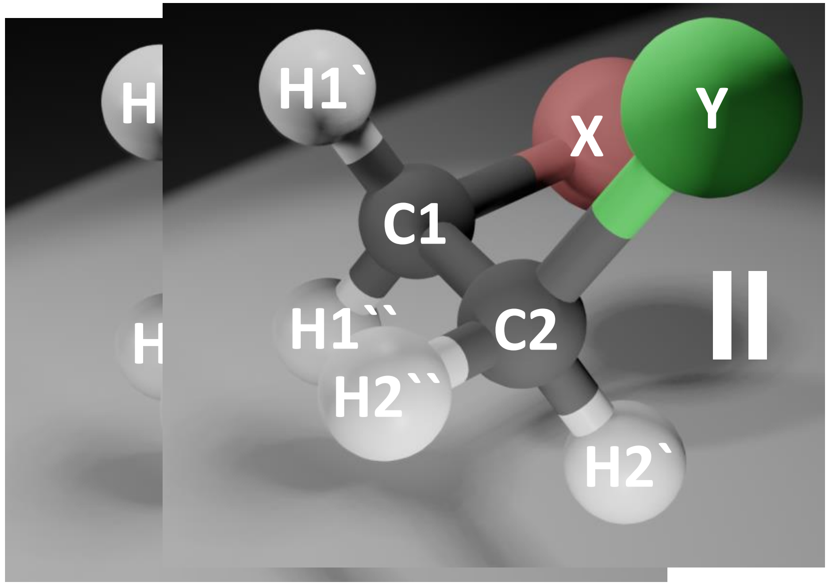


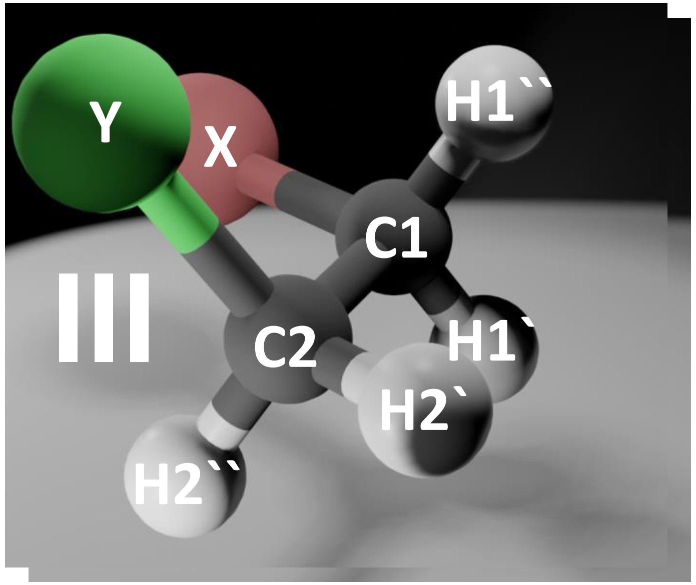
Let us reorder the three rotamers a little bit.

As you see there is a mirror plane inside rotamer **I** and no symmetry element inside the other two rotamers.

But on the other hand rotamer **II** and rotamer **III** are mirror images of each other.



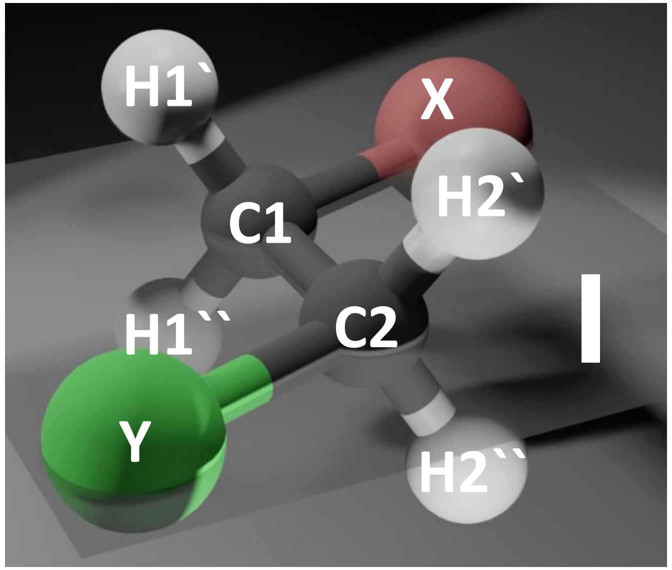


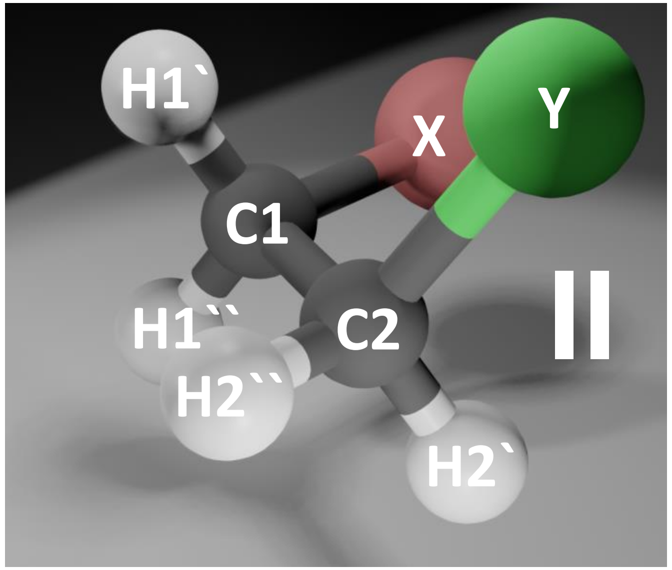


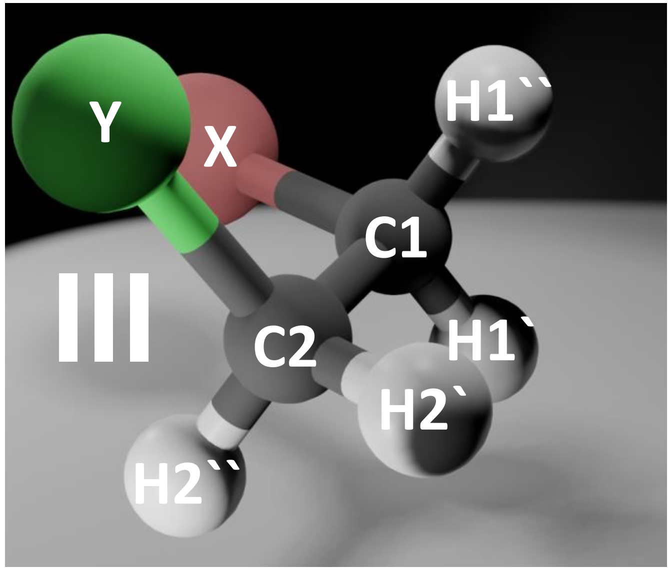
Symmetry

Are H2`and H2`` chemically equivalent?

And now let us paint the protons a little bit.



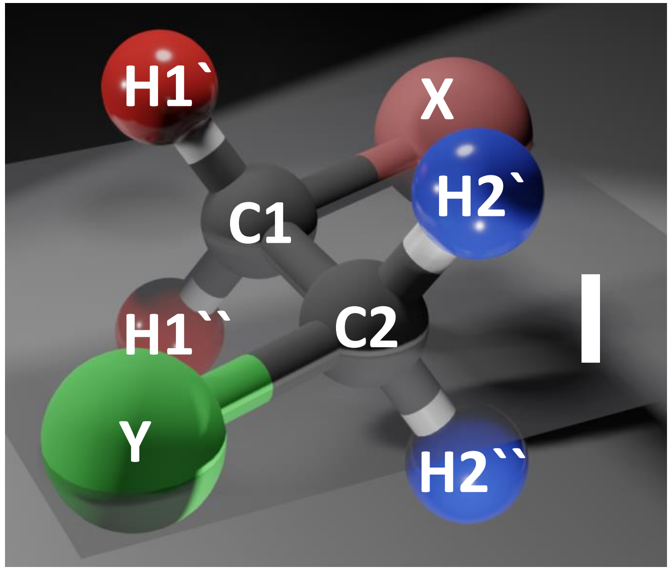




Symmetry

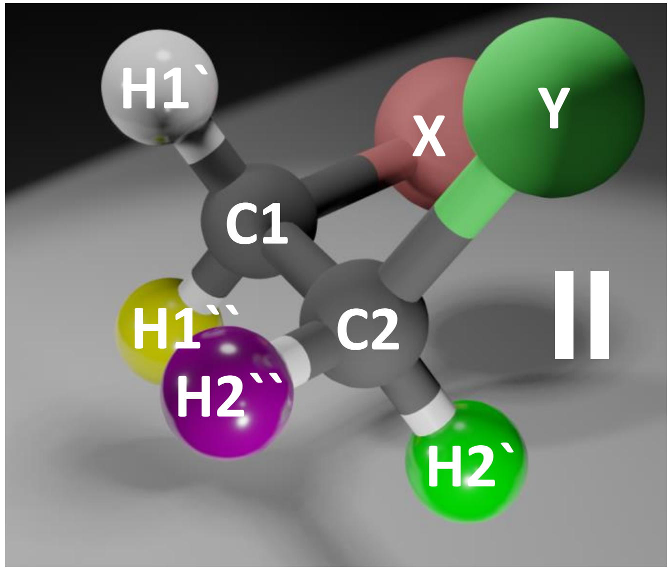
Are H2`and H2`` chemically equivalent?

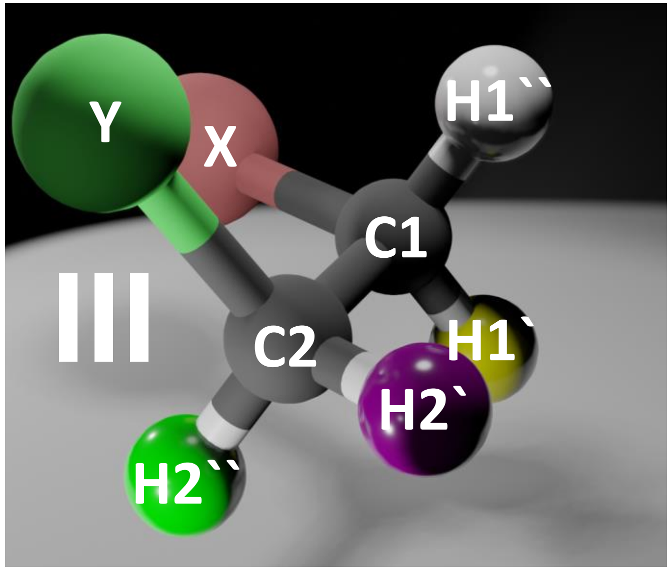
Different colours mean different chemical shifts, identical colours represent identical chemical shifts. Alltogether we have **six** different chemical shifts for the four protons inside the three rotamers.



As an example **H1`** and **H1``** in rotamer **I** are identical due to the internal mirror plane.

H2`` in rotamer **II** and **H2`** in rotamer **III** are identical, because rotamer **II** and rotamer **III** are mirror images.





Symmetry

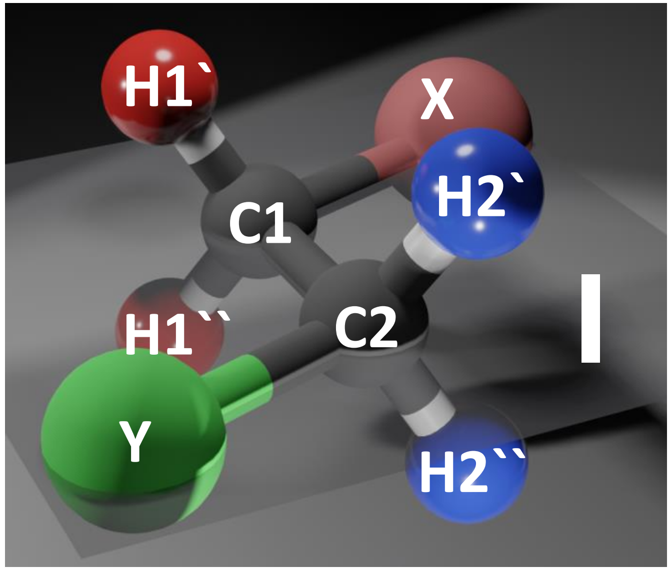
Are H1`and H1`` chemically equivalent?

The population of the rotamers is p_{I}, p_{II} and p_{III} with

$$p_{\mathrm{II}} = p_{\mathrm{III}}$$

and

$$p_{\mathrm{I}} + p_{\mathrm{II}} + p_{\mathrm{III}} = 1$$

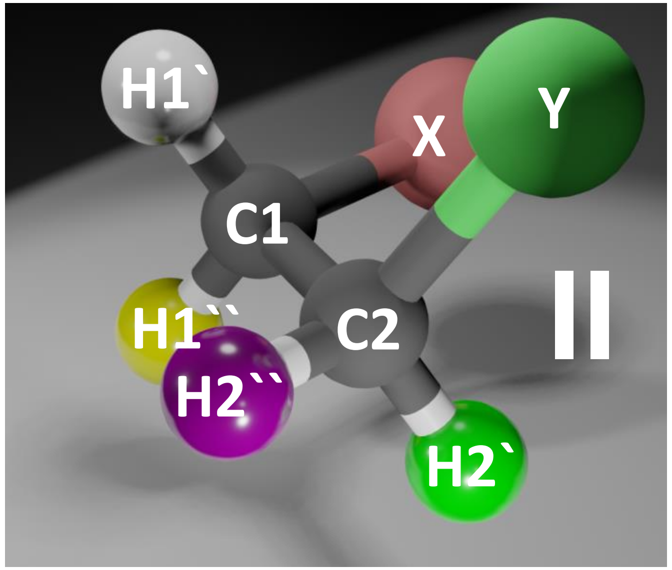


$\boldsymbol{p}_{\mathrm{I}}$
(rotamer population)

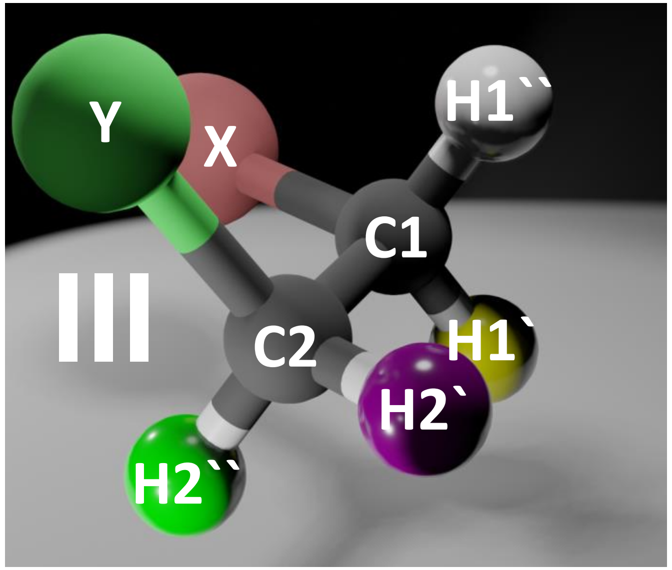
To keep the following equations short, we use single letters for the six different chemical shifts as follows:

$\delta_{H(red)} = R$
$\delta_{H(blue)} = B$
$\delta_{H(green)} = G$
$\delta_{H(yellow)} = Y$
$\delta_{H(purple)} = P$
$\delta_{H(white)} = W$ *(you wouldn‘t see a white letter)*

$\boldsymbol{p}_{\mathrm{II}}$



$\boldsymbol{p}_{\mathrm{III}}$



Symmetry

Are H2`and H2`` chemically equivalent?

Now we get for the four protons

$$\delta_{\mathrm{H1`}} = p_{\mathrm{I}} * R + p_{\mathrm{II}} * W + p_{\mathrm{III}} * Y$$
$$\delta_{\mathrm{H1``}} = p_{\mathrm{I}} * R + p_{\mathrm{II}} * Y + p_{\mathrm{III}} * W$$
$$\delta_{\mathrm{H2`}} = p_{\mathrm{I}} * B + p_{\mathrm{II}} * G + p_{\mathrm{III}} * P$$
$$\delta_{\mathrm{H2``}} = p_{\mathrm{I}} * B + p_{\mathrm{II}} * P + p_{\mathrm{III}} * G$$

With the boundary condition

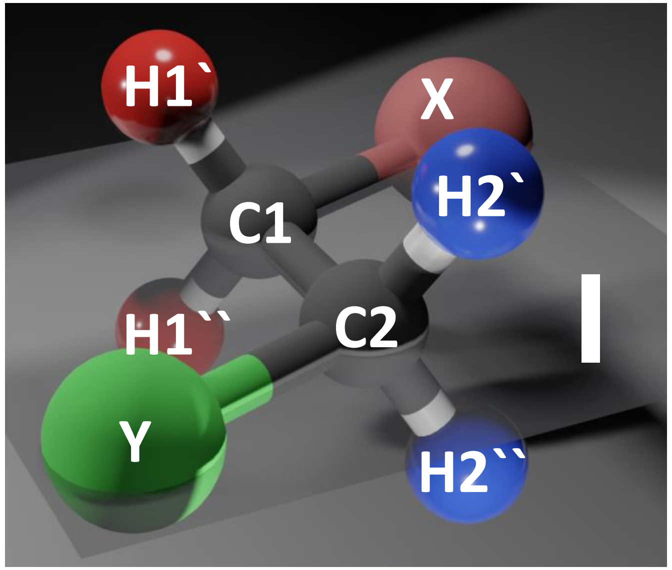
$$p_{\mathrm{II}} = p_{\mathrm{III}}$$

we get

$$\delta_{\mathrm{H2`}} = \delta_{\mathrm{H2``}}$$

and

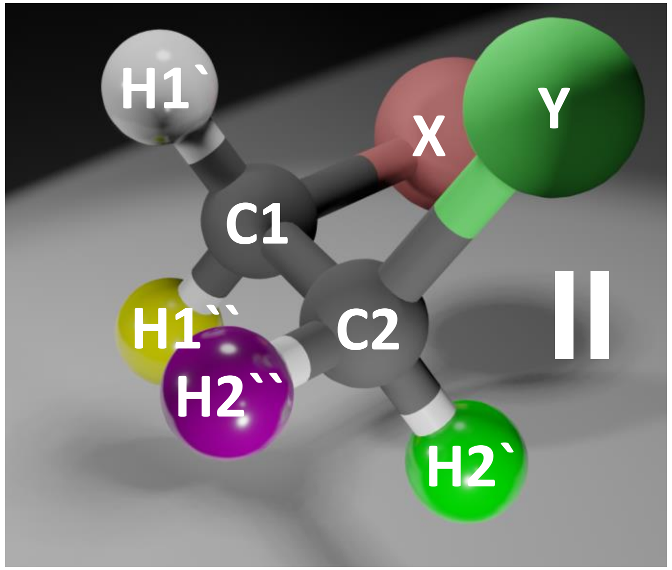
$$\delta_{\mathrm{H1`}} = \delta_{\mathrm{H1``}}$$



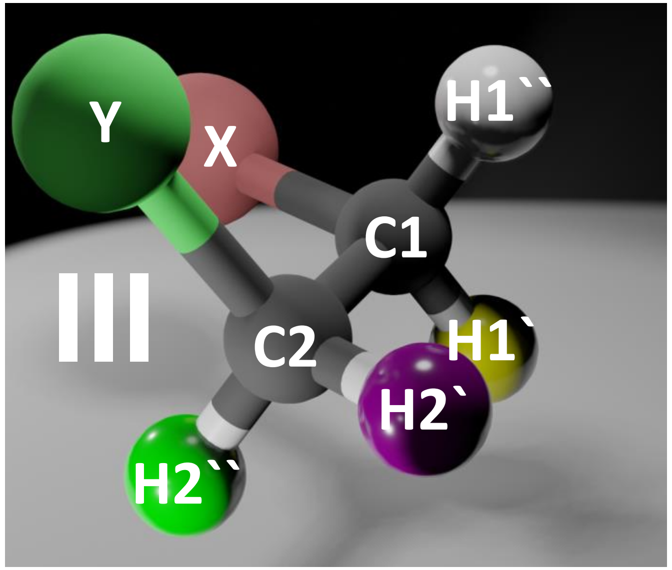
p_{I}

(rotamer population)

p_{II}



p_{III}



Symmetry

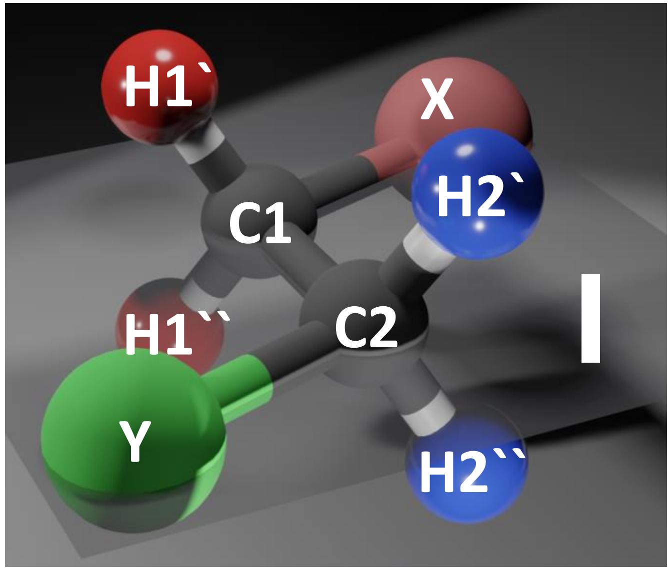
Are H2`and H2`` chemically equivalent?

We arrive at the result you expected from the beginning without all those difficult considerations.

But, just for your curiosity, try to repeat the calculation after replacing **H1``** with a third substituent **Z**, different from **X** and **Y**. In this case, there is no symmetry, no mirror plane inside rotamer **I** nor a mirror plane between the rotamers **II** and **III**.

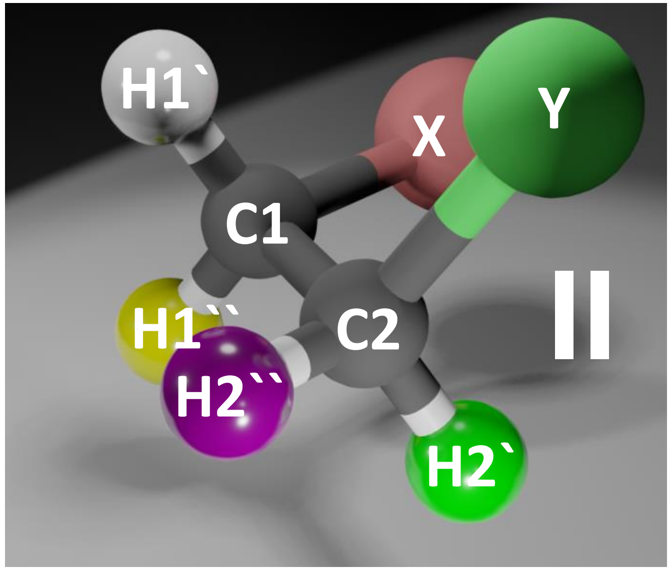
But, leaving that aside for the moment, let us return to the main question:

are **H2`** and **H2``** **magnetically** equivalent?

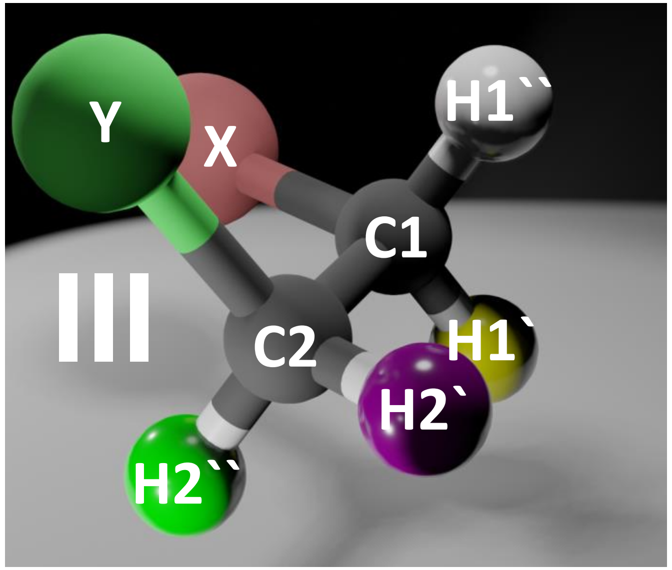


p_{I}
(rotamer population)

p_{II}



p_{III}



Symmetry

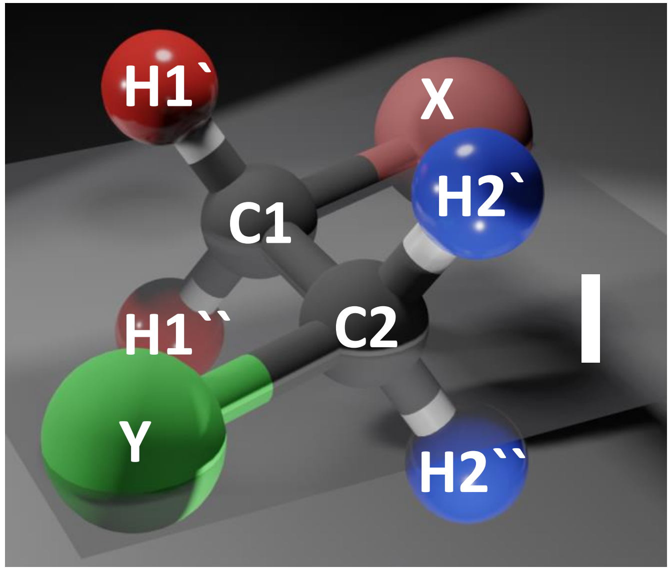
Are H2`and H2`` magnetically equivalent?

As we have seen, the protons **H2`** and **H2``** are chemically equivalent. They are magnetically equivalent as well, if the condition

$$^{3}J_{\text{H1`,H2`}} = {}^{3}J_{\text{H1`,H2``}}$$

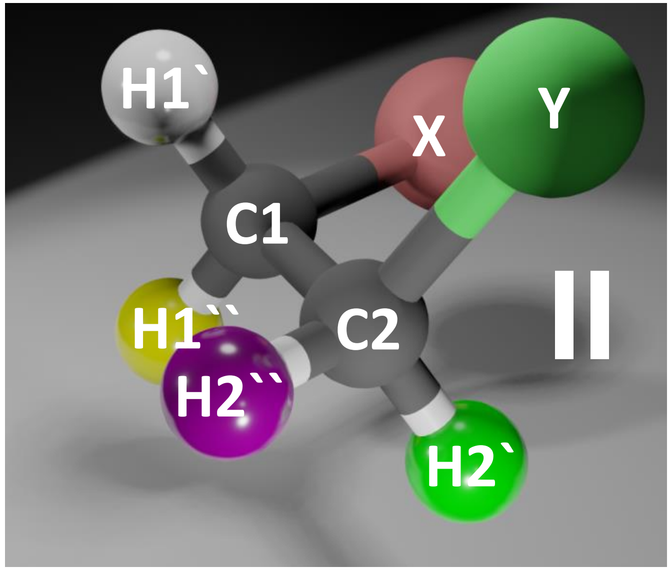
is fulfilled.
Of course the same has to be valid, if we replace **H1`** by **H1``** on both sides of the equation.

Let us see the geometric relations between **H1‘/H2`** and **H1`/H2``** one after the other for all three rotamers.

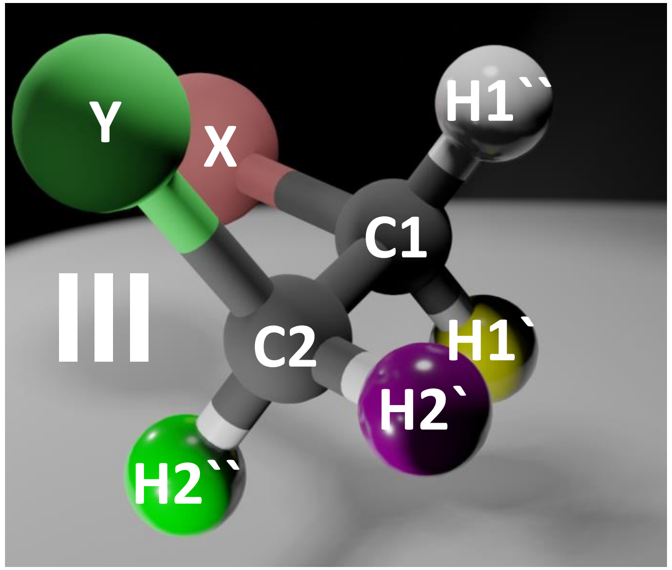


p$_{\text{I}}$
(rotamer population)

p$_{\text{II}}$



p$_{\text{III}}$



Symmetry

Are H2`and H2``
magnetically equivalent?

Let us start with the geometry between **H1`** and **H2`**. In all three rotamers **H1`** is labelled in black and **H2`** labelled in red.

We always have to focus on two planes. The first one is created from the atoms

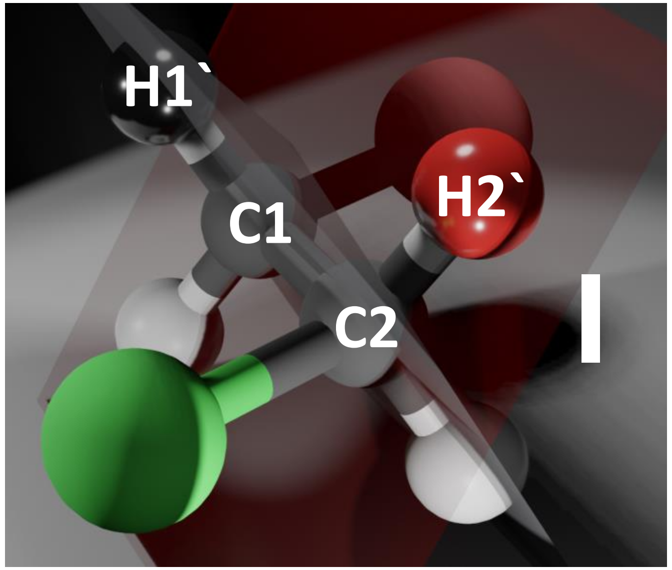
H1`, **C1** and **C2**,

the second one from the atoms

H2`, **C2** and **C1**.

The dihedral angles between these planes are

rotamer **I** – 60 degree
rotamer **II** – 180 degree
rotamer **III** – 60 degree

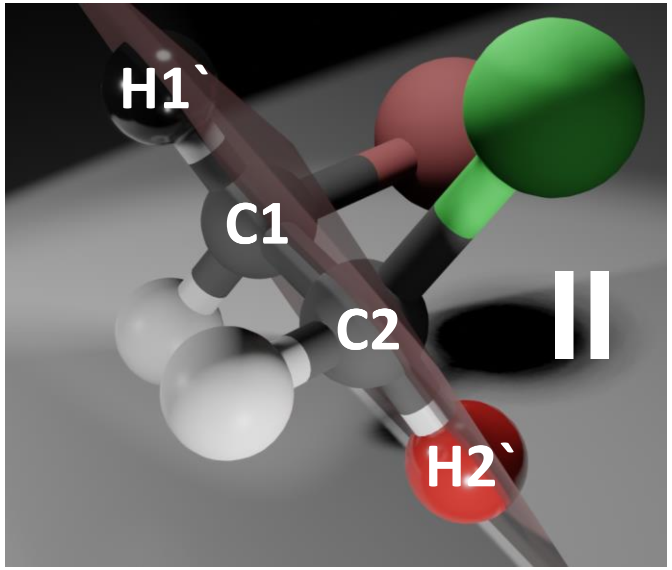


p_{I}
(rotamer probability)

dihedral angle
(H1`-C1-C2-H2`)
60°

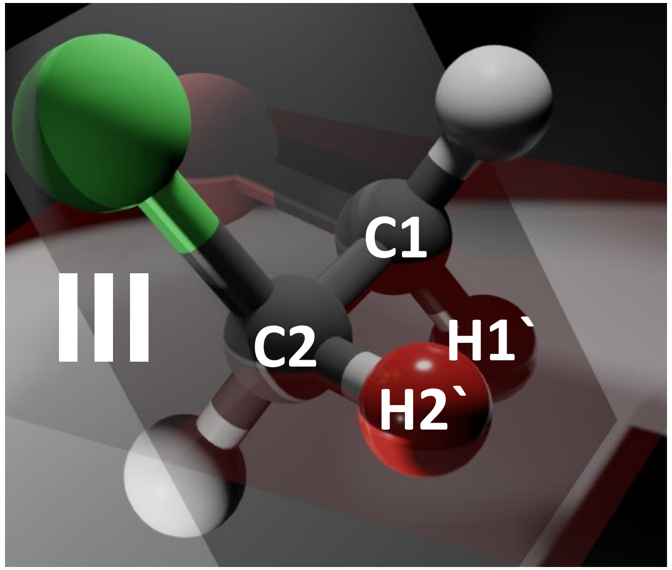
p_{II}

dihedral angle
(H1`-C1-C2-H2`)
180°



p_{III}

dihedral angle
(H1`-C1-C2-H2`)
60°



Symmetry

Are H2`and H2``
magnetically equivalent?

According to the Karplus equation, the vicinal coupling constant for a dihedral angle of 180 degree is significantly larger than the vicinal coupling constant in the case of a dihedral angle of 60 degrees.

Let us write for the coupling constants between **H1`** and **H2`**

$$J_{L\text{(arge)}}$$

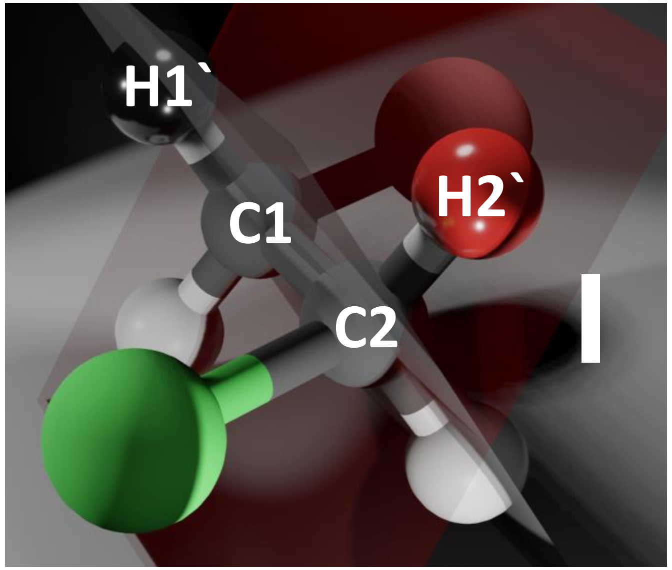
if the dihedral angle is 180 degree and

$$J_{S\text{(mall)}}$$

in the case of 60 degree.

$$J_{\text{H1`,H2`}} =$$
$$p_{\text{I}} * J_S + p_{\text{II}} * J_L + p_{\text{III}} * J_S$$

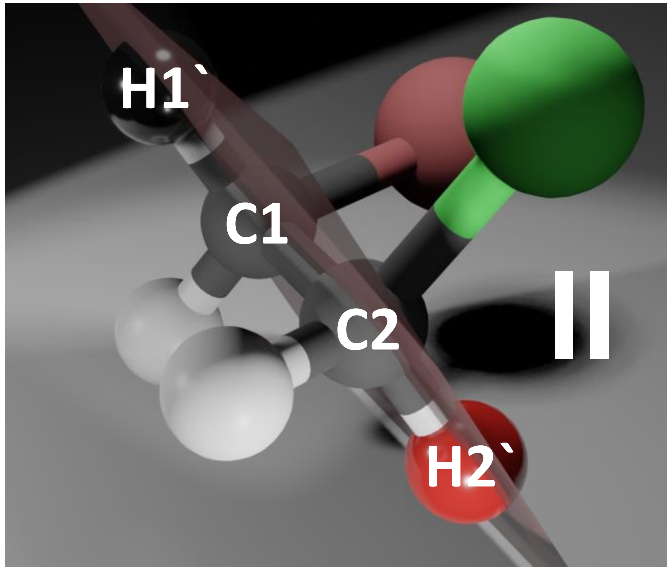
J_S



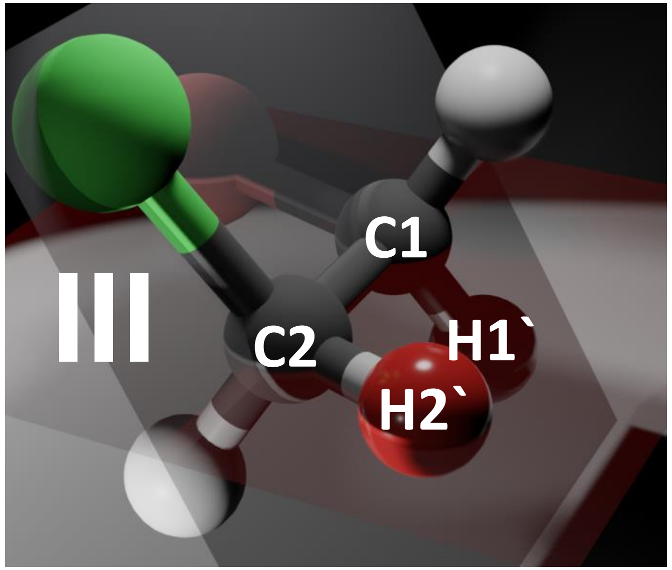
p_{I}
(rotamer probability)

dihedral angle
(H1`-C1-C2-H2`)
60°

p_{II} dihedral angle (H1`-C1-C2-H2`) 180° J_L



p_{III} dihedral angle (H1`-C1-C2-H2`) 60° J_S

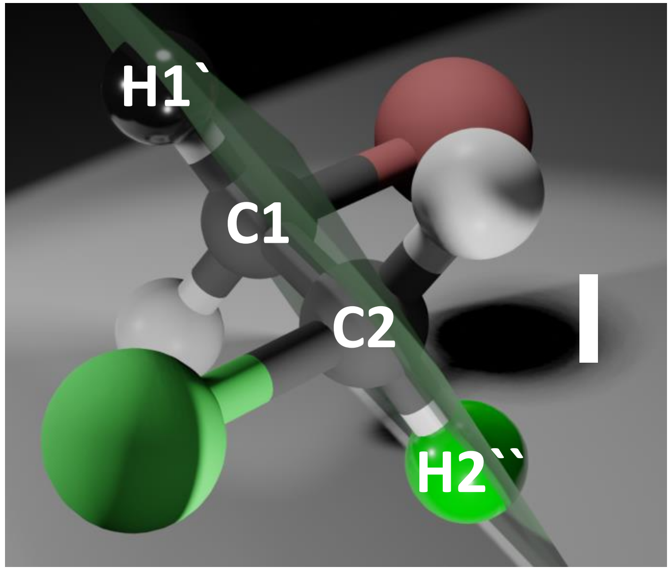


Symmetry

Are H2`and H2`` magnetically equivalent?

Let us repeat the same considerations for **H2``**, labelled in green.

J_L

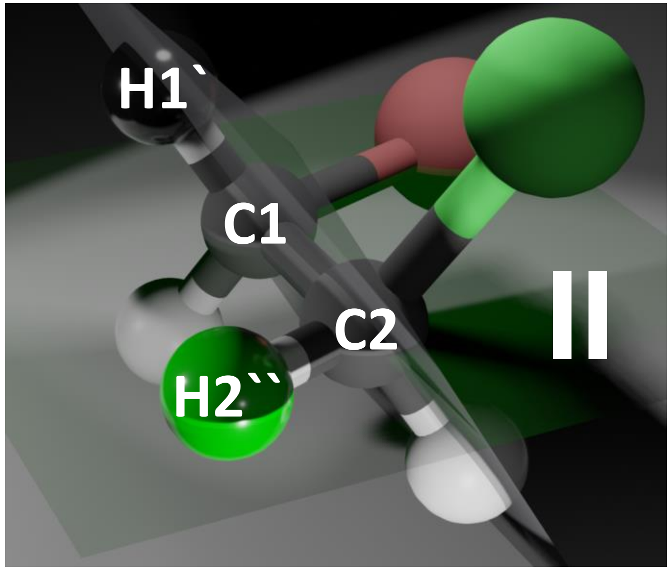


p_I (rotamer probability)

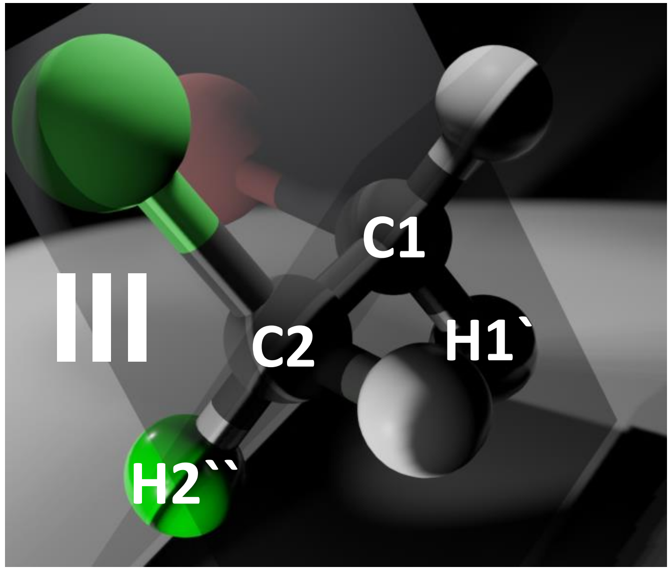
dihedral angle (H1`-C1-C2-H2``)

180°

p_{II} dihedral angle (H1`-C1-C2-H2``) **60°** J_S



p_{III} dihedral angle (H1`-C1-C2-H2``) **60°** J_S



$$J_{H1`,H2``} =$$
$$p_I * J_L + p_{II} * J_S + p_{III} * J_S$$

Symmetry

Are H2`and H2`` magnetically equivalent?

Finally we have

$$J_{\mathrm{H1`,H2``}} = p_{\mathrm{I}} * J_{\mathrm{L}} + p_{\mathrm{II}} * J_{\mathrm{S}} + p_{\mathrm{III}} * J_{\mathrm{S}}$$

$$J_{\mathrm{H1`,H2`}} = p_{\mathrm{I}} * J_{\mathrm{S}} + p_{\mathrm{II}} * J_{\mathrm{L}} + p_{\mathrm{III}} * J_{\mathrm{S}}$$

Now, please keep in mind the already known relations ($p_{\mathrm{II}} = p_{\mathrm{III}}$ and $p_{\mathrm{I}} + p_{\mathrm{II}} + p_{\mathrm{III}} = 1$) and play around a little bit with the population of rotamer **I**. Start with $p_{\mathrm{I}} = 0.333$.

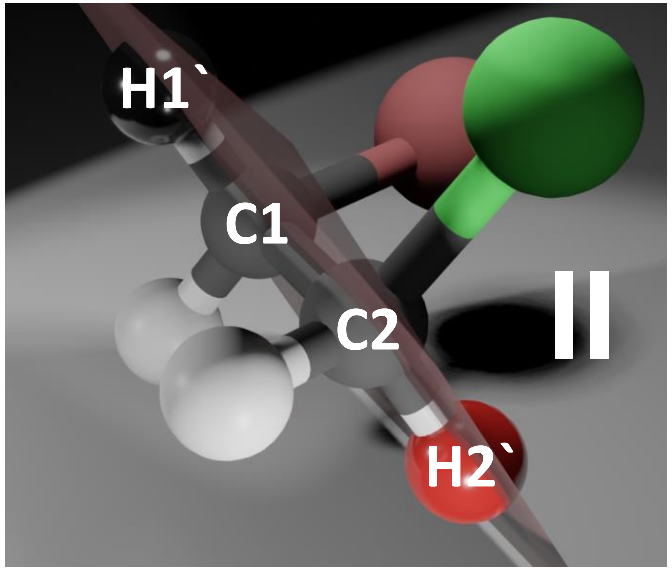
You will see how the two coupling constants vary in opposite directions with the population p_{I}.

The two coupling constants would only be identical in the case of $p_{\mathrm{I}} = p_{\mathrm{II}} = p_{\mathrm{III}}$, and with the two couplings we previously labelled as J_s being identical. But......

We made some simplifications. In principle no pair of the three rotamers result in identical coupling constants for either J_L *or* J_S. As an example see the environment for the two rotamers with dihedral angles of 180 degree between the coupling protons (J_L). In spite of an idential dihedral angle the coupling pathway is clearly different.
So if we did happen to find identical coupling constants in such a system it would be purely by luck!

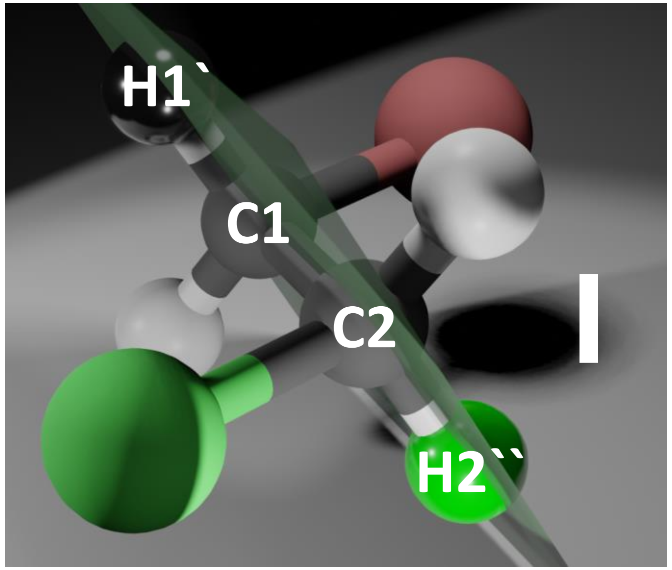
dihedral angle (H1`-C1-C2-H2`) **J_L**

180°



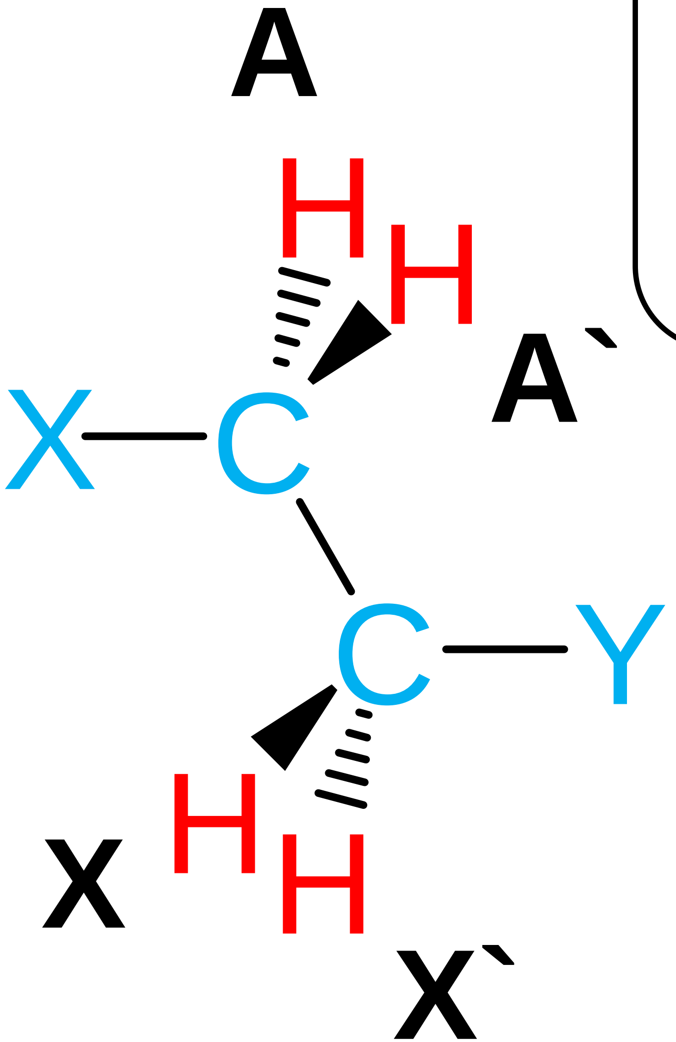
dihedral angle (H1`-C1-C2-H2`) **J_L**

180°



Symmetry

Conclusion



As soon as an asymmetrically substituted ethane is recognized as a structural fragment within an *achiral* compound, the methylene protons of this ethane fragment are **always** chemically equivalent and **always** magnetically non-equivalent.

Why *achiral*?

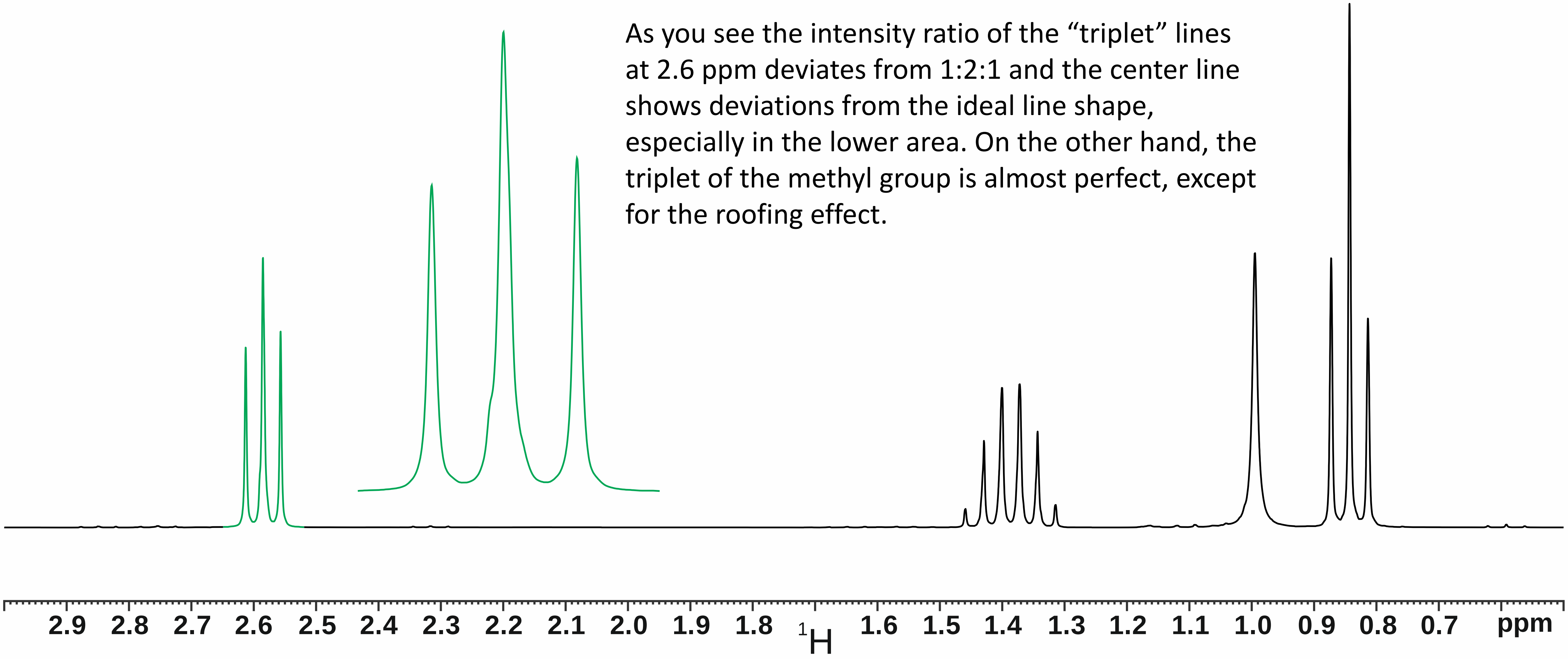
That‘s very simple. Within chiral compounds the methylene protons are chemically non-equivalent, which means, the question of magnetic equivalence doesn‘t appear.

Symmetry

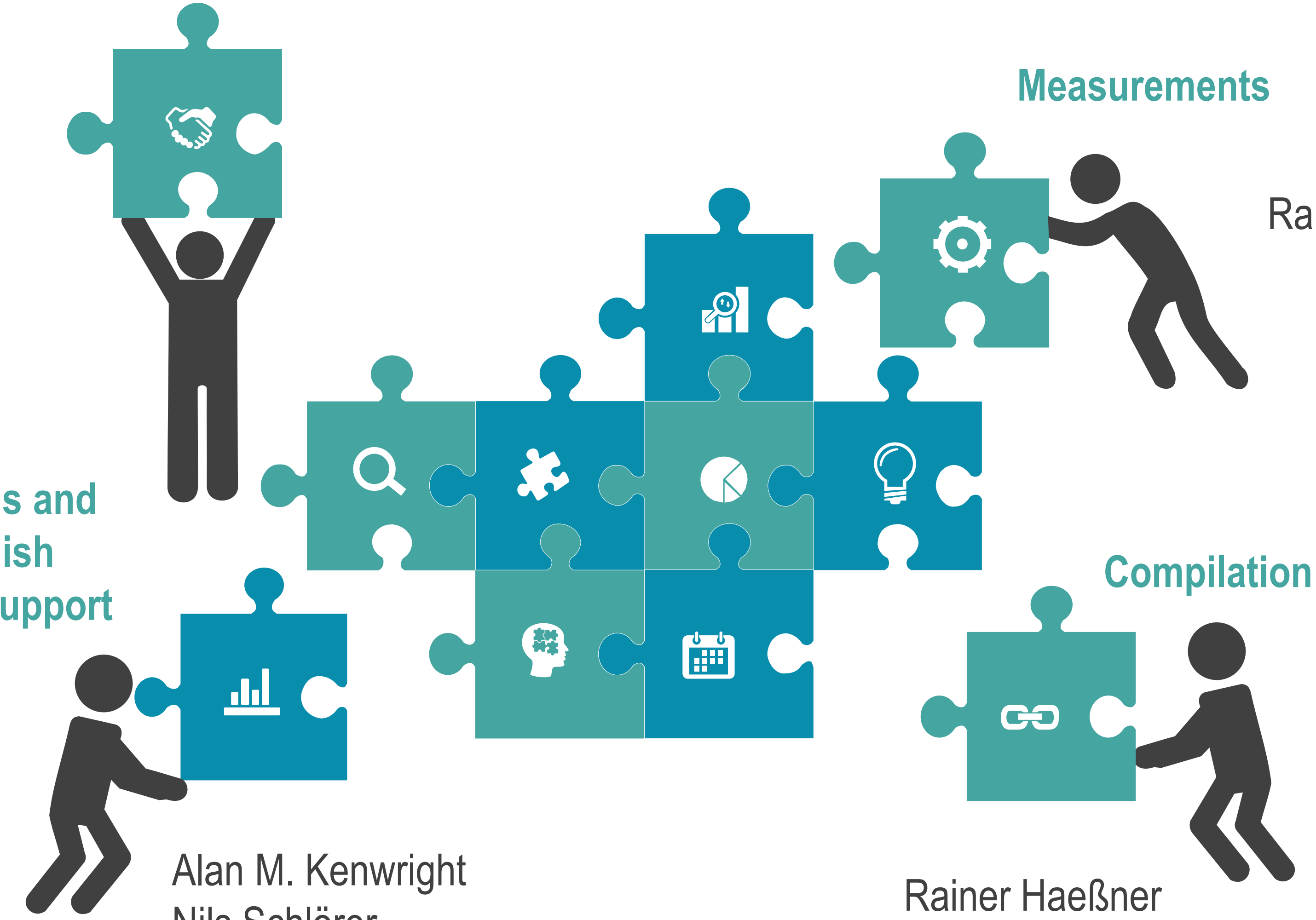
Keep your eyes open

Magnetic non-equivalence in alkyl chains is often not visible at a first glance. But with open eyes, you can see the effect almost everywhere, such as for example in the methylene group of propylamine.

As you see the intensity ratio of the “triplet” lines at 2.6 ppm deviates from 1:2:1 and the center line shows deviations from the ideal line shape, especially in the lower area. On the other hand, the triplet of the methyl group is almost perfect, except for the roofing effect.



Contributions



Spectrometer time

TU Munich

Measurements

Rainer Haeßner

Discussions and native English language support

Alan M. Kenwright
Nils Schlörer

Compilation

Rainer Haeßner

Contributions

Some special thanks.

This *problem of the month* is the result of an exciting discussion within the AMMRL mailing list.
It is not possible to mention all of the valuable feedback here - sorry - but some special contributions should be mentioned, I believe.

Svetlana Simowa provided an easy to understand explanation.

Novruz Akhmedov extracted the coupling constants used in the simulations from the raw data.

Hsin Wang contributed some text building blocks for the explanation using only a few words to focus on the essential details.

Karel Klika pointed out that, in principle, there is no perfect average even in the case of idential populations of all three rotamers.

Lukas Hintermann always provided immediate response to stereochemical questions of all kind.