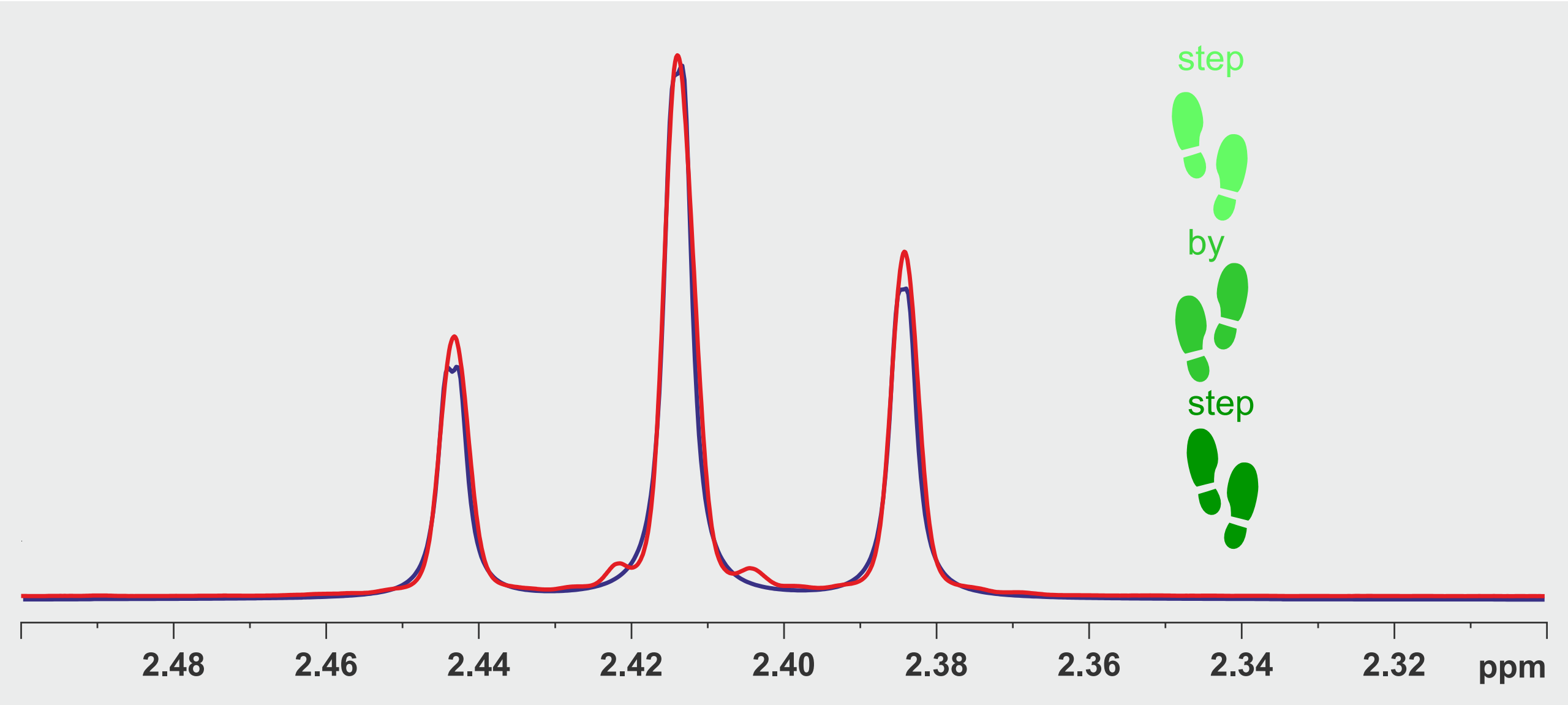
Übung plus Lösung – Schnellüberblick

Diese Version soll nur dem schnellen Überblick über die Fragestellung dienen. Sämtliche PowerPoint-Animationen fehlen, in einigen Fällen könnte die Umsetzung von PowerPoint auf PDF merkwürdig aussehen.
Die qualitativ hochwertigen PowerPoint-Originale stehen jederzeit zum freien Download zur Verfügung.

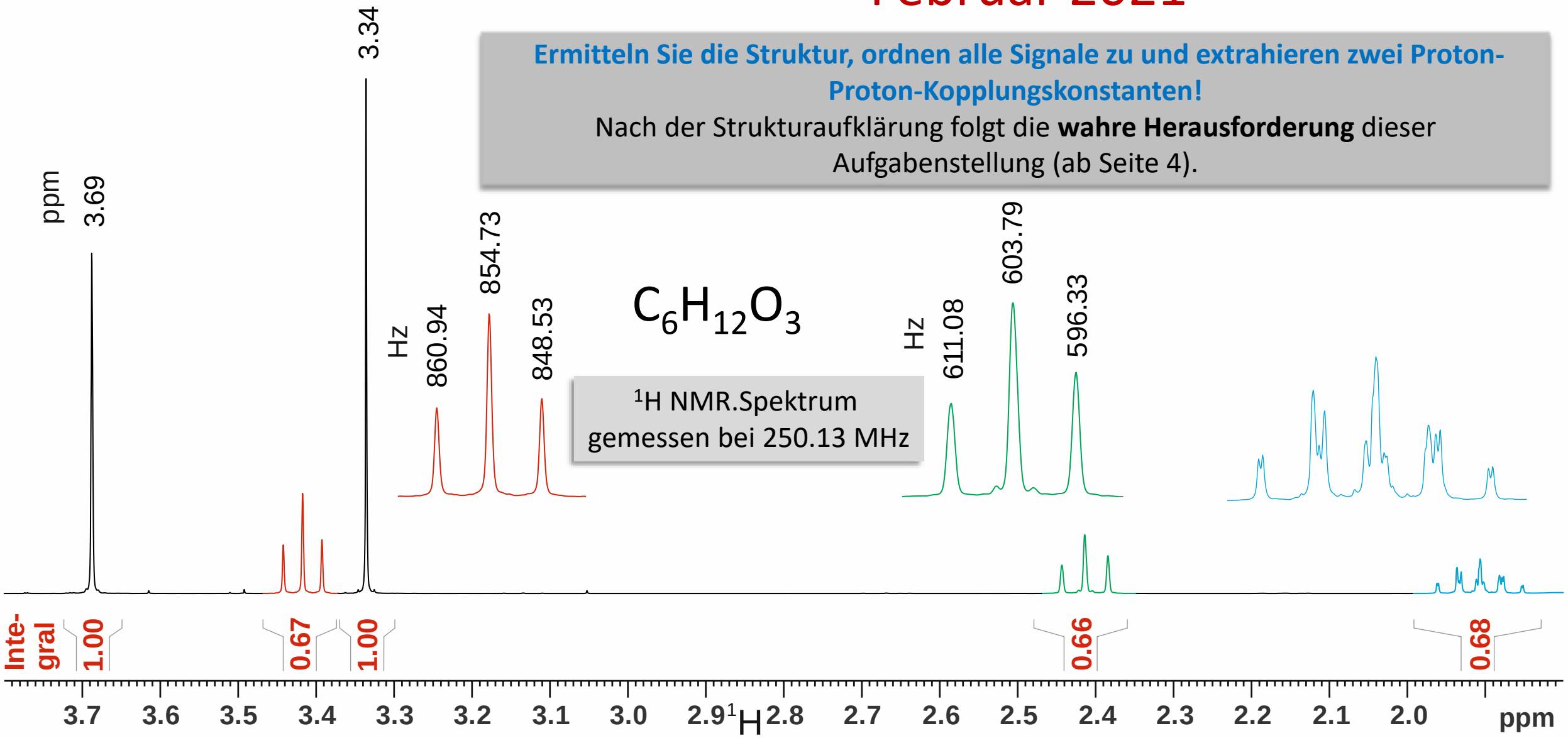


Herausforderung des Monats

Februar 2021

Ermitteln Sie die Struktur, ordnen alle Signale zu und extrahieren zwei Proton-Proton-Kopplungskonstanten!

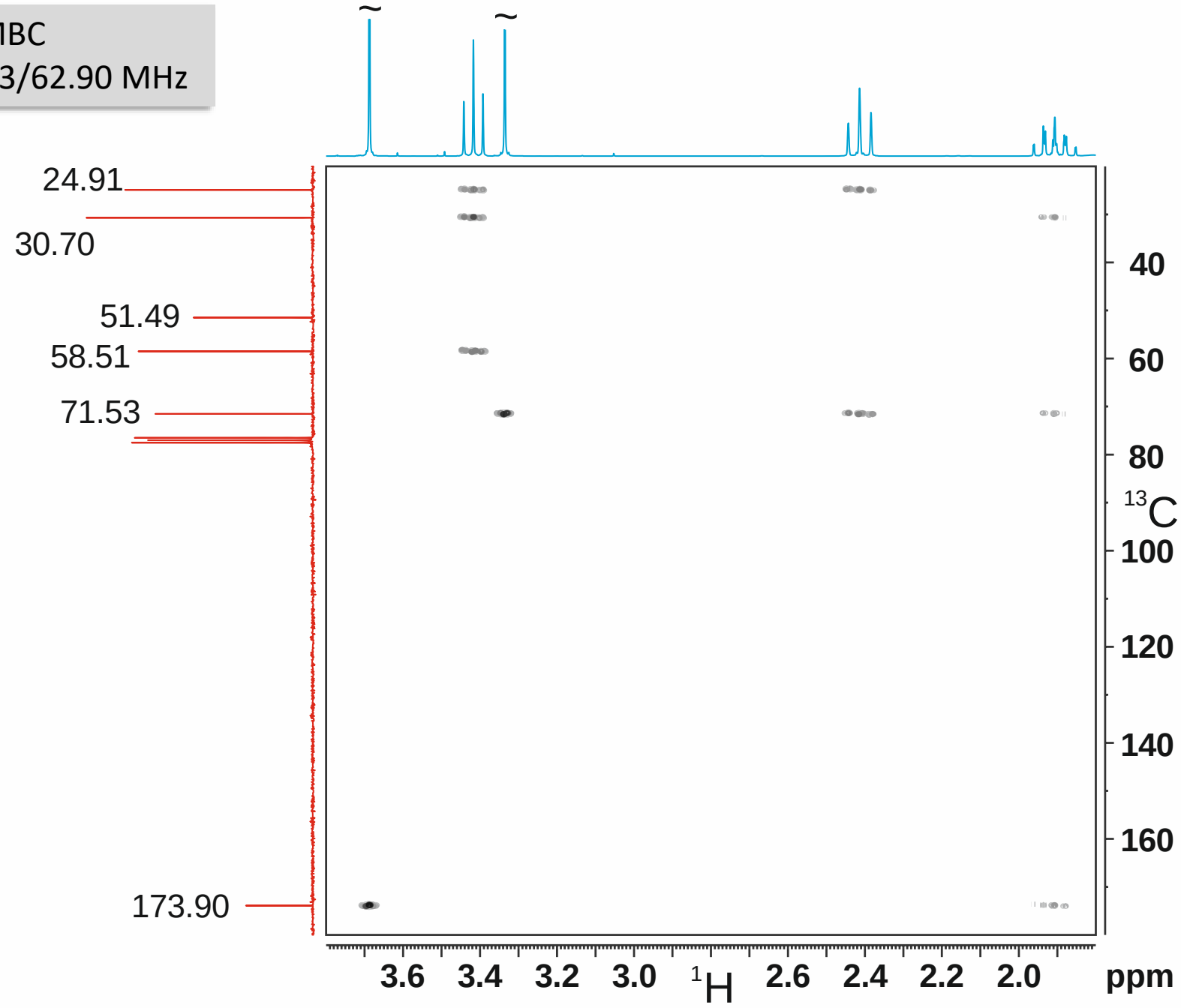
Nach der Strukturaufklärung folgt die **wahre Herausforderung** dieser Aufgabenstellung (ab Seite 4).



$C_6H_{12}O_3$

^{1}H NMR.Spektrum
gemessen bei 250.13 MHz

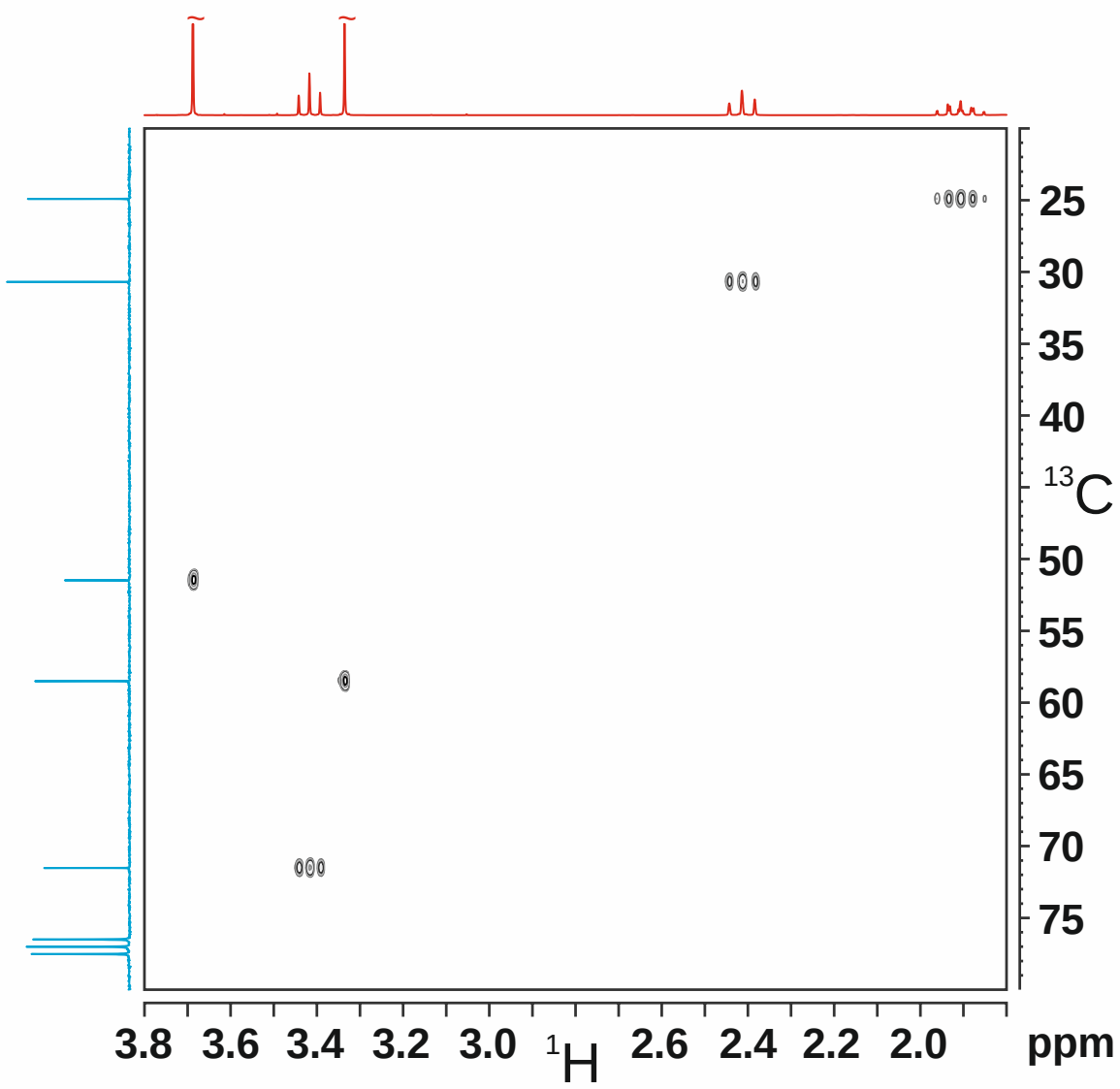
$^{1}H/^{13}C$-HMBC
gemessen bei 250.13/62.90 MHz



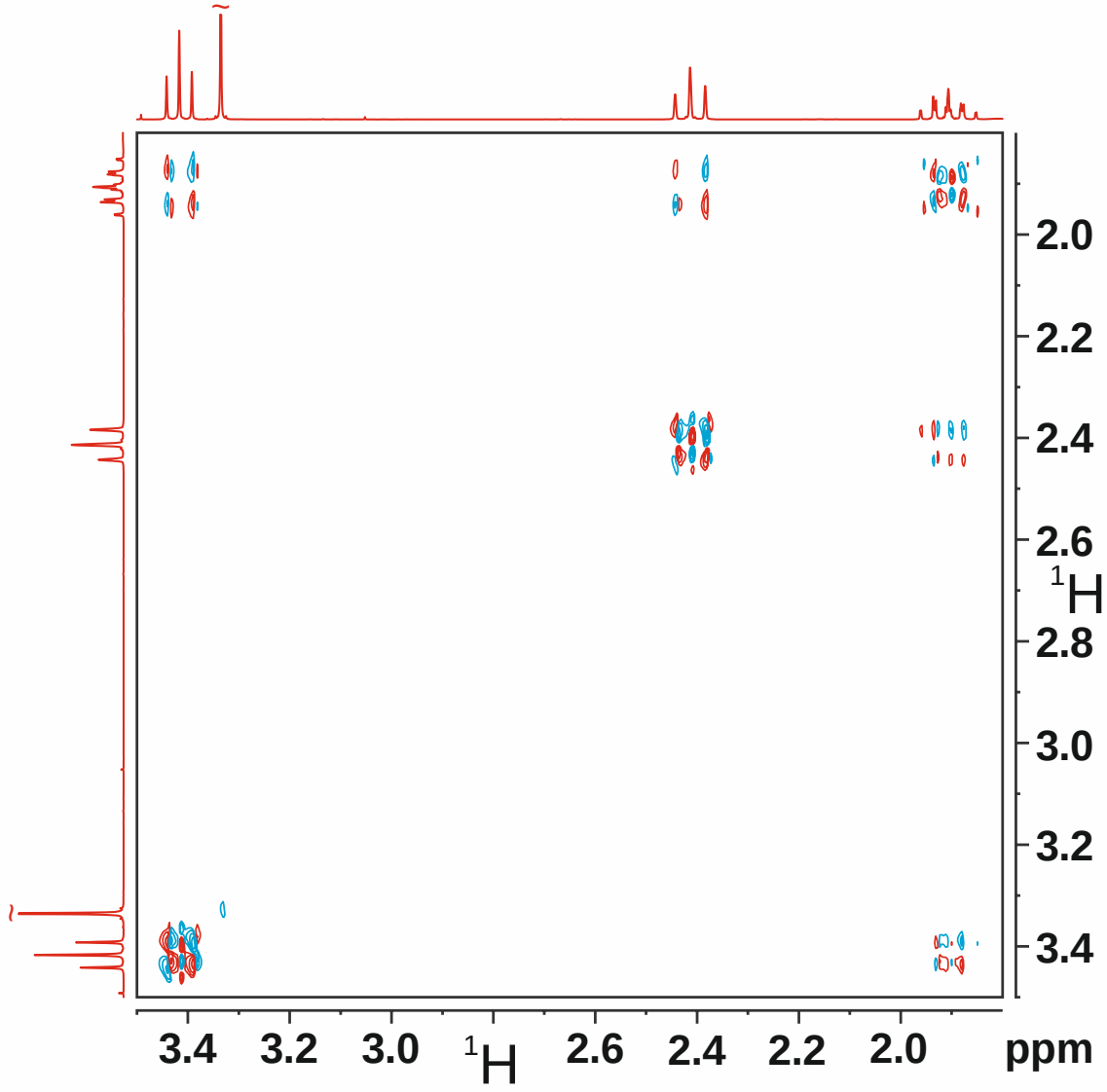
Die f_1-(Pseudo)projektion zeigt alle sechs Kohlenstoffsignale der Verbindung.

Ein separates eindimensionales Kohlenstoffspektrum wird nicht benötigt.

$^{1}H/^{13}C$-HSQC
gemessen bei 250.13/62.90 MHz



$^{1}H/^{1}H$-DQF-COSY
gemessen bei 250.13 MHz



Die unerwartete Herausforderung

Unter Verwendung von drei chemischen Verschiebungen und zwei Kopplungskonstanten kann man die drei Multipletts im Protonenspektrum simulieren. Bei ca. 3.4 ppm sind reales Spektrum und Simulation nahezu perfekt deckungsgleich, aber bei den beiden anderen Multipletts gibt es kleine, jedoch nicht zu vernachlässigende Abweichungen zwischen Simulation und Messung. Das gemessene Multiplett bei ca. 1.9 ppm sieht ein wenig komplexer aus als die Simulation.

Vor allem aber sollte man bei ca. 2.4 ppm ein sauberes Triplett erwarten.

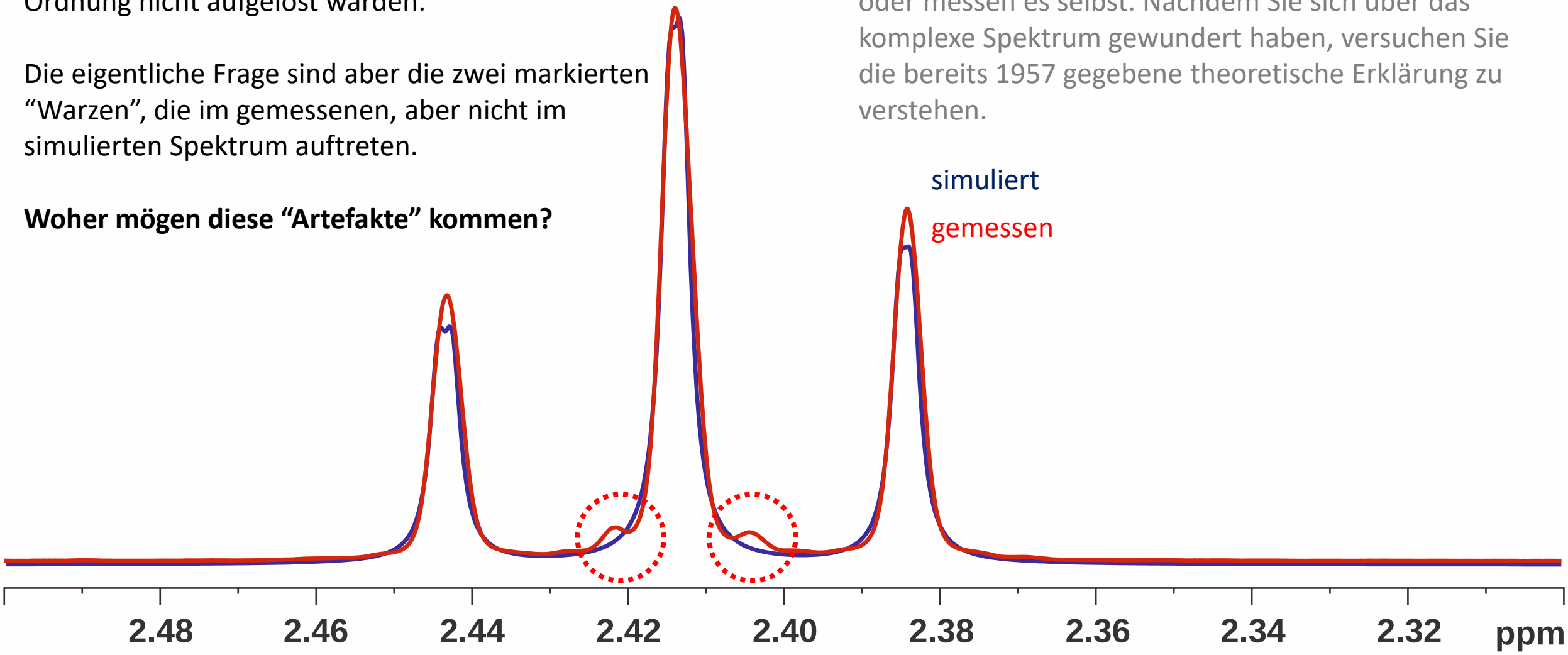
Die Feinaufspaltung resultiert aus der kleinen Differenz der chemischen Verschiebung zwischen 1.9 ppm und 2.4 ppm. Experimentell kann diese kleine Abweichung von einem Multiplett erster Ordnung nicht aufgelöst warden.

Die eigentliche Frage sind aber die zwei markierten “Warzen”, die im gemessenen, aber nicht im simulierten Spektrum auftreten.

Woher mögen diese “Artefakte” kommen?

Hinweis:

Zur Beantwortung dieser Frage suchen Sie bitte in der Literatur das Protonenspektrum von 1-Br-2-Cl-ethan oder messen es selbst. Nachdem Sie sich über das komplexe Spektrum gewundert haben, versuchen Sie die bereits 1957 gegebene theoretische Erklärung zu verstehen.

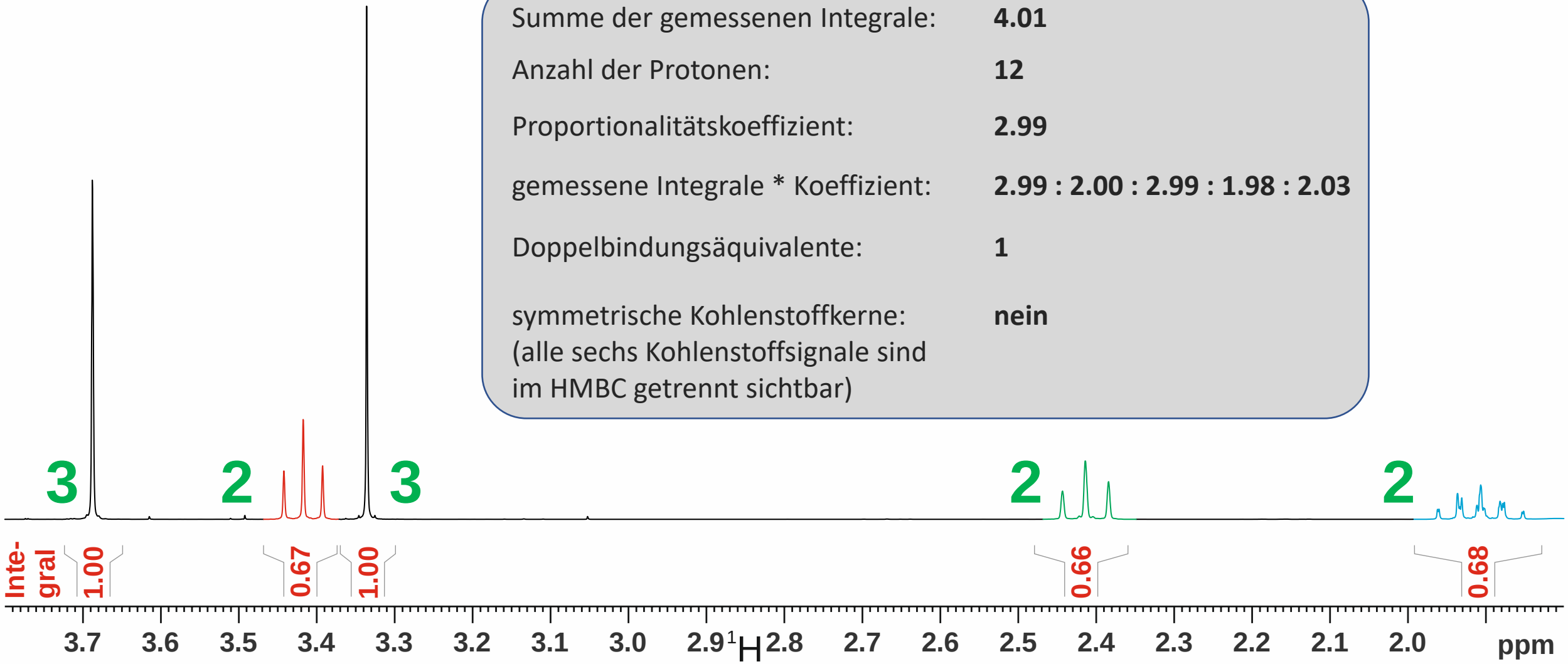


Basis

Integration, Doppelbindungs-
äquivalente, Symmetrie

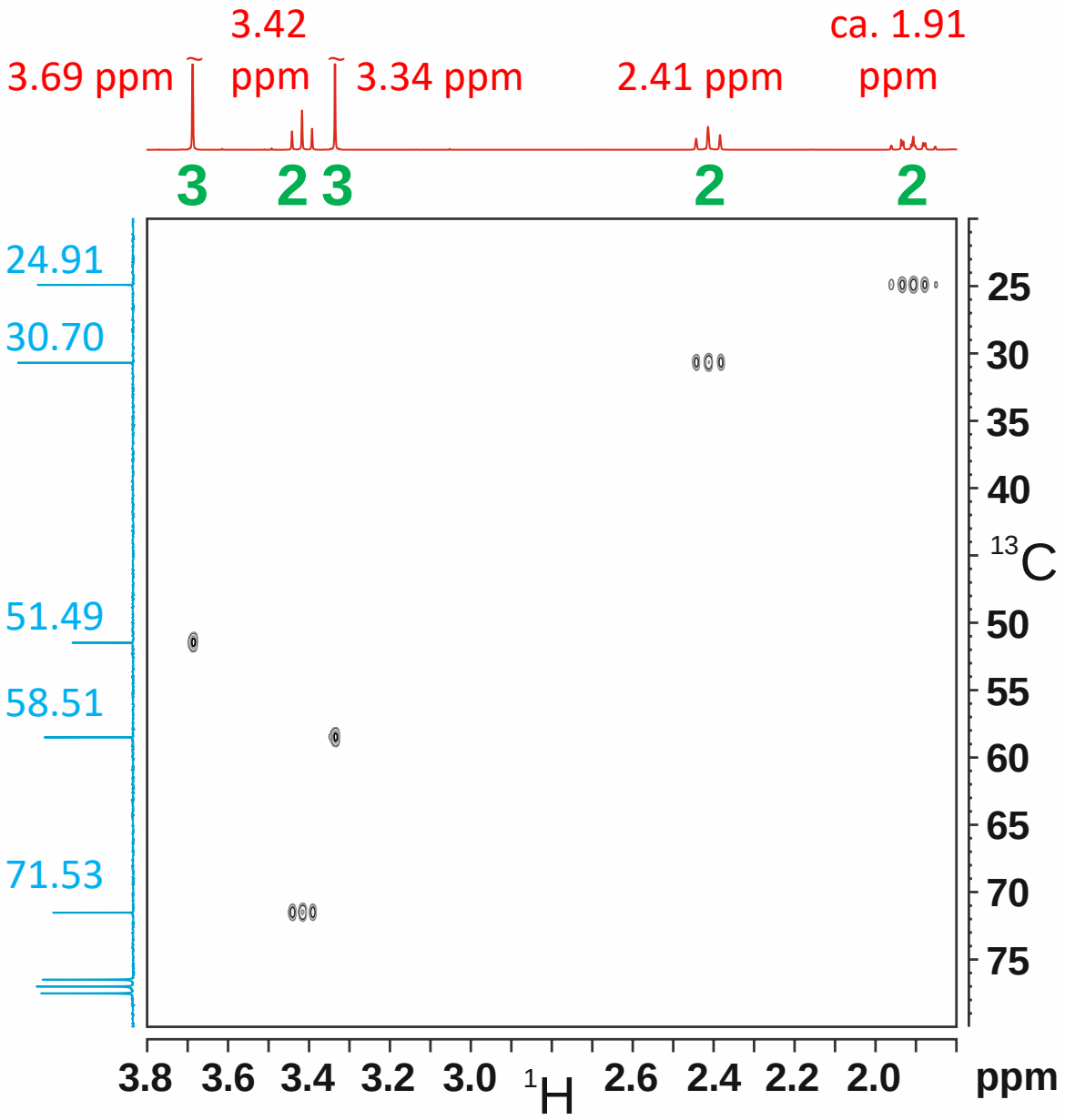
$C_6H_{12}O_3$

Summe der gemessenen Integrale:	**4.01**
Anzahl der Protonen:	**12**
Proportionalitätskoeffizient:	**2.99**
gemessene Integrale * Koeffizient:	**2.99 : 2.00 : 2.99 : 1.98 : 2.03**
Doppelbindungsäquivalente:	**1**
symmetrische Kohlenstoffkerne: (alle sechs Kohlenstoffsignale sind im HMBC getrennt sichtbar)	**nein**



Bausteine

CH_n-Fragmente



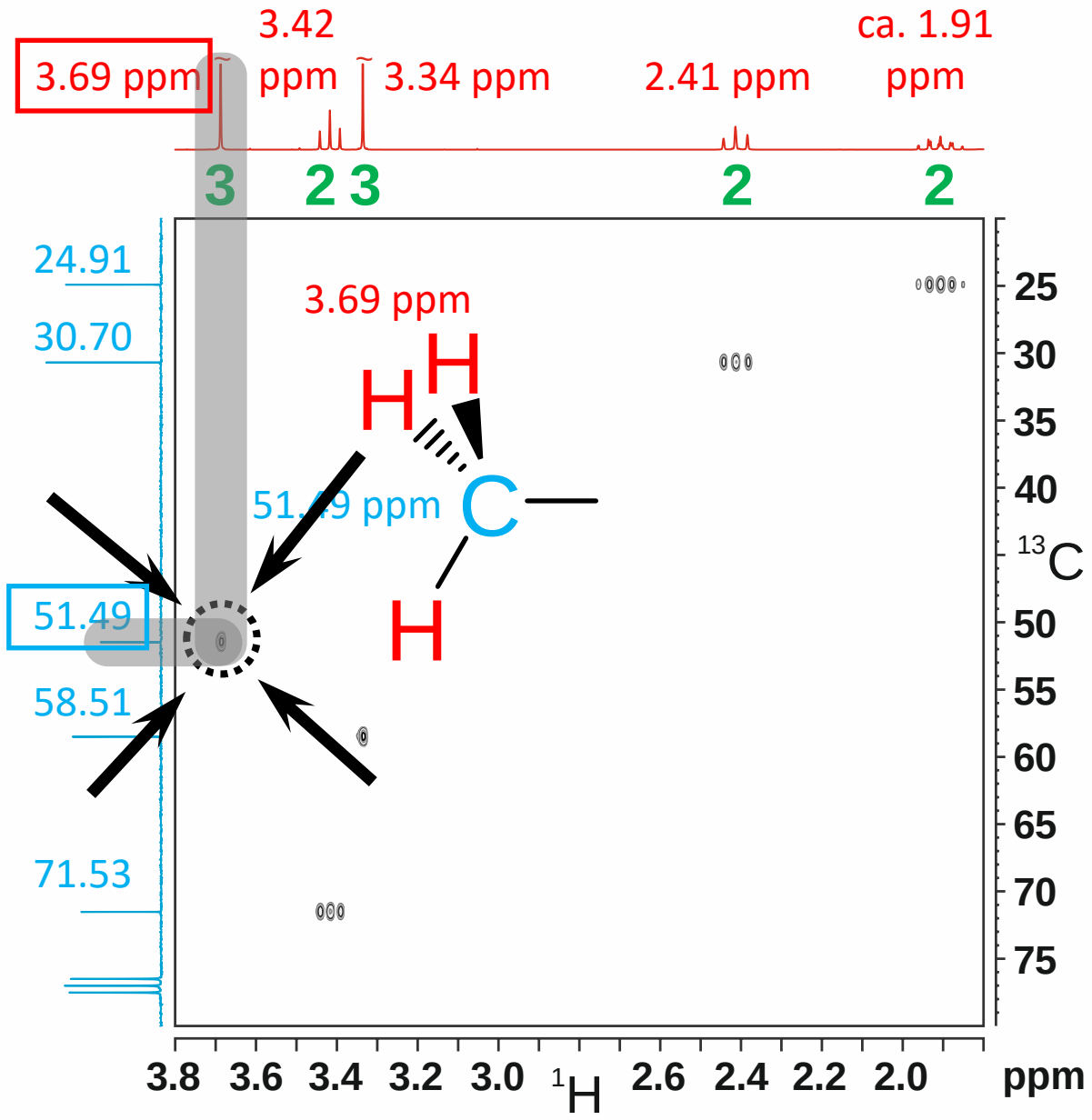
HSQCs sind sehr leicht auszuwerten. Natürlich ist die Empfindlichkeit kleiner als die eines eindimensionalen Protonenspektrums, aber andererseits höher als die eines eindimensionalen Kohlenstoffspektrums. Es ist immer zu empfehlen, ein HSQC zu messen, wenn sich die Gelegenheit dazu bietet.

Die ^{1}H-(Pseudo)projektion ergänzen wir um die Integrale und die chemischen Verschiebungen aus dem eindimensionalen Protonenspektrum. Für die ^{13}C-(Pseudo)projektion entnehmen wir die chemischen Verschiebungen dem eindimensionalen Kohlenstoffspektrum.

(Das eindimensionale Kohlenstoffspektrum erscheint nirgendwo als separates Spektrum, sondern nur als Pseudoprojektion für HSQC und HMBC verwendet.)

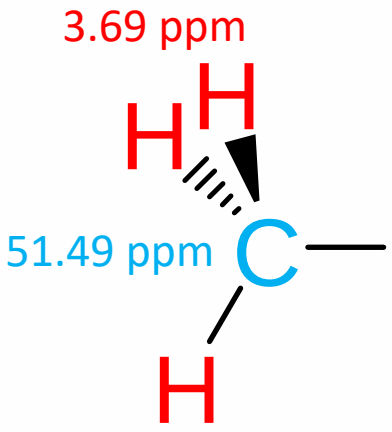
Bausteine

CH_n-Fragmente



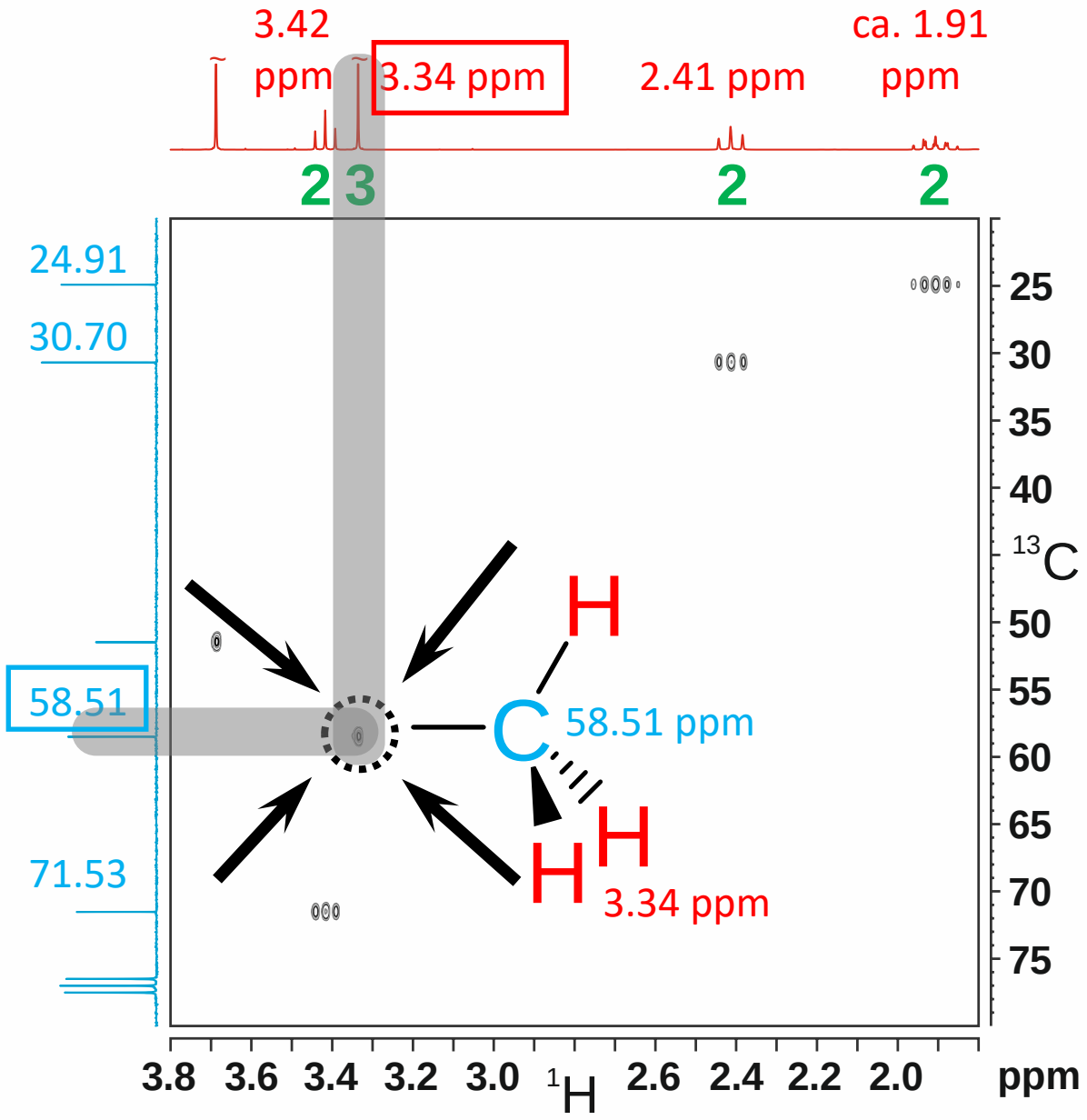
Die Protonensignale bei 3.69 ppm und 3.34 ppm können wegen ihres Integrals nur zu Methylgruppen gehören. Je drei symmetrische CH-Gruppen können wegen fehlender Symmetrie (Folie 1) ausgeschlossen werden.

Bitte fortsetzen zur zweiten Methylgruppe …



Bausteine

CH_n-Fragmente



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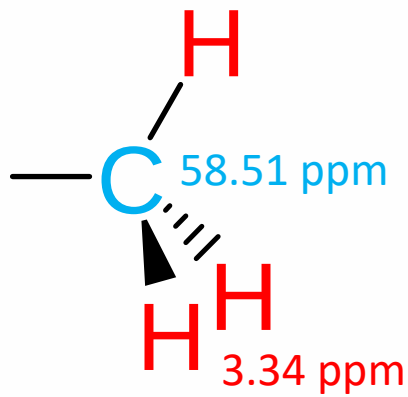
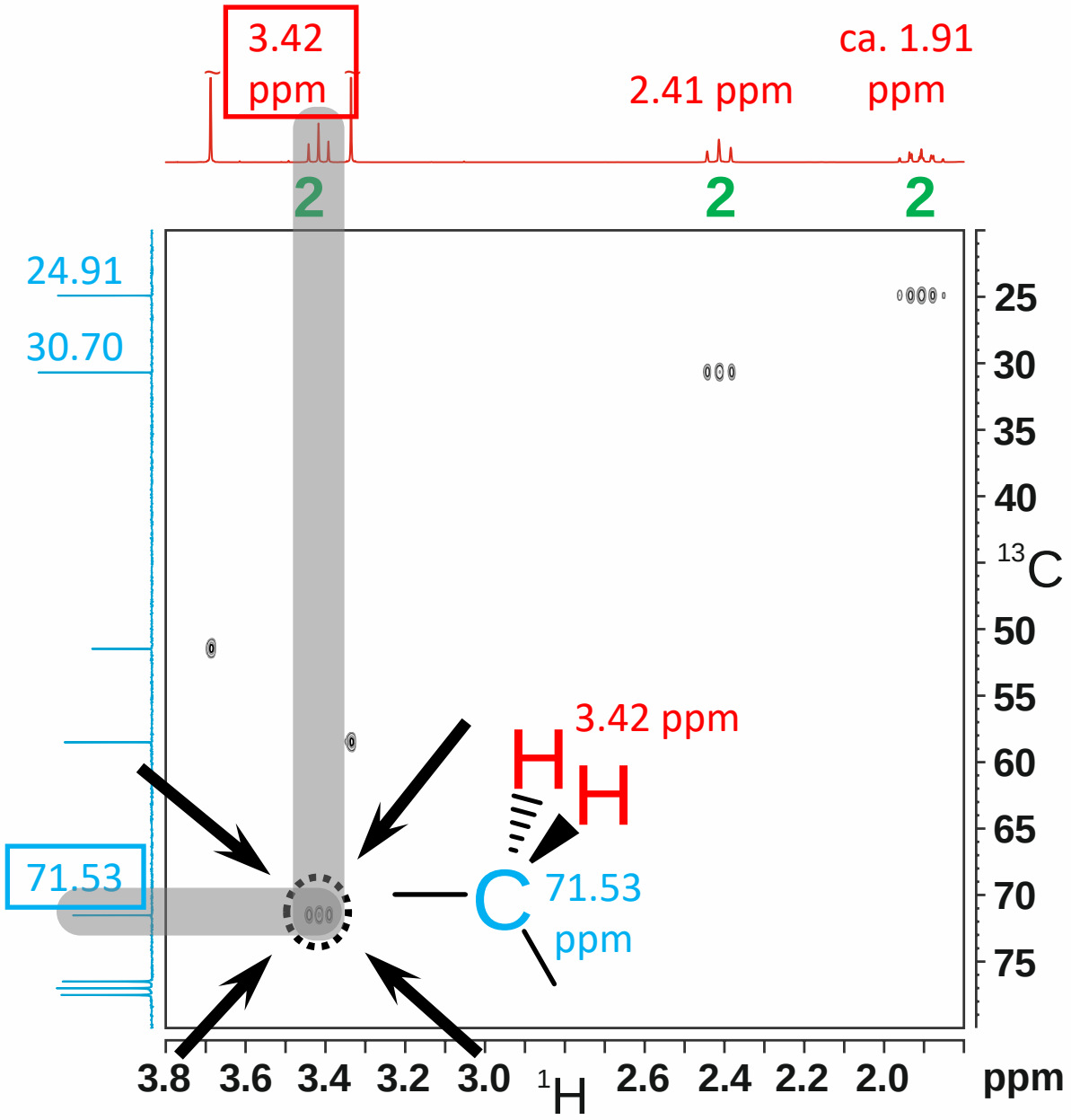
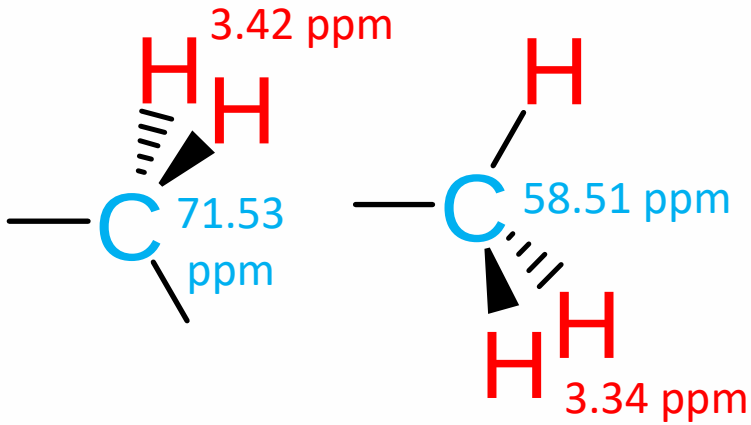


Bausteine

CH_n-Fragmente

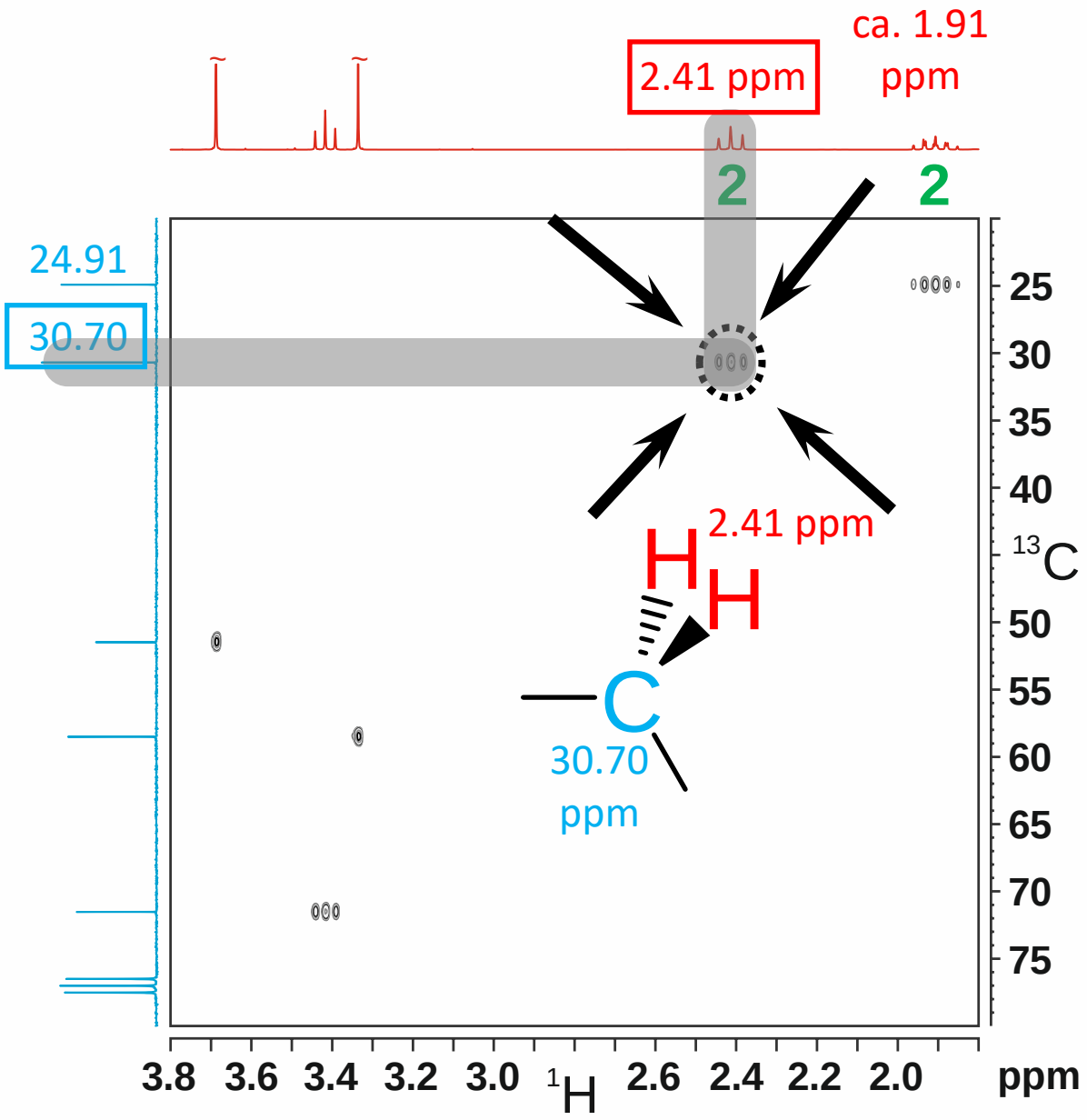


Die verbleibenden Kreuzpeaks gehören zu Methylengruppen. Extrahieren wir sie einen nach dem anderen.



Bausteine

CH_n-Fragmente



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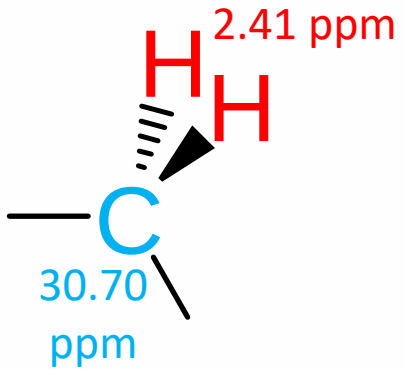

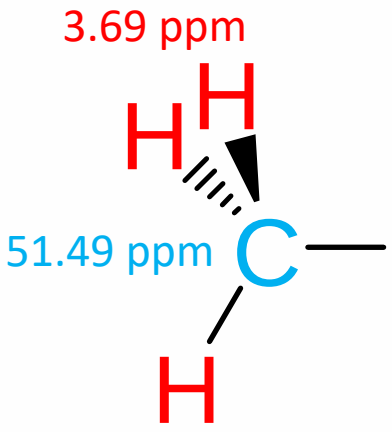

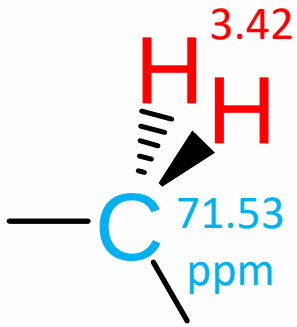

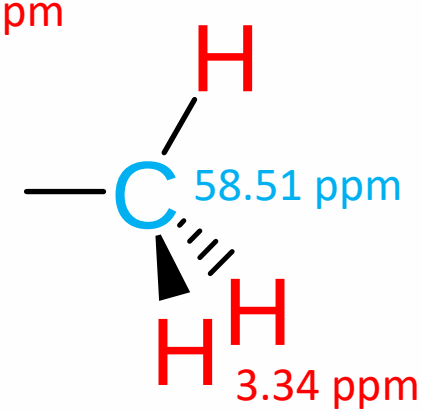

Bausteine

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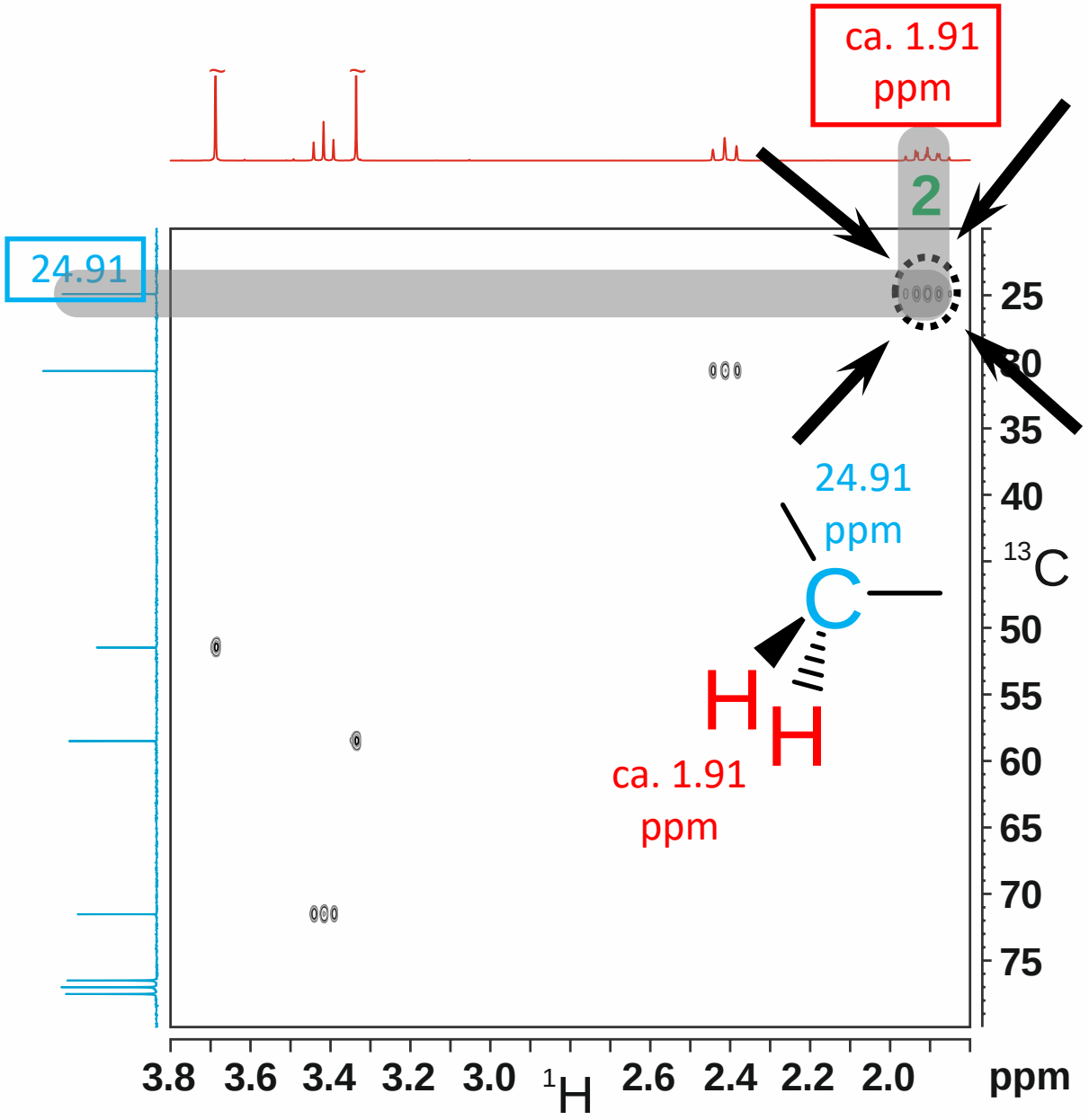

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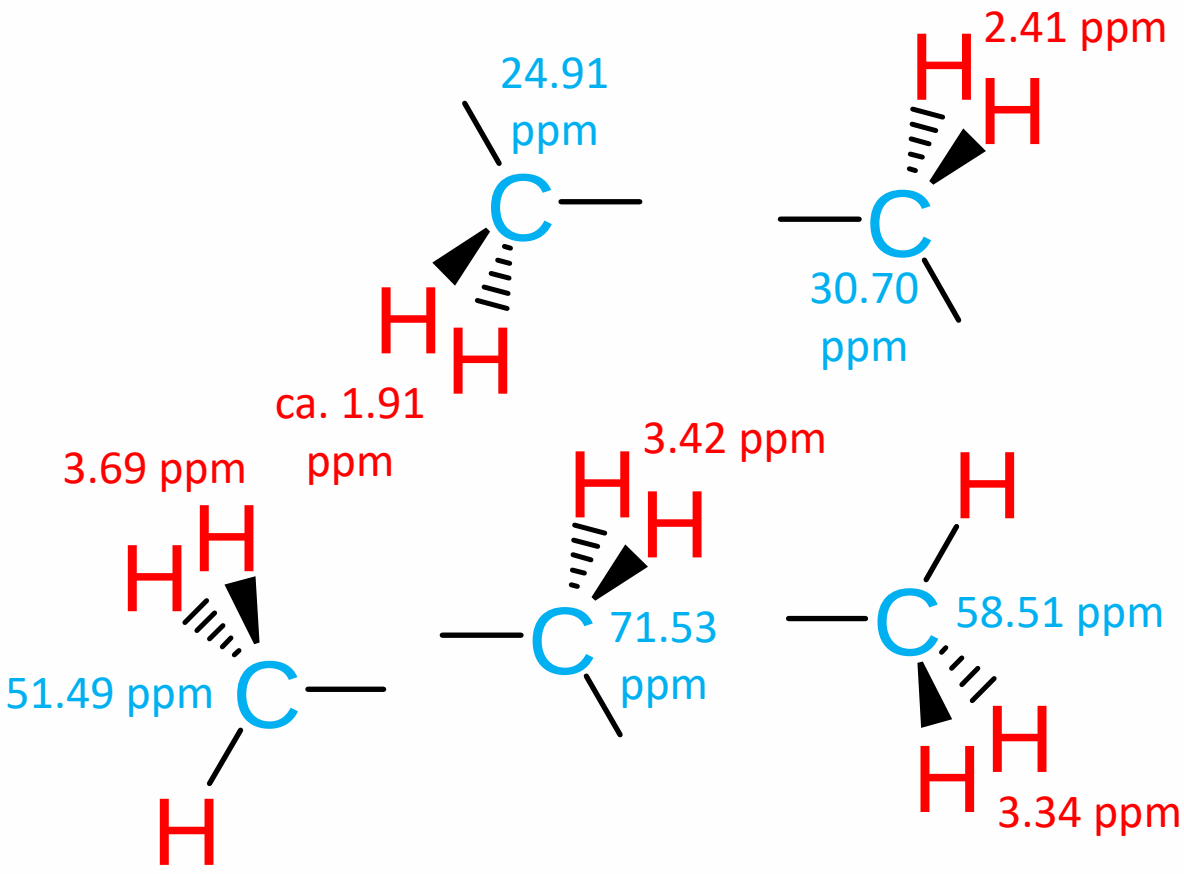
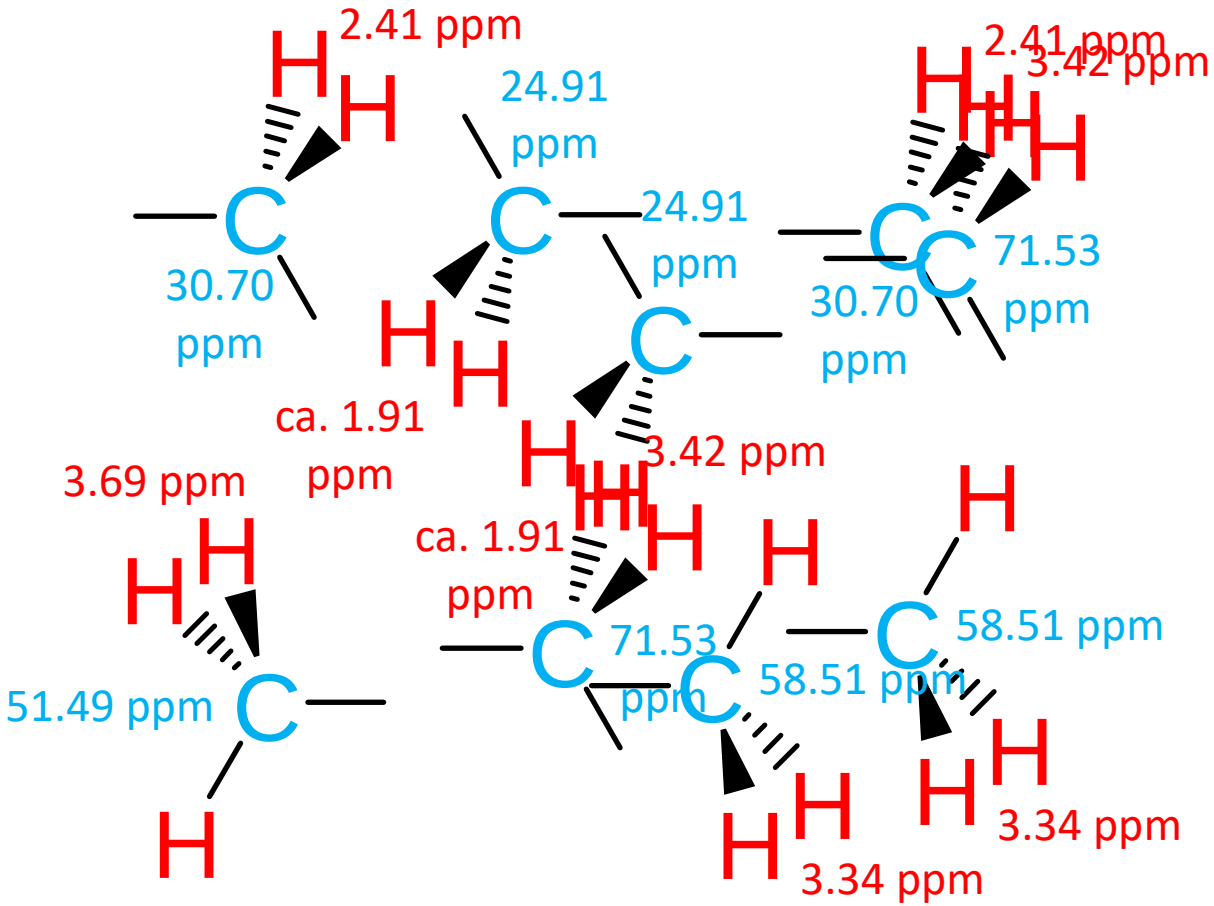


Verknüpfung der Bausteine

Teil 1 – Alkylkette

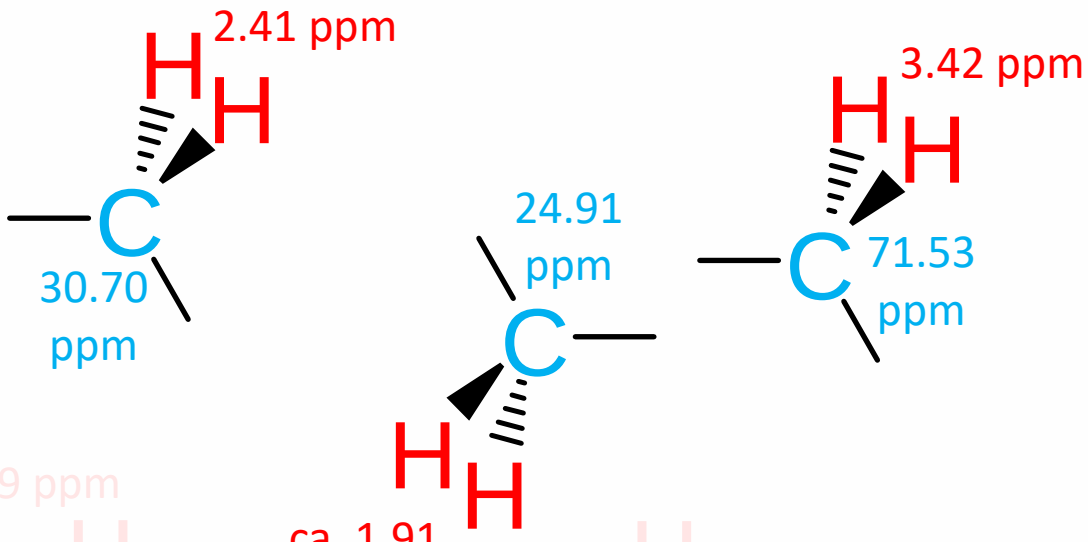
Beginnen wir damit, die Fragmente ein wenig umzuordnen. Dies erleichtert die nächsten Schritte.

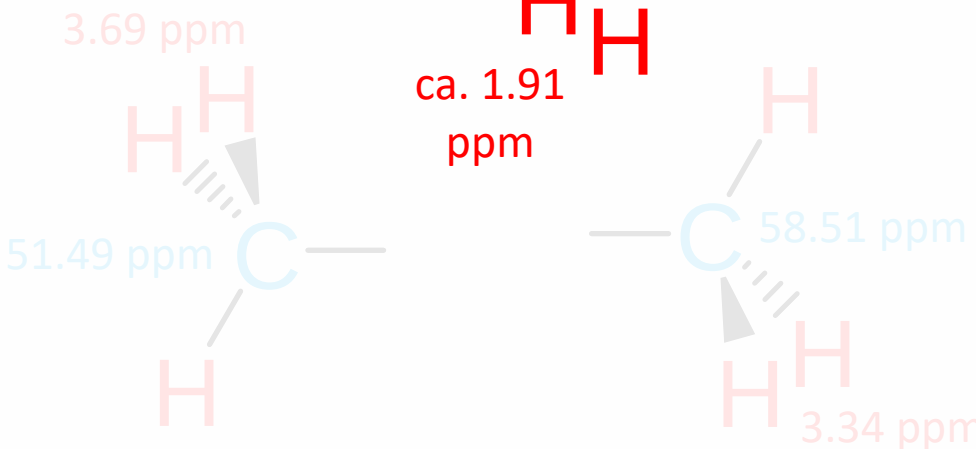


Verknüpfung der Bausteine

Teil 1 – Alkylkette

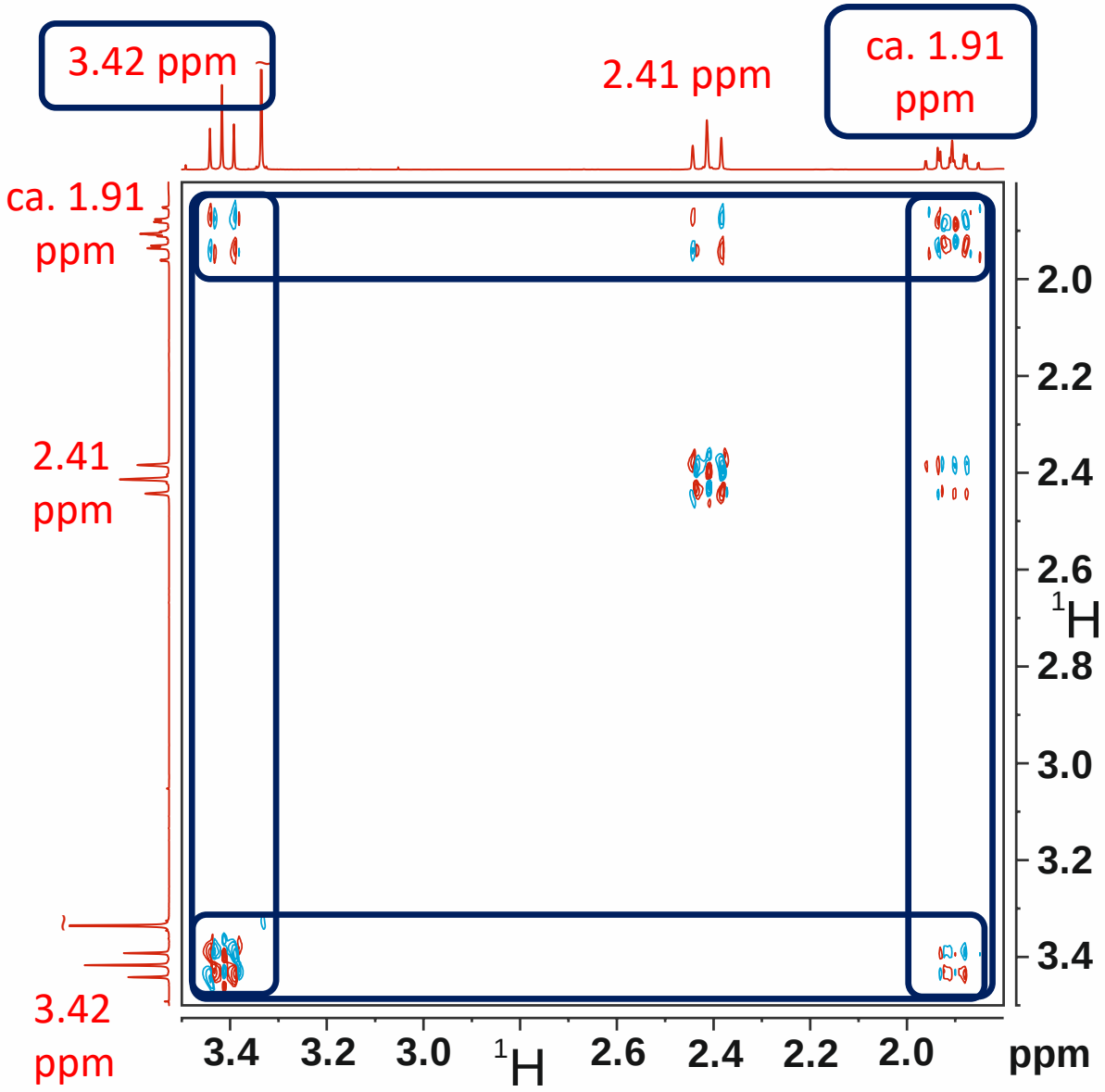
Aus dem COSY können wir keine Aussagen über die Verknüpfung der Methylgruppen ableiten.



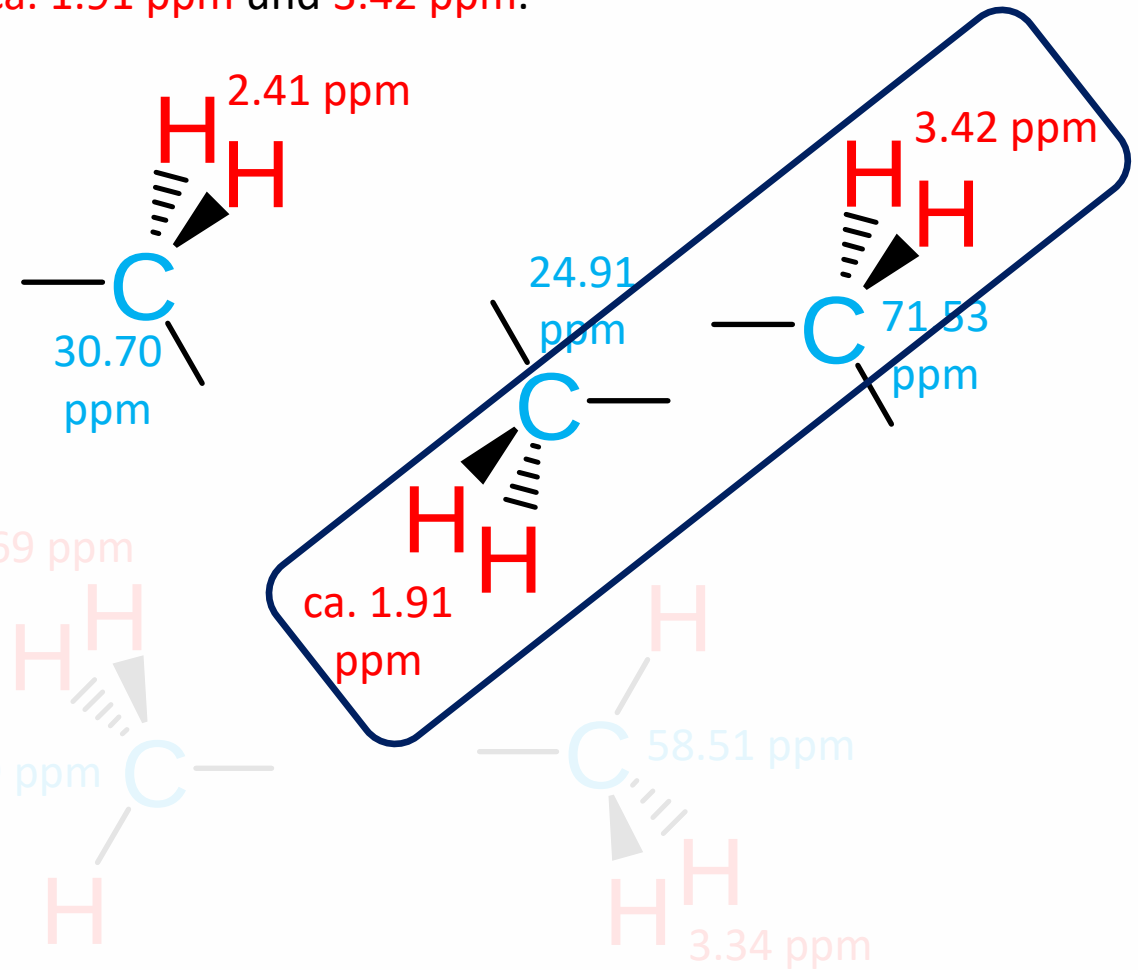


Verknüpfung der Bausteine

Teil 1 – Alkylkette

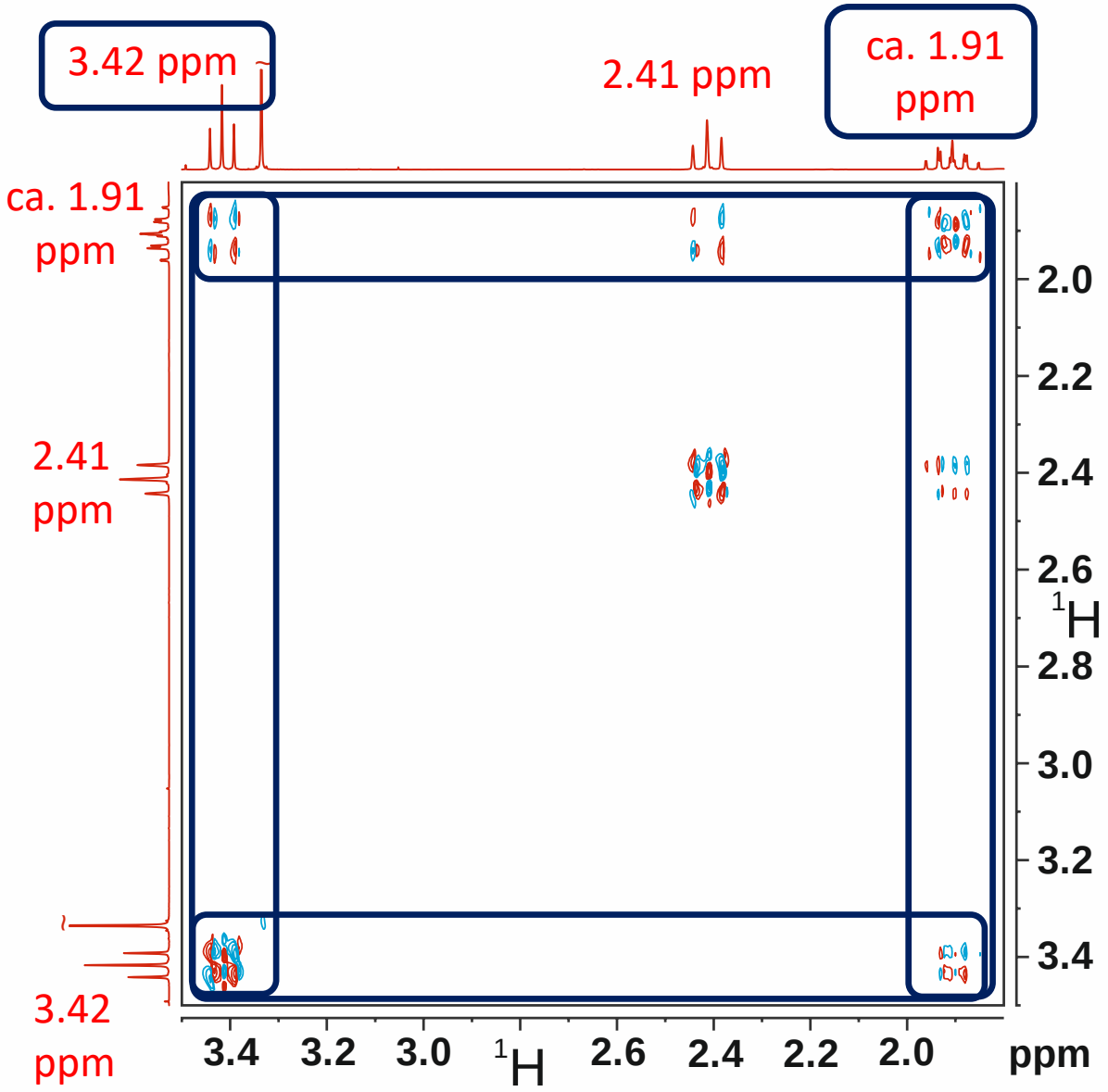


Eine erste Nachbarschaft beobachtet man im COSY für die Protonen mit den chemischen Verschiebungen von ca. 1.91 ppm und 3.42 ppm.



Verknüpfung der Bausteine

Teil 1 – Alkylkette



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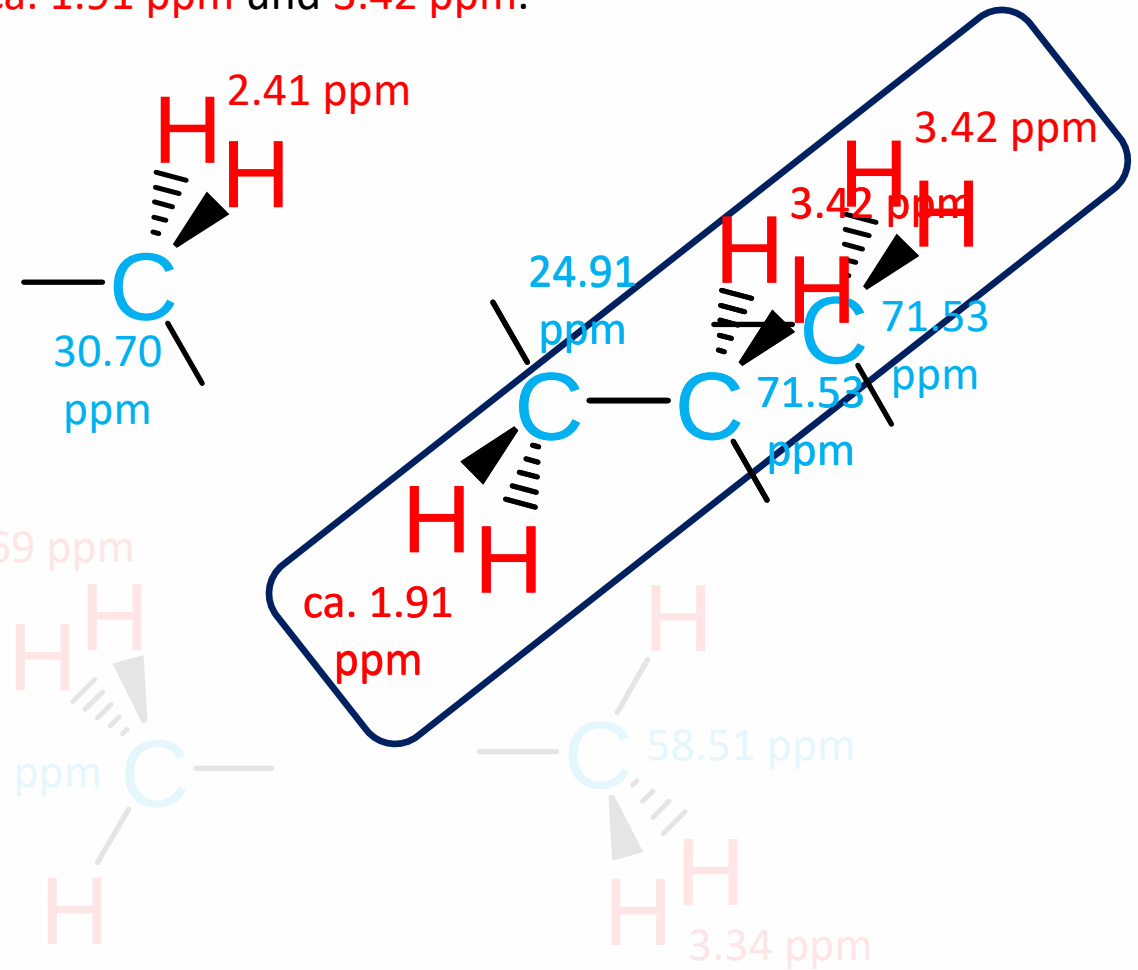
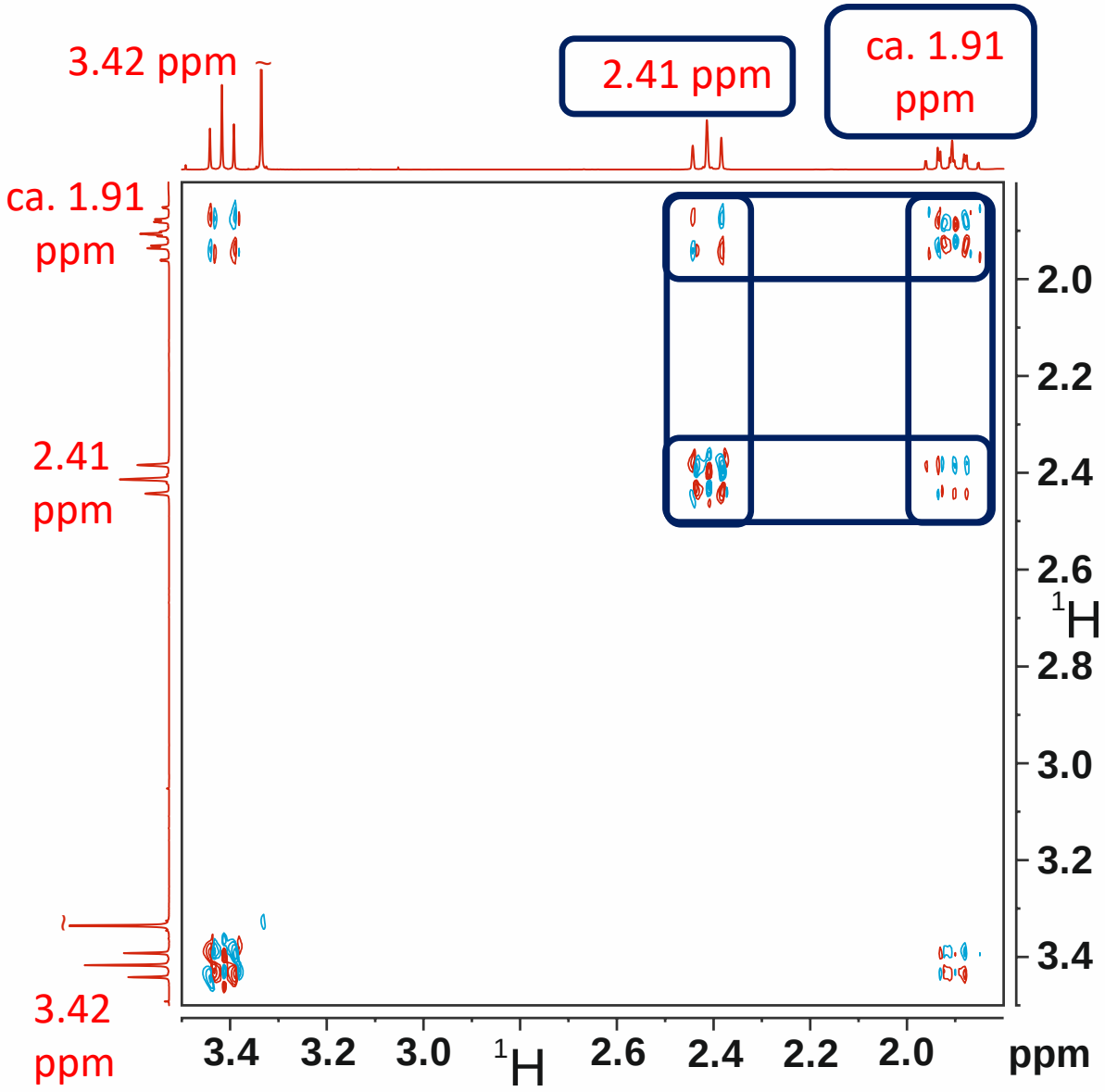
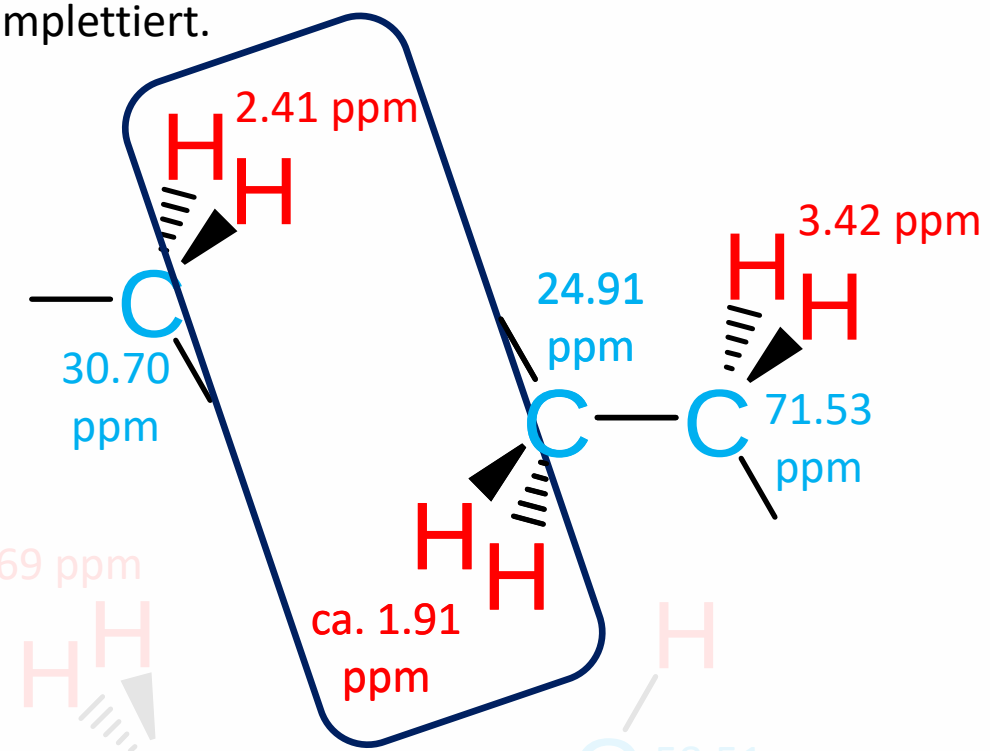


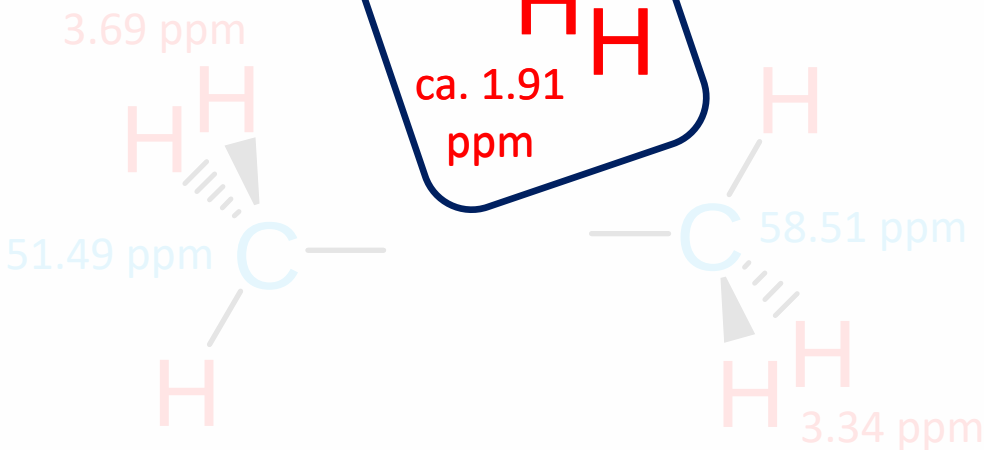
Verknüpfung der Bausteine

Teil 1 – Alkylkette

Gemäß den COSY-Kreuzpeaks sind die Protonen mit den chemischen Verschiebungen von ca. 1.91 ppm und 2.41 ppm ebenfalls benachbart. Das Alkylfragment wird damit komplettiert.







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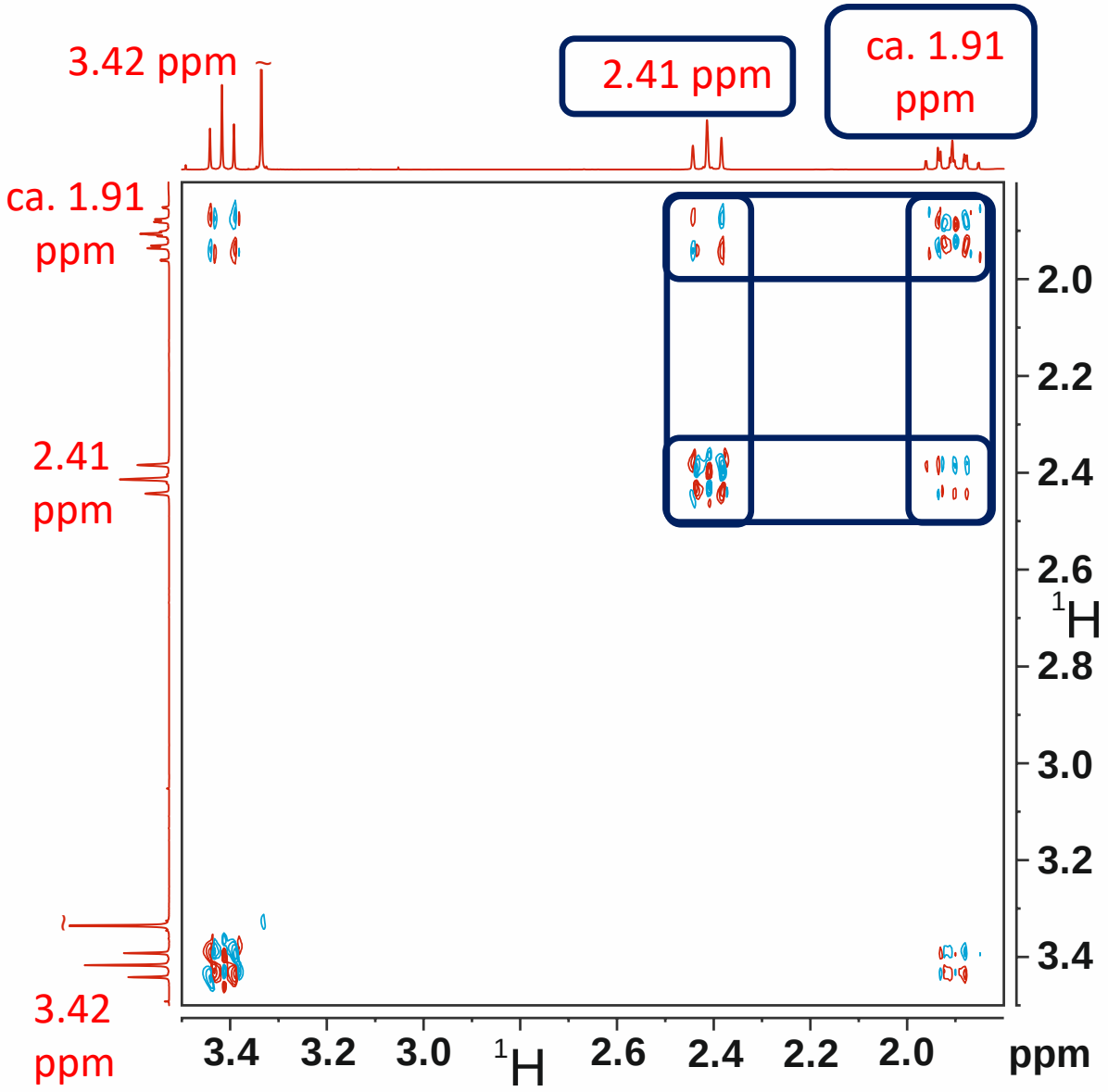
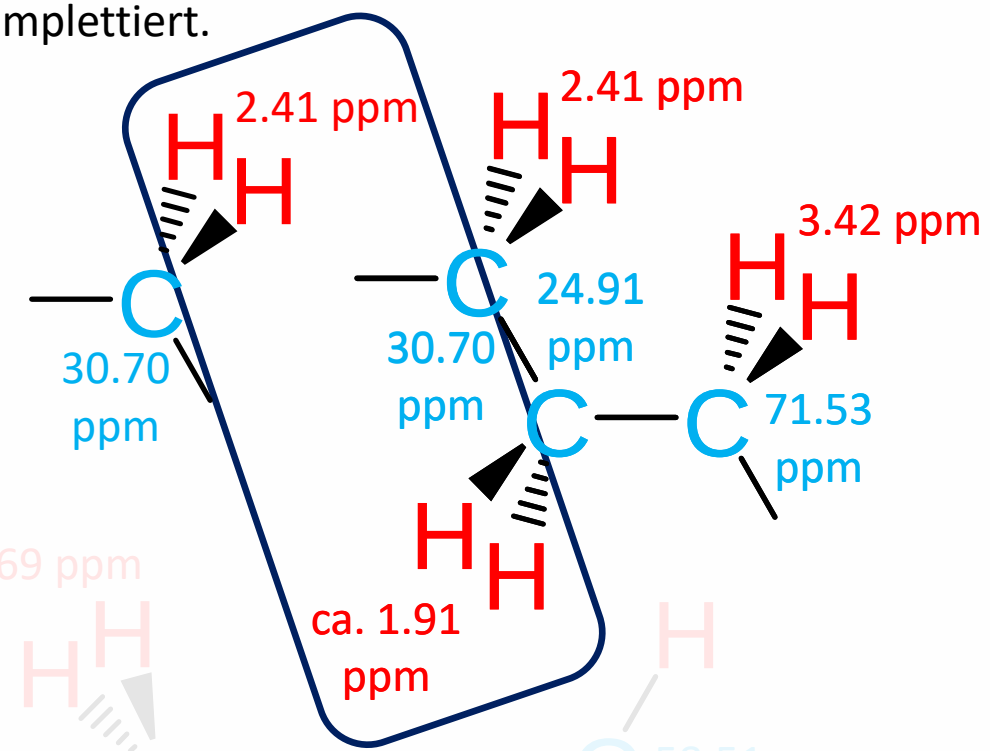


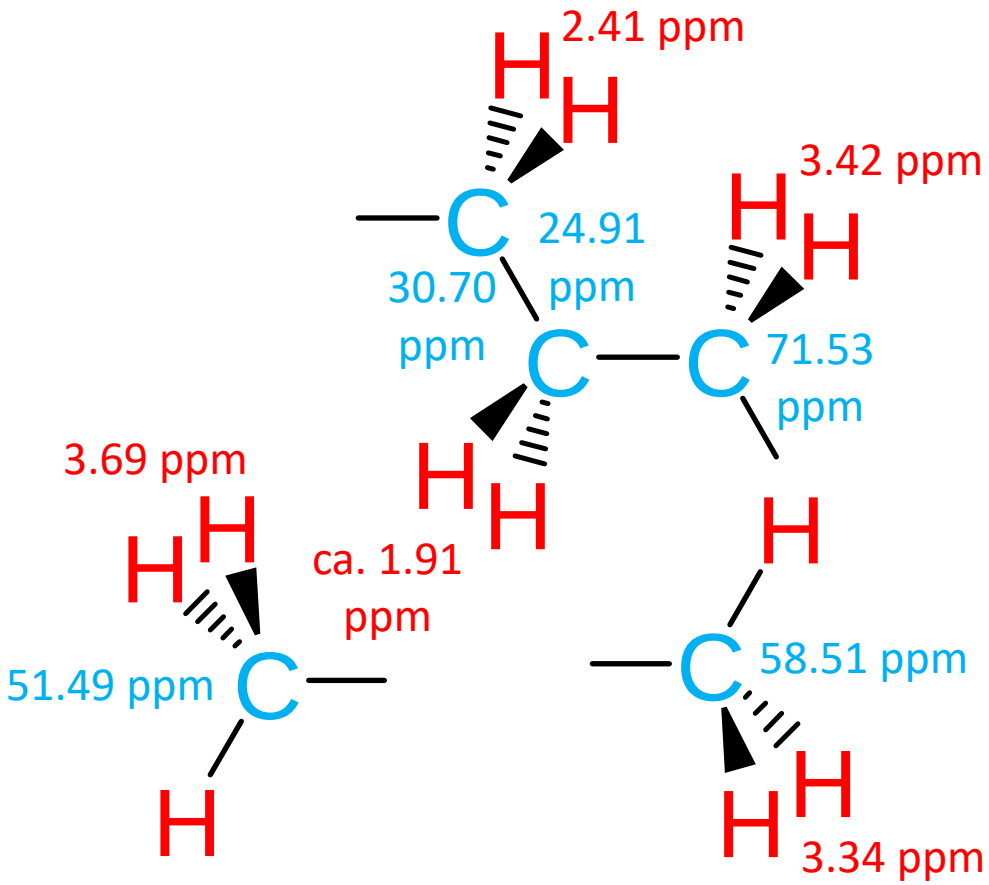


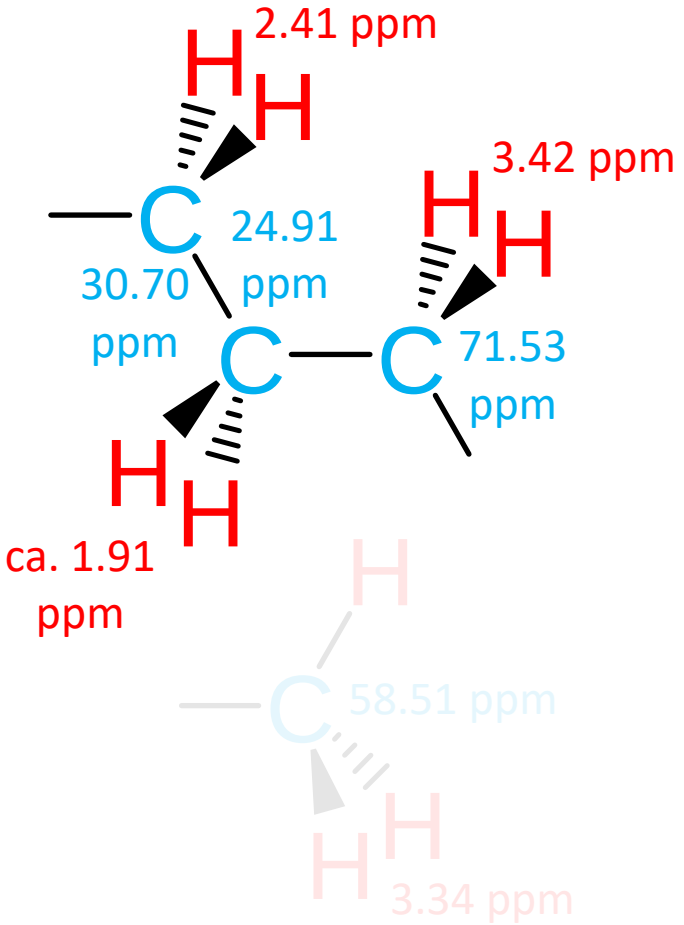
Was fehlt?

Eine kurze Bestandsaufnahme

Das COSY hilft jetzt nicht mehr weiter.

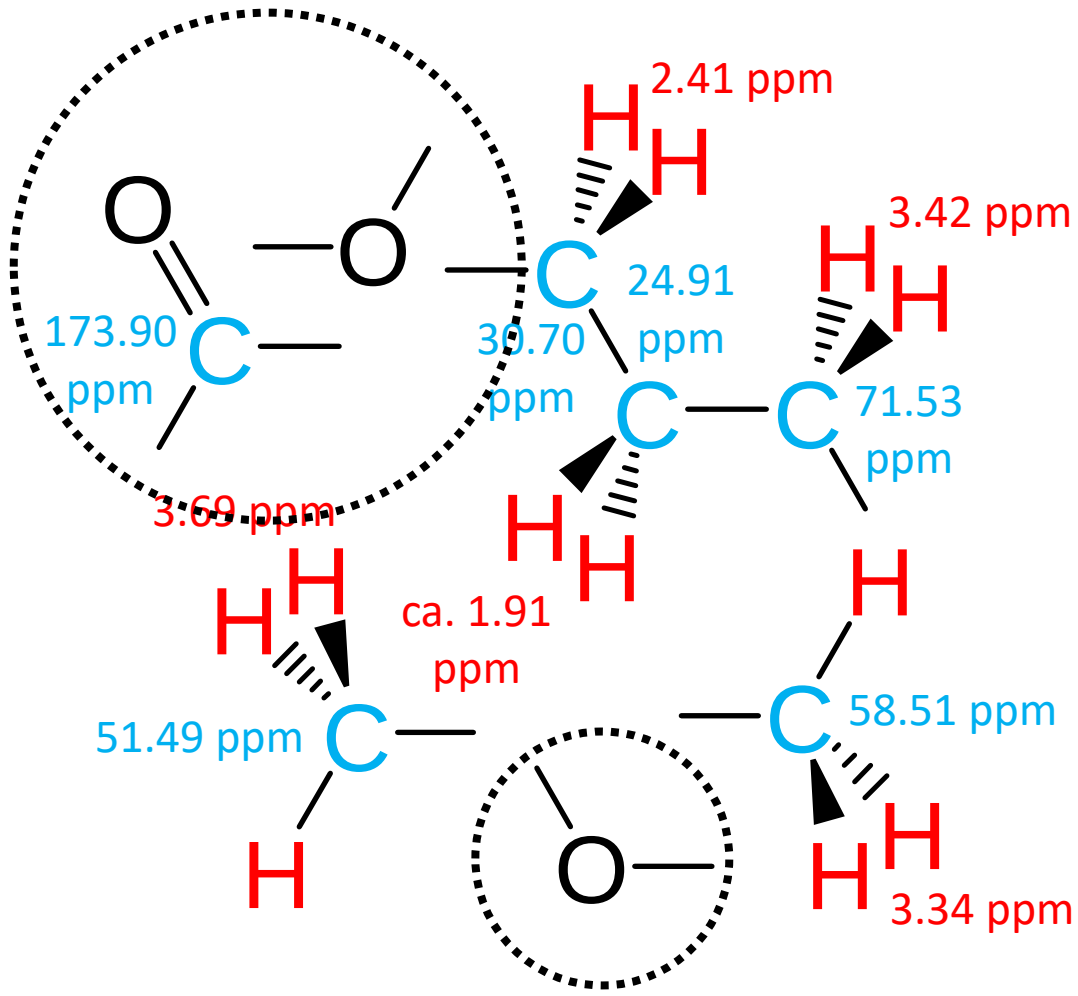
Ordnen wir die bisherigen Fragmente unter Verwendung der temporär verborgenen Methylgruppen ein wenig um.





Was fehlt?

Eine kurze Bestandsaufnahme



Summenformel	$C_6H_{12}O_3$
Bisher bekannte Bausteine	C_5H_{12}
Nicht zugeordnetes quartäres C-Atom	173.9 ppm
es fehlen …	CO_3 ein Doppel-bindungs-äquivalent

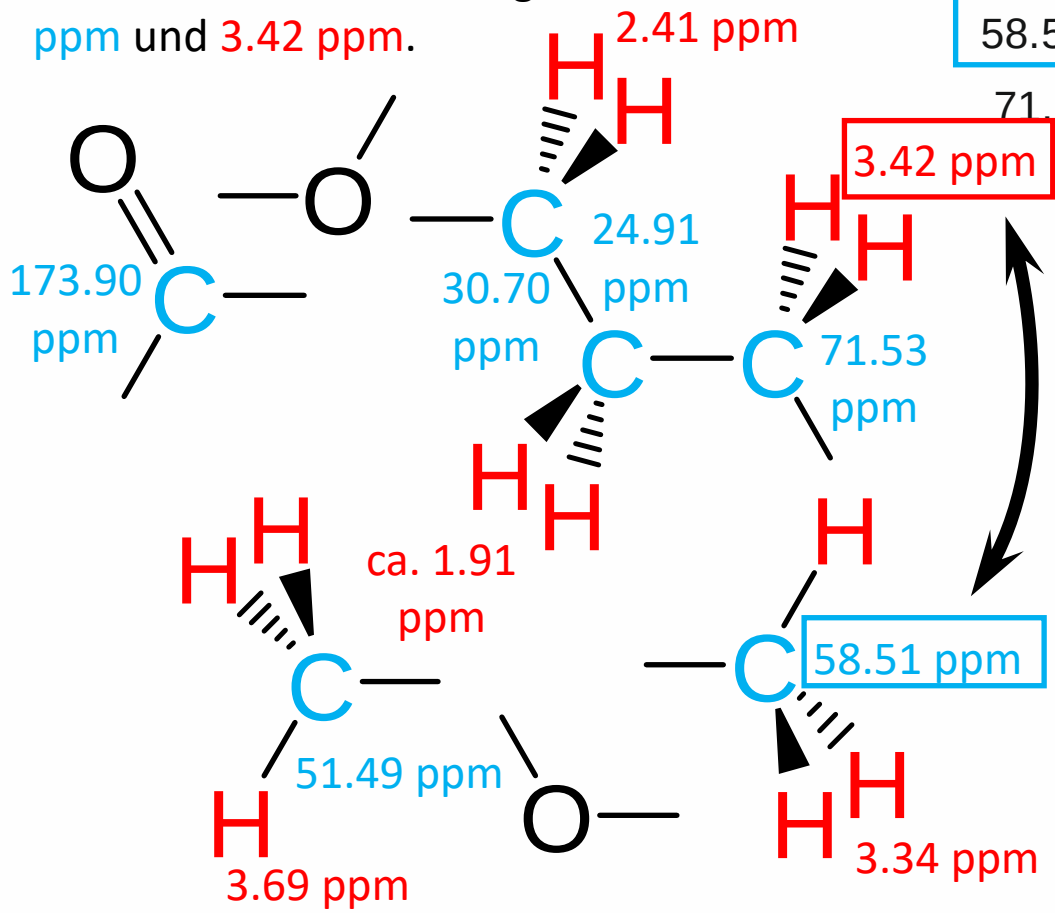
Aus den fehlenden Komponenten resultieren drei Fragmente, um die wir die ungeordnete Liste an Bausteinen ergänzen können.

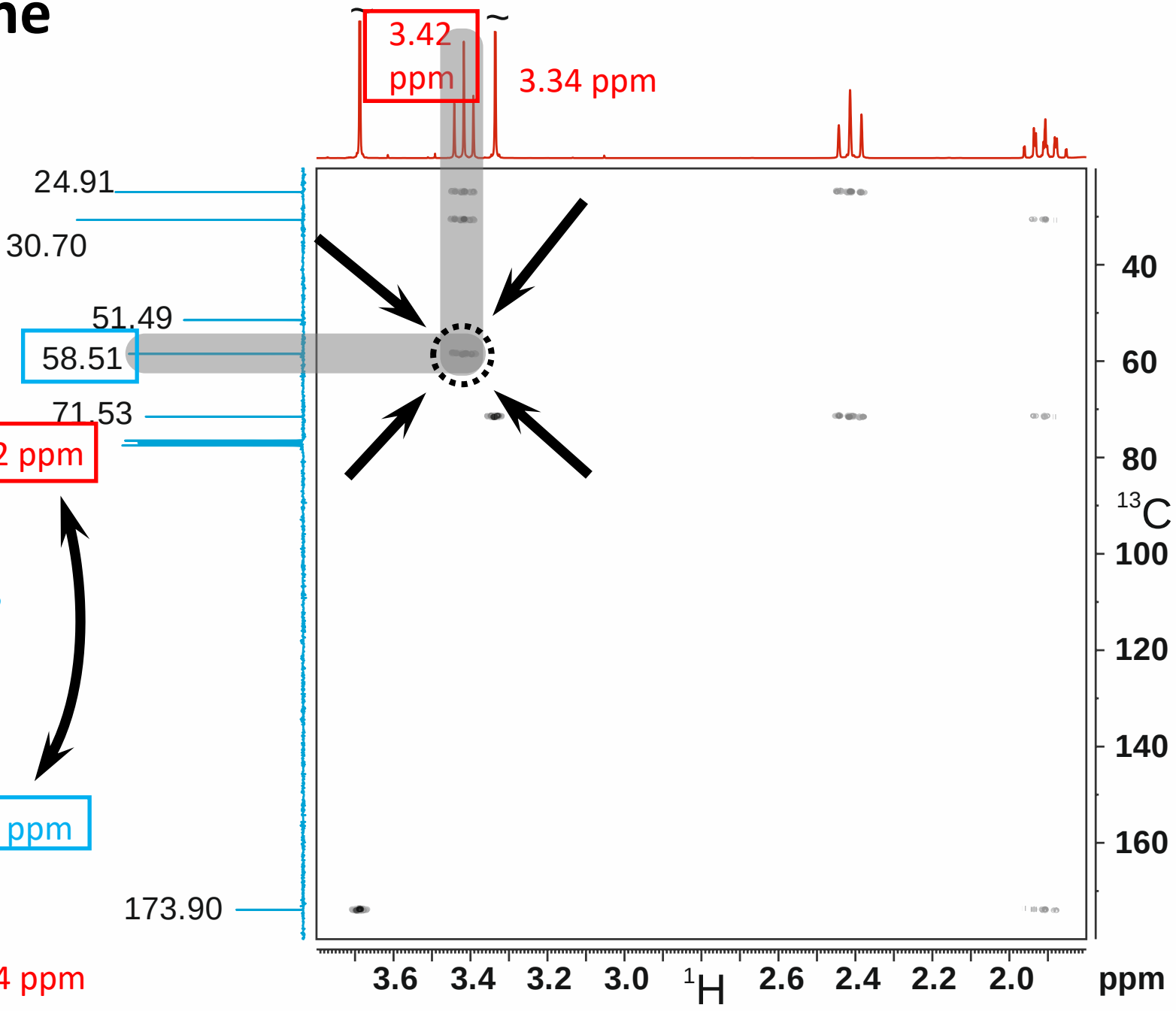
Verknüpfung der Bausteine

Das finale Puzzle

Zwei HMBC-Kreuzpeaks beinhalten sehr ähnliche Informationen.

Die erste Nachbarschaft beobachtet man zwischen den Signalen mit den chemischen verschiebungen von 58.51 ppm und 3.42 ppm.

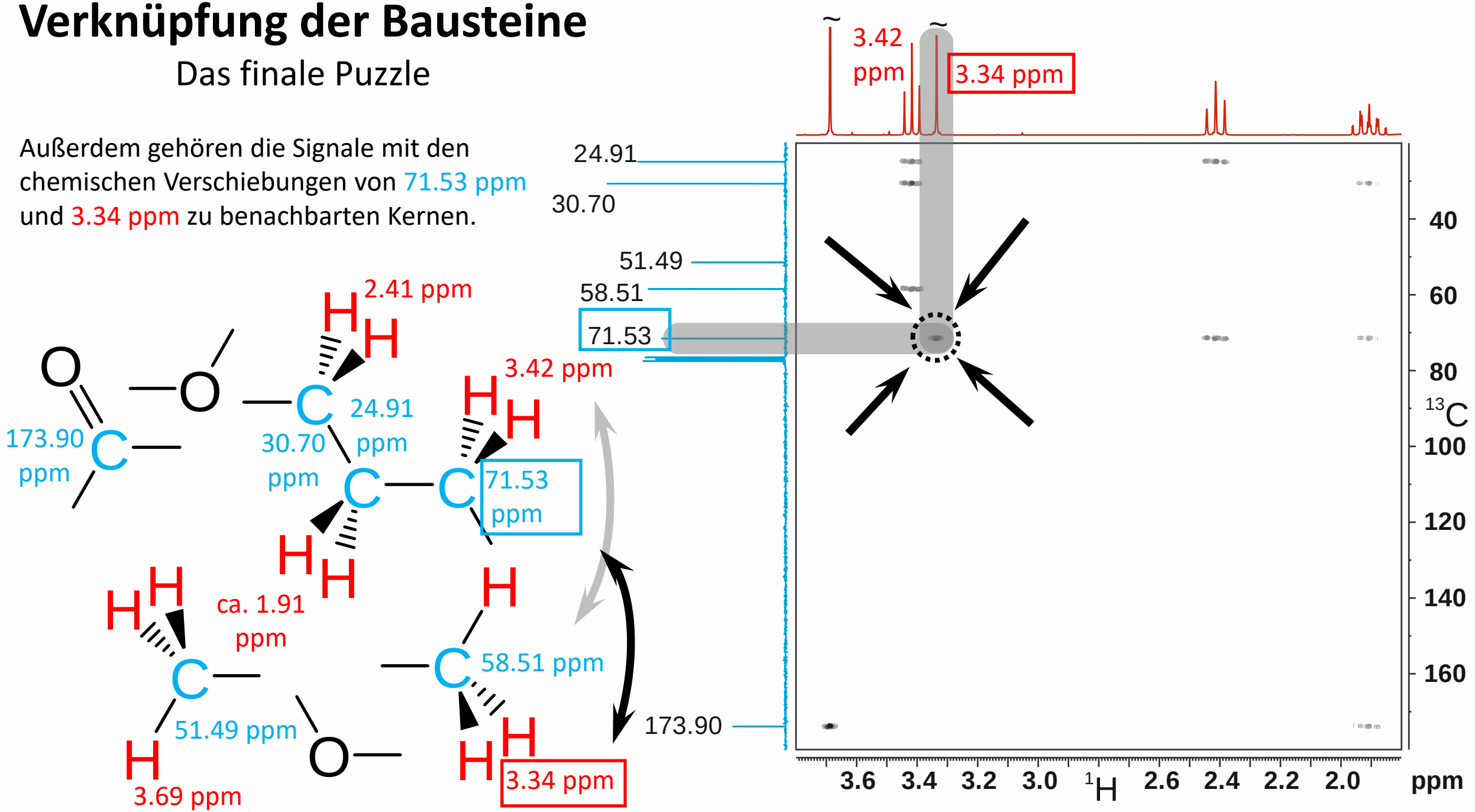




Verknüpfung der Bausteine

Das finale Puzzle

Außerdem gehören die Signale mit den chemischen Verschiebungen von 71.53 ppm und 3.34 ppm zu benachbarten Kernen.

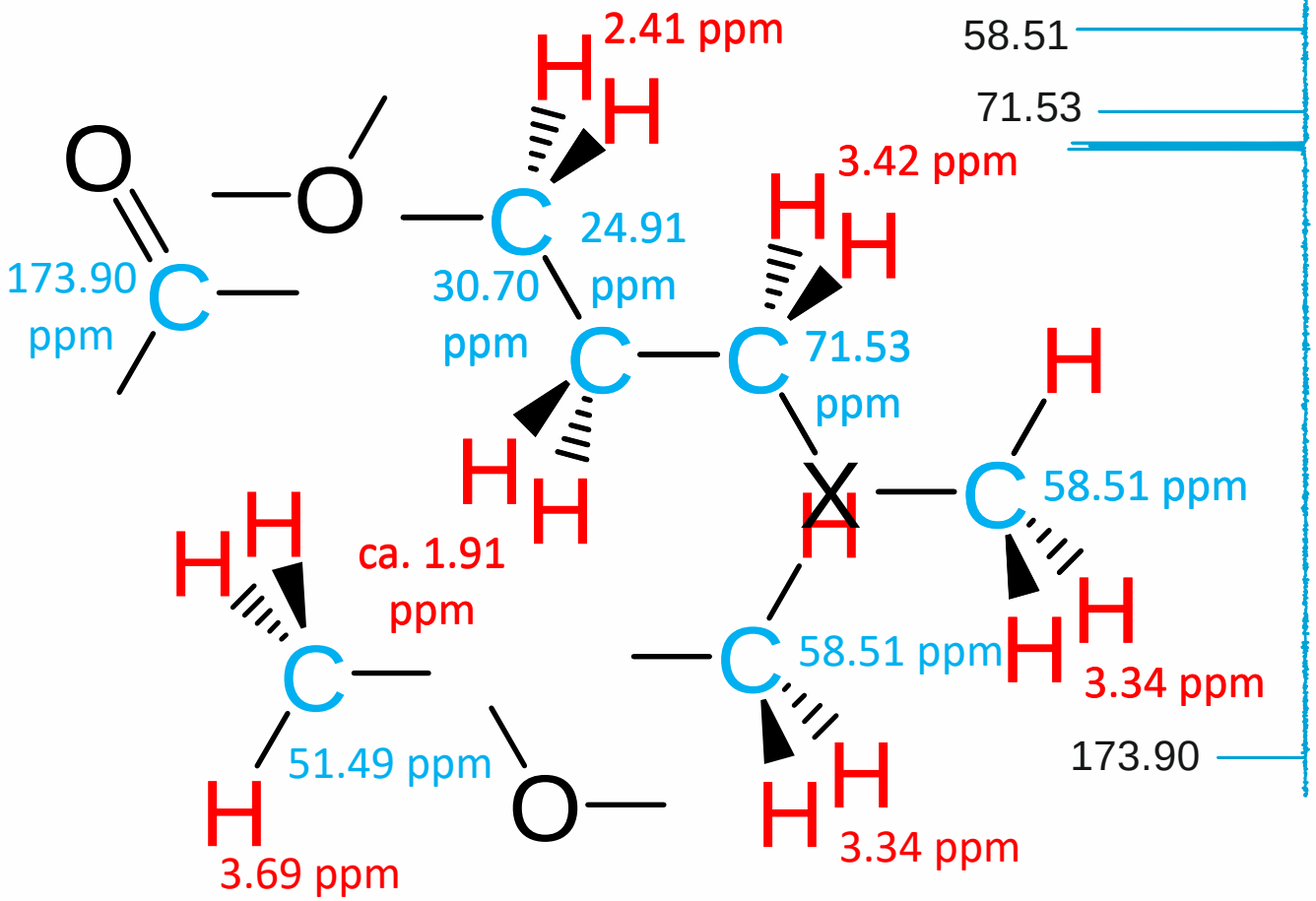


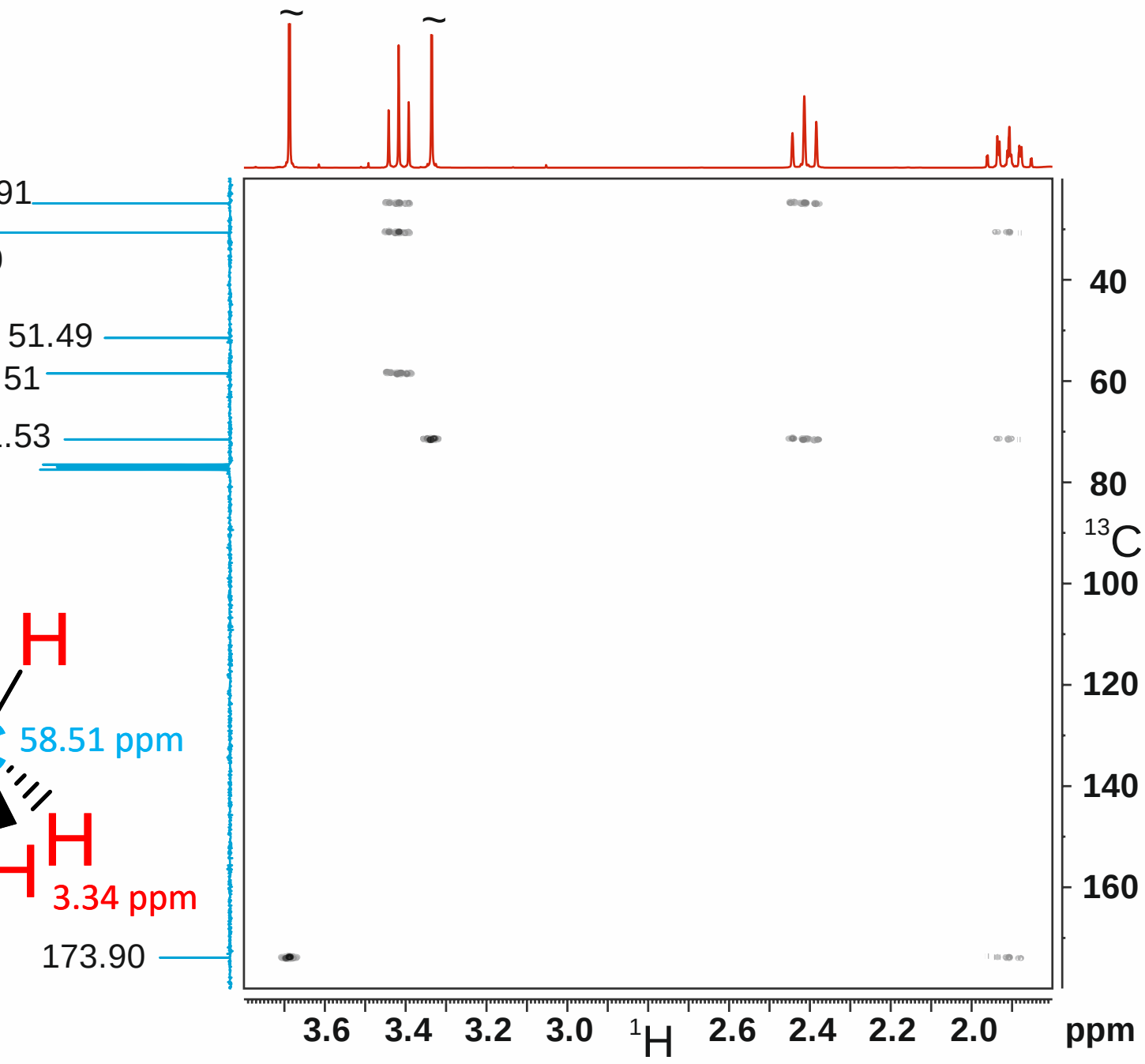
Verknüpfung der Bausteine

Das finale Puzzle

Eine Verknüpfungsmöglichkeit erklärt beide Kreuzpeaks.

X ist entweder - O - oder - CO -.



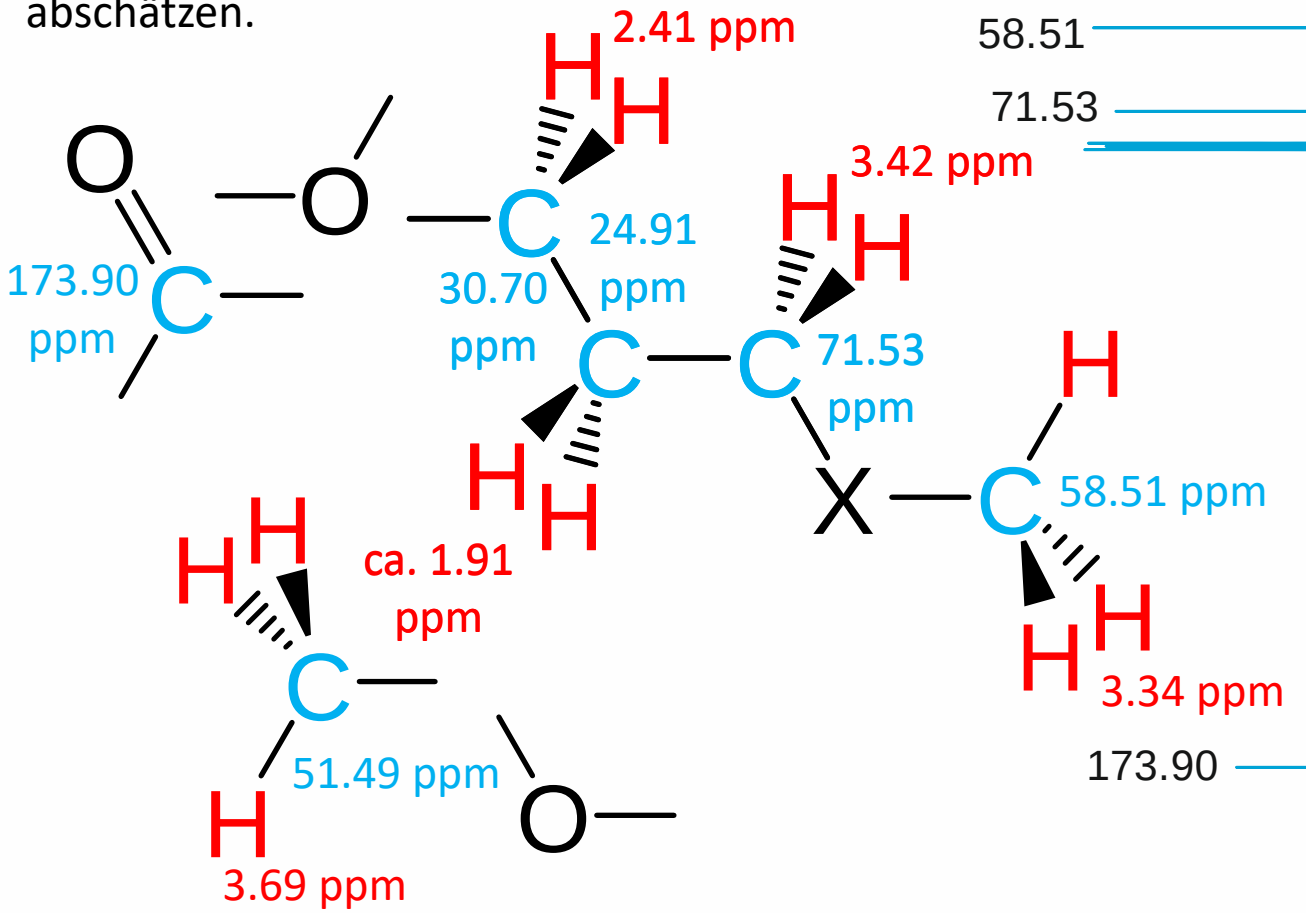


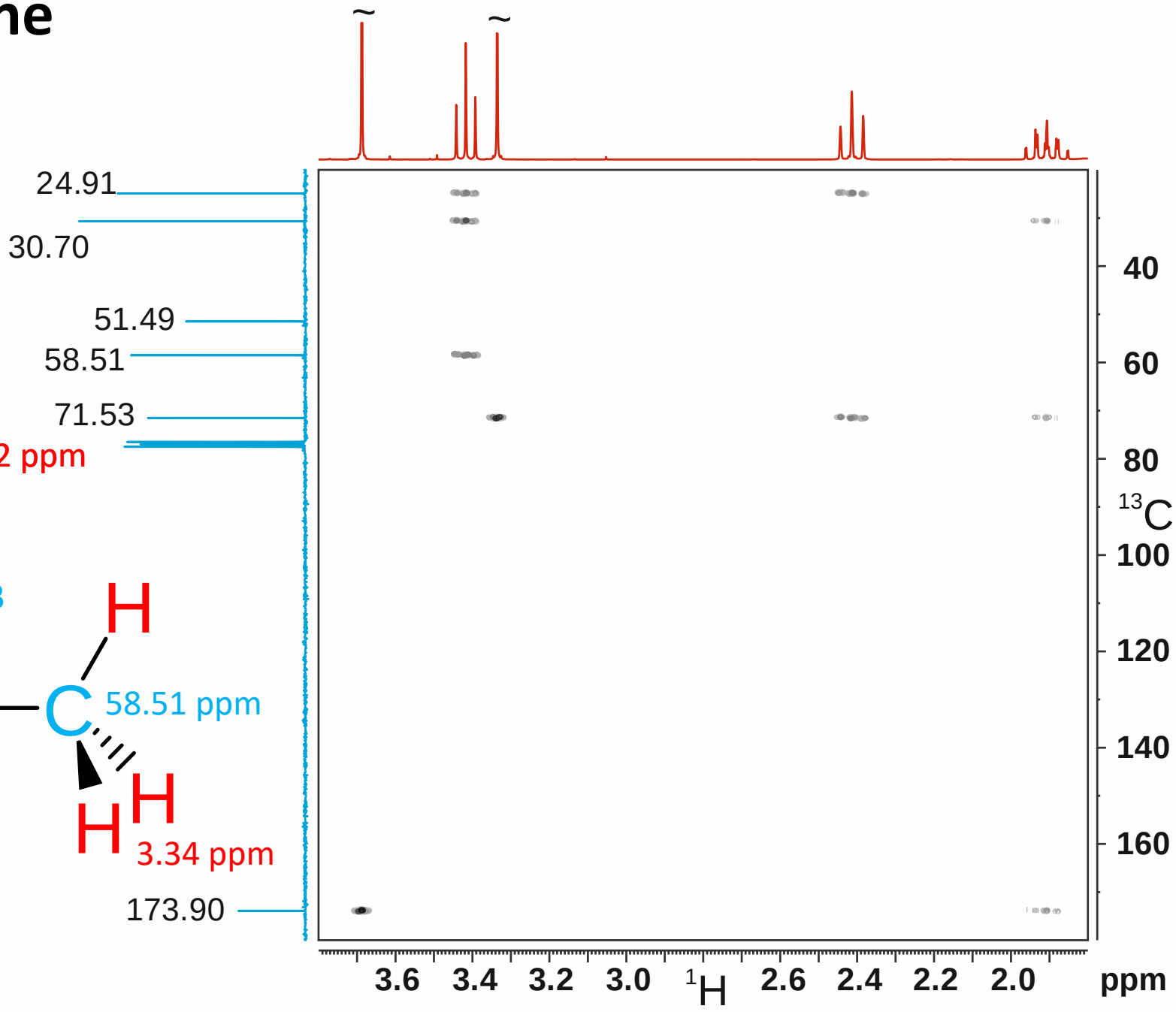
Verknüpfung der Bausteine

Das finale Puzzle

Wie wäre es mit **X** = - CO -?

Die chemische Verschiebung der Protonen der -CH_2-Gruppe direkt neben **X** kann man leicht mit Hilfe der Schoolery-Regeln abschätzen.





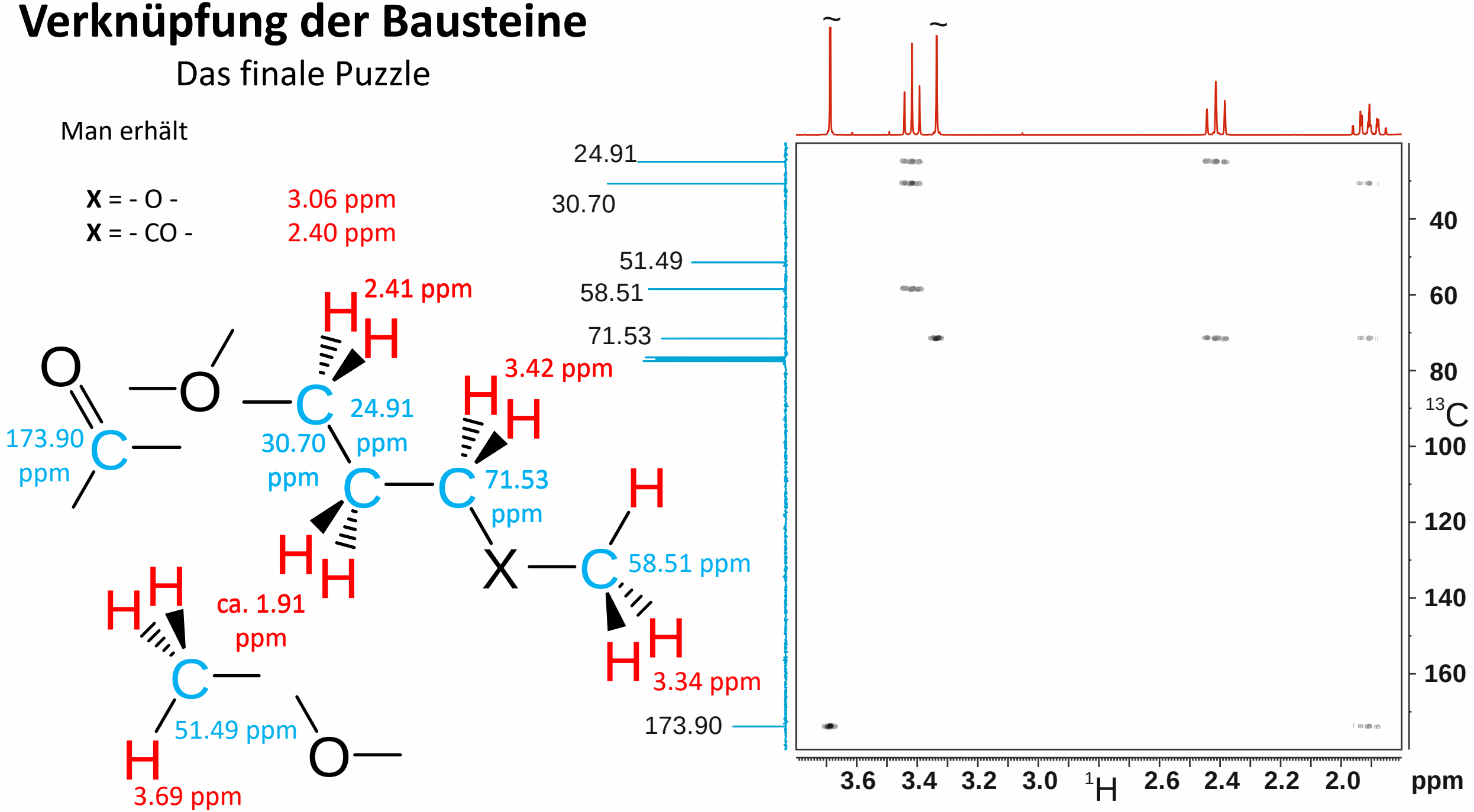
Verknüpfung der Bausteine

Das finale Puzzle

Man erhält

X = - O - 3.06 ppm

X = - CO - 2.40 ppm



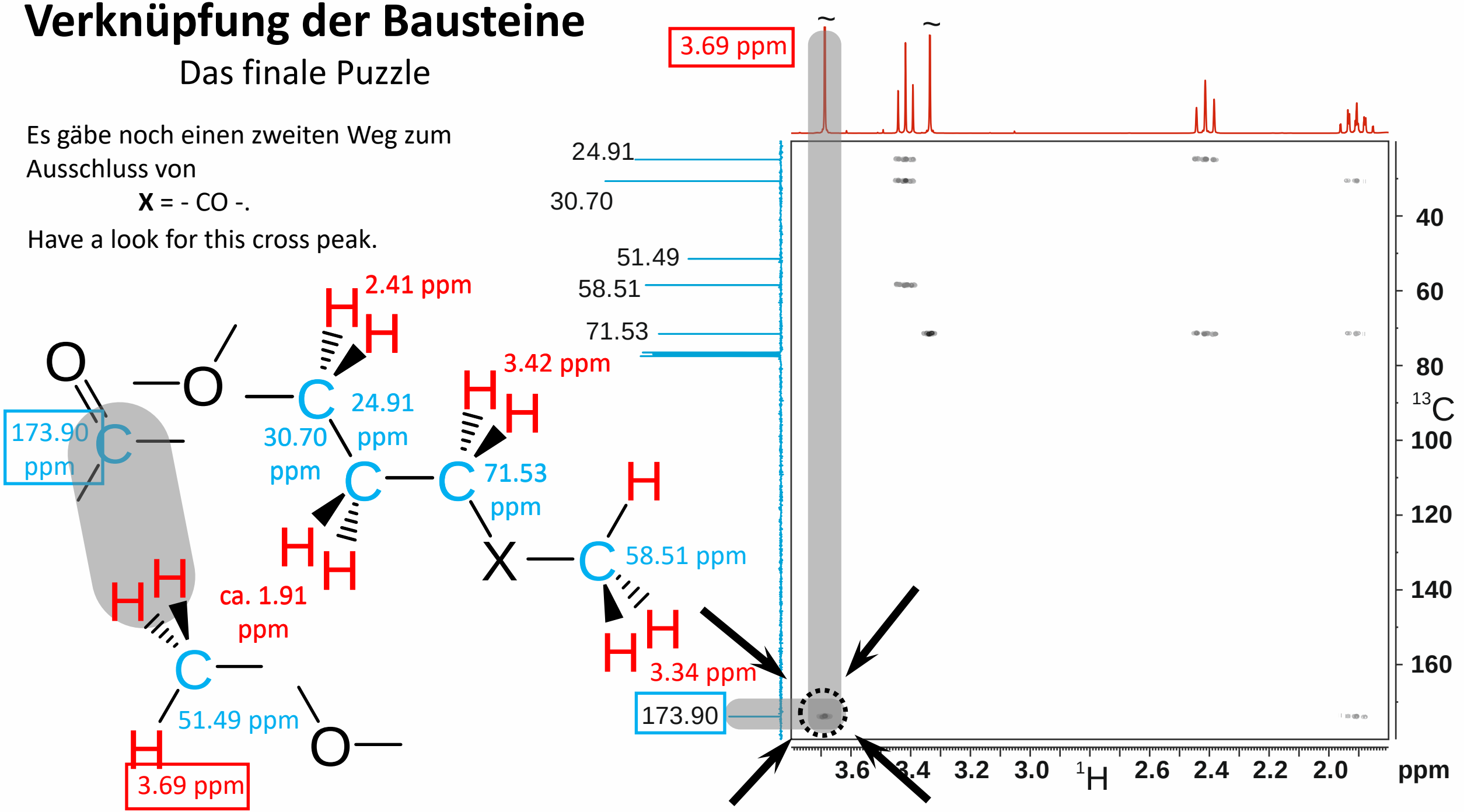
Verknüpfung der Bausteine

Das finale Puzzle

Es gäbe noch einen zweiten Weg zum Ausschluss von

X = - CO -.

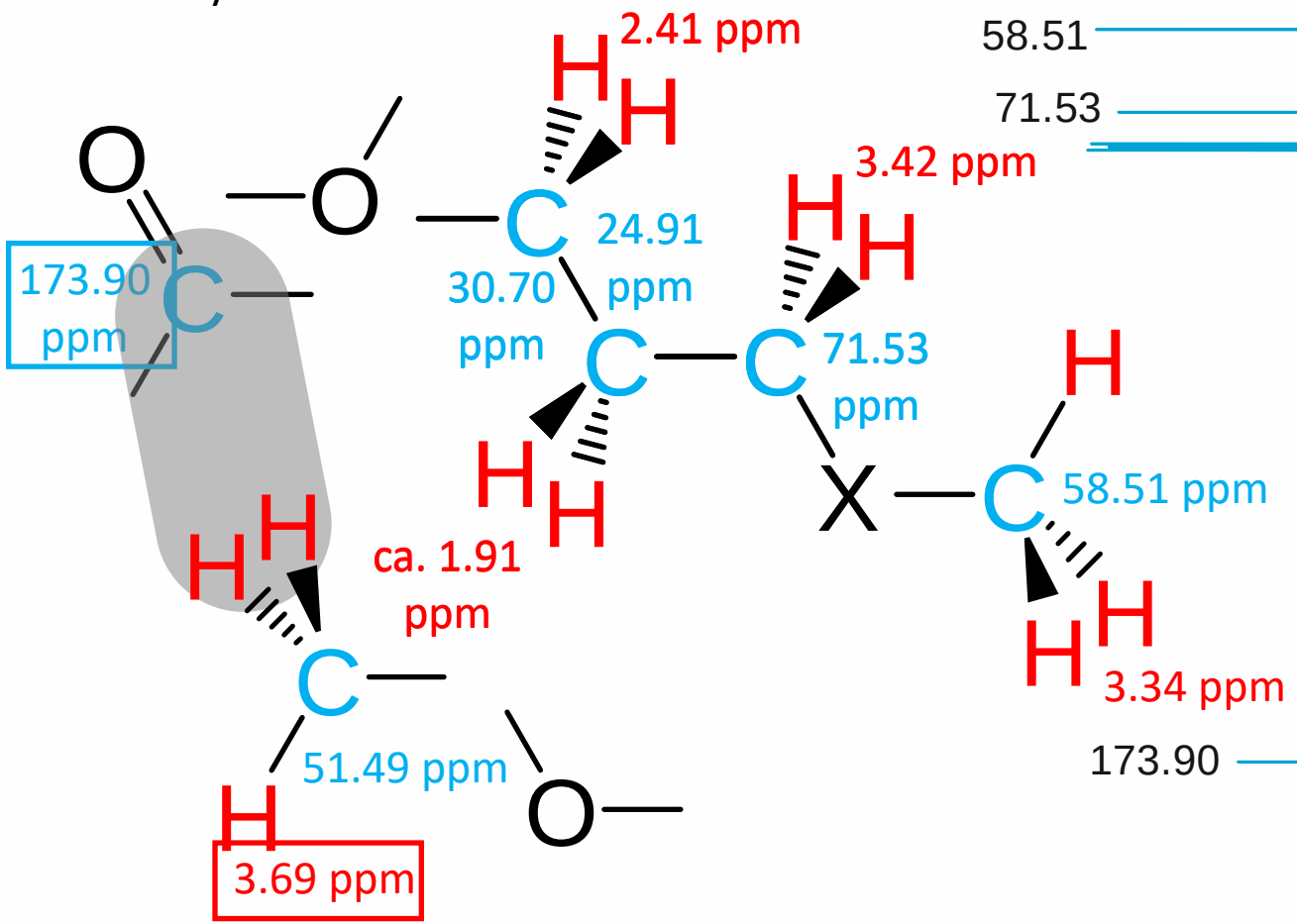
Have a look for this cross peak.

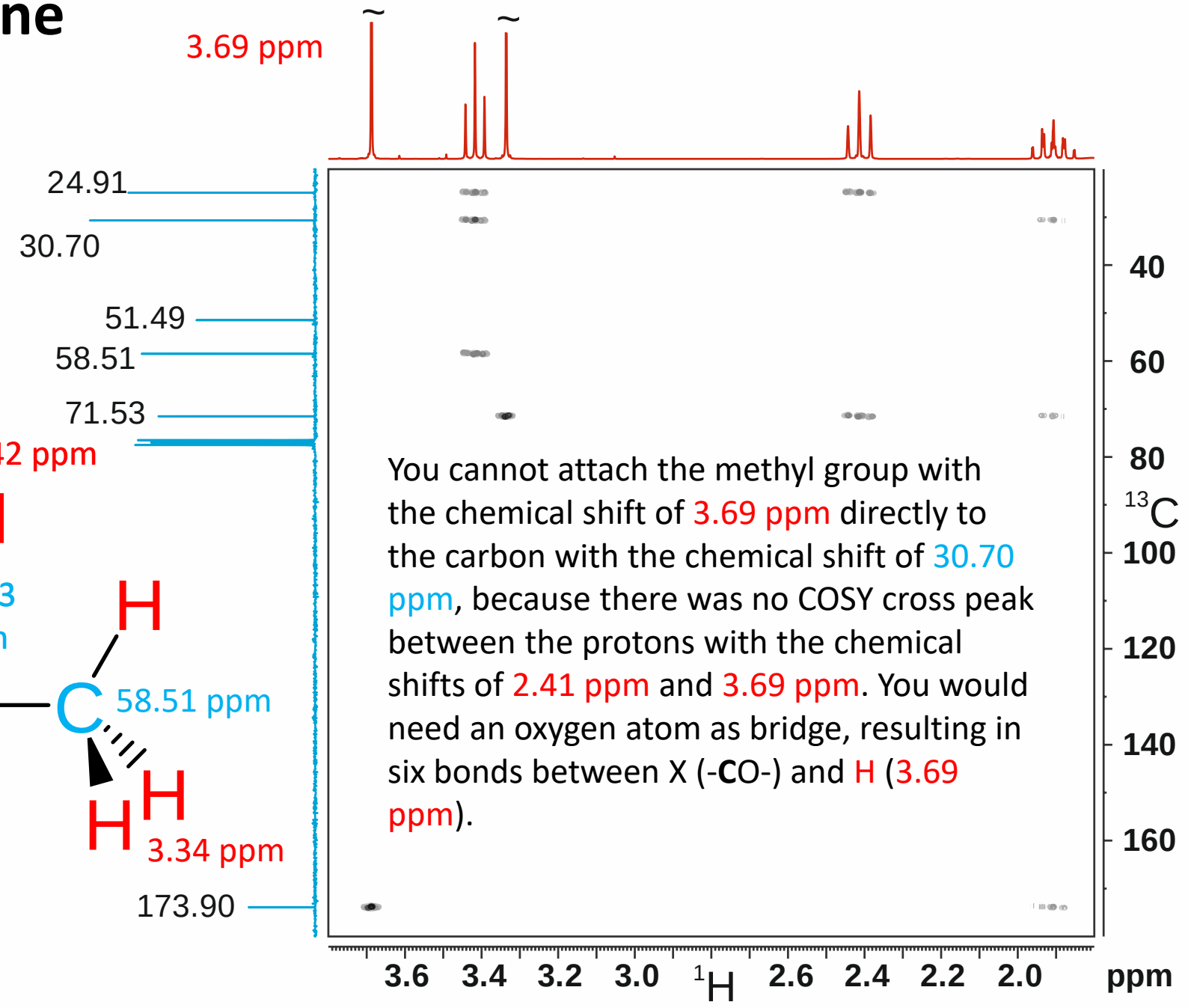


Verknüpfung der Bausteine

Das finale 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!

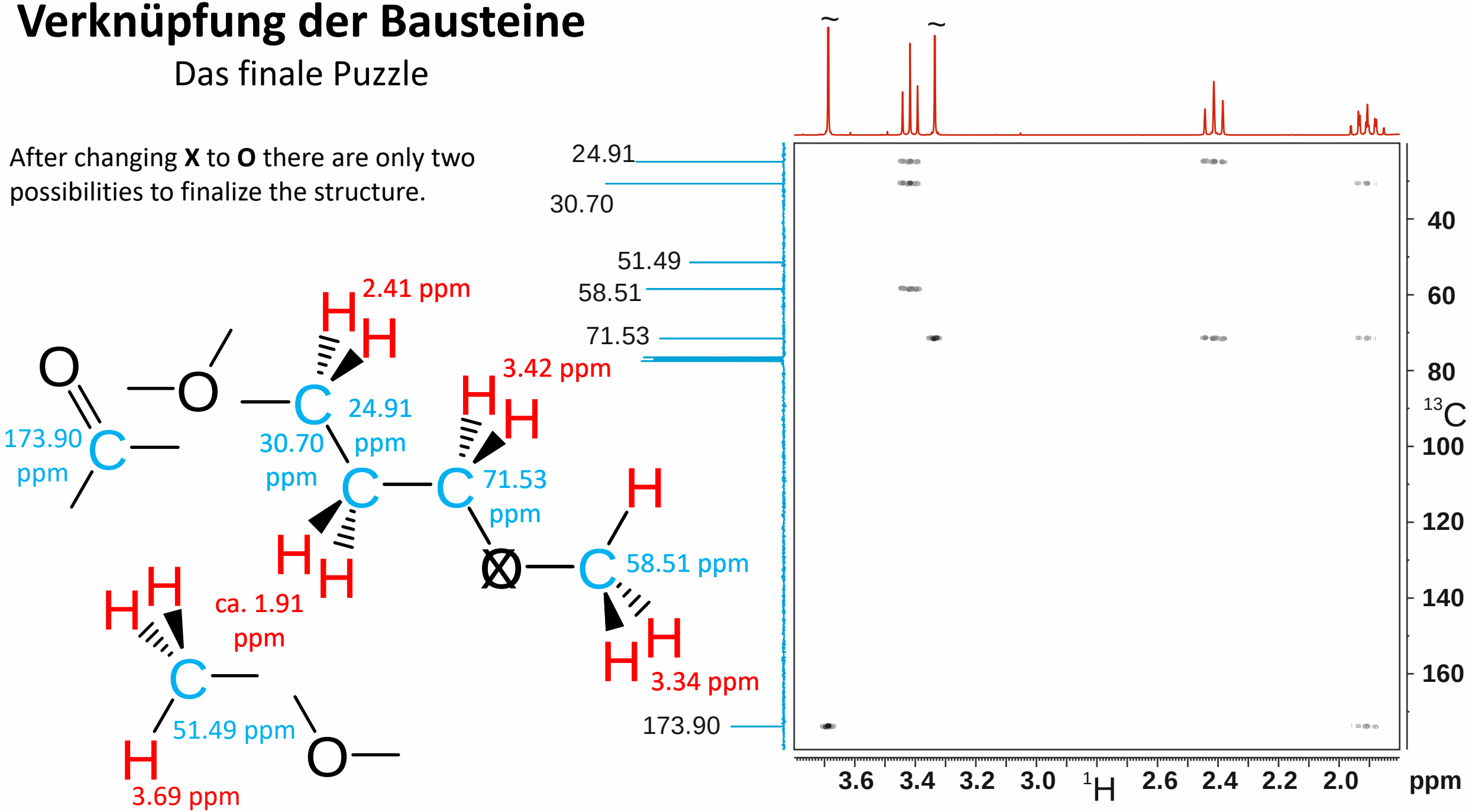




Verknüpfung der Bausteine

Das finale Puzzle

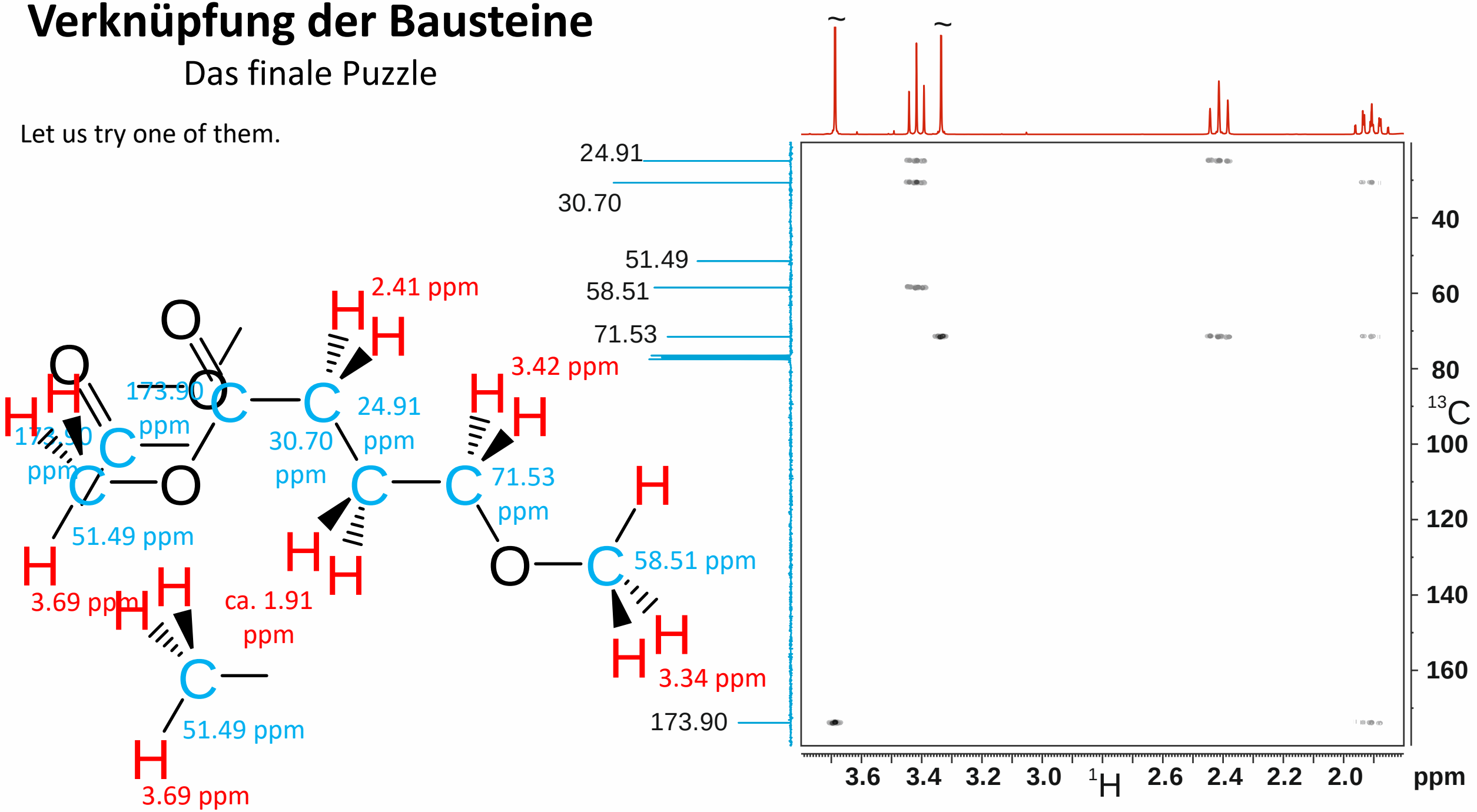
After changing **X** to **O** there are only two possibilities to finalize the structure.



Verknüpfung der Bausteine

Das finale Puzzle

Let us try one of them.

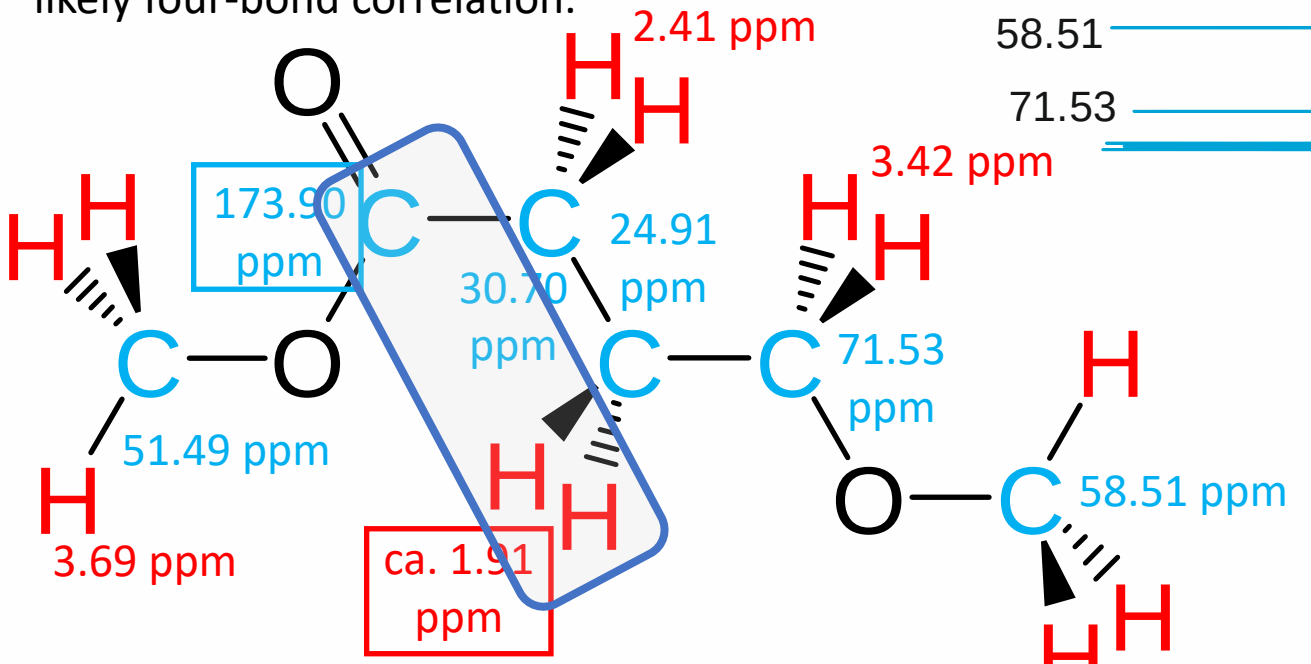


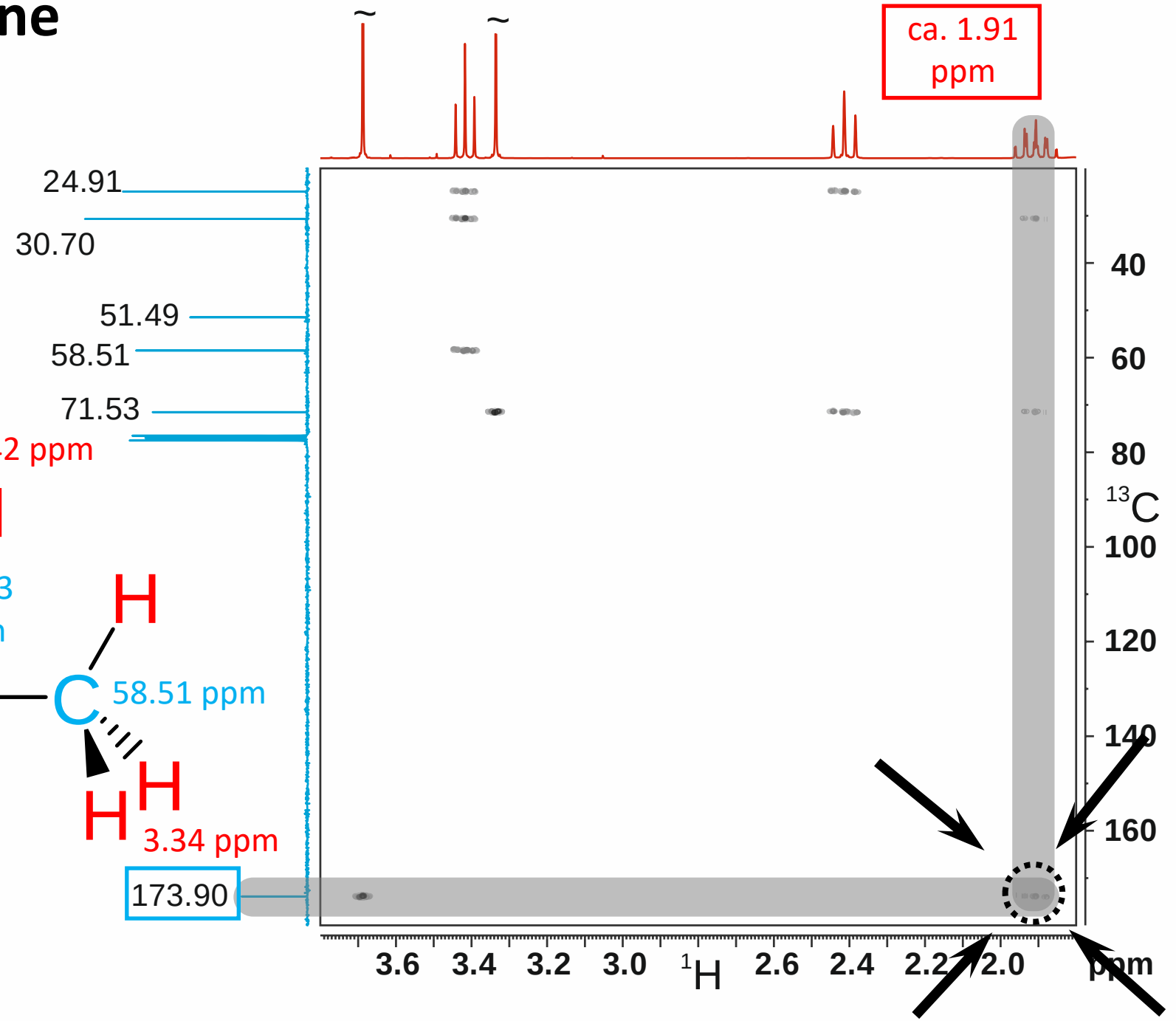
Verknüpfung der Bausteine

Das finale 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.

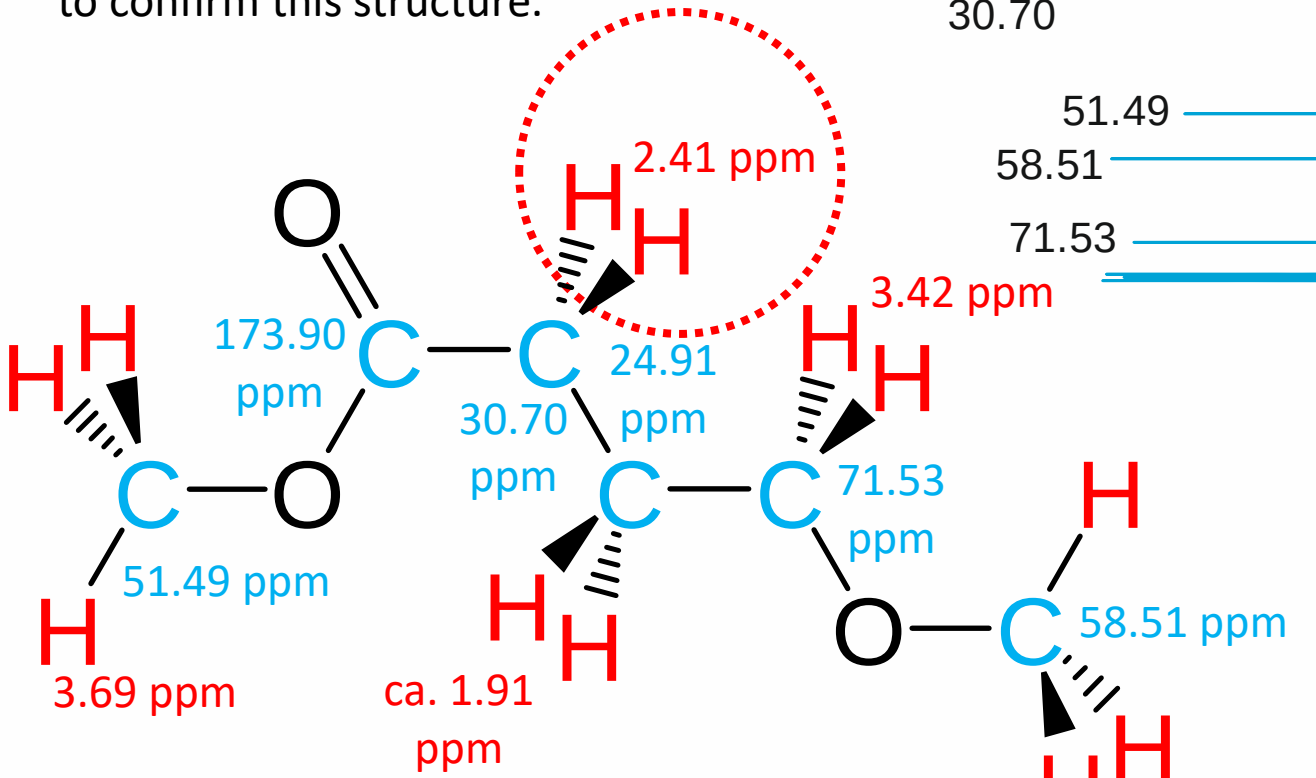


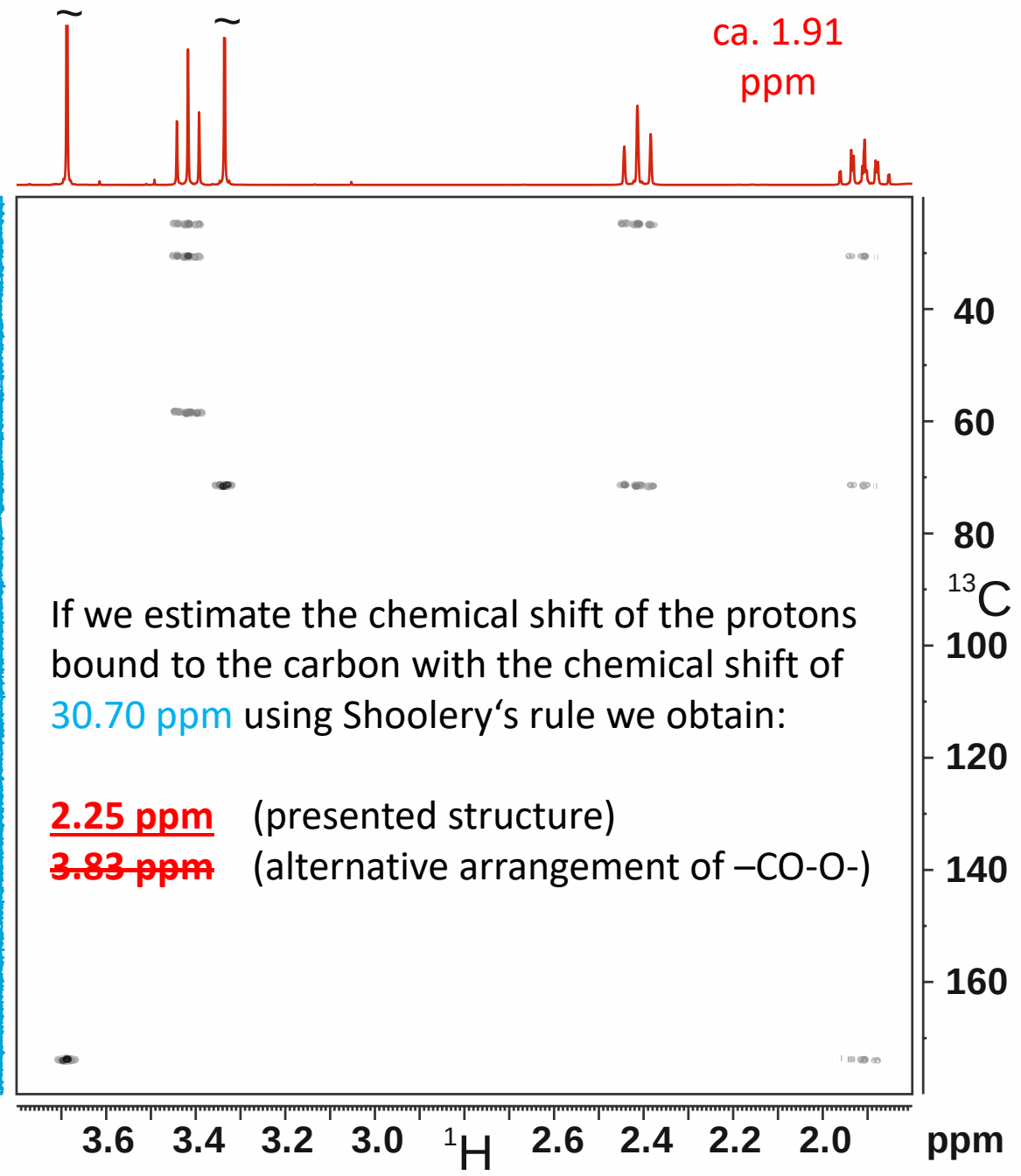


Verknüpfung der Bausteine

Das finale Puzzle

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





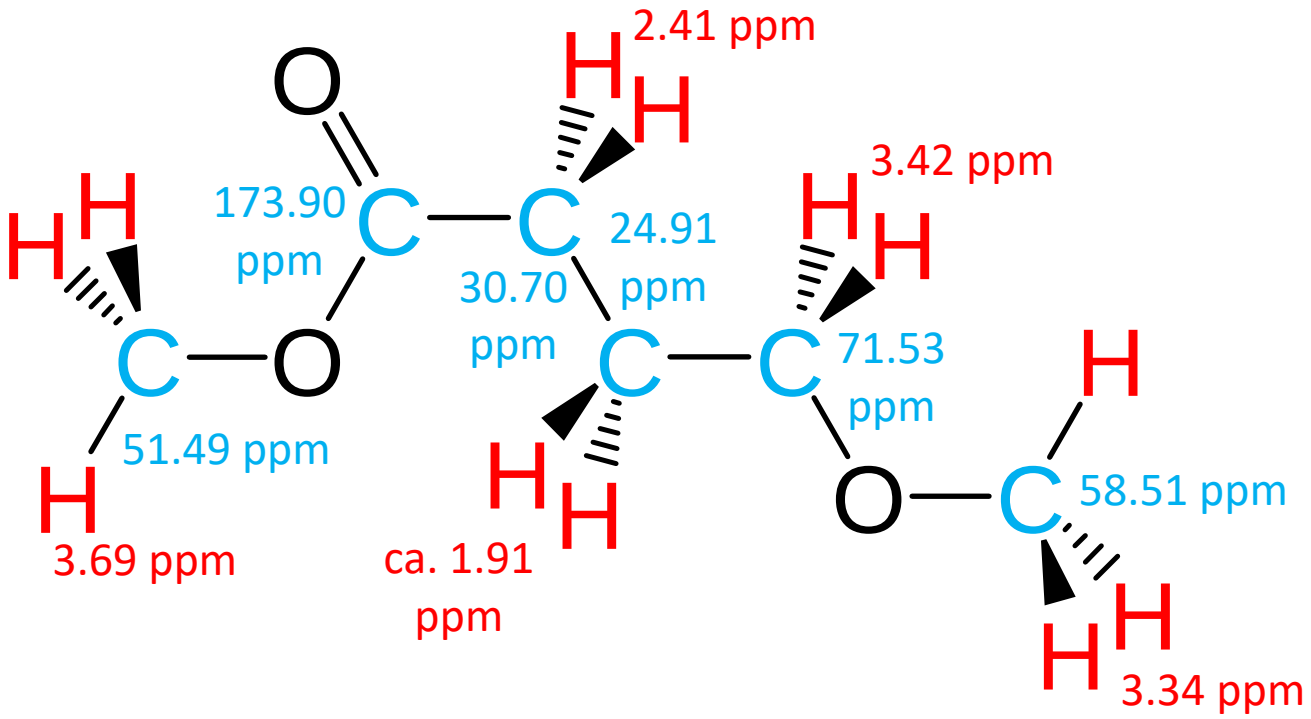
If we estimate the chemical shift of the protons bound to the carbon with the chemical shift of 30.70 ppm using Shoolery‘s rule we obtain:

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

Coupling constants

It looks simple, but it is not

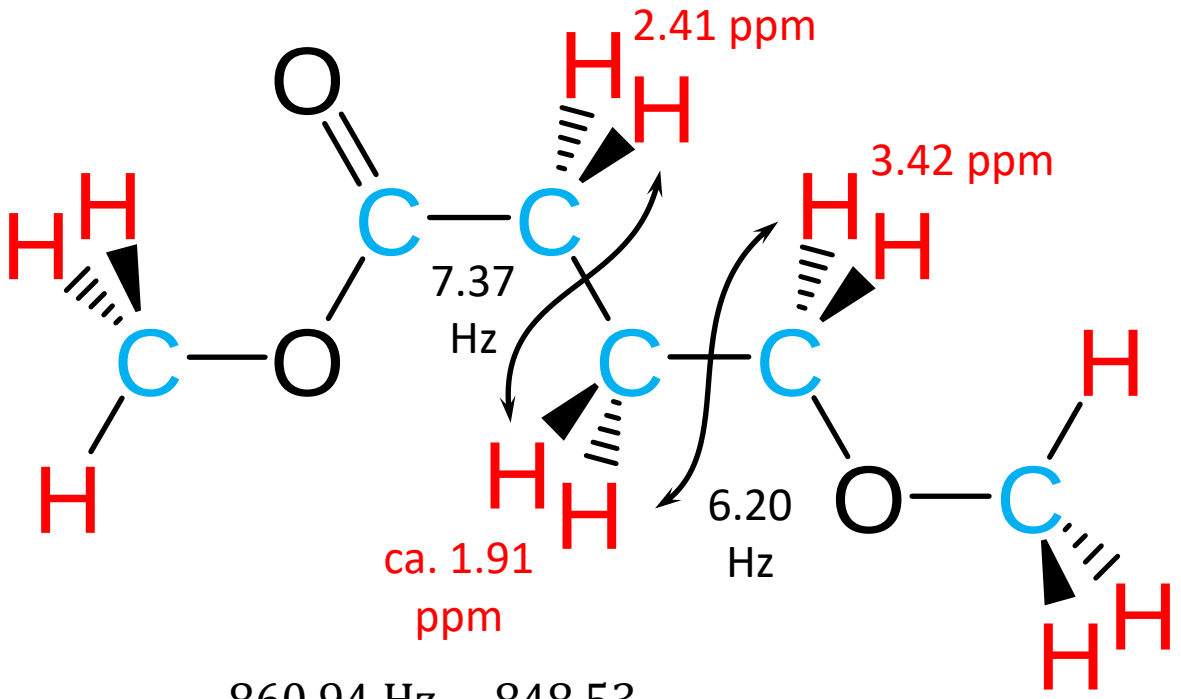
For the sake of clarity let us remove all carbon assignments and the proton assignments of both methyl groups. We don‘t need them anymore.

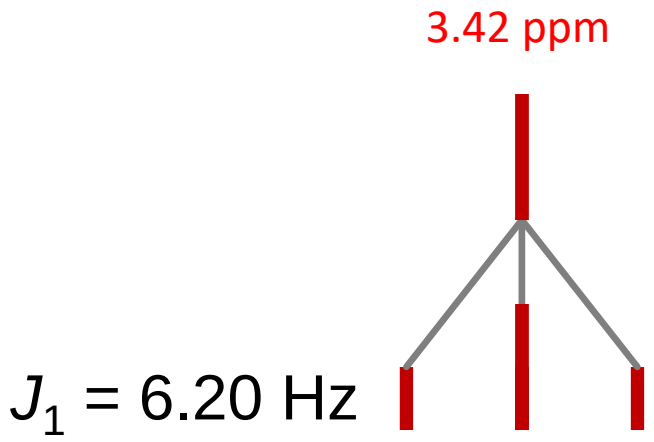


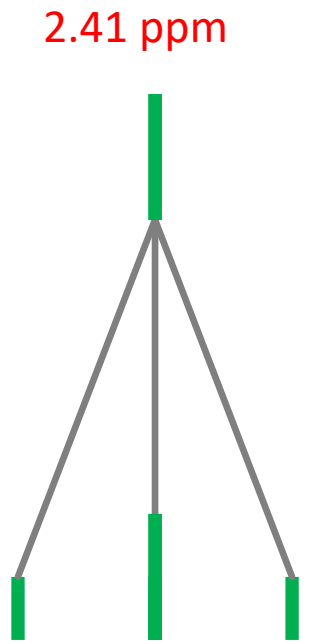
Coupling constants

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.

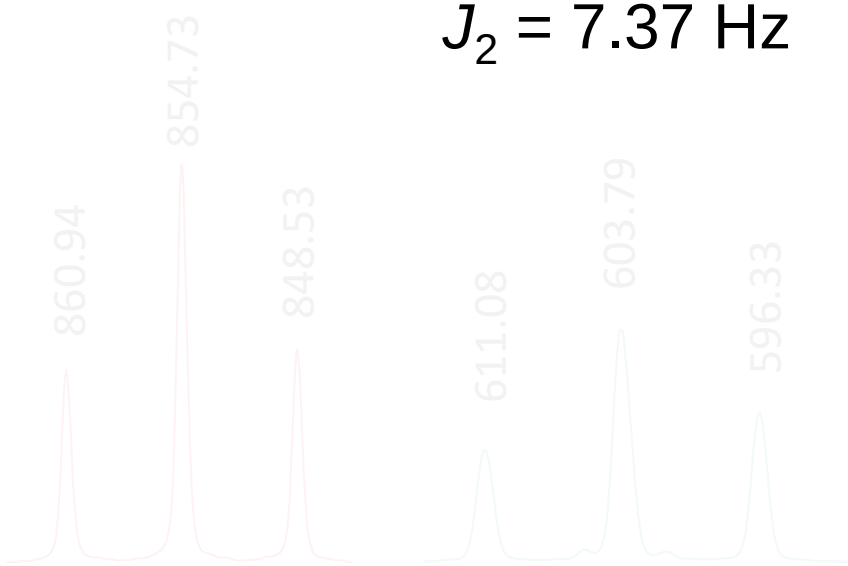






$$J_1 = \frac{860.94\ \text{Hz} - 848.53}{2} = \mathbf{6.20\ Hz}$$

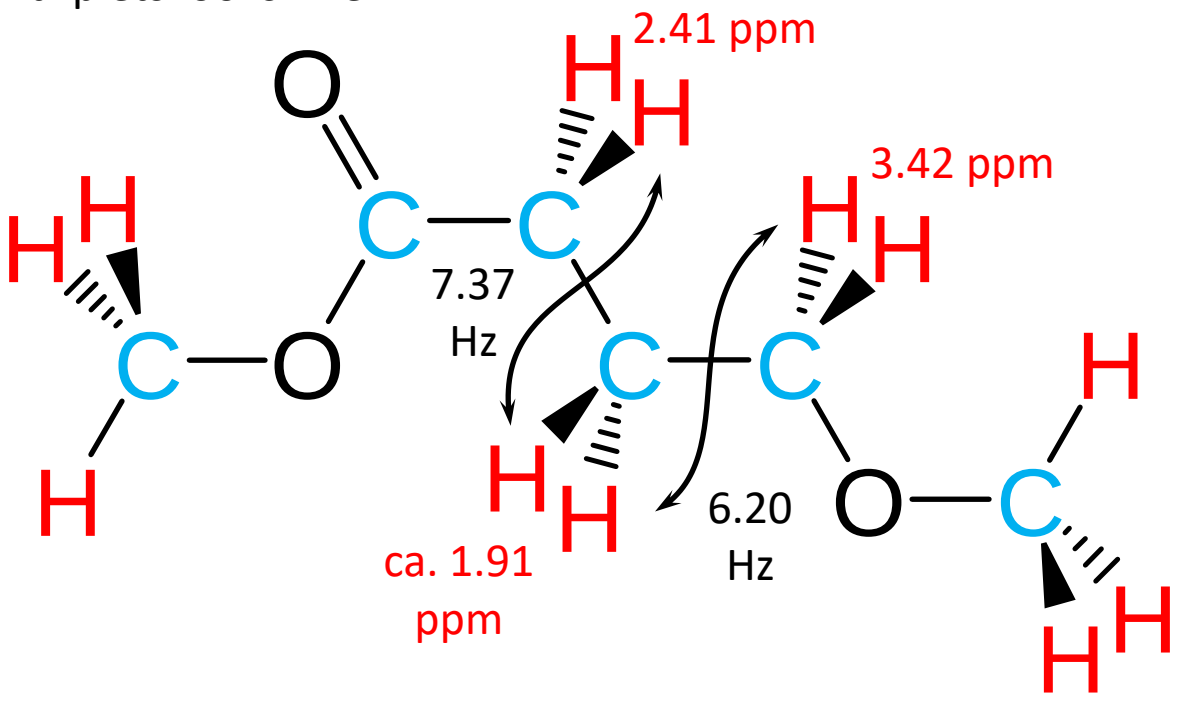
$$J_2 = \frac{611.08\ \text{Hz} - 596.33}{2} = \mathbf{7.37\ Hz}$$



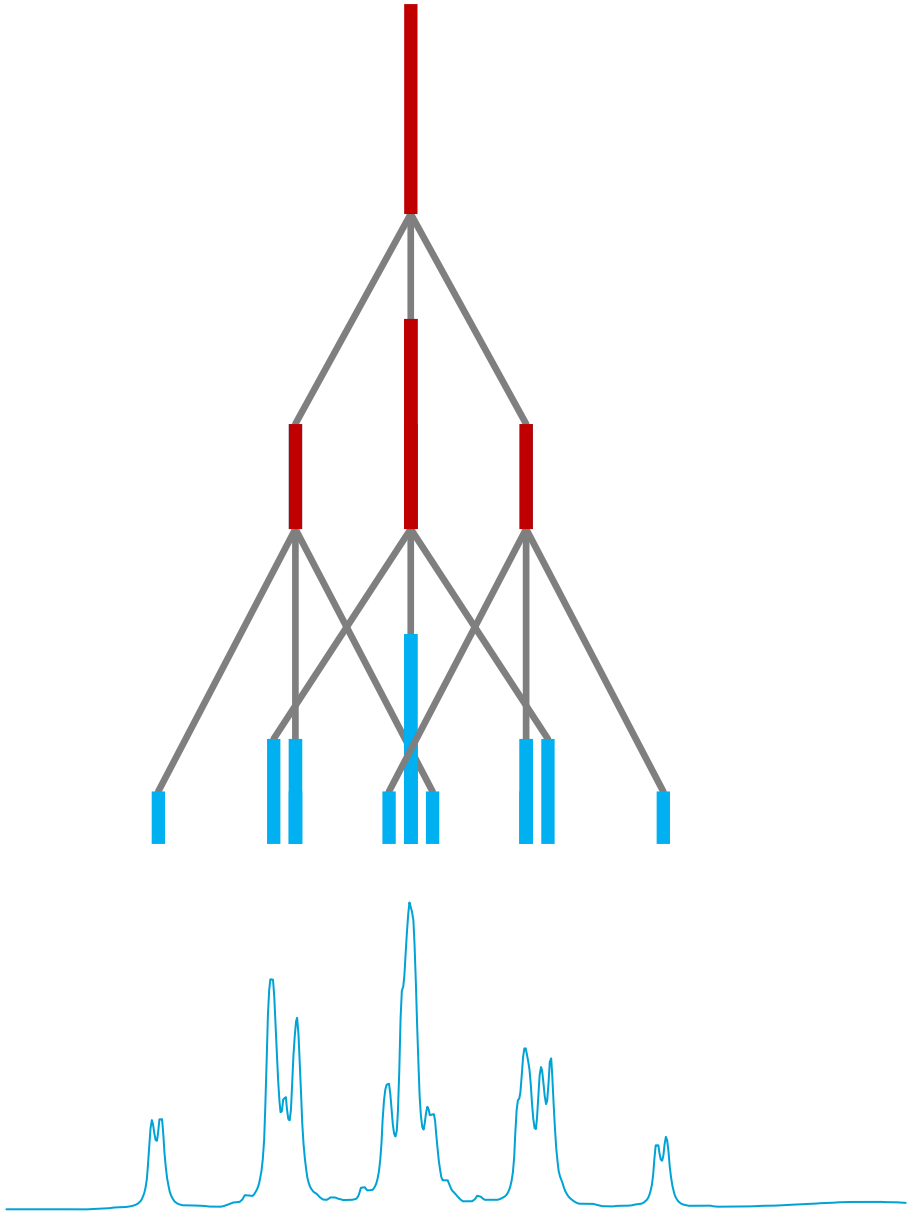
Coupling constants

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.



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



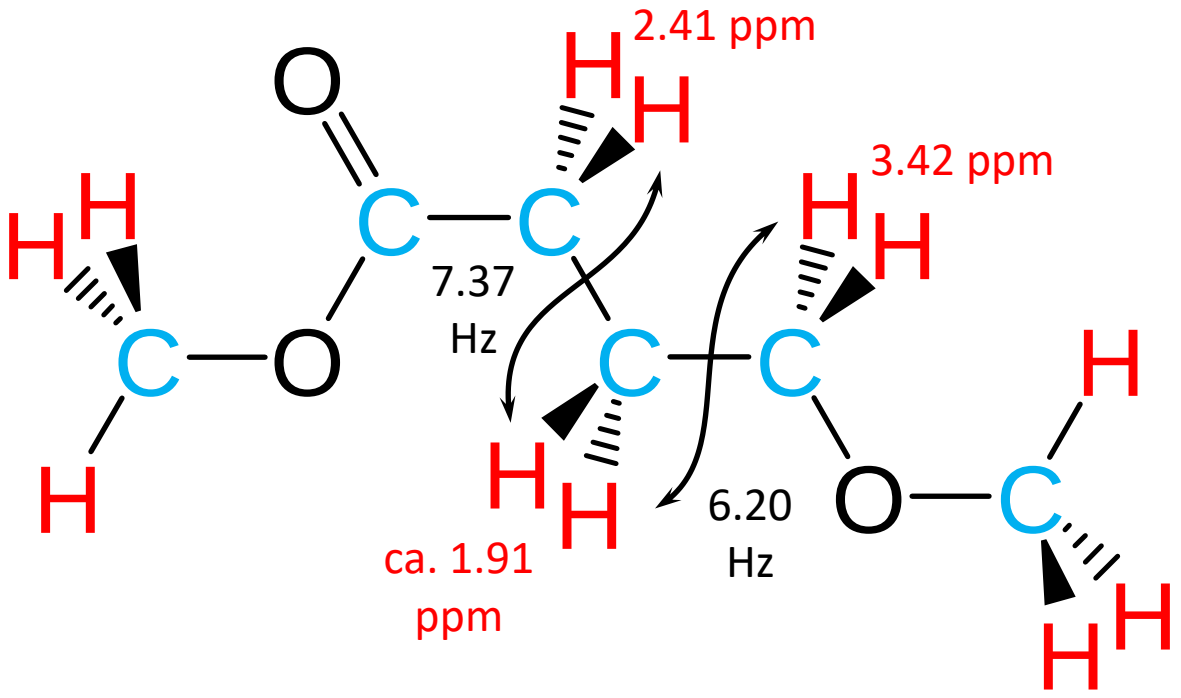
Coupling constants

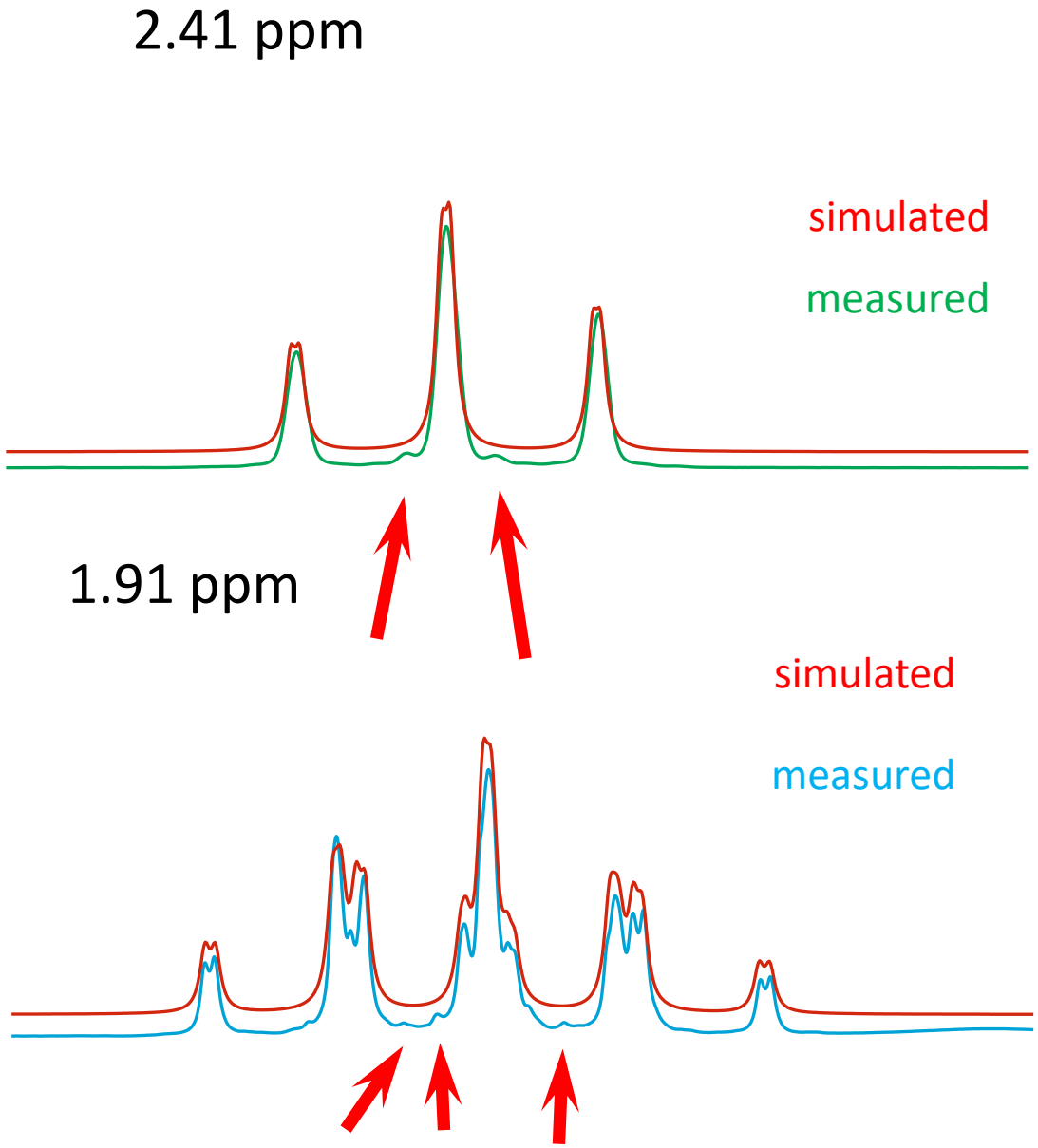
A last check

The simulation of two multiplets looks fine.

But … Have a closer look.

Some experimental details are missing in the simulation. Noise?

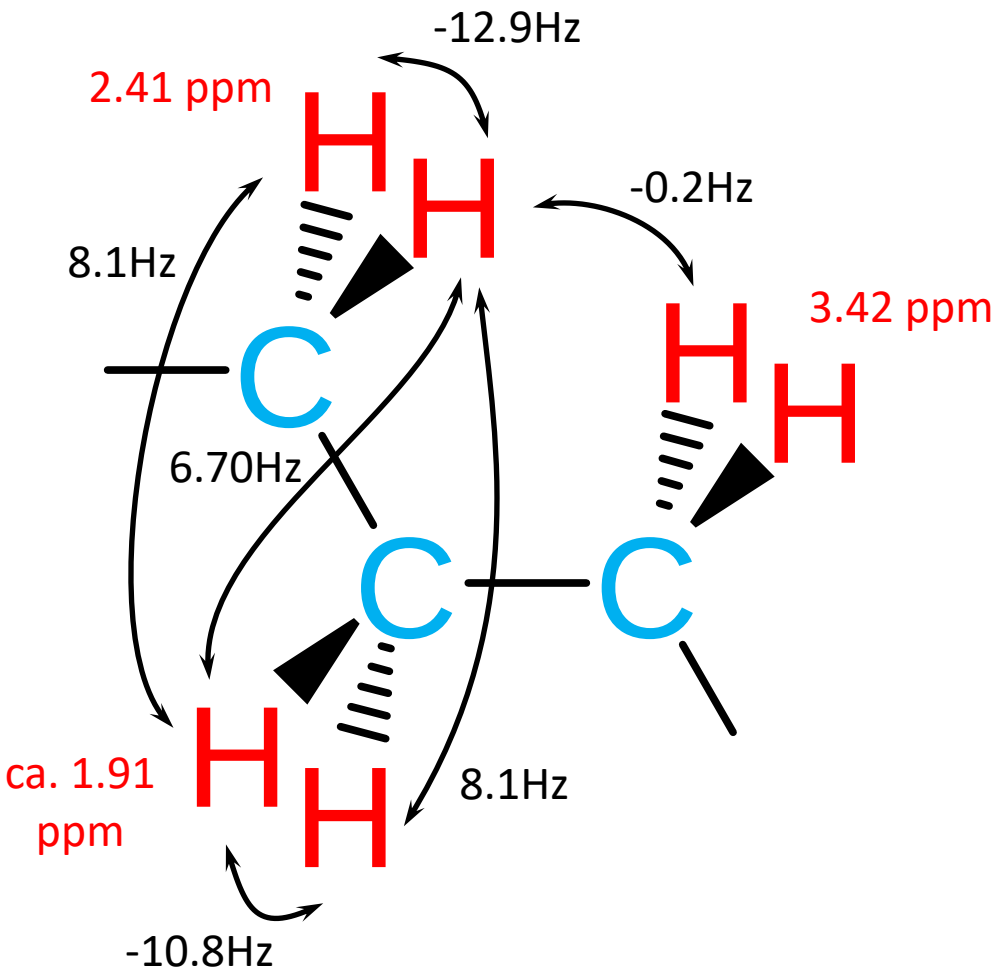




Coupling constants

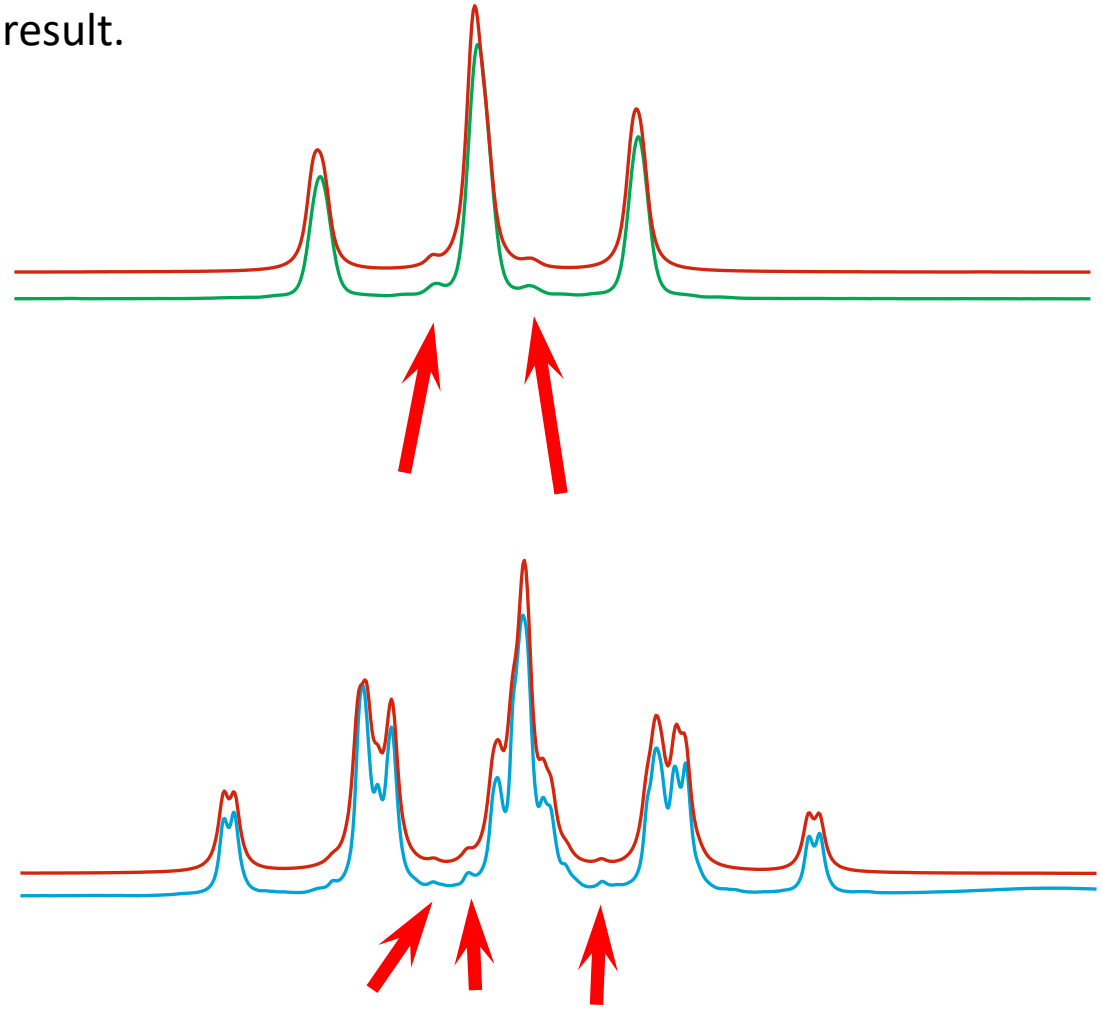
Some refinement

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



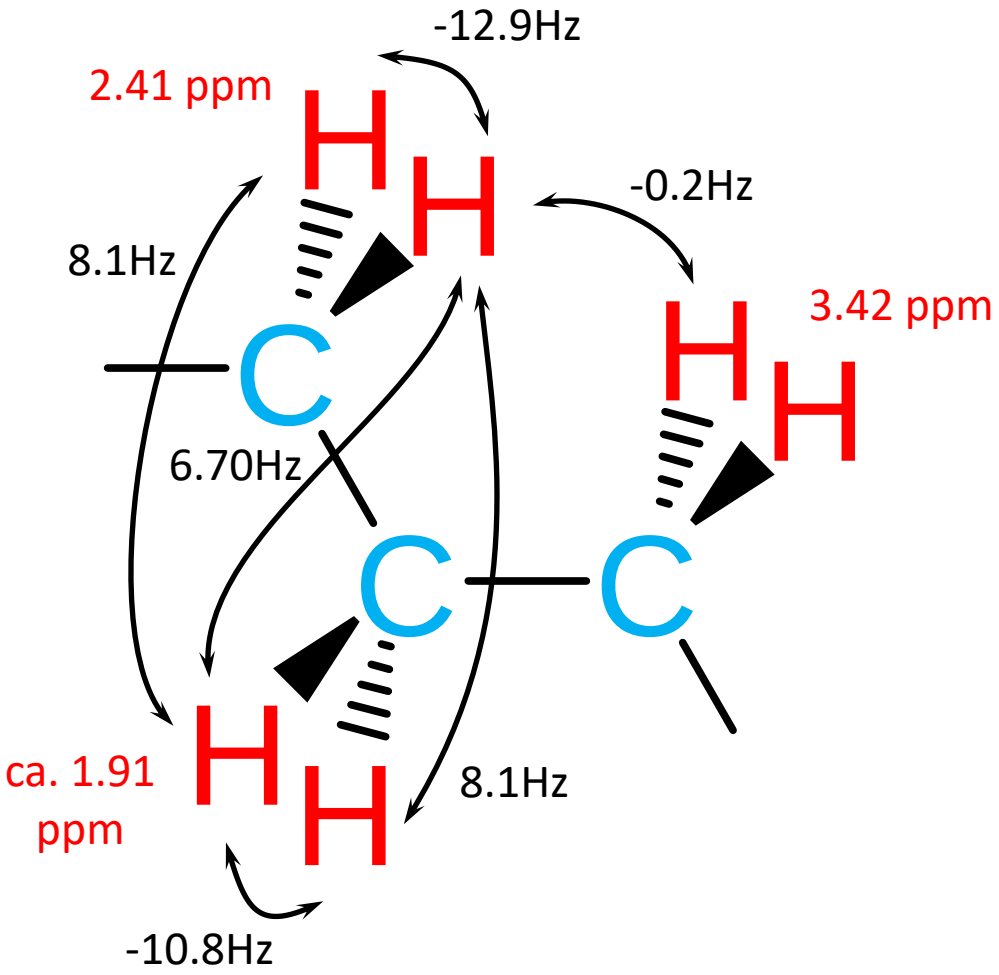
After changing some coupling constants and adding geminal coupling constants and a long rang coupling constant the „warts“ are simulated nearly perfectly.

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

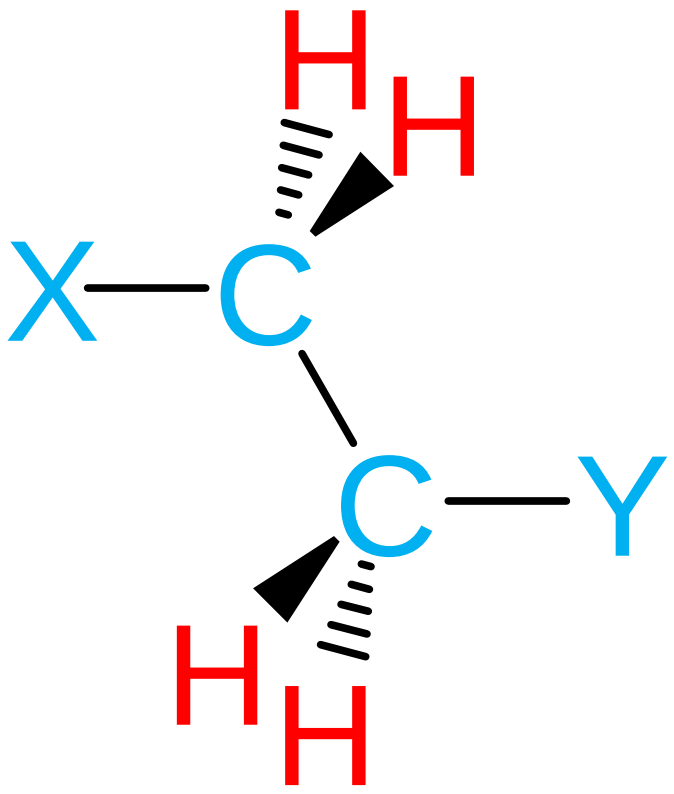


But …

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

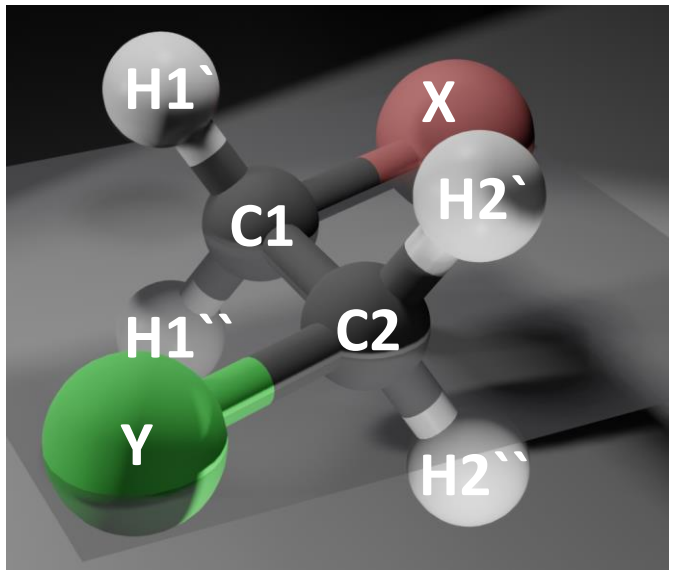


Let us reduce our molecule to a bisubstituted ethane derivative with two different substituents

X = -CO-O-CH_3

and

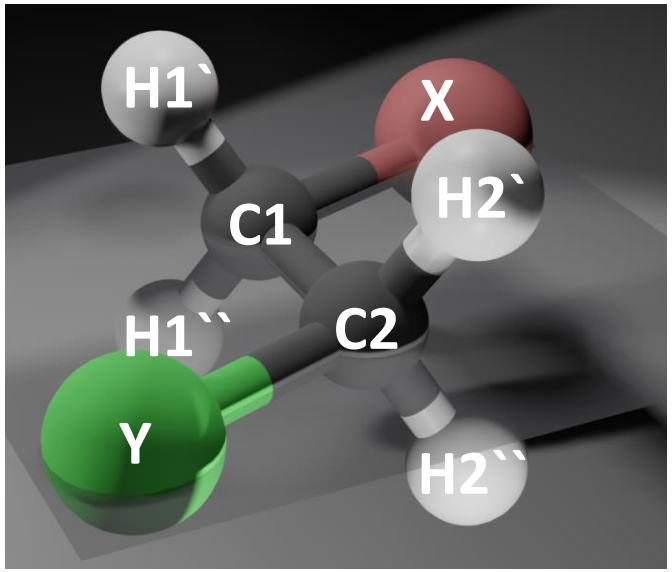
Y = -CH2-O-CH_3.



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.

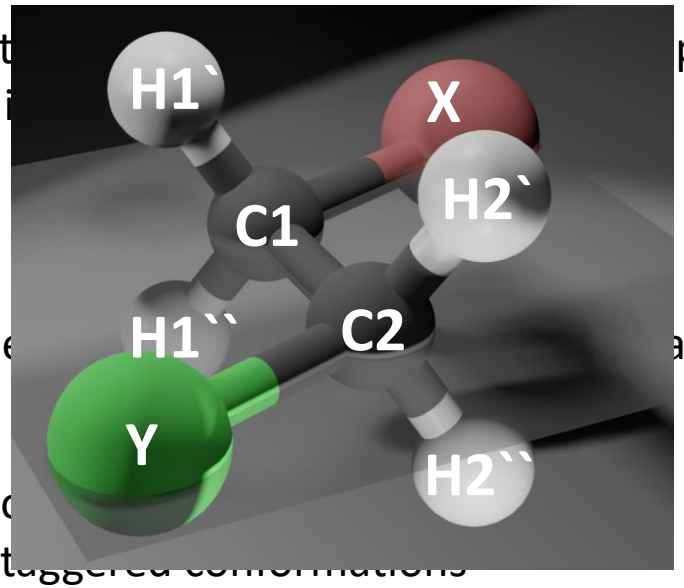
Symmetry

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 possible and the rotamer shown here i

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

- The first assumptio steric hindrance will favour the three staggered conformations
- 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

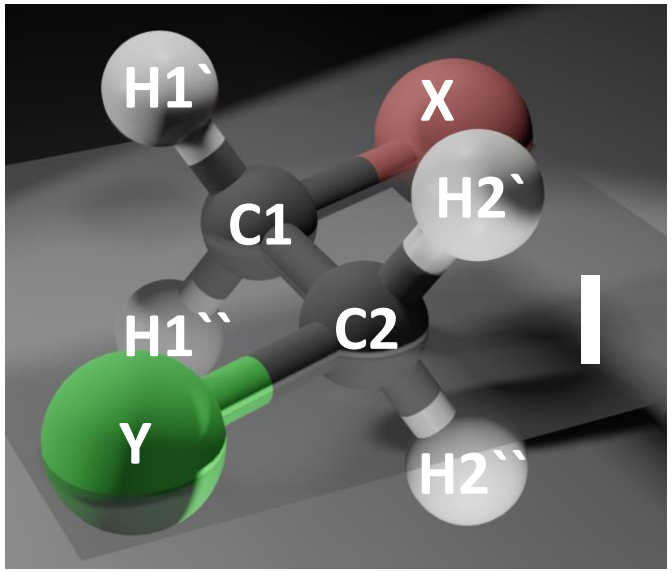
Are H2`and H2`` chemically equivalent?

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

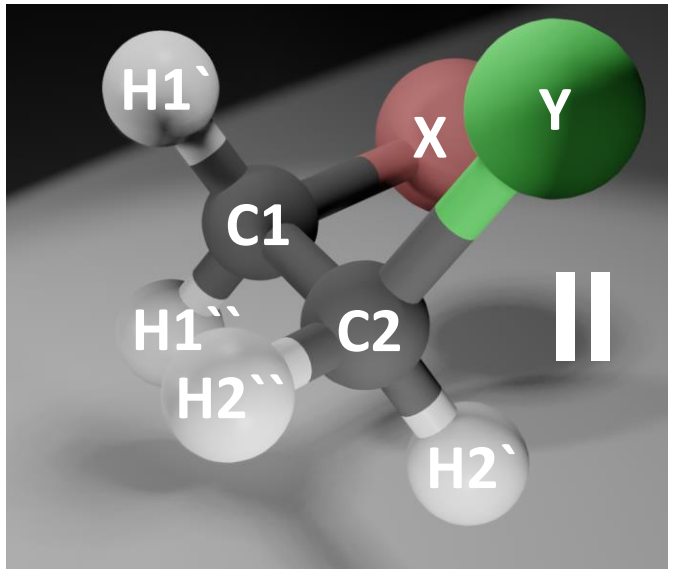
If we turn **C2** in rotamer **I** clockwise by 120 degree we get rotamer **II**.

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

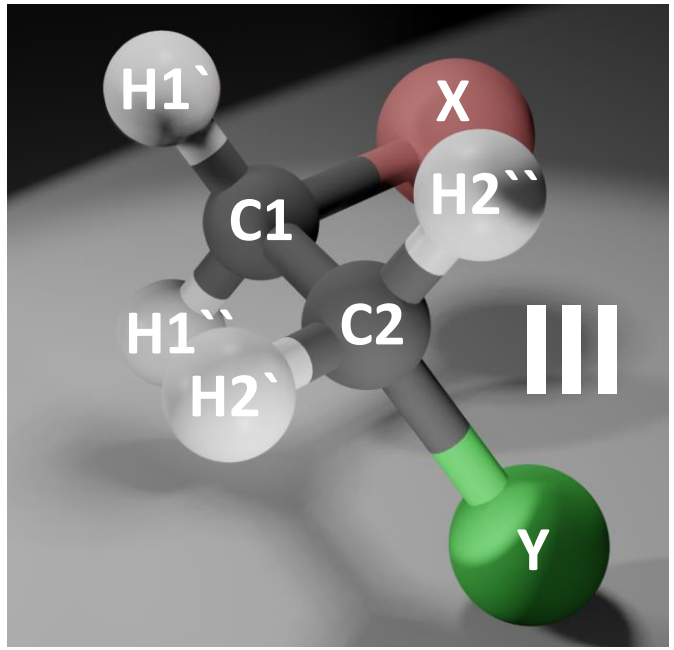
For rotamer **III** it is recommendable to change the viewpoint. Turn the whole molecule around the **C1**-**C2** bond by 180 degree and have a view to the molecule from the right side instead from the left side.



C2
120°

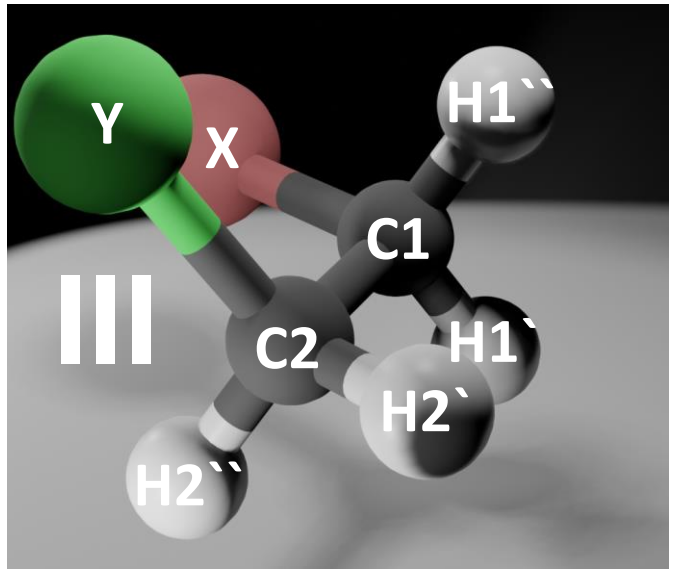


C2
120°



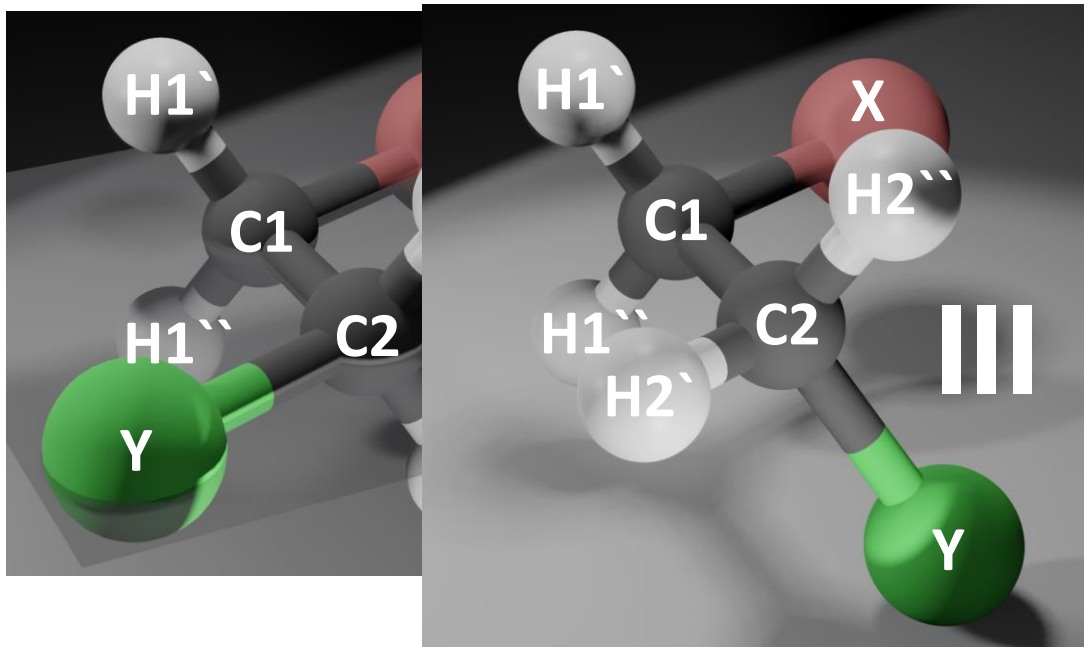
C1-C2 180°

change view to right side



Symmetry

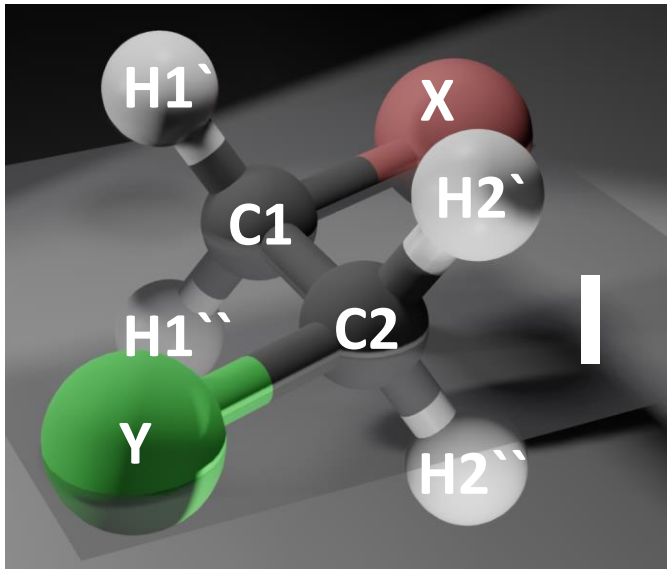
Are H2`and H2`` chemically equivalent?

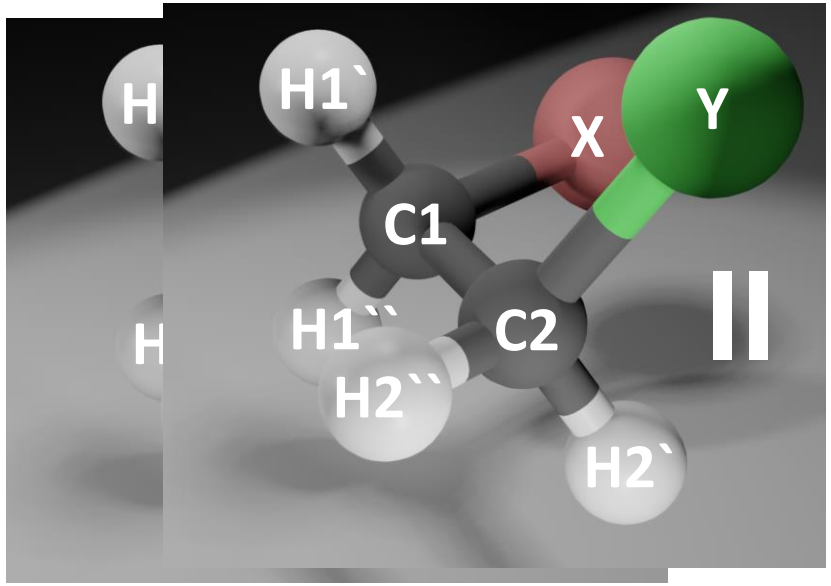


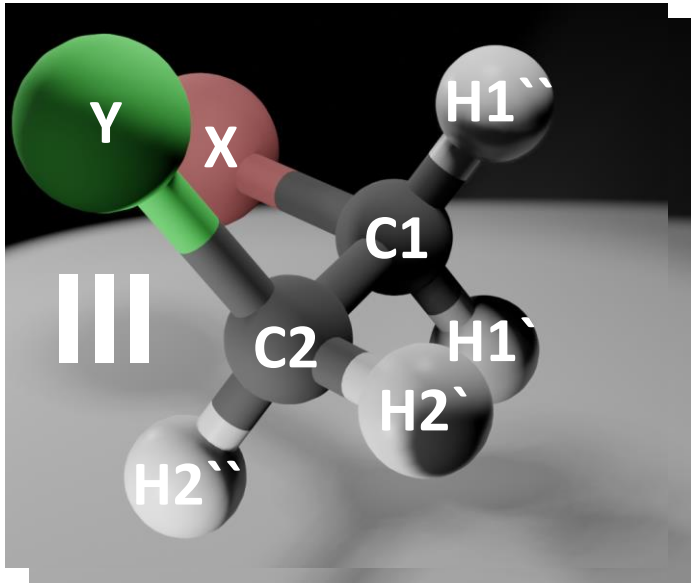
Let us reorder the three rotamers a little bit.

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.



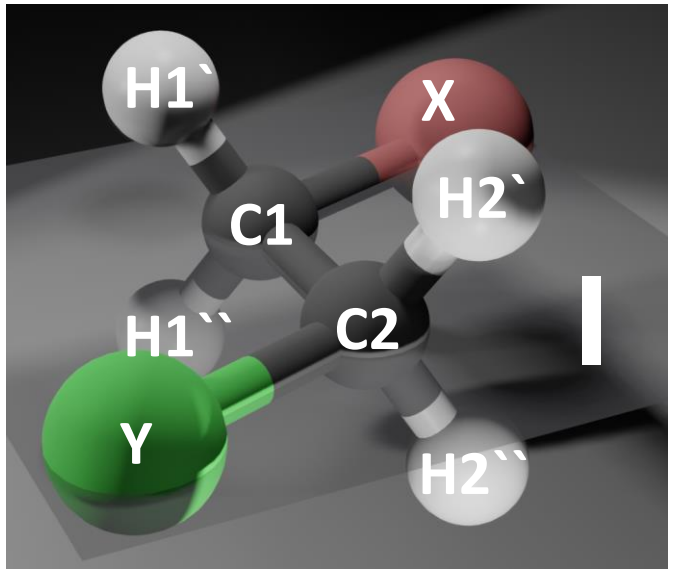


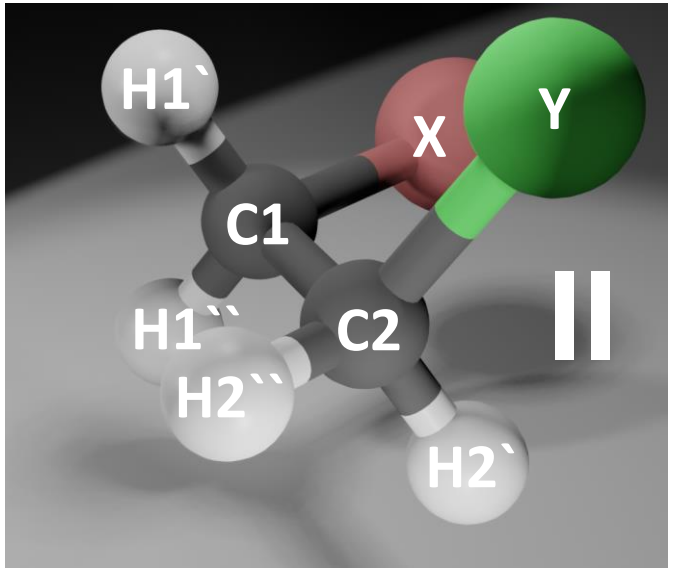


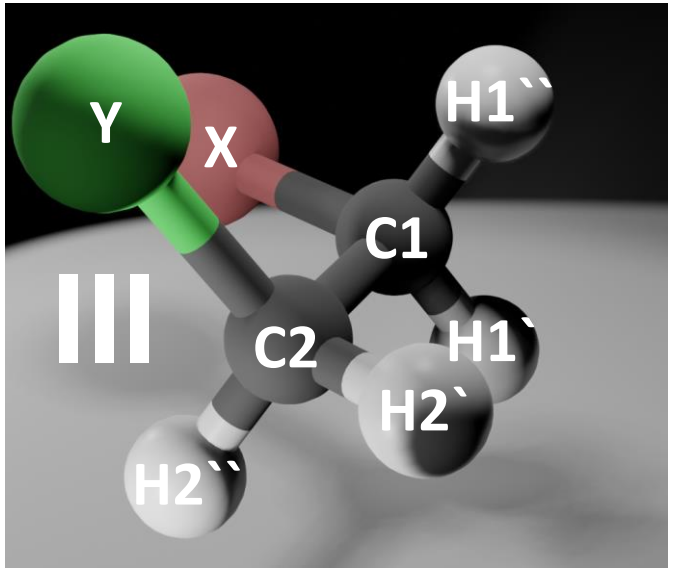
Symmetry

Are H2`and H2`` chemically equivalent?

And now let us paint the protons a little bit.



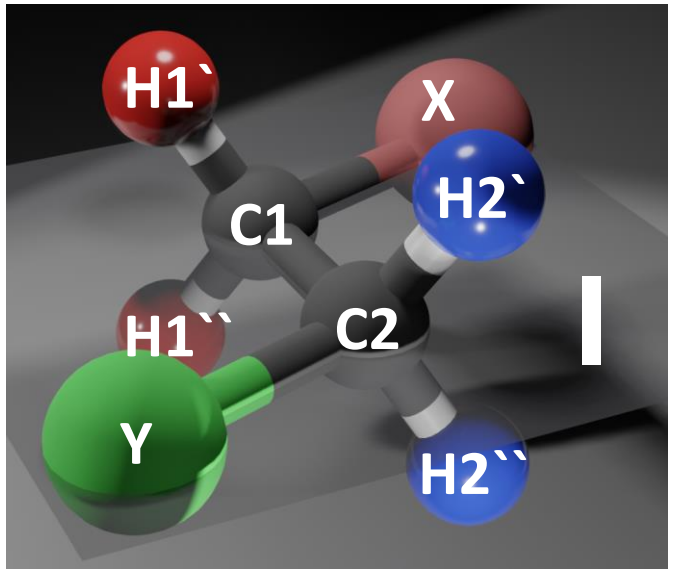




Symmetry

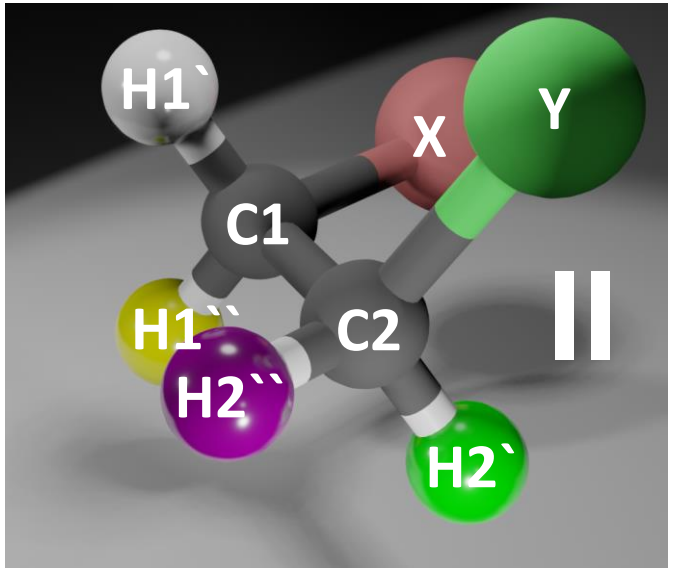
Are H2`and H2`` chemically equivalent?

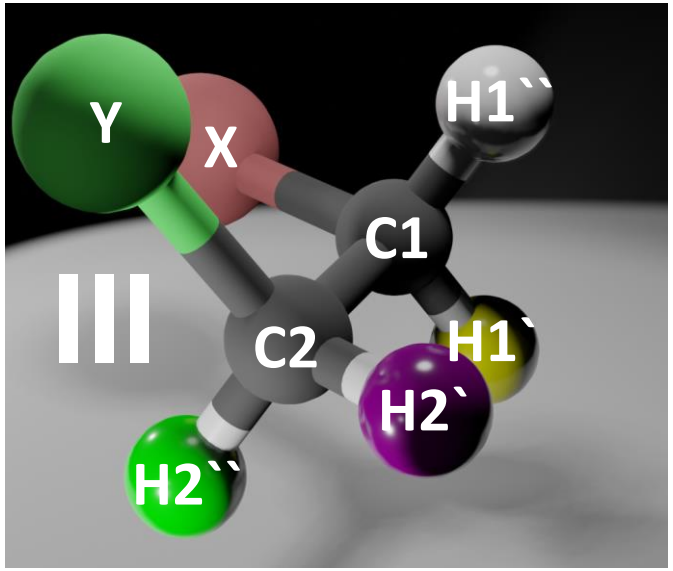
Different colours mean different chemical shifts, identical colours represent identical chemical shifts. Alltogether we have **six** different chemical shifts for the four protons inside the three rotamers.



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

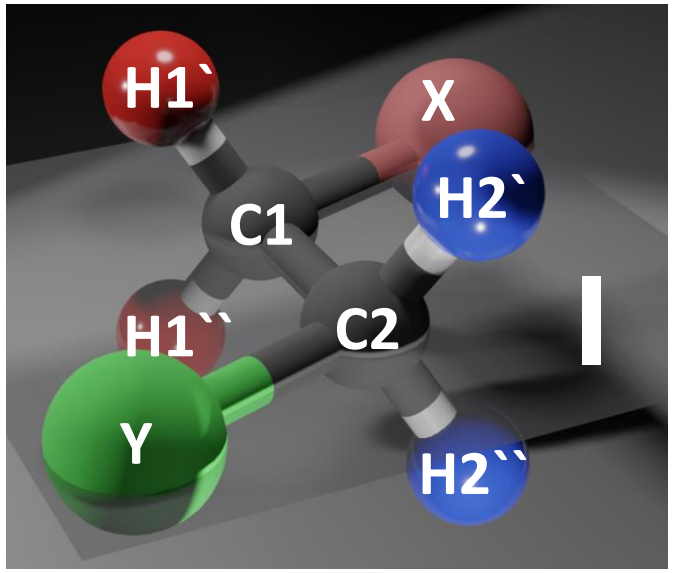
$$p_{II} = p_{III}$$

and

$$p_I + p_{II} + p_{III} = 1$$

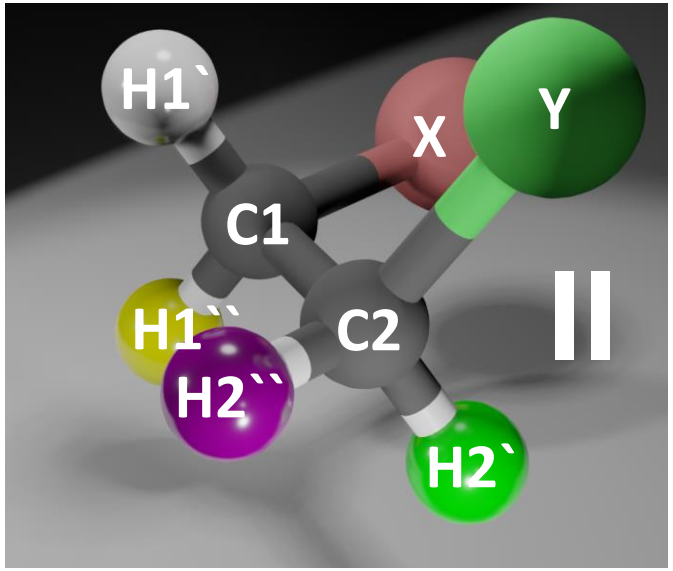
To keep the following equations short, we use single letters for the six different chemical shifts as follows:

$\delta_{H(red)}$ = **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)*

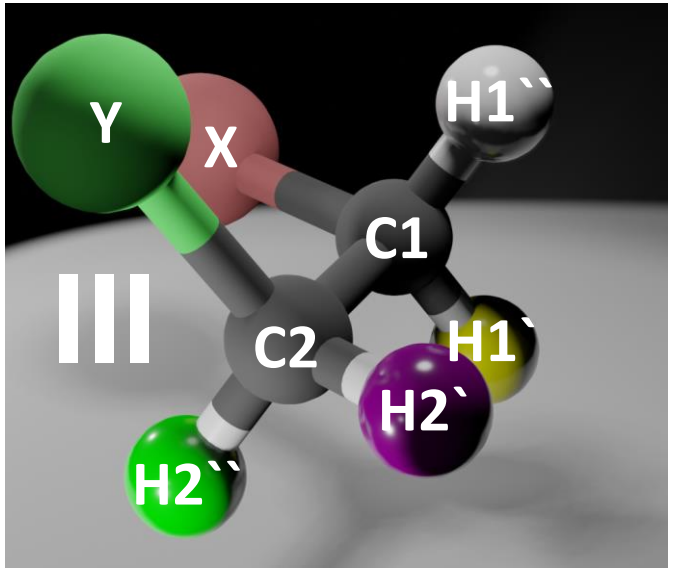


p_I (rotamer population)

p_{II}



p_{III}



Symmetry

Are H2`and H2`` chemically equivalent?

Now we get for the four protons

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

With the boundary condition

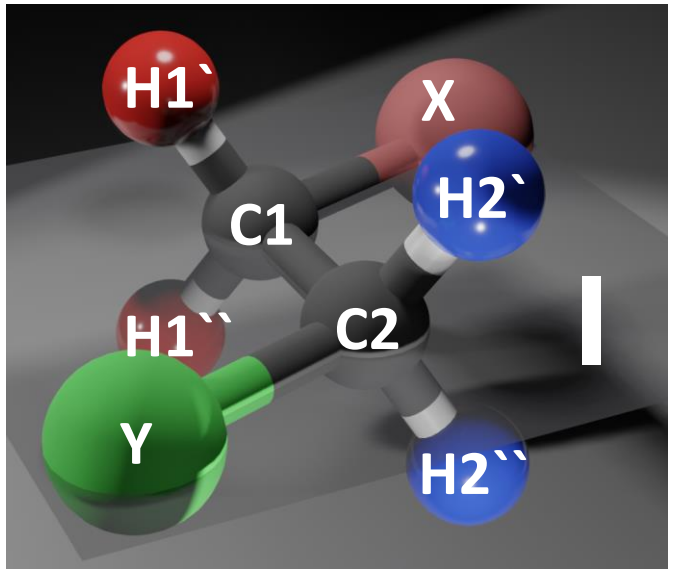
$$p_{II} = p_{III}$$

we get

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

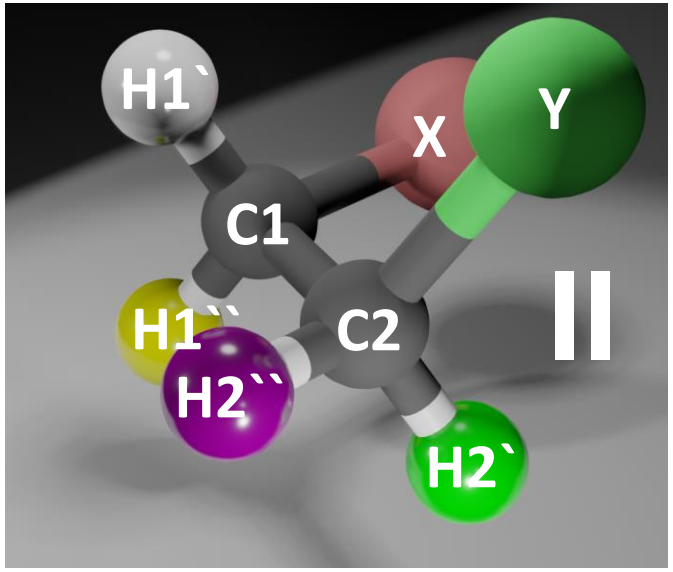
and

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

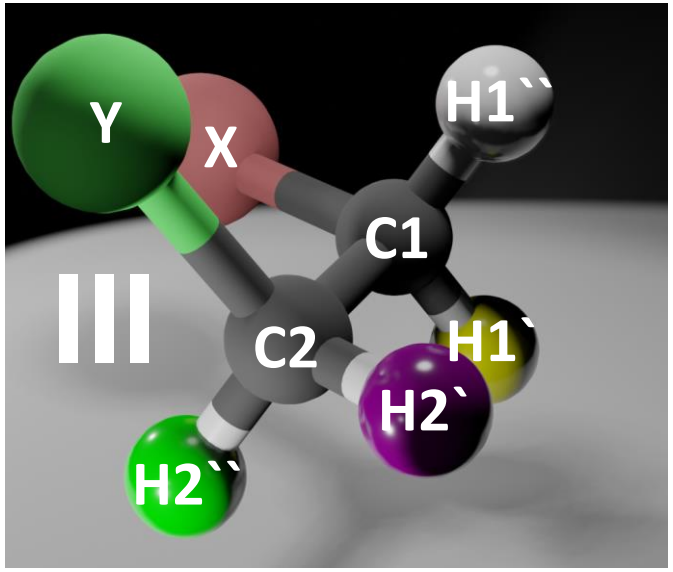


p_I (rotamer population)

p_{II}



p_{III}



Symmetry

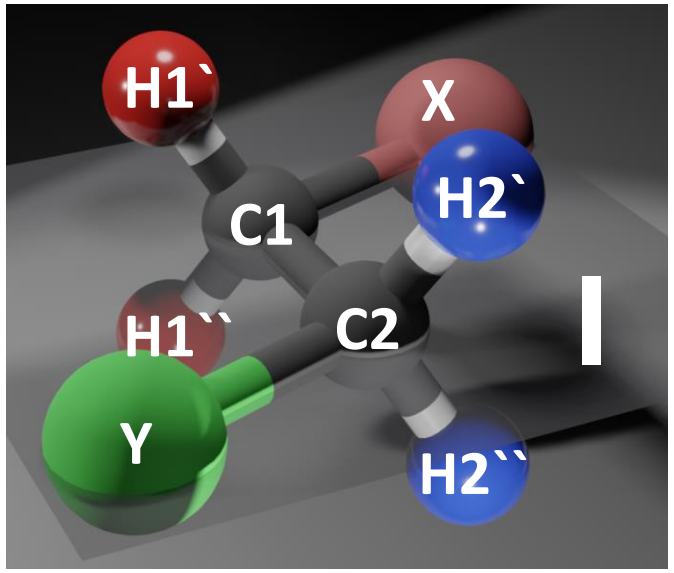
Are H2`and H2`` chemically equivalent?

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**.

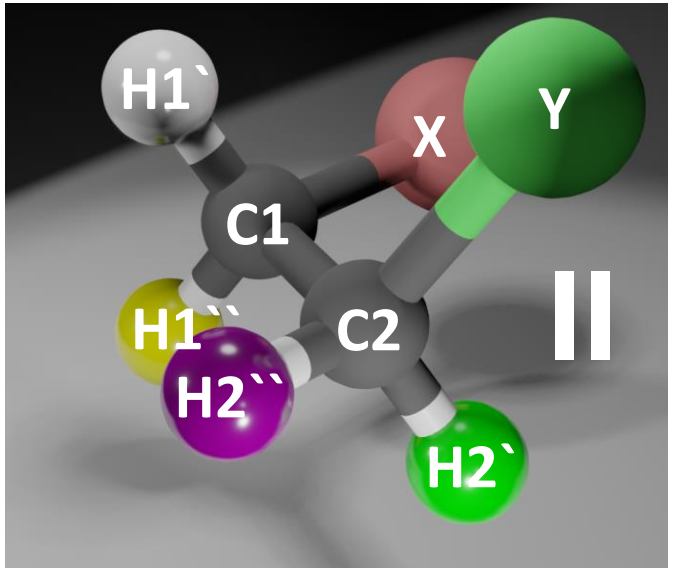
But, leaving that aside for the moment, let us return to the main question:

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

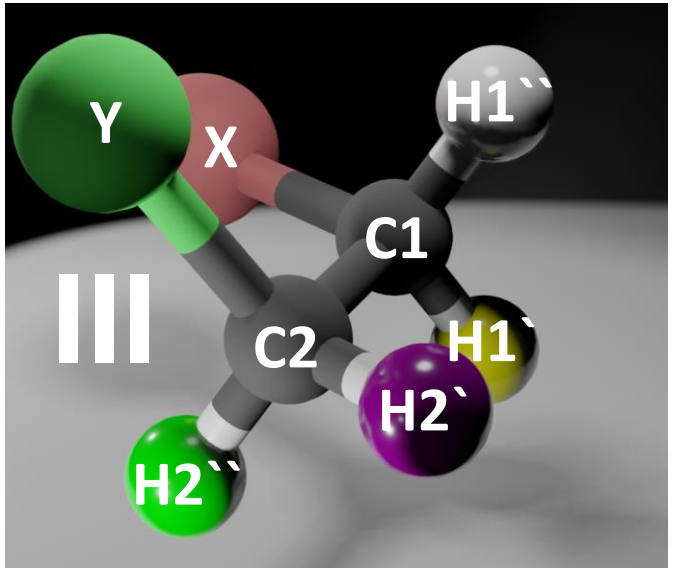


p_I (rotamer population)

p_{II}



p_{III}



Symmetry

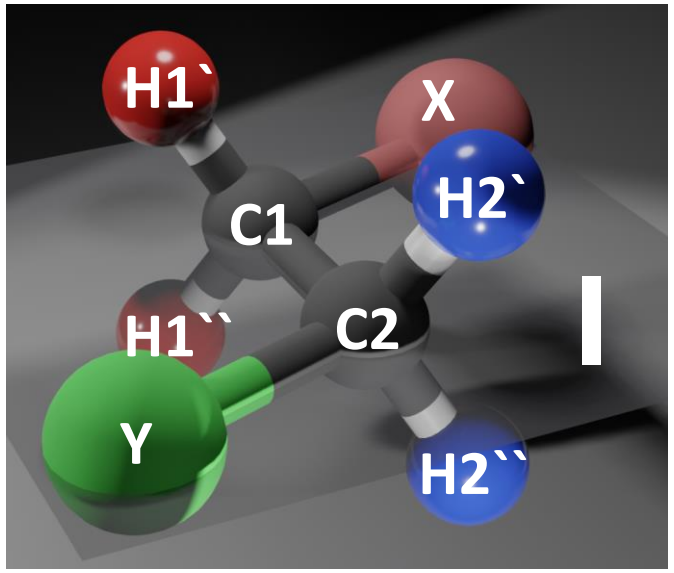
Are H2`and H2`` magnetically equivalent?

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

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

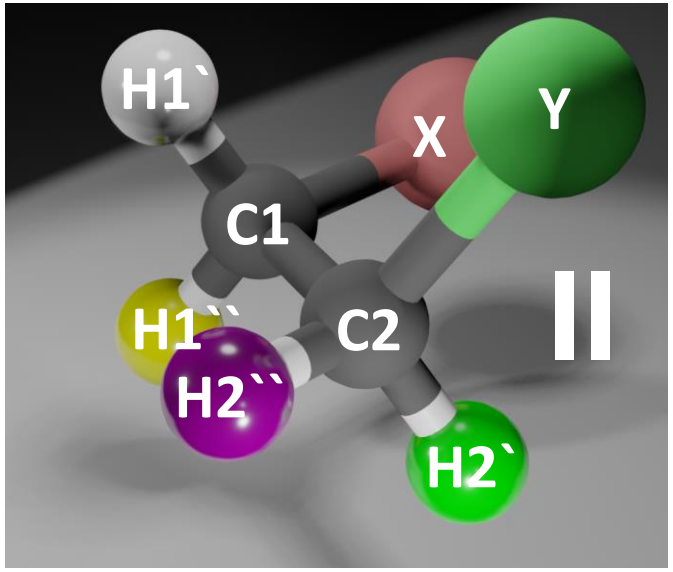
is fulfilled.
Of course the same has to be valid, if we replace **H1`** by **H1``** on both sides of the equation.

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

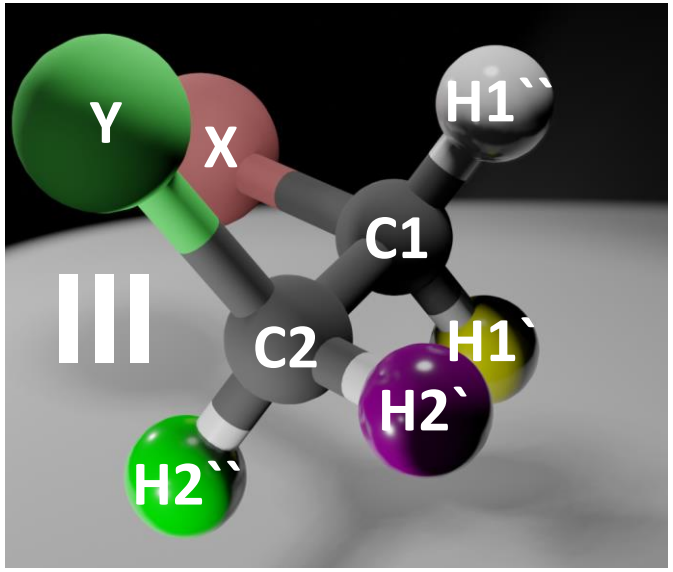


p_I (rotamer population)

p_{II}



p_{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

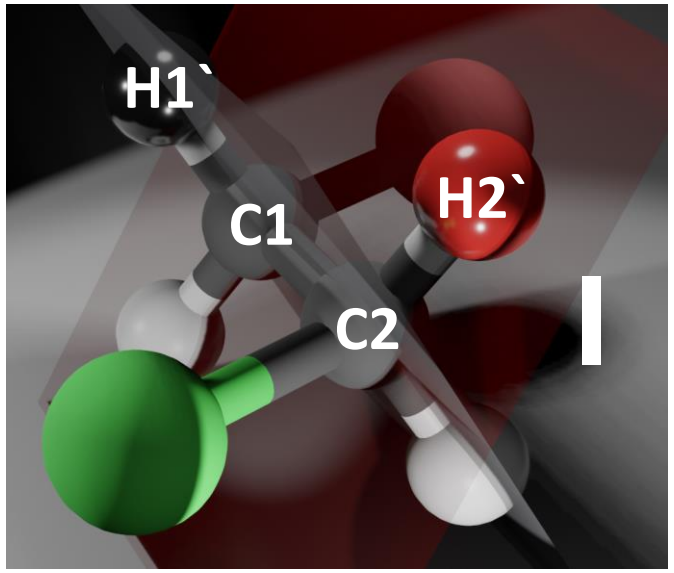
H1`, **C1** and **C2**,

the second one from the atoms

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

The dihedral angles between these planes are

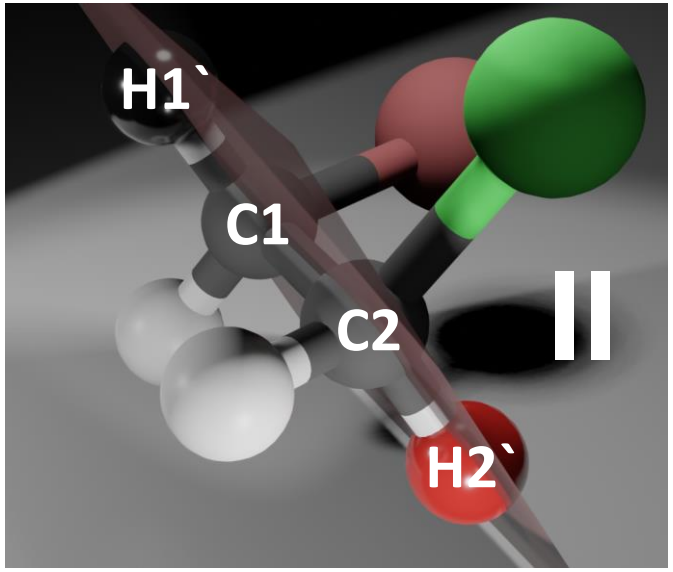
rotamer **I** – 60 degree
rotamer **II** – 180 degree
rotamer **III** – 60 degree



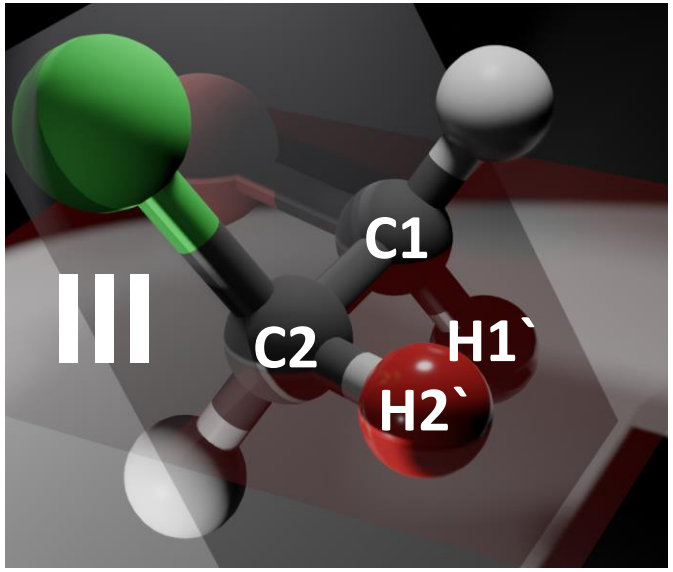
p_I (rotamer probability)

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`**

$J_{L(arge)}$

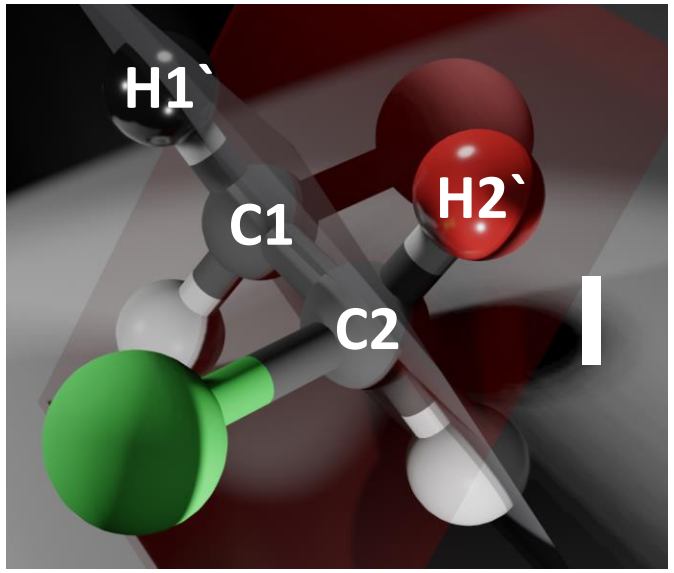
if the dihedral angle is 180 degree and

$J_{S(mall)}$

in the case of 60 degree.

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

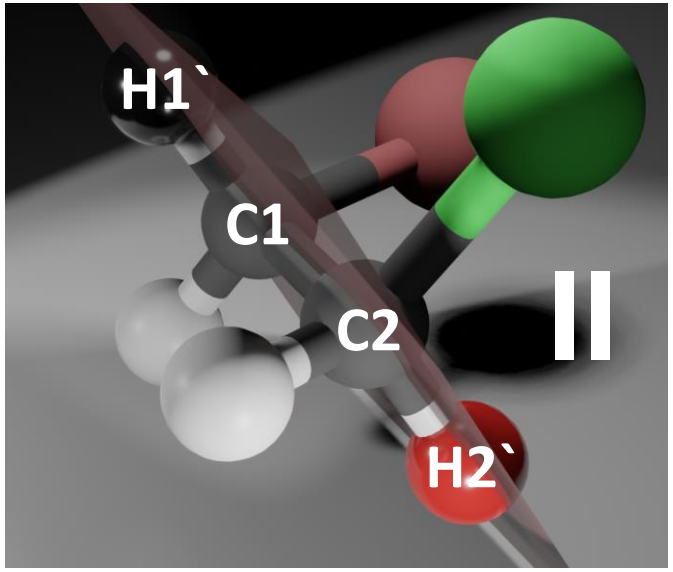
J_S



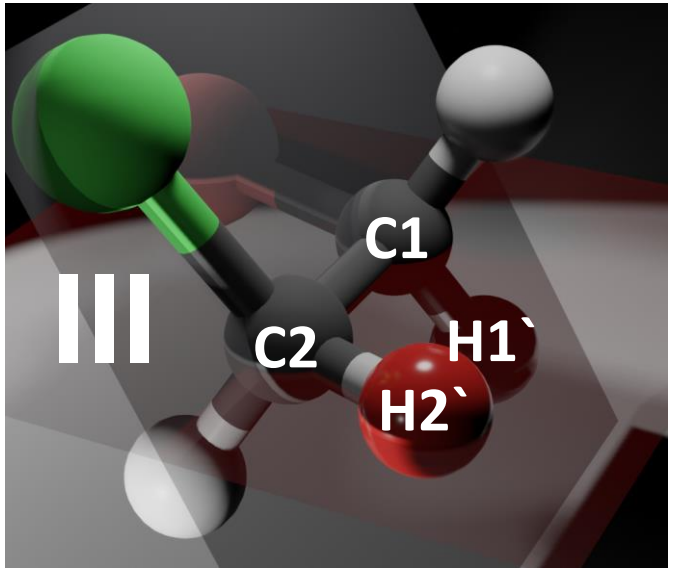
p_I (rotamer probability)

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

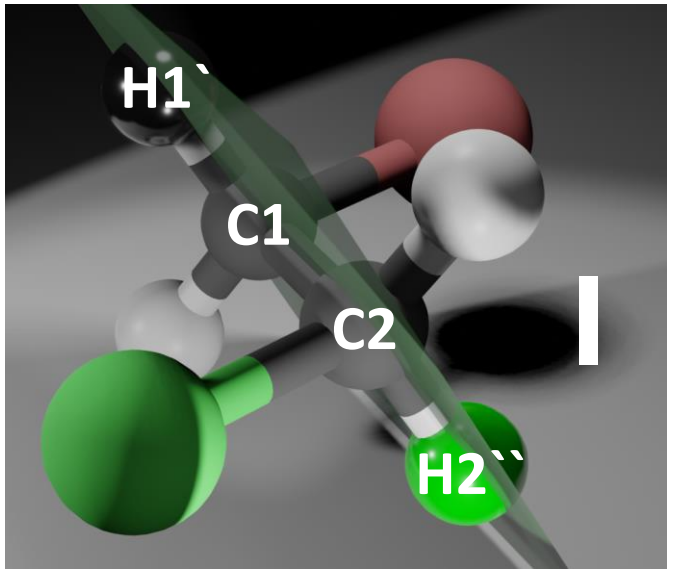


Symmetry

Are H2`and H2`` magnetically equivalent?

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

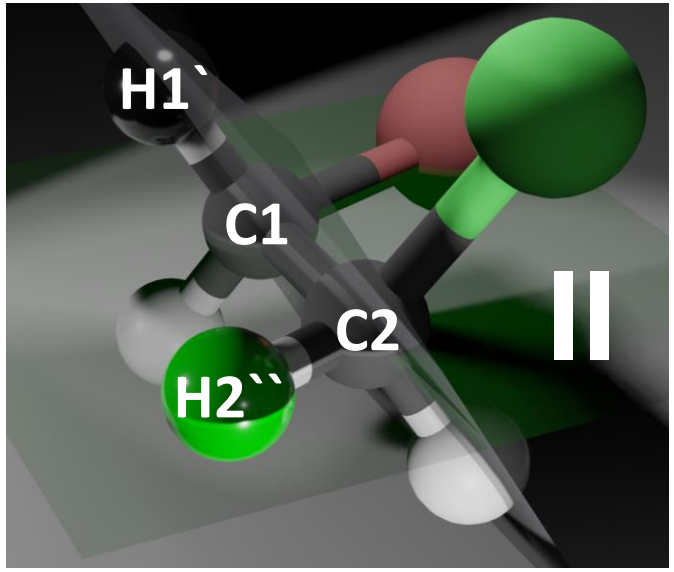
J_L



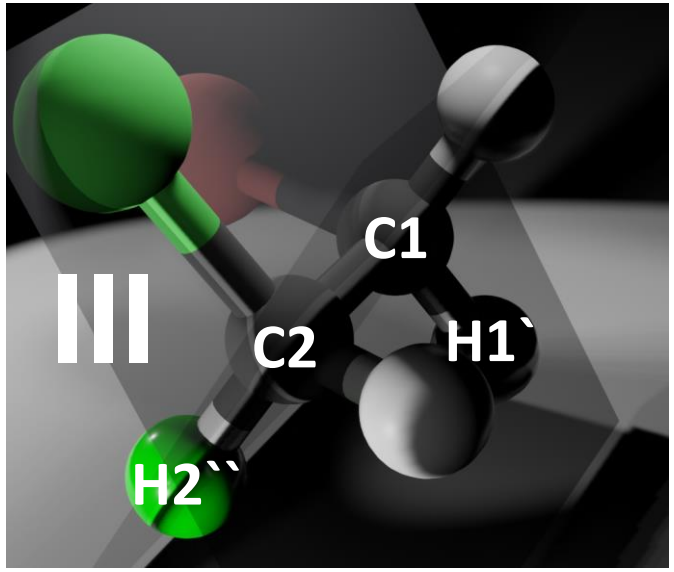
p_I (rotamer probability)

dihedral angle (H1`-C1-C2-H2``) **180°**

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



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



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

Symmetry

Are H2`and H2`` magnetically equivalent?

Finally we have

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

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

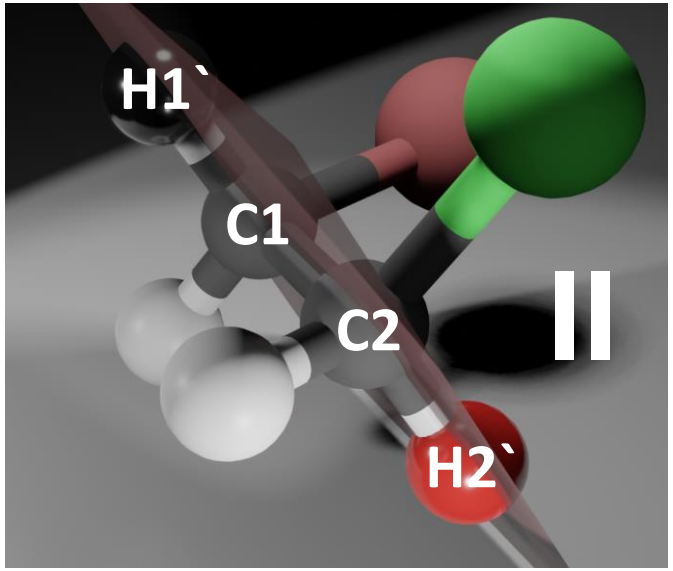
Now, please keep in mind the already known relations ($p_{II} = p_{III}$ and $p_I + p_{II} + p_{III} = 1$) and play around a little bit with the population of rotamer **I**. Start with $p_I = 0.333$.

You will see how the two coupling constants vary in opposite directions with the population p_I.

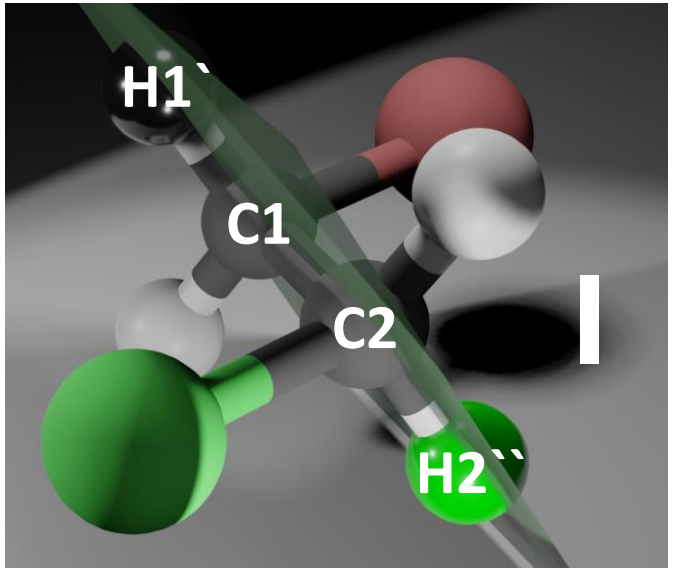
The two coupling constants would only be identical in the case of $p_I = p_{II} = p_{III}$, and with the two couplings we previously labelled as J_s being identical. But.....

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°

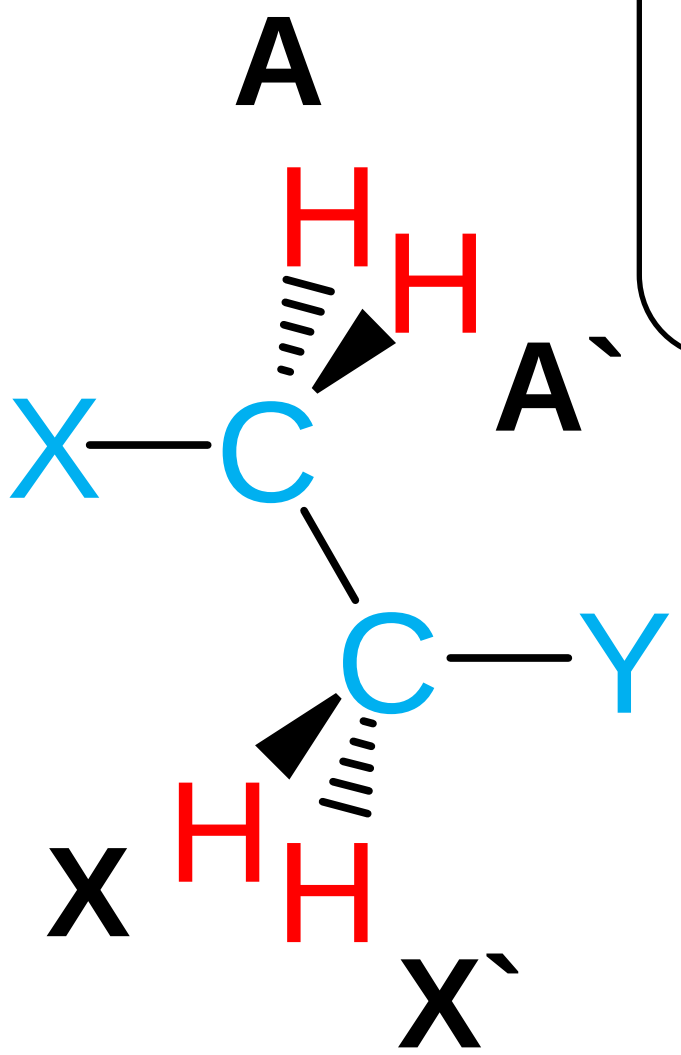


dihedral angle (H1`-C1-C2-H2`) J_L
180°



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*?

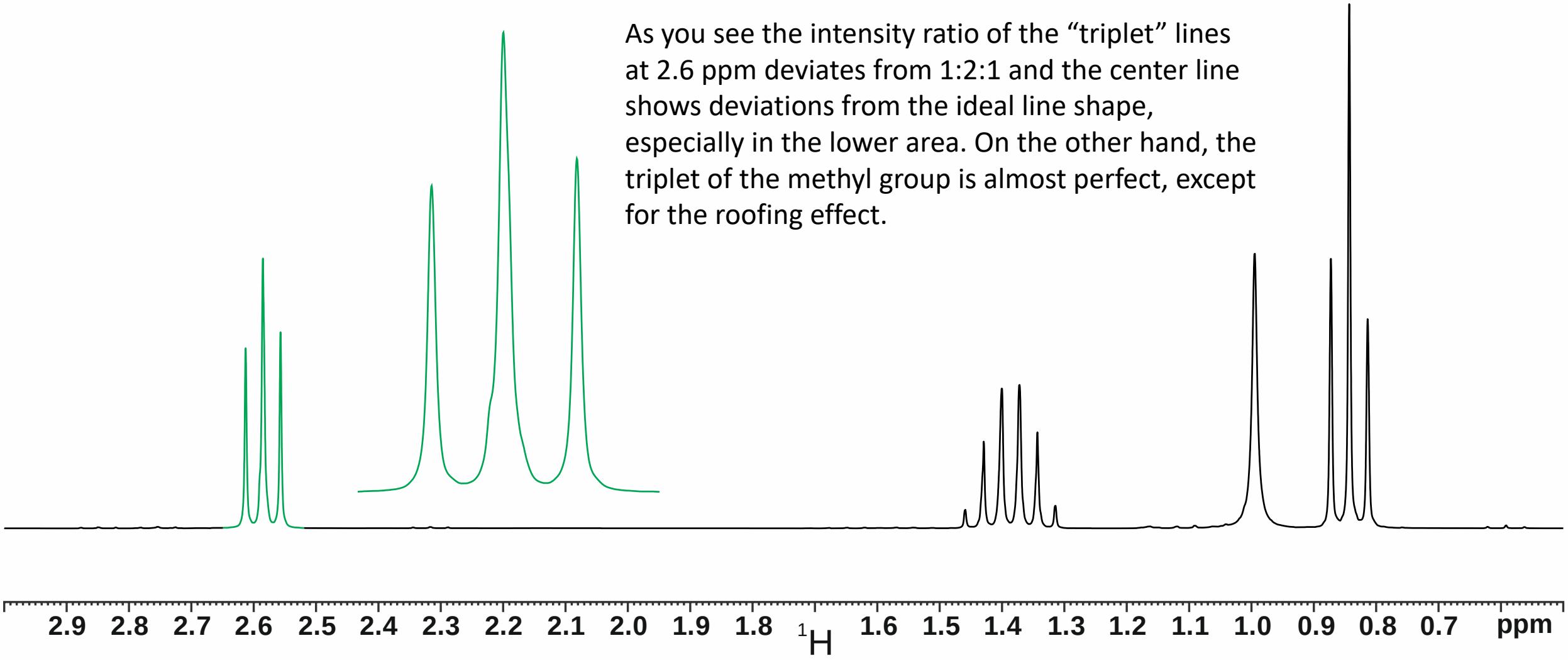
That‘s very simple. Within chiral compounds the methylene protons are chemically non-equivalent, which means, the question of magnetic equivalence doesn‘t appear.

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.



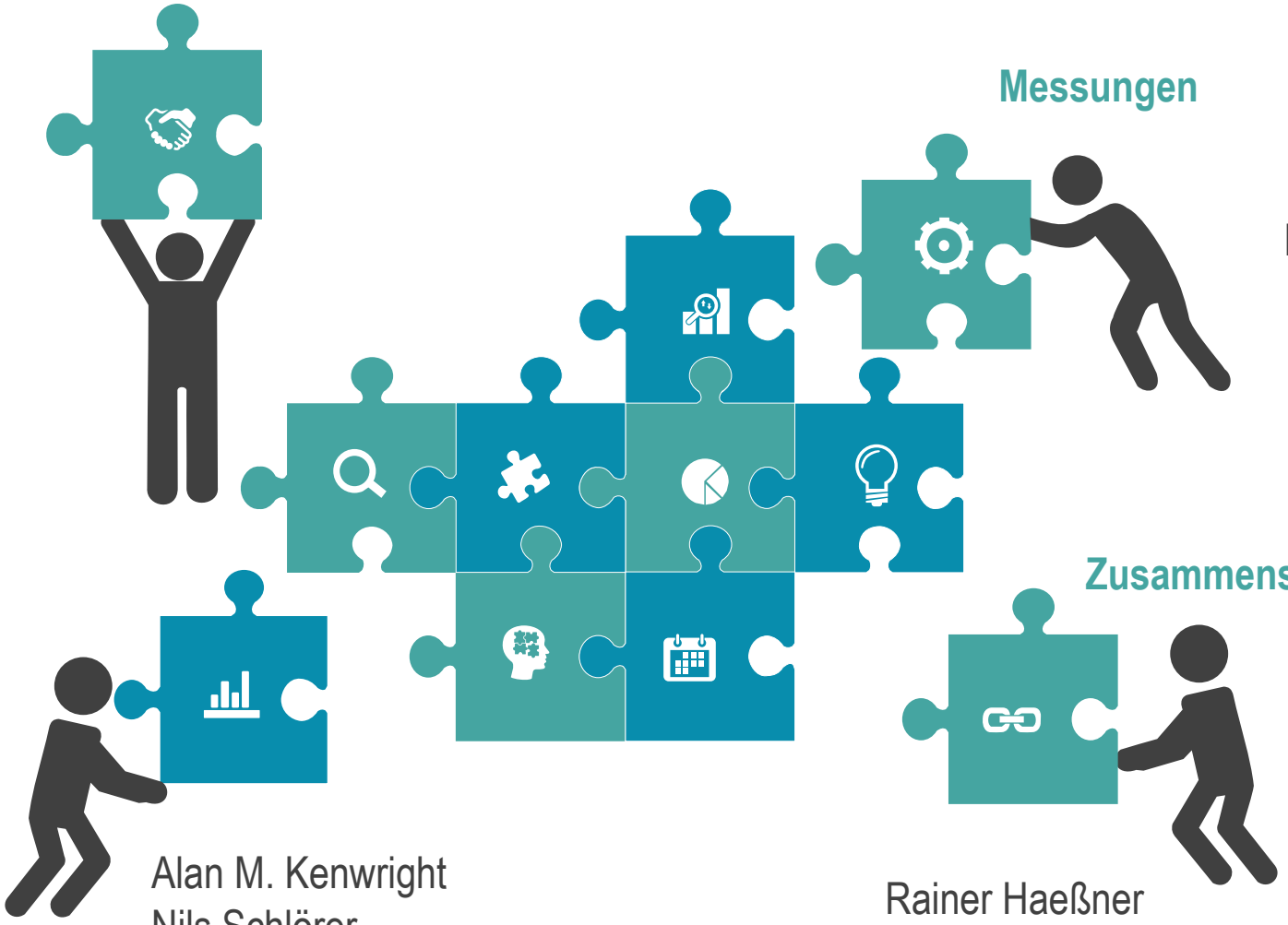
Beiträge

Spektrometerzeit

TU München

Messungen

Rainer Haeßner



Diskussionen

Alan M. Kenwright
Nils Schlörer

Zusammenstellung

Rainer Haeßner

Weitere Beispiele ...

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.