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The Synthesis of 6A,6B-Dideoxy-6 A,6B-(9,10-Dicyanoanthracenyl-2,3-Dimethylene)-beta-Cyclodextrin

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The Synthesis of $6^A,6^B$-Dideoxy-$6^A,6^B$-(9,10-Dicyanoanthracenyl-2,3-Dimethylene)-β-Cyclodextrin

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Abstract

$6^A,6^B$-Dideoxy-$6^A,6^B$-(9,10-dicyanoanthracenyl-2,3-dimethylene)- β- CD (cyclodextrin) was synthesized via the Wittig reaction of A, B-diformyl β-CD and the ylide of (9,10-dicyanoanthracenyl-2-methyl) triphenylphosphonium bromide. Features of this host molecule include a deeper pocket and more rigidity to the overall structure. The cavity was lengthened via a cap positioned perpendicularly to the face of the complex, and the increase in rigidity could be attributed to the olefinic bonds of the cap and its two points of attachment to the cyclodextrin.

The Synthesis of $6^A,6^B$-Dideoxy-$6^A,6^B$-(9,10-Dicyanoanthracenyl-2,3-Dimethylene)-β-Cyclodextrin

Introduction

Catalysts are able to increase the rate of reactions, without ever being exhausted. Often scientists attempt to imitate natural biological enzyme-substrate systems to understand their mechanisms and to explore possible applications for chemical catalysis. The applications of this strategy are wide and diverse. Drug delivery systems, bioremediation techniques, and fermentation methods are only a few examples.

Photocatalysis begins with the excitation of an electron from its ground state to an excited one. Photochemical reactions, however, are often hampered with inefficiency and a lack of stereo- or regioselectivity. Cyclodextrins, cyclic oligomers of glucose, are catalysts for a variety of non-photolysis reactions and some of their derivatives are photocatalysts. Cyclodextrins possess a pocket that is well defined and fairly constant, allowing them to mimic enzymatic specificity. Cyclodextrins covalently attached to one photochemical reactant can bind to a second reactant via weak intermolecular forces to promote catalysis. By effectively increasing the local concentrations of both reactants, the likelihood a reaction will occur is increased. Regioselectivity is enhanced because the attached reactant is held in a fairly stable position, while the other is fixed in a certain configuration. In this model, the cyclodextrin with the attachment is termed the host, while the reactant that is attracted to cyclodextrin is denoted the guest. Host-guest chemistry refers to the non-covalent interactions via a multiplicity of van der Waals contact points between a supramolecule and a small molecule.[1]

Biomimetic chemistry involves synthesis of model enzymes to meet or surpass the efficacy of biological enzymes. The overall goal of this project is to develop

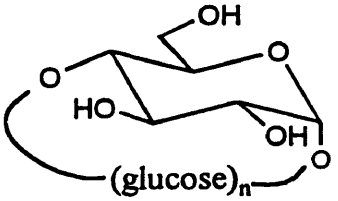
supramolecular hosts which can facilitate the photoinduced-electron-transfer oxidation of guests. Under this paradigm, light would excite the cyclodextrin host, and then electron transfer from the guest to the host would occur. The resulting oxidized guest would be susceptible to a nucleophilic attack, which should occur with enzyme-like regio- and stereoselectivity.

Background

Cyclodextrins

Cyclodextrins, cyclic oligomers of α-(1,4)-linked D (+)-glucopyranose units, were first discovered by Villiers in 1891 as byproducts of the action of *Bacillus macerans* amylase on starch. Several years later Schardinger provided a detailed description of the isolation and preparation of cyclodextrin.[2] Since the 1970's, interest in these organic molecules has surged due to their ability to form inclusion complexes, act as catalysts, and mimic enzymes. Industrial applications of cyclodextrin extend over a wide range, including the chemistry of food, cosmetics, pharmaceuticals, pesticides, and polymers.[3]

Cyclodextrins (CDs) consist of interconnected glucose units in the shape of a torus or donut. A system of nomenclature has been derived, based on their size, or more specifically the number of glucose units. CDs are denoted with the prefixes α-, ß,- and γ- for molecules consisting of 6, 7, and 8 sugar units. (Fig. 1) Sizes smaller



n = 6 => α
n = 7 => β
n = 8 => γ

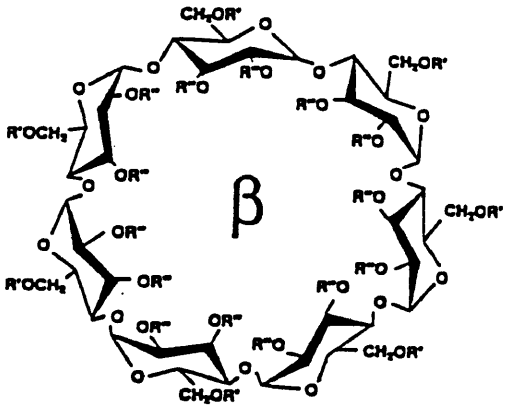


Figure 1. Representations of cyclodextrin

than these are too sterically strained for synthesis while those much larger are more synthetically elusive. The geometry of cyclodextrins resembles a truncated cone with two openings of different diameters. The smaller opening, or primary face, consists of primary

hydroxyl groups at the C6 position of the glucose, while the secondary face is constructed of secondary C2- and C3- hydroxyls. (Fig. 2)

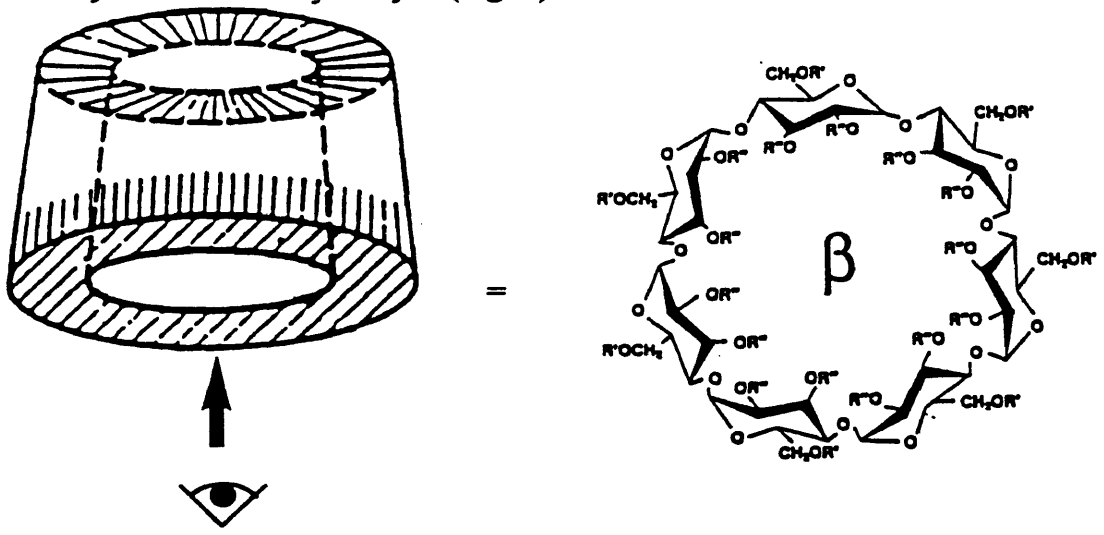


Figure 2. The faces of cyclodextrin

Numerous functionalities can be covalently attached to the cyclodextrin hydroxyl groups. Substituents tethered to cyclodextrin are attached with one bond. Tethers can be linked to the primary face or the secondary face. When two points of attachment are involved, then the substituent is called a cap. Currently, caps have only been attached to the primary face of cyclodextrin. Glucose units are labeled consecutively to indicate the points of attachment to the substituent functionalities. (Fig. 3)

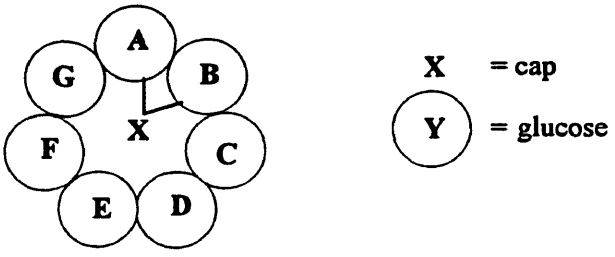


Figure 3. An example of the A, B- cap notation of cyclodextrin

Cyclodextrins serve as ideal enzyme models due to their apolar cavity, small size, and ease of functionalization. The hydrophobic inner cavity of the cone results from C-H

bonds and ether-like oxygens that connect the glucose units together. The dimensions of ß-cyclodextrin are 6.0 Å and 6.8 Å at the openings and 8.0 Å in height. The well-defined size and shape of the cavity contributes to the specificity of cyclodextrins. Various photochemically active cyclodextrin derivatives have been synthesized to date. In 1986, Neckers et al. reported the synthesis of a rose bengal-tethered cyclodextrin that had the capability of photooxygenating diphenyl dioxenes.[4] Six years later, Ye et al. synthesized a flavin-tethered CD that photooxidized benzyl alcohols.[5] Since then, Kuroda and coworkers have successfully photoreduced quinones to their corresponding hydroquinones with a benzophenone-attached cyclodextrin.[6] (Fig. 4)

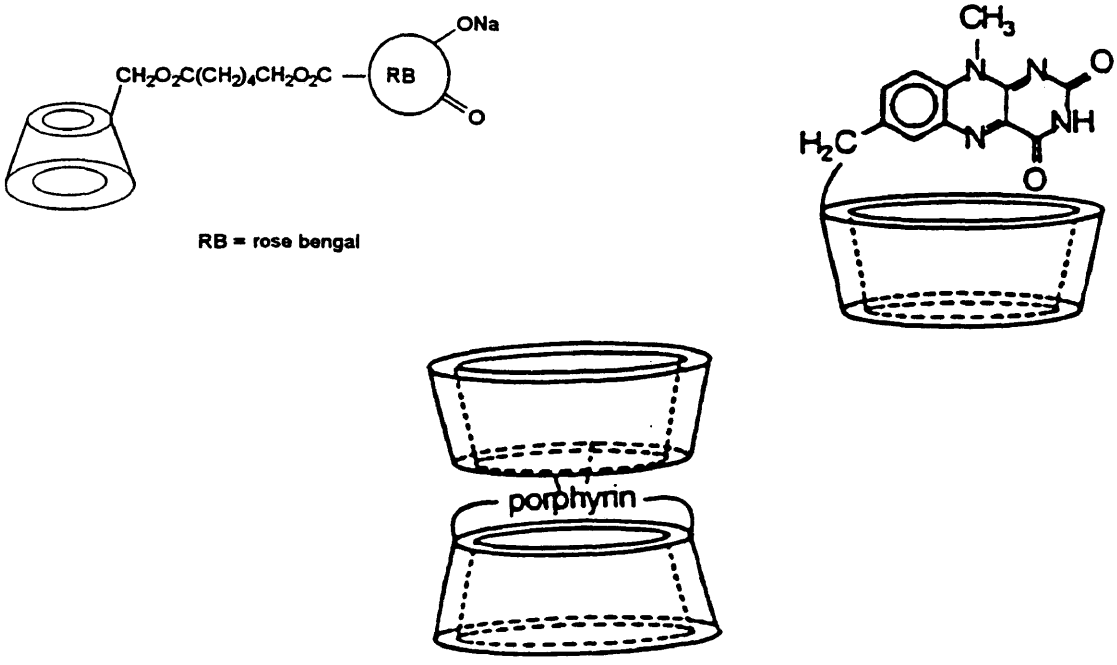


Figure 4. Some photochemically active cyclodextrin derivatives

Dicyanoanthracene

In photoinduced electron transfer oxidations, a reactant (acceptor) in solution is excited by light to enable abstraction of an electron from an encountered donor molecule.

In this work, the acceptor is the substituent attached to cyclodextrin and the donor molecule is the guest. Abelt and coworkers have previously attached anthraquinone and benzophenone functionalities to cyclodextrin, only to have the photoexcited functionality abstract hydrogen from the CD moiety.[7,8] This effectively quenched the host molecule, rendering it incapable of oxidizing the guest through electron transfer. As a result, Abelt chose to use a different functionality, 9,10-dicyanoanthracene (DCA), an electron-deficient sensitizer.[9-12] (Fig. 5) This aromatic was deemed an ideal cap/tether for two

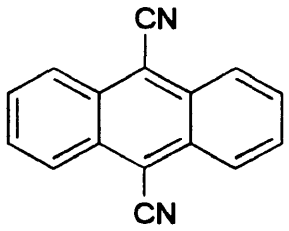


Figure 5. 9,10-Dicyanoanthracene

reasons. First, 9,10-dicyanoanthracene has a relatively low reduction potential of –0.82 V.[13] Second, DCA can be selectively excited at wavelengths longer than 400 nm.[14]

The thermodynamic Rehm-Weller equation describes the feasibility of electron transfer:

$$\Delta G \text{ (kcal/mol)} = 23.06\ (E_D^{ox} - E_A^{red} - e_o^2/a\varepsilon - \Delta E_{0,0})^{15}$$

where ΔG denotes the change in free energy; E_D^{ox} and E_A^{red} are the redox potentials of the donor and acceptor; $e_o^2/a\varepsilon$ is energy gained after bringing two radical ions to encounter distance a; ε is the dielectric constant of the solvent; and $\Delta E_{0,0}$ is the electron excitation of the acceptor or the zero-zero transition energy of the lowest excited singlet state of the acceptor. Based on the reduction potential and singlet excitation energy (2.89 eV and

66.6 kcal/mol) of DCA, electron transfers should be possible with donors whose oxidation potentials are less than ~2.0V.[16]

The Wittig Reaction

Wittig and Geissler first reported the conversion of benzophenone to 1,1-diphenylethylene using methylenetriphenylphosphorane.[17] Since then the facile conversion of a carbonyl group to a stereospecific alkene via a phosphonium ylide (known as the Wittig reaction) has been repeatedly demonstrated. (Fig. 6) The preliminary synthesis of

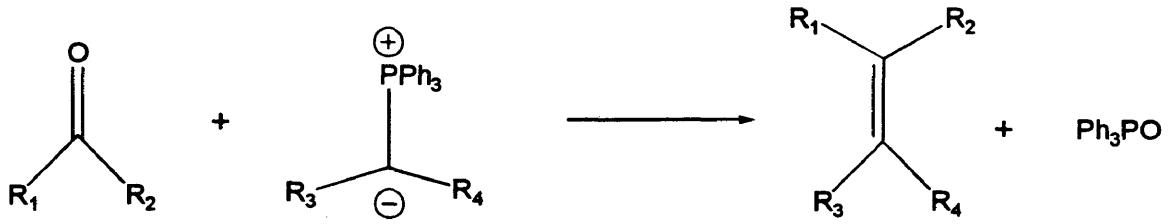


Figure 6. A general Wittig reaction- an alkylidene de-oxo bisubstitution

the phosphonium ylide involves the removal of an α-proton from the corresponding phosphonium salt using a base, whose strength depends on the acidity of the salt.[18] (Fig. 7)

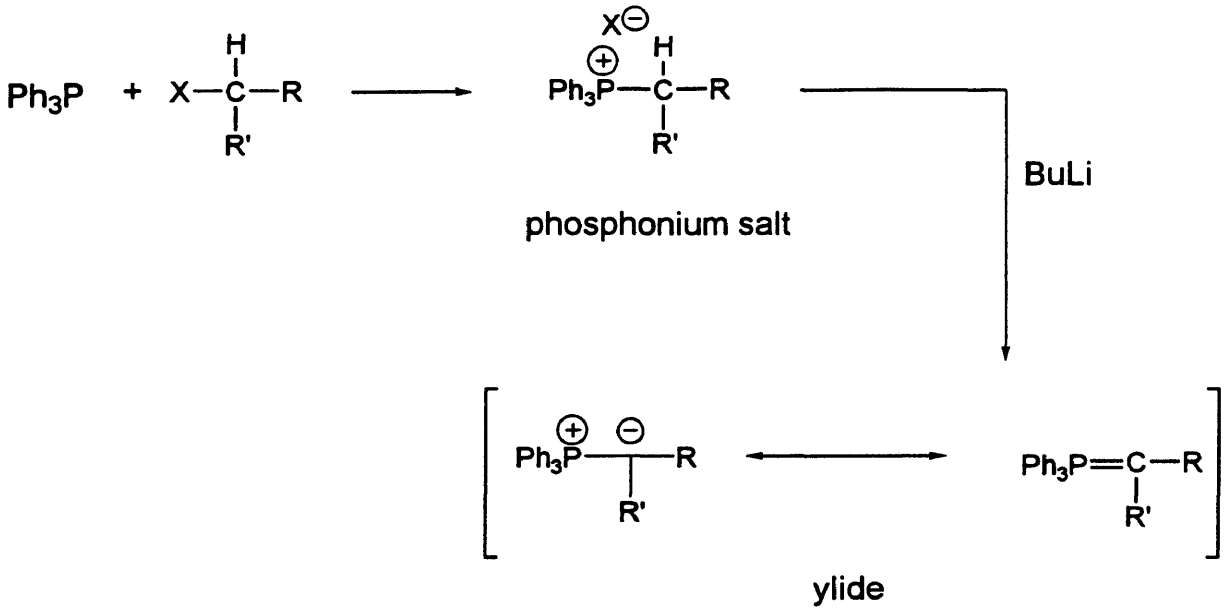


Figure 7. Ylide synthesis scheme

The ylide-anion can then perform a nucleophilic attack on the carbonyl. The initial adduct rearranges to a betaine, which then yields a phosphetan. This ultimately gives way to the alkene. (Fig. 8) Generally an unstabilized ylide is too reactive and reacts with the carbonyl

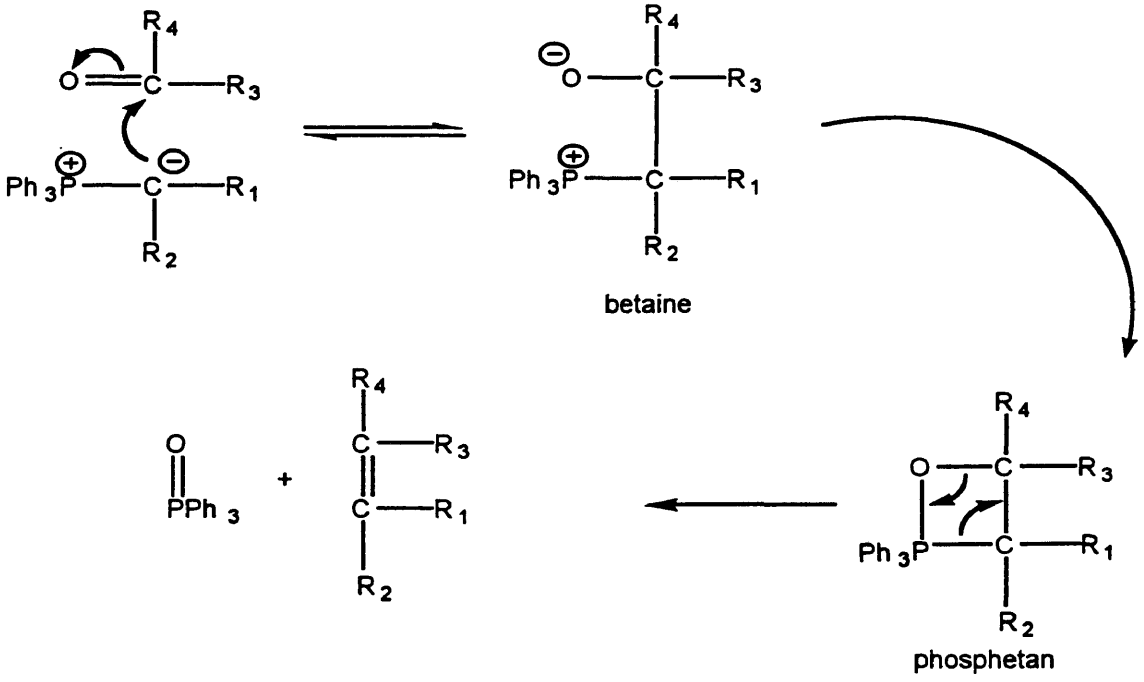


Figure 8. The Wittig reaction mechanism

group as well as water, oxygen, carbon dioxide, or alcohol. Stabilized ylides with electron-withdrawing groups in the α-position allow for reaction with aldehydes but react sluggishly and in low yield with ketones. In predicting the stereochemistry of the product, betaines with two asymmetric carbon atoms lead to two diastereomers; the more thermodynamically stable isomer will be dominant, provided that the betaine formation is reversible. This generally produces the *trans*-alkene. The amount of the *cis*-isomer can be increased using protic solvents, which decrease electrostatic interactions between the charged phosphorus and oxygen ions by solvating the oxygen anion of the betaines.

In 1997, Abelt and coworkers used the Wittig reaction to attach a 9,10-dicyanoanthracene to β-cyclodextrin with an olefinic bond.[19] (Fig. 9) The novelty of this

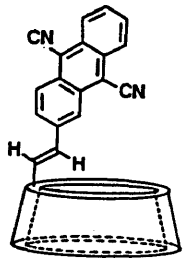


Figure 9. 6-Deoxy-6-(9,10-dicyanoanthracenyl-2-methylene)-β-cyclodextrin

application to carbohydrate chemistry was due to the difficulty one typically encounters in preventing the strongly basic ylide from reacting with the relatively acidic hydroxyl groups. A primary hydroxyl group on a glucose unit of cyclodextrin was protected as an aldehydic group, making 6-deoxy-6-formyl-β-cyclodextrin. The 2-bromomethyl-9,10-dicyanoanthracene was converted to a phosphonium salt with triphenylphosphine, and then to its corresponding ylide with potassium *t*-butoxide in dimethylsulfoxide. This

Wittig reagent was then added to the 6-deoxy-6-formyl-β-cyclodextrin *in situ*. The Wittig reaction is further explored here by similarly converting the dicyanoanthracene into an ylide and capping it to a cyclodextrin with two formyl groups.

The Nace Reaction

In 1959, Nace and Monagle found that sulfonates of primary alcohols could be reacted with dimethylsulfoxide to yield aldheydes.[20] (Fig. 10)

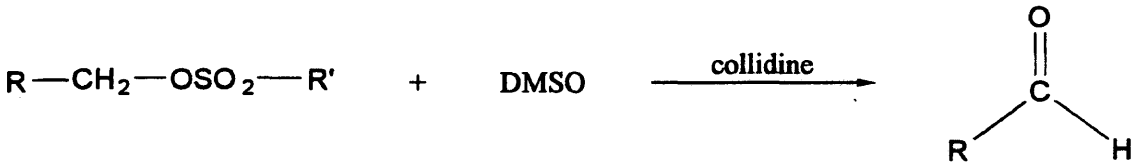


Figure 10. The general Nace reaction

In 1995, Yoon and coworkers reported the successful A,D-capping of cyclodextrin with a biphenyl-4,4'-disulfonyl.[21] After this the Nace reaction was utilized to modify the points of attachment at the cyclodextrin through the use of dimethylsulfoxide and collidine. Collidine served to abstract a proton and induce a rearrangement, which caused the exodus of the sulfonate groups and the production of aldehydic groups. (Fig. 11)

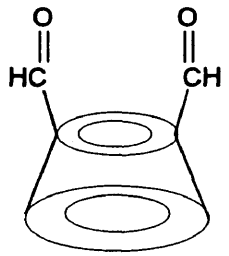


Figure 11. A,D-Diformyl-β-cyclodextrin

Ten years earlier, Tabushi et al. reported the successful A,B-regiospecific capping of cyclodextrin with a *m*-benzenedisulfonyl group.[22] (Fig 12) Based on Yoon's success,

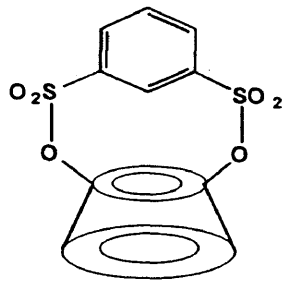


Figure 12. *m*-Benzenedisulfonyl capped cyclodextrin

a similar procedure involving the Nace reaction on Tabushi's *m*-benzene disulfonyl-capped β-cyclodextrin was attempted in order to produce A,B-diformyl β-cyclodextrin.

Experimental

β-cyclodextrin (Cerestar) was dried *in vacuo* (0.1 Torr) for twelve hours. Dimethylsulfoxide (DMSO) was distilled under reduced pressure from calcium hydride in an oil bath heated at 60°C. Chlorosulfonic acid was distilled and collected at 75 °C. Pyridine was distilled from calcium hydride, and the fraction distilling at 116 °C was collected. Collidine was fractionally distilled, and the fraction distilling at 170 °C was obtained.

Reversed phase column chromatography utilized LRP-2 C-18 bonded silica gel (37-53 μm) with gradient elution. Thirteen 100 mL solutions of acetonitrile and water were used with increasing acetonitrile content (0%, 1%, 2%, 4%, 6%, 8%, 10%, 15%, 20%, 30%, 40%, 50%, and 80%). Normal phase column chromatography utilized NP 100-200 mesh silica gel.

A Waters 244 system, equipped with an UV absorption detector (254 nm) and a Whatman Partisil 10 ODS-3 column, was used for all preparative high performance liquid chromatography. Ten minutes after sample injection, a gradient elution was applied from 17% aqueous acetonitrile to 42% over an hour.

Plates of 250 micron silica gel HLF (Uniplate™) with organic binder and UV254 were used for thin layer chromatography. A solution of *n*-butyl alcohol, ethanol, and water (5:4:3) was used for the eluant, and spots were detected using short wave UV light and vanillin.

Proton NMR studies were conducted on a GE QE-300 spectrometer.

4,6-Dimethoxybenzene-1,3-disulfonic acid

A chilled solution (-5°C) of 1,3-dimethoxybenzene (27.8 g, 0.20 mol) and methylene chloride (300 mL) was stirred while a solution of chlorosulfonic acid (35 mL, 2.5 mol) in methylene chloride (200 mL) was added dropwise over an hour. After stirring two hours at room temperature, the light purple solid (56.05 g, 0.19 mol, 94% yield) was filtered and washed with cold water (100 mL) and ether (2x100mL), and dried *in vacuo* (0.1 Torr).

4,6-Dimethoxybenzene-1,3-disulfonate dipyridinium salt

The solid 4,6-methoxybenzene-1,3-disulfonic acid (36.99 g, 124 mmol) was stirred in 186 mL of distilled pyridine for an hour, Buchner filtered, washed with ether twice (100mL), and then dried *in vacuo* (48.52 g, 129 mmol, 103% yield). ^{1}H NMR (Fig. 22)

4,6-Dimethoxybenzene-1,3-disulfonyl chloride

The dipyridinium disulfonate (2.03 g, 15.4 mmol) was mixed with PCl_5 (7.60 g, 36.7 mmol) and the reaction was heated to 60 °C for four hours. Crushed ice was added and the mixture was diluted with water (200mL). The mixture was filtered under reduced pressure, and the crude dimethoxybenzene-1,3-disulfonyl chloride was washed with cold water (100mL) and ether (2 x 100 mL) and dried *in vacuo* (4.46 g, 13.3 mmol, 86% yield). ^{1}H NMR (Fig. 23), mp. 174-178 °C

4,6-Dimethoxybenzene-1,3-disulfonyl-capped β-cyclodextrin

β-cyclodextrin (0.89 g, 0.784 mmol) was added to pyridine (50mL). Half of the solvent was distilled off and the solution was allowed to cool to 60 ° C. The dimethoxybenzene disulfonyl dichloride (0.29 g, 0.862mmol) was added to the solution and stirred for 1.5 hours at 60 ° C. After refrigeration overnight, the pyridine was distilled off under reduced pressure (0.1 Torr). The solid was collected on a Buchner funnel with acetone, and then the capped β-CD was dissolved in a minimal amount of hot water for a reprecipitation from 500 mL of acetone. The white solid was collected on a Buchner funnel, dried *in vacuo* (0.74 g, 0.57 mmol, 73 % yield) and purified via reversed phase gel chromatography. $R_f = 0.60$; ^1H NMR (Fig. 24)

A,B-Diformyl β-cyclodextrin

One gram of the capped β-CD (7.2 mmol) was dissolved in DMSO (20 ml, 7.6 mmol). Collidine (1mL) was added and the solution was heated to 135 °C for 1.5 hours. The DMSO was removed *in vacuo* to yield an orange solid. The solid was dissolved in a minimum amount of hot water and recrystallized in ethanol. The mixture was then chilled in the freezer overnight. The mixture was then Buchner filtered, and the resulting orange paste from the filter was dried *in vacuo* (0.47 g, 0.415 mmol, 58% yield).

9,10-Dicyanoanthracenyl-2,3-bis(methyl triphenylphosphonium bromide)

The 2,3-bis(bromomethyl)-9,10-dicyanoanthracene (0.32 g, 0.770 mmol) was dissolved in 75 mL of benzene under nitrogen. Recrystallized triphenylphosphine (0.40 g, 1.5 mmol)

was added and the solution was heated at reflux for three days at 100 °C. The resulting solid was then Buchner filtered to yield 0.55 g of yellow solid (0.59 mmol, 76 % yield). ^{1}H NMR (Fig. 25)

$6^A,6^B$-dideoxy-$6^A,6^B$-(9,10 dicyanoanthracenyl-2,3-dimethylene)- β- CD

The phosphonium salt (0.329 g, 0.35 mmol) was dissolved in DMSO (17 mL), under nitrogen. Potassium *t*-butoxide (0.109 g, 0.97 mmol) was added to the yellow solution, turning it green. The solution was stirred for 30 minutes. Next, the A,B-diformyl β-CD (0.55 g, 0.49 mmol) was added, and the mixture was heated and stirred overnight at 80 °C. Then the solvent was removed *in vacuo* (0.1 Torr). The Wittig-capped cyclodextrin was collected on a Buchner funnel and washed with acetone. It was dissolved in a minimum amount of hot water and reprecipitated from acetone to give 0.57 g of a black solid. The product was isolated using reversed-phase chromatography, normal phase chromatography, and high performance liquid chromatography (retention time of 24 minutes). After purification, the final mass amounted to 0.0008 g. (5.91×10^{-4} mmol, 0.2% yield). $R_f = 0.642$.

Results and Discussion

The synthetic pathway to $6^A,6^B$-dideoxy-$6^A,6^B$-(9,10-dicyanoanthracenyl-2,3-dimethylene)-β-CD was divided into three main steps. First, the β-CD needed to be modified into a precursor appropriate for the Wittig reaction, namely A,B-diformyl-β- CD. The second step required the synthesis of the cap, the ylide of 9,10-dicyanoanthracenyl-2,3-bis(methyl triphenylphosphonium bromide). In the final step, these reagents were combined together by the Wittig reaction.

In order to cap the disulfonyl chloride onto β-cyclodextrin, the precedent pathways developed by Yoon et al. and Tabushi and Nabeshima were modified.[21-22] Yoon et al. reported an A,D-cap of β-CD using a biphenyl-4,4'-disulfonyl group. He then modified the cyclodextrin derivative's sulfonyl groups to aldehydic ones in a Nace reaction. This converted the sulfonyls to aldehydic groups. Tabushi and Nabeshima capped β-CD with a benzene disulfonyl group at the adjacent hydroxyl groups (an A,B-cap). Knowing that an A,D-cap with sulfonyl linkages was modified to A,D-diformyl β-CD, and that an A,B-cap with sulfonyl linkages had been synthesized, a conversion of the A,B-cap to A,B-diformyl β-CD was proposed.

To insure an A,B modification of β-cyclodextrin, we relied on capping the CD with a derivative of *meta*-benzene disulfonyl chloride. The sulfonyl groups that attached to the primary hydroxyl groups of CD were forced to link in an A,B fashion due to their geometric constraints. Then modification of the linkages via the Nace reaction would produce adjacent aldehydes on the primary rim of cyclodextrin.

To prepare A,B diformyl β-cyclodextrin, three pathways to a *meta*-benzene disulfonyl chloride agent were attempted. The first involved the production of 4,6-dimethoxybenzene-1,3-disulfonyl chloride via the reaction of 4,6-dimethoxybenzene-1,3-disulfonic acid and thionyl chloride. The proton NMR (Fig. 26) of this confirms the desired structure. The methyl protons shift downfield to 4.20 by the electronegative oxygen. The aromatic protons, at 8.59 and 6.68, shift from their customary positions due to electron withdrawing groups (sulfonyls) and donating groups (methoxys), which alter the peak positions downfield and upfield respectively. When treated with β-CD in pyridine, the desired product could not be isolated from the resulting mixture.

A second pathway, capping β-cyclodextrin with *meta*-benzene disulfonyl chloride, was investigated. The disulfonyl chloride was synthesized via the reaction of 1,3-benzenedisulfonic acid disodium salt with thionyl chloride. Proton NMR (Fig. 27) verified the structure of the product. The C2 (Fig.13) aromatic proton singlet peak at

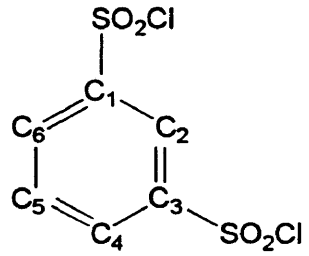


Figure 13. *meta*-Benzene disulfonyl chloride

8.69 shifts furthest downfield (8.69) because of its position between both sulfonyl groups. The other protons at the C4 and C6 positions (8.43) are identical and are expected to be split into doublets by the C5 proton. Due to fine coupling, the doublets are further split. The C5 proton is a triplet (7.99) due to coupling with the C4 and C6 protons. Capping

this disulfonyl chloride onto cyclodextrin was unsuccessful because of the hydrolytic lability of the sulfonyl groups, which occurred similarly in a cyclodextrin derivative synthesized by Abelt and coworkers in the past.[10]

The third pathway, which involved the preparation of 4,6-dimethoxybenzene-1,3-disulfonic acid (Fig. 14), was performed according to a literature method. The acid's

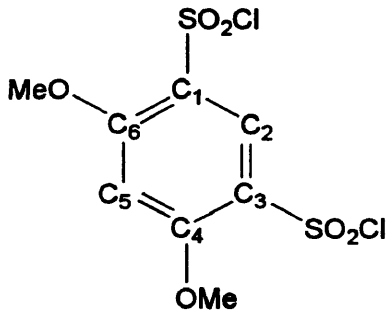


Figure 14. 4,6-Dimethoxybenzene-1,3-disulfonyl chloride

conversion to a disulfonate and ultimately 4,6-dimethoxybenzene-1,3-disulfonyl chloride was also accomplished using the aforementioned source. In this mechanism (Fig. 15), a double bond of the ring attacks the sulfur of chlorosulfonic acid, and displaces chloride. The cyclohexadienyl ring is stabilized by the electron-donating resonance of the methoxy groups. This chlorine then abstracts the proton connected to the carbon with the sulfur bond. This substitution is repeated at the C4 or C6 position of the benzene ring to yield 4,6-dimethoxybenzene-1,3-disulfonic acid (94% yield).

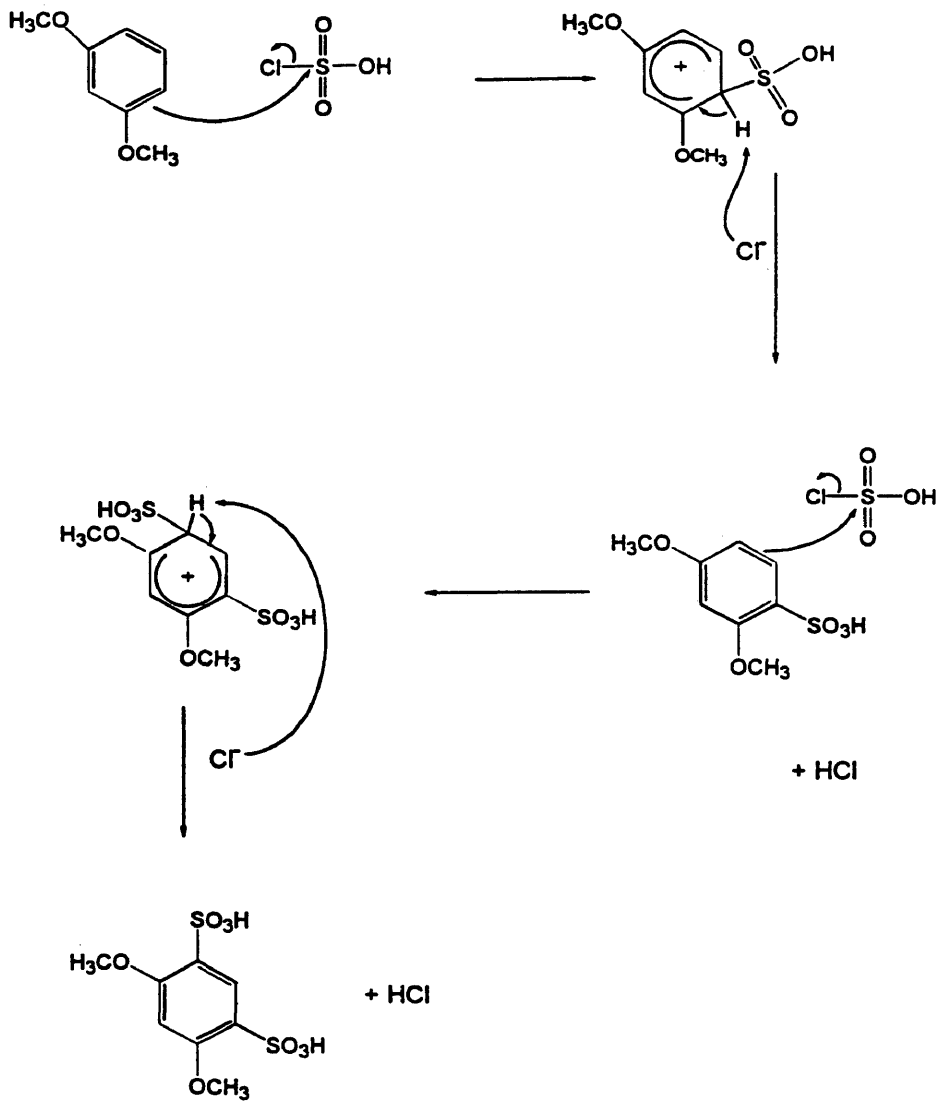


Figure 15. Synthesis of 4,6-dimethoxybenzene-1,3-disulfonic acid

The conversion of the disulfonic acid to a disulfonate salt (Fig. 16) involves the addition of pyridine, whose nitrogen lone pair abstracts a hydrogen from the hydroxyl groups at each sulfur (undried yield 103 %). These protons are acidic due to the resonance of the sulfonate group. The NMR (Fig. 22) reveals pyridinium protons far downfield at 8.01, 8.52 and 8.92; methyl protons as a large singlet at 3.73; and aromatic protons at 6.48 and 8.07. As before, the C5 proton shifts downfield by the sulfonyl group and the C2 proton shifts upfield by electron donating methoxy-substituents.

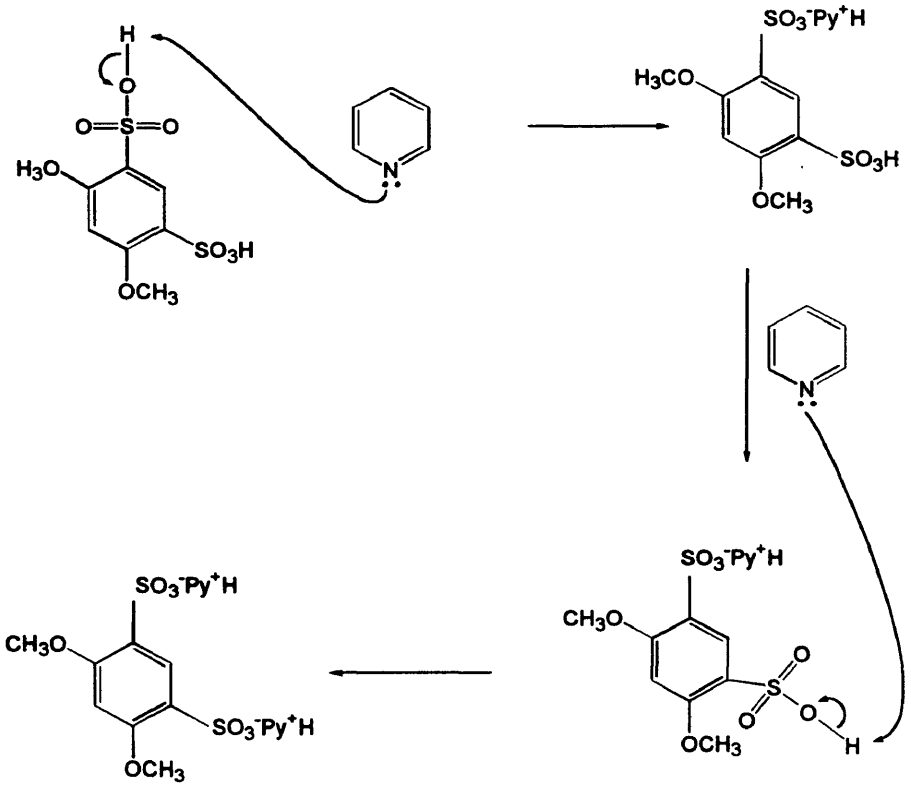


Figure 16. Synthesis of 4,6-dimethoxybenzene-1,3-disulfonate

To finally modify the disulfonate to disulfonyl chloride, a strong chlorinating agent, PCl_5, was used. (Fig. 17) The nucleophilic sulfonate anions attack phosphorus in a substitution reaction to displace a chloride. This chloride then attacks the sulfur to produce a phosphorus-oxygen double bond. As a result, another chloride is released from the PCl_4 functionality. This process is repeated with the remaining sulfonate group to give 4,6-dimethoxybenzene-1,3-disulfonyl chloride in a 86% yield. An NMR (Fig. 23) similar to that from the first synthetic pathway shows peaks at 8.58, 6.67, and 4.20.

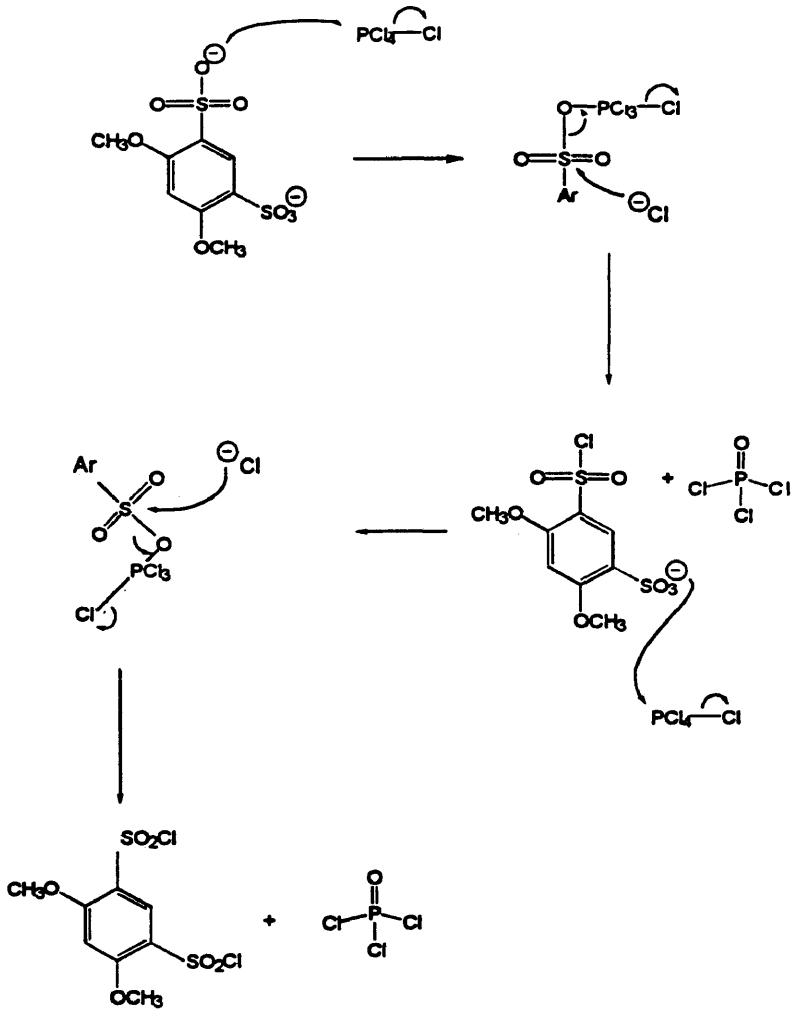


Figure 17. Synthesis of 4,6-dimethoxybenzene-1,3-disulfonyl chloride

The next phase of creating the β-CD precursor requires attaching the 4,6-dimethoxybenzene-1,3-disulfoyl chloride to β-CD. (Fig. 18) In this pathway, the nucleophilic pyridine bonds to sulfur and displaces chloride. A lone pair of electrons on an alcoholic oxygen of cyclodextrin serve to create a bond to the same sulfur, forcing pyridine to exit. The oxonium is then deprotonated by pyridine. This results in a sulfonyl tether of the disulfonyl chloride to β-cyclodextrin. Repeating this process yielded a capped β-CD derivative, which was analyzed via NMR (Fig. 24) after being isolated

through flash chromatography. The two aromatic peaks appear at 8.13 and 7.00 while the methoxy protons are at 4.09 and 4.05. The protons on the cyclodextrin's core structure appear at 3.57 and 3.36. On a thin layer chromatography plate, a spot with a ratio-to-front average of 0.60 was exhibited.

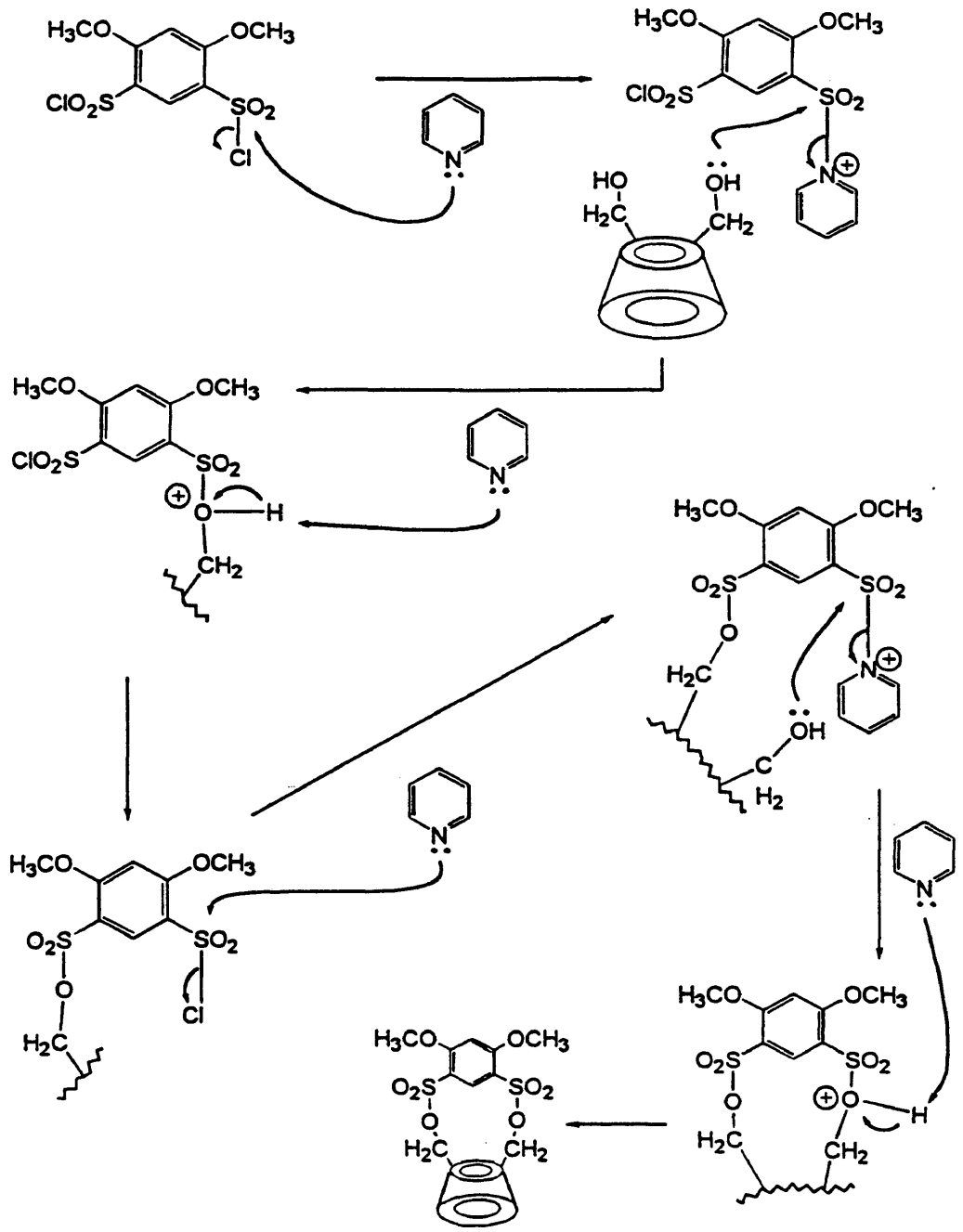
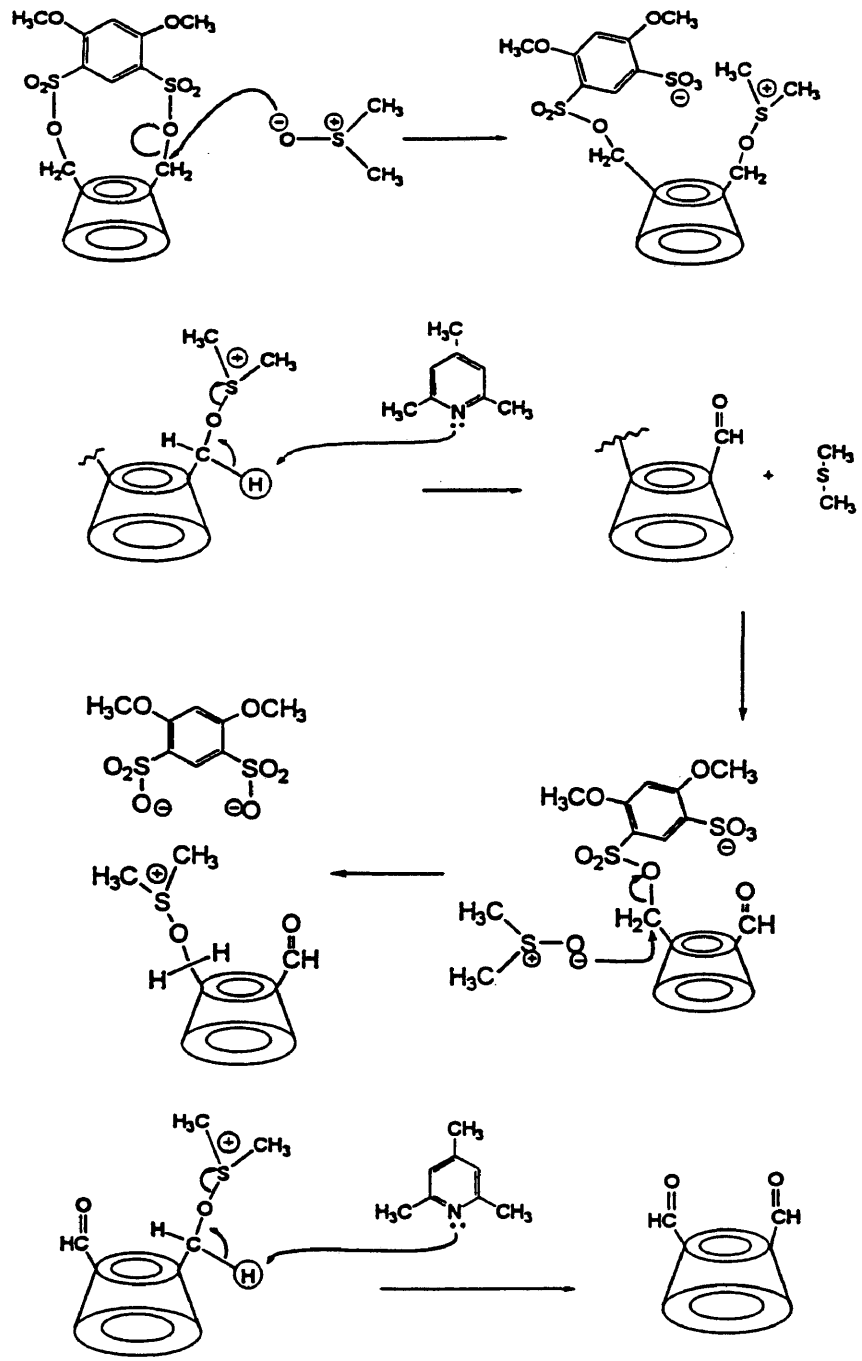


Fig. 18 Synthesis of 4,6-dimethoxybenzene-1,3-disulfonyl-capped β-cyclodextrin

The final phase of producing A,B-diformyl β-CD involved the Nace reaction. (Fig. 19) A resonance form of DMSO with an anionic oxygen attacks the carbon bonded to a sulfonate. The sulfonate is displaced and a repetition of this step uncaps the cyclodextrin. The lone pair of collidine abstracts a proton from this same carbon. This reaction produces an aldehyde and a dimethylsulfide as byproduct. Repetition of this process gives the desired A,B-diformyl β-cyclodextrin (58% yield). This product was not purified further, and, as a result, this may have contributed to the final product's low yield (see p.26).

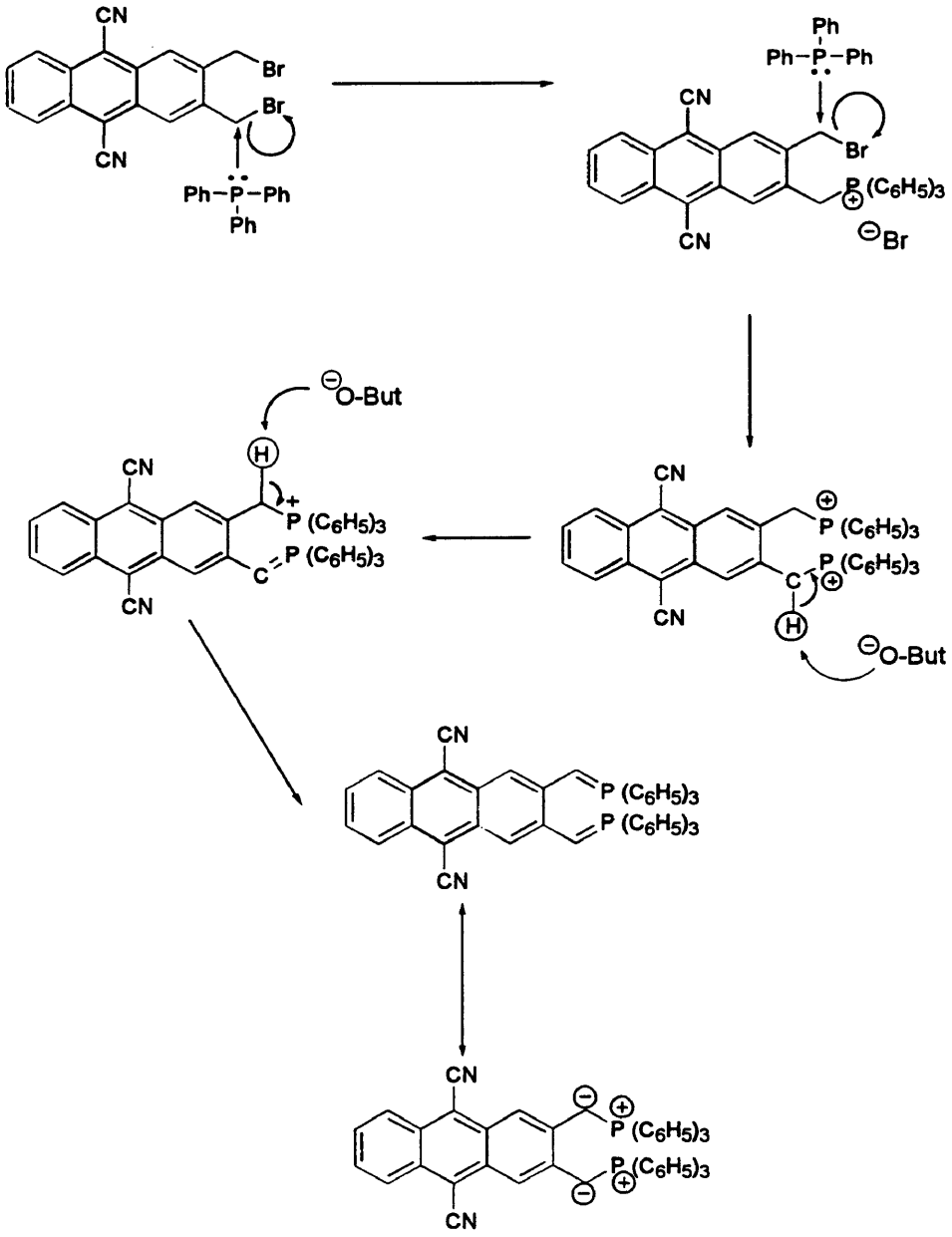
Figure 19. Synthesis of A,B-diformyl-β-cyclodextrin



The second step (synthesis of the Wittig capping agent) of the overall pathway was based on a similar construction of 9,10-dicyanoanthracenyl-2-methyl triphenylphosphonium bromide.[17] An alteration was made by doubling the quantity of

triphenylphosphine to create a bis-phosphonium salt. The phosphorus lone pair of triphenylphosphine attacks the brominated carbons of 2,3-bis(bromomethyl)-9,10-dicyanoanthracene to produce a salt. (Fig. 20) The *t*-butoxide then removes a hydrogen from the carbons to produce the ylide. A proton ^{1}H NMR (Fig. 25) of the ylide capping reagent (76% yield) verified the desired structure, as exemplified by peaks at 7.72, 7.83, and 7.99. The peak at 5.07 indicates a small amount of starting material remaining. The peak at 7.99 indicates aromatic hydrogens of DCA, and the remaining multiplets (7.83 and 7.72) point to the hydrogens of triphenylphosphine or hydrogens of 9,10-dicyanoanthracene.

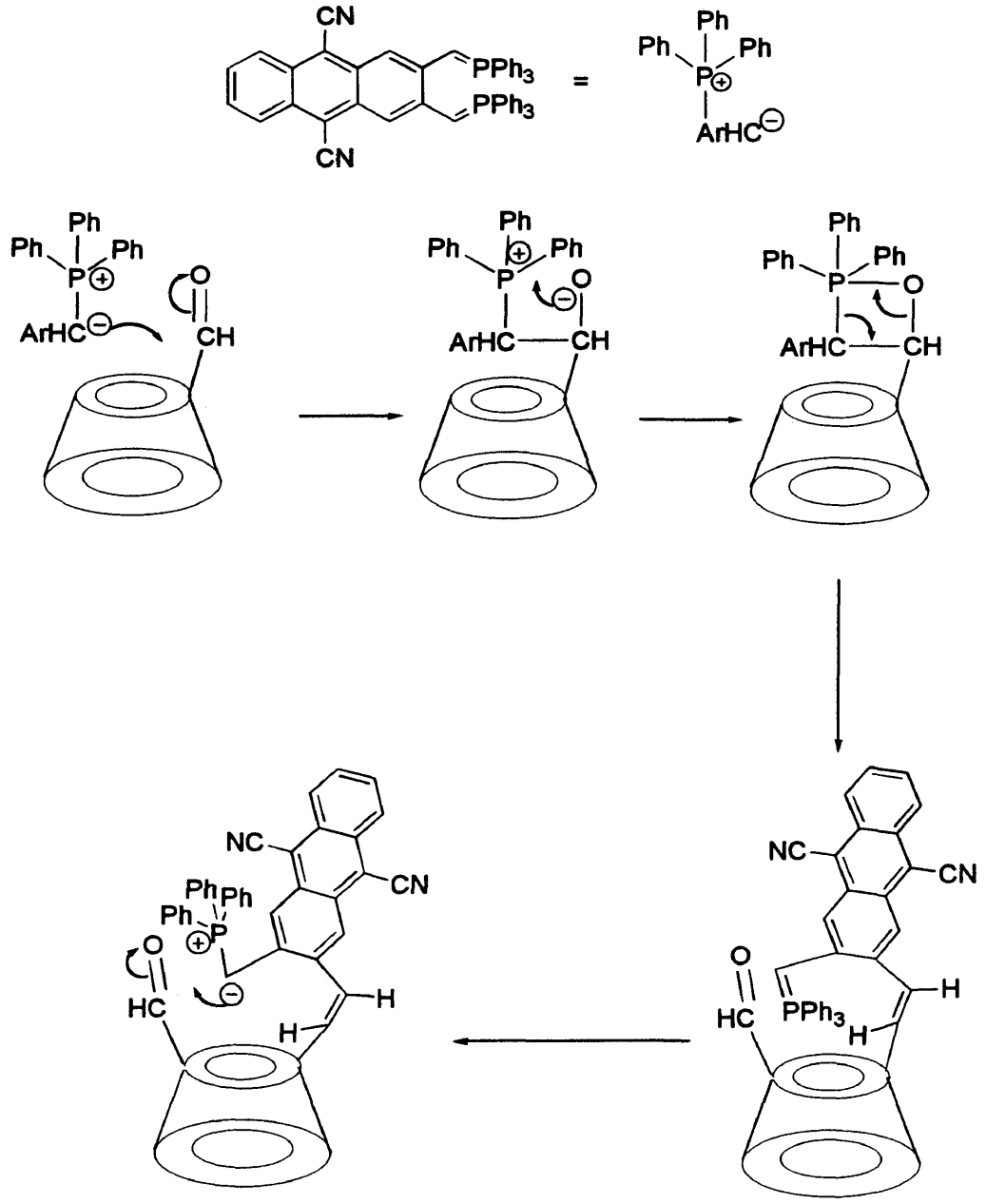
Figure 20. Synthesis of 9,10-dicyanoanthracenyl-2,3-bis(methyl triphenylphosphonium bromide)



The final step of attaching the ylide capping reagent to A,B-diformyl β-CD proceeded through the Wittig reaction. (Fig. 21) The bis-ylide reacts with the dialdehyde

in a multi-step synthesis. A betaine is produced when the lone pair of the carbanion adds to the carbonyl carbon, while an anionic oxygen is produced by a migration of the carbon-oxygen π-bond. One of the anionic oxygen lone pairs then serves to bridge phosphorus and oxygen together, yielding the phosphetan. The phosphetan then suffers fragmentation to produce a triphenylphosphine oxide and an olefinic bond between the two carbons. This process is repeated at the other aldehyde to give the capped final product, which is in the *E*-configuration due to the ylide's stabilization by the cyano groups. The low (0.2 %) yield can be attributed to impurities in both reagents (the dialdehyde and DCA). However, a small yield is expected since Abelt and coworkers were only able to produce a 20 % yield of the analogous olefinic tether. Squaring this yield provides a rough estimation (4 %) of the theoretical yield. The yellow hue of the final product *in situ* and its similar retention time to Abelt's 6-deoxy-6-(9,10-dicyanoanthracenyl-2-methylene)-β-cyclodextrin on the preparative HPLC grant a fair degree of confidence in this product. The possibility exists that the A,B-diformyl cyclodextrin could possibly contain only one aldehyde group and that only a single tether was created.

Figure 21. $6^A,6^B$-dideoxy-$6^A,6^B$-(9,10-dicyanoanthracenyl-2,3-dimethylene)-β-cyclodextrin



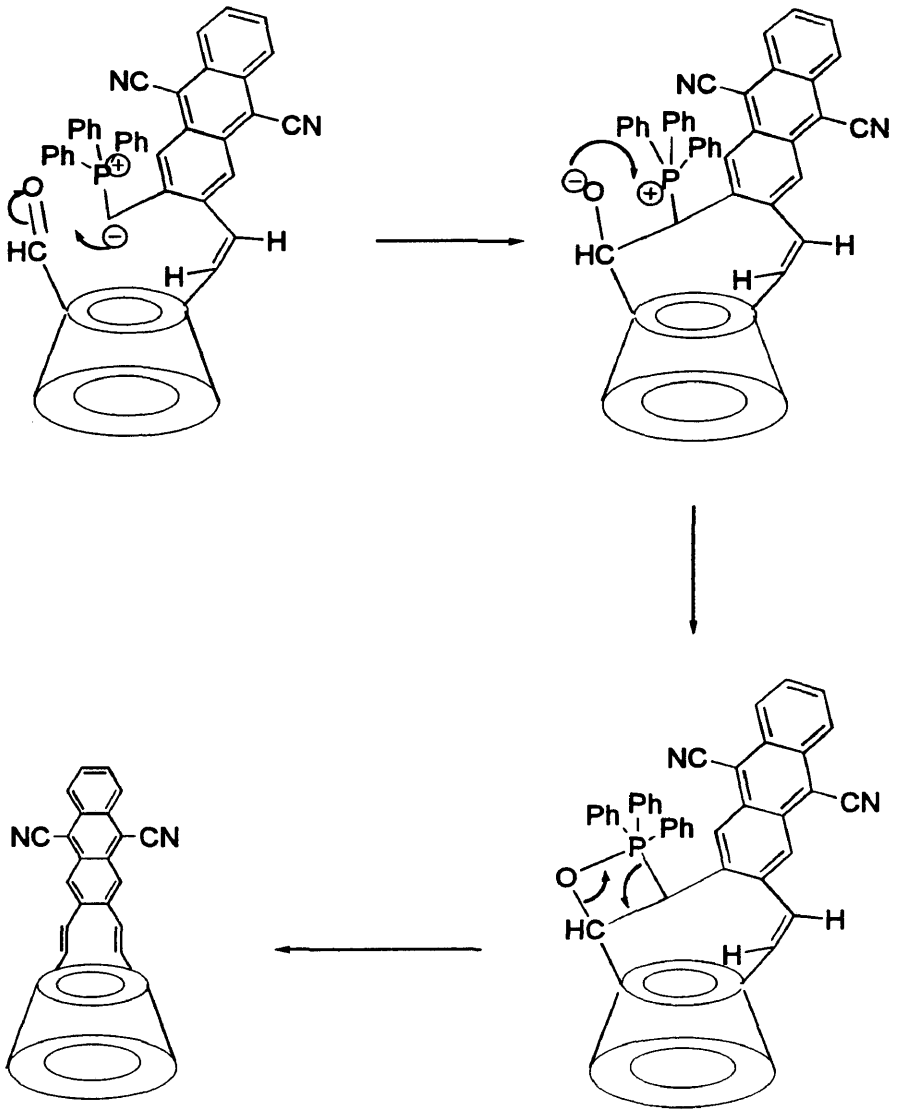


Figure 21. $6^A,6^B$-dideoxy-$6^A,6^B$-(9,10 dicyanoanthracenyl-2,3-dimethylene)-β-cyclodextrin (continued)

Conclusion

Although results are preliminary, synthesis of $6^A,6^B$-dideoxy-$6^A,6^B$-(9,10-dicyanoanthracenyl-2,3-dimethylene)-β-CD appears successful. To improve upon the research, the reaction needs to be scaled up. Second, faster, more efficient and effective ways of isolating the intermediates and reagents (4,6-dimethoxybenzene-1,3-disulfonyl-capped β-cyclodextrin, A,B-diformyl β-cyclodextrin, and the ylide of the dicyanoanthracene derivative) are necessary to streamline the process. Afterwards, the ability of the final product to act as a host would need to be assessed using fluorescence binding studies. Additional caps and tethers attached with an olefinic bond (via the Wittig reaction) at either face of the cyclodextrin need to be investigated.

Figure 22. ^{1}H NMR of 4,6-dimethoxybenzene-1,3-disulfonate dipyridinium salt in DMSO-d_6

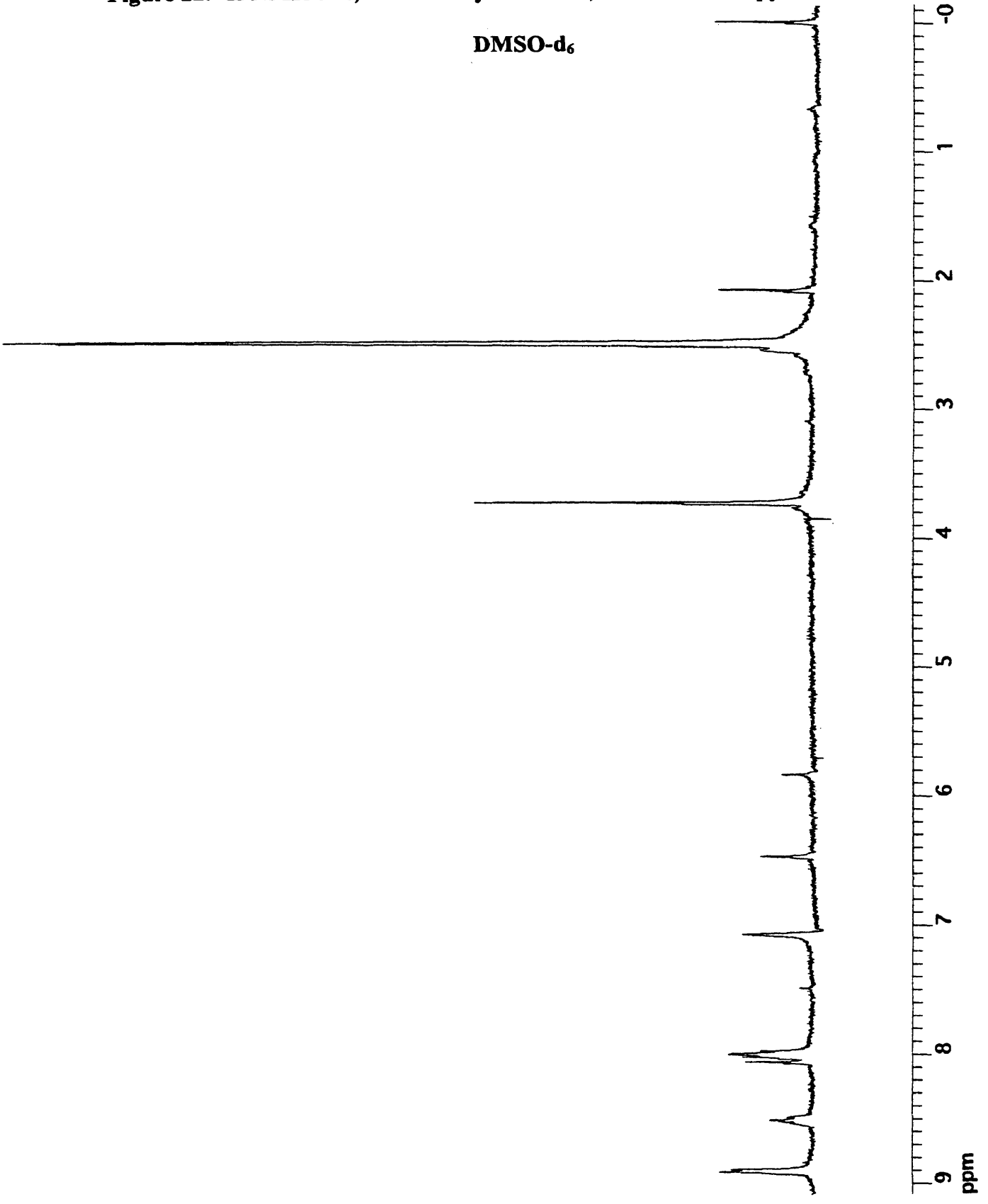


Figure 23. ^{1}H NMR of 4,6-dimethoxybenzene-1,3-disulfonyl chloride in $CDCl_3$

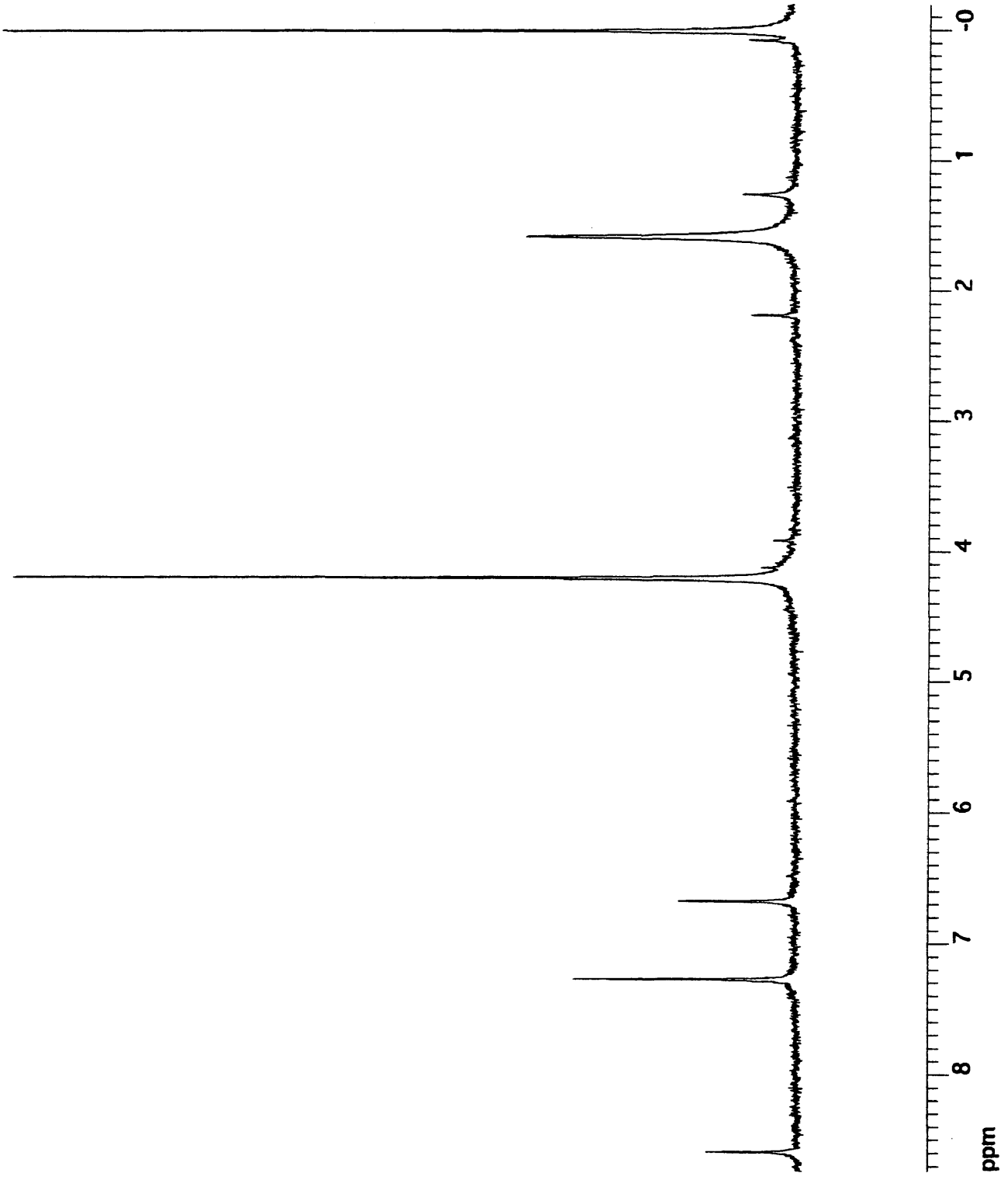


Figure 24. ^{1}H NMR of 4,6-dimethoxybenzene-1,3-disulfonyl-capped β-cyclodextrin in DMSO-d_6

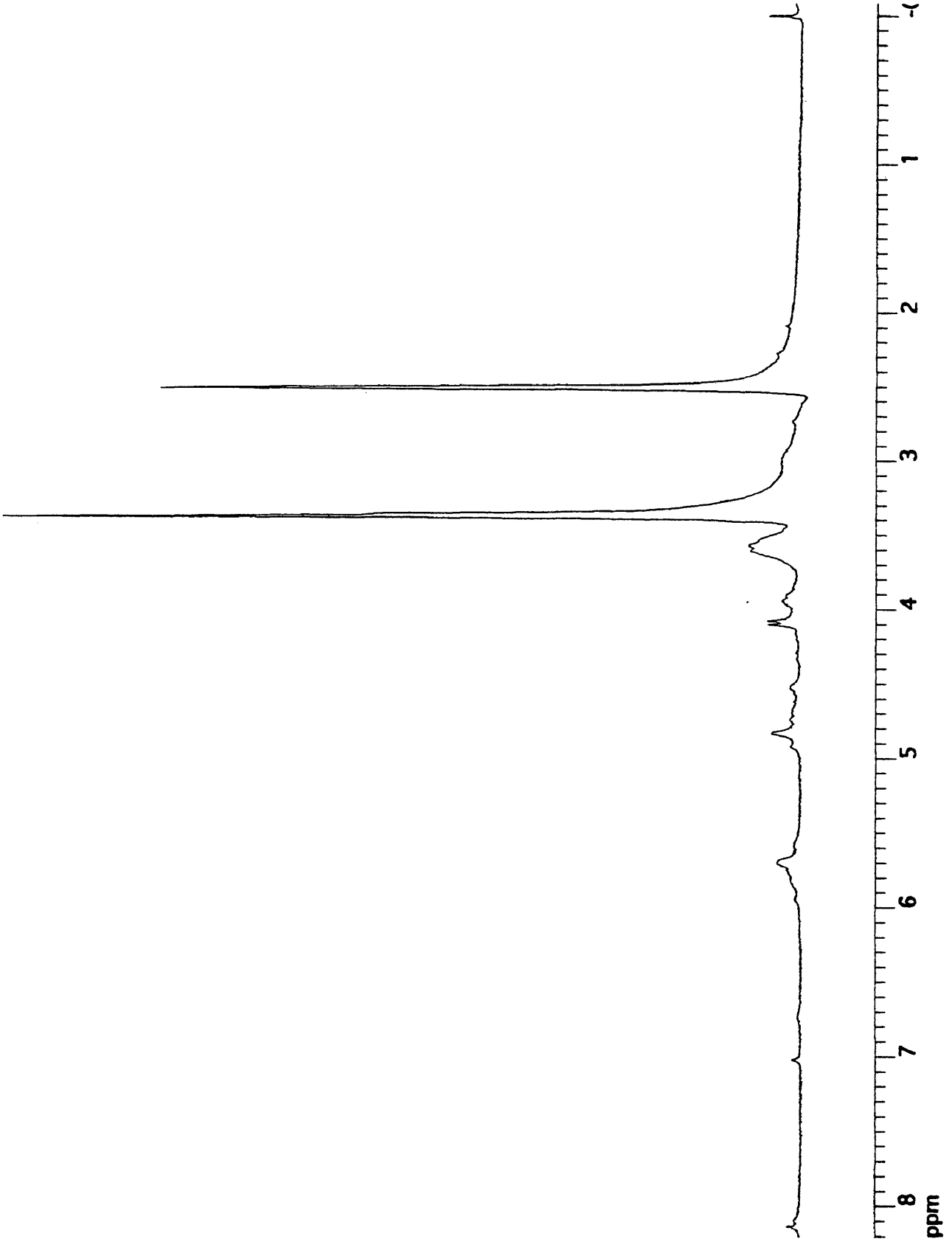


Figure 25. ^{1}H NMR of 9,10-dicyanoanthracenyl-2,3-bis(methyl triphenylphosphonium bromide) in $CDCl_3$

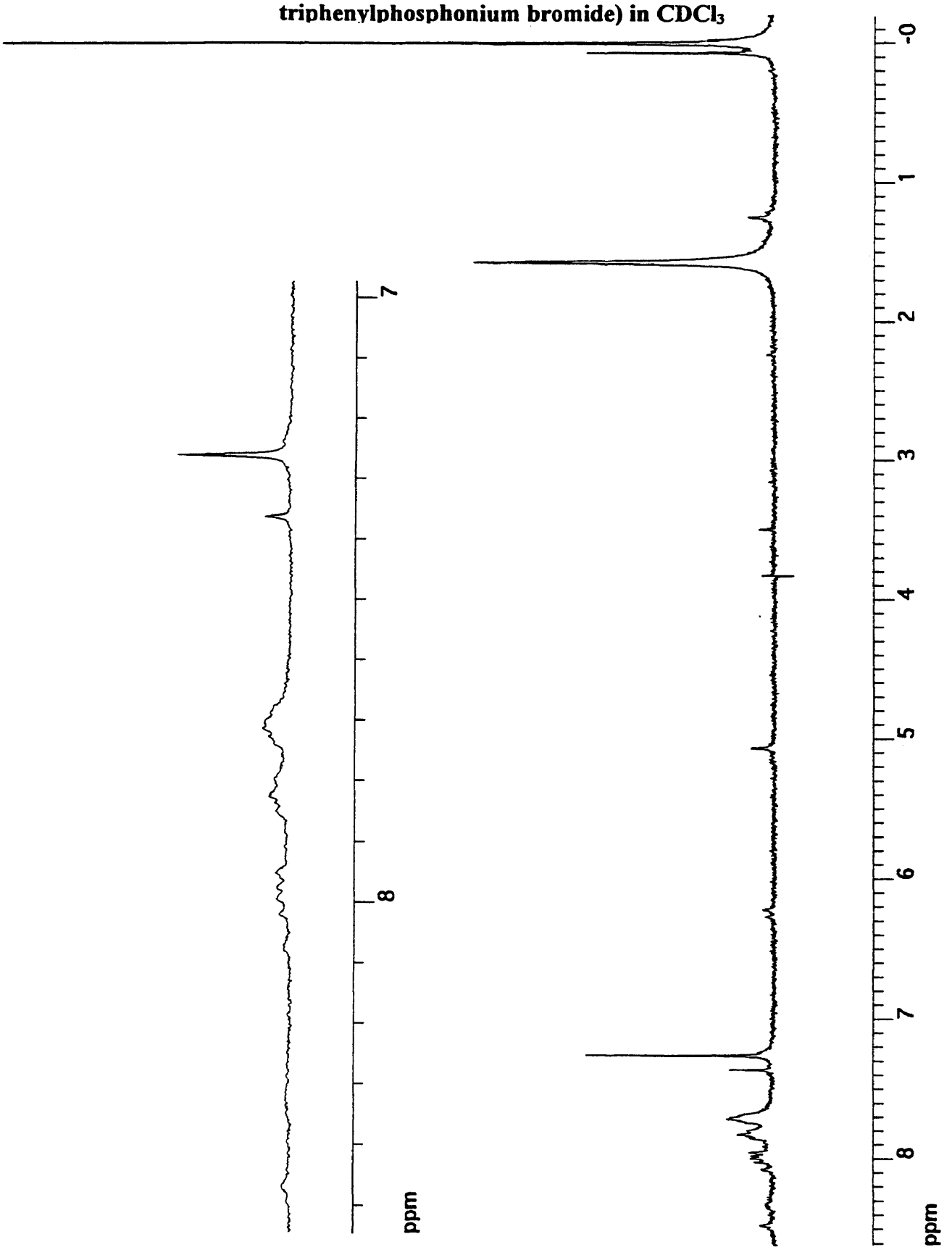


Figure 26. ^{1}H NMR of 4,6-dimethoxybenzen-1,3-disulfonyl chloride (from the first synthetic pathway) in $CDCl_3$

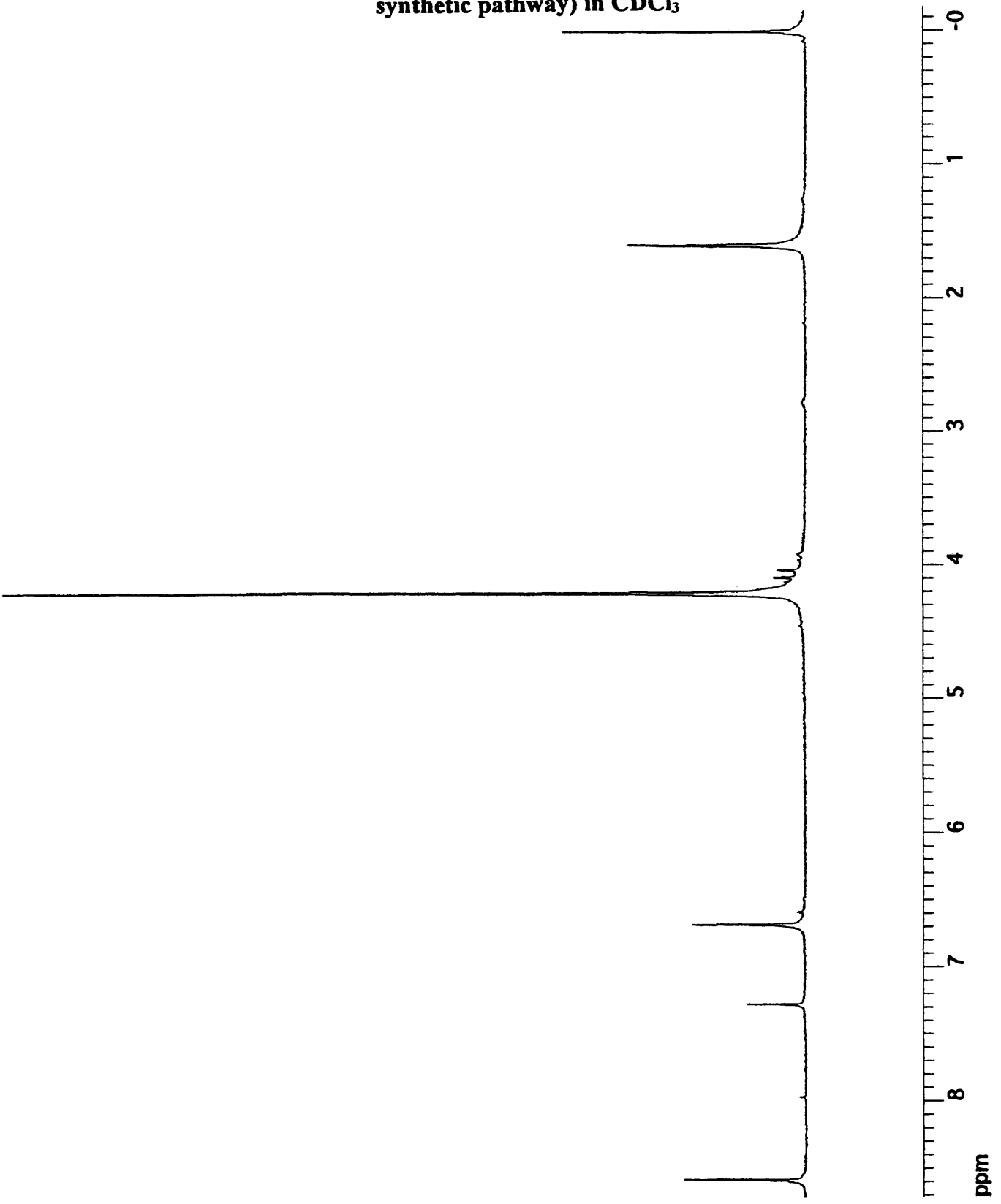
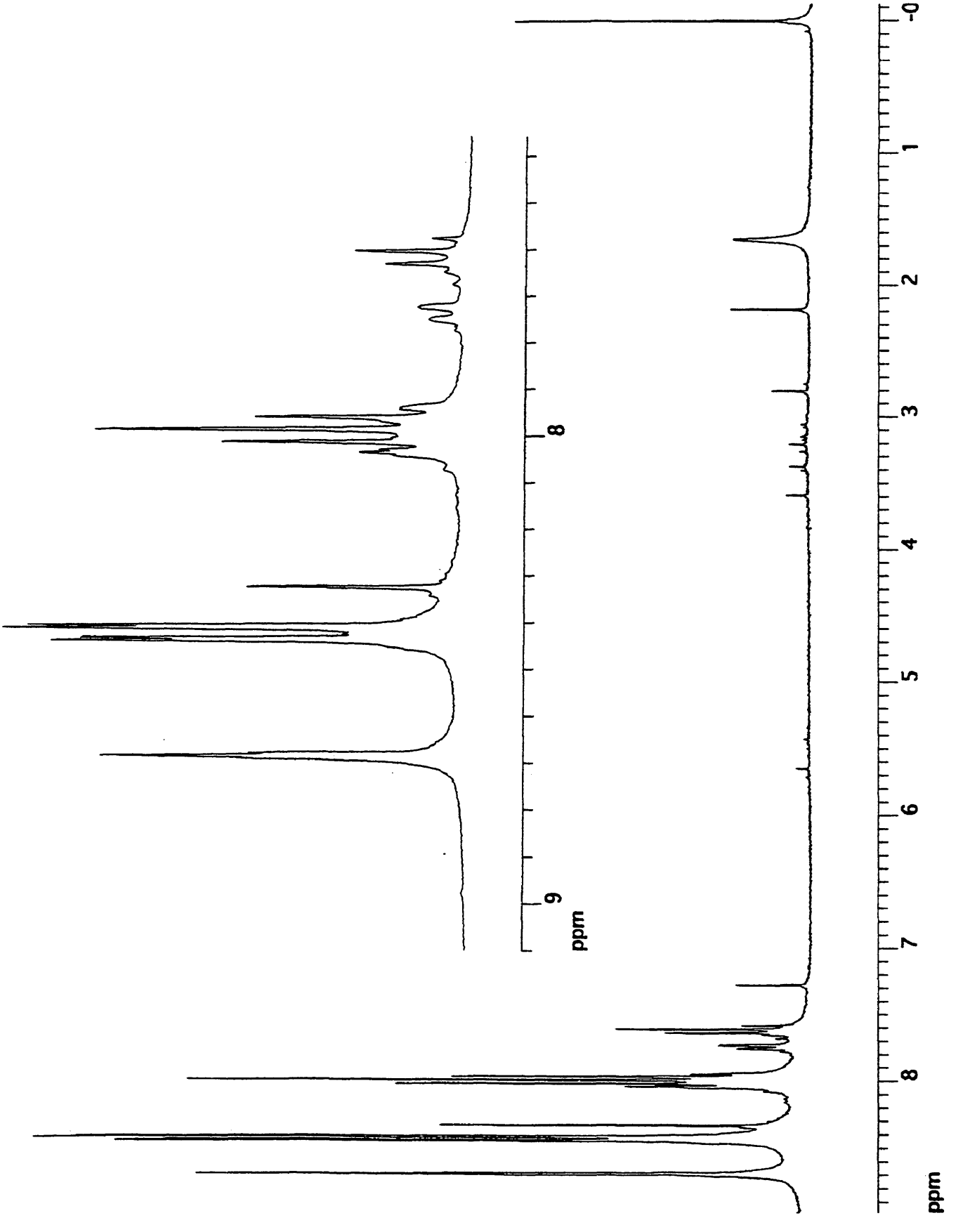


Figure 27. ^{1}H NMR of *meta*-benzene disulfonyl chloride in $CDCl_3$



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