INSTRUCTOR'S MANUAL

A GREENER APPROACH TO ASPIRIN SYNTHESIS USING MICROWAVE IRRADIATION

This experiment consists of two laboratory periods where the students will work individually with a specific catalyst that you should assign. During this experience, aspirin will be synthesized through the catalyzed esterification of salicylic acid with acetic anhydride in either an acidic or a basic medium. In this synthesis the microwave radiation is used as the energy source. The purpose of this experiment is to study the effect that irradiating with microwaves has on the catalysis of aspirin synthesis in terms of reaction time, purity, yield and formation of secondary products. Also, it introduces the students to the green chemistry concept. The students are asked to complete the following pre-laboratory assignment.

Pre-Laboratory Assignment:

1. Refer to Appendix I for the theory behind microwave synthesis.
2. Predict the expected ^{1}H NMR spectrum for aspirin (refer to Apendix II for NMR simulation exercise) and compare it with the experimental ^{1}H NMR spectrum (refer to Appendix III for spectroscopic characterization).

Note: To achieve the spectral visualization exercise, you need to download ChemSketch v. 8.0 which includes the I-Lab Add-on for ChemSketch 8.0. This freeware package is available at http://www.acdlabs.com/download/. To download the freeware package, your computer must be IBM compatible and have approximately 18.5 MB of free memory. In addition, visit the web page http://www.acdlabs.com/download/#Guide to obtain the ChemSketch v. 8.0 user's guide. You will find in appendix II an example of a simulated

spectrum of aspirin. Any other spectrum visualization package compatible with the jcamp spectrum file format and NMR spectral simulation capabilities can be used.

The student must complete the following physical properties table:

Reactants	Formula and Molecular structure	Boiling Point (°C)	Melting Point (°C)	Molecular Weight (g/mol)	Density (g/mL)
Salicylic Acid	$C_7H_6O_3$	211 in 200 mmHg	159	138.12	1.44
Acetic Anhydride	$C_4H_6O_3$	139.9	-73.1	102.09	1.08
Aspirin	$C_9H_8O_4$	------	135	180.17	------

Important Note:

"GENERAL SAFETY CONSIDERATIONS PRIOR TO USING A MICROWAVE OVEN IN AN OPEN VESSEL REACTIONS."

Some reactions performed in microwave ovens, when using open vessels, can boil over and splatter. If this situation occurs, remove the reaction mixture from the microwave oven as soon possible. Keep the inside surfaces of the microwave oven compartment clean and do not use microwave ovens to heat liquids to temperatures near their boiling points [1, 2].

It is very important to follow these safety considerations before using a microwave oven to irradiate a chemical reaction. However, the reaction to be studied in this experiment will be carried out under solvent-free conditions or "dry" media using an open vessel inside a domestic microwave oven [3]. Several studies have concluded that these are the best conditions to minimize the risks when using the technological advantages of microwave ovens. [1, 2].

WARNINGS:

- If any student is allergic to aspirin, you must not expose him or her to the compounds that will be used in this experiment.
- Be careful with the catalysts because they can be toxic and/or irritating, consult the MSDS before continuing with the experiment.

Table I: Reagents that will be used in the aspirin synthesis.

Reagents	*CAS Number*	*Warnings*
Acetic anhydride	108-24-7	Acetic anhydride is corrosive and a lachrymator. It can cause severe irritation and burns skin and eyes and may cause a skin allergy.
Salicylic acid	69-72-7	Causes irritation, avoid contact with eyes, skin or clothing.
Sulfuric acid	7664-93-9	Causes severe skin and eye burns. It is highly corrosive.
Phosphoric acid	7664-38-2	Causes severe skin and eye burns. It is highly corrosive.
Magnesium bromide etherate	29858-07-9	Flammable. After contact with skin, wash immediately with plenty of water.

Aluminum chloride hexahydrate	7784-13-6	Corrosive and causes burns.
Toluene	108-88-3	Flammable. Harmful by inhalation, irritating to skin and risk of serious damage to eyes.
4-*N,N*-dimethylaminopyridine	1122-58-3	Highly toxic to the skin. Causes burns. Risk of serious damage to eyes.
Triethylamine	121-44-8	Flammable. Corrosive and harmful by inhalation. Causes severe burns. Lachrymator.
Calcium carbonate	471-34-1	Irritant. Risk to serious damage to eyes. Hydroscopic.
Sodium acetate	127-09-3	Avoid contact and inhalation.
Ferric chloride hexahydrate	10025-77-1	Corrosive and causes burns.
Ethyl acetate	141-78-6	Flammable liquid.
Hexane	110-54-3	Flammable liquid and vapor. Toxic by inhalation and ingestion.
Aspirin	50-78-2	Teratogen and can affect you when breathed. Irritant. Burns to the eyes and scarring can occur. Decreases the

		ability of the blood to clot.
Acetone	67-64-1	Flammable liquid and vapor. Volatile substance. Irritant.
Ethyl ether	60-29-7	Flammable liquid and vapor. Volatile substance.
Petroleum ether	8032-32-4	Flammable and may cause lung damage if swallowed. Irritating to eyes, respiratory system and skin.

- The student must carry out the reaction inside the fume-HOOD and once the microwave is turn on, the HOOD's window must be down.
- Once the microwave oven stops, be careful not to inhale the vapors that are in the microwave oven.
- It is advisable to use safety gloves prior to removing the reaction mixture from the microwave oven because the beaker may be hot.
- It is recommended that all solid catalyst be stored in a desiccator.
- The triethylamine should be freshly distilled under calcium hydride and stored under nitrogen atmosphere or in a desiccator.

Possible irregularities which may occur in the experiment:

- If the crystals have not formed in 20 minutes, it is advisable to induce their recrystallization by tapping the beaker's sides with a glass stirrer, or by adding a seed crystal. The beaker must remain covered at all times during crystal growth; this avoids contamination with impurities during recrystallization.

- If your reaction turned brownish, you probably added an excess of catalyst (probably acid), which generated a polymer. It is advisable to start the reaction anew.
- If your reaction mixture turned viscous and yellowish (probably excess base), it is advisable to start a new reaction since this occurs when there is an excess of catalyst.
- Recrystallize carefully because adding too much solvent will retard the crystals' formation. It is advisable to add the hot solvent dropwise until the solid is dissolved.

Results:

Table II: Catalysts utilized in the synthesis of aspirin with conventional heating.

Catalyst	***Reaction time***	***Polymer formation***	***Melting point (°C)***	***% Yield***
None	No reaction	Negative	153-158 [a]	No reaction
H_2SO_4	5 min	Positive	130-133	39 %
H_3PO_4	5 min	Positive	133-135	35 %
$AlCl_3$	15 min	Negative	133-135	12 %
$MgBr_2 \cdot OEt_2$	19 min	Positive	133-135	28 %
$CaCO_3$	No reaction	Negative	150-153 [a]	No reaction
NaOAc	13 min	Negative	132-135	44 %
Et_3N	28 min	Negative	133-135	27 %
DMAP	22 min	Negative	134-136	46 %

a. Melting point of Salicylic Acid.

Once the experiment is completed, the students have to form groups to discuss results and to explain the effect of the catalyst in the reaction. It is expected that the students will collect results similar to the following ones:

Table III: Catalysts utilized in the synthesis of aspirin with microwave irradiation using recrystallization procedure and solvent-free approach.[a]

Catalyst	*Reaction time (min)*	*Polymer formation*	*Yield (%)*[b]	*Yield (%)*[c]
None	10-13	Negative	80	97
H_2SO_4	5	Positive	41	55
H_3PO_4	5	Positive	40	63
$AlCl_3$	6-7	Negative	65	66
$MgBr_2 \cdot OEt_2$	5	Positive	38	63
$CaCO_3$	5	Negative	77	92
NaOAc	9-10	Negative	52	85
Et_3N	8	Negative	61	90
DMAP	14	Negative	50	67

a. The melting points of aspirin obtained from recrystallization and solvent-free procedures are comparable (mp 132-135 ^oC).

b. Obtained yields from recrystallization procedure.

c. Obtained yields from solvent-free approach.

Spectroscopic data:

The spectroscopic data obtained from the product is as follows: FTIR (KBr), 3426-2996, 2868, 1752, 1692, 1687, 1306, 1184 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz), δ 10.20 (br. s, 1H), 8.12 (dd, J = 7.85, 1.62 Hz, 1H), 7.35 (t, J = 7.55 Hz, 1H), 7.62 (dt. J = 7.80, 1.62 Hz, 1H), 7.10 (d, J = 7.80 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 21.0 (q, C-9), 122.2 (d, C-6), 123.9 (s, C-2), 126.1 (d, C-4), 132.5 (d, C-3), 134.9 (d, C-5), 151.2 (s, C-7), 169.8 (s, C-8), 170.1 (s, C-1).

Discussion questions:

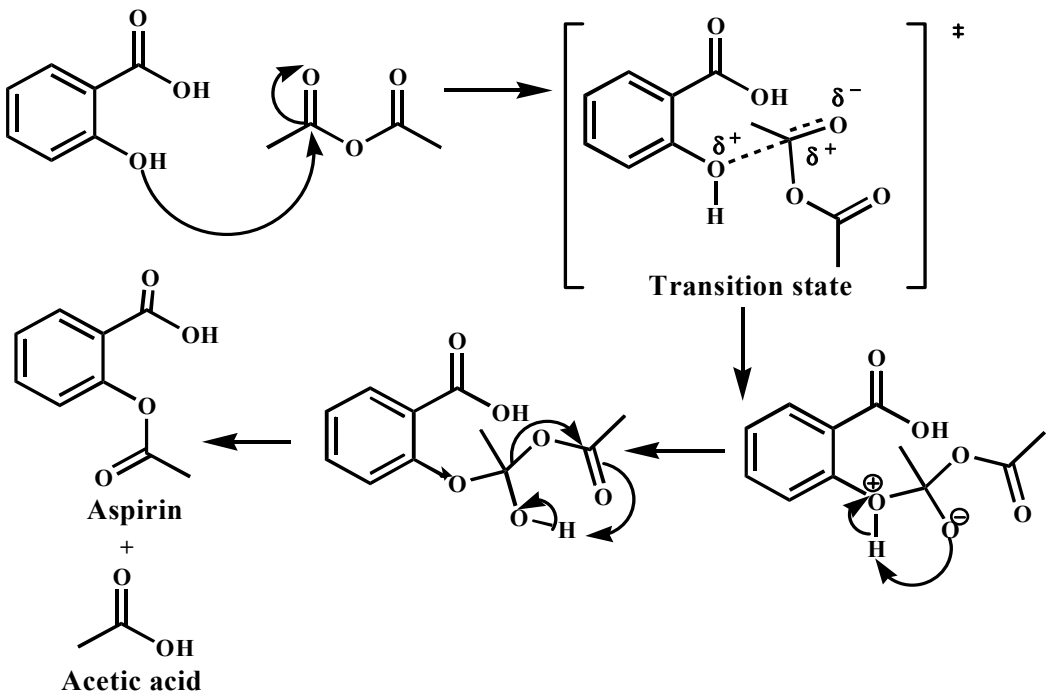
Once the experiment is completed, it is expected that students join in groups to discuss results and to be able to explain the effect of the catalyst on the reaction. Discussion questions are provided to the students to guide their reasoning.

1. Analyze the experimental results according to the data collected by the group.
2. Organize the different catalysts in order of decreasing effectiveness in:
    a. Reaction time
    b. Polymer formation
    c. Yield
    d. Product purity
3. Which is the best catalyst for this reaction? (Hint: Apply the green chemistry principles). Explain using the appropriate chemical and/or greener terminology, why your selected catalyst is the best.

Using these questions as a guide, the student might conclude that $CaCO_3$ could be the best catalyst, because in just 5 minutes they can obtain aspirin in 77 % and 92% yield (Table III), whilst without catalyst in 10-13 minutes they can obtain the same product in 80% and 97 % yield. This conclusion is correct as long as the reaction time is considered. However, if you want to guide the student to consider some aspects of green chemistry such as solvent-free reaction and atom economy, then the student should arrive at the conclusion that the best practical condition for aspirin synthesis is without catalyst.

4. Propose a reasonable reaction mechanism that supports your answer.

It is expected that the students will consider a reaction mechanism that proposes a charge separation in the reaction transition state, similar to the one presented in Scheme I.



Scheme I: Reaction mechanism suggested for the synthesis of aspirin under microwave condition without catalyst.

5. What effect does the microwave produce?

According to the literature, if there is an increase in the polarity of the media or charge separation in the reaction transition state, a faster reaction is observed under microwave irradiation, because the transition state is stabilized, decreasing the activation energy.

Literature cited:

1. Cresswell, S. L.; Haswell, S. J. *J. Chem. Educ.* **2001**, *78*, 900-904.

2. Loupy, A. *Microwaves in Organic Synthesis*, 1st edition; Wiley-VCH Verlag GmbH & Company KGaA, Weinheim, 2002, pp. 35, 115-116.

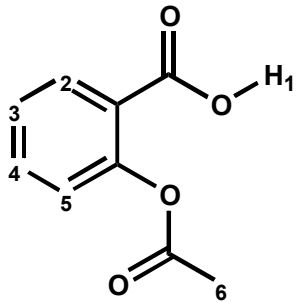
3. Mirafzal, G. A.; Summer, J. M. *J. Chem. Educ.* **2000**, *77*, 356-357.

APPENDIX II:

SIMULATION EXERCISE OF THE ^{1}H NMR SPECTRUM OF ASPIRIN

1. Perform a first order analysis of the ^{1}H NMR spectrum of aspirin, by predicting its spectrum or using the experimental data that were obtained from a real ^{1}H NMR spectrum (jcamp file) of that compound.

   Example: A first order analysis of aspirin.



Aspirin

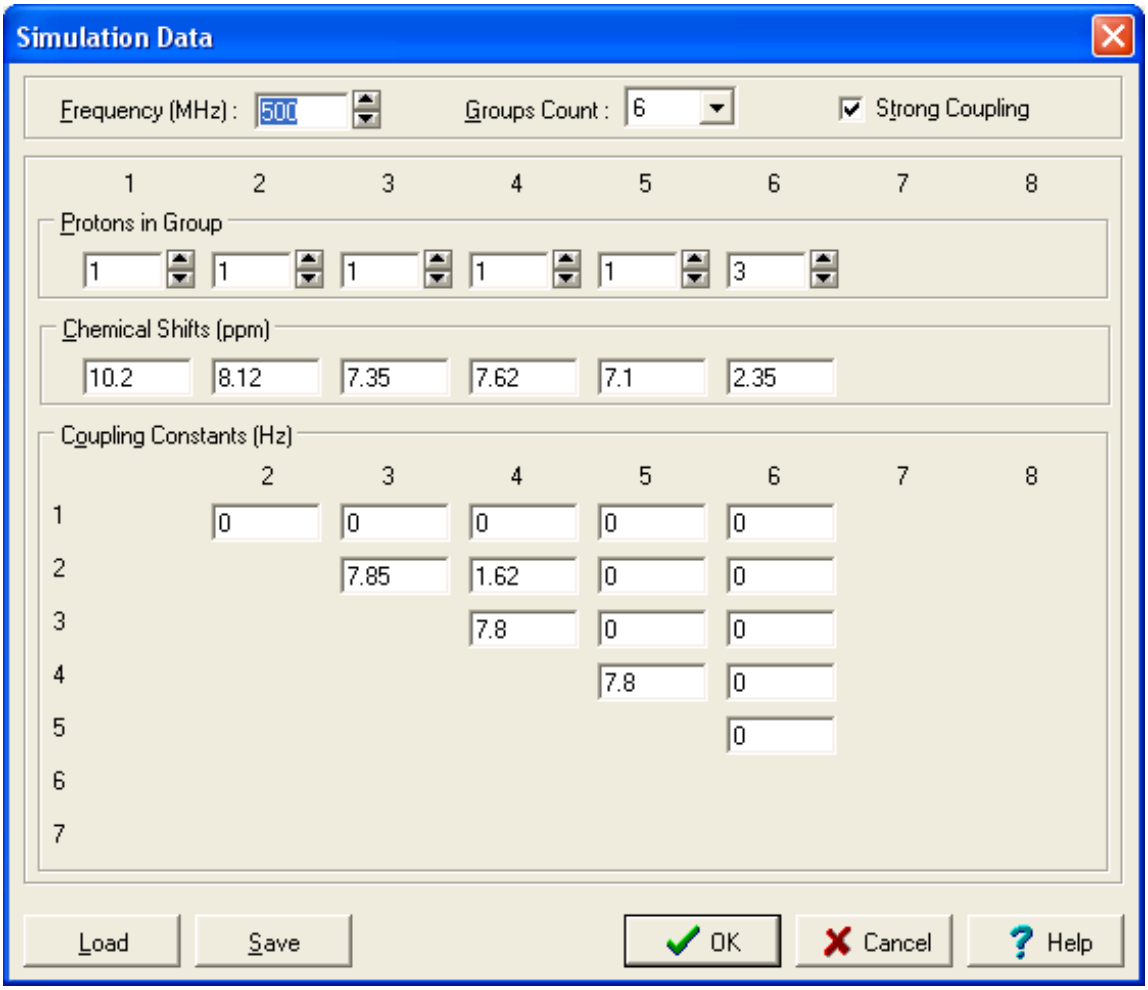
Proton group (H)	Spectral data
1	δ 10.20 (br. s, 1H)
2	δ 8.12 (dd, J = 7.85, 1.62 Hz, 1H)
3	δ 7.35 (t, J = 7.55 Hz, 1H)
4	δ 7.62 (dt, J = 7.80, 1.62 Hz, 1H)
5	δ 7.10 (d, J = 7.80 Hz, 1H)
6	δ 2.35 (s, 3H)

2. In the **Start** menu, 

select the program **HNMR Viewer** to simulate the ^{1}H-NMR of aspirin.

3. In the **Tools** menu, select the **simulation** option or click the **HNMR Spectrum Simulation** icon  to enter the coupling constant and chemical shift values for each proton group in the simulation window.

4. When you finish entering the data in the simulation window, press **OK.**



5. If you want to expand some signals, click **Zoom In**  . When you press that icon, a magnifying glass will appear in the cursor, which allows you to shade the desired signal doing a left click.

6. If you want to go back to the simulation spectrum window, click **Zoom Out**  .

7. Click the **Shift** icon  to label the chemical shift for all signals in your simulated spectrum.

8. Click the **Integrate Curve** icon  to integrate all signals in your simulated spectrum.

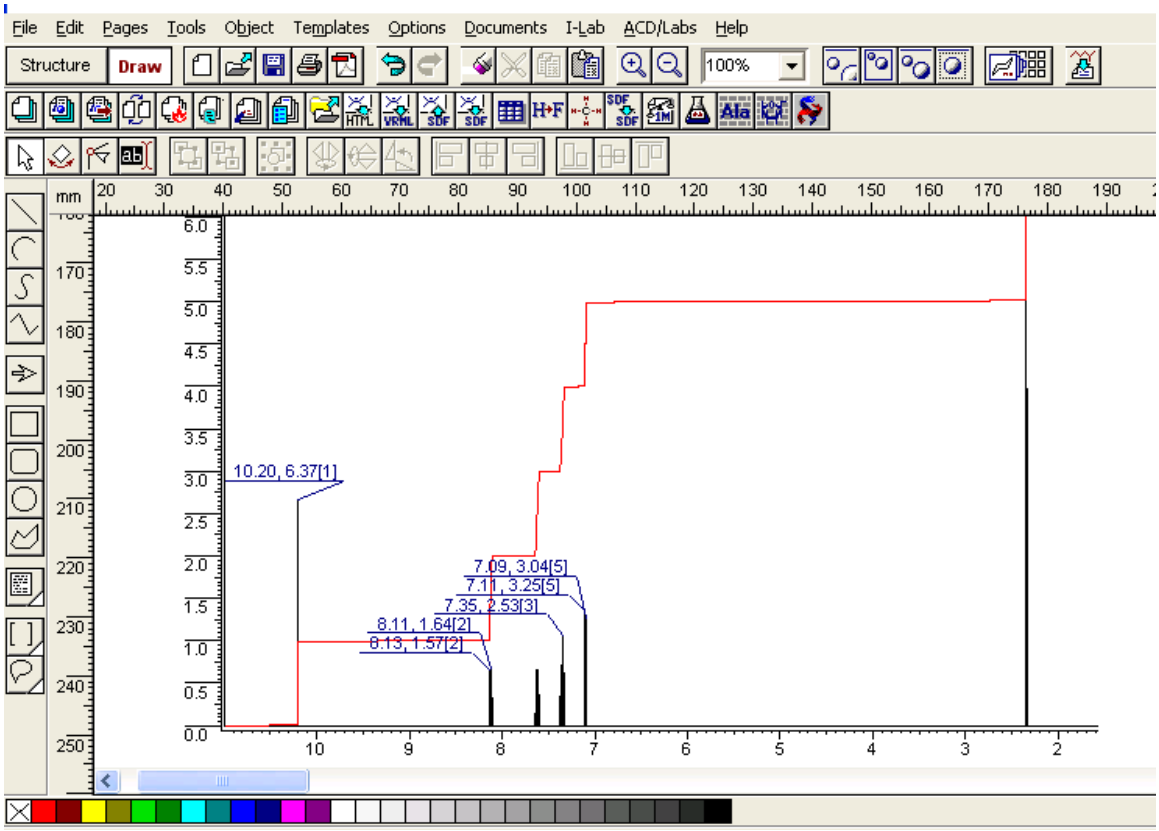
9. Click the **Hz** icon  to change the ppm scale to Hz scale in your simulated spectrum window.

10. Compare your simulated spectrum with an experimental spectrum of aspirin. If your simulation is not equal to the experimental spectrum in chemical shift and multiplicity terms, then you should go back to the simulation window (click **simulation** icon) and modify the coupling constant, chemical shift and/or proton group values.

11. Click **Show Realistic Lines**  if you want your spectrum to look realistic. On the other hand, if you want your signals be displayed as simple lines, click **Show Discrete Lines**  .

12. Click **Show Exchangeable Protons**  to see the exchangeable proton of the carboxylic group in aspirin.

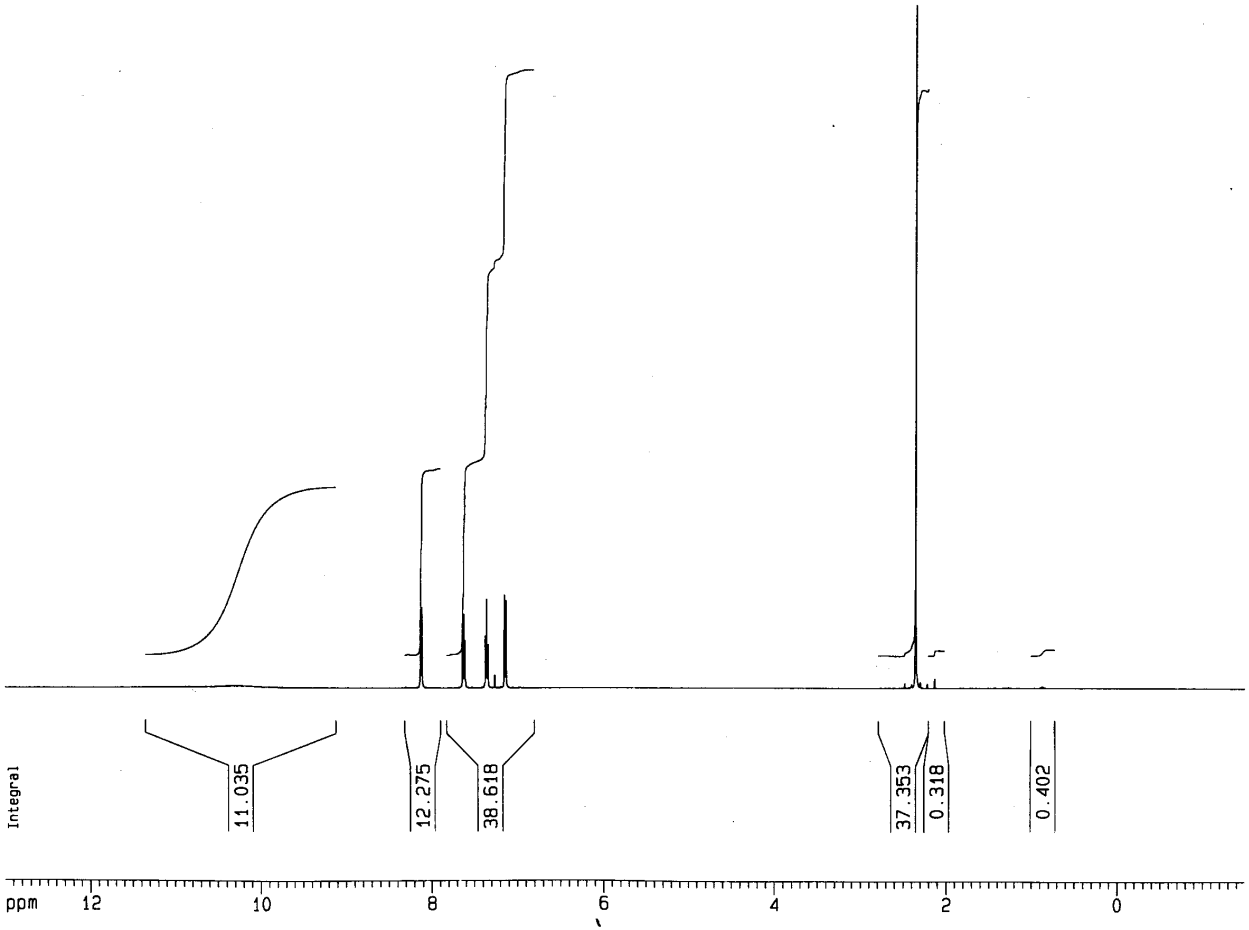
13. You can edit your spectrum pressing the **Copy Spectrum to Report Editor** icon  . With this option, you can carry the simulated spectrum to **ChemSketch**. If you press the **Structure** icon  you can draw the molecule of aspirin in the simulated spectrum (Refer to the **ChemSketch v. 8.0** user's guide).

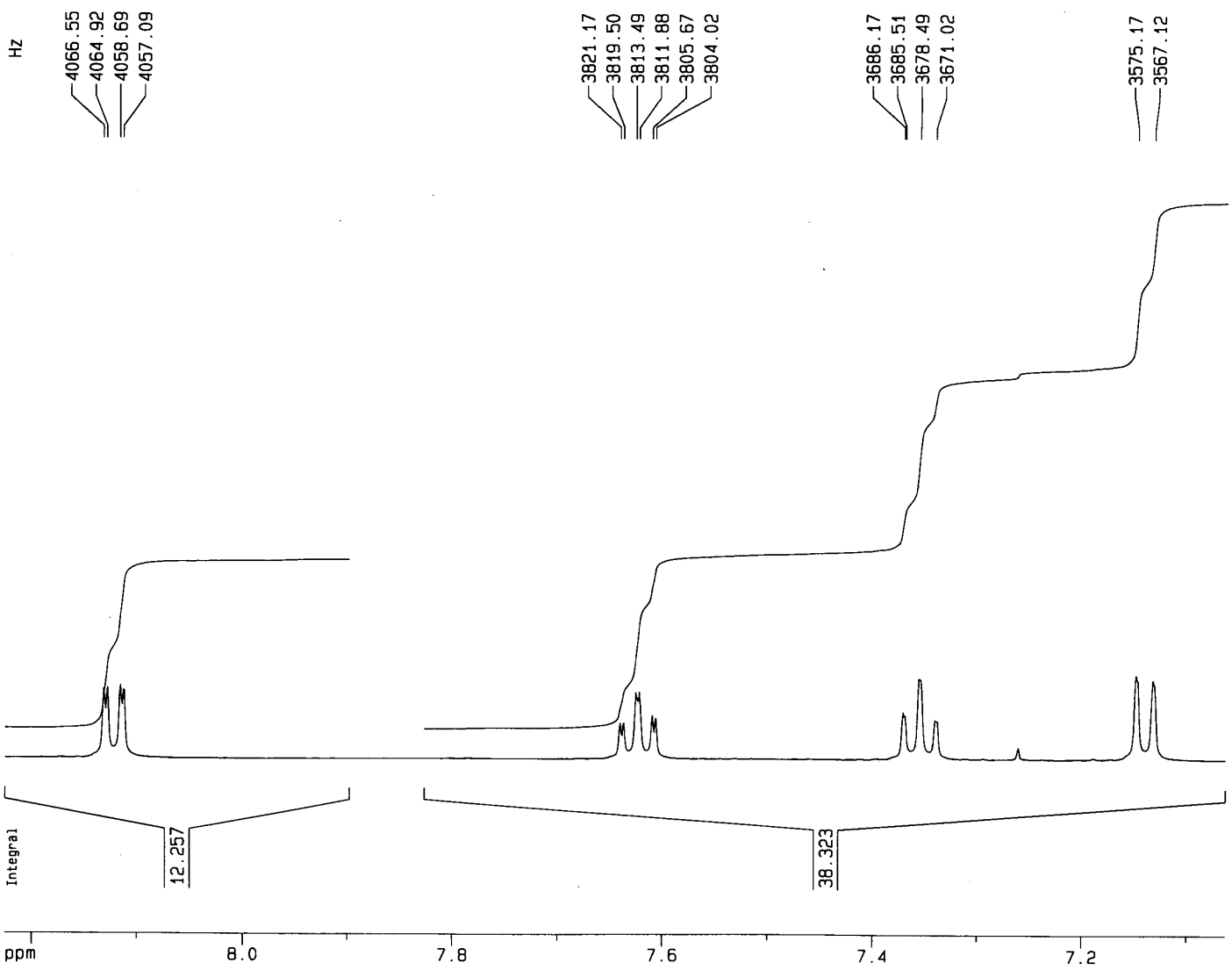


14. Click **Print**  if you want to print your edited spectrum data.

15. If you want to save your simulation data, click the **save** icon from the **File** menu.

APPENDIX III: SPECTROSCOPIC CHARACTERIZATION

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4058.69
4057.09
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3819.50
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3685.51
3678.49
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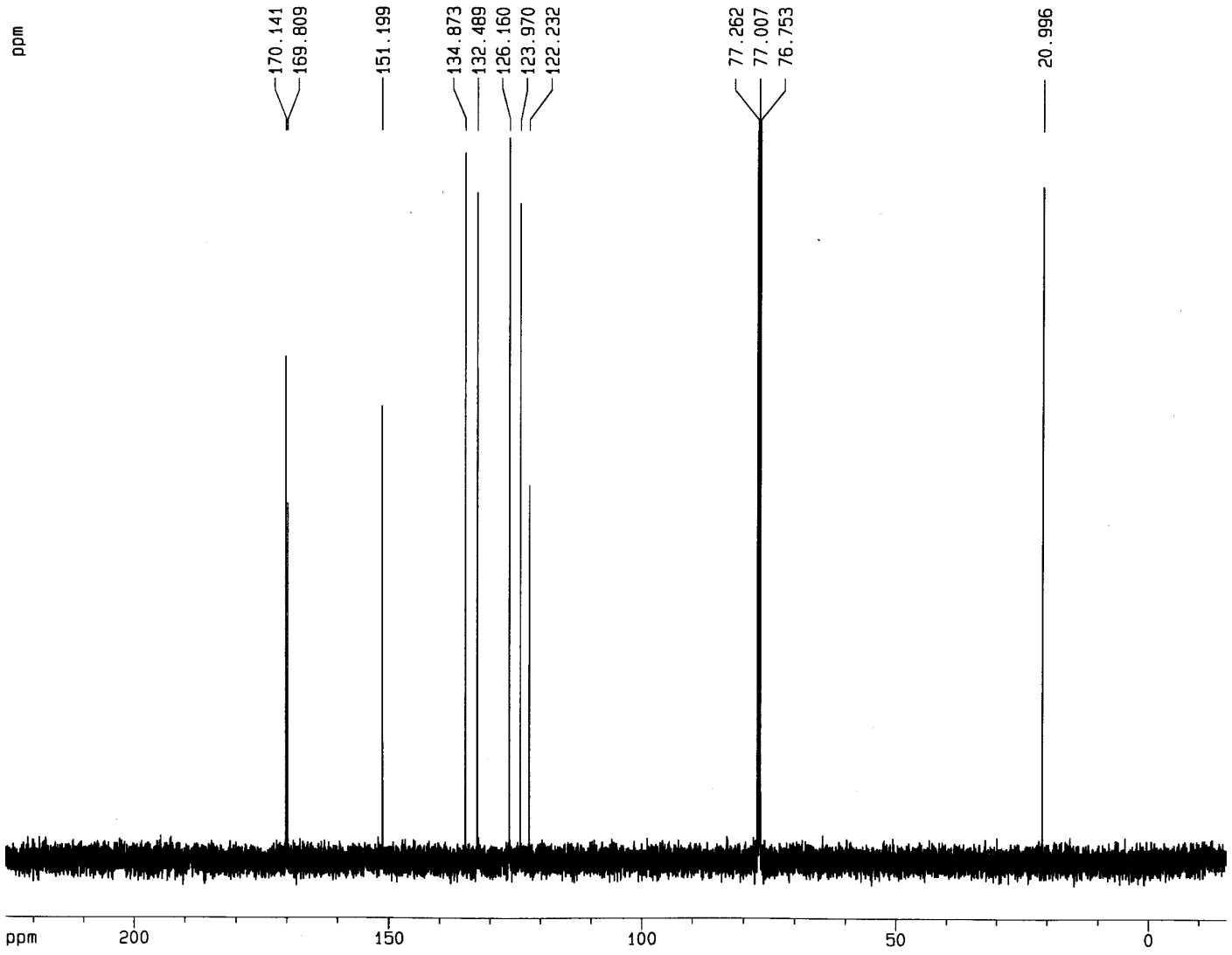
8.0
7.8
7.6
7.4
7.2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ppm
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150
100
50
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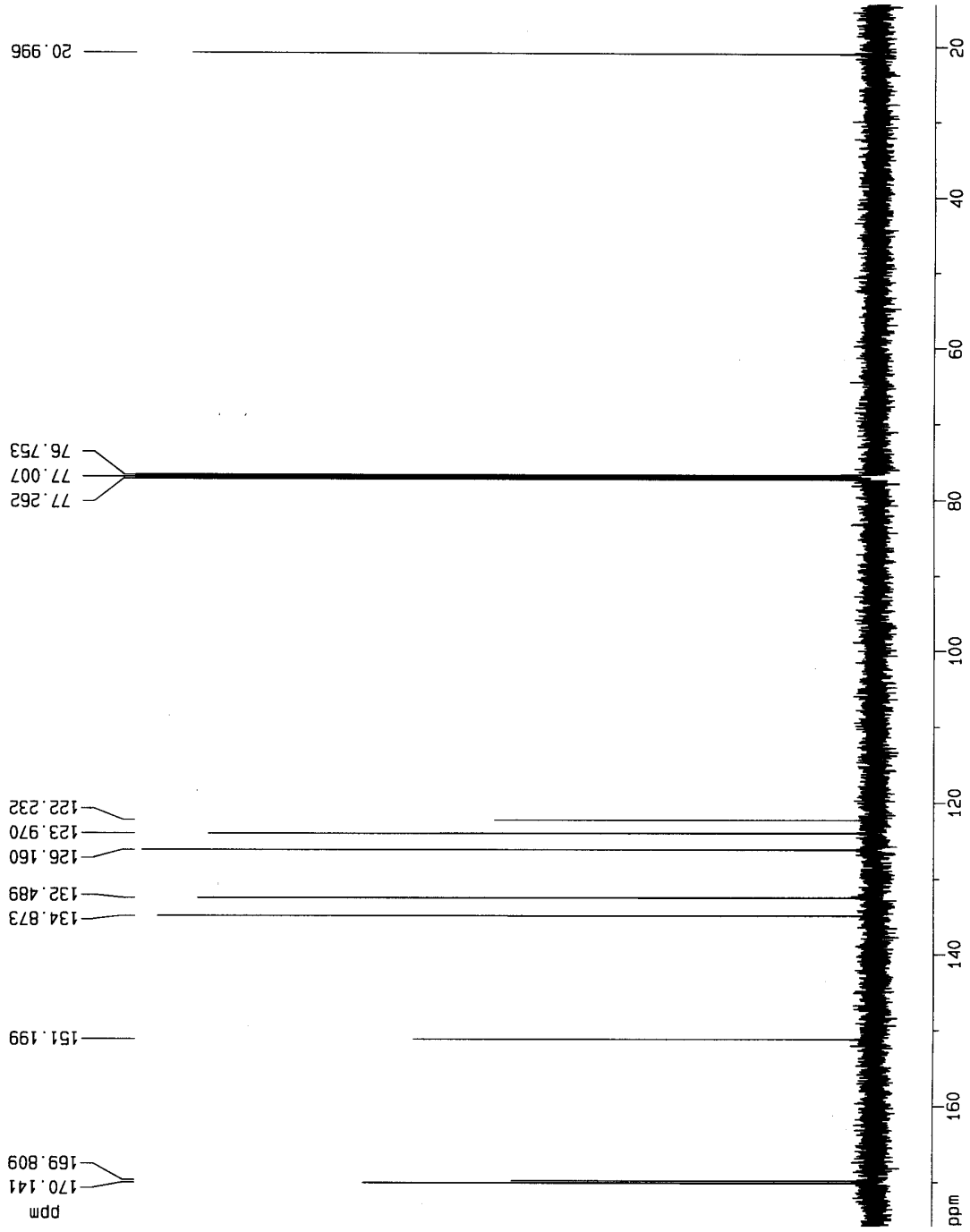
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122.232
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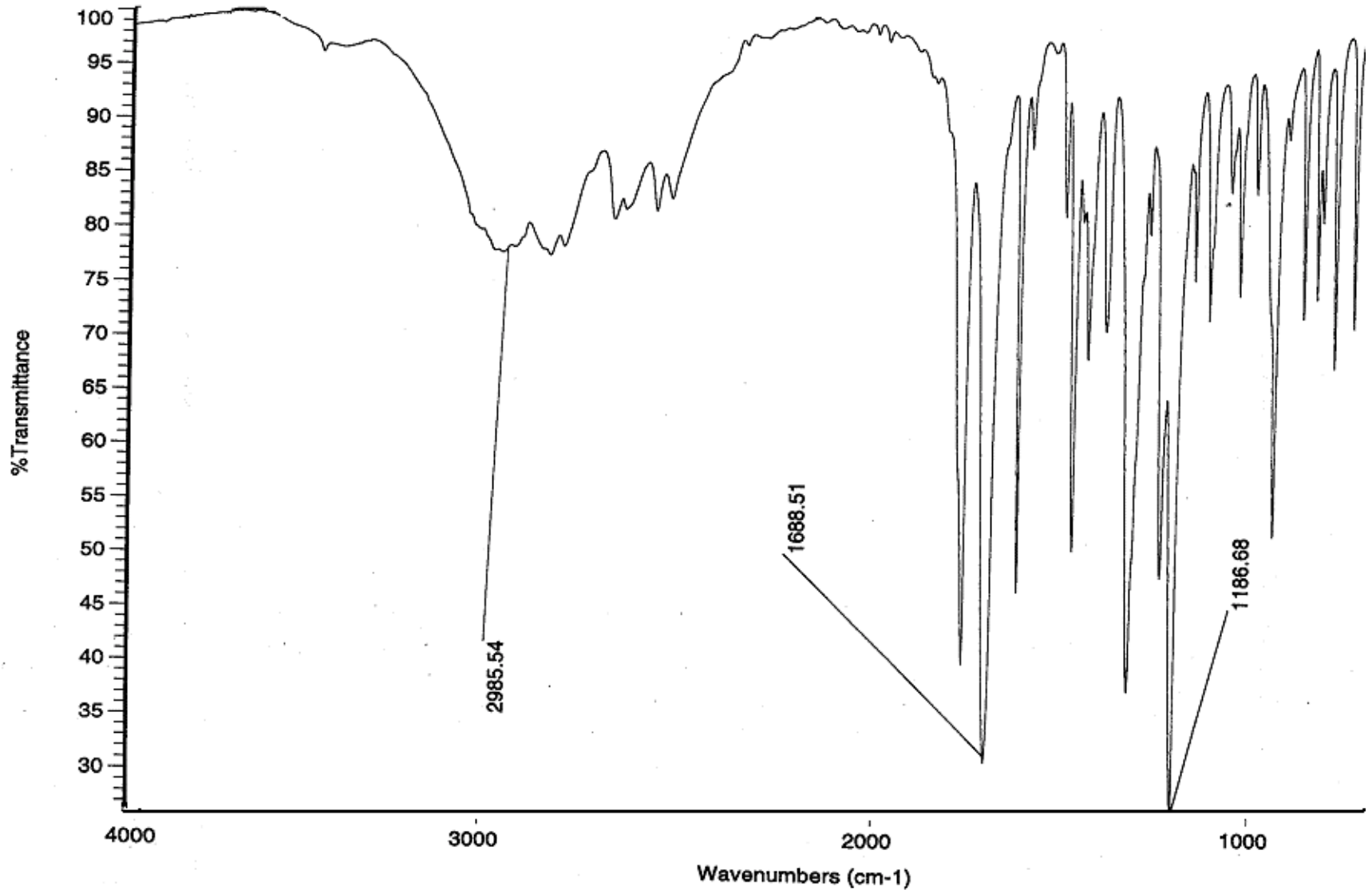
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95
90
85
80
75
70
65
60
55
50
45
40
35
30
2985.54
1688.51
1186.68
4000
3000
2000
1000
Wavenumbers (cm-1)

STUDENT'S MANUAL

A GREENER APPROACH TO ASPIRIN SYNTHESIS

USING MICROWAVE IRRADIATION

This experiment consists of two laboratory periods where the students will work individually with a specific catalyst, which will be assigned by the instructor. During this experience, aspirin will be synthesized through the catalyzed esterification of salicylic acid with acetic anhydride in either an acidic or a basic medium. In this synthesis microwave radiation is used as the energy source. The purpose of this experiment is to study the effect that irradiating with microwaves has on the catalysis of aspirin synthesis in terms of reaction time, purity, yield and formation of secondary products. Also, it introduces the students to the green chemistry concept.

Pre-Laboratory Assignment:

1. Refer to Appendix I for the theory behind microwave synthesis.
2. Read the following reference and answer the corresponding questions.

   Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686-694.

   Mention the basic principles of green chemistry and discuss those that best apply to this experiment.
3. You must be able to explain or define the following concepts:

   Lewis Acid

   Lewis Base

   Brönsted Acid

   Brönsted Base

Electromagnetic Spectrum

Microwaves

Dielectric Constant

Overheating Effect

4. Classify each of the following compounds as a Lewis or Brönsted acid or base:

   H_2SO_4

   H_3PO_4

   $MgBr_2 \cdot OEt_2$ (or $MgCl_2$)

   $AlCl_3$

   $CaCO_3$

   NaOAc

   NEt_3 (TEA)

   4-*N, N*-dimethylaminopyridine (DMAP)

5. Discuss the importance of microwaves in organic synthesis.
6. Describe the microwaves' effect in molecular terms.
7. Predict the microwaves' effect on solvents with high dielectric constants.
8. Describe the microwaves' effects on solvent-free reactions.
9. Establish the microwaves' specific effects in terms of Arrhenius' law.
10. Predict the microwaves' effect according to the reaction mechanism.
11. Predict the expected ^{1}H NMR spectrum for aspirin and compare it with the experimental ^{1}H NMR spectra.

Note: To achieve the spectral visualization exercise, you need to download ChemSketch v. 8.0 which include the I-Lab Add-on-for ChemSketch 8.0. This freeware package is

available at http://www.acdlabs.com/download/. To download the freeware package, your computer must be IBM compatible and have approximately 18.5 MB of free memory. In addition, visit the web page http://www.acdlabs.com/download/#Guide to obtain the ChemSketch v. 8.0 user's guide. You will find in appendix II an example of a simulated spectrum of p-methoxybenzaldehyde. Any other spectrum visualization package compatible with the jcamp spectrum file format and NMR spectral simulation capabilities can be used.

The student must complete the following physical properties table:

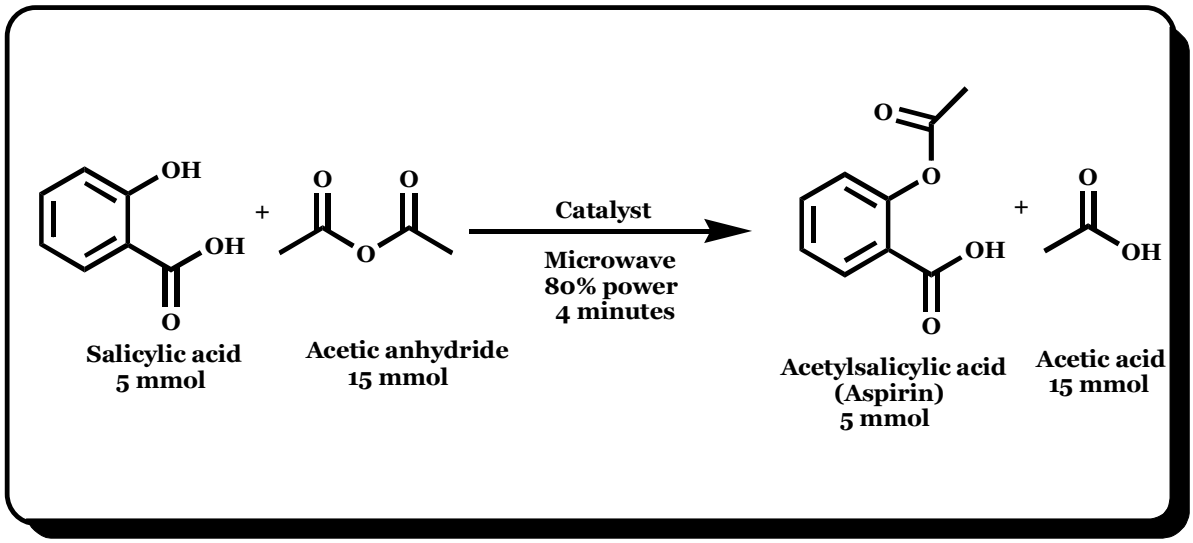
Reactants	**Formula and Molecular structure**	**Boiling Point (°C)**	**Melting Point (°C)**	**Molecular Weight (g/mol)**	**Density (g/mL)**
Salicylic Acid					
Acetic Anhydride					
Aspirin					

Important Note:

WARNING: IF YOU ARE ALLERGIC TO ASPIRIN, YOU MUST CONSULT WITH YOUR INSTRUCTOR BEFORE WORKING ON THIS EXPERIMENT. YOU MUST NOT EXPOSE YOURSELF TO THE COMPOUNDS THAT WILL BE USED IN THIS EXPERIMENT. BE CAREFUL WITH THE CATALYSTS BECAUSE THEY CAN BE TOXIC OR IRRITATING. CONSULT THE MSDS BEFORE CONTINUING WITH THE EXPERIMENT.

Procedure:

Reaction to be studied:



Prepare 5 mmoles of aspirin. Add 5 mmoles of salicylic acid, 15 mmoles of acetic anhydride (**WARNING: ACETIC ANHYDRIDE IS AN IRRITATING TOXIN AND A LACHRYMATOR SUBSTANCE)** and the assigned catalyst to a clean and dry 50-mL beaker. If the catalyst is a solid add 0.02-0.04 g, if it is a liquid add a single drop. The possible catalysts are: H_2SO_4, H_3PO_4, $MgBr_2{\cdot}OEt_2$ (or $MgCl_2$), $AlCl_3$, $CaCO_3$, NaOAc, NEt_3 and DMAP. **ADD THE CATALYST VERY CAREFULLY, IF TOO MUCH IS INADVERTENTLY ADDED, THE REACTION COULD BE SPOILED WHEN THE MICROWAVE IS USED.** Softly stir the reaction mixture and place it in the microwave (take care to place the beaker in the center of the microwave) and adjust the timer to 2 minutes at 80% power (for this adjustment press the "POWER" button and enter the number 8). Press "START" to run the two minute reaction process. Once the microwave oven stops **(WARNING: DO NOT INHALE THE VAPORS THAT ARE IN THE MICROWAVE)** remove the reaction mixture from the

microwave oven **(THE BEAKER MAY BE HOT!)** and stir the mixture for a few seconds before placing it in the center of the microwave again. Immediately adjust the timer for 2 minutes at 80% power and press "START". Once the microwave stops, note the time that the reaction was removed from the microwave and carry out a thin layer chromatography analysis (TLC) using a solution 8:2 v/v hexane-ethyl acetate as mobile phase and silica gel plates as stationary phase, followed by a ferric chloride ($FeCl_3$) test. These results will correspond to the "zero time". After five minutes have elapsed, carry out a thin layer chromatography analysis, followed by a ferric chloride ($FeCl_3$) test and repeat every five minutes until crystals form (refer to the table for the reaction progress). **IT IS IMPORTANT TO NOTE WHEN THE FIRST CRYSTAL FORMATION IS OBSERVED DURING THE REACTION'S PROGRESS.**

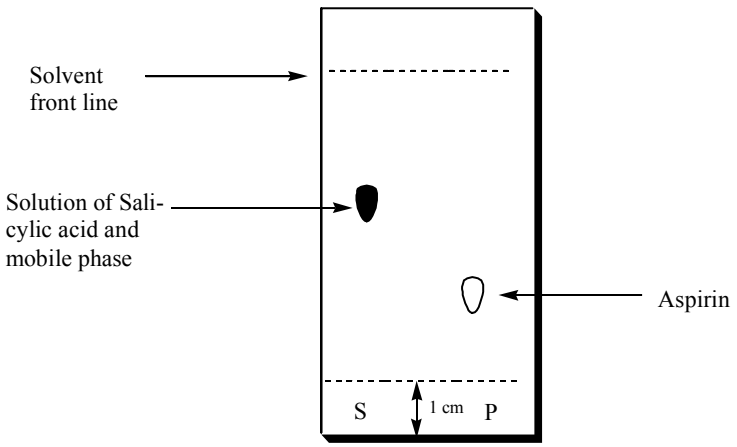
Once the crystals are formed, if your catalyst was a *base***,** proceed to acidify the medium using a 1M HCl solution. Add several drops of the HCl solution until litmus paper turns red. *Do not dip the litmus paper into the mixture.* After the acidification, save your crystals until the next laboratory period where you will recrystallize the product with the appropriate solvent. If your catalyst is an *acid***,** add 8 mL of a saturated sodium bicarbonate solution until it ceases to react. Stir, and then filter the solution using vacuum filtration. In a filtration flask, slowly add 3M HCl until it reaches an acidic pH, but do not add more than 8 mL as it can also hinder the solid's formation **(WARNING: DO NOT ADD WATER FOR THE TRANSFERENCE AS IT CAN HINDER THE ASPIRIN RECRYSTALLIZATION PROCESS).** The solution will begin to cloud up, which indicates the formation of aspirin crystals. Filter the solution and save the crystals until the next laboratory period where you will recrystallize the product. Finally, if you did not use a catalyst**,** then you may proceed directly with the recrystallization in the next laboratory period (**REMEMBER TO CARRY OUT SOLUBILITY TESTS TO**

DETERMINE THE BEST SOLVENT FOR RECRYSTALLIZATION). Finally dry the product in a preheated oven at 80 °C, determine its melting point, and yield (Table 1: Reaction progress).

This experimental procedure can be carried out following the principle of green chemistry for the preparation of 5 mmoles of aspirin. For this, the above experimental procedure is followed, with the exception of the recrystallization step. The crude product obtained from the reaction is washed with 25 mL of cold water to remove the excess acetic anhydride. Then, the product is filtered and dried in a preheated oven at 80 °C. The melting point and percent yield must be determined. Finally, NMR and other spectroscopic methods can be used to characterize the crude product (Table 2: Reaction progress).

Thin layer chromatography preparation:

Before you begin the reaction, you must already have prepared a chamber with mobile phase (a solution 8: 2 v/v hexane-ethyl acetate) for the thin layer chromatography and the silica plates. The plates must be cut and marked as shown in the following diagram before they are used:



Add 5 drops of 8:2 v/v hexane-ethyl acetate along with enough salicylic acid to slightly saturate it (the salicylic acid will not dissolve completely). The resulting solution will be used as the

starting material for the thin layer chromatography to monitor the reaction progress. However, if your product does not contain supernatant, you may carry out the test by dissolving a speck of the solid in 4-5 drops of the mobile phase (it will not dissolve completely). Once the thin layer chromatography is prepared, proceed to observe the markings under UV light. Determine the markings' R_f's and analyze the reaction's progress.

$FeCl_3$ Test:

Before you begin the reaction, prepare the test tubes to be used for the tests and have them organized and ready on a rack. There are a total of six test tubes, one for the starting material and five others (or more) to follow the reaction progress with the iron chloride test. To prepare the $FeCl_3$ test, add 5-6 drops of water to a test tube, followed by 3 drops of the $FeCl_3$ solution. Prepare the other four tests in the same way. When the reaction mixture is removed from the microwave oven, use a pipette to remove a drop and add it to a test tube. Follow this procedure every five minutes as long as no solid has formed or as long as there is enough supernatant when solids are beginning to form. Once the solid product is formed, remove a small amount of the solid with a microscale spatula and add this directly into the $FeCl_3$ test tube. If any change in color is observed, this is an indication that salicylic acid is still present in the mixture. It is important to remember that this test must be carried out immediately after removing the mixture from the microwave oven and then every five minutes to monitor the reaction progress. Why is a color change observed with the $FeCl_3$ test in the presence of salicylic acid?

Recrystallization process:

Recrystallize the product using the available solvents in the laboratory such as water, acetone, diethyl ether, petroleum ether and toluene. **WARNING: ACETONE, DIETHYL**

ETHER AND PETROLEUM ETHER ARE HIGH FLAMMABLE SOLVENTS, TO AVOID ITS VAPORS YOU SHOULD WORK IN THE FUME HOOD. USE A WATER BATH TO WARM THESE SOLVENTS. Remember, the beaker must remain covered at all times during crystal growing, this avoids contamination with impurities during the recrystallization process**.** Filter the crystals by suction filtration, dry them and determine their melting point and yield. Analyze your recrystallized product using Infrared, Nuclear Magnetic Resonance (^{1}H, ^{13}C) and UV-Visible light techniques.

Possible irregularities, which may occur in the experiment:

- If the crystals have not formed in 20 minutes, it is advisable to induce their recrystallization by tapping the beaker's sides with a glass stirrer, or by adding a seed crystal. The beaker must remain covered at all times during crystal growth; this avoids contamination with impurities during recrystallization.
- If your reaction turned brownish, you probably added an excess of catalyst (probably acid), which generated a polymer. It is advisable to start the reaction anew.
- If your reaction mixture turned viscous and yellowish (probably excess base), it is advisable to start a new reaction, since this also occurs when there is an excess of catalyst.
- Recrystallize carefully because adding too much solvent will retard the crystals' formation. It is advisable to add the hot solvent dropwise until the solid is dissolved**.**

Discussion questions:

1. Analyze the experimental results according to the data collected by the group.
2. Organize the different catalysts in order of decreasing effectiveness in:
    a. Reaction time

b. Polymer formation

c. Yield

d. Product purity

3. Which is the best catalyst for this reaction? (Hint: Apply the green chemistry principles). Explain using the appropriate chemical and/or greener terminology, why your selected catalyst is the best.
4. Propose a reasonable reaction mechanism that supports your answer.
5. What effect does the microwave produce?

Reaction progress table 1: Catalysts utilized in the synthesis of aspirin with microwaves using recrystallization procedure

Catalyst	Melting Pt. (°C)	% yield	0 minutes	5 minutes	10 minutes	15 minutes	20 minutes	Observations
H_2SO_4								
H_3PO_4								
$AlCl_3$								
$MgBr_2 \cdot OEt_2$								
None								
$CaCO_3$								
NaOAc								
Et_3N								
DMAP								

Reaction progress table 2: Catalysts utilized in the synthesis of aspirin with microwaves irradiation via a solvent-free approach

Catalyst	Melting Pt. (°C)	% yield	0 minutes	5 minutes	10 minutes	15 minutes	20 minutes	Observations
H_2SO_4								
H_3PO_4								
$AlCl_3$								
$MgBr_2 \cdot OEt_2$								
None								
$CaCO_3$								
NaOAc								
Et_3N								
DMAP								

APPENDIX I:

USE OF MICROWAVES IN ORGANIC CHEMISTRY

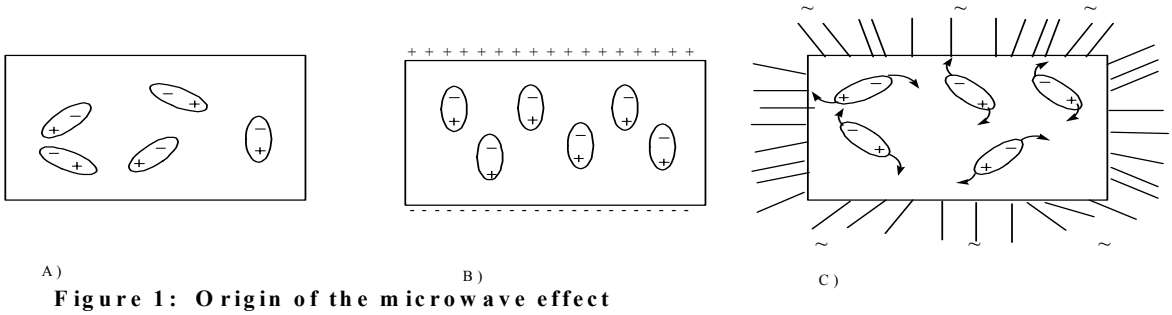
Before we discuss microwaves in a more detailed way, let us first talk about the main components of the electromagnetic spectrum and its relation with microwaves. The **electromagnetic spectrum** is the collection of radiations, ranging from very high and energetic frequencies, such as gamma rays and X-rays, to low frequency radiations, such as microwaves and radio waves [(1)], which contain lower energies.

When we use the term **microwaves**, we are referring to the name given to a specific part of the electromagnetic spectrum which is characterized by its low energy, which stems from the low frequency of its radiation. The wavelengths of the electromagnetic waves which comprise this type of radiation range from 0.75 to 3.75 mm. The usage of microwaves is widespread in home appliances and telecommunications applications; however, the unconventional source of energy microwaves provide is rapidly becoming a popular and very useful energy source for organic chemistry syntheses.

A microwave oven is an electric household appliance with a component named the magnetron. This vital component serves as the source of electromagnetic radiation in the microwave range. These microwaves generate movements in the molecules which make up food [(2)]; however these household appliances have also been successfully implemented in organic chemistry synthesis as a means of carrying out reactions more efficiently in terms of reaction time and purity.

Origin of the microwave effect [3, 4]**:**

A microwave oven is used to generate radiation that can induce the movement of molecules. When a substance is irradiated with microwaves, there is an interaction between the magnetic fields of molecules in movement and the magnetic field produced by the microwaves. This interaction produces a type of "friction" between the moving molecules which in turn produces heat. In the case of microwave ovens the frequency used is approximately 2450 MHz. This frequency is mostly absorbed by water or other substances with high dielectric constants (ε).



A) B) C)

Figure 1: Origin of the microwave effect

The **dielectric constant** is a measurement of the ability of a material to moderate the attraction forces between oppositely charged particles as compared to a standard [5]. The dielectric standard to be used for comparison is a vacuum whose assigned value ε is exactly equal to 1. Substances with high dielectric constants are classified as polar substances. As is to be expected, molecules that possess a dipole moment (charge separation), are able to absorb microwave radiation (Fig. 1-A and 1-B). In Figure 1-C, on the other hand, the molecules subjected to an alternating electric field begin spinning around themselves that generates friction between the molecules. They dissipate energy as heat as a result of agitation and intermolecular friction of molecules when dipoles change their mutual orientation at each alternation of the electric field at a very high

frequency [3]. In this context, an efficient absorption of the microwaves occurs in substances that possess high dielectric constants (polar substances) and high boiling points. According to the **intermolecular forces** theory, certain substances with high boiling points are composed of polar molecules which can have dipole-dipole interactions or hydrogen bonding; these interactions will be much stronger than those in molecules that possess only London dispersion forces. Let's analyze the following table:

Table 1: Some significant thermal effects of molecules that are subjected to microwave radiation using a 600 W household microwave oven [3, 6, 7].

Liquids	Temperature after 1 minute of irradiation (°C)	Boiling point (°C)	Dielectric constant (ε) at 25 °C	Dipole moment (Debye)
H_2O	81	100	80.1	5.9
EtOH	78	78	25.3	5.8
n-$C_5H_{11}OH$	106	137	15.1	5.7
CH_3CO_2H	110	119	6.2	5.6
DMF	131	153	36.7	10.8
n-C_6H_{14}	25	98	1.9	0.0
CCl_4	28	77	2.2	0.0

We can see from Table 1 that pentanol, if compared with water, has a higher boiling point because it can form a hydrogen bond and possesses an aliphatic chain, which allows for a greater surface area, which in turn, requires greater energy to separate its molecules. We can also appreciate that water, which also forms hydrogen bonds, absorbs microwaves

better than pentanol as it possesses a greater dipole moment and after a minute of irradiation reaches a temperature of 81 °C nearing its boiling point (100 °C). In the case of DMF, it possesses a greater dipole moment and dielectric constant, for this reason the microwave radiation brings its temperature the closest to boiling point in one minute. On the other hand, in the cases of hexane and carbon tetrachloride, no significant absorption of the microwave radiation occurs because their dipole moments are zero.

When the solvents reach average temperatures greater than their corresponding boiling points, the continued absorbance of microwaves produces what is called the **overheating effect** [8]. This effect is due to the dissipation of the microwaves over the liquid's volume. The efficiency of certain reactions reported in the literature has been attributed to this effect. The overheating effect is commonly observed in household systems in the absence of stirring. Figure 2 depicts the increase in temperature and the boiling point of methanol in a monomode system adjusted to 30 W. According to this figure, when methanol is exposed to microwave irradiation over a 100 s period, this solvent reaches temperatures greater than its boiling point (65 °C). When boiling chips were added to the overheated solvent, temperatures substantially dropped to nearly that of the boiling point of the solvent. This temperature decrease was expected because the boiling chips increase the number of nucleation sites, thus reduce the overheating effect [8].

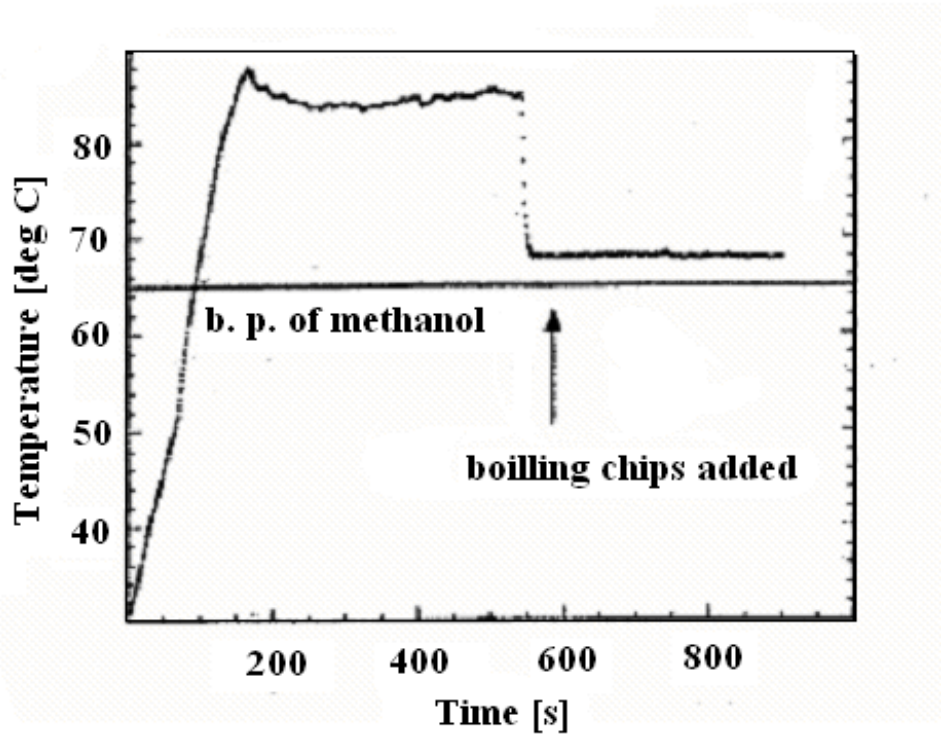


Figure 2: Temperature profile of methanol showing a dramatic decrease in temperature when boiling chips are added. (Adapted from 8)

Table 2 shows the results of the temperature measurements in a monomode system in the absence of stirring.

Table 2: Boiling points of some common polar solvents (°C) [9, 10].

Solvents	Normal Conditions	Microwave Exposure	Differences
Water	100	105	5
1-Butanol	117	138	21
2-Butanol	98	127	29
Methanol	65	84	19
1-Pentanol	136	157	21
1-Heptanol	176	208	32
Acetone	56	89	33
Ethyl acetate	77	102	25
Tetrahydrofurane	67	103	36
Acetonitrile	82	120	38

Specific effects of the microwaves

The microwaves' effects are not simply the thermal effects; there are factors other than the heating generated by the friction between molecules that can affect a reaction. These effects can be reasoned out using Arrhenius' law {$k = A \exp(-\Delta G/RT)$} in which every term of the law can have resultant modifications [3, 11].

1. ***Pre-exponential factor A.*** One of the specific effects of microwaves is the increase in the pre-exponential factor A, which is representative of the probability that the molecules will collide. The collision efficiency can be effectively influenced through the mutual orientation of the polar molecules involved in the reaction.

2. ***Activation energy ($\Delta G^{\neq}$)***. The main effect of the microwaves is the decrease in the activation energy ($\Delta G^{\neq}$). The activation energy is a value given by the relation $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$. The magnitude of the activation energy can be predicted with the term - $T\Delta S^{\neq}$, which can increase when the reaction is irradiated with microwave radiation. When it is exposed to microwaves, a reaction tends to be more organized in comparison to traditional heating due to the polarization present in molecules, which possess a dipole moment.

Effects of the medium [3]:

The microwaves' effects can be considered in terms of the medium of reaction. The effects of the solvent are of particular importance when studying the microwaves' effects.

1. If the solvent is polar and aprotic (i.e. DMSO, CH_3CN, DMF) or protic (i.e. alcohols), the main interactions occur between the microwaves and the polar molecules of the solvent. When this interaction occurs, the energy is transferred from the solvent (in excess) to the reaction mixture, resulting in the specific effects of the microwaves on the reactants (i.e. increase in the pre-exponential factor A and decrease in activation energy $\Delta G^{\neq}$). Because of this, in chemical reactions, the rate of reaction when microwaves are applied is similar to the rate of reaction when conventional heating is applied.
2. When the solvents are non-polar (i.e. xylene, toluene, carbon tetrachloride), they do not absorb microwaves efficiently. For this reason, these solvents allow a specific absorption by the reactants. The reactants, if they are polar molecules, have the capacity to transfer energy from themselves to the solvent.

3. The effects of the microwaves are mostly likely to be observed in reactions that are solvent-free [3]. Solvent-free reactions are carried out due to ecological and economical reasons. Nevertheless, when this type of reaction is carried out with microwave heating, the absorption is limited by the nature of the reactant molecules.

Microwave effects according to the reaction mechanism [3]:

The specific effects of the microwaves can be expected in polar reaction mechanisms, meaning that charge separation (be it formally or partially) occurs during any step of the reaction. When polarity increases during a reaction as the molecules change from a base state to their transition state, stabilization occurs in the transition state due to the interaction of the electromagnetic waves from the microwave with the electromagnetic waves generated by this state. This interaction results in an increase in reactivity due to the resultant decrease in activation energy. It is important to stress the fact that this stabilization of the transition state in polar mechanisms is not observed in reactions using traditional heat. The previous explanation can be observed qualitatively in Figure 3.

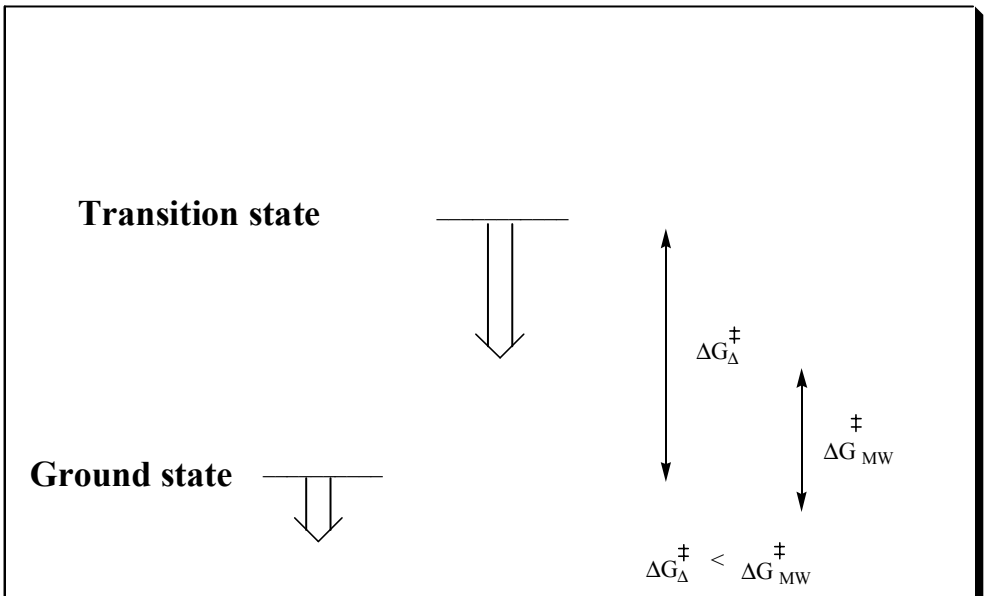
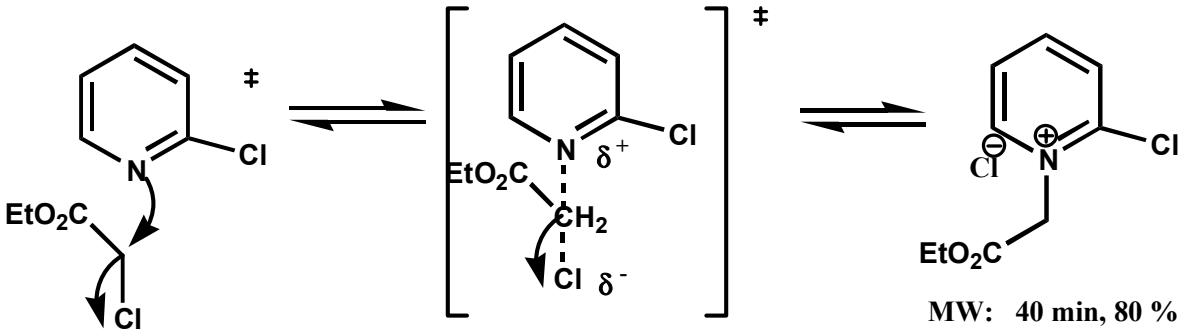


Figure 3: Relative stabilization of more polar transition state when compared to the ground state

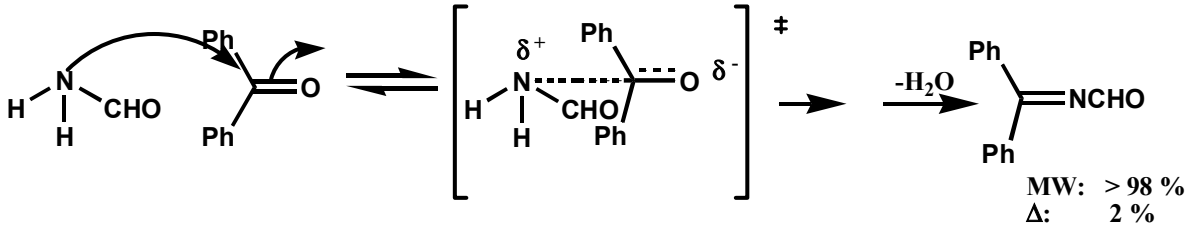
As can be observed in the previous figure, in the transition state for a polar mechanism, when traditional heat is applied, no stabilization of this state is observed judging by the activation energy of this reaction. On the other hand, when microwaves are applied to the same transition state, a decrease in activation energy is observed as compared to the activation energy when classic heat is applied, which favors the formation of the product in a shorter period of time. There are various reactions whose proposed mechanisms are polar and could be studied, most importantly among these are: **bimolecular nucleophilic substitution (S_N2), nucleophilic additions** to compounds that contain carbonyl groups, **imine synthesis, enamine synthesis, carboxylic acid amidations, Michael type additions,** and others [(12)].

Examples of some reactions carried out in microwaves [3]:

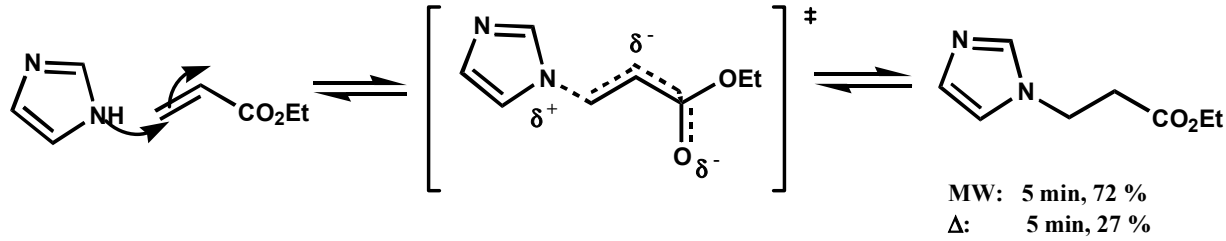
1. S_N2 Reactions:



2. Nucleophilic addition to a carbonyl compound:



3. Michael additions:



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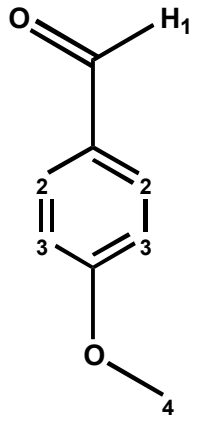
APPENDIX II:

SIMULATION OF ^{1}H-NMR SPECTRUM OF P-METHOXYBENZALDEHYDE

1. Conduct a first order analysis of *p*-methoxybenzaldehyde, through predicting its spectrum or using the experimental data that was obtained from a real ^{1}HNMR spectrum of that compound.

   Example: A first order analysis of *p*-methoxybenzaldehyde.



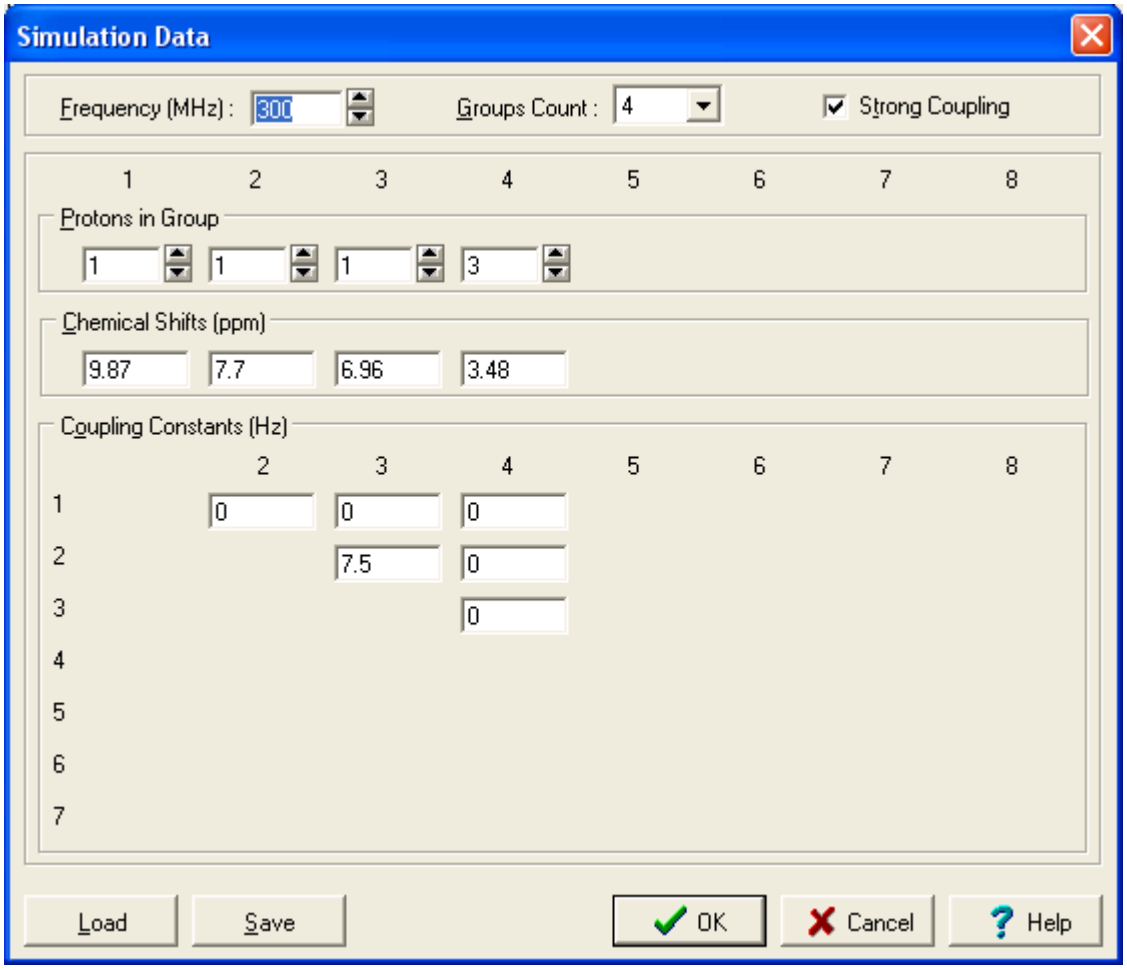
***p*-methoxybenzaldehyde**

Proton group (H)	Spectral data
1	δ 9.87 (s, J = 0 Hz, 1H)
2	δ 7.70 (d, J = 7.50 Hz, 2H)
3	δ 6.96 (d, J = 7.50 Hz, 2H)
4	δ 3.48 (s, J = 0 Hz, 3H)

2. In the **Start** menu,  select the program **HNMR Viewer** to simulate the ^{1}H-NMR of *p*-methoxybenzaldehyde.

3. In the **Tools** menu, select the **simulation** option or click the **HNMR Spectrum Simulation** icon  to enter the coupling constant and chemical shift values for each proton group in the simulation window.

4. When you finish entering all the data in the simulation window, press **Ok**.



5. If you want to expand some signals, click **Zoom In**  . When you press that icon, a magnifying glass will appear in the cursor, which allows you to shade the desired signal doing a left click.

6. If you want to go back to the simulation spectrum window, click **Zoom Out**  .

7. Click the **Shift** icon  to label the chemical shift for all signals in your simulated spectrum.

8. Click the **Integrate Curve** icon  to integrate all signals in your simulated spectrum.

9. Click the **Hz** icon  to change the ppm scale to Hz scale in your simulated spectrum window.

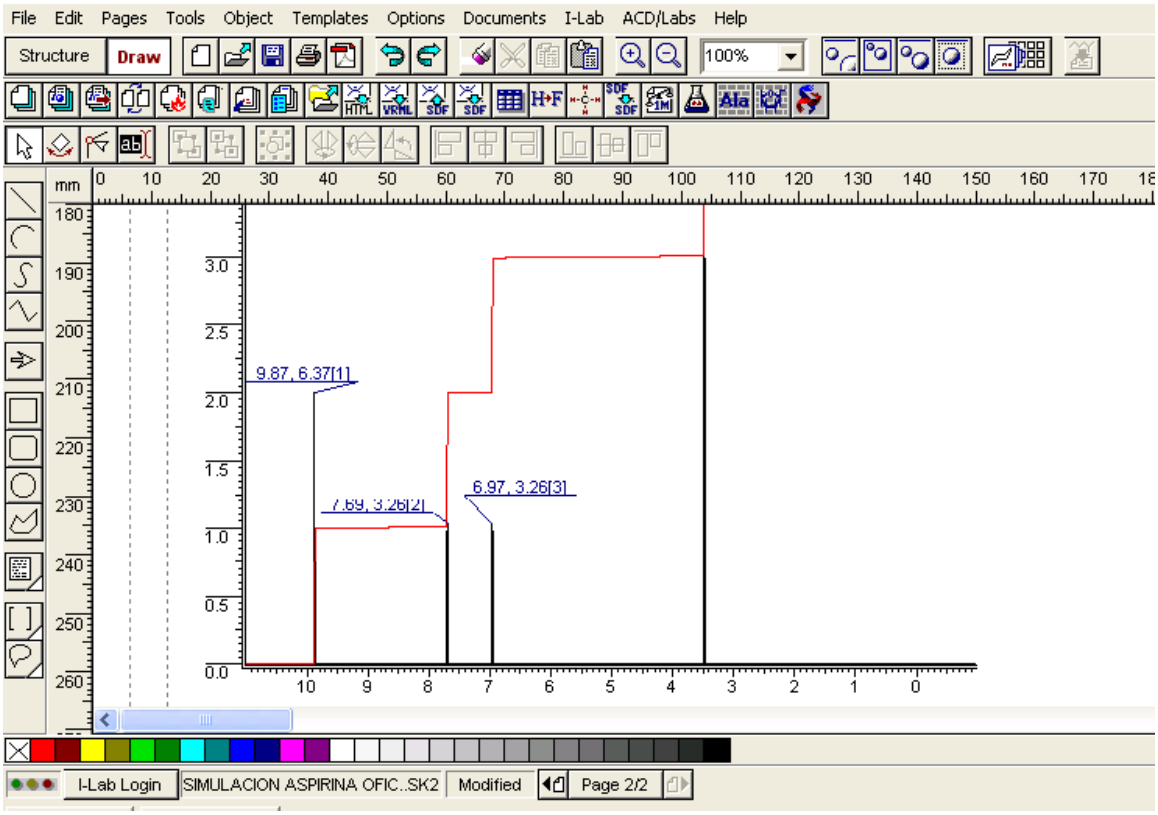
10. Compare your simulated spectrum with an experimental spectrum of *p*-methoxybenzaldehyde or its predicted spectrum. If your simulation doesn't equal to the experimental spectrum or its predicted spectrum in chemical shift and multiplicity terms, then you should go back to the simulation window (click **simulation** icon) and correct the coupling constant, chemical shift and/or proton group values.

11. Click **Show Realistic Lines**  if you want that your signals to have realistic lines. On the other hand, if you want that your signals have a simple lines, click **Show Discrete Lines**  .

12. Click **Show Exchangeable Protons**  to see the exchangeable protons.

13. You can edit your spectrum pressing the **Copy Spectrum to Report Editor** icon  . With this option, you can carry the simulated spectrum to **ChemSketch**. If you press the **Structure** icon 

you can draw the molecule of *p*-methoxybenzaldehyde in the simulated spectrum (Refer to the **ChemSketch v. 8.0** user's guide).



14. Click **Print**  if you want to print your edited spectrum data.

15. If you want to save your simulation data, click the **Save** icon from the **File** menu.