Cis-Cinnamonitriles: Synthesis, Separation, and Reaction with Diphenylphosphine

An Honors Thesis (HONRS 499)

by

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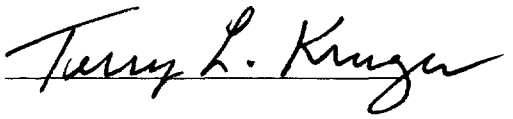

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Purpose of Thesis

The series of experiments described here was done in an attempt to study the reaction of diphenylphosphine with the *cis* isomer of variously substituted cinnamonitriles. This discussion begins with the synthesis of the cinnamonitriles and how they are characterized using various instruments. Also, the characterization of the diphenylphosphine is described. Next, the method of separation of the two isomers of the cinnamonitrile is illustrated. Lastly, the results of the diphenylphosphine addition to *p*-chlorocinnamonitrile is discussed.

Cis-Substituted Cinnamonitriles: Synthesis, Separation, and Reaction with Diphenylphosphine

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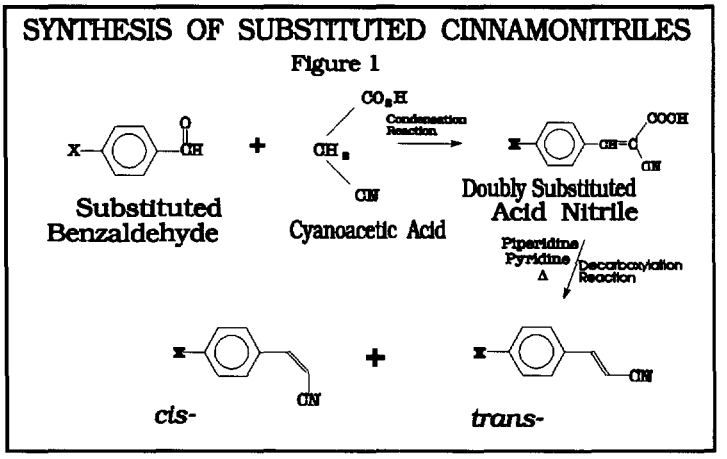
Introduction:

Substituted cinnamonitriles contain an electron poor alkene group which allows for the reaction with diphenylphosphine. The reaction of diphenylphosphine with this sort of alkene was first studied in the case of diphenylphosphine and acrylonitrile which yields 3-diphenylphosphino-propanonitrile. That reaction was conducted with acetonitrile as the polar solvent with aqueous potassium hydroxide added. Later, the reaction of cinnamonitriles with diphenylphosphine was carried out with deuterated chloroform as the non-polar solvent and without the necessity of basic catalyst. We present here a series of experiments dealing with variously substituted cinnamonitriles in an attempt to understand this apparently polar reaction that takes place in a non-polar and non-basic environment of deuterated chloroform.

Synthesis of Substituted Cinnamonitriles:

A Knoevenagel condensation reaction with a benzaldehyde of chosen substitution and an equal molar ratio of cyanoacetic acid in a solvent system containing both pyridine and piperidine produced the necessary cinnamonitriles. (Figure 1)



The reaction was run under an argon blanket at reflux which was set up in a round-bottomed flask equipped with condensor and an extraction apparatus with extraction thimble containing barium hydroxide (to remove excess water). As the reaction proceeded, the doubly substituted acid nitrile was decarboxylated to the substituted cinnamonitrile. The yield from this synthesis was fairly high -- about 60 percent. Also, the ratio of *cis* and *trans* products was usually about 50/50.

Although some of these substituted cinnamonitriles were available at a reasonable expense through chemical distribution companies, the amount of *cis*- isomer in the commercially produced product was very small. For unsubstituted cinnamonitrile, the commercially produced product is 99 percent *trans* while the product we synthesized by the above procedure was 55 percent *trans*. All of the substituted cinnamonitriles synthesized experimentally had a higher *cis*- percentage than the commercial

product from Aldrich.

The chosen substituent for the synthesis depended on what kind of electron effect was needed. Electron donating groups such as *p*-methyl- and *p*-methoxy-, donate electrons to the ring and affect the reactivity of the compound. Electron withdrawing groups, such as *p*-nitro-, *m*-nitro-, *p*-trifluoromethyl-, *p*-fluoro-, and *p*-cyano-, withdraw electrons from the ring structure thus affecting the reactivity in the opposite manner. Due to the electron differences in the substituents, the syntheses of the cinnamonitriles containing electron donating groups gave slightly higher yields. (Figure 2 & 3)

Characterization of Product:

The two instruments used to characterize the product were the nuclear magnetic resonance spectrometer (NMR) and the mass spectrometer. For the NMR, the peak with the most analytical utility was that corresponding to the vinylic hydrogen adjacent to the nitrile. The chemical shift of this set of two peaks (*cis/trans*) was between 5 and 6 parts per million. (Figure 3) Also, the two peaks not only distinguished the *cis*- and *trans*-isomers with the *trans*- isomer being shifted farther downfield but allowed estimation of relative amounts of the two isomers. A plot showing the correlation between the chemical shift of the vinylic hydrogen and the Hammett's Sigma value for the effect of substituents on the benzene ring has been plotted. A plot of this data shows a distinctly, separate linear correlation for

the *cis*- and *trans*- isomers. (Graph 1)

When looking at the spectrum of the cinnamonitrile, the two peaks corresponding the *cis*- and *trans*- isomers could be easily distinguished. By integrating these individual peaks, the relative amounts of *cis* and *trans* isomer available in that sample can be determined. Usually, the downfield peak representing the *trans*- isomer was of greater intensity in the samples. (Figure 3)

The mass spectrometer was also used to characterize the products. When using the chemical ionization feature of the mass spectrometer, the cinnamonitrile behaved as expected as only pseudomolecular ions and their complexes with common neutrals were observed. (Figure 4) For the *p*-methylcinnamonitrile, molecular weight 143 amu, the peak at m/e = 144 corresponds to the molecular weight of the compound and a proton. The peak at m/e = 185 corresponds to the molecular weight of the compound and the solvent, acetonitrile. Lastly, the peak at m/e = 287 corresponds to 2 molecular weights and one proton. All of these peaks are what was expected for the chemical ionization of *p*-methlycinnamonitrile. The chemical ionization of *p*-nitrocinnamonitrile followed a similar pattern. (Figure 5) However, additional peaks were found in that spectrum because of a mixture of two solvents were used to dissolve the sample.

Another type of ionization method in mass spectrometry is electron ionization. This method usually produces an extensive fragmentation pattern of the compound. For the unsubstituted cinnamonitrile, the major fragmentation is a loss of -HCN.

Further fragmentation results in a benzene ring peak at m/e = 78. (Figure 6) For *p*-chlorocinnamonitrile, two major fragmentation types were discovered. (Figure 7) One fragmentation, similar to the unsubstituted cinnamonitrile, was -HCN. The other fragmentation was chlorine loss. Because chlorine has two isotopes -- chlorine-35 and chlorine-37 -- two different peaks were found in a three to one ratio for the loss of chlorine. Although this pattern was different than the unsubstituted, the fragmentation pattern was what was expected.

To further this study on cinnamonitriles using the mass spectrometer, we plan to determine any differences in the fragmentation patterns for *cis*- and *trans*- isomers of the variously substituted cinnamonitriles.

Separation of *Cis*- and *Trans*- Isomers:

Once the substituted cinnamonitrile was synthesized, the compound was separated using a GOW-MAC series 550P gas chromatograph equipped with quarter inch column. This instrument model was chosen for its ejection port on the rear of the instrument, non-destructive detector type, quarter inch column, and other locational conveniences. Since a GC separates all the components of a mixture, the substances used on this instrument did not have to be pure to be separated into their respective isomers.

To begin separation, the given substituted cinnamonitrile had to be in liquid or solution form. Solids and gooey liquids

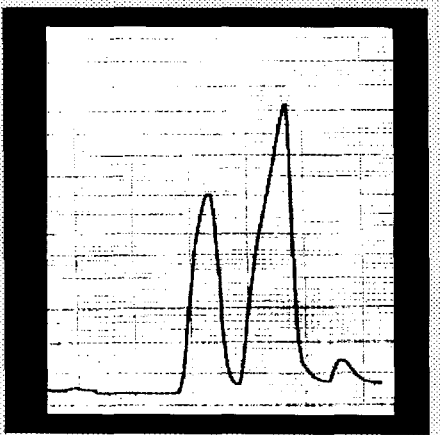
were dissolved in acetone. More fluid liquids were used without addition of solvent. The sample was injected into the instrument using a syringe containing an appropriate amount of sample. The amount of injection depended on the consistency of the sample. For example, the *p*-chlorocinnamonitrile flowed through the column in a reasonable amount of time; therefore, the injection amount was approximately 30 uL. However, for the *p*-nitrocinnamonitrile, the injection amount was lowered to approximately 5 uL to ensure that no compound corrupted the column. Table 1 shows the parameters for the running of the gas chromatograph with cinnamonitriles.

Table 1

Init. temp.	175°C
Ramp	0:25
Final temp	275°C
Time	4:00
Inj. temp.	300°C
Det. temp.	300°C
MA.	150 ma
Inj. amt.	Variable

As the sample flows across the detector, the integrator connected to the GC graphs the relative amount of that component in the sample. Also, the more volatile components go through the column first. The first component eluted was the solvent, acetone, which gave a strong peak on the integrator approximately two seconds after injection. A given while later, the substituted

Gas Chromatogram
Figure 8



Small peak on left corresponds to the *cis*
While the taller peak on the right is the *trans*

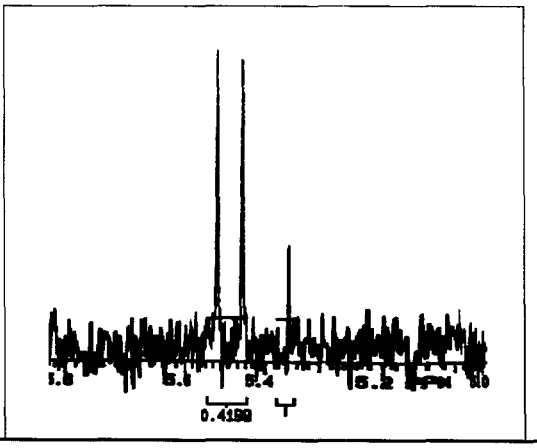
cinnamonitrile travels across the detector. (Figure 8) Since the *cis-* isomer is the more reactive isomer, it elutes before the *trans-* isomer. Therefore, the *cis-* isomer can be collected from the ejection port as the integrator is graphing the *cis-* peak. Also, the *trans-* isomer may be collected in the same manner.

The collection of the *cis-*isomer was done with a glass disposable Pasteur pipette with a little bit of glass wool in the larger end. The pipette was placed against the insulated ejection port and the sample was collected. The glass wool produces turbulence in the flowing gases which helped catch the liquid as the gas condenses. Since a very minuscule amount of sample was injected, a very small amount of each isomer was collected. Therefore, many collections of each isomer must be done to gain a sufficient sample for analysis.

The sample was removed from the pipette by rinsing deuterated chloroform through the pipette and into an NMR tube. The sample was analyzed for purity using NMR. (Figure 9) This technique allowed for high purity of separation with little expense.

Figure 9

This NMR is of cis-p-chlorocinnamonitrile The peak at 5.5 corresponds to the cis The purity of this technique is found by looking at the absence of a peak at 6 signifying nearly pure cis isomer.

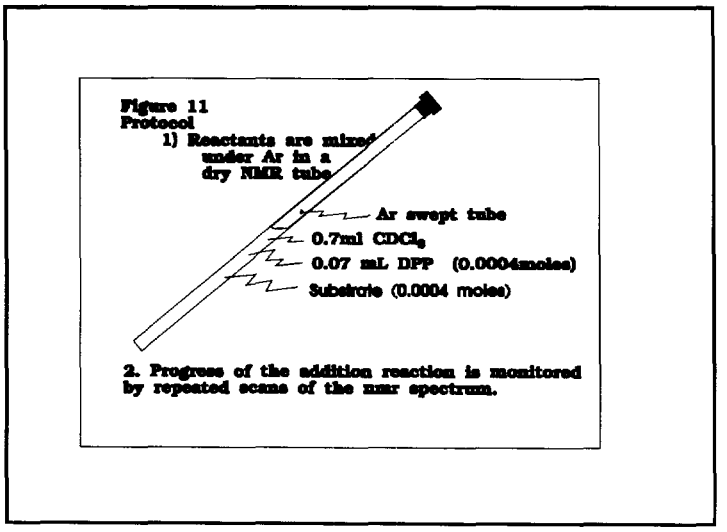


Characteristics Diphenylphosphine:

The reagent used to react with the variously substituted cinnamonitriles was diphenylphosphine (DPP). This reagent reacts violently with air and water, has a very nasty odor, and is light sensitive. Therefore, the handling of this reagent is very important. This nasty chemical is always stored in dark glass containers and stored and handled under argon.

Diphenylphosphine gives two distinct peaks on the NMR spectrum due to the spin-spin splitting of the phosphorous. (Figure 10) Also, a small peak farther downfield between 9 and 10 ppm corresponds to the partially oxidized portion of the molecule. When the spectrum is integrated, if the two sharp peaks are not eight times the oxidized peak, then the reagent cannot be used until the impurities of the oxidation have been removed or reduced.

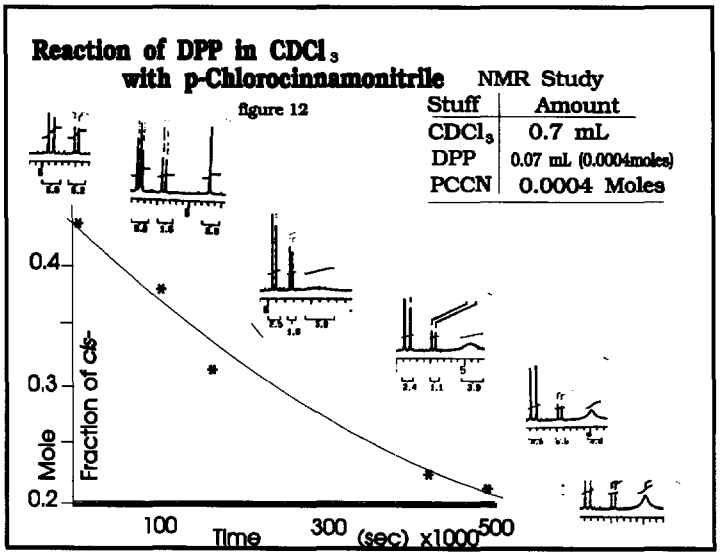
The reaction of diphenylphosphine with variously substituted cinnamonitriles was done in an NMR tube with deuterated chloroform as the solvent. Since diphenylphosphine is so nasty, the protocol for addition of the reagent is important. (Figure 11) Water in the deuterated chloroform can cause the diphenyl-phosphine to react with the water instead of the cinnamo-



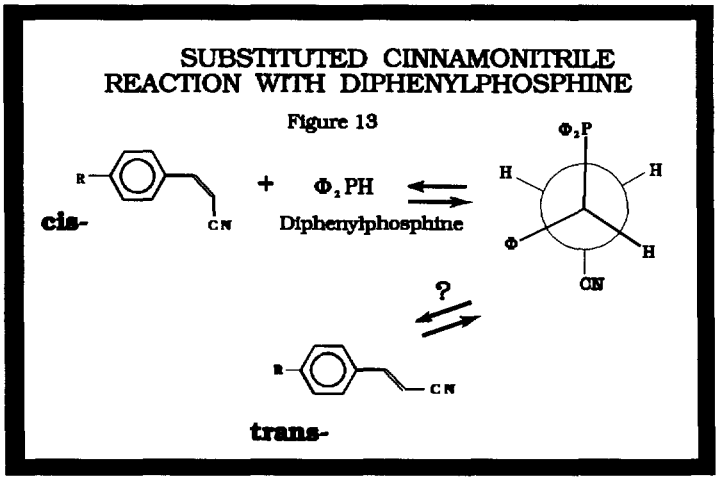
nitrile. Therefore, water must be avoided in the deuterated chloroform. Of course, the addition of diphenyl-phosphine must be done under an argon blanket. Therefore, the NMR tube with deuterated chloroform and cinnamonitrile must be swept with argon before addition of the diphenylphosphine. Also, the Epindorf Pipetter used to add the diphenylphosphine must have argon in the tip. Lastly, the diphenylphosphine must be kept under an argon blanket during the whole procedure.

Results of DPP Addition to Cinnamonitrile:

The reaction of diphenylphosphine with *p*-chloro-cinnamonitrile was done in deuterated chloroform with many NMR scans taken over the period of the reaction. (Figure 12) An equal molar ratio of the cinnamonitrile to the diphenylphosphine was used. The initial *p*-chlorocinnamonitrile had about 75 percent *trans*- isomer. The addition of DPP showed the characteristic two peaks of DPP. Over time, those peaks disappeared into the base line. Also, the mole fraction of the *cis*- decreases as the reaction proceeds. Lastly, a broad peak began to form at about 5.5 ppm. That peak became sharper as the reaction proceeded.



Discussion about DPP addition to *p*-Chlorocinnamonitrile:



Since the mole fraction of *cis*- decreased as the reaction progressed over time while the mole fraction of *trans* increased, then the *cis* isomer is reacting with the DPP. (Figure 13) This scheme suggests that DPP adds to the double bond of the *cis*-cinnamonitrile in a Michael type fashion. The possible equilibrium between the DPP-*cis*-cinnamonitrile complex and the *trans*-cinnamonitrile suggests that the DPP could be acting as a catalyst in the isomerization reaction.

Also, the change in shape of the peak corresponding to the possible product suggests something about the rate of reaction. Since the peak is very sharp when an abundance of *cis* is present and as the relative amount of cis declines the peak becomes broader, then the *cis*- could be the limiting factor for the reaction of DPP to cinnamonitriles.

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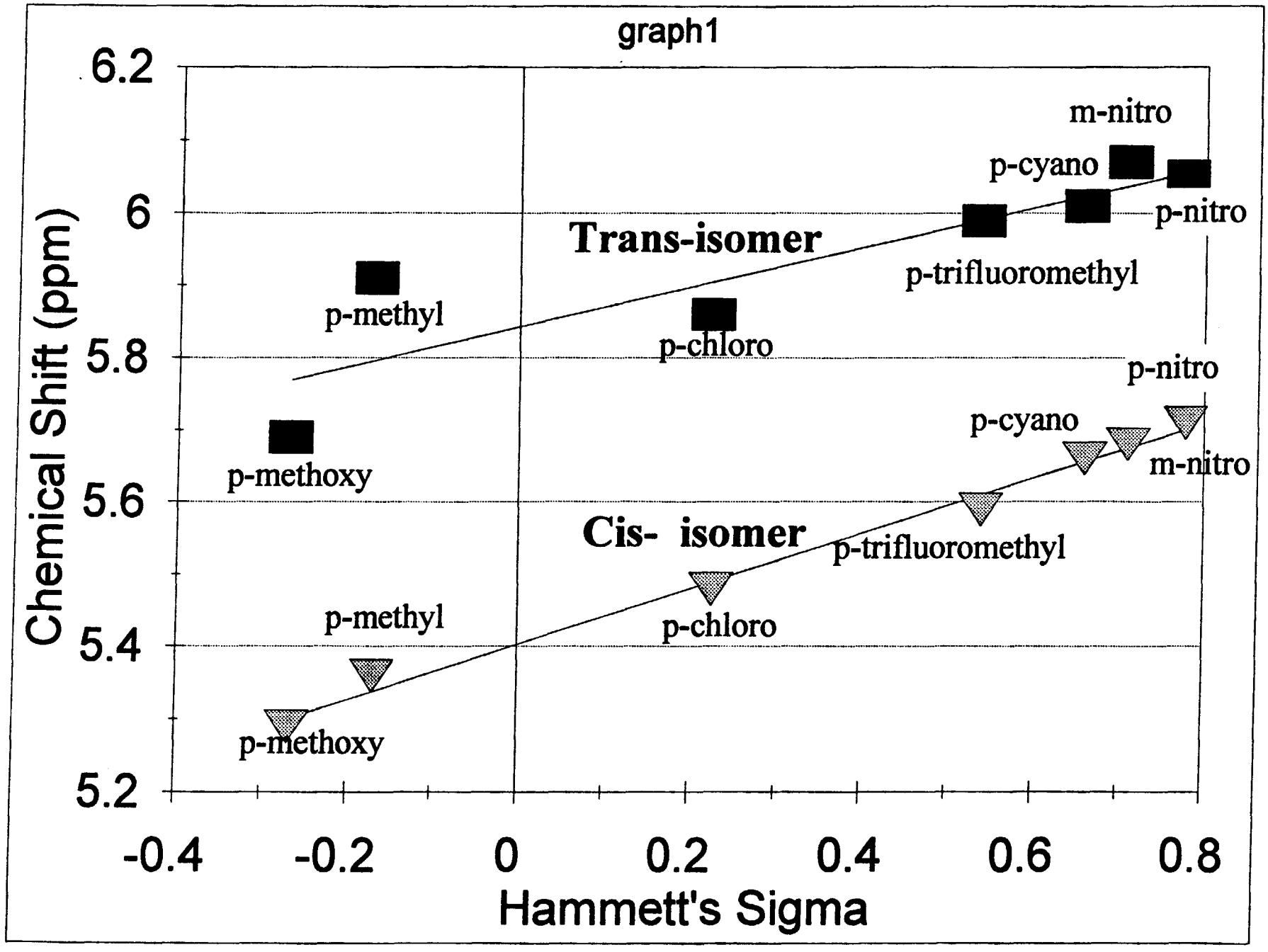

graph1
6.2
6
5.8
5.6
5.4
5.2
Chemical Shift (ppm)
-0.4
-0.2
0
0.2
0.4
0.6
0.8
Hammett's Sigma
m-nitro
p-cyano
p-nitro
Trans-isomer
p-trifluoromethyl
p-methyl
p-chloro
p-nitro
p-cyano
m-nitro
p-methoxy
Cis- isomer
p-trifluoromethyl
p-methyl
p-chloro
p-methoxy

Figure 2
This NMR shows the unsubstituted cinnamonitrile from Aldrich. Only the *trans* peak is apparent at 5.85 ppm.

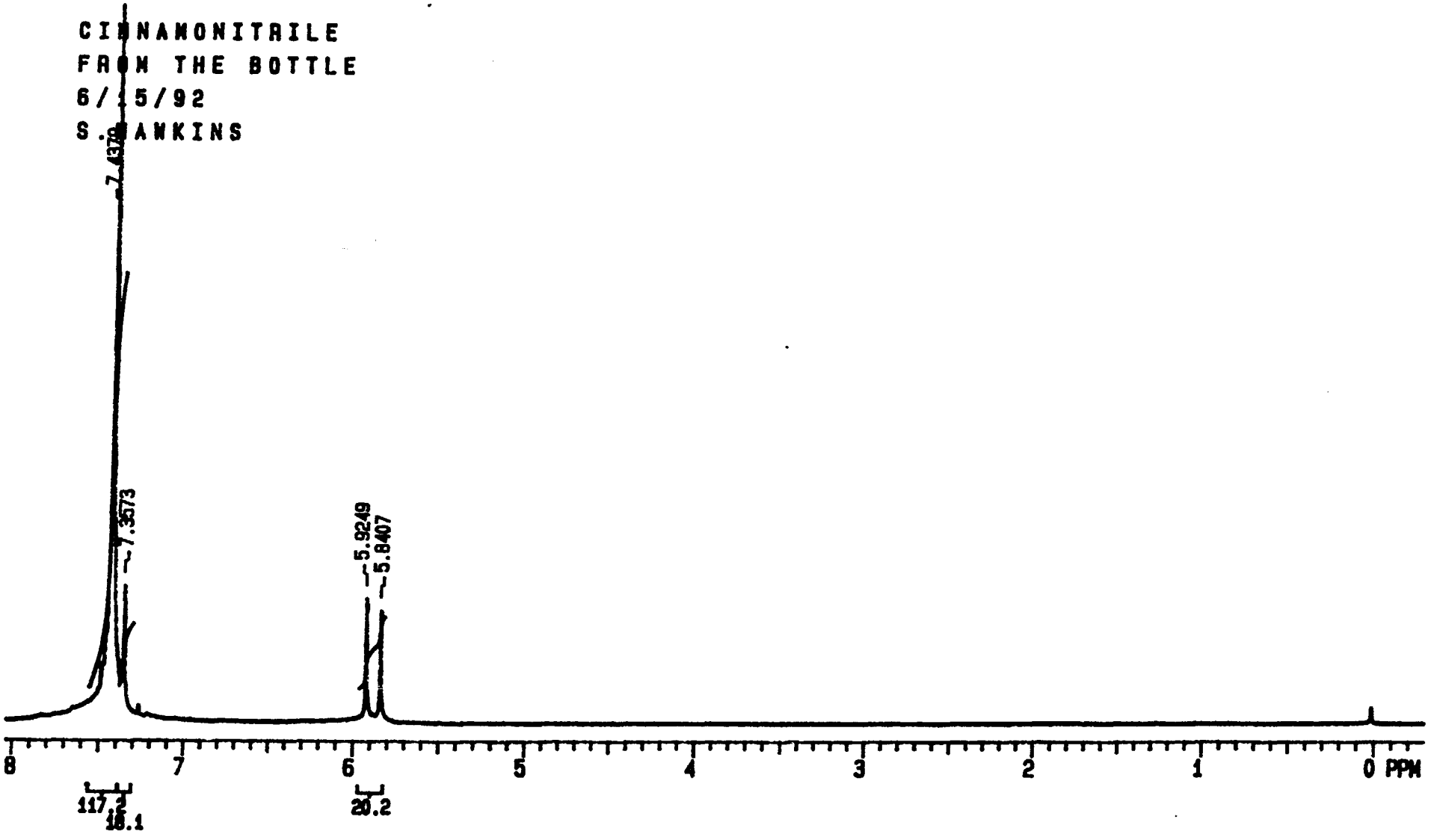
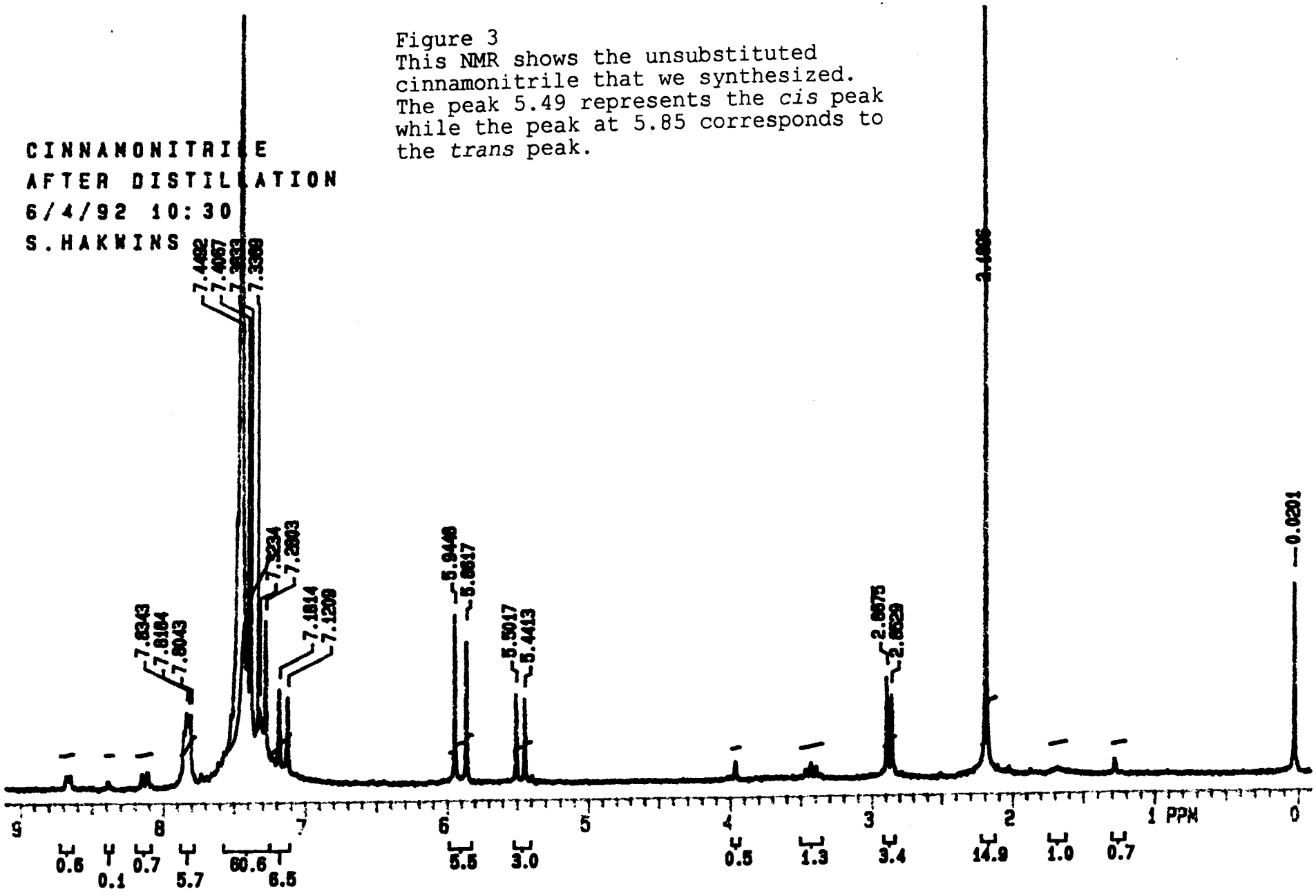


Figure 3
This NMR shows the unsubstituted cinnamonitrile that we synthesized. The peak 5.49 represents the *cis* peak while the peak at 5.85 corresponds to the *trans* peak.



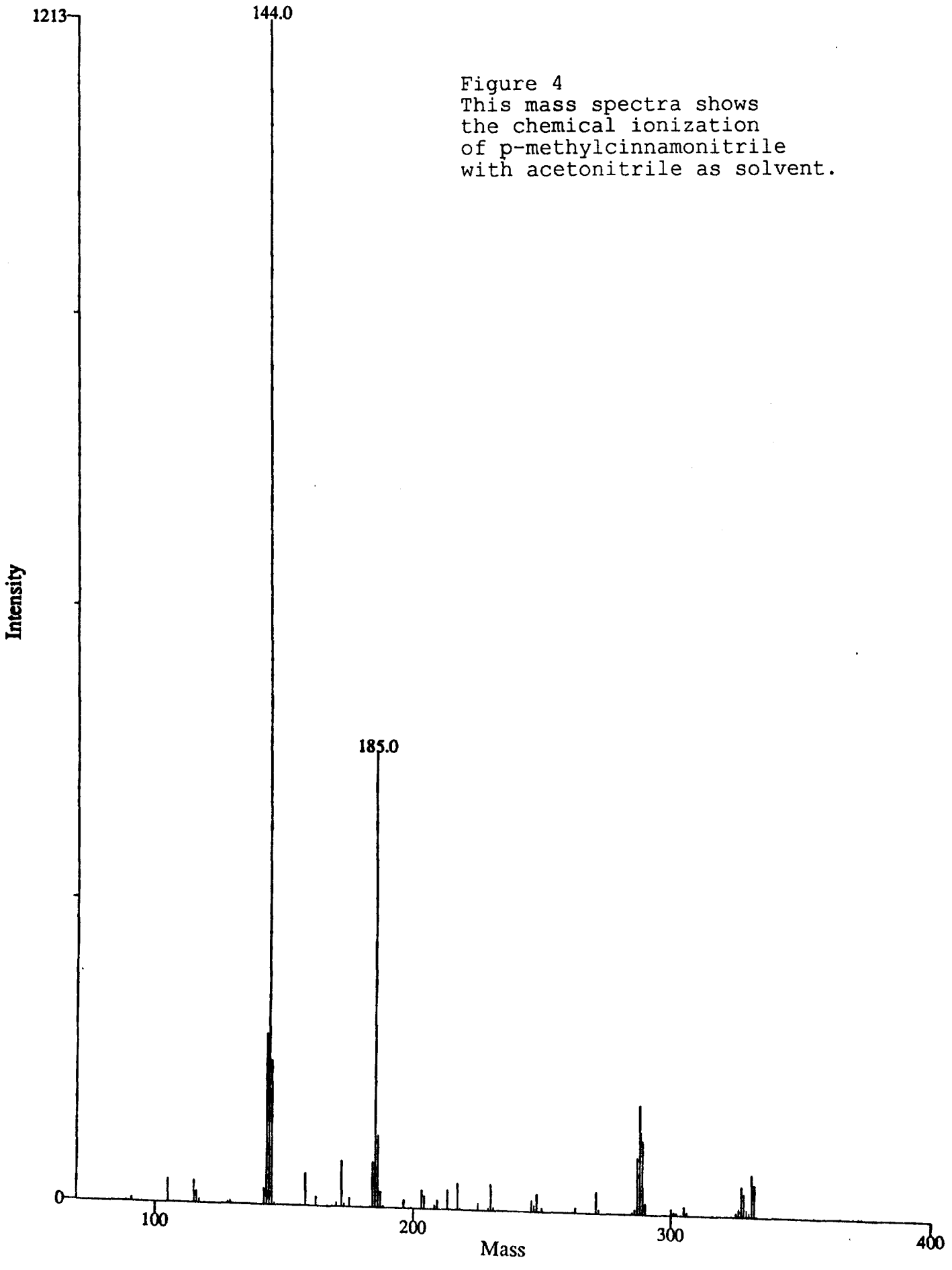


Figure 4
This mass spectra shows the chemical ionization of p-methylcinnamonitrile with acetonitrile as solvent.

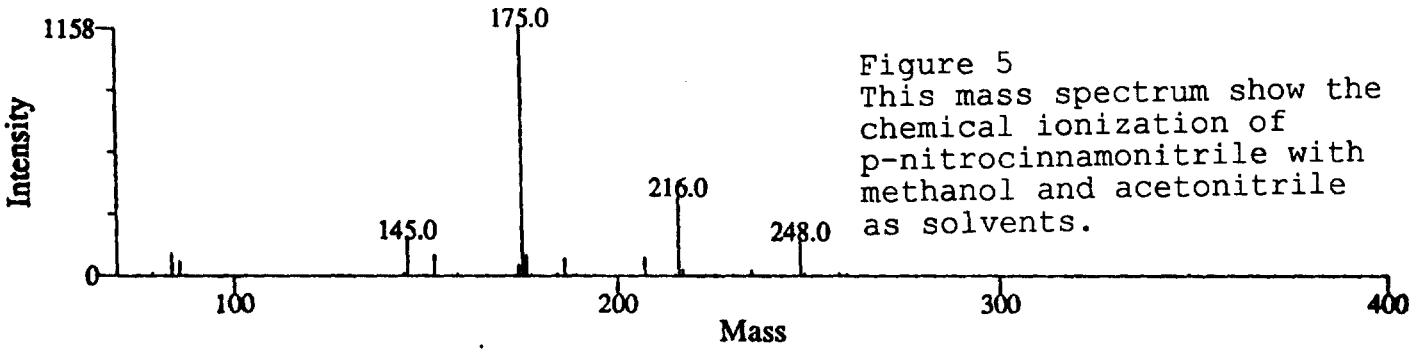
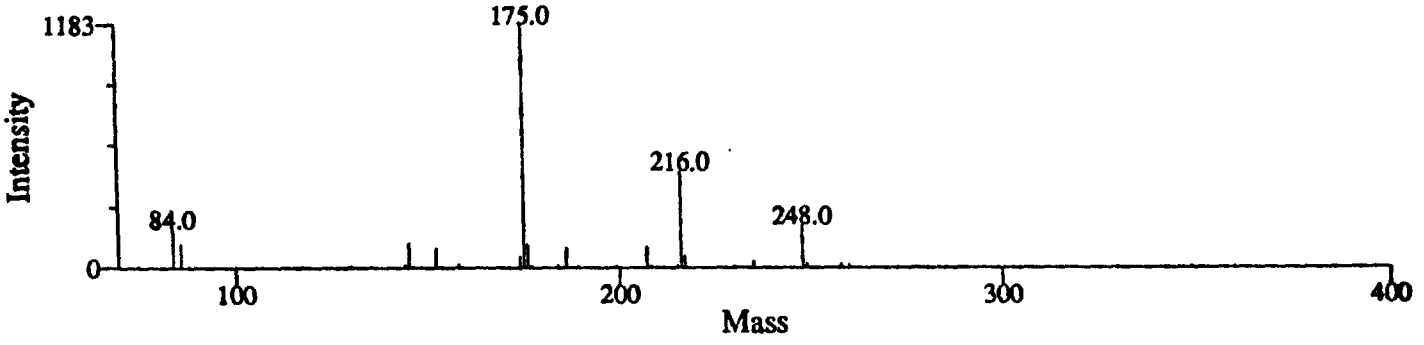
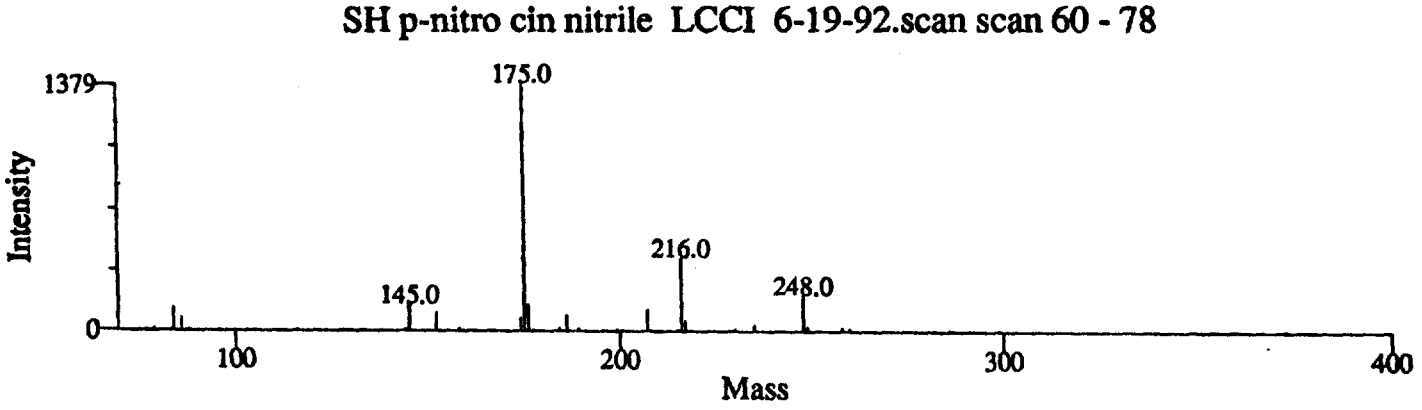
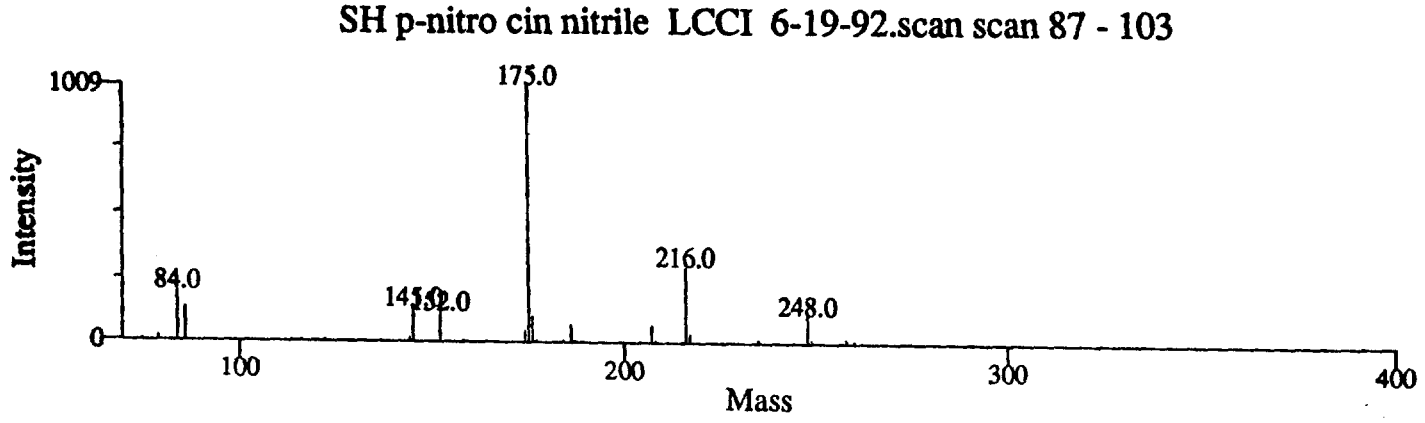


Figure 5
This mass spectrum show the chemical ionization of p-nitrocinnamonitrile with methanol and acetonitrile as solvents.







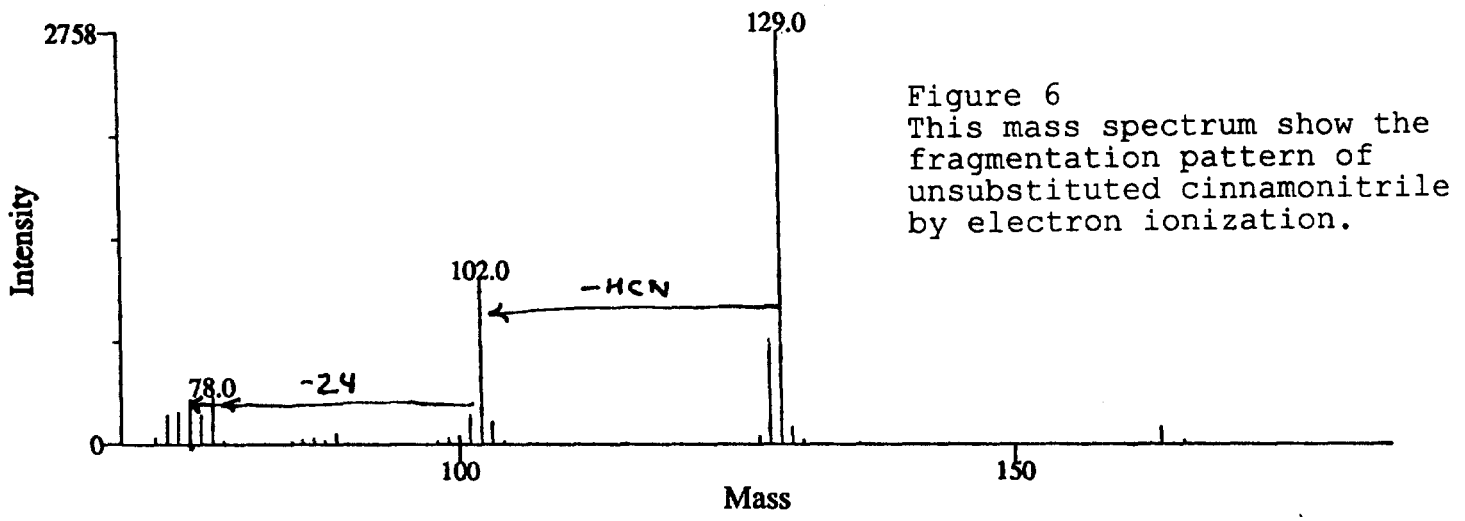
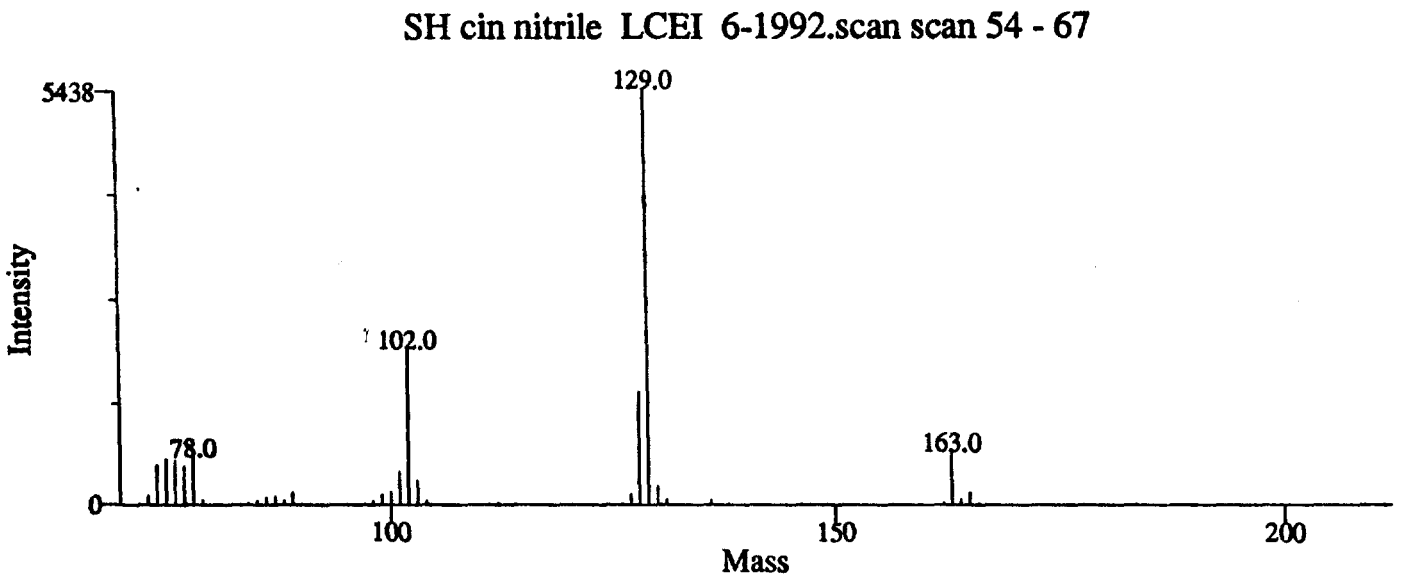
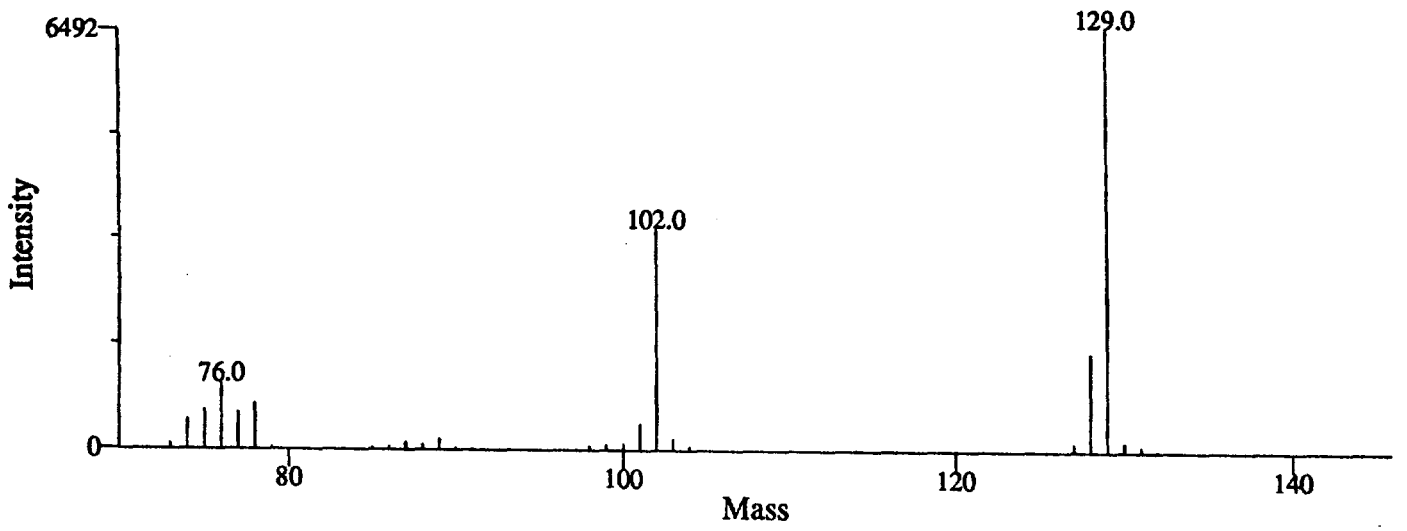


Figure 6
This mass spectrum show the fragmentation pattern of unsubstituted cinnamonitrile by electron ionization.





SH p-chlorocin nitrile LCEI 6-1992.scan scan 7 - 114

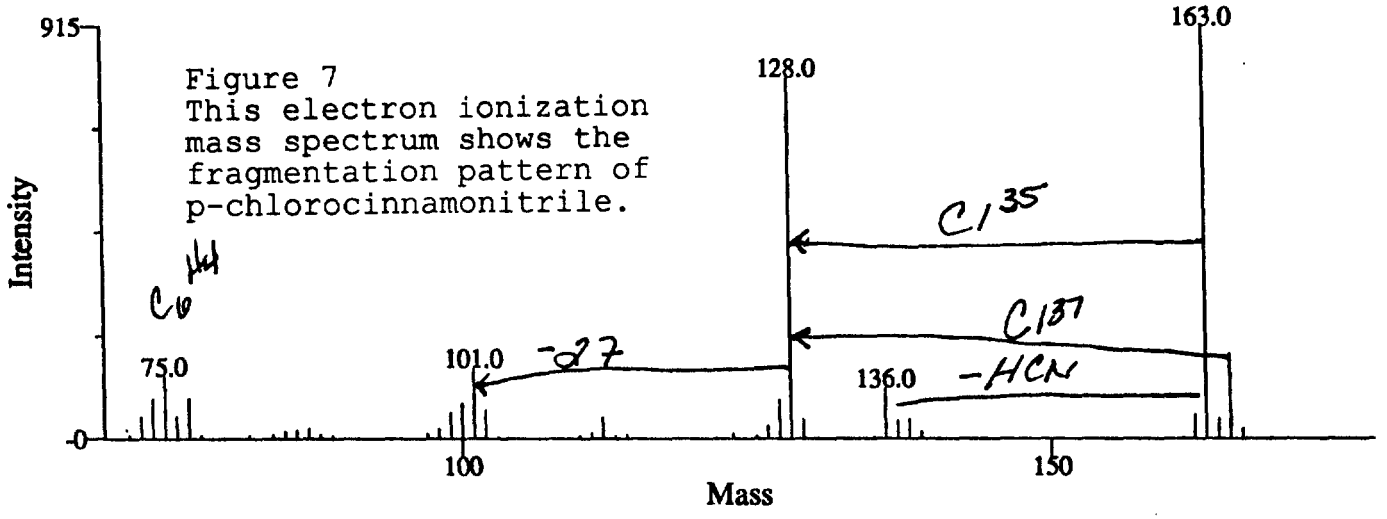
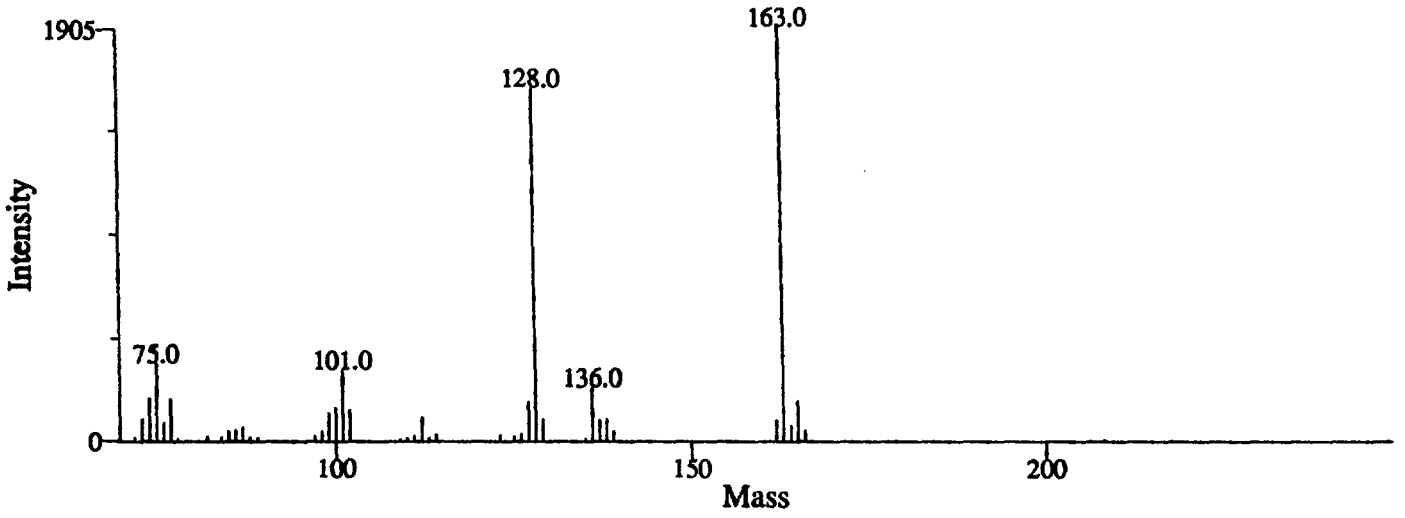
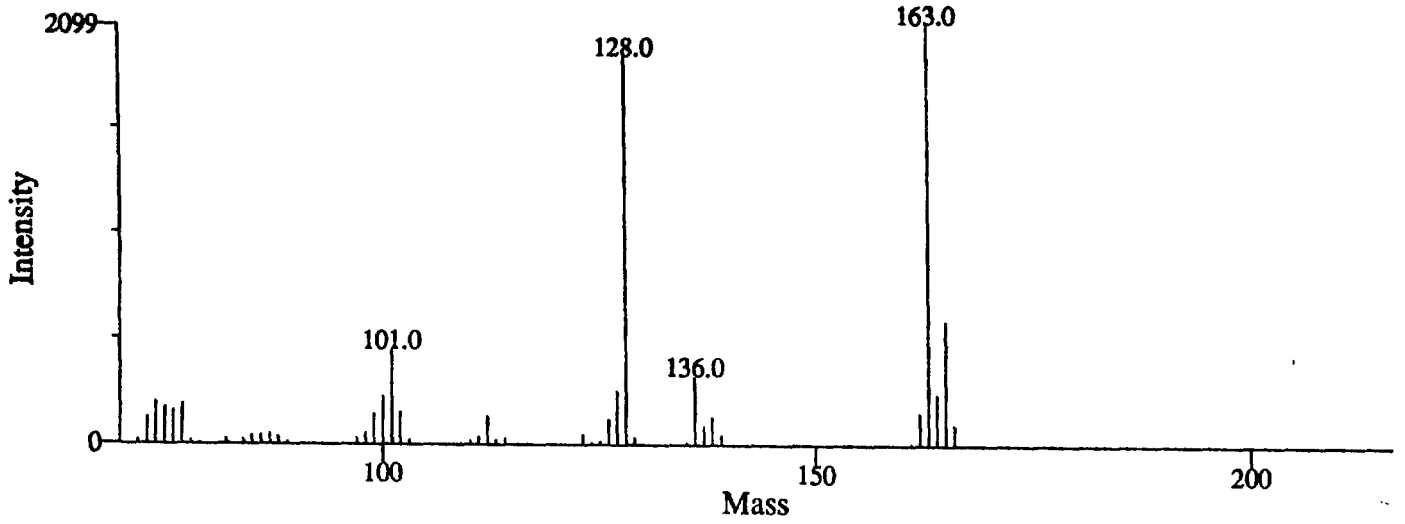


Figure 7
This electron ionization mass spectrum shows the fragmentation pattern of p-chlorocinnamonitrile.

SH p-chlorocin nitrile LCEI 6-1992.scan scan 45 - 57



SH p-chlorocin nitrile LCEI 6-1992.scan scan 81 - 88



// DPP plus Ethyl crotonate (RuL)

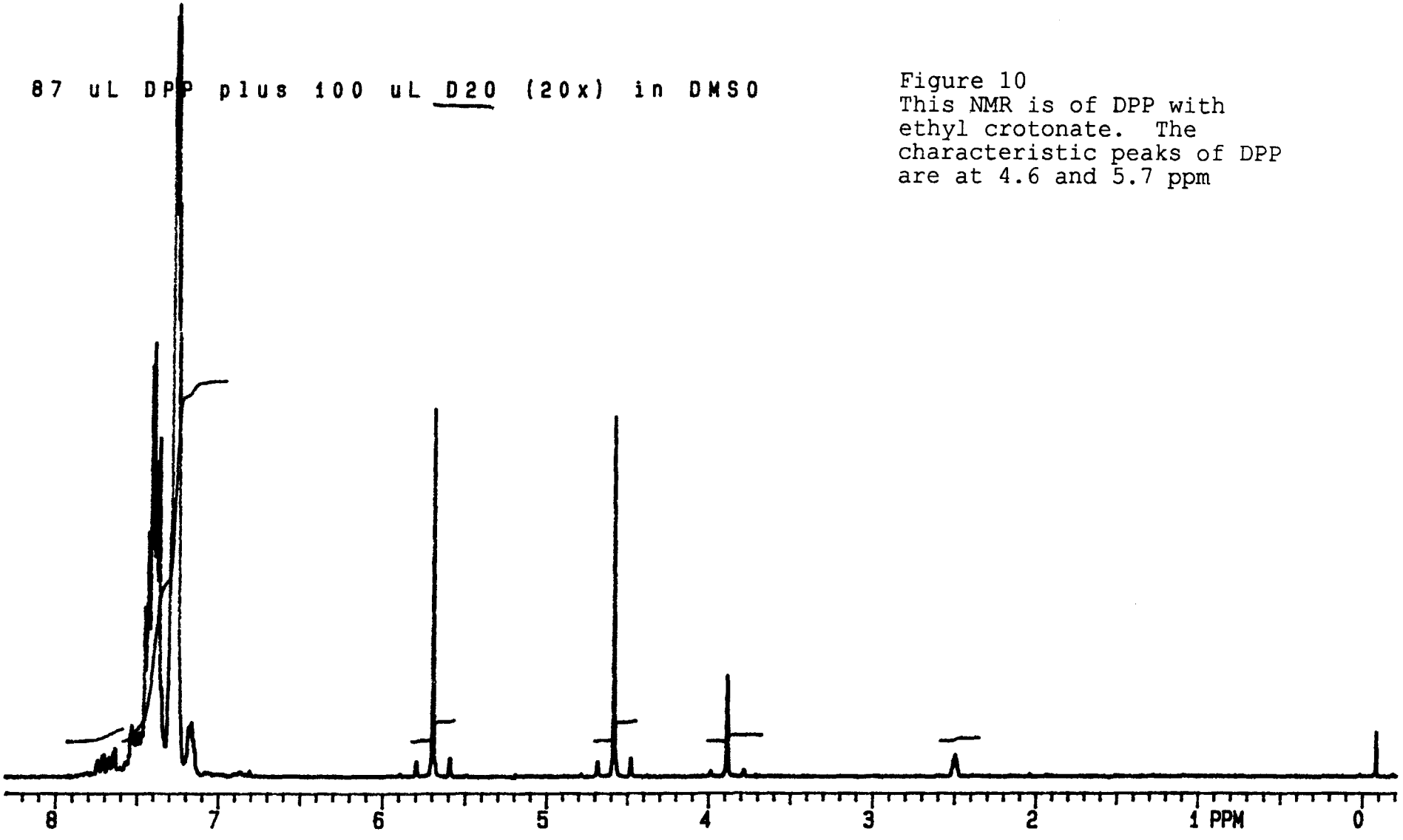


Figure 10
This NMR is of DPP with ethyl crotonate. The characteristic peaks of DPP are at 4.6 and 5.7 ppm