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Supporting Information

Raman spectroscopy as an in-situ tool to obtain kinetic data for organic transformations

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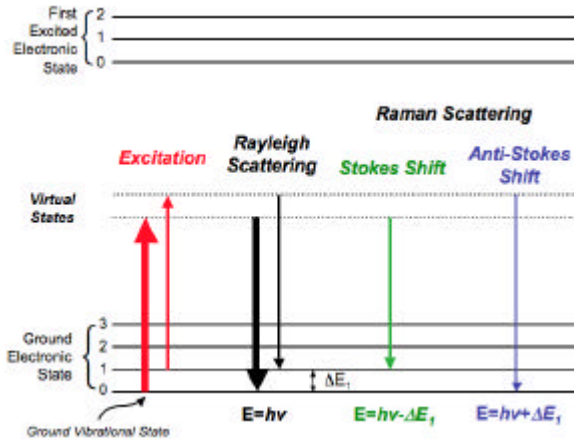
Supporting information

Background to Raman Spectroscopy as a tool for reaction monitoring

The basis behind Raman spectroscopy is the idea that when an incident photon strikes a molecule, an electron in that molecule may either absorb or impart some energy upon the incident photon. This energetically altered photon is then detected as a different wavelength. However, the fundamental principles of Raman spectroscopy dictate that this is a very unlikely phenomenon. Indeed, in comparison to IR spectroscopy, which may absorb up to 90% of the incident light in a 10^{-3} M sample, observance of a Raman scattering event is about 10^{10} times less likely to occur under similar conditions. Accordingly, most photons strike a molecule elastically and return to the detector unchanged, this being termed Rayleigh scattering. Also, Raman scattering has a second-order dependence on the frequency of the incident light. Firstly, it is dependent upon the electronic component of the light wave to momentarily polarize the electron cloud of a molecule. This depolarization, or deformation of the electronic field, is slightly higher energetically, but does not represent a quantized energy change (e.g. an electronic transition) and hence is termed a *virtual state*. It is only at this point that a second photon can encounter this excited molecule and impart some of its energy to activate a resonant vibrational oscillation of the molecule. The result is a lower-energy photon that is deflected and detected by the spectrometer with a longer wavelength and has been termed Stokes shift. Less likely at normal temperatures, the photon may strike an already-vibrationally excited molecule, absorbing energy and deactivating a vibrational oscillation, hence, returning to the detector higher in energy and with a shorter wavelength and has been termed anti-Stokes shift.



Schematic of Raman scattering fundamentals. Most photons (>99.9%) simply bounce back, unaltered, and give no information regarding the molecule (Rayleigh scattering). When a photon imparts some of its energy onto an electron in a low-energy virtual state, the detected wavelength of the returning photon is longer. This is termed the Stokes shift. When a photon absorbs some energy from an electron that is in a high-energy virtual state, the detected wavelength is shorter. This is termed anti-Stokes shift.

Raman signal strength is dependent upon a number of variables and can be described as shown in equation 1 where I = Signal Intensity (electrons), P_o = laser intensity (photons·sec^{-1}), β = Raman cross-section (cm^2·molecule^{-1}·sr^{-1}), D = number density (molecules·cm^{-3}), l = path length (cm), Ω = solid angle of

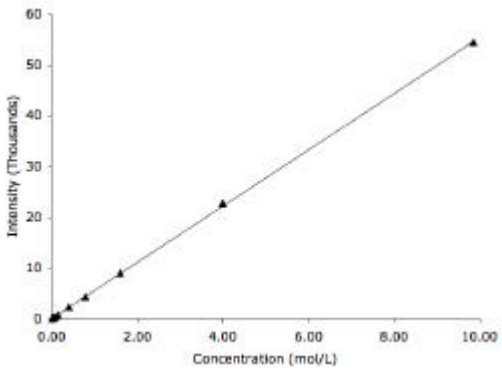
collection (sr), T = transmission factor - signal loss due to filters in system (unit-less), Q = quantum efficiency of detector (electrons·photon^{-1}), t_s = integration time (sec). It can be more simply expressed as shown in equation 2 where γ is treated as a constant equal to $P_o\beta\Omega TQ$. In a laboratory D, *l*, and t_s are easily manipulated or, more importantly, if holding all others constant then *changes* in any of these three variables should be observable.

$$I = P_o\ \beta\ D\ l\ \Omega\ T\ Q\ t_s$$

$$I = \gamma\ D\ l\ t_s$$

The number density term, while dependent on a number of factors, is most closely tied to the concentration of the sample. More concentrated solutions lead to stronger Raman signal. As a result, Raman spectroscopy is in theory an effective means to measure concentration changes in a dynamic system.

Confirming the relationship between signal strength and concentration. To probe the effects of concentration on signal strength in the Raman spectrum we recorded spectra of benzaldehyde at a wide range of concentrations from 0.0160 M to 9.847 M in ethanol. The plot of signal strength due to the peak at 1000 cm^{-1} versus the concentration of benzaldehyde (Figure 3) showed a linear relationship, R^2=0.9998, confirming that Raman spectroscopy is an effective means to measure concentration changes in a reaction.



Plot of Raman signal intensity at 1000 cm^{-1} for solutions of benzaldehyde in ethanol at nine different concentrations, ranging from 0.0160 M to 9.847 M, R^2=0.9998

Apparatus and experimental procedures

The Raman system used was an Enwave Optronics Spectrometer, Model EZRaman-L (www.enwaveopt.com). To interface the microwave unit and Raman spectrometer, the fiber-optic probe from the spectrometer was placed into the microwave cavity and the laser focused through a quartz light pipe. The fiber-optic probe tip was inserted so it touched the wall of the reaction vessel.

EXCITATION SOURCE: NIR, frequency stabilized, narrow linewidth diode laser at 785 nm. Laser power at sample ~200 mW. Linewidth < 2 cm^{-1}. Fiber-coupled laser output (100 µm, 0.22 NA).

FIBER-OPTIC PROBE: Permanently-aligned two single fiber combination 100 µm excitation fiber, 200 µm collection fiber (0.22 NA). Working distance: 8 mm (standard). Rayleigh rejection: O.D. > 7 at laser wavelength.

CCD DETECTOR: High sensitivity linear CCD array. Temperature regulated (at 13 °C) operation for long integration time and stable dark reference subtraction. Pixel Size: 14 µm x 200 µm (2048 pixels); 16 bit digitization.

SPECTROGRAPH: Symmetrical crossed Czerny-Turner design. Resolution: ~10 cm^{-1} at 785 nm. Excitation spectral coverage: 200 cm^{-1} to 2400 cm^{-1}. Built-in software calibration.

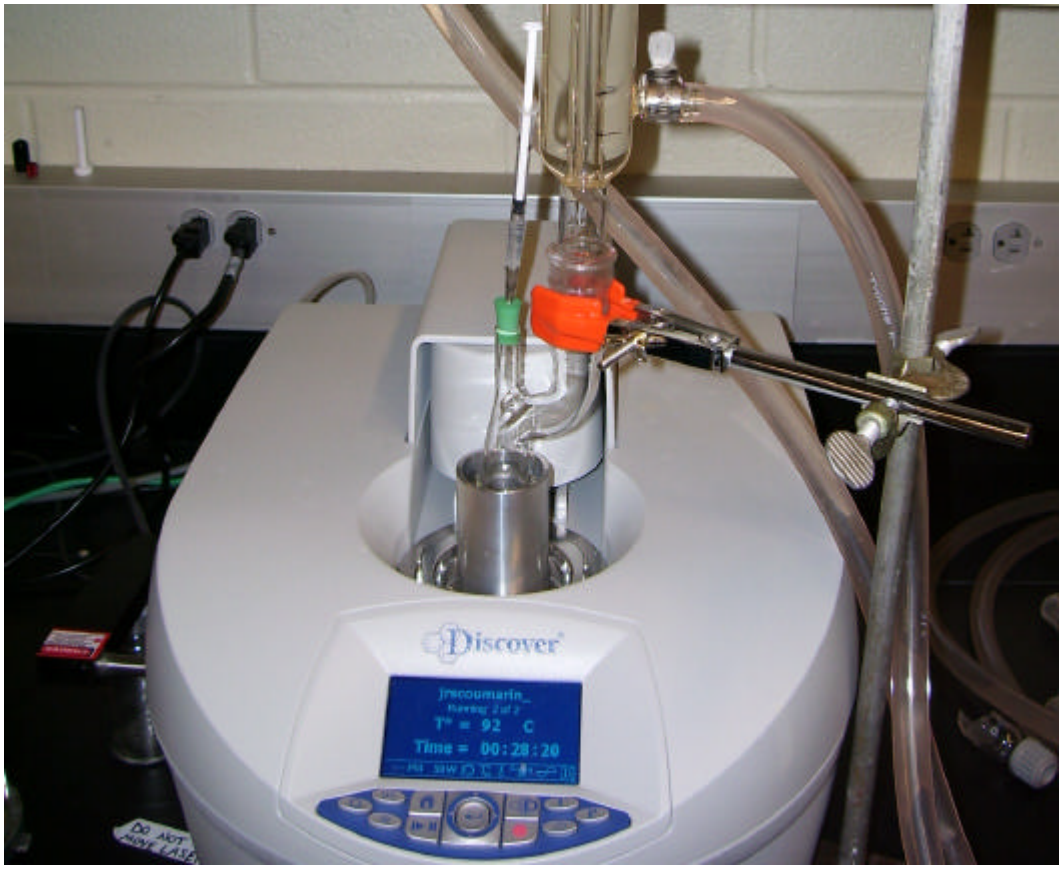
SYSTEM SOFTWARE: EZ Raman 3.5.4MAS. Data files exported into Microsoft Excel.

The microwave unit used was a CEM Discover® S-Class. The unit contains an acess port in the side of the cavity. Reactions can be performed in 10 mL or 35 mL glass tubes or open round-bottom flasks of up to 125 mL in volume. In the case of sealed-tube experiments a septum was attached and the pressure monitored by an automated load cell connected to the vessel. For open-vessel experiments, a reflux condenser could be attached to the top of the flask and an attenuator used to prevent microwave leakage. The temperature of the contents of reaction vessels was monitored using a calibrated infrared temperature control mounted under the vessel. The contents of the reactions vessel were stirred, when required, by means of an electromagnetic stirring mechanism located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure and power profiles were monitored using commercially available software provided by the microwave manufacturer.

Typical procedure for monitoring the formation of 3-acetylcoumarin.

Into a 50.00 ml volumetric flask was placed salicyaldehyde (6.106 g, 50.00 mmol) and ethyl acetoacetate (6.507 g, 50.00 mmol). The reagents were diluted to 50.00 ml with ethyl acetate. This solution was transferred to a 50 ml long-necked round bottom flask equipped with a Teflon-coated stirbar. The flask was placed into the microwave cavity, making sure that any company glassware markings were orthogonal to the Raman laser path. The microwave attenuator was then locked in place. A 2" adapter was connected to the round bottom flask to allow a Claisen adapter with septum inlet to be placed atop the reaction flask (Figure 18). A reflux condenser was placed on the Claisen adapter. The septum inlet was capped with a rubber stopper with a 22-gauge syringe needle inserted through. The Raman probe was inserted into the microwave cavity until the quartz light pipe just made contact with the side of the reaction flask. The reaction mixture was brought to reflux (83-84ºC) using a microwave power of 50 watts. Once at reflux, the microwave power was was dropped to 7 watts and the temperature was set artificially high at 90ºC to ensure the microwave was always applying continuous power and reflux was maintained. At this time, a background scan of the reaction was recorded. This background is automatically subtracted from all subsequent scans, removing any signal due to starting materials and solvent. The Raman spectrometer was set to acquire a spectrum every 10 s (actual observed acquisition rate was 12.2 s), with 10 s integration times, "boxcar" set to 3 and "average" set to 1. Continuous scans were then begun. After the first scan (t = 0), the piperidine catalyst (436 mg, 4.0 mmol, 8 mol%) was rapidly injected into the reaction mixture. As the reaction is dynamic and the change in concentration is initially linear, the first acquisition after the catalyst is injected was set to half of the observed aquisition rate (e.g. 6.1 s). Each subsequent acquisition is set to 6.1 + 12.2*n* seconds. After running the reaction for the requisite period of time the Raman data acquisition and the microwave heating were halted. The reaction mixture was allowed to cool to room temperature and the product isolated was stopped. Upon cooling, the product was collected by vacuum filtration and recrystallized from ethanol. Reactions carried out below reflux (35-75ºC) were done in a procedure analogous to the Knovenagel condensation procedure below. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.67 (m, 2H), 7.40 (m, 2H), 2.73 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 195.4, 159.2, 155.3, 147.4, 134.4, 130.2, 125.0, 124.5, 118.2, 116.7, 30.5.

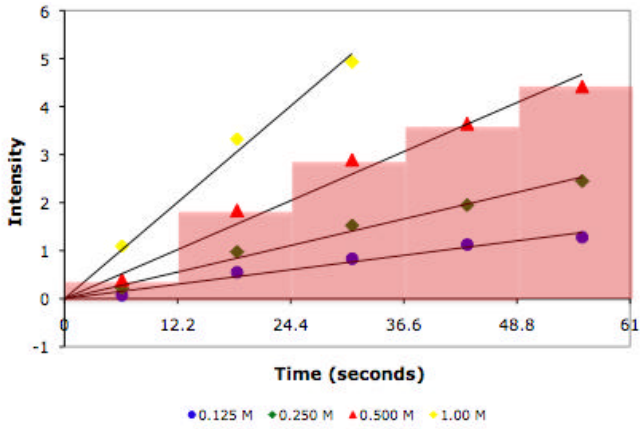
Experimental set-up for performing the kinetic measurements in an open vessel

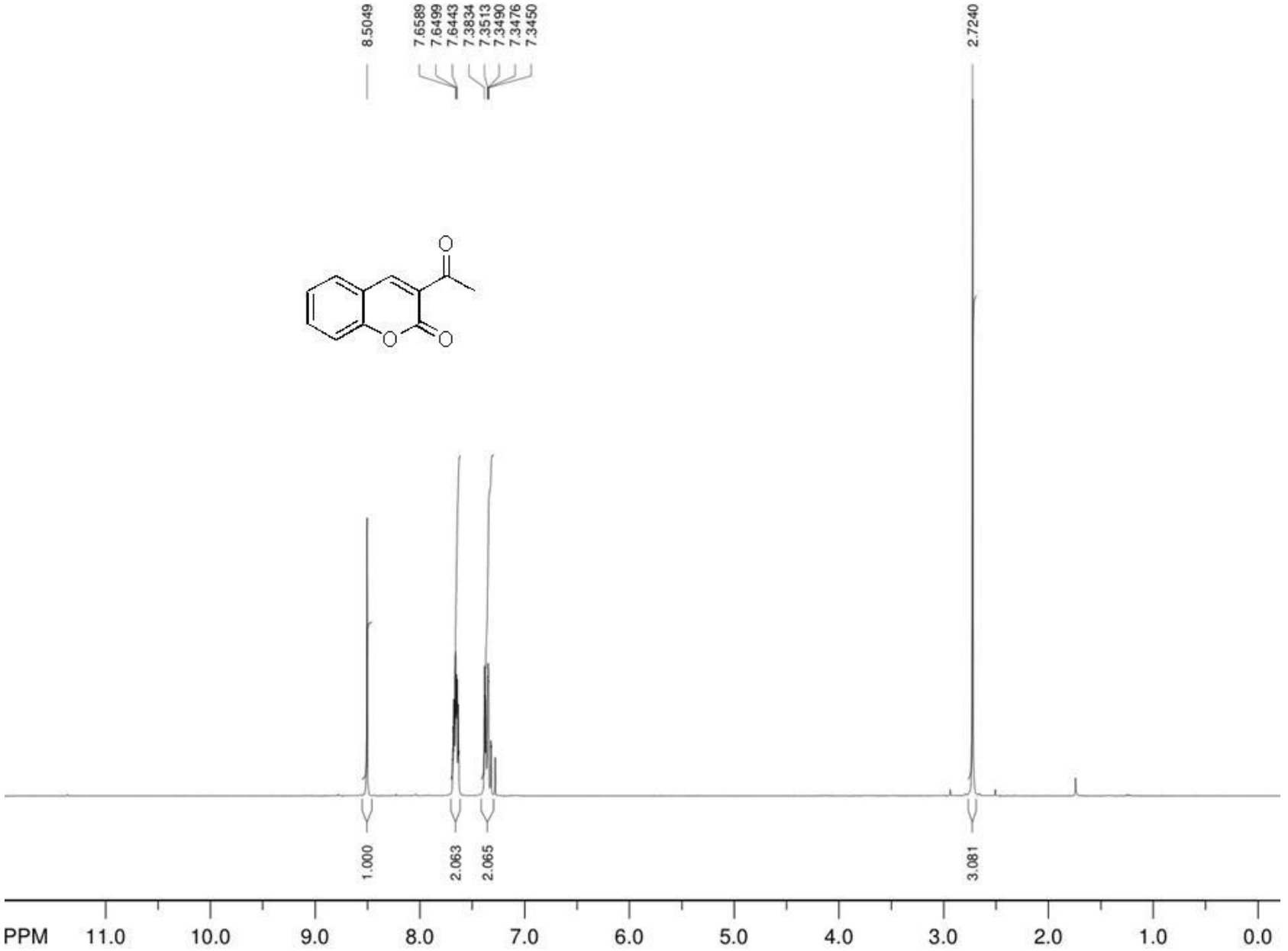

Discover
jrscoumarin_
T* = 92 C
Time = 00:28:20

Monitoring formation of ethyl-(E/Z)-2-acetyl-3-(2-methoxyphenyl)-acrylate.

Into a 50.00 ml volumetric flask were placed 2-methoxybenzaldehyde (6.808 g, 50.00 mmol) and ethyl acetoacetate (6.507 g, 50.00 mmol). The reagents were diluted to 50.00 ml with ethyl acetate. This solution was transferred to the 50 ml long-necked round bottom flask and placed into the microwave cavity. The reaction mixture was brought to the desired temperature (35-75ºC) at which point a background scan of the reaction that would be subtracted from all subsequent scans was taken. The Raman spectrometer was set to take continuous scans using the same parameters as with the 3-acetyl coumarin synthesis. Continuous scans were begun. After the first scan (t=0), the stopper was momentarily removed and the piperidine catalyst in toluene (4.0 M, 1.0 ml, 4.0 mmol, 8 mol%) was rapidly injected into the reaction mixture. Upon cooling, the reaction mixtures were combined. To drive the reaction to completion and thus allow for isolation and characterization, a portion of the reaction mixture was transferred to a 35 mL thick-walled reaction vessel, more ethyl acetoacetate added and then the vessel sealed and heated to 120ºC until completion was reached as judged by Raman monitoring (~12 min). The crude reaction mixture was poured over aqueous HCl (2.0M) and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and the solvent was removed under vacuum. The E/Z isomers co-distill (184°C @8-10 mmHg) so 500 mg of the distillate was placed on a 20-cm silica gel column (80 g silica gel) and eluted using 6:3:0.5 pet ether:DCM:ethyl acetate solvent system to separate the E and Z isomers. R_f=0.342 (Z-isomer), 0.210 (E-isomer)

For the plots of Raman signal intensity versus time (Figures 6 & 7), scans acquire data for 10 seconds, which results in a signal being produced every 12.2 seconds; 10 seconds of acquisition time plus approximately 2.2 seconds to relay information between the Raman unit and the PC. A linear approximation of the formation can be assumed at the onset of the reaction or for the first 60 seconds. Therefore, the first scan after the addition of catalyst (scan 2) that is produced at t=12.2 seconds more precisely represents the Raman signal strength and hence the concentration due to 3-acetylcoumarin formation at t=6.1 seconds. Below, a modified Figure 7 illustrates this.

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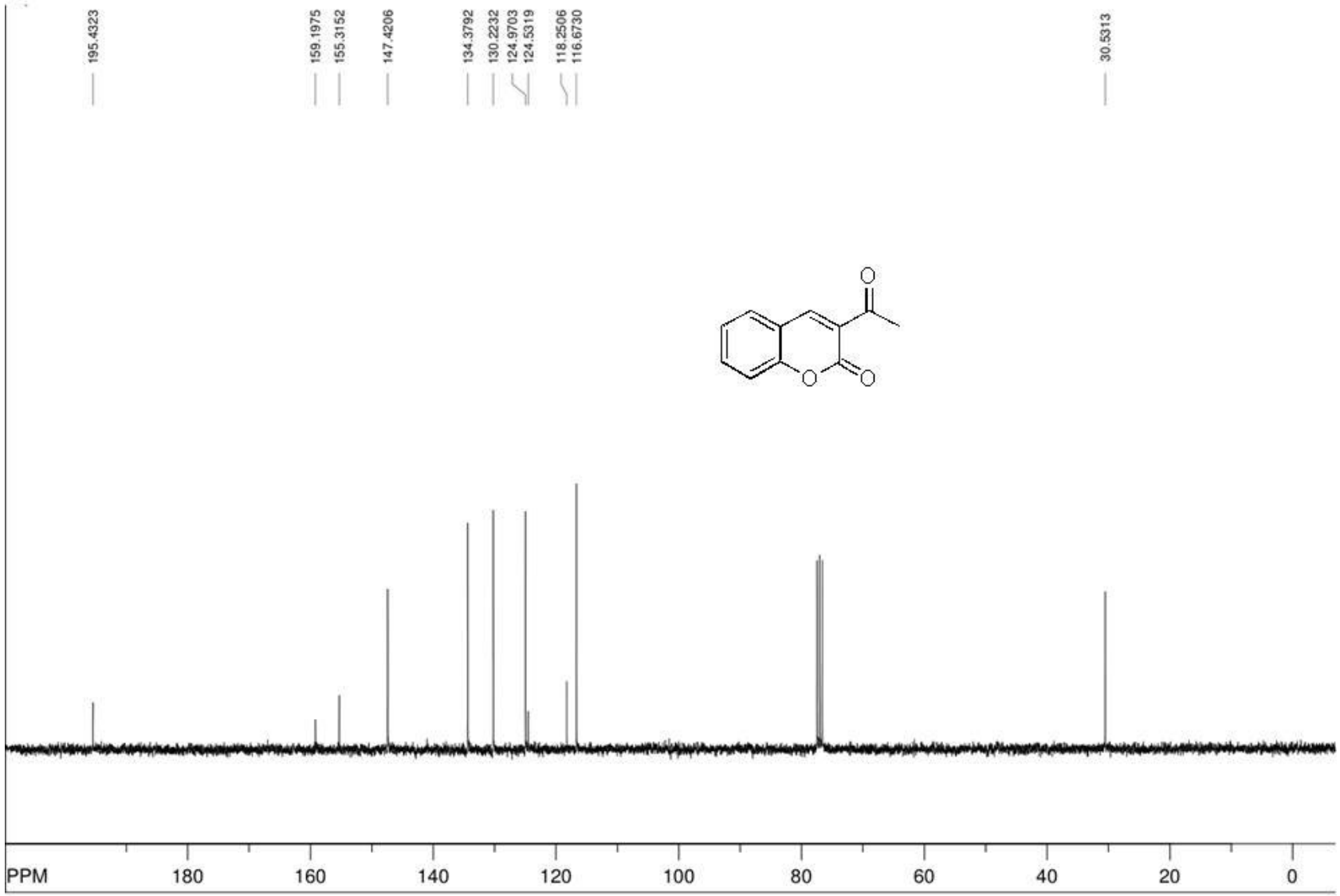
7.6589
7.6499
7.6443
7.3834
7.3513
7.3490
7.3476
7.3450
2.7240
1.000
2.063
2.065
3.081
PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0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159.1975
155.3152
147.4206
134.3792
130.2232
124.9703
124.5319
118.2506
116.6730
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O
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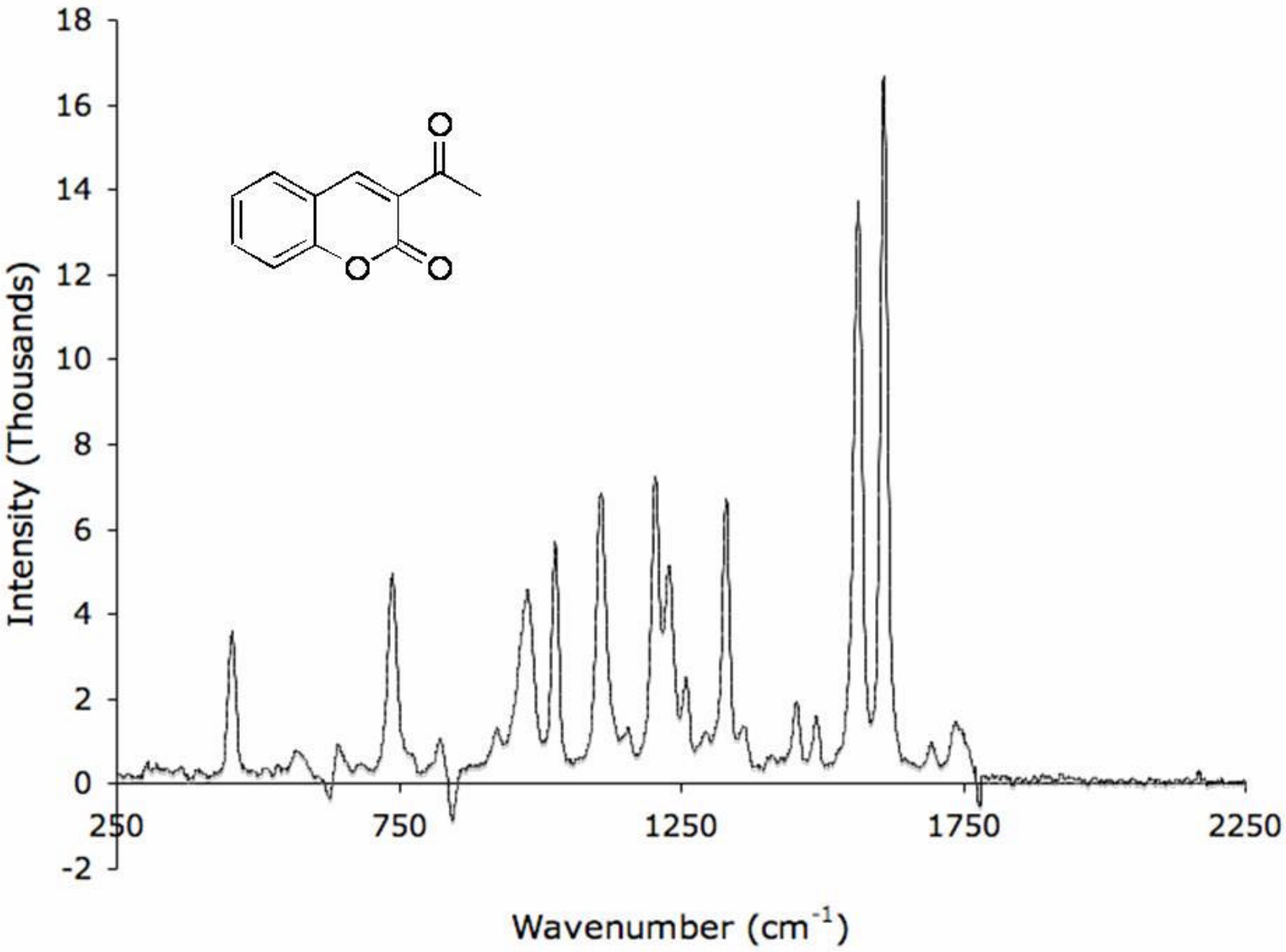
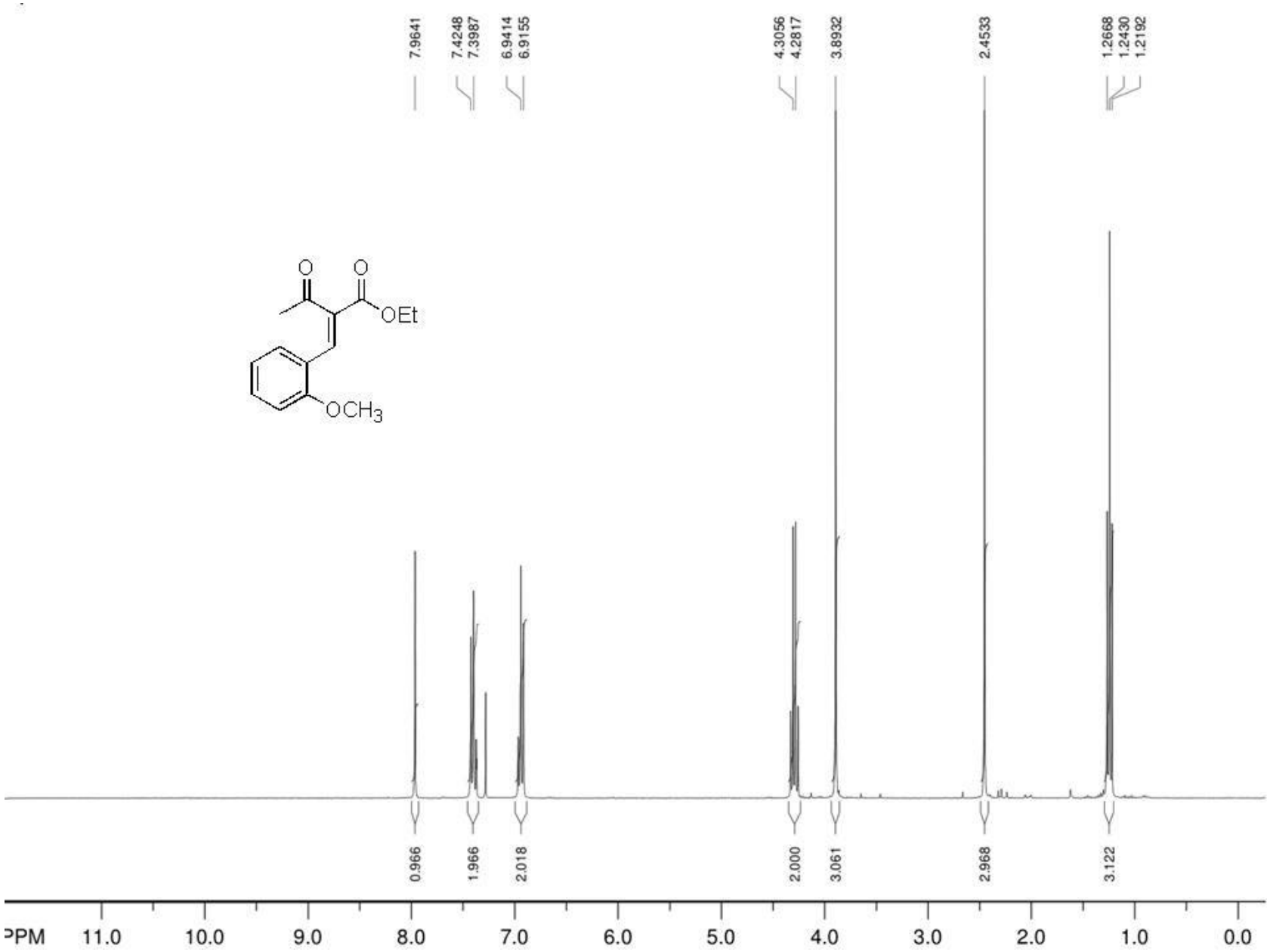
O
PPM
180
160
140
120
100
80
60
40
20
0


18
16
14
12
10
8
6
4
2
0
-2
Intensity (Thousands)
250
750
1250
1750
2250
Wavenumber (cm-1)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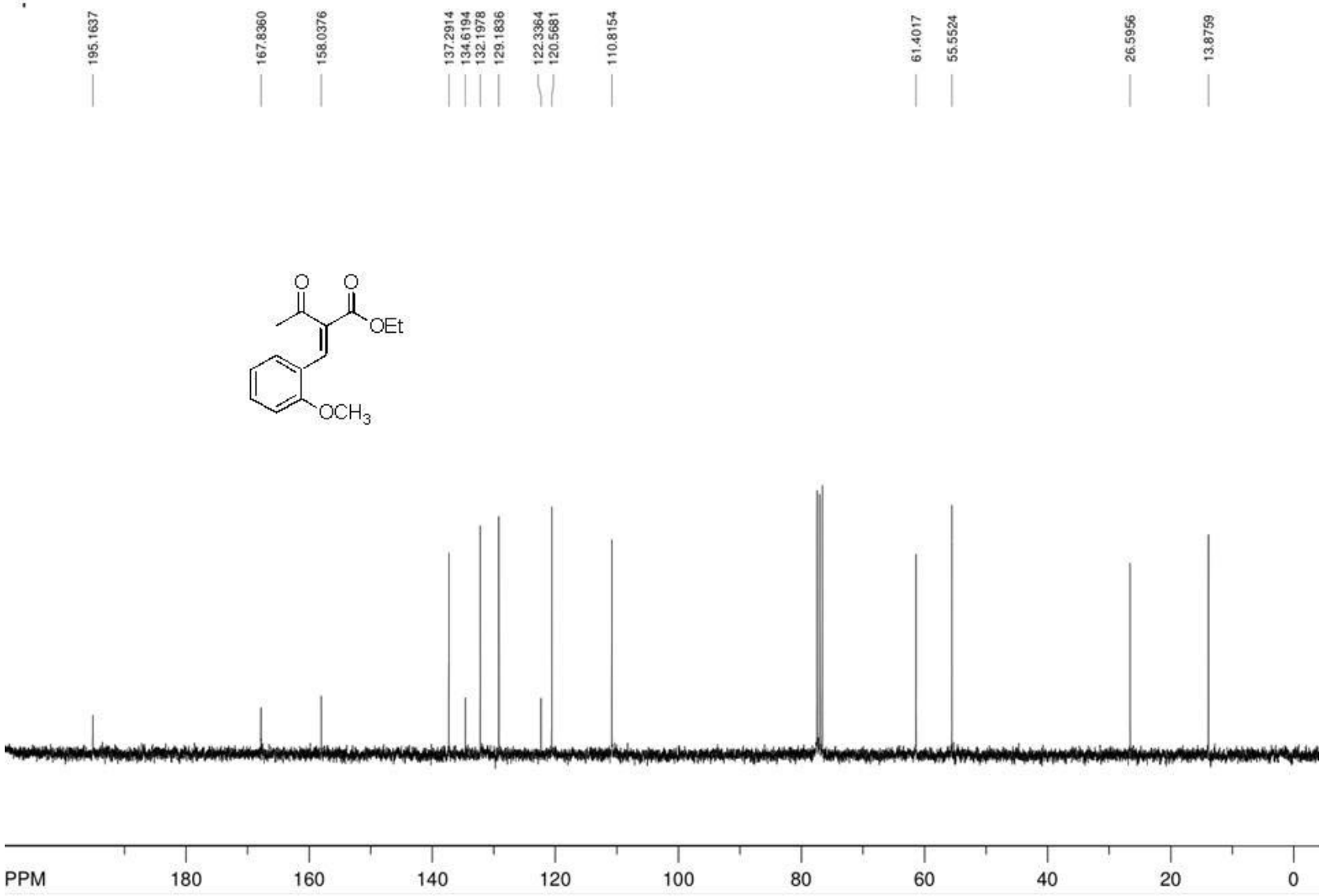
7.3987
6.9414
6.9155
4.3056
4.2817
3.8932
2.4533
1.2668
1.2430
1.2192
O
O
OEt
OCH3
0.966
1.966
2.018
2.000
3.061
2.968
3.122
PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0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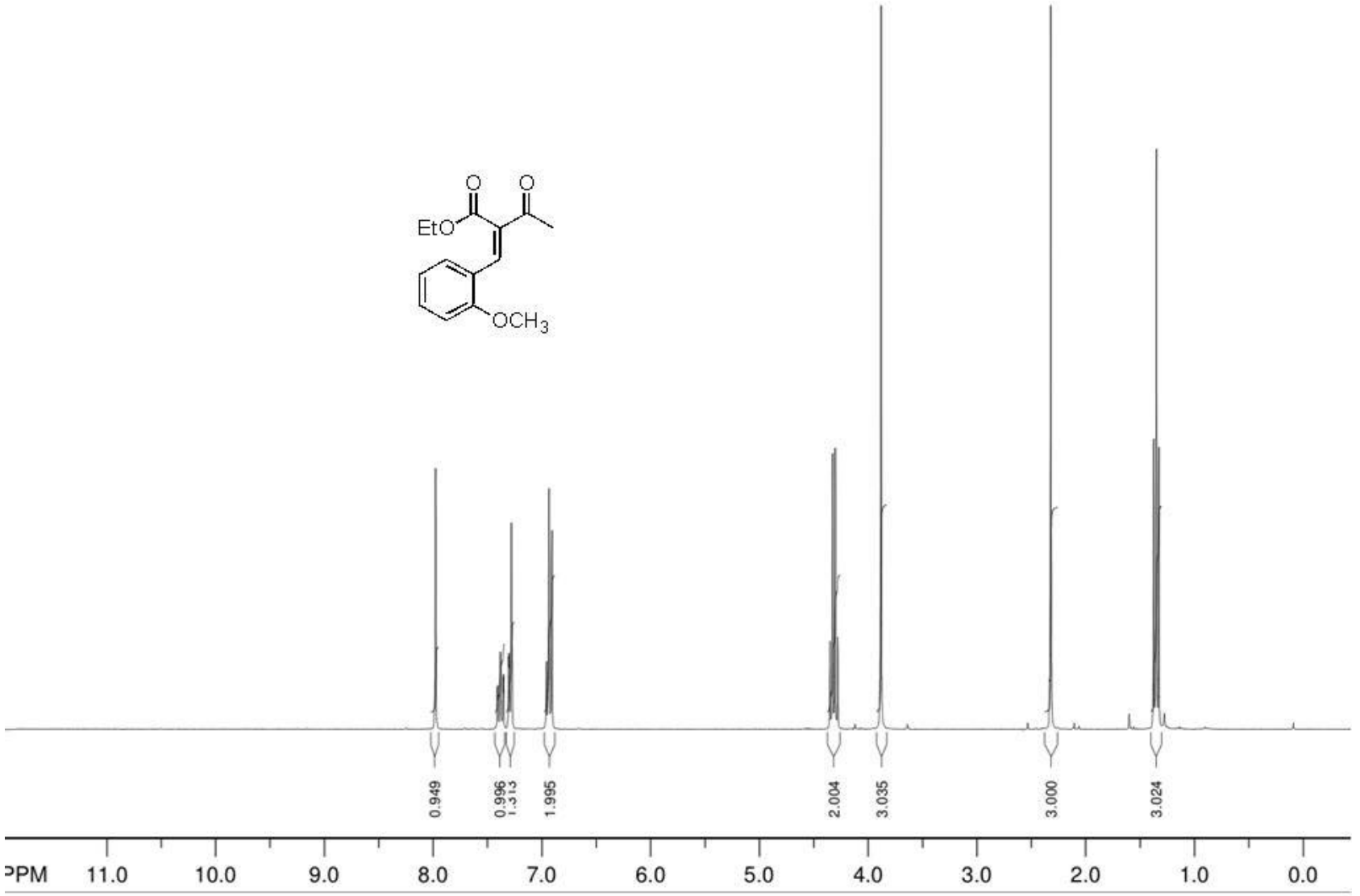
137.2914
134.6194
132.1978
129.1836
122.3364
120.5681
110.8154
61.4017
55.5524
26.5956
13.8759
O
O
OEt
OCH3
PPM
180
160
140
120
100
80
60
40
20
0


EtO
O
O
OCH3
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0.996
1.313
1.995
2.004
3.035
3.000
3.024
PPM
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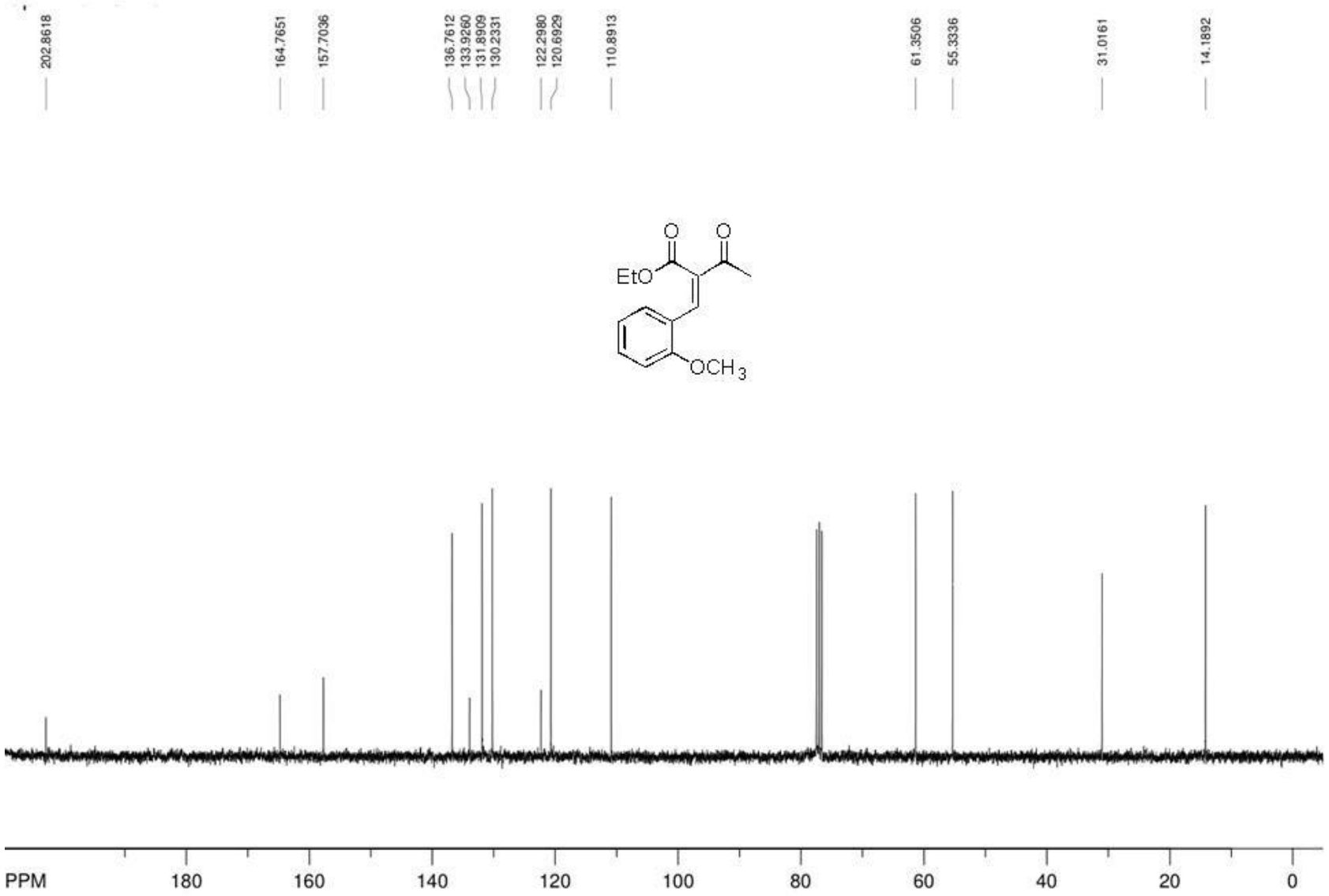
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0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55.3336
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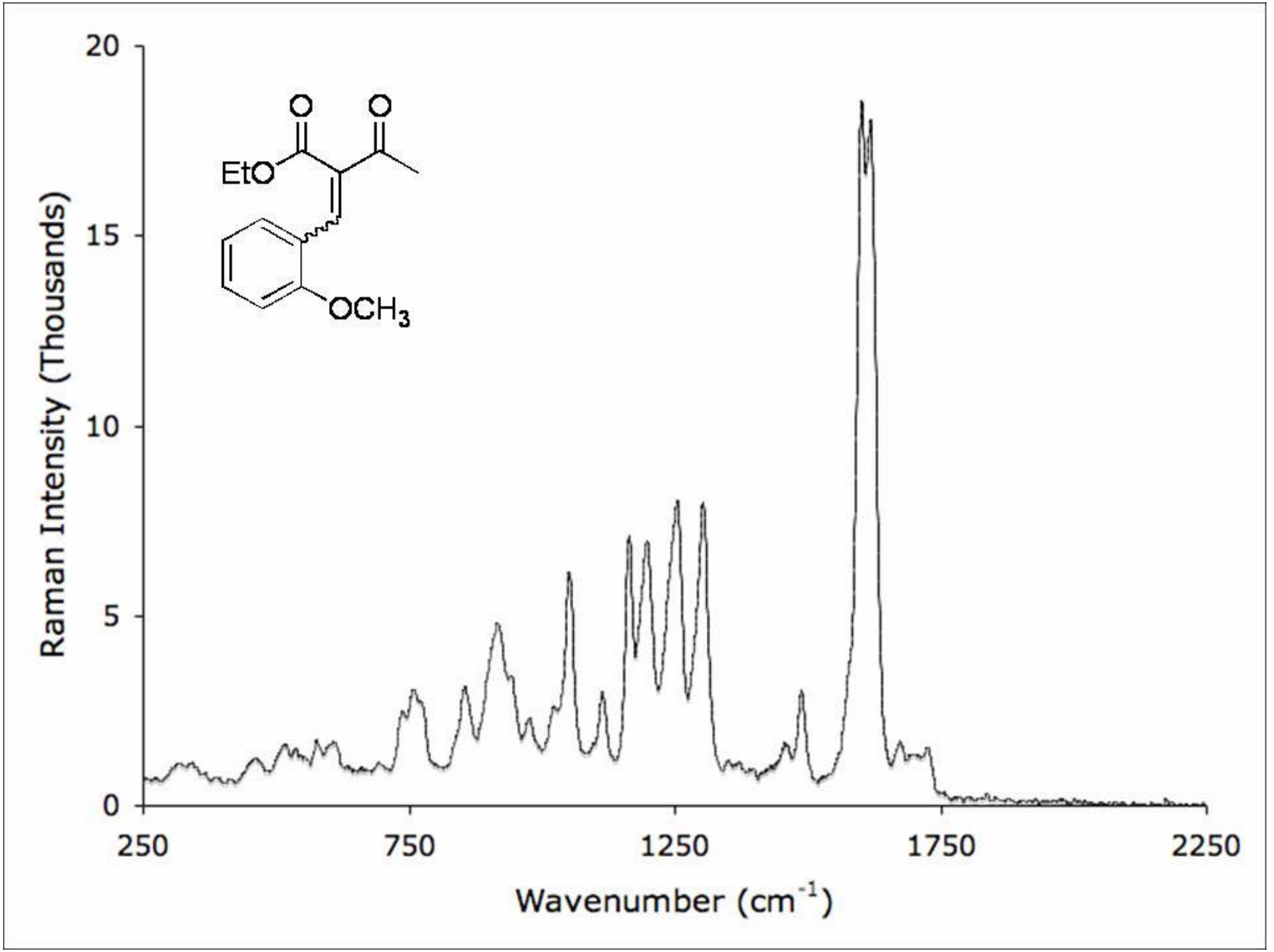
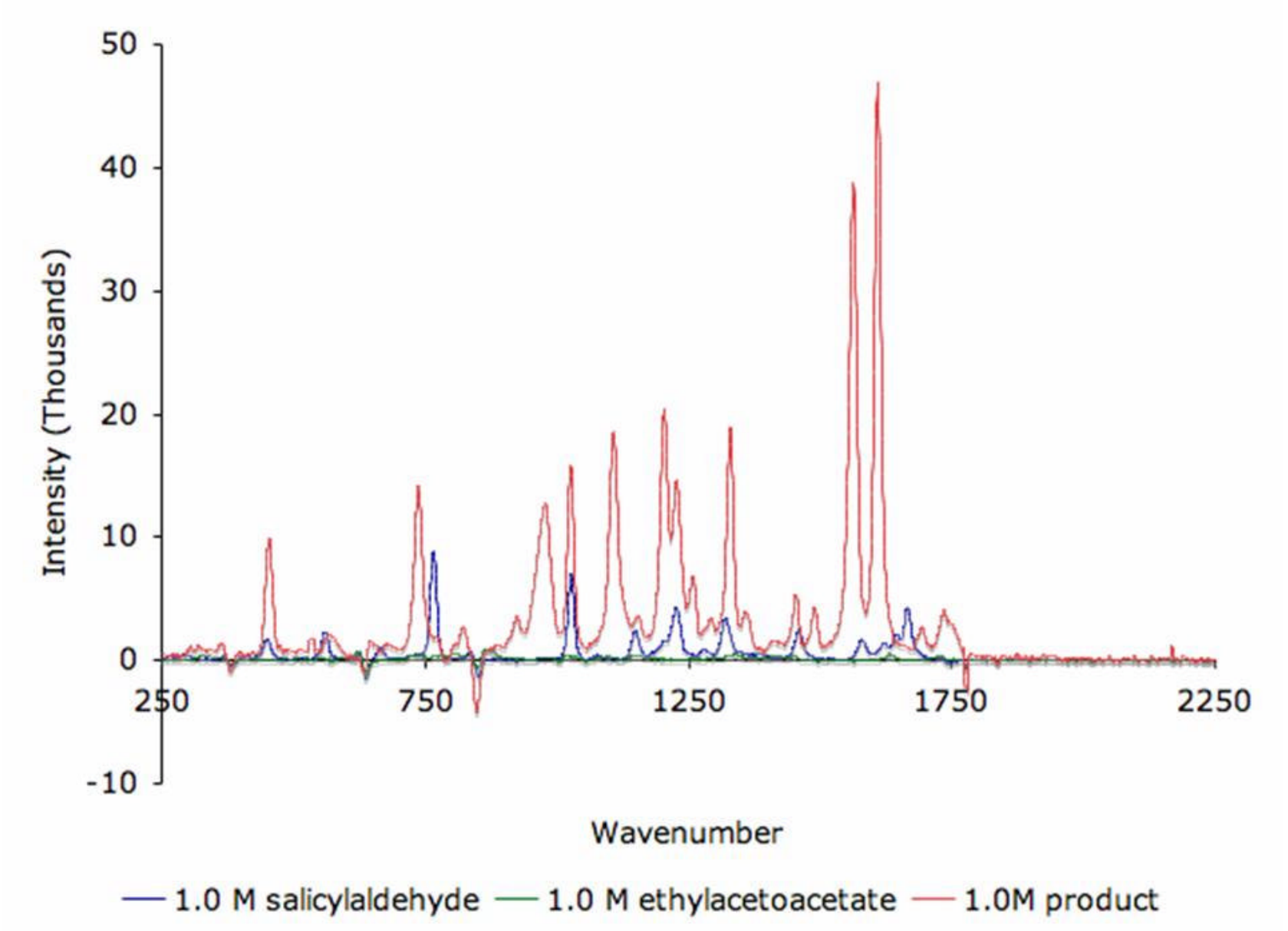
160
140
120
100
80
60
40
20
0


20
15
10
5
0
Raman Intensity (Thousands)
EtO
OCH3
250
750
1250
1750
2250
Wavenumber (cm-1)


50
40
30
20
10
0
-10
Intensity (Thousands)
250
750
1250
1750
2250
Wavenumber
1.0 M salicylaldehyde
1.0 M ethylacetoacetate
1.0M product