

**The Synthesis of 5-Benzoyl-1,3-Benzenediacids
for the Double-Capping
of β -Cyclodextrin**

A Thesis

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Daniel MacDougall Williams

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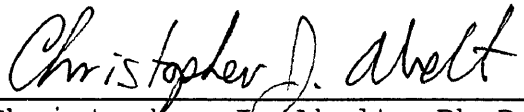
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Daniel M. Williams

Approved, August 1994



Christopher J. Abelt, Ph.D.



Deborah C. Bebout, Ph.D.



Robert D. Pike, Ph.D.

TABLE OF CONTENTS

ACKNOWLEDGMENTS.....	iv
LIST OF FIGURES.....	v
LIST OF TABLES.....	vi
LIST OF SPECTRA.....	vii
ABSTRACT.....	viii
INTRODUCTION.....	2
BACKGROUND.....	6
Cyclodextrins.....	6
Inclusion Complexes.....	8
Capping.....	11
Photochemistry of Benzophenone-capped β -Cyclodextrin...16	
Phase Transfer Catalysis.....	19
Other Synthetic Pathways.....	22
EXPERIMENTAL.....	27
Meta-xylene Dibromide.....	28
Copper (II) Cyanide.....	28
Tert-butyl Nitrite.....	29
Dimethyl 5-cyano-1,3-isophthalate.....	30
5-Cyano-1,3-isophthalic Acid.....	31
5-Cyano-1,3-benzenebis-4',4'-dimethyloxazoline.....	31
5-Nitro-1,3-benzenedisulfonic Acid.....	32
5-Amino-1,3-benzenedisulfonic Acid.....	32
5-Amino-1,3-isophthalic Acid.....	33
RESULTS AND DISCUSSION.....	34
SPECTRA.....	48
REFERENCES.....	64
VITA.....	67

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LIST OF FIGURES

Figure:

1. Desired Pinacolized Cap.....	4
2. Different Representations of Cyclodextrin.....	6
3. Dimensions of α , β and γ Cyclodextrins.....	7
4. Inclusion Complex Formation in α -Cyclodextrin.....	9
5. Effect of Capping on Cyclodextrin.....	11
6. Breslow's "Flexible Capping" of Cyclodextrin.....	12
7. First Discovered Cyclodextrin Cap.....	13
8. Tabushi's Regioisomeric Caps.....	13
9. Mechanism for Looper's Walk and Competing Telomerization.....	14
10. Photochemical Formation of Benzopinacol from Benzophenone.....	16
11. Importance of Solvent Choice.....	17
12. Radical-radical Reactions Under High Intensity Radiation.....	18
13. Possible Pinacol Products.....	19
14. Example of a Hofmann Elimination.....	21
15. 18-Crown-6 Chelating Potassium Ion.....	22
16. Formation of Diazonium Salt.....	22
17. Diazonium Salt to 5-Acetyl-1,3-Isophthalic Acid.....	23
18. Formation of Aryl Radical from Diazonium Salt.....	23
19. Monodimethyl Hydrazone to 5-Acetyl-1,3-Isophthalic Acid.....	24
20. Bromobenzenedialdehyde to 5-Acetyl-1,3-Isophthalic Acid.....	25
21. Direct Bromination to 5-Acetyl-1,3-Isophthalic Acid.....	26
22. Double Metal Halogen Exchange Method.....	26
23. Original Synthesis Pathway to Benzophenonediacid.....	34
24. Stoichiometry in Formation of Arylnitrile.....	35
25. Reason Proposed for Failure of Grignard Reaction.....	37
26. Three Grignard Attempts Using Phase Transfer Catalysis.....	39
27. Another Synthesis Pathway to the Benzophenonediacid.....	40
28. Result of Oxazolation of Aminodiacid.....	42
29. Formation of the Bisoxazoline from the Cyanodiacid.....	42
30. Result of Oxazolation of the Cyanodiester; Ring Closure Unsuccessful with Phenylisocyanate.....	43
31. First Steps of Route to Form Benzophenonedisulfonic Acid.....	44
32. Possible THF-soluble Oxazoline.....	45
33. Other Possible Synthetic Routes to Benzophenonediacid.....	46
34. Attempt at Novel Ether Capping.....	46

LIST OF TABLES

1. Variations on the Reaction of 5-amino-1,3-isophthalic acid with $\text{Cu}(\text{CN})_2$ and *t*-butyl nitrite yielding 5-cyano-1,3-isophthalic acid.....36

LIST OF SPECTRA

1. ¹ H NMR of <i>m</i> -xylylene dibromide.....	48
2. ¹³ C NMR of <i>m</i> -xylylene dibromide.....	49
3. ¹ H NMR of 5-nitro-1,3-benzenedisulfonic acid.....	50
4. ¹³ C NMR of 5-nitro-1,3-benzenedisulfonic acid.....	51
5. FT/IR of 5-nitro-1,3-benzenedisulfonic acid.....	52
6. ¹ H NMR of 5-amino-1,3-benzenedisulfonic acid.....	53
7. ¹³ C NMR of 5-amino-1,3-benzenedisulfonic acid.....	54
8. FT/IR of 5-amino-1,3-benzenedisulfonic acid.....	55
9. ¹ H NMR of dimethyl 5-cyano-1,3-isophthalate.....	56
10. ¹³ C NMR of dimethyl 5-cyano-1,3-isophthalate.....	57
11. ¹ H NMR of 5-cyano-1,3-isophthalic acid.....	58
12. ¹³ C NMR of 5-cyano-1,3-isophthalic acid.....	59
13. FT/IR of 5-cyano-1,3-isophthalic acid.....	60
14. ¹ H NMR of 5-amino-1,3-isophthalic acid.....	61
15. ¹ H NMR of 5-cyano-1,3-benzenebis-4',4'-dimethyloxazoline....	62
16. ¹³ C NMR of 5-cyano-1,3-benzenebis-4',4'-dimethyloxazoline...	63

ABSTRACT

Several synthetic routes for the formation of 5-benzoyl-1,3-benzenediacids were attempted. The synthetic pathways were unsuccessful owing to various difficulties, particularly solubility. The interest in these compounds lies in their potential ability to undergo a photochemical reaction to form the first capped cyclodextrin with covalent attachments to four glucose subunits.

**SYNTHESIS OF 5-BENZOYL-1,3-BENZENEDIACIDS
FOR THE DOUBLE CAPPING OF β -CYCLODEXTRIN**

INTRODUCTION

Cyclodextrins, which are cyclic molecules containing D(+)-glucopyranose subunits connected by α -(1,4) linkages, were discovered in 1891 by Villiers.¹ However, it was not until 30 years after Freudinger clarified the structure of cyclodextrins² in the 1940s that the amount of cyclodextrin research underwent a quantum leap as scientists developed a greater appreciation for its unique properties. This surge of interest occurred as chemists grasped that cyclodextrins were the first group of organic molecules known to complex other organic compounds.

The formation of inclusion complexes enables the host cyclodextrin to catalyze various classes of organic reactions on the guest organic molecule (or molecules) such as ester, amide and organophosphate hydrolysis.¹ As with enzyme-substrate complex formation, the formation of the inclusion complex in cyclodextrin increases the reaction rate because the probability of two molecules (be it two guest molecules or cyclodextrin and a guest molecule) colliding with each other in space at the correct orientation is increased considerably. Since cyclodextrins are intermediate in size between enzymes and organic molecules, they give valuable information about the molecular mechanisms of enzymatic activity.

Cyclodextrins have recently caught the eye of pharmaceutical companies interested in new ways of shuttling apolar drugs into the body. The interior of cyclodextrin is considerably less polar than water because it consists of only C-H groups and glycosidic oxygens. Since all cyclodextrins are somewhat water soluble, they may be used to transport nonpolar guest molecules (such as certain drugs) in an aqueous medium (such as body fluids). The guest organic molecule is in a dynamic equilibrium between being bound inside and being free outside of the cyclodextrin cavity. Once the drug reaches the part of the body where it is consumed, the drug is used up and the equilibrium shifts so that the drug is released from the torus. Luckily, the drug is not expelled prematurely into the body because the equilibrium favors the guest molecules residing inside the cavity.

Recently, the study of derivatized cyclodextrins has caught the attention of numerous research groups around the world. Cyclodextrins, while subject to cleavage in strong acids, are relatively stable in basic solutions. This fortunate fact allows functional groups to be attached to cyclodextrin with the aid of an alkaline catalyst.

Cyclodextrins containing an organic molecule attached to one glucopyranose residue are known as tethered cyclodextrins; if the organic molecule is attached to two or more glucose subunits, the cyclodextrin is said to be capped. Capping contiguous glucose residues is known as AB capping, capping glucose residues separated by one sugar subunit is known as AC capping, and so on. Numerous

tethers and caps have been studied.

Unfortunately, unsubstituted cyclodextrins, with their open top and bottom³, do not bind as specifically as enzymes and are therefore less effective catalysts. In certain cases, binding may be improved by derivatization because the substituent forms a hydrophobic floor inside the cyclodextrin. It has been shown that both capping⁴ and tethering⁵ molecules, when chosen judiciously, can significantly increase the ability of cyclodextrin to bind substrates. The strengthened binding is explained by examining one driving force for much of cyclodextrin host-apolar guest chemistry: hydrophobic interactions between the apolar interior of cyclodextrins and the guest molecule.

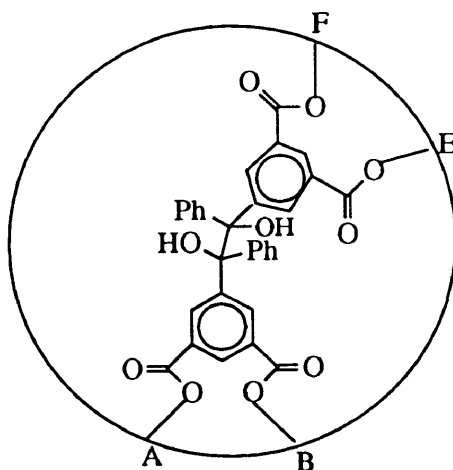


Fig. 1. Desired Pinacolized Cap

The main focus of this research was to prepare 3,5-benzophenone diacyl (or disulfonyl) chloride for the AB capping of β -cyclodextrin. Under low intensity radiation, it has been shown that two benzophenone molecules undergo a free-radical coupling reaction at 45°C in isopropanol to form benzopinacol.⁶ With two

benzophenone moieties AB capped to β -cyclodextrin, a successful photopinacolization would make the first cyclodextrin tetrasubstituted by one molecule (Fig. 1). This pinacolized product can exist as three different stereoisomers. Once isolated, these rigid and well-defined stereoconformers may prove to have better binding strength and specificity than other cyclodextrin caps.

BACKGROUND

Cyclodextrins:

Cyclodextrins are torus-shaped molecules (Fig. 2) which are also known as cycloamyloses, Schardinger dextrans or cycloglucans. Their size is denoted as follows: α -cyclodextrin has 6 glucopyranose subunits, β has 7 subunits, γ has 8, and so on (Figure 3). Alternatively, they may be called cyclohexaamyloses, cycloheptaamyloses, and so forth. Cyclodextrins with fewer than 6 residues are believed to be too sterically hindered to exist. Although cyclodextrins with more than 9 residues have been identified as components of mixtures, they have never been isolated and are considered to be too flexible to be of interest for binding and functionalization studies.

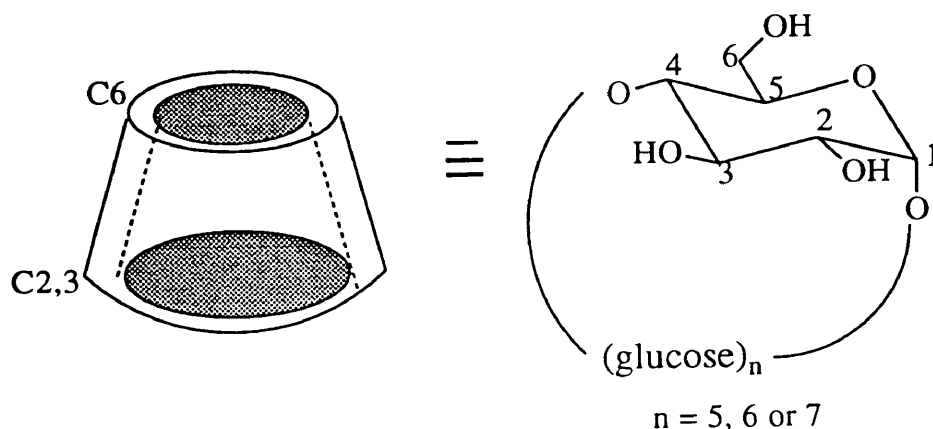


Fig. 2 Different representations of cyclodextrins

Cyclodextrins are commercially prepared by treating starch

with the enzyme amylase from the bacteria *Bacillus macerans* to form a crude digest containing α -, β - and γ -cyclodextrins plus a small amount of larger cyclodextrins. Isoamylase may be added to improve the reaction yield. From the digest, the four smallest cyclodextrins may be purified through selective precipitation or various chromatographic methods.

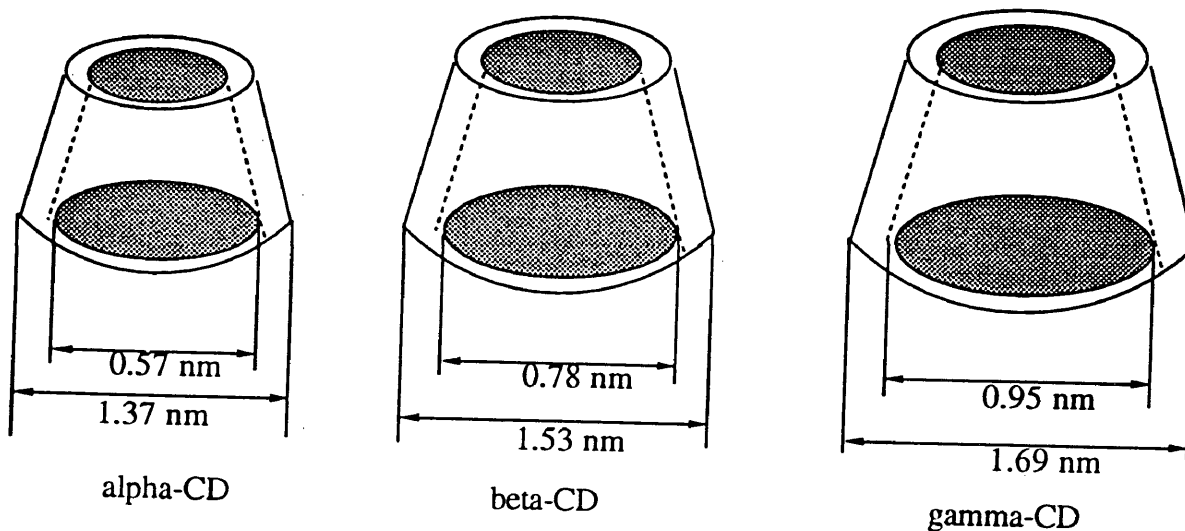


Fig. 3 Dimensions of α , β and γ cyclodextrins

Each glucopyranose subunit of cyclodextrin exists in an undistorted chair conformation. This conformation requires that the C6 primary hydroxyl groups be on one end of the torus (the primary face) and the C2 and C3 secondary hydroxyl groups be at the other end (the secondary face). The inherent flexibility of the primary hydroxyl groups allows them to rotate so as to partially block one opening to the cavity. On the contrary, the secondary hydroxyl groups have very little rotational freedom, not only because they are directly attached to the ring but also because most are hydrogen bonded to a hydroxyl group on a neighboring subunit. Cyclodextrin's cavity therefore is somewhat

"V"-shaped.

Hydrogen-deuterium exchange reactions show that every C2 and C3 hydroxyl group in β -cyclodextrin is involved in the intramolecular secondary hydroxyl H-bonding network. In order to reduce conformational strain in α -cyclodextrin, however, one of the glucopyranose units rotates out of the plane of the other residues, thereby eradicating two of the hydrogen bonds in the network. The flexibility of the γ - and δ -cyclodextrins diminishes the effectiveness of their hydrogen bonds. β -cyclodextrin is consequently the most rigid of all isolated cyclodextrins, which correlates with solubility studies which show that β -cyclodextrin is considerably less soluble in water than other cyclodextrins.⁷

Inclusion Complexes:

One of the most important features of cyclodextrins is their ability to act as a host for inclusion complexes. Cyclodextrins are known to include polar compounds such as some acids, amines and small ions and various apolar compounds, such as rare gases and aliphatic and aromatic hydrocarbons.¹

Various spectrophotometric methods may be used to verify the existence of inclusion complexes. Since ¹H NMR is so widely used and understood, it is a particularly common technique for detecting complex formation. Upon the addition of a guest benzoic acid derivative to a cyclodextrin solution, for example, ¹H NMR shows a substantial upfield shift of H-3 and H-5 atoms, but only a minor shift of the hydrogens at the H-1, H-2 and H-4 position. Since the

H-3 and H-5 atoms are located in the interior of cyclodextrin, the inclusion complex formation is thereby empirically verified. Titration, fluorescence and circular dichroism are examples of other techniques that may be used to determine inclusion complex formation.

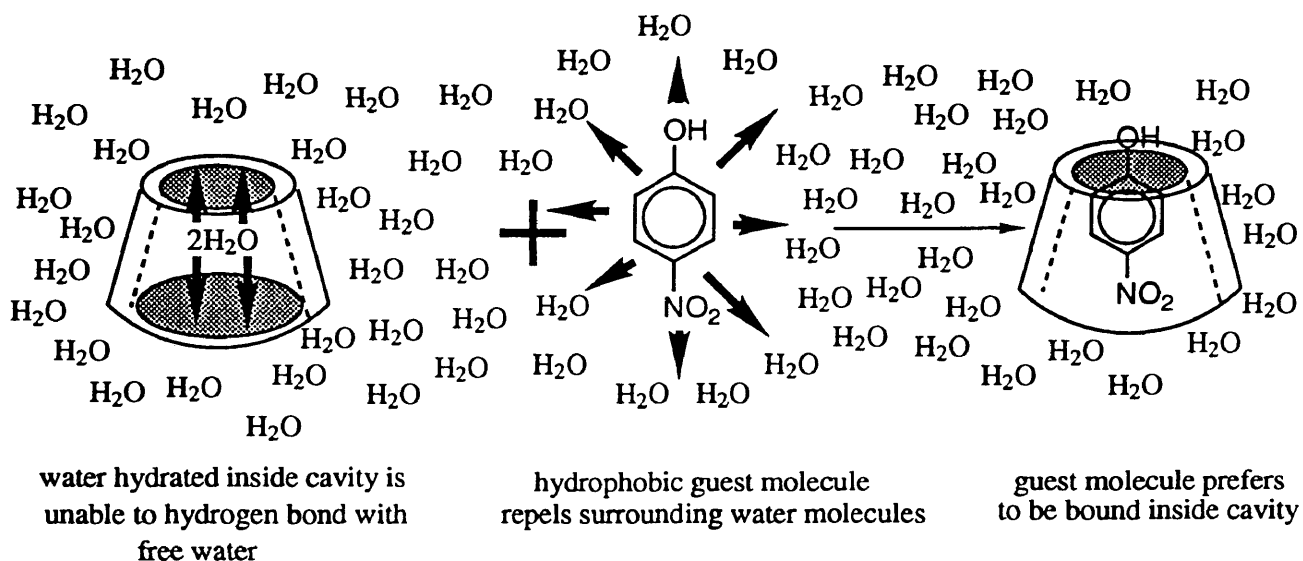


Fig 4. Inclusion complex formation in α -cyclodextrin

Researchers these past few decades have tried to rationalize the forces that allow cyclodextrin host-guest chemistry to occur. The hydrophobic effect, the release of high-energy water inside the cavity, the release of conformational strain energy, hydrogen bonding, and Van der Waals interactions have all been invoked to explain the formation of the inclusion complex.

When apolar molecules are placed in an aqueous solution, they become surrounded by water molecules. This ordering of water molecules around hydrophobic molecules is unfavorable entropically. To reduce this entropy loss, apolar compounds interact with each other, thereby allowing water ordering only around the apolar whole

rather than around each individual apolar molecule. For this reason, many aliphatic and aromatic hydrocarbons in solutions with cyclodextrins prefer to reside in the relatively apolar interior of the torus.

Hydrating water molecules are present in an "unincluded" cyclodextrin cavity in aqueous solution. Owing to the limited number of neighboring water molecules within adequate distance for effective hydrogen bonding, the included water is unable to hydrogen bond completely. Therefore, when these water molecules are replaced with an organic guest molecule and rejoin free water, a favorable enthalpy change occurs as the water molecules form their full complement of hydrogen bonds. According to this theory, the better a guest molecule fits into or fills the cavity, the more effectively it can displace the cavity water.⁸

As was stated previously, one glucose subunit of α -cyclodextrin lies out of the plane of its fellow subunits. However, as was demonstrated by X-ray crystallographic studies, when numerous different guest compounds replace the two water molecules hydrating the cyclodextrin cavity, the skewed subunit rejoins the plane of the others.⁹ The removal of angle strain along with the concomitant reformation of the hydrogen bonding network make the included α -cyclodextrin enthalpically favored over free α -cyclodextrin. For higher cyclodextrins, release in conformational energy obviously is not a factor in the formation of inclusion complexes since there are no out-of-plane glucose residues.

In a few cases, hydrogen bonding occurs between guest

molecules (such as hydroperoxides)¹⁰ and the primary hydroxyl groups of cyclodextrins. The involvement of Van der Waals forces on the other hand is much more widespread and is considered to be a very important factor in the inclusion of polar guest molecules.¹¹

p-Nitrobenzoic acid binds the cavity more weakly than benzoic acid. This result might seem surprising since the *p*-nitrobenzoic acid fills the cavity more completely than benzoic acid. In this case, the negative Van der Waals interactions between the interior of cyclodextrin and the nitro group supersede the ability of the guest cavity to displace the high-energy water or reduce the conformational strain. Also, it has been shown that *p*-nitrophenol can only enter the torus with the nitro end going in first. As the ring strain or high-energy water theories are not concerned with the means of penetration, again only Van der Waals forces explain this result.¹¹

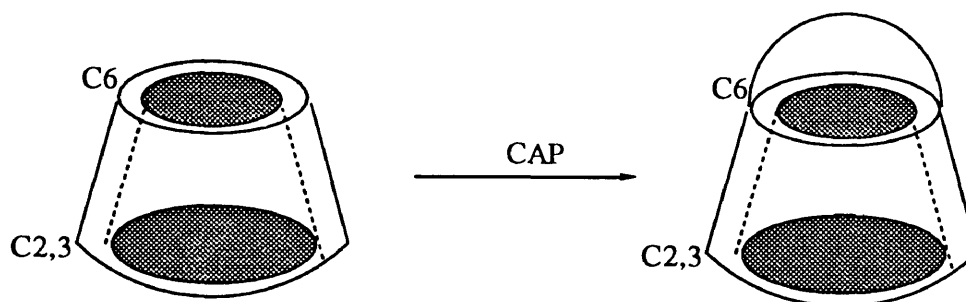


Fig. 5. Effect of Capping on Cyclodextrin

Capping:

Even though unmodified cyclodextrins bind compounds for the reasons mentioned above, they do not approximate enzymes in terms of binding strength and specificity because their open faces allow

guest molecules to leave and solvent molecules to enter the cavity more easily. Also, the presence of the glycosidic oxygens makes the cyclodextrin interior not completely apolar, thereby reducing the efficacy of the hydrophobic interactions.

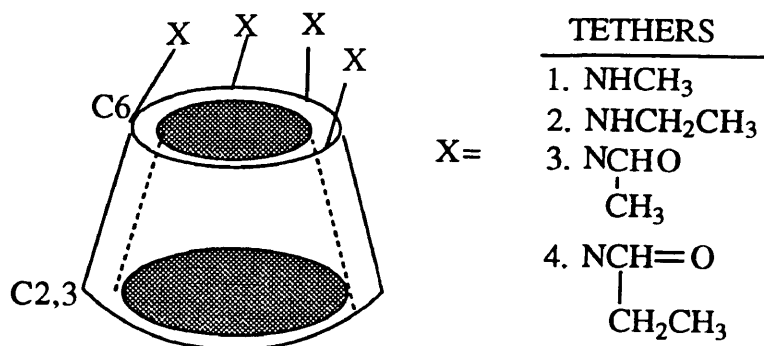


Fig. 6 Breslow's "Flexible Capping" of Cyclodextrin

With the desire to strengthen binding and improve specificity, Breslow and Emert attached different functional groups to all the C6 positions of the primary face of β -cyclodextrin (Fig. 6).¹² They predicted by molecular modeling and by considering hydrophobic forces that the alkyl groups of their substituents would bunch together on the inside of the cyclodextrin cavity to form what is known as a flexible cap. The guest 1-adamantanecarboxylic acid was shown to bind these modified cyclodextrins significantly better. However, several aromatic guests (including *m*-nitrophenyl acetate) were shown to bind the flexibly capped cyclodextrin equivalently or worse than the unmodified cyclodextrin. The flexible cap was believed to make the cyclodextrin cavity too shallow for these compounds to fit snugly into the cavity. The alkyl groups' inherent rotational freedom may also have diminished the rigidity and thereby the binding-effectiveness of the flexible cap.

One year later, Tabushi *et al* reported that his group had derivatized cyclodextrin at two positions using a bifunctionalized molecule which was mostly aromatic in character. A relatively rigid molecule, diphenylmethane-*p,p'*-disulfonyl chloride, was the first known "true" cyclodextrin cap (Fig. 7). And indeed, it was able to bind both 1-adamantanecarboxylic acid and *m*-nitrophenyl acetate more strongly.¹³

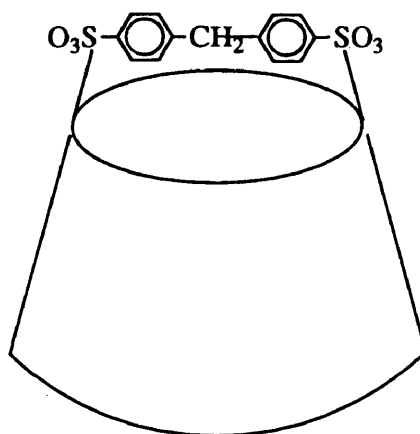


Fig. 7 The first discovered cyclodextrin cap

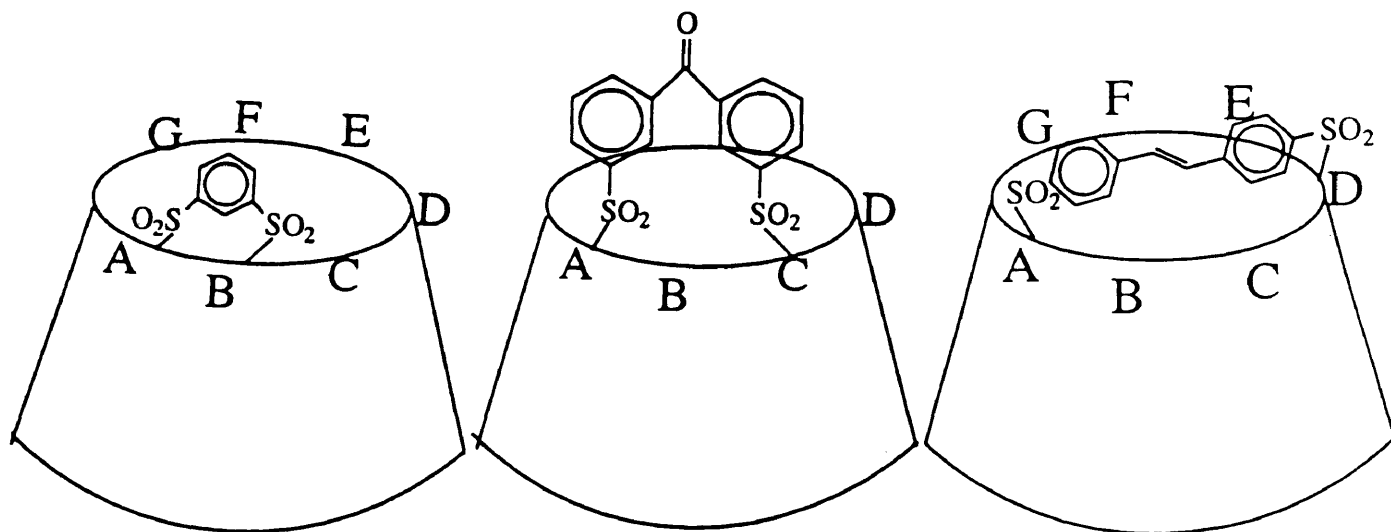


Fig. 8 Tabushi's Regioisomeric Caps

The mechanism proposed by Tabushi for the capping of

cyclodextrin is known as Looper's Walk (Fig. 9). First, one of the functional groups on the bifunctional capping molecule is attached to the C6 position of one glucose residue by an addition-elimination mechanism. The singly attached cap will then, based on its size, flexibility, direction of attack and so on, swing around and attach to another glucose residue.¹⁴

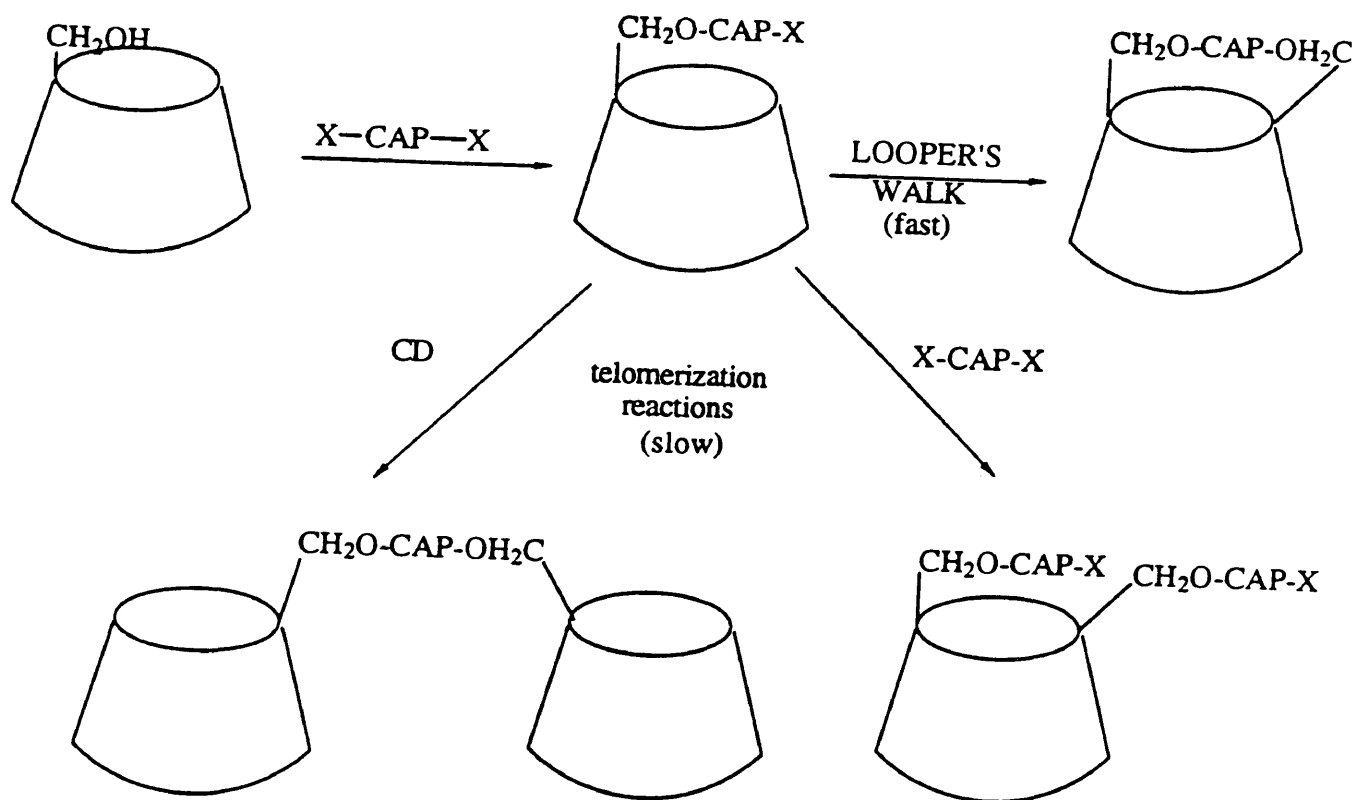


Fig. 9 Mechanism for Looper's Walk and Competing Telomerization

Unfortunately, this mode of capping is not always regiospecific and can often lead to a distribution of AB and AC or AC and AD regioisomeric caps. This complication occurs due to the flexibility of the capping molecule, the primary hydroxyl groups and the cyclodextrin molecule itself. For example, as was shown by molecular modeling studies¹⁵, this flexibility allows AC capping to

occur when the cap has an interfunctional group distance between 7.8 Å and 11.73 Å; AD capping is feasible if this distance is between 10.6 Å and 14.8 Å. The overlap between these two regioisomers is apparent.

The original cyclodextrin cap, owing to its flexible sp^3 carbon, produces a nice distribution of AC and AD isomers. Tabushi *et al* therefore set themselves to the task of synthesizing more rigid caps of an appropriate length to improve the regioisomeric selectivity. They found that *meta*-benzenedisulfonyl chloride¹⁶, benzophenone-3,3'-disulfonyl chloride and *trans*-stilbene-4,4'-disulfonyl chloride¹⁷ almost exclusively capped β -cyclodextrin in an AB, AC and AD fashion respectively (Fig. 8). Competing with the capping of cyclodextrin are the intermolecular condensation reactions or so-called telomerization reactions (Fig.9). Propitiously, telomerization reactions do not affect the regioisomeric distribution and are less favored than intramolecular capping.¹⁷

Reacting cyclodextrin with a 2.6 molar stoichiometric excess of benzophenone-3,3'-disulfonyl chloride, Tabushi *et al*. made the first doubly-capped cyclodextrin.¹⁸ Polycapping may be done successfully with AB and AC caps, but not with AD caps due to steric restrictions. It is hoped that via photochemical reaction, two photosensitive caps may be linked to form the first cyclodextrin with a single molecule attached at four glucopyranose subunits.

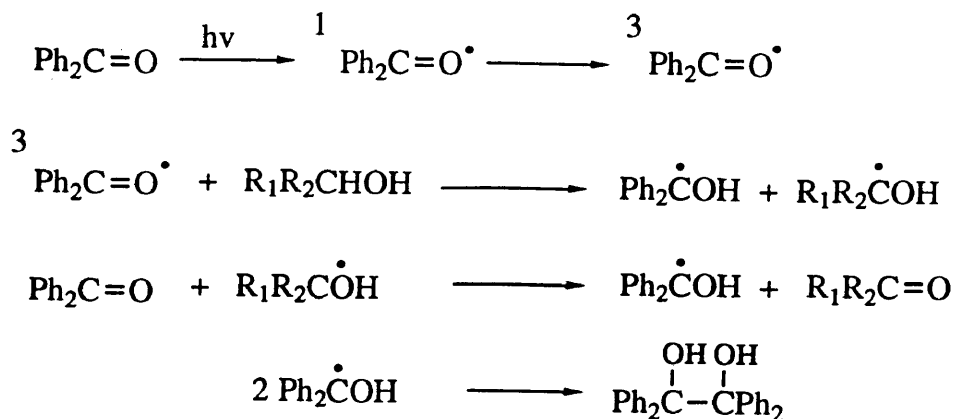


Fig. 10 Photochemical Formation of Benzopinacol From Benzophenone
Photochemistry of Benzophenone-capped β -cyclodextrin:

As a result of the simplicity of electromagnetic radiation, photochemical reactions are chaotic in nature. Owing to the great degree of contact between species in solution, there is little to stop a photoexcited molecule from interacting with any other photoexcitable species. For this reason, it is often desirable to perform photochemical reactions in an organized medium, such as the interior of cyclodextrin, where geometrical and steric factors will limit the scope of photochemical possibilities.

In 1900, Ciamician and Silber discovered that benzophenone, a nonenolizable ketone, could form benzopinacol when irradiated in ethanol.¹⁹ Once the reaction mechanism was characterized in 1920, the research on benzophenone chemistry grew exponentially. Eventually, it was discovered that benzopinacol yield is maximized using isopropanol as solvent, low-intensity radiation and an oxygen-free atmosphere.

Benzopinacol is formed by a mechanism in which photoexcited triplet benzophenone abstracts a hydrogen, either from the solvent or from some other H donor (Fig.10). In the 1940s, Bachmann

discovered that the yield of benzopinacol is nearly quantitative in isopropanol,²⁰ an improvement over the yield in ethanol. This result follows mechanistically since isopropanol forms a more stable radical upon hydrogen abstraction than ethanol forms. The reaction is therefore solvent-dependent as can be seen vividly by examining what can happen in solvents with no readily abstractable hydrogens. Upon irradiation in acetonitrile-water, for example, benzophenone-capped β -cyclodextrin abstracted a C6 hydrogen from a glucopyranose residue of cyclodextrin itself (Fig. 11). The result was diminished yield of coupled benzopinacol product and a complex reaction mixture since the C6 aldehyde may form numerous different pinacol products.²¹

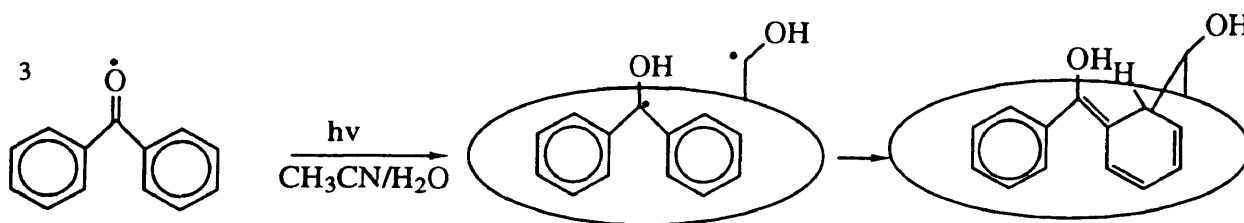


Fig.11 Importance of Solvent Choice

Since high intensity radiation increases the steady state concentration of radical intermediates, it also increases the probability of radical-radical reactions. Under these conditions, pinacolization still occurs, but it is now also possible that a ketyl radical will couple at the *ortho* and *para* positions of the benzhydryl radical to form light-absorbing transients (LATs).²² Not only do both LATs quench triplet benzophenone, but under an aerobic atmosphere, these LATs react with the ketyl radicals to form benzophenone and the alkyl ketone. Another complicating

possibility under large light flux is the occurrence of reverse hydrogen-transfer and the direct coupling of the benzhydrol radical with the hydrogen donor ketyl radical (Fig. 12). Oxygen is also problematic because it reacts with the ketyl radicals. Both oxygen and high intensity radiation therefore minimize the benzopinacol yield.

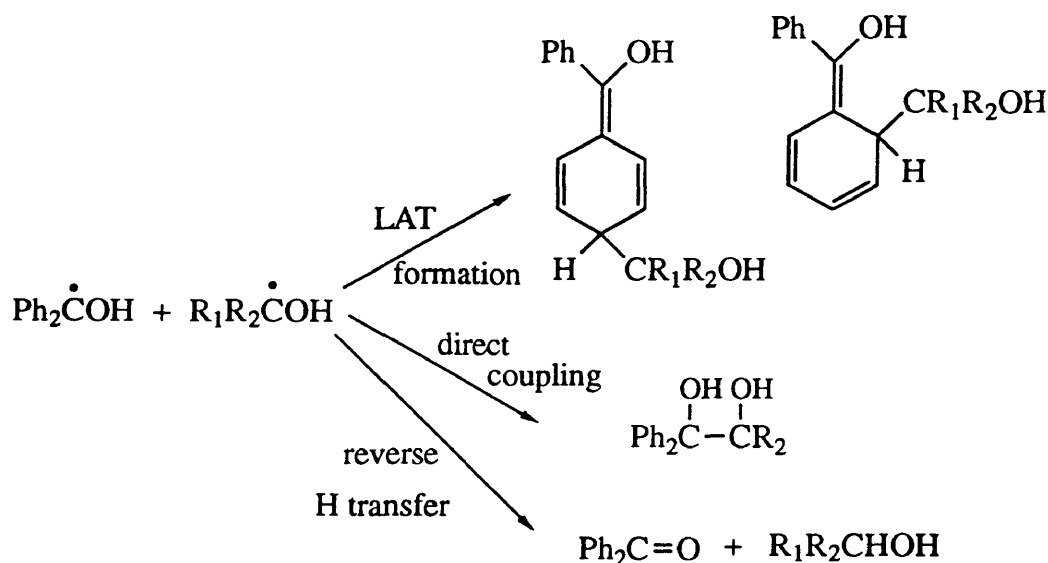


Fig. 12 Radical-radical reactions under high intensity radiation

Abelt *et al.* showed by HPLC that in aqueous isopropanol, irradiated benzophenone-capped β -cyclodextrin formed three major products. Since the benzophenone carbonyl has an endo and an exo face, endo-endo, exo-exo and endo-exo pinacol products (Fig. 13) can occur when the two radicals couple. The endo-exo form is the major product by simple statistics because it may be formed by two modes of attack, while the others are formed by only one.²⁰

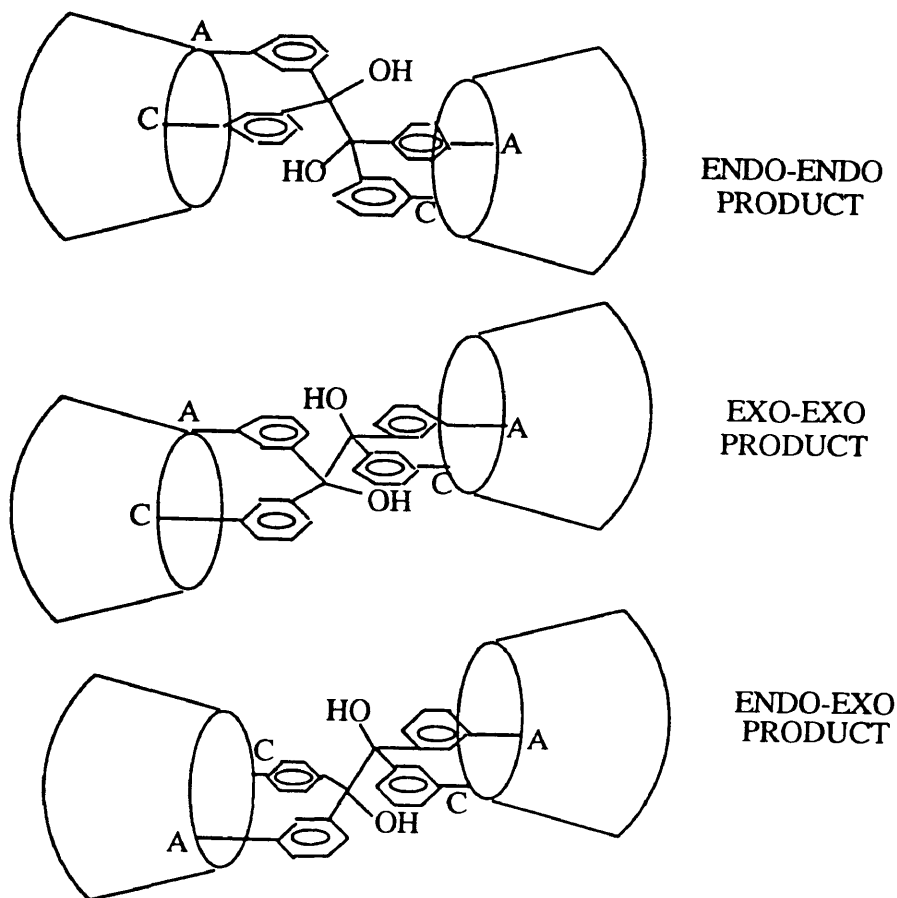


Fig. 13 Possible Pinacol Products

Phase Transfer Catalysis:

For bimolecular reactions to occur successfully, there must be collision between two reacting species.²³ Sometimes, however, collision is impossible because one of the two reactive entities does not dissolve in the desired solvent--a problem that occurs typically when one reactant is hydrophobic in character and the other is hydrophilic. This problem is typically circumvented by using a solvent that will dissolve both molecules. For example, solvents such as DMSO, DMF or acetonitrile, due to their dipolar, aprotic nature, are typically used to dissolve apolar and polar molecules simultaneously. However, these solvents are expensive and in some circumstances are reactive with the solute species.

In the late 1960s and early 1970s, several research groups gained insight on methods for bringing mutually insoluble molecules together for bimolecular reaction in the absence of acceptable reaction solvents. The term phase transfer catalysis, a method for bringing ions into organic media by either adding a counterion soluble in organic media or by complexing the counterion with an organic host, was coined in 1968 by Charles M. Starks.²⁴

The effectiveness of phase transfer catalysis is demonstrated through the reaction of 1-chlorooctane with sodium cyanide in an organic medium. After several days of heating and stirring this mixture, there was practically none of the desired 1-cyanooctane product formed. In the presence of an appropriate quaternary ammonium salt, however, 1-cyanooctane was formed with 100% yield after only 1 or 2 hours!²⁵

Phase transfer catalysis is necessary when a cation (in the case above, Na^+) that is only soluble in the aqueous layer restrains the anion from leaving that layer in order to maintain electric neutrality. The lithium cation, owing to its small size and unique properties, is somewhat soluble in some organic solvents and may be used to effect a phase transfer. A quaternary ammonium (or phosphonium) chloride, bromide or hydroxide also is used for phase transfer catalysis because it is typically completely alkylated or arylated which allows it to enter the organic layer. When the positively charged ammonium ion diffuses into this less polar layer, it requires a negatively charged molecule to enter the layer with it. In the case above, cyanide is more soluble in

nonpolar media than either the bromide, chloride or hydroxide anion, so to maintain electric neutrality, the cyanide ion enters the organic solvent and the bromide or chloride remain in the aqueous layer with the original cation. The cyanide is then able to react with the 1-chlorooctane.

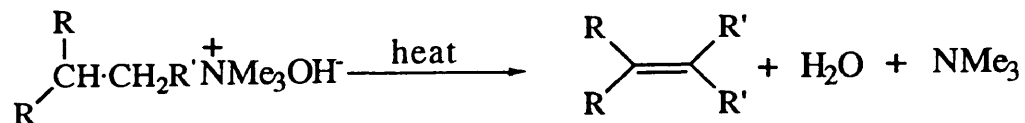


Fig. 14 Example of a Hofmann Elimination

Several principles are involved in choosing the appropriate quaternary ammonium salt for the phase transfer. Quaternary hydroxides, for example, may undergo Hofmann elimination (Fig. 14) at room temperature. Since a Hofmann elimination requires the presence of a hydrogen β to the nitrogen, the use of benzyl, methyl and phenyl substituents, for example, prevent this side reaction from occurring. Also, some hydrocarbon substituents are better than others for avoiding the cleavage of the quaternary ammonium hydroxide into the trisubstituted ammonia and alcohol.²⁴

Crown ethers and some of their analogues are useful in phase transfer catalysis because they are able to chelate ionic species of the appropriate size. For example, 18-crown-6 is able to complex the potassium ion (Fig. 15). Since these macroheterocycles are soluble in both aqueous and organic media, they shuttle complexed cations into the organic layer, allowing the anion to be transported along with it to maintain electric neutrality, thereby inducing the phase transfer catalysis.

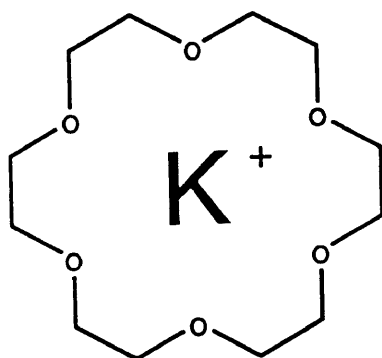


Fig. 15 18-crown-6 Chelating Potassium Ion

Other Synthetic Pathways:

While neither the synthesis of 3,5-benzophenonedicarbonyl chloride nor 3,5-benzophenonedisulfonyl chloride have been reported, there are two procedures in the literature for the synthesis of a closely related analogue, 5-acetyl-1,3-isophthalic acid. From this compound, the diacyl chloride is formed by the standard chlorination with thionyl chloride and DMF.

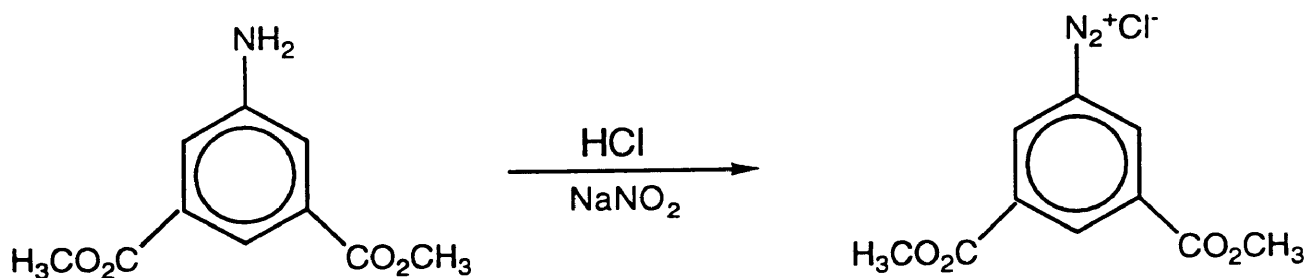


Fig. 16 Formation of Diazonium Salt

Clendinning prepared several alkyl derivatives of phthalic and isophthalic acid. The first step of his preparation of 5-acetyl-1,3-isophthalic acid transforms commercially available 5-amino-1,3-isophthalic acid into a diazonium salt by reacting it with HCl and NaNO_2 (Fig. 16). The diazonium salt is subsequently reduced to aryl radical indirectly by copper (II) sulfate and sodium bisulfite. Once the aryl radical is formed, it reacts with acetaldoxime to make the aryl oxime. The aryl oxime is then hydrolyzed to give the

desired 5-acetyl-1,3-isophthalic acid.²⁶ (Fig. 17) The published yield is 12% for this procedure.

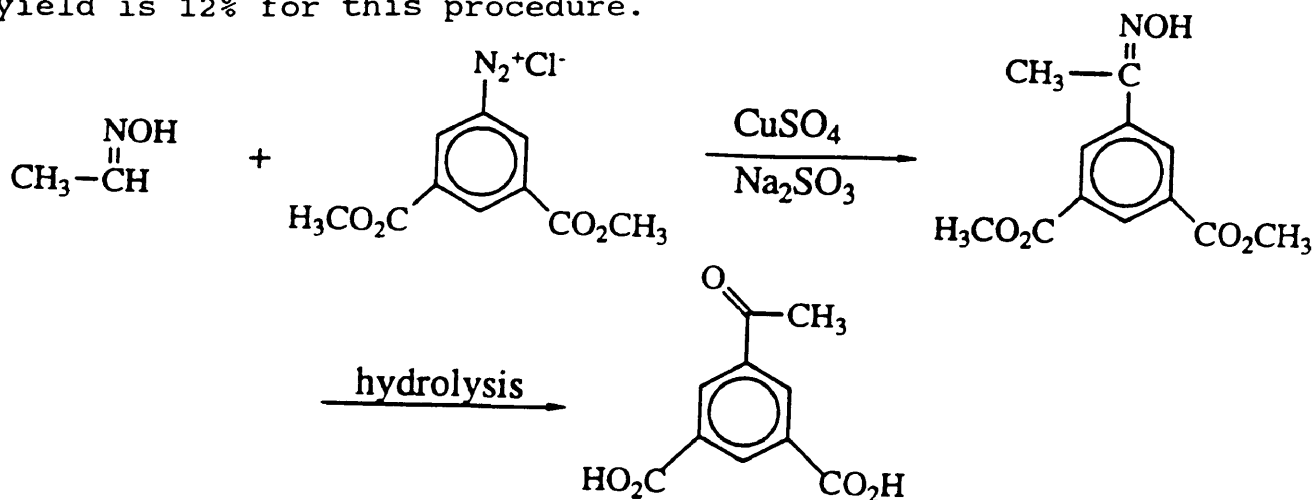


Fig. 17 Diazonium Salt to 5-Acetyl-1,3-isophthalic acid

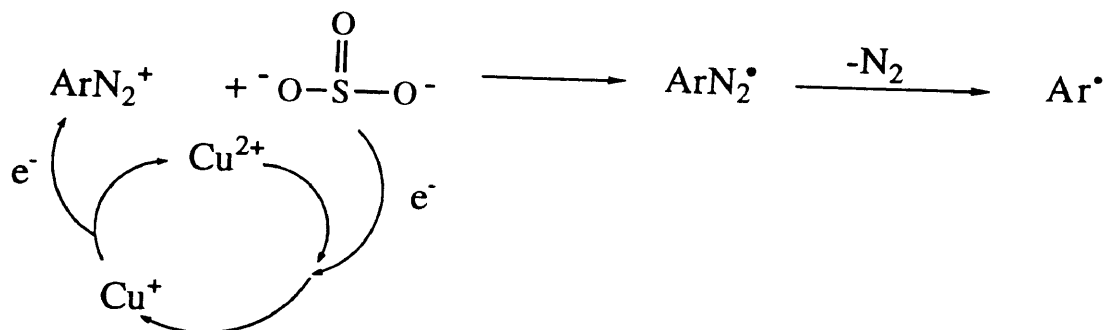


Fig. 18 Formation of Aryl Radical from Diazonium Salt

In the other reaction procedure (Fig. 19), the monodimethyl hydrazone of triacetyl benzene was prepared from one mole of triacetylbenzene, dimethyl hydrazine, and *p*-toluene sulfonic acid in benzene. In the following step, the acetyl groups are oxidized to the carboxylic acid using hypobromous acid. Acid hydrolysis then converts the hydrazone to an acetyl group. The yield for the oxidation and hydrolysis is very good (69%), but the hydrazone is formed in low yield (15%).²⁷

Several other pathways have been proposed for the formation of 5-acetyl-1,3-isophthalic acid. One synthetic possibility involves

the formation of 5-bromo-1,3-benzenedialdehyde (Fig. 20). Ethylene glycol will react with the aldehyde groups, changing them into the corresponding acetal. With the aldehyde groups thus protected, the arylmagnesium bromide may then be formed. This Grignard reagent is reacted with acetonitrile; after acid hydrolysis and chromic acid oxidation, the 5-acetyl-1,3-isophthalic acid is formed. However, this as yet unattempted synthetic route seems cumbersome at first glance. To start, the bromobenzenedialdehyde must be formed in two steps from 5-amino-1,3-isophthalic acid, making a total of seven steps. Second, both the bromination step and Grignard reactions are known to give relatively low percent yield. Therefore, it seemed highly questionable whether there would be much starting material to work with for the final oxidation.

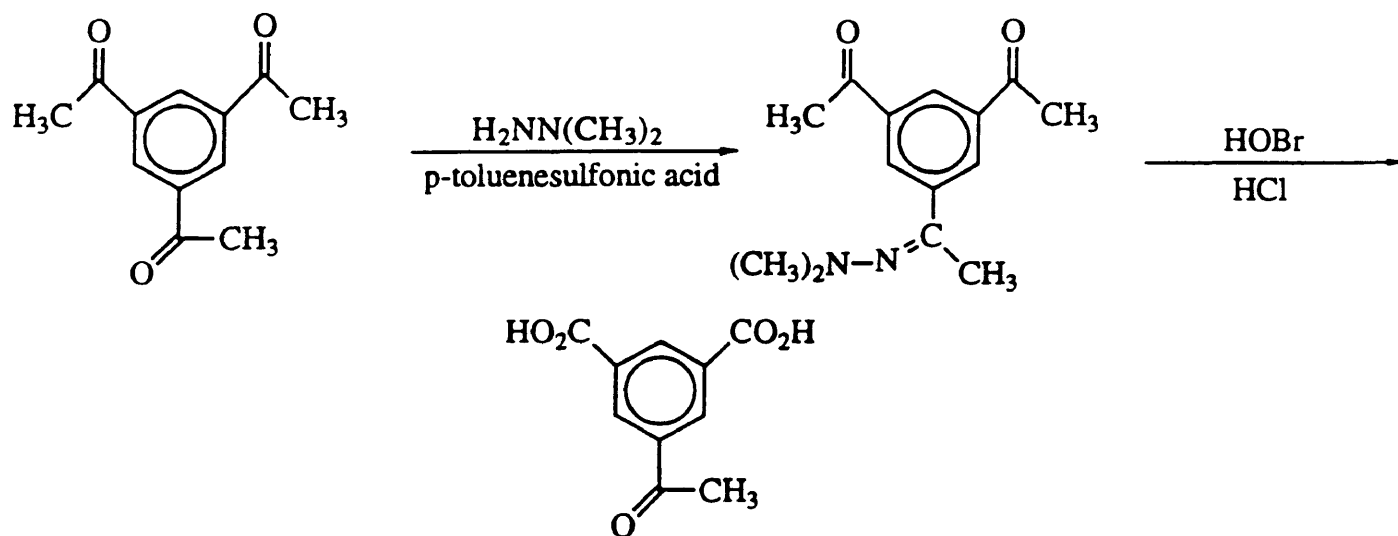


Fig. 19 Monodimethyl Hydrazone to 5-Acetyl-1,3-isophthalic acid

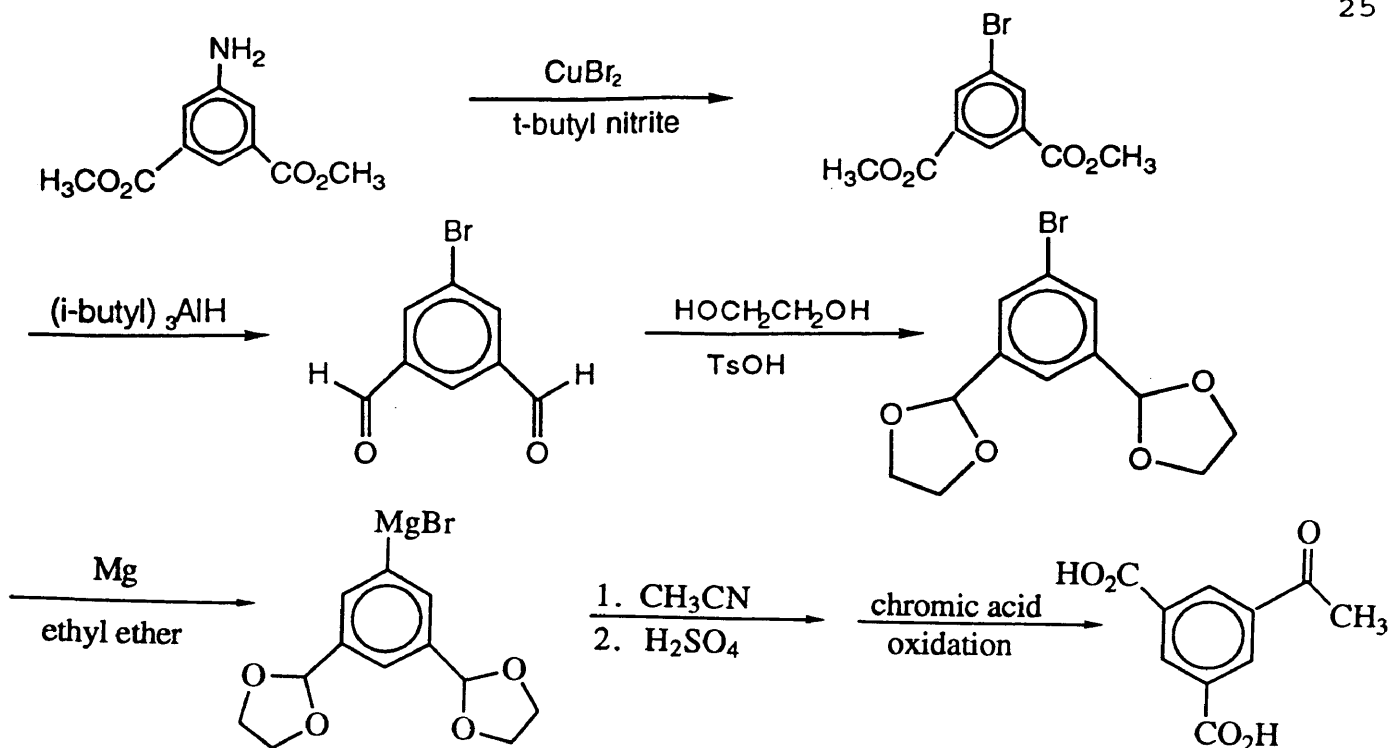


Fig. 20 Bromobenzenedialdehyde to 5-Acetyl-1,3-isophthalic acid

A second reaction scheme also uses an ethylene glycol acetal as a protecting group, this time for the carbonyl of 5-acetyl-1,3-dibromobenzene. This molecule then undergoes a double metal halogen exchange upon addition of two equivalents of *t*-butyl lithium and the bislithiate is formed (Fig. 21). The bislithiate then attacks carbon dioxide to form the diacid product. Yet another possible reaction scheme begins with the recently discovered²⁸ direct bromination of isophthalic acid with potassium bromate in sulfuric acid (Fig. 22). The arylmagnesium bromide is formed next, which attacks acetonitrile to give the desired product after hydrolysis.

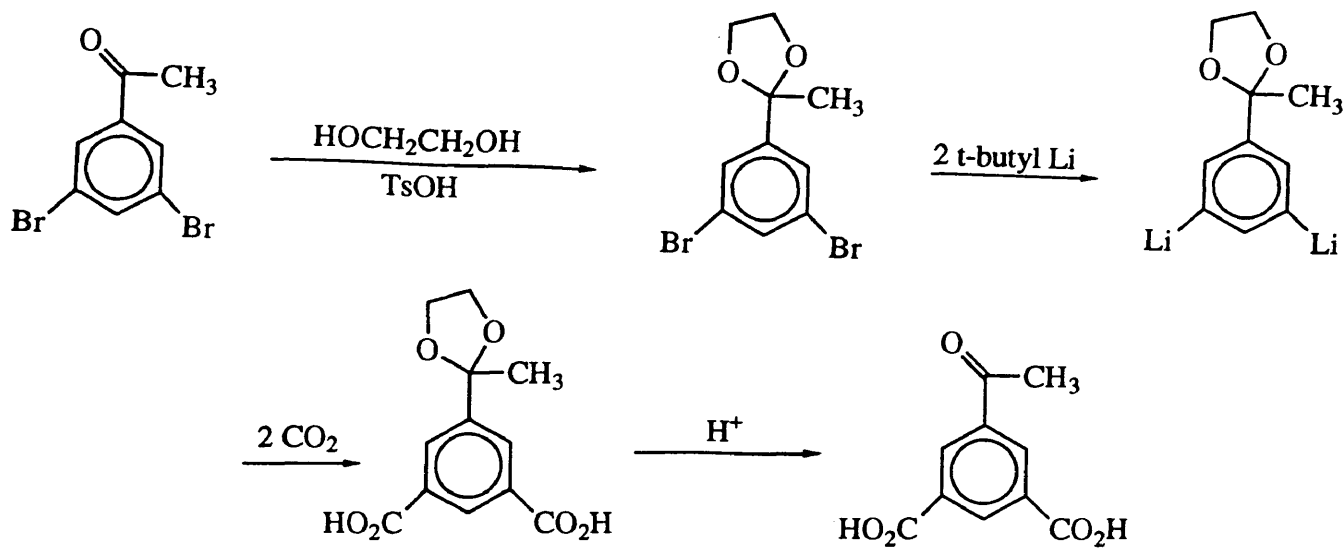


Fig. 21 Double Metal Halogen Exchange Method

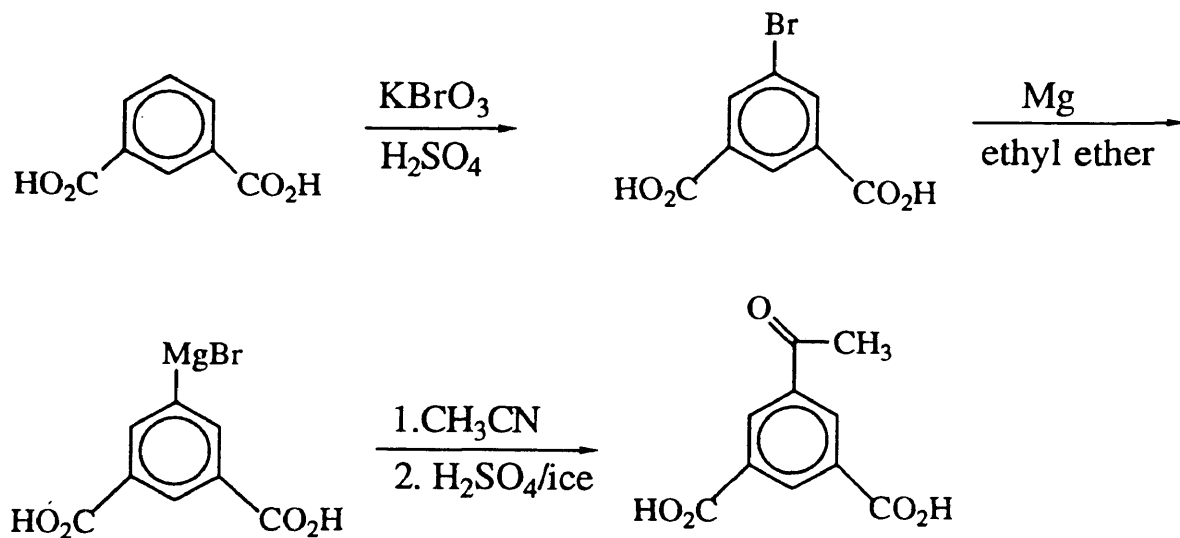


Fig. 22 Direct Bromination to 5-Acetyl-1,3-isophthalic acid

EXPERIMENTAL

Acetonitrile and pyridine were distilled from CaH_2 under CaCl_2 and used immediately. ^1H NMR and ^{13}C NMR data were obtained using a GE QE-300 spectrometer. NMR samples were dissolved in DMSO-d_6 and referenced to DMSO at 2.49 ppm for ^1H NMR and at 39.5 ppm for ^{13}C NMR. FT-IR spectra were obtained using a Perkin-Elmer 1600S spectrometer. Samples for IR analysis were cast as KBr pellets. Melting points were determined on a Mel-Temp capillary apparatus; the values are uncorrected.

meta-xylene dibromide²⁹

Meta-xylene (8 g, 75 mmol), benzoyl peroxide (0.25 g) and N-bromosuccinimide (27.5 g, 154 mmol) were placed in a round-bottom flask equipped with a condenser. Carbon tetrachloride (75 mL) was added to the solids and the resultant solution was heated at reflux with stirring for approximately 45 minutes under a flood light. The solution was cooled, filtered and concentrated *in vacuo* at 50°C. The oily pot residue was recrystallized from hexanes. The m-xylene dibromide (5.12 g, 48 mmol, 30% yield) precipitate was collected by vacuum filtration. The hard, white crystals melted at 75-76°C.

¹H NMR δ 4.48 (s 4H), 7.33 (s 3H), 7.43 (s 1H);

¹³C NMR δ 33.1, 129.3, 129.5, 129.8, 138.5.

Copper (II) Cyanide³⁰

Copper (II) sulfate pentahydrate (5.0 g, 20 mmol) was completely dissolved in water (100 mL). In a separate vessel, potassium cyanide (2.6 g, 40 mmol) was dissolved in water (25 mL). Distilled pyridine (1.6 mL, 20 mmol) was poured into the stirring copper solution. The solution should turn navy blue immediately. Next, the KCN solution was added under stirring to the copper solution. A green precipitate formed that was filtered with suction and then dried overnight at 50° C *in vacuo*.

tert-butyl nitrite³¹

In a three-neck flask fitted with a reflux condenser, thermometer and an addition funnel, sodium nitrite (38.0 g, 0.55mol) was dissolved in water (150 mL). The reaction vessel was then immersed in an ice-salt bath until the temperature of the nitrite solution dropped to 1°C. While maintaining the temperature of the stirring nitrite solution between 1°C and 5°C, a cold mixture (0-5°C) of t-butanol (50 mL, 0.53 mol), sulfuric acid (13.6 mL) and water (10 mL) was added below the surface of the nitrite solution over 3 hours from the addition funnel. Once the addition was complete, the stirring was stopped and layers formed. The solution was allowed to sit for several minutes and then was poured into a separatory funnel. The funnel was shaken and the aqueous (bottom) layer was discarded. The green organic layer was then washed with 10% aq. sodium bicarbonate (2 x 10 mL) and conc. aqueous NaCl (2 x 10 mL). The organic layer was distilled; the fraction boiling between 63°C and 70°C was collected and stored in the refrigerator until use.

Dimethyl 5-cyano-1,3-isophthalate

In a three-neck round bottom flask equipped with a thermometer and reflux condenser, copper (II) cyanide (3.35 g, 29 mmol) and t-butyl nitrite (4.3 mL, 35 mmol) were dissolved in acetonitrile (150 mL, distilled). The reaction mixture was heated to 50°C whereupon dimethyl 5-amino-1,3-isophthalic acid (5 g, 23 mmol) was added via powder funnel. The solution was heated to 65°C for a minimum of 3 hours. The solution turned from green to black during the course of the reaction. Gas evolution from the reaction was monitored by an oil bubbler. The reaction was allowed to continue for another hour after the bubbling terminated. The acetonitrile was then distilled off, leaving about 10 mL of liquid in the pot. The product mixture was then taken up in ether (400 mL) and about 20% aq. HCl (100 mL) and filtered with suction. Any solid which was collected was placed in a sublimator for later use. The ether filtrate was then washed with 20% aq. HCl (2 x 400 mL). The ether layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The remaining solid was combined with the above solid in the sublimator apparatus. The solids were then heated between 160°C and 180°C under vacuum (0.1 Torr) for several hours. The sublimation was continued until no more solid collected on the sublimator finger. The product was recrystallized from methanol and collected by filtration with suction. Dimethyl 5-cyano-1,3-isophthalate (1.38 g, 6.3 mmol, 22% yield) was isolated as a white solid. mp 170-172°C. ¹H NMR δ 8.65 (s 1H), 8.59 (s 2H), 3.9 (s 6H); ¹³C NMR δ 52.9, 113.1, 118.0, 131.5, 133.3, 136.7, 163.9.

5-cyano-1,3-isophthalic acid

Dimethyl 5-cyano-1,3-isophthalic acid (0.88 g, 4 mmol), 1N NaOH (8 mL, 8 mmol) and chloroform (10 mL) were heated to 40°C in ethanol (35 mL). The reaction mixture was stirred overnight. The next day, the solution was poured into water (80 mL) which was extracted with methylene chloride (2 x 75 mL). The aqueous layer was acidified with 10% HCl to at least pH 2 and was extracted with ethyl ether (2 x 75 mL). The ether layer was then dried with MgSO₄ and the ether was removed *in vacuo* and the solid was dried under vacuum (0.1 Torr) giving 5-cyano-1,3-isophthalic acid (0.58g, 3.04 mmol, 76% yield).

FT-IR cm⁻¹ 3085.5, 2239.3, 1730.8, 1713.8, 1273.5, 1196.6;

¹H NMR δ 8.64 (s 1H), 8.52 (s 2H);

¹³C NMR δ 112.7, 117.4, 132.7, 134.1, 136.5, 165.0.

5-cyano-1,3-benzenebis-4',4'-dimethyloxazoline

5-Cyano-1,3-isophthalic acid (0.77 g, 3.51 mmol) and 2-amino-2-methyl-1-propanol (8.5 g, 96 mmol) were dissolved in toluene (200 mL). The solution was heated at reflux overnight with azeotropic removal of water. The solution was cooled and the resultant precipitate was collected by suction giving 5-cyano-1,3-benzenebisoxazoline. mp 220-224°C.

¹H NMR δ 8.62 (s 1H), 8.10 (s 2H), 3.35 (s 4H), 1.16 (s 12H);

¹³C NMR δ 22.8, 53.9, 67.0, 109.5, 119.3, 132.9, 134.2, 140.3, 167.7.

5-nitro-1,3-benzenedisulfonic acid³²

Fuming nitric acid (50 mL) was added to 1,3-benzenedisulfonic acid (5 g, 21 mmol), and the mixture was heated at reflux with stirring overnight. The next day, the reaction mixture was cooled and poured over water (150 mL). The aqueous nitric acid was removed *in vacuo*; the solid residue was recrystallized from saturated aqueous NaCl. The 5-nitro-1,3-benzenedisulfonic acid (2.96 g, 10.4 mmol, 50% yield) precipitate was collected by suction filtration yielding thin, white needles. mp >400°C.

¹H NMR δ 8.25 (s 2H), 8.21 (s 1H);

¹³C NMR δ 120.0, 120.2, 129.6, 146.8, 149.7, 149.7;

FT-IR cm⁻¹ 1606.2, 1540.4, 1366.3, 1313.1, 1235.7, 1211.5, 1197.0, 1114.8, 1097.6, 1047.5, 993.0, 921.2, 895.0.

5-amino-1,3-benzenedisulfonic acid

5-Nitro-1,3-benzenedisulfonic acid (3.92 g, 13.8 mmol) was completely dissolved in 80 mL H₂O and placed into a Parr bottle. Palladium-on-carbon catalyst (0.25 g) was added to the solution. The Parr bottle was then shaken under a hydrogen (45 psi) atmosphere overnight. The palladium-on-carbon catalyst was removed by suction and was placed under a crystallizing dish to prevent ignition. The filtrate was distilled to dryness *in vacuo*; the solid that remained was 5-amino-1,3-benzenedisulfonic acid (3.08 g, 12.2 mmol, 88% yield). mp > 400°C.

¹H NMR δ 7.86 (s 1H), 7.52 (s 2H); ¹³C NMR δ 120.5, 122.5, 131.0, 149.1; FT-IR cm⁻¹ 3452.6, 1654.6, 1607.4, 1437.4, 1276.9, 1234.4, 1191.9, 1045.6.

5-amino-1,3-isophthalic acid

Commercially available dimethyl-5-amino-1,3-isophthalic acid (5 g, 23.9 mmol) was dissolved in ethanol (200 mL), 1N NaOH (47.8 mL, 47.8 mmol) and chloroform (50 mL). (The chloroform was used to dissolve the ester). The reaction mixture was heated at 40°C with stirring overnight. The next day, the solvents were removed *in vacuo*; the remaining solid was covered with 5% aqueous monobasic potassium phosphate (100 mL). Phosphoric acid was added to the phosphate solution until the solution was approximately pH 4. When the addition was complete, the resulting precipitate was filtered off *in vacuo*. The solution was refiltered the next day and the following day as more precipitate had formed. The precipitate was 5-amino-1,3-isophthalic acid. mp > 400°C.

$^1\text{H NMR } \delta$ 7.63 (s 1H), 7.36 (s 2H), 5.66 (s 2H).

RESULTS AND DISCUSSION

Although the objective of this research was to synthesize benzophenone 3,5-diacid chlorides for the capping and pinacolization of β -cyclodextrin, the entirety of this work was devoted to the synthesis of the diacids themselves. The synthesis was plagued by several stubborn problems, of which solubility was the most daunting. A primary focus of this research was to discover ways around these difficulties.

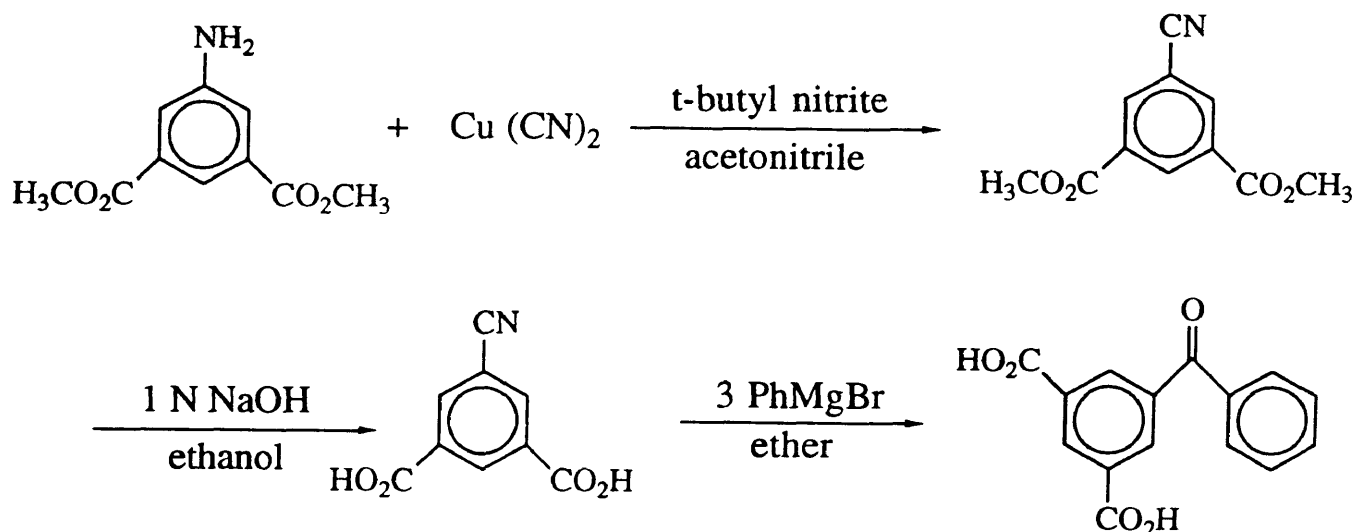


Fig. 23 Original Synthesis Pathway to the Benzophenonediacid

The initial step of the original reaction procedure was to replace the amino group of dimethyl 5-amino-1,3-isophthalic acid with a cyano group (Fig. 23). This reaction was pursued using *t*-butyl nitrite and $\text{Cu}(\text{CN})_2$ in acetonitrile, a technique that had previously been used successfully for the halogenation of arylamines using the appropriate cupric halide, but never before

for cyanation.³³ This novel reaction procedure was successful, but only gave 20% yield. Attempts therefore were made to optimize reaction conditions for the new cyanation technique.

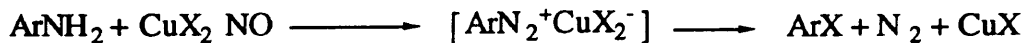
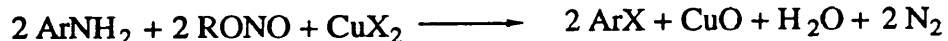


Fig. 24 Stoichiometry of Formation of Arylnitrile

Several explanations for the low yield of the cyanodiester initially seemed likely. First of all, the aminodiester did not dissolve particularly well in acetonitrile. This may have deterred the reaction from going to completion. Second, the temperature might not have been high enough or the reaction time long enough for the reaction to favor product formation. Finally, since nitro compounds are known to decompose at high temperatures, perhaps the *t*-butyl nitrite was destroyed at the elevated reaction temperature and therefore was unable to interact with the arylamine.

To remedy the solubility problem, the reaction was attempted in acetonitrile, plus just enough DMF or DMSO to dissolve the aminodiester. The reaction yield unfortunately was reduced considerably in these solvent mixtures, perhaps owing to side reactions between DMF or DMSO and reagents. The reaction was also attempted in acetonitrile and a small amount of water. The yield was practically nil for this reaction.

To increase the reaction temperature and perhaps improve dissolution, the cyanation was attempted in refluxing propionitrile. Propionitrile was chosen since its boiling point is 20°C higher than acetonitrile. In addition, since propionitrile is

the next largest molecule in the family of cyanoalkanes, it is slightly less polar than acetonitrile. It was speculated that this greater hydrophobicity might enable propionitrile to dissolve the organic aminodiester. Despite these theories, the product yield was nevertheless one tenth the yield in acetonitrile. Also, a study was done on the effect of reaction time on yield. It was discovered that at least 2 hours were necessary for maximum product yield.

Table 1. Variations on the reaction of 5-amino-1,3-isophthalic acid with $\text{Cu}(\text{CN})_2$ and *t*-butyl nitrite yielding 5-cyano-1,3-isophthalic acid.

Reaction conditions	Reaction yield
1 equiv. $\text{Cu}(\text{CN})_2$, 1.25 equiv. <i>t</i> -butyl nitrite in acetonitrile	22%
1 equiv. $\text{Cu}(\text{CN})_2$, 1.25 equiv. <i>t</i> -butyl nitrite in acetonitrile, DMF	10%
1 equiv. $\text{Cu}(\text{CN})_2$, 1.25 equiv. <i>t</i> -butyl nitrite in acetonitrile, DMSO	5%
1 equiv. $\text{Cu}(\text{CN})_2$, 1.25 equiv. <i>t</i> -butyl nitrite in acetonitrile, water	<1%
1 equiv. $\text{Cu}(\text{CN})_2$, 1.25 equiv. <i>t</i> -butyl nitrite in propionitrile	2%
1 equiv. $\text{Cu}(\text{CN})_2$, 5 equiv. <i>t</i> -butyl nitrite in acetonitrile	20%

In order to counteract the depletion of *tert*-butyl nitrite by decomposition, the reaction was done using a four molar excess of this compound. This ploy ensured that enough nitrite would be available to aid in the cyanation of the arylamine. However, this technique had no effect (within error) on the reaction yield.

The subsequent formation of the 5-cyano-1,3-isophthalic acid from dimethyl 5-cyano-1,3-isophthalate using 2 equivalents 1 N NaOH

in ethanol resulted in a nearly quantitative yield. The procedure was straightforward, containing only two minor variations from a technique for the formation of 3-cyano-1-naphthoic acid.³⁴ One variation was the removal of ethanol before the reaction workup, which led to a 16% increase in product yield. Secondly, since the cyanodiacid did not precipitate out in acidified water, the aqueous layer was instead washed with ether. The ether was removed *in vacuo* yielding the desired product.

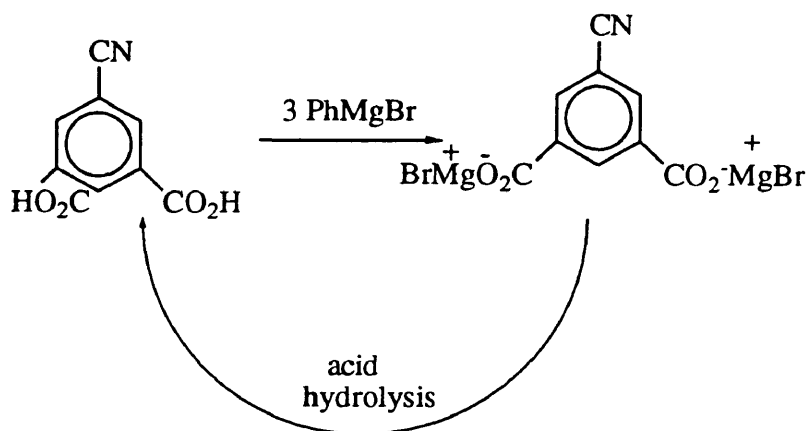


Fig. 25 Reason Proposed for Failure of Grignard Reaction

The subsequent Grignard reaction on the cyanodiacid, had it been successful, would have made the desired benzoyldiacid. Unfortunately, when the cyanodiacid was reacted with three molar equivalents of PhMgBr in ether followed by acid hydrolysis in refluxing 10% H₂SO₄, the result was the starting material, cyanodiacid. Oddly enough, as the reaction took place the reaction mixture went from gray to orange, and after hydrolysis, to yellow. These color changes seemed to indicate that a reaction was occurring. Several explanations seemed likely. Since considerable caution was taken to exclude water from the reaction system and

since the Grignard reagent itself was formed successfully, the possibility of water interacting with PhMgBr was dismissed. It seemed that the most probable scenario was that when the PhMgBr removed the protons from the carboxylic acids to form the carboxylate anions, the dianion precipitated out of the ether layer and therefore was no longer present for the third equivalent of PhMgBr to attack the cyano group (Fig. 25). Another possibility was that the reaction temperature was not high enough to effect the conversion of cyano to imine.

In an effort to improve solubility and increase the reaction temperature in one blow, the reaction was attempted first in distilled THF and then in benzene with an equivalent of ether. Canonne *et al.* showed that Grignard reagents reacted more successfully with nitriles in benzene than in ether.³⁵ Unfortunately, the reaction was successful in neither solvent. Solubility again appeared to be the spoiler.

Since solubility could not be improved in any Grignard-acceptable solvent, various phase transfer catalysts (PTC) were investigated in an attempt to bring the anions into an organic solvent. Benzyltrimethylammonium hydroxide (also known as Triton B) was locally available, so it was initially chosen as the PTC. Two molar equivalents of Triton B were reacted with 5-cyano-1,3-isophthalic acid to form the corresponding dicarboxylate salt. This molecule was then reacted with one equivalent of PhMgBr in THF and hydrolyzed. The resulting product was starting material. Since the dicarboxylate salt did not seem to dissolve at all in

THF, it can be assumed that the Grignard reagent and carboxylate dianion were not able to collide, and thereby react.

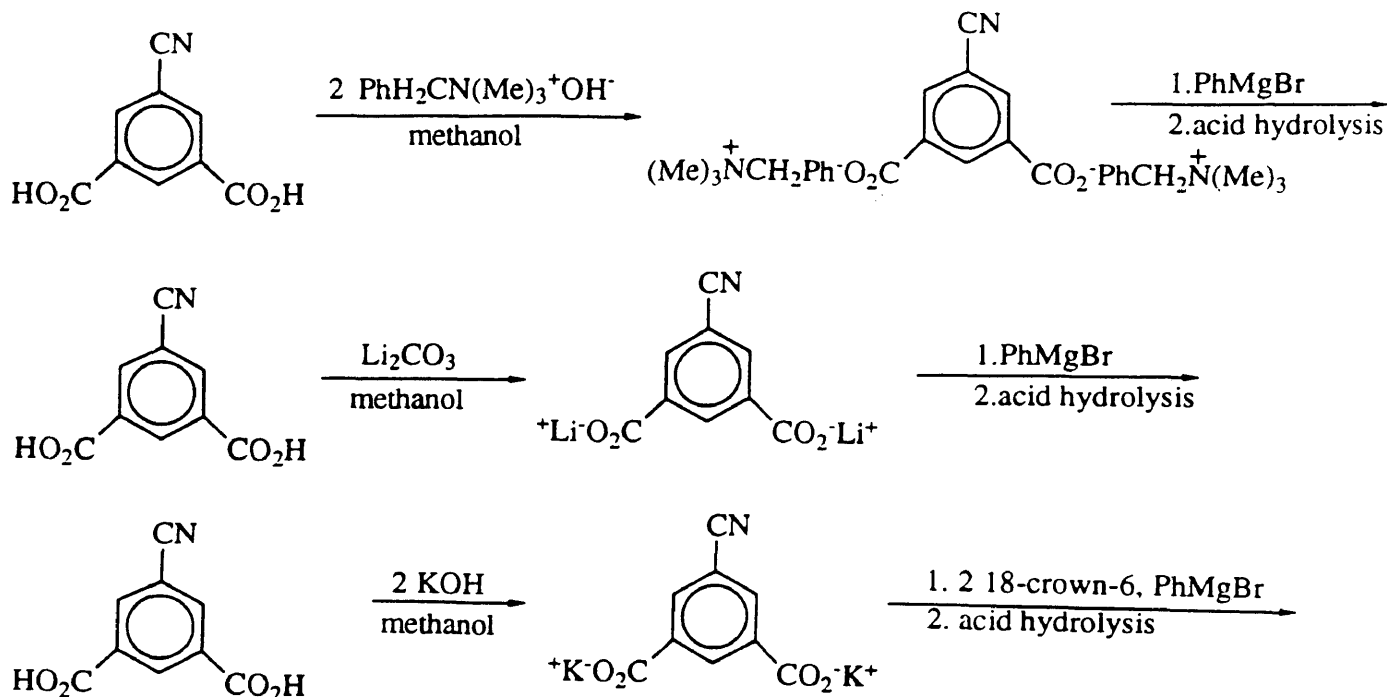


Fig. 26 Three Grignard Attempts Using Phase Transfer Catalysis

Next, the dicarboxylate dilithium salt was prepared from lithium carbonate and 5-cyano-1,3-isophthalic acid. This salt, when reacted with one molar equivalent of PhMgBr , did not effect the Grignard attack on the cyano group. Again, the lack of dissolution of the salt probably hindered the reaction. Finally, a last attempt at phase transfer catalysis was made, this time using 5-cyano-1,3-isophthalate dipotassium salt, two equivalents of 18-crown-6 and PhMgBr . It was speculated that the crown ether might induce phase transfer into THF, since they were both ethers and might have somewhat similar solubility properties. The reaction was again unsuccessful in making the benzophenonediacid, making instead the 5-cyano-1,3-isophthalic acid after hydrolysis.

Solubility appeared to be the culprit yet again.

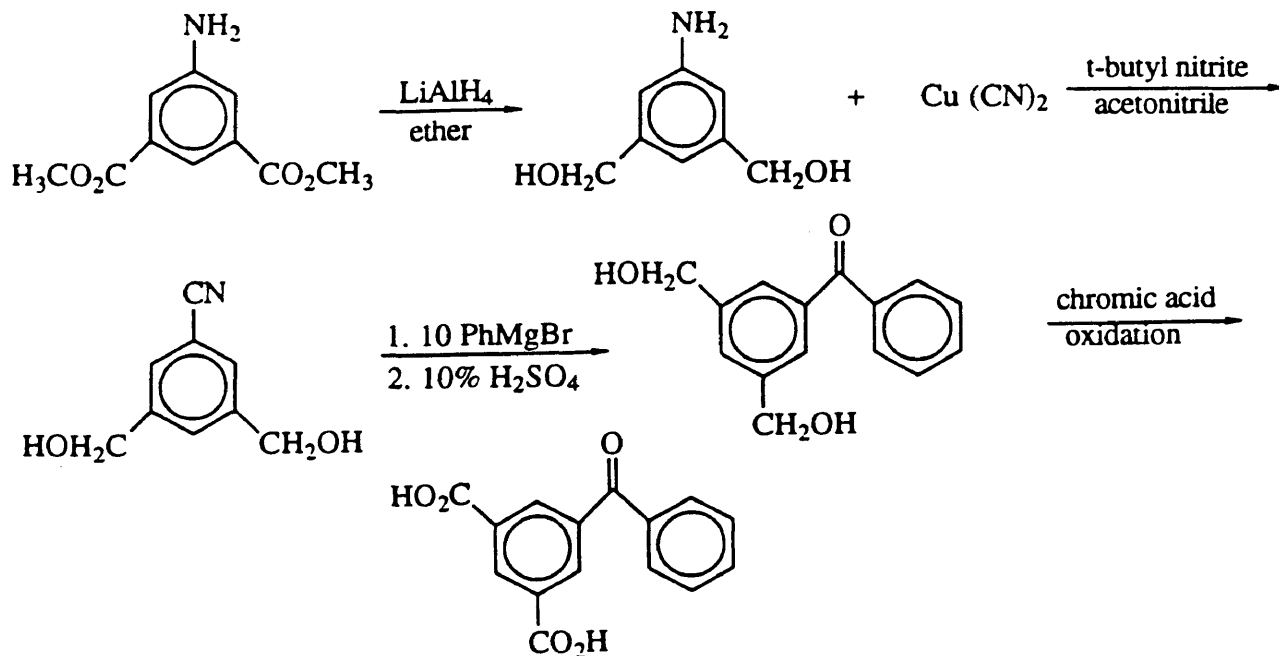


Fig. 27 Another Synthesis Pathway to the Benzophenonediacid

With all the possibilities for phase transfer catalysis used up, another strategy clearly needed to be devised. So, the next plan of attack was to try a different synthetic route completely. This pathway also began with dimethyl 5-amino-1,3-isophthalate (Fig. 27). The diester first was to be reduced to dimethanol using lithium aluminum hydride and then was to be cyanated with *t*-butyl nitrite and cupric cyanide. The reasoning behind this pathway choice becomes clear in the next step. In that subsequent step, PhMgBr attacks the cyano group of 5-cyano-1,3-benzenedimethanol in either ether or THF. When the PhMgBr deprotonates the benzylic hydroxyl moieties, the corresponding dianion is likely to be more soluble in organic solution than the dicarboxylate moieties and therefore will not precipitate out of solution. After the Grignard product is hydrolyzed, oxidation by chromic acid theoretically

should yield the desired benzophenonediacid.

Unfortunately, this new reaction pathway was hampered at the very first step. The lithium aluminum hydride reduction was unsuccessful. Instead of the desired dimethanol, a sludgy precipitate formed which may have contained aluminum complexed with the amino group of the starting material. In addition to possible complexation difficulties, the dimethyl 5-amino-1,3-isophthalate did not dissolve particularly well in the ether, perhaps deterring reaction.

Sodium borohydride is generally not used to reduce ester moieties. However, with longer reaction times and higher temperatures than are necessary for an equivalent lithium aluminum hydride reduction, sodium borohydride may be used to effect ester reductions in certain cases.³⁶ Therefore, the reduction of dimethyl 5-amino-1,3-isophthalate was attempted using sodium borohydride in first methanol and then 1-propanol. Both reactions were unsuccessful and produced starting material, probably owing to lack of solubility of starting material in both reaction solvents.

Since the synthesis pathway using dimethanol was fraught with difficulties, another solution clearly was necessary. A possible answer materialized when it was discovered that oxazolines are known to be effective in protecting carbonyl groups from Grignard attack.³⁷ With the successful formation of the 5-cyano-1,3-benzenebisoxaline, it was speculated that the Grignard would attack the cyano group and after acid hydrolysis (which would also cleave the oxazoline), the benzophenonediacid would be formed.

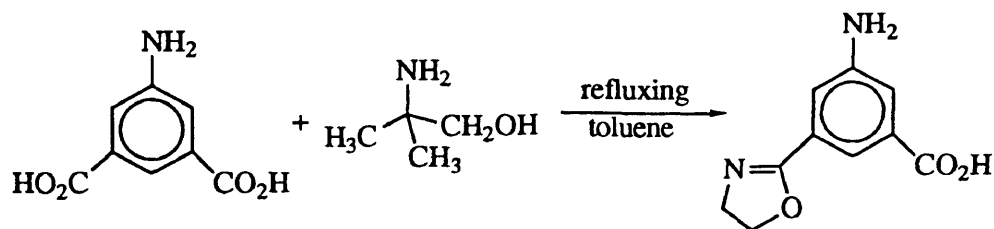


Fig. 28 Result of Oxazolinization of the Aminodiacid

The synthesis of a bisoxazoline was initially attempted with 5-amino-1,3-isophthalic acid and two equivalents of 2-amino-2-methyl-1-propanol in refluxing toluene. This reaction yielded mostly starting material plus a little monooxazoline. Subsequently, the reaction was attempted again, this time using a 16 molar excess of the aminoalcohol. That reaction yielded exclusively monooxazoline product, with not a trace of the bisoxazoline (Fig. 28). It was speculated that the formation of an ammonium-carboxylate zwitterion might have prevented the oxazoline from forming at the second carbonyl position.

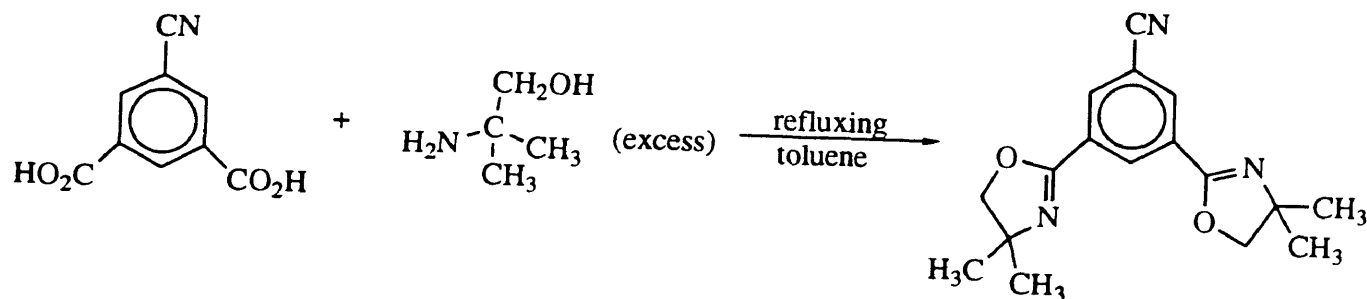
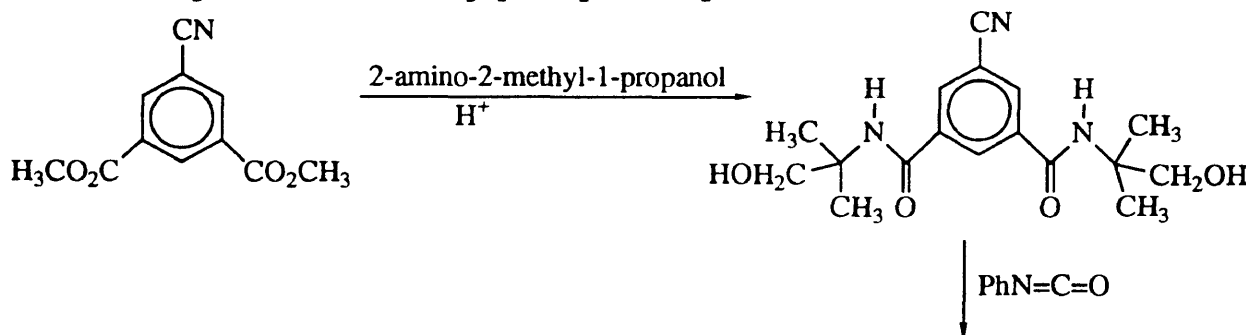


Fig. 29 Formation of the Bisoxazoline from the Cyanodiacid

The formation of the bisoxazoline was next attempted from 5-cyano-1,3-isophthalic acid, again using 2-amino-2-methyl-1-propanol in refluxing toluene. This reaction was successful, yielding 5-cyano-1,3-benzenediylbis(4,4-dimethyl-2-oxazolin-5-yl)carboxylic acid with nearly quantitative yield (Fig. 29). The bisoxazoline was then reacted with PhMgBr in THF, yielding 5-cyano-1,3-isophthalic acid after

hydrolysis. The problem appeared again to be solubility, since the bisoxazoline did not seem to dissolve in THF. The bisoxazoline also did not seem to dissolve in refluxing 1,4-dioxane, benzene or toluene, so none of those solvents were pursued as possibilities for the Grignard reaction.

The formation of the cyanobisoxazoline was also attempted directly from the cyanodiester in order to reduce one step in the synthetic pathway. This reaction was attempted using the usual aminoalcohol in refluxing toluene and a few drops of sulfuric acid. The reaction attached the aminoalcohol to the carbonyl of the ester, but ring closure did not occur (Fig. 30). An attempt to effect ring closure using phenylisocyanate was also not successful.



**Fig. 30 Result of Oxazolinization of the Cyanodiester;
Ring Closure Unsuccessful with Phenylisocyanate**

In addition to the synthesis of the benzophenonedicarboxylic acid, the synthesis of 3,5-benzophenonedisulfonic acid was attempted (Fig.31). From commercially available *m*-benzenedisulfonic acid, 5-nitro-1,3-benzenedisulfonic acid was prepared using refluxing fuming nitric acid as the reaction solvent. The nitro group was reduced to amino group with hydrogen, using palladium-on-carbon as a catalyst. Subsequently, a conversion from amino to cyano group was pursued using cupric

reaction was determined by ^1H NMR to be the cyanodisulfonic acid. It was speculated that this result was caused by the hydrolysis of the ester by water dissolved in methanol. At this point, however, this reaction pathway was pursued no further because the formation of 3,5-benzophenonedicarboxylic acid seemed much more promising.

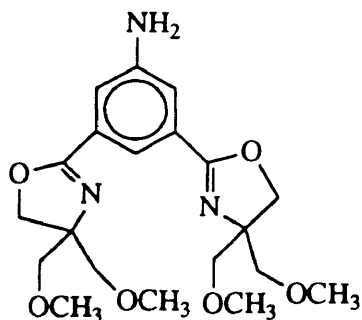


Fig. 32 Possible THF-soluble Oxazoline

Fortunately, there are possibilities for the future successful formation of 5-benzoyl-1,3-benzenedicarboxylic acids. One pathway is to make a THF-soluble bisoxazoline by reacting the cyanodiacid with a different aminoalcohol (Fig. 32). Another slightly different possibility presently being attempted by this research group is to react benzaldehydeoxime with the cyanodiester using *t*-butyl nitrite. The product formed from this reaction would hopefully give 5-benzoyl-1,3-isophthalic acid upon hydrolysis (Fig. 33). A third considered synthetic route begins with a completely different starting material, 5-bromo-1,3-dimethylbenzene. The Grignard reagent of that compound then attacks benzonitrile and after hydrolysis, 3,5-dimethyl-benzophenone is formed. The methyl groups would then be oxidized in chromic acid at 200°C to form 5-benzoyl-1,3-isophthalic acid (Fig. 33).

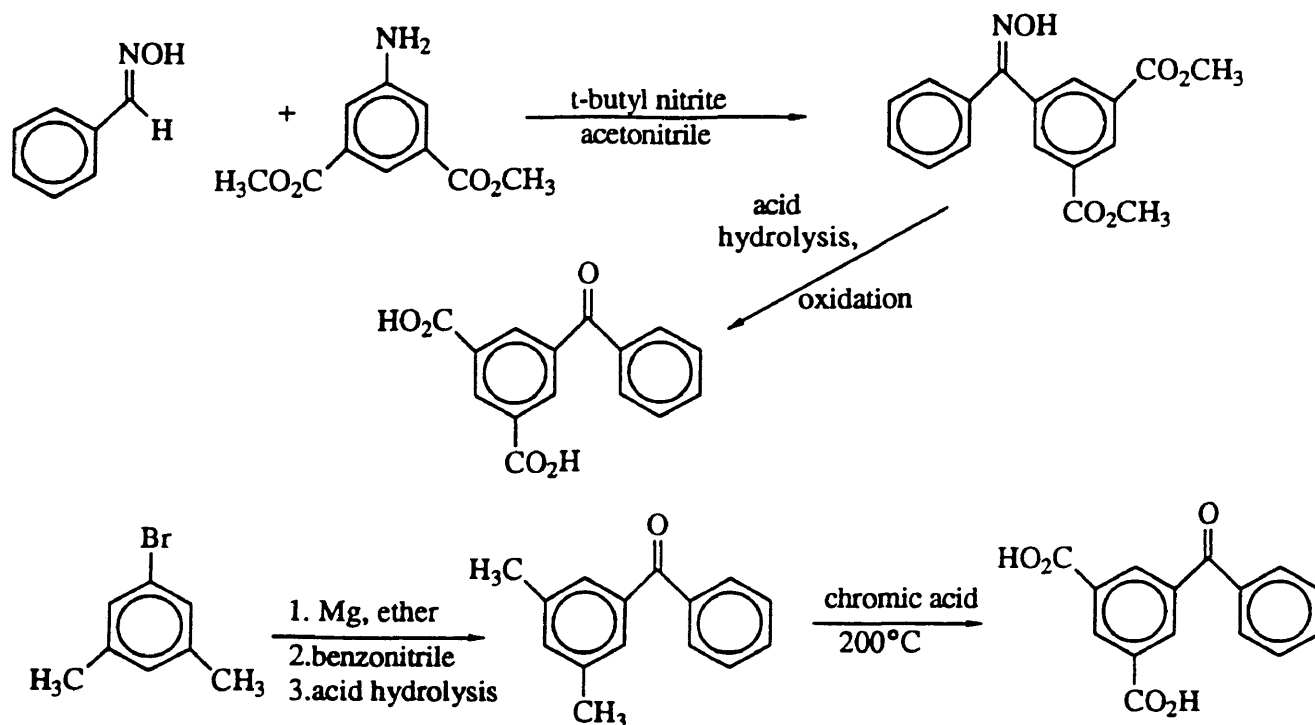


Fig. 33 Other Possible Synthetic Routes to Benzophenonediacid

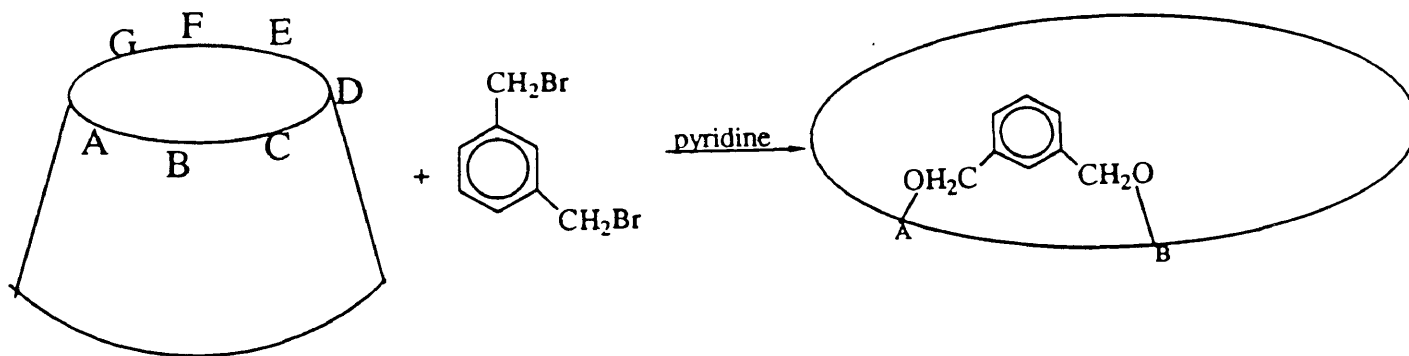
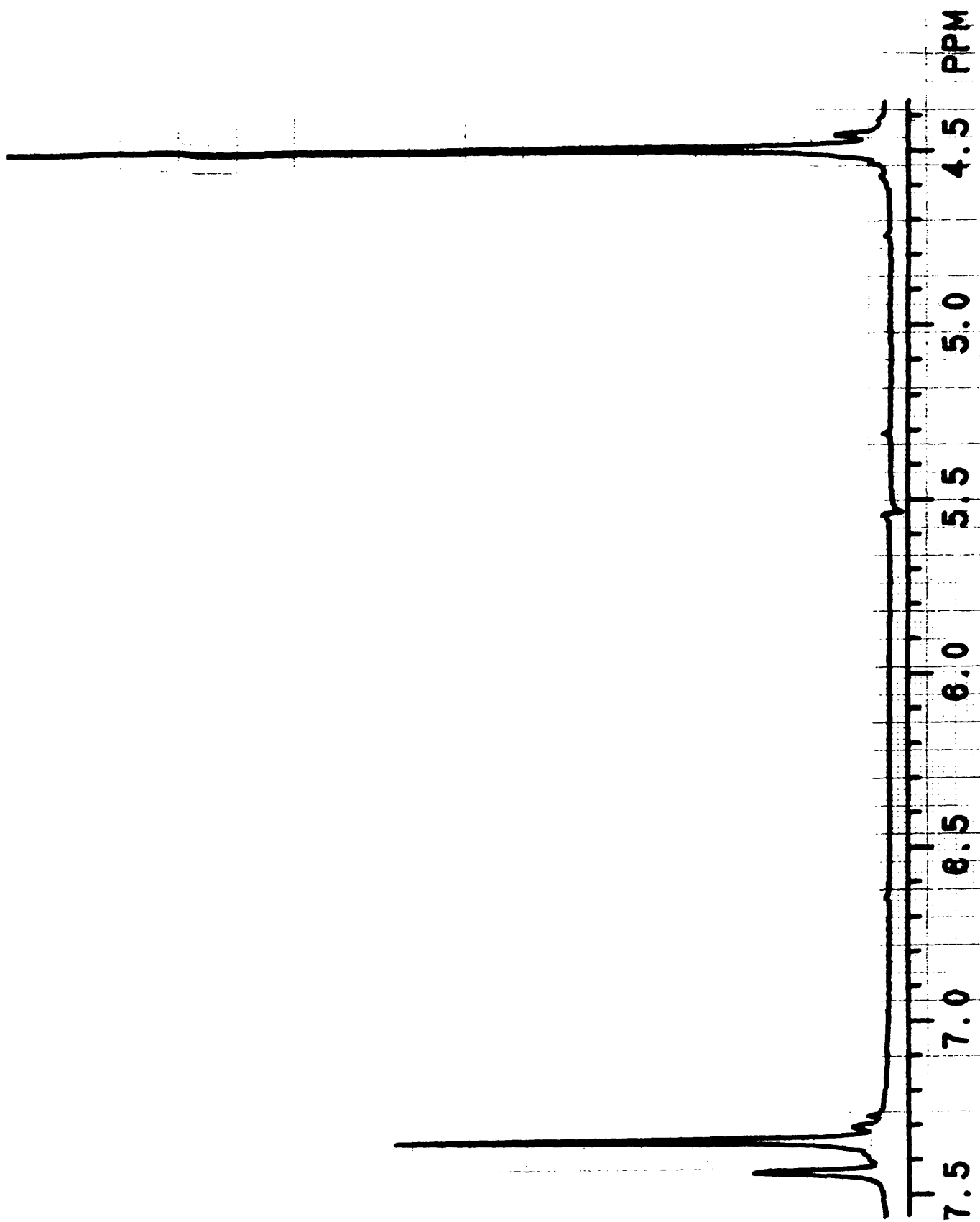


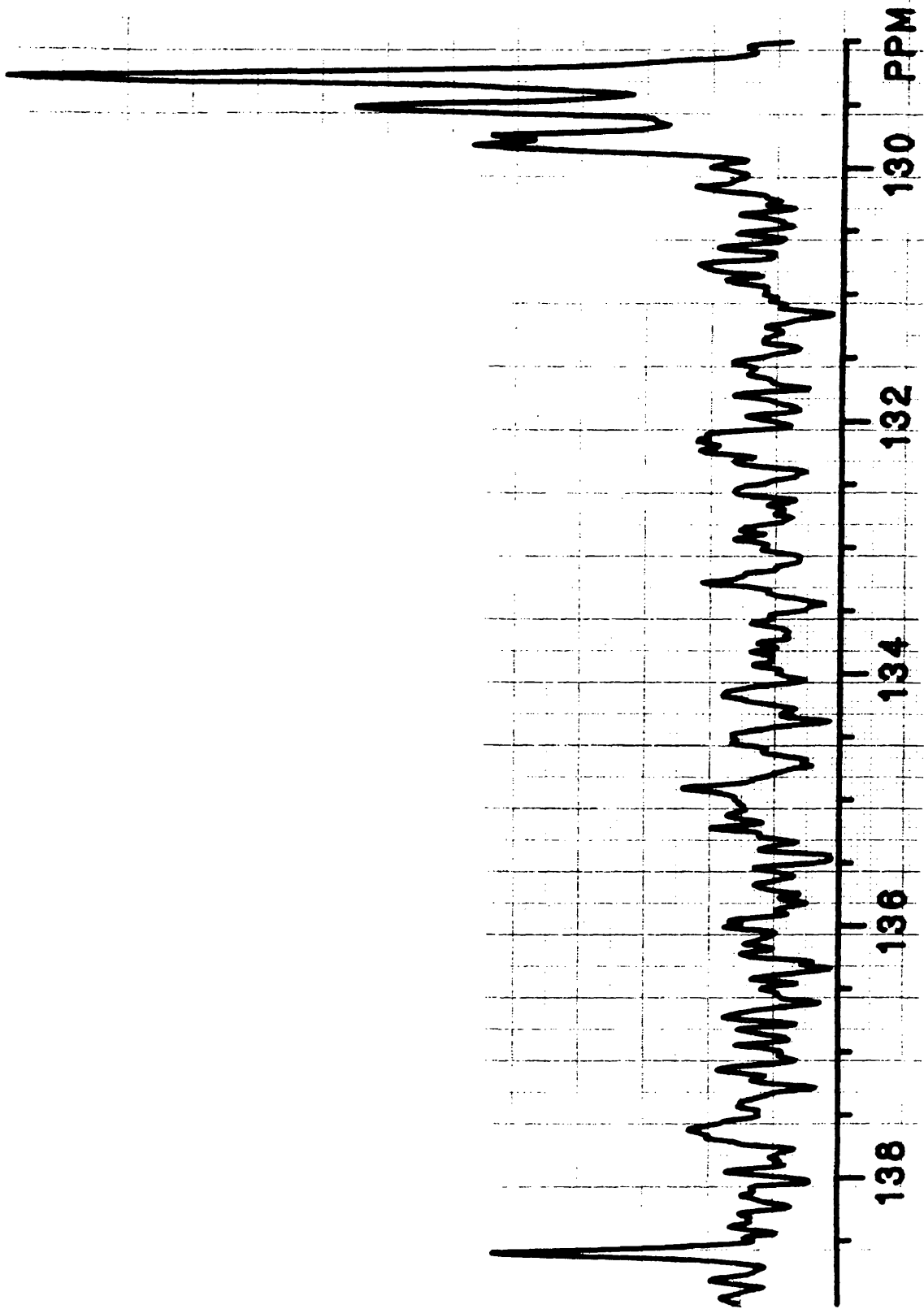
Fig. 34 Attempt at Novel Ether Capping

In addition to the synthesis of 5-benzoyl-1,3-benzenediacids, a novel method for capping cyclodextrin was attempted. To do this, an equimolar amount of *meta*-xylylene dibromide and β -cyclodextrin were heated in pyridine at 75°C overnight (Fig. 34). The desired product would have made the first cap attached by an ether linkage

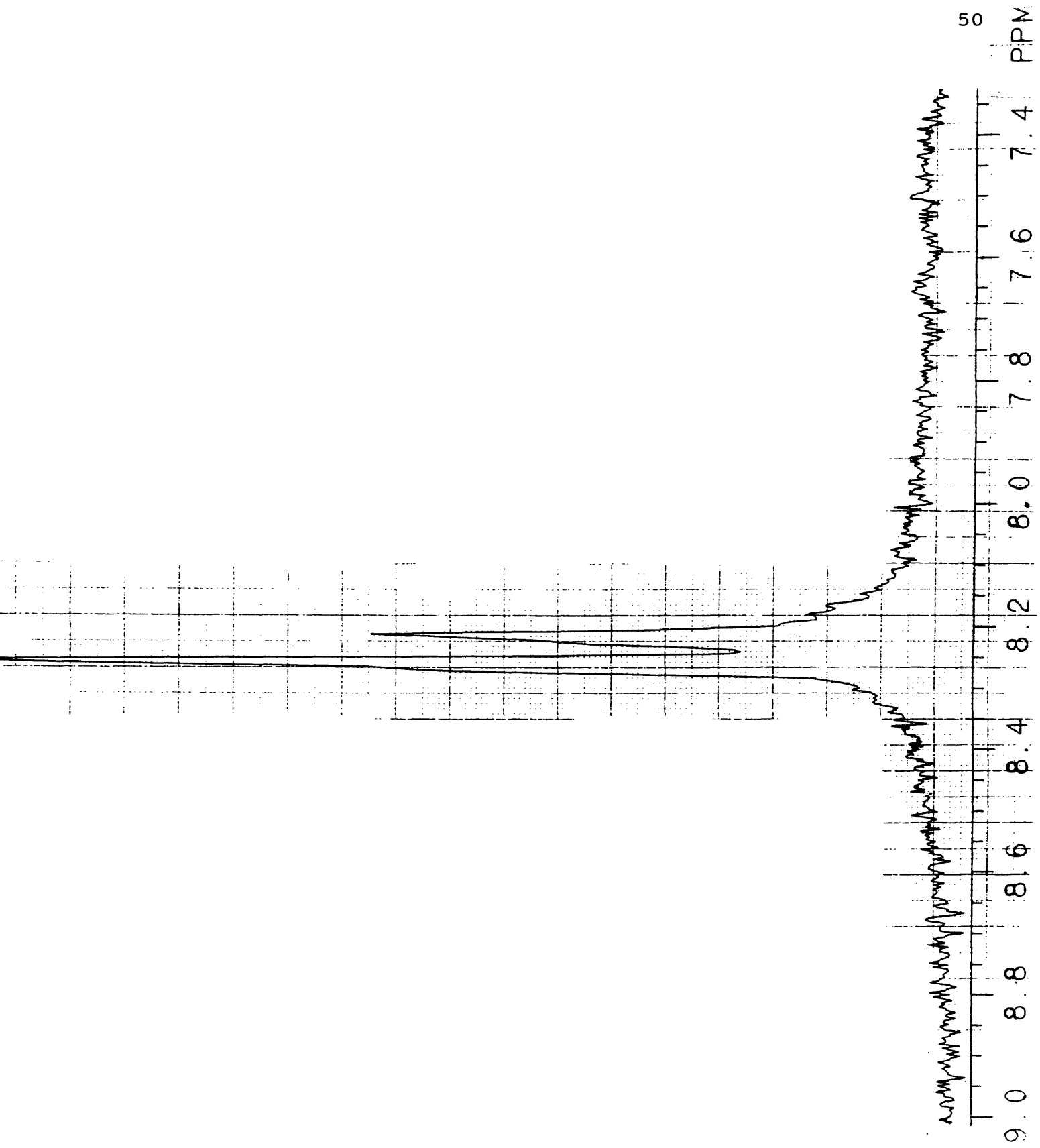
to the C6 hydroxy position of β -cyclodextrin. All preceding caps have been attached to cyclodextrin via an ester linkage. Unfortunately, the reaction was not successful and the bispyridinium salt of *meta*-xylene was formed instead (as determined by ^1H NMR).



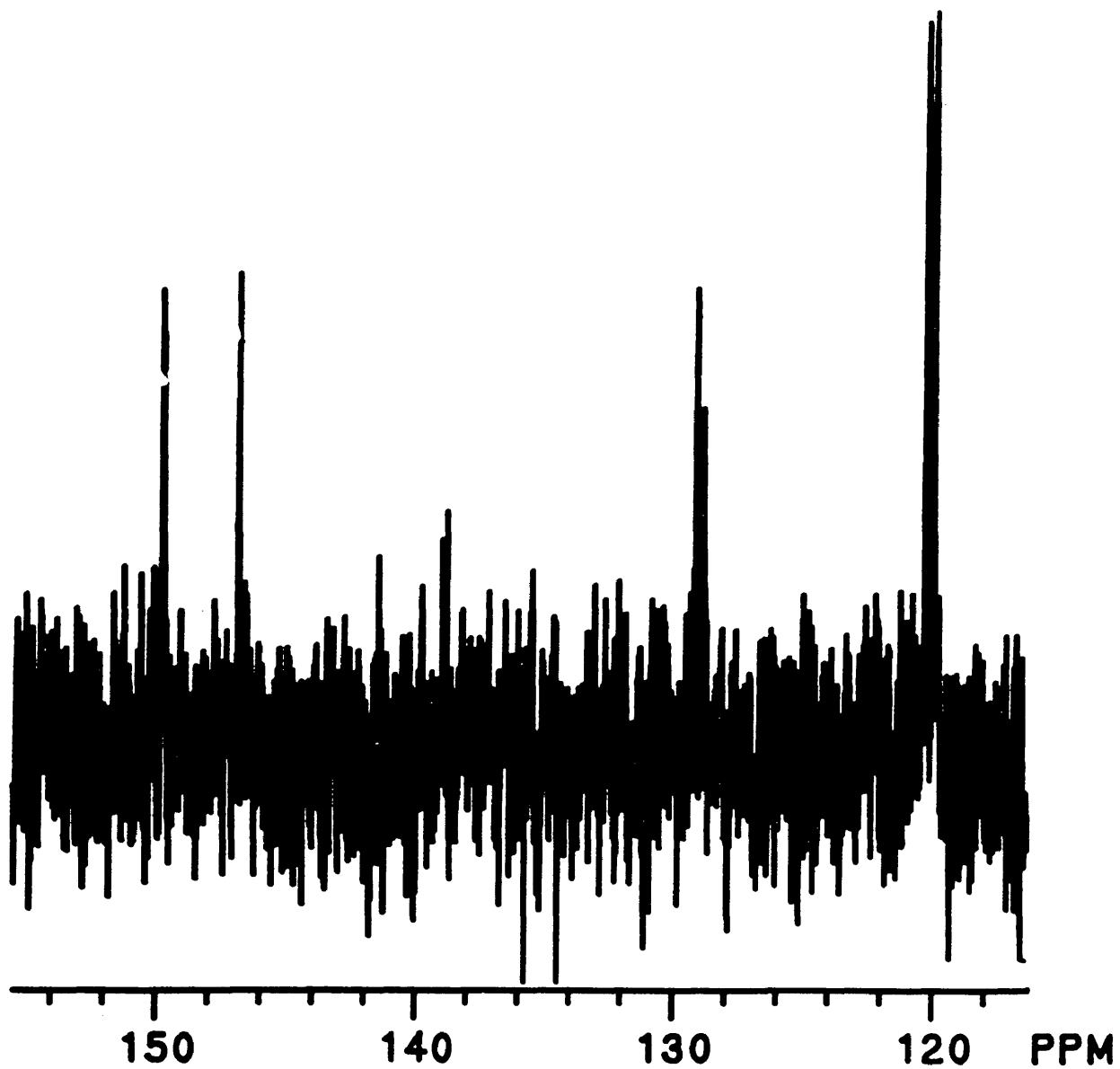
Spectra 1. ¹H NMR of *m*-xylylene dibromide



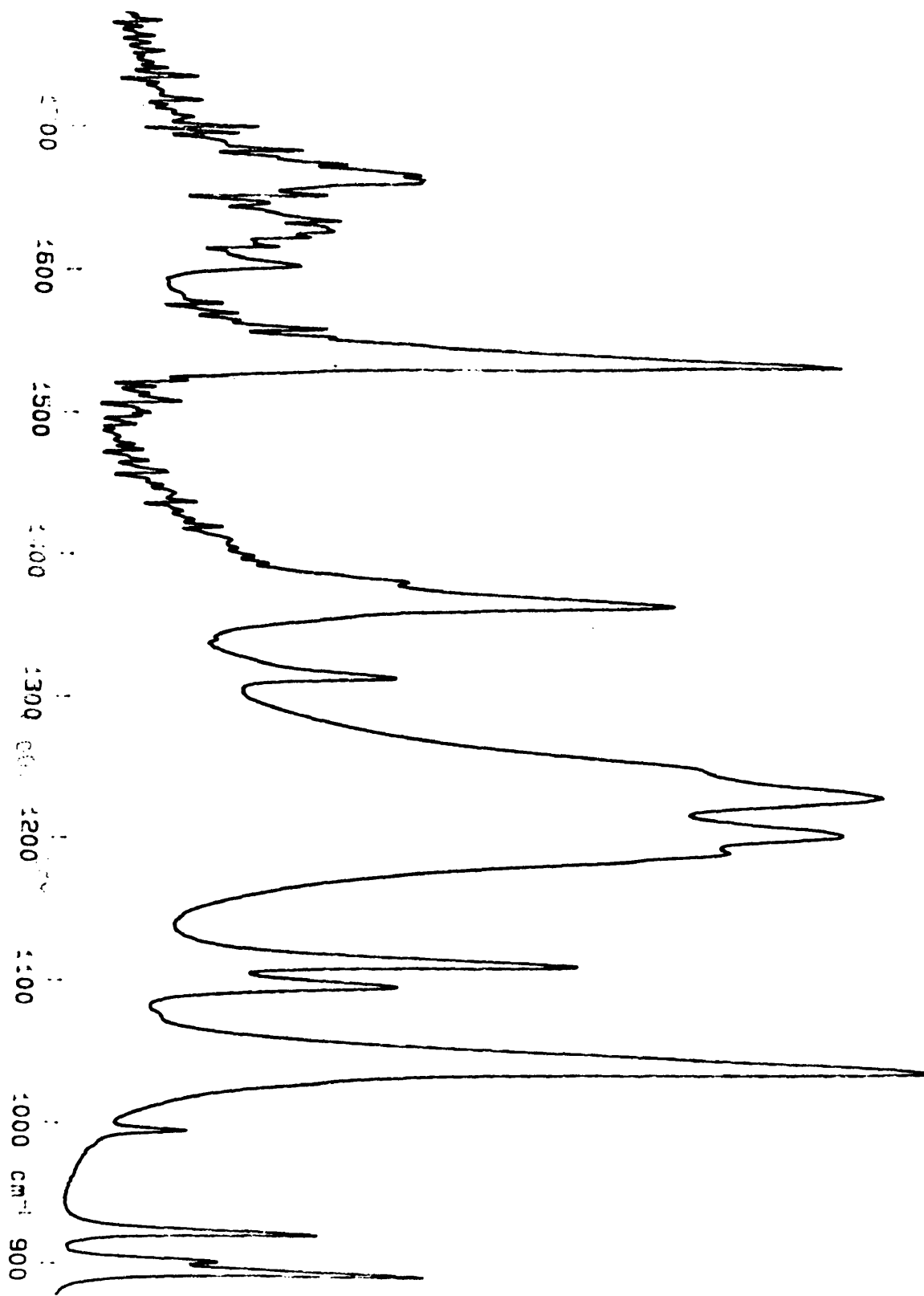
Spectra 2. ^{13}C NMR of *m*-xylylene dibromide



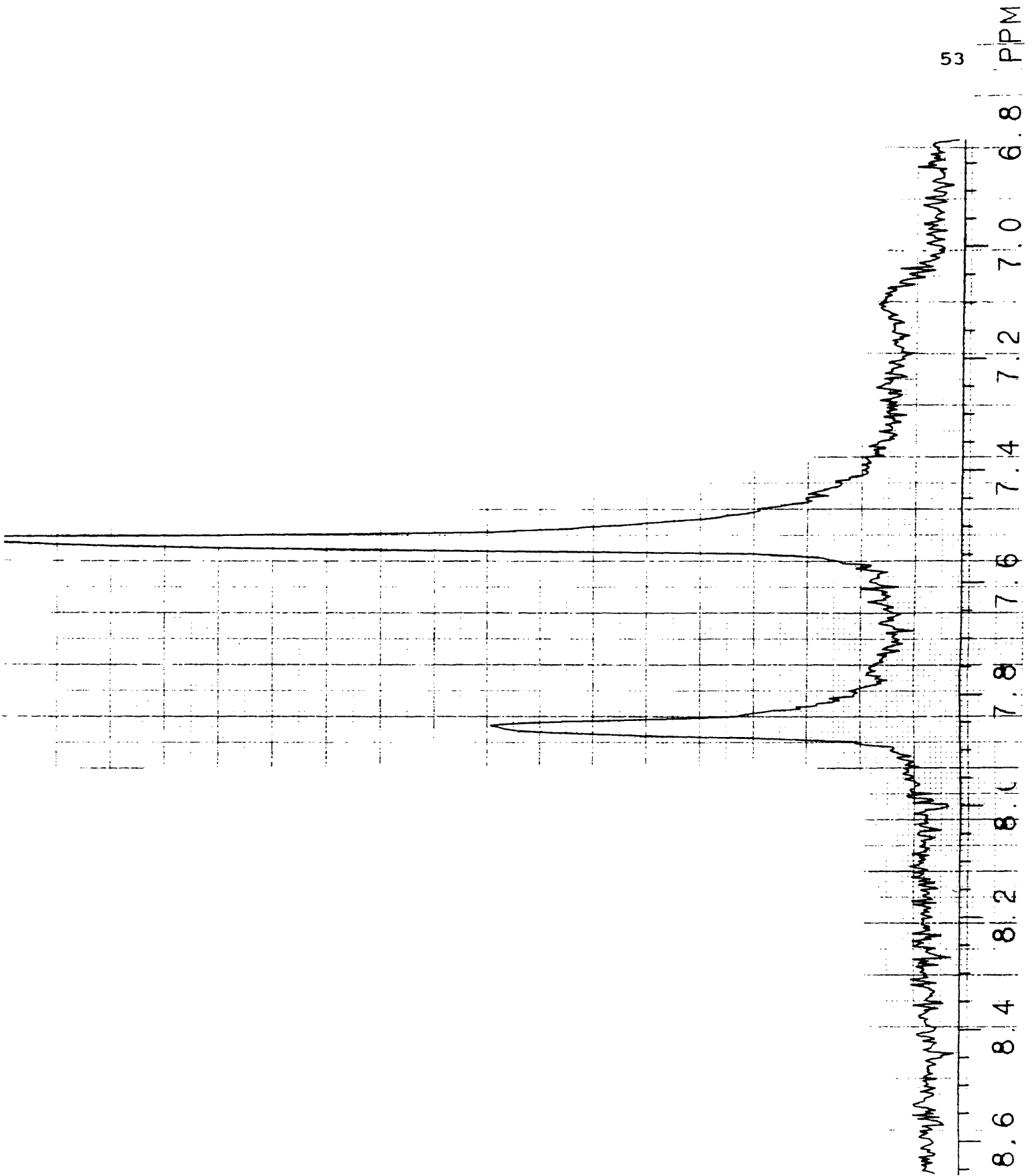
Spectra 3. ¹H NMR of 5-nitro-1,3-benzenedisulfonic acid



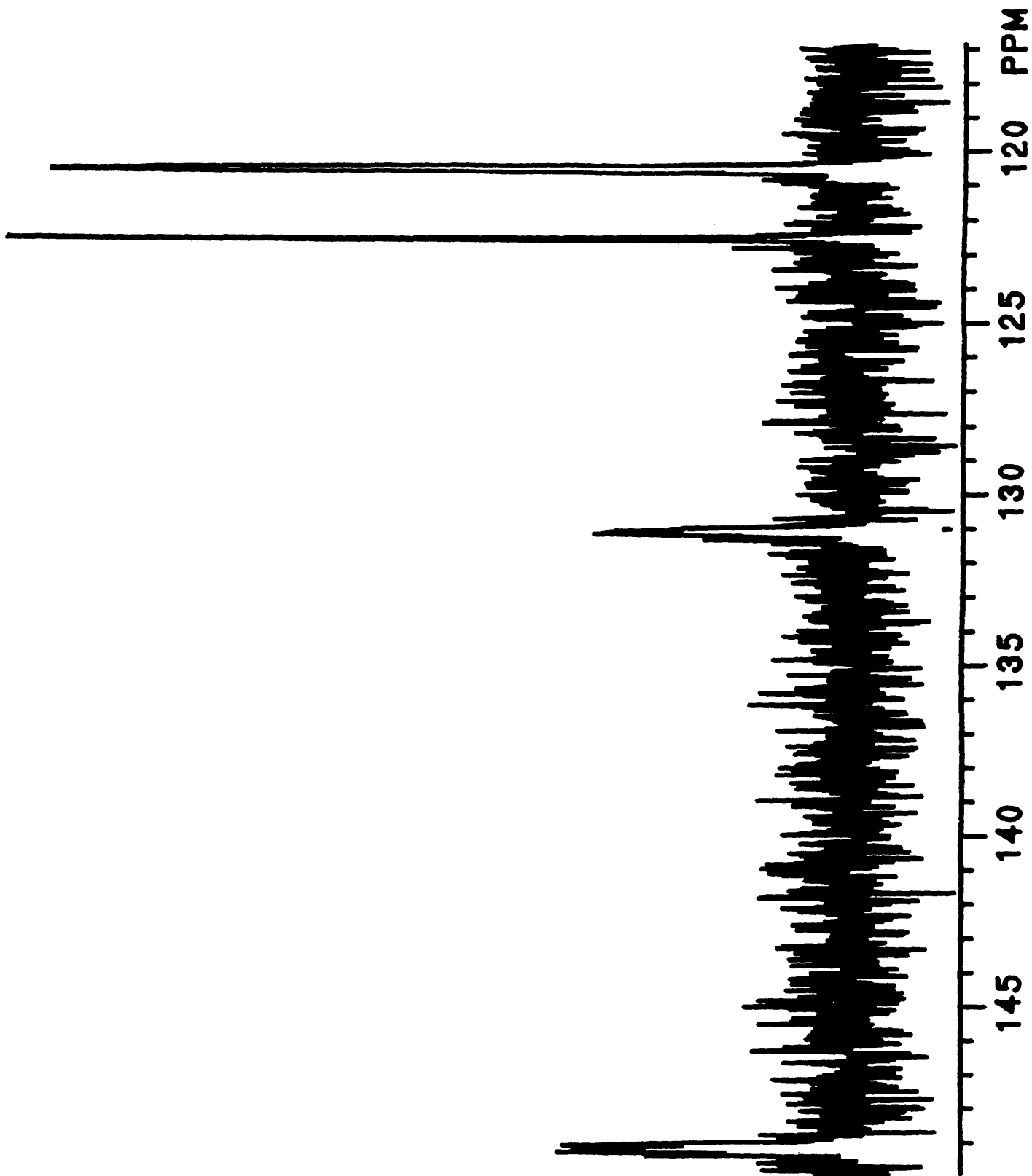
Spectra 4. ^{13}C NMR of 5-nitro-1,3-benzenedisulfonic acid



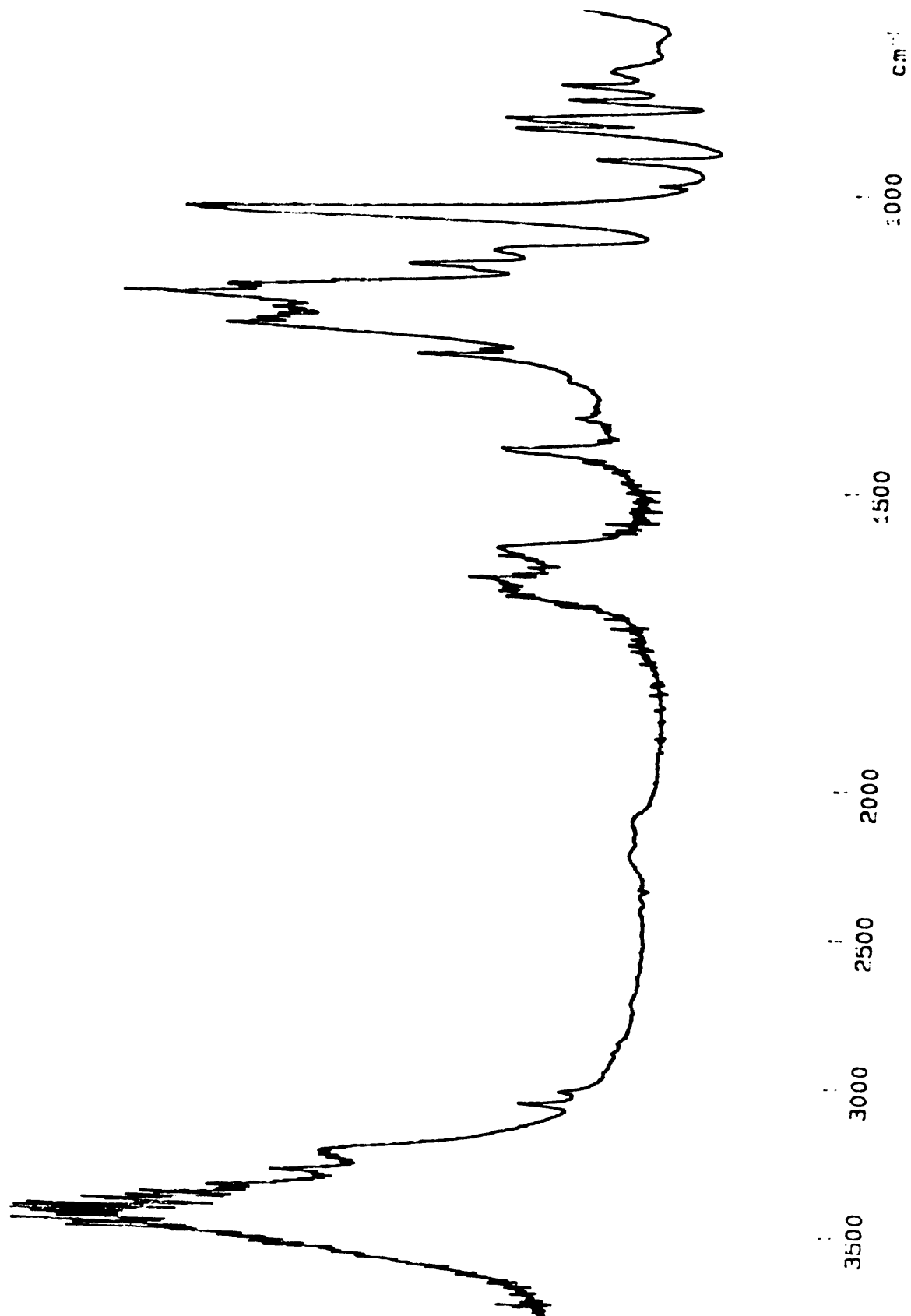
Spectra 5. FT/IR of 5-nitro-1,3-benzenedisulfonic acid



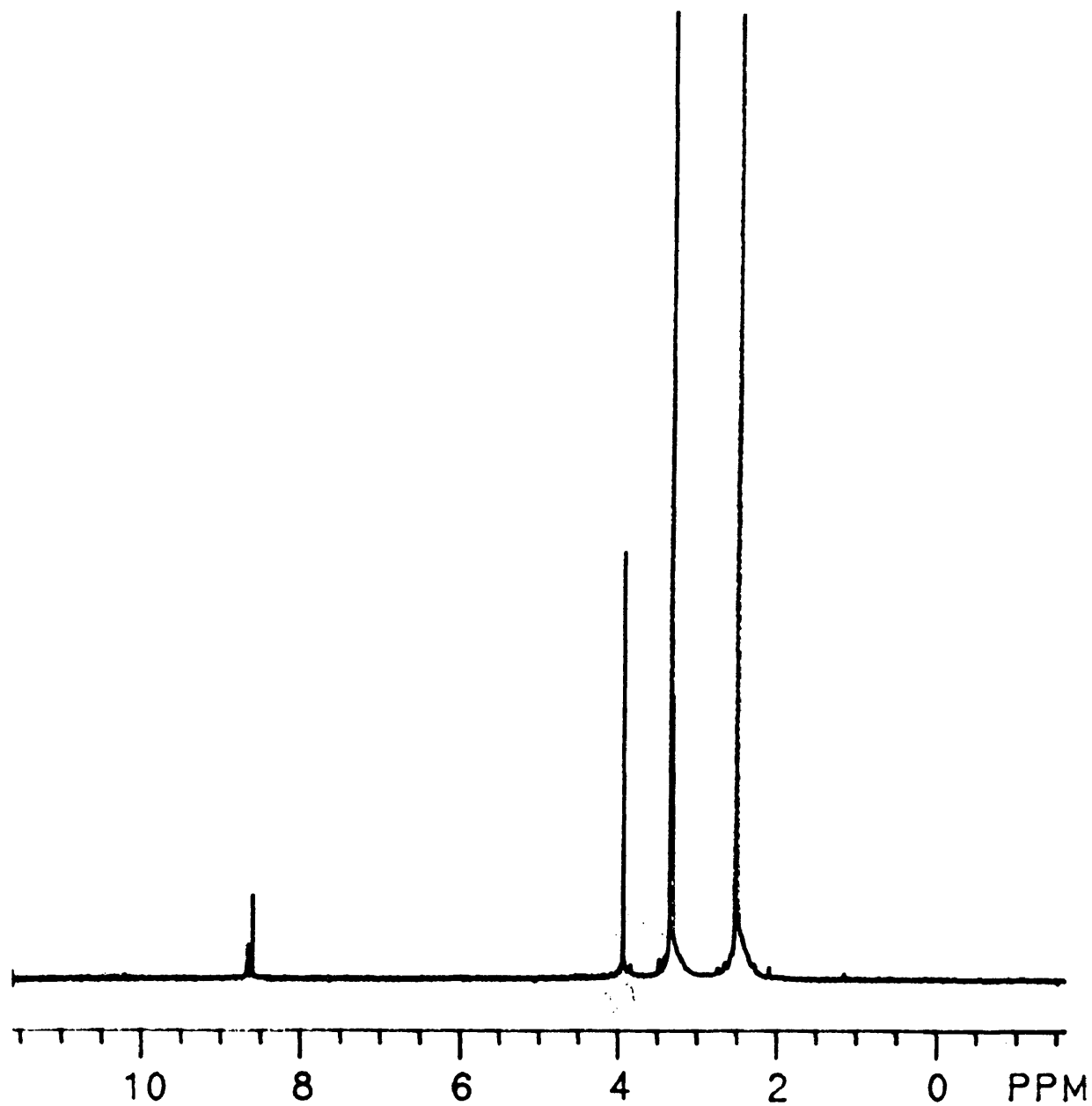
Spectra 6. ^1H NMR of 5-amino-1,3-benzenedisulfonic acid



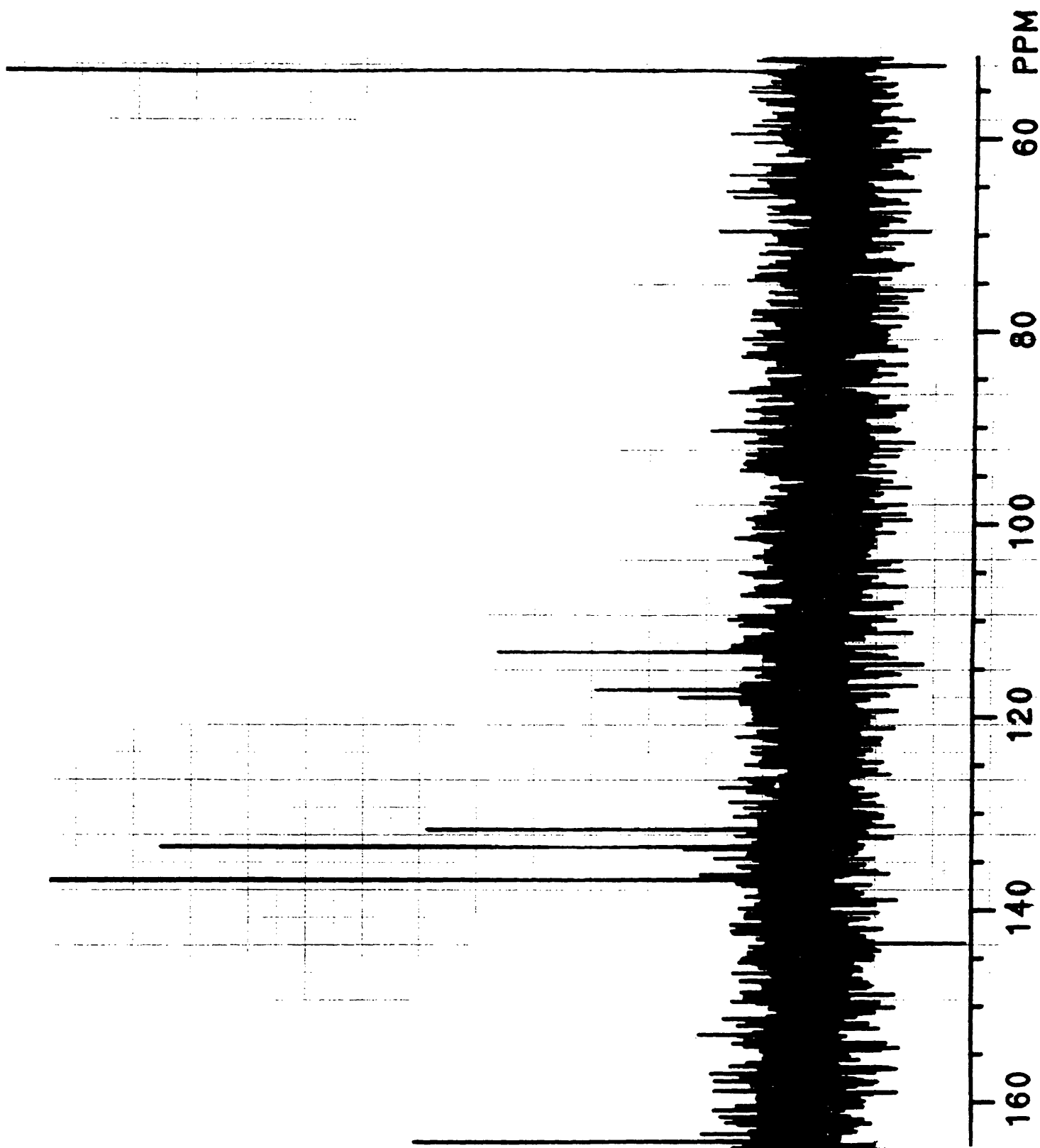
Spectra 7. ^{13}C NMR of 5-amino-1,3-benzenedisulfonic acid



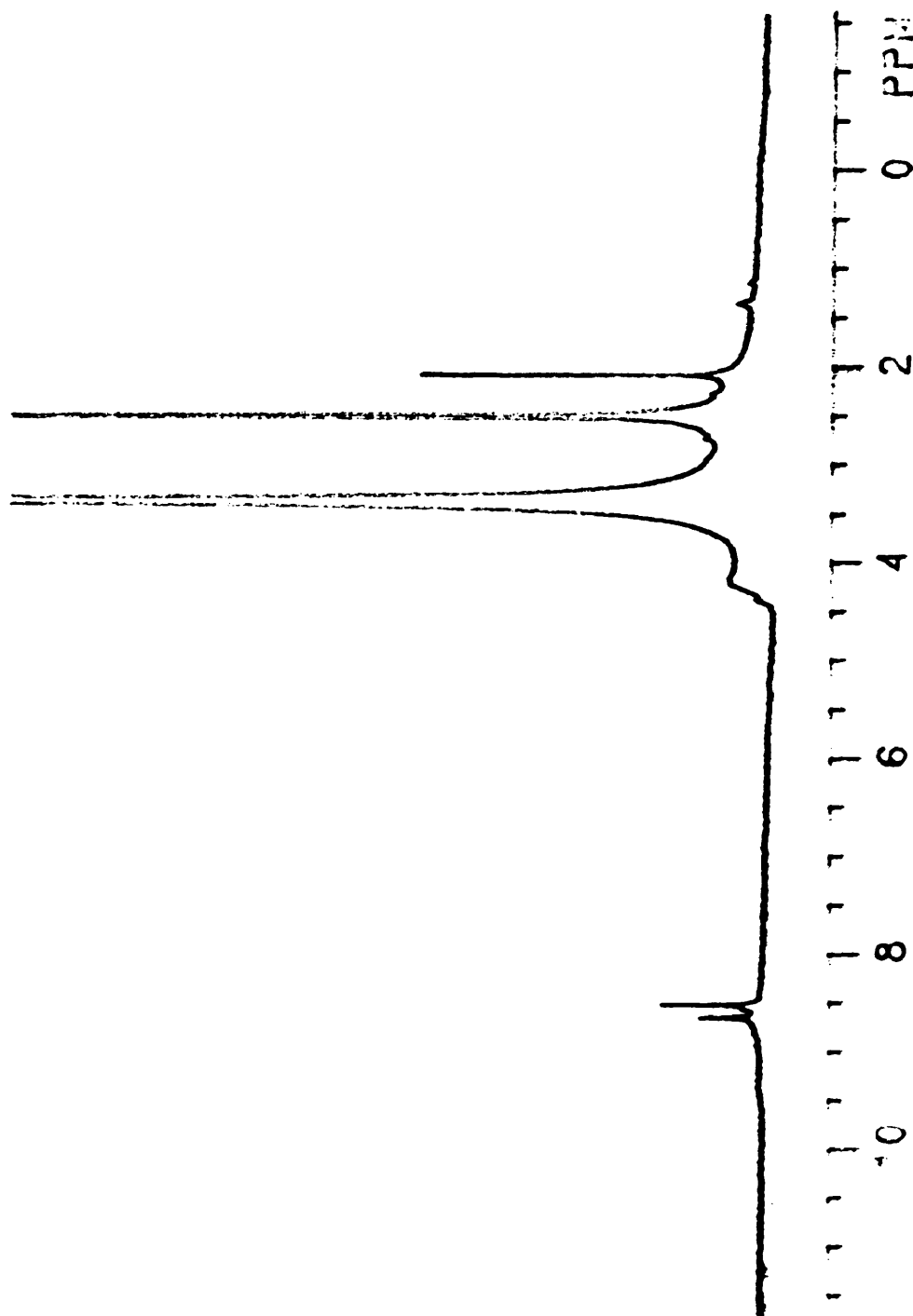
Spectra 8. FT/IR of 5-amino-1,3-benzenedisulfonic acid



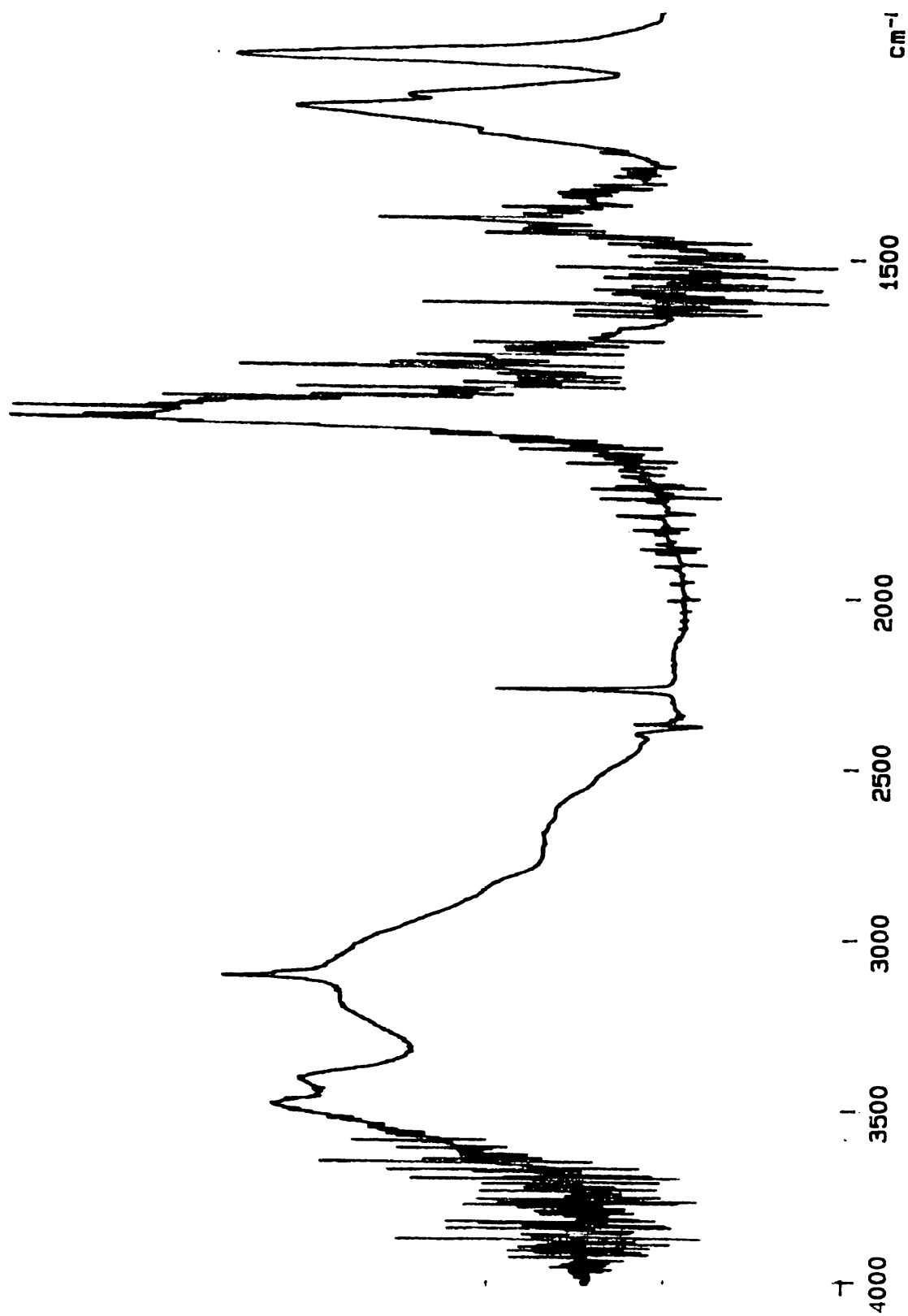
Spectra 9. ^1H NMR of Dimethyl 5-cyano-1,3-isophthalate



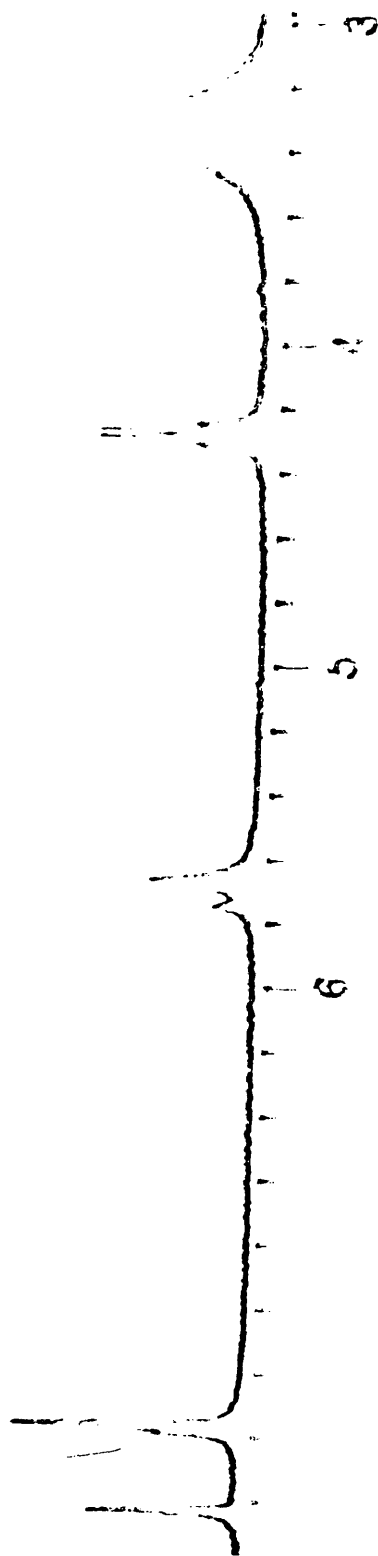
Spectra 10. ^{13}C NMR of Dimethyl-5-amino-1,3-isophthalate



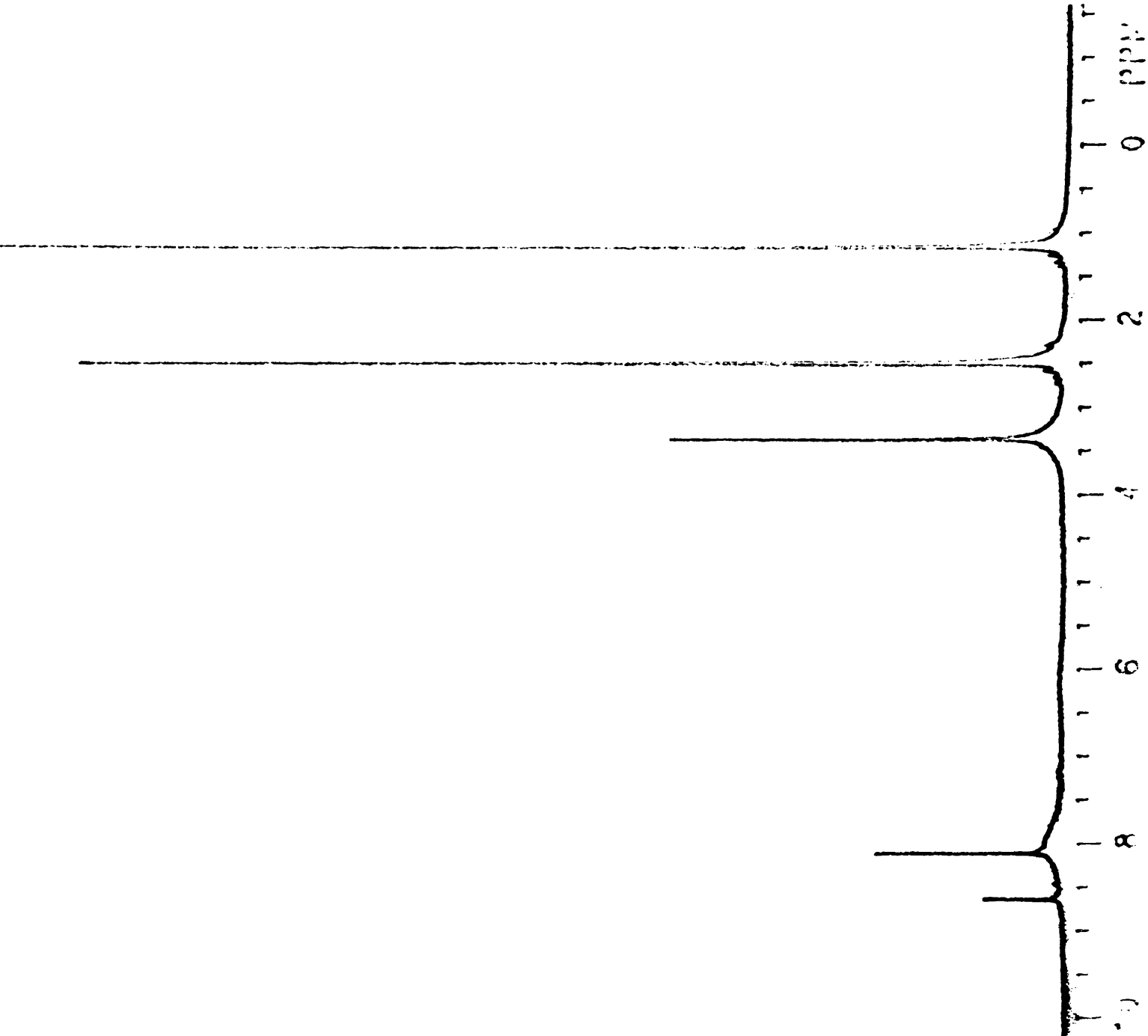
Spectra 11. ^1H NMR of 5-Cyano-1,3-isophthalic acid



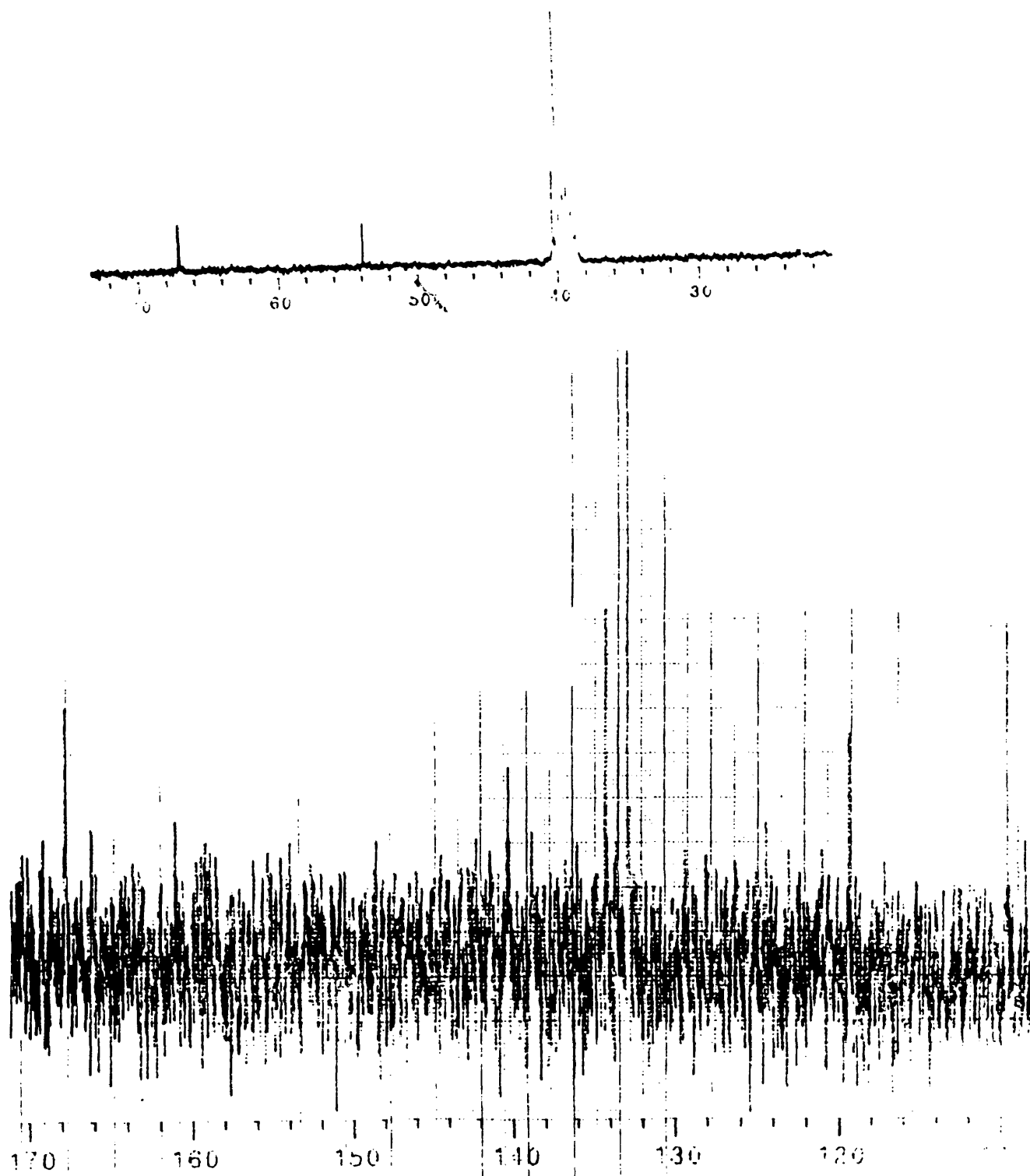
Spectra 13. FT/IR of 5-cyano-1,3-isophthalic acid



Spectra 14. ¹H NMR of 5-amino-1,3-isophthalic acid



Spectra 15. ¹H NMR of 5-Cyano-1,3-benzenebis-4',4'-dimethyloxazoline



Spectra 16. ^{13}C NMR of 5-cyano-1,3-benzenebis-4',4'-dimethyloxazoline

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VITAE**Daniel MacDougall Williams**

Born in Nairobi, Kenya, 7 July 1971 to David and Helen Williams. Graduated from McLean High School in McLean, Virginia in May 1989. Received a Bachelor of Science degree in chemistry at the College of William and Mary in May 1993. The author enrolled in the Master of Arts program at the College of William and Mary in June 1993.

After graduation, the author will begin his Ph.D. in chemistry at McGill University in Montreal, Canada.