DENDRIMER ASSEMBLY
VIA
NON-COVALENT INTERACTIONS

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B.S. in Chemistry, Boğaziçi University, 2005

Submitted to the Institute for Graduate Studies in
Science and Engineering in partial fulfillment of
the requirements for the degree of
Master of Science

Graduate Program in Chemistry
Boğaziçi University
2009

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ACKNOWLEDGEMENTS

First of all, I am grateful to my thesis supervisors Assist. Prof. Rana SANYAL and Assist. Prof. Amitav SANYAL for their guidance, suggestions and for all the support. I also extend my thanks to them for giving me the opportunity to work in their lab where I have learned and enjoyed so much.

I wish to express my thanks to Prof. İlknur DOĞAN, Prof. Safiye ERDEM, Prof. Selim KÜSEFOĞLU for their careful and constructive review of the final manuscript.

I would like to extend my thanks to Burcu SELEN ÇAĞLAYAN and Ayla TÜRKEKUL for their patience and help in running NMR experiments supporting my laboratory work.

I would also like to thank to Özge ÜNAL, A. Neren ÖKTE and Şerife AKALIN for their helps during running my UV-Vis experiments

I would also want to thank the entire chemistry department for supplying me this much of a fun and home like place.

Finally my deepest thanks go to my whole family and all my friends for their endless love

And ultimately, I would want to thank to all of the former and present SANYAL lab members for giving their friendships and coffee :D

This research has been supported by Bogaziçi University (BAP 08B505, 07HB502, 07M105), TÜBİTAK (105S353).

ABSTRACT

DENDRIMER ASSEMBLY VIA NON-COVALENT INTERACTIONS

Dendrimers are monodisperse and highly branched macromolecules which are built around a core. The segments that combine to form a dendrimer are called dendrons. The synthesis of dendrimers can be undertaken in a manner that all dendrons are grown from the core molecule. As an alternative, dendrons can be synthesized separately and later combined with a multivalent core molecule to obtain the dendrimer. The number of multivalency of the core determines the number of segments in the dendrimer. The attachment of the dendron segments to the core unit can be via a covalent or non-covalent interaction.

Non-covalent interactions based on hydrophobic effect can be exploited to yield a supramolecular dendrimer assembly. Assembly of dendrons in aqueous environment can be achieved by attachment of functional groups capable of forming host-guest complex at the focal point of the dendrons. Cyclodextrins having a hydrophobic interior cavity are capable of making supramolecular host-guest interactions with appropriate guests. A well known example is the inclusion complex of β-cyclodextrin and adamantane.

Two different types of dendrons were synthesized and functionalized with β-cyclodextrin and adamantane respectively. The adamantane containing polyester dendrons were synthesized using divergent synthesis. Novel methodology involving copper catalyzed Huisgen type Click chemistry was utilized to obtain the cyclodextrin containing polyether dendrons. Self-assembly of dendrons to provide segment-block dendrimers in aqueous environment was successfully demonstrated.

ÖZET

KOVALENT OLMAYAN ETKİLEŞİMLERLE DENDRİMER OLUŞUMU

Dendrimerler bir çekirdek etrafinda yapılanan, yüksek derecede dallanmış, tek dağılımlı moleküllerdir. Dendrimeri oluşturan parçalar dendron olarak adlandırılırlar. Genel kanı olarak dendrimerlerin, bütün dendronların tek bir çekirdek etrafında büyüyerek sentezlendiği düşünülür. Alternatif bir yol olarak dendronların ayrı ayrı sentezlenip daha sonra çok değerli bir çekirdek etrafinda birleştirilmesiyle de sentezlenebilirler. Çekirdekteki değerlik sayısı dendrimerdeki parçacık sayısını belirler. Dendronların çekirdeğe bağlanma biçimleri hem kovalent bir yolla hem de kovalent olmayan etkileşimler ile olabilir.

Hidrofobik etkileşimlere dayalı kovalent olmayan etkileşimlerden faydalanarak supramoleküler dendrimer oluşumu sağlamak mümkündür. Sulu ortamda dendronların bu oluşumu sağlamaları, dendronların odak noktalarına biri diğerinin içine girebilecek fonksiyonel gruplarin bağlanmasıyla başarılabilir. Hidrofobik iç boşluğa sahip olan siklodekstrinler bahsi geçen kompleksi uygun moleküller ile yapabilme yetisine sahiptirler.Bu çesit kompleksleşme alanında en bilinen örnek β-siklodekstrin ve adamantanın yaptığıdır.

İki farklı dendron sentezlenmiş ve sırasıyla β-siklodekstrin ve adamantan ile fonksiyonelleştirilmiştir. Adamantan barındıran poliester dendronları içten dışa sentez metoduyla sentezlenmiştir. Özgün bir metot olan bakır katalizörlü Huisgen tipi Klik kimyası kullanılarak, β-siklodekstrin barındıran poliaril eter dendronları sentezlenmiştir. Sulu ortamda, parça bloklu dendrimerlerin, oluşumunun dendronların kendiliğinden bir araya gelmesi yolu ile gerçekleştiği başarı ile gösterilmiştir.

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LIST OF ABBREVIATIONS

ACN	Acetonitrile
Bis-MPA	2,2-bis(hydroxymethyl)propionic acid
β-CD	Beta-Cyclodextrin
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
D_2O	Deuterated water
DCC	Dicyclohexylcarbodiimide
DMAP	N,N Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl Acetate
FT-IR	Fourier Transform Infrared
HPLC	High Performance Liquid Chromatography
MeOH	Methanol
NMR	Nuclear Magnetic Resonance
PAMAM	Polyamidoamine
PEG	Poly(ethylene glycol)
py	Pyridine
TEA	Triethylamine
TEG	Triethyleneglycol
THF	Tetrahydrofuran

1. INTRODUCTION

1.1. Dendrimers

Dendrimers are monodisperse globular macromolecules that are built around a core with successive geometrically symmetric branching units [1]. When divided into segments the central part is the core and the outer part is the periphery and each branching unit building the structure from the core to the periphery is the indication of generation (Figure 1.1). In Figure 1.1 two generations are designated, namely first generation (G-1), and second generation (G-2).

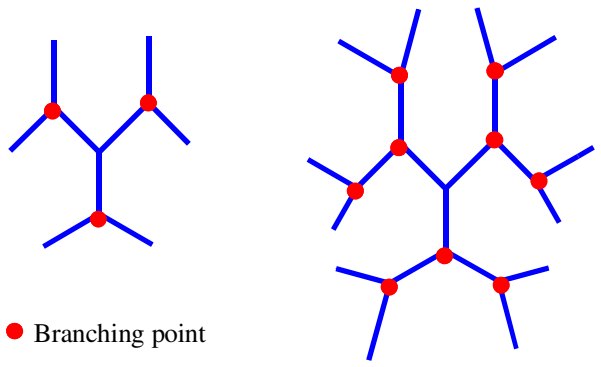


Figure 1.1. Dendrimers

A part of a dendrimer starting from a core and ending at the periphery is called a dendron. The generations of dendrons are defined exactly in the same way that of a dendrimer (Figure 1.2). Dendrons can be synthesized by two methods, one beginning from the peripheral unit and building through the inner part, focal point, and one beginning from a focal point and growing through the periphery. The first method is called as convergent synthesis and the latter method called divergent synthesis of a dendron. Also some has an

interesting property of being able to be synthesized by both of the routes that is in interest [2], [3].

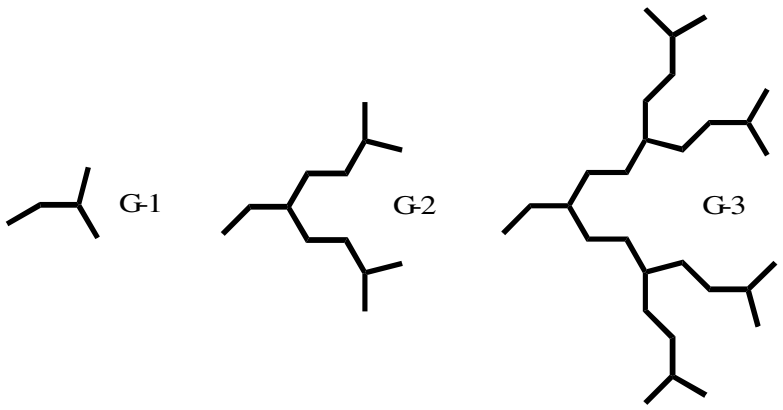


Figure 1.2. Generations of dendrons

Dendrons that are synthesized using either the convergent or the divergent route can be combined together to form a dendrimer. The selection of dendrons that combine to form a dendrimer results in the formation of a symmetrical dendrimer, or an unsymmetrical dendrimer. This combination of dendrons can be either via covalent bond forming reaction between their focal points or via non-covalent interactions.

1.2. Dendrimers Formed by Covalent Bonds

Dendrimer can be built by combination of dendrons by a reaction between their focal points which bears specific reactive groups. Most of the time the synthesis of the dendrons does not include this reactive units at the focal point. However another functionizable group that doesn't interfere with the growing synthesis of the dendron, ensures the further functionalization of the focal point to the desired functionality.

1.2.1. Irreversible Covalent Bonding

Dendrimers can be synthesized by choosing the covalent bond between the focal points of dendrons to be reversible or irreversible. Such a choice provides dendrons that are either thermally stable or unstable. Unless thermoreversibility is desired, dendrons are linked by non-reversible covalent bonds. Lee *et. al.* has shown a (1,3) Huisgen dipolar cycloaddition reaction between a polyarylether dendron and a polyamidoamide (PAMAM) dendron to form an orthogonal unsymmetrical dendrimer [4]. This reaction is carried out between an azide group bearing polyarlyether dendron **1** and an acetylene group bearing PAMAM dendron **2**. The resulting dendrimer **3** has an irreversible covalent bond (Figure 1.3). The further orthogonal multifunctionalization can be succeeded by the formation of the orthogonal unsymmetrical dendrimer, as an advantage.

Another important property that (1,3) Huisgen cycloaddition offers is that the reaction conditions are mild enough to serve the availability of usage of any biological unit carrying dendrons [5].

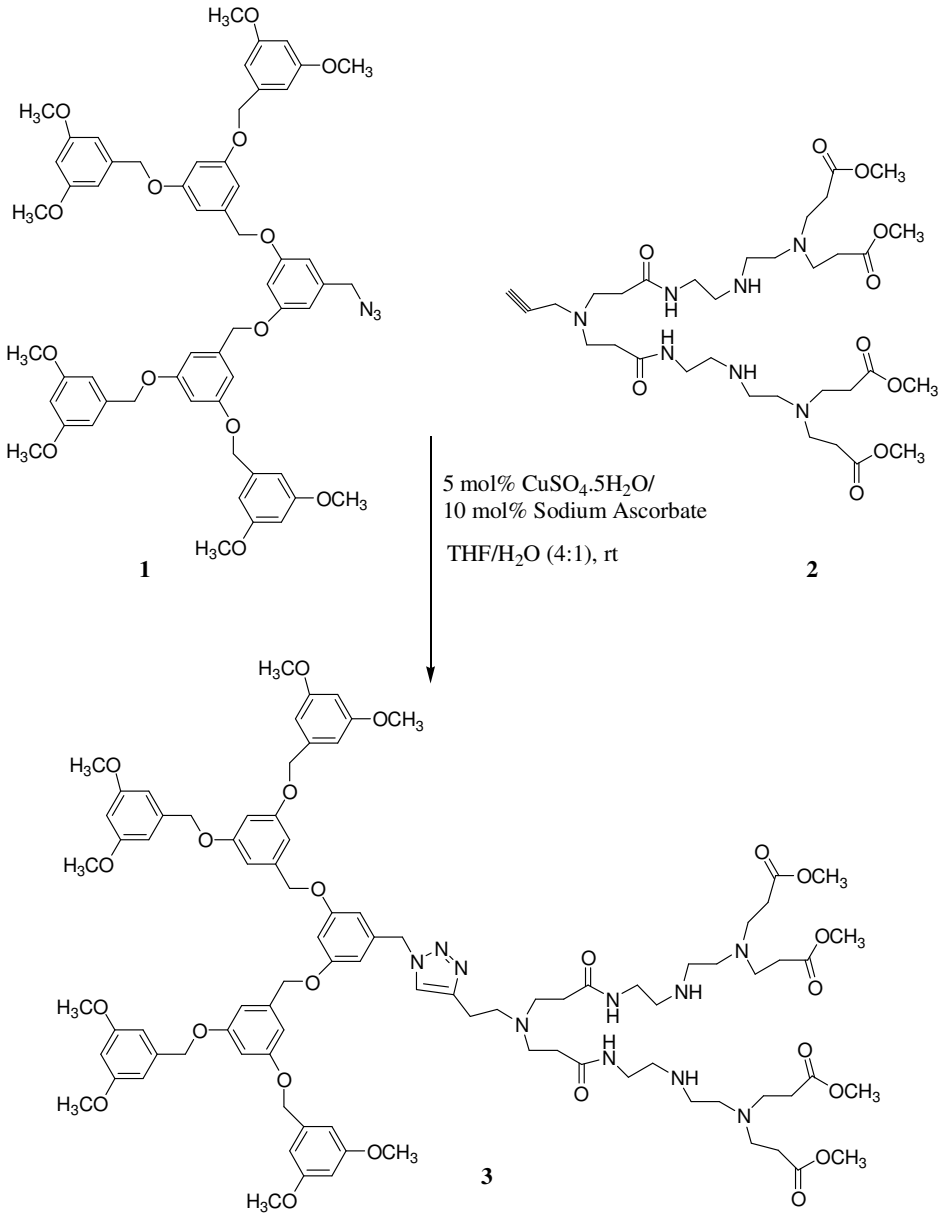


Figure 1.3. Synthesis of a dendrimer via (1,3) huisgen cycloaddition

1.2.2. Reversible Covalent Bonding

Another class of click reactions is the [4+2] Diels-Alder cycloaddition reaction between an electron rich diene and electron poor dienophile. Recently Sanyal *et. al.* reported that the synthesis of dendrimers that can be transformed back to the dendrons, by utilizing the advantage of thermoreversibility of Diels-Alder reaction [6]. Dendrimers **6** were synthesized using Diels-Alder reaction between a furan functionality bearing

polyarylether dendron **4** and a maleimide functionalized polyester dendron **5** (Figure 1.4). One of the most importing aspect of this synthesis is reported such that, as well as the thermoreversibility of the product is achieved, carrying out the reaction without any other reagents is also succeeded.

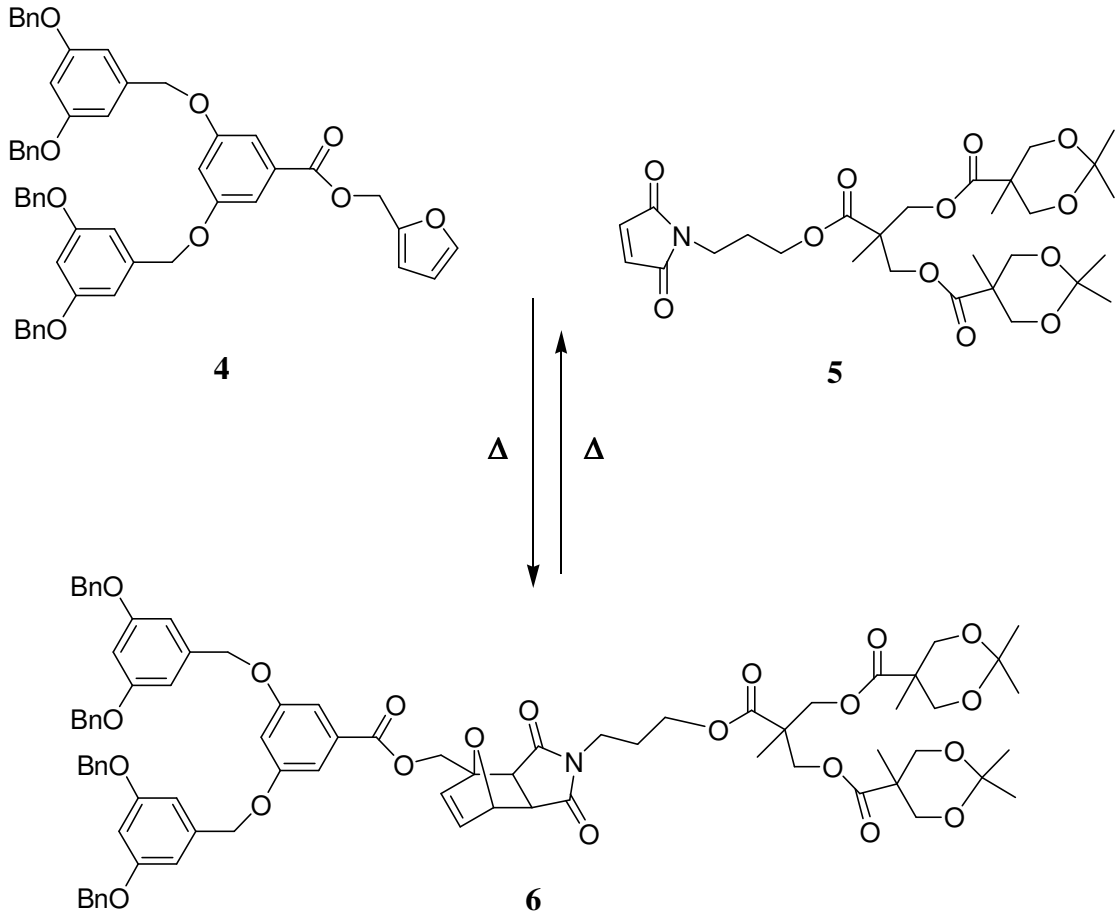


Figure 1.4. The synthesis of dendrimer via diels-alder reaction

1.3. Dendrimers Formed by Noncovalent Interactions

Utilizing all the benefits that the supramolacular chemistry offers, the idea of building dendrimer with desired properties can be achieved by connecting the dendrons via strong noncovalent interactions.

As an example, consider the vital tool necessary for the successful production of the new generation of our body cells: Deoxyribo Nucleic Acid (DNA); the reversibility and the specificity, and the orthogonality are the key properties (Figure 1.5). In fact these 3 property are the powerful benefits that the supramolecular chemistry offers [7].

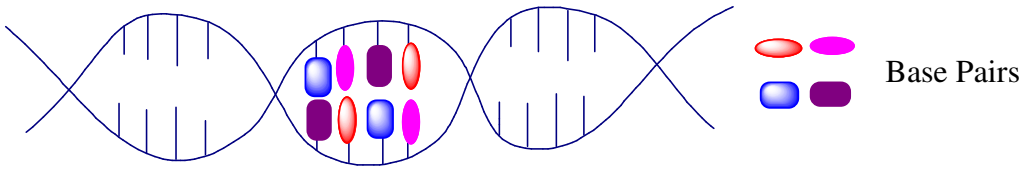


Figure 1.5. The DNA representation

The reversibility indicates that when environmental conditions that stabilizes the supramolecule changes the supramolecule is divided back into its building blocks or vice versa. Interestingly, the property that makes this reversibility more powerful and beneficial special to the case is the successive repeatability of reversibility. As an another important aspect, the specificity brings the ability to build the desired design but no other. Again referring to DNA molecule, the specificity issue is held by the capability of number of hydrogen bonds that DNA bases can do. This leads the DNA molecule directly to the desired supramolecular helix structure. Thirdly orthogonality offers the ability to build unique structures from distinct building blocks, as again in the case of DNA molecules. Although the two helix structures are distinct and unique, they can combine orthogonally to form the complete helix structure.

All these beneficial aspects are utilized in supramolecular dendrimer chemistry. Hydrogen bonding , ion-ion interactions, π-π stacking, and hydrophobic interactions are the most commenly used noncovalent forces while building up a supramolecular design [8].

Zimmerman *et. al.* has functionalized the focal point of a polyarylether dendron with a 2-point hydrogen bonding capable rigid structure [9]. The rigid structure has four

carboxylic acid moities (Figure 1.6). When functionalized dendrons **7** allowed to self assemble in an organic solvent the dendrons form a linear supramolecular polymer aggregate by simply utilizing their hydrogen bonding capability. Interestingly they have further reported that, when the generation of the dendrons increases the supramolacular shape changes into a hexameric form **8** [10].

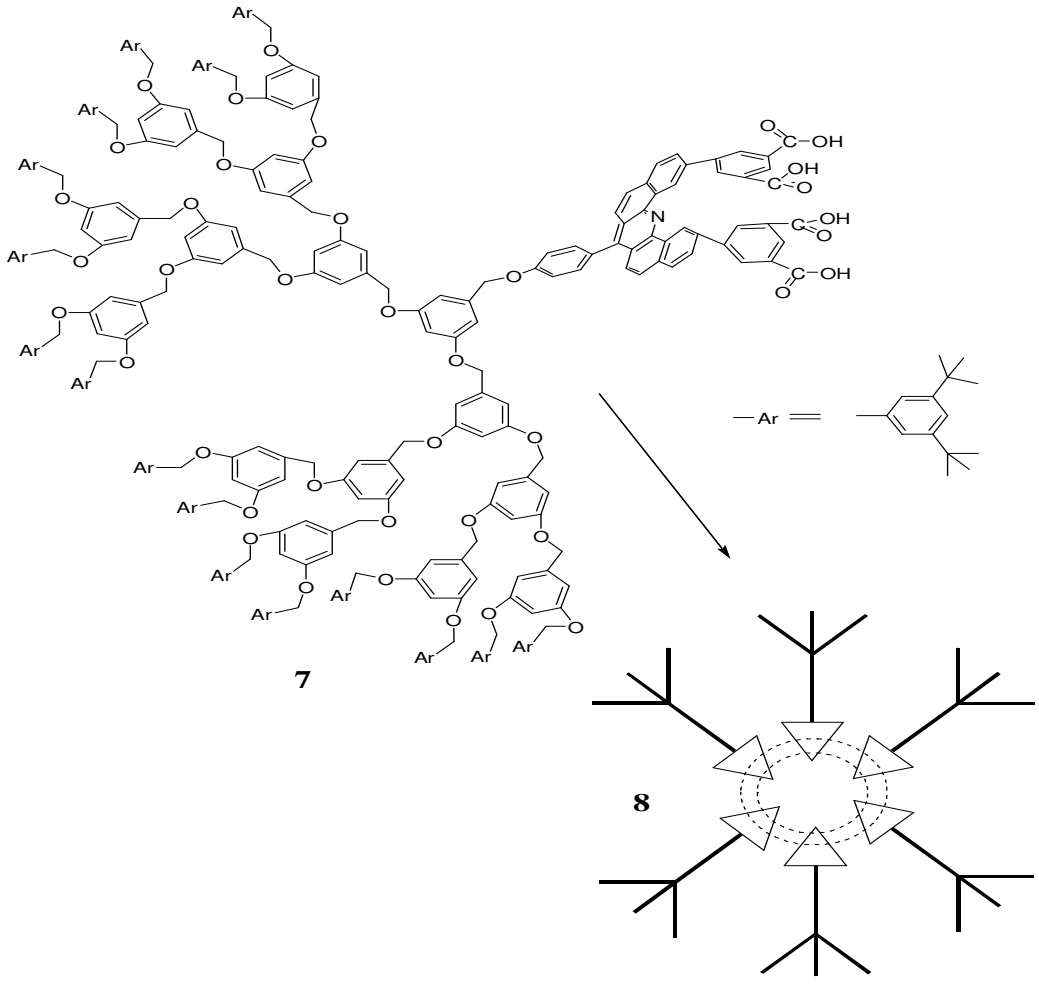
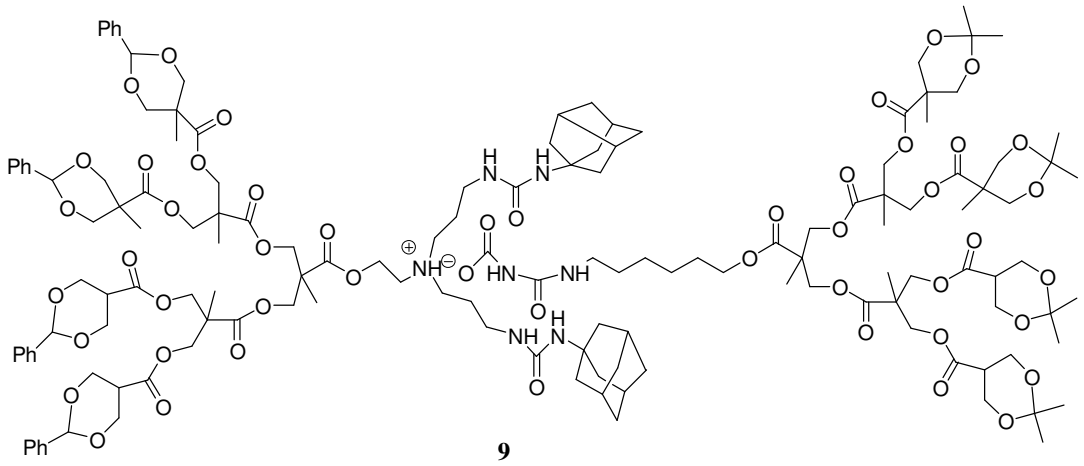


Figure 1.6. The hexameric dendrimer self-assembly

It is possible to use multiple distinct interactions in a single supramolecular self assembly. This will increase the selectivity and stability of the desired product. Fréchet and co-workers reported the supramolecular assembly **9** built up by using both ion-ion interactions and multiple hydrogen bonding between urea moities [11].



9

Figure 1.7. The bow-tie dendrimer assembly

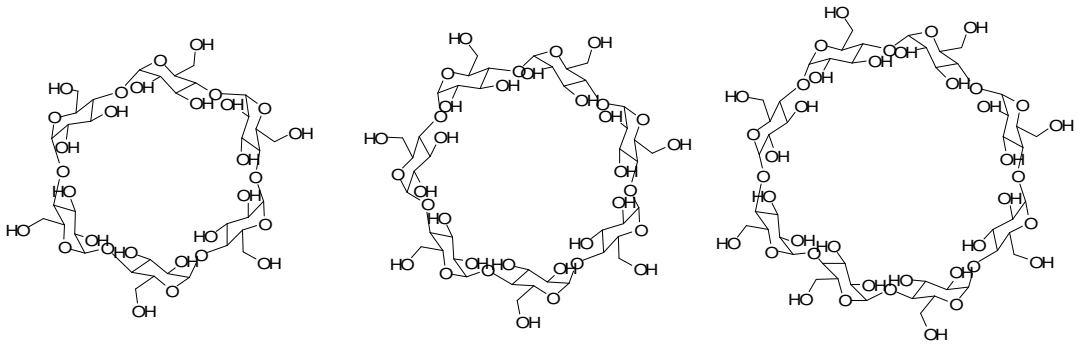
As seen in Figure 1.7 the multiple hydrogen bonds between urea moities is the common force for the supramoleculer structure to be stable in organic solvent. However, the specificity is satisfied by the ion-ion interaction. In other words the ion-ion interaction between carboxylate and quaternernary amine dictates an A-B type orthogonality instead of possible self assembly of each of the functionalized dendrons

1.4. Cyclodextrins and Supramolecular Assemblies

Another important type of interaction that leads to the formation of a supramolecular systems is the hydrophobic interaction. This interaction is simply driven in a way such that the building blocks stacks together in order to minimize their energies in a non-hydrophobic environment. One of the most common building blocks used for supramolecular assembly in aqueous environment are a family of cyclic oligosaccharides called cyclodextrins.

Cyclodextrins are naturally occurring molecules synthesized by a bacteria called "*Bacillus macerans*" from starch [12]. The resulting crystalline structure synthesized by bacteria, is a mixture of cyclodextrins. In Figure 1.8 the family of cyclodextrins are shown.

The one with a 6 repeating unit is α-cyclodextrin **10**, with 7 repeating unit is called β-cyclodextrin **11** and with 8 repeating unit is called γ-cyclodextrin **12**.



10 **11** **12**

Figure 1. 8. The cyclodextrin family

Among the naturally synthesized mixture, β-cyclodextrin is the most abundant species with a 7 repeating sugar units. The number of repeating sugar units defines the physical and chemical properties of cyclodextrins [12], [13]. All cyclodextrins have a hydrophilic surface and a hydrophobic interior cavity. The hydrophilic surface leads to water solubility whereas the hydrophobic interior is capable of making a host guest complex via hydrophobic interaction.

This property is responsible for widespread use of cyclodextrins in drug formulations [14]. Bioavailability of hydrophobic drug molecules is increased due to complexation of drug molecule with hydrophilic cyclodextrin. However the physical and chemical property differences among the family is a selection method for the desired chemical route for the functionalization and the host guest complexation process.

The difference of the repeating unit number among the family leads to the dimensional differences of the interior hydrophobic cavity of the entities. In Figure 1.9. the schematic representation of α, β, and γ-cyclodextrins are shown respectively. The α-

cyclodextrin's **13** hydrophobic cavity has a diameter of 0.57 nm, β-cyclodextrin's **14** has 0.78 nm, and γ-cyclodextrin's **15** has 0.95 nm.

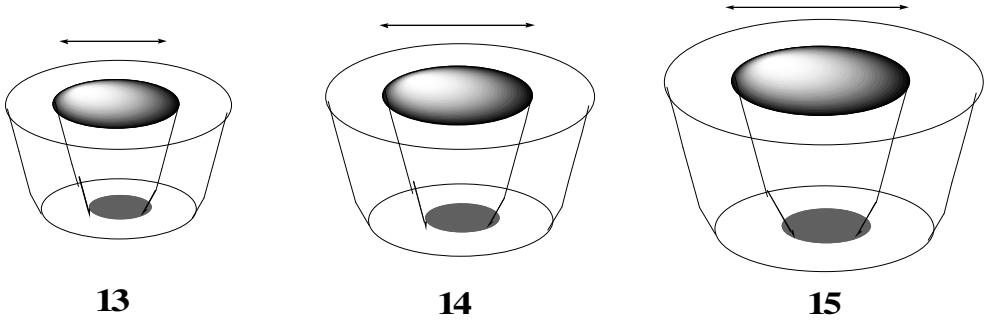


Figure 1.9. The Schematic representation of cyclodextrins

Dimensions of the interior cavity of cyclodextrins play an important role in the hydrophobic complexation. The match between the dimension of the guest molecule and the cavity dimension of the selected cyclodextrin will define the stability of the supramolecular. If the complexation constant is not high enough the complex will be loose, more susceptible to fall apart furthermore any other prospective guest or impurity that can bind to that cavity will participate in competitive binding.

Taking into consideration of this fact, some guests presents a best fit for the distinct cyclodextrins. As an example adamantane is a very good guest for β-cyclodextrin and polyethylene glycol is a good match for α-cyclodextrin.

Cyclodextrins are used in complexation not only in their native forms but also after further functionalizations. The β-cyclodextrin has 7 primary hydroxyl groups and 14 secondary hydroxyl groups. One can attain selective functionalization arising from the chemical reactivity difference between primary and secondary hydroxyl groups.

The selection between the primary and secondary hydroxyls for further functionalization is obvious such that the strength of the base to generate alkoxy groups from hydroxyls will determine either the primary or the secondary hydroxyl will react [13]. Interestingly, 6 of the 7 primary hydroxyl groups are hydrogen bonded intramolecularly. Thus only one out of 7 hydroxyl groups is capable of undergoing facile chemical reaction [15].

Petter and co-workers has mono functionalized a β-cyclodextrin by a nucleophilic substitution reaction between the cyclodextrin itself and a 4-toluol sulfonyl chloride in the presence of sodium hydroxide [16]. After the allocation of a good leaving group, further functionalization is carried by using sodium azide as nucleophile to afford azido cyclodextrins (Figure 1.10).

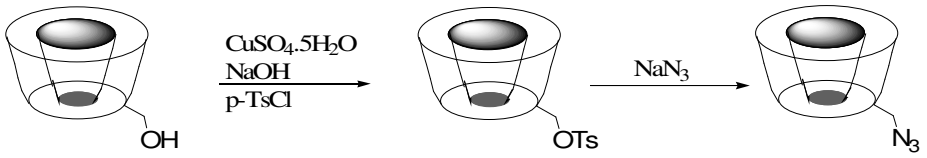


Figure 1.10. The Functionalization of a Primary Hydroxyl

1.4.1. Cyclodextrin Based Self Assemblies

Both having the ability of making inclusion complexes and having the capability of functionalization, made the cyclodextrins widely used in supramolecular chemistry as building blocks. As a result of water solubility property, most of the complexes are stable in water medium.

Van de Manakker *et. al*. has shown that by the use of cholesterol's ability of binding to the β-cyclodextrins's hydrophobic cavity, self assembled hydrogels can be synthesized [16].

The synthesis of self assembled hydrogels involves end functionalization of polyethylene glycol **16**, with cholesterol **17** via esterification to yield 8 armed cholesterol functionalized polymers **18**, and end functionalization of same type polymer, with amino β-cyclodextrin hydro chloride (βCD-NH_2.HCl) **19** via amidation to yield 8 armed βCD functionalized polymers **20** (Figure 1.11).

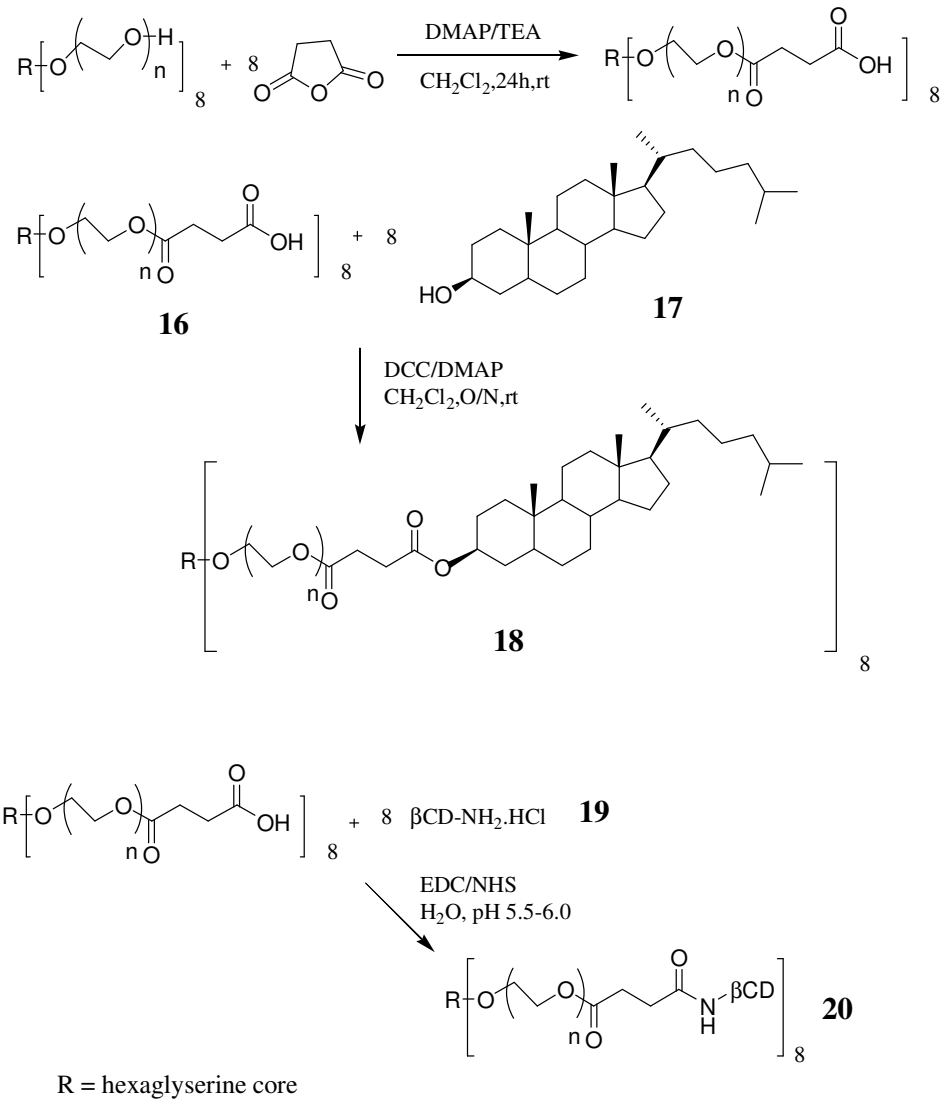


Figure 1.11. Self assembled hydrogel synthesis

After the synthesis of the building block polymers, the polymer mixture has been dissolved in NH_4OAc buffer, then the solution is lyophilized and the lyophilized mixtures were hydrated in order to obtain hydrogels.

With a similar point of view Kaifer and co-workers crosslinked the gold nanoparticles and obtain aggregates by making use of the ability of ferrocene units being capable of binding the β-cyclodextrin cavity [17].

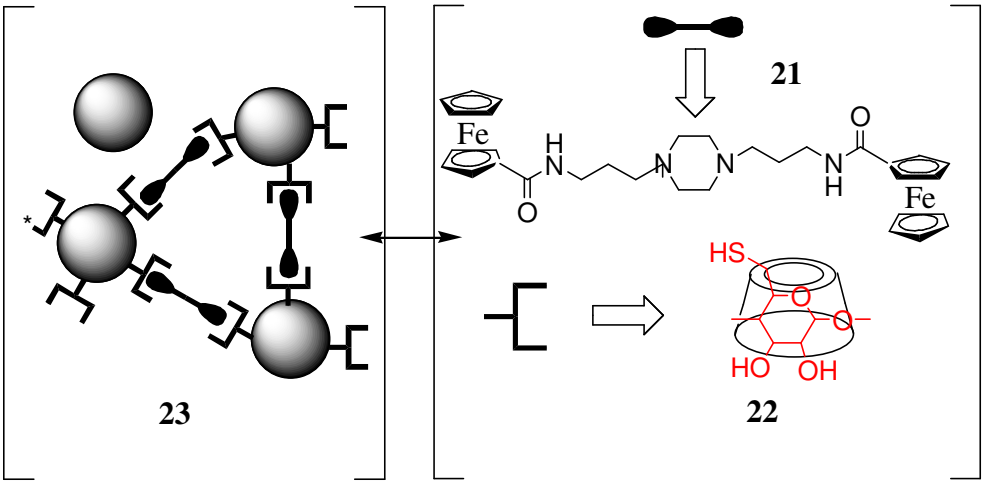


Figure 1.12. Supramolecular gold nanoparticle aggregate

Gold nanoparticles are prepared from the thiol functionalized β-cyclodextrins **22** and aggregation **23** is achieved by the addition of di-ferrocene functionality **21** addition into the medium (Figure 1.12). In order to justify both the competitiveness and the reason for aggregation is the result of inclusion; free cyclodextrins were added into the medium. And is it observed that the aggregation of gold nanoparticles collapses due to the competitive binding of di-ferrocene units and free cyclodextrins.

1.4.2. Cyclodextrin Dendrimer Self Assemblies

Being both functionalizable and having the ability to form complexes to supramolecular assemblies, cyclodextrins draw attention in the fields of dendrimers as well as polymer they do in the field of polymer conjugates.

Newkome *et. al.* has shown a conifer-shaped dendrimer assembly by making use of the good match between adamantane and β-cyclodextrin [18]. The dendron synthesized in a convergent manner, and focal point was further functionalized with an adamantane. The synthesized water soluble dendron and β-cyclodextrin was mixed 1:1 molar ratio in D_2O and the desired supramolecular dendrimer assembly **24** formed. The new type of dendron cyclodextrin assembly can be represented as a tree in a bucket (Figure 1.13).

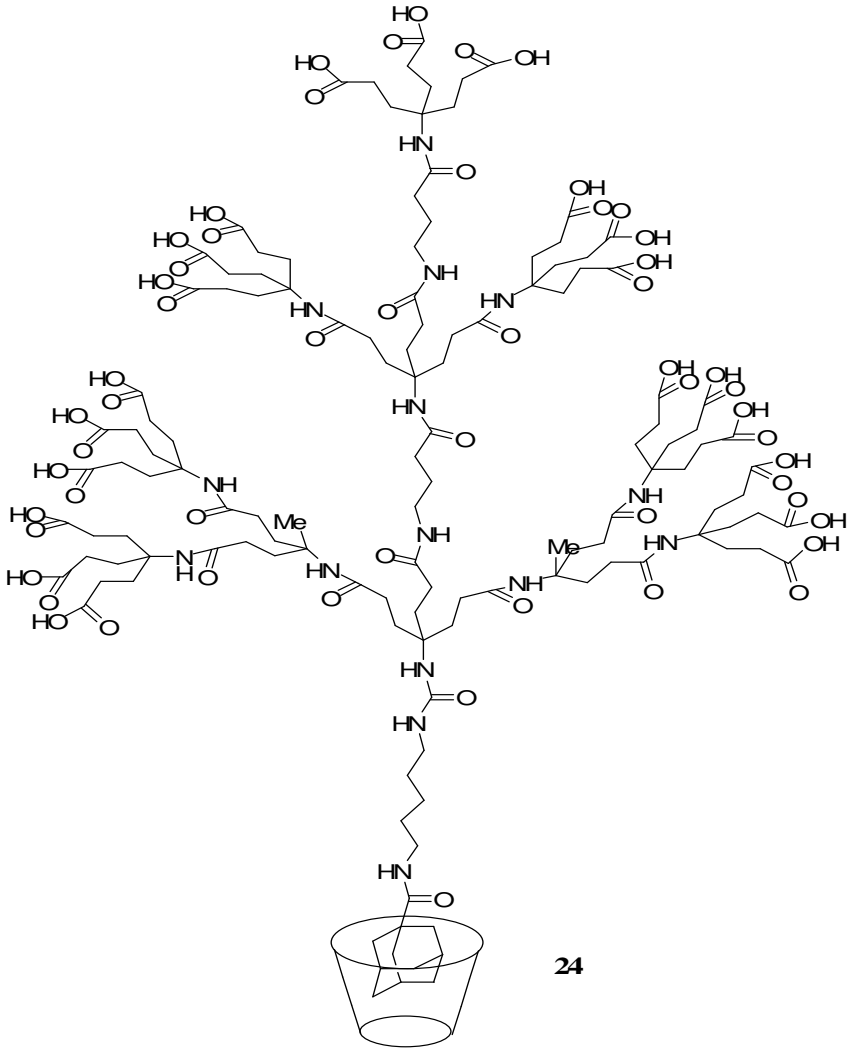


Figure 1.13. Conifer shaped dendrimer assembly

It is also possible to use orthogonal interaction types together with cyclodextrin assemblies. In Figure 1.14. Newkome *et. al.* first synthesized the dendritic structure based on complexation on Ruthenium [19]. After the self assembled metallodendrimer **25** has formed, β-cyclodextrin **26** and metallodendrimer were self assembled to yield a new dendrimer **27** that has two orthogonal non-covalent interactions.

Although the metallodendrimer itself is completely water insoluble, the property of β-cyclodextrin being water soluble is used to achieve the self assembly in water medium. To fulfill the desired product's formation, a strategy that involves the usage of excess β-cyclodextrin with respect to the adamantane functionalized end groups has chosen.

The orthogonality of the used two non-covalent interactions implies that when two of the interactions are performed, the interactions do not interfere. In other words step by step building is possible. This property is also proven in the work done.

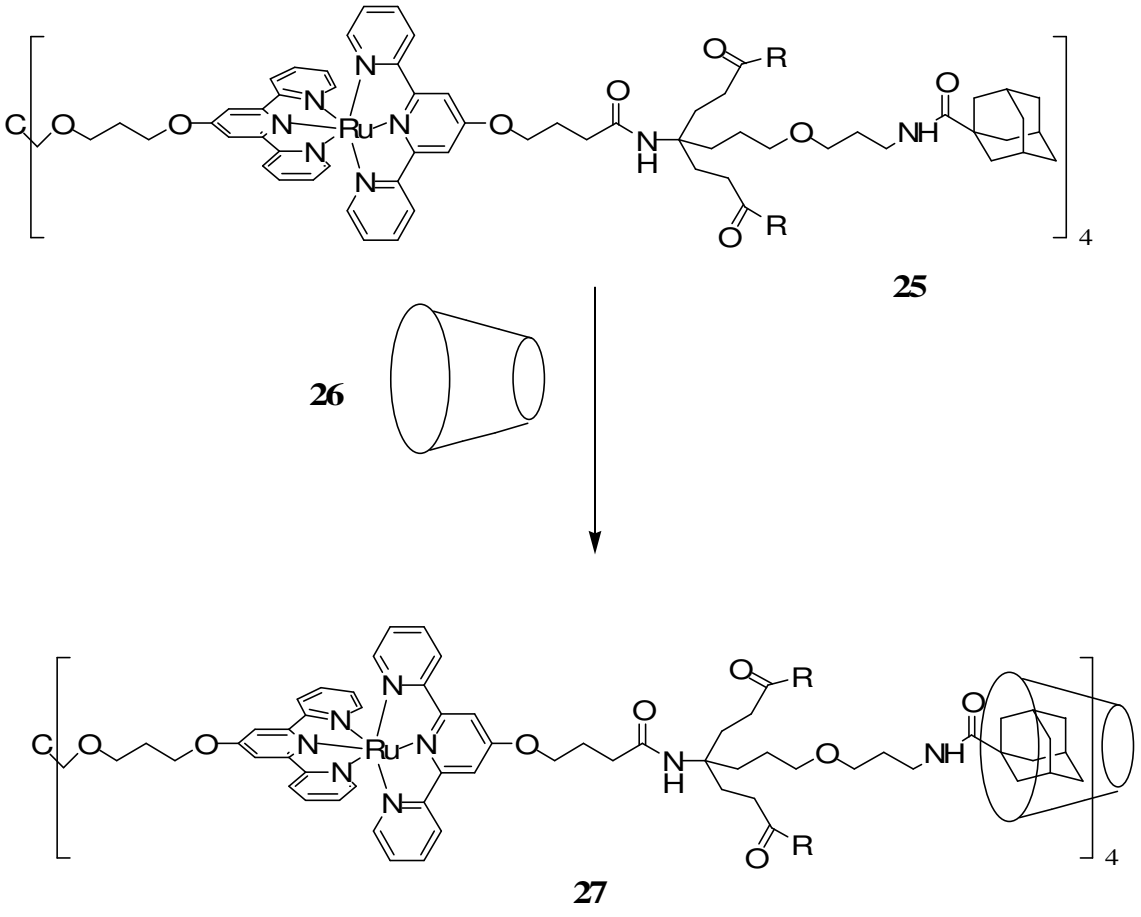
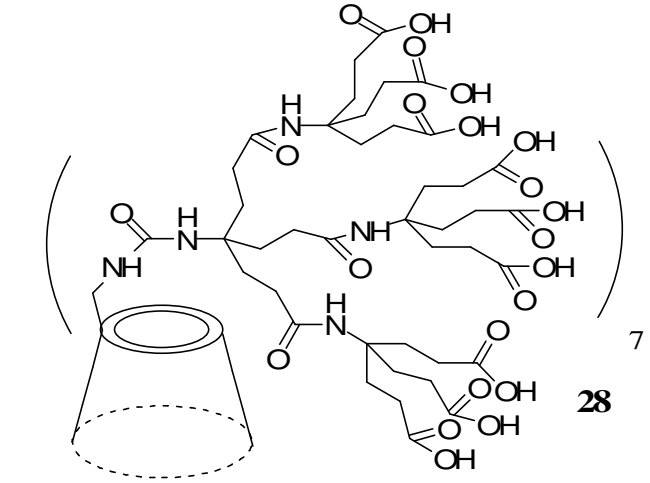


Figure 1.14. Self assembled metallodendrimer

In both of the examples the properties of β-cyclodextrin are used to build up supramolecular self assemblies without accomplishing any further functionalization of β-cyclodextrin itself.

As an another approach, Newkome et. al. has first functionalized the β-cyclodextrin with dendritic moieties to afford a self assembled dendrimer [20]. The functionalization of β-cyclodextrin is performed from the primary hydroxyl groups where the secondary hydroxyl groups remained untouched.

Synthesis involved the allocation of seven water soluble dendrimers to the seven primary hydroxyl groups of the β-cyclodextrin. As a result covalently linked supramolecular cyclodextrin dendron derivative **28** has been obtained. In order to self assemble this dendron modified structures a di-adamantane functionalized template **29** has been synthesized (Figure 1.15). The occurring self-assembled dendrimer is a symmetrical dendrimer and can not be subjected to orthogonal functionalization of each of the dendron-cyclodextrin adducts.



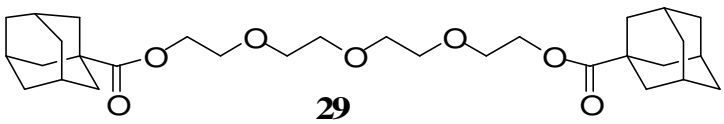


Figure 1.15. The dendron functionalized β-cyclodextrin

2. AIM OF THE STUDY

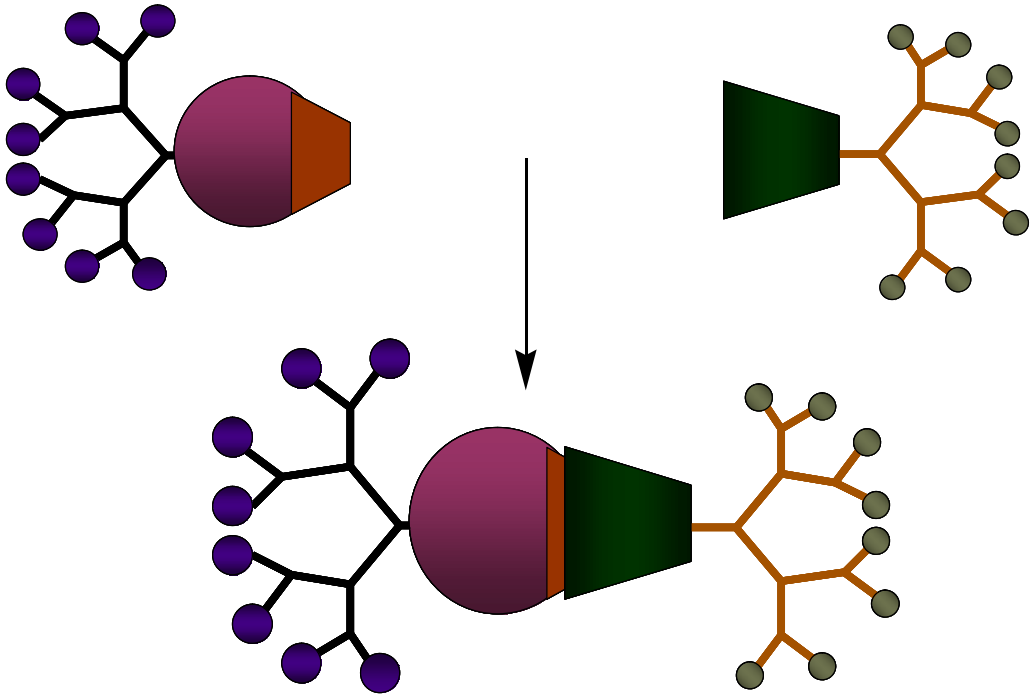


Figure 2.1. Orthogonal dendrimer supramolecular assembly

This study aims the synthesis of A-B type segment block dendrimers via non-covalent interactions. There are some sub-aims to fulfill this goal. One is to synthesize an adamantane functionalized polyester dendron by divergent route. This step will finalize the synthesis of one out of two dendrons, that will further contribute to the dendrimer assembly.

Second sub-aim is to synthesize acetylene functionalized polyaryl ether dendrons which bear methyl protected triethylene glycol at their surfaces. The acetylene functionality aims the further functionalization of the dendrons via click chemistry. The purpose of the methyl protected triethylene glycol units is to increase the water solubility

behavior of the dendrons. The water solubility plays a very important role in the self-assembly process.

Thirdly, to build up the second dendron which will contribute to the dendrimer assembly a host molecule to the adamantane functionalized is synthesized. This molecule is β-cyclodextrin. The β-cyclodextrin is mono functionalized with an azide group in order to attach to the acetylene functionalized polyaryl ether dendron.

After the synthesis of both of the dendrons, the self assembly of dendrimer will be carried out in water medium.

3. EXPERIMENTAL

3.1. Methods and Metarials

All chemicals were used as received from manufacturer (Merck, Aldrich, Alfa Aesar, Riedel de Haen). Dry solvents (CH_2Cl_2, THF, toluene) was obtained from ScimatCo Purification System, other dry solvents were dried of molecular sieves. Column chromatography was performed using silicagel-60 (43-60 nm). Thin layer chromatography was performed using silica gel plates (Kiesel gel 60 F254, 0.2mm, Merck). Plates were viewed under 254nm UV lamp otherwise plates are developed either by $KMnO_4$ stain or $EtOH/H_2SO_4$ (95:5). Infrared spectroscopy was carried out on Thermo Scientific Nicolet 380 FT-IR spectrophotometer. Removing water from cyclodextrins was accomplished with LabConco lyophilizer. ^1H NMR (operating at 400 MHz) and ^{13}C NMR (operating at 100 MHz) were recorded on Varian Mercury-MX in either D_2O or $CDCl_3$ as solvent at the Advanced Technologies Research and Development Center at Boğaziçi University.

3.2. Synthesis

The synthesis of the dendrimer has four main parts which are: synthesis of generations of polyester dendrons carrying adamantane (AD) functionality at the focal point, synthesis of polyaryl ether dendron carrying triethyleneglycolmonomethylether (MeOTEG) functionalities at the periphery, synthesis of mono functionalized β-cyclodextrin (β-CD) having azide functionality, and combining the β-CD and the generations of polyaryl ether dendrons via click chemistry.

The synthesis of polyester dendrons were carried out in a divergent manner i.e. starting from the focal point which is AD functionality and growing through the surface via Steglich Esterification. The final dendrons that will be used in supramolecular assembly are all in deprotected forms carrying hydroxyl groups at their peripheries in order to enhance water solubility (Figure 3.1). The triethylene glycol linker (TEG) between the AD and the polyester dendron not only further enhances the water solubility but also brings

flexibility and supplies the sufficient distance from the dendron to overcome the steric factors thus increasing the availability of AD for hydrophobic complexation.

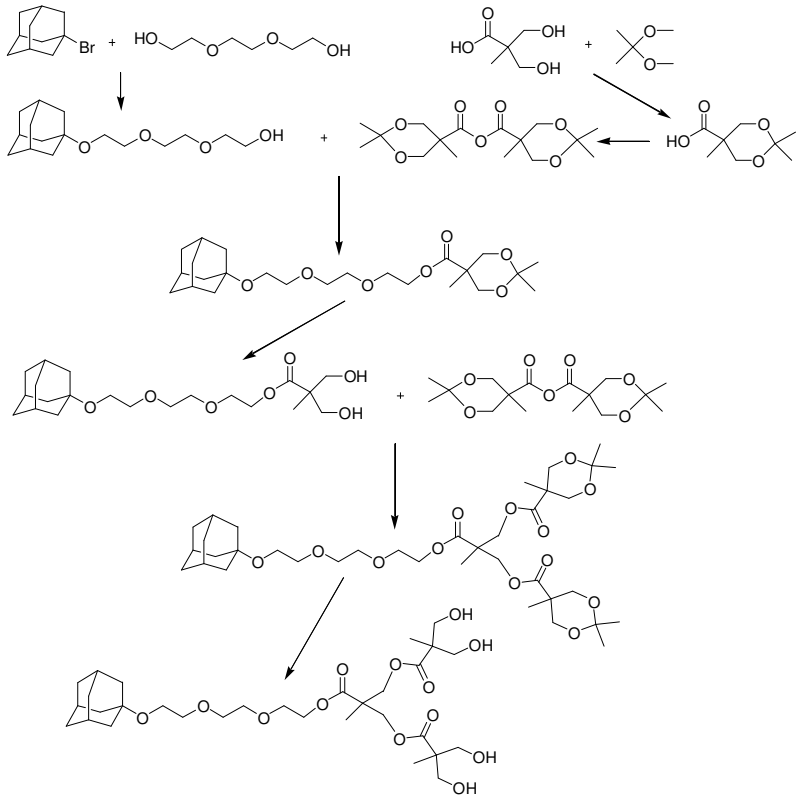


Figure 3.1. Synthesis route of AD-TEG polyester dendrons

As opposed to the polyester dendron synthesis, polyaryl ether dendrons were synthesized in a convergent manner, meaning starting from the MeOTEG units at the periphery and growing towards to the focal point. After the synthesis of two generations of dendrons the generations' focal points were further functionalized with acetylene units which will be utilized in click chemistry. The MeOTEG units at the periphery greatly enhance the water solubility of hydrophobic polyaryl ether dendrons.

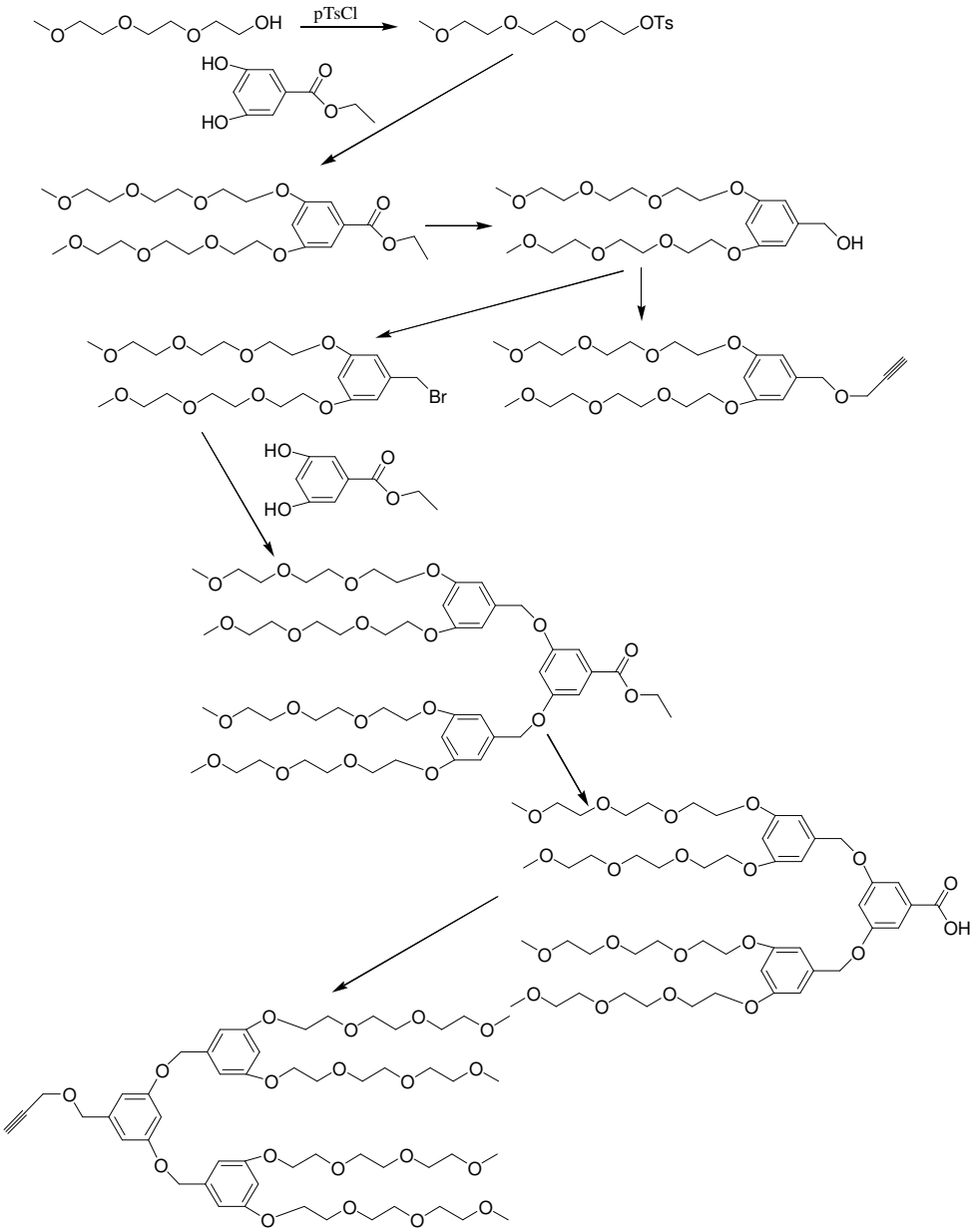


Figure 3.2. Synthesis route of MeOTEG polyaryl ether dendrons

The other constitutional compound that will contribute to the click chemistry, β-CD, was mono functionalized by azide moiety. In the synthesis strategy the intra-molecular hydrogen bonding between 6 primary hydroxyl groups out of 7 was exploited. The intra-molecular hydrogen bonding causes a decrease in the tendency of reacting which favors a mono functionalization in a dilute reaction medium. Azide functionality is achieved by nucleophilic substitution reaction following conversion of relatively more reactive hydroxyl group to a leaving group (Figure 3.3).

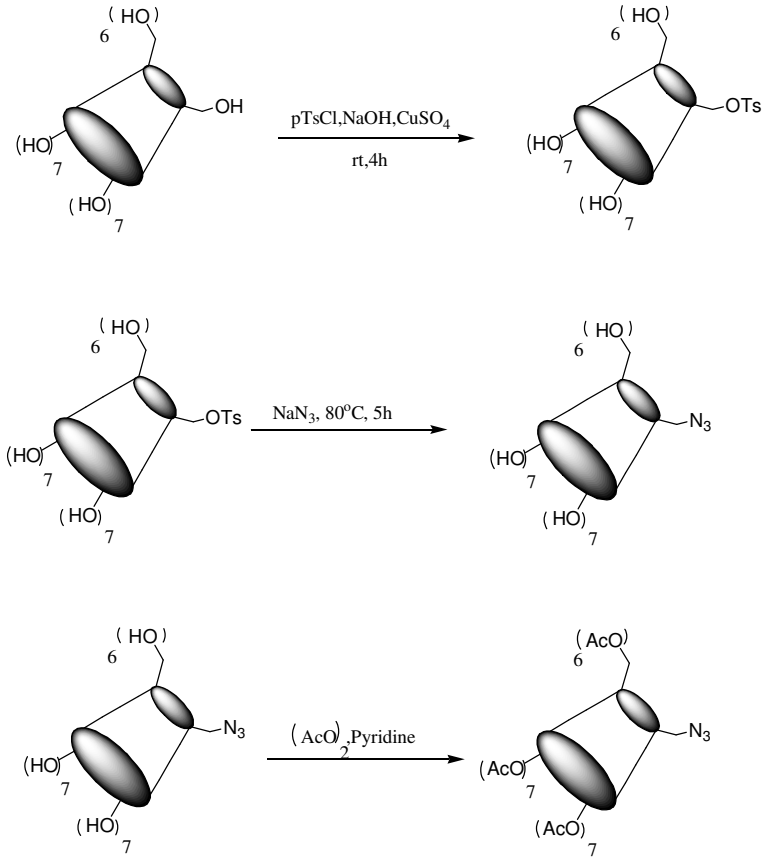


Figure 3.3. Synthesis route for β-CD modification

3.2.1. Synthesis of Polyester Dendrons

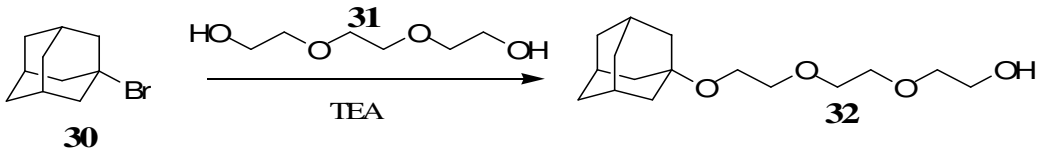


Figure 3.4. The synthesis of adamantane triethylene glycol

3.2.1.1. Synthesis of Adamantane Triethylene Glycol **32**. Adamantyl bromide **30** (0.5 g, 2.32 mmol) was dissolved in TEG **31** (10 mL) and triethylamine (TEA) (98 µL, 6.52 mmol) added. The mixture was allowed to react for 48 h at 120 °C. The reaction mixture was diluted with 25 mL CH_2Cl_2 and extracted with 1M HCl (2 x 25 mL) and then H_2O (3 x

25 mL). The residue was dried over Na_2SO_4, filtered and volatiles evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (65:35) to yield adamantane triethylene glycol **32** (AD-TEG) (0.55 g, 83 % yield) as yellow oil. Synthesis adopted from literature [21]. ^{1}H NMR ($CDCl_3$) δ 3.71 – 3.57 (m, 12H), 2.12 (bs, 3H), 1.73 (bs, 6H), 1.63 – 1.55 (m, 6H) (Figure A.1.)

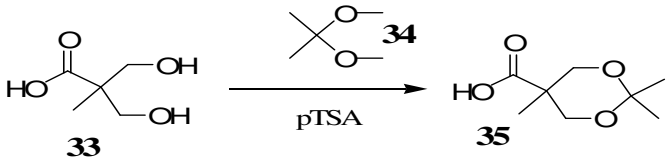


Figure 3.5. Synthesis of isopropylidene-2,2-bis(oxymethyl)propionic acid

3.2.1.2. Synthesis of Isopropylidene-2,2-bis(oxymethyl)propionic acid **35**. Bishydroxymethyl propionic acid **33** (Bis-MPA) (5 g, 37.28 mmol) , 2,2-dimethoxypropane **34** (6.9 mL, 55.92 mmol) and p-toluenesulfonic acid mono hydrate (pTSA) (0.36 g, 1.87 mmol) were dissolved in dry acetone (25 mL) under nitrogen atmosphere. The mixture allowed to react for 2h at room temperature. The catalyst was neutralized by the addition of 0.4 mL TEA and the solvent evaporated under *vacuo*. The residue was dissolved in 50 mL CH_2Cl_2 and extracted with H_2O (2 x 25 mL). The residue was dried over Na_2SO_4, filtered and volatiles evaporated under *vacuo* in order to yield Isopropylidene-2,2-bis(methoxy)propionic acid **35** (4.2 g, 65 % yield) as white solid. ^{1}H NMR data corresponds to the literature values [22].

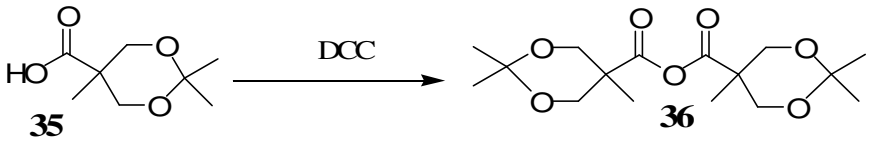


Figure 3.6. Synthesis of Isopropylidene-2,2-bis(oxymethyl)propionic anhydride

3.2.1.3. Synthesis of Isopropylidene-2,2-bis(oxymethyl)propionic anhydride **36**. To a suspension of isopropylidene-2,2-bis(methoxy)propionic acid **35** (4.21 g, 24.15 mmol) in 14 mL dry CH_2Cl_2, a solution of 1,3-dicyclohexylcarbodiimide (DCC) (2.49 g, 12.08 mmol) in 5 mL dry CH_2Cl_2 was added. The mixture was allowed to react for 4 h at room temperature. The dicyclohexyl urea (DCC) was removed through a glass filter and the solvent evaporated under *vacuo*. The residue was dissolved in small amount of cold ethyl acetate (EtOAc) and the remaining DCC filtered through glass filter again. The volatiles removed under *vacuo* in order to yield isopropylene-2,2-bis(oxymethyl)propionic anhydride **36** (3.91g, 98 % yield) as a viscous oil. ^{1}H NMR data corresponds to the literature values [23].

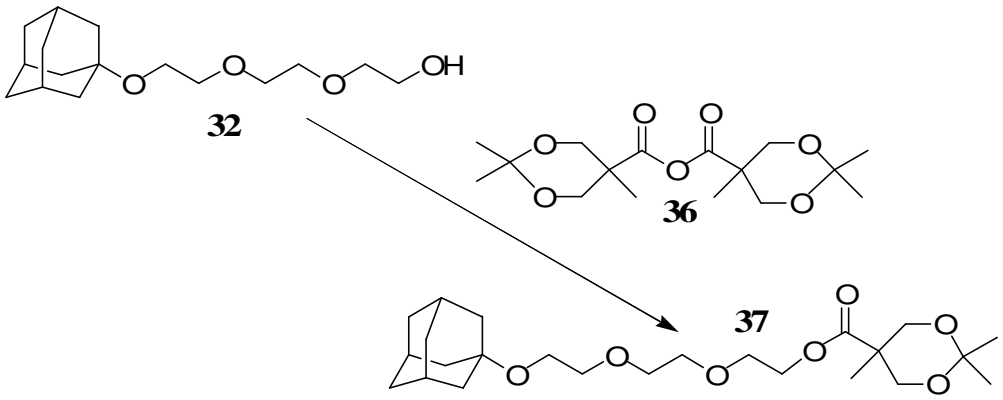


Figure 3.7. Synthesis of AD-TEG-G1 acetal

3.2.1.4. Synthesis of AD-TEG-G1 acetal **37**. To a solution of AD-TEG **32** (0.44 g, 1.56 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.095 g, 0.78 mmol) in dry CH_2Cl_2, (17 mL) isopropylene-2,2-bis(oxymethyl)propionic anhydride **36** (0.77 g, 2.34 mmol) and 1.3 mL pyridine (py) was added and the mixture was stirred at room temperature for 12 h. The excess anhydride was quenched by addition of 2.3 mL py:H_2O (1:1) for 6 h. The reaction mixture was diluted with 30 mL CH_2Cl_2 and extracted with $NaHSO_4$ (3 x 20 mL), 10 % Na_2CO_3 (3 x 20 mL) and saturated brine (3 x 20 mL). The organic residue was dried over Na_2SO_4, filtered and the volatiles removed under *vacuo*. The residue was purified by column chromatography with ethyl acetate:hexane (1:4) in order to yield AD-TEG-G1 acetal **37** (0.36 g, 53 % yield). ^{1}H NMR ($CDCl_3$) δ 4.28 (t, 2H, J = 4.6 Hz), 4.18 (d, 2H, J =

11.8 Hz), 3.70– 3.55 (m, 10H), 2.12 (bs, 3H), 1.72 -1.71 (m, 6H), 1.64 – 1.55 (m, 6H), 1.41 (s, 3H), 1.37 (s, 3H), 1.20 (s, 3H). IR: ν = 1730.3, cm^{-1} (Figure A.1., A.2.).

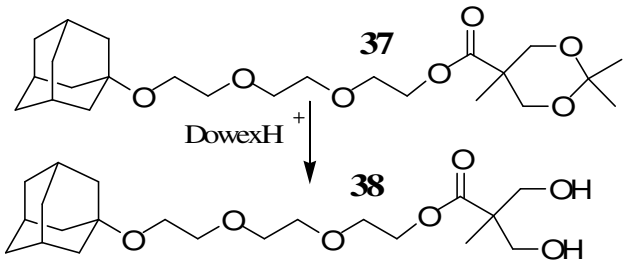


Figure 3.8. Synthesis of AD-TEG-G1

3.2.1.5. Synthesis of AD-TEG-G1 **38**. AD-TEG-G1 acetal **37** (0.33 g, 0.75 mmol) was dissolved in methanol (10 mL). To the solution, resin was added $DowexH^+$ and the mixture was stirred for 3 h. The resin was filtered and the volatiles were removed under *vacuo*. The organic residue was purified by column chromatography with ethyl acetate:hexane (65:35) to yield AD-TEG-G1 **38** (0.17 g, 56 % yield) as a yellow oil. ^1H NMR ($CDCl_3$) δ 4.33 (t, 2H, J = 4.7 Hz), 3.84 – 3.70 (m, 6H), 3.62 (s, 4H), 3.56 (bs, 4H), 2.12 (bs, 3H), 1.72 – 1.55 (m, 12H), 1.09 (s, 3H). IR: ν = 3432.7, 1726.7, cm^{-1} (Figure A.3., A.4.).

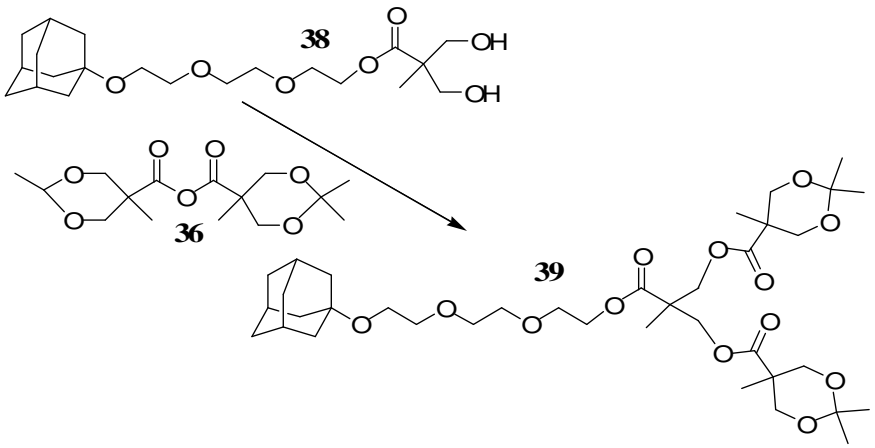


Figure 3.9. Synthesis of AD-TEG-G2 acetal

3.2.1.6. Synthesis of AD-TEG-G2 acetal **39**. To a solution of AD-TEG-G1 **38** (0.116 g, 0.29 mmol) and DMAP (0.035 g, 0.29 mmol) in dry CH_2Cl_2 (3.2 mL) was added isopropylene-2,2-bis(oxymethyl)propionic anhydride **36** (0.29 g, 0.87 mmol) and 0.25 mL py and the mixture was stirred at room temperature for 12 h. The excess anhydride was quenched by addition of the 0.22 mL py:H_2O (1:1) for 6 h. The reaction mixture was diluted with 7 mL CH_2Cl_2 and extracted with $NaHSO_4$ (3 x 10 mL), 10 % Na_2CO_3 (3 x 10 mL) and saturated brine (3 x 10 mL). The organic residue was dried over Na_2SO_4, filtered and the volatiles removed under *vacuo*. The residue was purified by column chromatography with ethyl acetate:hexane (1:4) in order to yield AD-TEG-G2 acetal **39** (0.20 g, 97 % yield).

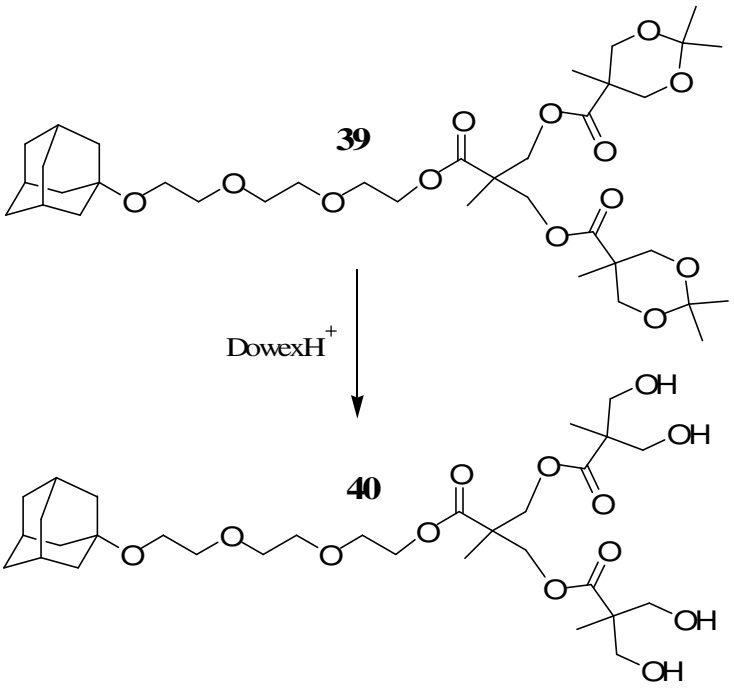


Figure 3.10. Synthesis of AD-TEG-G2

3.2.1.7. Synthesis of AD-TEG-G2 **40**. AD-TEG-G2 acetal **39** (0.20 g, 0.28 mmol) was dissolved in methanol (10 mL). To the solution, was added Dowex,H^+ resin and the mixture was stirred for 3 h. The resin was filtered and the volatiles removed under *vacuo*. The organic residue was purified by column chromatography with ethyl acetate:hexane (65:35) to yield AD-TEG-G2 **40** (0.18 g, 96 % yield) as a yellow oil.

3.2.2 Synthesis of Polyaryl Ether Dendrons

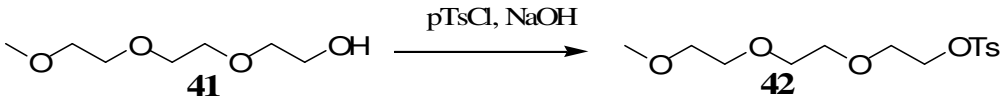


Figure 3.11. Synthesis of triethylene glycol monomethyl ether tosylate

3.2.2.1 Synthesis of Triethylene Glycol Monomethyl Ether Tosylate **42**. Triethylene glycol monomethyl ether **41** (MeOTEG) (5 mL, 31.88 mmol) and NaOH (2.44 g, 60.89 mmol) were dissolved in THF:H_2O (40 mL, 1:1) and a solution of pTsCl (6.08 g, 31.88 mmol) in THF (60 mL) was added. The mixture was stirred for 24 h at room temperature. THF was removed under *vacuo* and the remaining water solution was extracted with CH_2Cl_2 (3 x 25 mL). The organic solution was dried over Na_2SO_4, filtered and volatiles removed under *vacuo*. Organic residue was purified by column chromatography with ethyl acetate:hexane (35:65) to yield triethylene glycol monomethyl ether tosylate **42** (MeOTEGOTs) (6.9 g, 68 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 2H, *J* = 8.3 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 4.14 (t, 2H, *J* = 4.8 Hz), 3.66 (t, 2H, *J* = 4.8 Hz), 3.60 – 3.57 (m, 6H), 3.52 – 3.49 (m, 2H), 3.35 (s, 3H), 2.42 (s, 3H) (Figure A.5).

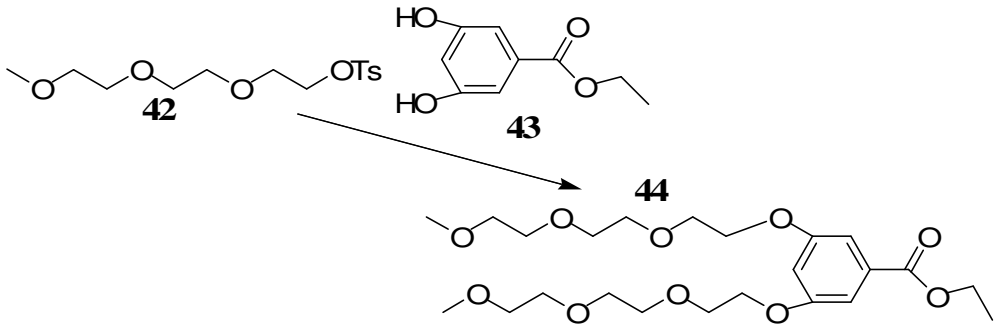


Figure 3.12. Synthesis of MeOTEG-G1 ester

3.2.2.2. Synthesis of MeOTEG-G1 ester **44**. MeOTEGOTs **42** (5.08 g, 15.95 mmol), ethyl 3,5-dihydroxybenzoate **43** (1.16 g, 6.38 mmol), K_2CO_3 (0.88 g, 6.38 mmol) and 18-C-6 (0.084 g, 0.32 mmol) were dissolved in dry acetone (50 mL). The mixture was refluxed for 12 h. The mixture was filtered in order to remove K_2CO_3, and acetone was removed under *vacuo*. The organic residue was dissolved in CH_2Cl_2 (30 mL) and extracted with H_2O (3 x 30 mL). The organic solution was dried over Na_2SO_4, filtered and volatiles were removed under *vacuo*. The organic residue was purified by column chromatography with ethyl acetate:hexane (7:3) to yield MeOTEG-G1 ester **44** (2.15 g, 71 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.17 (s, 2H), 6.66 (s,1H), 4.33 (q, 2H, *J* = 7.1 Hz), 4.12 (t, 4H, *J* = 4.5 Hz), 3.8 (t 4H), 3.72 – 3.62 (m, 12H), 3.53 (t, 4H, *J* = 4.5 Hz), 3.36 (s, 6H), 1.36 (t, 3H, *J* = 7.1 Hz) (Figure A.6).

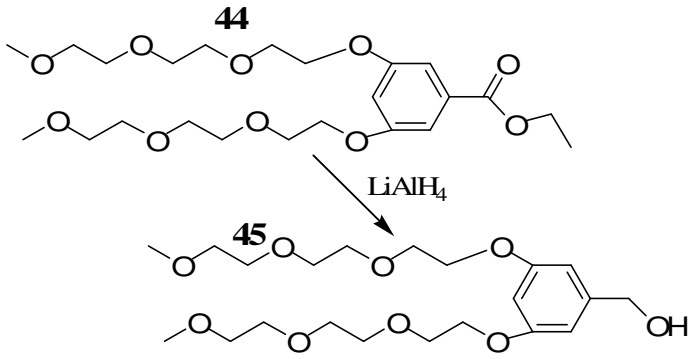


Figure 3.13. Synthesis of MeOTEG-G1-ol

3.2.2.3. Synthesis of MeOTEG-G1-ol **45**. MeOTEG-G1 ester **44** (2.00 g, 4.21 mmol) was dissolved in THF (40 mL), and lithium aluminum hydride ($LiAlH_4$) (0.48 g, 12.63 mmol) was added at 0°C. The mixture was stirred for 24 h at room temperature. Excess $LiAlH_4$ was quenched with 20% NaOH (15 mL) and H_2O (20 mL). The mixture was then extracted with EtOAc (3 x 30 mL). The organic solution was dried over Na_2SO_4, filtered and volatiles was removed under *vacuo*. The organic residue was purified by column chromatography with ethyl acetate:hexane (4:1) to yield MeOTEG-G1-ol **45** (1.47 g, 80 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.52 (s, 2H), 6.39 (s,1H), 4.58 (d, 2H, *J* = 6.0 Hz), 4.09 (t, 4H, *J* = 4.0 Hz), 3.81 (t, 4H, *J* = 3.9 Hz), 3.70 – 3.52 (m, 16H), 3.35 (s, 6H), 1.81 (t, 1H, *J* = 6.0 Hz) (Figure A.7).

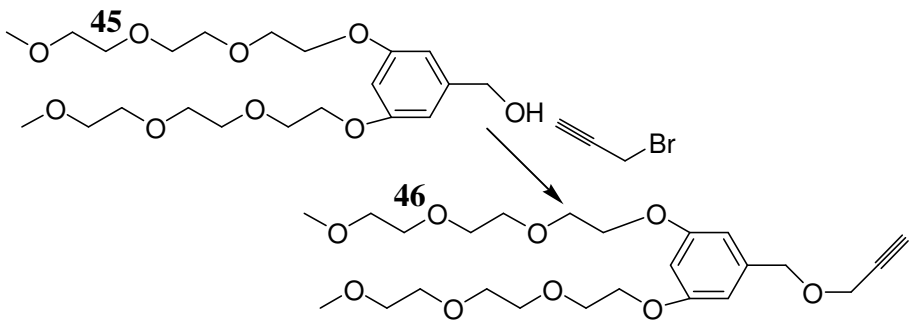


Figure 3.14. Synthesis of MeOTEG-G1 acetylene

3.2.2.4. Synthesis of MeOTEG-G1 acetylene **46.** MeOTEG-G1-ol **45** (0.3 g, 0.69 mmol) and sodium hydride (NaH) (0.050 g, 2.08 mmol) were dissolved in THF (10 mL) and to this mixture was added propargyl bromide (119 μL, 1.38 mmol) and the mixture was refluxed for 15 h. Excess NaH was quenched by H_2O and volatiles were removed under *vacuo*. The residue was extracted with CH_2Cl_2 (2 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and solvent evaporated under *vacuo*. The organic residue was purified by column chromatography with ethyl acetate:hexane (1:1) to yield MeOTEG-G1 acetylene **46** (0.27 g, 82 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.50 (s, 2H), 6.41 (s, 1H), 4.51 (s, 2H), 4.13 (s, 2H), 4.08 (t, 4H, *J* = 4.0 Hz), 3.82 (t, 4H, *J* = 4.0 Hz), 3.71 – 3.62 (m, 12H), 3.53 (t, 4H, *J* = 4.0 Hz), 3.36 (s, 6H), 2.43 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 160.0, 139.5, 106.6, 101.2, 79.6, 74.6, 71.9, 71.6, 70.8, 70.7, 70.6, 69.7, 67.5, 59.0, 57.0. IR: ν = 3246.5, 2872.7, 1447.3 (Figure A.8, A.9, A.10).

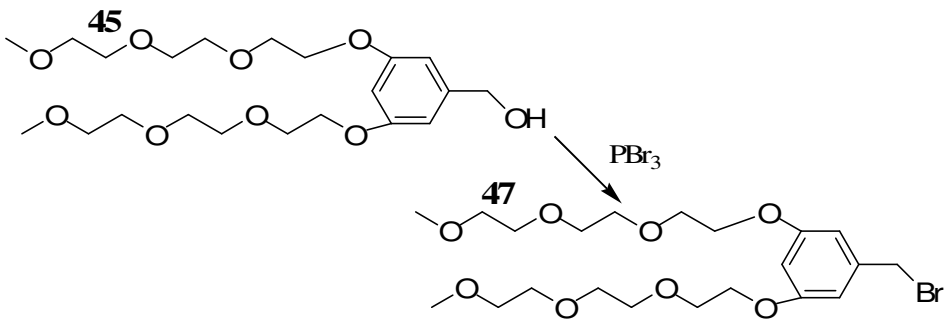


Figure 3.15. Synthesis of MeOTEG-G1 bromide

3.2.2.5. Synthesis of MeOTEG-G1 bromide **47**. MeOTEG-G1-ol **45** (1.47 g, 3.40 mmol) was dissolved in toluene (20 mL). The solution was brought to 0 ^{o}C and tribromo phosphine (PBr_3) (133 μL, 1.40 mmol) was added. The temperature raised to room temperature and stirred for 3 h. Excess PBr_3 was quenched with equivolume of ice-H_2O mixture. The mixture was extracted with $CHCl_3$ (3 x 30 mL). The organic layer was dried over Na_2SO_4, filtered and volatiles were removed under *vacuo*. The organic residue was purified with column chromatography with ethyl acetate:hexane (3:2) to yield MeOTEG-G1 bromide **47** (1.17 g, 69 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.52 (d, 2H, *J* = 2.2 Hz), 6.40 (t, 1H, *J* = 2.2 Hz), 4.37 (s, 2H), 4.08 (t, 4H, *J* = 4.9), 3.83 – 3.82 (m, 4H), 3.71 – 3.70 (m, 4H), 3.67 – 3.62 (m, 8H), 3.54 – 3.51 (m, 4H), 3.36 (s, 6H), (Figure A.11).

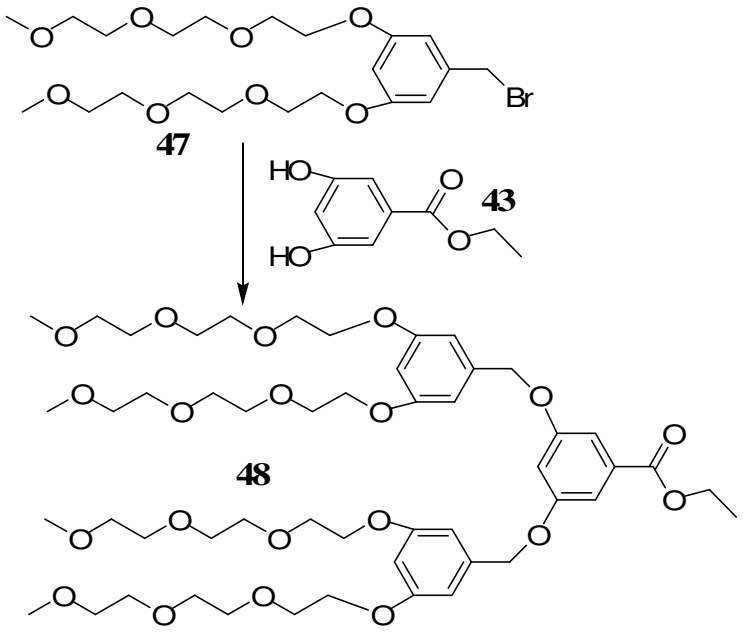


Figure 3.16. Synthesis of MeOTEG-G2 ester

3.2.2.6. Synthesis of MeOTEG-G2 ester **48**. MeOTEG-G1 bromide **47** (1.1 g, 2.22 mmol), ethyl 3,5-dihydroxybenzoate **43** (0.16 g, 0.89 mmol), K_2CO_3 (0.31 g, 2.22 mmol) and 18-C-6 (0.012 g, 0.04 mmol) were dissolved in dry acetone (30 mL). The mixture was refluxed for 12 h. The mixture was filttered in order to remove K_2CO_3, and acetone was removed under *vacuo*. The organic residue was dissolved in CH_2Cl_2 (20 mL) and extracted

with H_2O (3 x 20 mL). The organic solution was dried over Na_2SO_4, filtered and volatiles were removed under *vacuo*. The organic residue was purified by column chromatography with ethyl acetate:hexane (7:3) to yield MeOTEG-G2 ester **48** (0.77 g, 86 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 2H, *J* = 2.4 Hz)6.74 (t, 1H, *J* = 2.4 Hz), 6.57 (d, 4H, *J* = 2.4 Hz), 6.43 (t, 2H, *J* = 2.4 Hz), 4.96 (s, 4H), 4.34 (q, 2H, *J* = 7.1 Hz), 4.09 (t, 8H, *J* = 4.9 Hz), 3.82 (t, 8H, *J* = 4.9 Hz), 3.73 – 3.52 (m, 32H), 3.35 (s, 12H), 1.37 (t, 3H, J = 7.1 Hz). IR: ν = 1715.7 cm^{-1}, (Figure A.12, A.13).

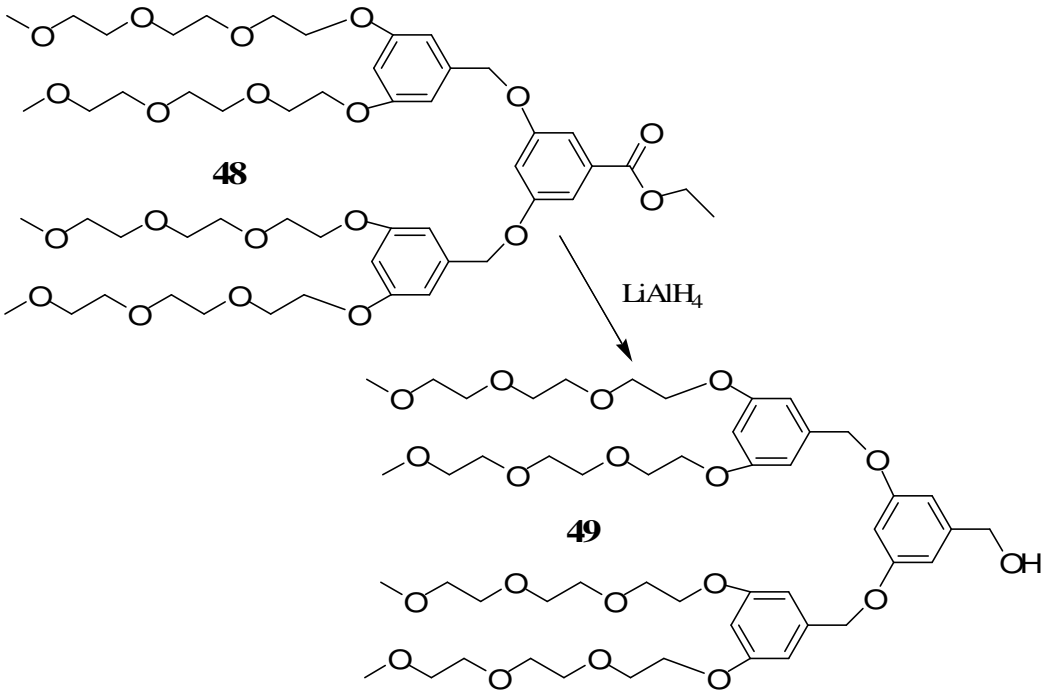


Figure 3.17. Synthesis of MeOTEG-G2-ol

3.2.2.7. Synthesis of MeOTEG-G2-ol **49**. MeOTEG-G2 ester **48** (0.71 g, 0.70 mmol) was dissolved in THF (40 mL), and lithium aluminum hydride ($LiAlH_4$) (0.08 g, 2.11 mmol) was added at 0°C. The mixture was stirred for 24 h at room temperature. Excess $LiAlH_4$ was quenched with 20 % NaOH (15 mL) and H_2O (20 mL). The mixture was then extracted with EtOAc (3 x 30 mL). The organic layer was dried over Na_2SO_4, filtered and volatiles were removed under *vacuo*. The organic residue was purified by column chromatography with ethyl acetate:hexane (4:1) to yield MeOTEG-G2-ol **49** (0.63 g, 93 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.56 (s, 6H), 6.48 (s, 1H), 6.42 (s, 2H), 4.94 (s,

4H), 4.59 (s, 2H), 4.09 (bs, 8H), 3.82 (bs, 8H), 3.70 – 3.52 (m, 32H), 3.35 (s, 12H) (Figure A.14).

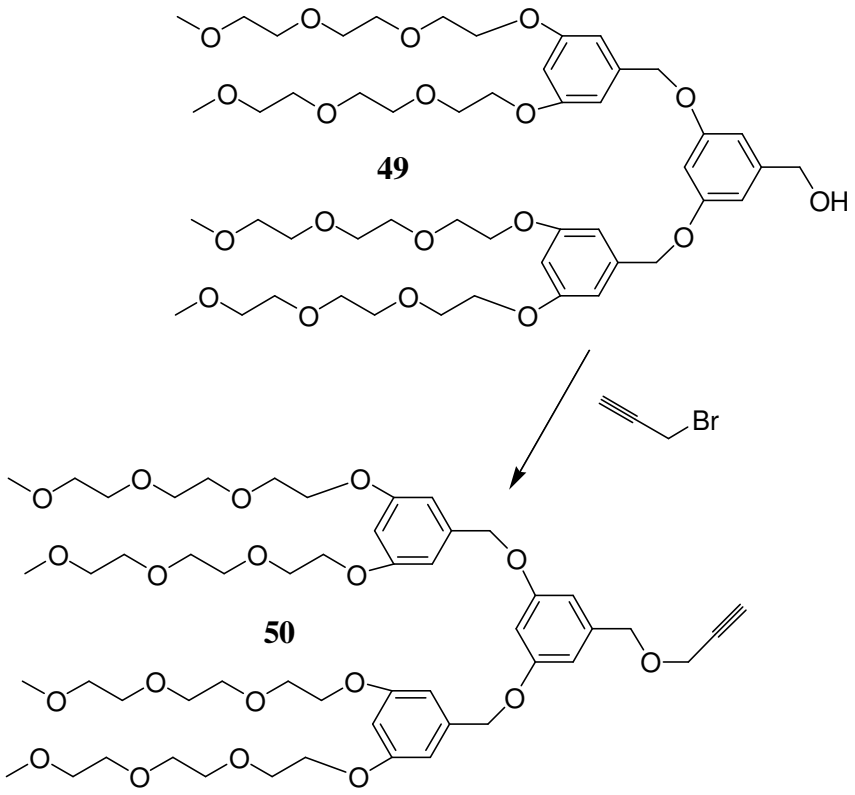


Figure 3.18. Synthesis of MeOTEG-G2 acetylene

3.2.2.8. Synthesis of MeOTEG-G2 acetylene **50**. MeOTEG-G2-ol **49** (0.22 g, 0.22 mmol) and sodium hydride (NaH) (0.026 g, 0.67 mmol) were dissolved in THF (7 mL) and to this mixture was added propargyl bromide (38 μL, 0.45 mmol) and the mixture was refluxed for 15h. Excess NaH was quenched by H_2O and volatiles were removed under *vacuo*. The residue then extracted with CH_2Cl_2 (2 x 25 mL). The organic part was dried over Na_2SO_4, filtered and solvent evaporated under *vacuo*. The organic residue was purified by column chromatography with ethyl acetate to yield MeOTEG-G2 acetylene **50** (0.27 g, 82 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.57 (s, 6H), 6.51 (s,1H), 6.43 (s, 2H), 4.93 (s, 4H), 4.52 (s, 2H), 4.14 (t, 2H, J = 2.3 Hz), 4.09 (t, 8H), 3.82 (t, 8H), 3.72 – 3.52 (m, 32H), 3.35 (s, 12H), 2.46 (t, 1H, J = 2.3 Hz). ^{13}C NMR ($CDCl_3$) δ 159.9, 139.5, 139.0, 106.7, 106.0,

101.5, 101.0, 79.5, 74.8, 71.8, 71.3, 70.7, 70.6, 70.5, 69.8, 69.6, 67.4, 59.0, 57.0. IR: ν = 3247.9, 2871.9, 1593.2 cm^{-1} (Figure A.15, A.16, A.17).

3.2.3. Modifications of β-Cyclodextrin

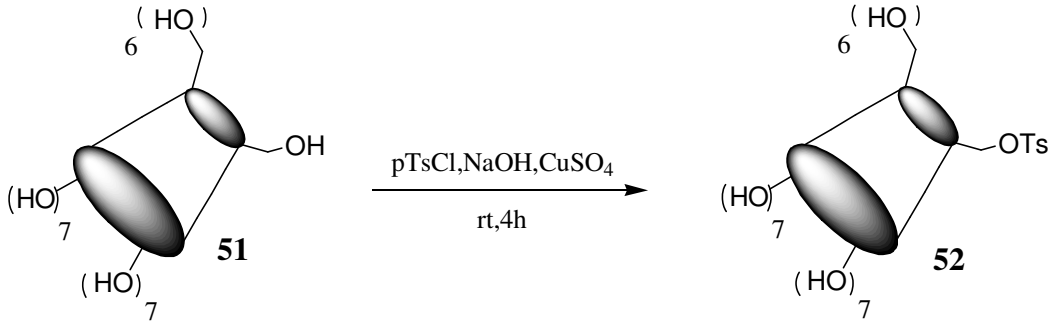


Figure 3.19. Mono tosylation of β-CD

3.2.3.1. Mono Tosylation of β-CD **52**. To a solution of β-CD **51** (3.78 g, 3.33 mmol) in H_2O (166.67 mL), a solution of $CuSO_4.5H_2O$ (2.5 g, 10 mmol) in H_2O (250 mL) and a solution of NaOH (3.33 g, 83.25 mmol) in H_2O (83.33 mL) was added. To this solution, was added a solution of pTsCl (5 g, 26.33 mmol) in acetonitrile (ACN) (33.3 mL) dropwise in 2.2 h and the solution was stirred for 4.5 h more at room temperature. The reaction was stopped by setting the pH to 7 by the addition of HCl (1 M). The mixture was filtered and the filtrate was crystallized at 0 ^oC for 12 h. The crystals were filtered, washed with cold diethylether (25 mL) and then with cold acetone (25 mL) and dried to yield mono tosyl β-CD (β-CDOTs) **52** (0.97 g, 23 % yield) as white powder. ^1H NMR data corresponds to the literature values [24].

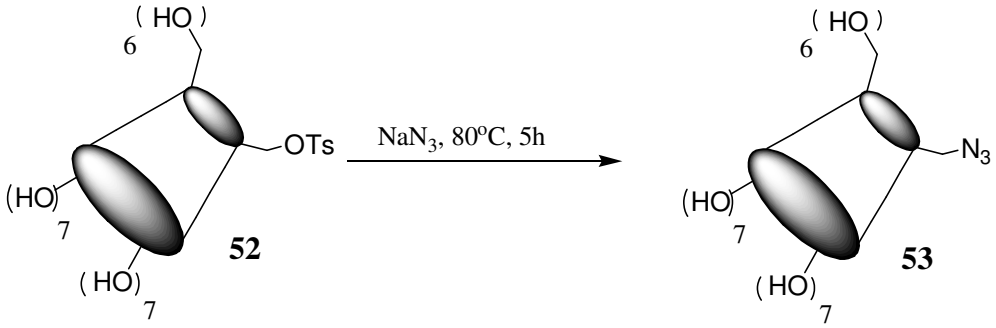


Figure 3.20. Synthesis of β-CD azide

3.2.3.2. Synthesis of β-CD Azide **53**. To a solution of sodium azide (0.1 g, 1.64 mmol) in H_2O (3 mL), β-CDOTs **52** (0.1 g, 0.08 mmol) was added. The solution was allowed to react at 80°C for 5h. The solution was precipitated in acetone:water (6:1), and filtered to yield β-CD azide **53** (β-CDN_3)(0.73 g, 83 % yield) as a white solid. ^{1}H NMR data corresponds to the literature values [24].

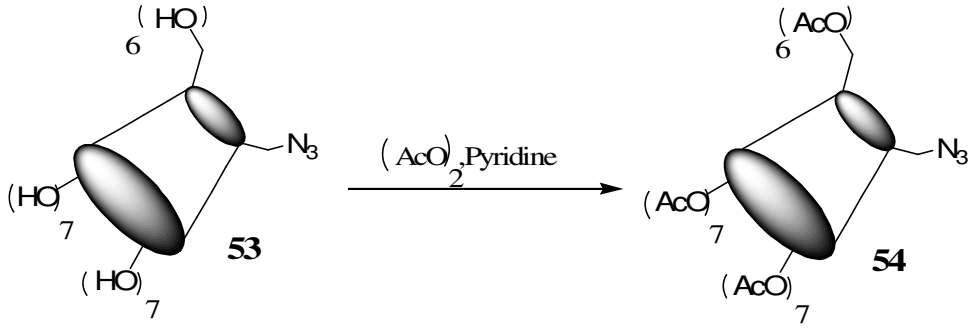


Figure 3.21. Synthesis of acetylated β-CDN_3

3.2.3.3. Synthesis of Acetylated β-CDN3 **54**. β-CDN_3 **53** (0.1 g, 0.086 mmol) was dissolved in acetic anhydride ($(AcO)_2$), pyridine mixture (1:2, 27 mL) and stirred at 80 °C overnight. Mixture concentrated and extracted with 10 % HCl (3 x 10 mL) and H_2O (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered, and volatiles were removed under vacuo. The organic layer was purified by column chromatography with benzene:ethanol (16:1) to yield acetylated β-CDN_3 **54** (0.04 g, 23 % yield) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.31 - 5.28 – 5.00 (m, 12H), 4.82 – 4.73 (m, 6H), 4.58 – 4.50

(m, 6H), 4.30 – 4.03 (m, 12H), 3.78 – 3.62 (m, 8H), 2.15 – 2.00 (m, 60H). IR: ν = 2104, 1738.7 cm^{-1} (Figure A.18,A.19).

3.2.4. β-CD and Polyaryl Ether Dendron Click

To synthesize the second dendron that will contribute to self assembly to afford the supramolecular dendrimer, the azido cyclodextrins and acetylene functionalized polyaryl ether dendrons were combined via click chemistry. The first generation polyaryl ether dendron readily reacts with a non-acetylated azido cyclodextrin to afford the dendron with a high yield. Unfortunately, this is not true for the second generation polyaryl ether dendron and non-acetylated azido cyclodextrin. To overcome this problem, acetylated cyclodextrin was used.

3.2.4.1. β-CDN3 53 and MeOTEG-G1 acetylene 46 Click (G-1 Click) **55**. β-CDN_3 **53** (0.03 g, 0.026 mmol), MeOTEG-G1 acetylene **46** (0.015 g, 0.032 mmol) and copper iodide (0.003 g, 0.016 mmol) were dissolved in dry dimethyl formamide (DMF) (0.75 mL) under nitrogen atmosphere. To the solution N,N diisopropylethylamine (DIPEA) (13 μL, 0.16 mmol) was added and the solution was heated to 125 ^{o}C for 30 minutes in microwave. DMF was removed under *vacuo* and the reaction mixture was purified by column chromatography with methyl ethyl ketone (MEK):methanol:H_2O (6:1:1) to yield G-1 Click **55** (0.035 g, 83 % yield) as a white solid. ^{1}H NMR (D_2O) δ 7.46 (s, 1H), 6.63 (s, 2H), 6.44 (s, 1H), 5.27 – 5.09 (m, 8H), 4.11 (s, 4H), 3.90 – 3.53 (m, 71H), 3.32 (s, 6H) (Figure A.20).

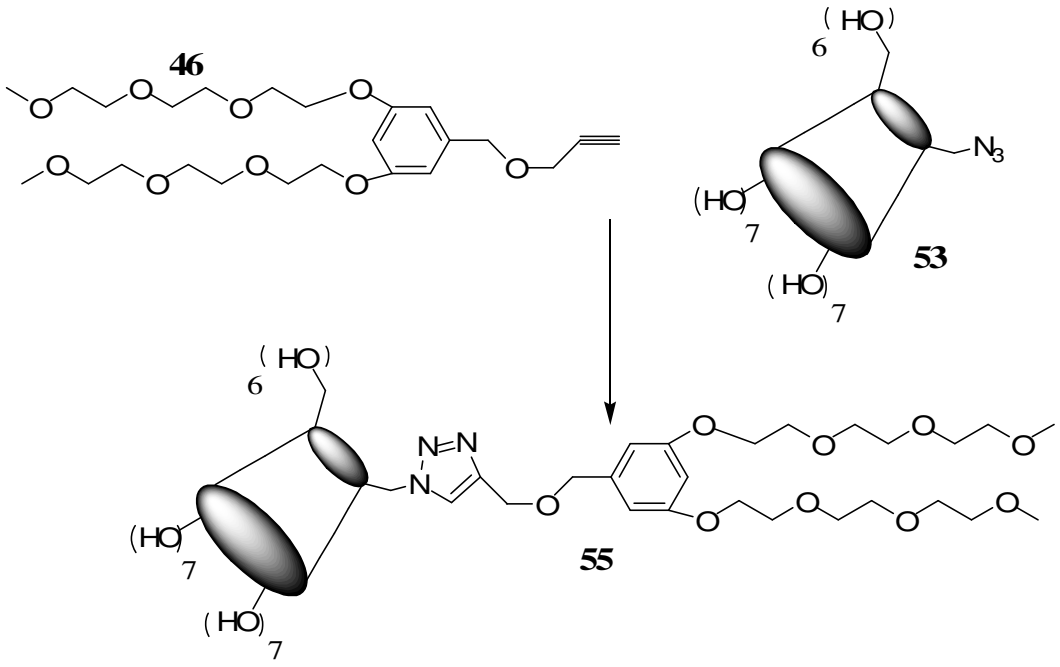


Figure 3.22. β-CDN$_3$ and MeOTEG-G1 acetylene click (G-1 Click)

3.2.4.2. Acetylated β-CDN3 54 and MeOTEG-G2 acetylene 50 Click (G-2 Click) **56**. Acetylated β-CDN$_3$ **54** (0.124 g, 0.062 mmol), MeOTEG-G2 acetylene **50** (0.075 g, 0.074 mmol) and copper iodide (0.007 g, 0.037 mmol) were dissolved in dry toluene (0.8 mL) under nitrogen atmosphere. To this solution, was added DIPEA (63.7 μL, 0.37 mmol) and the solution was heated to 125 ^{o}C for 30 minutes in microwave (Figure A.21.).

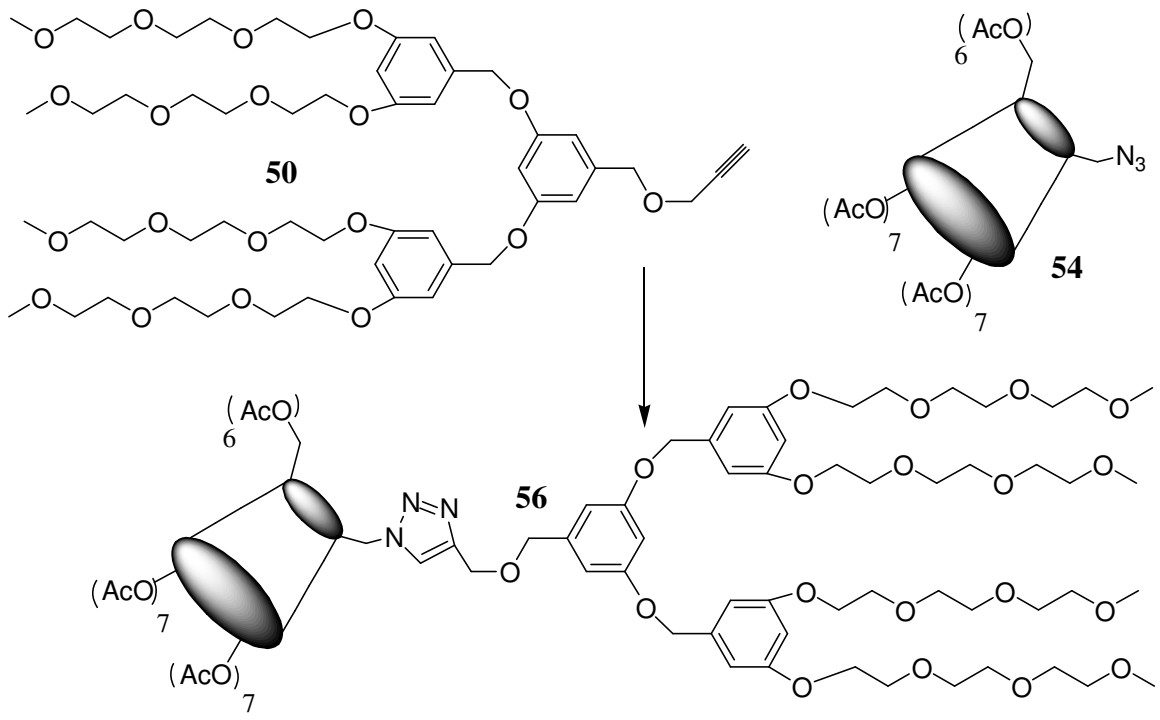


Figure 3.23. Acetylated β-CDN$_3$ and MeOTEG-G2 acetylene Click (G-2 Click)

3.3. Dendrimer Self Assembly

The complexation has been accomplished in NaOH – NaHCO3 buffer at pH 10.50 with ionic strength 0.6 [21]. In order to justify the formation of cyclodextrin based self assembled dendrimer a control UV-Vis experiment has been carried out exactly at the same complexation conditions. In the UV-Vis experiment phenolphthalein **57** selected as a dye which has the ability to bind to the β-cyclodextrins hydrophobic cavity. When the complexation between the dendronized β-cyclodextrin **58** and the phenolphthalein takes place at that pH the initial purple color of the dye solution diminishes. This is due to the Van der Waals interactions, hydrogen bonding, and hydrophobic interactions [22]. Thus the diminishing of absorbance proves the inclusion of the dye into the β-cyclodextrin's hydrophobic cavity (Figure 3.24).

Upon addition of the 2-amino adamantane **59**, there is a restoration of the purple color. This is due to the fact that, the 2-amino adamantane has replaced the dye to form a new self assembly **60**.

The supramolecular assemblies that both the dye and the 2-amino adamantane form with dendronized β-cyclodextrin are reversible. Another fact is that, the match between 2-amino adamantane and dendronized β-cyclodextrin is much more appropriate in size than that of phenolphthalein and β-cyclodextrin.

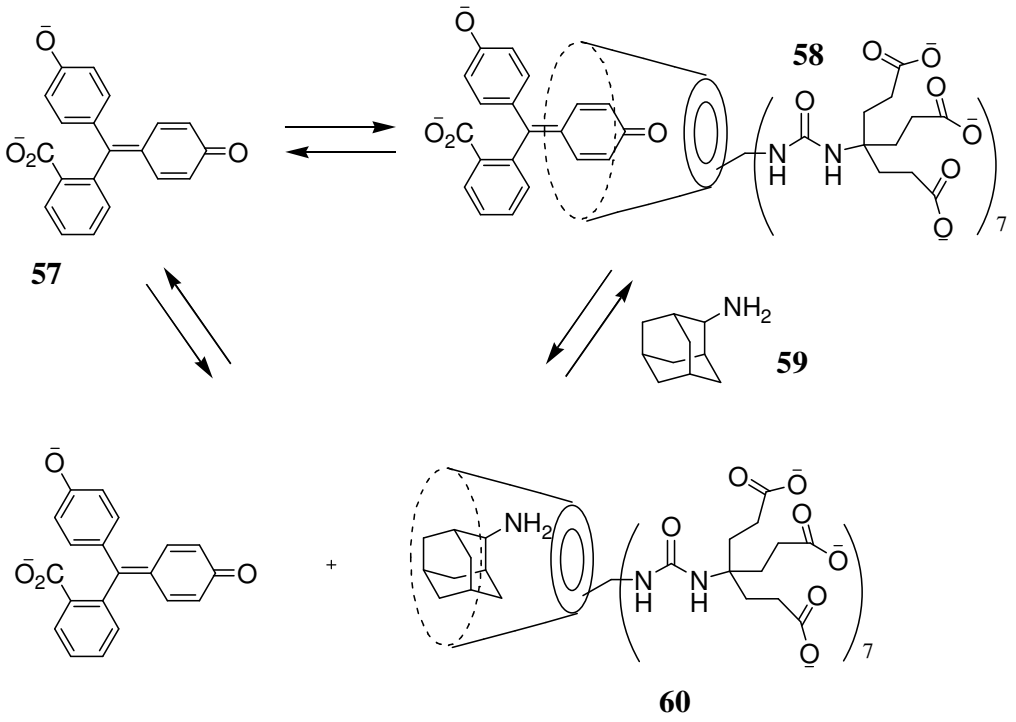


Figure 3.24. The competitive complexation

To justify the dendrimer assembly, exactly the same idea was used which is described above. To a phenol phtalein dye solution (30 μM), 60 moles fold cyclodextrin modified dendron was added. Due to the reason of decrease in absorption, it is proven that the phenol phtalein dye which has a nice pink color at buffer pH was complexed with β-CD's hydrophobic cavity. Upon addition of adamantane functionalized dendron (2.5 moles fold with respect to β-CD) the absorption of dye (color) was enhanced greatly. The restoration of absorption indicates that there is a competition for binding between the dye and the adamantane dendron thus proving the supramolecular dendrimer self assembly. The intention of using excess adamantane rises from the dynamic and competitive nature of self assembly. In Figure 3.26 and Figure 3.27 the self assemblies between a G-1 Click

dendron and 1st and 2nd generations of adamantyl functionalized dendrons were shown respectively.

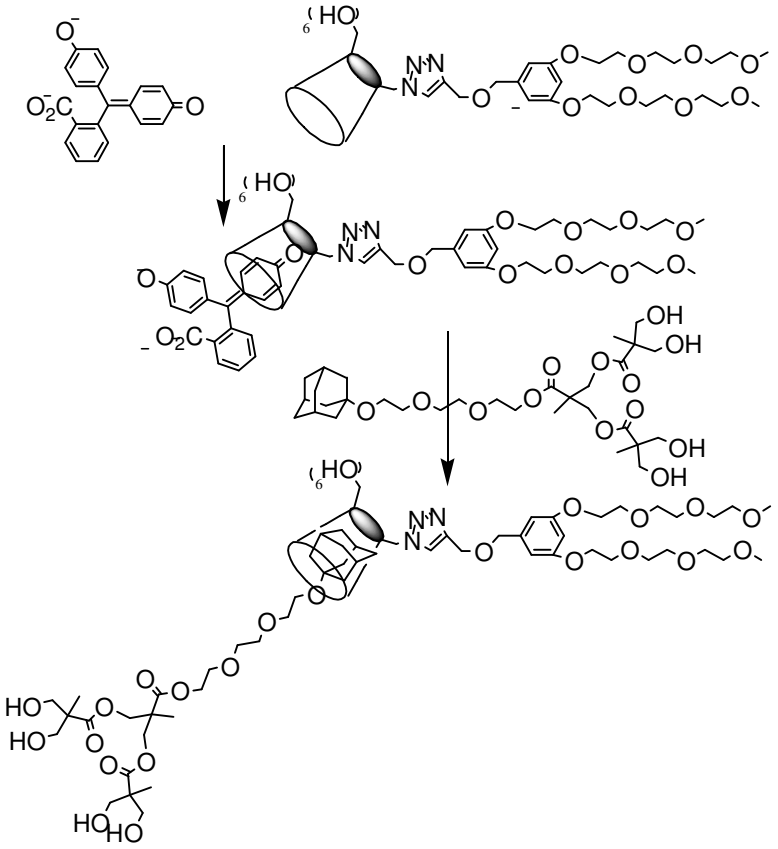


Figure 3.25. The non-covalent dendrimer assembly

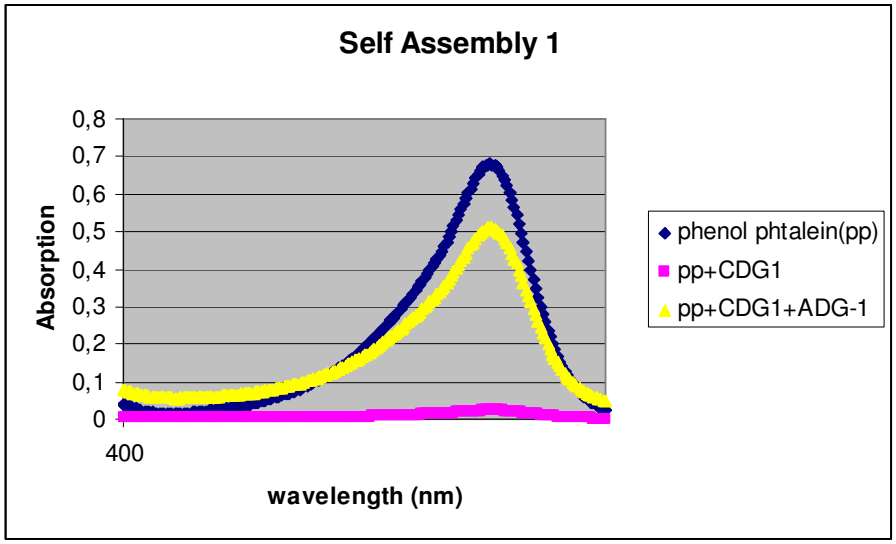


Figure 3.26. G-1 Click AD-G1 dendrimer assembly

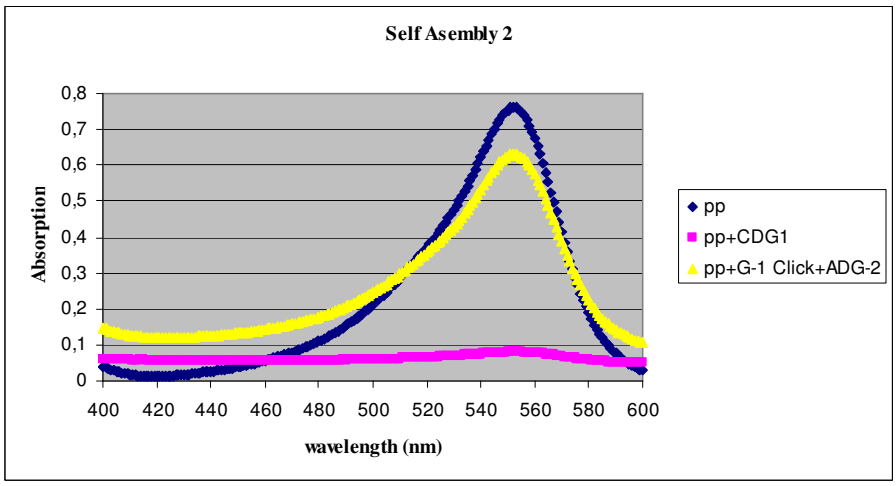


Figure 3.27. G-1 Click AD-G2 dendrimer assembly

4. RESULTS AND DISCUSSION

For the synthesis of AD-TEG-G1 acetal, ^{1}H NMR justifies the molecule in a way such that the (–CH_2) protons are chemically different (δ4.18 (d, 2H, J = 11.8 Hz)) due to the six membered ring conformation. One of the protons is on axial position and the other one is on equatorial position on the plane so that they experience different chemical environment on time scale. For this reason they appear as a doublet with a high coupling constant (Figure A.1.). Another fact which proves the formation of the desired molecule is the disappearance of (-OH) stretch in IR spectrum (Figure A.2.).

Upon hydrolysis of acetal functionality in the synthesis of AD-TEG-G1 ol, with the disturbance of six membered ring, the (-CH_2) protons becomes chemically equivalent and the doublet in the ^{1}H NMR disappears (Figure A.3.). Another fact that justifies the molecule is the restoration of (-OH) stretch in the IR spectrum (Figure A.4.). The facts that are mentioned above are also valid for the second generation dendron.

The adamantyl moiety on the focal point of polyester dendron is responsible for the complexation with the β-CD. The triethylene glycol linker that is present between the adamantane and the polyester dendron not only provides water solubility to the whole dendron but also increases the availability of adamantane for the complexation by decreasing the steric hinderance.

The triethylene glycol monomethyl ether functionalized polyaryl ether dendrons were further functionalized with alkyne moiety with propargyl bromide in order to react with an azide moiety of the β-CD via click reaction. The accomplishment of the placement of alkyne terminality has been proven via ^{1}H NMR spectroscopy. In the first generation case, the terminal alkyne proton (≡C-H) appears as a triplet (2.46 (t, 1H, J = 2.3 Hz)) and has an integration value of one. The same concept is valid for the second generation dendron

where the terminal alkyne proton (≡C-H) appears as triplet (2.46 (t, 1H, J = 2.3 Hz)), and again has an integration value of one.

The purpose of the peripheral MeOTEG functionalities is to provide water solubility to the dendron which has hydrophobic aromatic rings. These functionalities were achieved not after the whole dendron was synthesized but alternatively, by selecting a convergent route for the dendron synthesis, which starts from these peripheral MeOTEG units and grows towards to the focal point. The fact that proves the attachment of two of these functionalities per peripheral aromatic ring is the integration ratio of methyl (-CH_3) groups to the aromatic protons which is calculated from the ^{1}H NMR spectrum. The integration ratio for both the first generation dendron and the second generation dendron is two to one.

The other component that will couple with the acetylene dendrons is the mono azido functionalized β-CD. Apart from the other two members of cyclodextrin family, β-CD has lower water solubility.This property arises from the fact that the six out of seven primary hydroxyl units are hydrogen bonded intramolecularly. Hydrogen bonding also causes a decrease in reactivity of the hydroxyl groups which are responsible for it. Thus the one out of seven hydroxyl groups is more reactive. This fact was exploited in order to mono functionalize the cyclodextrin ring.

β-CD dendron conjugate was synthesized via click chemistry. The product, synthesized by combining first generation dendron and β-CD, was justified by ^{1}H NMR. The proton on the triazole ring which is formed after cycloaddition reaction, appears on the aromatic reagion and has an integral value of one. However same reaction conditions didn't hold for the second generation dendron,. To overcome this problem the remaining 20 (-OH) groups were protected with acetyl groups, and then click reaction was performed for the second generation dendron. It can be seen from ^{1}H NMR that the click reaction was working. But there was remaining unreacted second generation dendron even after prufication with column chromatography. Thus, to simplify the purification, current efforts are for deprotection of the acetyl protection groups.

After two unsymmetrical dendrons has been synthesized, supramolecular assembly was carried on in aqueous buffer solution. Two prove the dendrimer supramolecular assembly, UV-vis titration was used. In the UV-Vis titration, the disappearance of pink color of phenol phtalein dye solution upon addition of CDG1 click dendron proves two concepts. Phenol phtalein dye can make inclusion complex with the hydrophobic cavity of β-CD, and β-CD has the ability of making host-guest interactions even after chemical modification. When the adamantane containing dendron was added the pink color was restored. This is mainly because the nature of self assembly is reversible and the occurring inclusion complex has a dynamic equilibrium. Adamantane has a better affinity towards the hydrophobic interior cavity of β-CD and it simply replaces the phenol phtalein dye. Thus the supramolecular segment block dendrimer assembly occurs.

5. CONCLUSIONS

Water soluble polyester dendrons bearing adamantane functionality at the focal point were synthesized. Surface functionalized polyaryl ether dendrons were synthesized and further functionalized with acetylene moieties. Mono functionalization of β-CD with azide moiety was achieved. Acetylene functionalized polyaryl ether dendron and β-CDN_3 were combined to afford dendron oligosaccharide conjugate by utilizing click chemistry. Unfortunately, the conditions that yield to first generation dendron β-CD conjugate, did not hold for the second generation of polyaryl ether dendron conjugate. To avoid this problem, hydroxyl groups on the β-CD was protected and current efforts concentrate on the deprotection of the acetyl groups of the conjugate. The supramolecular dendrimer assemblies were carried out for the first generation of β-CD conjugated dendron and two generations of adamantly functionalized polyester dendrons. The supramolecular assemblies were proven via UV-Vis spectroscopy.

APPENDIX A: SPECTROSCOPY DATA

^{1}H, ^{13}C NMR and IR spectroscopy of the synthesized products are included. Necessary expansions were made on the NMR data.

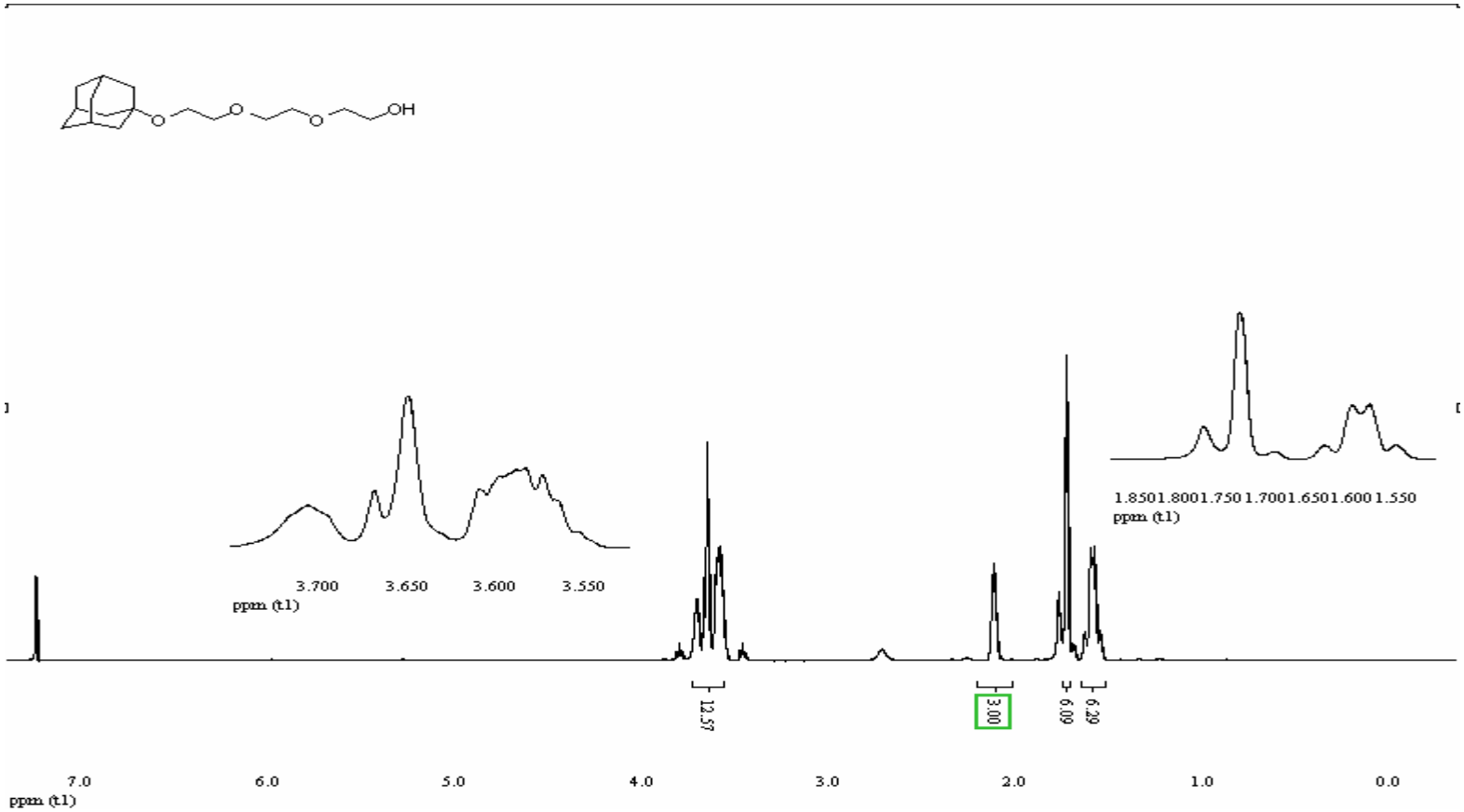


Figure A.1. Synthesis of Adamantane Triethylene Glycol **32**

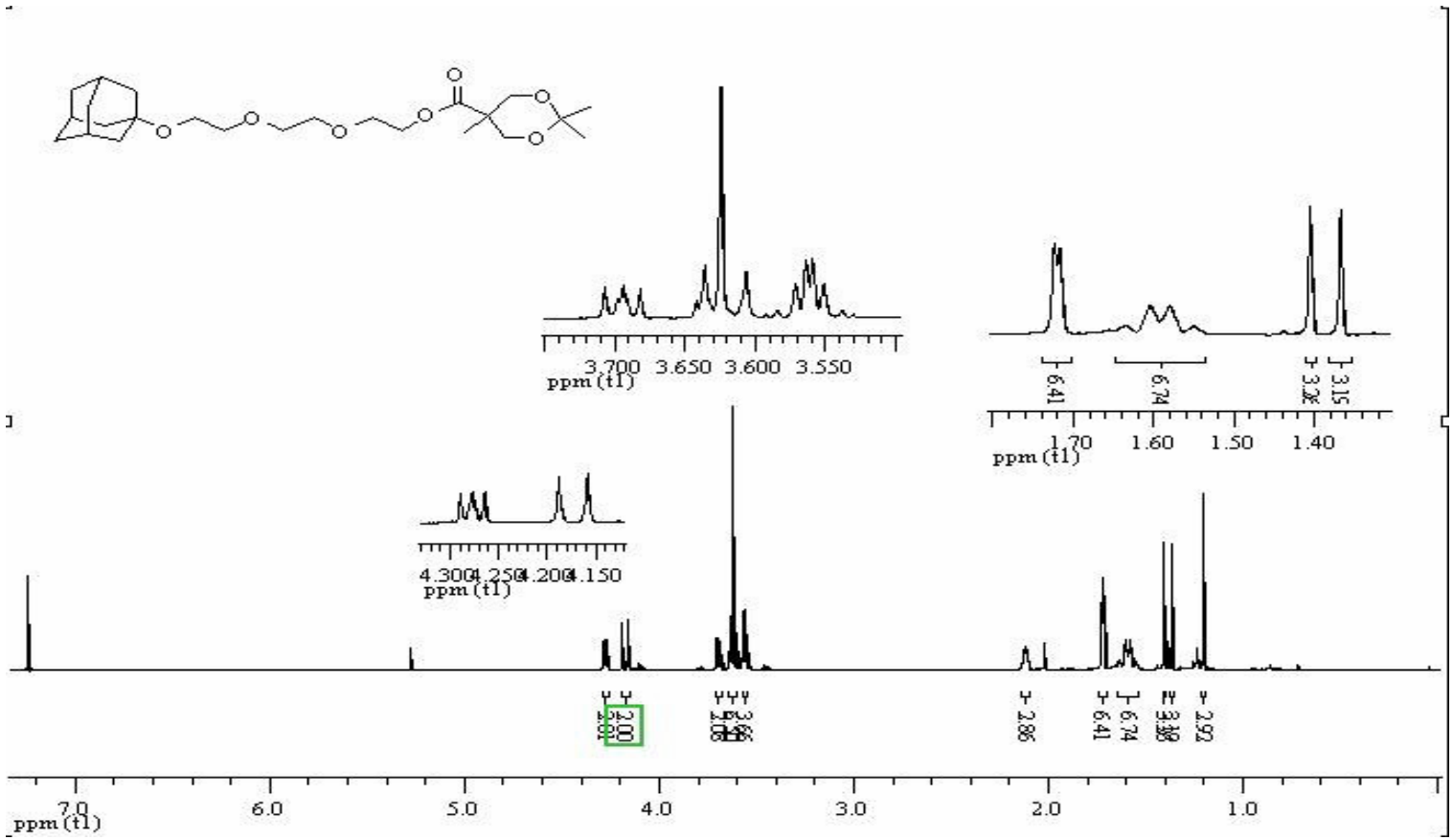


Figure A.2. ^{1}H NMR of AD-TEG-G1 acetal **37**

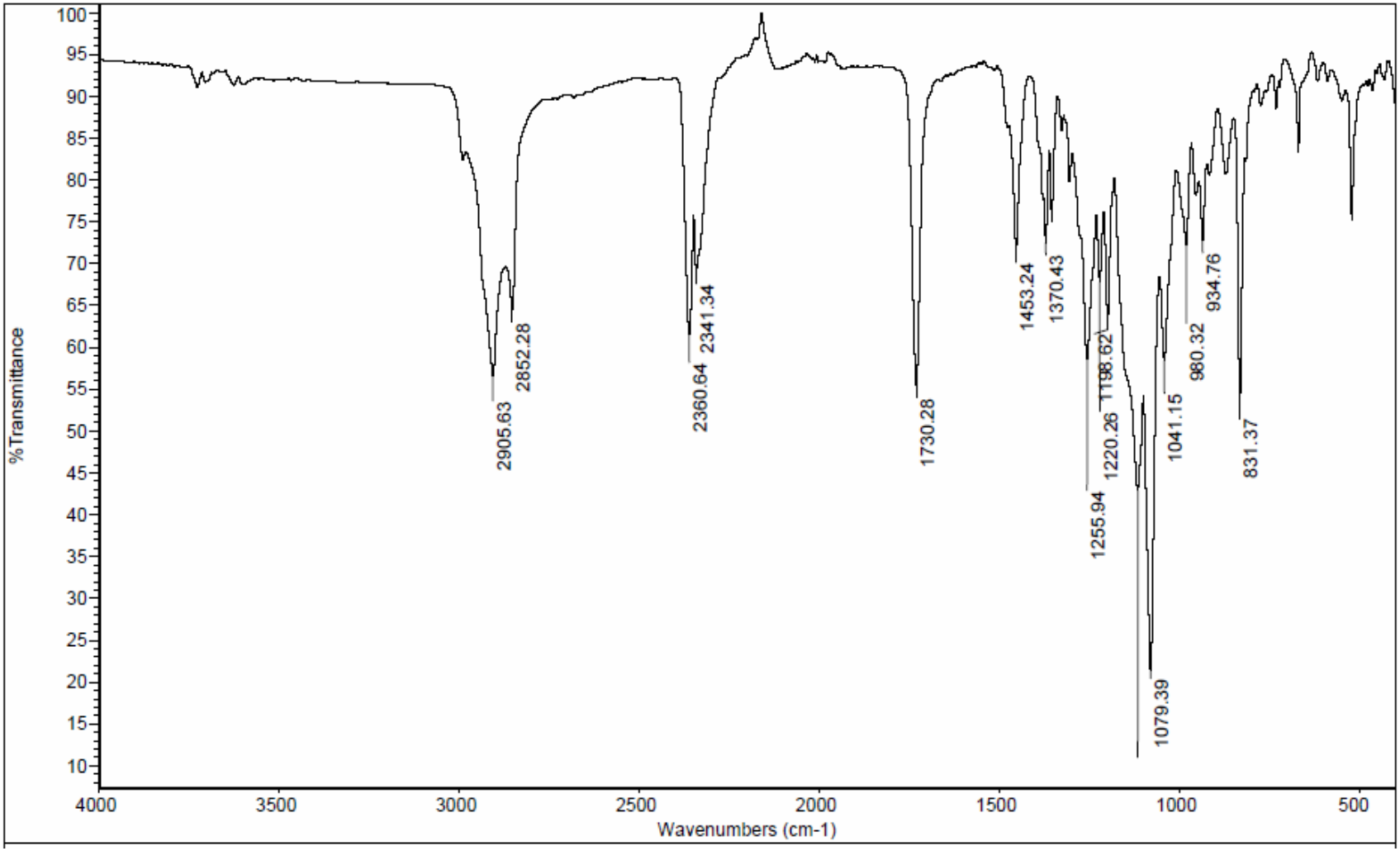


Figure A. 3. IR spectrum of AD-TEG-G1 acetal **37**

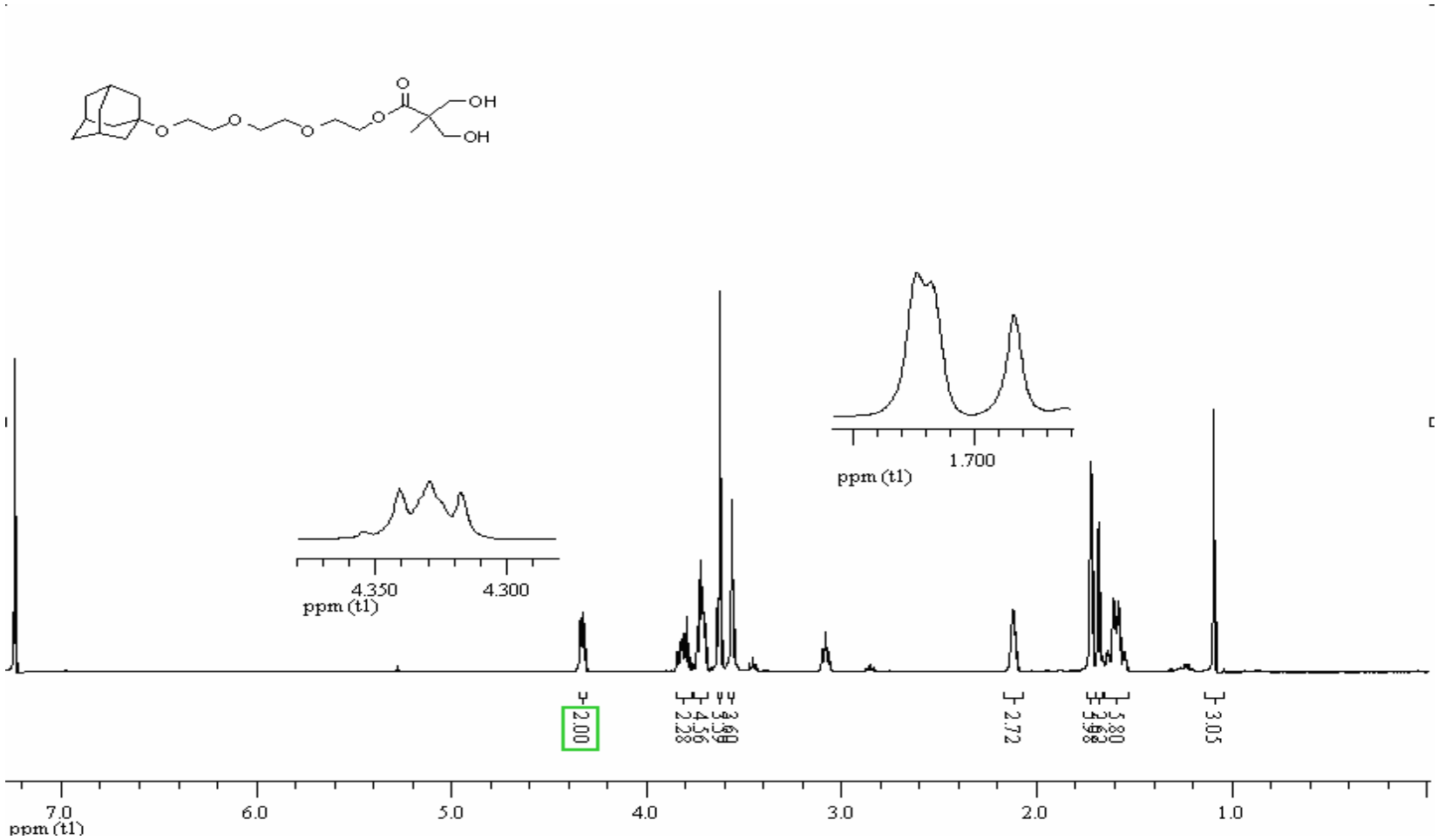


Figure A.4. ^{1}H NMR of AD-TEG-G1 **38**

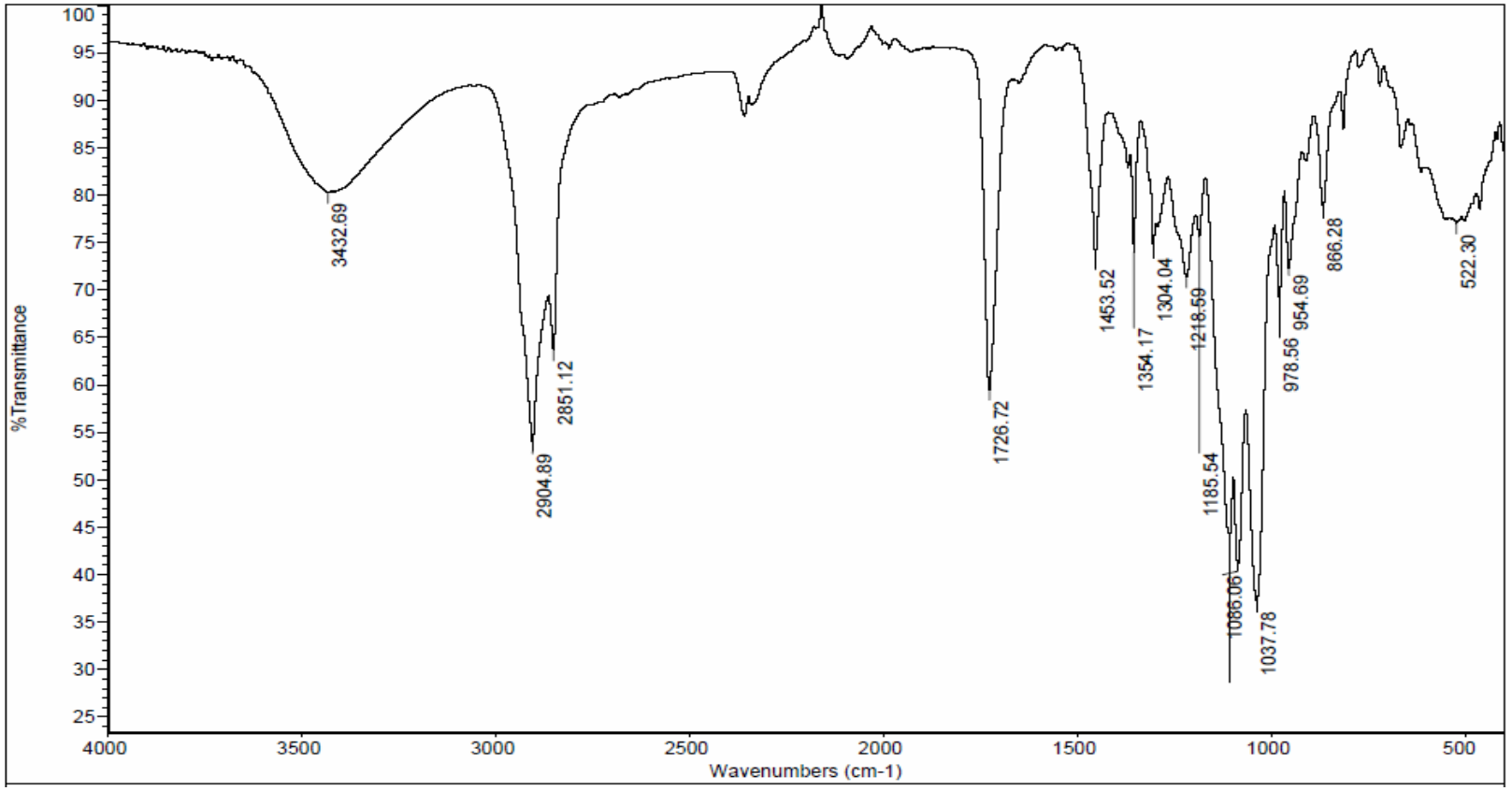


Figure A.5. IR spectrum of AD-TEG-G1 **38**

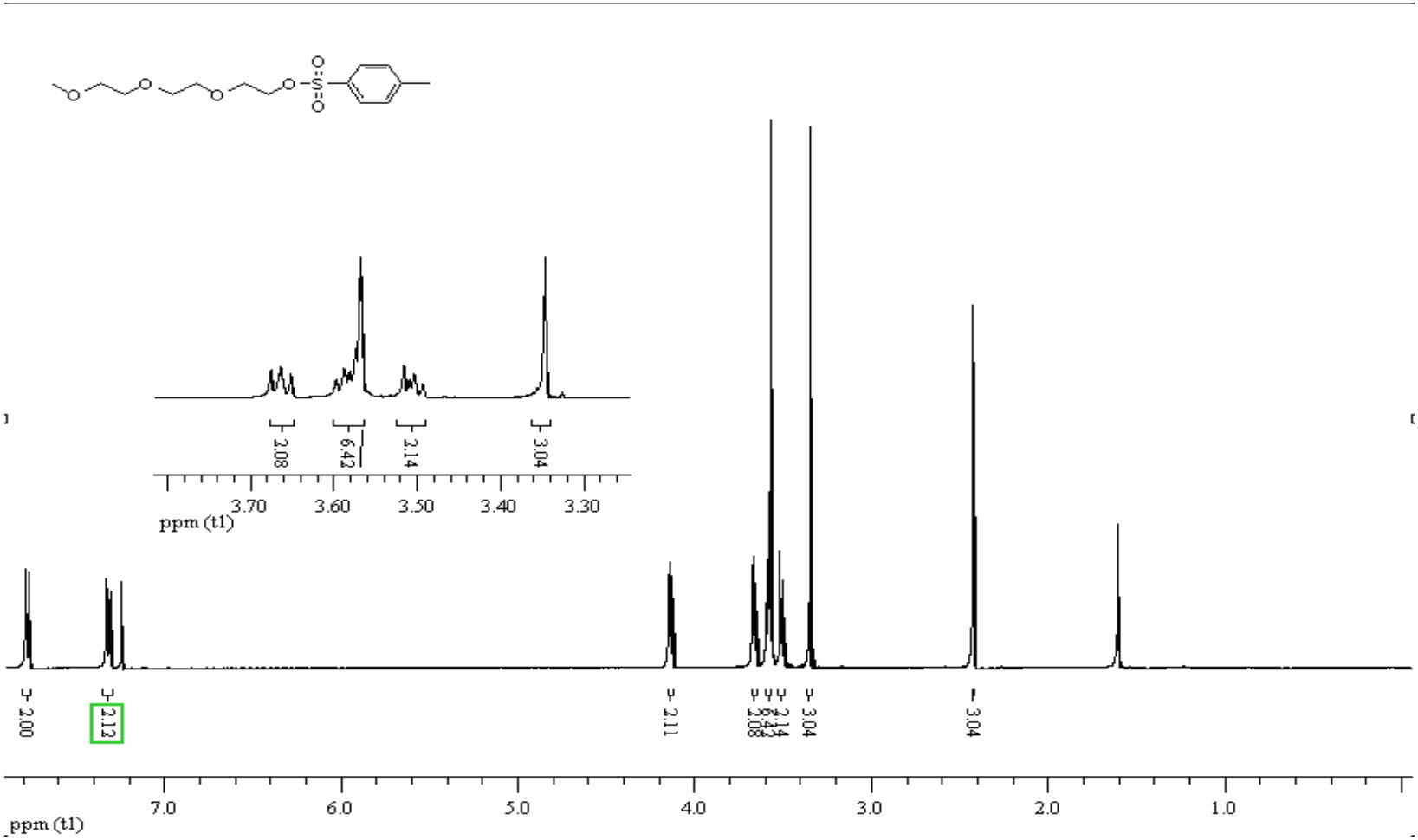


Figure A.6. 1H NMR of MeOTEGOTs **42**

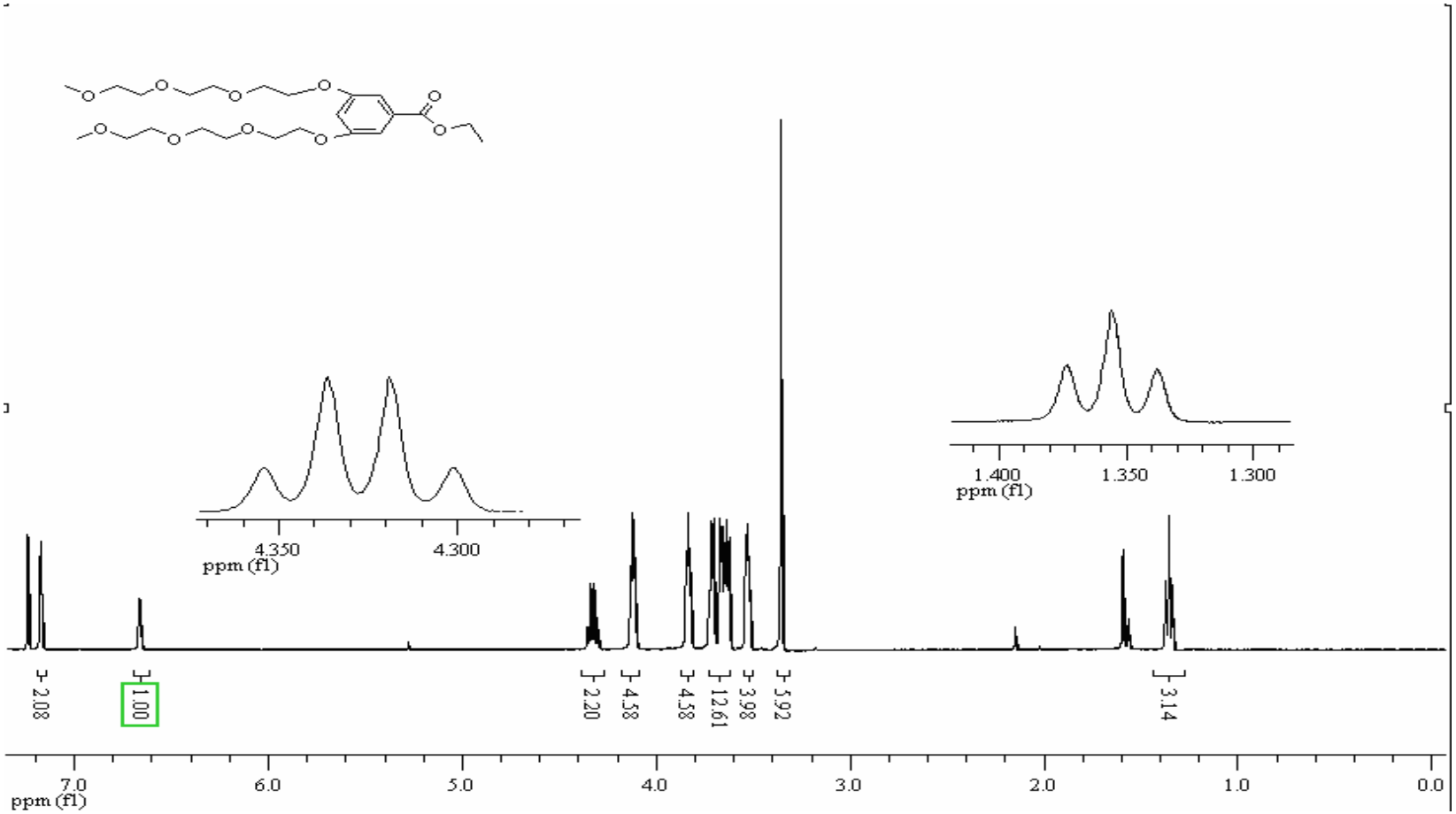


Figure A.7. ^{1}H NMR of MeOTEG-G1 ester **44**

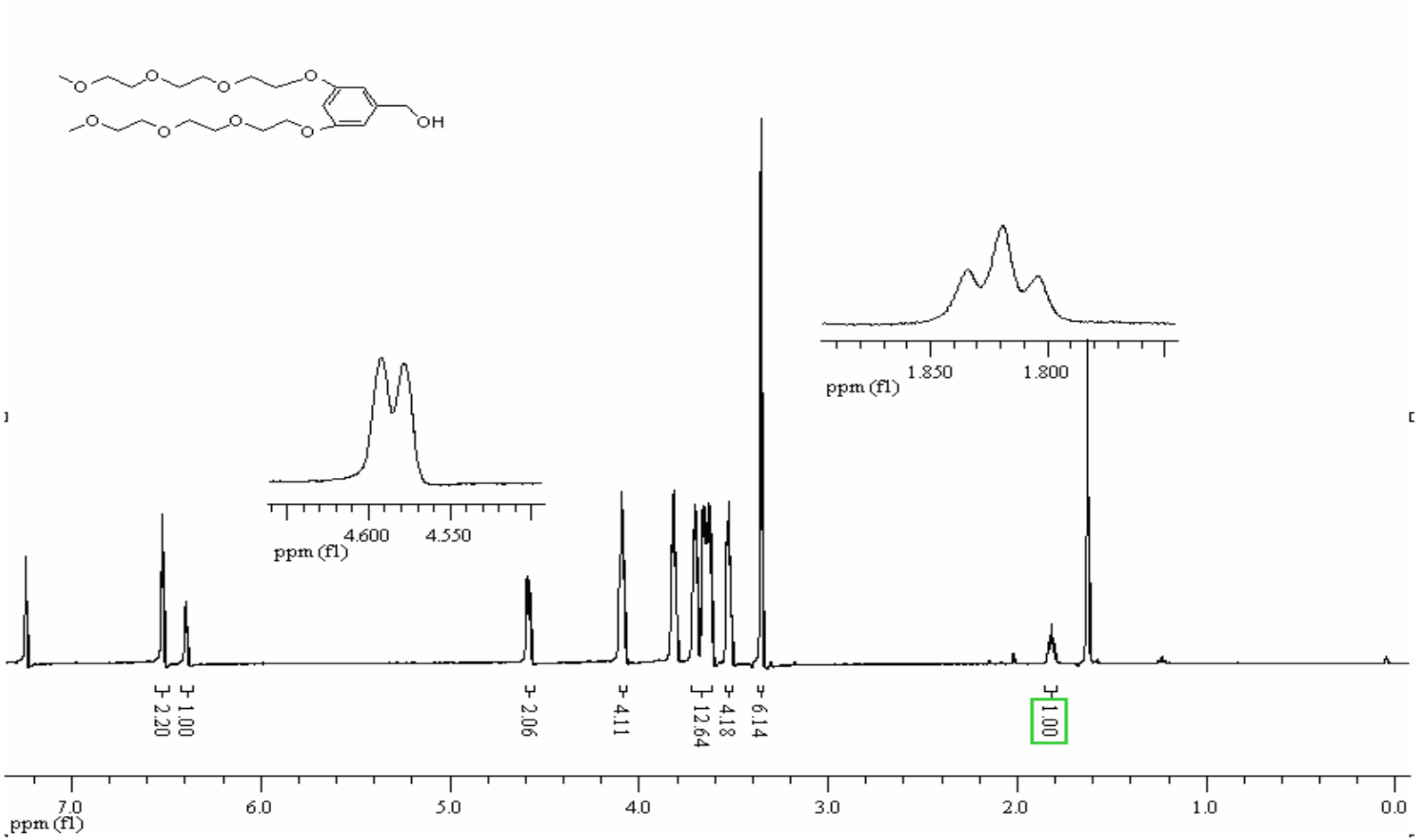


Figure A.8. ^{1}H NMR of MeOTEG-G1-ol **45**

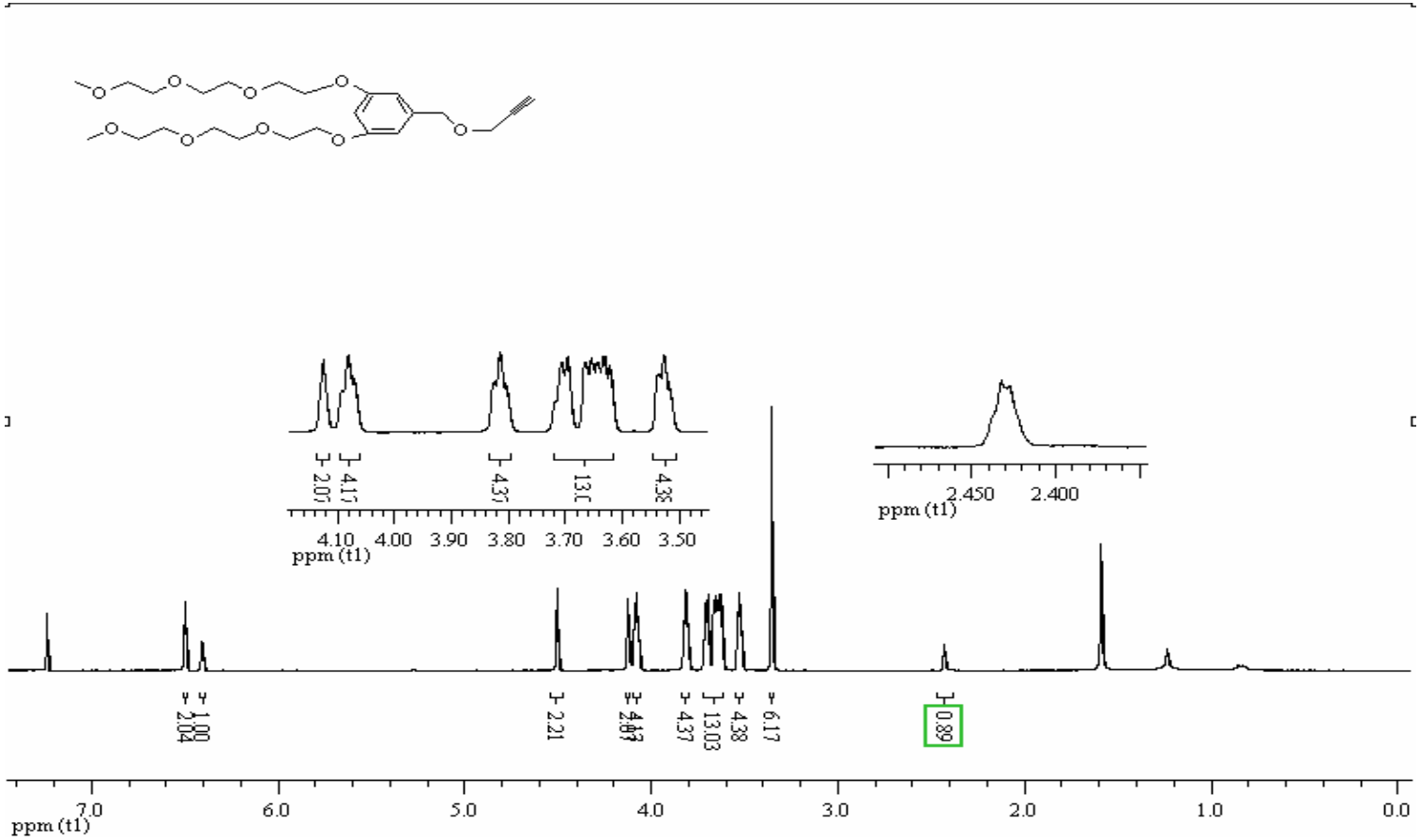


Figure A.9. ^{1}H NMR of MeOTEG-G1 acetylene **46**

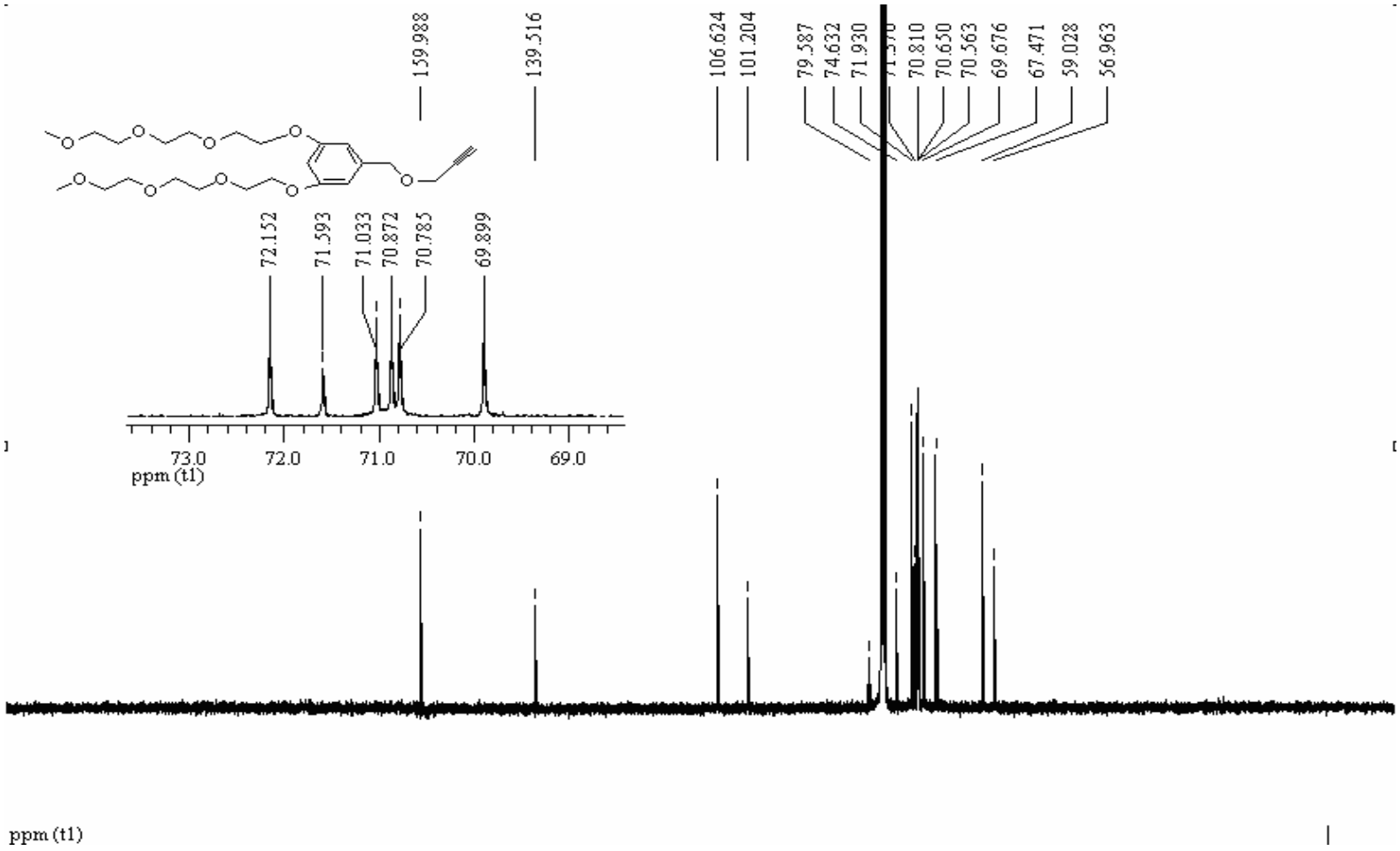


Figure A.10. ^{13}C NMR of MeOTEG-G1 acetylene **46**

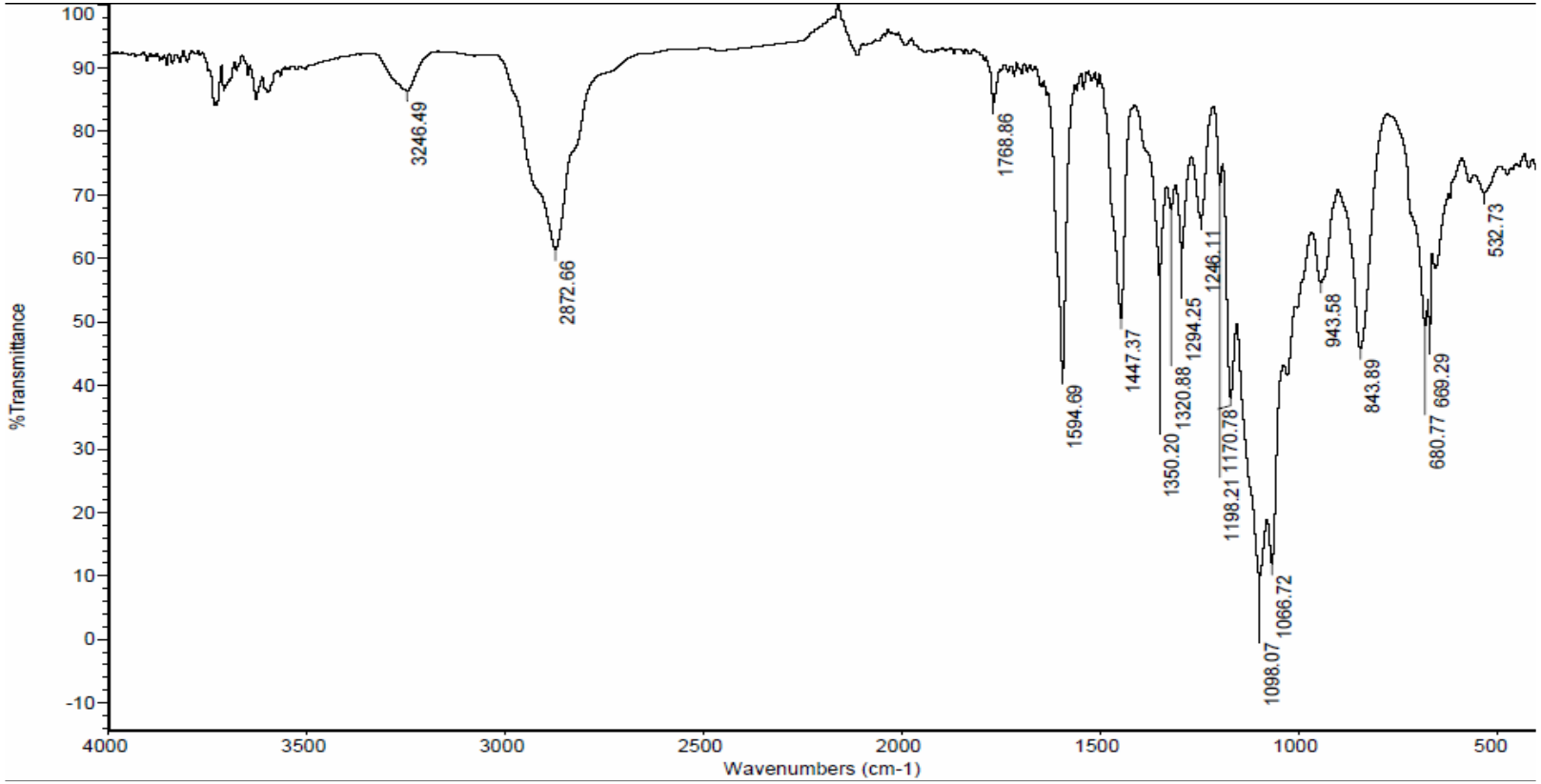


Figure A.11. IR spectrum of MeOTEG-G1 acetylene **46**

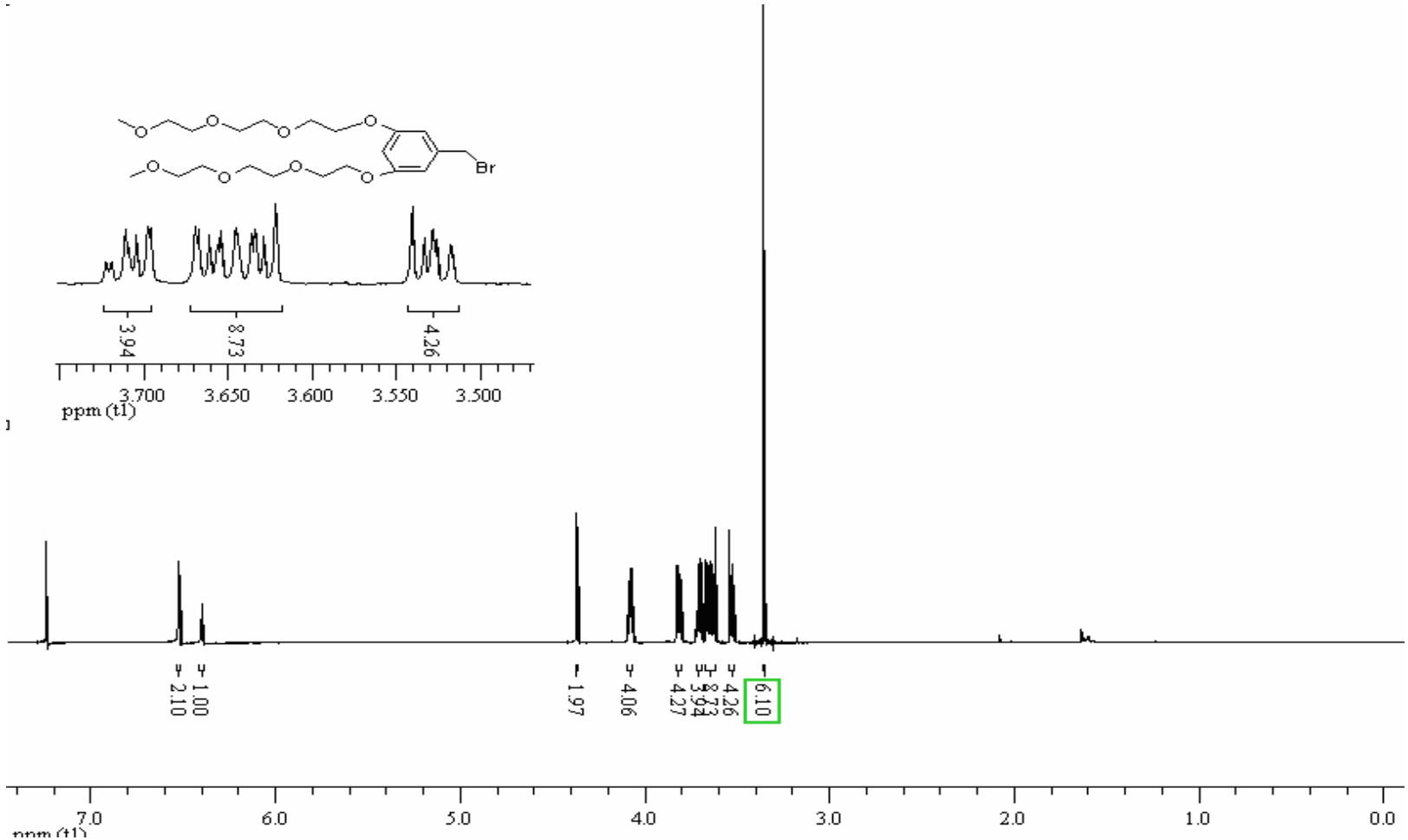


Figure A.12. ^{1}H HMR of MeOTEG-G1 bromide **47**

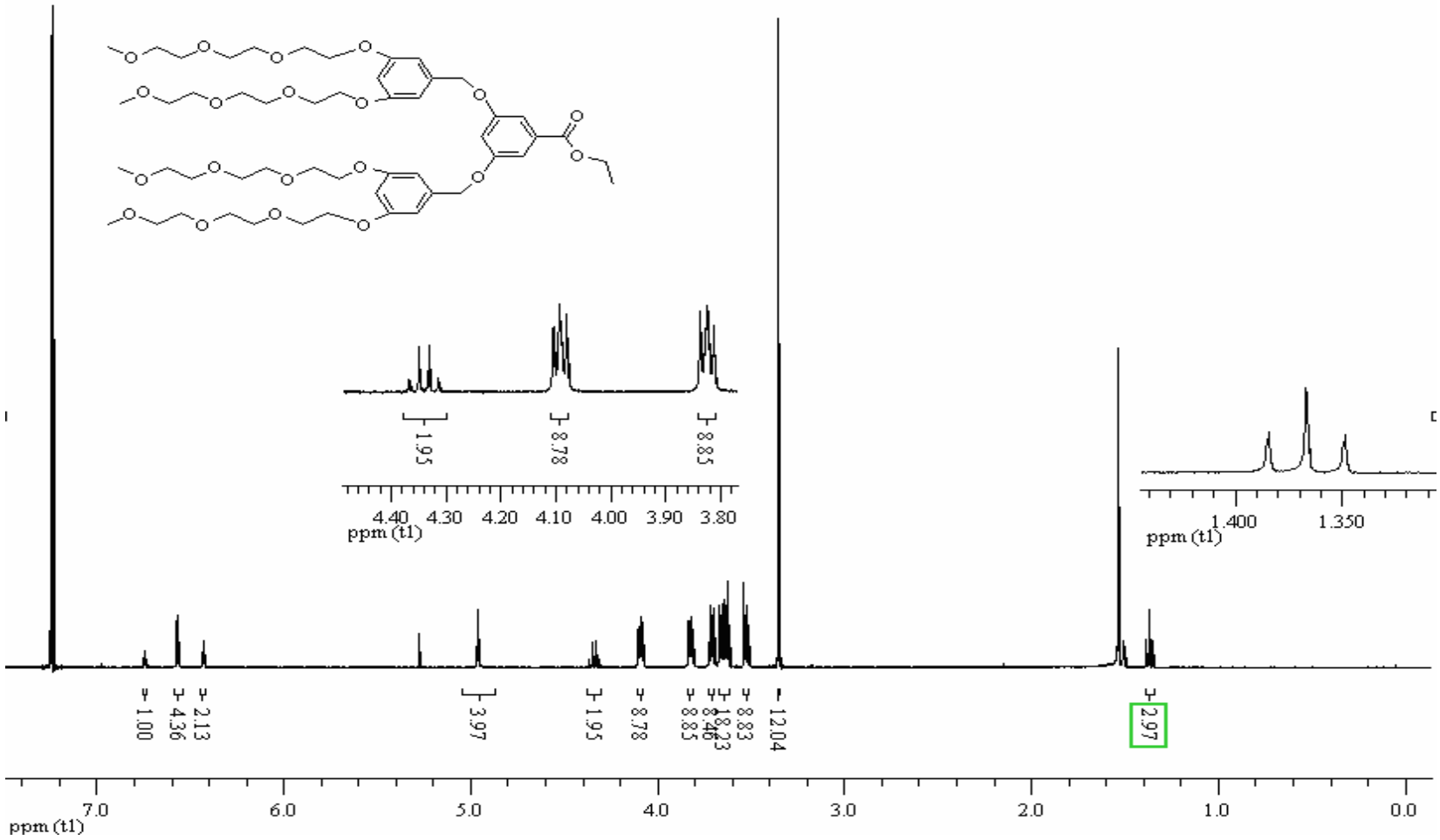


Figure A.13 ^{1}H NMR of MeOTEG-G2 ester **48**

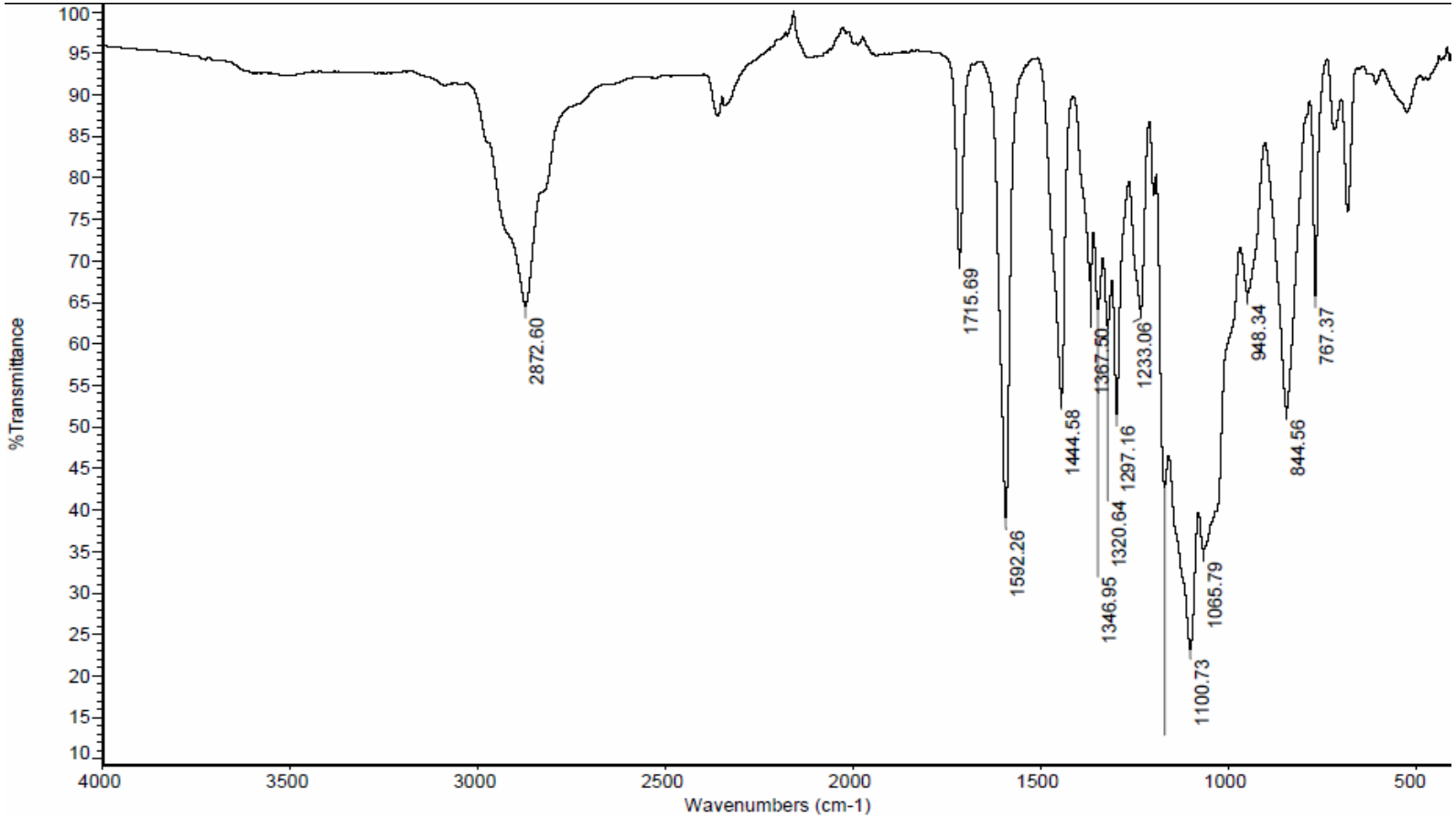


Figure A.14. IR spectrum of MeOTEG-G2 ester **48**

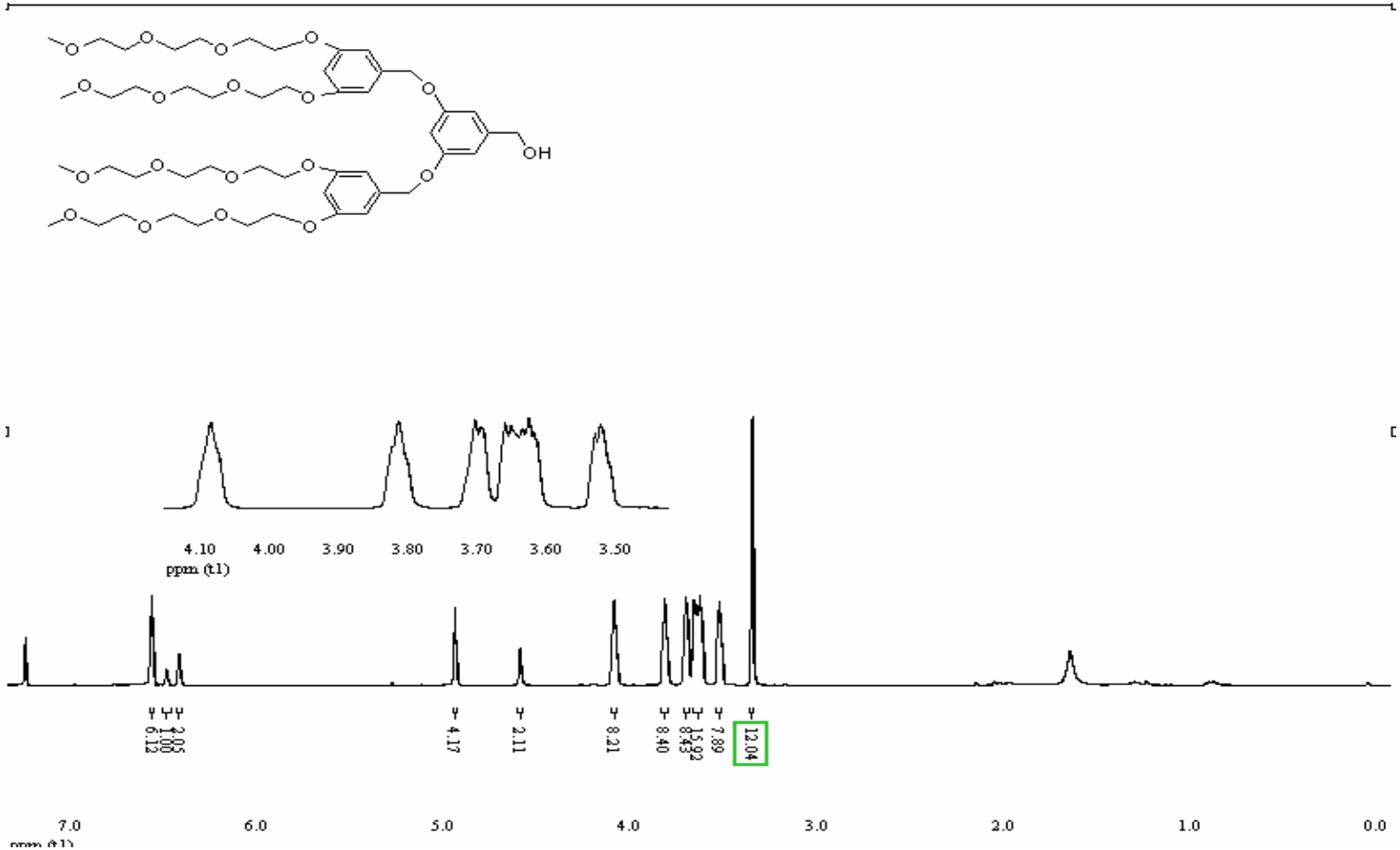


Figure A. 15. 1H NMR of MeOTEG-G2-ol **49**

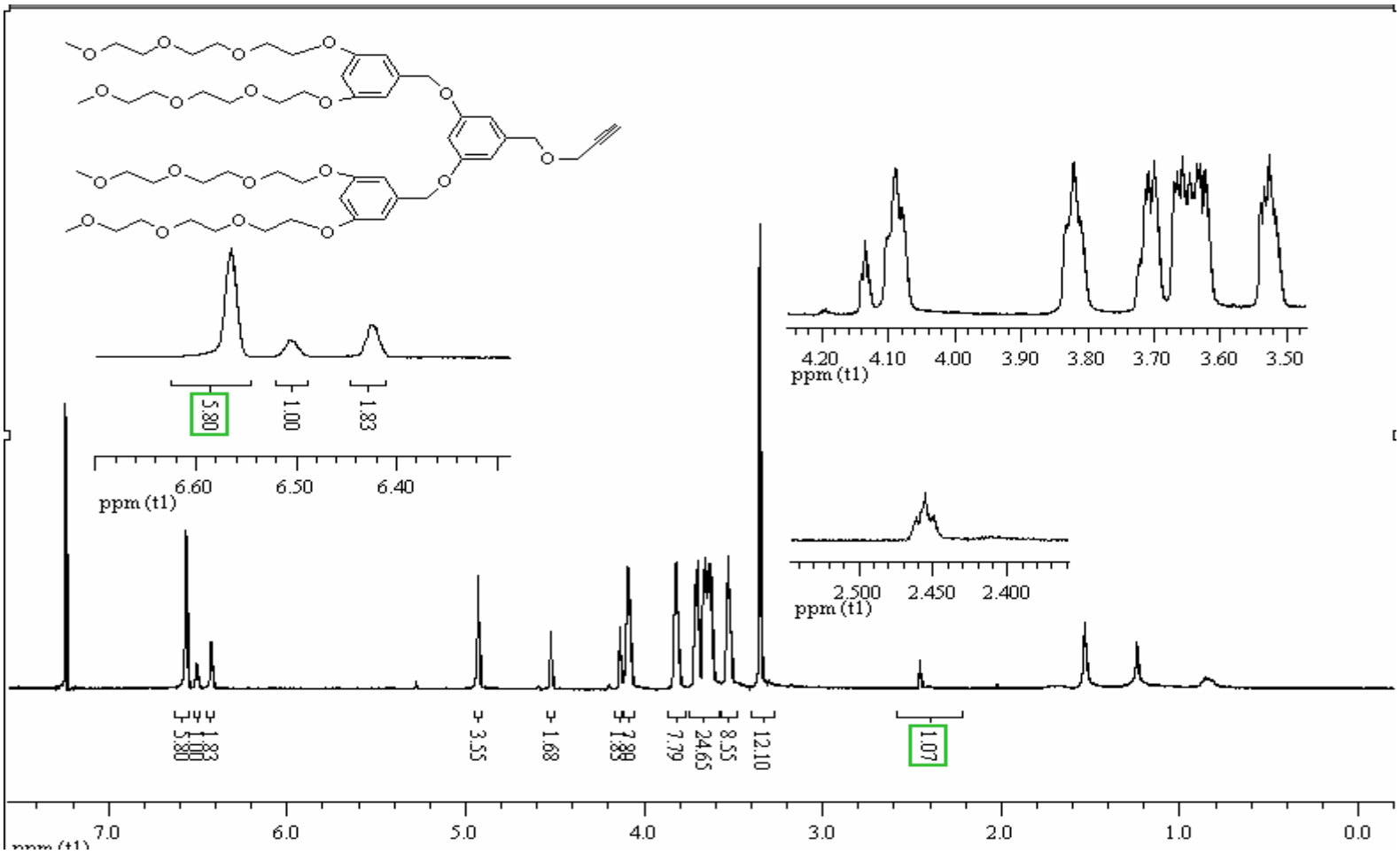


Figure A.16. ^{1}H NMR of MeOTEG-G2 acetylene **50**

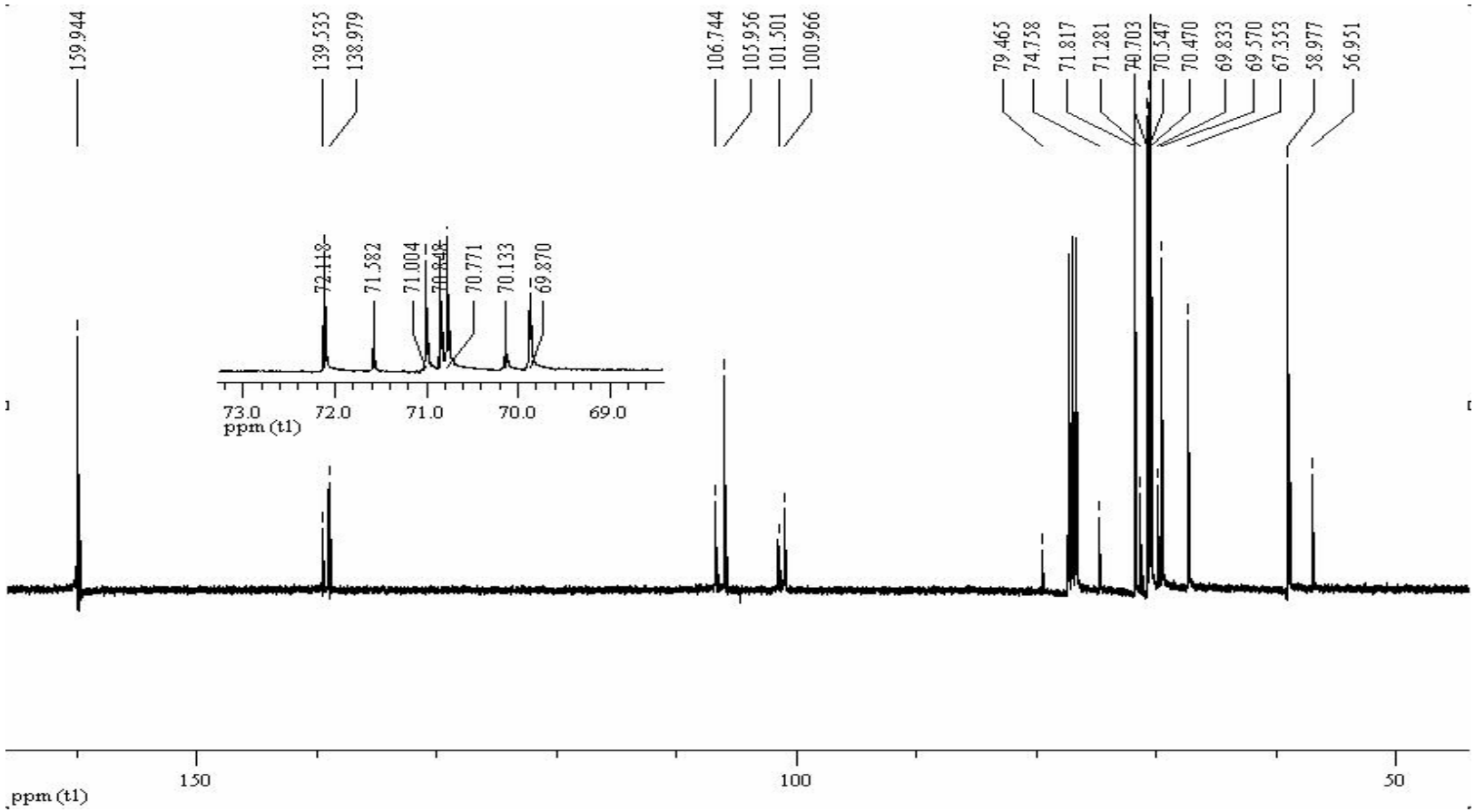


Figure A.17. ^{13}C NMR of MeOTEG-G2 acetylene **50**

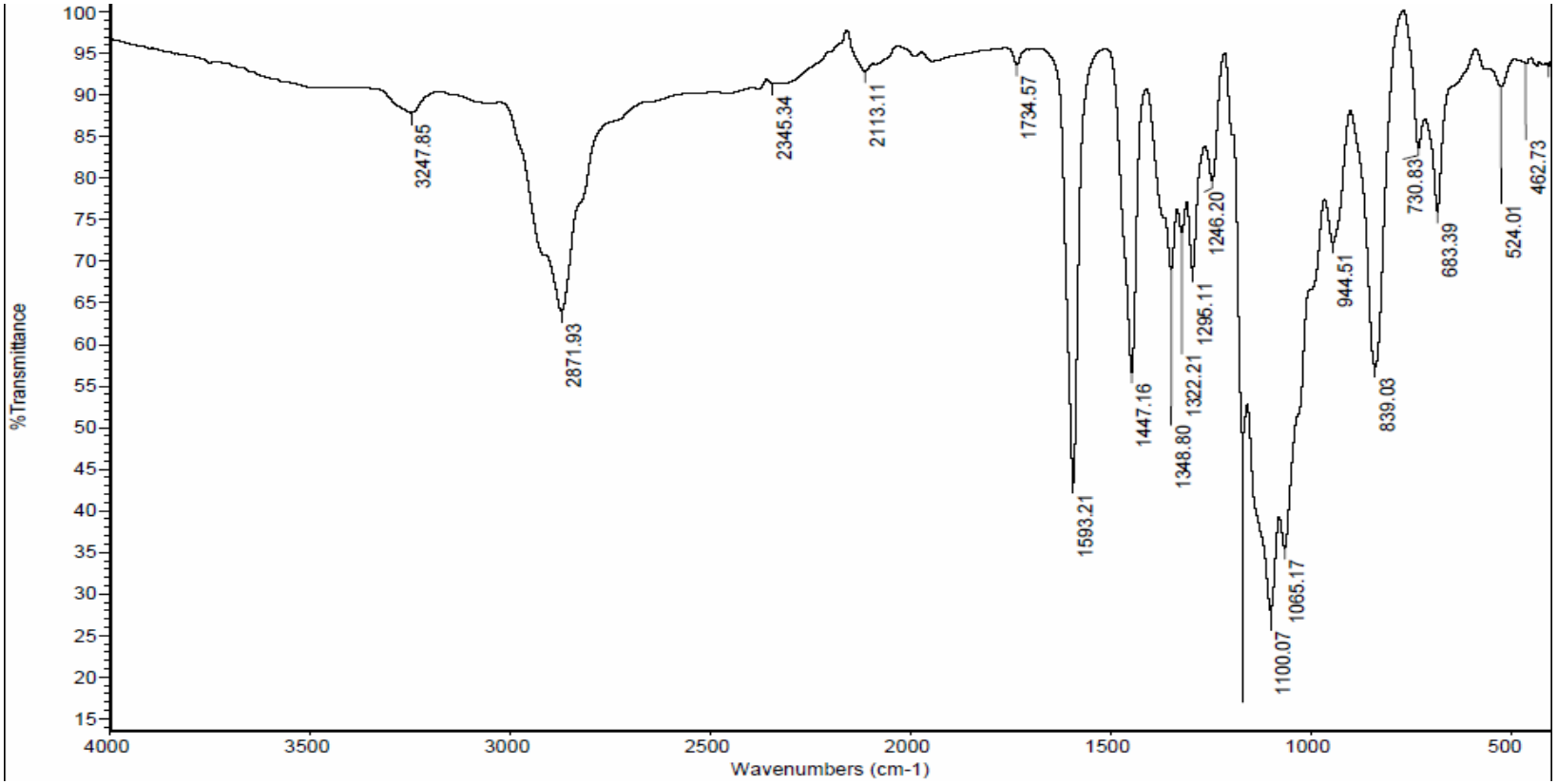


Figure A.18. IR spectrum of MeOTEG-G2 acetylene **50**

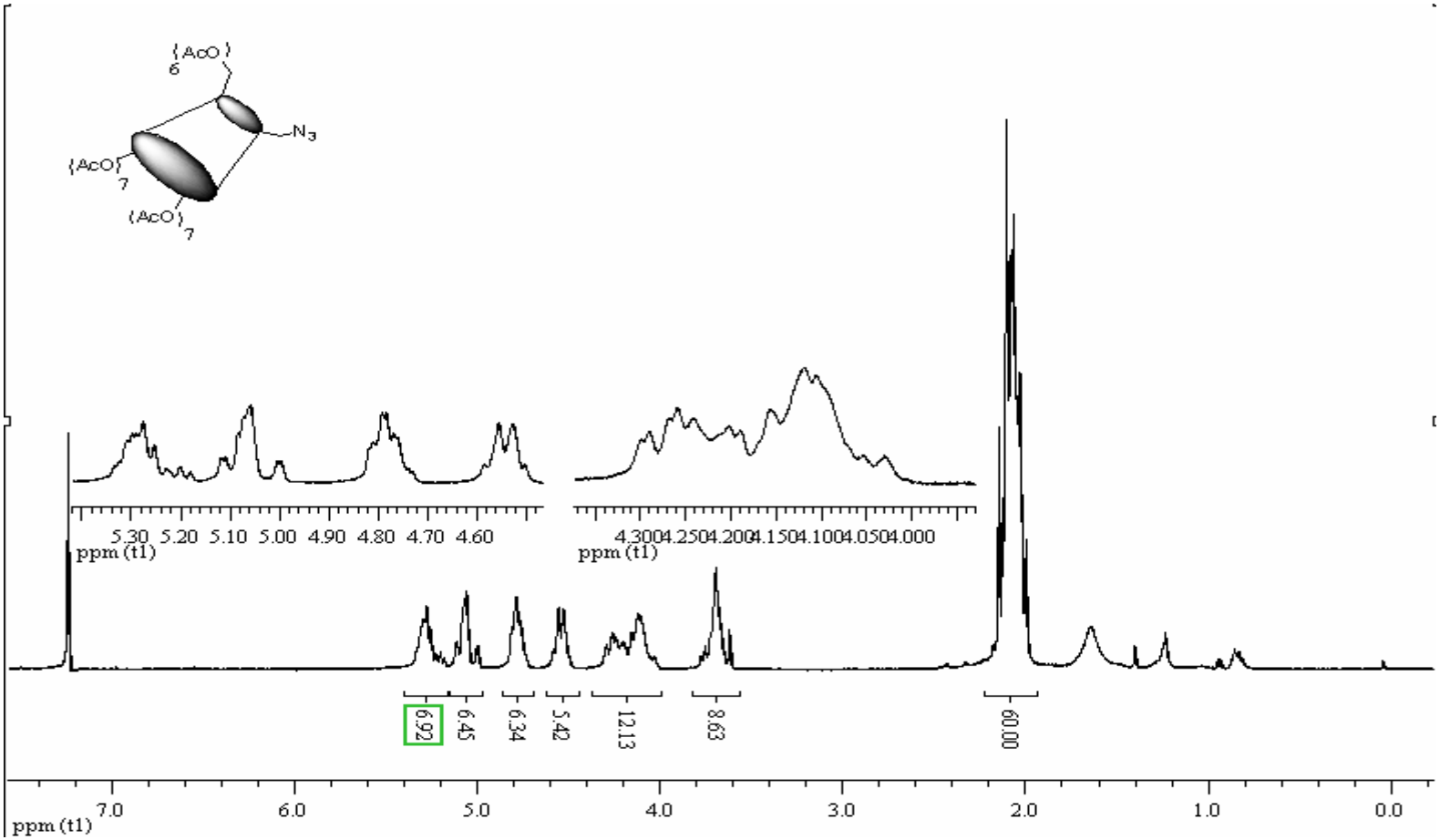


Figure A.19. 1H NMR of β-CDOAc **54**

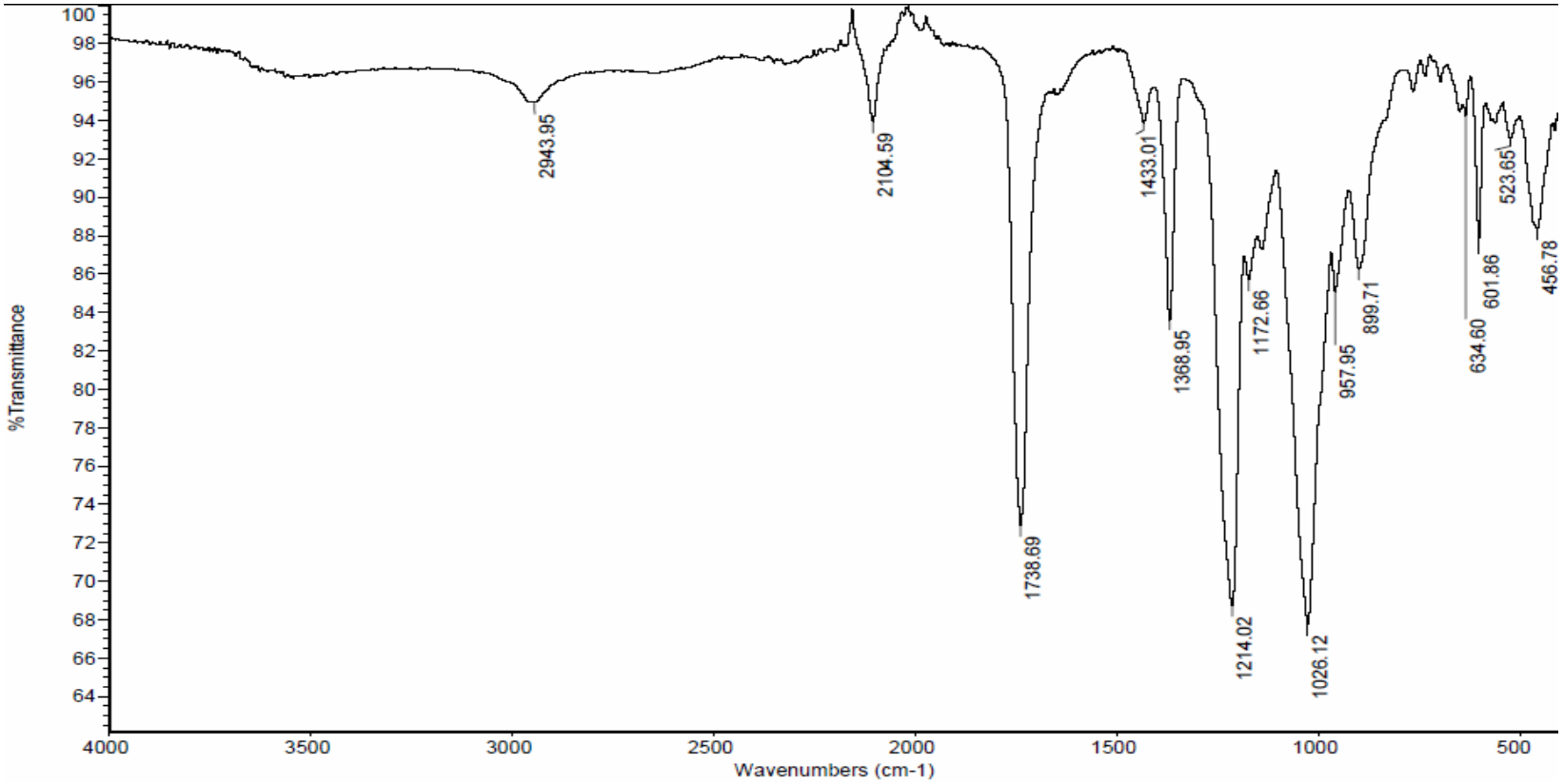


Figure A. 20. IR spectrum of β-CDOAc **54**

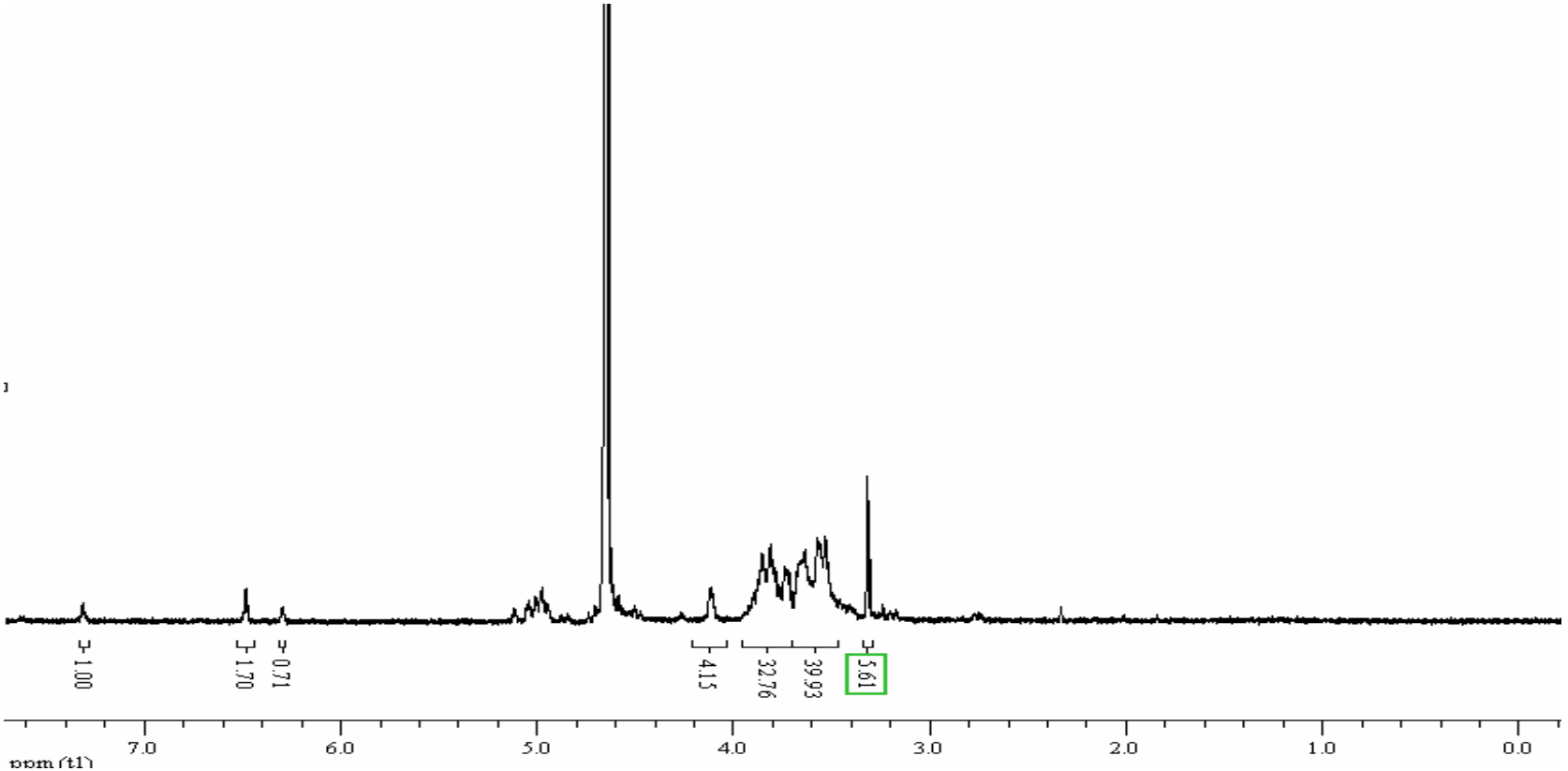


Figure A.21. ^{1}H NMR of G-1 Click **54**

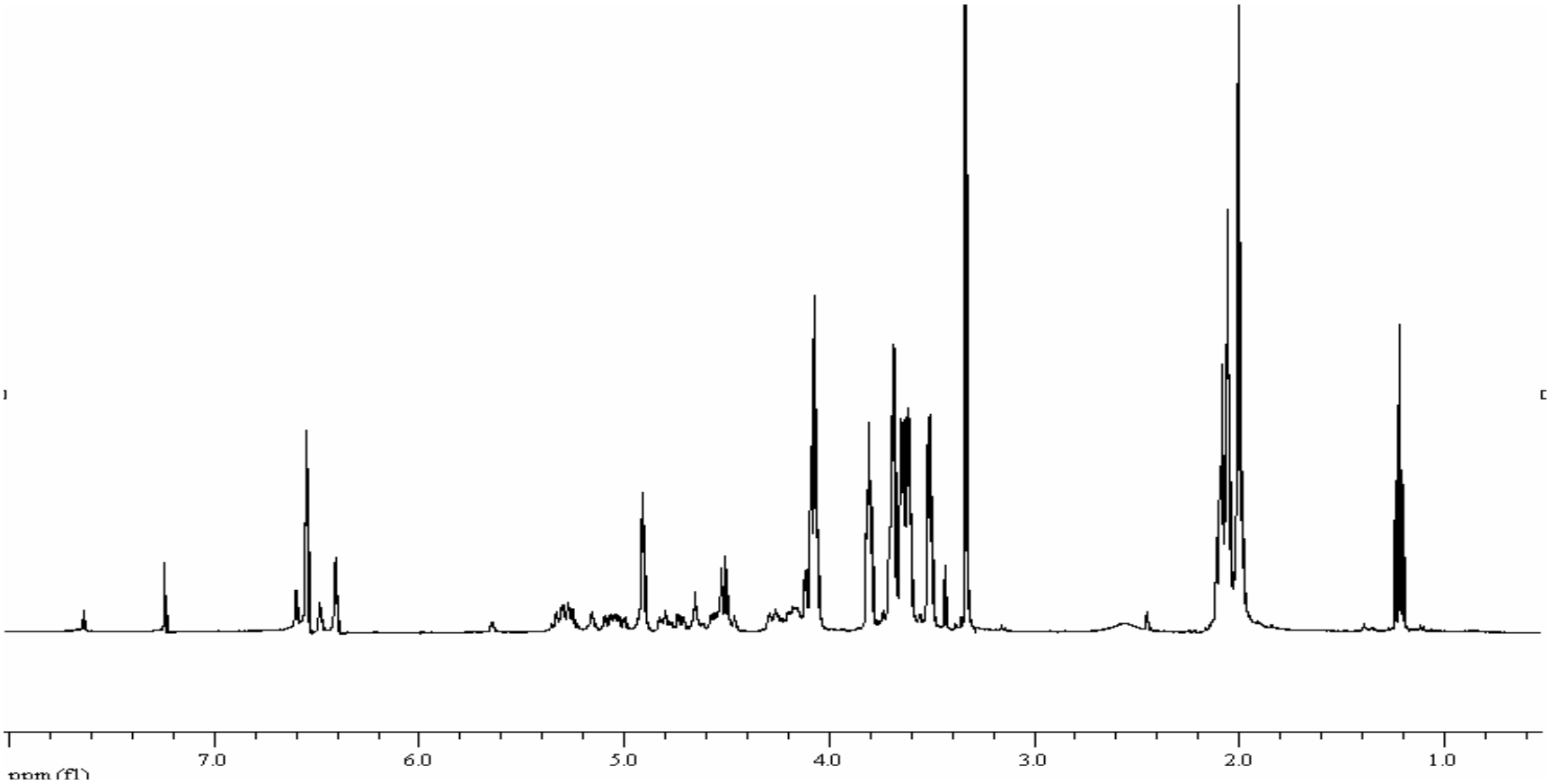


Figure A.22. ^{1}H NMR of G-2 Click **55**

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