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The Synthesis of Benzophenane 3,5-Dicarboxylic Acid for the Double Capping of beta-Cyclodextrin

Jaydee Dones Cabral
College of William & Mary - Arts & Sciences

The Synthesis of
Benzophenone 3,5-Dicarboxylic Acid
for the Double Capping of β-Cyclodextrin

A Thesis

Presented to

The Faculty of the Department of Chemistry

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In Partial Fulfillment

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Master of Arts

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by

Jaydee D. Cabral

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APPROVAL SHEET

This thesis is submitted in partial fulfillment of

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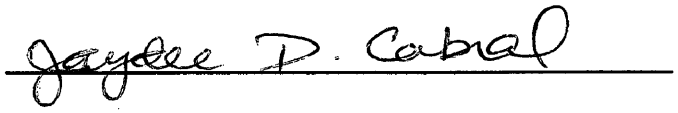

Jaydee D. Cabral

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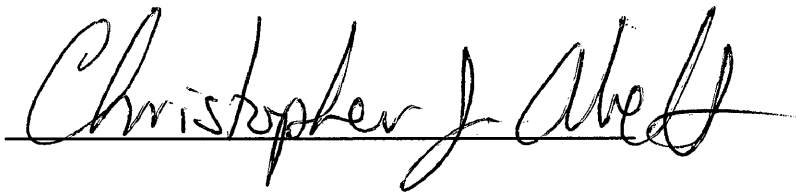
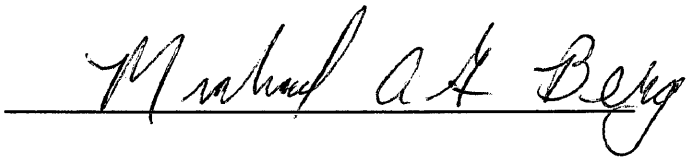
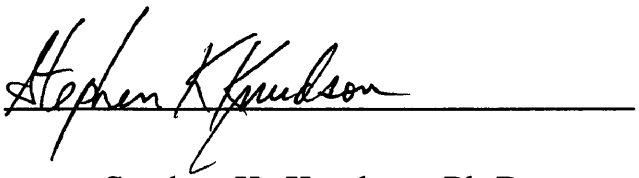


Christopher J. Abelt, Ph.D.



Michael A.G. Berg, Ph.D.



Stephen K. Knudson, Ph.D.

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The writer wishes to express her appreciation to Professor Christopher J. Abelt under whose guidance this investigation was conducted, for his patient guidance and criticism throughout the investigation. The author is also indebted to Professors Stephen K. Knudson and Michael A.G. Berg for their careful reading and criticism of the manuscript.

ABSTRACT

Synthetic routes into benzophenone-3,5-dicarboxylic acid were explored. The most promising route involved a three step synthesis starting from commercially available 2,4-dimethylaniline. The last step, the oxidation of methyl groups in 3,5-dimethylbenzophenone, was investigated under various reaction conditions.

Of the several oxidation methods tried, the one involving CrO_3 in acetic acid was the most promising. The benzophenone-3,5-dicarboxylic acid is to be used as a double capping agent for β-cyclodextrin.

SYNTHESIS OF BENZOPHENONE 3,5-DICARBOXYLIC ACID FOR THE DOUBLE CAPPING OF β-CYCLODEXTRIN

INTRODUCTION

Cyclodextrins, which are composed of D-(+)-glucopyranose subunits connected by α-(1,4)-linkages, were discovered in 1891 by Villiers.[1] After the structures of cyclodextrins[2] were elucidated by Freudinger in the 1940s, interest in cyclodextrin research grew as scientists developed a greater appreciation for the molecule's unique properties. Notable structural features of the compound include their toroidal shape, hydrophobic cavity and outer surface, and hydrophillic faces.[3]

The formation of inclusion complexes is one of the most important characteristics of cyclodextrins. Guest compounds, ranging from polar molecules such as acids, amines, and small ions to highly apolar compounds like aliphatic and aromatic hydrocarbons, can be included within the cavity of cyclodextrin.[1] Inclusion complexes are useful in that they can catalyze various organic reactions on guest organic molecules. Similar to an enzyme-substrate arrangement, the formation of the inclusion complex in cyclodextrin increases the reaction rate by raising the probability that two molecules will collide in the correct spatial orientation. These collisions can occur between two guest molecules, or cyclodextrin and a guest molecule. Cyclodextrin, being intermediate in size between that of enzymes and organic molecules, mimics enzymatic activity and provides valuable insight into enzyme molecular mechanism.

In addition to accelerating chemical transfer reactions, cyclodextrins display hydrophobic interactions, form stereospecific complexes, and provide an interior surface with dielectric properties different from that of an outside aqueous solution.[4] All of these uncommon properties have generated an increased interest not only from the scientific community, but from the industrial community as well.

More specifically, the pharmaceutical industry uses cyclodextrins for a variety of purposes. A main focus of research centers on the transport of apolar drugs into the body.[4] Torus-shaped in nature, the cyclodextrin interior is considerably less polar than water. The interior consists primarily of nonpolar C-H groups and secondary glycosidic oxygens. All cyclodextrins are somewhat water soluble which enables them to transport nonpolar guest molecules. A guest molecule, for example, a nonpolar drug, may be easily transported through a body's aqueous medium. Once the drug reaches the part of the body where it is to be expended, the equilibrium shifts so that the drug is released from the torus. Premature expulsion is rare because the equilibrium favors the guest molecules residing inside the cavity.

Along with its industrial applications, the study of derivatized cyclodextrins is currently being investigated by numerous research groups around the world. Cyclodextrins, although subject to cleavage in strong acids, are fairly stable in basic solutions. This important fact enables functional groups to be attached to cyclodextrin with the assistance of an alkaline catalyst.

A cyclodextrin with an organic molecule attached to one glucopyranose subunit, is called a tethered cyclodextrin. If the organic molecule is attached to two or more glucopyranose subunits the cyclodextrin is said to be capped. Capping adjacent glucose residues is known as AB capping, caps separated by one sugar is known as AC capping, and so on. Many tethered and capped cyclodextrins have been explored.

The importance of capping is demonstrated by the fact that an unsubstituted cyclodextrin, with its open top and bottom, is not able to bind substrates as specifically as enzymes, and are therefore less effective catalysts. It has been shown that both capping[5] and tethering[6] molecules, when carefully chosen, can significantly increase the ability of cyclodextrins to bind substrates. In some cases, derivitization improves binding by forming a hydrophobic floor inside the cyclodextrin. Increased binding ability is explained by hydrophobic interactions that occur in aqueous solution between the apolar interior of cyclodextrins and the guest molecule.

The main focus of this research was to prepare benzophenone 3,5-dicarboxylic acid 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 in isopropanol to form benzopinacol.[7] Having two benzophenone molecules AB capped to β-cyclodextrin would result in the first cyclodextrin tetrasubstituted by one molecule. Four different stereoisomers exist

of this pinacolized product. Once isolated, benzopinacol may prove to be the best cap known in terms of binding effectiveness and specificity.

BACKGROUND

Cyclodextrins:

Cyclodextrins are cyclic oligosaccharides which are sometimes referred to as cycloamylases, Schardinger dextrins or cycloglucans.[1] They are torus-shaped molecules containing from six to twelve α-(1,4)-linked glucose units. Their size is indicated as follows: α-cyclodextrin has 6 glucopyranose subunits, β has 7 subunits, γ has 8, and so on. Subsequently, they may also be called cyclohexaamyloses, cycloheptaamyloses, and so forth. Cyclodextrins possessing fewer then 6 residues do not occur because they are too sterically hindered to exist. While cyclodextrins with more than 9 residues have been identified as components of mixtures, they have never been isolated. Larger cyclodextrins are often too flexible to be of interest for binding and functionalization studies.

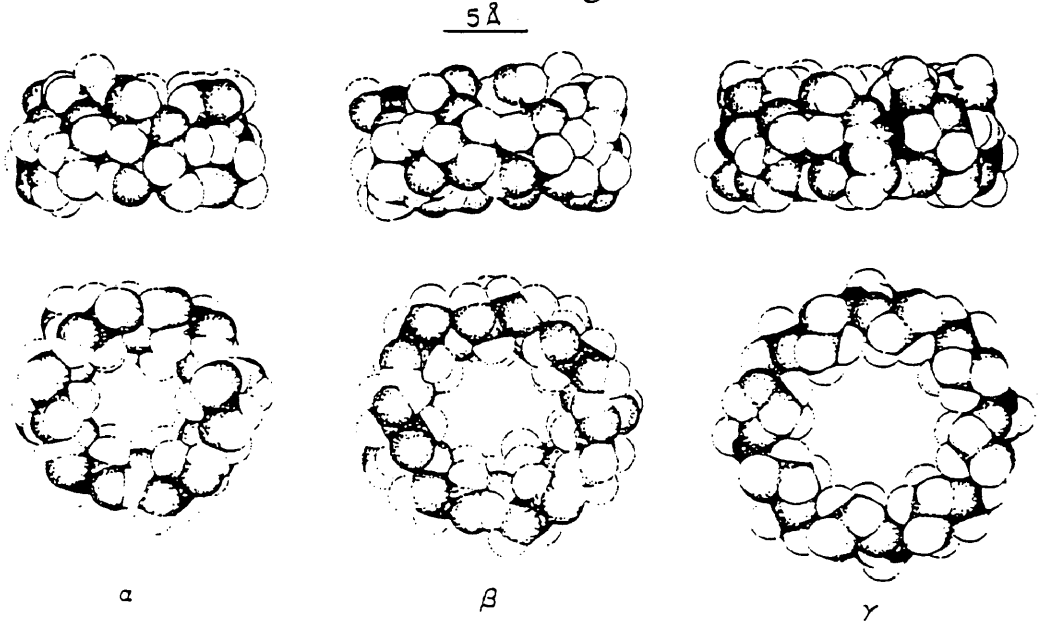


Fig.1 Structures of α-, β-, and γ- cyclodextrins

By treating starch with the enzyme amylase from the bacteria *Bacillus macerans* cyclodextrins can be commercially prepared by forming a crude digest consisting of α-, β-, and γ-cyclodextrins in addition to a small amount of larger cyclodextrins. Isoamylase may be added to enhance the reaction yield. Purification of the four smallest cyclodextrins from the digest is done by selective precipitation or by variuos chromatographic techniques.

All of the glucopyranose subunits of cyclodextrin exist in an undistorted chair conformation. This constraint dictates a special arrangement of functional groups with areas of hydrophilic and hydrophobic regions within the cyclodextrin molecule. The primary face of the torus consists of C6 primary hydroxyl groups. On the other end of the torus, the secondary face, consists of C2 and C3 secondary hydroxyl groups. With hydroxyl groups occupying both ends of the torus, cyclodextrins are rendered soluble in aqueous solution. On the other hand, the inside of the cavity is hydrophobic because it is lined by C3 and C5 hydrogens and by the ether-like oxygens. In solution, therefore, these cavities provide a hydrophobic matrix in hydrophillic surroundings, described as a "microheterogenous environment".[3]

In addition, the primary C6 hydroxyl groups are able to rotate freely, allowing them to partially block one opening of the cavity. Adversely, the secondary hydroxyl groups are relatively rigid not only due to their direct attachment to the ring, but also due to an intramolecular hydrogen bond formed

with another hydroxyl group on a neighboring subunit. Cyclodextrin cavities are therefore slightly "V" shaped with the secondary hydroxyl side more open than the primary hydroxyl side.[1] That is, the primary face possesses a slightly more narrow circumference than the secondary face.

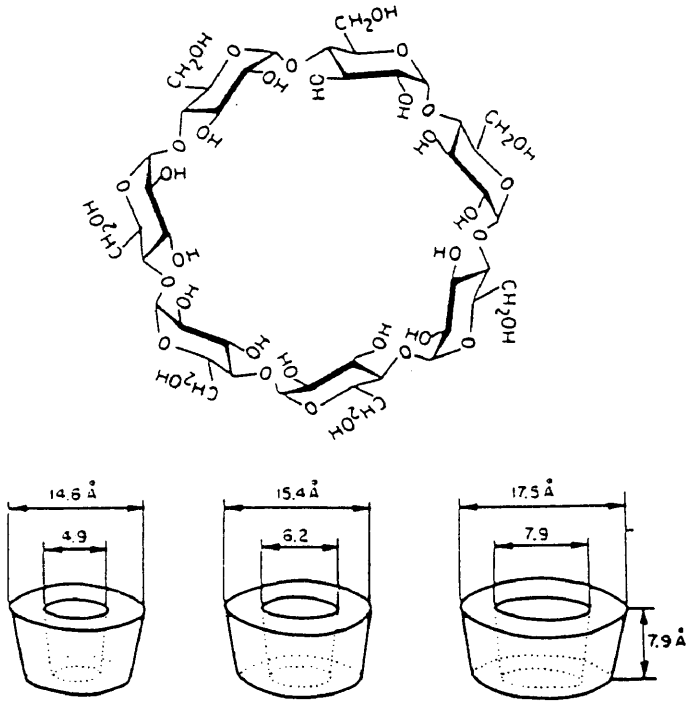


Fig.2 Structure of β-cyclodextrin, and molecular dimensions of α-, β-, and γ-cyclodextrins[3]

The limited rotation of the secondary hydroxyl groups allows cyclodextrin to be strengthened by hydrogen bonding. Studies on the hydrogen-deuterium exchanges of β-cyclodextrin prove that each C2 and C3 hydroxyl group is involved in an intramolecular secondary H-bonding network. α-Cyclodextrin, on the other hand, must eliminate two of its hydrogen bonds in order to minimize conformational strain. The flexibility of the γ- and δ-cyclodextrins significantly

decreases the effectiveness of their hydrogen bonds. β-cyclodextrin, however, is the most rigid of all the isolated cyclodextrins. This rigidity correlates well with solubility studies which show that β-cyclodextrin is notably less soluble in water than other cyclodextrins.[8]

Inclusion Complexes:

One of the most important features of cyclodextrins is the formation of inclusion complexes in which the cavity of cyclodextrin serves as a host for a variety of organic, guest molecules. Guest compounds include polar reagents such as acids, amines, or small ions and extend to various nonpolar molecules, such as aliphatic and aromatic hydrocarbons and rare gases.[1]

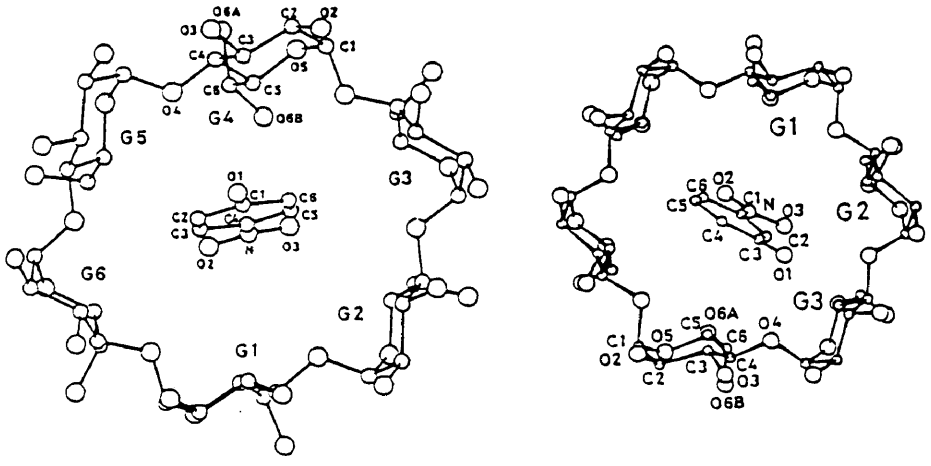


Fig. 3 Inclusion complex formation of α-cyclodextrin with p- and m-nitrophenol[3]

Inclusion complexes are able to form in aqueous solutions because they are enthalpically and entropically favored. Several proposals have been made to explain the large, favorable enthalpy change that results from cyclodextrin complex formation. Suggestions include van der Waals interactions between the guest and host molecules, the effect of hydrogen bonding between the guest and hydroxyl groups of cyclodextrin, the hydrophobic effect, the release of high energy water molecules from the cyclodextrin cavity, and the release of strain energy in the macromolecular cyclodextrin ring.[1] The last two factors explain why inclusion complexes are able to develop easily in an aqueous environment.

In an aqueous solution, nonpolar molecules become surrounded by water molecules. The ordering of water molecules around hydrophobic molecules is not favored entropically. To compensate for this energy loss, nonpolar molecules aggregate around one another, allowing the water molecules to order themselves around the nonpolar whole instead of each individual nonpolar molecule. It is for this reason that many aliphatic and aromatic hydrocarbons in solution with cyclodextrin prefer to reside within the apolar core of the torus.

Water molecules that are trapped within the cyclodextrin cavity possess high potential energies due to the fact that they cannot fully hydrogen bond with the limited number of neighboring water molecules which are also present inside the torus. Once a guest molecule enters the cavity, releasing these high energy water molecules, a favorable entropy change occurs as the water molecules rejoin free

water and form their full ensemble of hydrogen bonds. According to this theory, the better a guest molecule fits into the cavity, the more effectively it can displace the cavity water.[9]

Although guest molecule size can range from noble gases to fatty acid Coenzyme A derivatives, the stability of the resulting complexes vary with the size of both guest and host. If a substrate is too large, it will simply not fit and, therefore, will not bind to cyclodextrin.[3] The fact that the guest molecule is actually contained within the cavity was first shown by X-ray studies. However, further proof was required before it could be established that this occurred in solution. Therefore, NMR spectroscopic data was used to clarify the host-guest constitution.

In addition to NMR, a multitude of spectrophotometric methods can be used to examine the molecular nature of inclusion complexes. Some other methods include UV absorption, circular dichroism, and fluorescence. ^{1}H NMR, however, being a common technique, is widely used for inclusion complex detection. For example, when substituted benzoic acids were added to a solution of α-cyclodextrin, the H-3 and H-5 atoms, which are directed toward the interior of the cavity, showed a pronounced upfield shift. On the other hand, the H-1, H-2, and H-4 atoms, located on the exterior of the cavity, showed only a marginal upfield shift.[1] Therefore, by means of ^{1}H NMR, inclusion complex formation can be empirically confirmed.

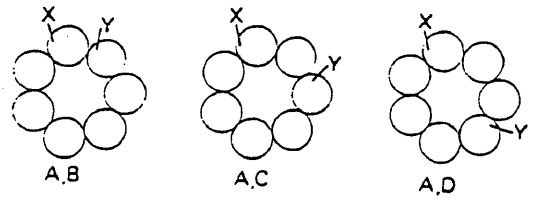


Fig. 4 AB-, AC-, and AD capping in β-cyclodextrin

Capping:

In cyclodextrin chemistry, considerable attention has been focused on developing techniques to modify primary hydroxyl groups through the attachment of caps. Bifunctional modifying reagents or "capping" reagents possess rigid skeletal structures that may symmetrically disubstitute β-cyclodextrin. Capped β-cyclodextrins have been shown to exhibit remarkably enhanced binding capability with many organic substrates as compared to parent (ie. uncapped) cyclodextrins.[3]

Capping boosts the binding strength of various inclusion complexes by increasing the nonpolar nature of the cavity. Without the cap, both ends of the torus are open, allowing guest molecules to escape easily, thereby decreasing complexation rates. The cylindrical cavity with open ends does not immobilize a bound substrate, so the cyclodextrin-substrate complex does not have the well-defined geometry required to produce large intracomplex rates.

Breslow and Emert, in order to increase binding strength and reactivity, affixed various functional groups to the C6 positions of the primary face of β-

cyclodextrin.[9] They speculated by use of molecular modeling and consideration of hydrophobic interactions that the alkyl groups of their derivatives would cluster on the inside of the cyclodextrin cavity and form a "flexible cap". 1-Adamantanecarboxylic acid was shown to bind strongly with these modified cyclodextrins. Reactions with m-nitrophenol acetate and m-*tert*-butyl acetate resulted in binding with the flexibly capped cyclodextrin equally or worse than the unmodified cyclodextrin. Molecular models suggested that the cavity was simply too shallow for the substrates to bind effectively. In addition, the alkyl groups being able to rotate freely, may have also reduced the rigidity, and subsequently, the binding ability of the flexible cap.

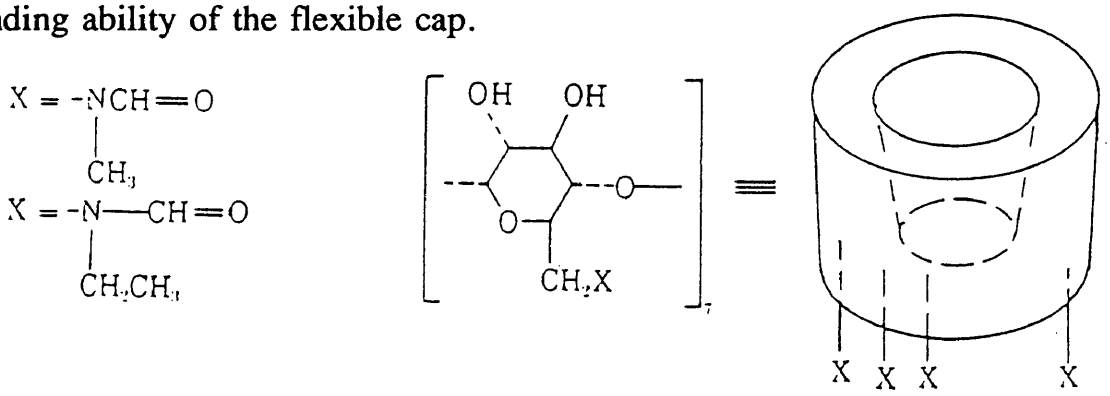


Fig. 5 Breslow's "Flexible Capping" of β-cyclodextrin[9]

Although Breslow's modified cyclodextrin greatly increased its binding strength, Tabushi *et al* sought to further refine this method, and a year later, reported that his group had succesfully derivatized cyclodextrin at two positions using a bifunctionalized molecule. The first known "true" cyclodextrin cap, diphenylmethane-p,p-disulfonyl chloride, was a fairly rigid molecule which was able to bind both 1-adamantecarboxylic acid in addition to m-nitrophenyl acetate

more strongly.[10]

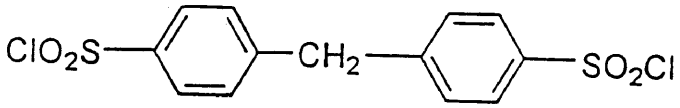


Fig. 6 First "True" cyclodextrin cap

Bifunctionalized caps were researched due to their ability to create more rigid geometries enhancing catalytic rates and substrate binding. The capping reaction mechanism proposed by Tabushi, known as a "looper's walk", transpires via an addition-elimination reaction where one of the functional groups on the bifunctional capping reagent binds to the C6 position of one glucose subunit. The tethered cap will then bind at either the B, C, or D glucopyranose moiety based on a variety of factors. Important factors include the size and flexibility of the molecule, the direction of approach of the entering group, and so on.[11] Regiospecficity can be achieved by selectively choosing caps which possess the appropriate interfunctional group distance. Molecular modeling studies showed that caps which surpass an appropriate distance can result in a variety of regioisomers.[12]

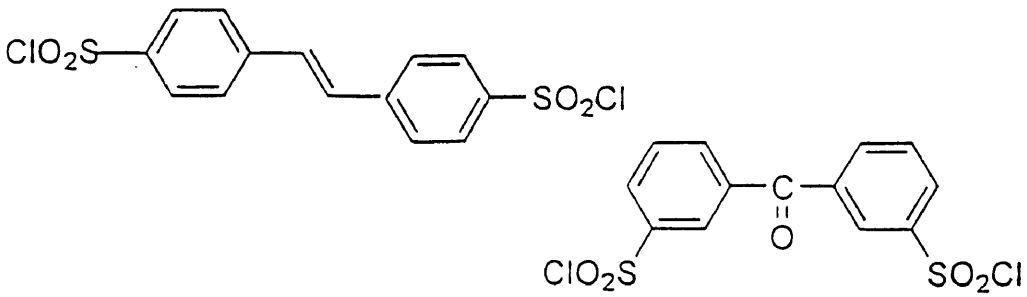


Fig. 7 Tabushi's regiospecific caps

In addition to the bifunctionalization of β-cyclodextrin, Tabushi *et al* attempted to synthesize more rigid caps of a specific length to further improve the regioisomeric selectivity. By reacting cyclodextrin with benzophenone-3,3'-disulfonyl chloride, one could successfully tetrasubstitute cyclodextrin producing the A,C-A',C' regioisomer. They also reported that *trans*-stilbene-4,4'-disulfonyl chloride successfully double capped cyclodextrin forming the A,D-A',D' regioisomer. This double capping further increases the rigidity of γ-cyclodextrin, creating a cavity with a significantly more well defined geometry.[13] It is believed that in the future, two photosensitive caps may be bound via a photochemical reaction and used to form the first cyclodextrin with a single molecule attached at four glucopyranose residues.

Photochemistry:

The goal of this project is to photochemically reduce a double capped benzophenone cyclodextrin to the benzopinacol in the presence of a hydrogen donor. This newly formed benzopinacol would then be a tethered anchor for β-cyclodextrin.

Photochemical reactions occur when atoms or molecules absorb light. The absorption of light causes the molecules, which normally exist in a minimum state of electronic energy, to be raised to a less stable state or an excited state. All substances are selective in their absorption of radiation. The absorbing molecule

must, therefore, possess an excited state which corresponds with the energy of radiation in order to undergo excitation. Due to the inherently chaotic nature of photochemical reactions, where a photoexcited molecule may interact randomly with any other photoexcitable species, it is desirable to perform photochemical reactions in an organized environment. Cyclodextrin's interior provides such a structured surrounding thereby limiting other photochemical possibilities.

Ciamician and Silber in 1900 discovered that benzophenone could form benzopinacol when irradiated in ethanol.[14] After the reaction mechanism was characterized in 1920, interest in benzophenone research grew tremendously. It was learned that by using isopropanol as the solvent and performing the reaction under low intensity radiation in an oxygen free atmosphere one could maximize benzopinacol yields.

Benzopinacol formation occurs when benzophenone is irradiated resulting in an excited singlet state. This singlet state then undergoes intersystem crossing and converts to the triplet state. Benzophenone in its triplet state may now abstract a hydrogen atom from an alcohol, thereby breaking the carbonyl π-bond and creating a carbon-centered radical on benzophenone and the alcohol. The radical center of the alcohol then donates a hydrogen atom to an unexcited benzophenone so as to form a more resonance stabilized radical center. Two radical centers on the benzophenone can now combine to form the pinacol.[15]

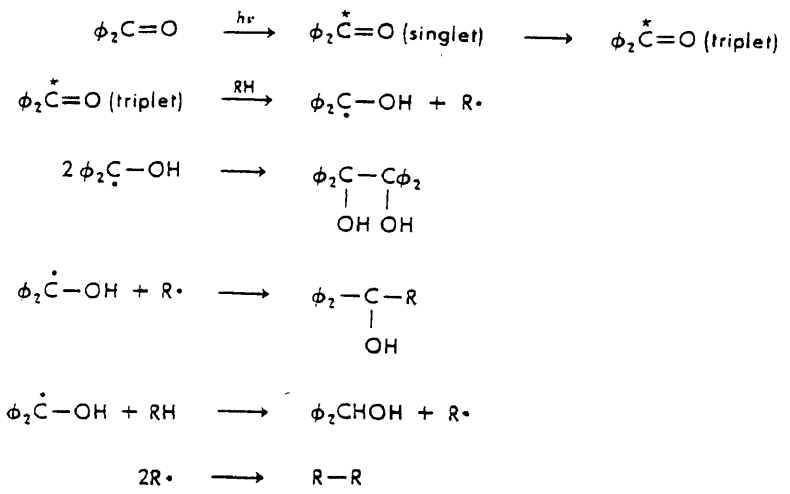


Fig. 8 Benzopinacol formation[15]

Under high intensity radiation, the probability of radical-radical interactions increases. Pinacolization can occur under such conditions but additional reactions also result. One possible reaction involves the coupling of two ketyl radicals at the *ortho* and *para* positions of the aromatic ring which form light-absorbing transients (LATs).[16] LATs not only quench triplet benzophenone, but in the presence of oxygen produce benzophenone and the alkyl ketone. Another possibile reaction is the occurrence of reverse hydrogen transfer. Oxygen, once again, disrupts synthesis by reacting with the ketyl radicals. In all, both oxygen and high intensity radiation reduce benzopinacol yields.

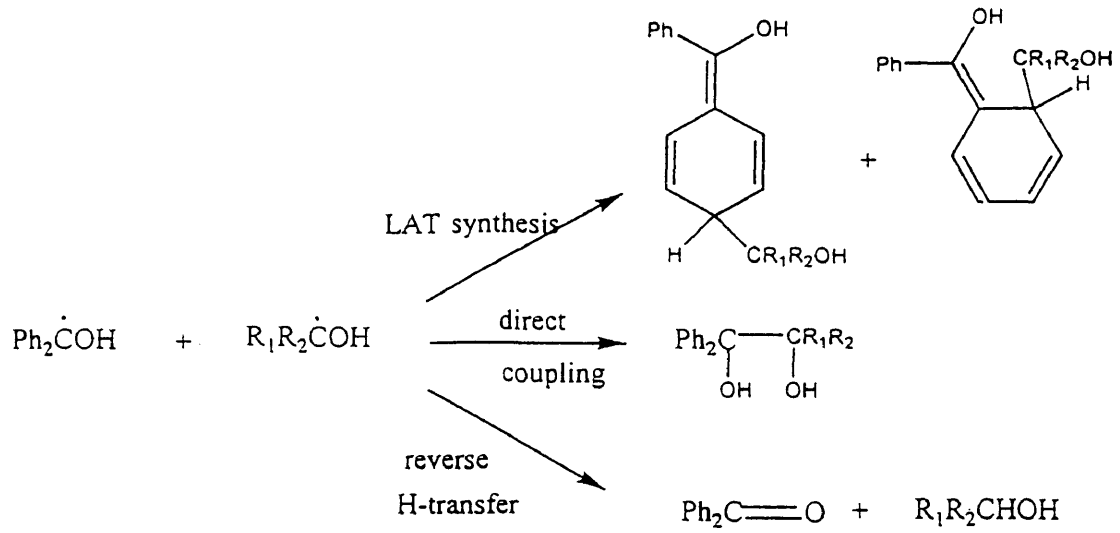


Fig. 9 Radical-Radical reactions under high intensity radiation

Abelt *et al* showed by HPLC that irradiated benzophenone capped β-cyclodextrin in aqueous isopropanol formed three major products. The benzophenone carbonyl, possessing an endo and an exo face can produce endo-endo, exo-exo, and endo-exo pinacol products when the two benzophenone radicals couple. The endo-exo form is the major product simply because it may be formed by two modes of attack, while the others are formed by only one.[17]

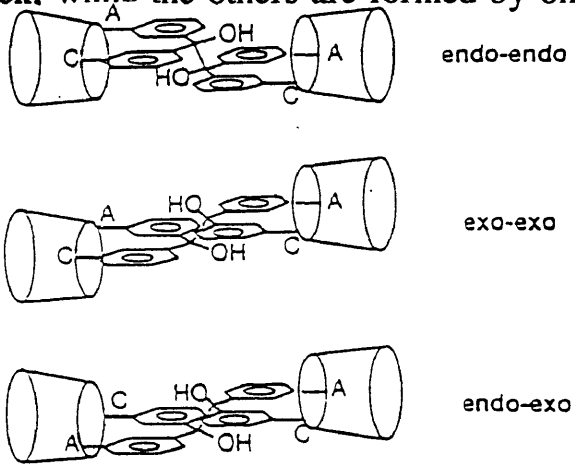


Fig.10 Three major pinacol products

Previous Synthetic Pathways:

There is no reported synthesis of benzophenone 3,5-dicarboxylic acid. However, there have been previous unpublished reports concerning the synthesis of other aromatic carboxylic acid derivatives for the double capping of β-cyclodextrin.

In 1993, Sharma reported the attempted synthesis of 5-acetylisopthalic acid.[18] Although several attempts were made, the most promising route involved a six step synthesis starting with 4'-aminoacetophenone. The procedure was successful up until the fourth step where 1-(3',5'-dicyanophenyl) ethanol was synthesized, but in poor yields. Sharma was therefore unable to further oxidize and then hydrolyze 1-(3',5'-dicyanophenyl) ethanol to the desired acetylisophthalic acid.

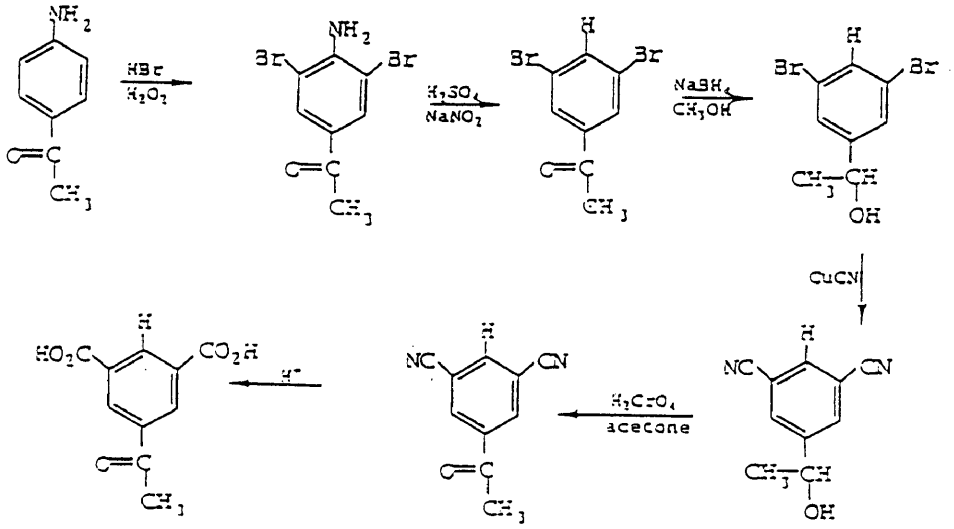


Fig. 11 Proposed acetylisopthalic acid synthesis

In 1994, Williams attempted to synthesize 3,5-benzophenone diacyl (or

disulfonyl) chlorides.[19] The bulk of this work was devoted to the synthesis of the diacids themselves. The synthesis was troubled by several problems, of which solubility, proved to be the most disappointing. His most successful endeavor involved replacing the amino group of dimethyl 5-amino-1,3-isophthalic acid with a cyano group. This reaction was pursued using t-butyl nitrite and $Cu(CN)_2$ in acetonitrile and gave a 20% yield.

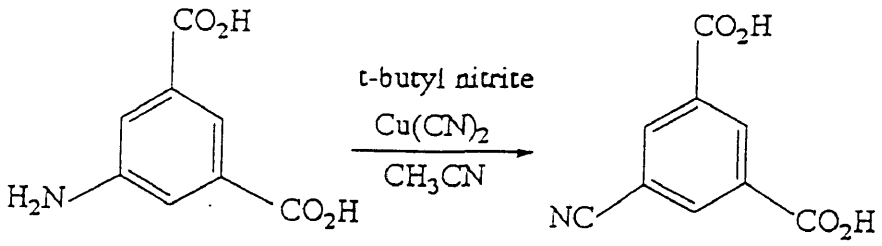


Fig. 12 Synthesis of 5-cyano-1,3-isophthalic acid

EXPERIMENTAL

Tetrohydrofuran was distilled from Na°/benzophenone. ^{1}H NMR and ^{13}C NMR data were obtained using a QE-300 spectrometer. NMR samples were dissolved in $CDCl_3$ and referenced to TMS at 0 ppm. Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. GE halogen 90W flood light was used as low intensity radiation source.

1-bromo-3,5-dimethylbenzene[18]

To a 1L three-neck round bottom flask fitted with a thermometer, reflux condenser, and addition funnel was added 21.07 g (0.174 mol) of 2,4-dimethylaniline, 400 mL of water, and 48% HBr (36.7g, 0.455 mol). The reaction was heated with stirring to 70°C whereupon 30% H_2O_2 (18 mL, 0.176 mol) was added dropwise via addition funnel. The heat was then removed, and the exothermic reaction raised the temperature to 85°C. When the reaction cooled to 70°C, the solution was filtered, extracted with methylene chloride, and washed with water and an aqueous solution of Cu(II)Br_2 to remove peroxides. The solvent was removed *in vacuo*.

The remaining bromodimethylaniline was combined with 95% ethanol (500 mL) in a 1L three-neck round bottom flask fitted with a stir bar, thermometer, and condenser. The mixture was heated with stirring as H_2SO_4 (18 mL) was added slowly via pipet. A solution of sodium nitrate (30.9 g in 270 mL of water) was then added dropwise via an addition funnel along with a catalytic amount of copper powder (0.20 g). The resulting solution was heated at reflux with stirring for approximately 2 hours, after which time, the procedure is repeated. The solution was extracted with hexane, washed with water, concentrated *in vacuo*, and the organic layer vacuum distilled. The fraction boiling between 90°C and 95°C under aspirator vacuum was collected and stored at room temperature. The product was a light, brown liquid (10.42 g, 56.3 mmol, 49% yield). ^{1}H NMR δ

7.12 (s, 2H), 6.88 (s, 1H), 2.30 (s, 6H); ^{13}C NMR δ 20.8, 121.0, 128.1, 129.0, 139.8.

N,N-diethylbenzamide[20]

A three-necked 250 mL round bottom flask equipped with an addition funnel, $CaCl_2$ drying tube, and magnetic stir bar was placed in an ice bath for the duration of the reaction. Diethylamine (11.45 g, 156.6 mmol) and $CHCl_3$ (100 mL) were placed in the flask. Benzoyl chloride (10 g, 71.2 mmol) was then added dropwise via an addition funnel. The reaction was stirred for 3 hours. The organic layer was then separated, dried with $CaCl_2$, concentrated *in vacuo*, and then distilled under vacuum (0.1 Torr). The fraction boiling between 87°C and 91°C was collected. The product was a clear liquid (7.89 g, 44.8 mmol, 69% yield).

^1H NMR δ 7.33, 7.30, 7.28, 3.24 (d, 2H), 1.15 (s, 3H), 1.00 (s, 3H);

^{13}C NMR δ 13.85, 39.26, 43.3, 126.75, 128.67, 129.26, 138.28, 170.47.

3,5-dimethylbenzophenone[21]

Distilled THF (400 mL) and 1-bromo-3,5-dimethylbenzene (12.14 g, 65.6 mmol) were placed in a three-neck, 1L round bottom flask equipped with a stir bar, cold temperature thermometer, N_2 line, and addition funnel. The flask was placed in a dewar bath filled with an ethyl ether/liquid nitrogen slurry. BuLi (45

ml, 1.6 M) was added slowly so that the reaction temperature did not exceed -90°C. The mixture was stirred for 45 minutes, after which time, N,N-diethylbenzamide (15.75 g, 89.0 mmol) was added dropwise. The mixture was then allowed to warm to room temperature and was stirred for an additional 45 minutes. A dilute NH_4Cl solution (16 g in 200 ml of water) followed by a NaCl solution (17 g in 200 ml of water) was then added to quench the reaction. The aqueous layer was extracted with several portions of ether, dried with anhydrous $CaCl_2$, concentrated *in vacuo*, and distilled under vacuum (0.1 Torr). The fraction boiling between 120°C and 127°C was collected, and recrystallized from 95% ethanol. The product was a white solid (6.30 g, 34.0 mmol, 52% yield): mp 62-65°C. ^1H NMR δ 2.37 (s, 6H), 7.39 (s, 2H), 7.44 (s, 1H), 7.50 (m, 2H), 7.58 (m, 1H), 7.78 (d, 2H); ^{13}C NMR δ 21.04, 127.89, 129.83, 131.97, 133.80, 137.87, 138.16, 138.32, 196.40.

3,5-*bis*-bromomethyl benzophenone[22]

In a 250 mL three-necked round bottom flask equipped with a stir bar, addition funnel, thermometer, N_2 line, and reflux condenser was placed 1 g (4.76 mmol) of 3,5-dimethylbenzophenone and 40 mL of benzene. A flood light was placed approximately 1 cm from the reaction flask and the reaction was heated to 80°C. Bromine (1.83 g, 11.42 mmol) in benzene (10 mL) was added dropwise at a rate such that the bromine color is removed as fast as it is added

(approximately 48 hours of reflux with a slow manual addition). The reaction was allowed to cool at room temperature, and was then washed with a sodium bisulfite solution followed by a sodium bicarbonate solution (performed in hood due to formation of noxious fumes). The organic layer was dried with anhydrous calcium chloride, filtered, and the solvent removed *in vacuo*. The product was a brown oil (1.89 g, 5.11 mmol) and contained a mixture of the desired product (68%), dibrominated methyl groups (8%), and starting material (24%). Relative amounts of each were determined using integration data from the ^{1}H NMR. ^{1}H NMR δ 2.37 (s, 3H), 4.50 (s, 2H), 6.65 (s, 1H), 6.85 (s, 1H), 7.35-7.88 (8H).

Benzophenone-3,5-dicarboxaldehyde[23]

To a 100 mL round bottom equipped with a reflux condenser was added 3,5-*bis*-bromomethyl benzophenone (1.89 g, 5.11 mmol) and 1 mg of sodium bicarbonate dissolved in 9 ml of DMSO. The reaction mixture was heated 160°C for 3.5 hours using an oil bath. The solution was cooled to room temperature and poured into ice water, and then extracted with diethyl ether. The ether extractions were washed with water to remove any excess DMSO. The organic layer was dried with anhydrous $CaCl_2$ and the solvent removed *in vacuo*. The product was a yellow oil (1.06 g, 4.45 mmol) and contained a mixture of the desired product (35 %) and starting material (65%). Relative amounts of each were determined using integration data from the ^{1}H NMR. ^{1}H NMR δ 2.50 (s, 3H), 7.52-8.60 (8H),

10.0 (s, 1H), 10.2 (s, 1H).

Benzophenone-3,5-dicarboxylic acid[24]

In a 1L three-necked round bottom flask fitted with a stir bar, reflux condenser, and thermometer was added benzophenone 3,5-dicarboxaldehyde (1.06 g, 4.45 mmol) in water (400 mL). The reaction mixture was heated to approximately 100°C. NaOH (7.0 g, 0.175 mmol) in water (88 mL) and $KMnO_4$ (0.939 g 5.94 mmol) in water (100 mL) was rapidly added. The reaction was boiled overnight. After which time, sodium bisulfite was added to the solution followed by H_2SO_4 (7 mL). A clear, light brown solution resulted. The solution was extracted with CH_2Cl_2, the organic layer washed with water, dried with anhydrous $CaCl_2$, and the solvent removed *in vacuo*. The product was recrystallized from ethanol giving a white solid (0.50 g, 1.89 mmol) containing a mixture of the desired dicarboxylic acid, monocarboxylic acid, and starting material. ^1H NMR δ 2.37 (s, 6H), 2.69 (s, 1H), 2.72 (s, 1H), 7.40-8.6 (8H), 10.2-11.2 (broad, 2H).

Benzophenone-3,4-dicarboxylic acid[25]

In a three-necked 100 mL round bottom flask equipped with a stir bar, addition funnel, reflux condenser, and thermometer was placed 3,4-dimethylbenzophenone (1.00 g, 4.76 mmol) dissolved in acetic acid (5 mL). The reaction mixture was heated to approximately 100°C. A solution of chromium oxide (2.6 g, 0.026 mol) in water(3 mL), acetic acid (5 mL), and sulfuric acid (1 mL) was added slowly. The reaction was boiled for a week. After which time, the solution was allowed to cool to room temperature and decanted into cold water (55 mL). The mixture was extracted with CH_2Cl_2, dried with anhydrous $CaCl_2$, and the solvent removed *in vacuo*. The product was a brown liquid (4.50 g) containing a small amount of starting material (5%) and monocarboxylated (15%) benzophenone. Relative amounts of each were determined using integration data from the ^1H NMR. ^1H NMR δ 2.33 (s, 6H), 2.68 (s, 3H), 2.72 (s, 3H), 7.31-8.48 (8H), 11.62 (s, 1H).

Benzophenone-3,5-dicarboxylic acid

The same procedure was used as above. The product was a light green solid (0.28 g, 1.06 mmol) giving a 28% yield with 83% conversion. mp 280-286°C. ^1H NMR δ 2.44 (s), 7.57 (m,5H), 8.00 (d), 8.13 (s, 2H), 8.67 (s, 1H). ^{13}C NMR δ 20.48, 128.37, 128.42, 128.54, 129.30, 129.38, 131.75, 132.59, 133.27, 133.37, 137.74, 138.63, 165.64, 194.19.

Benzophenone-3,4-dicarboxylic acid[26]

In a 250 mL round bottom flask equipped with a stir bar was placed of 3M NaOCl solution (50 mL), 3,4-dimethylbenzophenone (1.00 g, 4.76 mmol), $Bu_4N^+Br^-$ (0.077 g, 0.24 mmol), $RuCl_3 \cdot 3H_2O$ (0.048 mmol, 0.0099 g), and of CH_2Cl_2 (40 mL). The mixture was stirred for 2 days at room temperature and the pH maintained between 8-10.5 by the addition of potassium dihydrogen phosphate and phosphoric acid. During the course of the reaction, the solution remained yellow, but then turned black when all the RuO_4 had reacted. The solution was acidified with sulfuric acid, then extracted with CH_2Cl_2. The product was a yellow liquid (1.38 g) containing a mixture of starting material (75%), monocarboxylated benzophenone (20%), and the desired dicarboxylic acid (5%). Relative amounts of each were determined using integration data from the ^1H NMR. ^1H NMR δ 2.32 (s, 3H), 2.37 (s, 3H), 2.45 (s, 3H), 2.89 (s, 3H), 7.30-7.89 (m, 8H), 8.22 (s, 1H).

RESULTS AND DISCUSSION

The principal goal of this research project was to synthesize benzophenone-3,5-dicarboxylic acid for the double capping of β-cyclodextrin and subsequent photopinacolization of the benzophenones. Generation of the carboxylic acid groups proved to be difficult and became the main focus of the project.

The synthetic pathway involved the formation of the desired dicarboxylic acid from 3,5-dimethylbenzophenone via oxidation of the methyl groups. The synthesis of the 3,5-dimethylbenzophenone proved to be fairly successful resulting in 50 to 60% yields. The dimethylbenzophenone was prepared from 1-bromo-3,5-dimethylbenzene and N,N-diethylbenzamide via a BuLi exchange reaction. Both 1-bromo-3,5-dimethylbenzene and the N,N-diethylbenzamide were synthesized.

Starting with commercially available 2,4-dimethylaniline, the aromatic ring was brominated using 48% HBr and H_2O_2. The reagents, 48% HBr and H_2O_2, were chosen to prevent any side chain brominations from occurring. 48% HBr in H_2O_2 is a stronger brominating agent than bromine causing the aromatic ring to be attacked instead of the side chain methyl groups. The amino group of the 6-bromo-2,4-dimethylaniline was then removed via a diazotization reaction giving 1-bromo-3,5-dimethylbenzene in 49% yield. N,N-diethylbenzamide was easily prepared via an addition-elimination reaction using benzoyl chloride and

diethylamine in 69% yield.

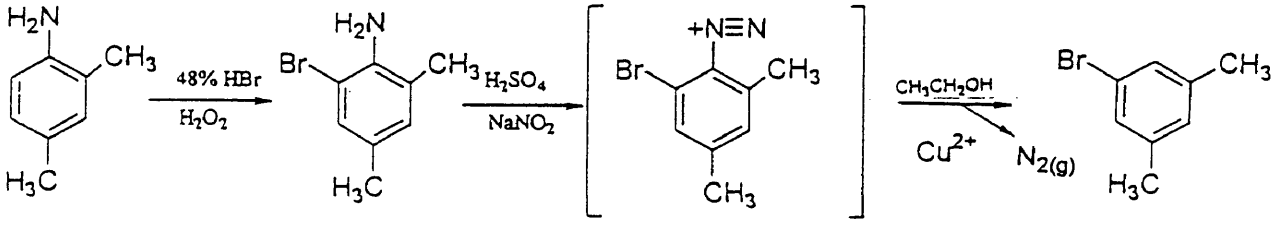


Fig. 13 Synthesis of 1-bromo-3,5-dimethylbenzene

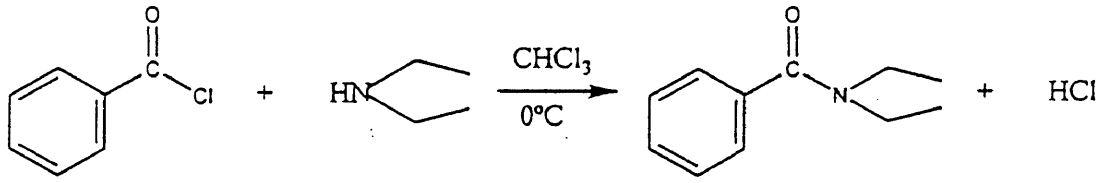


Fig. 14 Synthesis of N,N-diethylbenzamide

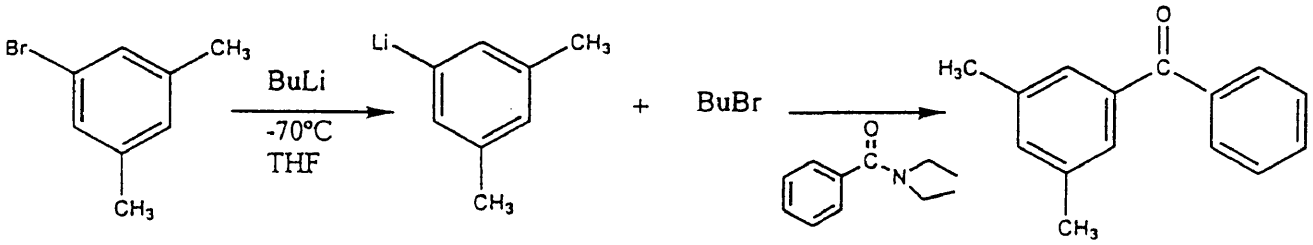


Fig. 15 Synthesis of 3,5-dimethylbenzophenone

The BuLi reaction, as diagramed above, had low yields due to the fact that fresh BuLi was not available and the titration method used to determine the

molarity of the available BuLi proved to be inaccurate. The titration method for BuLi involved two separate titrations using potassium hydrogen pthalate as the primary standard solution. One titration determined the amount of total base present using a titrating solution composed of BuLi, isopropanol, and water. The other titration, which determined the amount of LiOH present, used a solution composed of ethyl ether, benzyl bromide, isopropanol, and water. By subtracting the amount of total base from the amount of LiOH present one could determine the concentration of active BuLi. Repeated attempts using this procedure revealed that the BuLi had degraded slightly. But, a considerable amount of degradation must have occurred because LiOH could be seen in the cloudy appearance of the BuLi solution.

Another reaction pathway explored for the synthesis of 3,5-dimethylbenzophenone utilized a Grignard reagent. The procedure called for 1-bromo-3,5-dimethylbenzene to be reacted with Mg° to form the Grignard. The Grignard reagent was then reacted with benzonitrile and sulfuric acid to form dimethylbenzophenone. This approach failed because the Grignard reagent could not be synthesized. Attempts made to facilitate its formation by activating the Mg° via washings with HCl failed. It was speculated that in the preparation of the 1-bromo-3,5-dimethylbenzene, although distilled from CaH_2, there remained some unknown material which inhibited the Grignard reagent's formation.

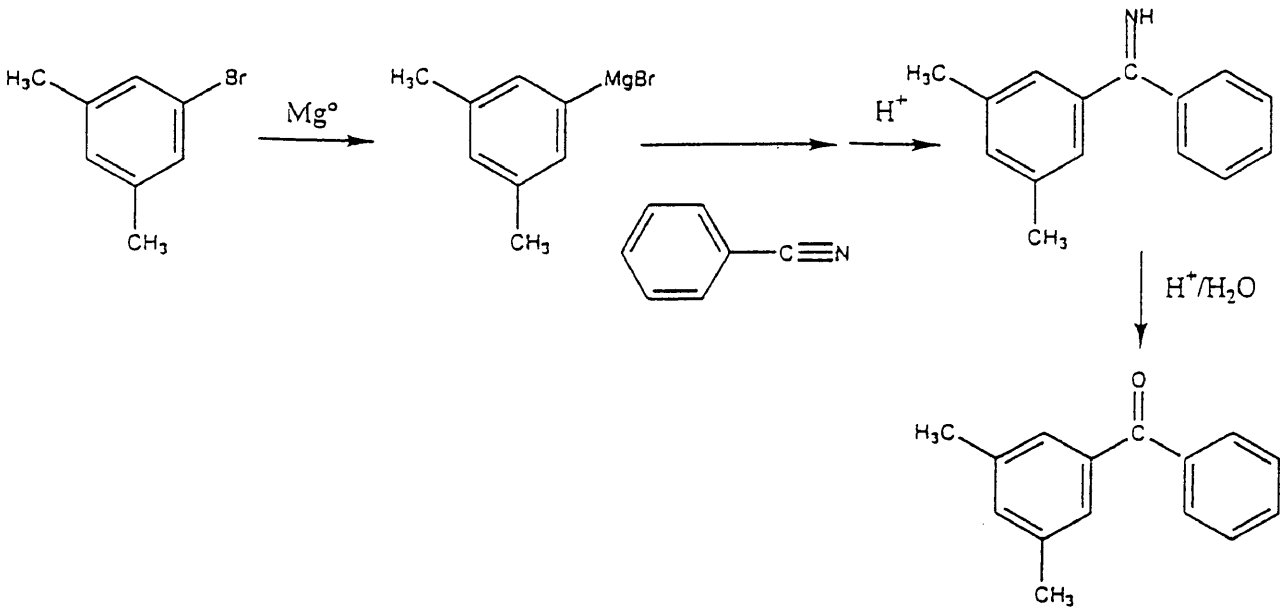


Fig. 16 Failed Grignard pathway

Having successfully synthesized 3,5-dimethylbenzophenone from the lithation route, various oxidizing agents and pathways were explored. Initial oxidation experiments were performed using 3,5-dimethylbenzophenone. But, as time passed, and precious quantities of the 3,5-dimethylbenzophenone were being used up in unsuccessful oxidation attempts, it was decided that future experiments would be performed using the commercially available regioisomer 3,4-dimethylbenzophenone.

Early attempts were made using sodium dichromate dihydrate under various reaction conditions. All reactions performed with this oxidizing agent, as indicated by ^{1}H NMR spectra, showed minimal or partial oxidation of the methyl groups

(Table 1). The reasoning behind the failure to satisfactorily oxidize may be explained by the specificity of reaction conditions required in order for sodium dichromate dihydrate to work effectively. Reaction conditions such as acidity, order of reagent addition, temperature, and so on have to be precisely right for oxidation to occur. Unfortunately, these prime conditions still remain a mystery, and subsequently, the use of sodium dichromate dihydrate as an oxidizing reagent was abandoned.

Table 1. Variations on the reaction of 3,4-dimethylbenzophenone with $Na_2Cr_2O_7 \cdot 2H_2O$ yielding benzophenone 3,4-dicarboxylic acid

Reaction Conditions	Reaction Yield
4.86 equiv. $Na_2Cr_2O_7 \cdot 2H_2O$ in H_2O, sealed tube at 200°C	12%
1.75 equiv. $Na_2Cr_2O_7 \cdot 2H_2O$ in H_2SO_4 at 30°C	20%
0.625 equiv. $Na_2Cr_2O_7 \cdot 2H_2O$ in acetic acid, acetic anhydride at 60°C	18%

A new procedure was then proposed which involved a three-step synthesis pathway. In order to convert the methyl group to a more oxidizable form, it was decided to tribrominate the methyl groups and hydrolyze to form the desired carboxylic acid. The first step, the tribromination, carried out using 6.0

equivalents of bromine, failed presumably due to overbromination of the aromatic ring. The tribromination pathway was therefore abandoned, and replaced by a monobromination procedure, which would then be followed by hydrolysis and oxidation to the carboxylic acid. Once again, bromine was used, but only 2.4 equivalents in a carbon tetrachloride solution. The monobromination was considerably more successful resulting in 68% yield. Dibromination of approximately 7% of the 3,5-dimethylbenzophenone had also occurred. As indicated by the 68% yield, there remained a considerable amount of 3,5-dimethylbenzophenone in the product mixture. Being unable to separate the starting material from the desired product, the methyl groups were present throughout each of the following steps of the pathway toward the carboxylic acid. The same monobromination procedure was also explored using N-bromosuccimide. Both free radical brominations gave similar yields, but the bromine method had a slightly higher yield and was an easier reaction to work-up.

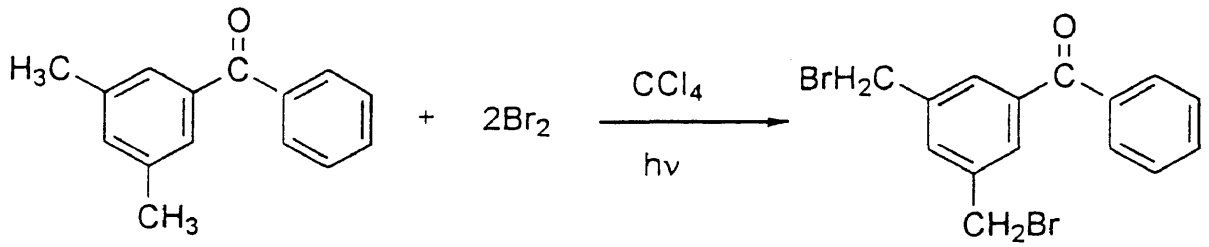


Fig. 17 3,5-*bis*-bromomethyl benzophenone synthesis

The second step of the synthesis pathway, the formation of the

corresponding aldehyde, was pursued via a nucleophilic displacement reaction using the aprotic solvent DMSO. Primary alkyl halides have been known to be oxidized easily into aldehydes with DMSO. Its effectiveness is due to its poor solvation of anions. The anions are therefore poorly stabilized and highly reactive. As expected, the reaction converted the bromomethyl groups into aldehyde groups.

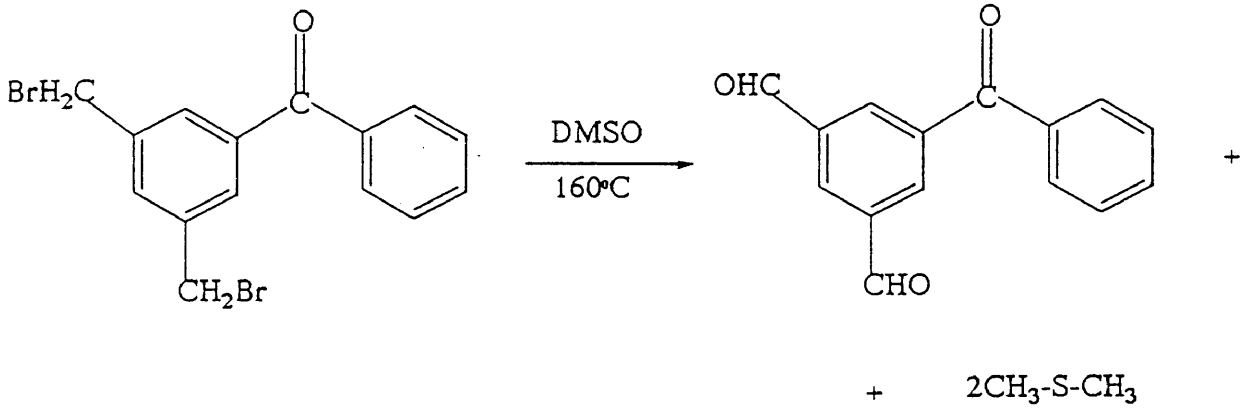


Fig. 18 Synthesis of benzophenone-3,5-dicarboxaldehyde

The last step of the procedure, the oxidation to the carboxylic acid, was carried out using $KMnO_4$ in aqueous NaOH. Previous attempts under acidic conditions failed, resulting in minimal oxidation. Potassium permanganate's success under basic conditions is counterintuitive since $KMnO_4$ has a lower reduction potential when under basic conditions than under acidic conditions. In

base, $KMnO_4$ is not protonated and, therefore, possesses a negative charge which hinders electron-transfer away from a substrate of interest. The reason for success under basic conditions, however, can be explained by the base reacting with the benzophenone 3,5-dicarboxaldehyde to activate the $KMnO_4$ to perform a hydride transfer. The ^1H NMR spectrum revealed the presence of carboxylic acid protons at 10.2 ppm.

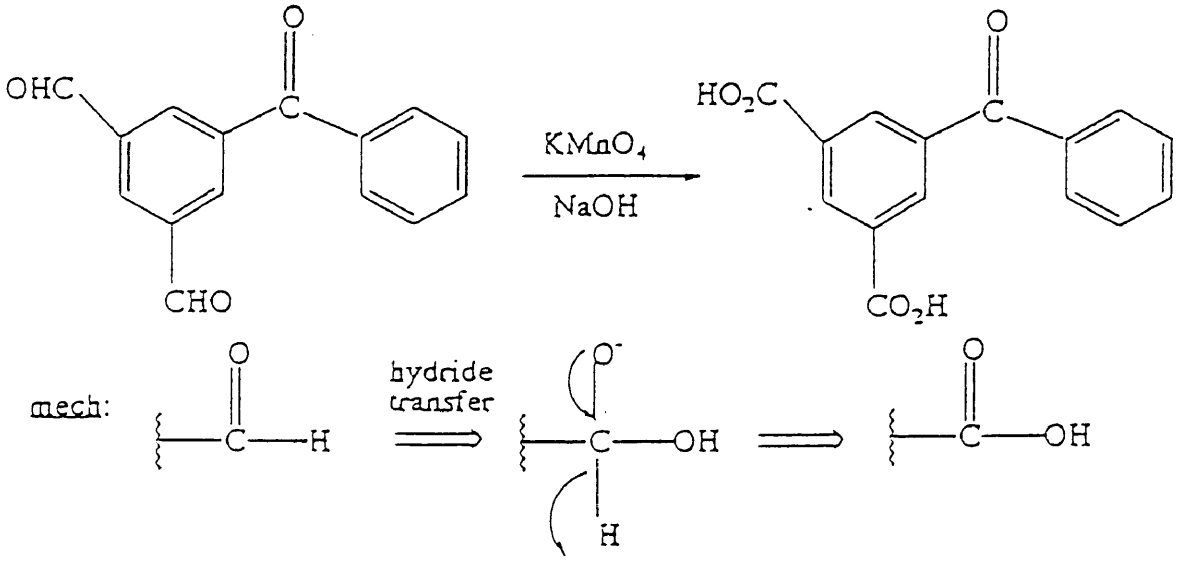


Fig. 19 Benzophenone-3,5-dicarboxylic acid synthesis

Studies involving chromium (VI) oxide were also being investigated as a direct synthesis pathway for obtaining the benzophenone 3,5-dicarboxylic acid. Under strong acidic conditions, such as in a solution of H_2SO_4, minimal or partial oxidation occurred with no peak present at 10.2 ppm in the ^1H NMR spectrum.

But, in a solution consisting mostly of aqueous acetic acid and H_2SO_4, and after a week of continuous heating and stirring, the CrO_3 procedure produced the best results. A strong, broad peak was seen at 11.6 ppm with no methyl group peaks present at 2.37 ppm in the ^1H NMR spectrum.

Due to the success of the CrO_3 procedure with the 3,4-dimethylbenzophenone model compound, the procedure was then repeated on the 3,5-dimethylbenzophenone. As indicated by the ^1H NMR spectrum, the reaction proved to be a success resulting in 83% conversion and 28% yield. No methyl peaks were present in the 2.3-2.4 ppm region and a 2 to 1 ratio of two aromatic proton peaks at 8.67 and 8.41 ppm were also found, consistent with the benzene-3,5-dicarboxylic acid group. A mysterious doublet appeared at 8.0 ppm, possibly indicating the presence of starting material or aromatic ring oxidation. An ^1H-^1H COSY spectrum was obtained on the sample showing no coupling between aromatic protons and methyl groups. Starting material may be present in such minute amounts that the methyl groups could not be detected.

In the oxidation of the methyl groups of the compounds 3,4- and 3,5-dimethylbenzophenone, chromium (VI) oxide is believed to proceed via a free radical mechanism. The exact nature of the mechanism is unknown, but, it is thought to occur via one of the following three methods: direct electron transfer, hydride transfer, or hydrogen-atom transfer. The hydrogen-atom transfer, however, is the most favored possibility due to the fact that a very similar

radical mechanism. The exact nature of the mechanism is unknown, but, it is thought to occur via one of the following three methods: direct electron transfer, hydride transfer, or hydrogen-atom transfer. The hydrogen-atom transfer, however, is the most favored possibility due to the fact that a very similar oxidizing reagent, chromyl chloride, as proposed by Etard[27], proceeds via this process. Many oxidation reactions are free-radical substitutions and involve the transfer of a hydrogen atom. In the CrO_3 case, after the hydrogen-atom transfer occurs forming a free radical, an -OAc group is added and then hydrolyzed to form the corresponding primary alcohol. The alcohol is then turned into a chromate ester intermediate via an ionic process, subsequently forming the desired carboxylic acid.

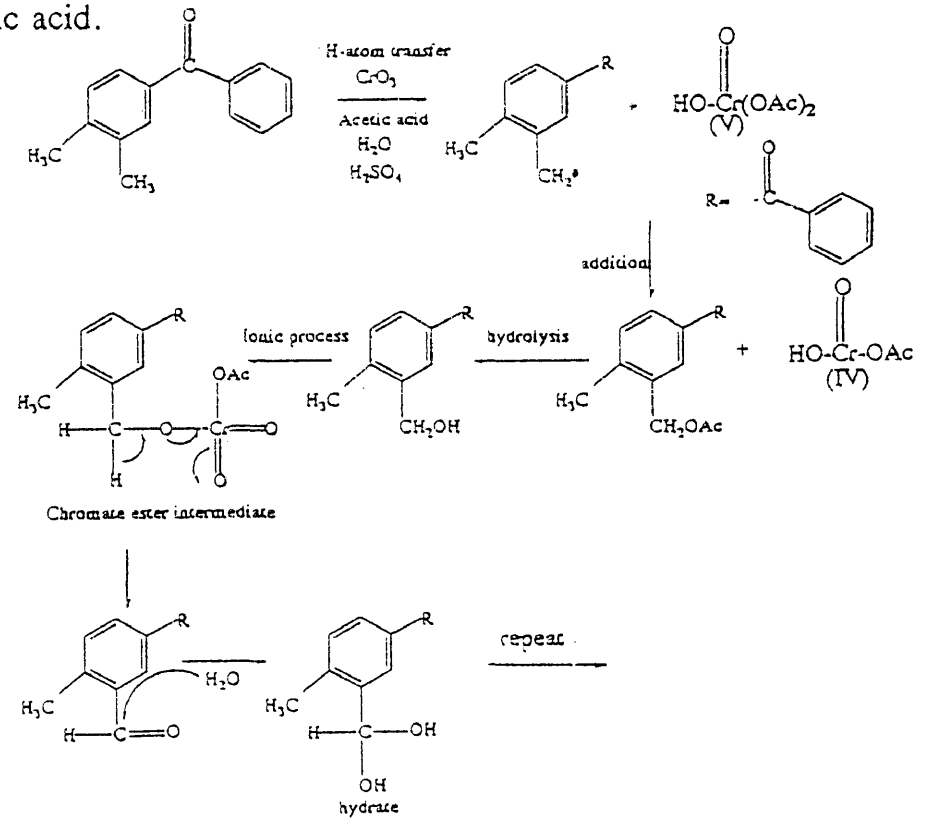
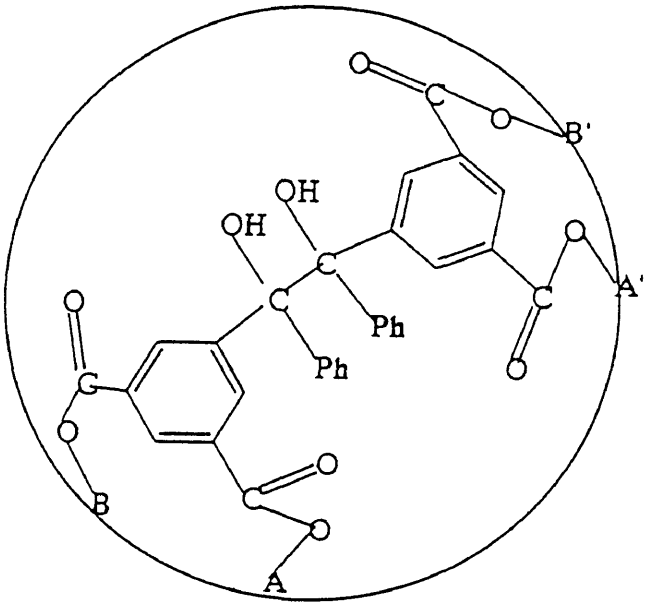


Fig. 20 benzophenone-3,4-dicarboxylic acid synthesis

CONCLUSION

Although several methods for synthesizing benzophenone-3,5-dicarboxylic acid were explored, the CrO_3 procedure in acetic acid proved to be the most successful. Complete oxidation of both methyl groups was accomplished with minimal traces of starting material present in the reaction mixture. It is conceivable that in the near future this method may be further refined resulting in higher percent yields and conversions.

Having successfully synthesized benzophenone-3,5-dicarboxylic acid, it can now be used as a double-capping agent for β-cyclodextrin. Photopinacolization reaction would result in a benzopinacol which would AB-A'B'cap β-cyclodextrin via ester linkages at the C6 hydroxy position of four glucopyranose subunits.



Top view of Primary face

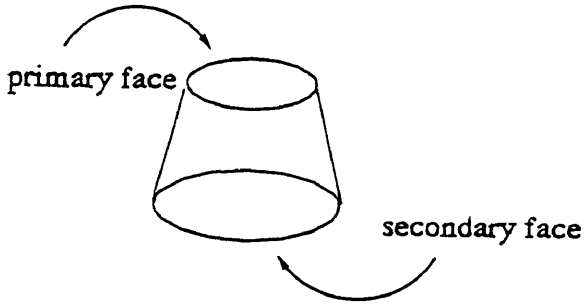
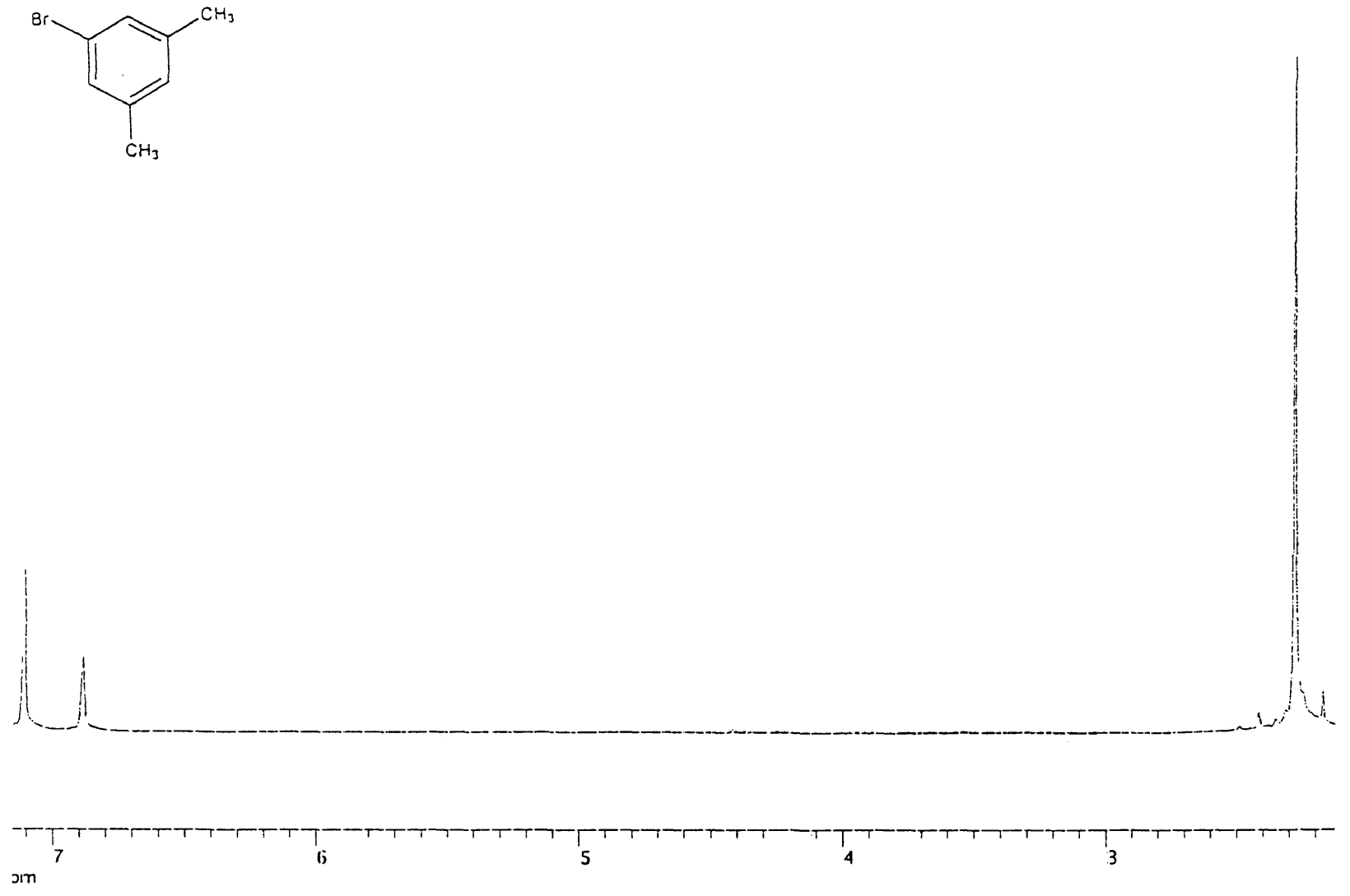
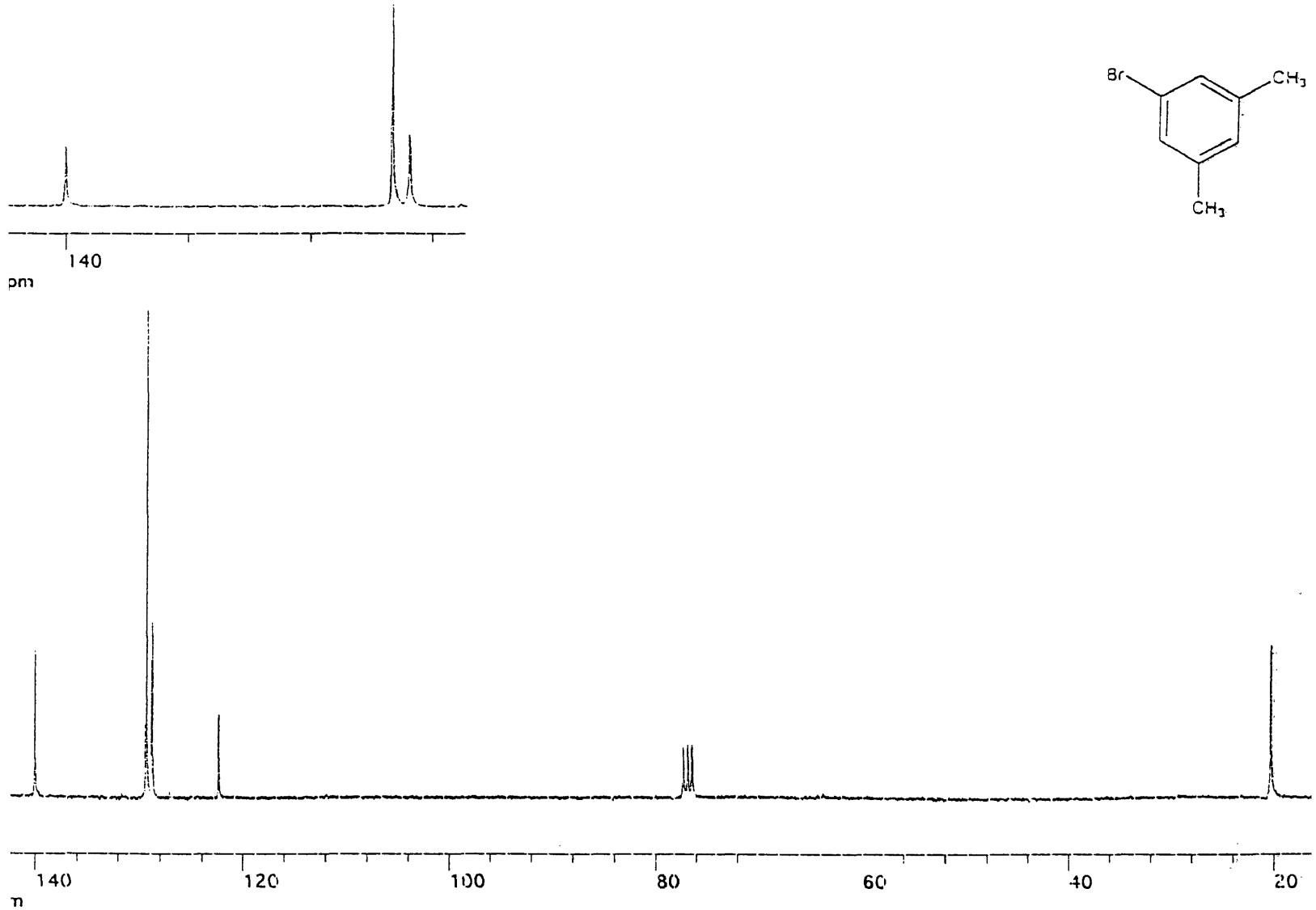


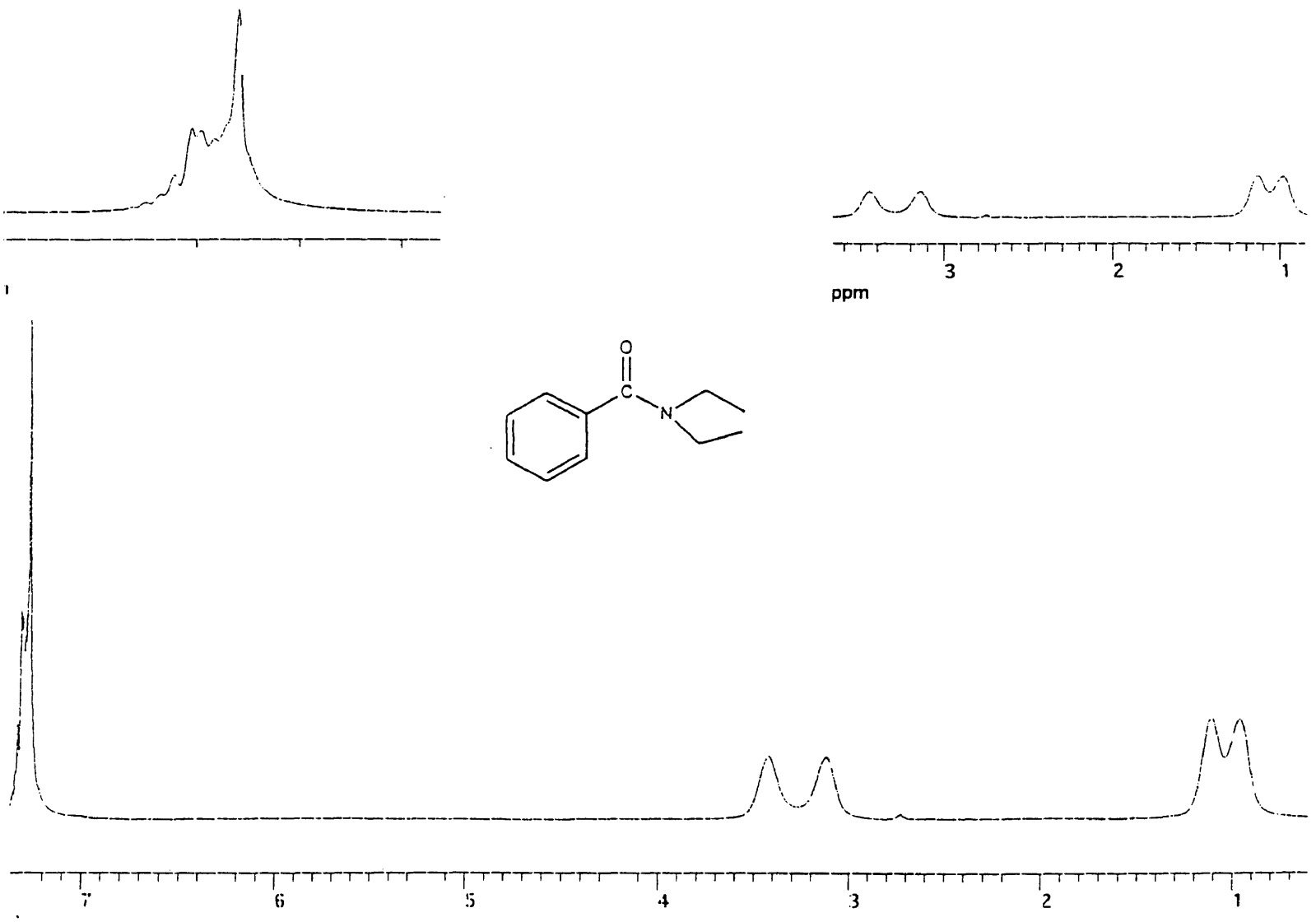
Fig.21 Double capping of Benzophenone-3,5-Dicarboxylic Acid to β-cyclodextrin



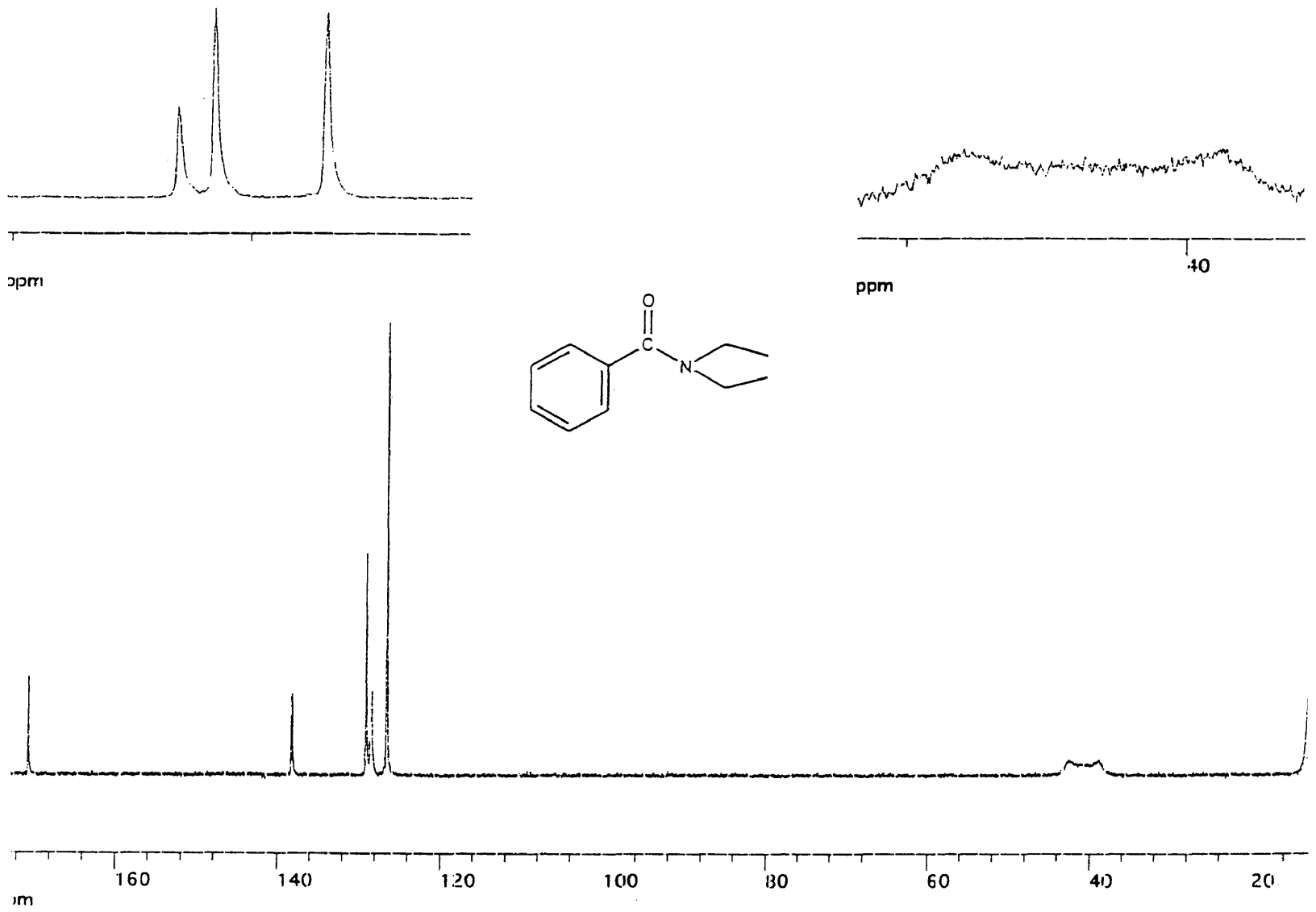
Spectra 1. ^{1}H NMR of 1-bromo-3,5-dimethylbenzene



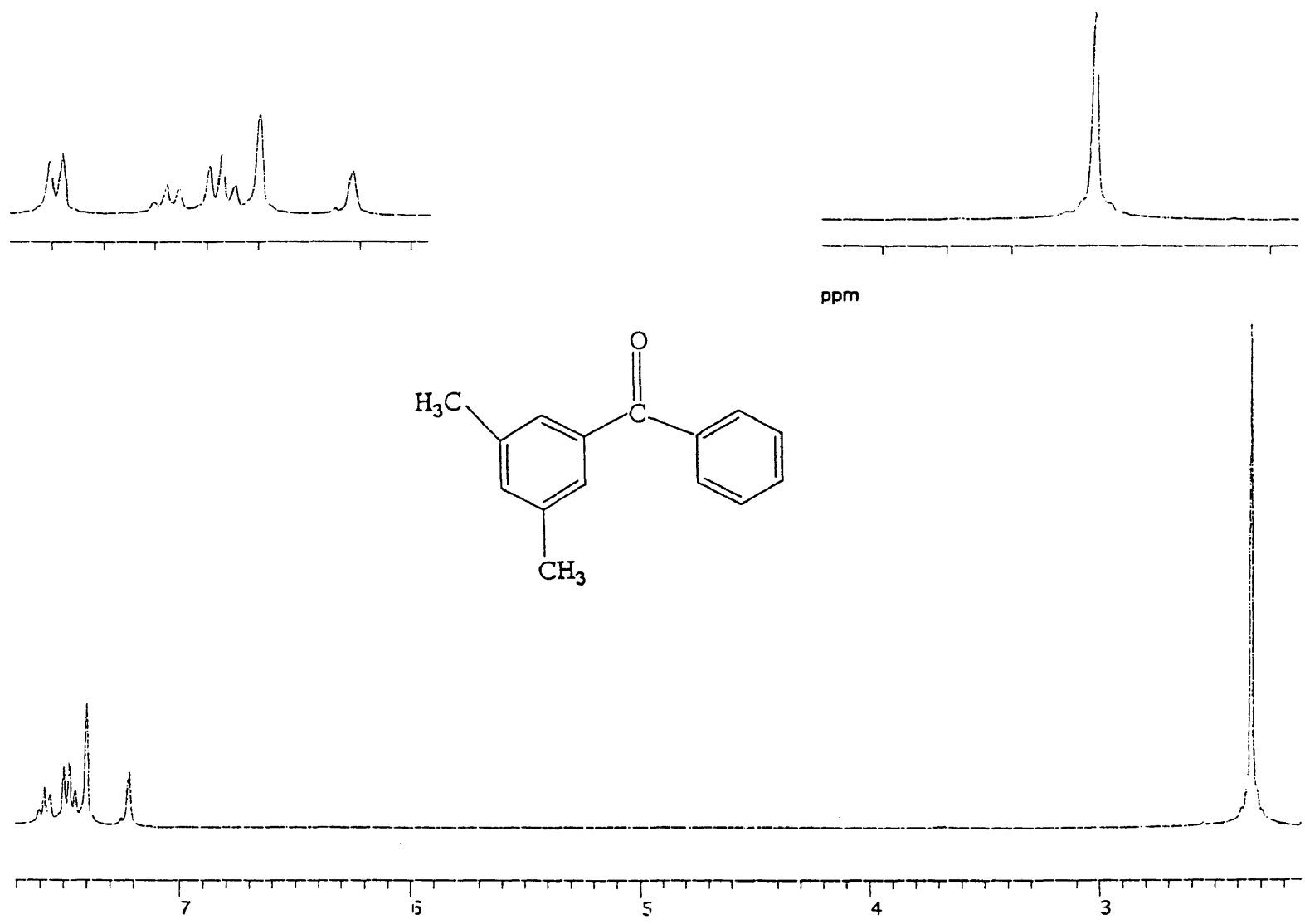
Spectra 2. ^{13}C NMR of 1-bromo-3,5-dimethylbenzene



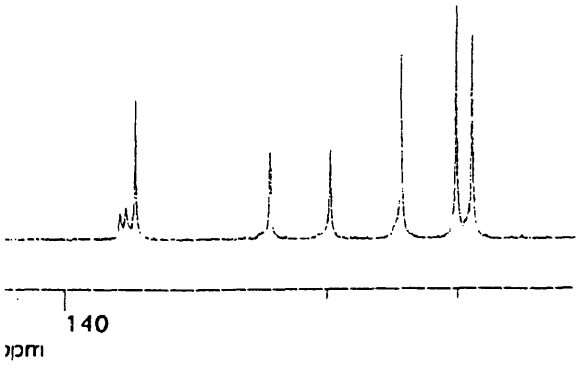
Spectra 3. ^{1}H NMR of N,N-diethylbenzamide

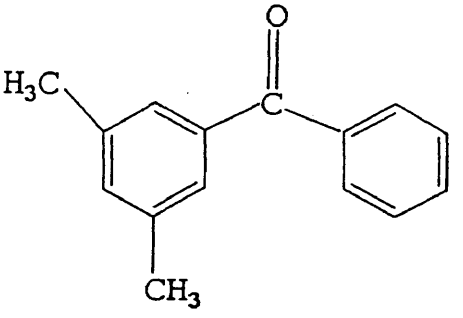


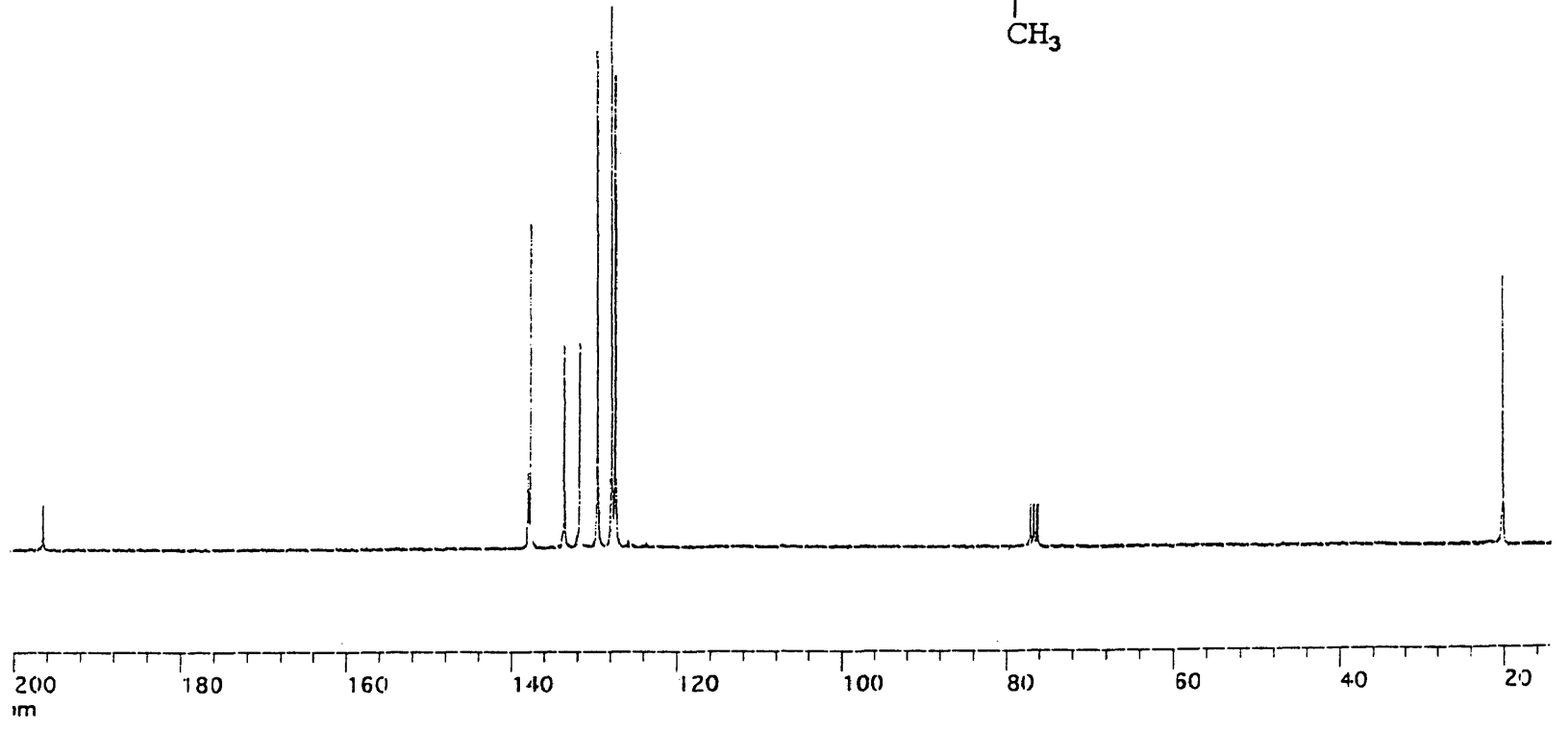
Spectra 4. ^{13}C NMR of N,N-diethylbenzamide



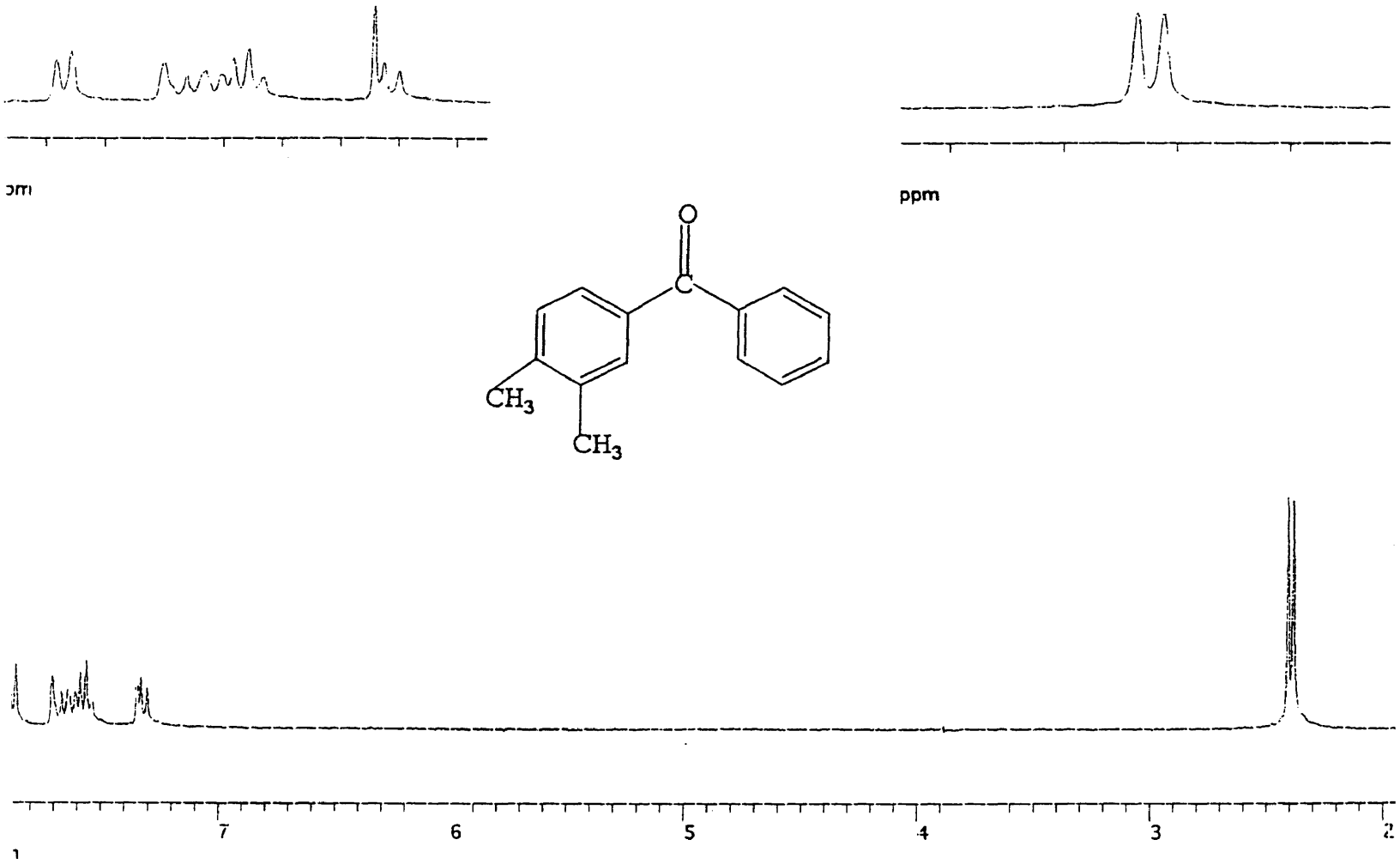
Spectra 5. ^{1}H NMR of 3,5-dimethylbenzophenone



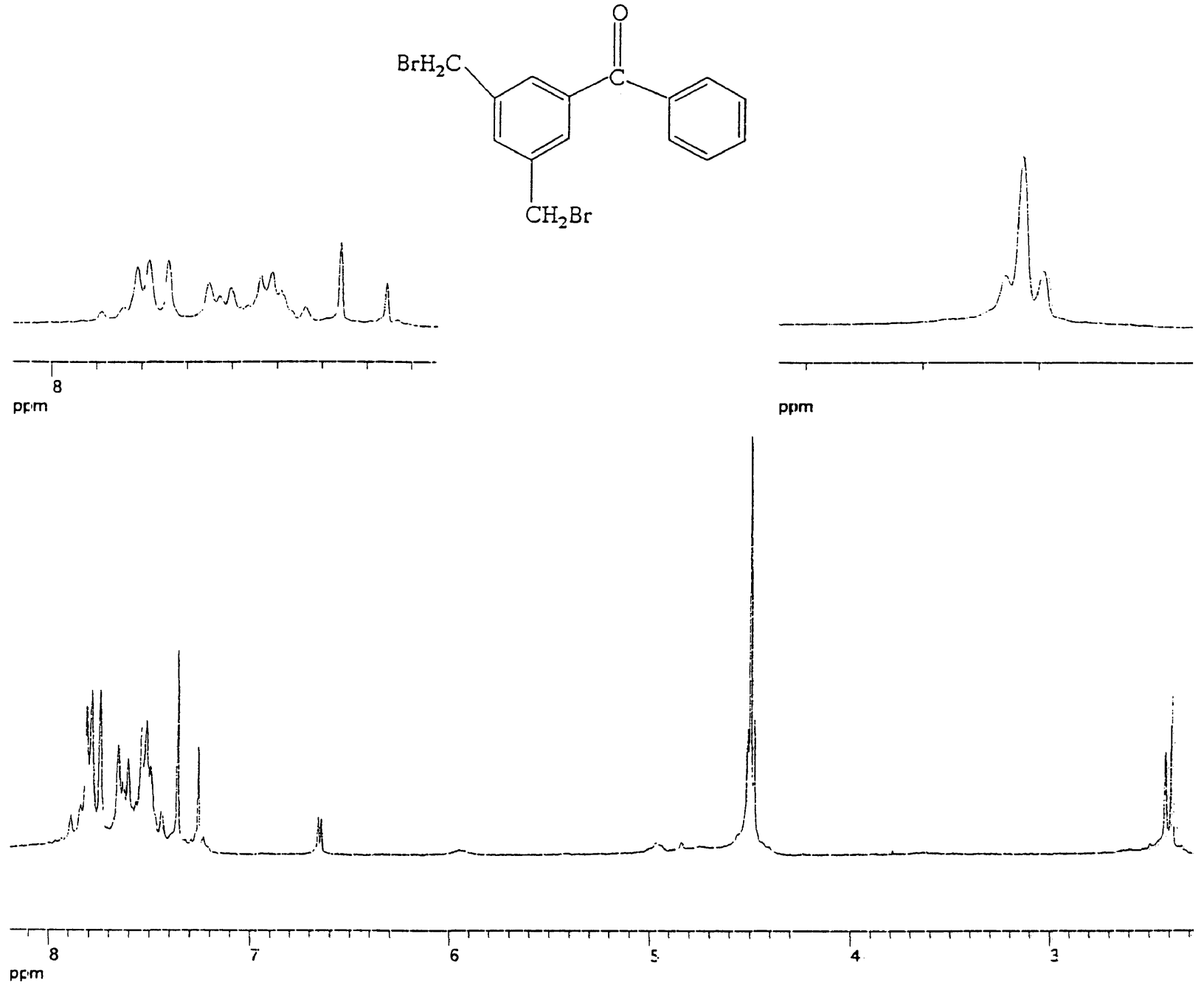




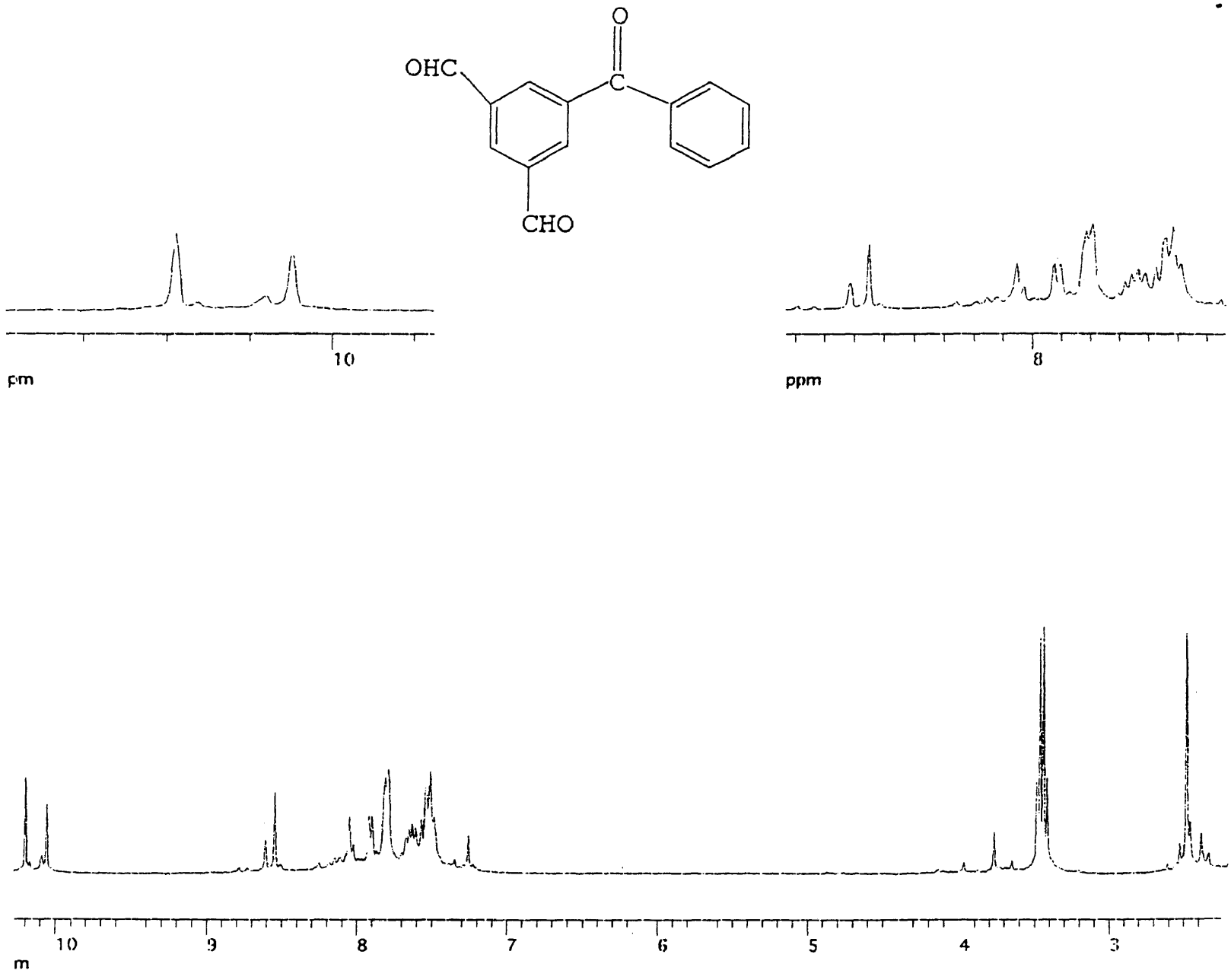
Spectra 6. ^{13}C NMR of 3,5-dimethylbenzophenone



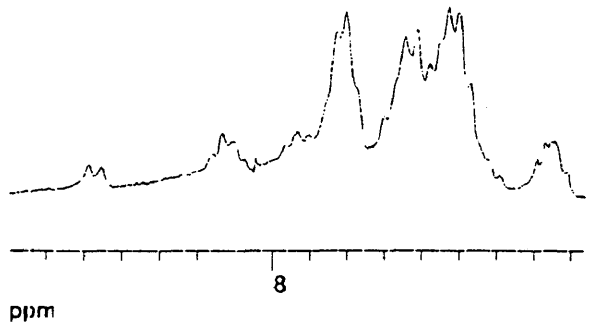
Spectra 7. ^{1}H NMR of 3,4-dimethylbenzophenone

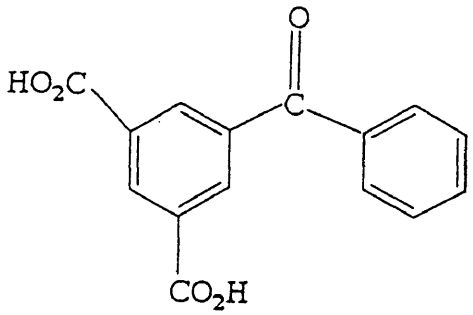


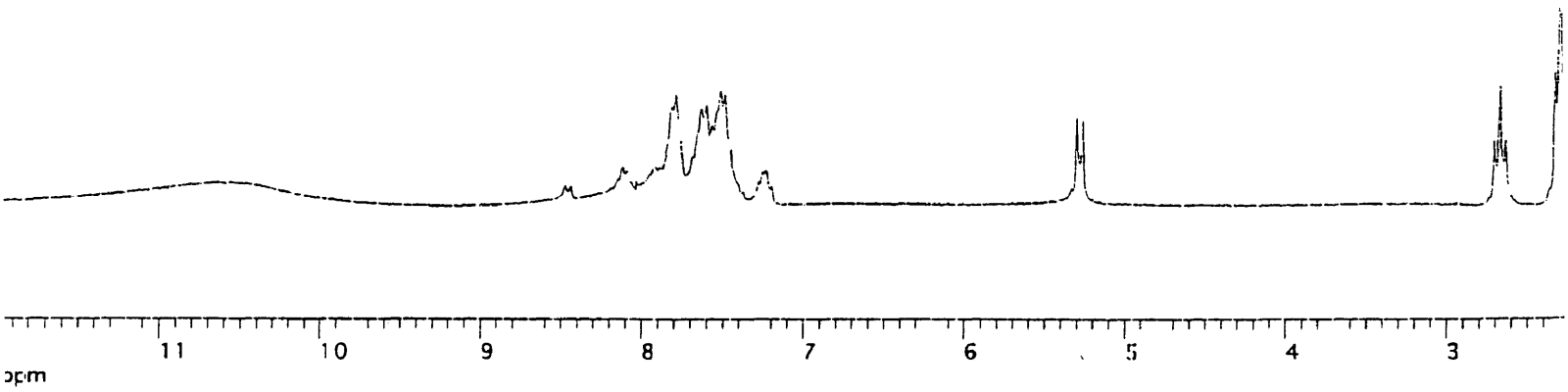
Spectra 8. ^{1}H NMR of 3,5-*bis*-bromomethyl benzophenone



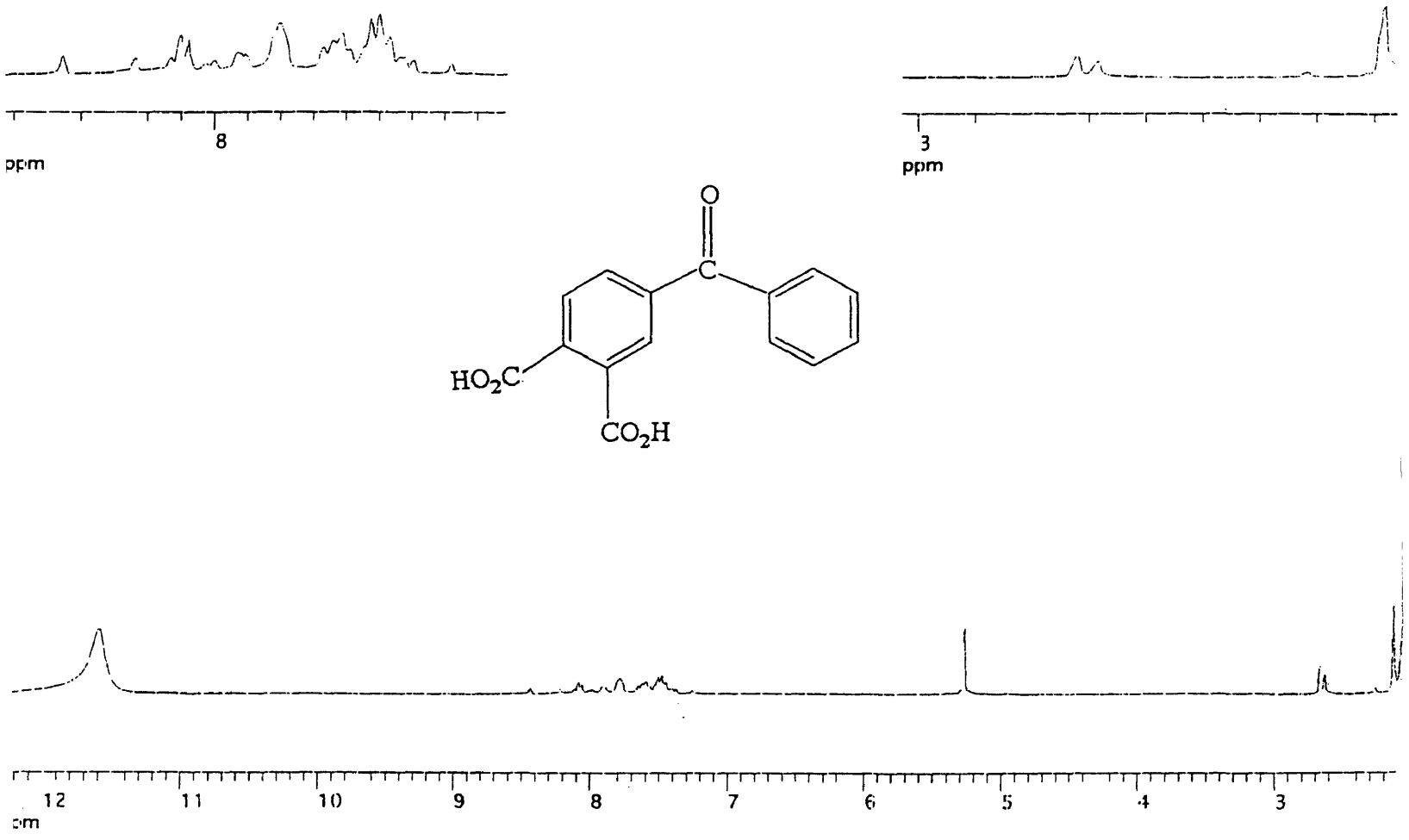
Spectra 9. ^{1}H NMR of benzophenone 3,5-dicarboxaldehyde



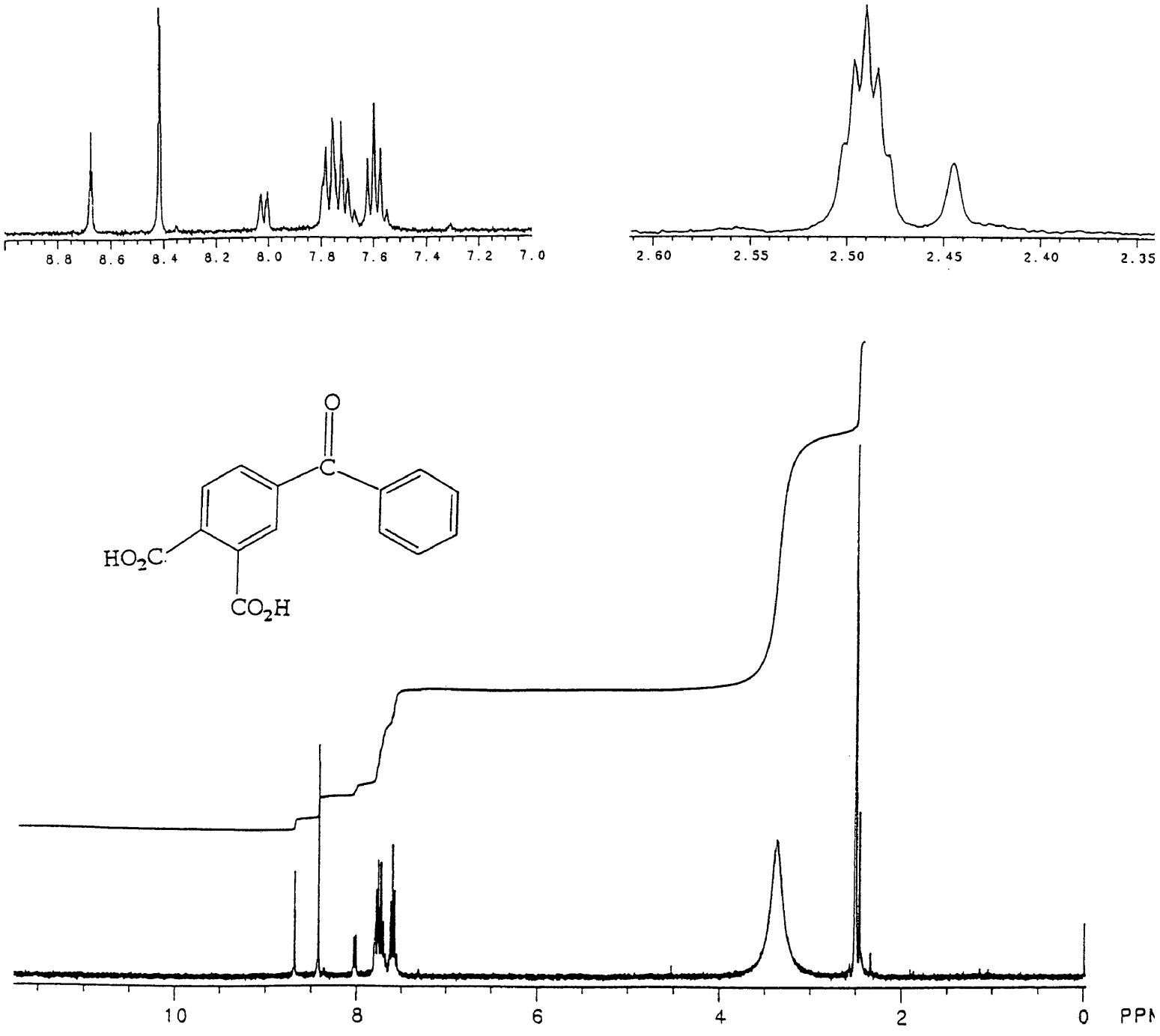




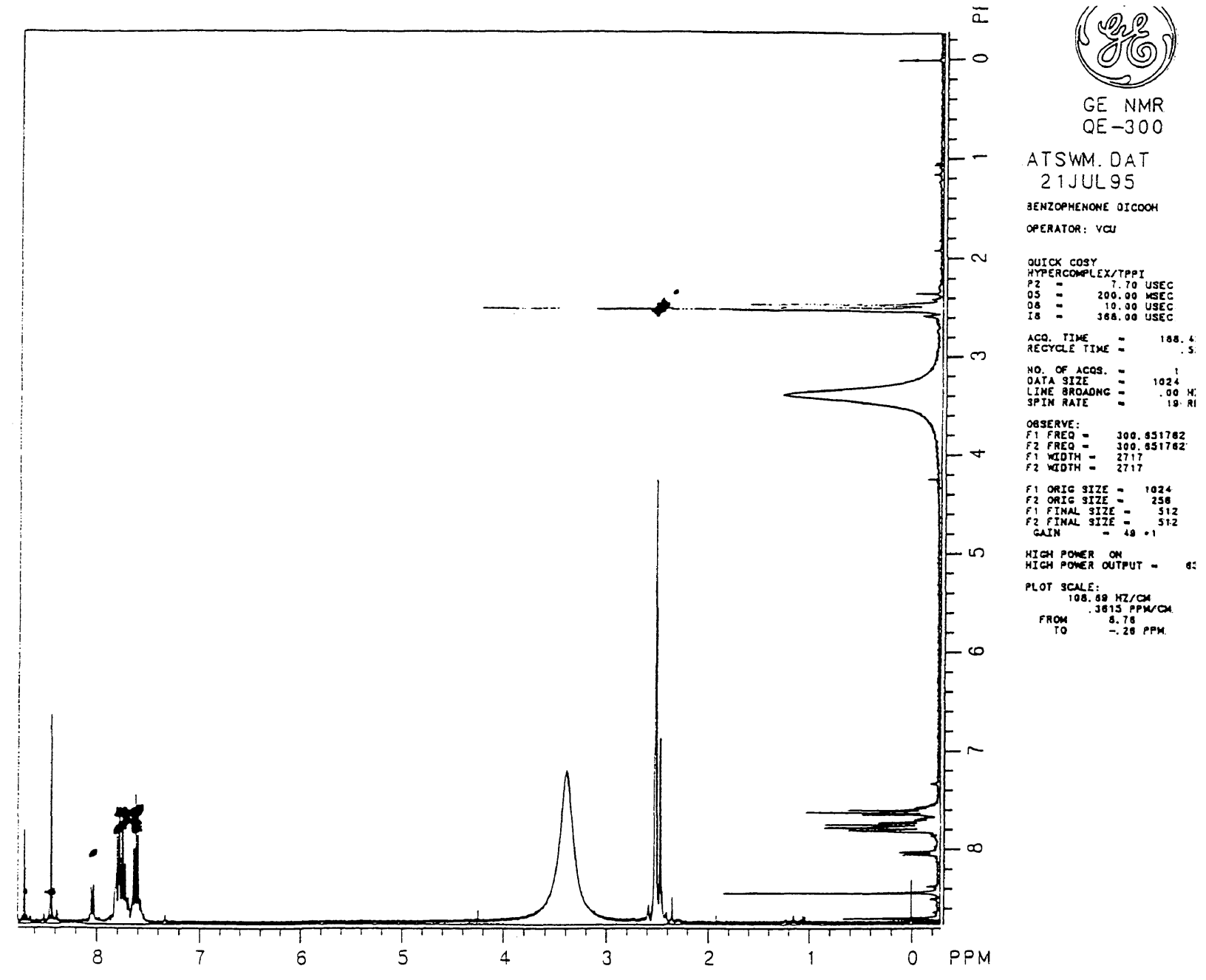
Spectra 10. ^{1}H NMR of benzophenone-3,5-dicarboxylic acid



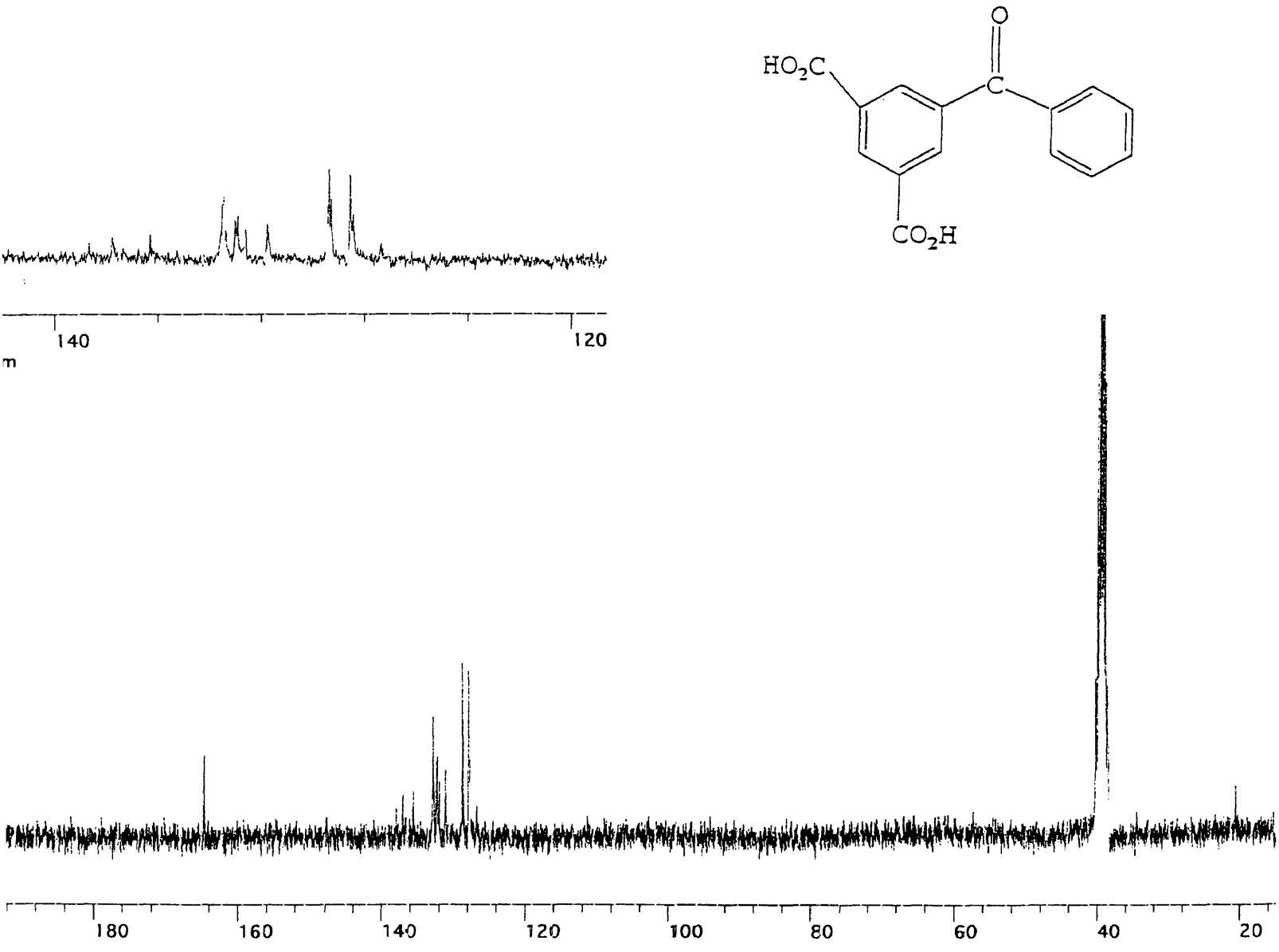
Spectra 11. ^{1}H NMR of benzophenone-3,4-dicarboxylic acid



Spectra 12. ^{1}H NMR of Benzophenone-3,5-dicarboxylic acid



Spectra 13. ^{1}H-^{1}H COSY of Benzophenone-3,5-dicarboxylic acid



Spectra 14. ^{13}C NMR of Benzophenone-3,5-dicarboxylic acid

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VITAE

Jaydee Dones Cabral

Born in San Francisco, California, 26 June 1972 to Gil and Carmelita Cabral. Graduated from Salem High School in Virginia Beach, Virginia in June 1990. Received a Bachelor of Science degree in chemistry at the College of William and Mary in May 1994. The author enrolled in the Master of Arts program at the College of William and Mary in August 1994.

After graduation, the author will begin her Ph.D. in biomedical sciences at Eastern Virginia Medical School in Norfolk, Virginia.