Supporting Information

On the rational design of microwave-actuated organic reactions

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1.1 General procedure for benzylation of *p*-xylene in an oil bath

2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (10.0 mg, 0.0094 mmol) is added to a clean, dry 10-mL test tube equipped with a triangular-shaped stir bar. To the salt is added 2.0 mL of *p*-xylene *via* syringe (2 x 1.0 mL aliquots). A heat gun is used to gently heat the test tube while stirring. Once the solid is dissolved, a 3-drop aliquot is removed (using a 9" disposable borosilicate glass Pasteur pipette) to ensure no reactivity prior to subjection to the reaction conditions. The test tube is then submerged in an oil bath preheated to two degrees (ºC) above the desired reaction temperature—the time of reaction begins at this point. Thee-drop aliquots are removed at the desired intervals according to the prescribed conditions, returning any excess solution to the reaction test tube. Aliquots removed are stored in small glass vials with a phenolic cap. After all aliquots have been collected, NMR samples are prepared in 0.5 mL of DMSO-d_6 and immediately analyzed using a Bruker 400 MHz Ultrashield NMR Spectrometer and processed with Bruker Topspin software.

1.2 General procedure for the benzylation of *p*-xylene in a microwave reactor

2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (10.0 mg, 0.0094 mmol) is added to a clean, dry, quartz 10-mL microwave reaction tube equipped with a triangular-shaped stir bar. To the salt is added 2.0 mL of *p*-xylene *via* syringe (2 x 1.0 mL aliquots). A heat gun is used to gently heat the tube while stirring. Once the solid is dissolved, a three-drop aliquot is removed (using a 9" disposable borosilicate glass Pasteur pipette) to ensure no reactivity prior to subjection to the reaction conditions. The reaction tube is then placed into a CEM Discover Benchmate microwave reactor. The prescribed reaction conditions are programmed into the instrument using Synergy software as an open-vessel reaction allowing for timed-aliquots to be removed without interruption of the experiment. The reaction is started and aliquots are removed at

desired intervals by inserting a glass pipette momentarily to remove the correct approximate amount needed. Excess solution is quickly transferred back in to the reaction vessel. Aliquots removed are stored in small glass vials with a phenolic cap. After all aliquots are collected, NMR samples are prepared in 0.5 mL of DMSO-d_6 and immediately analyzed using a Bruker 400 MHz Ultrashield NMR Spectrometer and processed with Bruker Topspin software.

1.3a. General procedure for the benzylation of toluene in refluxing toluene in an oil bath

2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (150.0 mg, 0.1410 mmol) is added to a clean, dry, quartz roundbottom flask with an elongated neck equipped with a stir bar. To the salt is added 30.0 mL of dry toluene *via* a graduated 60.0 mL syringe. The flask is fitted with a condenser, followed by submersion in to a preheated oil bath (125ºC or 145ºC). Timing of the experiment begins when the solvent begins to reflux. After reacting for the prescribed interval, the roundbottom flask is removed from the oil bath immediately, followed by removal of a three-drop aliquot (using a 9" disposable borosilicate glass Pasteur pipette) as soon as the reflux line fell below the reflux condenser joint. NMR samples are prepared in 0.5 mL of DMSO-d_6 and immediately analyzed on a Bruker 400 MHz Ultrashield NMR spectrometer and processed with Bruker Topspin software.

1.3b. General procedure for the benzylation of toluene in refluxing toluene in a microwave reactor

2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (150.0 mg, 0.1410 mmol) is added to a clean, dry, quartz roundbottom flask with an elongated neck equipped with a stir bar. To the salt is added 30.0 mL of dry toluene *via* a graduated 60.0 mL syringe. The flask is warmed gently with a heat gun while stirring to dissolve the solid. Once the solid is dissolved, a three-drop aliquot is removed (using a 9"

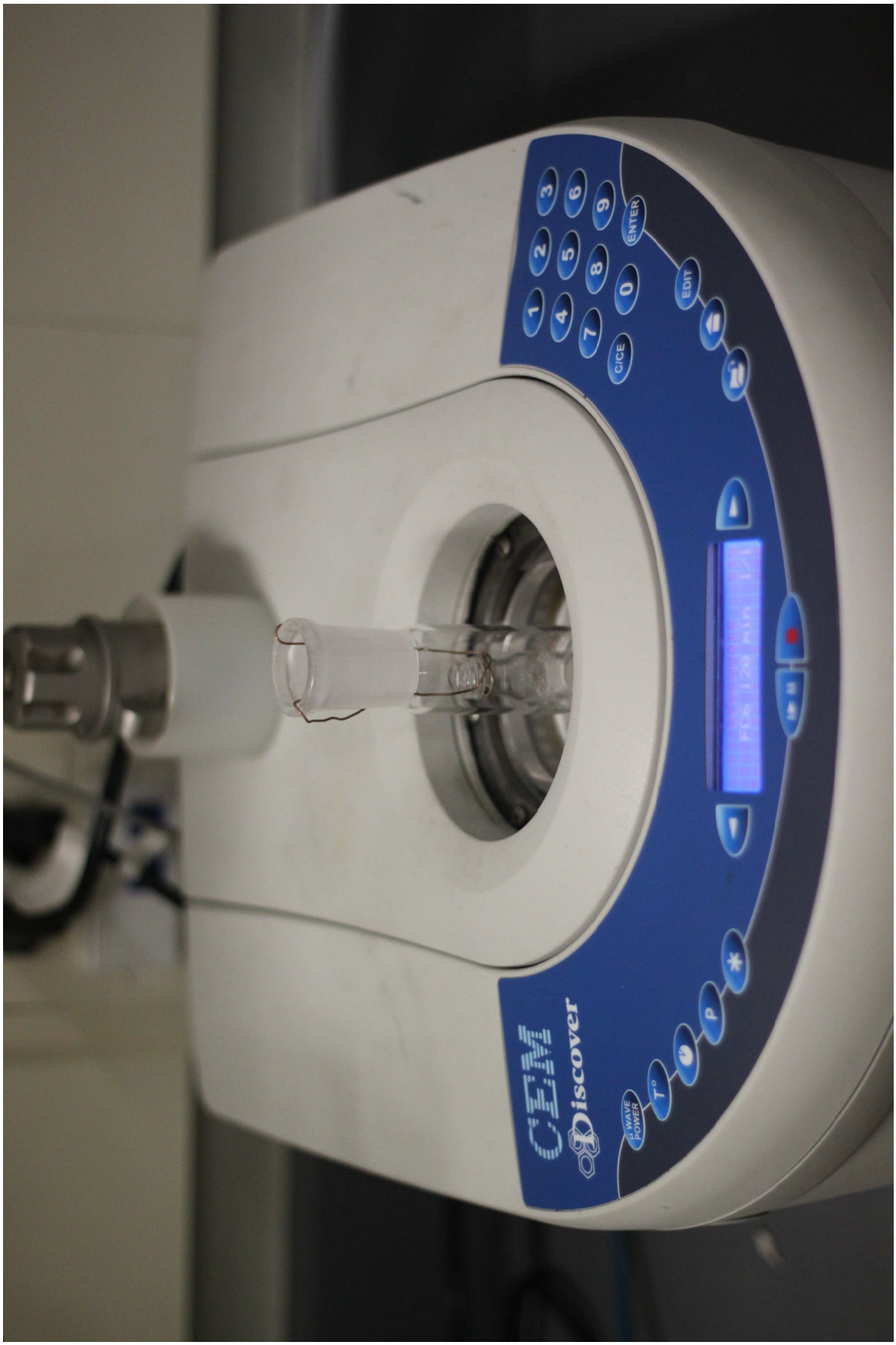
disposable borosilicate glass Pasteur pipette) to ensure no reactivity prior to subjection to the reaction conditions. The quartz roundbottom flask is then placed in the microwave reactor, followed by placement of the open vessel microwave attenuator. A condenser is then fitted with a condenser, followed by subjection to microwave irradiation (300W). Timing of the experiment begins when the solvent begins to reflux (visible from the top of the instrument though the open-vessel attenuator). After reacting for the prescribed interval, the microwave irradiation is ceased. A three-drop aliquot is removed (using a 9" disposable borosilicate glass Pasteur pipette) as soon as the reflux line falls below the reflux condenser joint. NMR samples are prepared in 0.5 mL of DMSO-d_6 and immediately analyzed on a Bruker 400 MHz Ultrashield NMR spectrometer and processed using Bruker Topspin software.

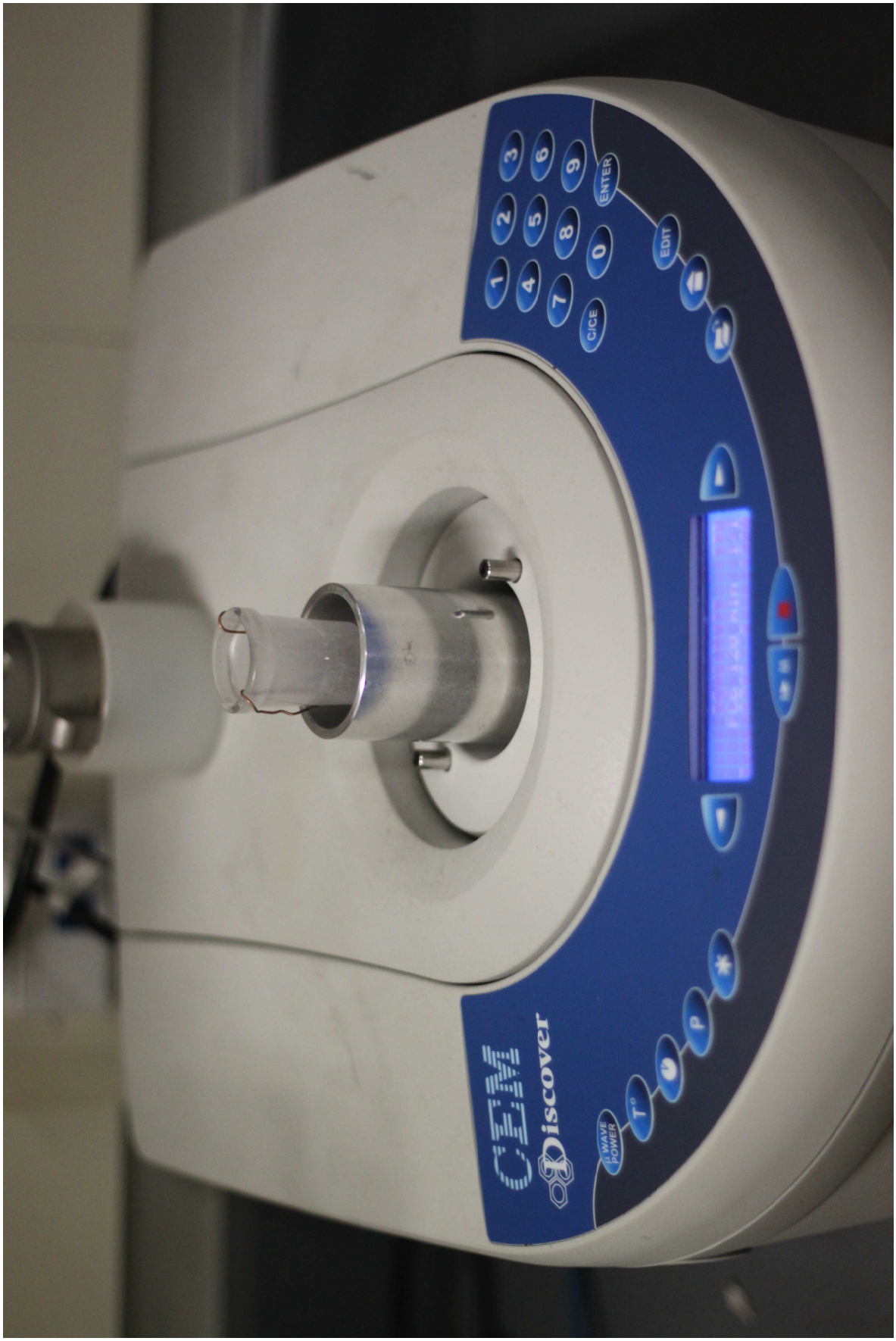
1.4a General Procedure for the benzylation of *p*-xylene in a propylene glycol bath within a microwave reactor

2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (10.0 mg, 0.0094 mmol) is added to a clean, dry, quartz microwave reaction tube equipped with an oval-shaped stir bar. To the salt is added 2.0 mL of *p*-xylene *via* syringe (2 x 1.0 mL aliquots). A heat gun is used to gently heat the tube while stirring. Once the solid is dissolved, a three-drop aliquot is removed (using a 9" disposable borosilicate glass Pasteur pipette) to ensure no reactivity prior to subjection to the reaction conditions. The tube is suspended in a custom-made quartz roundbottom flask filled with propylene glycol and equipped with a stir bar using copper wire (see section 1.4b [pp. S7-S9]). The roundbottom flask is then placed into a CEM Discover Benchmate microwave reactor. The prescribed reaction conditions are programmed in to the instrument using Synergy software as an open-vessel reaction allowing for timed-aliquots to be removed without interruption of the experiment. The reaction is started and aliquots were removed at desired intervals by

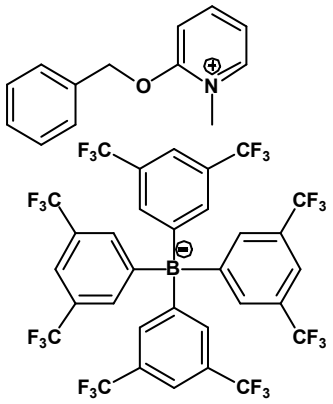
inserting a glass pipette momentarily to remove the correct approximate amount needed. Excess solution is quickly transferred back in to the reaction vessel. Aliquots removed are stored in small glass vials with a phenolic cap. After all aliquots are collected, NMR samples are prepared in 0.5 mL of DMSO-d_6 and immediately analyzed using a Bruker 400 MHz Ultrashield NMR Spectrometer and processed with Bruker Topspin software.

1.4b Photographs illustrating the use of custom-made glassware as a propylene glycol bath in a microwave reactor





1.5 Procedure for the synthesis of 2-benzyloxy-1-methylpyridinium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (4)



Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF, 2.29g, 2.58 mmol) was added to a clean, dry 100-mL roundbottom flask equipped with a stir bar and flushed with nitrogen. Separately, 2-benzyloxy-1-methylpyridinium triflate (BnOPT, 0.900g, 2.58 mmol) was added to a clean, dry 250-mL roundbottom flask equipped with a stir bar and flushed with nitrogen. Tetrahydrofuran was added *via* syringe to each flask (~50mL per flask). Each flask was heated in an oil bath set at 40ºC and stirred. THF was gradually added *via* syringe until no solid particles remained in either flask. Once dissolved, both flasks were opened, and the NaBArF-THF solution was quickly poured in to the BnOPT-THF solution, using a magnet to prevent transfer of the stir bar. The solution was again capped and allowed to stir under nitrogen over night.

After stirring, the THF was removed under reduced pressure to yield a clear yellow oil. α,α,α-Trifluorotoluene ($PhCF_3$) was added to make a clear, yellow solution with a precipitate. The precipitate was removed by gravity filtration and recrystallization from the $PhCF_3$ solution was attempted by adding hexane. Too much $PhCF_3$ was present to allow for an efficient recrystallization, so the solution was concentrated to a smaller volume. Hexane was added until the solution became cloudy and was then placed on ice. The resultant

precipitate was filtered off as a yellow solid. A second recrystallization from $PhCF_3$/hexanes yielded a fine, shiny-white solid in a 63% yield (~1.7g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.04 (s, 3H), 5.66 (s, 2H), 7.47-7.53 (m, 3H), 7.60-7.62 (m, 4H), 7.65 (broad s, 8H), 7.76 (broad s, 4H), 7.85-7.87 (d, 1H), 8.53-8.58 (dt, 1H), 8.72-8.74 (dd, 1H) ppm. ^{19}F NMR (400 MHz, DMSO-d_6): δ -64.18 (s, 24F) ppm.

1.6. Procedure for the calibration of the IR temperature probe for microwave reaction vessels in the CEM Discover Benchmate microwave reactor

The desired reaction vessel to be calibrated is filled with propylene glycol and equipped with a stir bar. The volume used is matched to the volume that would be used for solvents during actual experiments (vials- 2.0 mL, quartz roundbottom flask- 30.0 mL). The sample is heated using microwave irradiation to approximately 120 ºC. After reaching 120 ºC, microwave irradiation is halted and a thermocouple probe is inserted[1] in to the propylene glycol. F*or vials*—As the temperature gradually cools to 70 ºC[2] according to the thermocouple probe, the instrument is calibrated to read the same temperature. *For the roundbottom flask*—As the temperature gradually cools to 100 ºC according to the thermocouple probe, the instrument is calibrated to read the same temperature. The reaction vessels are calibrated at temperatures close to the temperatures used during actual experiments. Using elevated temperatures should help to increase the accuracy at elevated temperatures. Once calibrated, the accuracy of the IR probe is tested by heating to 120 ºC using microwave irradiation. Once at 120 ºC, microwave irradiation is halted and the thermocouple probe inserted. The thermocouple probe confirms accurate

[1] As the thermocouple probe is not intended for use with microwaves, no thermocouple probe readings were made while the vial/flask was under microwave irradiation

[2] Ideally the vial would have been calibrated at 100 ºC. As the temperature decreased too rapidly at 100 ºC, accurate calibrations could not be made. Once calibrated at 70 ºC, vials were heated to 120 ºC for calibration accuracy testing. No temperature discrepancies were noted between the thermocouple probe and the IR probe as the vial cooled from 120 ºC to room temperature.

temperature measurement at 120 ºC down to room temperature as the propylene glycol gradually cools. No temperature discrepancies are observed at any point during the cooling process.

A note on the limitations of external IR sensors:

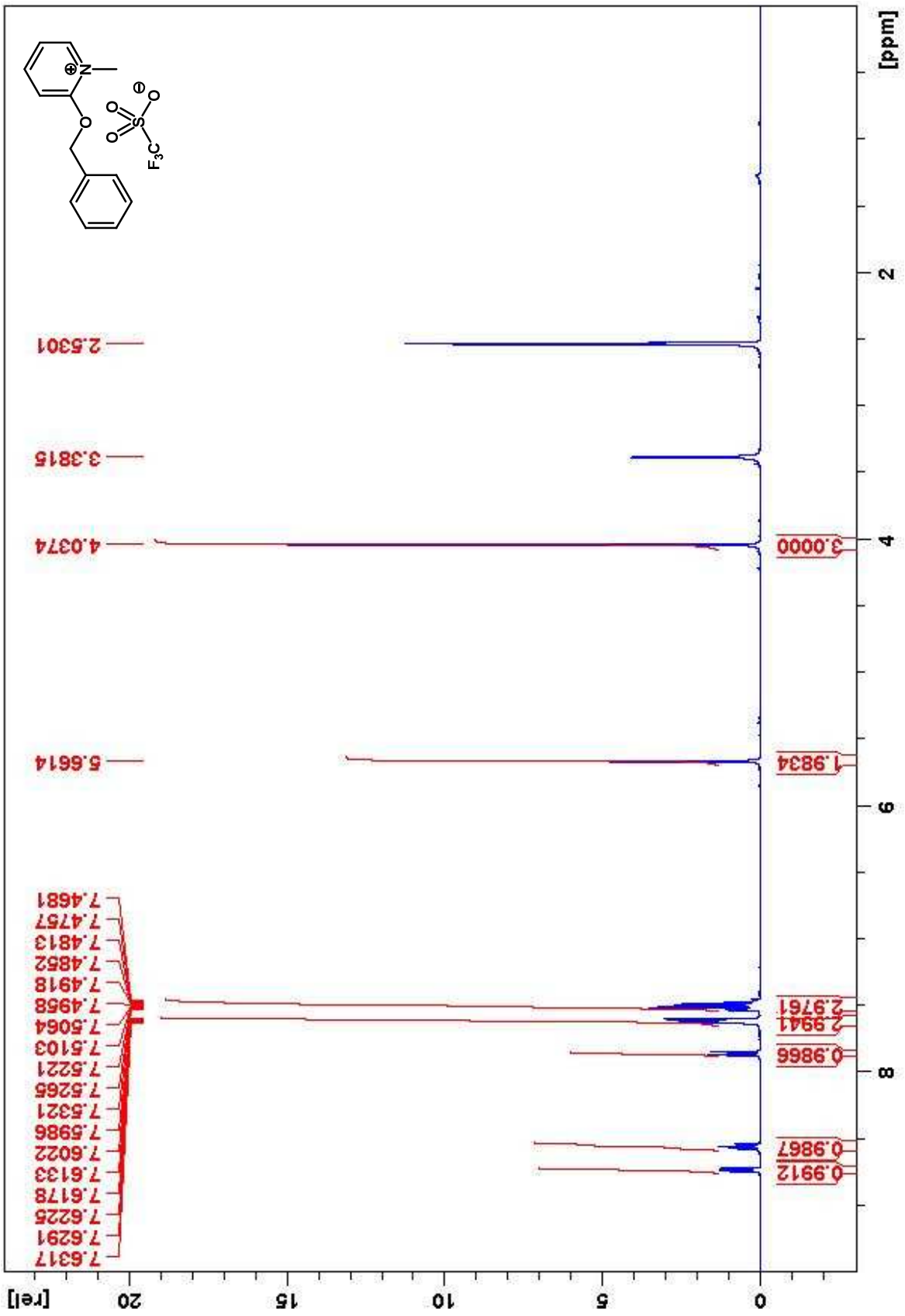
The sensor is basically measuring the temperature of the flask, calibrated to match the solution temperature. However, if the solution heats (or cools) faster than the flask, then the external sensor will not provide an accurate measure. This is especially problematic when heating a highly polar solvent (e.g., ionic liquid) using the constant temperature control setting on the MW reactor. High power is automatically applied to heat the system and then power is reduced as the flask temperature approaches the prescribed value, but the rapidly heated solution may have already exceeded the desired temperature.

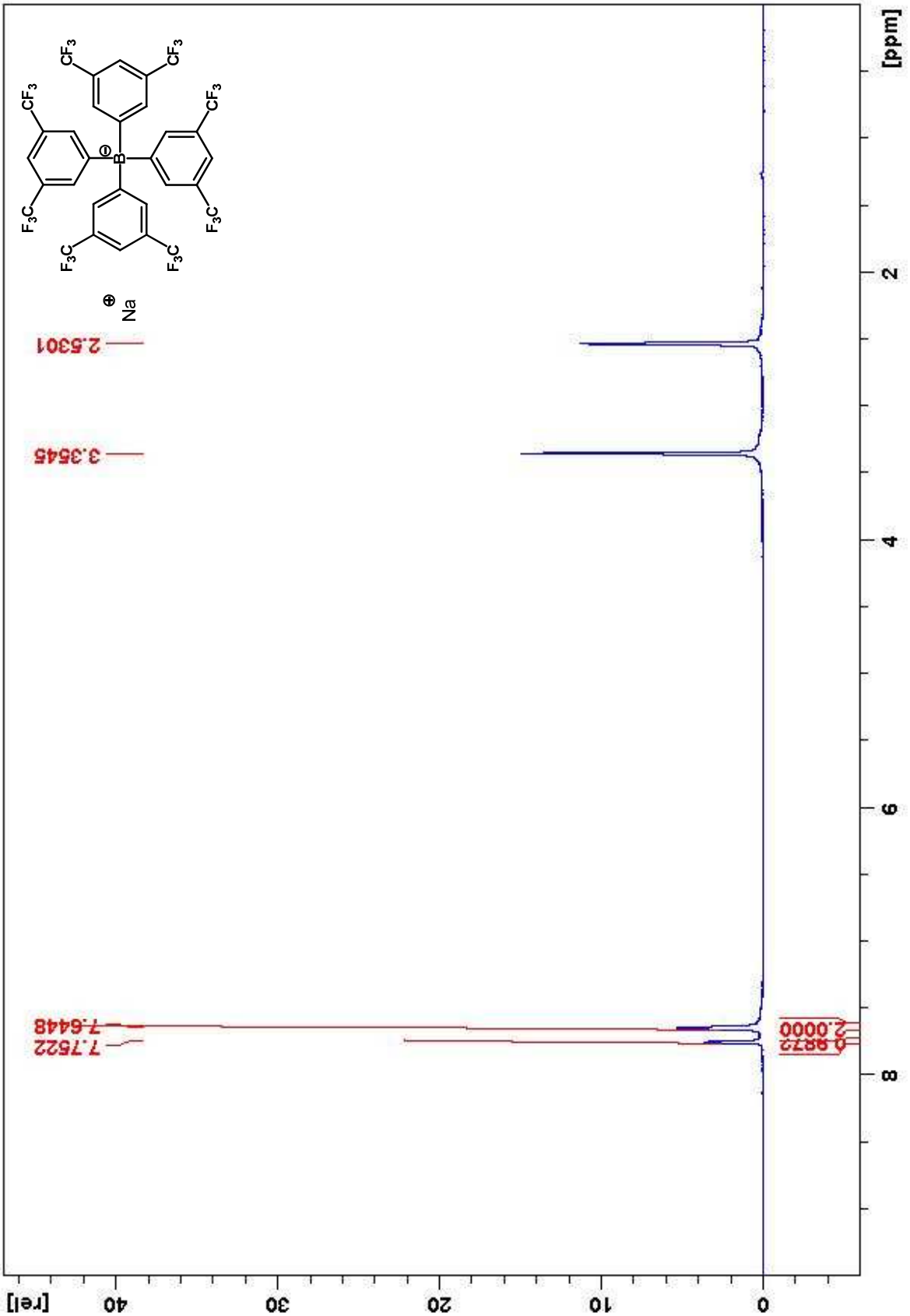
How this limitation affects measurements in our specific system:

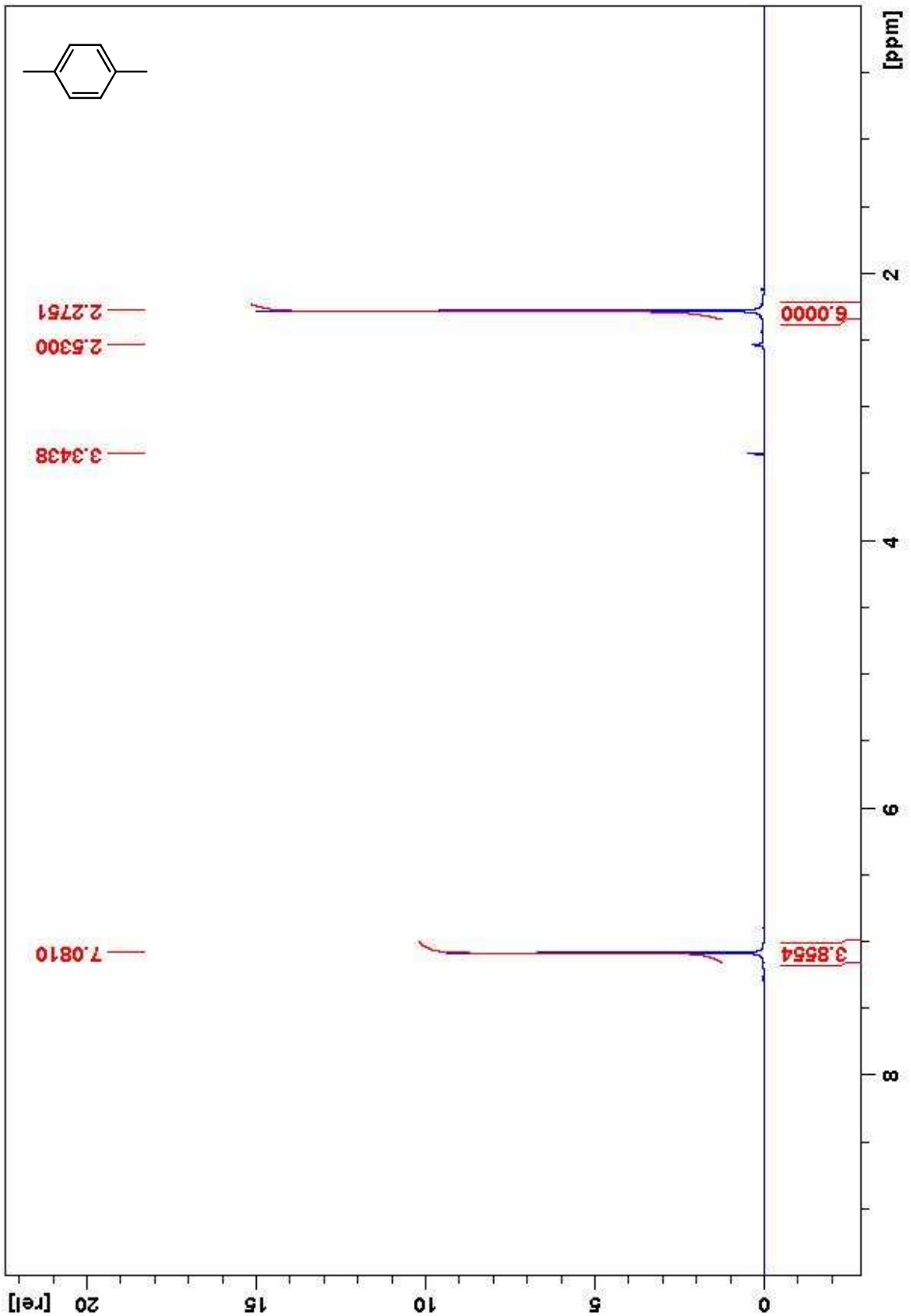
Our system is different (cf Scheme 2 and Figure 2, constant power experiments). There is no risk of "overshooting" the prescribed temperature when none is prescribed. We irradiated a relatively non-polar (poorly MW-absorbing) solution at constant power to reach the maximum possible temperature. The temperature of the system increased and fluctuated more slowly (over minutes, not seconds) than what is observed from polar solutions, and constant power was applied regardless. The duration of the experiment (30 min) provided ample time for the system (solution and flask) to equilibrate. With proper calibration as described above, the external sensor can record the solution temperature with good accuracy and precision.

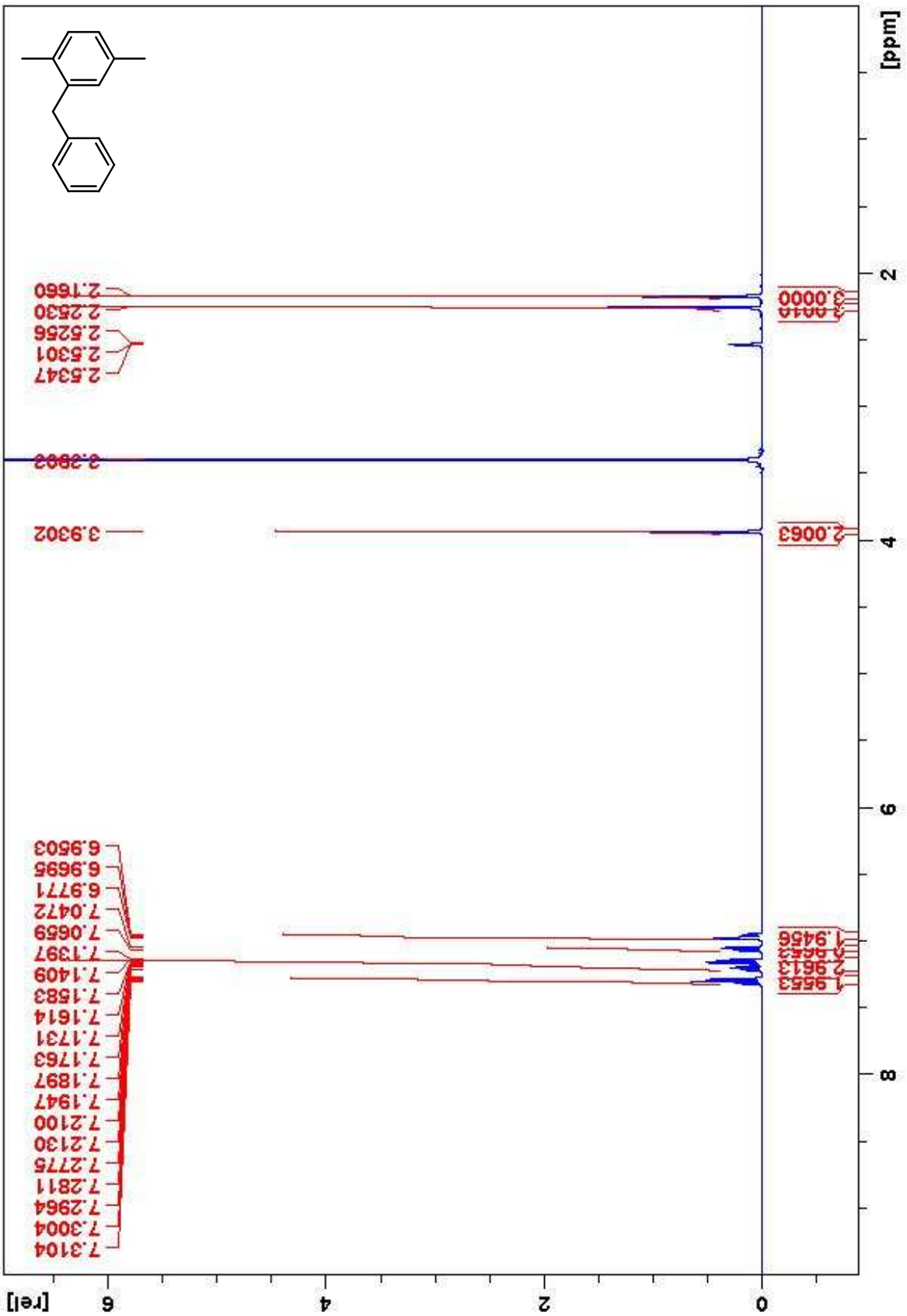
For the experiments described in Scheme 2 and Figure 2, the applied MW power was not sufficient to heat the system to 100 °C within the allotted time. At 200 W of power, the maximum recorded temperature over the 30-min experiment was 95 °C (ave temp = 85 °C). At 300 W, the max temp after 30 min was 97 °C (ave = 86 °C; plots of recorded temp vs. time can be found on pages S26 and S28.) Given careful calibration as described above, there is no good reason to suspect that the bulk solution temperature reached or exceeded 100 °C, the temp to which the corresponding oil bath experiments were subjected for the duration.

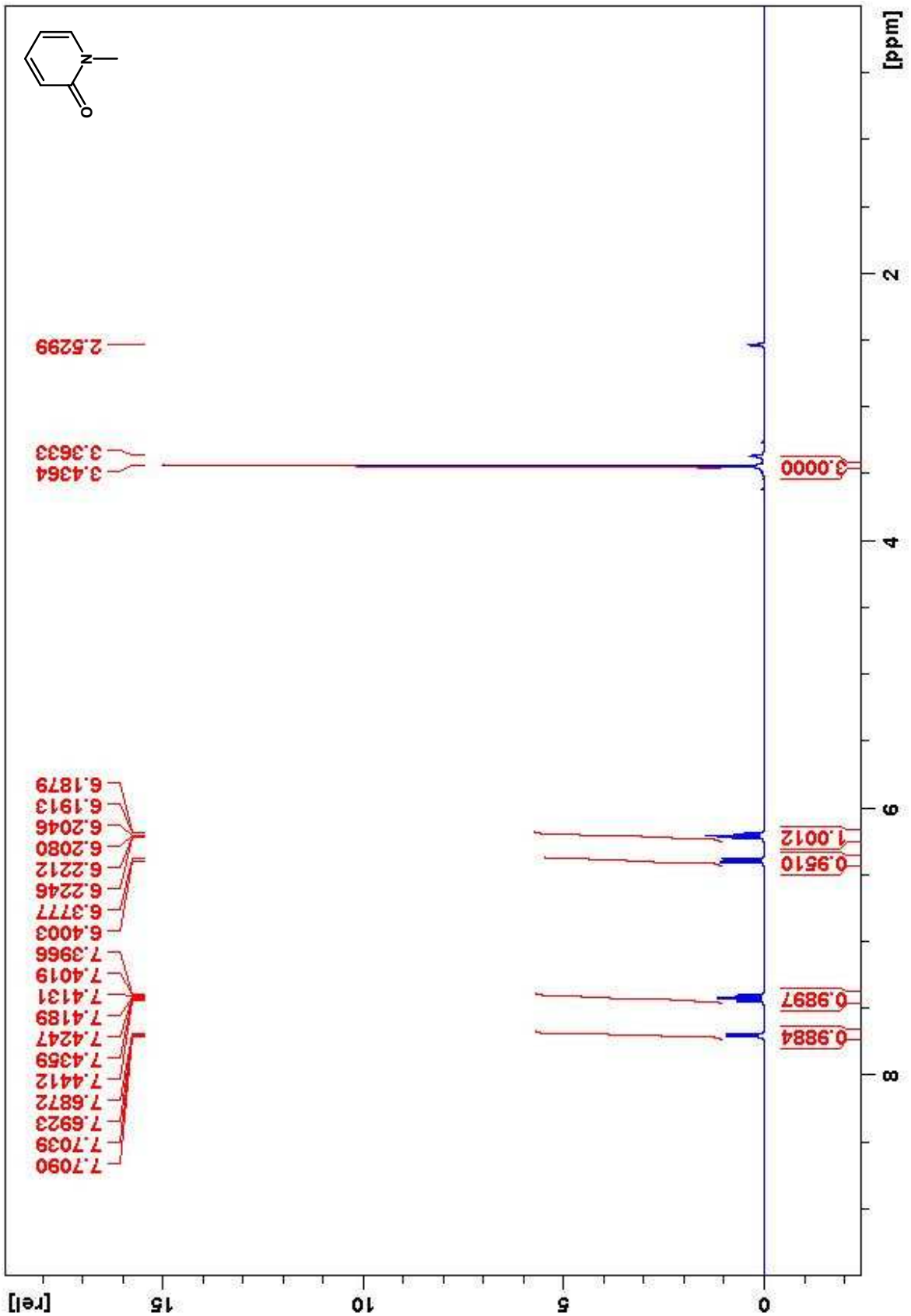
2.1 ^{1}H NMR Spectra for known compounds in DMSO-d_6



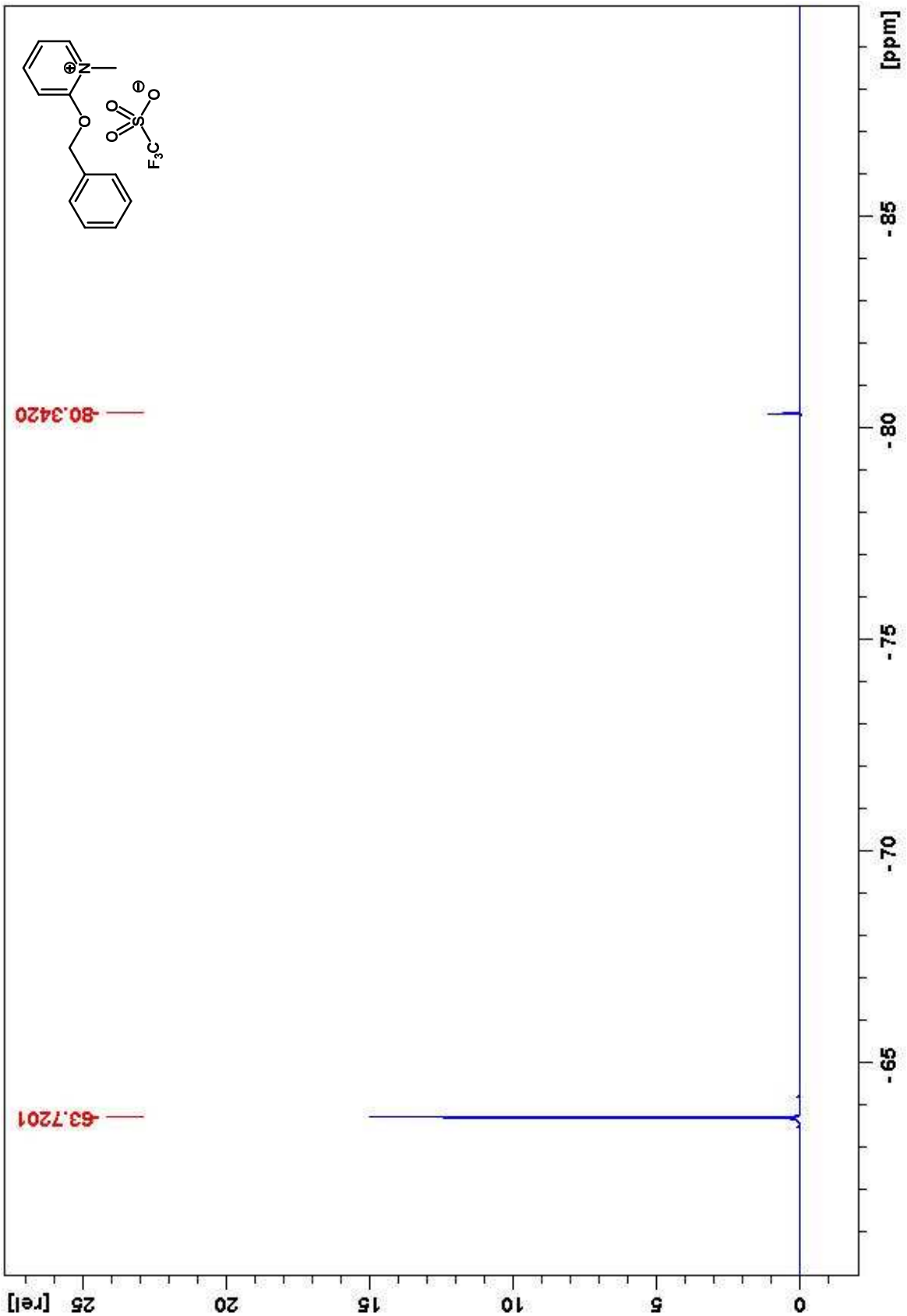


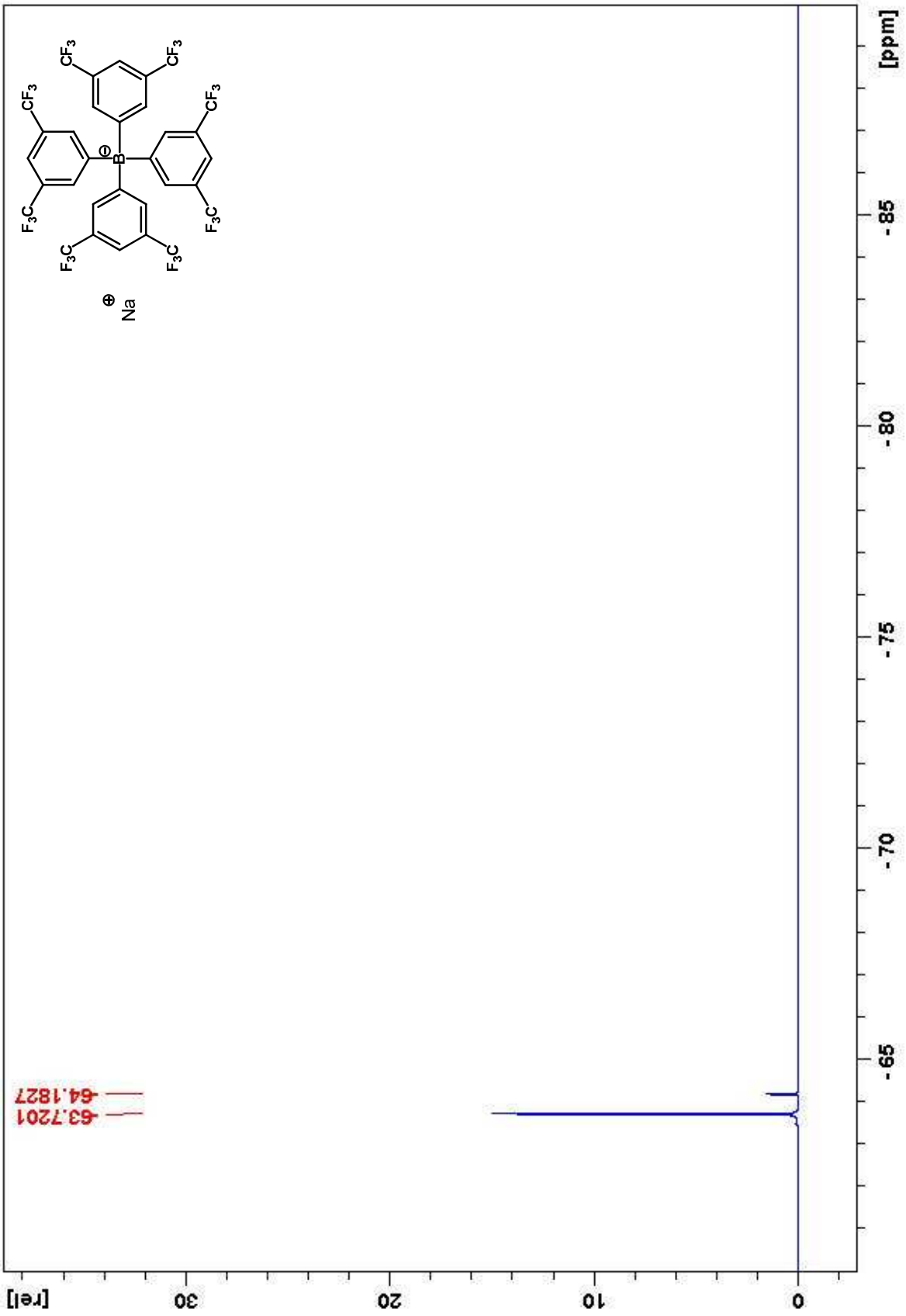




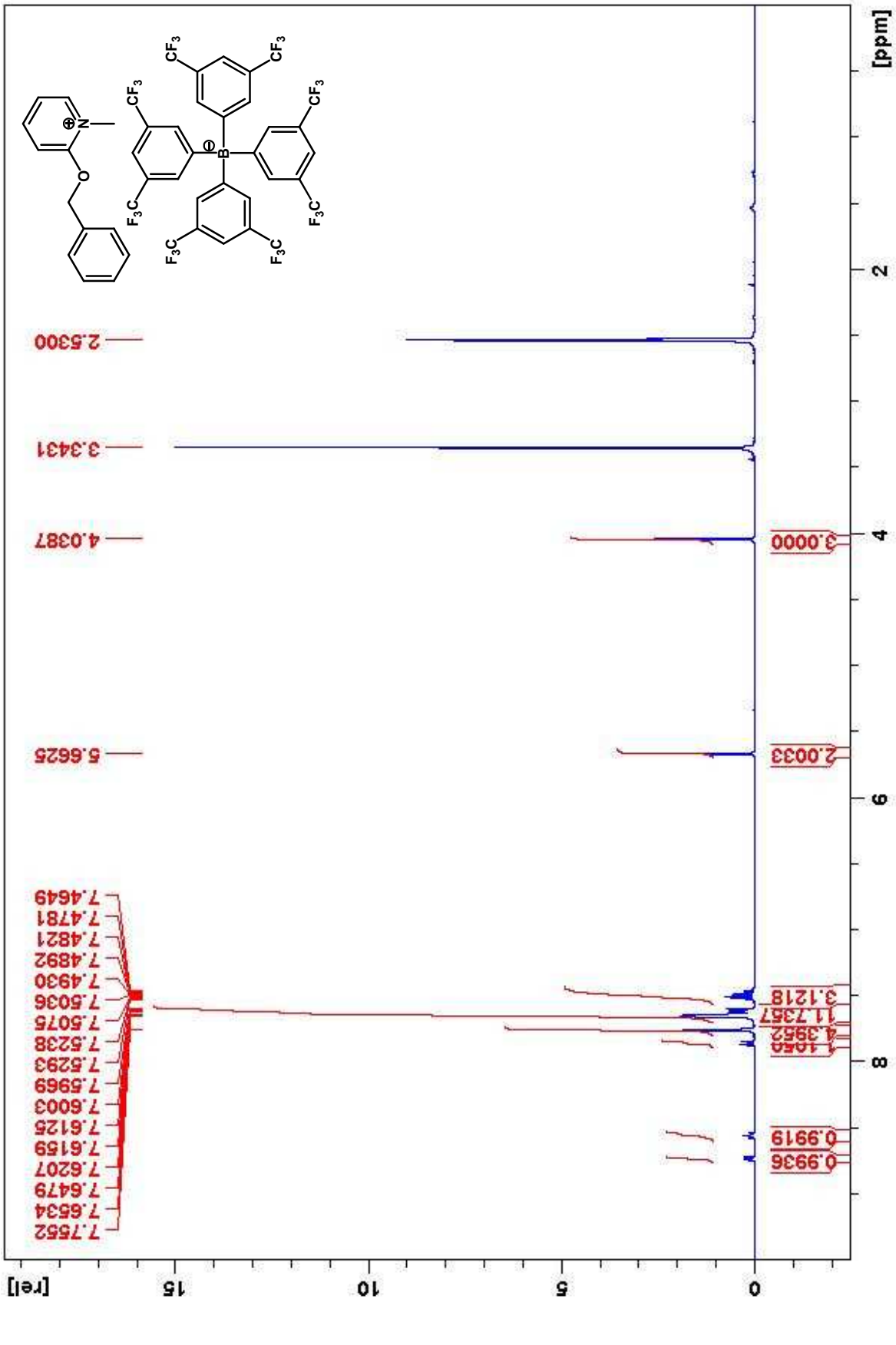


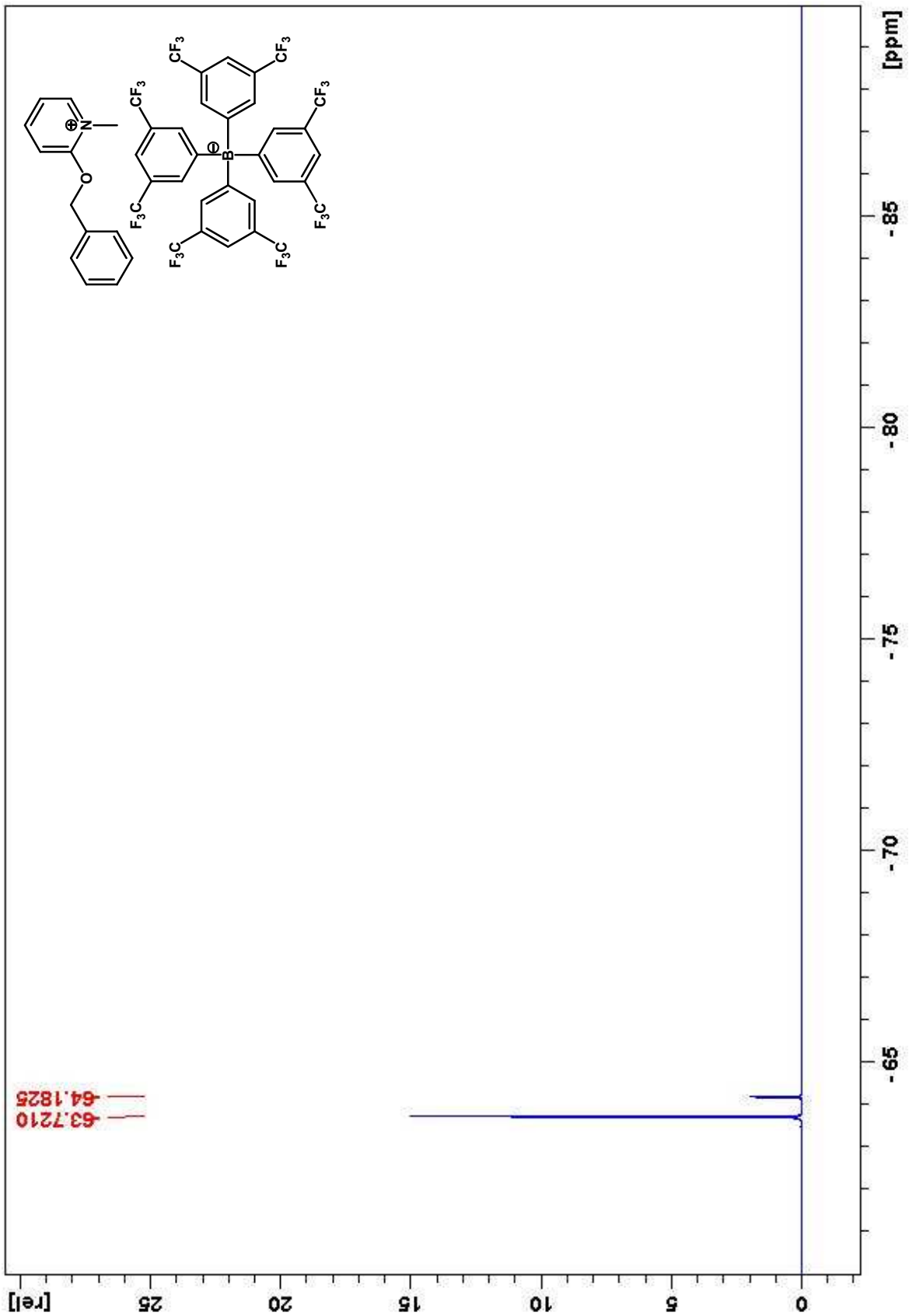
2.2 ^{19}F NMR Spectra for known compounds in DMSO-d$_6$



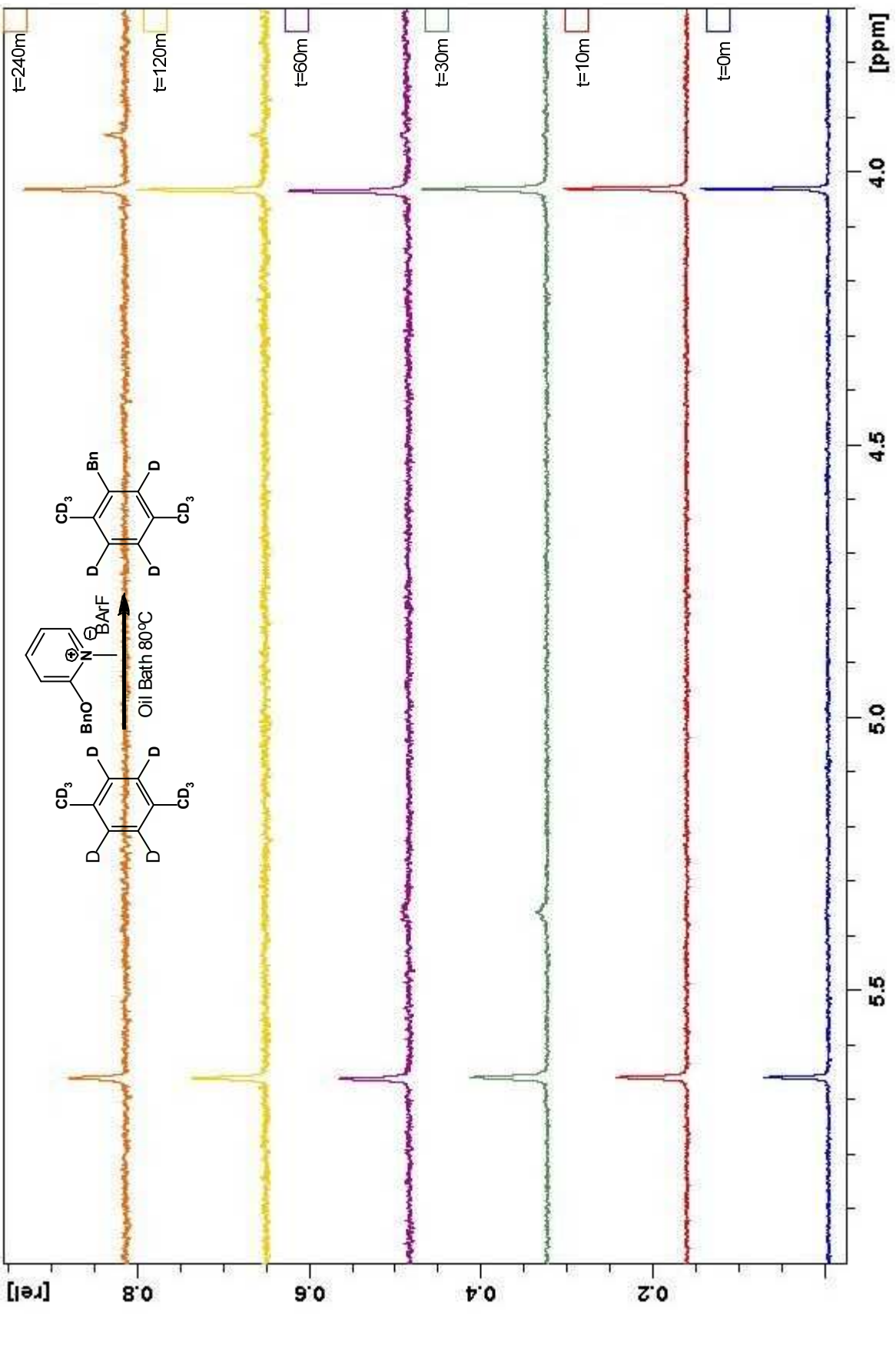


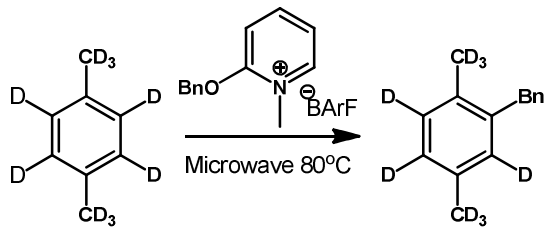
2.3 ^{1}H and ^{19}F NMR Spectra for 2-benzyloxy-1-methylpyridinium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate in DMSO-d_6 (4)

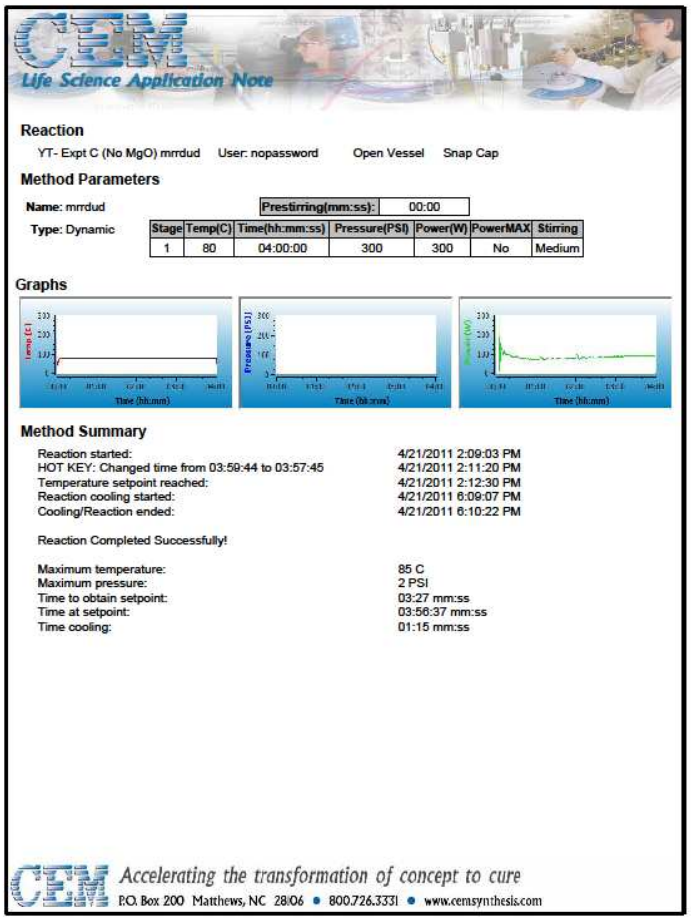




3.1 Summary of all reactions with condensed ^{1}H NMR Data (see sections 3.2-3.10 (pp. S35-S83) for individual spectra and integrations)







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Reaction

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Method Parameters

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Graphs

Method Summary

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Maximum pressure:	2 PSI
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Time at setpoint:	03:56:37 mm:ss
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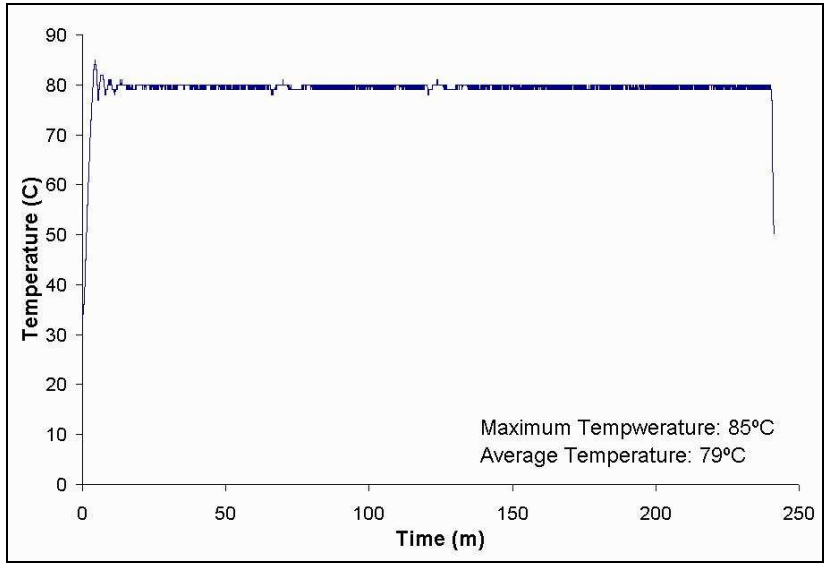

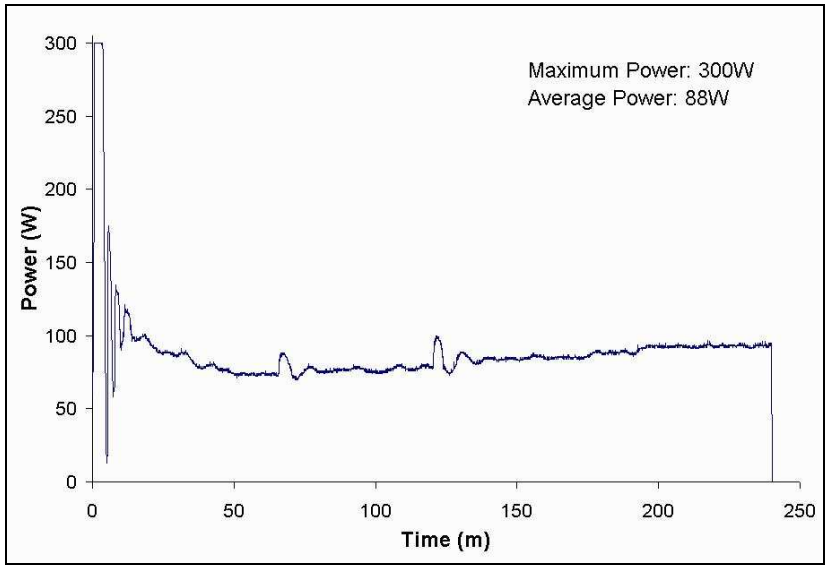

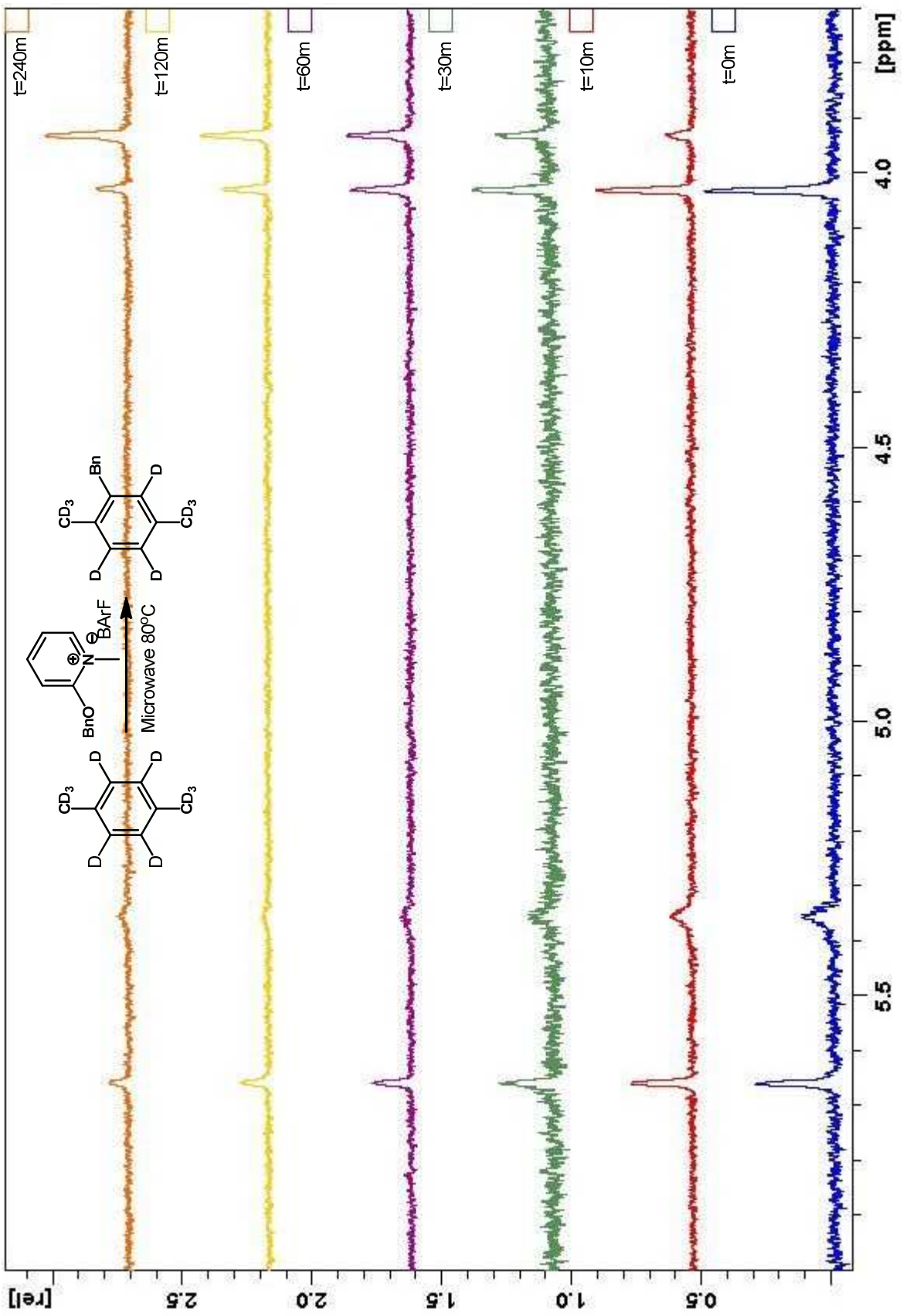

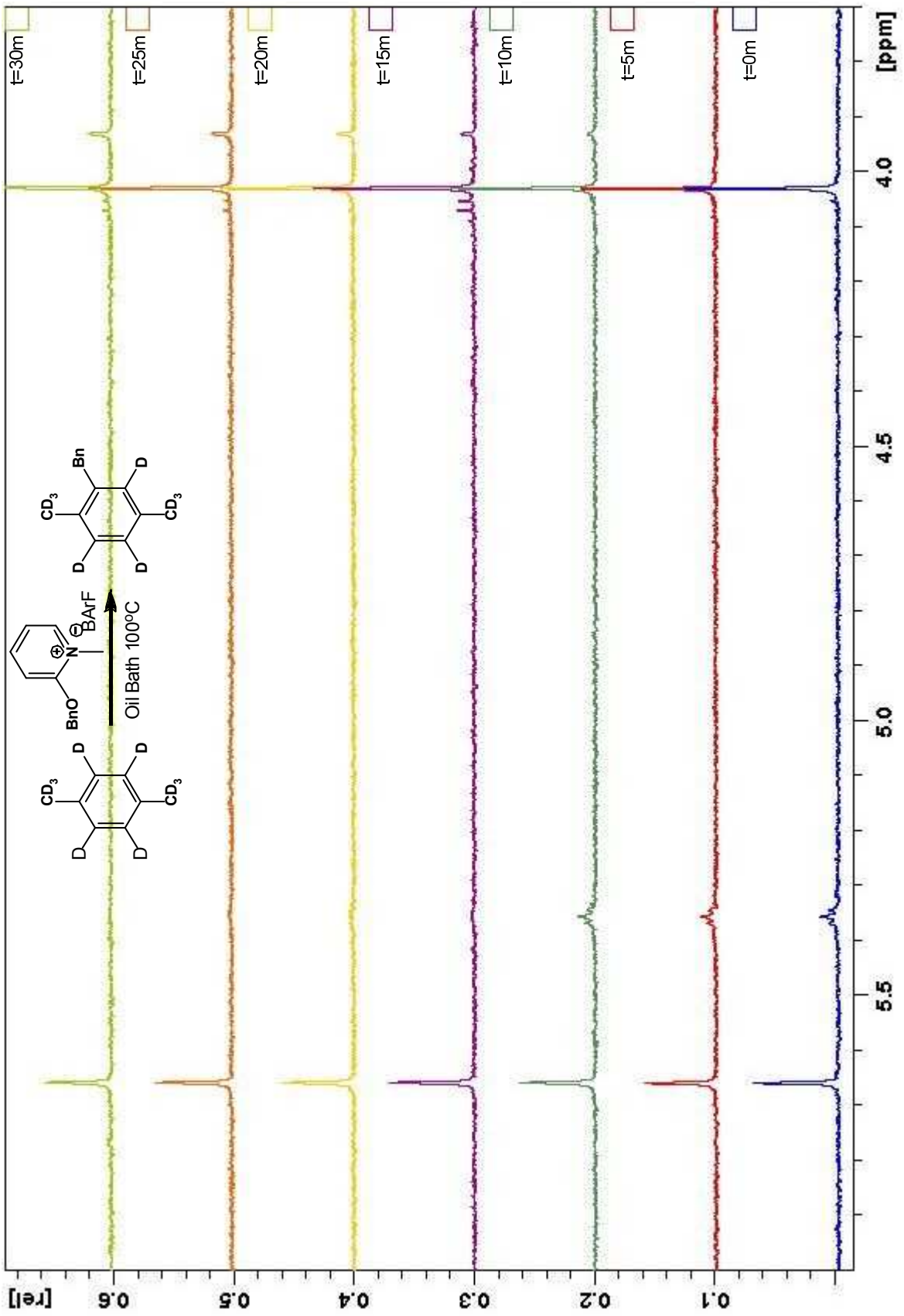

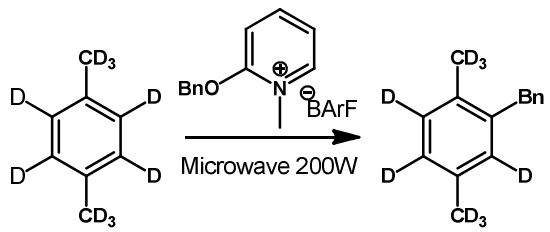

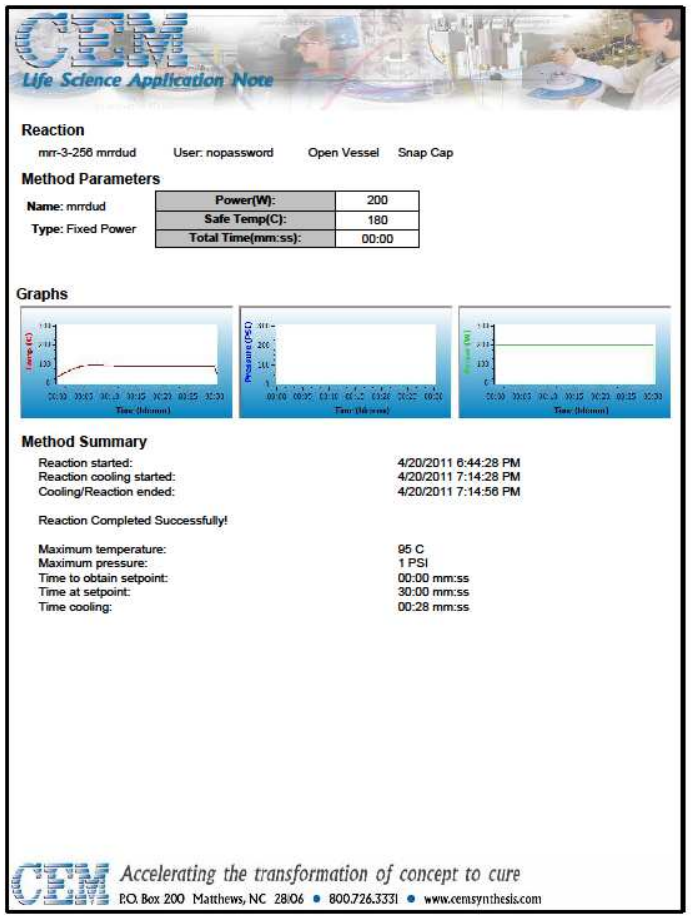

Life Science Application Note

Reaction

mrr-3-256 mrrdud User: nopassword Open Vessel Snap Cap

Method Parameters

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Graphs

Method Summary

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Cooling/Reaction ended:	4/20/2011 7:14:56 PM

Reaction Completed Successfully!

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Time at setpoint:	30:00 mm:ss
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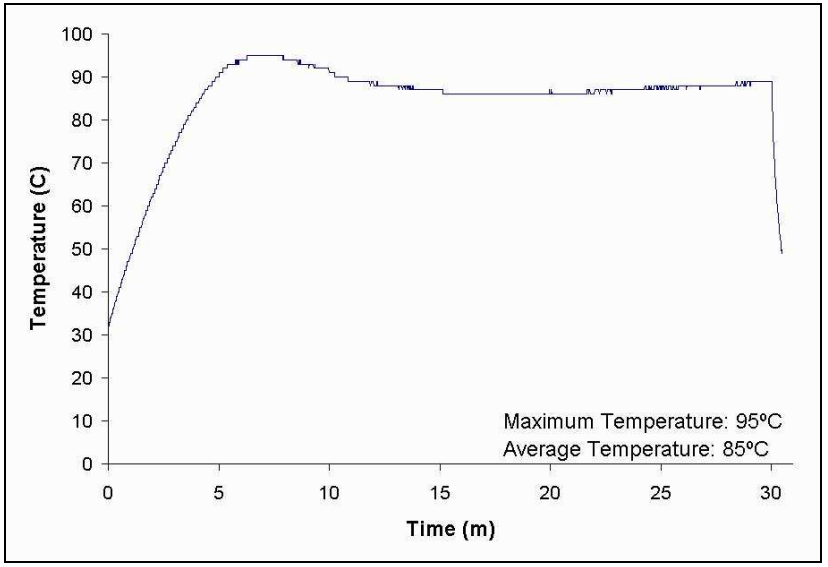

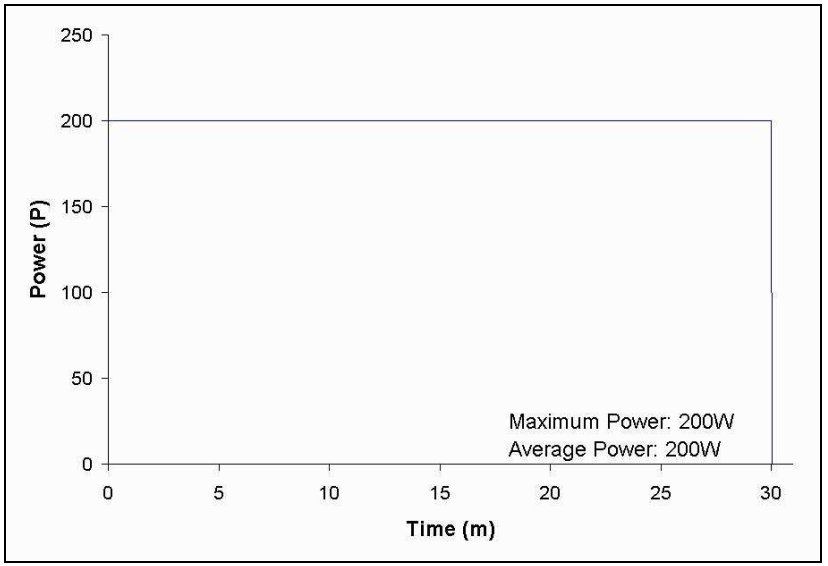

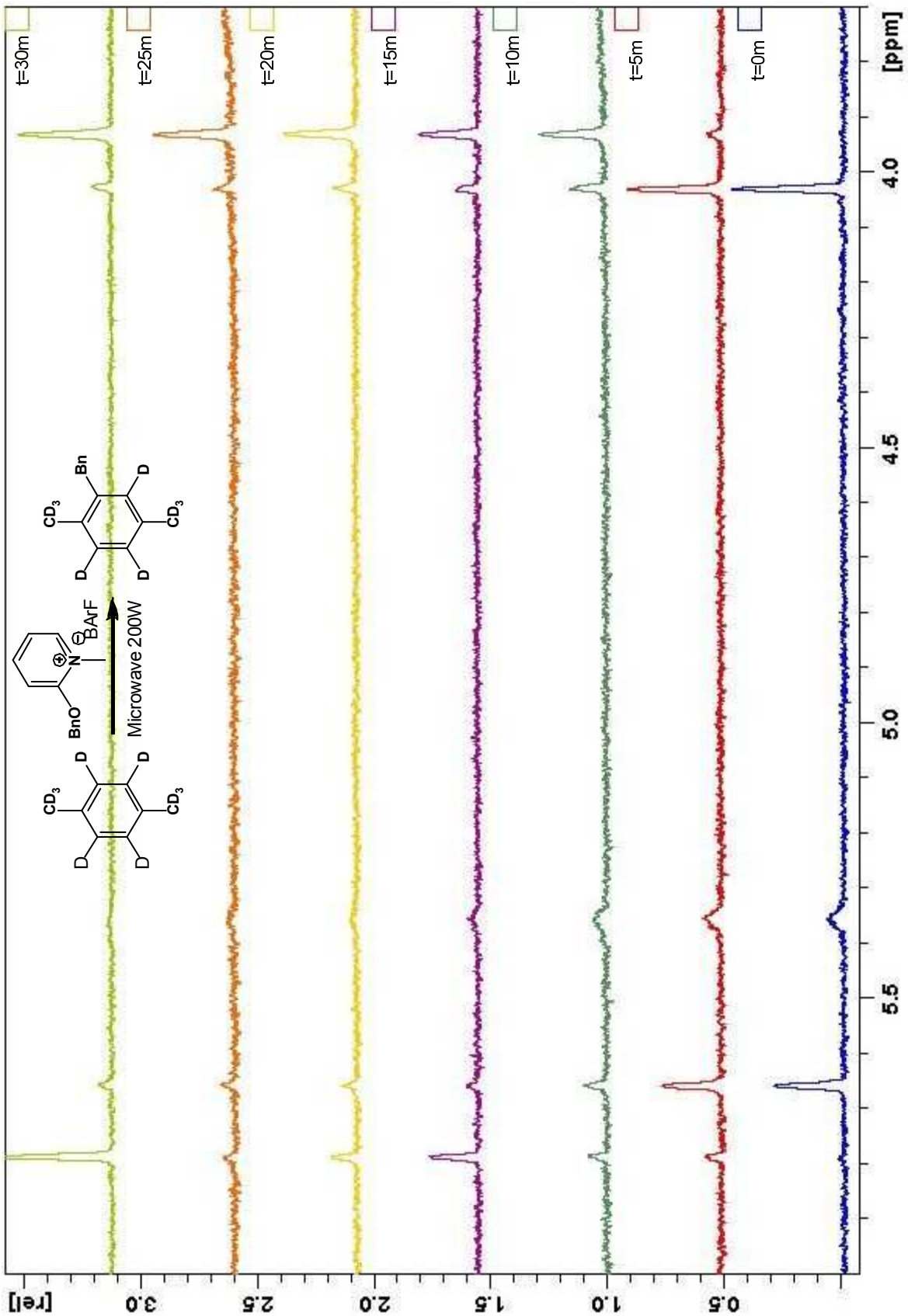

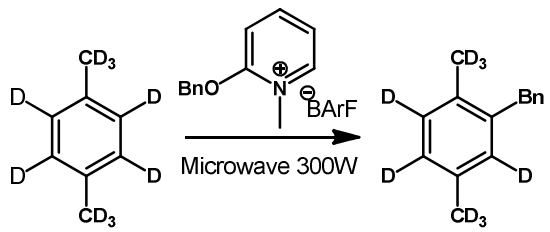

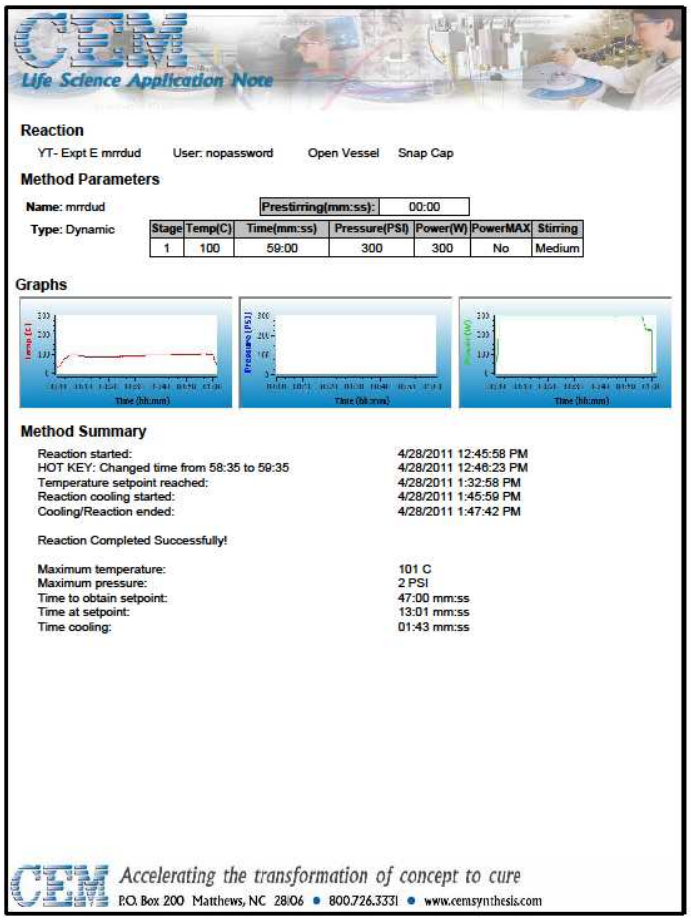

Life Science Application Note

Reaction

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Graphs

Method Summary

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Cooling/Reaction ended:	4/28/2011 1:47:42 PM

Reaction Completed Successfully!

Maximum temperature:	101 C
Maximum pressure:	2 PSI
Time to obtain setpoint:	47:00 mm:ss
Time at setpoint:	13:01 mm:ss
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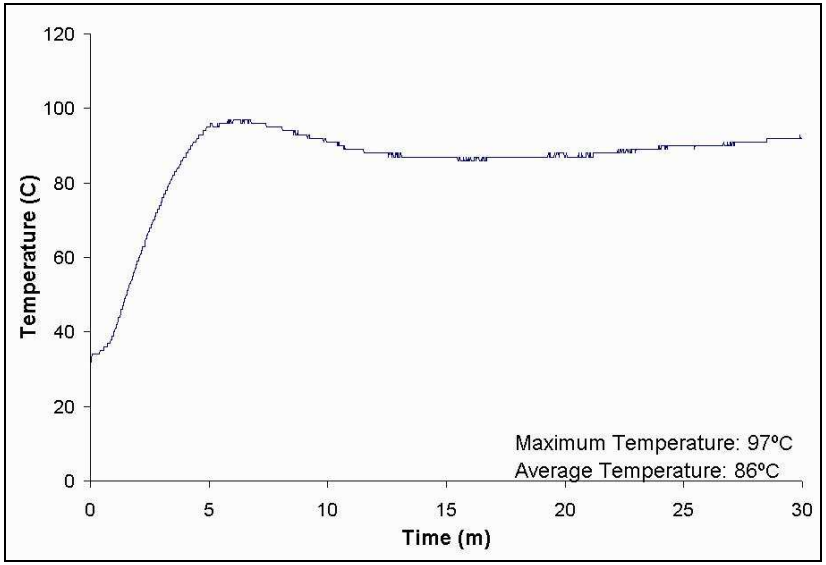

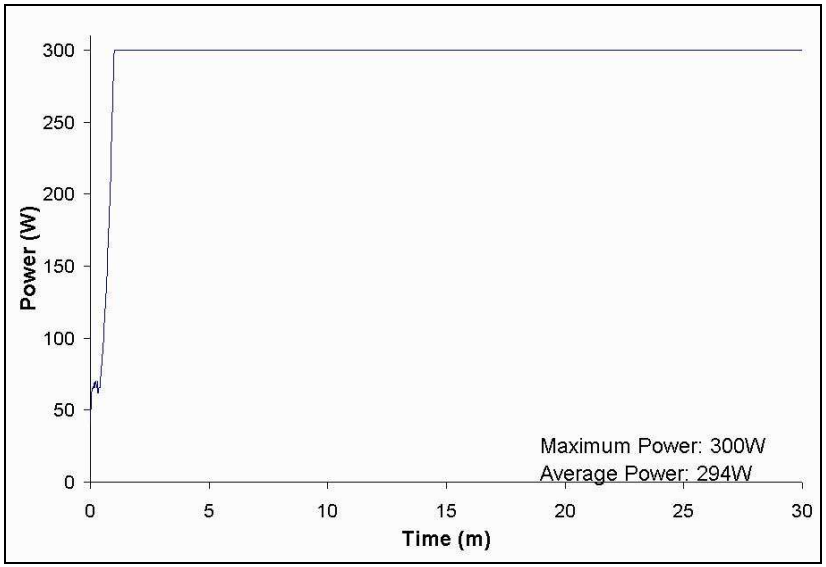

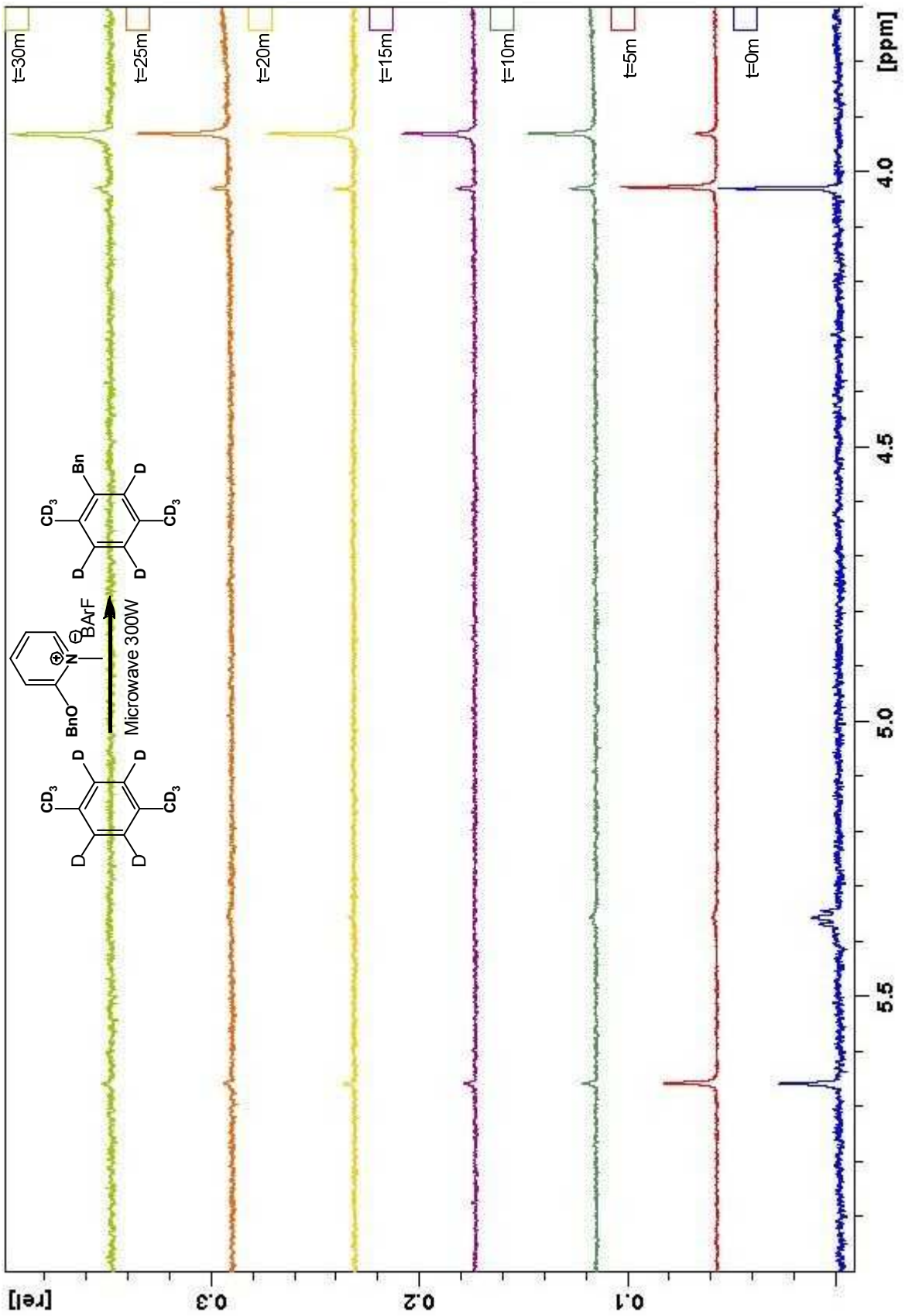

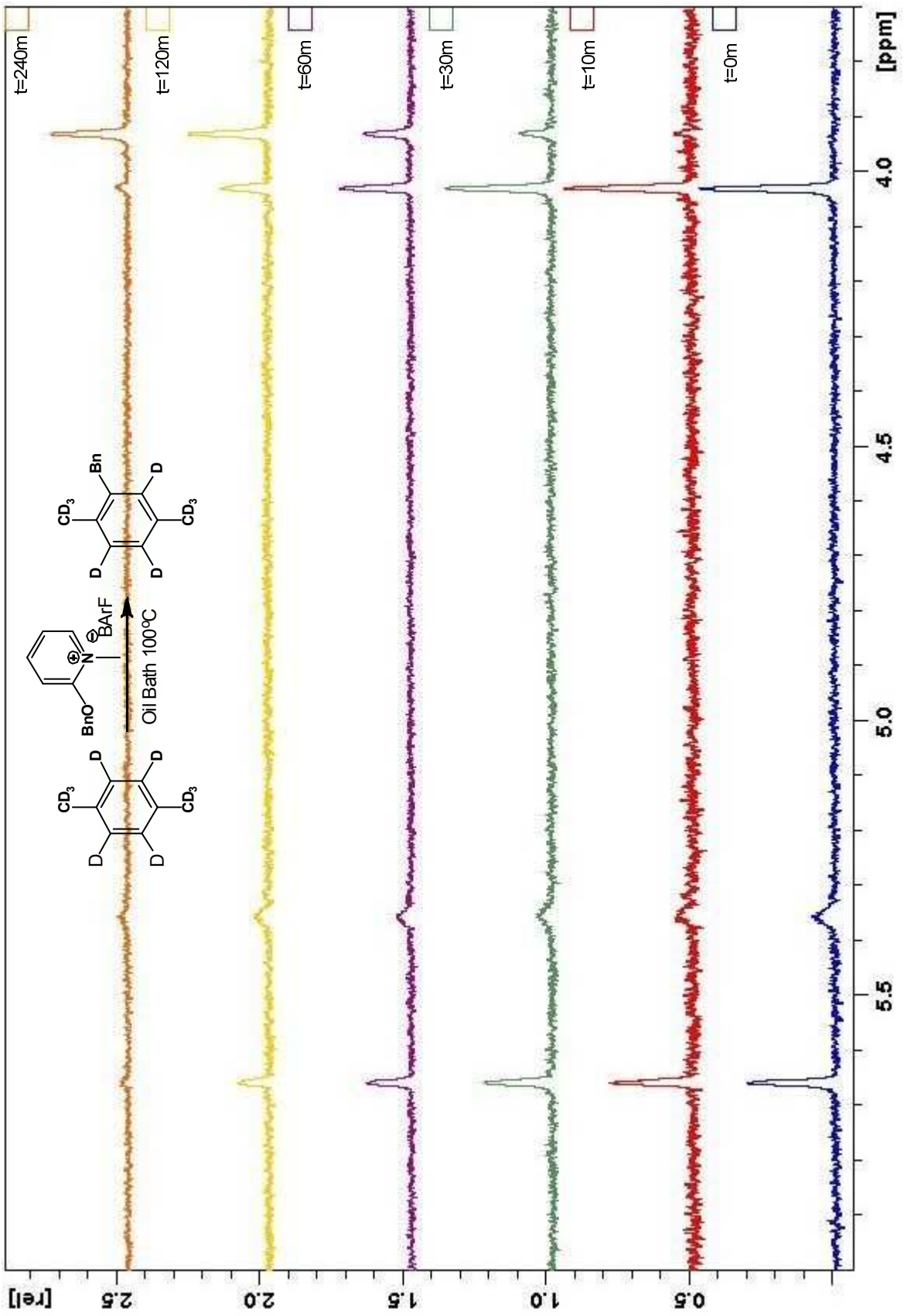

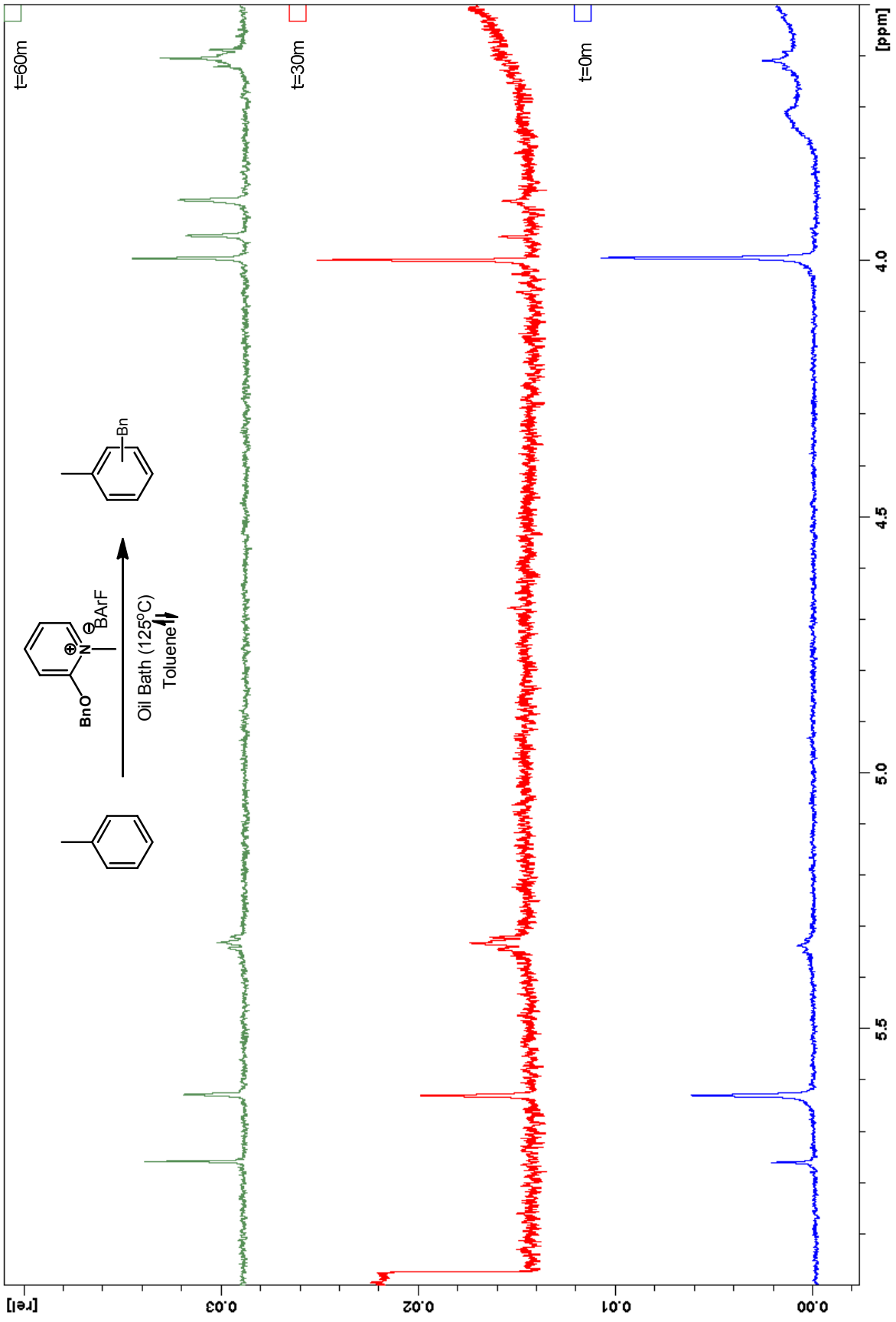

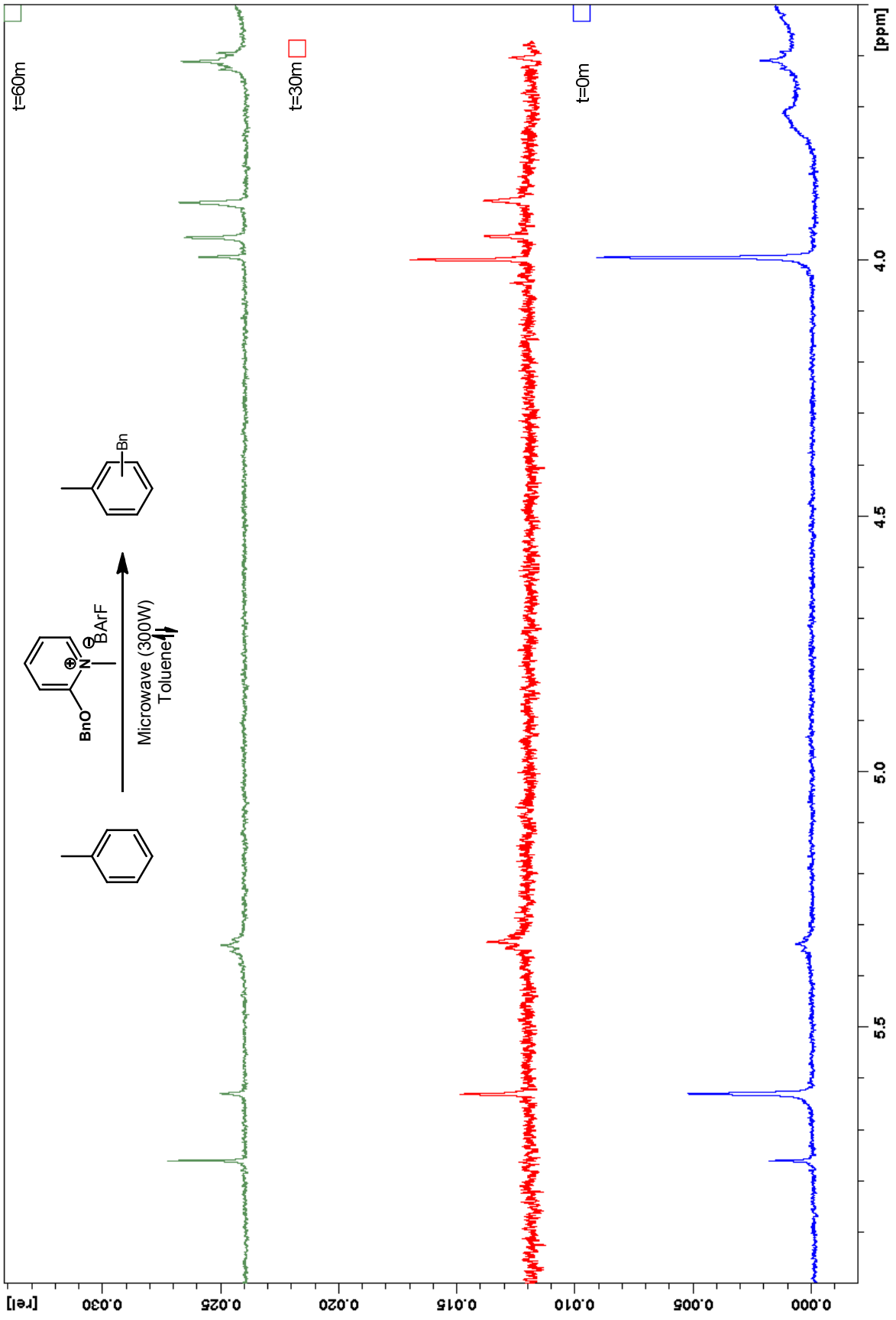

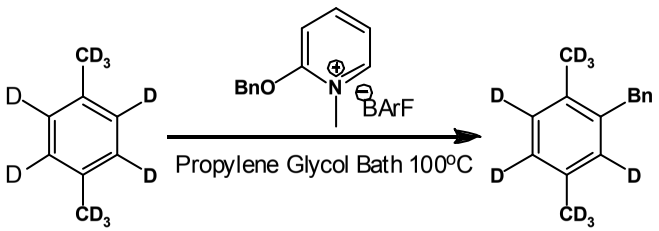

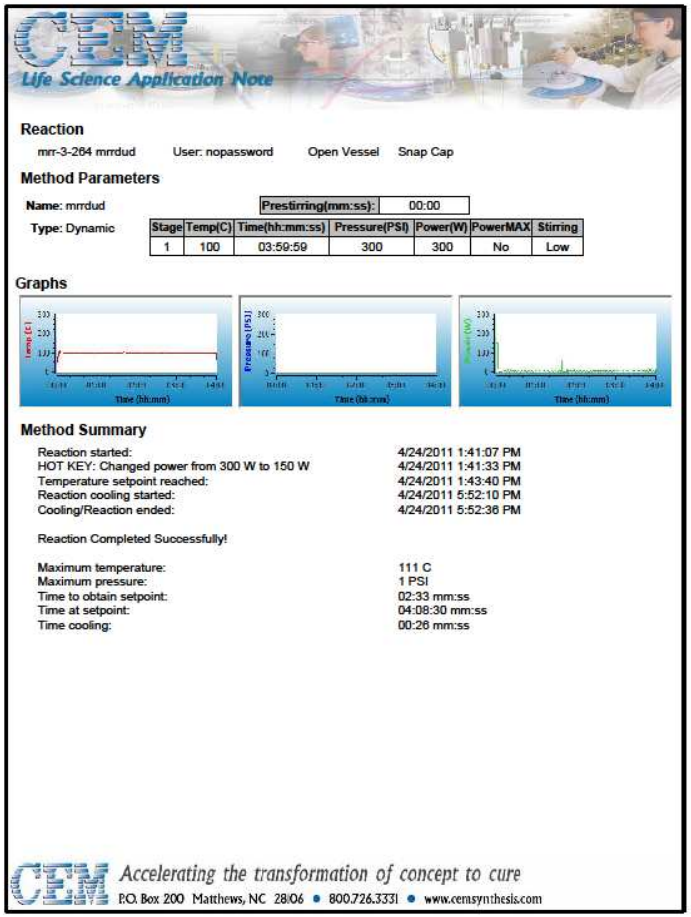

Life Science Application Note

Reaction

mrr-3-264 mrrdud User: nopassword Open Vessel Snap Cap

Method Parameters

Name: mrrdud

Type: Dynamic

Prestirring(mm:ss):	00:00

Stage	Temp(C)	Time(hh:mm:ss)	Pressure(PSI)	Power(W)	PowerMAX	Stirring
1	100	03:59:59	300	300	No	Low

Graphs

Method Summary

Reaction started:	4/24/2011 1:41:07 PM
HOT KEY: Changed power from 300 W to 150 W	4/24/2011 1:41:33 PM
Temperature setpoint reached:	4/24/2011 1:43:40 PM
Reaction cooling started:	4/24/2011 5:52:10 PM
Cooling/Reaction ended:	4/24/2011 5:52:36 PM

Reaction Completed Successfully!

Maximum temperature:	111 C
Maximum pressure:	1 PSI
Time to obtain setpoint:	02:33 mm:ss
Time at setpoint:	04:08:30 mm:ss
Time cooling:	00:26 mm:ss

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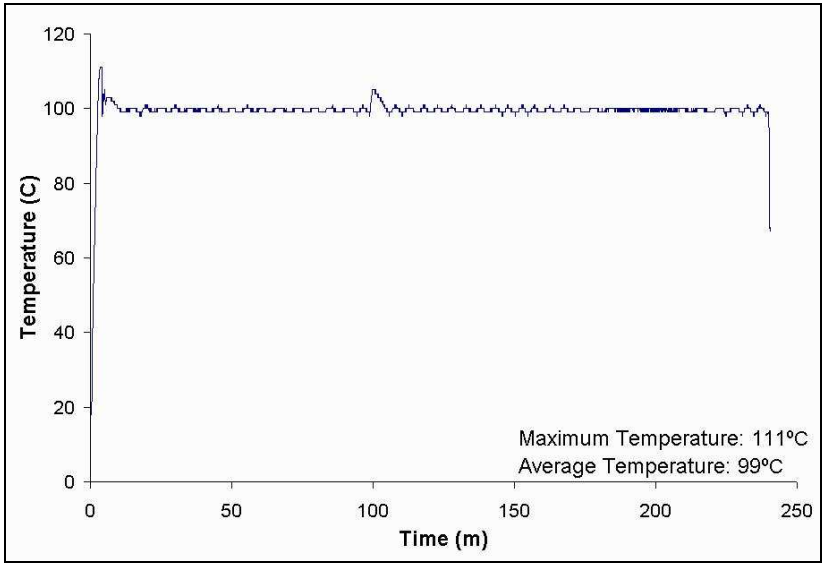
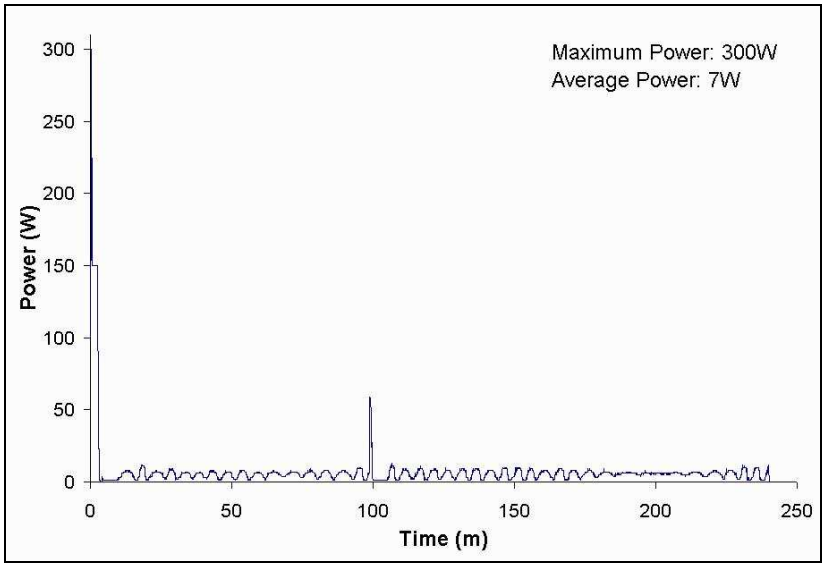
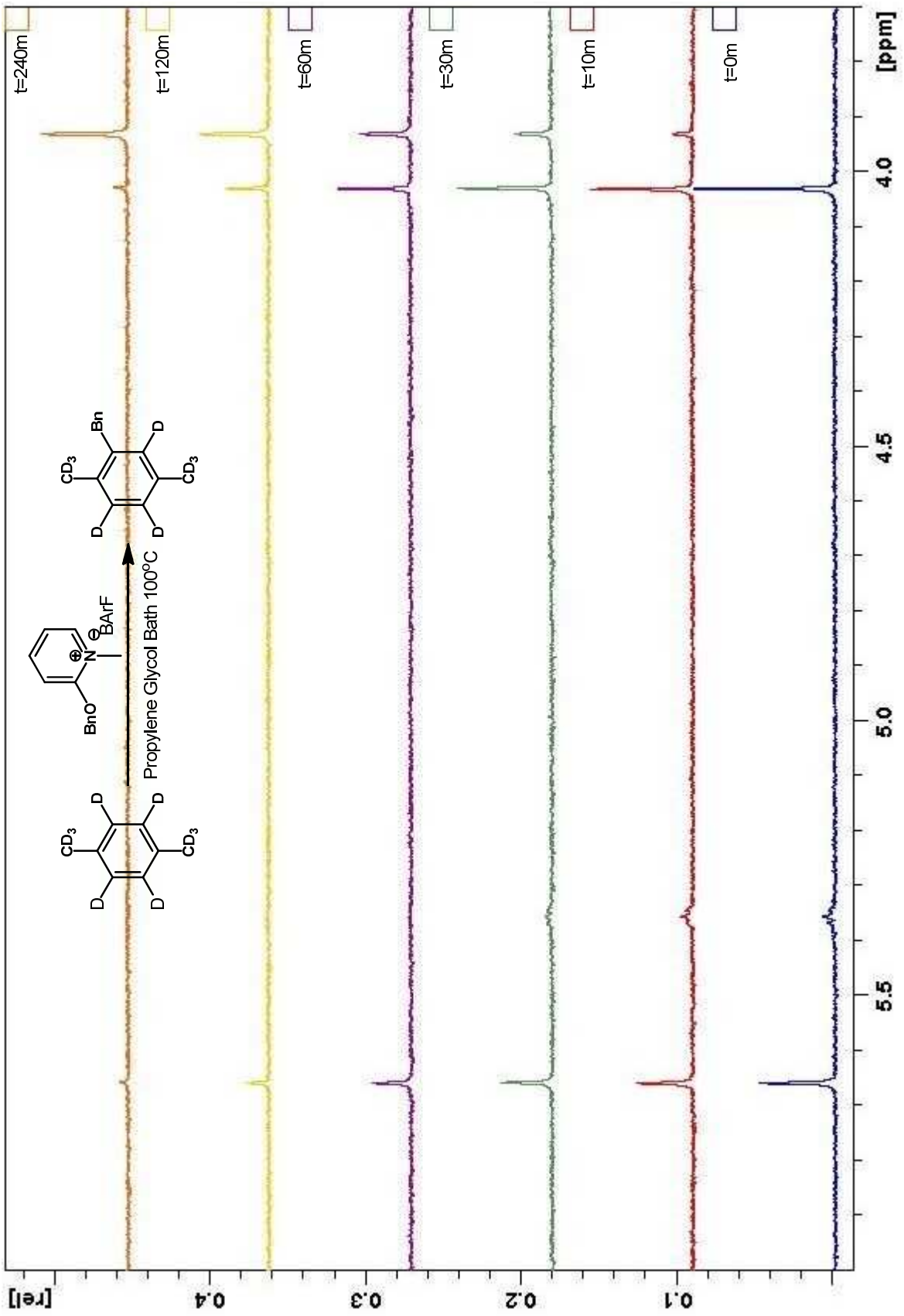
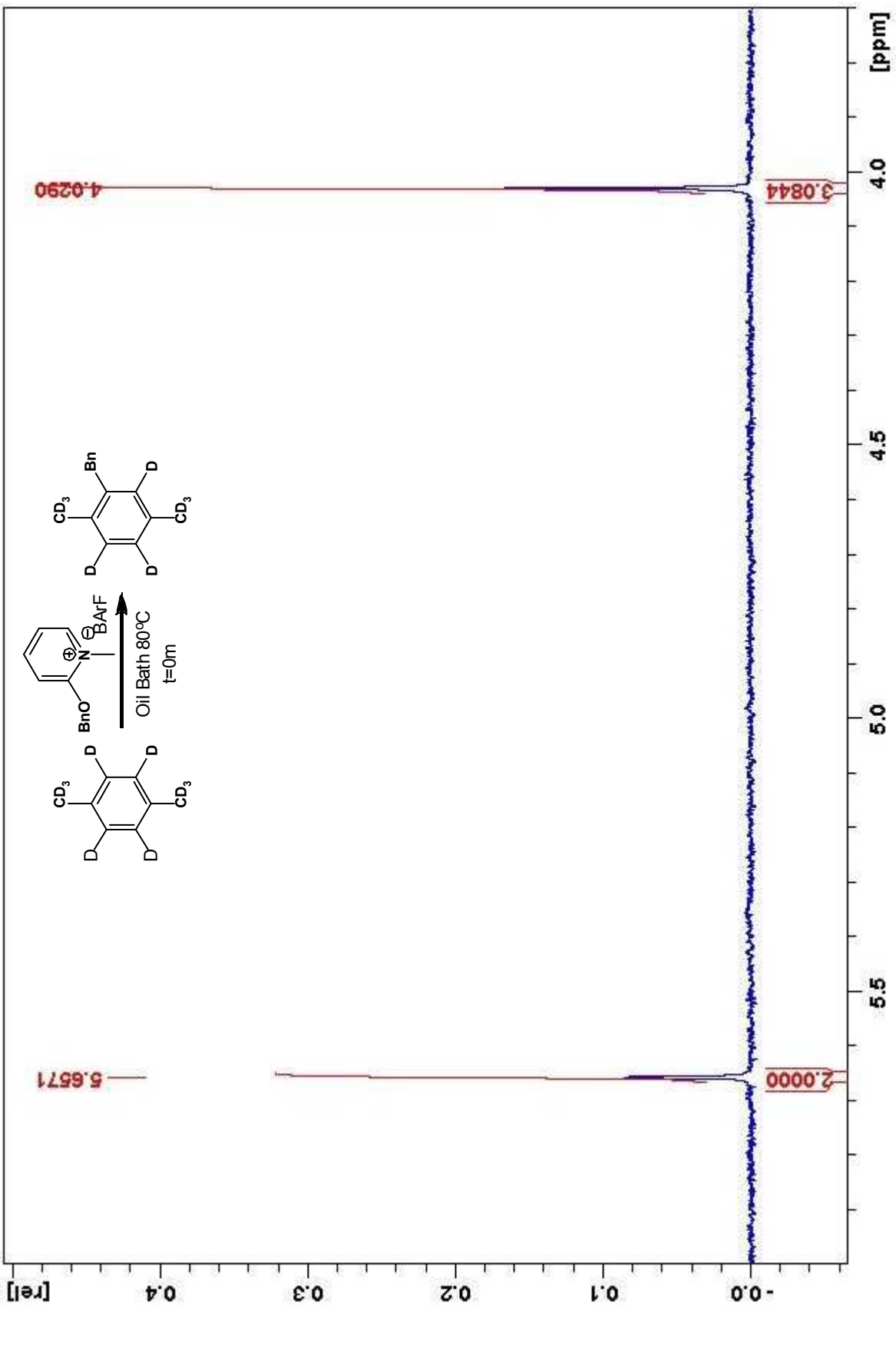
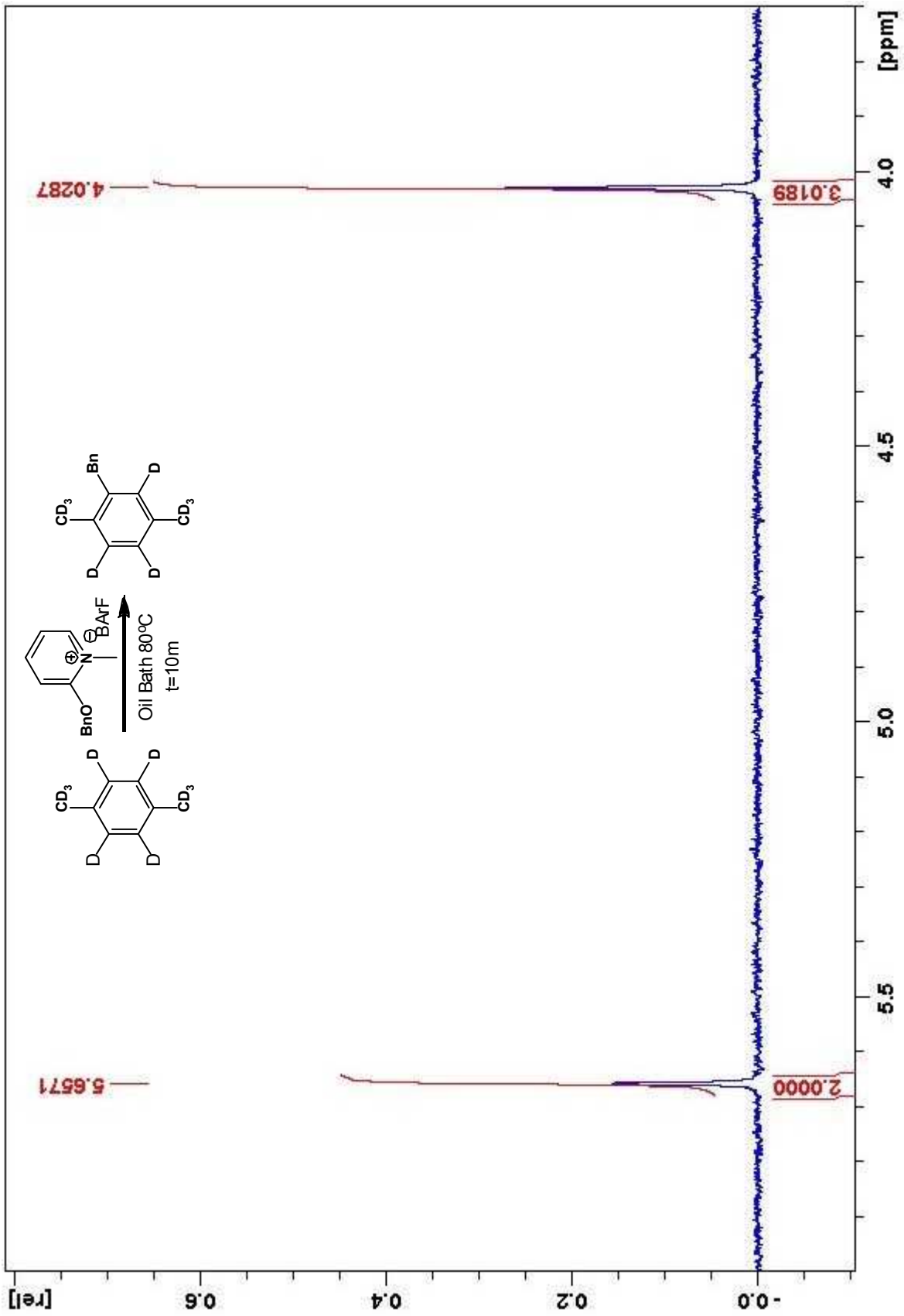


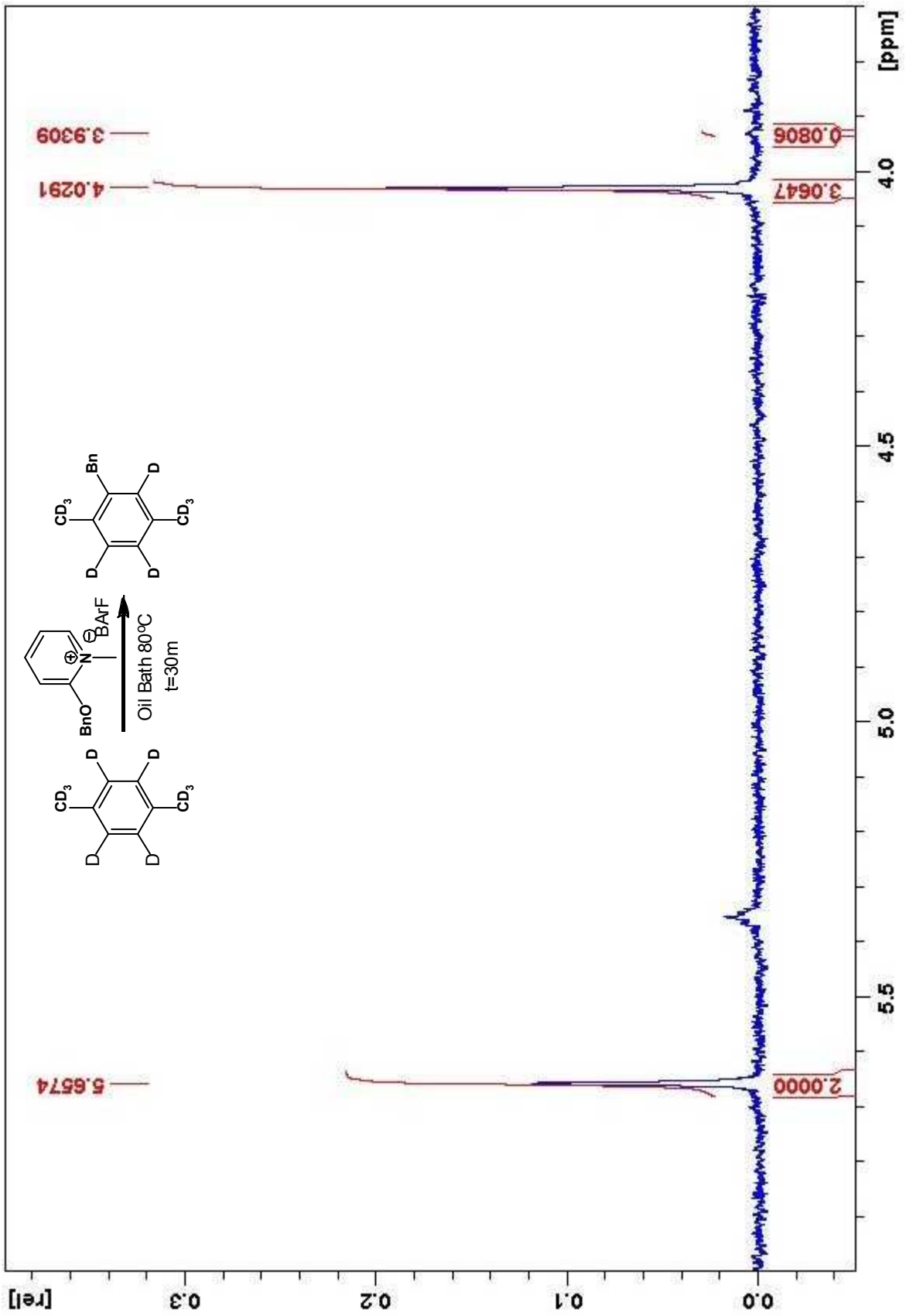


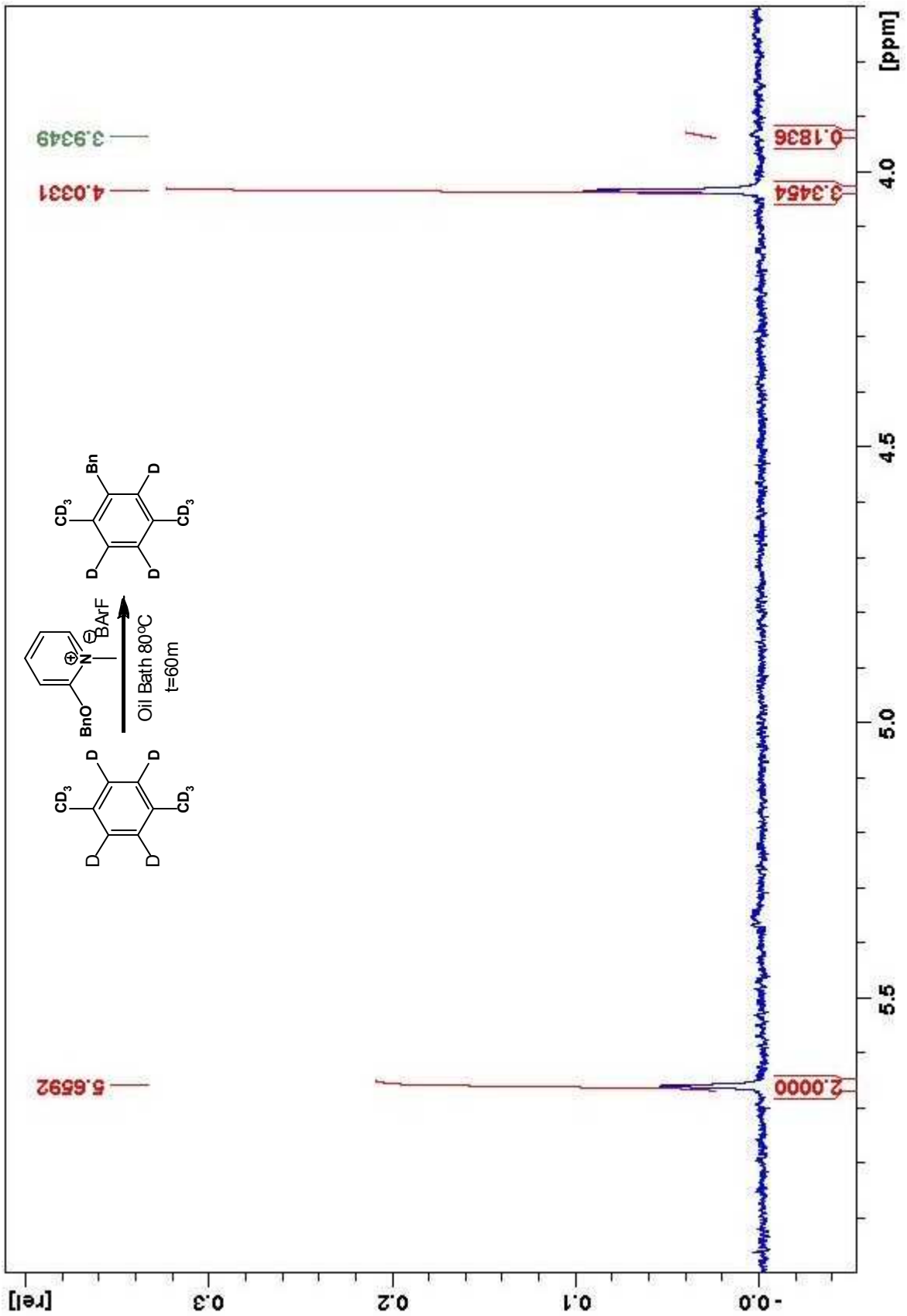


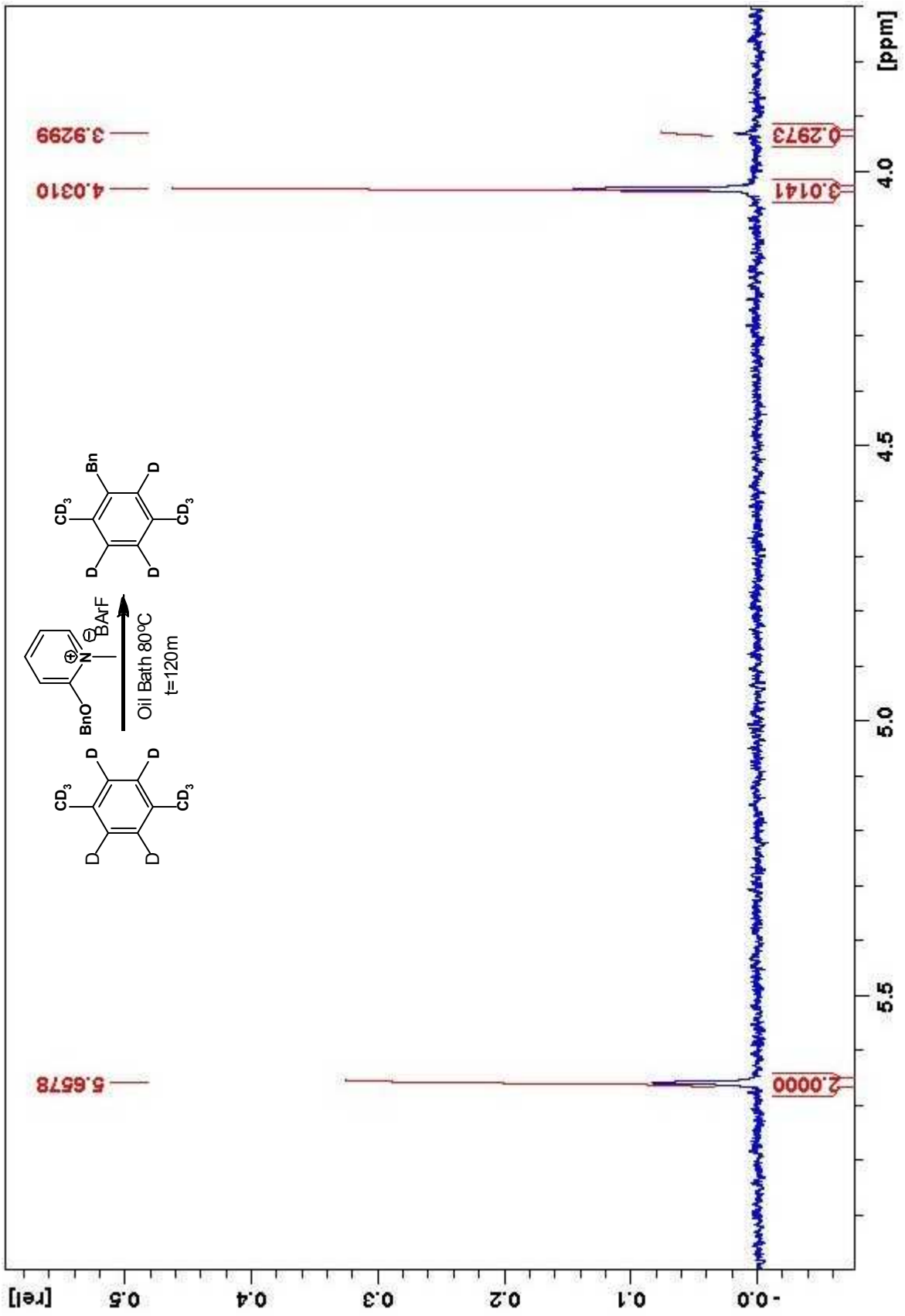
3.2 Individual ^{1}H NMR data- Oil Bath at 80°C from 0m to 240m (see p. S22 for condensed ^{1}H NMR Data)

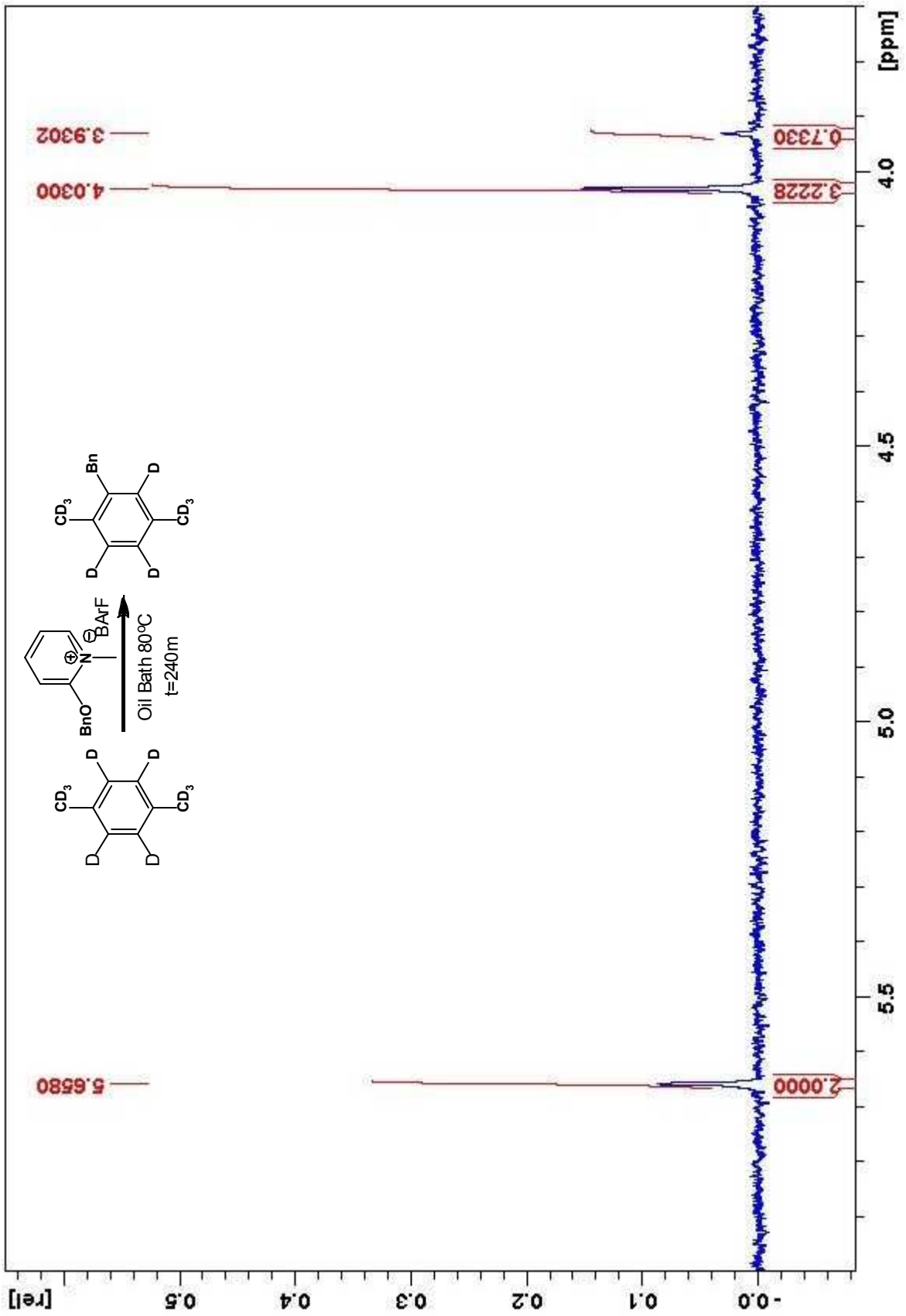




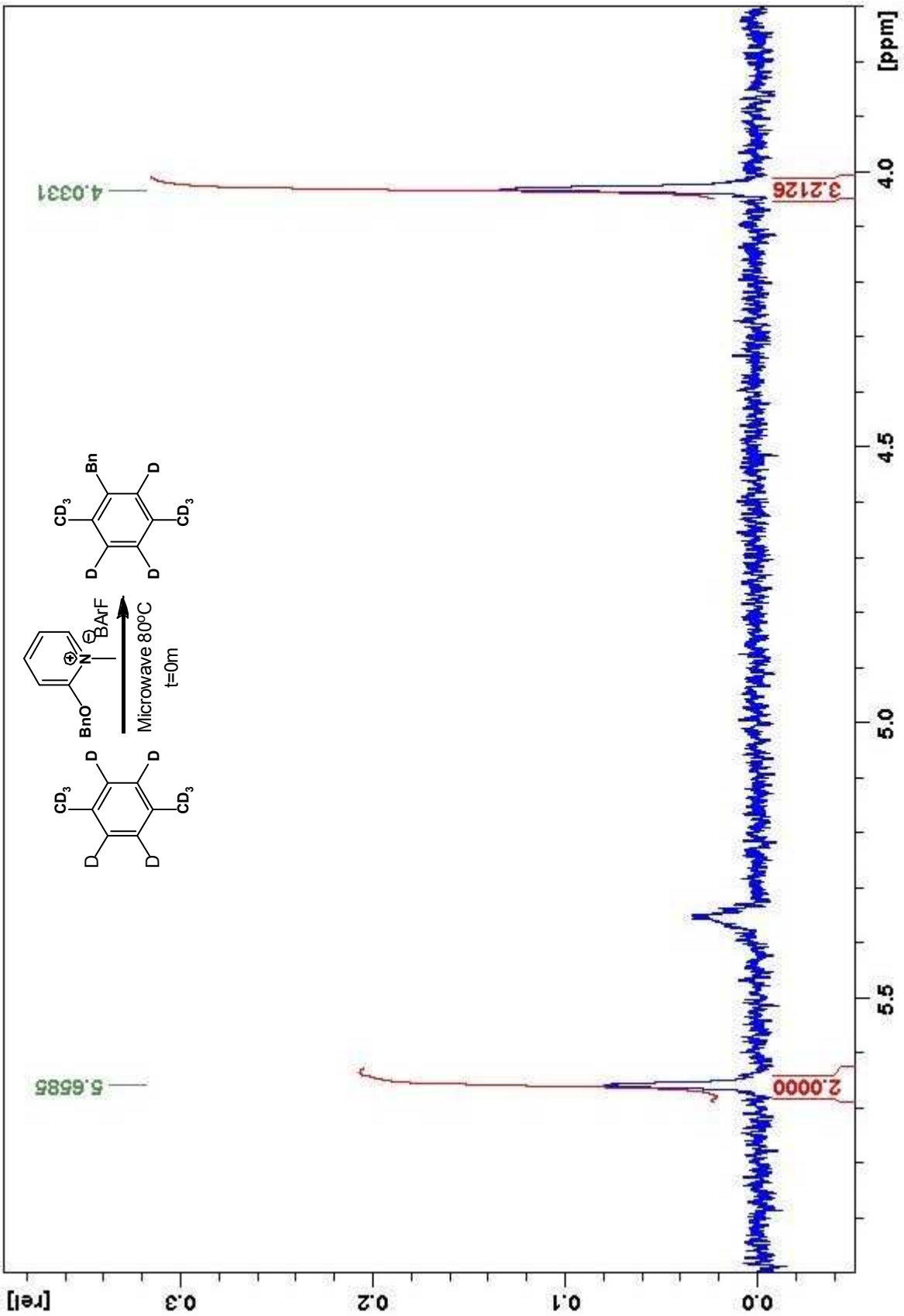


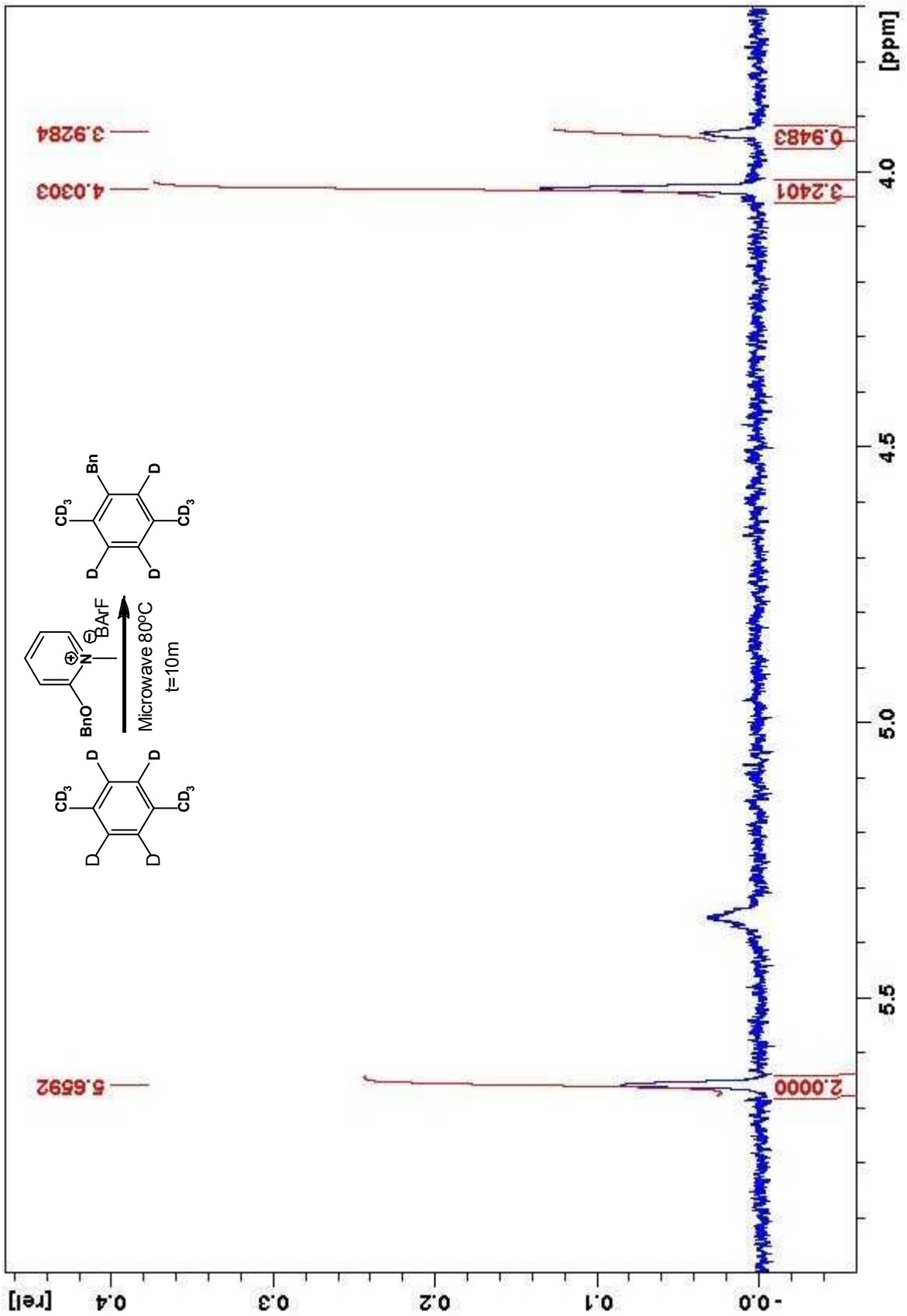


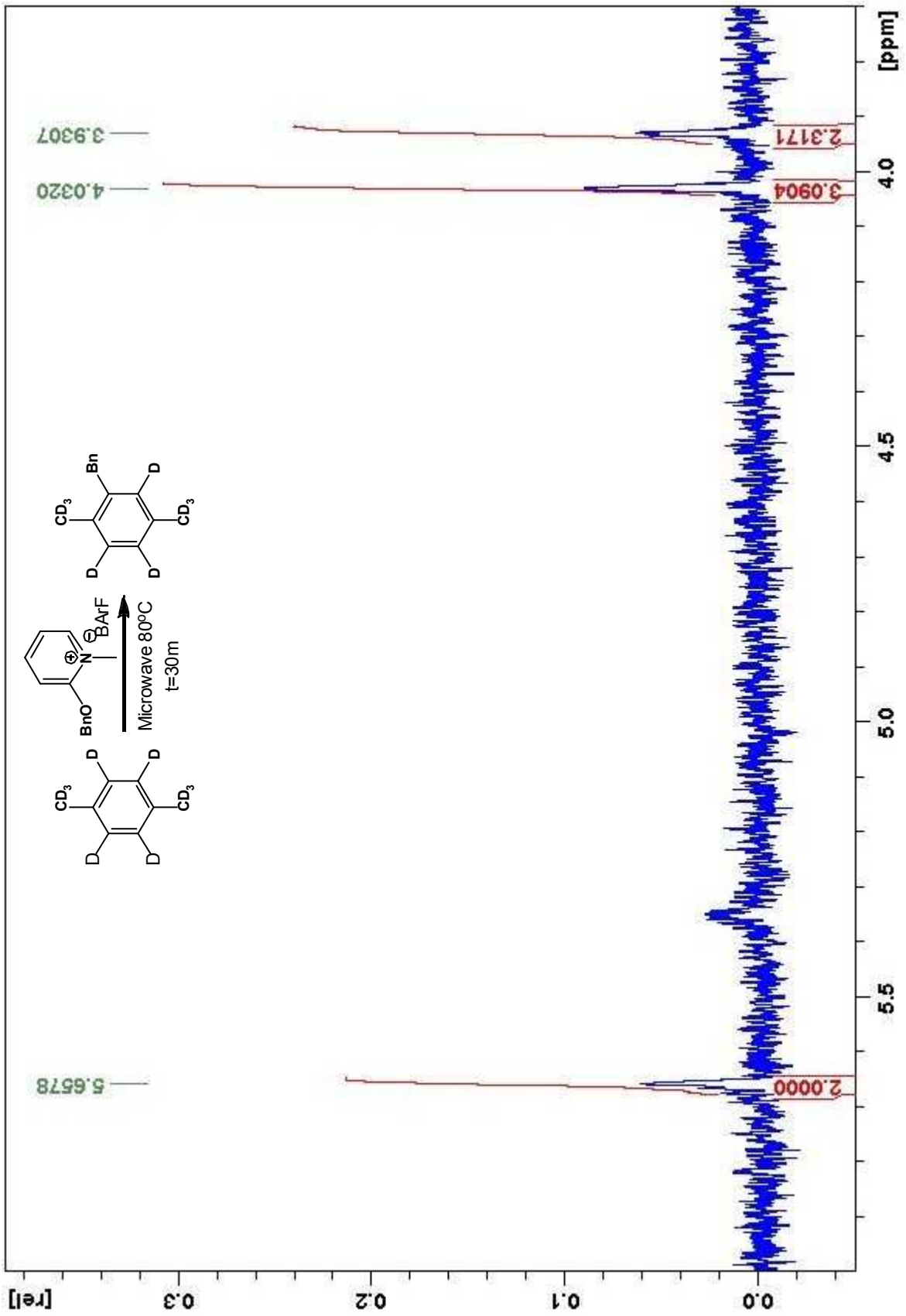


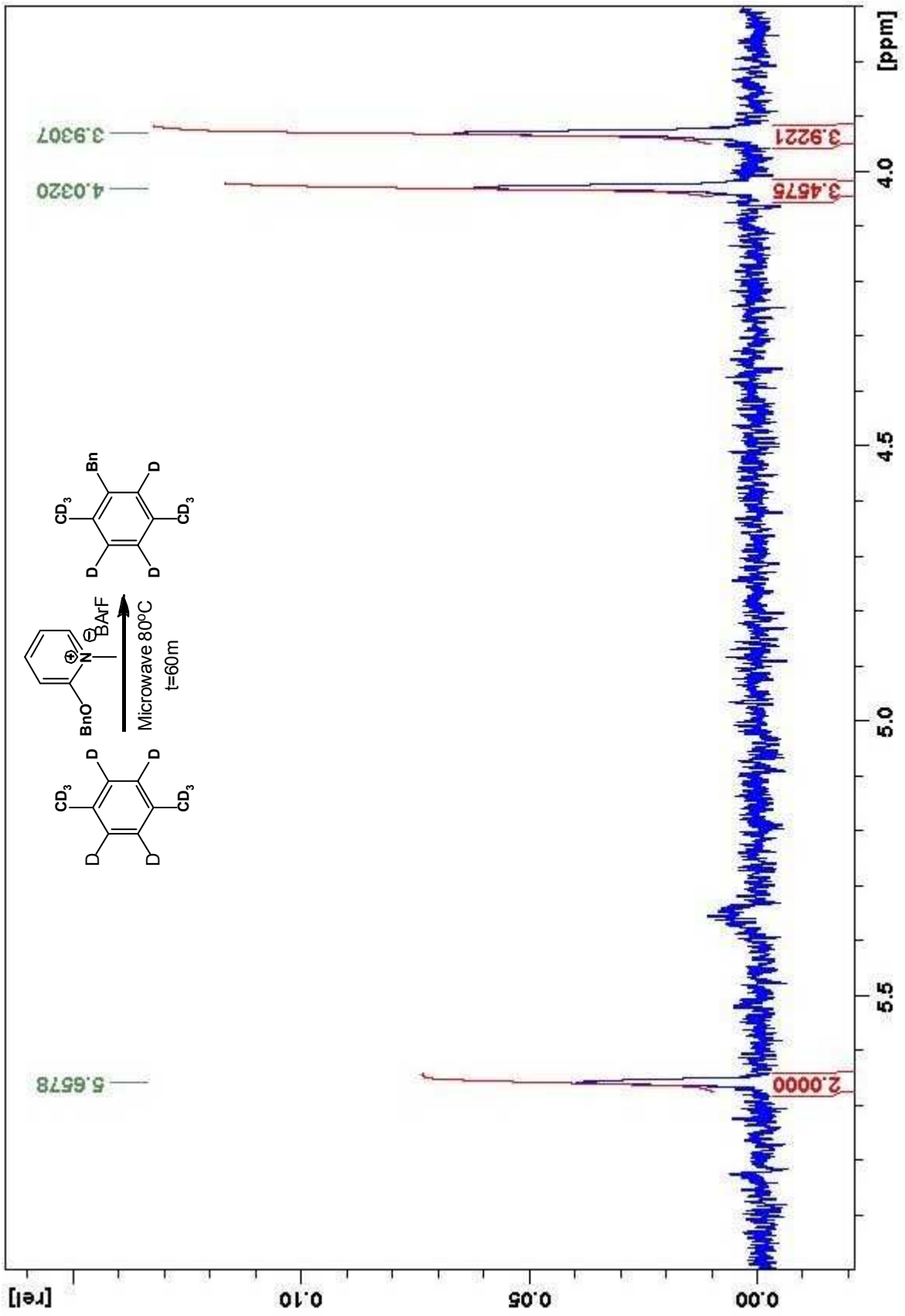


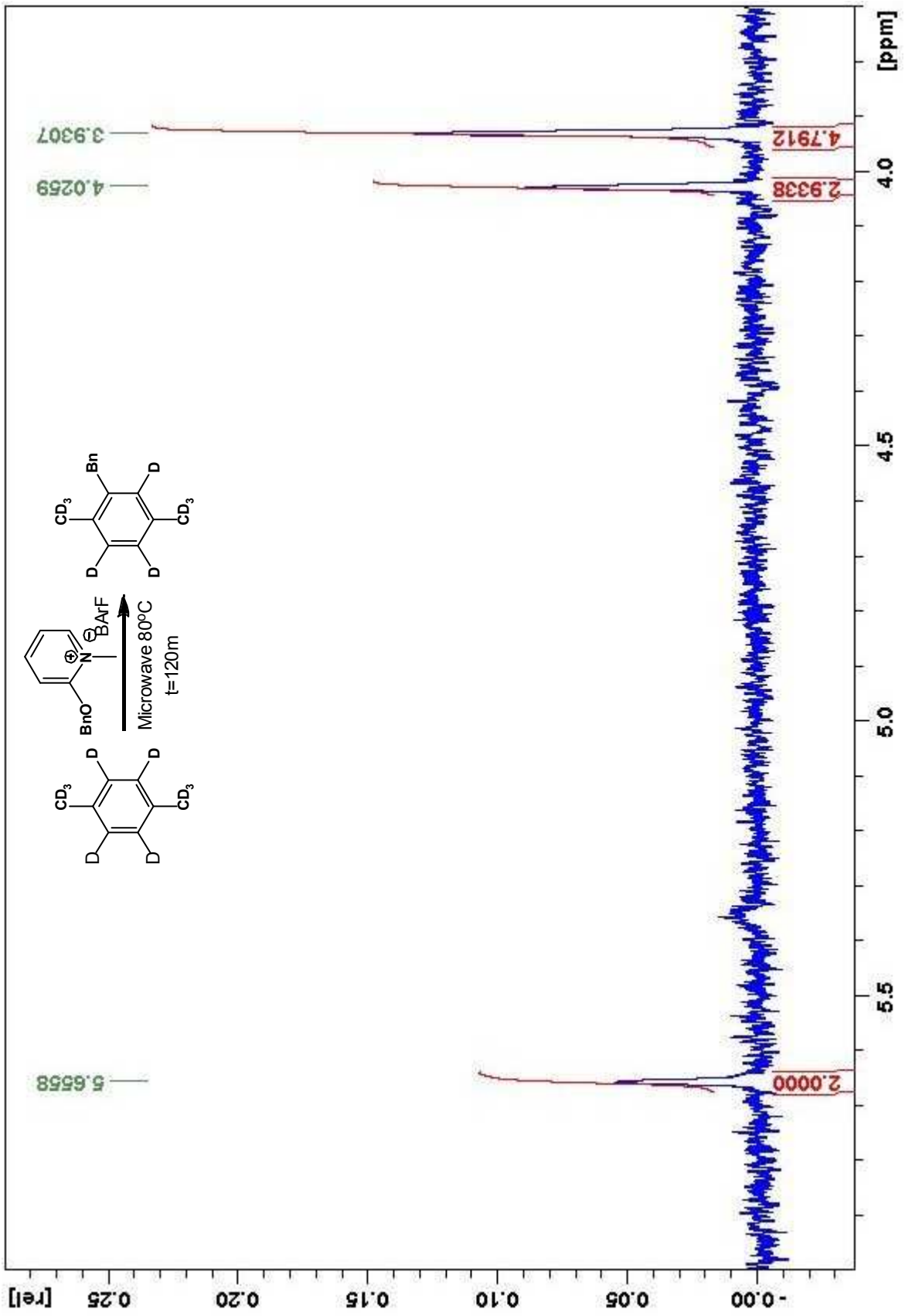
3.3. Individual ^{1}H NMR data- Microwave at 80°C from 0m to 240m (see pp. S23-S24 for condensed ^{1}H NMR Data)

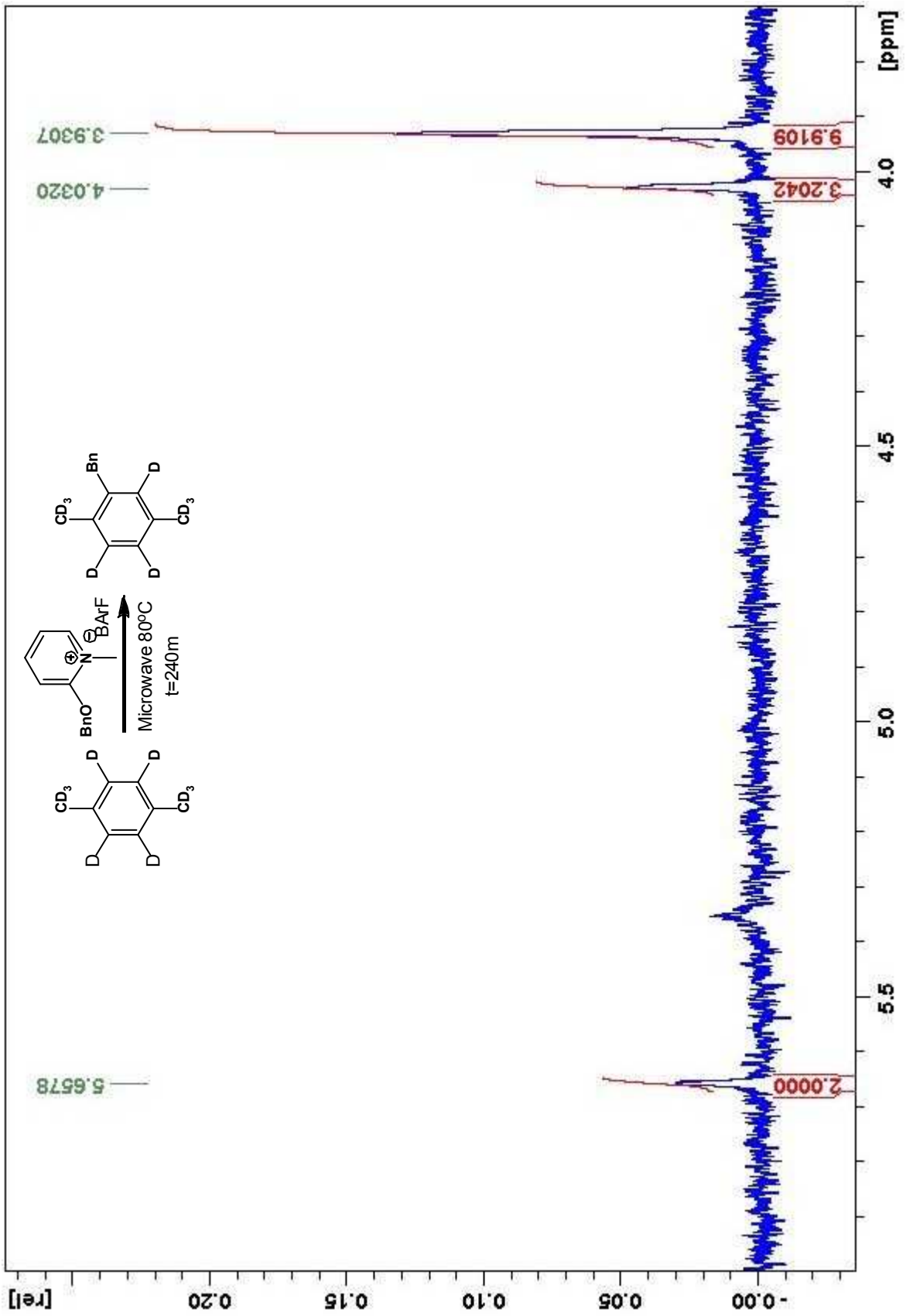




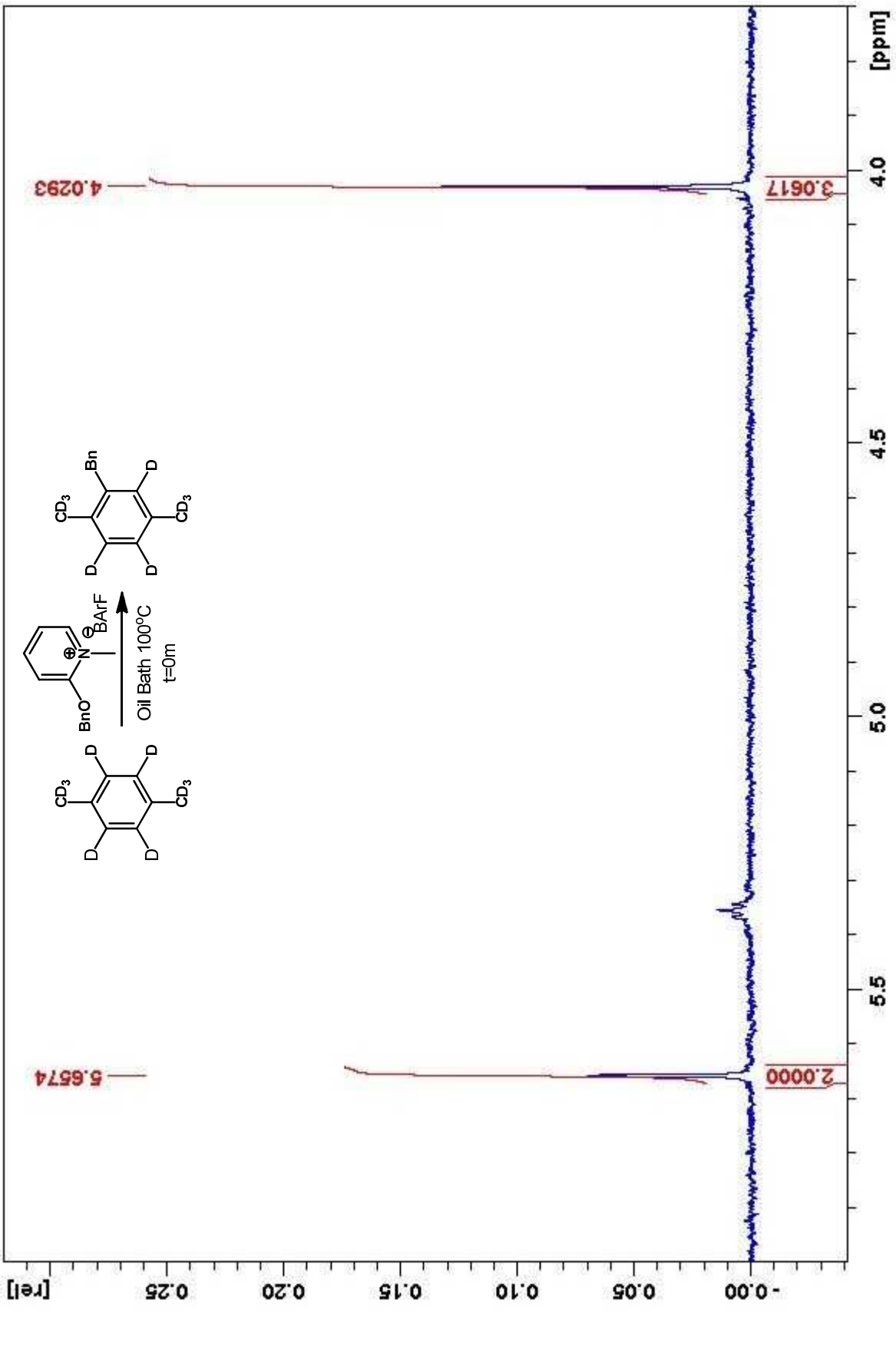


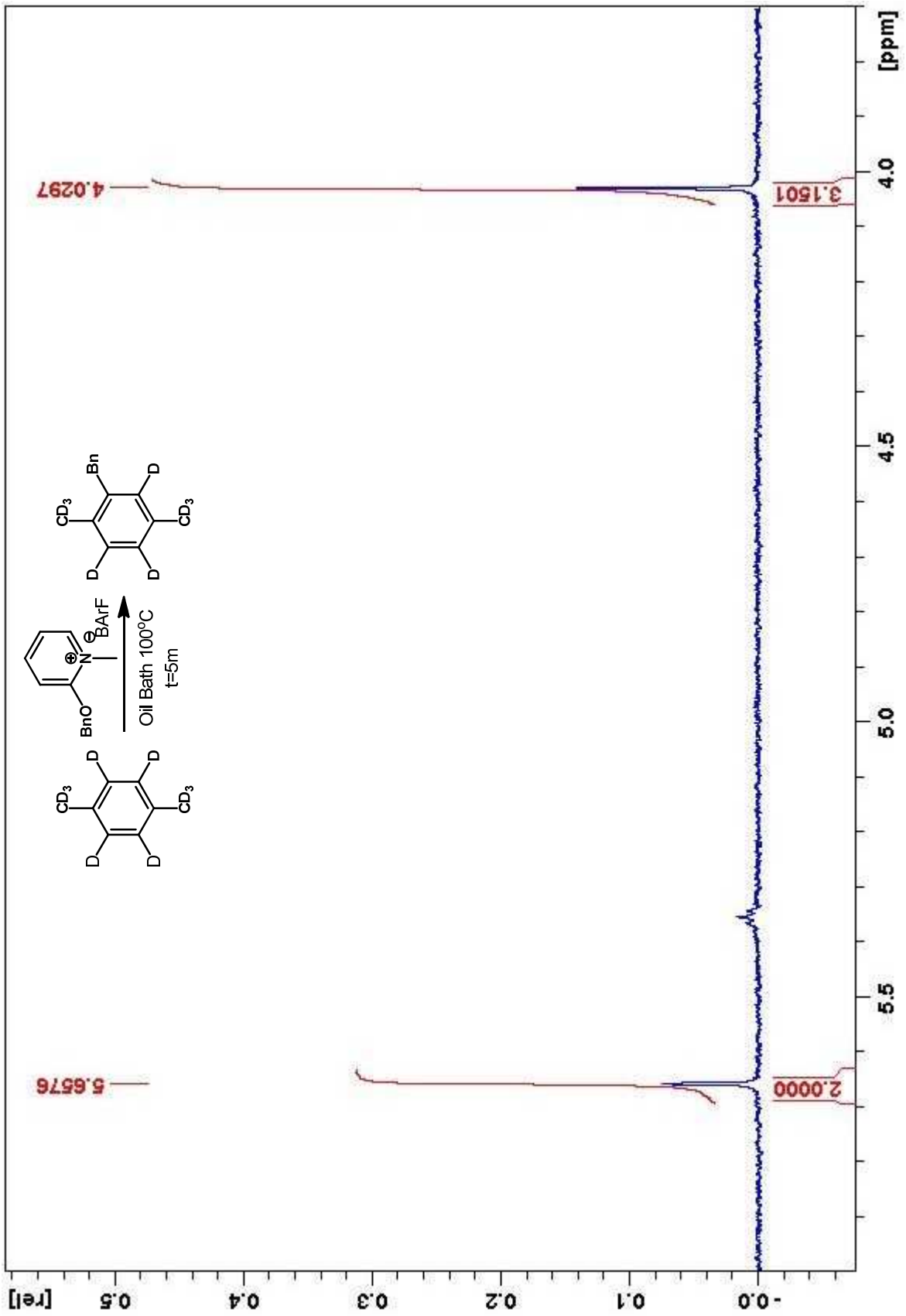


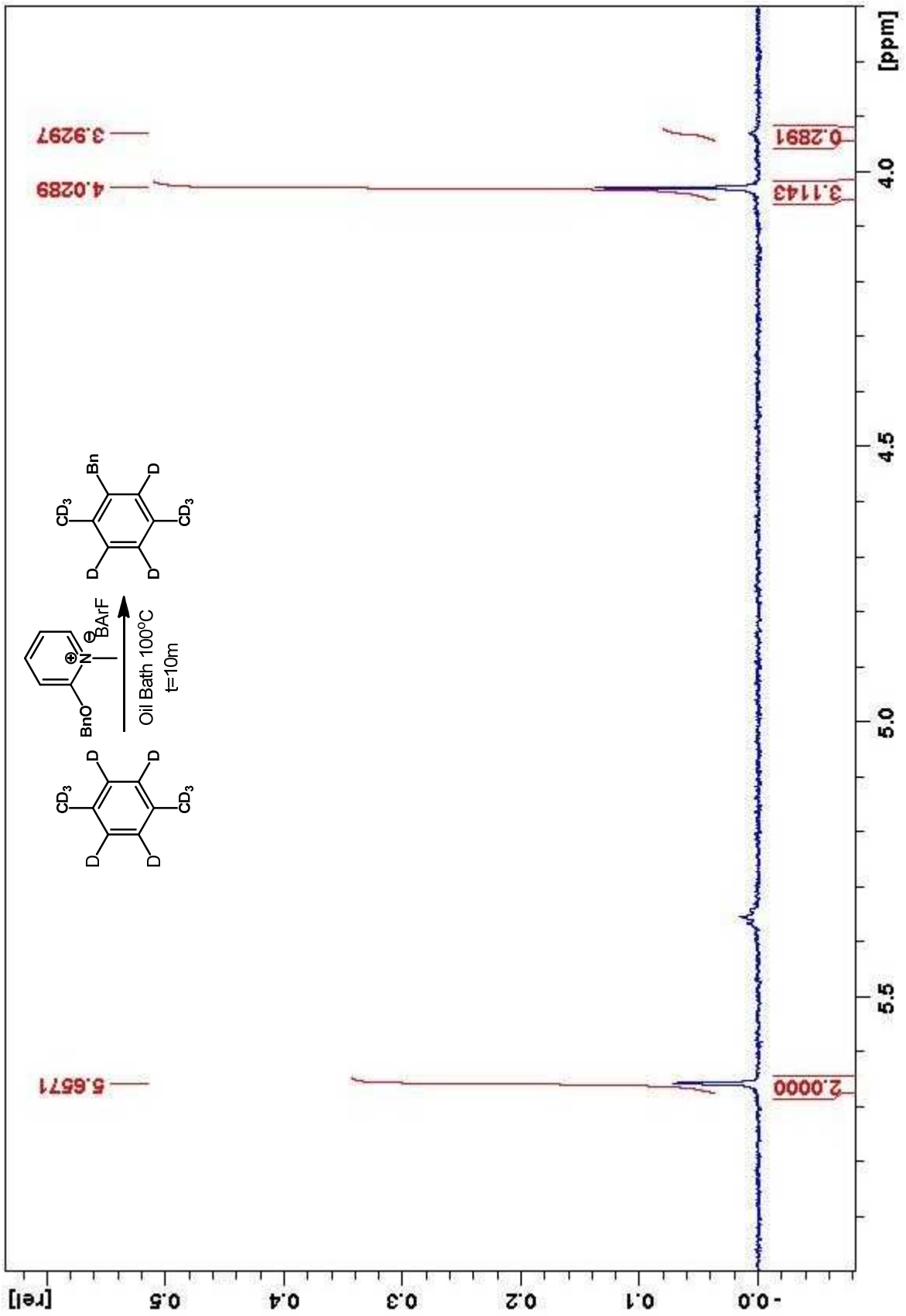


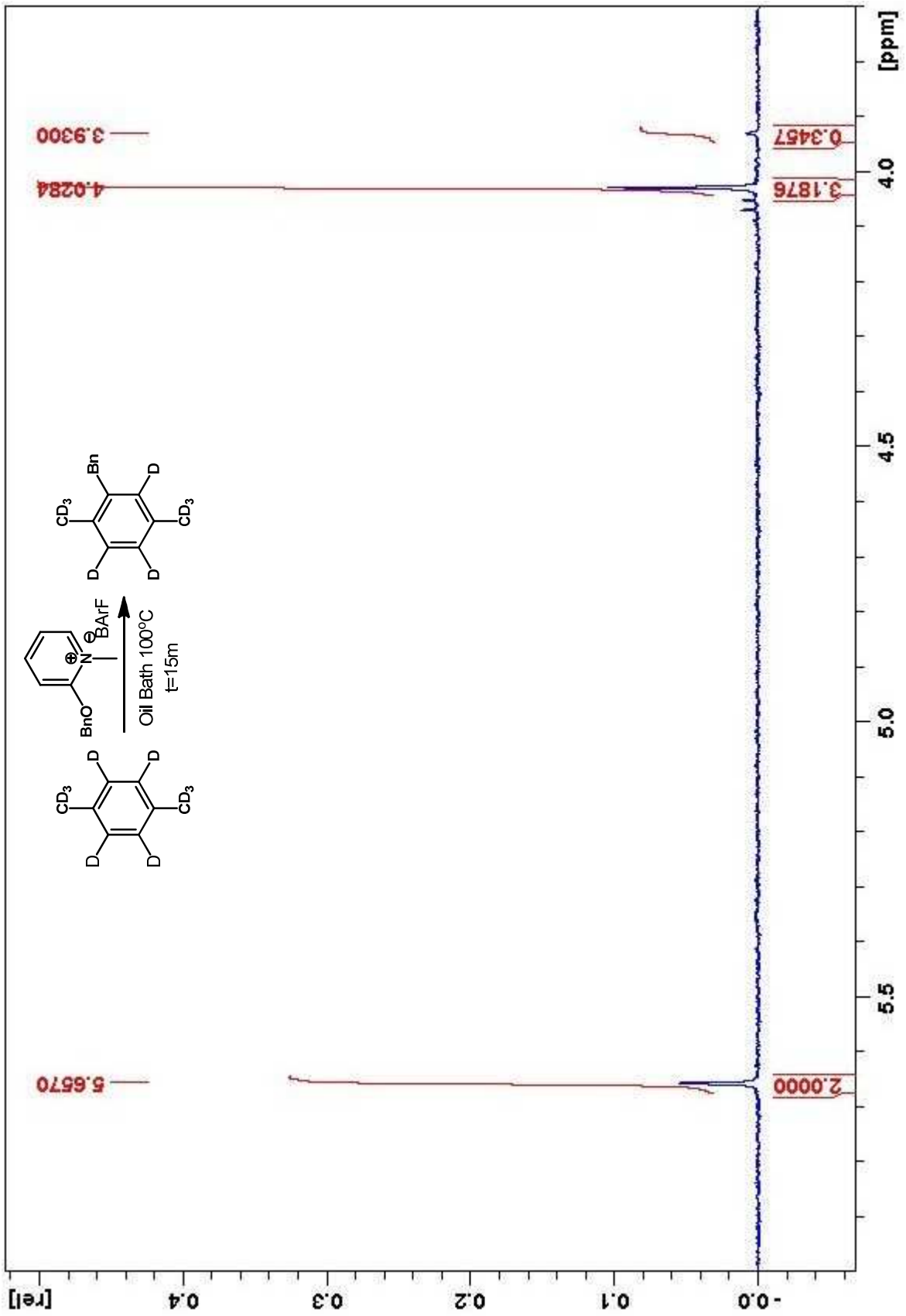


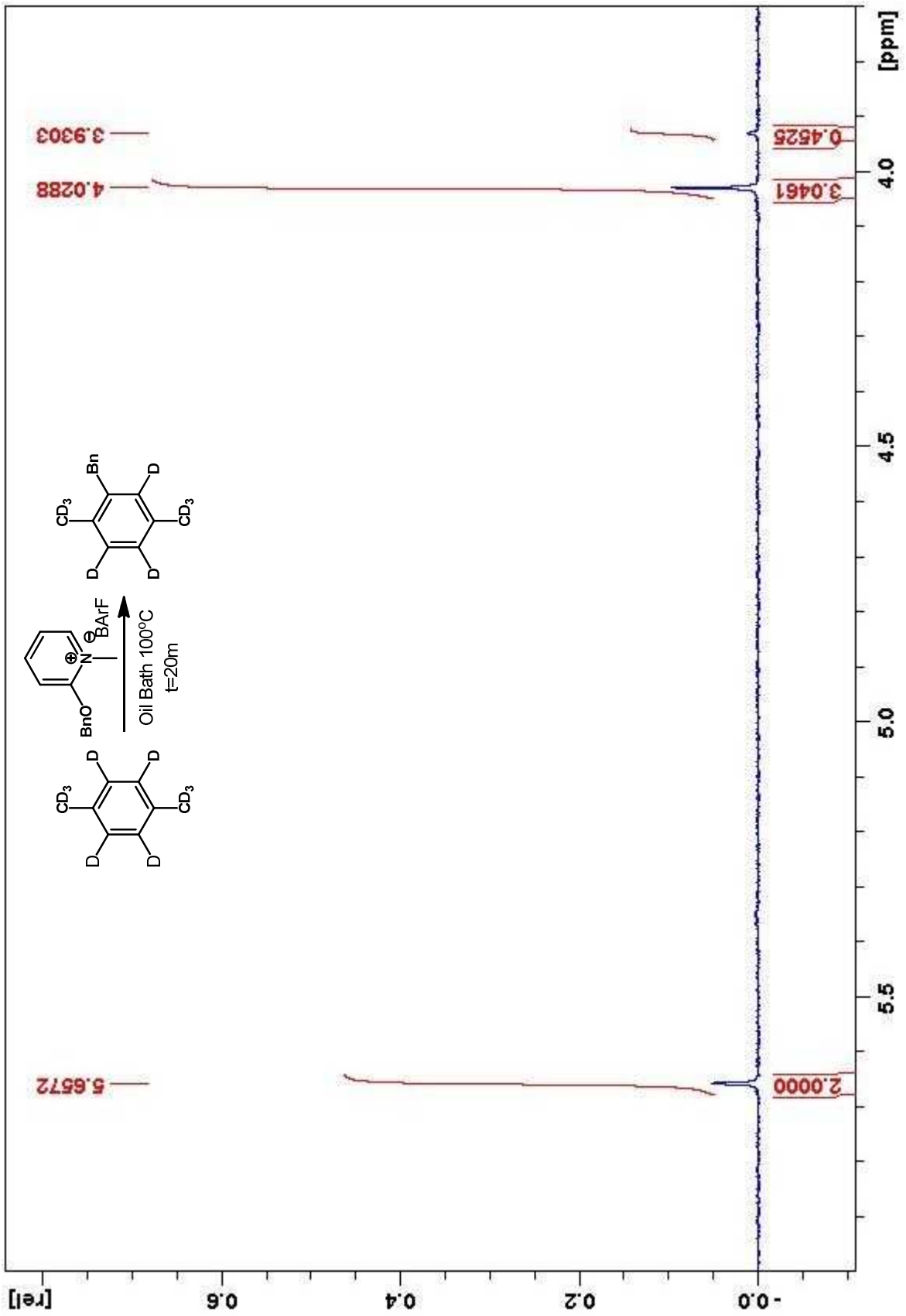
3.4 Individual ^{1}H NMR data- Oil Bath at 100°C from 0m to 30m (see p. S25 for condensed ^{1}H NMR Data)

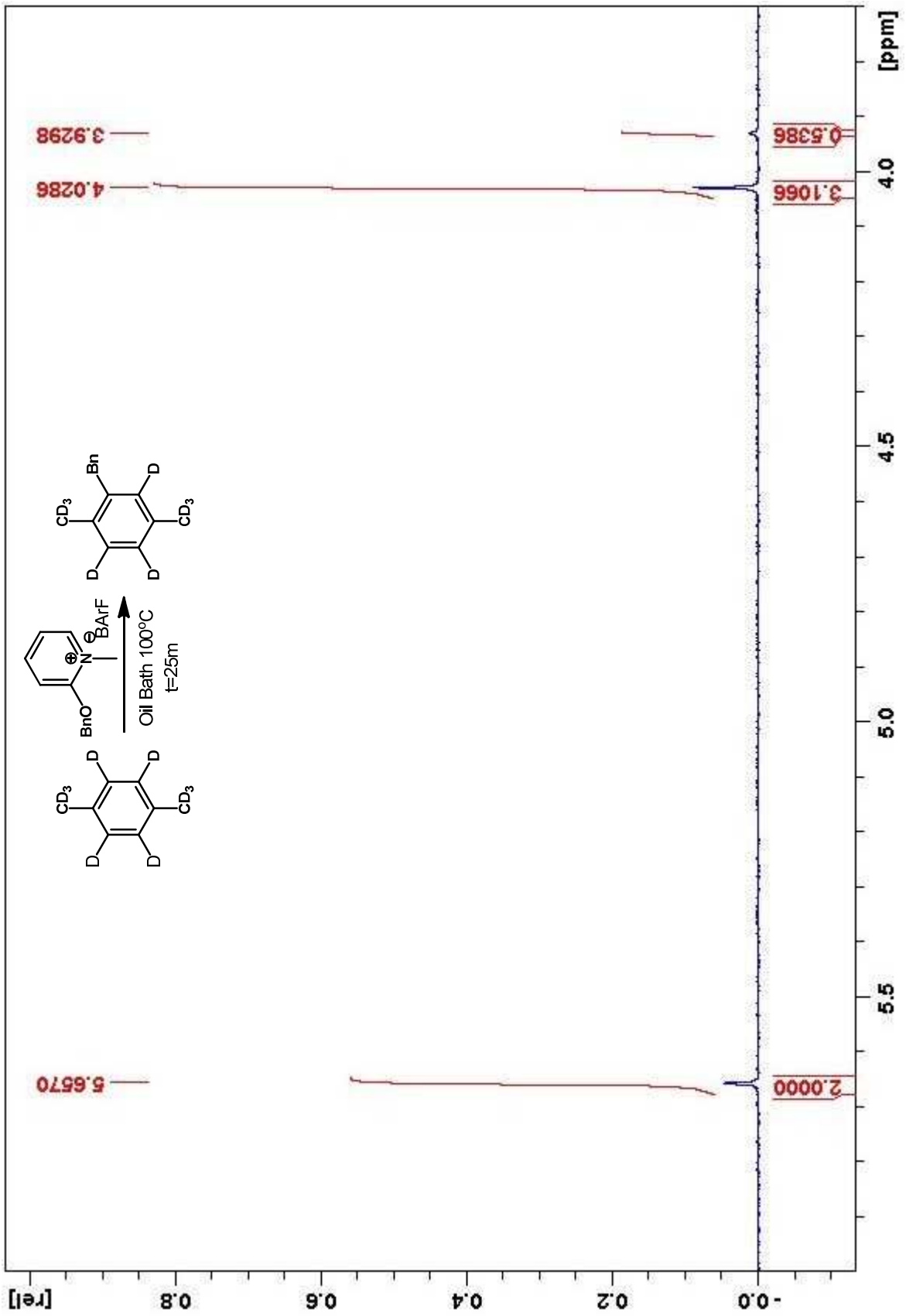


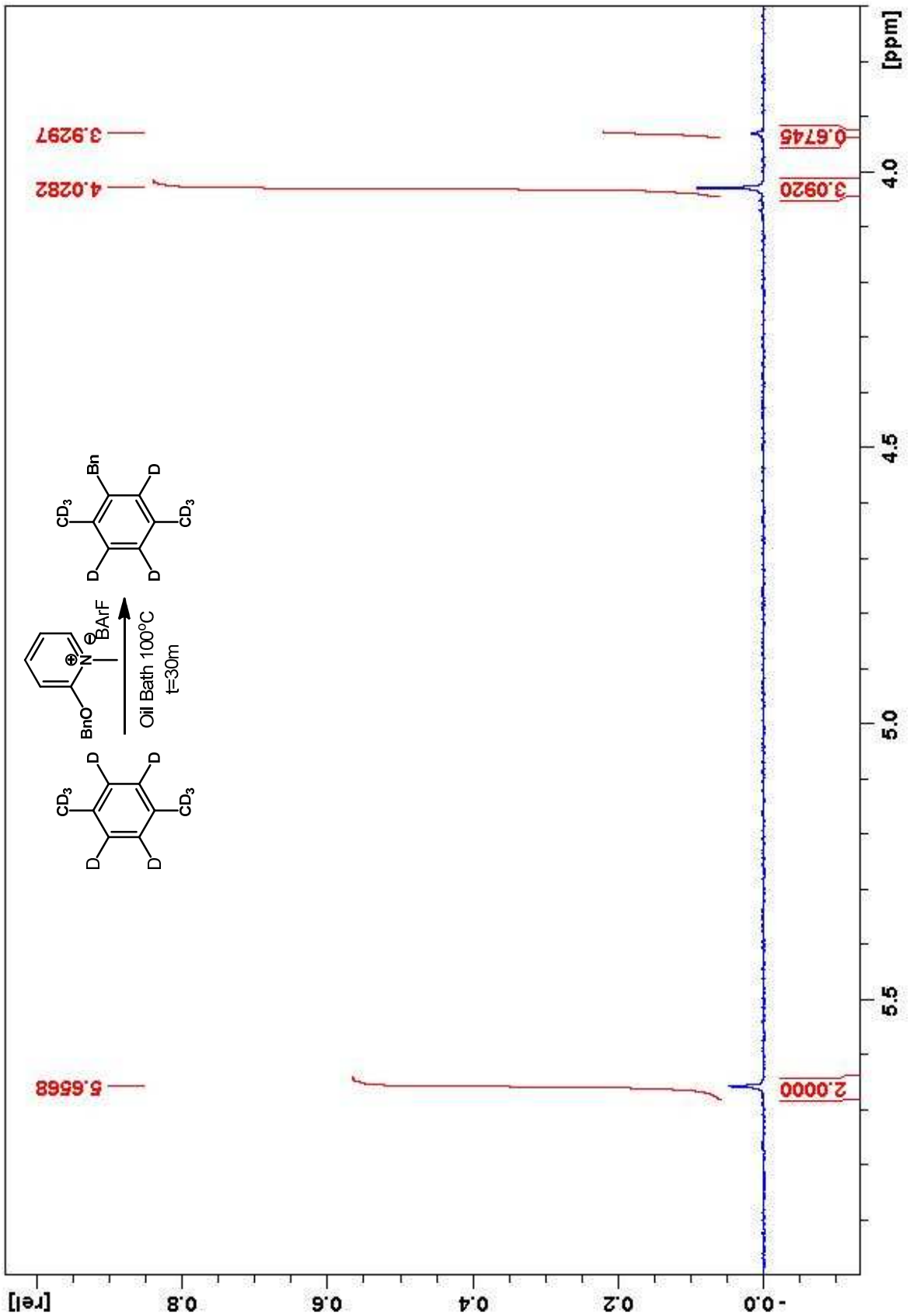




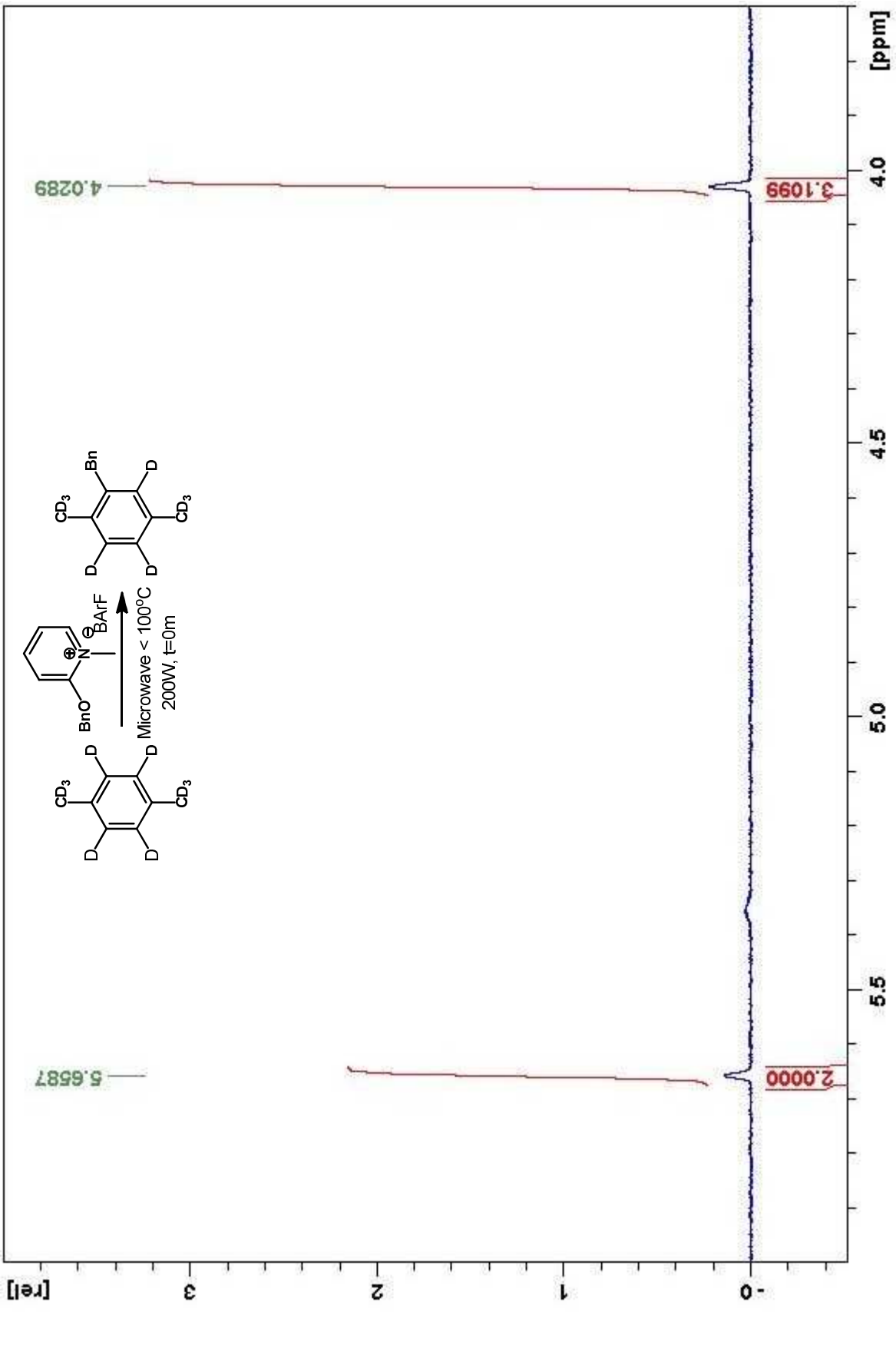


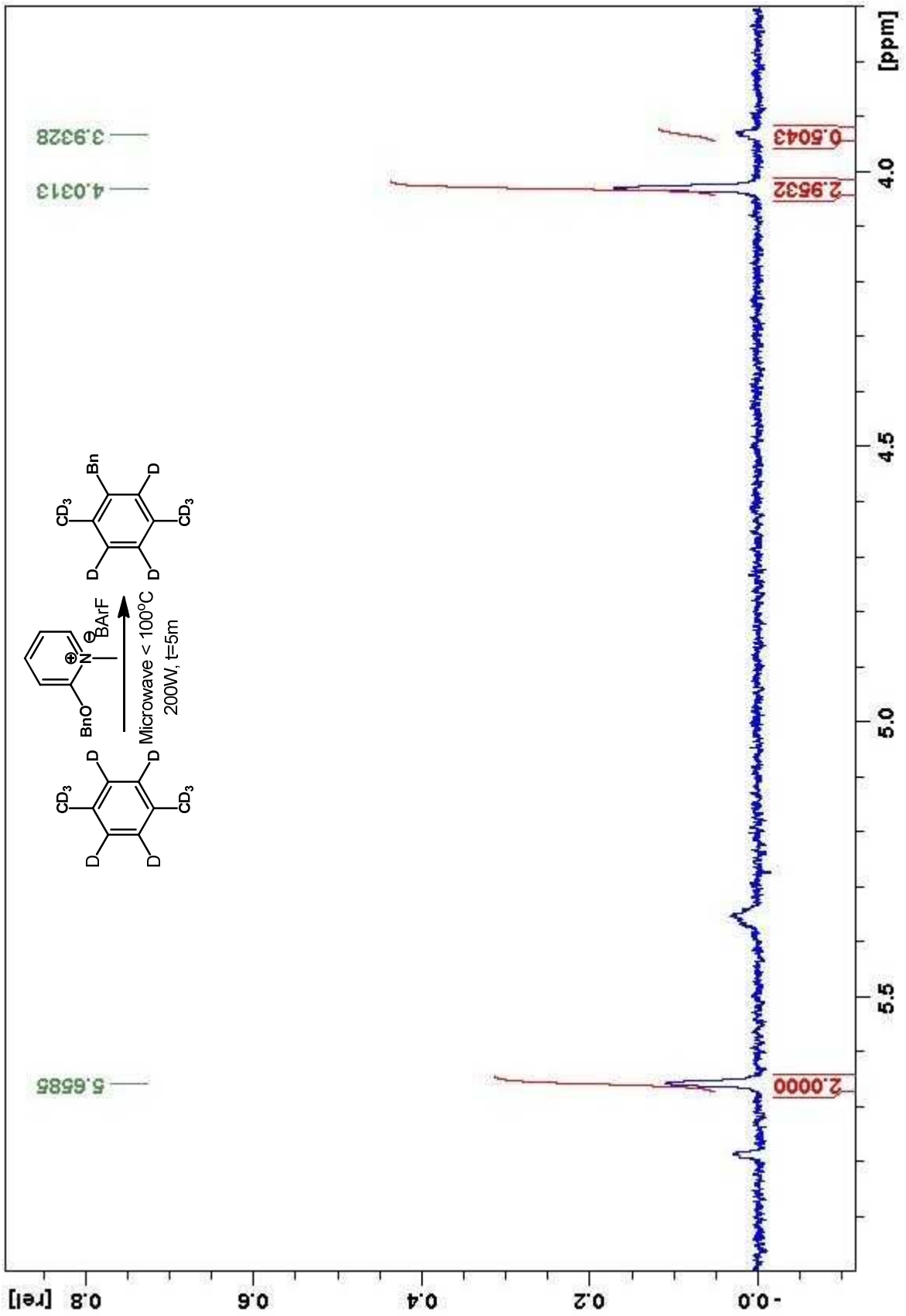


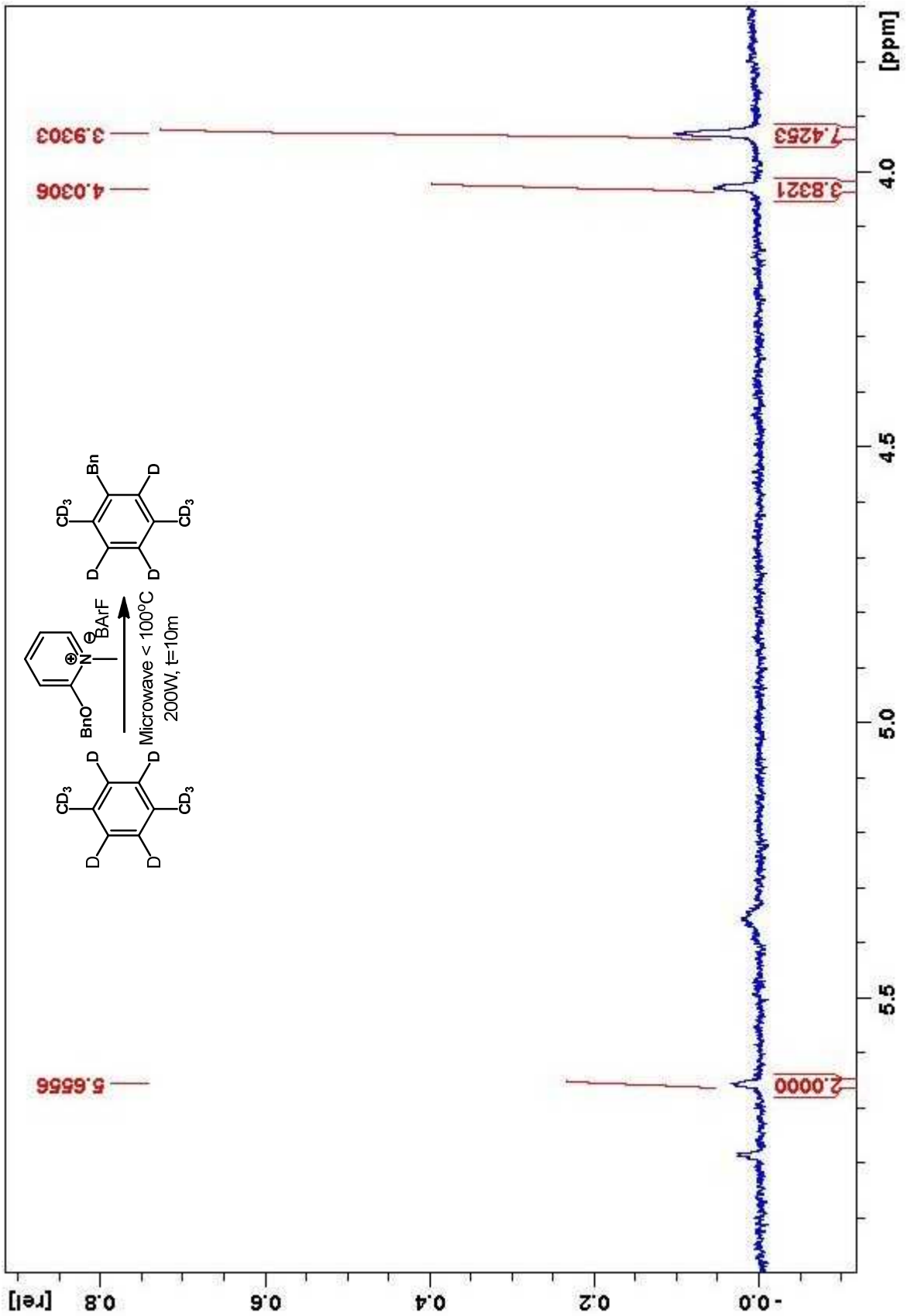


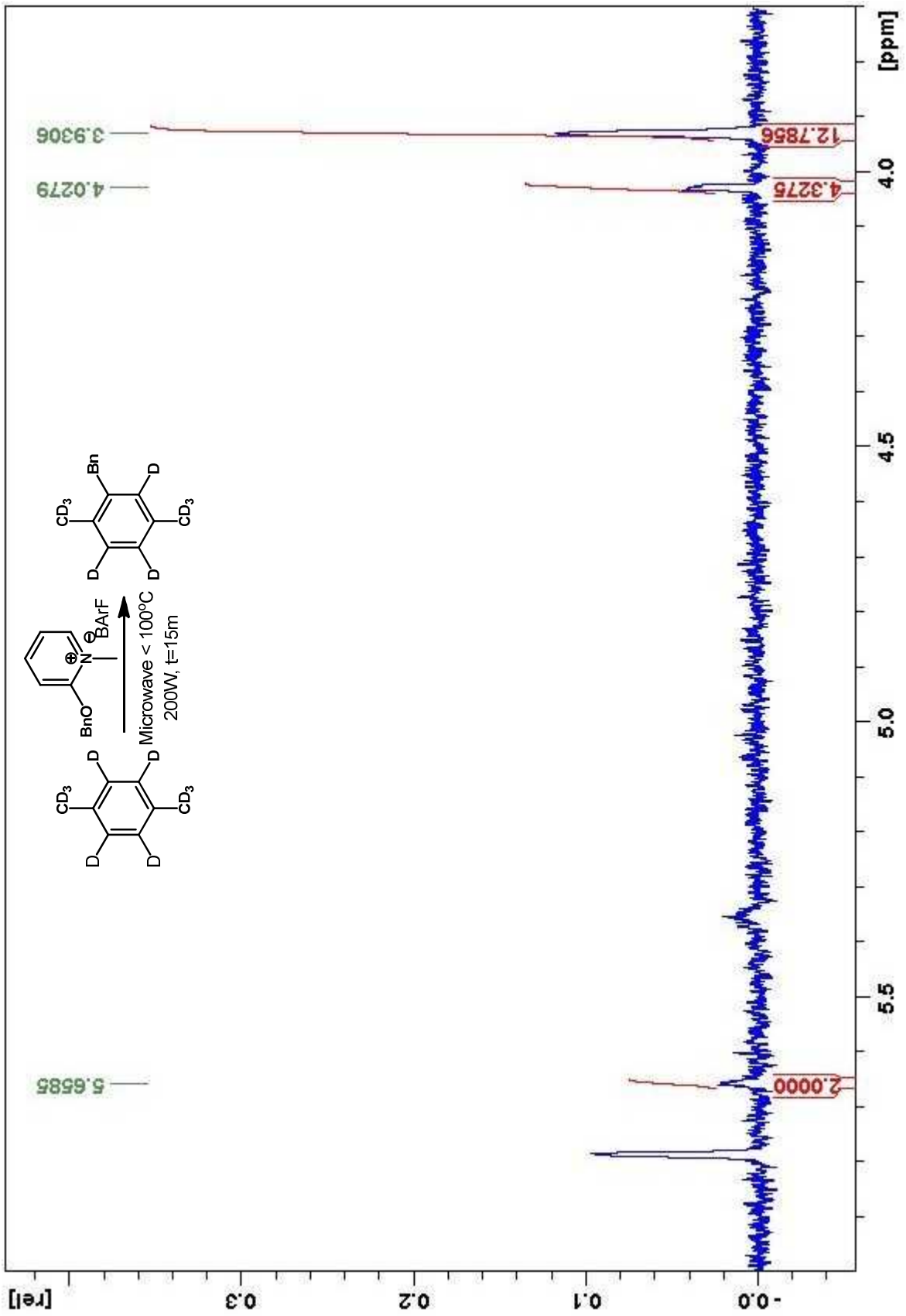


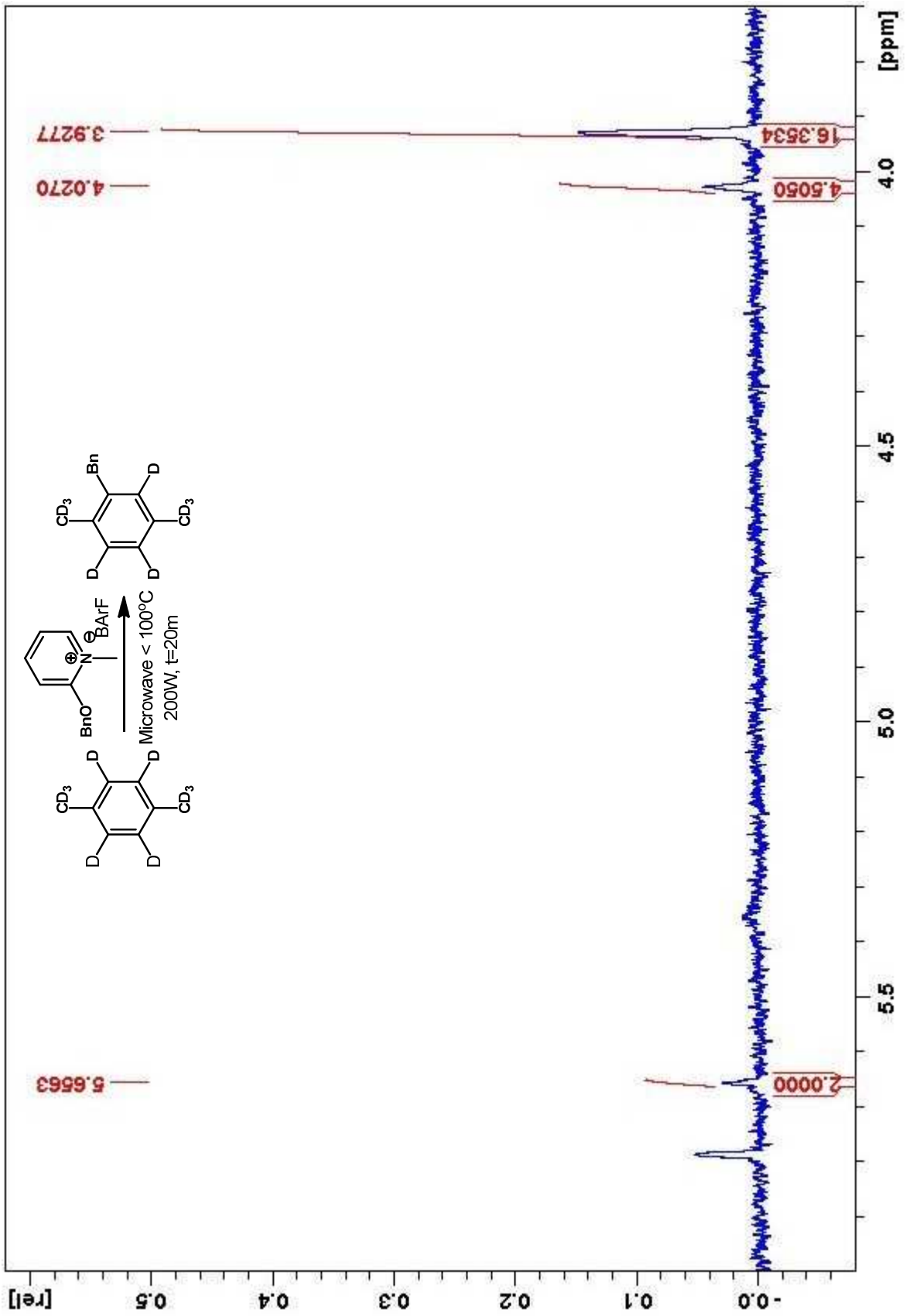
3.5 Individual ^{1}H NMR data- Microwave at < 100°C (200W) from 0m to 30m (see pp. S26-S27 for condensed ^{1}H NMR Data)

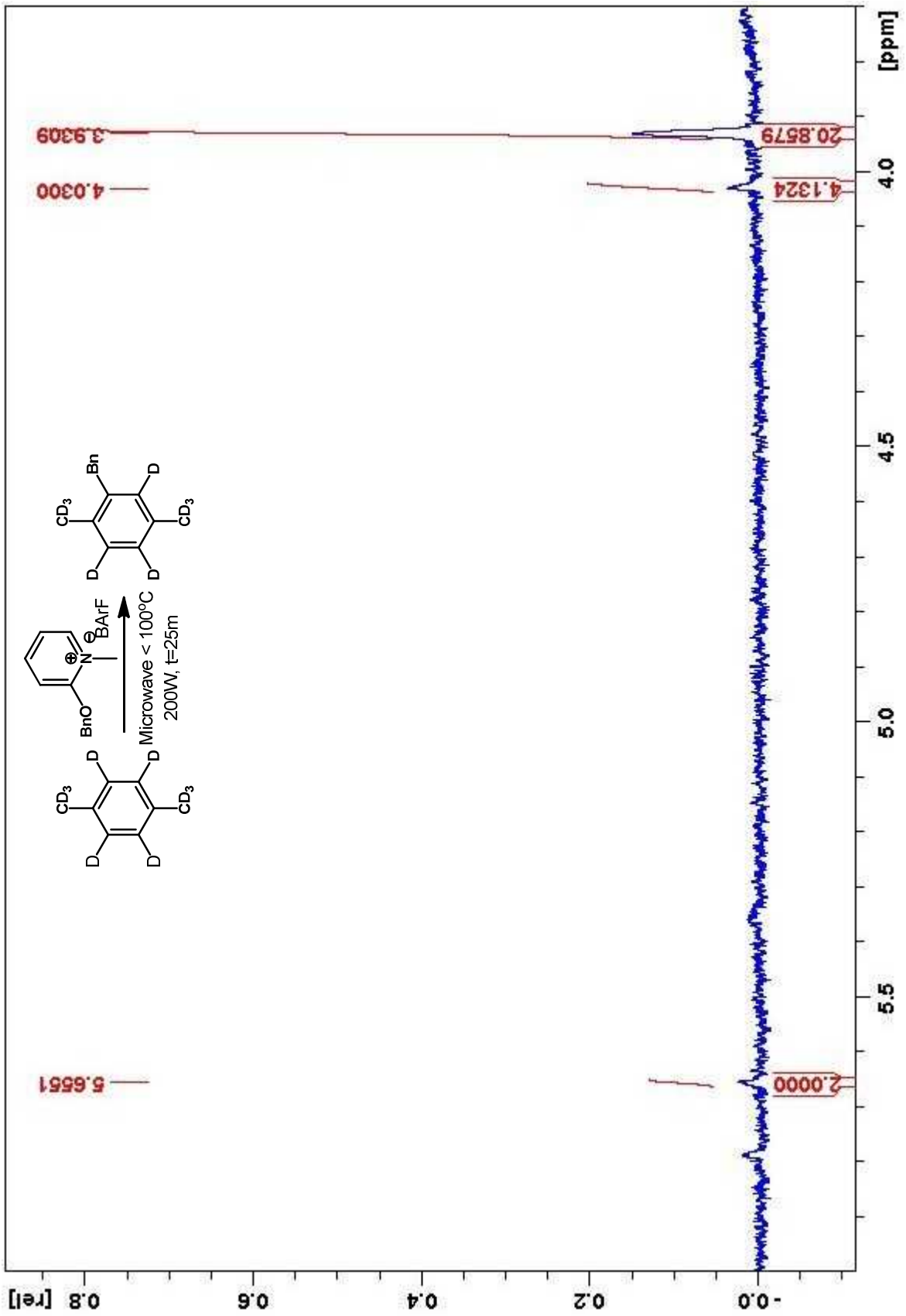


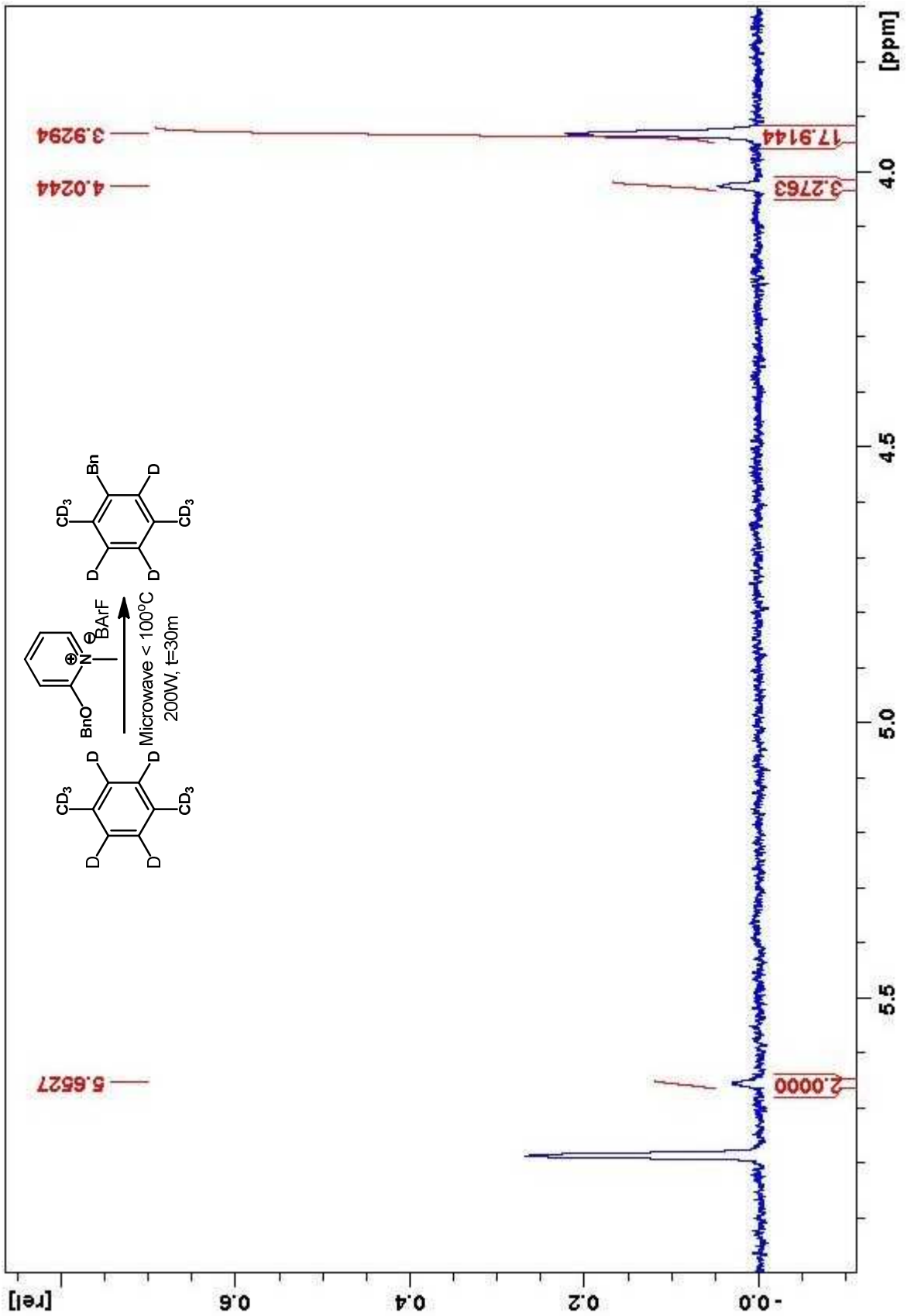



5.6556
4.0306
3.9303
3.8321
7.4253
2.0000
[rel]
[ppm]
BnO
BArF
Microwave < 100°C
200W, t=10m
Bn
D
CD3

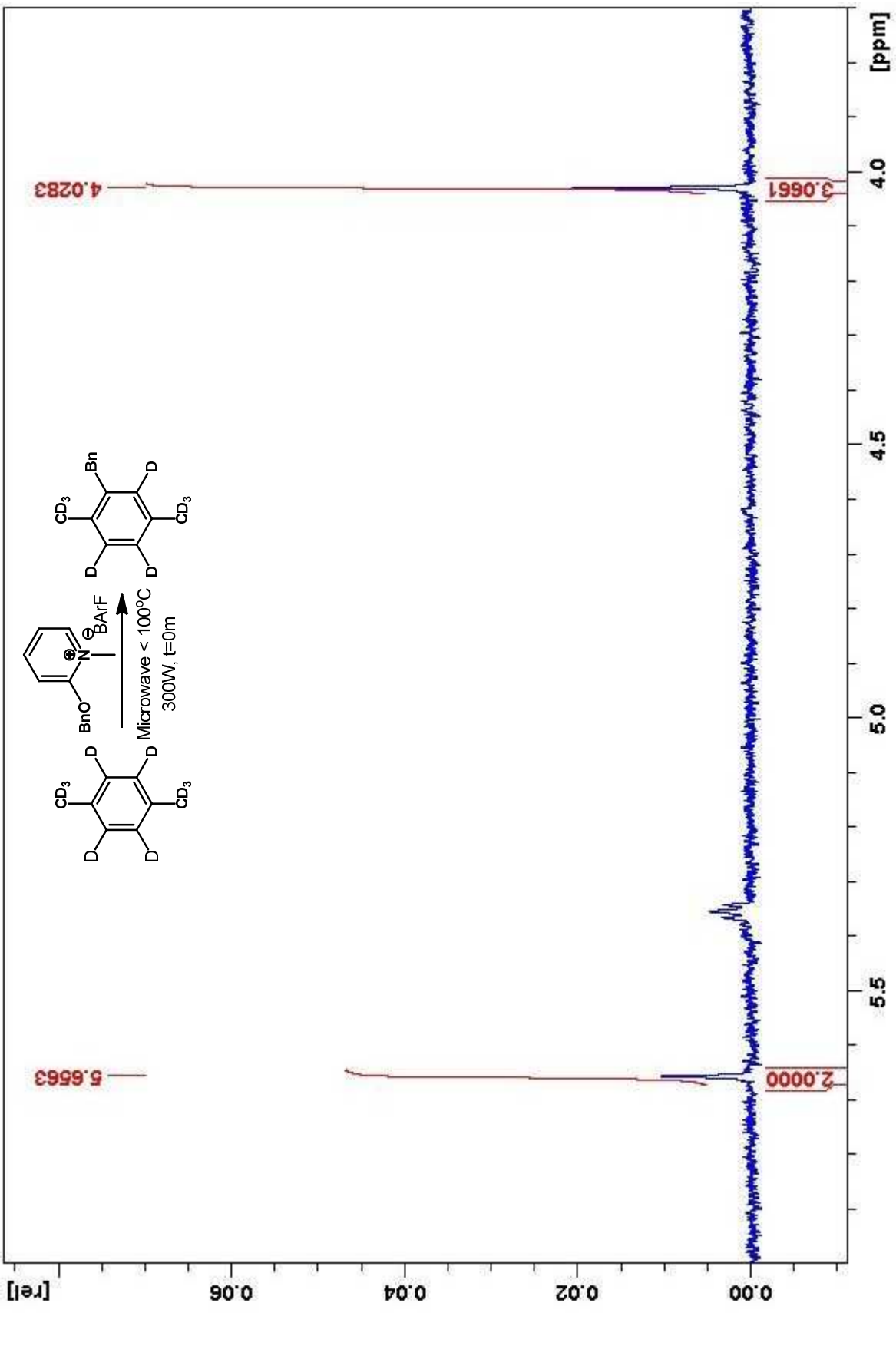


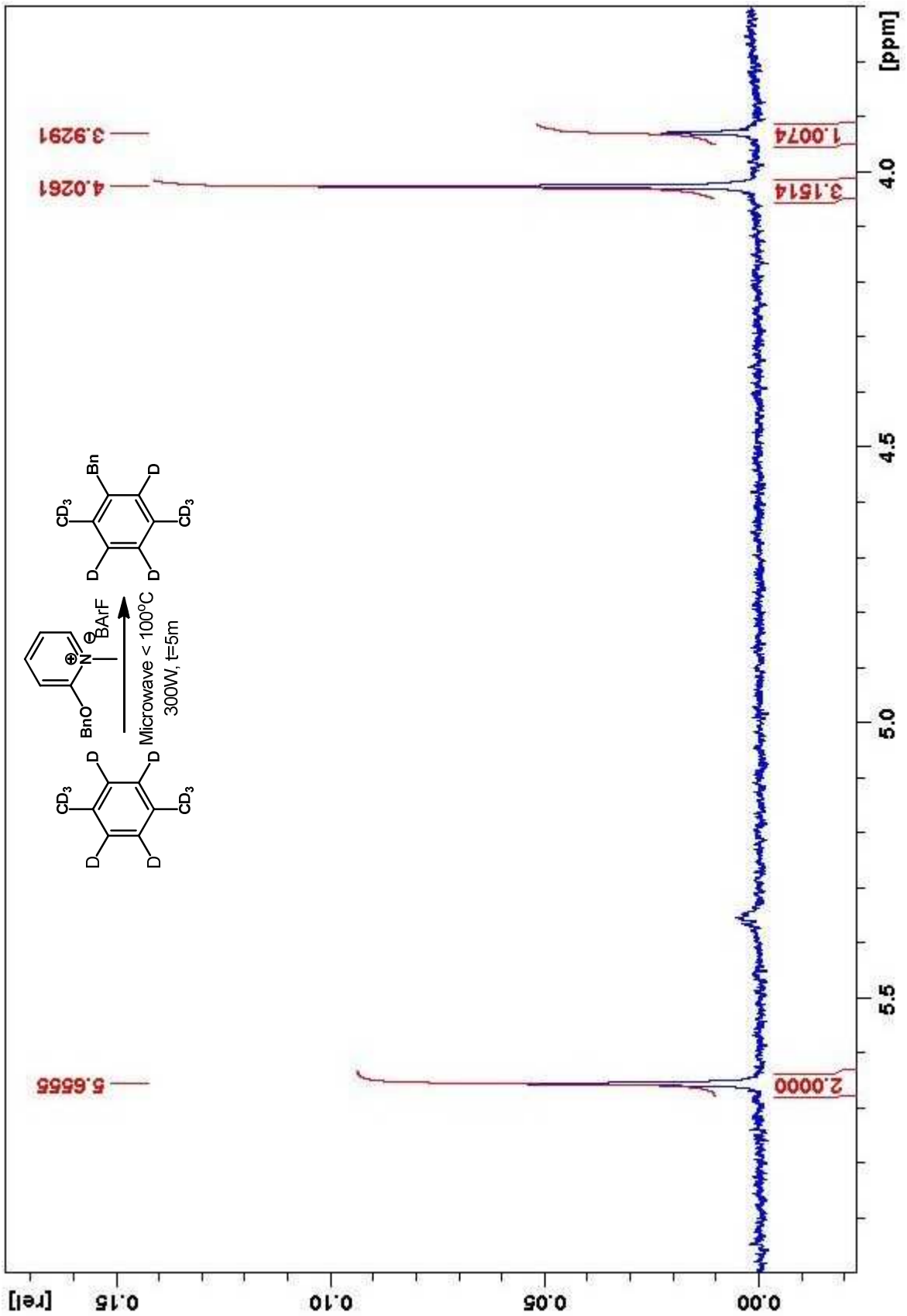


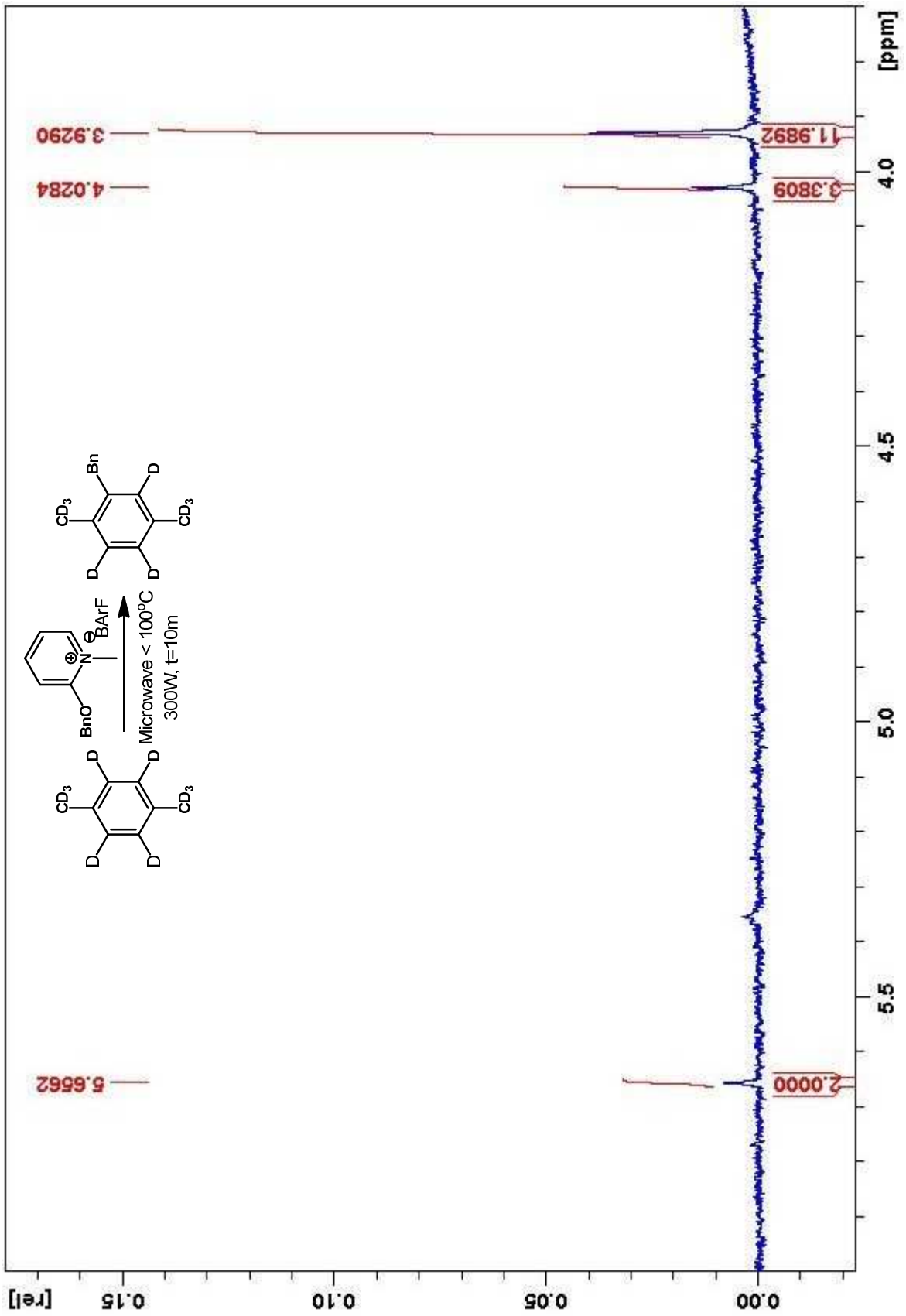


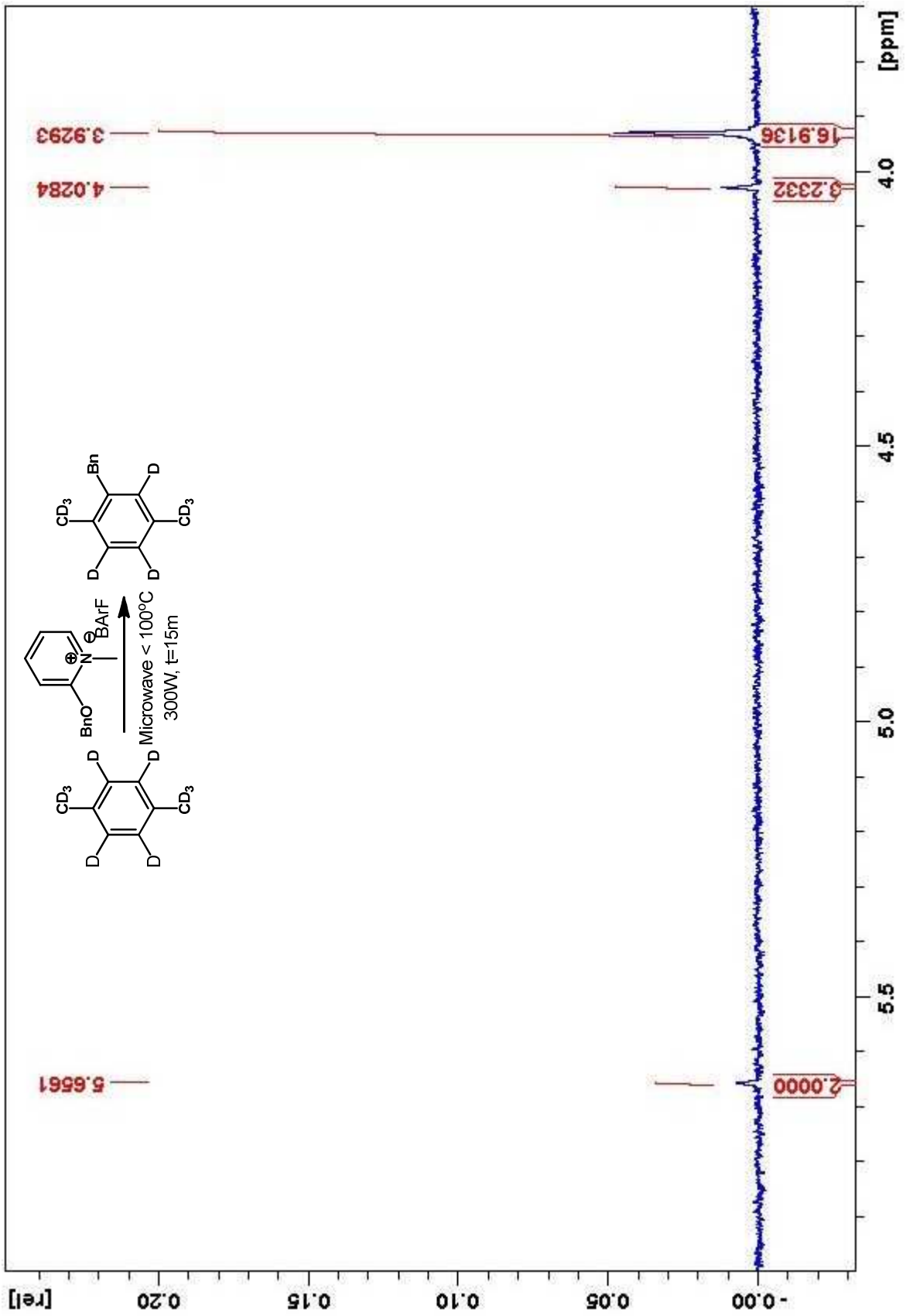


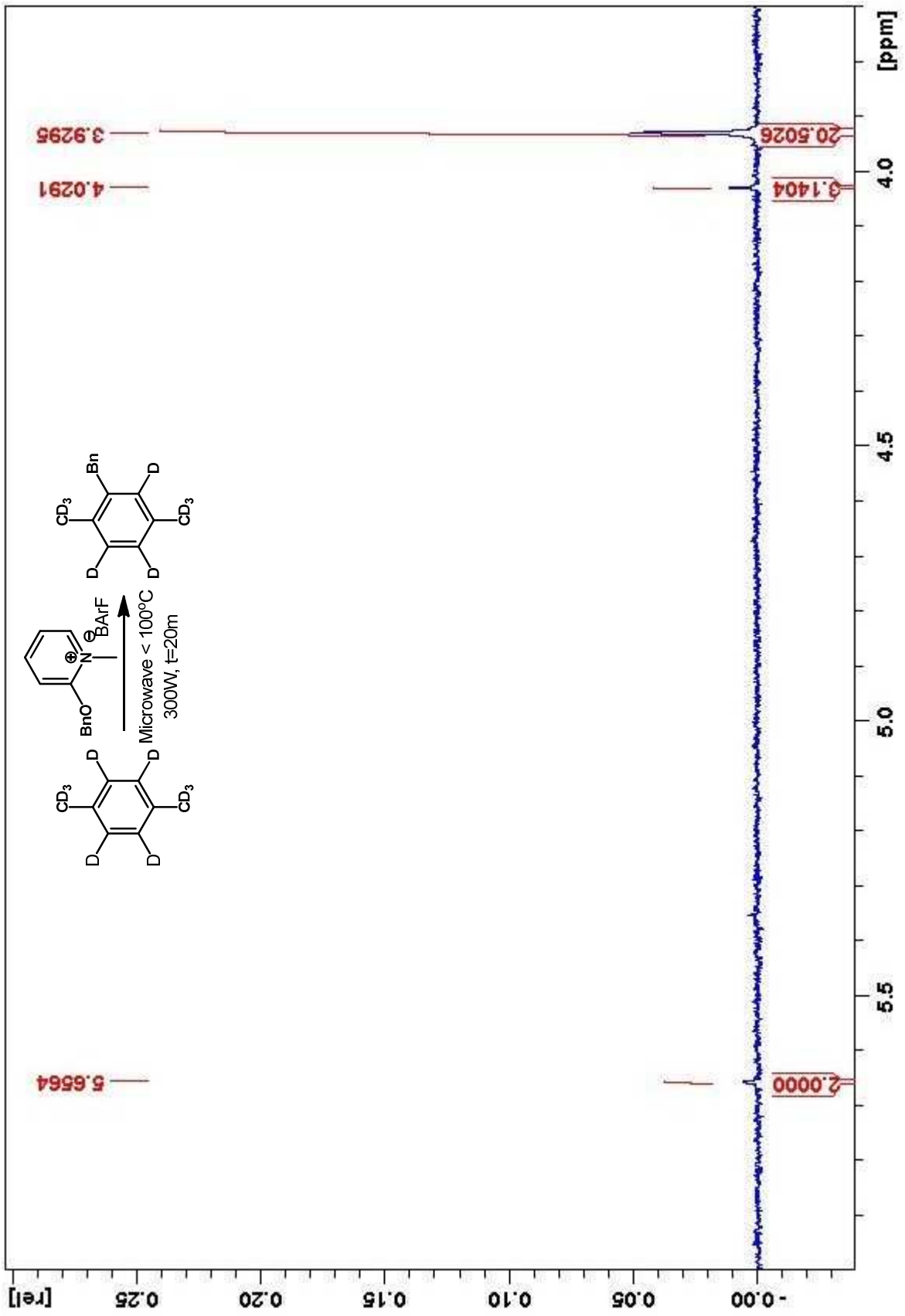
3.6 Individual ^{1}H NMR data- Microwave at < 100°C (300W) from 0m to 30m (see pp. S28-S29 for condensed ^{1}H NMR Data)

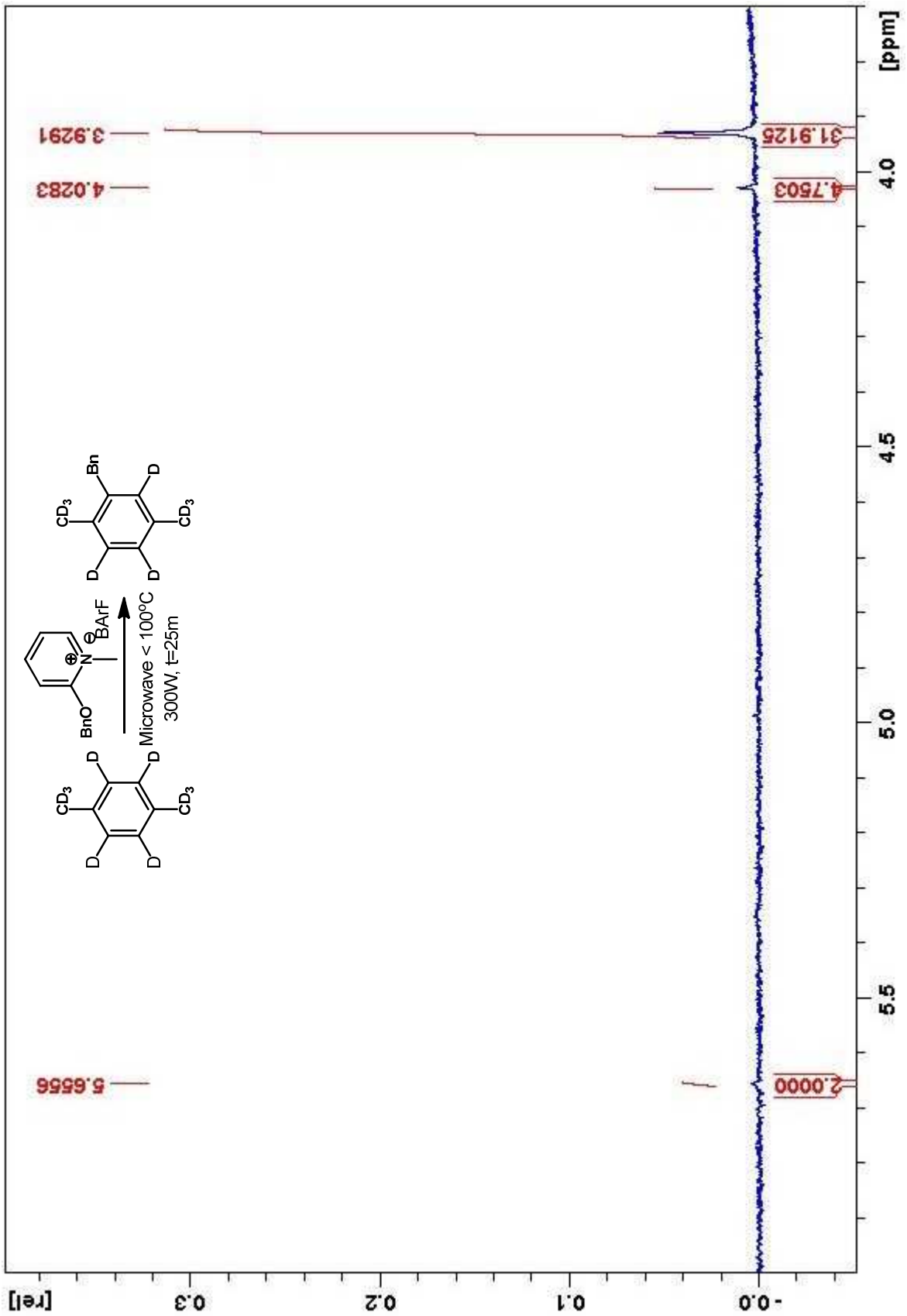


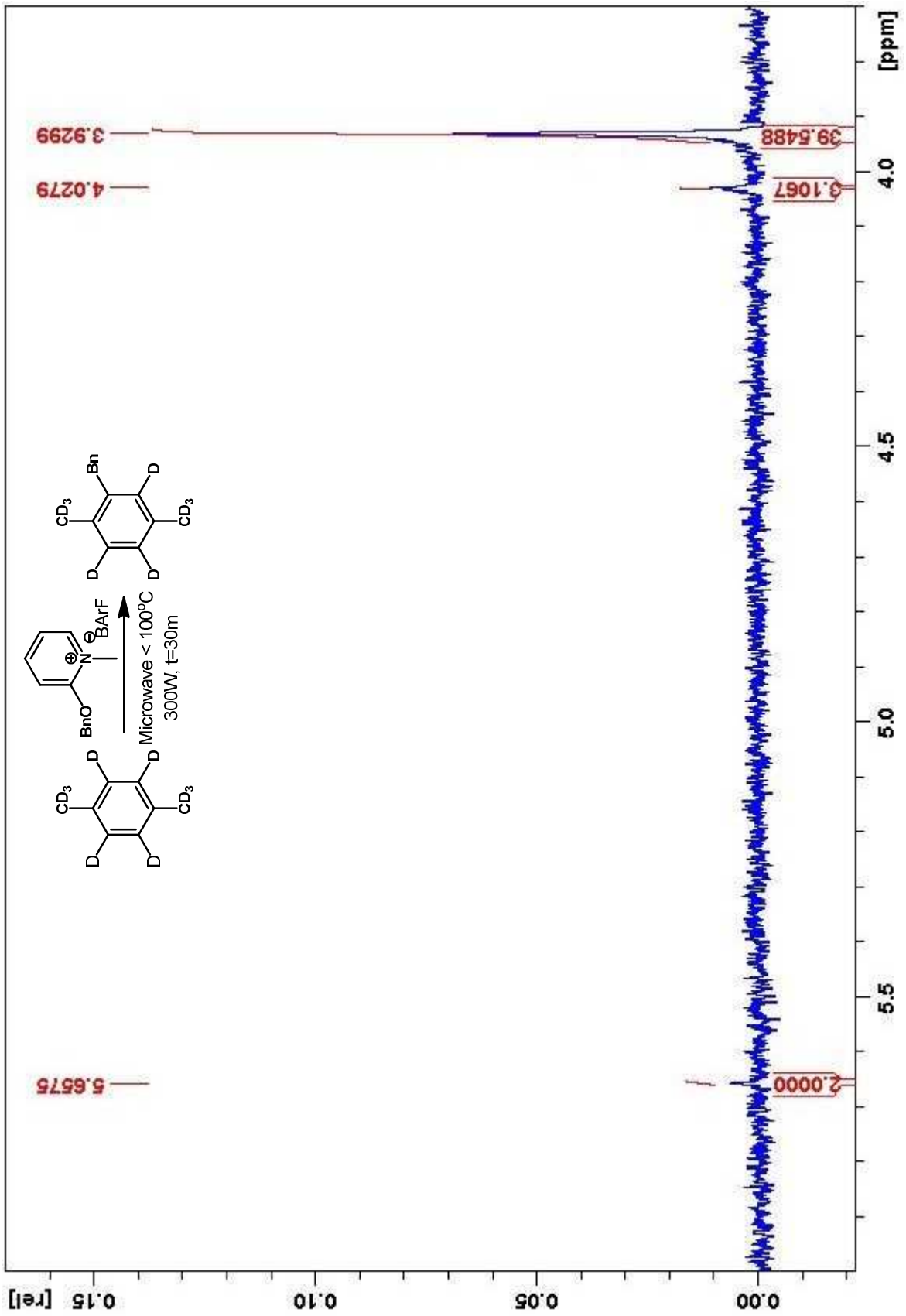




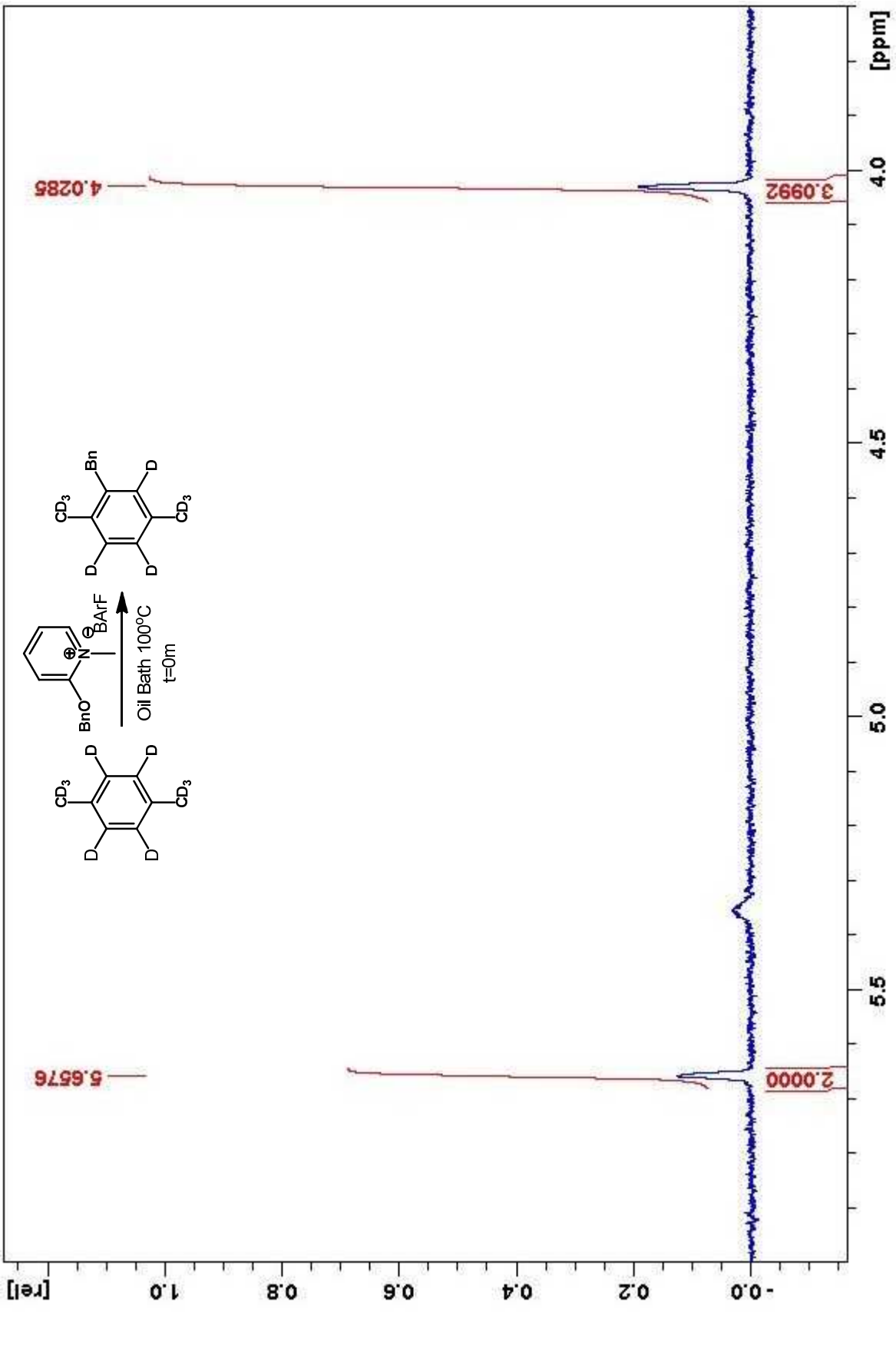


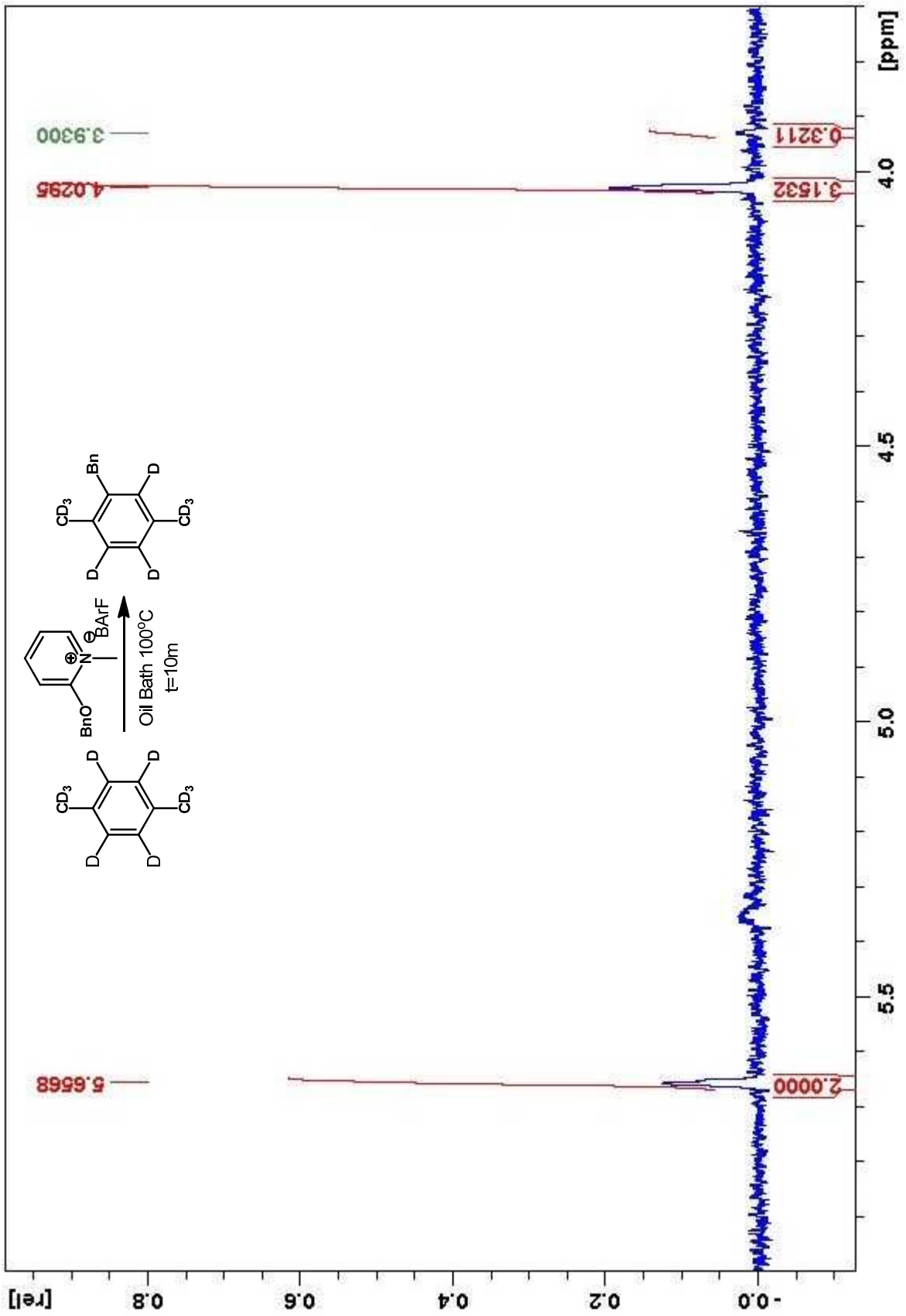


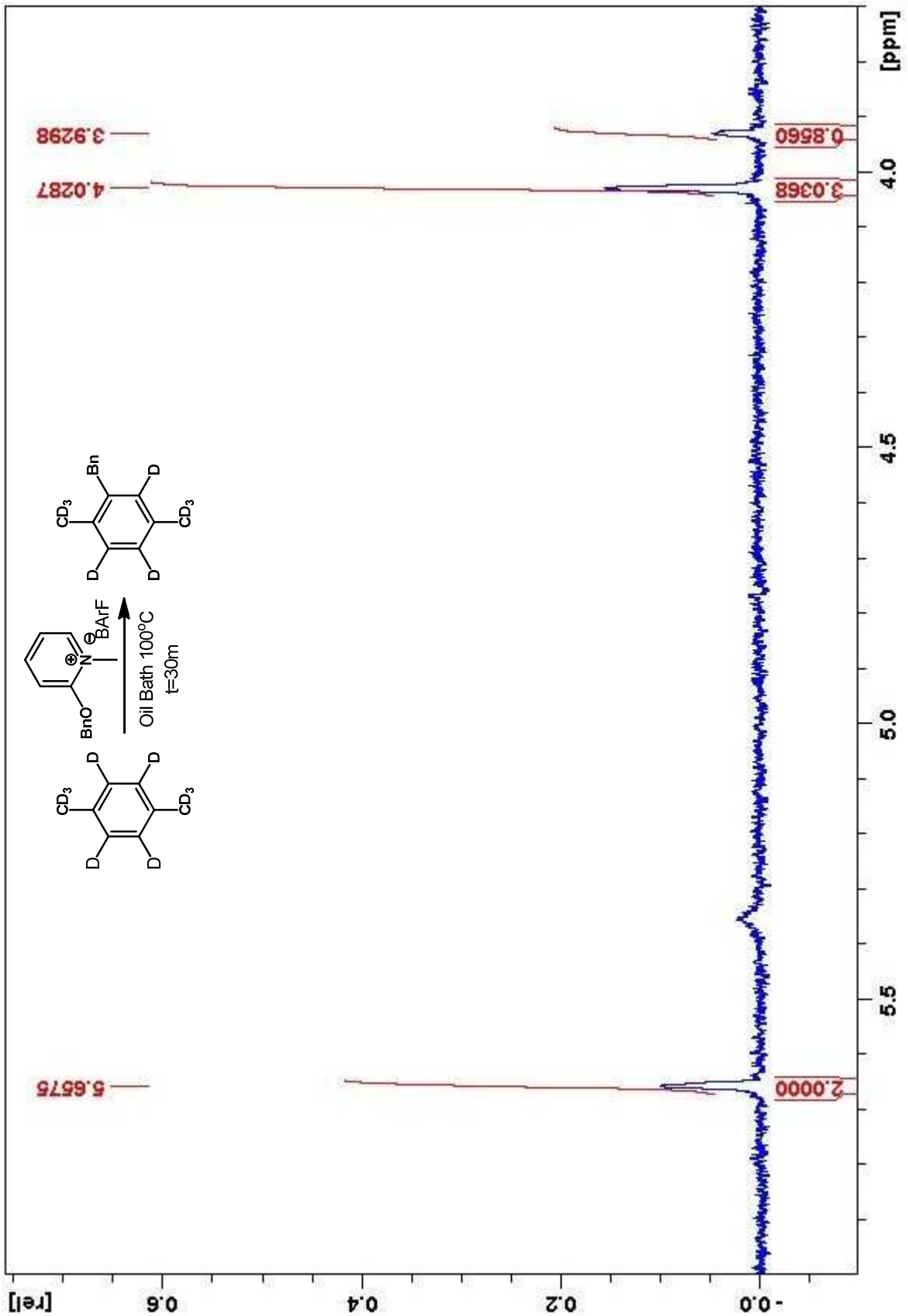


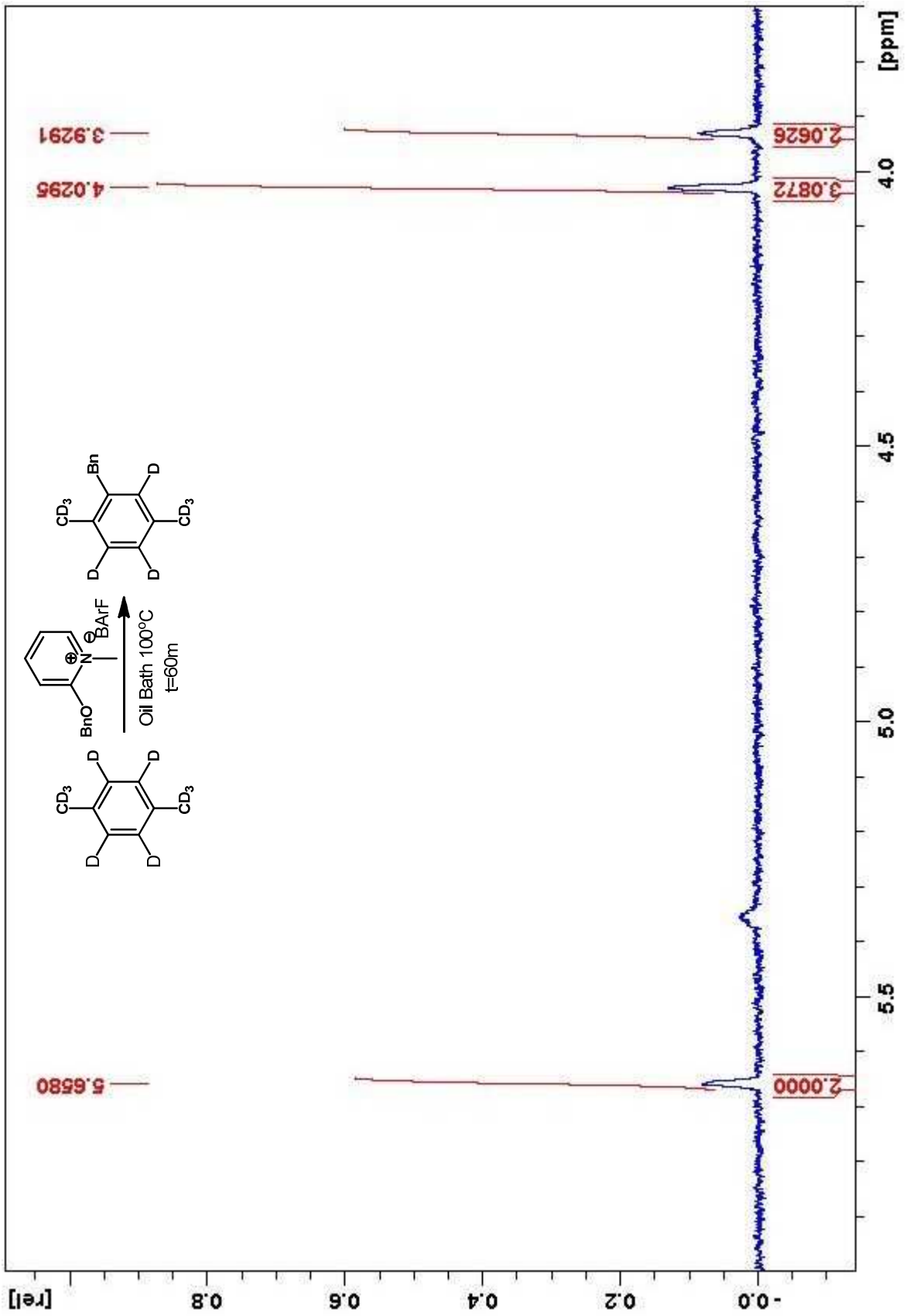


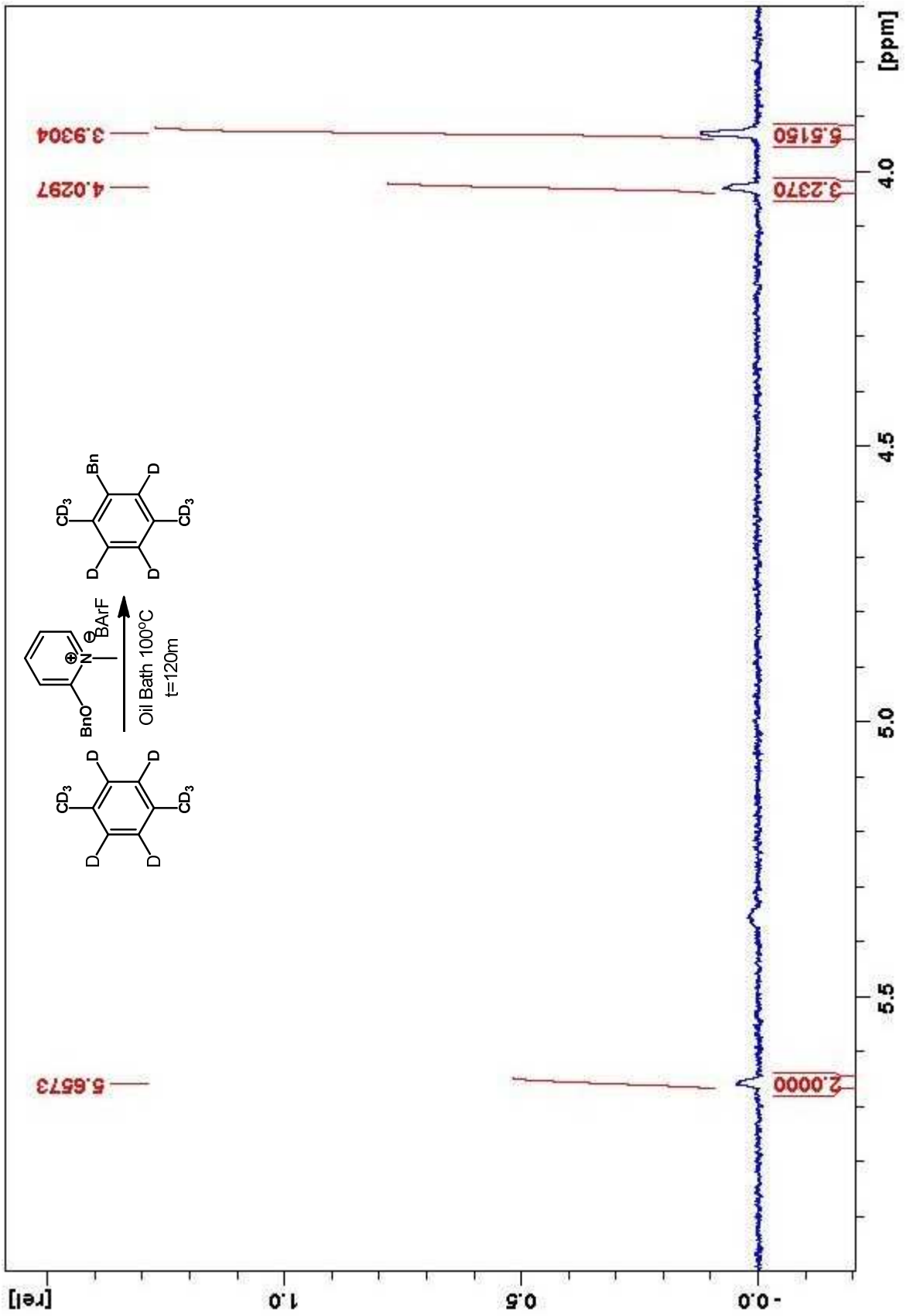
3.7 Individual ^{1}H NMR data- Oil Bath at 100°C from 0m to 240m (see p. S30 for condensed ^{1}H NMR Data)

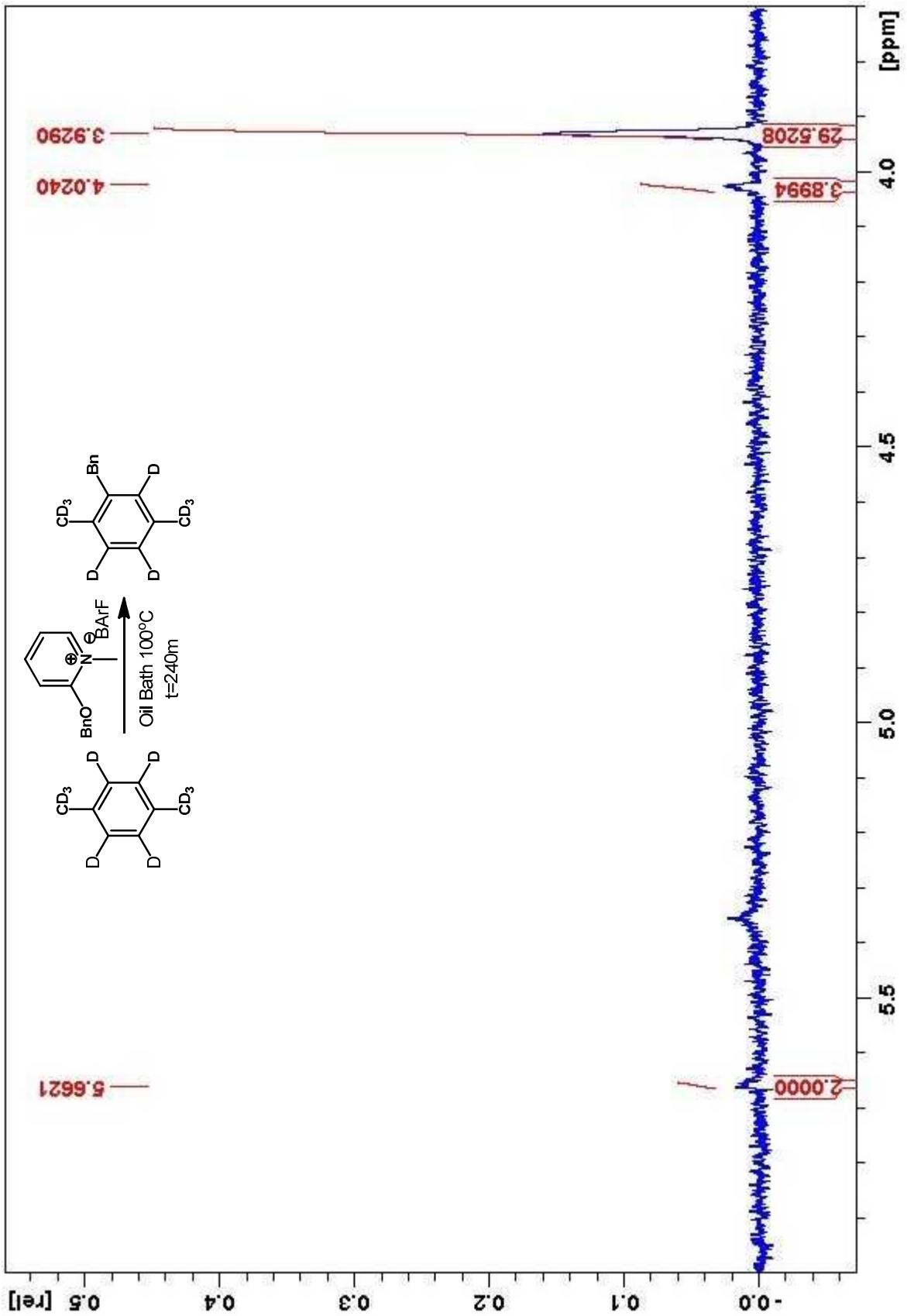




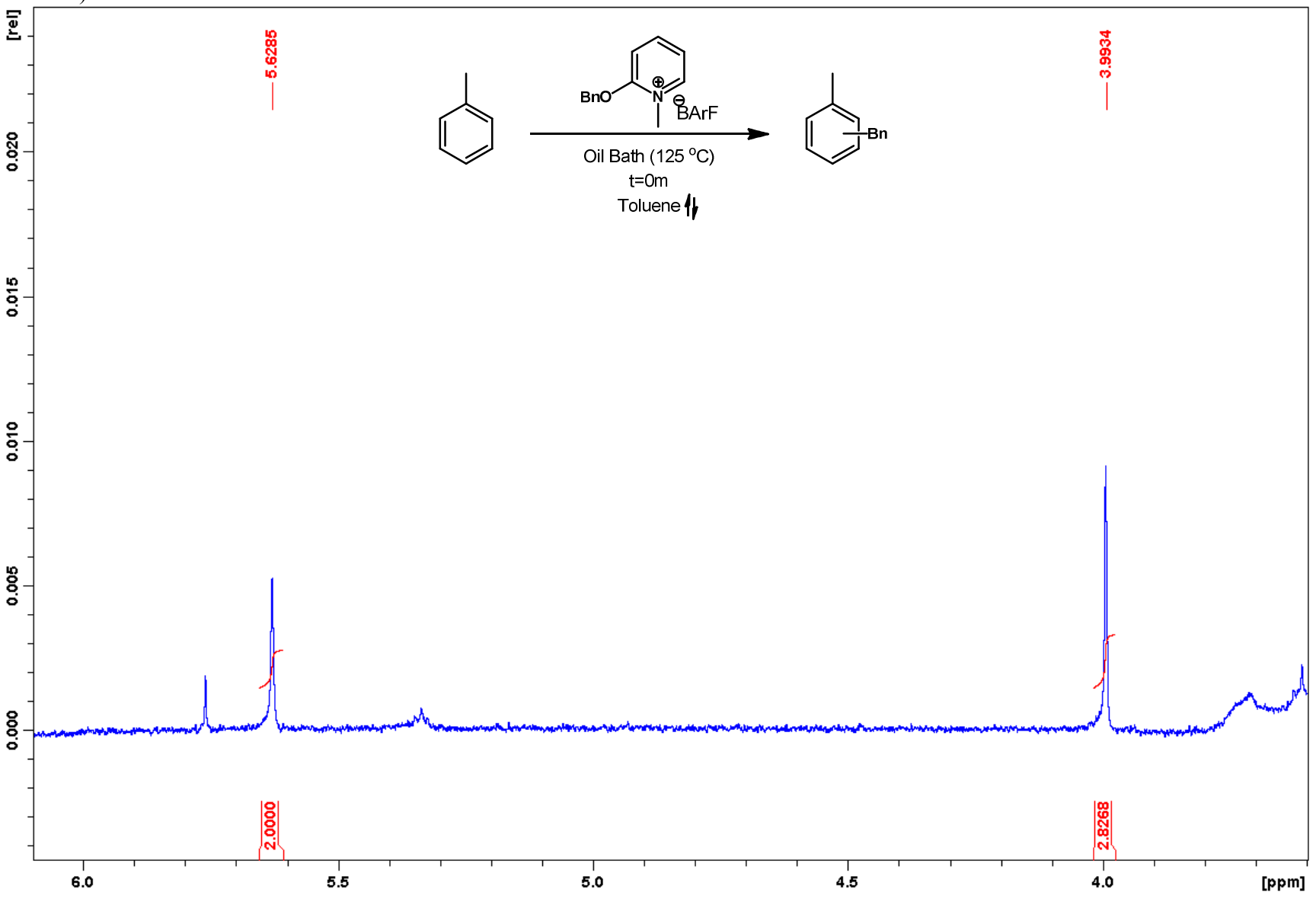


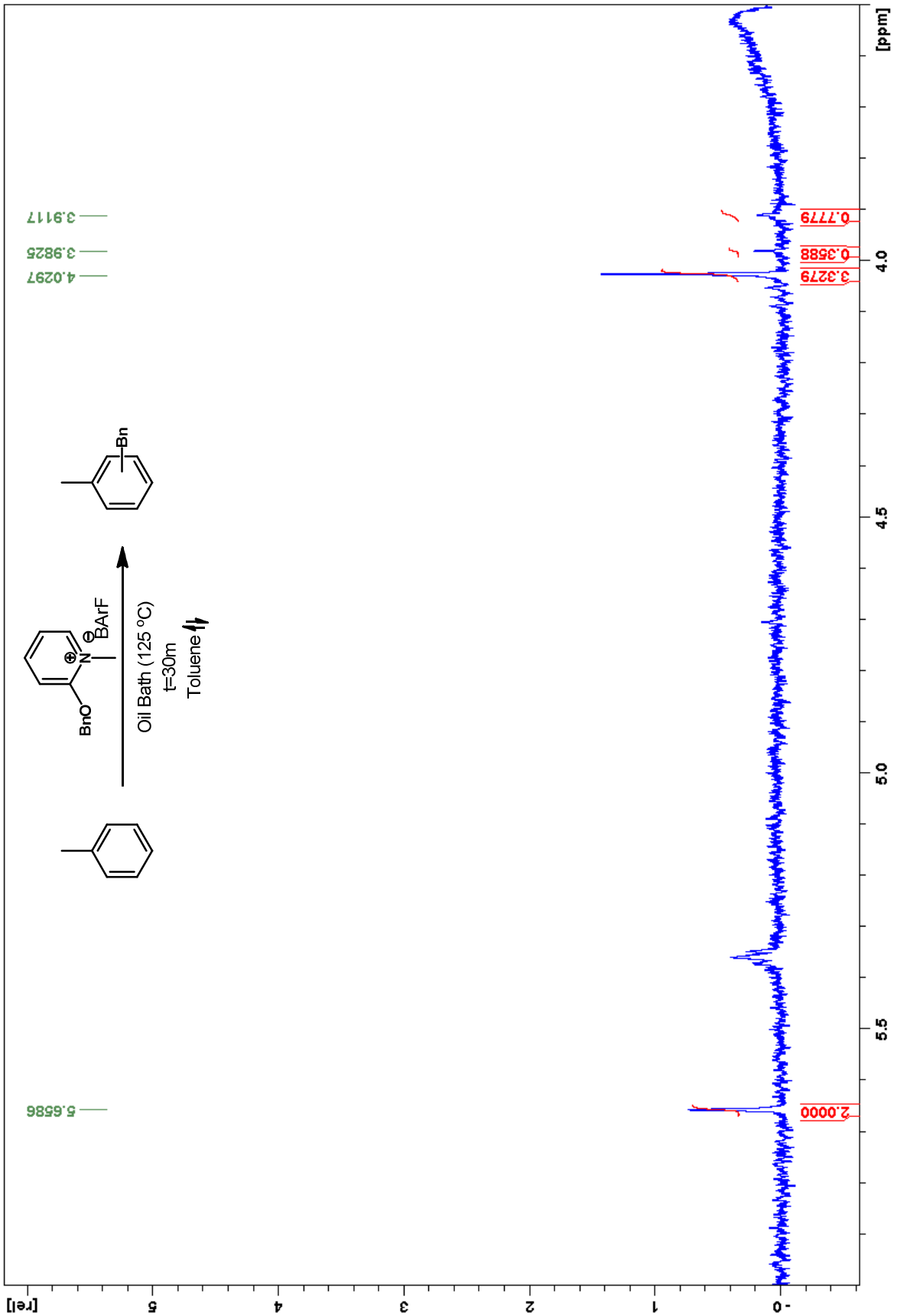


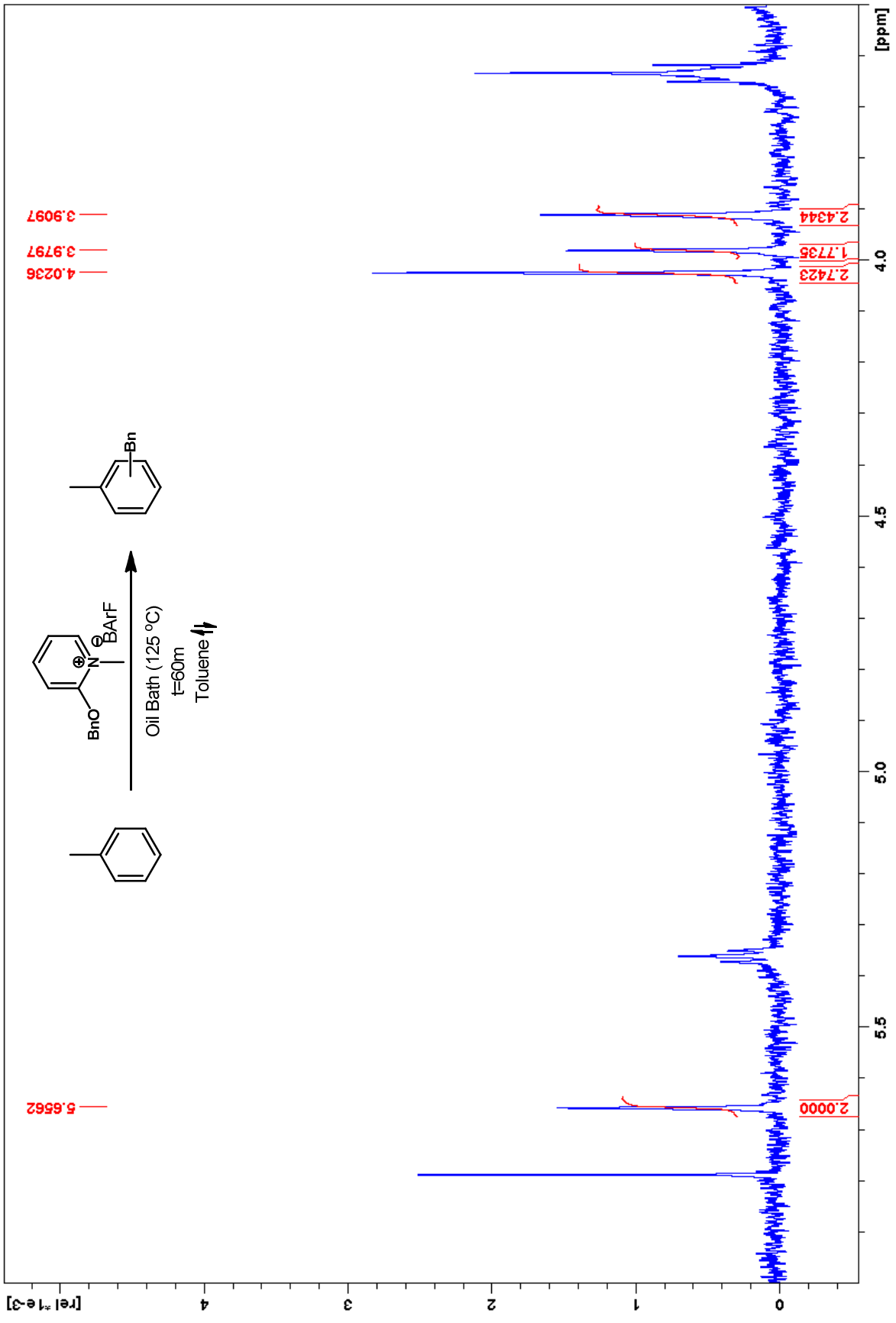




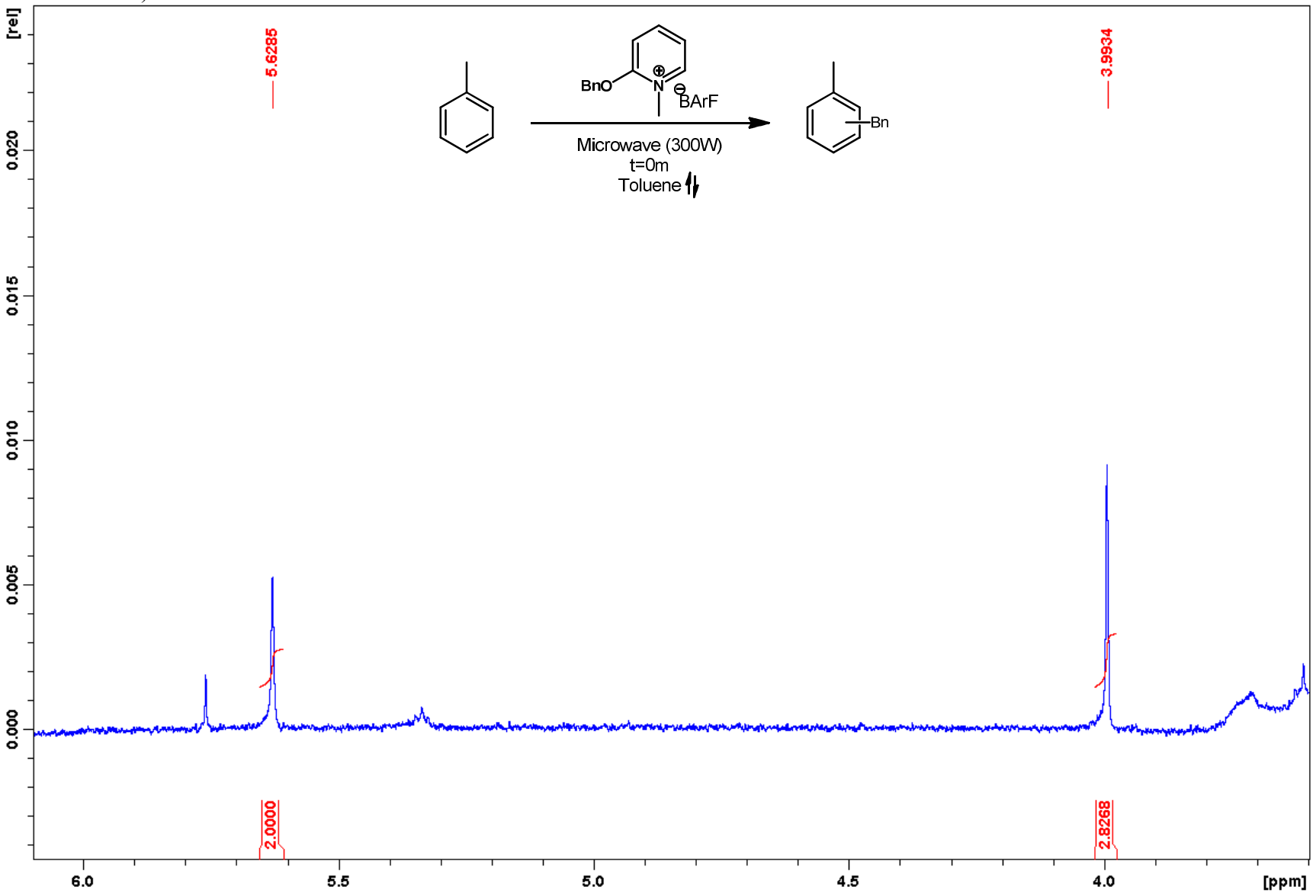
3.8 Individual ^{1}H NMR data- Benzylation of toluene in refluxing toluene in an oil bath from 0-60m (see pp. 31 for condensed ^{1}H NMR Data)

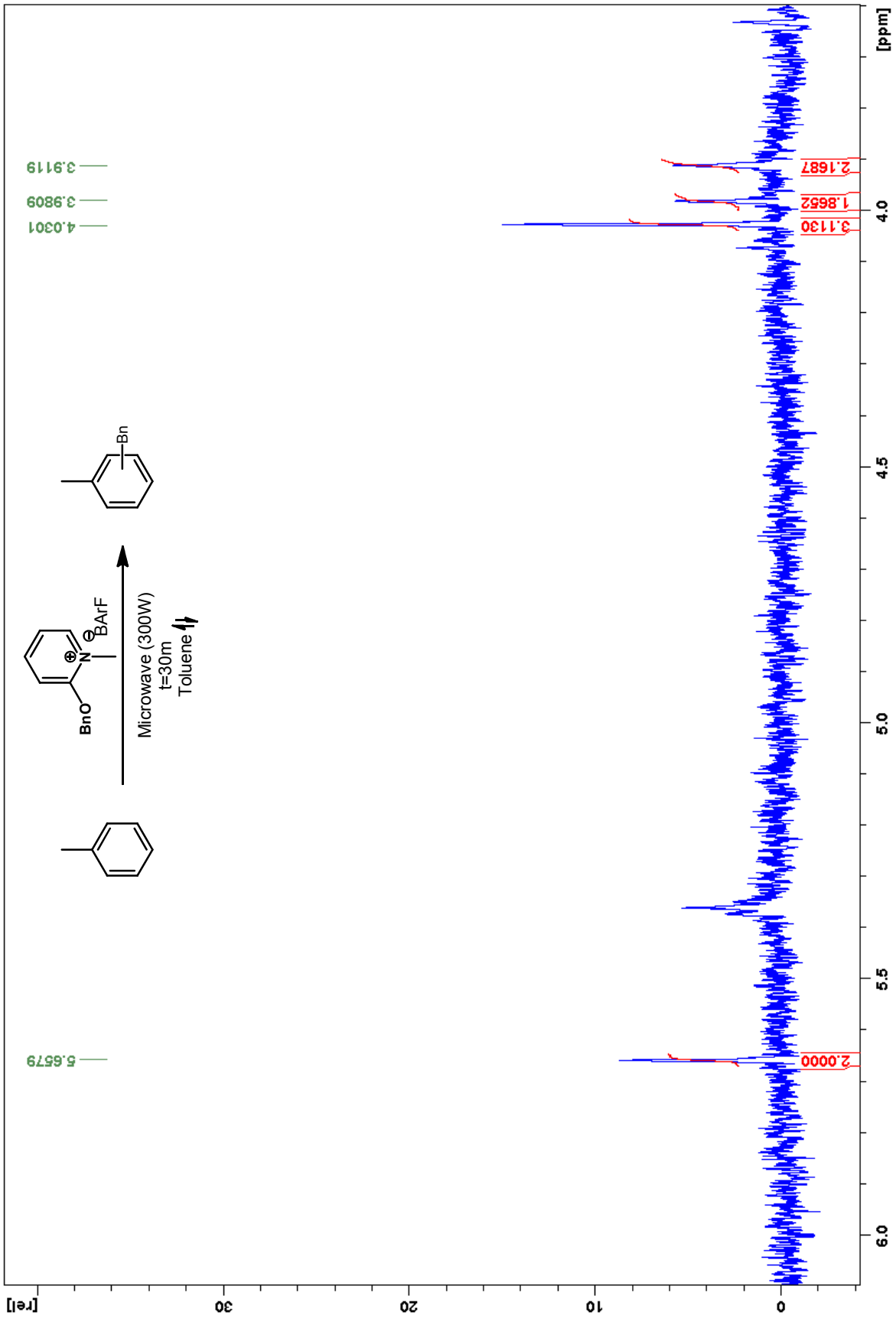


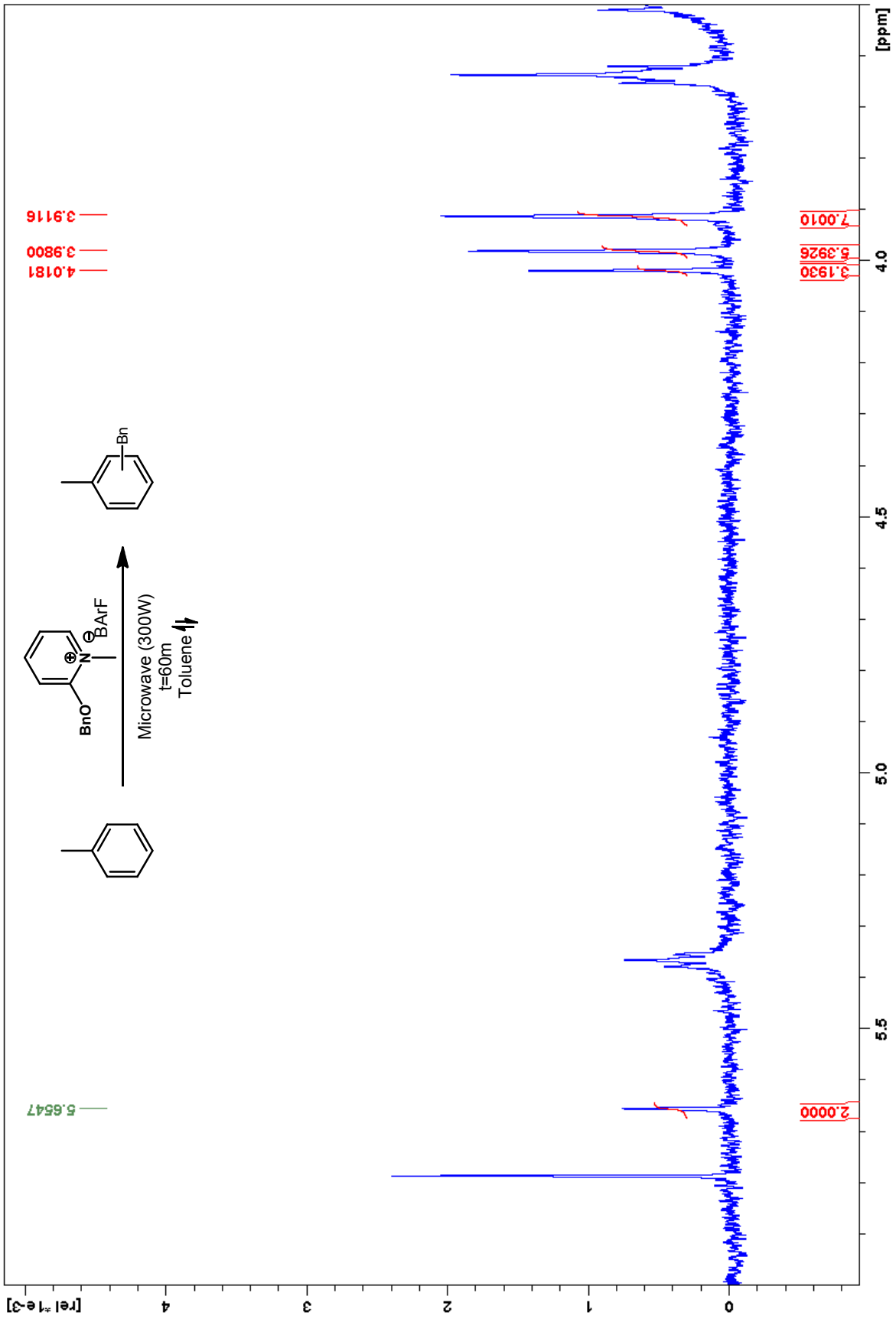




3.9. Individual ^{1}H NMR data- Benzylation of toluene in refluxing toluene in an oil bath from 0-60m (see pp. S32 for condensed ^{1}H NMR Data)







3.10 Individual ^{1}H NMR data- Propylene Glycol Bath at 100°C from 0m to 240m (see pp. S33-S34 for condensed ^{1}H NMR Data)