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Selective Oxidations of Alcohols and Indoles Using the Oxammonium Cation

Joseph C. Qiu, B. S.

University of Connecticut, 2011

A general procedure for the oxidation of primary alcohols to carboxylic acids, via an aldehyde intermediate, has been developed that supplements a general procedure for the oxidation of alcohols to either aldehydes or ketones. The mechanism of the oxidation of alcohols to generate aldehydes and ketones, as well as the oxidation reaction to generate acids, was explored in a series of relative rate studies. These studies have shown selectivity in the oxammonium cation oxidations, which was demonstrated by sequential, selective oxidation of a compound possessing two different primary alcohol functionalities.

The reactions of the oxammonium cation with nitrogen heterocycles, specifically indole and a few of its derivatives, was also briefly explored. Investigations were done in both aqueous and anhydrous conditions.

Selective Oxidations of Alcohols and Indoles Using the Oxammonium Cation

Joseph Cheng-hao Qiu

A Thesis

Submitted in Fulfillment of the

Requirements for Graduation as

University Scholar and Honors Scholar

at the

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2011

Approval Page

Honors Thesis

Selective Oxidations of Alcohols and Indoles Using the Oxammonium Cation

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2011

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- To my mother and family for their constant support throughout my undergraduate career.
- Most importantly, to the Lord God almighty for giving me the endurance and wisdom to support my zealotic passion for chemical research, as well as protecting me from any potentially fatal chemical accidents.

皆さん、神様、本当にありがとうございました！

女士們**,** 先生們**,** 神**,** 我非常感謝你**!**

Thank You, Everybody! Thank You, God!

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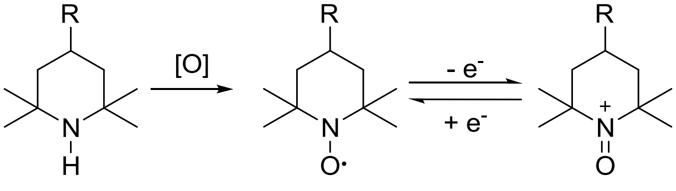
CHAPTER I: INTRODUCTION

OXAMMONIUM CATIONS

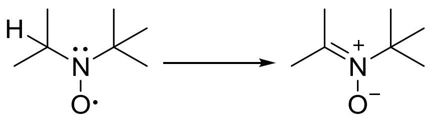
The oxammonium cation, an example of which is **1**, was first described by Golubev et al. in 1965.[1] It might be noted that the oxammonium cation has been termed iminoxyl,[1] immonium oxide,[1] oxopiperidinium, [2] 1-oxo-piperidinium, [3] nitrosonium, [4] and oxoiminium[5] in the literature. The oxammonium cation (**1**) is generated via a one-electron oxidation of the corresponding nitroxide radical (**2**). Nitroxide radicals are generally prepared by the corresponding amine, as shown in Scheme 1.1.



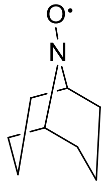
2 **1**

Scheme 1.1

Nitroxide radicals are one of a few radical species that are stable, and they have been used as electron spin resonance spin labels and as radical traps.[6] In order to generate a nitroxide radical from an amine, the amine must not possess any α-hydrogens. Should the amine possess an α-hydrogen, the nitroxide radical can rearrange to form a nitrone (Scheme 1.2).[6] There are exceptions to this generalization, as nitroxide radical **3** possesses α-hydrogens, but formation of the nitrone would be in violation of Bredt's rule without opening the ring.[6]



Scheme 1.2



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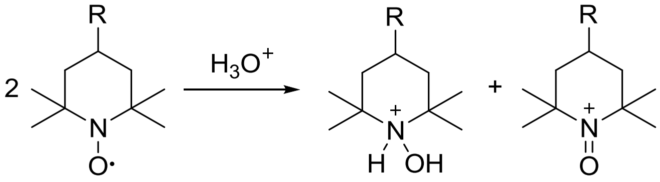
As noted above, the oxammonium cation is generated by a one-electron oxidation of the corresponding nitroxide. An alternative method for generating the oxammonium cation is to treat the nitroxide with a strong acid. In the presence of a strong acid, such as tetrafluoroboric acid or perchloric acid, the nitroxide disproportionates to give the oxammonium cation and the corresponding hydroxylammonium cation (Scheme 1.3).[5,7] Treatment of the hydroxylammonium cation with bleach gives the oxammonium cation via a two-electron oxidation.[8]



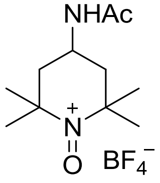
Scheme 1.3

OXAMMONIUM CATIONS AS OXIDIZING AGENTS FOR ALCOHOLS

The oxammonium cation is typically used as an oxidizing agent for alcohols. There are several methods of using or generating the oxammonium cation for this purpose. One of the more common methods is to generate the oxammonium cation *in situ* from a catalytic amount of nitroxide and a secondary oxidant, such as bleach.[9] Due to the high cost of most commercially available nitroxides, this is the one of the more cost effective methods.

Another method is to use a stoichiometric amount of the nitroxide with a strong acid. The acid causes the nitroxide to disproportionate and generates the oxammonium cation *in situ*, which then performs the oxidation.[10] It is also possible to use a peracid, such as MCPBA, along with the strong acid to oxidize the hydroxylammonium cation to the nitroxide,[11] however, undesirable side reactions may take place due to the presence of the peracid. Due to the high cost of most commercially available nitroxides, however, this acid disproportionation method is not as common as the nitroxide catalysis method.

The method that this project utilized involves the use of stoichiometric amounts of the oxammonium salt at neutral pH. Stoichiometric oxidations may also be done in acidic or basic media,[9] but these conditions were not used in any of the experiments in this project. A disadvantage of using a stoichiometric oxidation is the fact that commercially available oxammonium salts are expensive. However, the oxammonium salt used in this project (**4**) is easily prepared on a large scale from cheap, readily available 4-amino-2,2,6,6-tetramethylpiperidine.[8]



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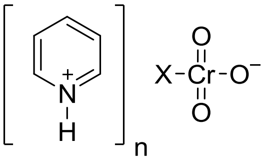
COMPARISON TO OTHER OXIDATION METHODS

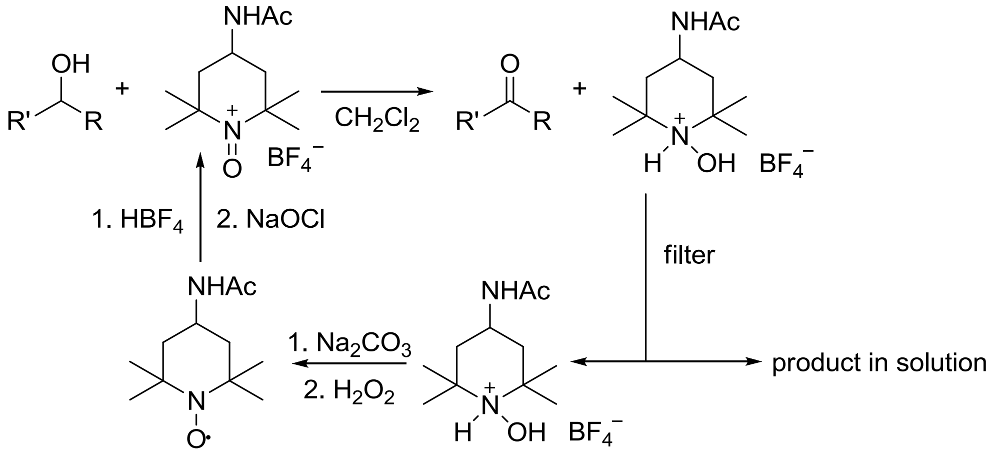
The oxammonium cation is one of the more environmentally-friendly reagents used to oxidize alcohols. One of the most commonly used methods for the oxidation of alcohols involves the use of heavy metals, such as chromium or manganese, neither of which are desirable in the environment. Furthermore, many chromium reagents, such as pyridinium chlorochromate (**5**) or pyridinium dichromate (**6**), contain chromium(VI), which is known to be a carcinogen.[12] The advantage of using these chromium reagents is that they are commercially available and are relatively inexpensive. In addition, chromium reagents have been widely used as oxidizing agents for alcohols for nearly a century, so there is a wealth of knowledge on their use.[13] The disadvantage to using chromium reagents, aside from their toxicity, is that chromium-laden tars are obtained as byproducts of the reaction. Undesirable side reactions may also occur which may result in necessitating the use of column chromatography to isolate the product. There is also a chance for over-oxidation to occur with chromium reagents. When using the oxammonium salt, however, the product of the reaction can simply be



5: n = 1, X = Cl

6: n = 2, X = CrO_3^-

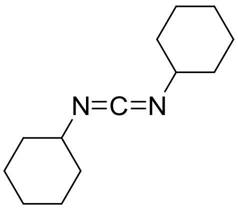
separated from the hydroxylammonium salt byproduct via filtration (Scheme 1.4).[7,8] The product can be recovered from the filtrate by evaporation of the solvent, while the oxammonium salt can be regenerated from the hydroxylammonium salt via the nitroxide (Scheme 1.4).[7,8]



Scheme 1.4

The other heavy metal often used in the oxidation of alcohols is manganese(IV) as manganese dioxide, which needs to be activated. Oxidations using manganese dioxide are comparable to oxidations using the oxammonium salt in that the product can be isolated from the byproduct by simple filtration. In both cases, the product is pure enough to be used without further purification. The advantage of using activated manganese dioxide is that it is commercially available. However, much like the chromium reagents, it produces a 'messy' reaction mixture and chromatography needs to be done to monitor the reaction.[9] In contrast, the oxammonium salt reaction is colorimetric; that is, there is a color change from a yellow slurry at the start of the oxidation to a white slurry when the reaction is complete. This makes monitoring the reaction a trivial matter, as long as stoichiometric amounts of the oxammonium salt are used. Manganese dioxide oxidation works well only with certain alcohols,[14] whereas the oxammonium salt oxidizes nearly any primary or secondary alcohol.

One alternative method of oxidizing alcohols that does not involve the use of a heavy-metal reagent is the Swern oxidation, as well as the older and similar Moffatt oxidation.[15] Both oxidations use dimethyl sulfoxide as the oxidizing agent with either oxalyl chloride or trifluoroacetic anhydride as an initiator for the Swern oxidation, or dicyclohexylcarbodiimide (DCC, **7**) as an initiator for the Moffatt oxidation.[16] These oxidations are performed at low temperatures and generate foul-smelling dimethyl sulfide as a by-product. Due to the use of water-sensitive initiating agents, the reaction must also be done in anhydrous solvents. In stark comparison, the oxammonium salt oxidation can be performed at ambient temperatures and the solvent does not necessarily need to be dry. Furthermore, no foul-smelling by-products are produced in the reaction.



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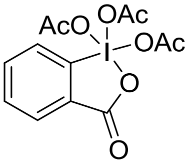
Another common alternative method of oxidizing alcohols that does not involve the use of heavy-metal reagents is the Dess-Martin oxidation.[17] This method uses the Dess-Martin periodinane (**8**), a hypervalent iodine species produced from 2-iodobenzoic acid. The main problem with this reagent is that it is potentially explosive and it is rather difficult to prepare.[18] It is commercially available; however, it is quite expensive on a per mole basis due to its high



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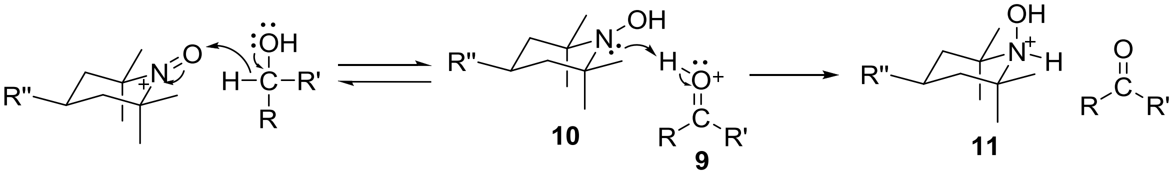
molecular mass. In comparison, the oxammonium cation itself is not explosive, although certain counter-anions, such as perchlorate, can make it capable of detonating. Although most oxammonium salts are not commercially available, they are relatively easy to synthesize.

MECHANISM OF REACTION WITH ALCOHOLS

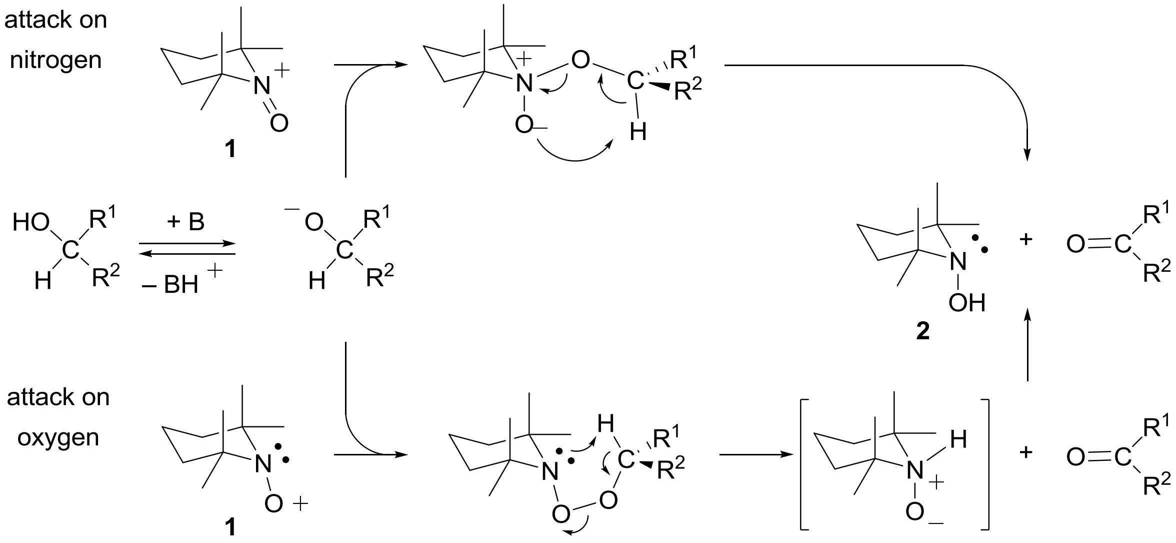
One of the aims of this project was to confirm what is believed to be the mechanism of the reaction of the oxammonium cation with alcohols at neutral pH (Scheme 1.5).[9,19] The oxammonium cation abstracts a hydride from the alcohol,



Scheme 1.5

which puts a positive charge on the carbon (not shown in Scheme 1.5) that is stabilized by resonance with the oxygen to give protonated carbonyl intermediate **9**.

Hydroxyamine **10** can deprotonate this intermediate to give hydroxylammonium cation **11** and the carbonyl product. This mechanism applies to both primary and



Scheme 1.6

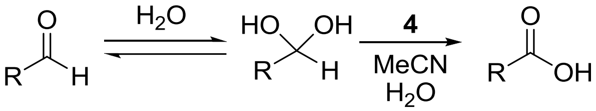
secondary alcohols, but it only operates in neutral or acidic media.

In basic media, the reaction is thought to proceed via a different mechanism (Scheme 1.6).[9,19] Under basic conditions, the alcohol is readily deprotonated to generate the corresponding alkoxide. The alkoxide can attack either the nitrogen or the oxygen of the oxammonium cation to generate a complex, although nitrogen attack is more likely.[9] The resonance structure with the positive charge on the oxygen has the oxygen lacking an octet, an unfavorable situation.

It has been found that the oxidation reaction proceeds much more quickly under basic conditions than in either neutral or acidic conditions.[9,19] This may be due to the formation of a complex between the negative alkoxide and the positive oxammonium cation, which allows the alcohol and the oxammonium cation to remain close enough to react. In neutral or acidic conditions, this complex cannot form since there is no alkoxide present; therefore, the alcohol and the oxammonium cation will stay in close proximity for only a short time. With the addition of silica gel the reaction in acidic and neutral media is accelerated,[7,9] presumably because the silica gel adsorbs both the oxammonium cation and the alcohol, keeping them close enough to each other for the reaction to take place.

OXAMMONIUM CATIONS AS OXIDIZING AGENTS FOR ALDEHYDES

As is the case for most aldehyde oxidations, aside from air, the oxammonium cation does not oxidize the aldehyde directly. Instead, it oxidizes the aldehyde hydrate, which is in equilibrium with the aldehyde, to give the corresponding carboxylic acid. This accounts for the requirement that aqueous conditions must be used for the reaction (Scheme 1.7). Aldehydes are also oxidized by the oxammonium cation in the presence of pyridine bases, such as 2,6-lutidine, however, the products are not carboxylic acids.



Scheme 1.7

Since the aldehyde hydrate is the species being oxidized to the carboxylic acid by the oxammonium salt, the equilibrium between the aldehyde and the aldehyde hydrate partially determines the rate at which the aldehyde is oxidized. If an aldehyde is conjugated to a double bond, as is the case for benzaldehydes and α,β-unsaturated aldehydes, the equilibrium lies strongly in favor of the aldehyde, since the aldehyde prefers to remain conjugated to the rest of the π-system. Therefore, it can be assumed that benzaldehydes and α,β-unsaturated aldehydes will be oxidized rather slowly by the oxammonium cation. If the aldehyde is isolated and unhindered, like formaldehyde or acetaldehyde, it is easy for a water molecule to approach the carbonyl and add to form the hydrate (Figure 1.1). If the aldehyde is sterically hindered, but still isolated, like in pivalaldehyde, the water molecule has a limited number of approaches to the carbonyl, so hydrate formation

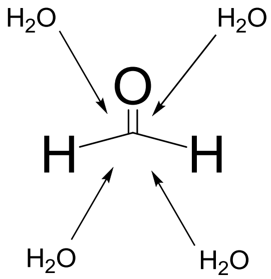


Figure 1.1

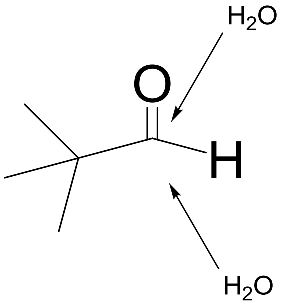


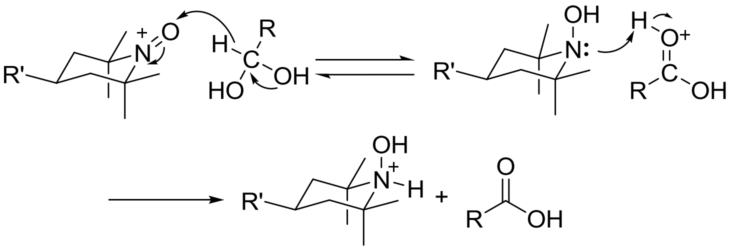
Figure 1.2

is less likely (Figure 1.2). However, an isolated, sterically-hindered aldehyde still has a higher chance of forming a hydrate than a conjugated aldehyde.

MECHANISM OF REACTION WITH ALDEHYDES

While the aldehyde-hydrate equilibrium may determine the rate at which the aldehyde is oxidized to the corresponding carboxylic acid, it is not the only factor that will determine the rate. Although a mechanism for the oxidation of aldehydes using the oxammonium cation has yet to be reported, it can be inferred based on the proposed mechanism for the oxidation of alcohols.[9,19]

As noted above, the species that is being oxidized by the oxammonium cation is the aldehyde hydrate, not the aldehyde itself. An aldehyde hydrate is essentially a geminal diol. Therefore, the mechanism for the oxidation of alcohols can also apply to the oxidation of the aldehyde hydrate (Scheme 1.8).

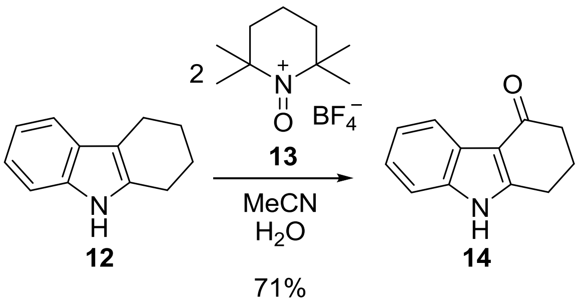


Scheme 1.8

It should be noted that, unlike the alcohol oxidations that are carried out in methylene chloride and lead to a precipitate of hydroxylammonium salt byproduct, the aldehyde oxidations are carried out in aqueous acetonitrile. In this medium, both the oxammonium salt and the hydroxylammonium salt are soluble. Since both species will be in solution, the oxammonium cation can comproportionate with the hydroxylammonium cation to generate the nitroxide. However, as there is acid present, any nitroxide that may be generated should quickly disproportionate again to give the oxammonium cation. However, there will always be some nitroxide remaining. In addition, nitroxide will be generated during the reaction due to the presence of hydrogen peroxide formed via oxidation of water by the oxammonium salt. Hydrogen peroxide is used to convert the hydroxyamine to the nitroxide, as shown in Scheme 1.4.

MISCELLANEOUS REACTIONS OF OXAMMONIUM CATIONS

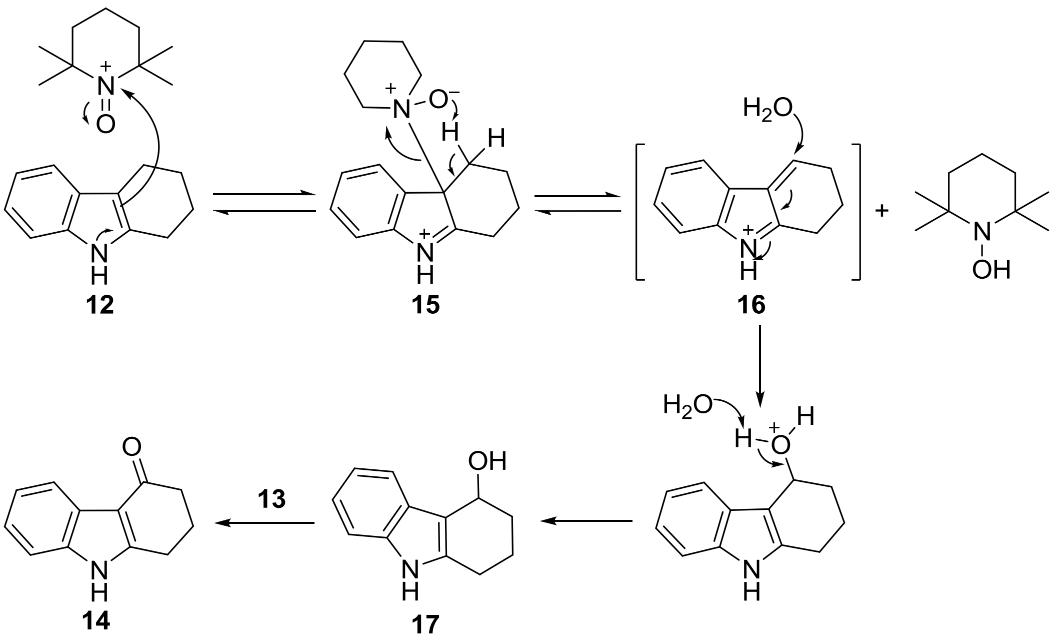
Although the oxammonium cation has been primarily used to oxidize alcohols to aldehydes or ketones, it has other potential uses as an oxidizing agent. One such use that was briefly investigated in this project involves the oxidation of



Scheme 1.9

indole alkaloids using oxammonium salt **4**. This reaction has been briefly investigated by Bobbitt et al.[20] As illustrated in Scheme 1.9, 1,2,3,4-Tetrahydrocarbazole (**12**) was treated with two stoichiometric equivalents of oxammonium salt **13** in aqueous acetonitrile to give ketone **14** in respectable yield.[20]

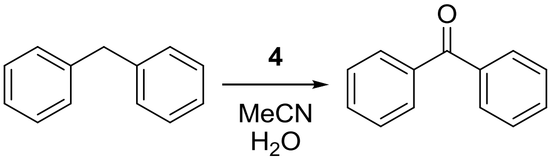
The mechanism of the reaction is believed to involve nucleophilic attack on the positive nitrogen of the oxammonium cation by the indole ring to give intermediate **15** (Scheme 1.10).[20] The oxygen on the tethered oxammonium cation can deprotonate the nearest carbon to give unsaturated imine **16**. Nucleophilic attack on this same carbon by a molecule of water gives alcohol **17**, which is then oxidized to **14** by one stoichiometric equivalent of the oxammonium cation. Re-



Scheme 1.10

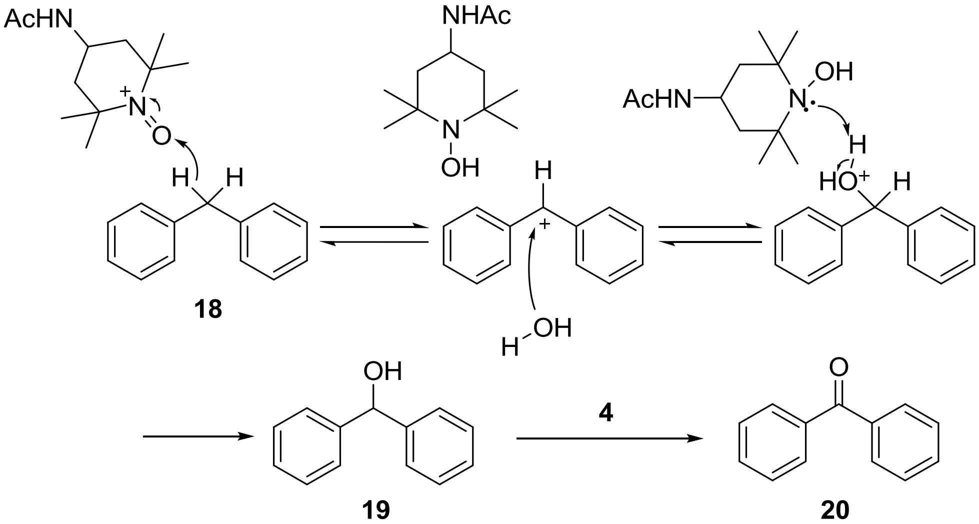
aromatization of the indole is presumably the driving force for the transformation of **16** to **17**.

Another transformation that was investigated was functionalization of the C-H bond in diphenylmethane to give benzophenone via benzhydryl alcohol (Scheme 1.11). Such a transformation has not been performed using the oxammonium salt, but it is not without precedent.[21] It appears to be similar to the oxidation of 1,2,3,4-tetrahydrocarbazole to ketone **14**, but it likely operates under a different mechanism.



Scheme 1.11

Although the mechanism of this reaction is not currently known, it can be



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19

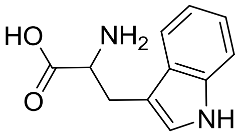
20

Scheme 1.12

inferred based on the mechanism for the oxidation of alcohols (Scheme 1.12). A rather stable carbocation can be obtained by abstraction of hydride from diphenylmethane (**18**). Nucleophilic attack by a molecule of water followed by deprotonation of the oxonium ion gives benzhydryl alcohol (**19**). Another equivalent of the oxammonium salt then oxidizes benzhydryl alcohol to benzophenone (**20**).

INDOLE OXIDATION CHEMISTRY

There is a relative large number of natural products containing the indole moiety. This is due to the fact that one of the 20 essential amino acids, tryptophan (**21**), possesses the indole moiety, and many of these indole-containing natural products are biologically prepared from tryptophan. Indole itself is an aromatic nitrogen heterocycle that is composed of a pyrrole ring fused in a [2,3] fashion to a benzene ring. There are two resonance forms of indole that are important in its chemistry (Figure 1.3). Indole is considered an electron-rich heterocycle due to the lone pair of electrons on the nitrogen contributing to the aromaticity, as opposed to



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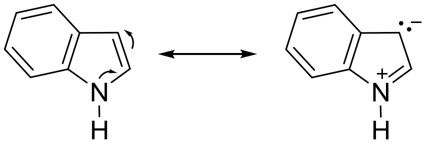
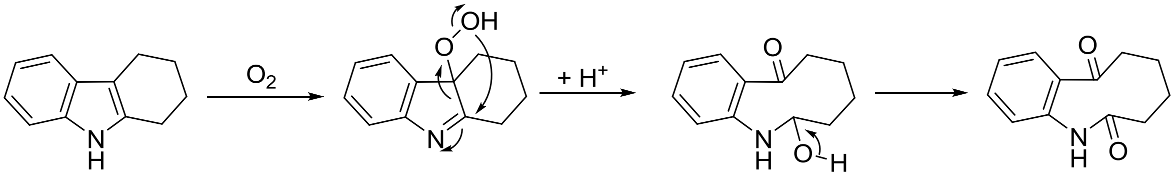


Figure 1.3

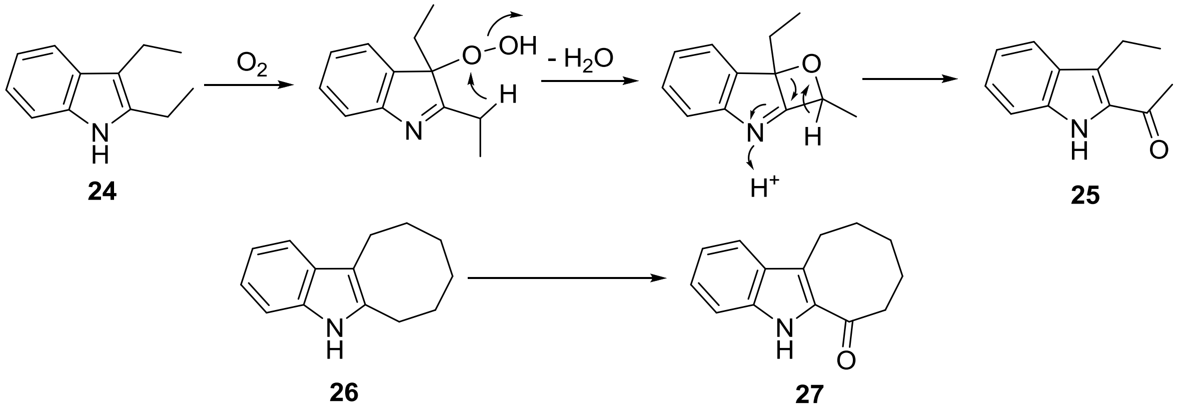
the lone pair in an electron-poor heterocycle, such as pyridine, which does not contribute to the aromaticity.

The electron-rich nature of the indole ring makes it highly susceptible to electrophilic substitution. As depicted in Figure 1.3, there is a significant amount of electron density at the C-3 position of indole due to resonance. It has been shown that the C-3 position is the most reactive site toward electrophilic substitution.[19] However, delocalization of the electron density from the nitrogen atom to the C-3 position means that indole is not as likely to accept a proton, making it a weak base (pK_a of the conjugate acid has been quoted as -2.5)[22] compared to pyridine (pK_a of the pyridinium cation has been quoted as 5.2)[23] where the lone pair remains localized on the nitrogen. Protonation of the indole ring leads to a loss of aromaticity, a highly unfavorable process.



Scheme 1.13

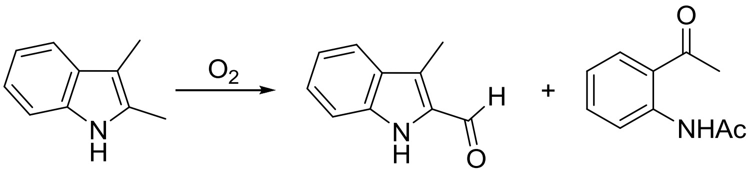
Indole oxidation chemistry was first investigated in the early 1950's, beginning with the autoxidation of 1,2,3,4-tetrahydrocarbazole in the presence of oxygen gas to generate hydroperoxide **22**.[24] Witkop and Patrick have shown that **22** is cleaved to give product **23** under neutral or slightly acidic conditions via the mechanism shown in Scheme 1.13.[24] This transformation is relevant to oxidations of indoles using the oxammonium cation as the reactions were conducted in neutral solution; therefore, some products of this type are to be expected in the oxammonium cation oxidations. Heating indole hydroperoxides in water increases the chance of cleavage.



Scheme 1.14

Another relevant reaction that can occur due to the formation of indole hydroperoxides has been observed on several occasions. Leete observed that 2,3-diethylindole (**24**) exposed to air and light for several days turned from a crystalline solid to a viscous liquid that showed strong IR absorption in the carbonyl range: the product was identified as 2-acetyl-3-ethylindole (**25**).[25] Witkop et al. observed a similar transformation with indole derivative **26** to give ketone **27**.[26]

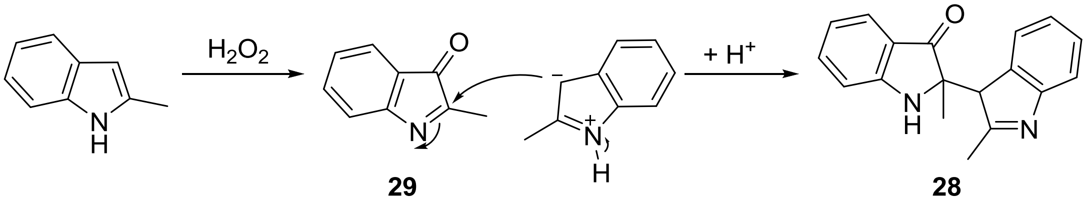
Both of these transformations are depicted in Scheme 1.14, along with the



Scheme 1.15

proposed mechanism for the reaction.[25] Aldehydes can also be generated by the same mechanism, as observed by Taylor for 2,3-dimethylindole (Scheme 1.15).[27] It should be noted that the major product of the autoxidation of 2,3-dimethylindole was the cleaved product.[27]

Peroxides often cleave the indole ring in the same fashion as shown in Scheme 1.13. However, it has been observed that oxidative coupling occurs with

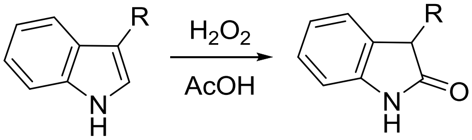


29

28

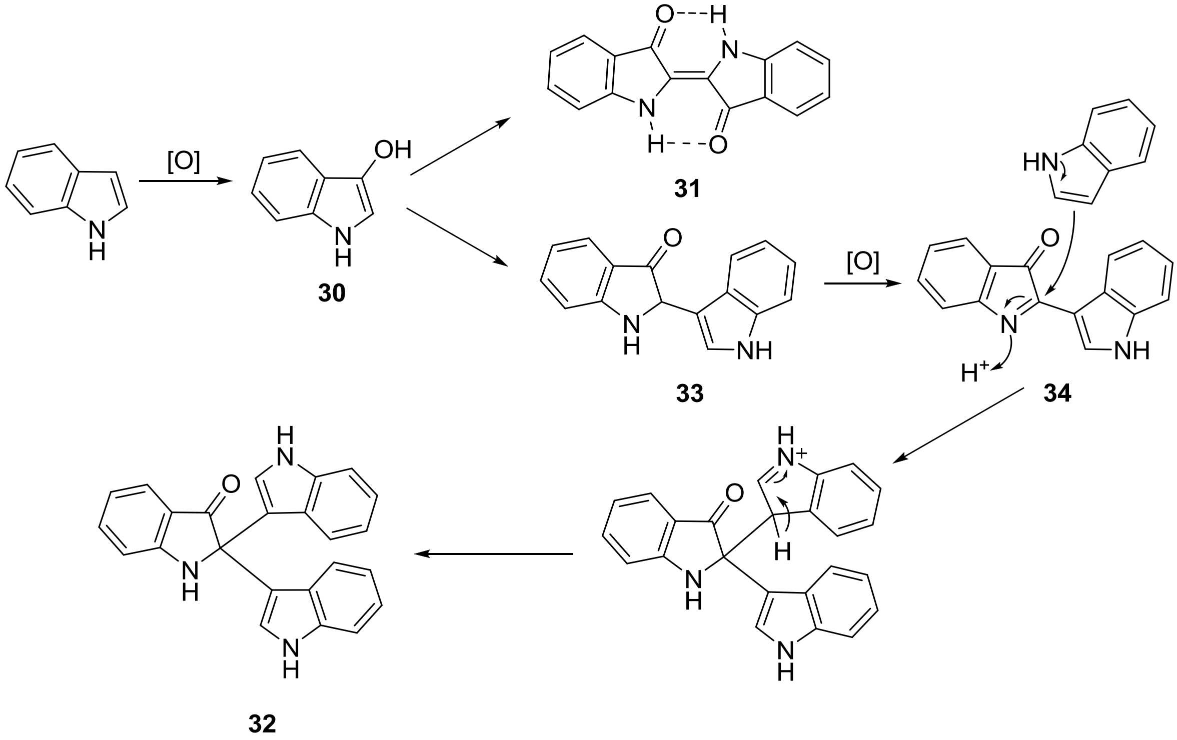
Scheme 1.16

2-methylindole to give bisindole **28**.[28] It should be noted that 2-methylindole is first oxidized to indoxyl **29**, to which 2-methylindole can couple via nucleophilic attack



Scheme 1.17

due to greater electron density at the C-3 position, courtesy of the methyl group via induction (Scheme 1.16).[28] Similar oxidations of 3-methylindole and tryptophan to give the corresponding oxindoles have also been observed, although no coupling occurs (Scheme 1.17).[29] Since the oxammonium cation can react with any water that is present in the reaction solution to give hydrogen peroxide, these reactions may be expected to occur.



Scheme 1.18

Indole itself can also autoxidize in the presence of air and light or in the presence of peroxides.[28] As shown in Scheme 1.18, the product of autoxidation is indoxyl (**30**), which can further react to form indigo (**31**) or even a trimeric product (**32**).[28] The formation of the trimeric product has been suggested to result from oxidation of leucoindoxyl red (**33**) to indoxyl red (**34**).[28] The C-2 position of the indoxyl portion of **34** is susceptible to nucleophilic attack by the C-3 carbon of indole, giving **32**.[28]

A number of oxidations of indole derivatives using the oxammonium cation have already been performed. As mentioned above, Bobbitt et al. has oxidized tetrahydrocarbazole and similar analogues to their respective ketones in aqueous acetonitrile using oxammonium salt **13**.[20] However, these reactions have not been investigated in anhydrous conditions. To this end, this project briefly explored the reaction of oxammonium salt **4** with various indoles in anhydrous methylene chloride.

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CHAPTER II: RESULTS AND DISCUSSION

RELATIVE RATES OF OXIDATION OF ALCOHOLS

The experimental data and calculations for the relative rates of oxidation of primary alcohols by the oxammonium cation. Most experiments were repeated multiple times to ensure reproducibility, so average values have been reported along with their standard deviations. In the case of *para*-nitrobenzyl alcohol and *para*-fluorobenzyl alcohol, some of the multiple experiments were competition reactions between three, or four, primary alcohols. Each competition reaction was between 2 mmol of each alcohol with 2 mmol of the oxammonium salt. The experimental data was determined at the end of each experiment, when the reaction was considered to be complete.

Aromatic Primary Alcohols with Different *para*-Substituents

para-Anisyl Alcohol vs. Benzyl Alcohol

Experiment 1

peak	**shift, δ**	**area**
benzaldehyde-aldehyde (1H)	9.98	1.00
p-anisaldehyde-aldehyde (1H)	9.83	5.76
p-anisyl alcohol-methoxy (3H)	3.76	7.50
p-anisaldehyde-methoxy (3H)	3.85	20.71

Extent of Reaction Calculations

Initial *p*-anisyl alcohol (A_0) = Final *p*-anisyl alcohol (A) + Final *p*-anisaldehyde (A’)

compound	area (methoxy)	percent	mmol
p-anisyl alcohol	7.50	26.6%	0.539
p-anisaldehyde	20.71	73.4% = conversion	1.49
initial	28.21	100.0%	2.03

Total aldehyde in reaction mixture = Final *p*-anisaldehyde + Final benzaldehyde

compound	area	percent	mmol
p-anisaldehyde	5.76	85.2%	1.49
benzaldehyde	1.00	14.8%	0.26
total	6.76	100.0%	1.75 (86.2% of 2.03)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B’)

compound	percent	mmol
benzyl alcohol	87.3%	1.78
benzaldehyde	12.7% = conversion	0.26
initial	100.0%	2.04

Ratio of Conversions: Anisyl alcohol: Benzyl alcohol = 5.78:1

Ratio of Aldehyde peaks: Anisaldehyde: Benzaldehyde = 5.76:1

Average/St. Dev.: 5.77(±0.01; 0.25%):1

Experiment 2

peak	shift, δ	area (after 0.5 mmol)	area (after 1.0 mmol)	final area
benzaldehyde-aldehyde (1H)	9.98	0.10	0.11	0.19
p-anisaldehyde-aldehyde (1H)	9.83	1.00	1.00	1.00

p-anisyl alcohol-methoxy (3H)	3.76	16.90	9.20	1.45
p-anisaldehyde-methoxy (3H)	3.85	3.39	3.59	3.33

Extent of Reaction Calculations after first 0.50 mmol

Initial *p*-anisyl alcohol (A_0) = Final *p*-anisyl alcohol (A) + Final *p*-anisaldehyde (A')

compound	area (methoxy)	percent	mmol
p-anisyl alcohol	16.90	83.3%	1.68
p-anisaldehyde	3.39	16.7% = conversion	0.34
initial	20.29	100.0%	2.02

Total aldehyde in reaction mixture = Final *p*-anisaldehyde + Final benzaldehyde

compound	area	percent	mmol
p-anisaldehyde	1.00	91.2%	0.337
benzaldehyde	0.10	8.8%	0.033
total	1.10	100.0%	0.370 (74.0% of 0.50)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B')

compound	percent	mmol
benzyl alcohol	98.4%	2.01(1)
benzaldehyde	1.6% = conversion	0.03(3)
initial	100.0%	2.04(4)

Ratio of Conversion: Anisyl alcohol: Benzyl alcohol = 10.5:1

Ratio of Aldehyde peaks: Anisaldehyde: Benzaldehyde = 10.4:1

Average/St. Dev.: 10.45(±0.07; 0.68%):1

Extent of Reaction Calculations after second 0.50 mmol

Initial *p*-anisyl alcohol (A_0) = Final *p*-anisyl alcohol (A) + Final *p*-anisaldehyde (A')

compound	area (methoxy)	percent	mmol
p-anisyl alcohol	9.20	71.9%	1.45
p-anisaldehyde	3.59	28.1% = conversion	0.57

initial	12.79	100.0%	2.02

Total aldehyde in reaction mixture = Final *p*-anisaldehyde + Final benzaldehyde

compound	area	percent	mmol
p-anisaldehyde	1.00	89.8%	0.567
benzaldehyde	0.11	10.2%	0.065
total	1.11	100.0%	0.632 (63.1% of 1.00)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B’)

compound	percent	mmol
benzyl alcohol	96.8%	1.97(9)
benzaldehyde	3.2% = conversion	0.06(5)
initial	100.0%	2.04(4)

Ratio of Conversion: Anisyl alcohol: Benzyl alcohol = 8.87:1

Ratio of Aldehyde peaks: Anisaldehyde: Benzaldehyde = 8.76:1

Average/St. Dev.: 8.82(±0.08; 0.88%):1

Extent of Reaction Calculations after final 1.00 mmol

Initial *p*-anisyl alcohol (A_0) = Final *p*-anisyl alcohol (A) + Final *p*-anisaldehyde (A’)

compound	area (methoxy)	percent	mmol
p-anisyl alcohol	1.45	30.4%	0.61
p-anisaldehyde	3.33	69.6% = conversion	1.41
initial	4.78	100.0%	2.02

Total aldehyde in reaction mixture = Final *p*-anisaldehyde + Final benzaldehyde

compound	area	percent	mmol
p-anisaldehyde	1.00	84.0%	1.40
benzaldehyde	0.19	16.0%	0.27
total	1.19	100.0%	1.67 (83.5% of 2.00)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B')

compound	percent	mmol
benzyl alcohol	86.9%	1.77
benzaldehyde	13.1% = conversion	0.27
initial	100.0%	2.04

Ratio of Conversion: Anisyl alcohol: Benzyl alcohol = 5.31:1

Ratio of Aldehyde peaks: Anisaldehyde: Benzaldehyde = 5.25:1

Average/St. Dev.: 5.28(±0.04; 0.80%):1

Experiment 3

peak	shift, δ	area (after 1.00 mmol)	final area
benzaldehyde-aldehyde (1H)	9.98	0.10	0.20
p-anisaldehyde-aldehyde (1H)	9.83	1.00	1.00
p-anisyl alcohol-methoxy (3H)	3.76	9.69	1.44
p-anisaldehyde-methoxy (3H)	3.86	4.20	4.35

Extent of Reaction Calculations after first 1.00 mmol

Initial *p*-anisyl alcohol (A_0) = Final *p*-anisyl alcohol (A) + Final *p*-anisaldehyde (A')

compound	area (methoxy)	percent	mmol
p-anisyl alcohol	9.69	69.75%	1.40
p-anisaldehyde	4.20	30.25% = conversion	0.61
initial	13.89	100.0%	2.01

Total aldehyde in reaction mixture = Final *p*-anisaldehyde + Final benzaldehyde

compound	area	percent	mmol
p-anisaldehyde	1.00	90.8%	0.607
benzaldehyde	0.10	9.2%	0.062
total	1.10	100.0%	0.669 (66.9% of 1.00)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B')

compound	percent	mmol
benzyl alcohol	96.9%	1.94(2)
benzaldehyde	3.1% = conversion	0.06(2)
initial	100.0%	2.00(4)

Ratio of Conversion: Anisyl alcohol: Benzyl alcohol = 9.82:1

Ratio of Aldehyde peaks: Anisaldehyde: Benzaldehyde = 9.84:1

Average/St. Dev.: 9.83(±0.01; 0.14%):1

Extent of Reaction Calculations after second 1.00 mmol

Initial *p*-anisyl alcohol (A_0) = Final *p*-anisyl alcohol (A) + Final *p*-anisaldehyde (A')

compound	area (methoxy)	percent	mmol
p-anisyl alcohol	1.44	24.9%	0.50
p-anisaldehyde	4.35	75.1% = conversion	1.51
initial	5.79	100.0%	2.01

Total aldehyde in reaction mixture = Final *p*-anisaldehyde + Final benzaldehyde

compound	area	percent	mmol
p-anisaldehyde	1.00	83.7%	1.51
benzaldehyde	0.20	16.3%	0.29
total	1.20	100.0%	1.80 (90.0% of 2.00)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B')

compound	percent	mmol
benzyl alcohol	85.3%	1.71
benzaldehyde	14.7% = conversion	0.29
initial	100.0%	2.00

Ratio of Conversion: Anisyl alcohol: Benzyl alcohol = 5.11:1

Ratio of Aldehyde peaks: Anisaldehyde: Benzaldehyde = 5.12:1

Average/St. Dev.: 5.115(±0.007; 0.138%):1

Experiment 4

peak	shift, *δ*	area
benzaldehyde-aldehyde (1H)	9.98	0.17
p-anisaldehyde-aldehyde (1H)	9.83	1.00
p-anisyl alcohol-methoxy (3H)	3.76	1.46
p-anisaldehyde-methoxy (3H)	3.85	4.33

Extent of Reaction Calculations

Initial *p*-anisyl alcohol (A_0) = Final *p*-anisyl alcohol (A) + Final *p*-anisaldehyde (A')

compound	area (methoxy)	percent	mmol
p-anisyl alcohol	1.46	25.3%	0.51
p-anisaldehyde	4.33	74.7% = conversion	1.51
initial	5.79	100.0%	2.02

Total aldehyde in reaction mixture = Final *p*-anisaldehyde + Final benzaldehyde

compound	area	percent	mmol
p-anisaldehyde	1.00	85.5%	1.51
benzaldehyde	0.17	14.5%	0.26
total	1.17	100.0%	1.77 (87.2% of 2.03)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B')

compound	percent	mmol
benzyl alcohol	87.4%	1.77
benzaldehyde	12.6% = conversion	0.26
initial	100.0%	2.03

Ratio of Conversion: Anisyl alcohol: Benzyl alcohol = 5.94:1

Ratio of Aldehyde peaks: Anisaldehyde: Benzaldehyde = 5.90:1

Average/St. Dev.: 5.92(±0.03; 0.48%):1

Average/St. Dev. (prop. error): 5.66(±0.05; 0.93%):1

para-Nitrobenzyl Alcohol vs. Benzyl Alcohol

Experiment 1

peak	shift, *δ*	area
benzaldehyde	9.98	1.00
p-nitrobenzaldehyde	10.11	0.11

Experiment 2

peak	shift, *δ*	area
benzaldehyde	9.97	7.91 (1.00)
p-nitrobenzaldehyde	10.11	1.00 (0.08[7])

para-Fluorobenzyl Alcohol vs. Benzyl Alcohol

Experiment 1

peak	shift, *δ*	area
benzaldehyde	9.98	1.22 (1.00)
p-fluorobenzaldehyde	9.92	1.00 (0.82)

para-Anisyl Alcohol vs. *para*-Nitrobenzyl Alcohol vs. Benzyl Alcohol

Experiment 1

peak	**shift, *δ***	**area**
benzaldehyde	9.98	1.00
p-nitrobenzaldehyde	N/A	0.09(0)
anisaldehyde	9.83	6.22

para-Anisyl Alcohol vs. *para*-Nitrobenzyl Alcohol vs. *para*-Fluorobenzyl Alcohol vs. Benzyl Alcohol

Experiment 1

peak	**shift, *δ***	**area**
benzaldehyde	9.97	1.00
p-nitrobenzaldehyde	N/A	0.08(3)
anisaldehyde	9.82	6.58
p-fluorobenzaldehyde	9.91	0.71

Primary Alcohols with Different Functionalities

1-Octanol vs. Benzyl Alcohol

Experiment 1

peak	**shift, *δ***	**area**
benzaldehyde-aldehyde (1H)	9.98	1.00
octanal-aldehyde (1H)	9.69	0.07(9)
benzyl alcohol-methylene (2H)	4.63	0.53
1-octanol-methylene (2H)	3.55	3.63
octanal-methylene (2H)	2.36	0.24

Extent of Reaction Calculations

Initial 1-octanol (A_0) = Final 1-octanol (A) + Final octanal (A')

compound	area (methylene)	percent	mmol
1-octanol	3.63	93.8%	1.88
octanal	0.24	6.2% = conversion	0.12
initial	3.87	100.0%	2.00

Total aldehyde in reaction mixture = Final octanal + Final benzaldehyde

compound	area	percent	mmol
octanal	0.08	7.3%	0.12
benzaldehyde	1.00	92.7%	1.58
total	1.08	100.0%	1.70 (85.0% of 2.00)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B')

compound	percent	mmol
benzyl alcohol	21.2%	0.42
benzaldehyde	78.8% = conversion	1.58
initial	100.0%	2.00

Ratio of Conversion: 1-Octanol: Benzyl alcohol = 0.079:1

Ratio of Aldehyde peaks: Octanal: Benzaldehyde = 0.079:1

Average/St. Dev.: 0.079:1

Experiment 2

peak	shift, δ	area
benzaldehyde-aldehyde (1H)	9.98	1.00
octanal-aldehyde (1H)	9.69	0.07(5)
benzyl alcohol-methylene (2H)	4.63	0.47
1-octanol-methylene (2H)	3.55	3.43
octanal-methylene (2H)	2.36	0.24

Extent of Reaction Calculations

Initial 1-octanol (A_0) = Final 1-octanol (A) + Final octanal (A')

compound	area (methylene)	percent	mmol
1-octanol	3.43	93.6%	1.87
octanal	0.24	6.4% = conversion	0.13
initial	3.67	100.0%	2.00

Total aldehyde in reaction mixture = Final octanal + Final benzaldehyde

compound	area	percent	mmol
octanal	0.08	7.0%	0.13
benzaldehyde	1.00	93.0%	1.72
total	1.08	100.0%	1.85 (92.5% of 2.00)

Initial benzyl alcohol (B_0) = Final benzyl alcohol (B) + Final benzaldehyde (B')

compound	percent	mmol
benzyl alcohol	14.1%	0.28
benzaldehyde	85.9% = conversion	1.72
initial	100.0%	2.00

Ratio of Conversion: 1-Octanol: Benzyl alcohol = 0.075:1

Ratio of Aldehyde peaks: Octanal: Benzaldehyde = 0.075:1

Average/St. Dev.: 0.075:1

Cinnamyl Alcohol vs. Benzyl Alcohol

Experiment 1

peak	shift, δ	area
benzaldehyde	9.96	1.00
cinnamaldehyde	9.65	6.58

Experiment 2

peak	shift, *δ*	area
benzaldehyde	9.98	1.00
cinnamaldehyde	9.67	5.65

Expeirment 3

peak	shift, *δ*	area
benzaldehyde	9.98	1.00
cinnamaldehyde	9.66	6.94

Neopentyl Alcohol vs. Phenylpropargyl Alcohol vs. *para*-Nitrobenzyl Alcohol

Experiment 1

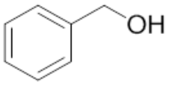
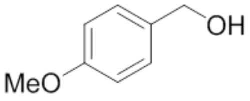
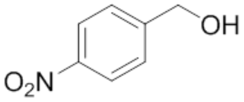
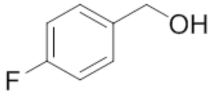
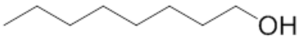
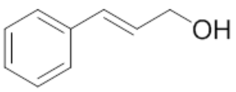
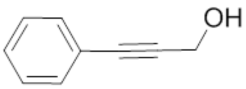
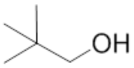
peak	shift, *δ*	area
phenylpropiolaldehyde	9.38	0.11
p-nitrobenzaldehyde	10.11	0.10
pivalaldehyde	N/A	0.01(1)

Average Product Distributions for Aromatic Alcohols (Benzyl Alcohol = 1.00)

trial	*p*-methoxy	*p*-nitro	*p*-fluoro
1	5.77	0.11	0.82
2	5.28	0.09	0.71
3	5.115	0.09	
4	5.92	0.08	
5	6.22		
6	6.58		
average	5.81	0.09 (~0.10)	0.77 (~0.75)
st. dev.	0.55 (9.47%)	0.01 (13.6%)	0.08 (10.2%)

Average Product Distributions for Primary Alcohols (Benzyl alcohol = 1.00; *p*-Nitrobenzyl alcohol = 0.10)

trial	**1-octanol**	**cinnamyl**	**phenylpropargyl**	**neopentyl**
1	0.079	6.58	0.11	0.011
2	0.075	5.65		
3		6.94		
average	0.077	6.39		
st. dev.	0.002 (3.7%)	0.67 (10.4%)		

Primary Alcohol	**Average Relative Rate**
	1.00
	5.81 ± 0.55
	0.09 ± 0.01
	0.77 ± 0.08
	0.077 ± 0.002
	6.39 ± 0.67
	0.11
	0.011

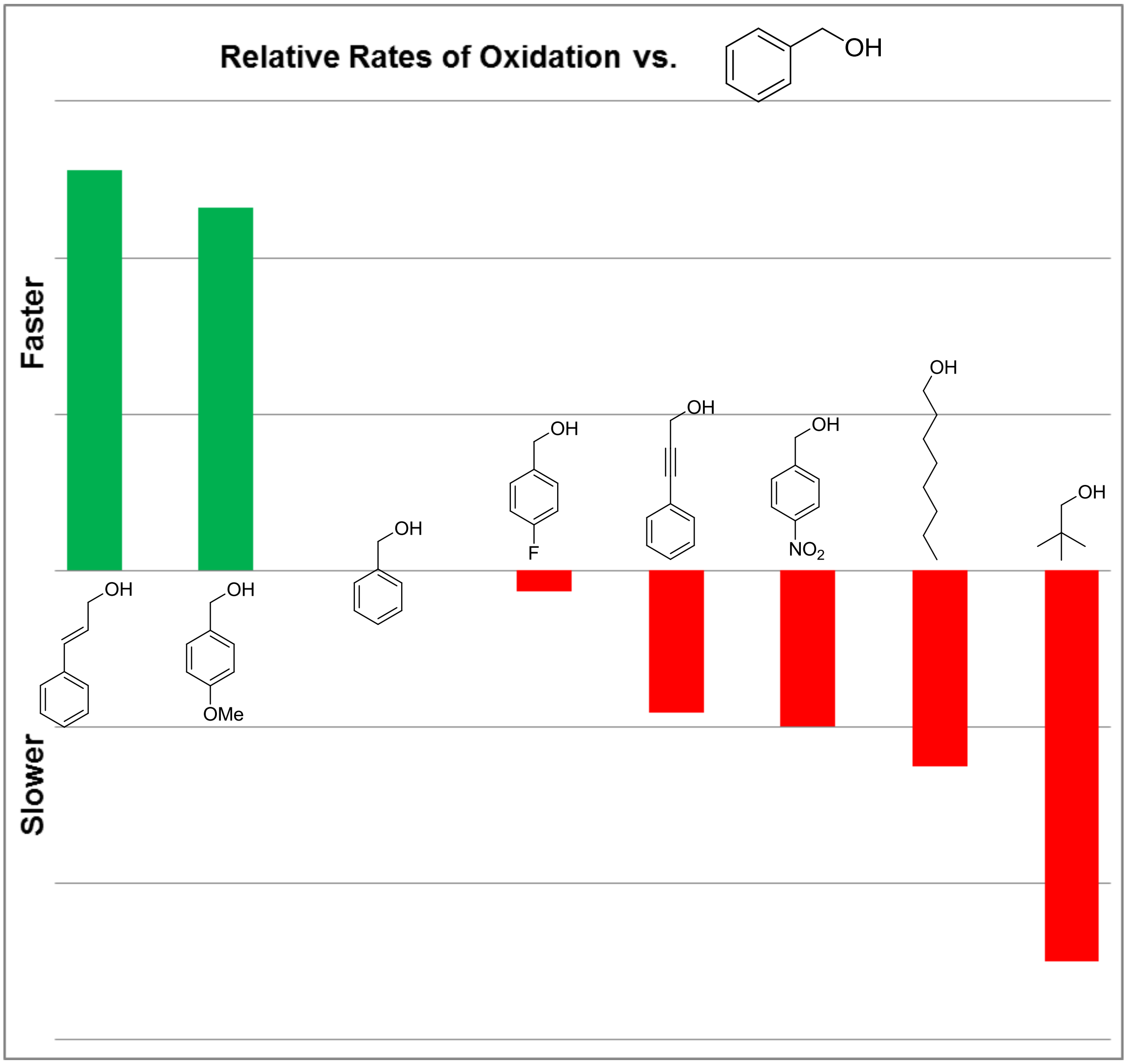


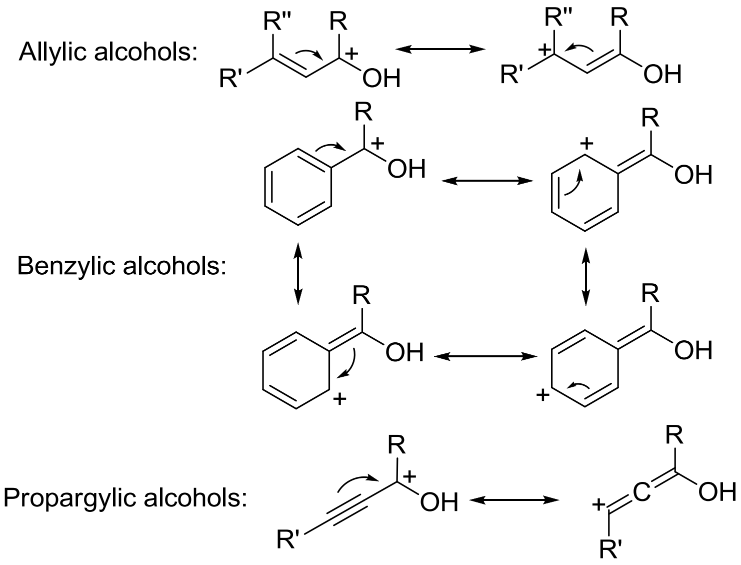
Figure 2.1

The relative rates of oxidation of the primary alcohols were determined by the integration of the aldehyde proton peaks in the ^{1}H NMR spectra. To confirm that this was a suitable method for determining the relative rates, the conversions for the oxidations of both *p*-anisyl alcohol and 1-octanol in comparison to the extent of reaction of benzyl alcohol were also determined. As both methods gave essentially equivalent results, the relative rates for the remaining alcohols were determined using the simpler method of comparing the areas of the aldehyde protons of the respective aldehydes.

The point of reference in most of the competition reactions was benzyl alcohol. In the case of those alcohols that oxidized slowly (such as neopentyl alcohol) *p*-nitrobenzyl alcohol was used as a reference. Benzyl alcohol was chosen as the point of reference because previous relative rate studies also used benzyl alcohol as a point of reference.[1]

As depicted in Figure 2.1, primary benzylic alcohols and primary allylic alcohols are oxidized much faster than are primary aliphatic alcohols and primary propargylic alcohols. The exception, *p*-nitrobenzyl alcohol, was found to oxidize at the approximately same rate as phenylpropargyl alcohol. The fact that *p*-nitrobenzyl alcohol is oxidized slowly highlights the dramatic effect that substitution *para* to the benzylic alcohol can have on the rate of oxidation.[4] Electron-donating groups, such as the methoxy group in *p*-anisyl alcohol, increase the rate of oxidation, whereas electron-withdrawing groups, such as the nitro group in *p*-nitrobenzyl alcohol, decrease the rate of oxidation.

Since the mechanism of the oxidation most likely proceeds via a carbocation intermediate, and formation of this carbocation intermediate is the rate-determining step of the reaction,[2,3] alcohols that can generate stable carbocations should react much faster than alcohols that cannot generate stable carbocations. As carbocations are essentially electron-deficient carbon centers, anything that can donate electron density to the carbocation will stabilize it. Therefore, electron-rich functional groups, such as aromatic rings or double bonds, that are directly attached to the carbocation can stabilize the positive charge by donating electron density.[5a-b] In the case of benzylic and allylic alcohols, electron density is donated via resonance, which delocalizes the positive charge, a highly stabilizing process (Scheme 2.1).[5a-b] This resonance stabilization also applies to propargylic carbocations; however, delocalization of the positive charge will result in a reasonably electronegative sp^2-hybridized carbon bearing the positive charge,



Scheme 2.1

which destabilizes the carbocation (Scheme 2.1) and should decrease the rate of oxidation, as was the case.[5a] If the carbocation is isolated and cannot engage in resonance to delocalize the positive charge, as is the case for aliphatic alcohols, the carbocation intermediate will be less stable and there is a much higher energy barrier that must be overcome in order to form this intermediate.

As mentioned above, there is a large difference in the rates of oxidation of *p*-anisyl alcohol and *p*-nitrobenzyl alcohol, with the former oxidizing nearly 60 times faster than the latter. The methoxy group in *p*-anisyl alcohol is a strongly electron-donating group and enhances the electron density of the benzene ring, leading to a more stabilized carbocation intermediate more than in benzyl alcohol. As a result, the rate of oxidation of *p*-anisyl alcohol should be increased relative to benzyl alcohol, as was the case.

On the other hand, the nitro group in *p*-nitrobenzyl alcohol is a strongly electron-withdrawing group and reduces the electron density of the benzene ring. Consequently, the rate of oxidation of *p*-nitrobenzyl alcohol should be decreased relative to benzyl alcohol, as was the case.

The stability of the carbocation intermediate was not the only factor that was found to influence the rate of oxidation. It was observed that neopentyl alcohol was oxidized more slowly than 1-octanol, despite the fact that a primary aliphatic carbocation would be generated in both cases. However, neopentyl alcohol possesses the sterically bulky *tert*-butyl group, whereas 1-octanol possesses a less bulky *n*-heptyl group. As the proposed mechanism in Scheme 1.5 implies, the oxammonium cation, which is sterically hindered itself, must be able to approach the alcohol in order to abstract a hydride. If the alcohol is also sterically encumbered, as is the case for neopentyl alcohol, the oxammonium cation cannot approach the alcohol as easily. The result is that the sterically bulky alcohol should be oxidized more slowly than a similar, less hindered alcohol, which was found to be the case.

RELATIVE RATES OF OXIDATION OF ALDEHYDES

The experimental data and calculations for the relative rates of oxidation of aldehydes by the oxammonium cation are shown below. The extents of reaction of the aldehydes were calculated in the same manner as the extents of reaction of *p*-anisyl alcohol and 1-octanol. Most experiments were repeated multiple times to ensure reproducibility, so average values have been reported along with standard deviations. The rates shown in Figure 2.2 are relative to benzaldehyde. Each competition reaction was between 2 mmol of each aldehyde with 2 mmol of the oxammonium salt. The experimental data was determined after 24 hours.

Aromatic Aldehydes with Different *para*-Substituents

p-Anisaldehyde vs. Benzaldehyde

Experiment 1

peak	shift, *δ*	area
benzaldehyde-aldehyde (1H)	10.07	6.61
p-anisaldehyde-aldehyde (1H)	9.92	7.68
p-anisaldehyde-methoxy (3H)	3.96	23.57
p-anisic Acid-methoxy (3H)	3.93	3.64

Conversion:

compound	conversion
benzaldehyde	25.87%
p-anisaldehyde	13.38%
ratio vs. benzaldehyde	0.517

Experiment 2

peak	shift, *δ*	area
benzaldehyde-aldehyde (1H)	10.07	5.53
p-anisaldehyde-aldehyde (1H)	9.92	7.14
p-anisaldehyde-methoxy (3H)	3.96	22.98
p-anisic acid-methoxy (3H)	3.93	2.94

Conversion:

compound	conversion
benzaldehyde	30.97%
p-anisaldehyde	11.34%
ratio vs. benzaldehyde	0.366

Experiment 3

peak	shift, *δ*	area
benzaldehyde-aldehyde (1H)	10.07	5.68
p-anisaldehyde-aldehyde (1H)	9.92	7.40
p-anisaldehyde-methoxy (3H)	3.96	23.64
p-anisic acid-methoxy (3H)	3.93	3.52

Conversion:

compound	**conversion**
benzaldehyde	32.97%
p-anisaldehyde	12.96%
ratio vs. benzaldehyde	0.393

***p*-Anisaldehyde vs. *p*-Nitrobenzaldehyde**

Experiment 1

peak	**shift, *δ***	**area**
p-nitrobenzaldehyde-aldehyde (1H)	10.20	19.81
p-anisaldehyde-aldehyde (1H)	9.91	13.43
p-anisaldehyde-methoxy (3H)	3.96	40.93
p-anisic acid-methoxy (3H)	3.93	5.84

Conversion:

compound	**conversion**
p-nitrobenzaldehyde	40.94%
p-anisaldehyde	12.49%
ratio vs. *p*-anisaldehyde	3.28
ratio vs. benzaldehyde	1.39

Experiment 2

peak	**shift, *δ***	**area**
p-nitrobenzaldehyde-aldehyde (1H)	10.20	17.95
p-anisaldehyde-aldehyde (1H)	9.91	14.57
p-anisaldehyde-methoxy (3H)	3.96	45.31
p-anisic acid-methoxy (3H)	3.92	3.52

Conversion:

compound	conversion
p-nitrobenzaldehyde	28.43%
p-anisaldehyde	7.21%
ratio vs. *p*-anisaldehyde	3.94
ratio vs. benzaldehyde	1.68

Experiment 3

peak	shift, *δ*	area
p-nitrobenzaldehyde-aldehyde (1H)	10.19	9.64
p-anisaldehyde-aldehyde (1H)	9.91	13.33
p-anisaldehyde-methoxy (3H)	3.95	42.18
p-anisic acid-methoxy (3H)	3.92	3.14

Conversion:

compound	conversion
p-nitrobenzaldehyde	32.18%
p-anisaldehyde	6.93%
ratio vs. *p*-anisaldehyde	4.73
ratio vs. benzaldehyde	2.01

p-Nitrobenzaldehyde vs. *p*-Fluorobenzaldehyde vs. *p*-Anisaldehyde

Experiment 1

peak	shift, *δ*	area
p-nitrobenzaldehyde-aldehyde (1H)	10.20	10.21
p-fluorobenzaldehyde-aldehyde (1H)	10.02	12.99
p-anisaldehyde-aldehyde (1H)	9.91	13.70
p-anisaldehyde-methoxy (3H)	3.95	44.55
p-anisic acid-methoxy (3H)	3.92	2.96

Conversion:

compound	conversion
p-nitrobenzaldehyde	30.17%

p-anisaldehyde	6.23%
p-fluorobenzaldehyde	11.10%
ratio vs. *p*-anisaldehyde	NO_2 – 4.84; F – 1.78
ratio vs. benzaldehyde	NO_2 – 2.06; F – 0.758

Experiment 2

peak	**shift, *δ***	**area**
p-nitrobenzaldehyde-aldehyde (1H)	10.19	5.51
p-fluorobenzaldehyde-aldehyde (1H)	10.02	7.42
p-anisaldehyde-aldehyde (1H)	9.90	7.69
p-anisaldehyde-methoxy (3H)	3.95	23.93
p-anisic acid-methoxy (3H)	3.92	2.12

Conversion:

compound	**conversion**
p-nitrobenzaldehyde	34.12%
p-anisaldehyde	8.14%
p-fluorobenzaldehyde	11.40%
ratio vs. *p*-anisaldehyde	NO_2 – 4.19; F – 1.40
ratio vs. benzaldehyde	NO_2 – 1.78; F – 0.596

p-Fluorobenzaldehyde vs. *p*-Anisaldehyde

Experiment 1

peak	**shift, *δ***	**area**
p-fluorobenzaldehyde-aldehyde (1H)	10.02	15.35
p-anisaldehyde-aldehyde (1H)	9.92	16.37
p-anisaldehyde-methoxy (3H)	3.96	51.50
p-anisic acid-methoxy (3H)	3.93	4.70

Conversion:

compound	**conversion**
p-fluorobenzaldehyde	12.93%

p-anisaldehyde	8.36%
ratio vs. *p*-anisaldehyde	1.55
ratio vs. benzaldehyde	0.658

***p-tert*-Butylbenzaldehyde vs. *p*-Anisaldehyde**

Experiment 1

peak	shift, *δ*	area
p-*t*-Butylbenzaldehyde-aldehyde (1H)	10.01	29.69
p-Anisaldehyde-aldehyde (1H)	9.91	35.57
p-Anisaldehyde-methoxy (3H)	3.95	113.41
p-Anisic Acid-methoxy (3H)	3.92	13.41

Conversion:

compound	conversion
p-*t*-butylbenzaldehyde	15.75%
p-anisaldehyde	10.57%
ratio vs. *p*-anisaldehyde	1.49
ratio vs. benzaldehyde	0.63

Aldehydes with Different Functionalities

***p*-Anisaldehyde vs Hexanal**

Experiment 1

peak	shift, *δ*	area
hexanal-aldehyde (1H)	9.75	0.59
p-anisaldehyde-aldehyde (1H)	9.92	18.72
p-anisaldehyde-methoxy (3H)	3.96	58.48
p-anisic acid-methoxy (3H)	3.92	1.18

Conversion:

compound	**conversion**
hexanal	96.93%
p-anisaldehyde	1.98%
ratio vs. *p*-anisaldehyde	49.0
ratio vs. benzaldehyde	20.8

Experiment 2

peak	**shift, *δ***	**area**
hexanal-aldehyde (1H)	9.75	1.62
p-anisaldehyde-aldehyde (1H)	9.91	18.35
p-anisaldehyde-methoxy (3H)	3.96	55.71
p-anisic acid-methoxy (3H)	3.92	0.97

Conversion:

compound	**conversion**
hexanal	91.49%
p-anisaldehyde	1.71%
ratio vs. *p*-anisaldehyde	53.5
ratio vs. benzaldehyde	22.7

Experiment 3

peak	**shift, *δ***	**area**
hexanal-aldehyde (1H)	9.76	1.35
p-anisaldehyde-aldehyde (1H)	9.93	19.62
p-anisaldehyde-methoxy (3H)	3.97	59.82
p-anisic acid-methoxy (3H)	3.94	1.08

Conversion:

compound	**conversion**
hexanal	93.26%
p-anisaldehyde	1.77%
ratio vs. *p*-anisaldehyde	52.6

ratio vs. benzaldehyde	22.4

***p*-Anisaldehyde vs. *trans*-Cinnamaldehyde**

Experiment 1

peak	shift, *δ*	area
cinnamaldehyde-aldehyde (1H)	9.73 (J = 7.6 Hz)	0.87
p-anisaldehyde-aldehyde (1H)	9.92	1.00
p-anisaldehyde-methoxy (3H)	3.96	3.09
p-anisic acid-methoxy (3H)	3.93	0.25

Conversion:

compound	conversion
cinnamaldehyde	19.53%
p-anisaldehyde	7.49%
ratio vs. *p*-anisaldehyde	2.61
ratio vs. benzaldehyde	1.11

Experiment 2

peak	shift, *δ*	area
cinnamaldehyde-aldehyde (1H)	9.74 (J = 7.6 Hz)	14.10
p-anisaldehyde-aldehyde (1H)	9.92	15.82
p-anisaldehyde-methoxy (3H)	3.96	47.90
p-anisic acid-methoxy (3H)	3.93	3.82

Conversion:

compound	conversion
cinnamaldehyde	17.92%
p-anisaldehyde	7.39%
ratio vs. *p*-anisaldehyde	2.43
ratio vs. benzaldehyde	1.03

Experiment 3

peak	**shift, *δ***	**area**
cinnamaldehyde-aldehyde (1H)	9.73 (J = 7.6 Hz)	16.33
p-anisaldehyde-aldehyde (1H)	9.92	18.68
p-anisaldehyde-methoxy (3H)	3.96	56.44
p-anisic acid-methoxy (3H)	3.93	4.76

Conversion:

compound	**conversion**
cinnamaldehyde	19.68%
p-anisaldehyde	7.78%
ratio vs. *p*-anisaldehyde	2.53
ratio vs. benzaldehyde	1.08

p-Anisaldehyde vs. Pivalaldehyde

Experiment 1

peak	**shift, *δ***	**area**
pivalaldehyde-aldehyde (1H)	9.52	2.41
p-anisaldehyde-aldehyde (1H)	9.92	18.44
p-anisaldehyde-methoxy (3H)	3.96	56.08
p-anisic acid-methoxy (3H)	3.93	3.53

Conversion:

compound	**conversion**
pivalaldehyde	74.67%
p-anisaldehyde	5.92%
ratio vs. *p*-anisaldehyde	14.8
ratio vs. benzaldehyde	6.30

Experiment 2

peak	**shift, *δ***	**area**

pivalaldehyde-aldehyde (1H)	9.53	4.36
p-anisaldehyde-aldehyde (1H)	9.93	18.13
p-anisaldehyde-methoxy (3H)	3.97	55.98
p-anisic acid-methoxy (3H)	3.93	3.30

Conversion:

compound	conversion
pivalaldehyde	66.99%
p-anisaldehyde	5.57%
ratio vs. *p*-anisaldehyde	13.9
ratio vs. benzaldehyde	5.90

Experiment 3

peak	shift, *δ*	area
pivalaldehyde-aldehyde (1H)	9.52	4.71
p-anisaldehyde-aldehyde (1H)	9.92	15.80
p-anisaldehyde-methoxy (3H)	3.96	48.98
p-anisic acid-methoxy (3H)	3.93	2.44

Conversion:

compound	conversion
pivalaldehyde	61.54%
p-anisaldehyde	4.75%
ratio vs. *p*-anisaldehyde	15.1
ratio vs. benzaldehyde	6.42

Average Product Distributions for Aromatic Aldehydes (Benzaldehyde = 1.00)

trial	*p*-methoxy	*p*-nitro	*p*-fluoro	*p*-*tert*-butyl
1	0.517	2.01	0.758	0.63
2	0.366	2.06	0.596	
3	0.393	1.78	0.658	
average	0.425	1.95	0.671	

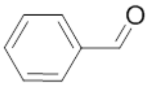
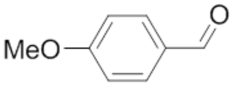
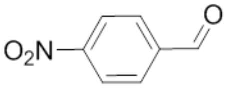
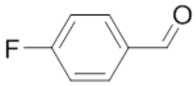
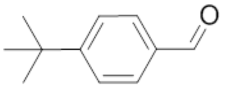
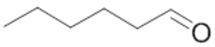
st. dev.	0.08 (18.9%)	0.17 (8.7%)	0.115 (17.1%)	

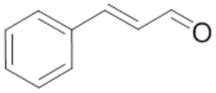
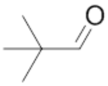
Average Product Distributions for Aldehydes with Different Functionalities

(Benzaldehyde = 1.00)

trial	**hexanal**	***trans*-cinnamaldehyde**	**pivalaldehyde**
1	20.8	1.11	6.30
2	22.7	1.03	5.90
3	22.4	1.08	6.42
average	22.0	1.07	6.21
st. dev.	1.0 (4.7%)	0.09 (8.39%)	0.28 (4.57%)

Table 2.2

Aldehyde	**Average Relative Rate**
	1.00
	0.43 ± 0.08
	1.95 ± 0.17
	0.67 ± 0.12
	0.63
	22.0 ± 1.0

	1.07 ± 0.09
	6.21 ± 0.28

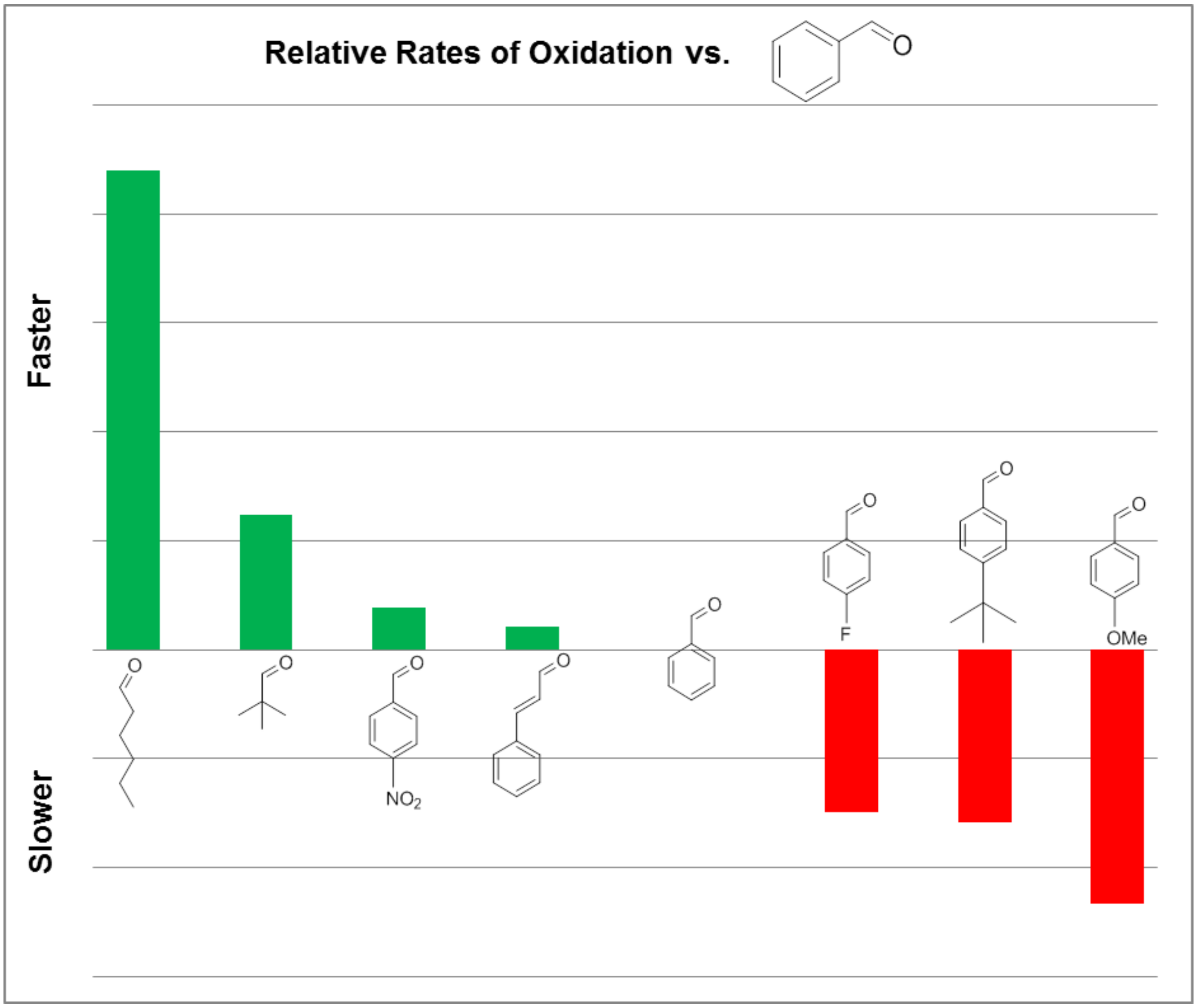


Figure 2.2

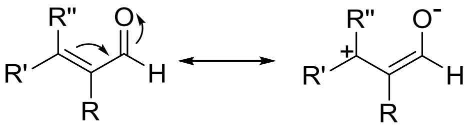
Compared to the relative rates of oxidation of primary alcohols to aldehydes, the determination of the relative rates of oxidation of aldehydes to carboxylic acids was substantially more difficult, as the appearance of the acid proton peaks could not be monitored in deuterated water. Therefore, the conversions of the aldehydes needed to be computed in order to determine the relative rates. The computation of the conversions of aldehydes to acids was done in the same fashion as the computation of the conversions of alcohols to aldehydes.

The reference point in these competition reactions was *p*-anisaldehyde, rather than benzaldehyde, although the relative rates of oxidation are reported relative to benzaldehyde. *p*-Anisaldehyde was used as the reference point because the appearance of the corresponding carboxylic acid, *p*-anisic acid, could be monitored via the appearance of the methoxy protons of the acid, which have a slightly different chemical shift compared to the methoxy protons of the aldehyde. Based on the peak integrations for each of the methoxy peaks, the amounts of both the aldehyde and the acid, as well as the extent of reaction of *p*-anisaldehyde, could be determined.

Once the amount of *p*-anisaldehyde had been determined, the amount of the second aldehyde could also be determined based on the ratios of the aldehyde proton peaks. When the amount of the second aldehyde was known, the amount of the corresponding acid could be found, which also gave the extent of reaction of the second aldehyde. This method was also found to work for competition reactions between three aldehydes.

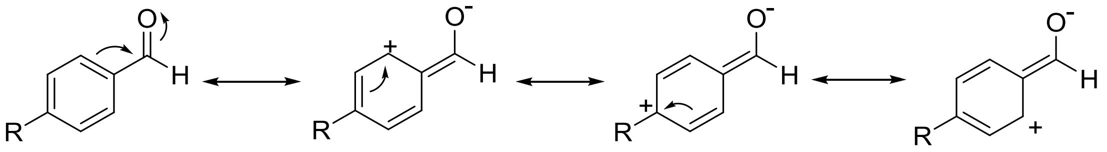
Examination of the results summarized in Figure 2.2 reveals that the trend in reactivity observed in the oxidation of primary alcohols has been reversed in the oxidation of aldehydes: that is, aliphatic aldehydes are oxidized much faster than are conjugated aldehydes. Furthermore, among the aldehydes studied, electron-donating groups, such as methoxy, seem to decrease the rate of oxidation, while electron-withdrawing groups, such as nitro, seem to increase the rate of oxidation. *p*-Fluorobenzaldehyde was unusual in that it possessed an electron-withdrawing group, but was still oxidized more slowly than benzaldehyde.

These results give some insight as to the what the mechanism of the reaction could be. The mechanism, depicted in Scheme 1.8, shows the hydrate of the aldehyde, rather than the aldehyde itself, as the species being oxidized. As the reaction requires the presence of water in order to proceed, this is a reasonable hypothesis. The trend in the reactivity of the aldehydes studied seems to support this hypothesis.



Scheme 2.2

Aliphatic aldehydes are known to favor hydrates more than conjugated aldehydes, although the aldehyde-hydrate equilibrium for most aliphatic aldehydes still lies heavily on the side of the aldehyde.[6] The reason for this is because conjugated aldehydes can engage in resonance, as shown in Scheme 2.2, which serves to stabilize the aldehyde relative to the hydrate and to delocalize electron density over the carbonyl carbon, making it less electrophilic. The decreased electrophilicity of the carbonyl carbon means that it is no longer as open to nucleophilic attack by a molecule of water, which must occur in order for the hydrate to form. With less hydrate present, the conjugated aldehydes will not oxidize as rapidly as the aliphatic aldehydes.



Scheme 2.3

It should be noted that in Scheme 2.2, the resonance form on the right has a carbon that bears a positive charge. Should the aldehyde be an aromatic aldehyde, additional resonance forms are possible where the positive charge is delocalized around the ring as depicted in Scheme 2.3. The stability of these resonance forms will depend on the electronic nature of the substituent on the benzene ring. If the substituent is electron-donating, as is the case for *p*-anisaldehyde, these resonance forms will be significantly stabilized, meaning that the aldehyde is far more favored than the hydrate. Hence, aromatic aldehydes that possess electron-donating substituents should oxidize much more slowly than benzaldehyde and other related aromatic aldehydes.

On the other hand, if the substituent is electron-withdrawing, as is the case for *p*-nitrobenzaldehyde, the resonance forms in Scheme 2.3 will be destabilized. Thus, although the aldehyde will be favored at equilibrium, there should be more hydrate present in the case of a benzaldehyde bearing an electron-withdrawing substituent. Hence, aromatic aldehydes that possess electron-withdrawing substituents should oxidize more rapidly than benzaldehyde.

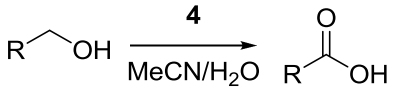
Halogen substitution on the aromatic ring is rather unusual because halogens are electron-withdrawing, but the substituent decreases the rate of oxidation of the substituted benzaldehyde relative to that of benzaldehyde. Although halogens are known to be electron-withdrawing due to their high electronegativity, halogens also possess lone pairs that may easily stabilize a carbonyl as depicted in Scheme 2.3. As a result, although the halogens are electron-withdrawing, the aldehyde is still more far more favored over the hydrate. Both of these electronic effects will influence the rate of oxidation of the halogen-substituted aromatic.

Since fluorine and carbon are of similar size, there is high orbital overlap in the C-F bond. Fluorine can easily donate electrons to an electrophilic carbon, which should result in a substantial decrease in the rate of oxidation of *p*-fluorobenzaldehyde. However, fluorine is highly electronegative and withdraws electron density; this should result in an increase in the rate of oxidation of *p*-fluorobenzaldehyde. Assuming that all aromatic hydrates are oxidized at the same rate, the electron-donating behavior of fluorine outweighs its electron-withdrawing nature, as *p*-fluorobenzaldehyde was oxidized slower than benzaldehyde. Further investigation using Hammett plot analysis (inductive σ-values vs. resonance σ-values) is needed to determine whether this is true or not.[7]

The difference in the reactivity of hexanal and pivalaldehyde lies only partially in their ability to form hydrates. Since pivalaldehyde is more sterically hindered than hexanal, there are a limited number of approaches a molecule of water can take in order to form a hydrate with pivalaldehyde as compared to hexanal. Therefore, pivalaldehyde should react more slowly than hexanal.

As proposed in Scheme 1.8, once the hydrate is formed, the oxidation occurs in the same fashion as the oxidation of an alcohol, via a hydride abstraction to generate a carbocation. Therefore, just as in the alcohol oxidations, where sterically encumbered alcohols are oxidized more slowly than are similar, unhindered alcohols, sterically encumbered hydrates are also oxidized more slowly than are similar, unhindered hydrates. Applying the same reasoning to the different aromatic aldehydes, hydrates with electron-donating groups should be oxidized faster than hydrates with electron-withdrawing groups. This may explain why relative rate difference between *p*-anisaldehyde and *p*-nitrobenzaldehyde (about 4 times) is relatively small compared to the relative rate difference between *p*-anisyl alcohol and *p*-nitrobenzyl alcohol (about 60 times).

OXIDATION OF PRIMARY ALCOHOLS TO CARBOXYLIC ACIDS



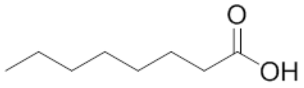
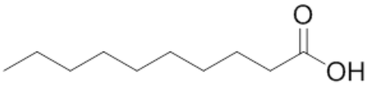
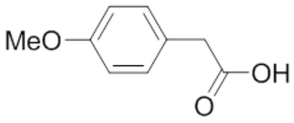
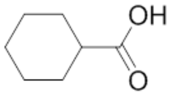
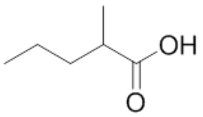
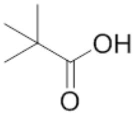
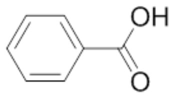
carboxylic acid	yield, %	time
	97	3 d
	97	3 d
	98	3 d
	96	3 d
	89	3 d
	88	20 d
	69	20 d

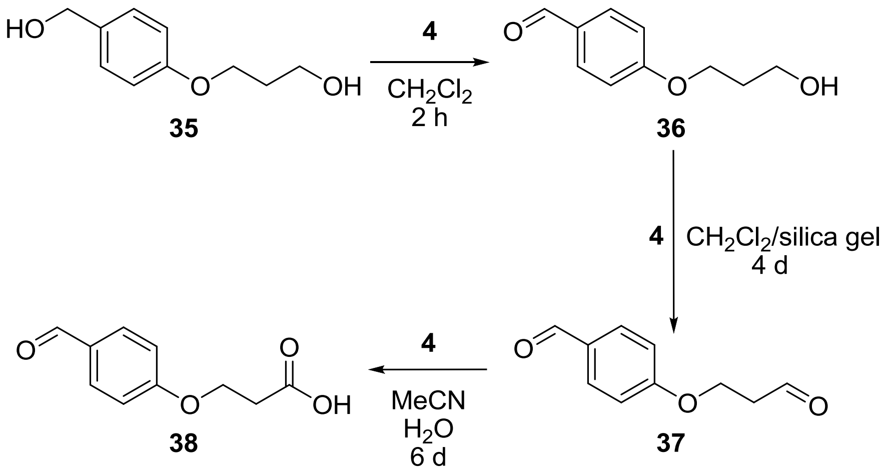
Table 2.3

Carboxylic acids can be generated in a reasonable amount of time from primary aliphatic alcohols by reaction with the oxammonium cation in 10% aqueous acetonitrile. The exception to this is the sterically bulky neopentyl alcohol, presumably due to the fact that the oxidation of neopentyl alcohol to pivalaldehyde is very slow. It should be noted that the general oxidation procedure is carried out in 10% aqueous acetonitrile at higher concentrations than either of the relative rate studies (0.25 M vs. 0.08 M). Solvent effects on the relative rates of oxidation of primary alcohols was not considered; however, they cannot be ignored because methylene chloride and acetonitrile have different solvating capabilities. It is safe to assume that the trend will be similar regardless of the solvent due to the proposed mechanism of the reaction.

As shown in Table 2.3, while primary aliphatic alcohols are usually oxidized to give quantitative yields of their corresponding carboxylic acids in a relatively short amount of time, benzyl alcohol gave only 70% conversion to benzoic acid even after three weeks of stirring. The remainder of the isolated material was benzaldehyde. By extension, it can be assumed that the other benzylic alcohols studied will also require equally long reaction times to give decent conversion to the corresponding acid.

When working up the reaction, it is essential to wash the ether extracts with an aqueous solution of HCl, typically 10% by volume. When extracting with ether, it must be kept in mind that the acetonitrile in the reaction is also extracted into the ether. The nitroxide, which is a byproduct of the reaction, is soluble in acetonitrile, and it will undoubtedly be in the ether layer after extraction. The purpose of washing the ether layer with a strong acid is to cause the nitroxide to disproportionate into the oxammonium salt and the hydroxylammonium salt, both of which have high solubility in water. Indeed, the aqueous, acidic layer turns yellow after the acid wash. If one omits the acid wash, the product will be contaminated with the nitroxide and be of lower purity as a result.

SELECTIVITY OF THE OXAMMONIUM CATION



Scheme 2.4

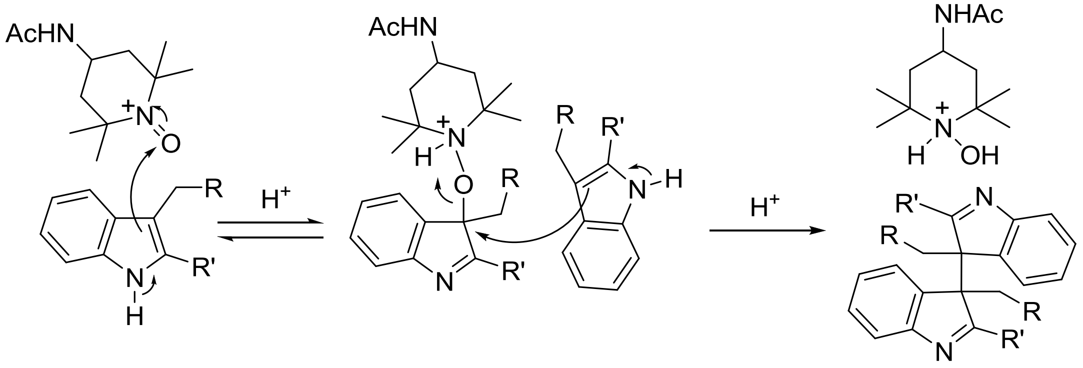
Both the relative rates of oxidation of primary alcohols and the relative rates of oxidation of aldehydes suggests that there is selectivity in these oxidations. In order to confirm the selectivity suggested by the relative rate studies, a compound (**35**) possessing two alcohols showing different reactivity toward the oxammonium cation was prepared and subjected to sequential, stoichiometric oxidations using **4** as depicted in Scheme 2.4.

The benzylic alcohol of diol **35**, which is functionally similar to *p*-anisyl alcohol, should oxidize much more quickly than the aliphatic alcohol of diol **35**, which is functionally similar to 1-octanol. This is confirmed by the experimental results: the first molar equivalent of **4** selectively oxidizes the benzylic alcohol in 2 h to generate **36** in 99% yield in about two hours. In comparison, oxidation of the aliphatic alcohol in **36** by the second molar equivalent of **4** to give dialdehyde **37** required the addition of silica gel to catalyze the reaction via what is believed to be surface immobilization of the reactants. Even with the addition of silica gel to the reaction mixture, the reaction required a four-day reaction period to generate **37** in 97% yield. Clearly, there is strong evidence to support the claim that the oxammonium cation shows selectivity in the oxidation of alcohols.

As noted above, the trend in reactivity toward the oxammonium cation shown by the oxidations of primary alcohols is reversed in the case of the oxidations of aldehydes. The aliphatic aldehyde in dialdehyde **37**, which is similar to hexanal in terms of functionality, should oxidize preferentially to the benzaldehyde in dialdehyde **37**, which is similar to *p*-anisaldehyde in terms of functionality, with the third, and final, molar equivalent of **4**. This is confirmed by the experimental results: acid **38** was generated in 95% yield with a six-day reaction period. Clearly, there is also strong evidence to support the claim that the oxammonium cation shows selectivity in the oxidation of aldehydes.

INDOLE OXIDATIONS

It was originally thought that indole and its derivatives would undergo oxidative coupling when reacted with the oxammonium cation as illustrated in Scheme 2.5. The electron-rich C-3 position of the indole ring can attack the oxammonium cation in a manner similar to that suggested in the mechanism depicted in Scheme 1.10.[8] However, as the reaction is run under anhydrous conditions, there are no water molecules around to act as nucleophiles to generate the product shown in Scheme 1.10. Therefore, a second molecule of the indole may act as a nucleophile and substitute at the C-3 position of the first molecule of the indole, releasing the hydroxylammonium cation as the byproduct. A second potential dimer, shown in Figure 2.3, was observed by Bobbitt in the electrochemical oxidation of tetrahydrocarbazole.[9]



Scheme 2.5

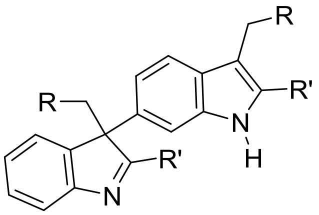
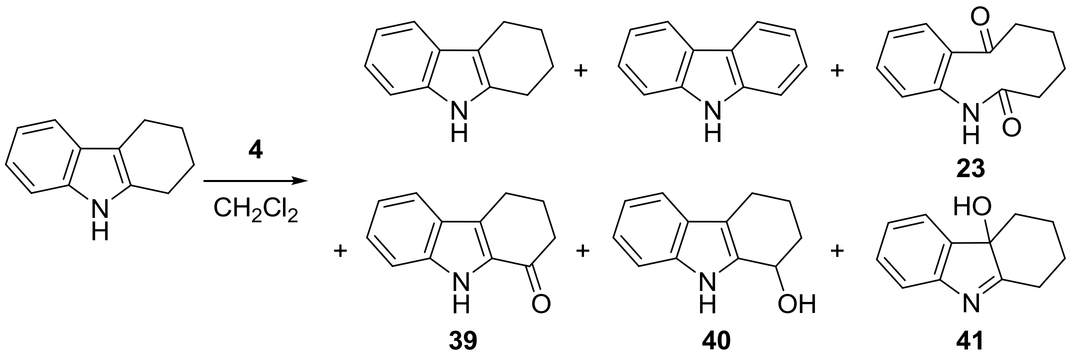


Figure 2.3

However, such dimers were not observed in the products of the oxidations of indole and tetrahydrocarbazole by **4** in anhydrous methylene chloride. Instead, the oxidation products that would be expected from either air oxidation or peroxide oxidation were found in both cases. It might be noted that, in the case of tetrahydrocarbazole, the oxidation products were characterized by GC-MS rather than by NMR spectroscopy. This outcome was surprising as none of the reactions was exposed to air, nor was any peroxide present in the reaction mixtures.

Oxidation of Tetrahydrocarbazole

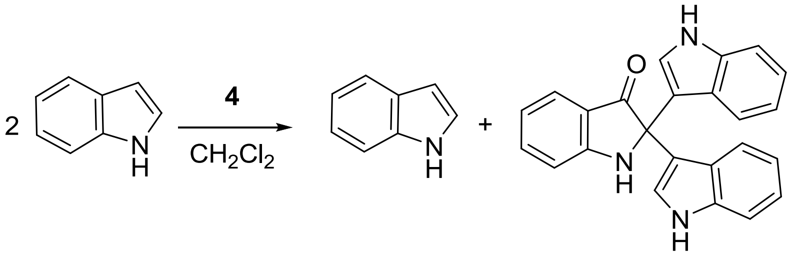


Scheme 2.6

Separation of the oxidation products by column chromatography allowed identification of 4-acetamido-2,2,6,6-tetramethylpiperidine as one of the products of oxidation of tetrahydrocarbzole. It is possible that the source of the oxygen in oxidation products **23**, **39**, **40**, and **41**, all of which may be derived from hydroperoxide **22**,[10] was the oxammonium cation. This would result in the formation of the piperidine. The nitroxide is also a possible source of the oxygen, as one of the main impurities in the oxammonium salt is nitroxide that had not been washed away during the isolation of the oxammonium salt.[11] Since this transformation of the oxammonium cation and related compounds has not been reported in the literature, no mechanism has been suggested for the reaction and further studies are needed to settle this question. Regardless of the source of the oxygen in the oxidation products, it has been found that oxidation of tetrahydrocarbazole under anhydrous conditions proceeds in the same fashion as oxidation in the presence of oxygen or peroxides.

Another product of the oxidation of tetrahydrocarbazole that was identified by GC-MS was carbazole. There is no literature report of tetrahydrocarbazole being oxidized to carbazole. Presumably, the reaction first proceeds via the mechanism shown in Scheme 1.10 until reaching intermediate **16**. Further studies are needed in order to elucidate the mechanism of this reaction.

Oxidation of Indole

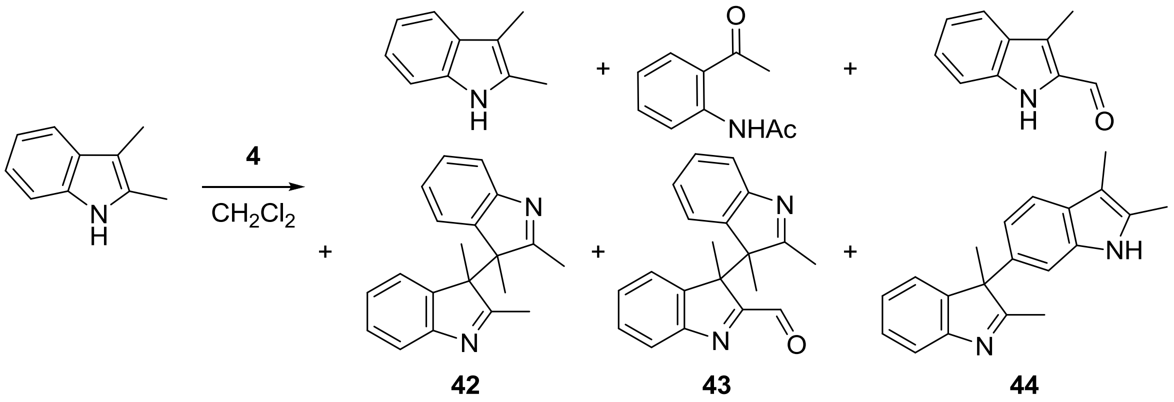


32

Scheme 2.7

The oxidation of indole by the oxammonium cation under anhydrous conditions gave products that were surprisingly simple to separate. Although the desired dimerization of indole did not occur under these conditions, indole did form a different set of oligomers that was consistent with the oxidation products observed by Witkop and Patrick.[12] The dominant product isolated was the trimer **32**, which was identified by NMR spectroscopy[13] and by its distinct behavior when heated close to its melting point.[12,13] Unreacted indole was also recovered from the reaction, which indicates that more oxammonium salt is needed to bring the reaction to completion.

Oxidation of 2,3-Dimethylindole



Scheme 2.8

The oxidation of 2,3-dimethylindole generated several dimeric species as evident from the molecular ion peaks for three of the oxidation products. Two of the products possessed molecular ions with a mass of 288, which corresponds to a dimer of 2,3-dimethylindole. The locations of the dimerization in both compounds could not be determined as the compounds could not be separated by chromatography. Instead, the locations were inferred based on the results from the electrochemical oxidations of tetrahydrocarbazole and its derivatives by Bobbitt et al.[9a-b] The final product possesses a molecular ion with a mass of 302, which corresponds to a heterodimer of 2,3-dimethylindole and 2-formyl-3-methylindole. The location of the dimerization was inferred as a pure sample of the compound could not be obtained.[9]

It seems reasonable to assume that the oxammonium cation oxidation of 2,3-dimethylindole should generate products that correspond to those from autoxidation via air or peroxides. In fact, the aldehyde shown in Scheme 2.8, along with the acetophenone, have been observed as products of autoxidation of 2,3-dimethylindole.[14] If oxammonium cation oxidations under anhydrous conditions do indeed give the same products as autoxidation, then it is reasonable to believe that the compounds shown in Scheme 2.8 are indeed the products of the oxidation of 2,3-dimethylindole.

CONCLUSIONS

The relative rates of oxidation of primary alcohols depends heavily on the stability of the carbocation intermediate generated. For this reason, primary benzylic alcohols and primary allylic alcohols, both of which generate carbocation intermediates stabilized by resonance, are oxidized much more rapidly than are primary aliphatic alcohols. Primary propargylic alcohols oxidize relatively slowly despite generating a carbocation intermediate that is resonance-stabilized because the resonance form of the propargylic cation is not as stable due to delocalization of the positive charge onto an sp^2-hybridized carbon.

Substituent effects play a role in the relative rates of oxidation of various benzylic alcohols. Electron-donating groups, such as methoxy, enhance the ability of the aromatic ring to stabilize the carbocation intermediate via resonance and result in an increase in the rate of oxidation. Electron-withdrawing groups, such as nitro, have the opposite effect and result in a decrease in the rate of oxidation.

In addition to electronic effects, steric hindrance can also affect the rate of oxidation of a primary alcohol. The reason for this is that the oxammonium cation must approach the alcohol in order for the reaction to occur. Sterically bulky primary alcohols are less accessible to the oxammonium cation and will oxidized slower as a result.

The relative rates of oxidation of aldehydes depends primarily on the aldehyde-hydrate equilibrium, as the hydrate is the species being oxidized by the oxammonium cation. If the aldehyde is conjugated to a double bond or an aromatic ring system, the equilibrium will favor the aldehyde rather than the hydrate. With less hydrate available, the aldehyde will not be oxidized as quickly: this is the case for the aromatic aldehydes and the α,β-unsaturated aldehydes. On the other hand, with more hydrate available, an aliphatic aldehyde will be oxidized much more rapidly.

The relative rates of oxidation of aldehydes are also influenced by the same factors that affect the relative rates of oxidation of primary alcohols. Therefore, the electronic effects and steric effects that affect the alcohol oxidations will also affect the aldehyde oxidations.

The relative rate studies for both the oxidation of primary alcohols to aldehydes and the oxidation of aldehydes to carboxylic acids have shown that the oxammonium cation can be used to selectively oxidize one alcohol, or aldehyde, in the presence of another alcohol, or aldehyde, that oxidizes more slowly.

Although further investigation is required, it appears that the oxidation of indoles by the oxammonium cation under anhydrous conditions gives products that are expected to form via autoxidation in the presence of oxygen or peroxides. Only in the case of 2,3-dimethylindole has oxidative coupling occurred.

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CHAPTER III

EXPERIMENTAL

General Procedure

Relative rate studies of oxidation of primary alcohols to aldehydes were competition reactions performed in methylene chloride using 0.08 M solutions of the alcohols. An NMR sample of each competition reaction was prepared from the filtered methylene chloride solution upon completion of the reaction, indicated by a white slurry and by a negative KI-starch test, with $CDCl_3$ in a sealed capillary tube as an external standard. NMR analysis of each sample was done with suppression of the methylene chloride signal at δ 5.30 ppm. The residual methylene chloride signal after suppression was used as a reference point.

Relative rate studies of oxidation of aldehydes to carboxylic acids were competition reactions performed under “ultra-high pure” grade argon in 10% aqueous acetonitrile using 0.08 M solutions of the aldehydes. Deuterated water was used in place of regular water in these reactions. After 24 h of stirring, an NMR sample of each competition reaction was prepared from the aqueous acetonitrile solution with $CDCl_3$ in a sealed capillary tube as an external standard. NMR analysis of each sample was done with suppression of the acetonitrile signal at δ 2.06. The residual acetonitrile signal after suppression was used as a reference point.

Gas-liquid chromatography was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a thermal conductivity detector and fitted with a 10-w x 0.53-mm, 0.5-μm Quadrex 007-1 (100% dimethylpolysiloxane) fused silica glass capillary column (Quadrex Corporation). Helium was used as the carrier gas.

Gas-liquid chromatography-mass spectrometry was performed on a Hewlett-Packard 5890 gas chromatograph fitted with a 25-w x 0.20-mm, 0.33-μm DB-5MS (5% diphenyl / 95% dimethylpolysiloxane) fused silica glass capillary column (J & W Scientific) and interfaced with a Hewlett-Packard 5971 mass selective detector (electron impact, EI). Helium was used as the carrier gas.

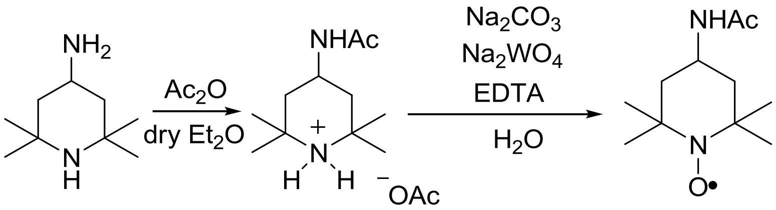
Flash column chromatography was performed on silica gel (Sorbent Technologies), 40-63 μm (200 – 400 mesh), in glass columns. Flash columns were packed using a plug of cotton and the slurry method.

^{1}H and ^{13}C NMR spectra were acquired either on a Bruker DRX-400 spectrometer or on a Bruker Avance 300 spectrometer. The NMR solvents used were $CDCl_3$ and DMSO-d_6. Proton and carbon spectra taken in $CDCl_3$ were referenced at δ 7.26 and 77.23 for the residual ^{1}H resonance of the solvent and the center line of the ^{13}C absorption of the solvent, respectively. Proton and carbon spectra taken in DMSO-d_6 were referenced at δ 2.50 and 39.51 for the residual ^{1}H resonance of the solvent and the center line of the ^{13}C absorption of the solvent, respectively. All chemical shifts are reported relative to Me_4Si at δ 0.00.

Preparation of 4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxammonium tetrafluoroborate

The preparation of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxammonium tetrafluoroborate (**4**) involved three steps as described below.

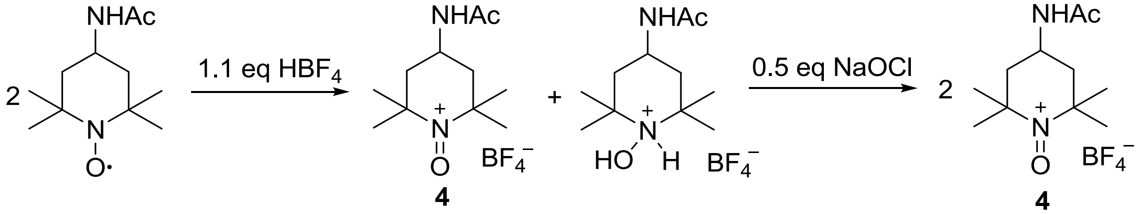
4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl



The preparation of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl was done following the procedure of Bobbitt,[1] with minor modifications. A solution of 156 g (1.00 mol) of 4-amino-2,2,6,6-tetramethylpiperidine in 560 mL of dry ethyl ether in a 4-L beaker was cooled in an ice bath while being stirred vigorously. A solution of 318 g (3.10 mol) of acetic anhydride in 140 mL of dry ethyl ether was added over a period of 30 min via an addition funnel. Any clumps that formed during the addition were broken apart using a wooden rod. Following addition of the anhydride solution, the reaction mixture was stirred for 3 h. The mixture was then filtered through a sintered glass filter and the resultant white solid was air-dried overnight to give 264 g (102%) of 4-acetamido-2,2,6,6-tetramethylpiperidinium acetate.

The acetate was suspended in approximately 2 L of water to give a 0.5M solution of the acetate. The solution was slowly made basic using 159 g (1.50 mol) of sodium carbonate. To catalyze the reaction, 17.8 g (54.0 mmol) of sodium tungstate and 12.6 g (43.2 mmol) of ethylenediaminetetraacetic acid were added to the solution, and 114 mL of 30% hydrogen peroxide solution (approximately 1.0 mol) was added slowly, with stirring, to the solution. The reaction mixture was stirred overnight and a red precipitate, which may be isolated by filtration, was observed. This was repeated until the red precipitate no longer appeared after stirring overnight, which takes a total of four 114-mL portions of 30% hydrogen peroxide (4.0 mol). The precipitate collected after filtration was air dried to give 117 g of the title compound; mp 141-146 °C [lit.[1] 147-148 °C]. The remaining red solution was extracted with methylene chloride until the solution had a faint yellow hue. The methylene chloride was removed by rotary evaporation to give 69.9 g of the title compound; mp 142-146 °C. The total yield of the title compound was 187 g (88%).

4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxammonium tetrafluoroborate (4)



The preparation of 4-acetamide-2,2,6,6-tetramethylpiperidine-1-oxammonium tetrafluoroborate was done following the procedure by Bobbitt.[2] A slurry of 100 g (0.468 mol) of 4-acetamido-2,2,6,6-tetramethylpiperidin-1-oxyl in 200 mL of water was made in a 4-L beaker. An aqueous solution of HBF_4 (48% by weight; 70.8 mL; 0.540 mol) was added dropwise via addition funnel to the vigorously stirring red-orange slurry. The slurry slowly turned black as the HBF_4 solution was added, but eventually gave a yellow precipitate once all of the acid had been added. The yellow slurry was stirred until no orange color could be detected. A commercial sodium hypochlorite solution (Clorox® bleach; 6.00% NaOCl) (250 mL; 0.221 mol) was added dropwise to the stirring yellow slurry over an hour. The slurry was then cooled in an ice bath and stirred for another 2 h in the ice bath. The yellow slurry was then filtered and the precipitate washed with small portions of water and methylene chloride to remove NaCl and leftover nitroxide, respectively. The precipitate was allowed to dry overnight. The product is obtained as a bright yellow powder (102 g; 0.340 mol; 72.6%; mp 193.5-196 °C;[3] lit.[2] 184-185 °C).

Relative Rates of Oxidation of Primary Alcohols to Aldehydes

A tared 50-mL Erlenmeyer flask was charged with a 0.08M solution of benzyl alcohol (or *para*-nitrobenzyl alcohol in the case of alcohols that oxidize slowly) in dichloromethane. A separate, tared, 25-mL Erlenmeyer flask, was charged with a 0.08 M solution of a different primary alcohol in dichloromethane. This can be repeated for three or four primary alcohols, provided that the total amount of dichloromethane used does not exceed 25 mL. The alcohol solutions were combined and a background NMR spectrum was taken as a starting point, and 2.00 mmol of **4** was added to the reaction mixture. The resulting yellow slurry was stirred and the color of the solution was monitored every 5 min until the slurry was white and gave a negative starch-KI test. Once the reaction was complete, an aliquot was filtered through cotton into an NMR tube for NMR analysis.[4] Deuterated chloroform, sealed in a closed capillary and inserted into the NMR tube, was used as an external standard.

General Procedure for the Oxidation of Alcohols to Carboxylic Acids

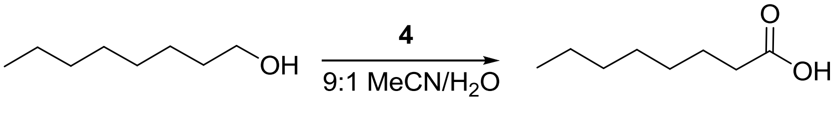
A 0.25 M solution of primary alcohol in 9:1, by volume, acetonitrile and water was prepared in a 50-mL Erlenmeyer flask. Between 2.0 and 2.2 molar equivalents of **4** were added to give an orange-colored solution and the solution was allowed to stand at room temperature for a period of time. Once the orange color disappears, the reaction mixture was diluted to twice its volume with deionized water. The diluted aqueous solution was extracted with five portions of ethyl ether. The combined organic layers were washed with 5 mL of 10% HCl to remove any nitroxide. The ether was then dried with 10 mL of brine and $MgSO_4$. The ether was removed under vacuum to constant weight to isolate the product.

Relative Rates of Oxidation of Aldehydes to Carboxylic Acids

A tared 50-mL Erlenmeyer flask was charged with 2.00 mmol of *p*-anisaldehyde dissolved in 12 mL of a 9:1 (by vol) mixture of acetonitrile and deuterium oxide. A separate, tared 25-mL Erlenmeyer flask was charged with 2.00 mmol of a different aldehyde dissolved in 12 mL of the same solvent. The two solutions were combined and the reaction vessel was flushed with argon. An aliquot was taken and analyzed by NMR to give a starting point. The aliquot was then returned to the reaction mixture and 2.00 mmol of **4** was added to the reaction mixture. The reaction vessel was then sealed and allowed to stir for 24 h before an aliquot was removed for NMR analysis[5] with 1% $CHCl_3$ in $CDCl_3$ sealed in a capillary tube as a standard.

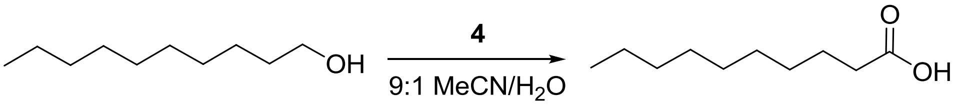
Oxidation of Alcohols[6]

Octanoic Acid from 1-Octanol



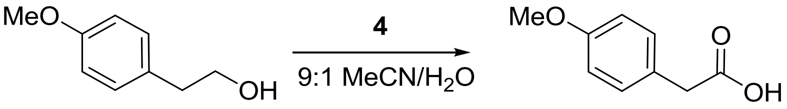
Following the general procedure, 130.0 mg (1.00 mmol) of 1-octanol was oxidized with 600.0 mg (2.00 mmol) of **4**. After 3 d, the reaction was worked up as described to give 140 mg (0.972 mmol, 97%) of octanoic acid as a clear, light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (1H, br s), 2.35 (2H, t, J = 5.0 Hz), 1.62 (2H, q, J = 5.0 Hz), 1.32-1.28 (8H, m), 0.88 (3H, t, J = 5.0 Hz);[7] ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 34.2, 31.7, 29.1, 29.0, 24.8, 22.7, 14.1.[8]

Decanoic Acid from 1-Decanol



Following the general procedure, 791.6 mg (5.00 mmol) of 1-decanol was oxidized with 3.00 g (10.0 mmol) of **4**. After 3 d, the reaction was worked up as described to give 835.7 mg (4.85 mmol, 97%) of decanoic acid as a clear, light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (2H, t, J = 7.0 Hz), 1.65-1.58 (2H, m), 1.29-1.25 (12H, m), 0.86 (3H, t, J = 7.0 Hz);[9] ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 34.3, 32.0, 29.5, 29.3, 29.2, 24.8, 22.8, 14.2.[9]

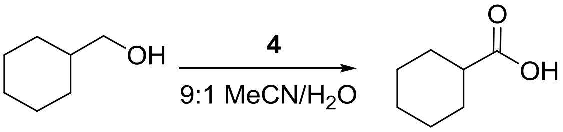
p-Methoxyphenylacetic Acid from *p*-Methoxyphenylethanol



Following the general procedure, 765.0 mg (5.03 mmol) of *p*-methoxyphenylethanol was oxidized with 3.00 g (10.0 mmol) of **4**. After 3 d, the reaction was worked up as described to give 820.5 mg (4.94 mmol, 98%) of *p*-

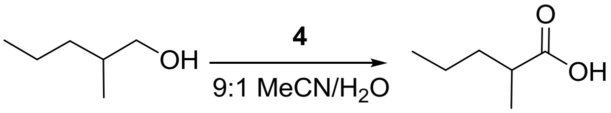
methoxyphenylacetic acid as a pale yellow solid (mp 79-81 °C, lit.[10] 77-79 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (1H, br s), 7.20 (2H, d, J = 8.3 Hz), 6.87 (2H, d, J = 8.3 Hz), 3.80 (3H, s), 3.59 (2H, s);[11] ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 159.0, 130.6, 125.6, 114.3, 55.4, 40.3.[11]

Cyclohexanecarboxylic Acid from Cyclohexylmethanol



Following the general procedure, 232.0 mg (2.03 mmol) of cyclohexylmethanol was oxidized with 1.32 g (4.4 mmol) of **4**. After 3 d, the reaction was worked up as described to give 248.9 mg (1.94 mmol; 96%) cyclohexanecarboxylic acid as a clear, light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (1H, br s), 2.33 (1H, t, J = 11.2 Hz), 1.93 (2H, d, J = 12.4 Hz), 1.76 (2H, d, J = 11.6 Hz), 1.65 (1H, d, J = 8.0 Hz), 1.45 (2H, q, J = 10.8 Hz), 1.37-1.14 (3H, m);[12] ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.8, 43.0, 28.9, 25.5, 25.2.[12]

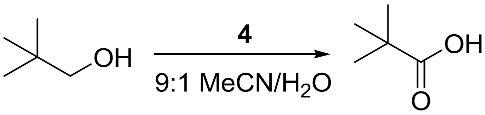
2-Methylpentanoic Acid from 2-Methylpentan-1-ol



Following the general procedure, 409.2 mg (4.00 mmol) of 2-methylpentan-1-ol was oxidized with 2.43 g (8.10 mmol) of **4**. After 3 d, the reaction was worked up as described in the general procedure to give 412.7 mg (3.55 mmol; 89 %) of 2-

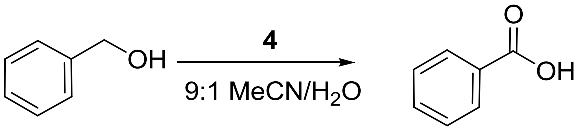
methylpentanoic acid as a clear, light yellow oil, some lost during removal of ether: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (1H, br s), 2.47 (1H, m), 1.67 (1H, m), 1.52-1.26 (3H, m), 1.18 (3H, d, *J* = 6.0 Hz), 0.92 (3H, m);[13] ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 39.3, 35.7, 20.4, 16.9,14.0.[14]

Pivalic Acid from Neopentyl Alcohol



Following the general procedure, 274.0 mg (3.11 mmol) of neopentyl alcohol was oxidized with 1.98 g (6.60 mmol) of **4**. After 20 d, the reaction was worked up as described in the general procedure to give 278 mg (2.72 mmol, 88%) of pivalic acid as a clear, slightly colored oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.79 (1H, s), 1.23 (9H, s);[15] ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 38.8, 27.2.[15]

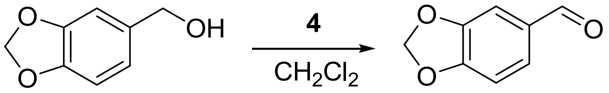
Benzoic Acid from Benzyl Alcohol



Following the general procedure, 215.1 mg (1.99 mmol) of benzyl alcohol was oxidized with 1.32 g (4.00 mmol) of **4**. After 20 d, the reaction was worked up as described in the general procedure, except the ether was not removed. Analysis of the ether solution by gas chromatography indicated that 31% of benzaldehyde remained in the product.

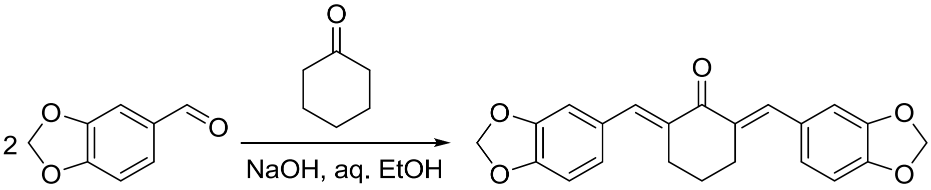
Demonstration of Multi-step Reaction Using the Oxammonium Cation

Piperonal from Piperonyl Alcohol



A 50-mL Erlenmeyer flask was charged with 760.1 mg (5.00 mmol) of piperonyl alcohol dissolved in 25 mL of methylene chloride. A mixture of 1.65 g (5.50 mmol) of **4** and 3.00 g of silica gel was added to the vigorously stirring alcohol solution. The yellow slurry became white after about 30 min of stirring. The white slurry was filtered through a thin layer of silica gel and filter paper. The filter cake was rinsed several times with methylene chloride. Evaporation of the solvent gave 654.0 mg (4.36 mmol; 87%) of 3,4-methylenedioxybenzaldehyde (piperonal) as a clear oil. The product was used in the next step with no further purification: ^{1}H NMR (400 MHz, CH_2Cl_2 + $CDCl_3$) δ 9.78 (1H, s, CHO), 7.40 (1H, d, *J* = 8.0 Hz, H-6), 7.29 (1H, s, H-2), 6.93 (1H, d, *J* = 8.0 Hz, H-5), 6.06 (2H, s, OCH_2O);[16] ^{13}C NMR (100 MHz, CH_2Cl_2 + $CDCl_3$) δ 190.3 (CHO), 153.3 (C-4), 149.0 (C-3), 132.2 (C-1), 128.7 (C-6), 108.5 (C-2), 106.8 (C-5), 102.6 (OCH_2O).[16]

Aldol Condensation of Piperonal with Cyclohexanone

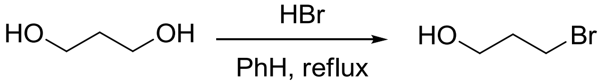


In a 50-mL Erlenmeyer flask, 624.9 mg (4.16 mmol) of piperonal was mixed with 209.1mg (2.13 mmol) of cyclohexanone. In a separate 50-mL beaker, 5 pellets of sodium hydroxide (566.0 mg; 14.4 mmol) were dissolved in 10 mL of 1:1 ethanol/water.

Half of the aldehyde/ketone mixture was added to the ethanolic sodium hydroxide solution. After about 15 min of stirring, the remaining aldehyde/ketone mixture was added. The flask that contained the mixture was rinsed with ethanol to ensure that all of the aldehyde/ketone mixture had been added. The reaction was stirred for two d. The yellow precipitate that formed was isolated by filtration. The filter funnel used was rinsed with methylene chloride to recover more product. The filtrate was then concentrated on a steam bath and the residue collected. The combined yield of 2,6-bis-(3,4-methylenedioxybenzylidene)cyclohexan-1-one was 470 mg (1.30 mmol; 63%); mp 186.0 °C (lit.[17] 182-183 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, s, C=CH), 7.0 (2H, d, J = 8.4 Hz, Ar H-6), 6.99 (2H, s, Ar H-2), 6.85 (2H, d, J = 7.8 Hz, Ar H-5), 6.00 (4H, s, OCH_2O), 2.90 (4H, t, J = 5.5 Hz, H-3 + H-5), 1.80 (2H, m, J = 6.0 Hz, H-4);[17] ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (C=O), 148.2 (Ar C-3), 147.9 (Ar C-4), 136.9 (C-2 + C-6), 134.9 (C=**C**-Ar), 130.4 (Ar C-1), 126.0 (Ar C-6), 110.3 (Ar C-5), 108.6 (Ar C-2), 101.6 (OCH_2O), 28.7 (C-3 + C-5), 23.2 (C-4).[17]

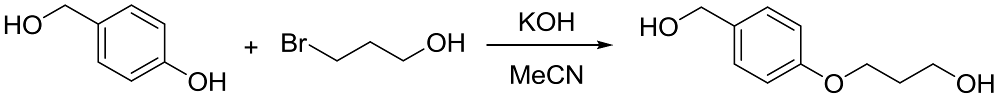
Demonstration of Oxammonium Cation Selectivity

Preparation of 3-Bromopropan-1-ol



Following the procedure of Kang,[18] 7.61 g (100 mmol) of 1,3-propanediol was suspended in 200 mL of benzene in a 500-mL, 2-necked RB flask equipped with a Dean-Stark trap, a condenser, and an addition funnel and 12.5 mL of 48% aq. HBr (8.90 g; 110 mmol) was added slowly via the addition funnel while the solution was heated at reflux. After 28 h, the benzene solution was allowed to cool to room temperature, washed sequentially with 20 mL of 6 M aq. NaOH, 20 mL of 10% aq. HCl, four 20-mL portions of water, and 20 mL of brine. The solution was dried ($MgSO_4$) and concentrated to give 7.21 g (51.9 mmol; 52%) of a clear liquid that was identified as the product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (2H), 3.52 (2H, t, *J* = 6.5 Hz), 2.07 (2H, quintet, *J* = 6.2 Hz);[18] ^{13}C NMR (300 MHz, $CDCl_3$) δ 60.5, 35.2, 30.5.[19]

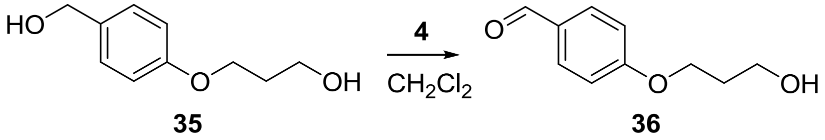
Preparation of 3-(4-hydroxymethylphenoxy)-propan-1-ol



35

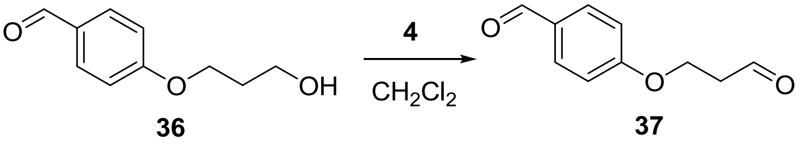
Following the procedure of Linares,[20] 6.29 g (49.1 mmol) of 97% 4-hydroxybenzyl alcohol was dissolved in 55 mL of acetonitrile, 3.12 g (55.6 mmol) of powdered KOH was added, and the resulting solution was stirred for 30 min at room temperature before addition of 7.21 g (51.9 mmol) of 3-bromopropan-1-ol. The reaction mixture was stirred for 3 days. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was chromatographed over silica gel using 1:1 EtOAc/hexanes as the eluent to afford 6.10 g (33.5 mmol, 68%) of the title compound as a white solid; mp 70−71 °C (lit.[20] 77.8−78 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 8.8 Hz), 6.89 (2H, d, *J* = 8.4 Hz), 4.62 (2H, d, *J* = 5.6 Hz), 4.12 (2H, t, *J* = 6.0 Hz), 3.86 (2H, q, *J* = 5.6 Hz), 2.04 (2H, quintet, *J* = 5.8 Hz);[20] ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.6, 133.6, 128.9, 114.8, 66.0, 65.3, 60.7, 32.2.[20]

Oxidation of 3-(4-Hydroxymethylphenoxy)propan-1-ol to 4-(3-Hydropropoxy)benzaldehyde



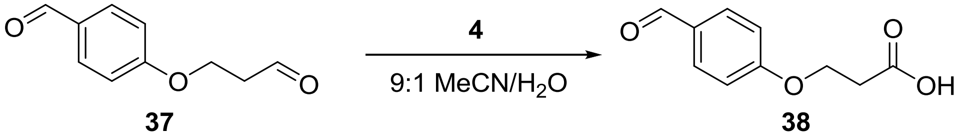
A 50-mL Erlenmeyer flask was charged with 546.7 mg (3.00 mmol) of **35** dissolved in 25 mL of CH_2Cl_2. To this solution, 985.0 mg (3.28 mmol) of **4** was added and the resulting yellow slurry was stirred at room temperature for 2 h at which time the yellow slurry had become white. The slurry was filtered and the filter cake was rinsed with CH_2Cl_2. The filtrate was passed through a short column of silica gel, and concentrated to give 536.4 mg (99% crude yield) of 4-(3-hydroxypropoxy)benzaldehyde (**36**) as a clear, slightly yellow liquid. An NMR sample was prepared from 18.0 mg of this crude product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (1H, s, C**H**O), 7.79 (2H, d, *J* = 8.3 Hz, H-2,6), 6.97 (2H, d, *J* = 8.5 Hz, H-3,5), 4.18 (2H, t, *J* = 6.1 Hz, H-α), 3.85 (2H, t, *J* = 5.9 Hz, H-γ), 2.21 (1H, br s, O**H**), 2.06 (2H, quintet, *J* = 6.0 Hz, H-β);[21] ^{13}C NMR (400 MHz, $CDCl_3$) δ 191.1 (**C**HO), 164.2 (C-4), 132.2 (C-2,6), 130.0 (C-1), 114.9 (C-3,5), 65.7 (C-α), 59.7 (C-γ), 32.0 (C-β).[21]

Oxidation with 4-(3-Hydropropoxy)benzaldehyde to 4-(3-Oxopropoxy)benzaldehyde



A 50-mL Erlenmeyer flask was charged with 518.4 mg (2.88 mmol) of **36** dissolved in 25 mL of CH_2Cl_2. To this solution, 985.0 g (3.28 mmol) of **4** and 2.12 g of silica gel were added and the resulting yellow slurry was stirred for 4 d at which time the slurry had become white. The mixture was filtered, the filter cake was rinsed with CH_2Cl_2, the filtrate was passed through a short column of silica gel, and concentrated to give 499.2 mg (97% crude yield) of 4-(3-oxopropoxy)benzaldehyde (**37**) as a clear, slightly yellow liquid. An NMR sample was prepared from 20.3 mg of this crude product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (2H, s, Ar-C**H**O + CH_2C**H**O), 7.83 (2H, d, *J* = 8.7 Hz, H-2,6), 7.00 (2H, d, *J* = 8.6 Hz, H-3,5), 4.39 (2H, t, *J* = 6.1 Hz, H-α), 2.97 (2H, t, *J* = 6.0 Hz, H-β);[22] ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.5 (CH_2**C**HO), 191.1 (Ar-**C**HO), 163.6 (C-4), 132.2 (C-2,6), 130.3 (C-1), 114.9 (C-3,5), 61.9 (C-α), 43.1 (C-β).[23]

Oxidation of 4-(3-Oxopropoxy)benzaldehyde to 3-(4-Formylphenoxy)propanoic Acid

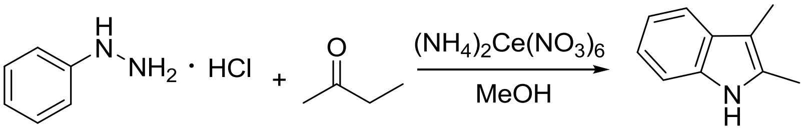


A 50-mL Erlenmeyer flask was charged with 468.9 mg (2.63 mmol) of **37** dissolved in 10.5 mL of 9:1 MeCN/H_2O and 867.9 mg (2.89 mmol) of **4** was added. The mixture was stirred for 6 d and then diluted with 9 mL of water. The resulting solution was extracted sequentially with two 10-mL portions of ether and four 5-mL portions of ether. The combined ether extracts were washed with 10 mL of 10% aq. HCl and the ether was then extracted with 10 mL of saturated aq. $NaHCO_3$ solution. The aqueous extract was made acidic to litmus paper by addition of 12 M HCl and extracted with four

10-mL portions of ether. The ether extracts were washed with 10 mL of brine, dried ($MgSO_4$), and concentrated to give 482.9 mg (95% crude yield) of 3-(4-formylphenoxy)propanoic acid (**38**) as a white solid; mp 128.5−129.5 °C (lit.[24] 127−128 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.87 (1H, s, Ar-C**H**O), 7.85 (2H, d, *J* = 9 Hz, H-3,5), 7.12 (2H, d, *J* = 9 Hz, H-2,6), 4.28 (2H, t, *J* = 6 Hz, H-γ), 2.74 (2H, t, *J* = 6 Hz, H-β);[25] ^{13}C NMR (300 MHz, $CDCl_3$) δ 191.3 (Ar-**C**HO), 172.0 (**C**OOH), 163.3 (C-1), 131.8 (C-3,5), 129.7 (C-4), 114.9 (C-2,6), 64.2 (C-β), 33.9 (C-α).[26]

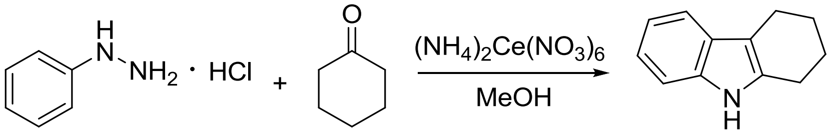
Indole Syntheses

2,3-Dimethylindole



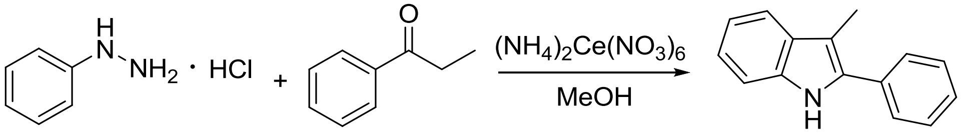
Following the procedure of Varma,[27] a solution of 2.89 g (20.0 mmol) of phenylhydrazine hydrochloride and 1.44 g (20.0 mmol) of 2-butanone in 30 mL of methanol was prepared. After addition of 2.19 g (4.00 mmol) of ceric ammonium nitrate to the stirring solution, the reaction mixture was heated at reflux for 3 h, then allowed to cool to room temperature. The reaction mixture was poured into a beaker containing 100 mL of water and a large amount of precipitate was formed. The precipitate was isolated by filtration and air-dried to give 2.65 g (18.3 mmol, 91%) of 2,3-dimethylindole as a white powder; mp 100-103.5 °C (lit.[28] 104 °C); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.67 (1H, br s), 7.51 (1H, d, *J* = 7.2 Hz), 7.28 (1H, dd, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 7.13 (2H, m), 2.39 (3H, s), 2.27 (3H, s);[29] ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.4, 130.8, 129.6, 121.1, 119.2, 118.1, 110.2, 107.3, 11.7, 8.6.[29]

1,2,3,4-Tetrahydrocarbazole



Following the procedure of Varma,[27] a solution of 3.61 g (25.0 mmol) of phenylhydrazine hydrochloride and 2.45 g (25.0 mmol) of cyclohexanone in 40 mL of methanol was prepared. After addition of 2.74 g (5.00 mmol) of ceric ammonium nitrate to the stirring solution, the reaction mixture was heated at reflux for 2 h, then allowed to cool to room temperature. The reaction mixture was poured into a beaker containing 100 mL of water and a large amount of precipitate formed. The precipitate was isolated by filtration and air-dried to give 3.52 g (20.6 mmol, 82%) of 1,2,3,4-tetrahydrocarbazole as a white powder; mp 116.5-117.5 °C (lit.[30] 118.5-119.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, br s), 7.47 (1H, d, J = 7.5 Hz), 7.28 (1H, d, J = 7.5 Hz), 7.10 (2H, m), 2.73 (4H, dd, J_1 = 11.9 Hz, J_2 = 4.9 Hz), 1.91 (4H, m);[31] ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 134.3, 128.0, 121.2, 119.3, 117.9, 110.5, 110.4, 23.5, 23.4(5), 23.4(2), 21.1.[31]

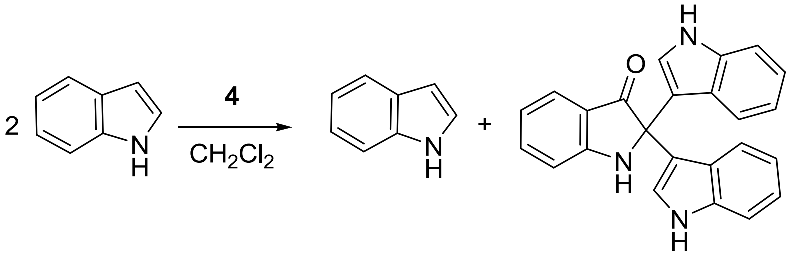
3-Methyl-2-phenylindole



Following the procedure of Varma,[27] a solution of 14.46 g (0.100 mol) of phenylhydrazine hydrochloride and 13.81 g (0.100 mol) of propiophenone in160 mL of methanol was prepared. After addition of 10.96 g (0.020 mol) of ceric ammonium nitrate to the stirring solution, the reaction mixture was heated at reflux overnight, then allowed to cool to room temperature. The reaction mixture was then poured into a beaker containing 400 mL of water. A dark oil formed on the surface which slowly solidified. The precipitate was isolated by filtration and air-dried to give 17.42 g (0.084 mol, 84%) of 3-methyl-2-phenylindole as a slightly red powder; mp 92-93 °C (lit.[32] 92-94 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, br s), 7.64 (3H, t, J = 7.1 Hz), 7.52 (2H, t, J = 7.4 Hz), 7.40 (2H, t, J = 7.4 Hz), 7.29-7.17 (2H, m), 2.51 (3H, s);[29] ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 134.2, 129.0, 128.0, 127.5, 122.5, 119.8, 119.2, 110.9, 108.9, 9.9.[29]

Indole Oxidations[33]

Oxidation of Indole



32

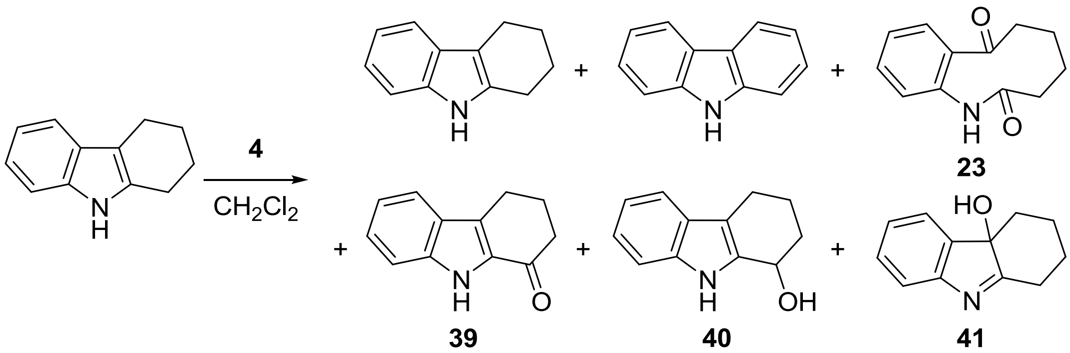
A 50-mL Erlenmeyer flask was charged with a suspension of 1.65 g (5.50 mmol) of **4** in 20 mL of methylene chloride. Indole (1.17 g, 10.0 mmol) was slowly added to this solution. The solution, which soon turned dark green, and was stirred for 3 d. The precipitate which had formed was isolated by filtration and rinsed with methylene chloride. The white color of the precipitate identified it as the hydroxylammonium salt byproduct. The filtrate was concentrated to a fraction of its volume (~5 mL), and the concentrated filtrate was chromatographed over silica gel using 2% methanol in methylene chloride as the eluent.

One of the two compounds that was isolated was identified as unreacted indole (396.4 mg, 3.38 mmol); mp 53-54 °C (lit.[34] 52.5-53 °C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.05 (1H, br s, 1H-indole), 7.54 (1H, d, J = 7.9 Hz), 7.40 (1H, d, J_1 = 8.1 Hz), 7.33 (1H, t, J = 2.8 Hz), 7.08 (1H, t, J = 7.5 Hz), 6.99 (1H, t, J = 7.9 Hz), 6.42 (1H, m), 3.35 (1H, s);[35,36] ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 135.8, 127.6, 125.1, 120.8, 119.9, 118.7, 111.3, 100.9.[35]

Addition of ether to the second compound resulted in the formation of a precipitate in addition to a red-colored ether solution. The precipitate was isolated by filtration and air-dried to give 301.6 mg (0.830 mmol) of **32** as a yellowish-brown solid; mp[37] 245-246 °C (lit.[38] 243-245.5 °C); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.97 (2H, br s), 8.14 (1H, br s), 7.50 (2H, t, J = 9.0 Hz), 7.36 (4H, t, J = 9.4 Hz), 7.12 (2H, d, J = 2.4 Hz), 7.04 (2H, t, J = 7.4 Hz), 6.96 (1H, d, J = 8.4 Hz), 6.85 (2H, t, J = 7.4 Hz), 6.74 (1H, t, J = 7.4 Hz);[39] ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 200.8, 160.6, 137.4, 136.9, 125.6, 124.4, 124.0, 121.0, 120.5, 118.3, 117.8, 117.0, 114.0, 111.8, 111.6, 67.6.[40]

The red ether solution was concentrated to give 230.5 mg of a dark solid (mp 120-121 °C). ^{1}H NMR analysis shows that there is a small amount of **32** present, but the remaining components could not be identified.

Oxidation of 1,2,3,4-Tetrahydrocarbazole



A 50-mL Erlenmeyer flask was charged with a suspension of 1.65 g (5.50 mmol) of **4** in 10 mL of methylene chloride and a solution of 856.7 mg (5.00 mmol) of 1,2,3,4-tetrahydrocarbazole in 10 mL of methylene chloride was added dropwise to the stirring suspension. After 3 d of stirring at room temperature, the reaction mixture was filtered to give a precipitate that became white after rinsing with methylene chloride. The filtrate was concentrated and chromatographed over silica gel using 2% methanol in methylene chloride as the eluent. A single fraction, which gave 614.0 mg of an orange solid that did not have a sharp melting point, was obtained; GC analysis indicated that this fraction contained several compounds. These compounds could not be separated using column chromatography. Identification of these compounds was done via GC-MS:[41]

Unreacted 1,2,3,4-tetrahydrocarbazole; GC-MS *m/z*: 171 [M^+].

Carbazole; GC-MS *m/z*: 167 [M^+].

Cleaved product **23**; GC-MS *m/z*: 203 [M^+].

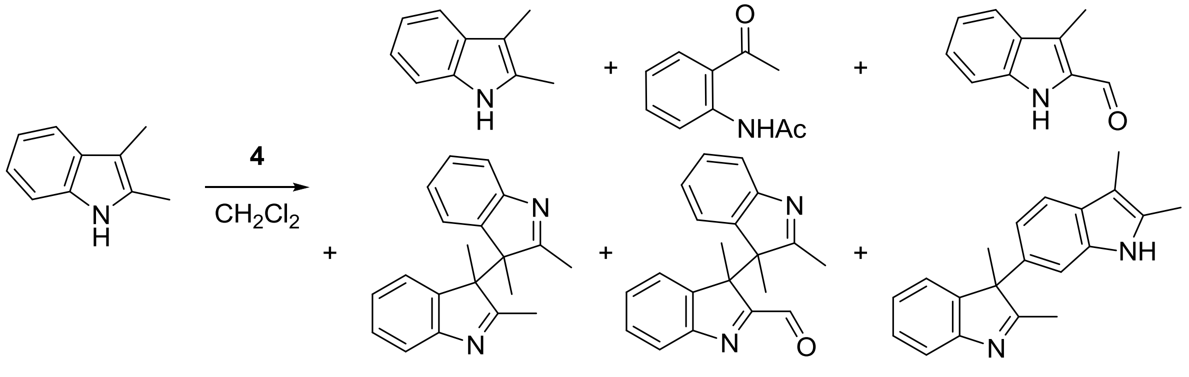
Ketone **39**, which corresponds to the products in Scheme 1.14; GC-MS *m/z*: 185 [M^+].

Alcohol **40**, which is can be oxidized to **39**; GC-MS *m/z*: 187 [M^+].

Alcohol **41**, formed via the hydroperoxide; GC-MS *m/z*: 187 [M^+].

4-Acetamido-2,2,6,6-tetramethylpiperidine; GC-MS *m/z*: 183 [M^+].

Oxidation of 2,3-Dimethylindole



42 **43** **44**

A 50-mL Erlenmeyer flask was charged with a suspension of 1.65 g (5.50 mmol) of **4** in 10 mL of CH_2Cl_2 and a solution of 726.3 mg (5.00 mmol) of 2,3-dimethylindole in 10 mL of CH_2Cl_2 was added dropwise to the stirring suspension. After 3 d of stirring at room temperature, the reaction mixture was filtered to give a precipitate that became white after rinsing with methylene chloride. The filtrate was concentrated and chromatography over silica gel using 2% methanol in methylene chloride as the eluent. Two separate fractions were obtained, but both fractions contained multiple compounds that could not be separated using column chromatography. Identification of these compounds was done via GC-MS:

Fraction 1

Unreacted 2,3-dimethylindole; GC-MS *m/z*: 145 [M^+], 144 [M – H].

2-Formyl-3-methylindole;[42] GC-MS *m/z*: 159 [M^+].

Fraction 2

2-Acetamidoacetophenone; GC-MS *m/z*: 177 [M^+].

Dimer **42**; GC-MS *m/z*: 288 [M^+].

Dimer **43**; GC-MS *m/z*: 302 [M^+].

Dimer **44**; GC-MS *m/z*: 288 [M^+].

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3. The oxammonium salt decomposes rapidly upon melting.

4. All NMR analyses done for the oxidations to aldehydes were done with suppression of the CH_2Cl_2 peak at δ 5.30 ppm. The appearance of the aldehyde proton peaks was monitored.

5. All NMR analyses done for the oxidations to acids were done with suppression of the CH_3CN peak at δ 2.06 ppm. The disappearance of the aldehyde proton peaks and the appearance of the methoxy group protons in *para*-anisic acid were monitored.

6. ^1H NMR relative to δ 7.26 ppm for $CDCl_3$ and ^{13}C NMR relative to δ 77.23 ppm for $CDCl_3$.

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23. No ^{13}C NMR spectrum reported.

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26. No ^{13}C NMR spectrum reported.

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33. Indole is the only compound studied that gave pure compounds via column chromatography. The other indoles gave compounds that could not be separated.

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36. 1H-Indole is in equilibrium with 3H-indole.

37. The solid turns black at 206 °C, but does not melt.

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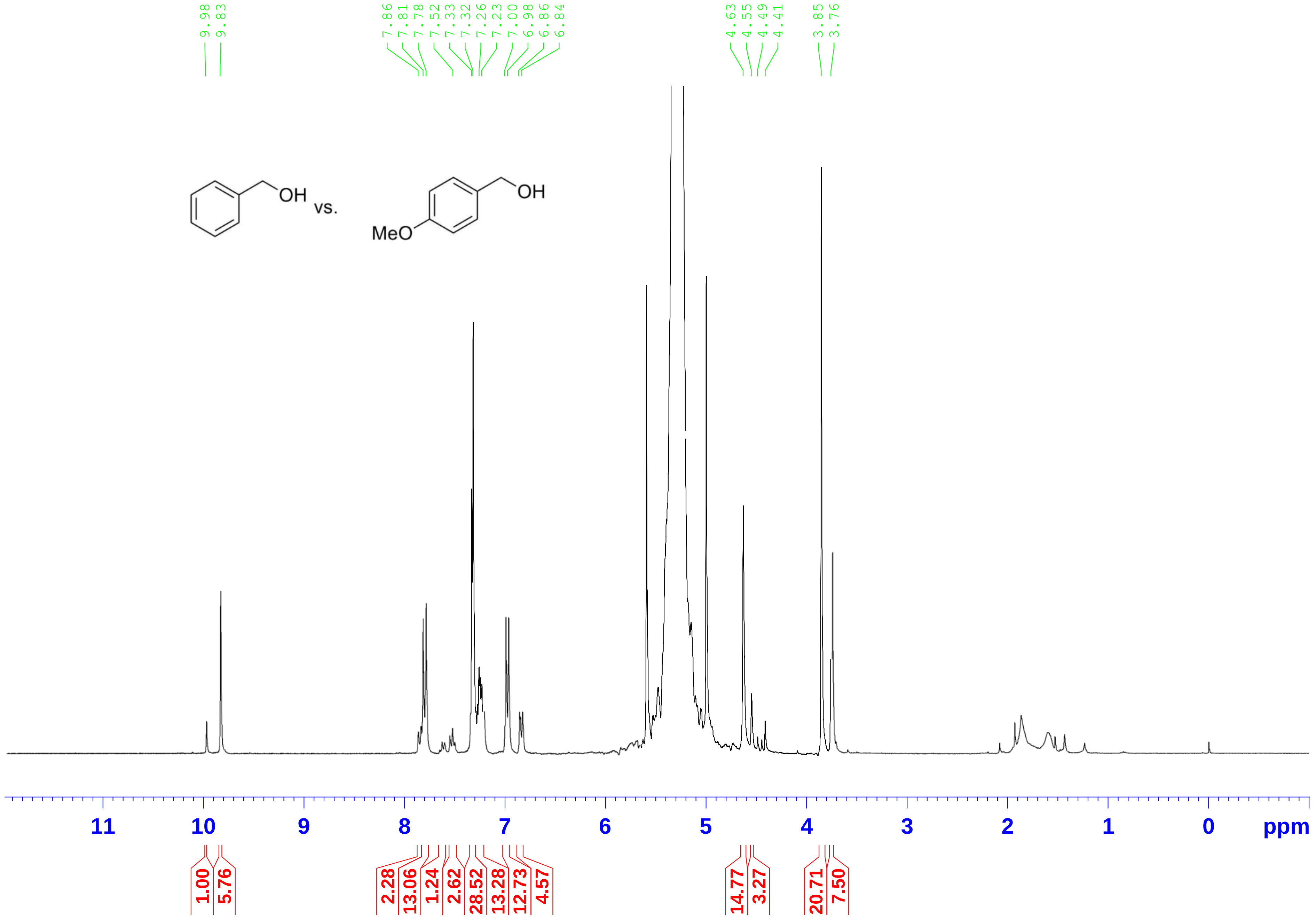
40. No ^{13}C NMR spectra reported.

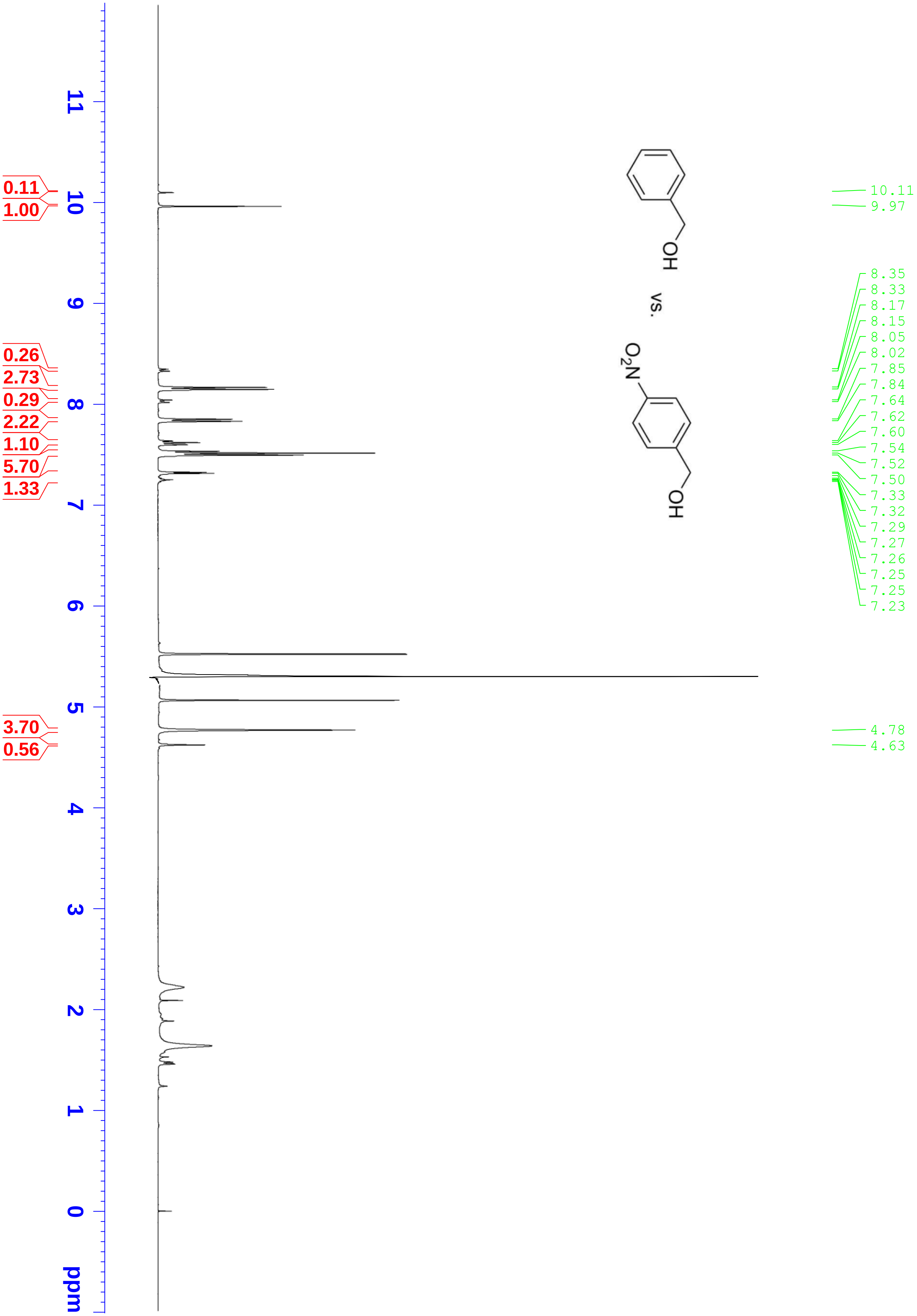
41. There are peaks that correspond to compounds that are not products of the oxidations of tetrahydrocarbazole and 2,3-dimethylindole. Most of these are simply preservatives that were present in the starting materials in the syntheses of these indoles.

42. The material may also be 3-formyl-2-methylindole; refer to the “Results and Discussion” section for a detailed explanation on which isomer was formed.

APPENDIX: NMR SPECTRA AND GC-MS DATA



9.98
9.83
7.86
7.81
7.78
7.52
7.33
7.32
7.26
7.23
7.00
6.98
6.86
6.84
4.63
4.55
4.49
4.41
3.85
3.76
OH
vs.
MeO
OH
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
5.76
2.28
13.06
1.24
2.62
28.52
13.28
12.73
4.57
14.77
3.27
20.71
7.50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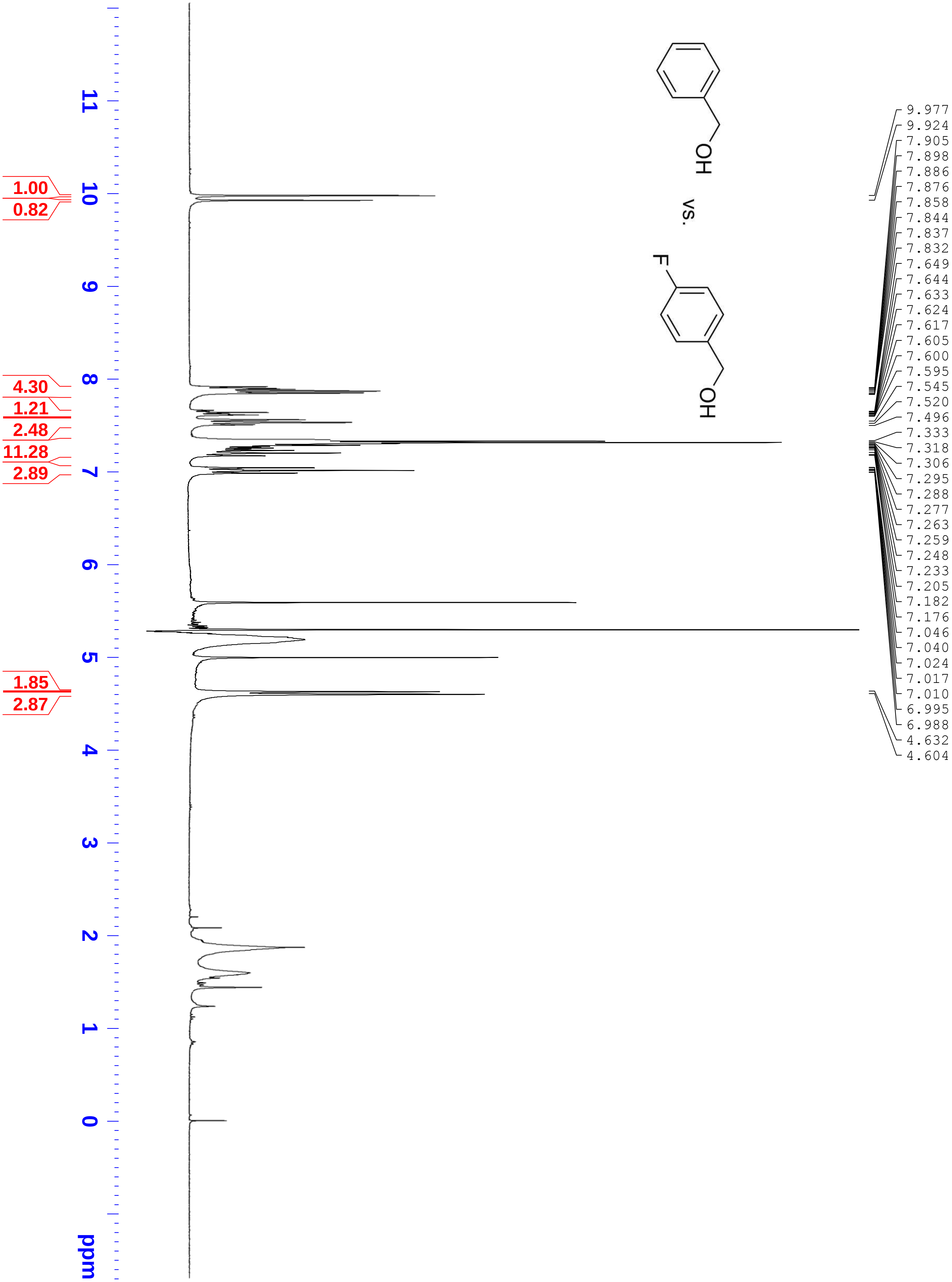
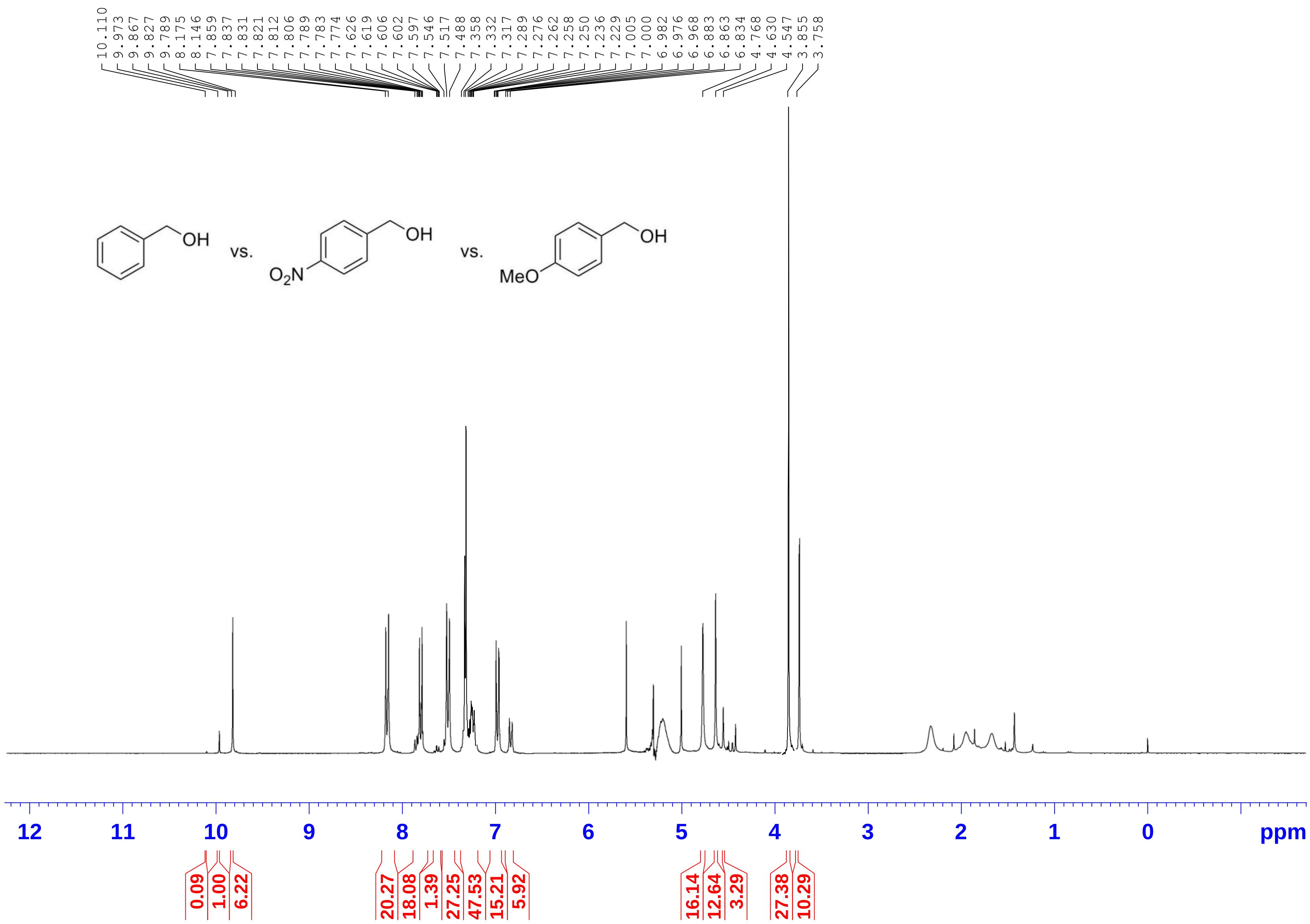
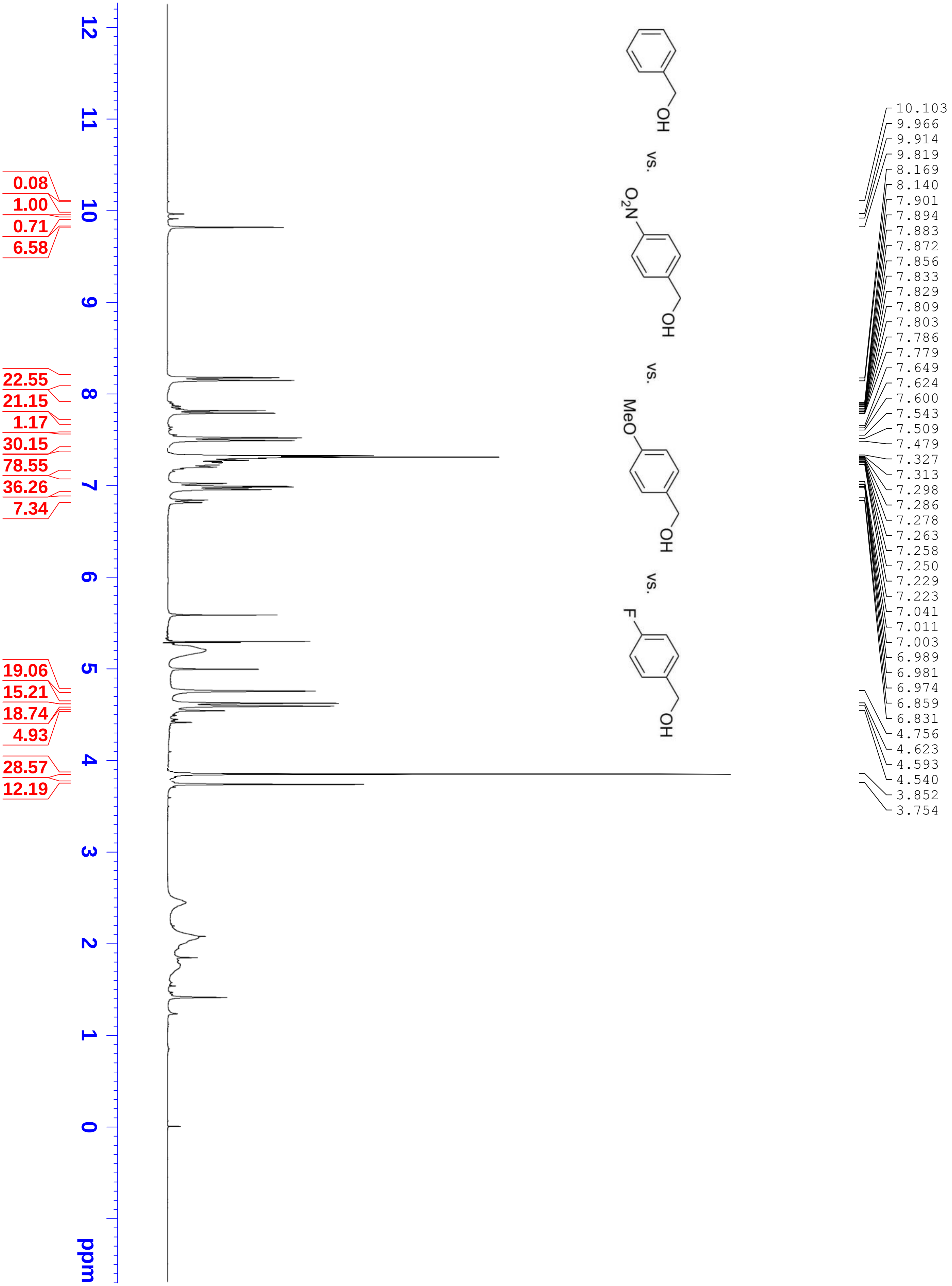
vs.
O_2N
OH
10.11
9.97
8.35
8.33
8.17
8.15
8.05
8.02
7.85
7.84
7.64
7.62
7.60
7.54
7.52
7.50
7.33
7.32
7.29
7.27
7.26
7.25
7.25
7.23
4.78
4.63
0.11
1.00
0.26
2.73
0.29
2.22
1.10
5.70
1.33
3.70
0.56
11
10
9
8
7
6
5
4
3
2
1
0
ppm



OH
vs.
F
OH
1.00
0.82
4.30
1.21
2.48
11.28
2.89
1.85
2.87
11
10
9
8
7
6
5
4
3
2
1
0
ppm
9.977
9.924
7.905
7.898
7.886
7.876
7.858
7.844
7.837
7.832
7.649
7.644
7.633
7.624
7.617
7.605
7.600
7.595
7.545
7.520
7.496
7.333
7.318
7.306
7.295
7.288
7.277
7.263
7.259
7.248
7.233
7.205
7.182
7.176
7.046
7.040
7.024
7.017
7.010
6.995
6.988
4.632
4.604



10.110
9.973
9.867
9.827
9.789
8.175
8.146
7.859
7.837
7.831
7.821
7.812
7.806
7.789
7.783
7.774
7.626
7.619
7.606
7.602
7.597
7.546
7.517
7.488
7.358
7.332
7.317
7.289
7.276
7.262
7.258
7.250
7.236
7.229
7.005
7.000
6.982
6.976
6.968
6.883
6.863
6.834
4.768
4.630
4.547
3.855
3.758
OH
vs.
O2N
OH
vs.
MeO
OH
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.09
1.00
6.22
20.27
18.08
1.39
27.25
47.53
15.21
5.92
16.14
12.64
3.29
27.38
10.29


OH
vs.
O2N
OH
vs.
MeO
OH
vs.
F
OH
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.08
1.00
0.71
6.58
22.55
21.15
1.17
30.15
78.55
36.26
7.34
19.06
15.21
18.74
4.93
28.57
12.19
10.103
9.966
9.914
9.819
8.169
8.140
7.901
7.894
7.883
7.872
7.856
7.833
7.829
7.809
7.803
7.786
7.779
7.649
7.624
7.600
7.543
7.509
7.479
7.327
7.313
7.298
7.286
7.278
7.263
7.258
7.250
7.229
7.223
7.041
7.011
7.003
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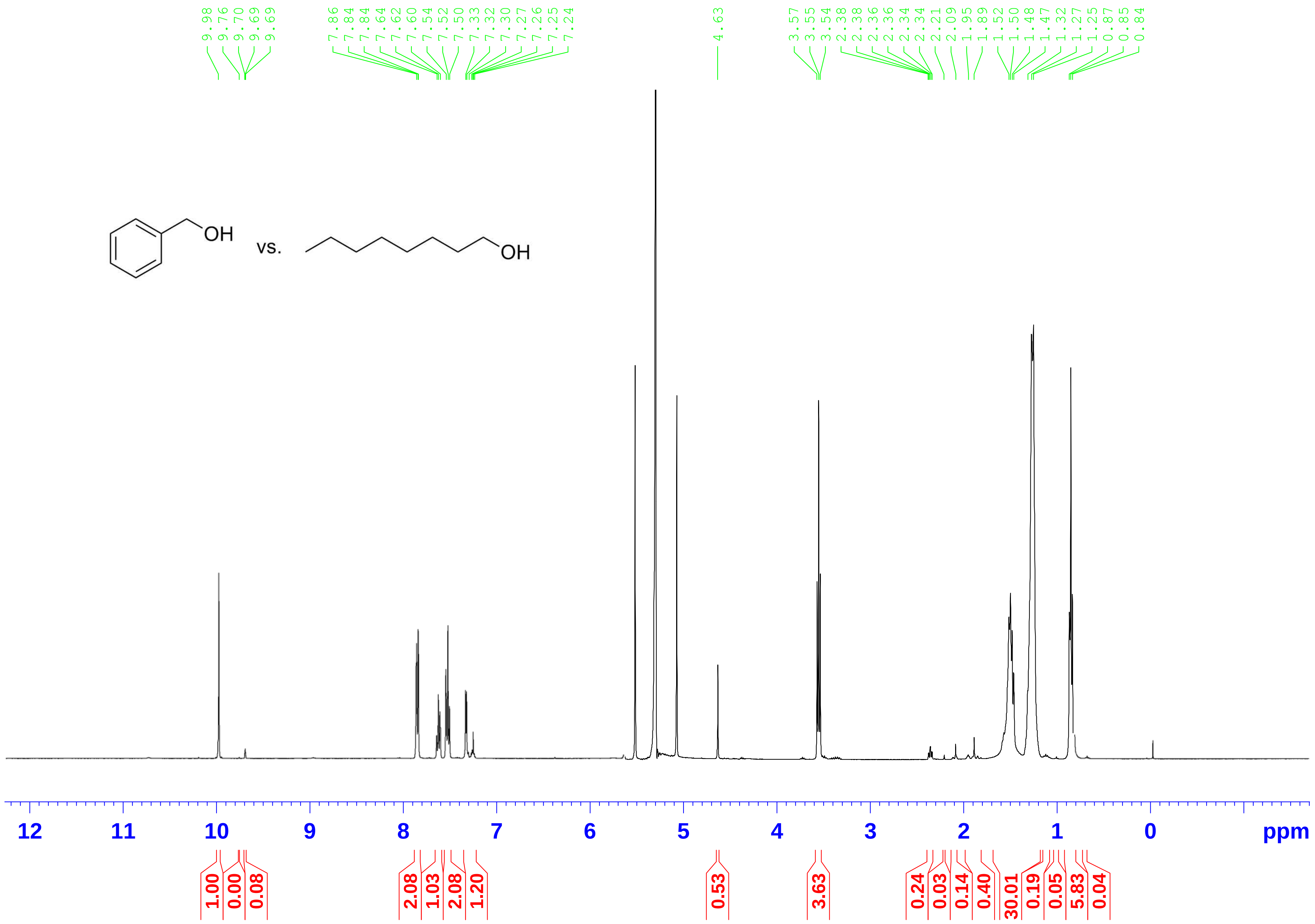
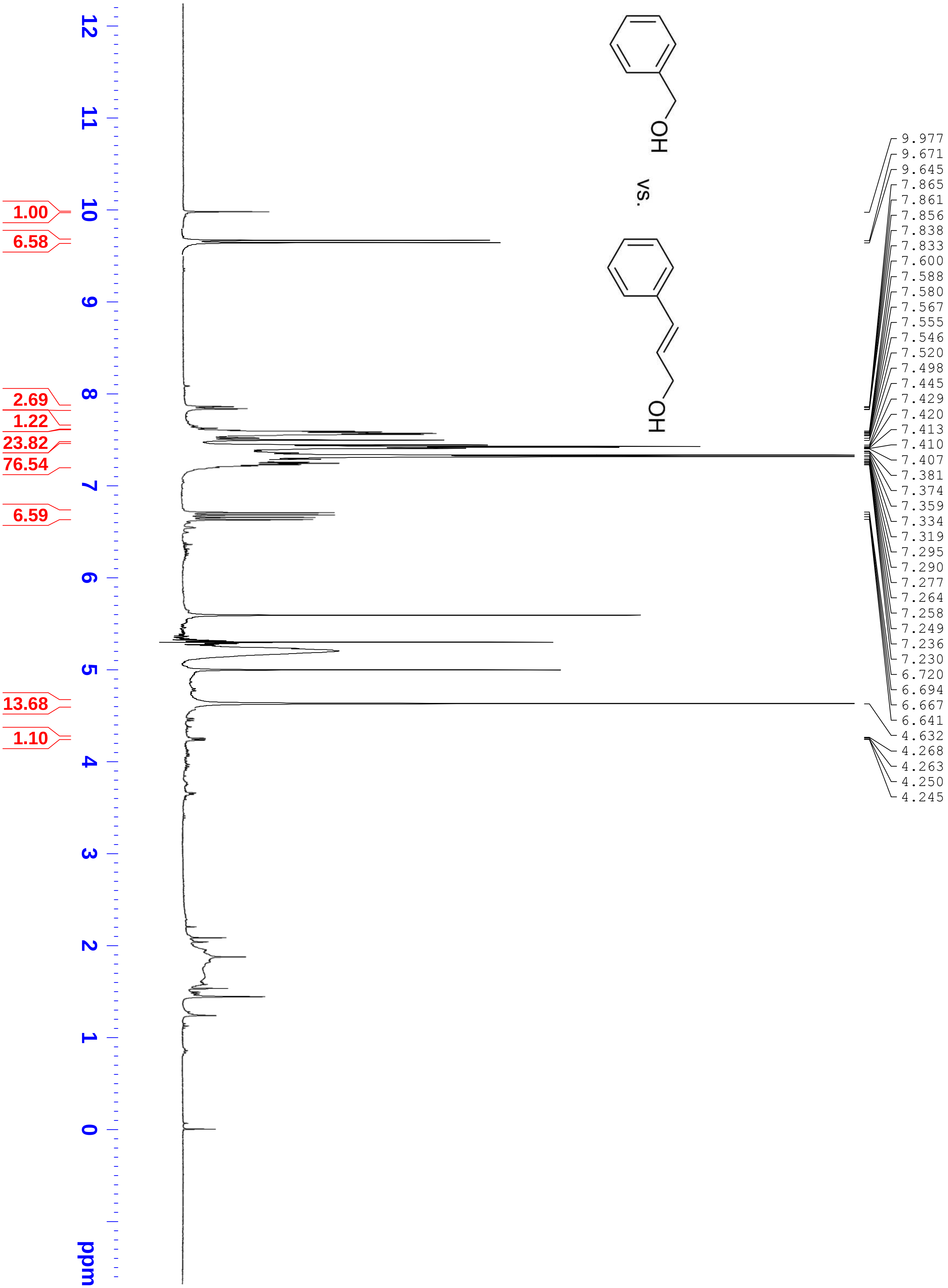
3.852
3.754



9.98
9.76
9.70
9.69
9.69
7.86
7.84
7.84
7.64
7.62
7.60
7.54
7.52
7.50
7.33
7.32
7.30
7.27
7.26
7.25
7.24
4.63
3.57
3.55
3.54
2.38
2.38
2.36
2.36
2.34
2.34
2.21
2.09
1.95
1.89
1.52
1.50
1.48
1.47
1.32
1.27
1.25
0.87
0.85
0.84
OH
vs.
OH
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.00
0.08
2.08
1.03
2.08
1.20
0.53
3.63
0.24
0.03
0.14
0.40
30.01
0.19
0.05
5.83
0.04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vs.
OH
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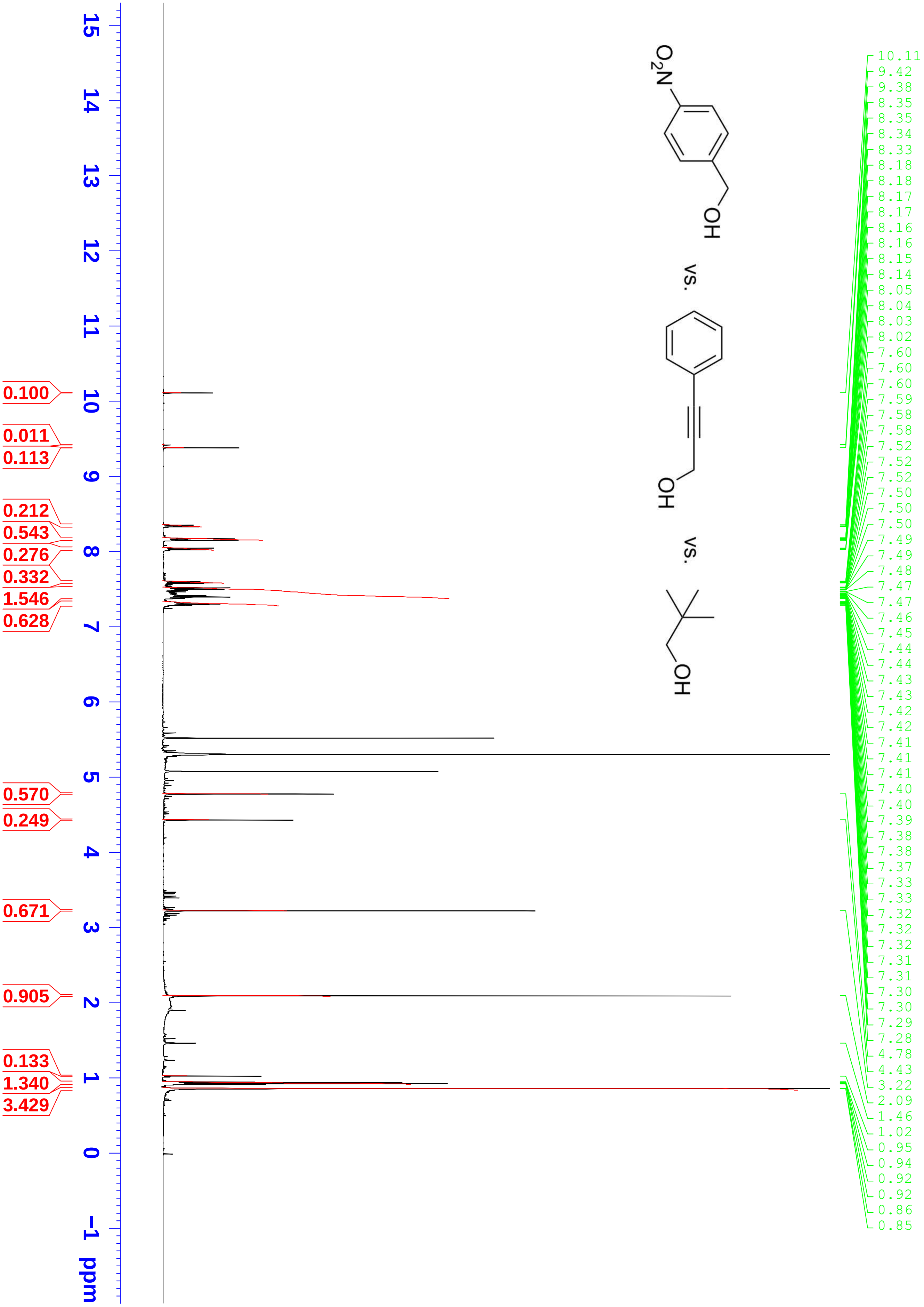
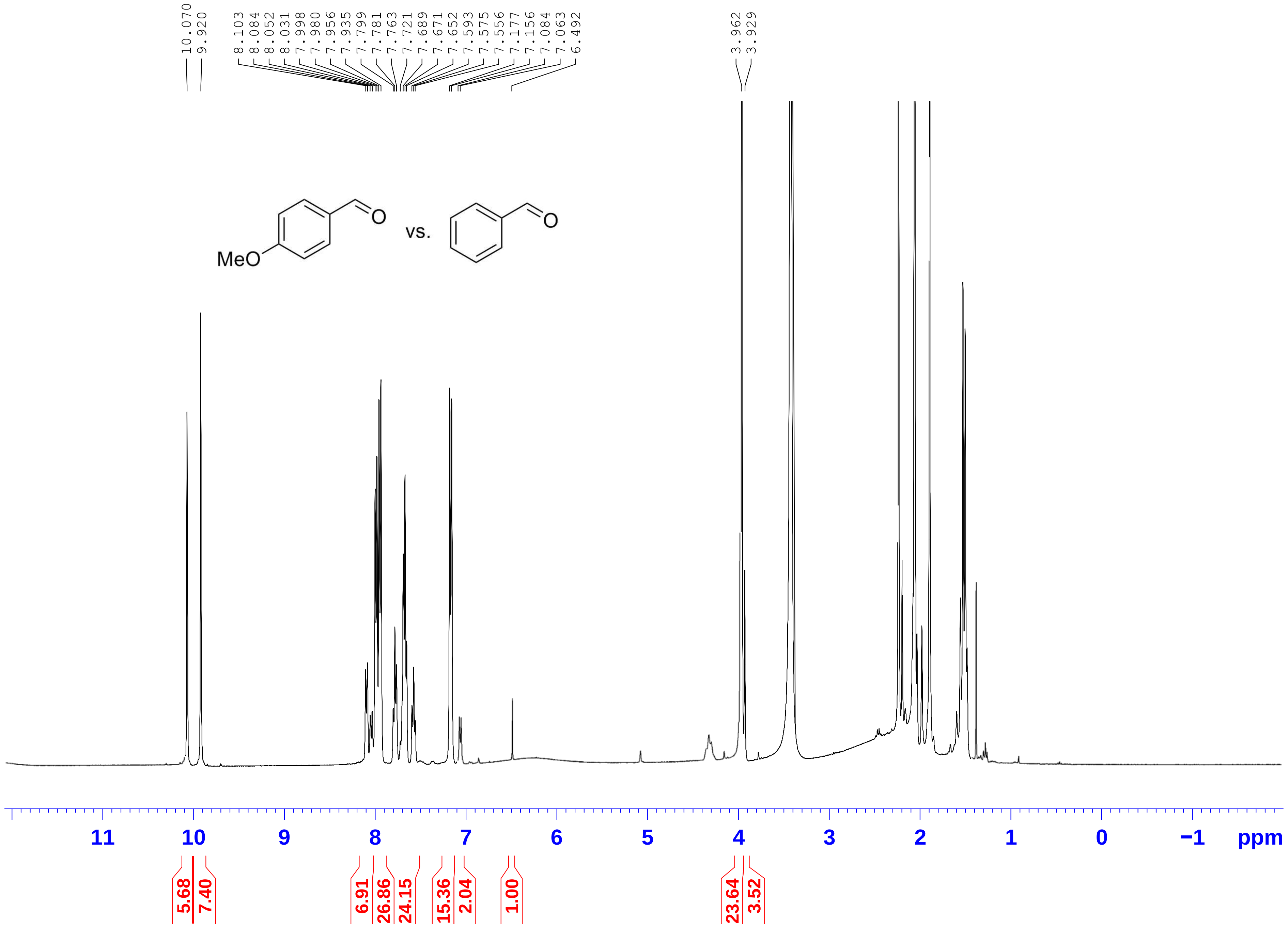
7.865
7.861
7.856
7.838
7.833
7.600
7.588
7.580
7.567
7.555
7.546
7.520
7.498
7.445
7.429
7.420
7.413
7.410
7.407
7.381
7.374
7.359
7.334
7.319
7.295
7.290
7.277
7.264
7.258
7.249
7.236
7.230
6.720
6.694
6.667
6.641
4.632
4.268
4.263
4.250
4.245
1.00
6.58
2.69
1.22
23.82
76.54
6.59
13.68
1.10
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

O2N
OH
vs.
OH
vs.
OH
10.11
9.42
9.38
8.35
8.35
8.34
8.33
8.18
8.18
8.17
8.17
8.16
8.16
8.15
8.14
8.05
8.04
8.03
8.02
7.60
7.60
7.60
7.59
7.58
7.58
7.52
7.52
7.52
7.50
7.50
7.50
7.49
7.49
7.48
7.47
7.47
7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.28
4.78
4.43
3.22
2.09
1.46
1.02
0.95
0.94
0.92
0.92
0.86
0.85
0.100
0.011
0.113
0.212
0.543
0.276
0.332
1.546
0.628
0.570
0.249
0.671
0.905
0.133
1.340
3.429
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm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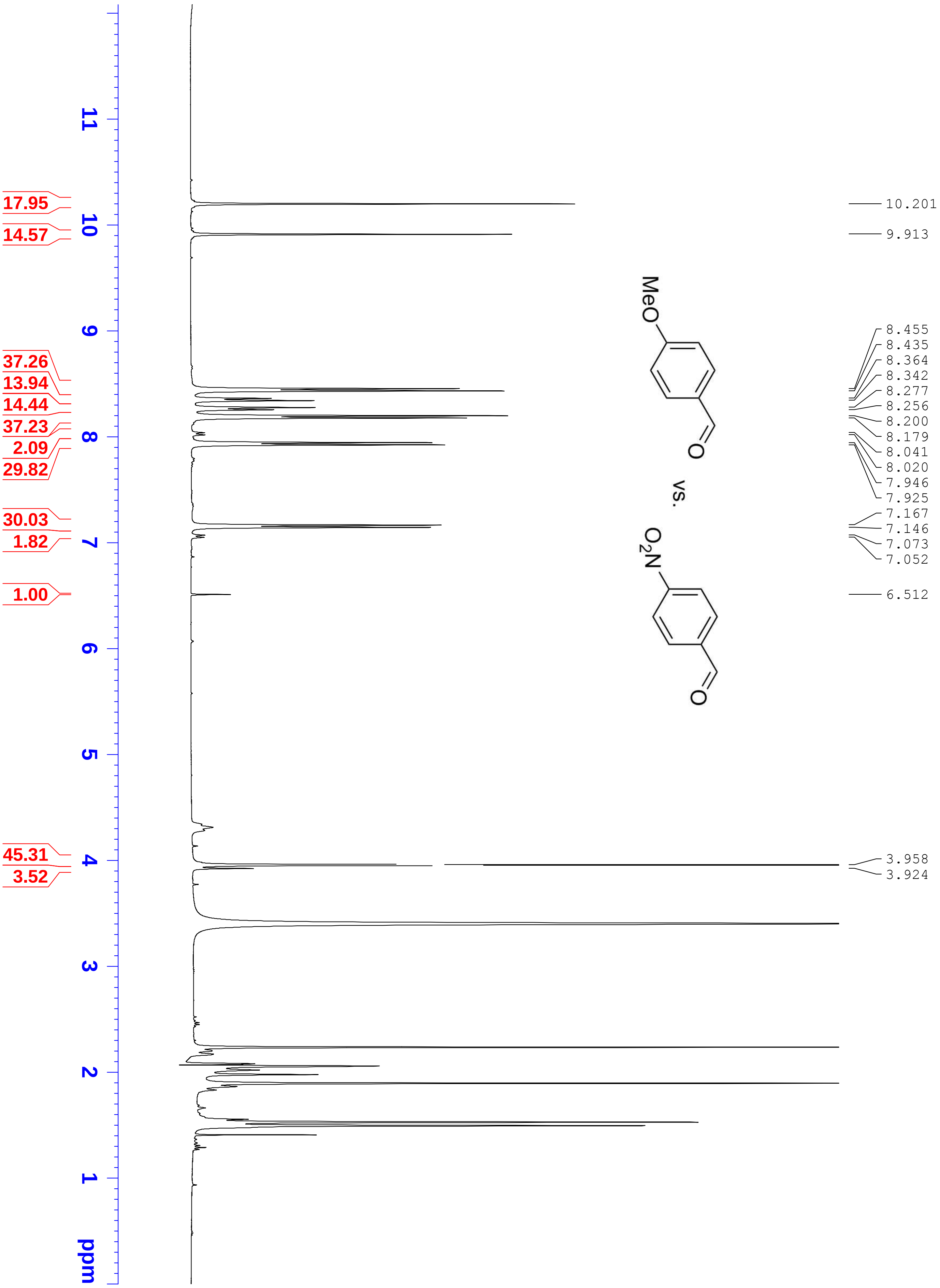
8.084
8.052
8.031
7.998
7.980
7.956
7.935
7.799
7.781
7.763
7.721
7.689
7.671
7.652
7.593
7.575
7.556
7.177
7.156
7.084
7.063
6.492
3.962
3.929
MeO
O
vs.
O
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
5.68
7.40
6.91
26.86
24.15
15.36
2.04
1.00
23.64
3.52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37.26
13.94
14.44
37.23
2.09
29.82
30.03
1.82
1.00
45.31
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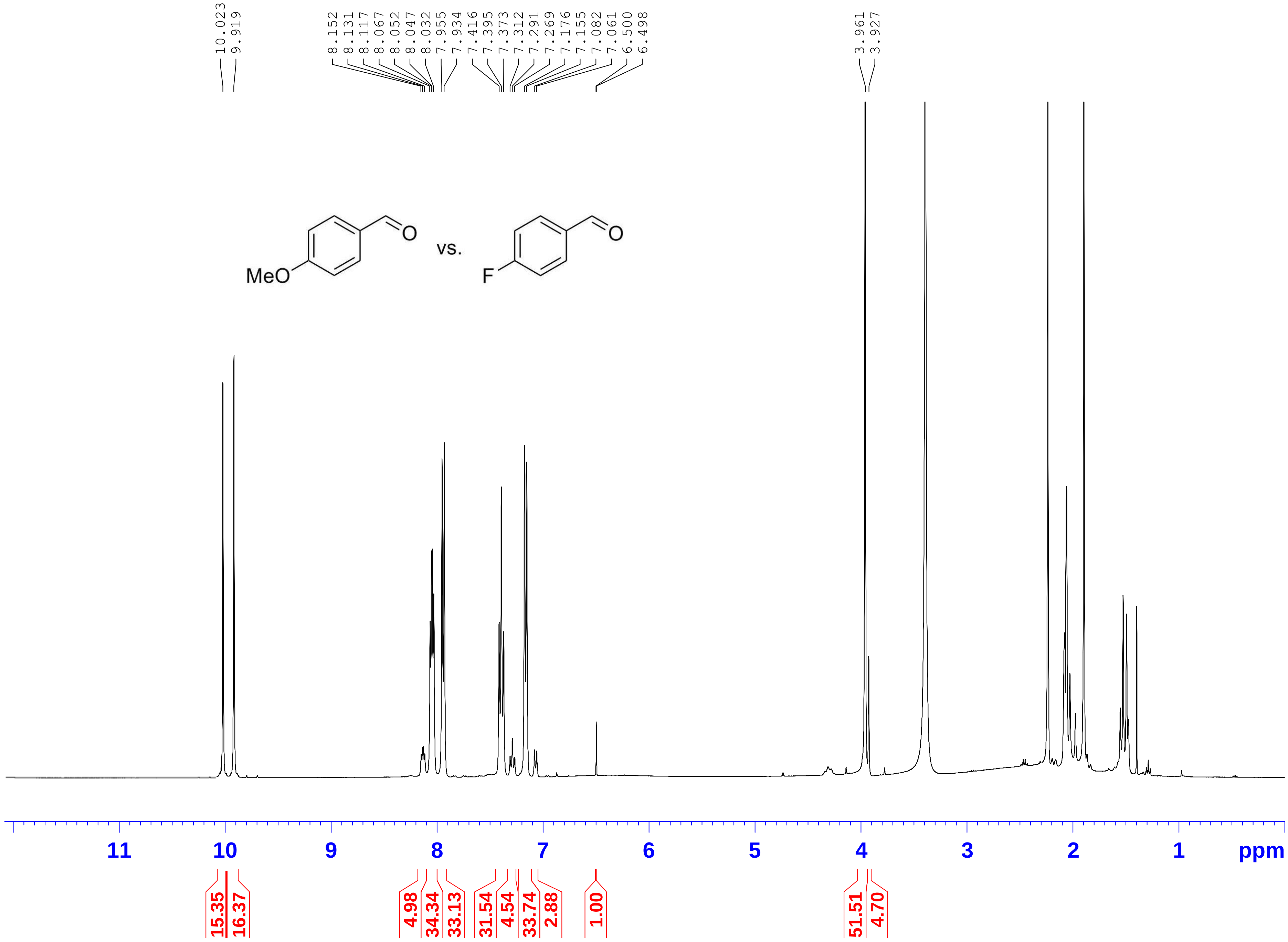
11
10
9
8
7
6
5
4
3
2
1
ppm
10.201
9.913
8.455
8.435
8.364
8.342
8.277
8.256
8.200
8.179
8.041
8.020
7.946
7.925
7.167
7.146
7.073
7.052
6.512
3.958
3.924
MeO
O
vs.
O2N
O


10.023
9.919
8.152
8.131
8.117
8.067
8.052
8.047
8.032
7.955
7.934
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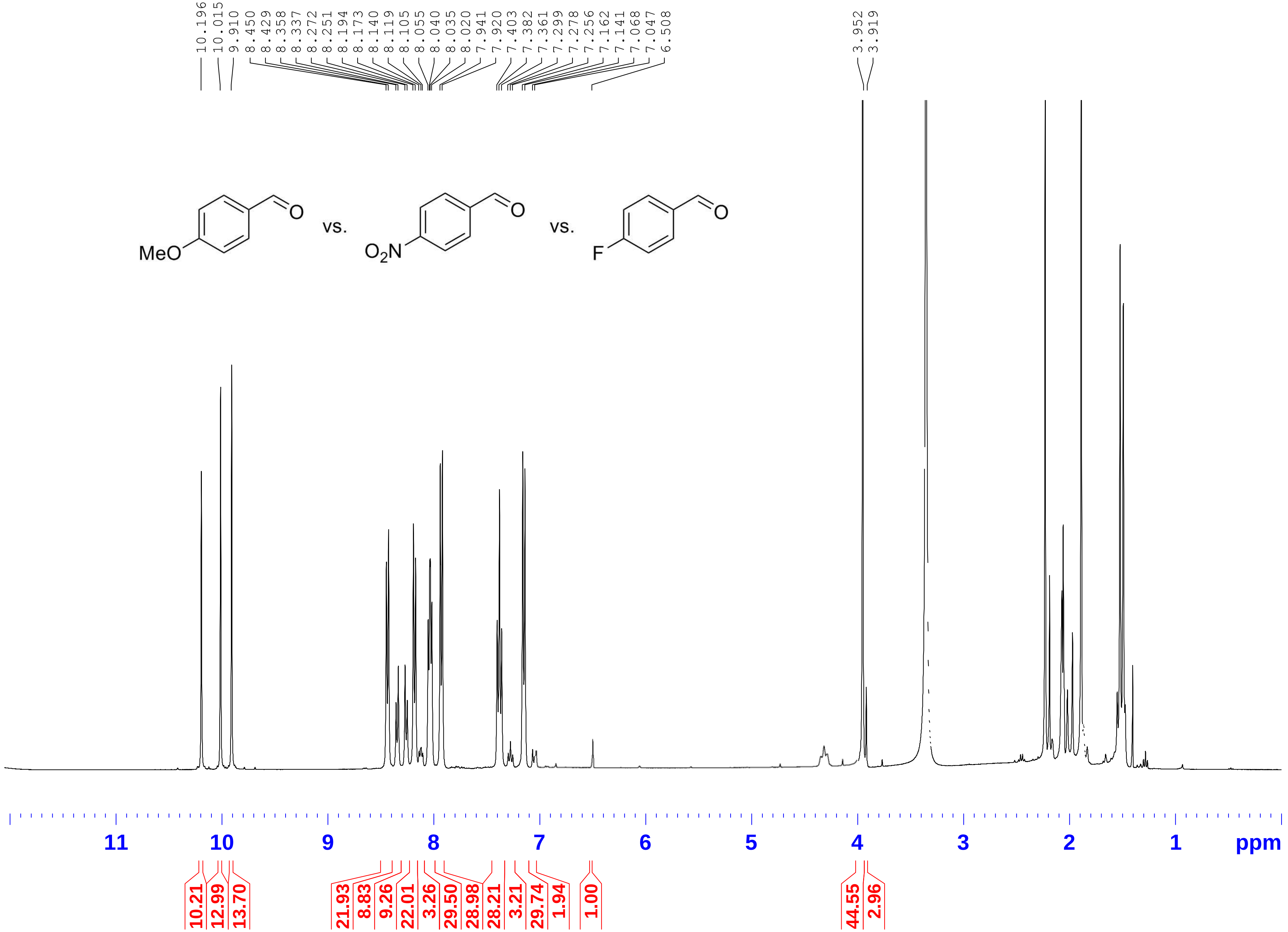
7.395
7.373
7.312
7.291
7.269
7.176
7.155
7.082
7.061
6.500
6.498
3.961
3.927
MeO
O
vs.
F
O
11
10
9
8
7
6
5
4
3
2
1
ppm
15.35
16.37
4.98
34.34
33.13
31.54
4.54
33.74
2.88
1.00
51.51
4.70



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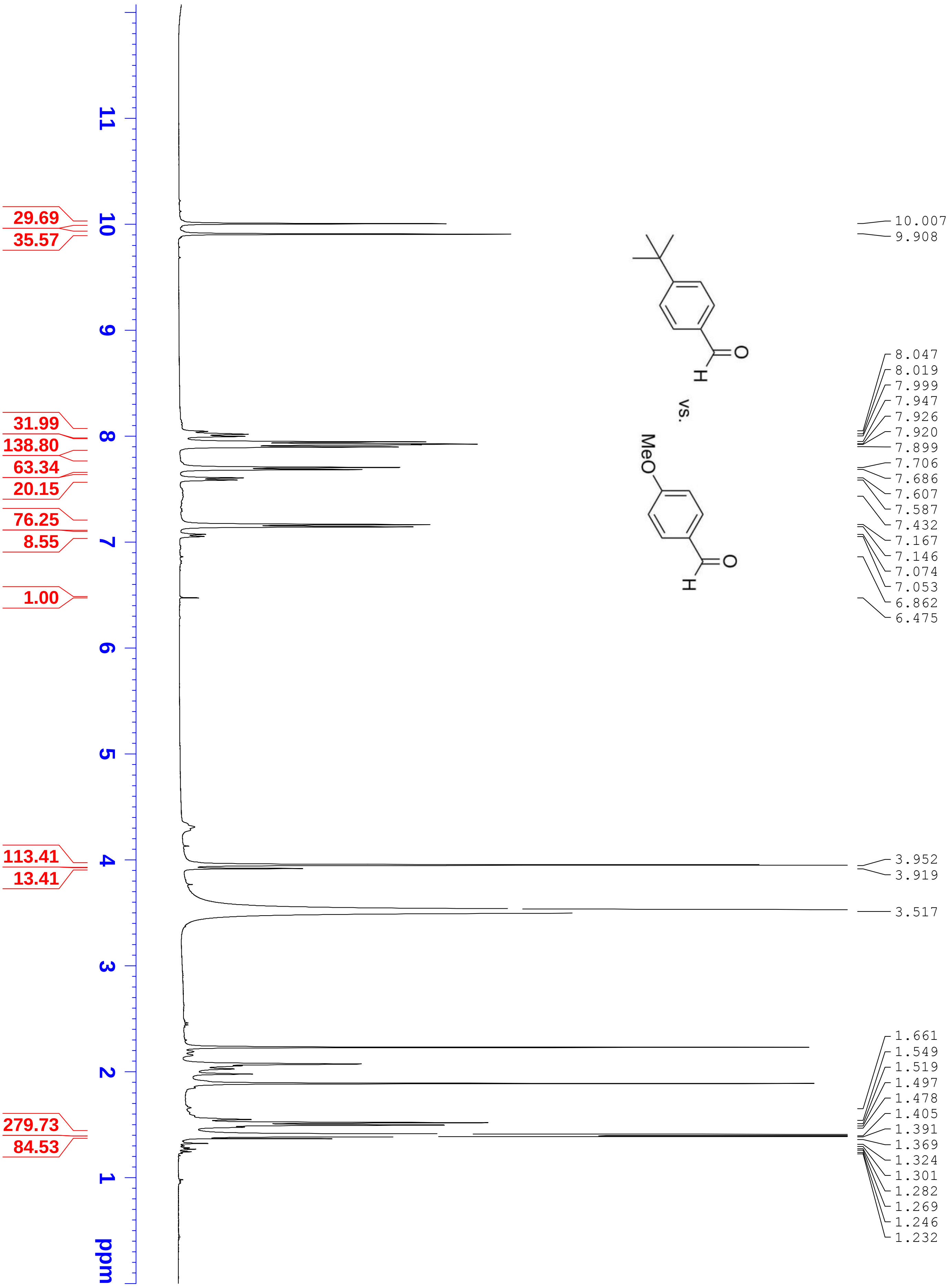
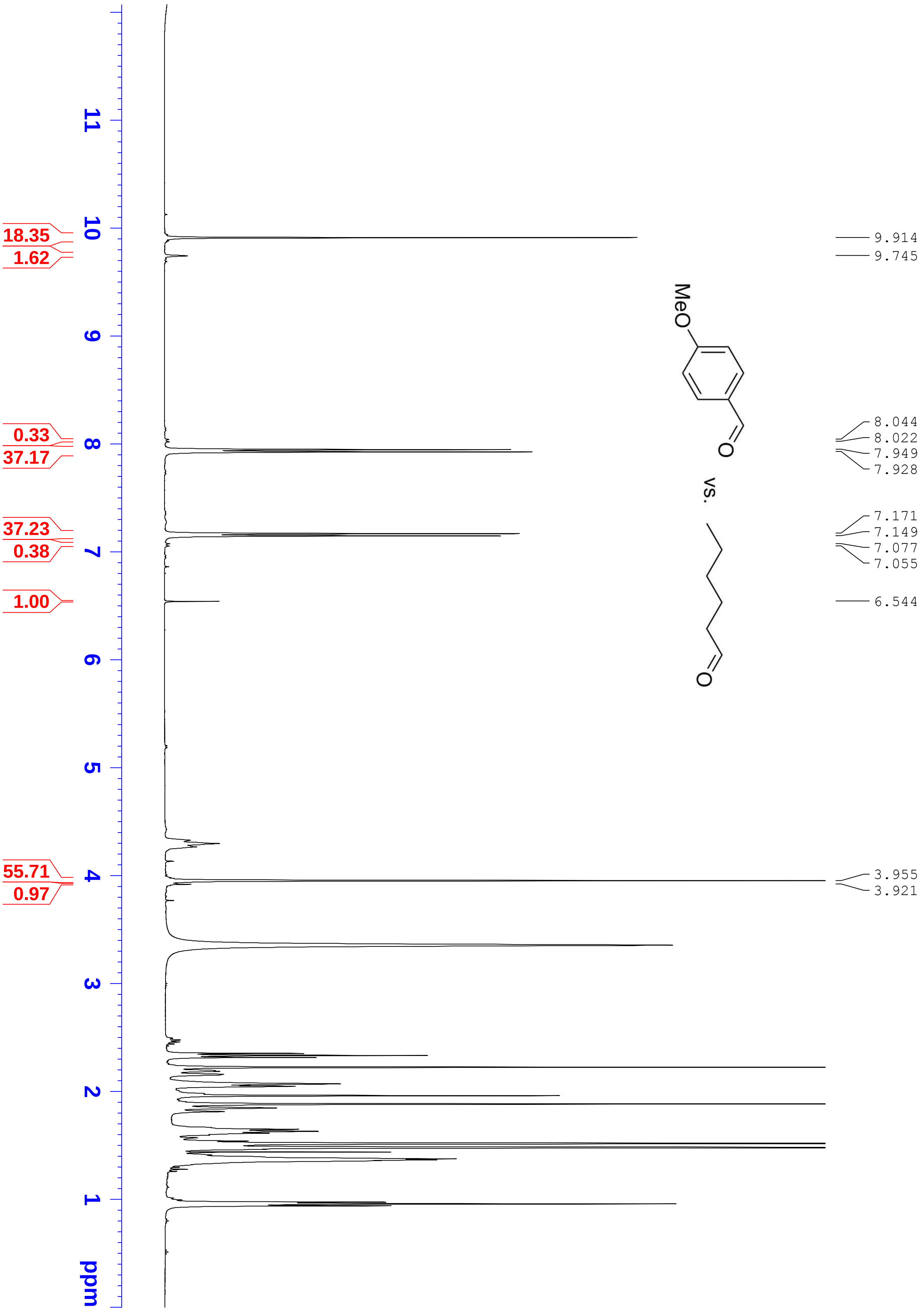
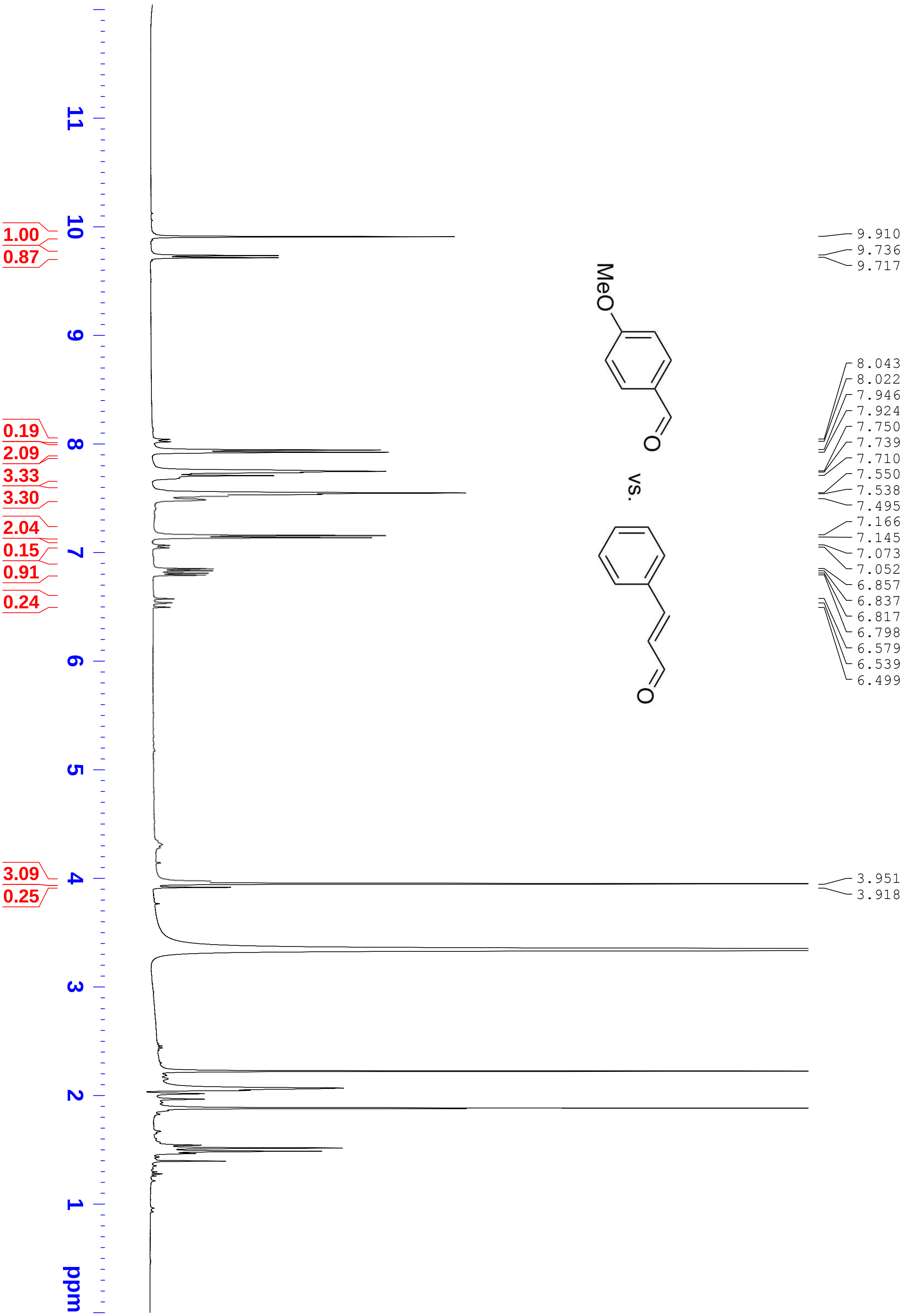
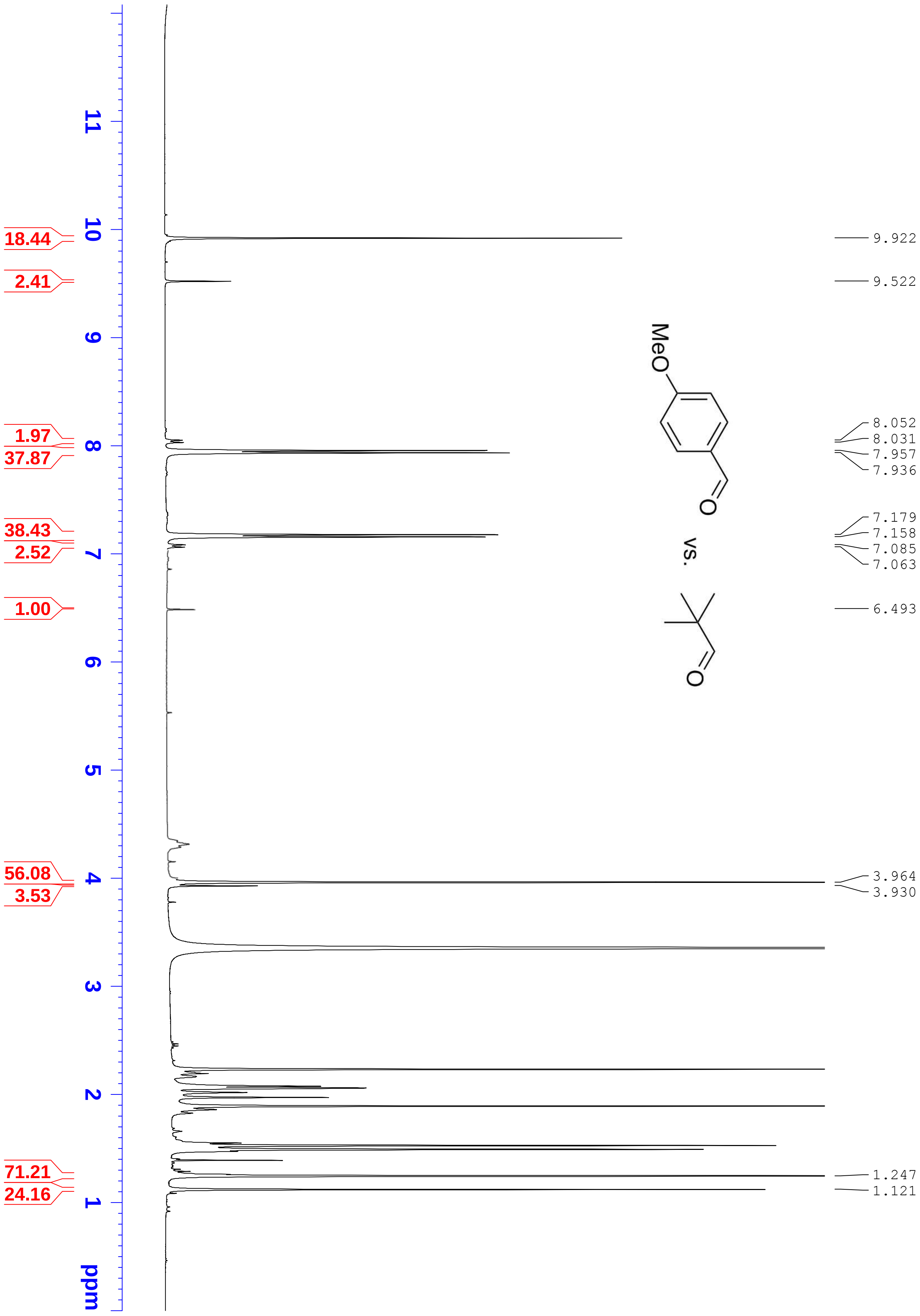
10.015
9.910
8.450
8.429
8.358
8.337
8.272
8.251
8.194
8.173
8.140
8.119
8.105
8.055
8.040
8.035
8.020
7.941
7.920
7.403
7.382
7.361
7.299
7.278
7.256
7.162
7.141
7.068
7.047
6.508
3.952
3.919
MeO
O
vs.
O_2N
O
vs.
F
O
11
10
9
8
7
6
5
4
3
2
1
ppm
10.21
12.99
13.70
21.93
8.83
9.26
22.01
3.26
29.50
28.98
28.21
3.21
29.74
1.94
1.00
44.55
2.96



MeO
vs.
H
O
29.69
35.57
31.99
138.80
63.34
20.15
76.25
8.55
1.00
113.41
13.41
279.73
84.53
11
10
9
8
7
6
5
4
3
2
1
ppm
10.007
9.908
8.047
8.019
7.999
7.947
7.926
7.920
7.899
7.706
7.686
7.607
7.587
7.432
7.167
7.146
7.074
7.053
6.862
6.475
3.952
3.919
3.517
1.661
1.549
1.519
1.497
1.478
1.405
1.391
1.369
1.324
1.301
1.282
1.269
1.246
1.232


MeO
O
vs.
O
9.914
9.745
8.044
8.022
7.949
7.928
7.171
7.149
7.077
7.055
6.544
3.955
3.921
18.35
1.62
0.33
37.17
37.23
0.38
1.00
55.71
0.97
11
10
9
8
7
6
5
4
3
2
1
ppm


MeO
O
vs.
O
1.00
0.87
0.19
2.09
3.33
3.30
2.04
0.15
0.91
0.24
3.09
0.25
11
10
9
8
7
6
5
4
3
2
1
ppm
9.910
9.736
9.717
8.043
8.022
7.946
7.924
7.750
7.739
7.710
7.550
7.538
7.495
7.166
7.145
7.073
7.052
6.857
6.837
6.817
6.798
6.579
6.539
6.499
3.951
3.918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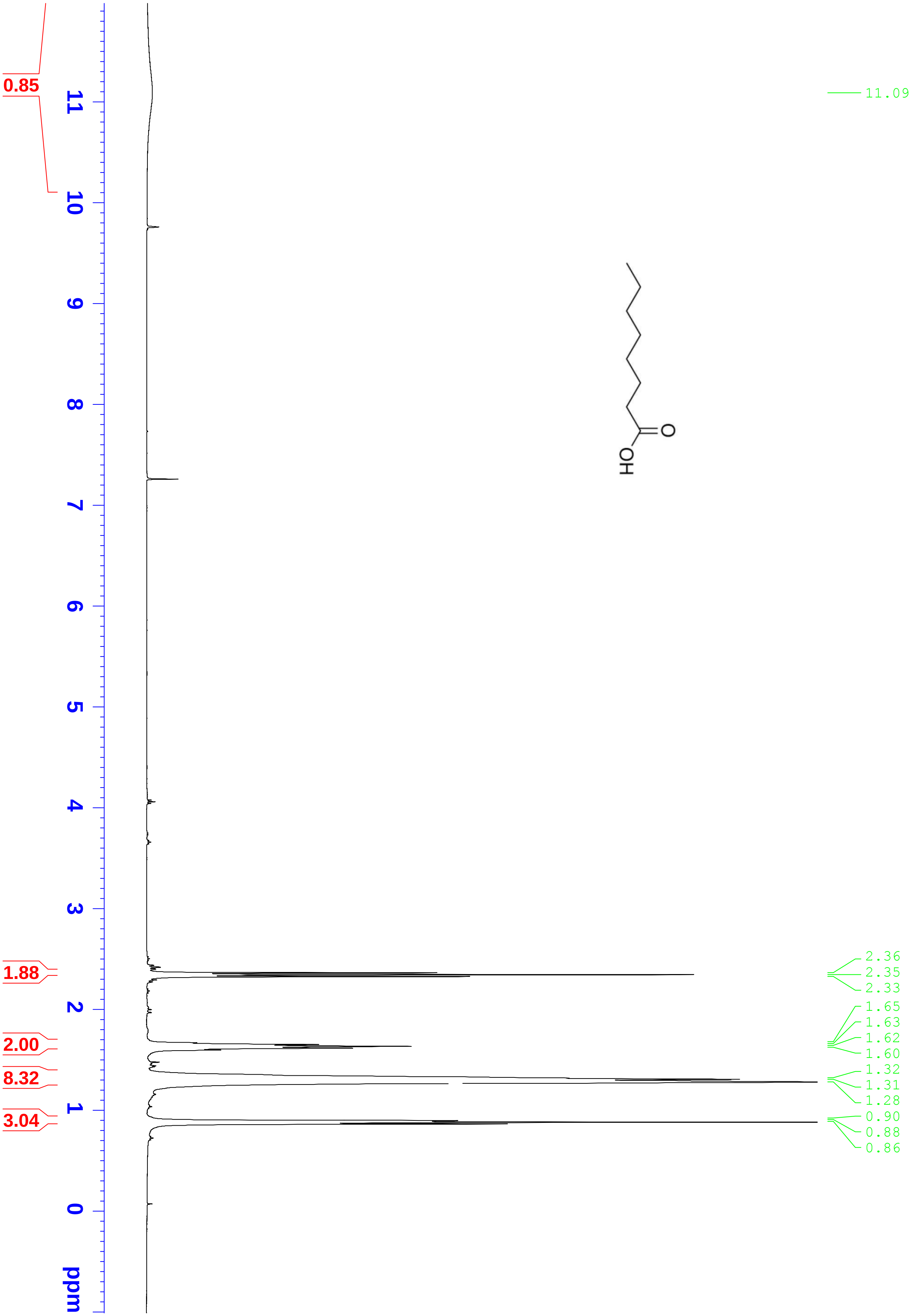
2.41
1.97
37.87
38.43
2.52
1.00
56.08
3.53
71.21
24.16
11
10
9
8
7
6
5
4
3
2
1
ppm
9.922
9.522
8.052
8.031
7.957
7.936
7.179
7.158
7.085
7.063
6.493
3.964
3.930
1.247
1.121
MeO
O
vs.
O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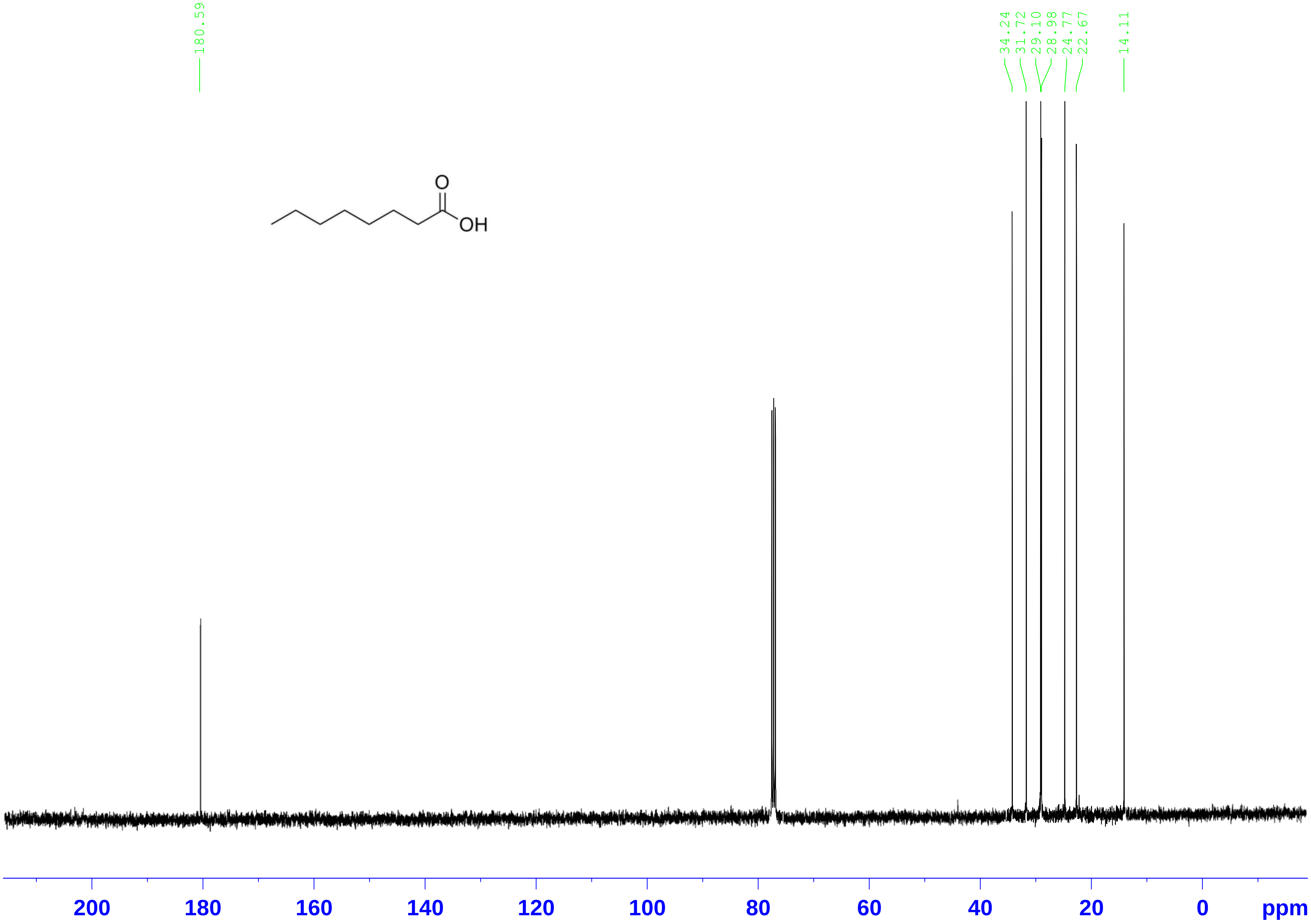
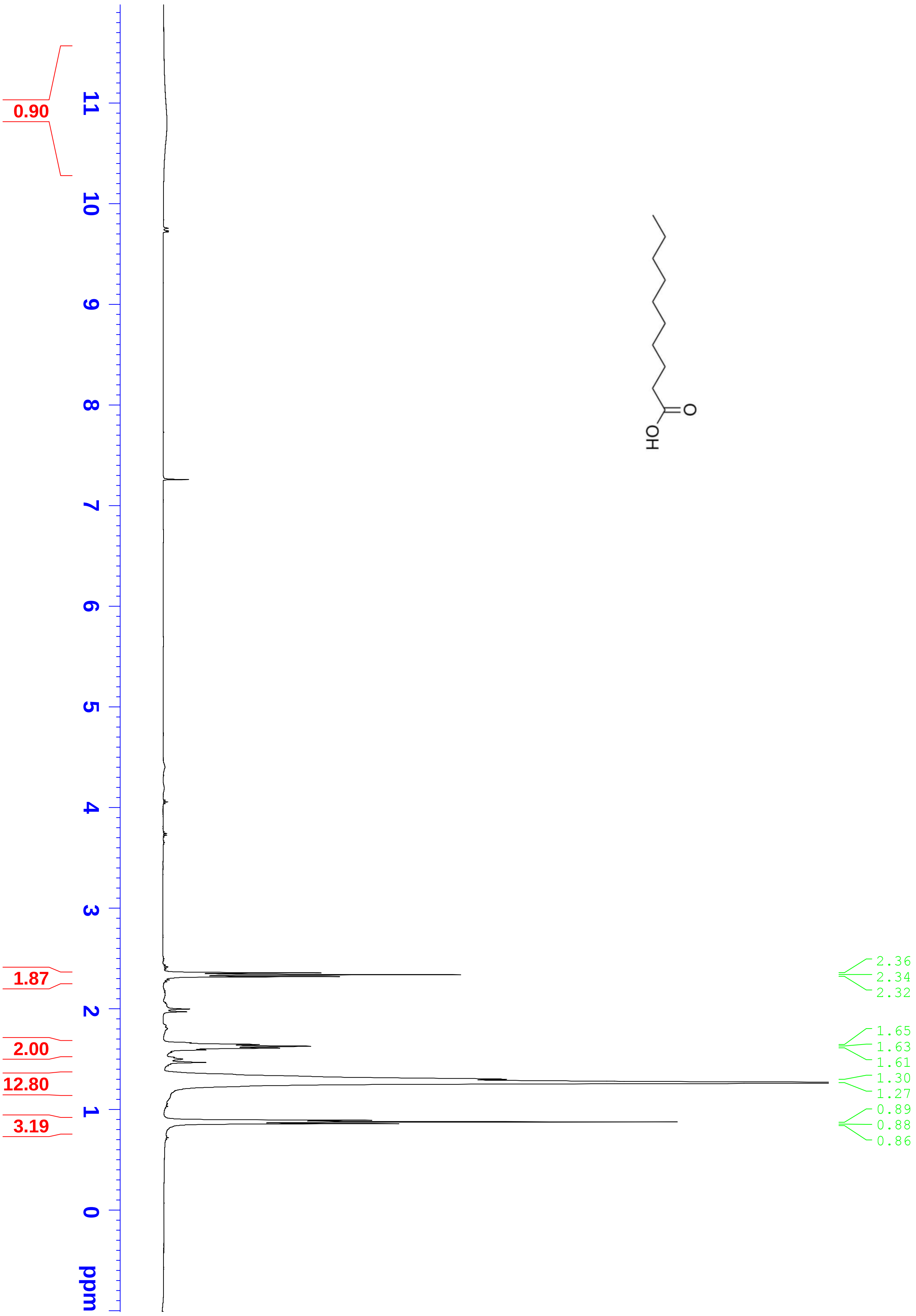
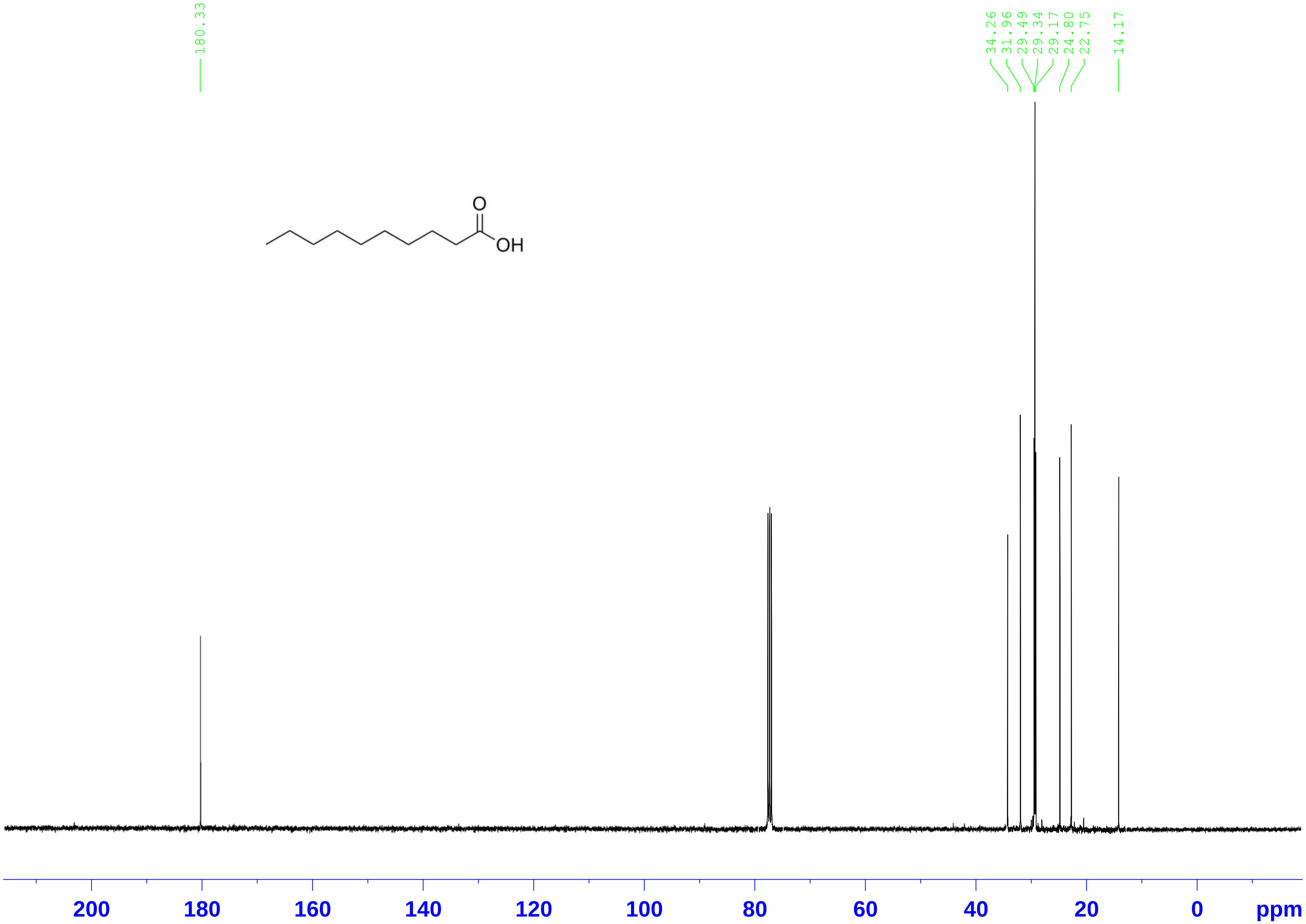
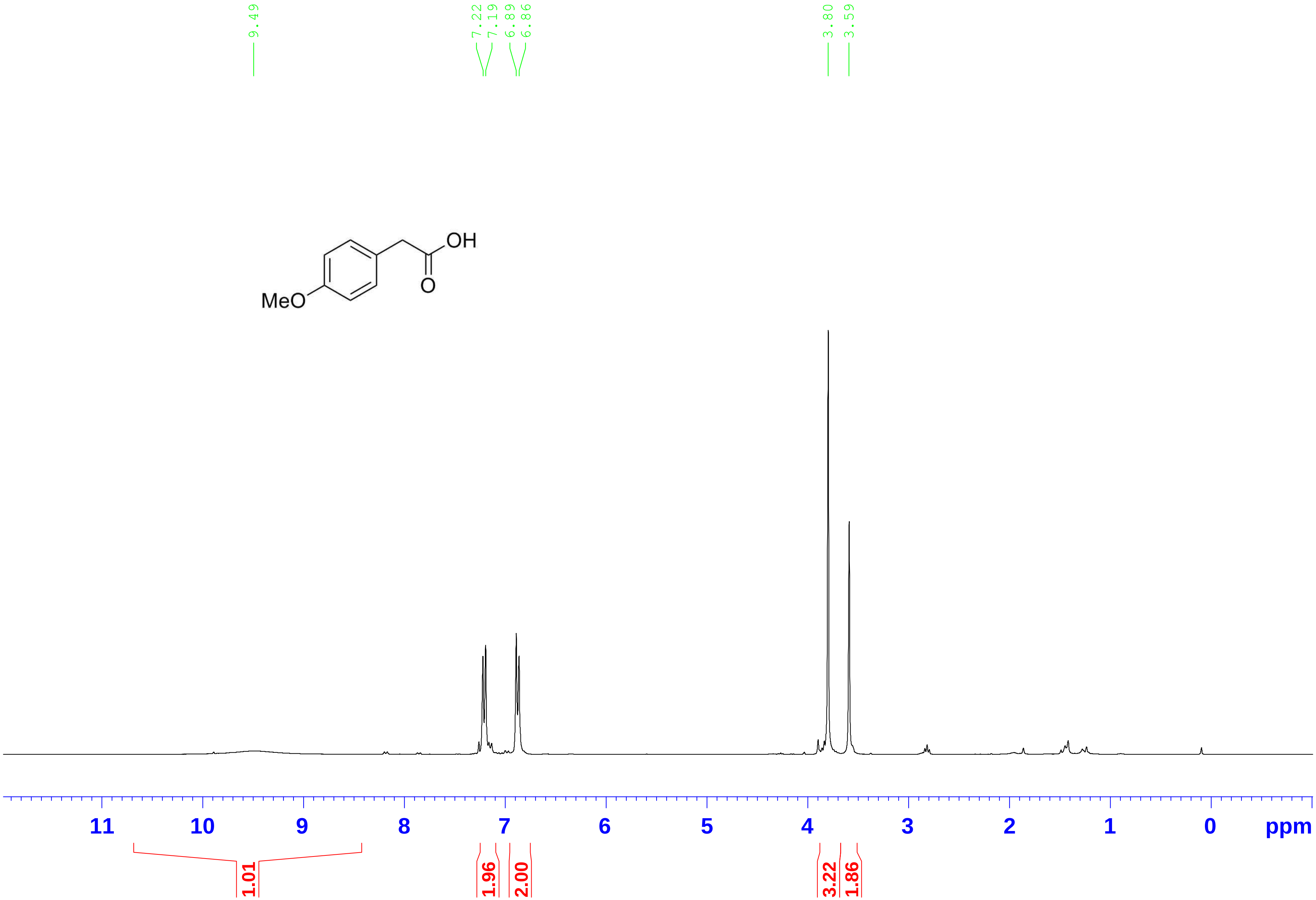
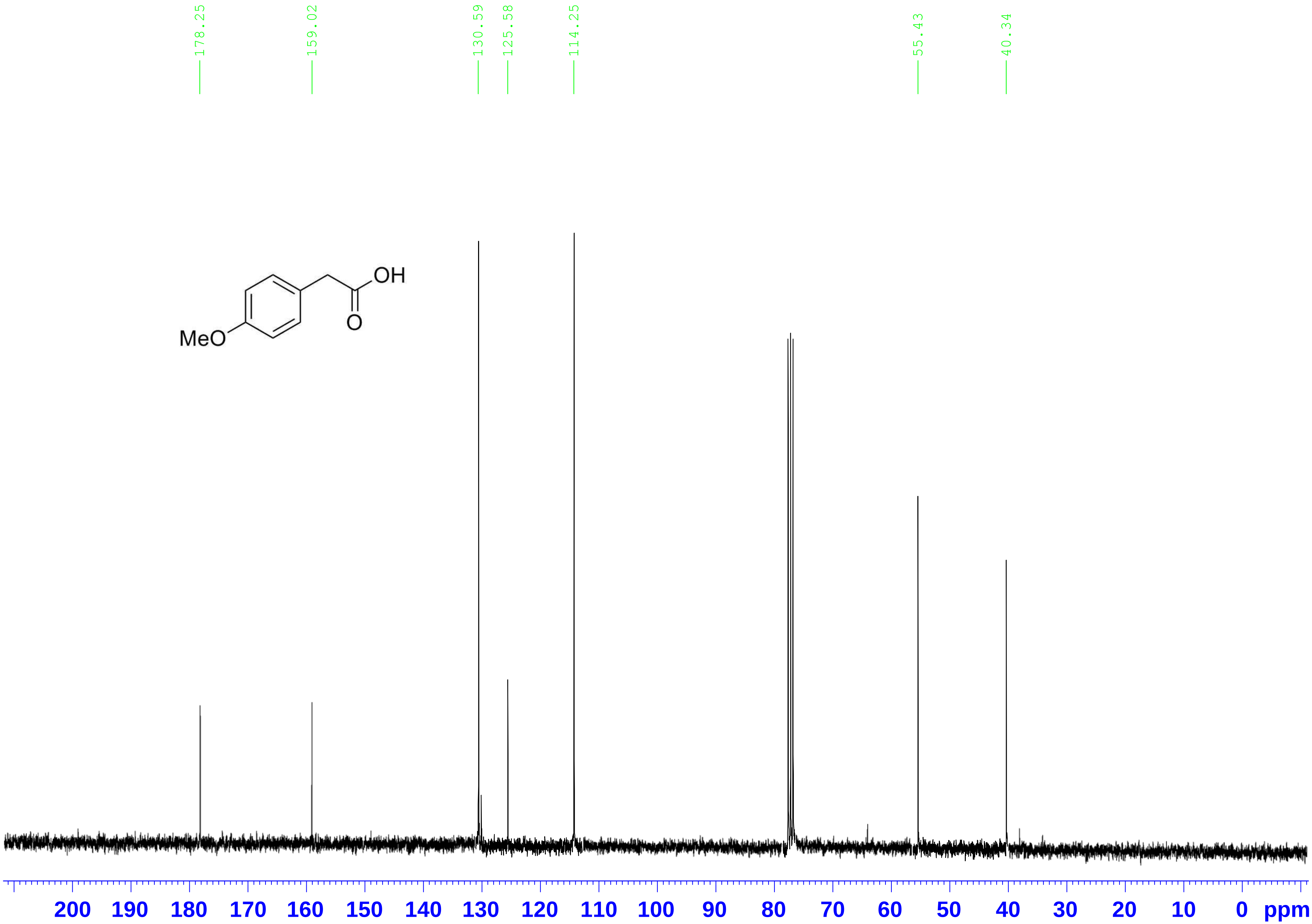
1.88
2.00
8.32
3.04
11
10
9
8
7
6
5
4
3
2
1
0
ppm
OH
O
11.09
2.36
2.35
2.33
1.65
1.63
1.62
1.60
1.32
1.31
1.28
0.90
0.88
0.86


180.59
34.24
31.72
29.10
28.98
24.77
22.67
14.11
O
OH
200
180
160
140
120
100
80
60
40
20
0
ppm


0.90
1.87
2.00
12.80
3.19
11
10
9
8
7
6
5
4
3
2
1
0
ppm
OH
O
2.36
2.34
2.32
1.65
1.63
1.61
1.30
1.27
0.89
0.88
0.86


180.33
34.26
31.96
29.49
29.34
29.17
24.80
22.75
14.17
O
OH
200
180
160
140
120
100
80
60
40
20
0
ppm


9.49
7.22
7.19
6.89
6.86
3.80
3.59
OH
O
MeO
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.01
1.96
2.00
3.22
1.86


178.25
159.02
130.59
125.58
114.25
55.43
40.34
OH
O
MeO
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
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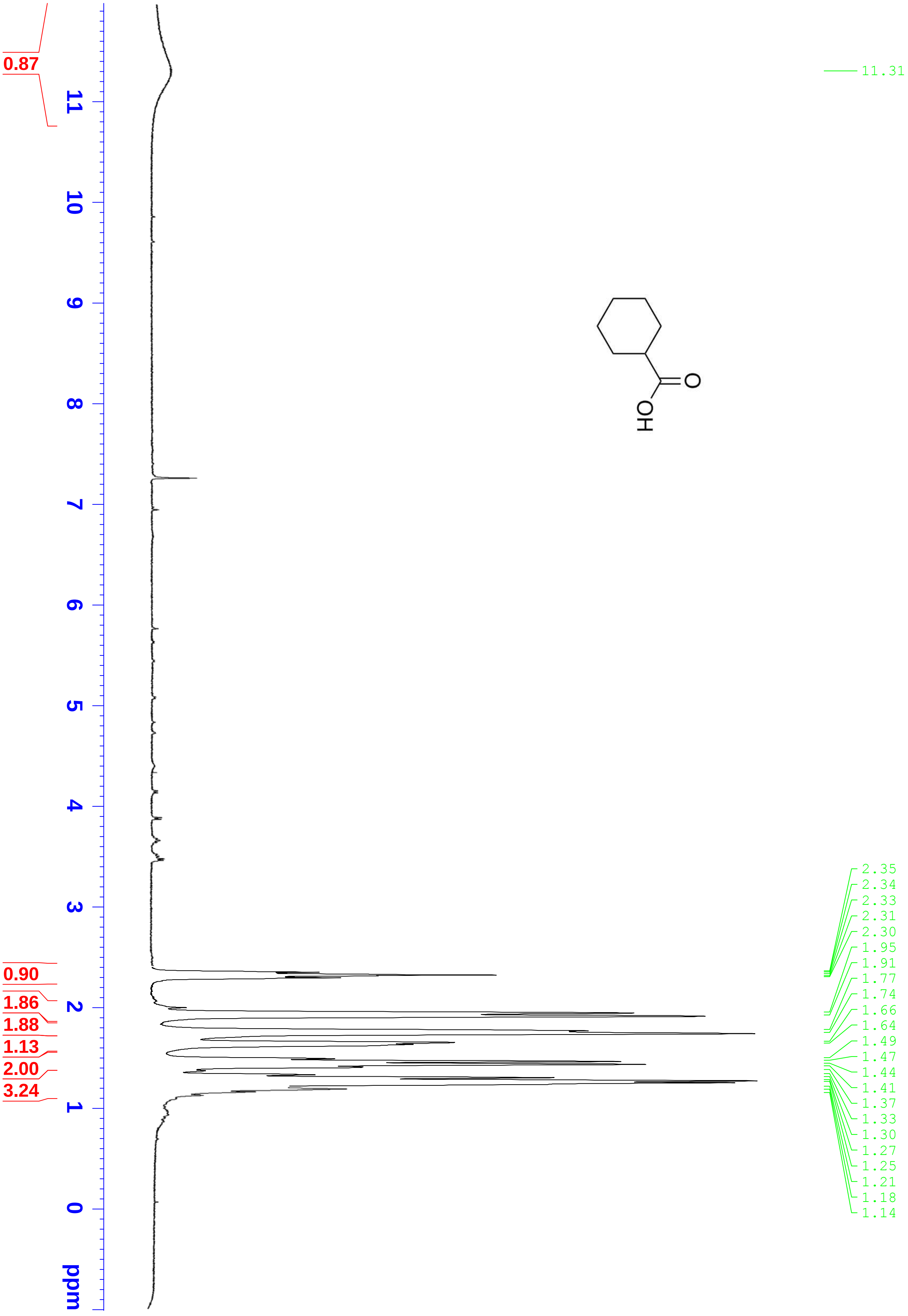
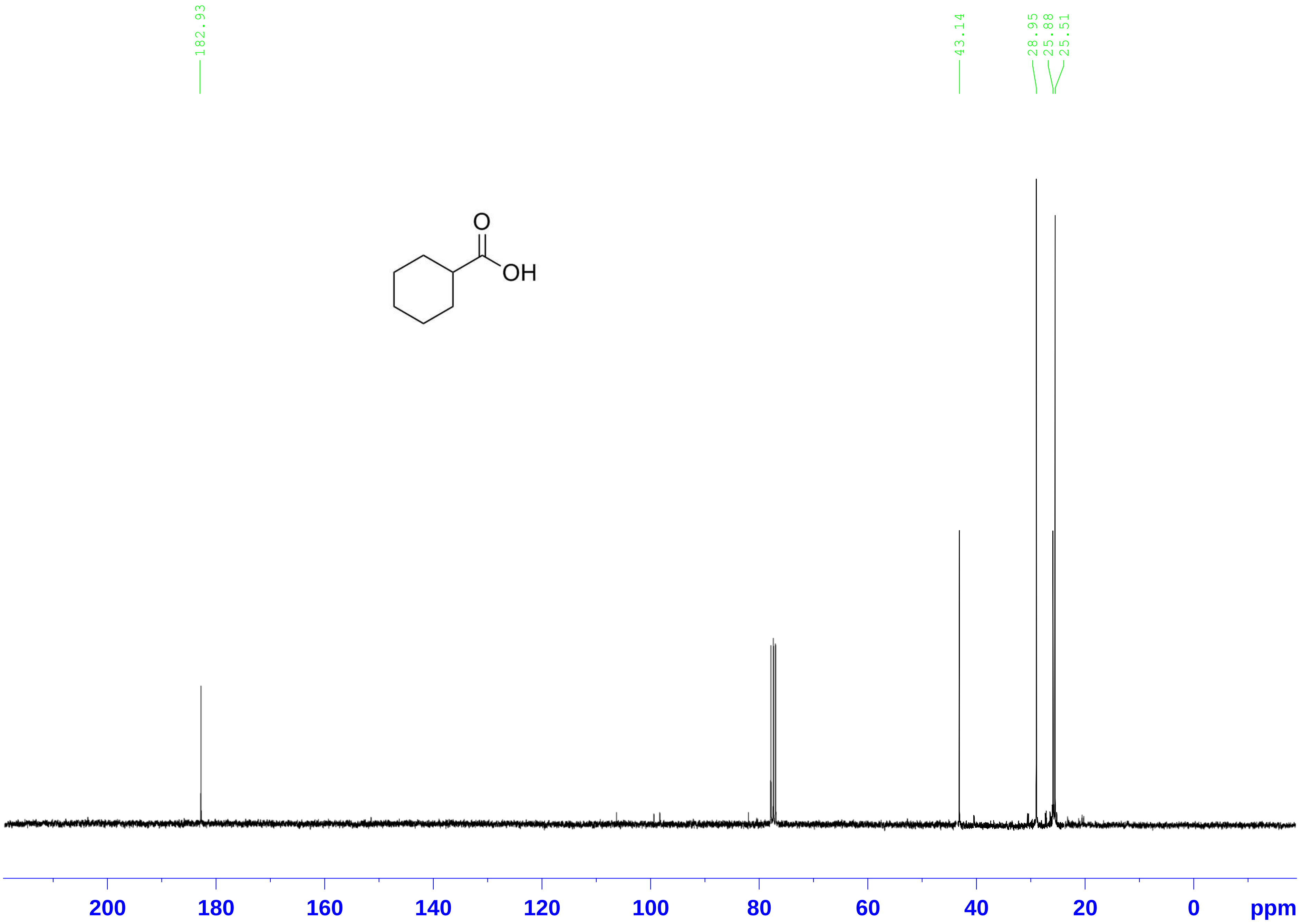
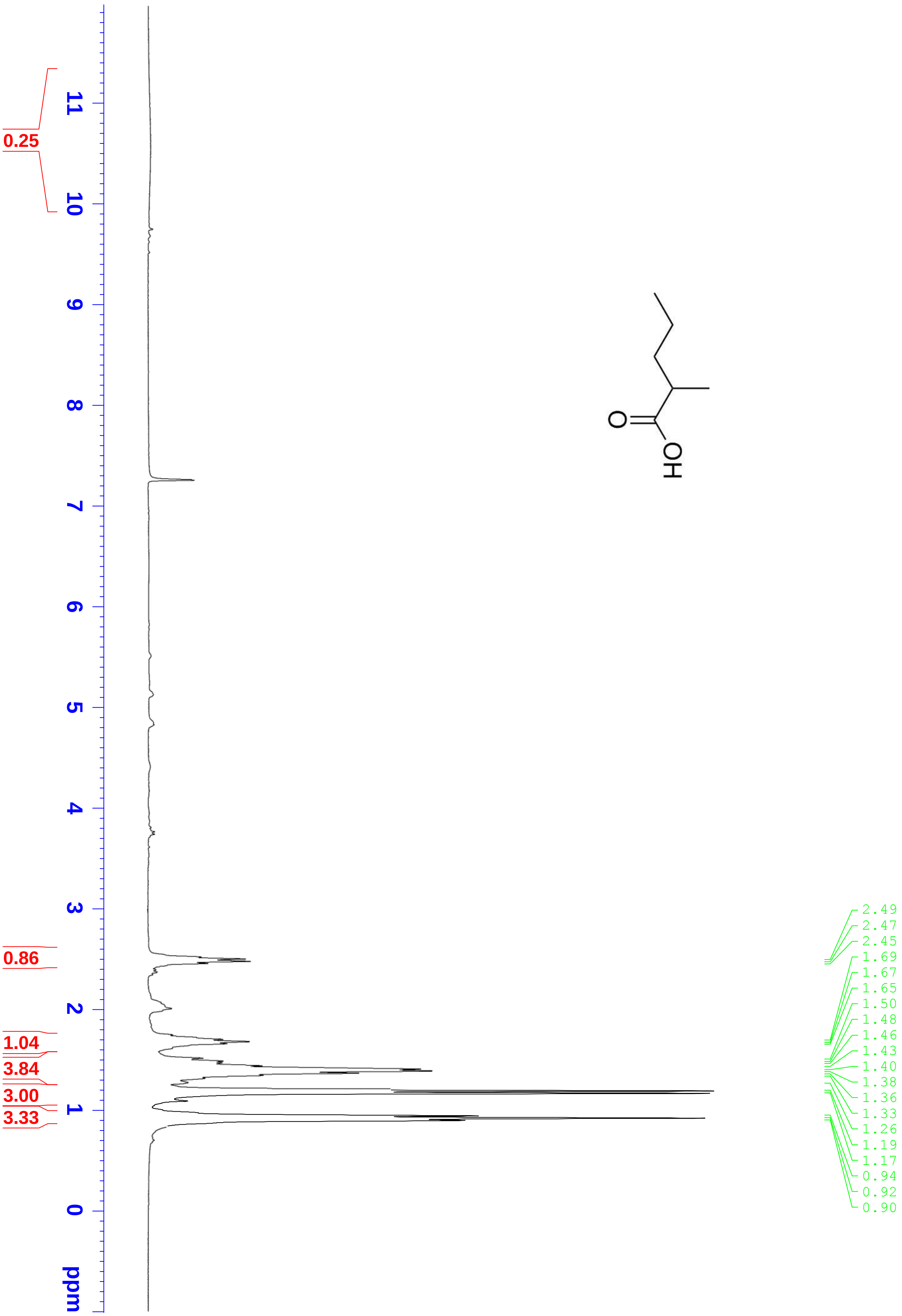
30
20
10
0
ppm

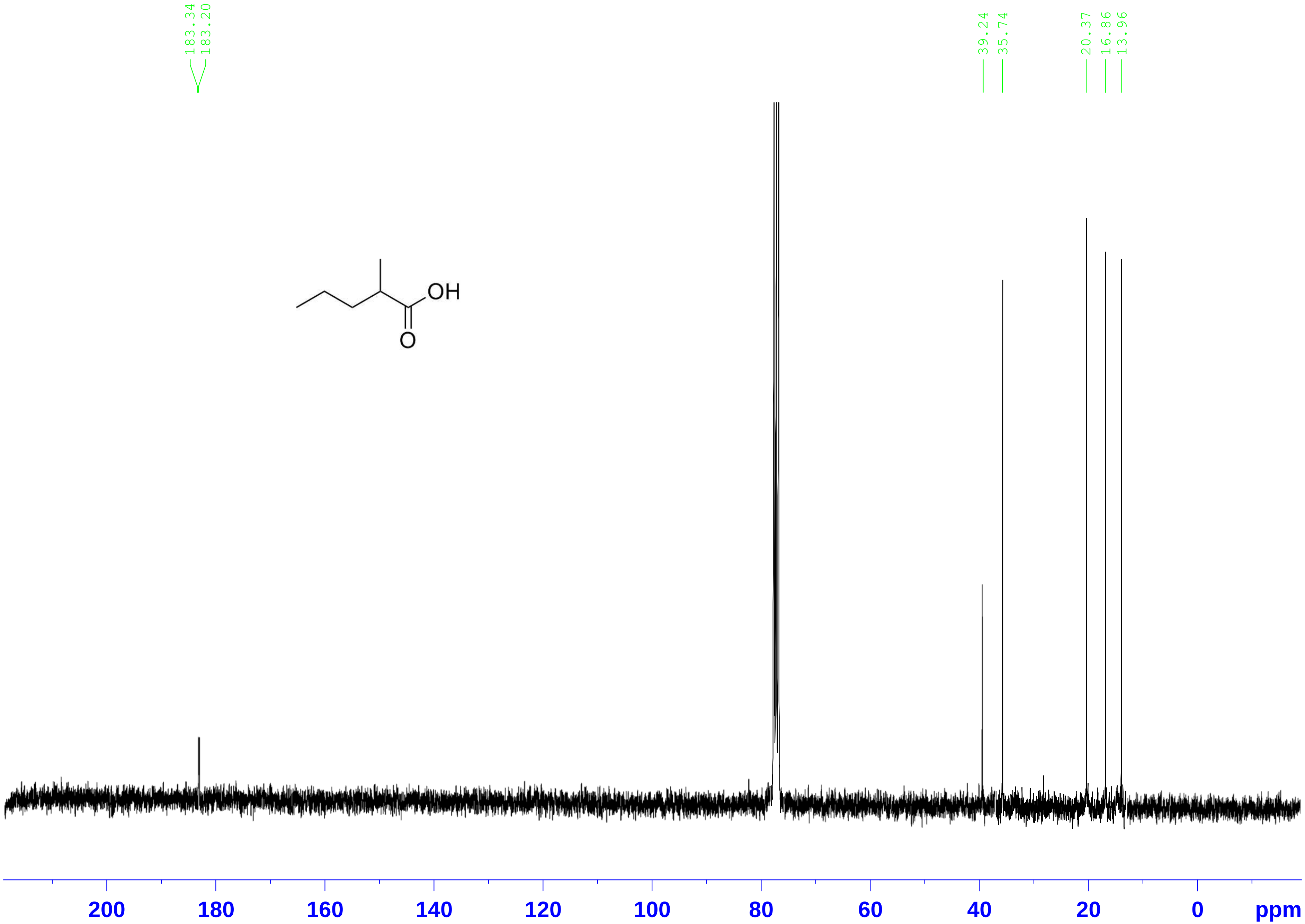


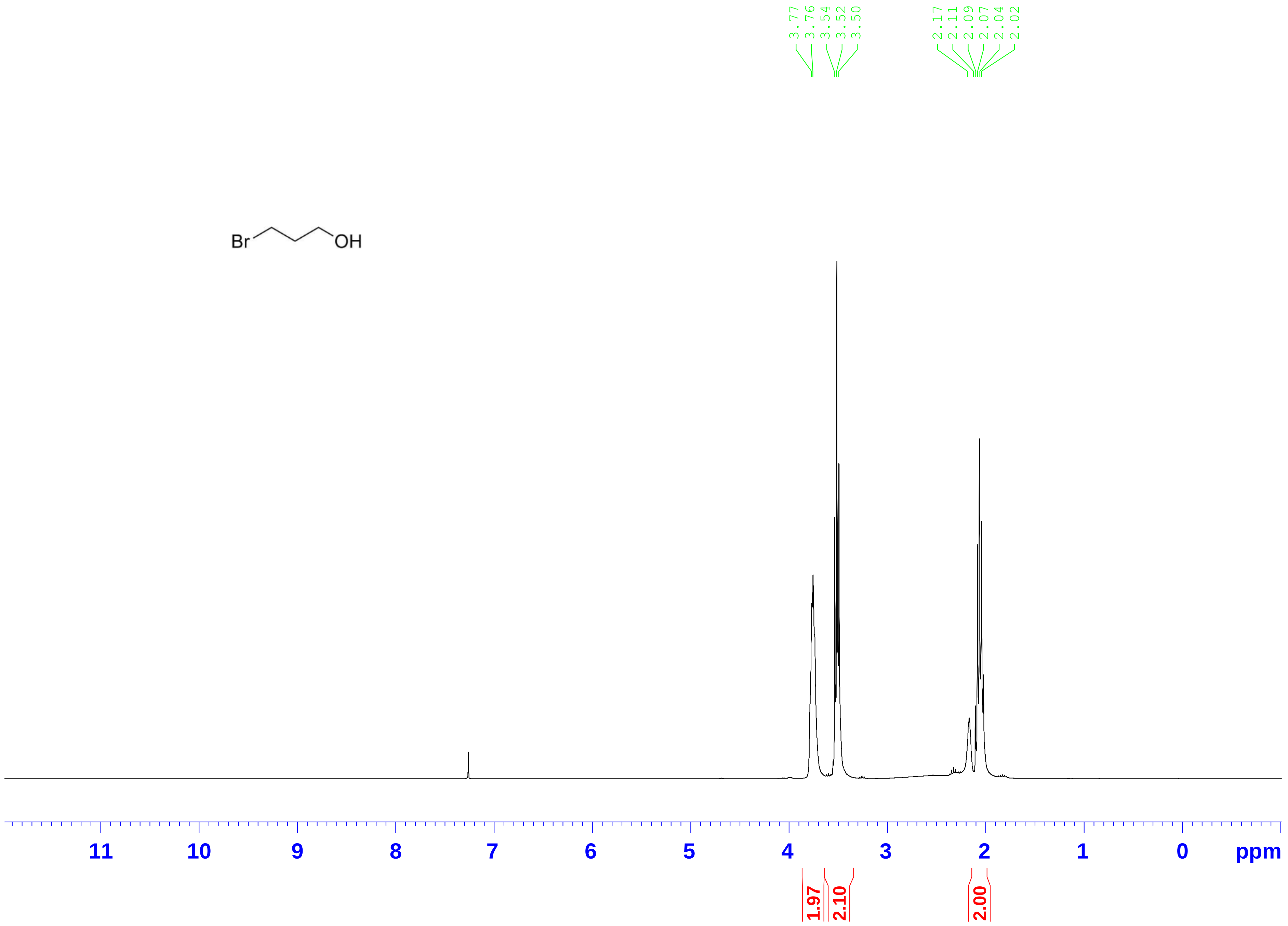
11.31
2.35
2.34
2.33
2.31
2.30
1.95
1.91
1.77
1.74
1.66
1.64
1.49
1.47
1.44
1.41
1.37
1.33
1.30
1.27
1.25
1.21
1.18
1.14
0.87
0.90
1.86
1.88
1.13
2.00
3.24
11
10
9
8
7
6
5
4
3
2
1
0
ppm
O
HO

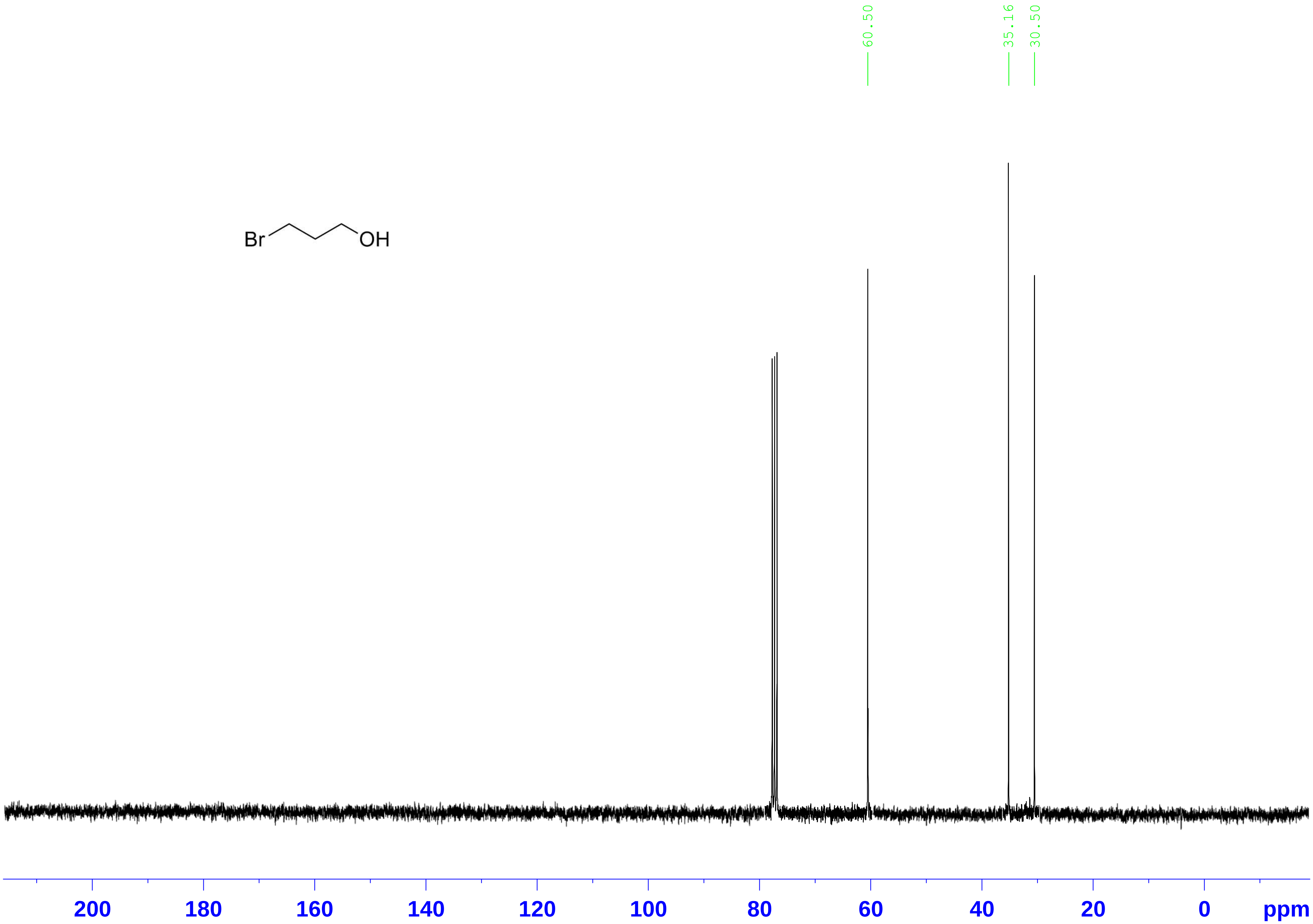

182.93
43.14
28.95
25.88
25.51
O
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

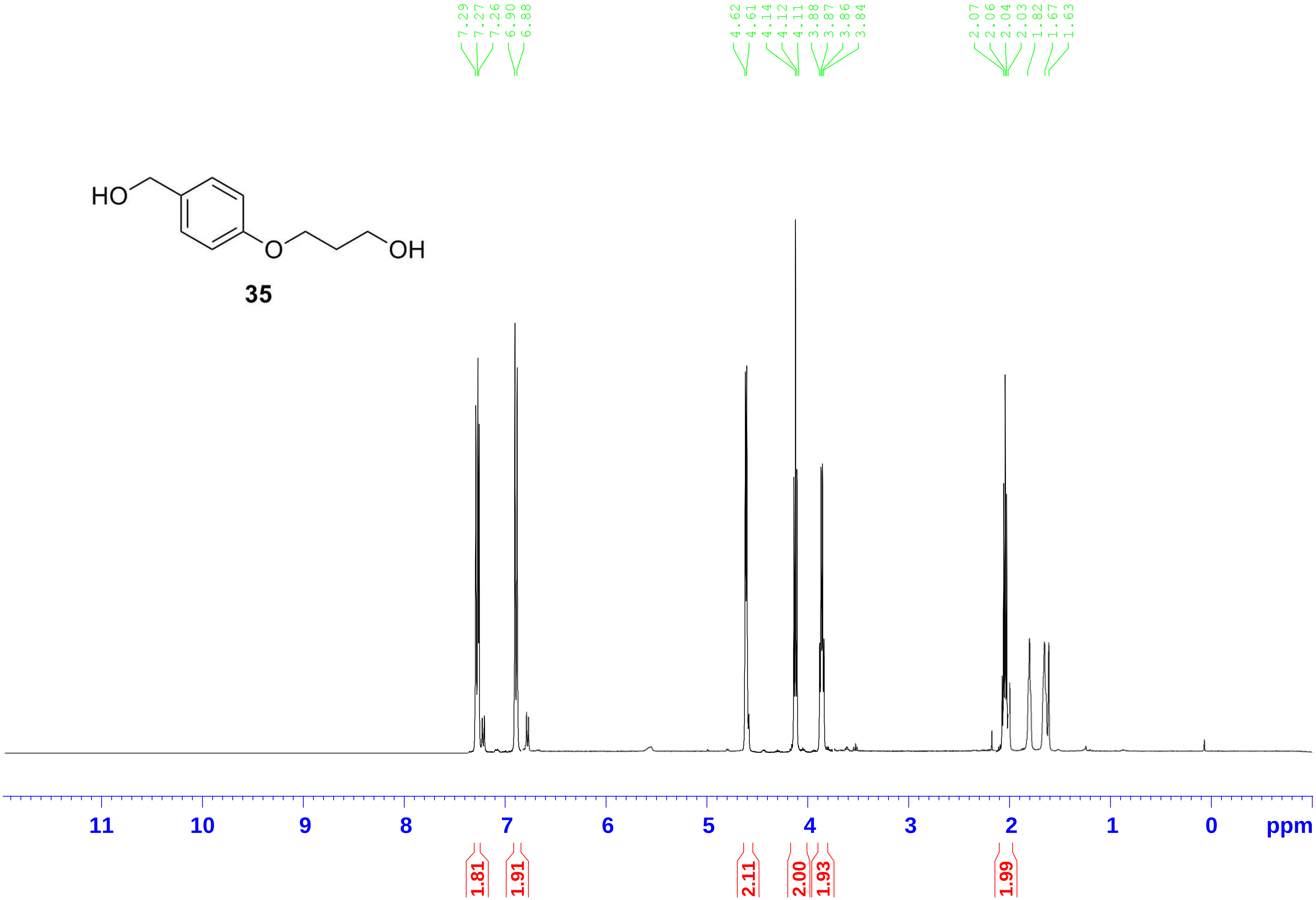


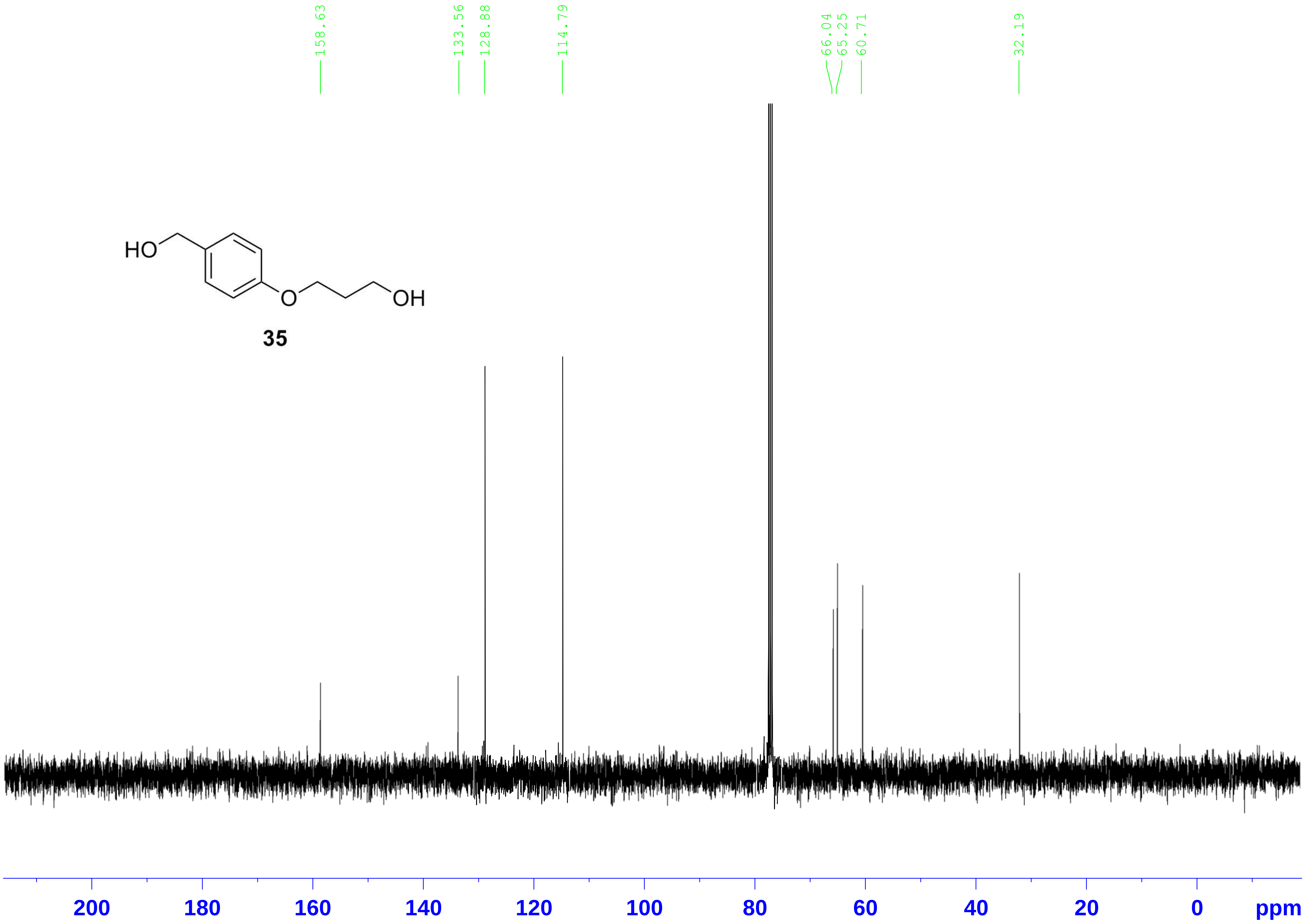
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.25
0.86
1.04
3.84
3.00
3.33
2.49
2.47
2.45
1.69
1.67
1.65
1.50
1.48
1.46
1.43
1.40
1.38
1.36
1.33
1.26
1.19
1.17
0.94
0.92
0.90
O
OH

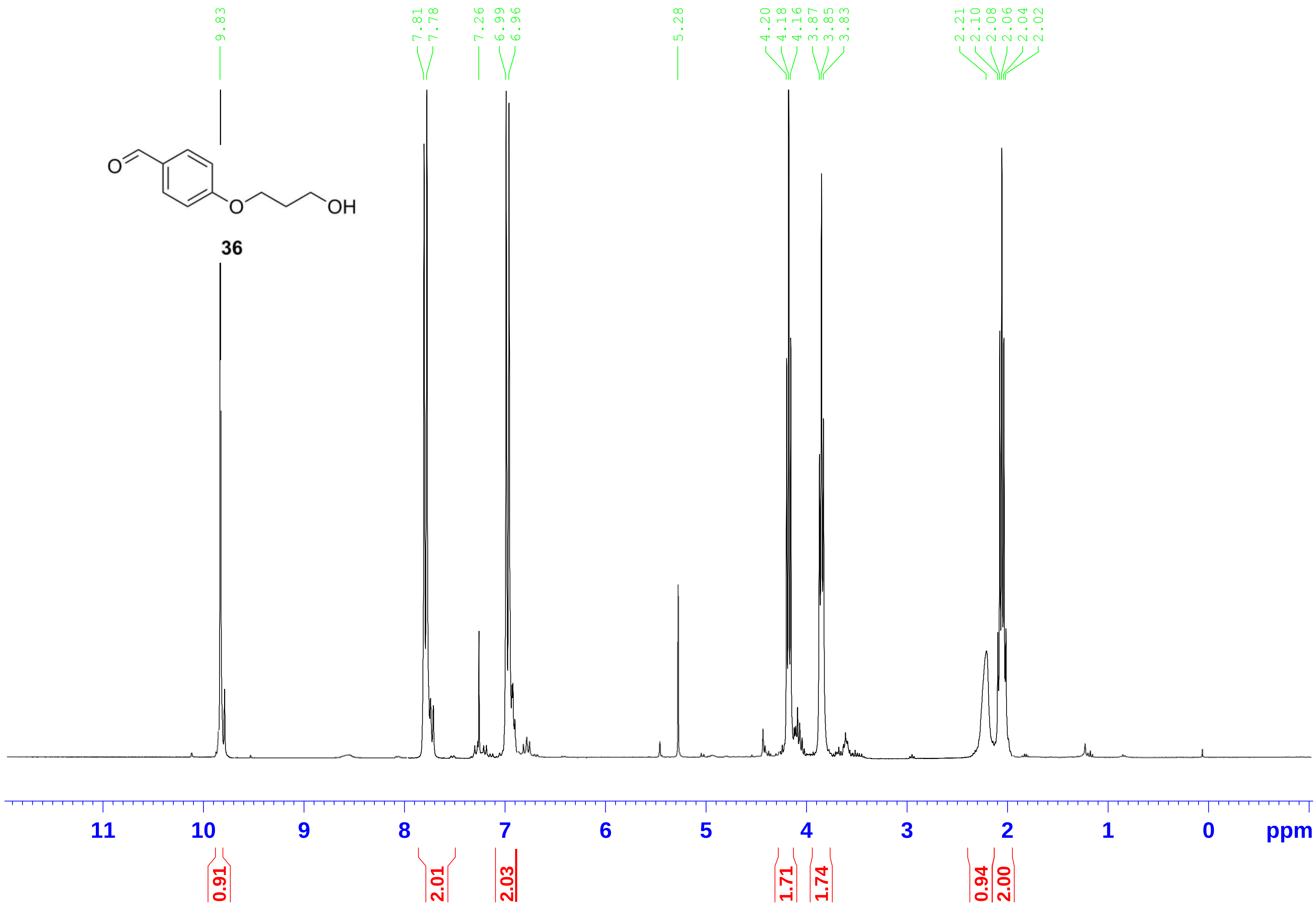

183.34
183.20
39.24
35.74
20.37
16.86
13.96
OH
O
200
180
160
140
120
100
80
60
40
20
0
ppm

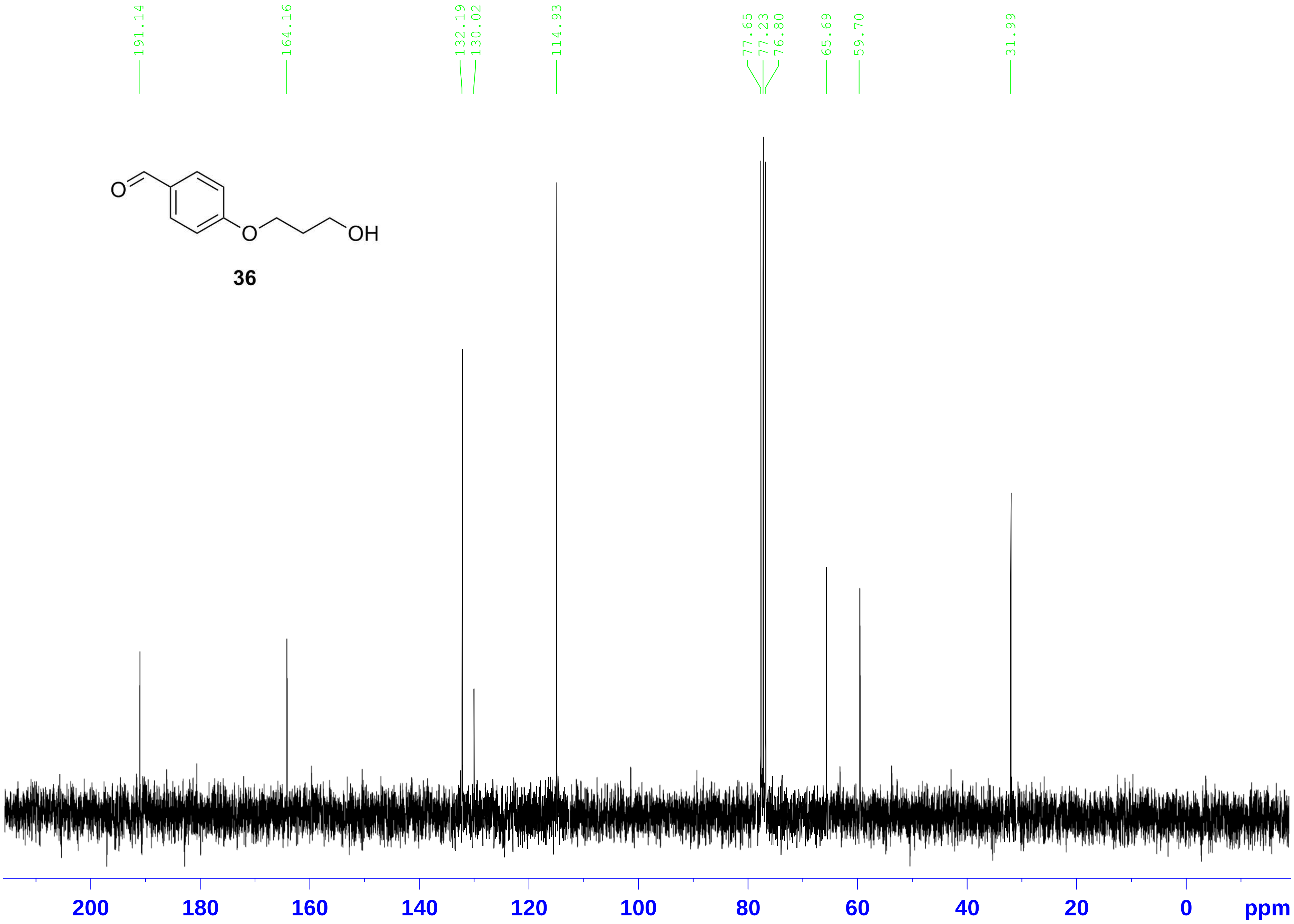

Br
OH
3.77
3.76
3.54
3.52
3.50
2.17
2.11
2.09
2.07
2.04
2.02
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.97
2.10
2.00

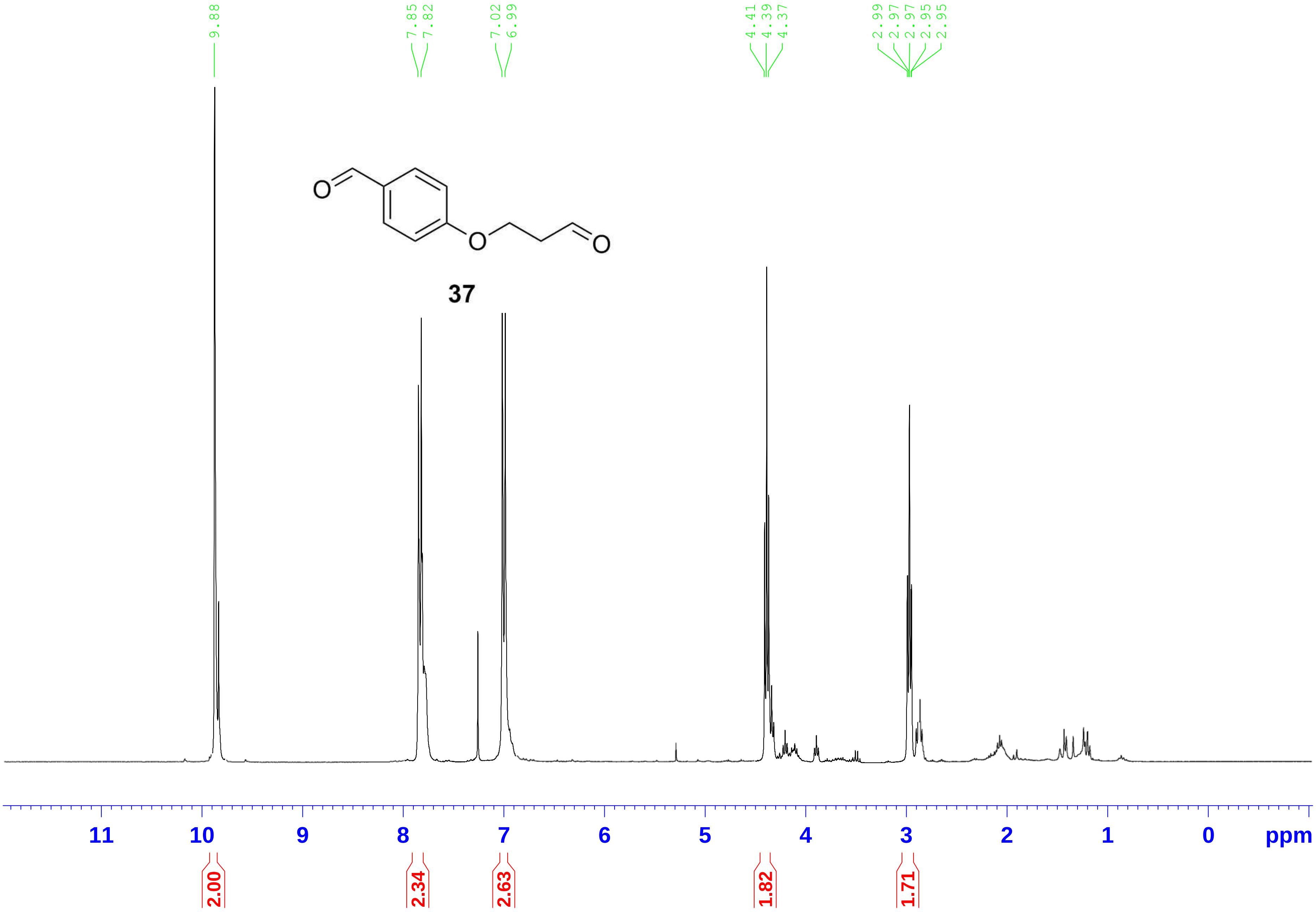

60.50
35.16
30.50
Br
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

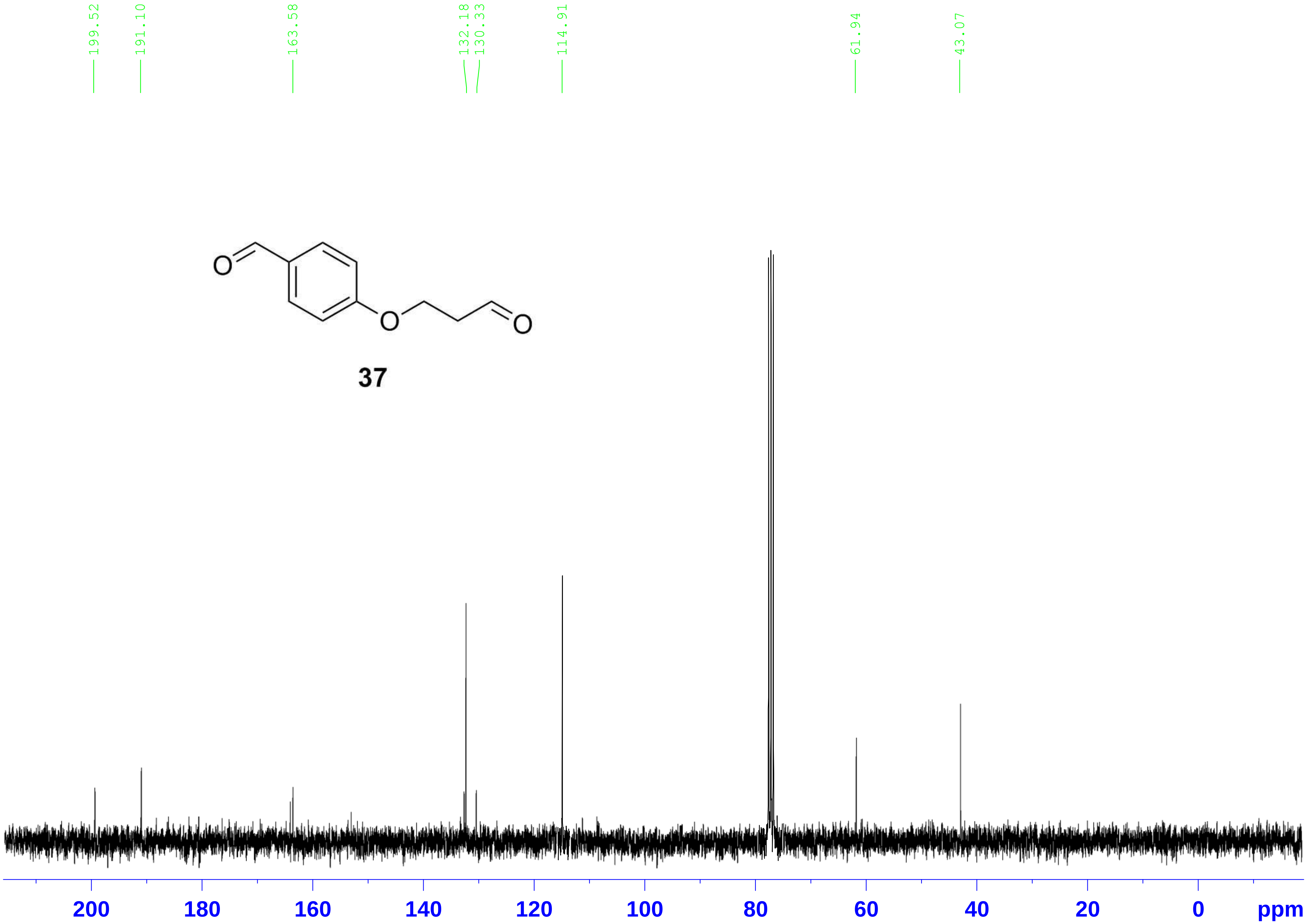

35
HO
O
OH
7.29
7.27
7.26
6.90
6.88
4.62
4.61
4.14
4.12
4.11
3.88
3.87
3.86
3.84
2.07
2.06
2.04
2.03
1.82
1.67
1.63
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.81
1.91
2.11
2.00
1.93
1.99


158.63
133.56
128.88
114.79
66.04
65.25
60.71
32.19
HO
O
OH
35
200
180
160
140
120
100
80
60
40
20
0
ppm


9.83
7.81
7.78
7.26
6.99
6.96
5.28
4.20
4.18
4.16
3.87
3.85
3.83
2.21
2.10
2.08
2.06
2.04
2.02
O
O
OH
36
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.91
2.01
2.03
1.71
1.74
0.94
2.00


191.14
164.16
132.19
130.02
114.93
77.65
77.23
76.80
65.69
59.70
31.99
O
O
OH
36
200
180
160
140
120
100
80
60
40
20
0
ppm


37
9.88
7.85
7.82
7.02
6.99
4.41
4.39
4.37
2.99
2.97
2.97
2.95
2.95
O
O
O
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.34
2.63
1.82
1.71


199.52
191.10
163.58
132.18
130.33
114.91
61.94
43.07
37
200
180
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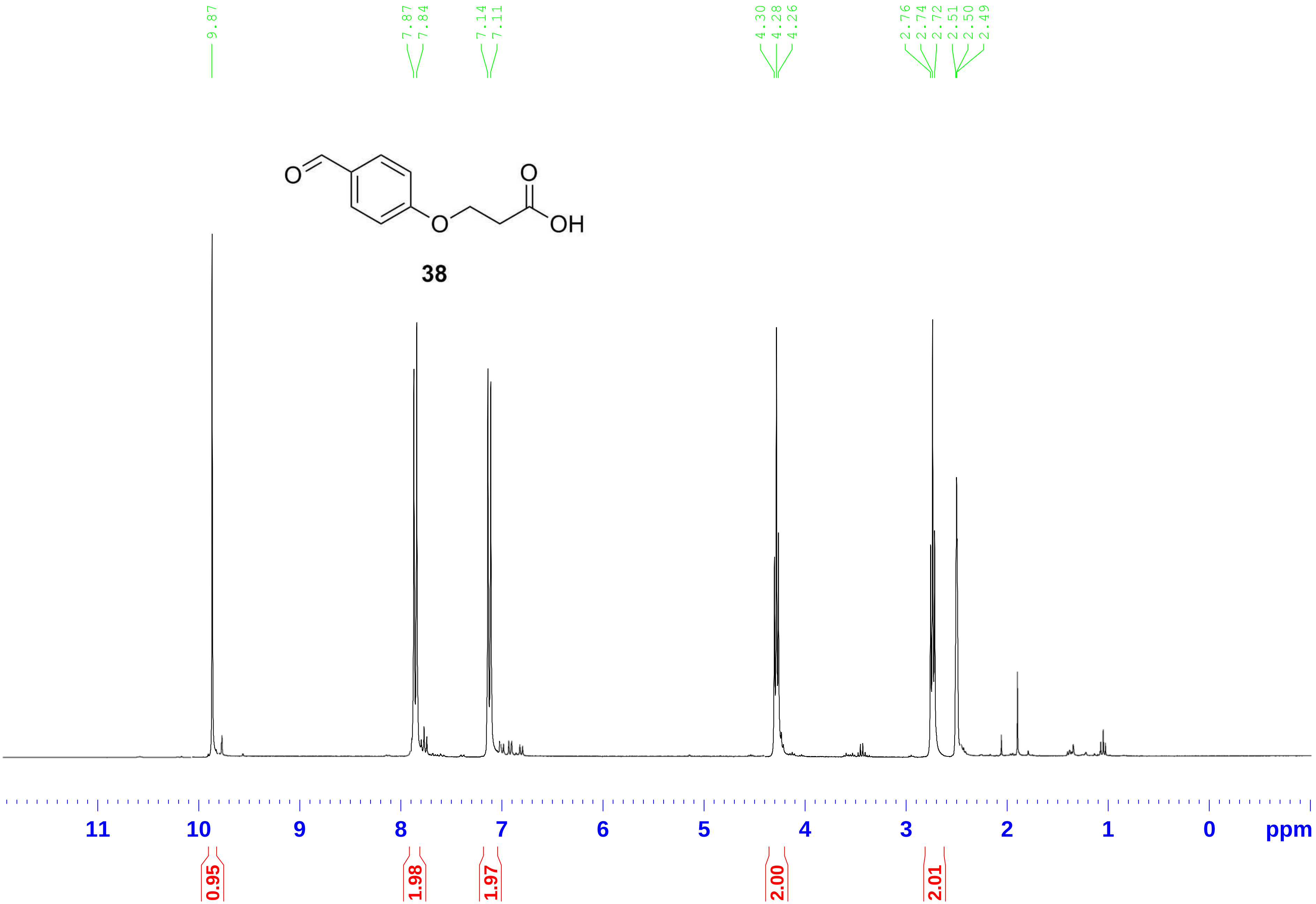
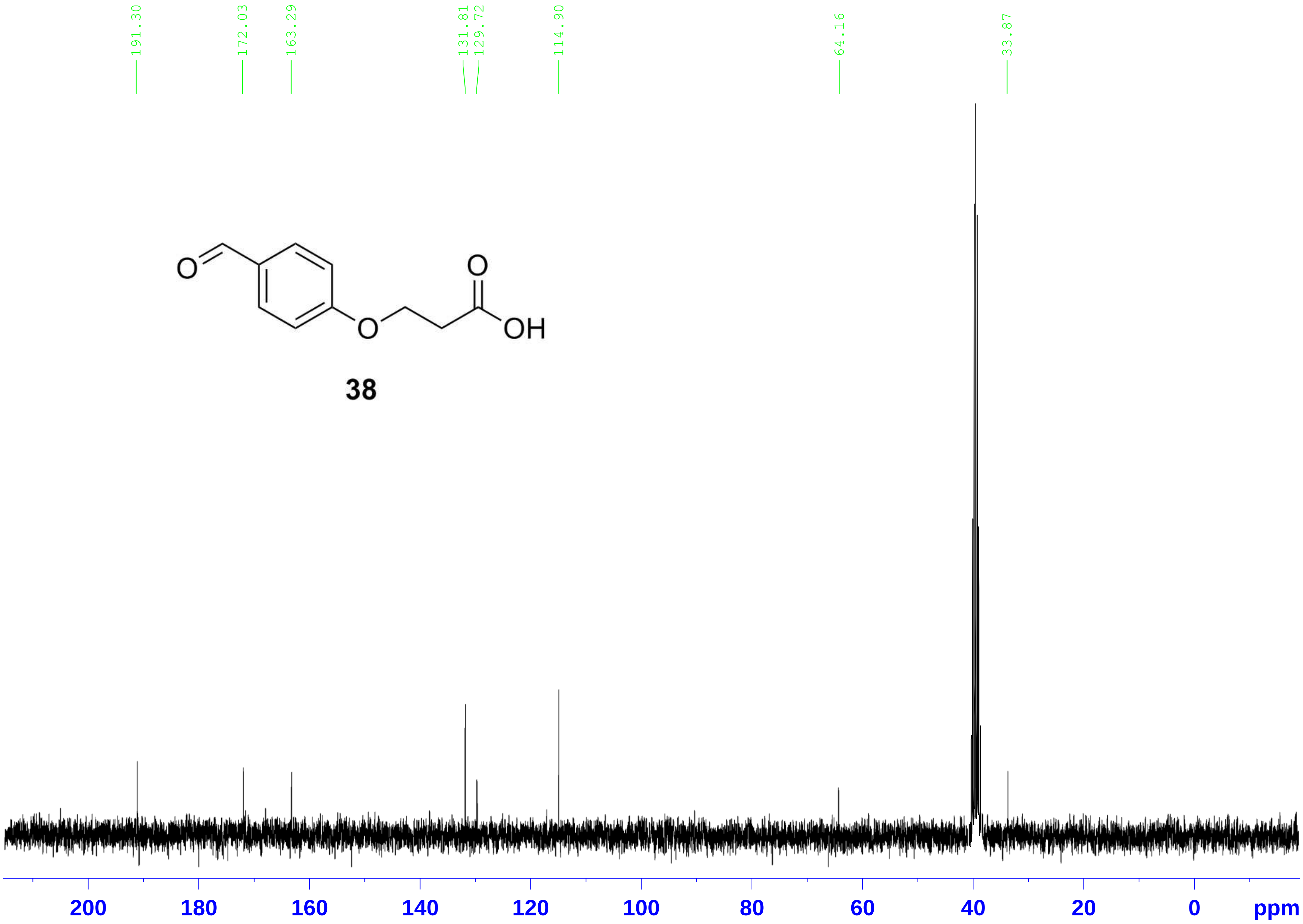
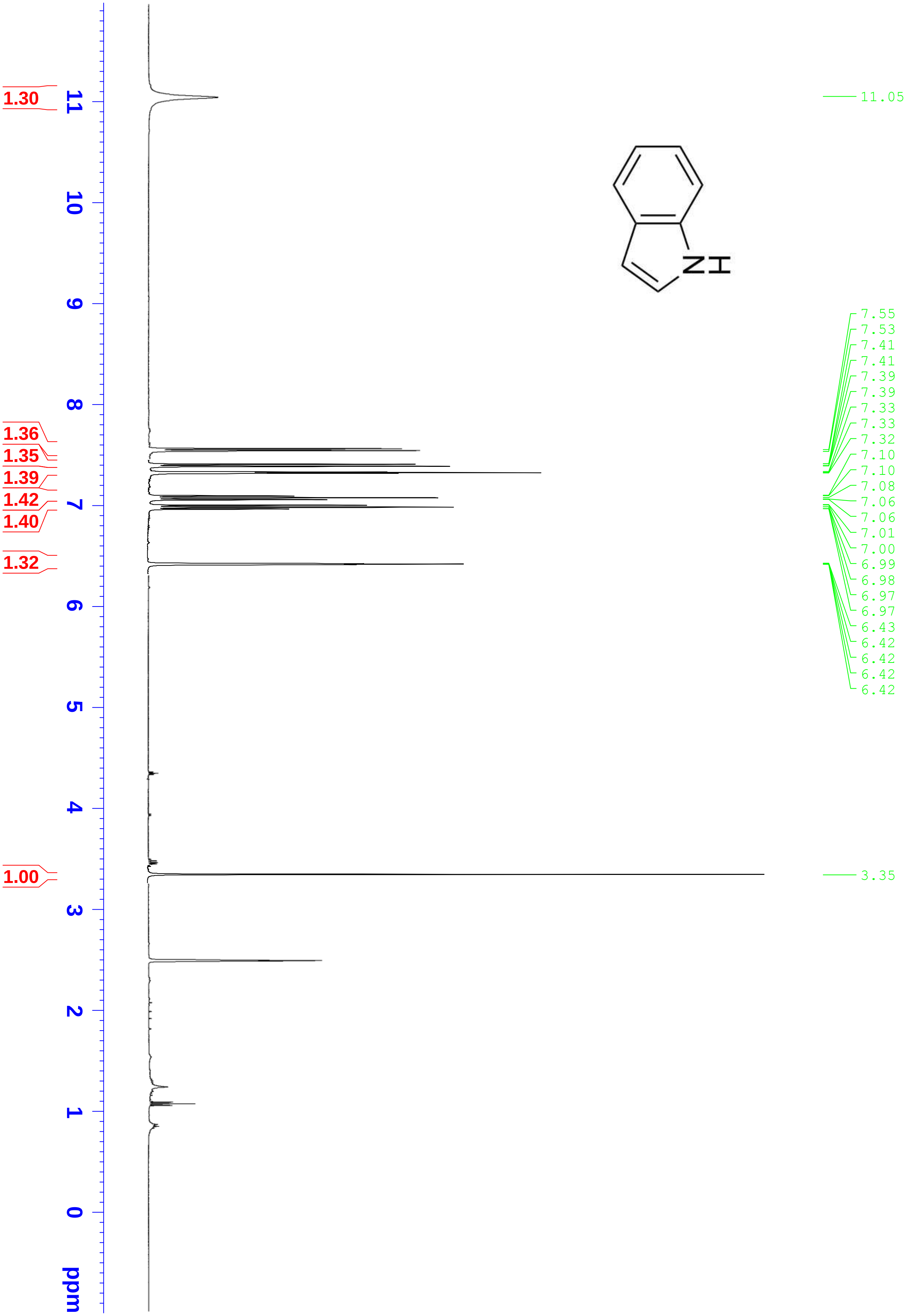
140
120
100
80
60
40
20
0
ppm


9.87
7.87
7.84
7.14
7.11
4.30
4.28
4.26
2.76
2.74
2.72
2.51
2.50
2.49
O
O
OH
38
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.95
1.98
1.97
2.00
2.01


191.30
172.03
163.29
131.81
129.72
114.90
64.16
33.87
O
O
OH
O
200
180
160
140
120
100
80
60
40
20
0
ppm

38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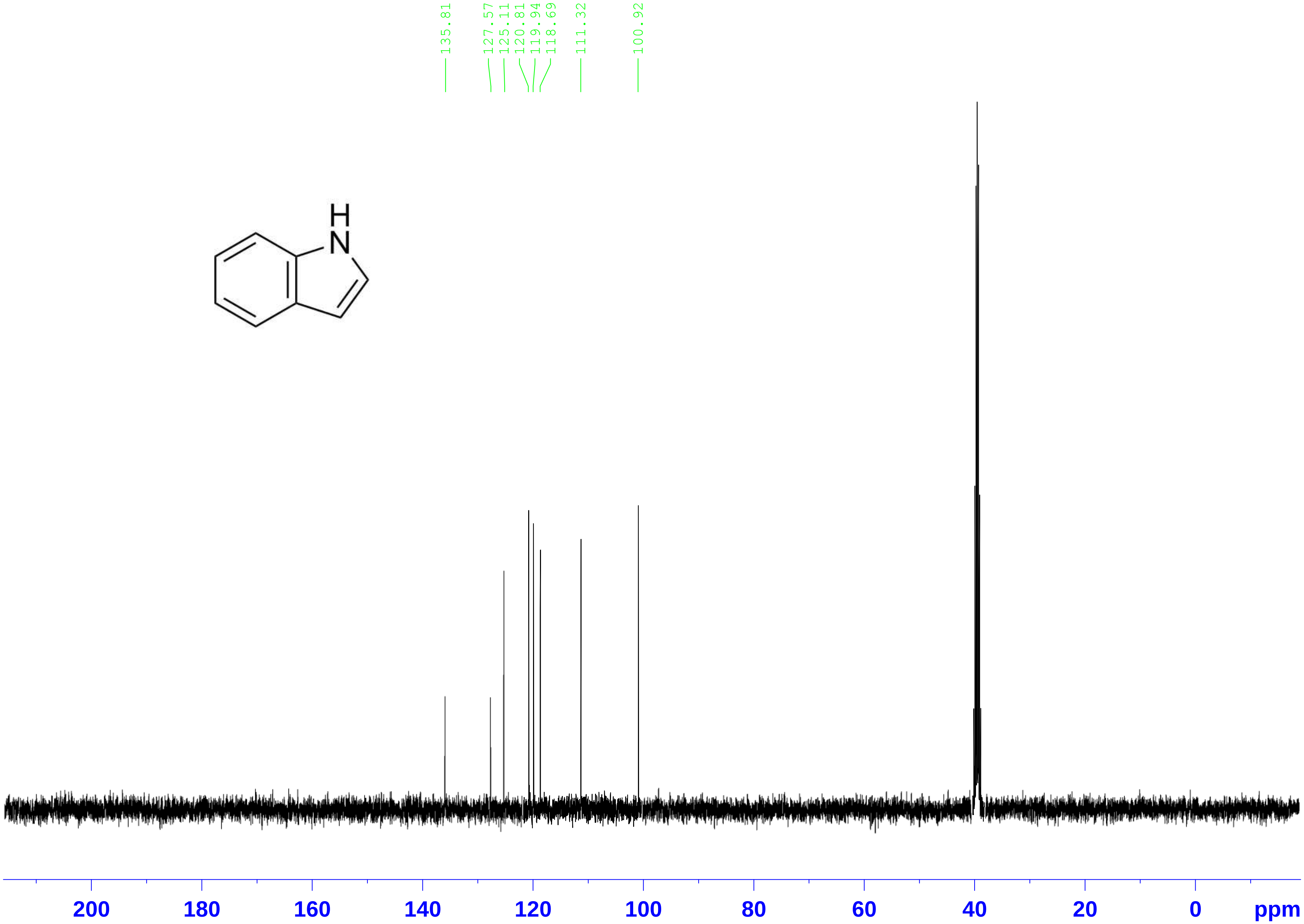
1.36
1.35
1.39
1.42
1.40
1.32
1.00
11
10
9
8
7
6
5
4
3
2
1
0
ppm
11.05
7.55
7.53
7.41
7.41
7.39
7.39
7.33
7.33
7.32
7.10
7.10
7.08
7.06
7.06
7.01
7.00
6.99
6.98
6.97
6.97
6.43
6.42
6.42
6.42
6.42
3.35
NH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127.57
125.11
120.81
119.94
118.69
111.32
100.92
H
N
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180
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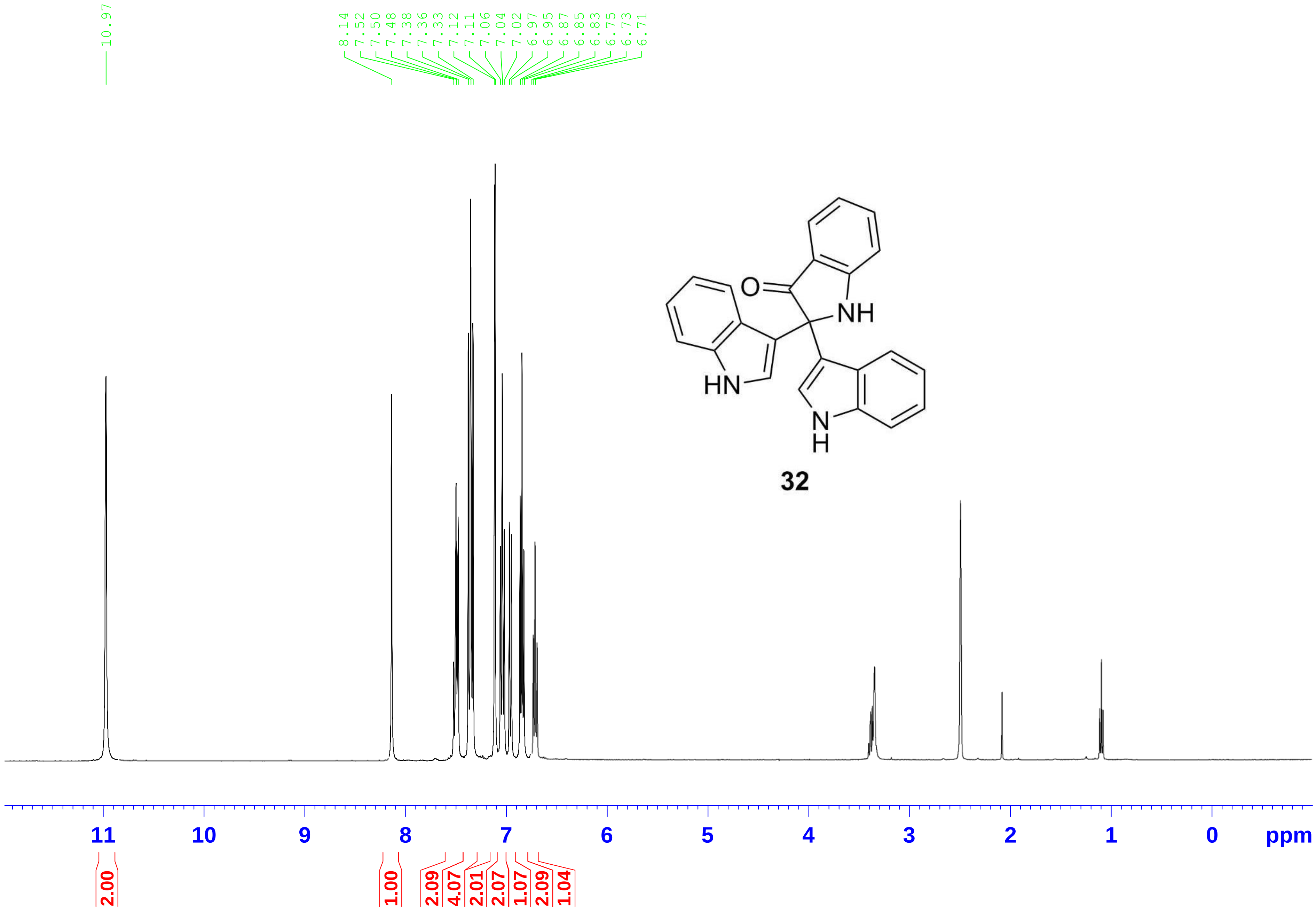
140
120
100
80
60
40
20
0
ppm


32

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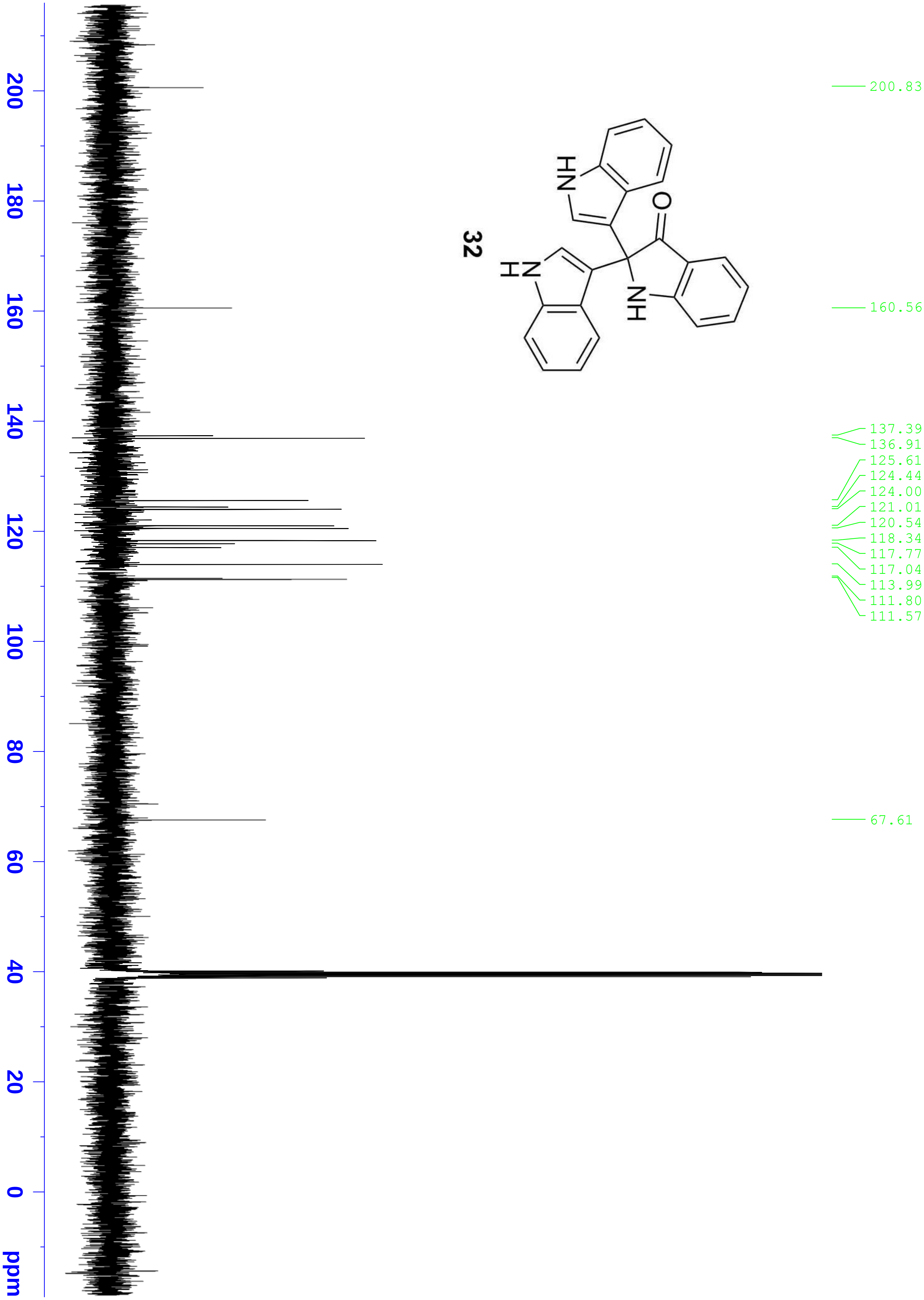
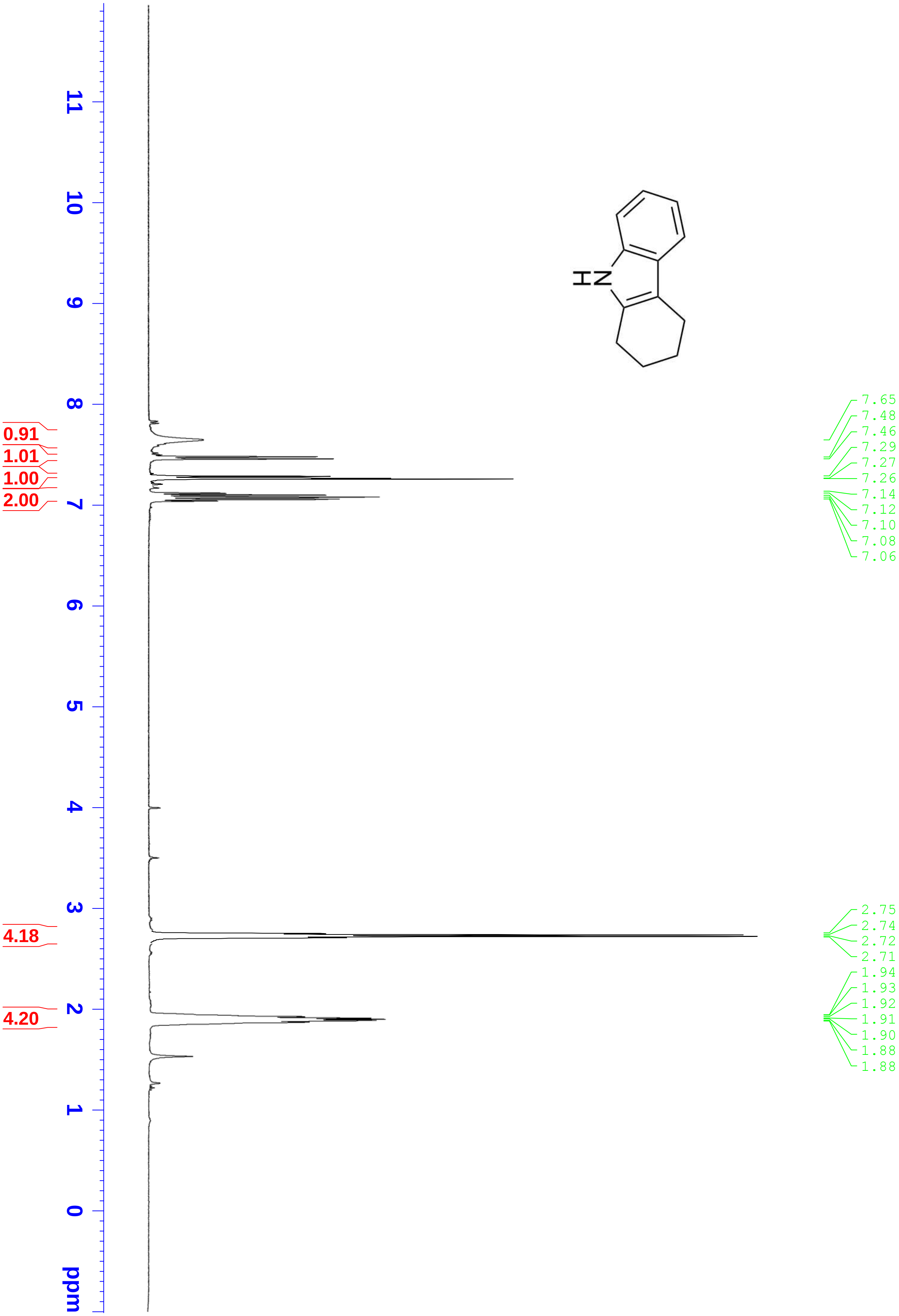
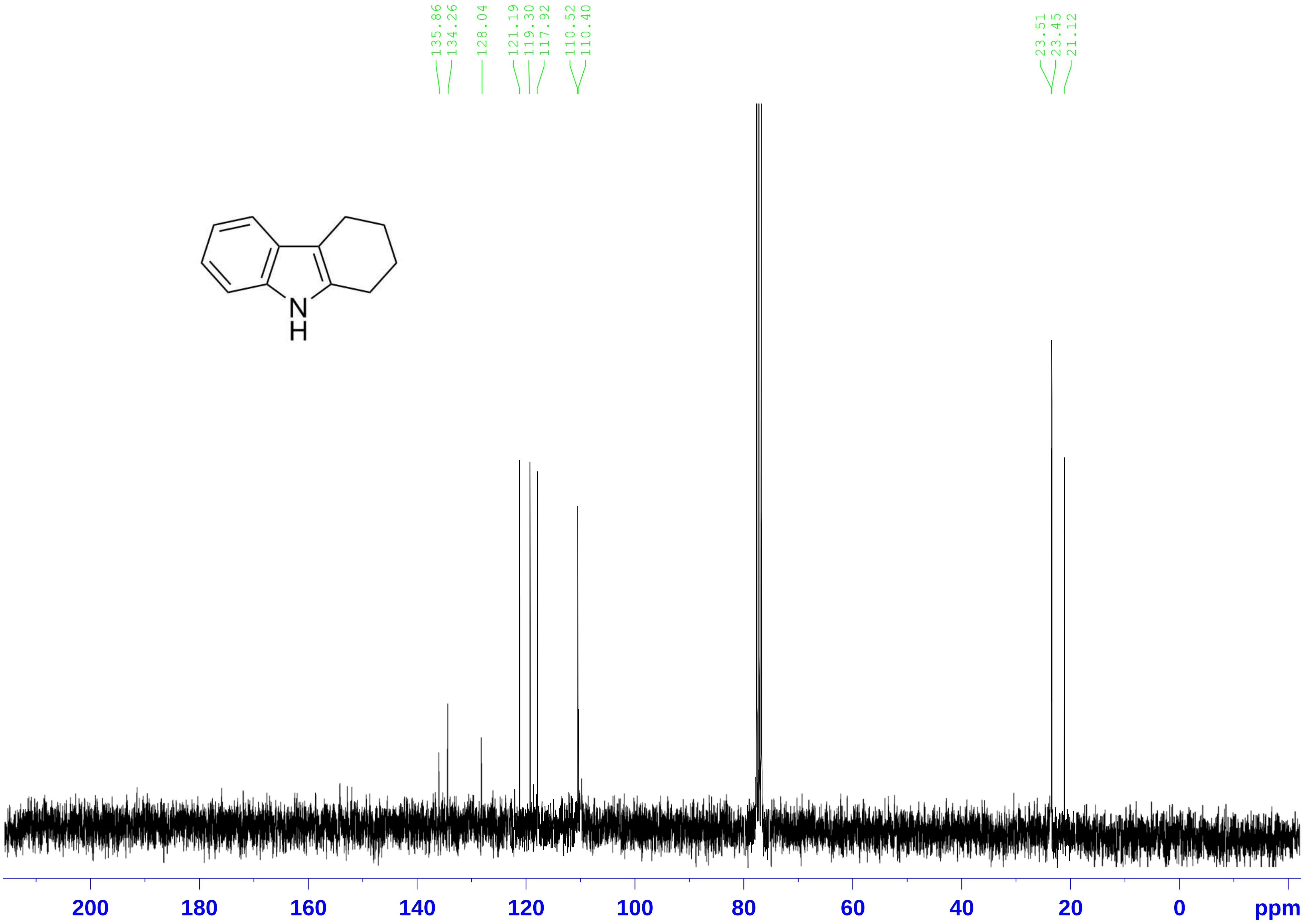
8.14
7.52
7.50
7.48
7.38
7.36
7.33
7.12
7.11
7.06
7.04
7.02
6.97
6.95
6.87
6.85
6.83
6.75
6.73
6.71
O
NH
HN
N
H
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.00
2.09
4.07
2.01
2.07
1.07
2.09
1.04

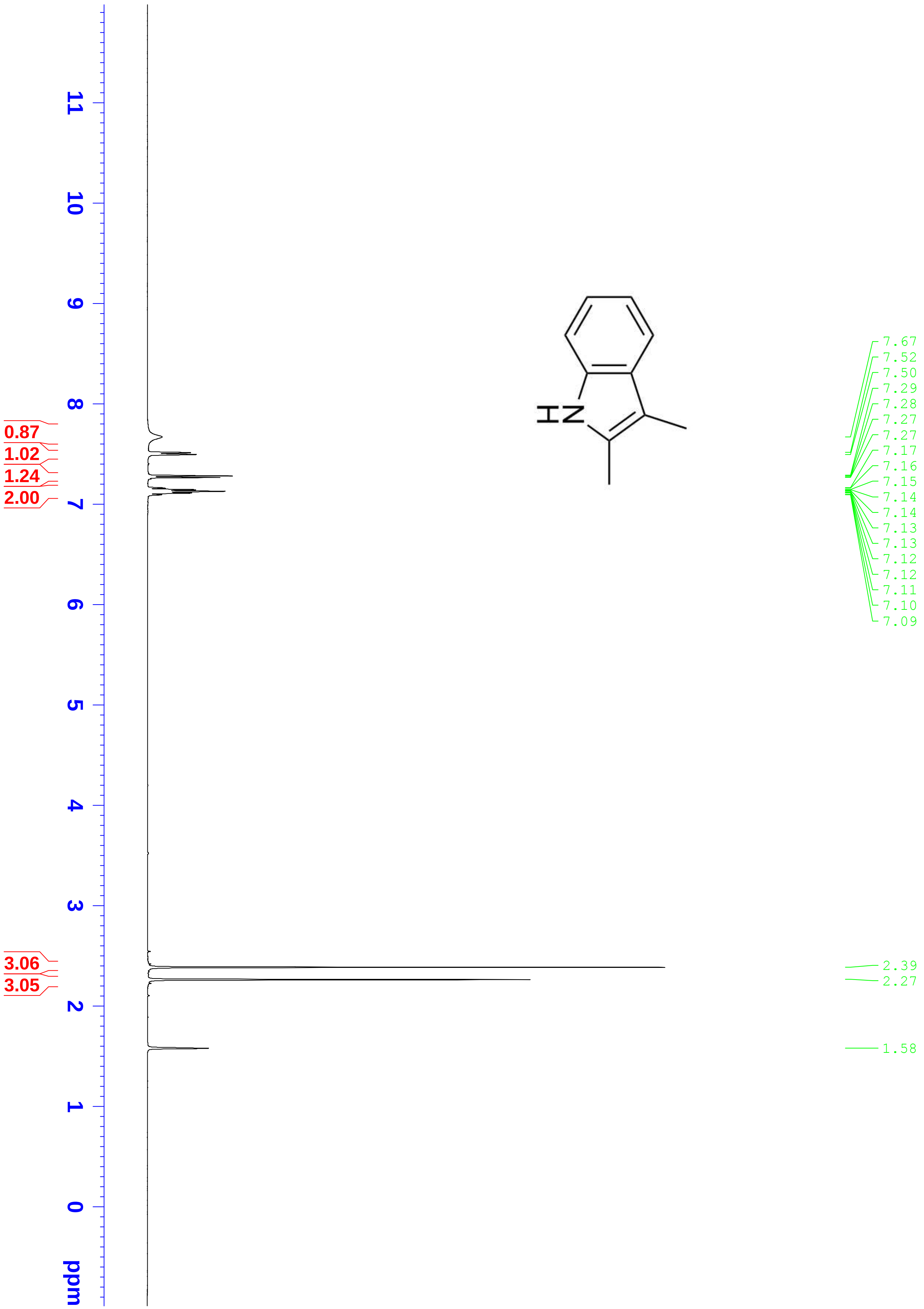

200.83
160.56
137.39
136.91
125.61
124.44
124.00
121.01
120.54
118.34
117.77
117.04
113.99
111.80
111.57
67.61
200
180
160
140
120
100
80
60
40
20
0
ppm
O
NH
HN
N
H

32

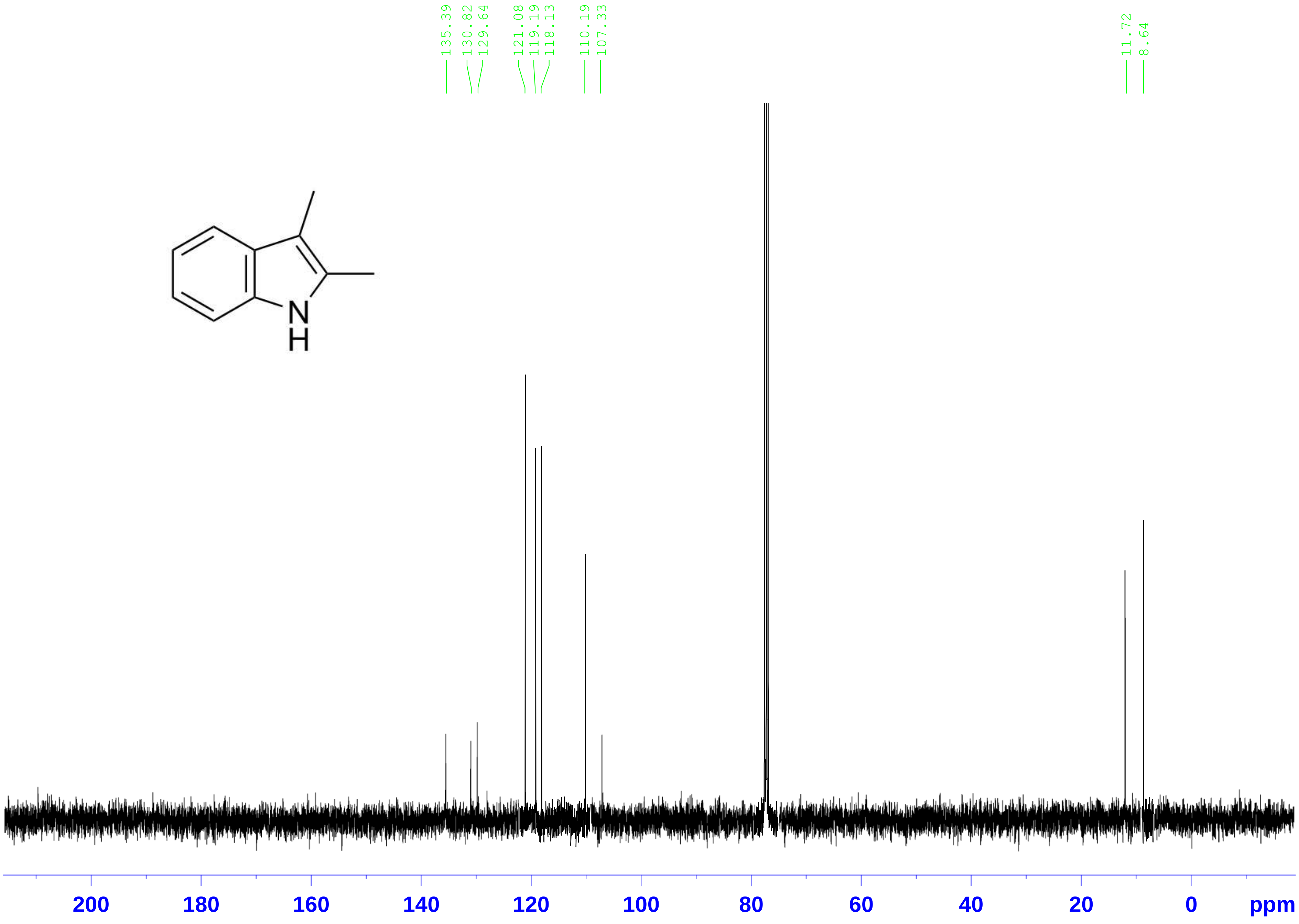


7.65
7.48
7.46
7.29
7.27
7.26
7.14
7.12
7.10
7.08
7.06
2.75
2.74
2.72
2.71
1.94
1.93
1.92
1.91
1.90
1.88
1.88
0.91
1.01
1.00
2.00
4.18
4.20
HN
11
10
9
8
7
6
5
4
3
2
1
0
ppm


135.86
134.26
128.04
121.19
119.30
117.92
110.52
110.40
23.51
23.45
21.12
N
H
200
180
160
140
120
100
80
60
40
20
0
ppm



11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.87
1.02
1.24
2.00
3.06
3.05
7.67
7.52
7.50
7.29
7.28
7.27
7.27
7.17
7.16
7.15
7.14
7.14
7.13
7.13
7.12
7.12
7.11
7.10
7.09
2.39
2.27
1.58
HN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130.82
129.64
121.08
119.19
118.13
110.19
107.33
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N
H
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180
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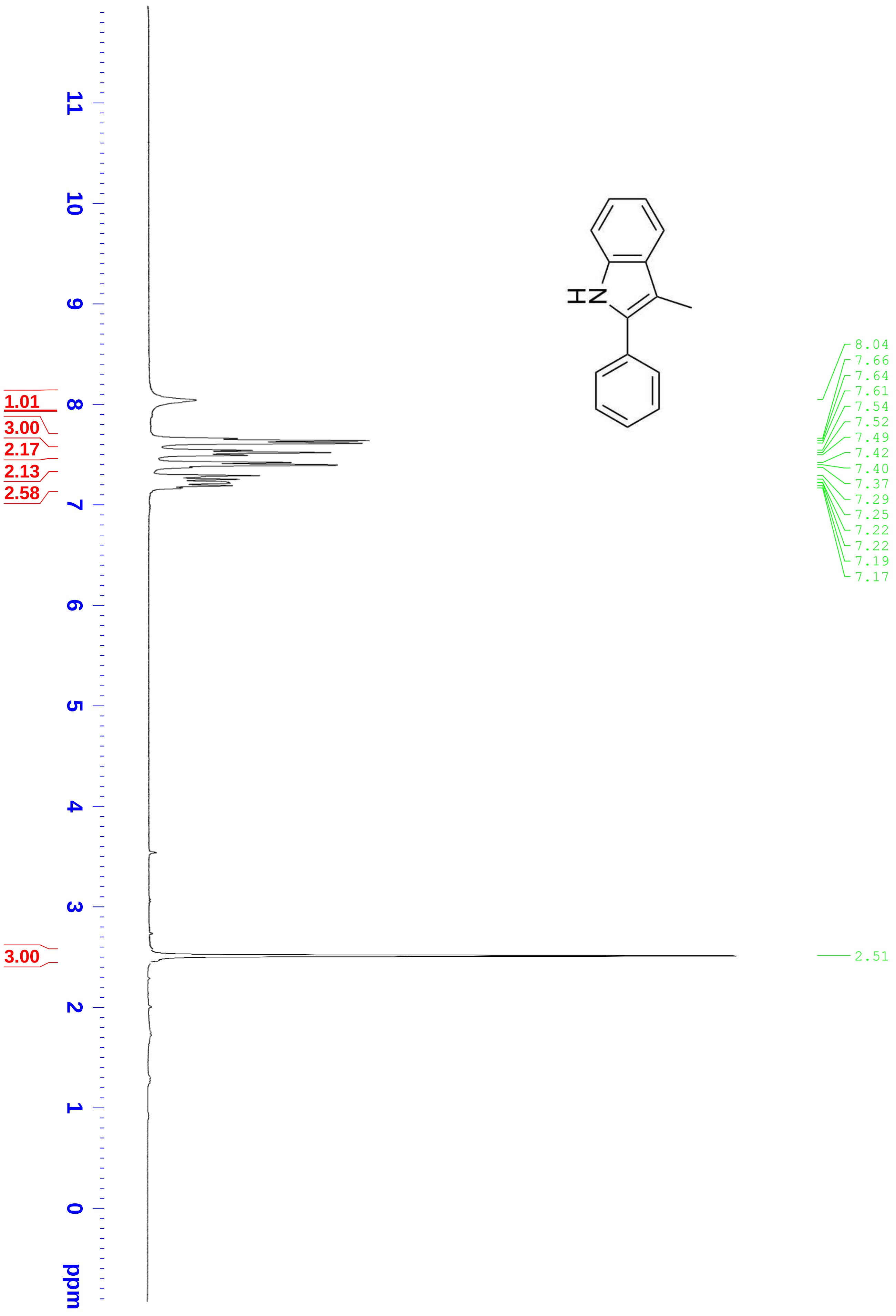
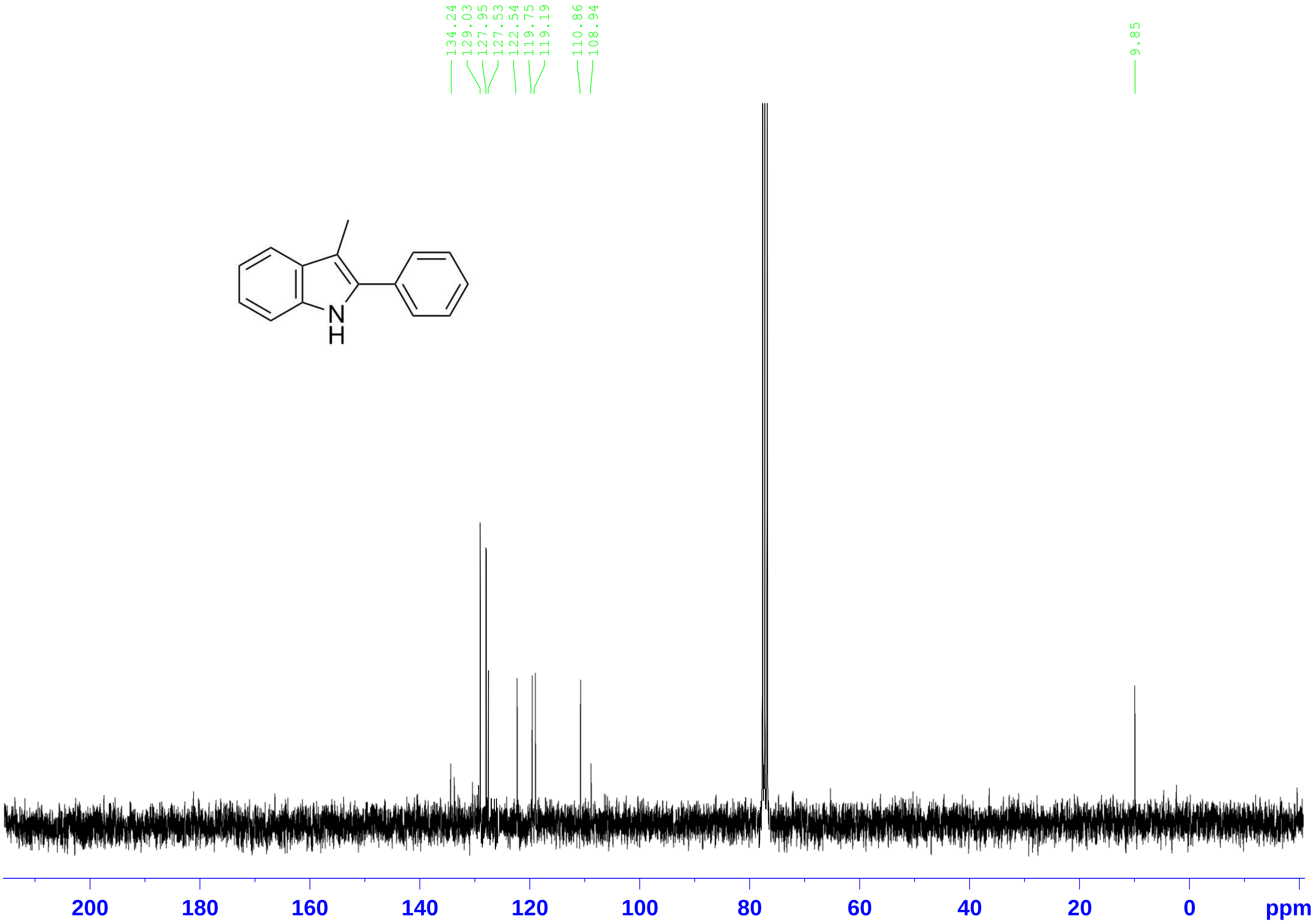
140
120
100
80
60
40
20
0
ppm


8.04
7.66
7.64
7.61
7.54
7.52
7.49
7.42
7.40
7.37
7.29
7.25
7.22
7.22
7.19
7.17
2.51
1.01
3.00
2.17
2.13
2.58
3.00
HN
11
10
9
8
7
6
5
4
3
2
1
0
ppm


134.24
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127.95
127.53
122.54
119.75
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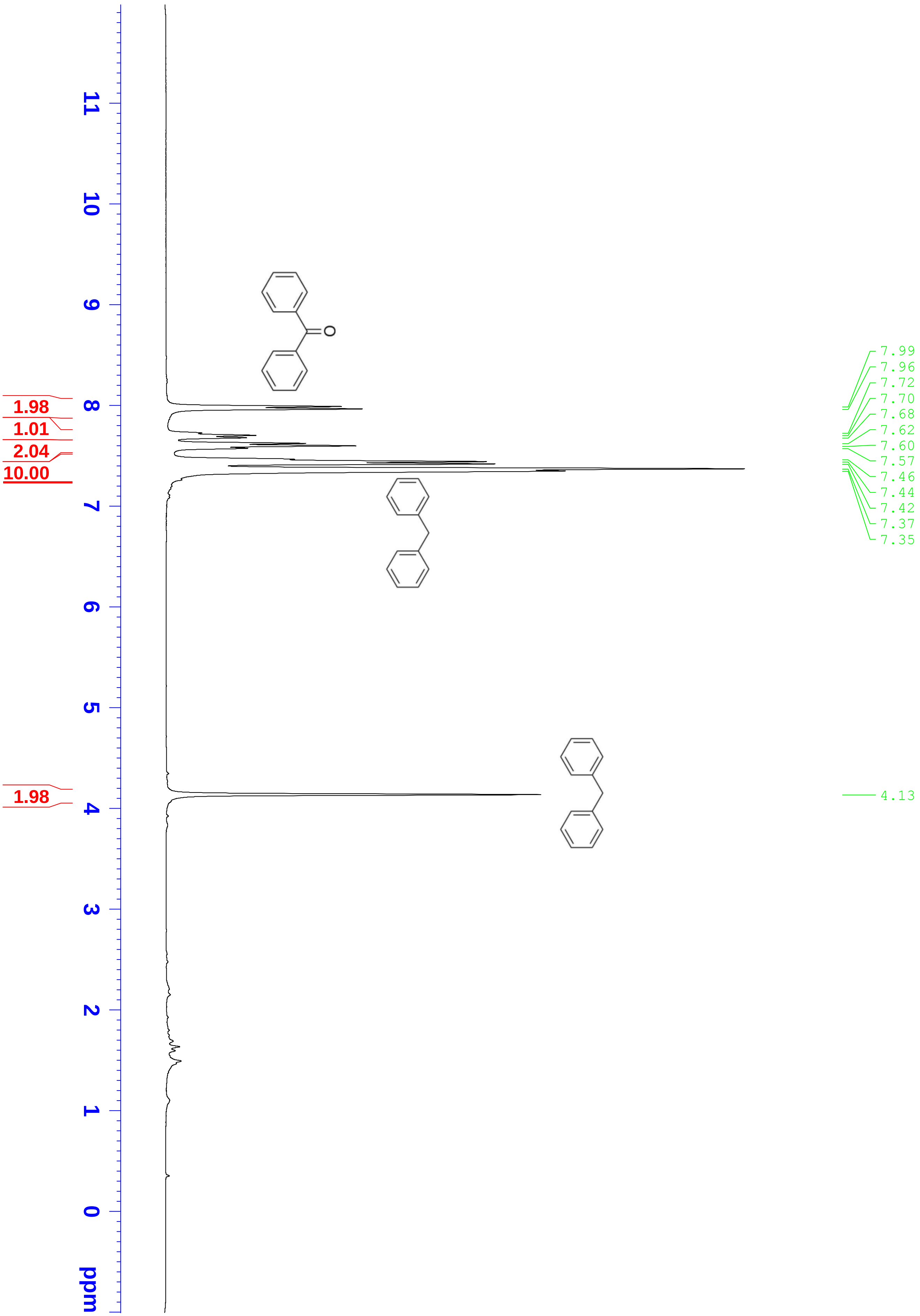
140
120
100
80
60
40
20
0
ppm


7.99
7.96
7.72
7.70
7.68
7.62
7.60
7.57
7.46
7.44
7.42
7.37
7.35
4.13
1.98
1.01
2.04
10.00
1.98
11
10
9
8
7
6
5
4
3
2
1
0
ppm
O