MICROWAVE-ASSISTED SYNTHESIS OF NOVEL PAMAM TYPE DENDRIMERS AND THEIR ANALYTICAL APPLICATIONS

by

Cemil DIZMAN

A Thesis Submitted to

the Graduate Institute of Sciences and Engineering

of

Fatih University

In Partial Fulfillment of
The Requirements for the degree of

Master of Science

in

Chemistry

January 2009
Istanbul, Turkey

APPROVAL PAGE

Student **:** Cemil DIZMAN

Institute **:** Institute of Sciences and Engineering

Department **:** Chemistry

Thesis Subject: Microwave-Assisted Synthesis of Novel Pamam Type Dendrimers and Their Analytical Applications

Thesis Date **:** January 2009

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

Assist. Prof. Dr. Metin TÜLÜ
Head of Department

This is to certify that I have read this thesis and that in my opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

Assist. Prof. Dr. Metin TÜLÜ
Supervisor

Examining Committee Members

Assist. Prof. Dr. Metin TÜLÜ …….

Assoc. Prof. Dr. Ayhan Bozkurt …….

Dr. Fikret Koç …….

It is approved that this thesis has been written in compliance with the formatting rules laid down by the Graduate Institute of Sciences and Engineering.

Assist. Prof. Dr. Nurullah ARSLAN
Director

MICROWAVE-ASSISTED SYNTHESIS OF NOVEL PAMAM TYPE DENDRIMERS AND THEIR ANALYTICAL APPLICATIONS

Cemil DIZMAN

M. S. Thesis-Chemistry
January 2009

Supervisor: Assist. Prof. Dr. Metin TÜLÜ

ABSTRACT

Dendrimers are highly branched three dimensional macromolecules with well-defined structures constructed around a multifunctional central core. These structural characteristics exhibit good physical and chemical properties. Their synthesis are arising from a core, symmetrically additions of new groups help the dendrimer to grow exponentially. The functionalities of the dendrimers depend on cores, terminal groups and void spaces. In this study, the effects of these parameters have been analyzed by using different cores, terminal groups and void internals. Most of the synthesized dendrimers have been achieved by microwave assisted technique.

In this study, poly (ethylene glycol) diacid, poly (oxypropylene) triamine, Trimesic acid and tris (2-aminoethyl) amine have been chosen as dendritic cores. Methyl acrylate was added to the amine cores by the Michael addition reaction in order to obtain related esters. The esters have been converted to carboxylic acids in the presence of formic acid. Then two, three, and four branched PAMAM type dendrimers have been synthesized by using different dendrons. The syntheses are carried out mostly by applying microwave irradiation technique and correlated with conventional methods. Synthesized materials were characterized via FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

As analytical applications, metal complexations of mentioned dendrimers were performed at different pH values.

Keywords: PAMAM Dendrimer, Microwave, Michael Addition, Metal Complexation

MİKRODALGA KULLANILARAK YENİ PAMAM TİPİ DENDRİTİK MOLEKÜLLERİN SENTEZİ VE ANALİTİK UYGULAMALARI

Cemil DIZMAN

Yüksek Lisans Tezi - Kimya
Ocak 2009

Tez Yöneticisi: Yrd. Doç. Dr. Metin TÜLÜ

ÖZ

Dendrimerler çok fonksiyonlu bir merkezden büyüyen çok düzgün bir yapıya sahip çok dallı ve üç boyutlu makromoleküllerdir. Bu yapısal özellikler ile oldukça ilginç fiziksel ve kimyasal özelliklere sahiptirler. Çekirdekten başlayarak simetrik bir şekilde yeni grupların eklenmesi dendrimerlerin üstel olarak büyümesini sağlar. Dendrimerlerin işlevselliği kullanılan çekirdeklere, son gruplara ve boşluklu alanlara bağlıdır. Bu çalışmada bu parametreler göz önüne alınarak yeni dendrimerler sentezlenmiştir. Dendrimerlerin sentezi mikrodalga yardımıyla yapılmıştır.

Bu çalışmada poli (etilen glikol) diasit, poly(oksipropilen) triamin, Trimezik asit ve tris (2-aminoetil) amin çekirdek olarak seçildi. Michael ekleme reaksiyonu ile aminli çekirdeklere metil akrilat eklenerek esterlerin oluşumu sağlandı. Oluşan esterler formik asitle hidroliz edildi. Farklı dendronlar kullanılarak iki, üç ve dört dallı PAMAM tipi dendrimerler sentezlenmiştir. Sentezler genelde mikrodalga yöntemiyle yapılıp klasik yöntemlerle de korrelasyonu yapılmıştır. Sentezlenen maddelerin karakterizasyonu FT-IR, ^{1}H NMR ve ^{13}C NMR spektroskopisi yardımıyla yapılmıştır.

Analitik uygulama olarak sentezlenen dendrimerlerin farklı pH'larda metal iyonlarıyla etkileşimi incelendi.

Anahtar Kelimeler: PAMAM Dendrimerler, Mikrodalga, Michael Ekleme, Metal Kompleksleşmeler

Dedicated to my family.

“*No pain, no gain”*

ACKNOWLEDGEMENT

I would like to express my special thanks to my supervisor Assist. Prof. Dr. Metin Tülü, who helped me during my research by presenting helpful suggestions, encouraged me and increased my moral and motivation to write this thesis.

I also want to thank to Prof. Dr. Muhammad Naz Aghatabay and to my lab mate Tezcan Paralı for his contributions to my research by sharing his experiences and helpful thoughts.

My thanks also go to the second year students, Suat Tüysüz, Mihriban Mutlu, Rabia Kolat, Ümran Kurtan, Sevim Feyza Yardımcı and Kemal Çetin, whose helps when doing experiments accelerated my research and shorten the time to learn whether I was in the right way or not.

I would like to express my thanks to all my friends and to my family for their meaningful and useful suggestions.

I want to express my special thanks to my fiancée for her understanding and support to me while writing this thesis.

Finally, I want to thank to The Graduate Institute of Sciences and Engineering of Fatih University for funding my thesis with the P50020703.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS AND ABBREVIATIONS

SYMBOL/ABBREVIATION

NMR	:	Nuclear Magnetic Resonance
FT-IR	:	Fourier Transform Infrared Spectroscopy
TLC	:	Thin Layer Chromatography
PAMAM	:	Poly(amidoamine)
PPI	:	Poly(propyleneimine)
Ply	:	Polylysine
PEG	:	Polyethylene glycol
PEI	:	Polyethylene imine
Triton B	:	Benzyltrimethylammonium hydroxide
Jeffamine®	:	poly(oxypropylene triamine)
DCC	:	N,N'-Dicyclohexyl-Carbodiimide
HOBT	:	N-Hydroxybenzotriazole
EtOH	:	Ethanol
MeOH	:	Methanol
Et_3N	:	Triethylamine
THF	:	Tetrahydrofuran
EtOAc	:	Ethylacetate
DCM	:	Dichloromethane
DMF	:	Dimethylformamide
$EtNO_2$	:	Nitroethane
$MetNO_2$	:	Nitromethane
G	:	Generation of a Dendrimer
TMA	:	Trimesic acid
TREN	:	Tris (2-aminoethyl)amine

CHAPTER 1

INTRODUCTION

Dendrimers are a new class of artificial highly branched macromolecules with several attractive properties, such as narrow size distribution, extremely low polydispersity, regular and high degree of branching, multi-valency, nano-sized scale, globular architecture, well-defined molecular weight and ease of derivatization via the peripheral functional groups. The structure of these materials has a great impact on their physical and chemical properties. Because of unusual physical properties and ease of syntheses they have attracted much attention by many scientists for two decades. As a result of their unique behavior dendrimers are suitable for a wide range of biomedical and industrial applications [1,2,3].

1.1 HISTORY AND DEVELOPMENTS

Dendrimer that was coined by Tomalia et al. was derived from the Greek words dendri-(tree branch-like) and meros (part of) [4]. They are tree-like structures. There is a core in the center and each layer up from the core dendrimers has shells of branched molecules. The core is called as “generation 0” and repeatedly addition of branched molecules to each branch forms the next generation, “generation 1”, “generation 2”,and so on until the terminating generation (Figure 1.1).

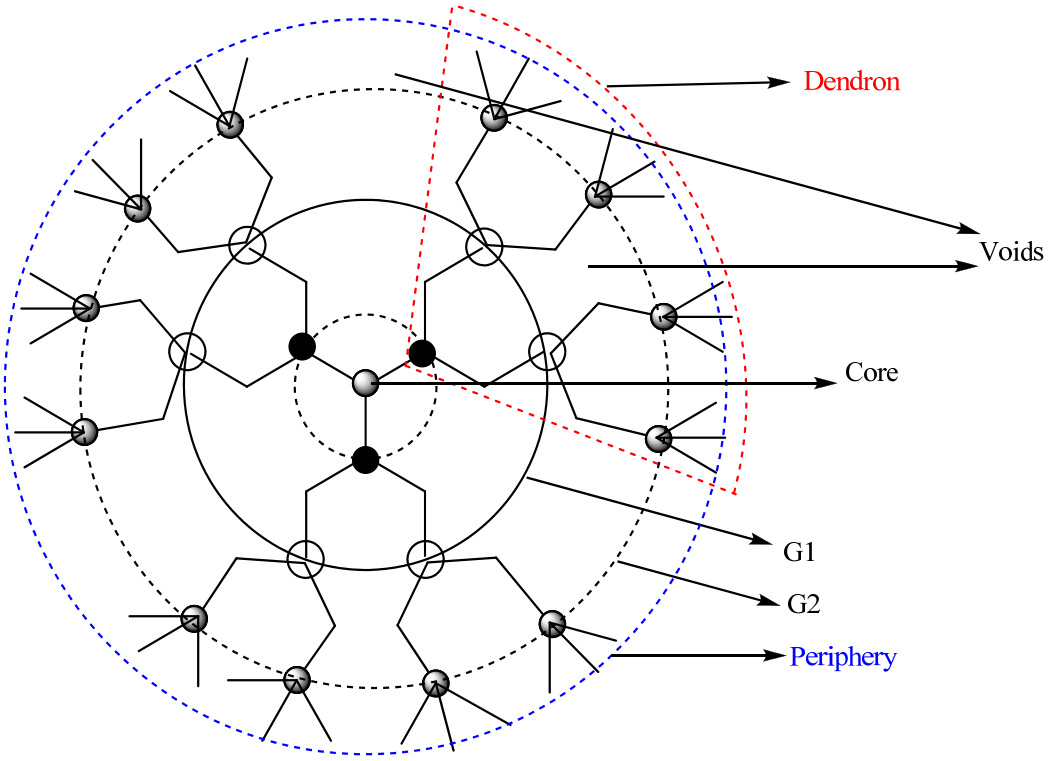
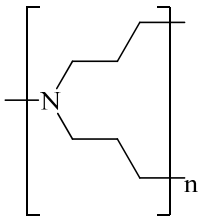


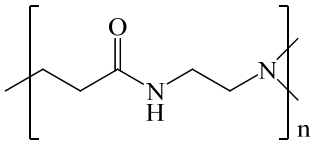
Figure 1.1 A schematic representation of a spherical dendrimer composed of two "generations" (G1 and G2) is shown above. One tree-like unit of a dendrimer is called "dendron".

The size of a dendrimer increases with generation number. Small generations have expanded or open conformations but as the size increases, because of the increasing number of surface functional groups, dendrimers adopt spherical or globular structure.[5] The cores and the functional groups on the terminal focal points of dendrimers and the voids among the branches make them extremely useful for the production of novel molecules and lots of applications [1,6].

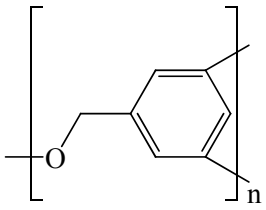
From the first dendrimer synthesis by Vögtle [7], over 100 compositions (families) of dendrimers have been synthesized. Today different dendrimers can be prepared by changing the repeating units and the cores. By the addition of one type of branching units to the others the dendrimers that have mixing repeating units can be prepared. Some repeating units are summarized in Table 1. The Frechet-type polyether compositions and the Tomalia-type PAMAM (Poly (amido amine)) dendrimers are the most extensively characterized and the best understood dendrimers [8]. Arborols or Newkome-type dendrimers became popular after the publications of Newkome group [9].



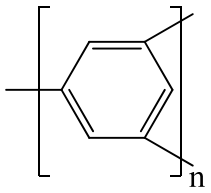
Vögtle and co-workers (1978) [10]. Double Michael-type addition of acrylonitrile to a primary amine; reduction of a nitrile to an amine.



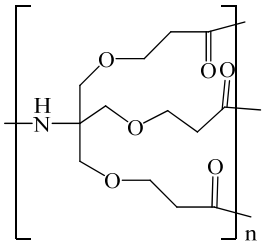
Tomalia et al. (1985) [11]. Double Michael addition to a primary amine; the reaction of an ester with an excess of amine to give an amide.



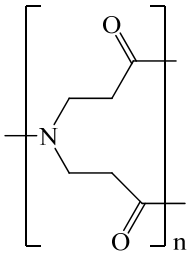
Hawker and Frechet (1990) [12]. Reaction of a phenol with a benzylic bromide; bromination of a benzylic alcohol with PPh_3 and CBr_4.



Miller, Neenan and co-workers (1992) [13]. Aryl Grignard reagents or Suzuki coupling for linking units; the transformation of an aryl trimethylsilane into an arylboronic acid with BBr_3.



Newkome et al. (1985) [14]. Use of "tris" DCC/HOBT coupling; base-promoted hydrolysis of an ester in the presence of amide bonds. This and similar "tris" based branching have been used by many researchers.



Uhrich and Frechet (1992) [15]. DMAP-catalyzed DCC coupling; BOC deprotection with TFA.

Table 1 Some repeating units used for the synthesis of dendrimers [16].

Different synthetic methodologies have been demonstrated for the syntheses of dendrimers such as convergent, divergent, 'Double Exponential' and 'Mixed' Growth, 'Hypercores' and 'Branched Monomers' etc. [17]. Convergent and divergent procedures are the most common ones (Figure 1.2) [5]. In the divergent approach, the dendrimer grows from a core by the addition of the branching units. Then inactive sites on the branching units are activated in order to get higher generation dendrimers by repeatedly addition of branching units to the formed branched molecules. In the convergent approach, firstly dendritic branches named dendrons are produced. Dendron that has an inactive site is grown from the active sites. After sufficient growth the inactive site on the dendrons is activated in order to be reactive to be able to react with the desired cores. Then the dendrons are added into the cores [18,19].

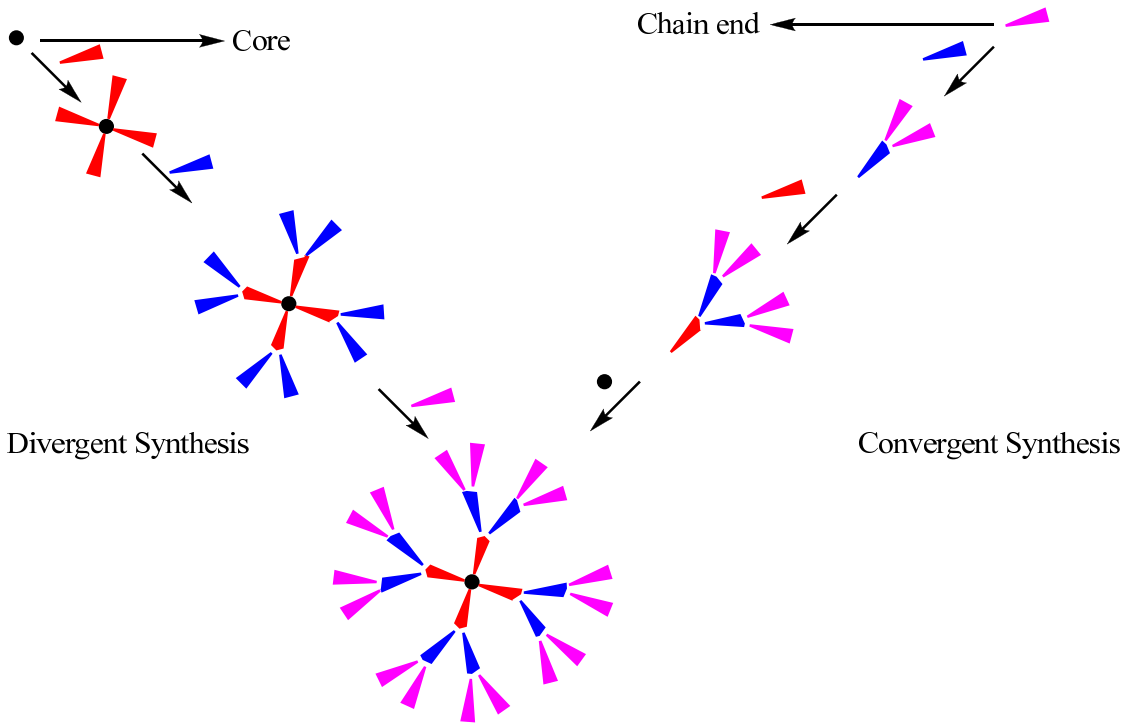


Figure 1.2 A schematic representation of the divergent and convergent synthesis.

Convergent, divergent and the other growing methods can be used for the production of new dendrimers that include specific functional groups on their surfaces and branching points such as PAMAM (poly (amido amine)), PPI (poly(propylene imines)),

phosphorous, polylysines dendrimers etc... PAMAM-type dendrimers have been received great attention for their capability in biomedical applications [20] and complexation studies [21,22,23].

Poly (amido amine) dendrimers are the first synthesized, characterized, and commercialized dendrimer families. They are prepared by consecutive addition of methyl acrylate to the diamine core by the Michael reaction and the amidation of resulting esters with ethylene diamine. PAMAM dendrimes with different cores and branched molecules have been also reported [24]. The PAMAM dendrimers have been extensively studied especially for their drug delivery, gene carrier and antibacterial properties [25,26].

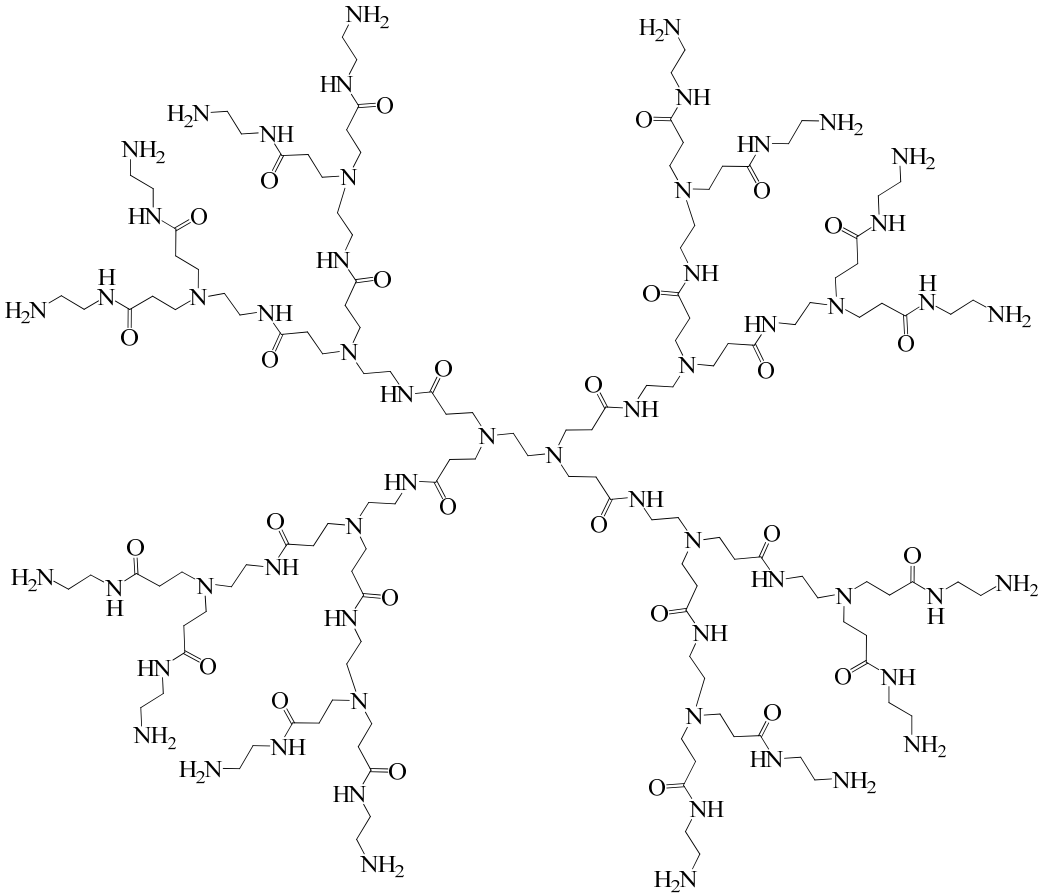


Figure 1.3 Generation 2 PAMAM dendrimers.

PAMAM dendrimers possess perfect solubility in a large number of solvents, particularly in water. Non-polar cavities in PAMAM dendrimers in combination with their

hydrophilic exterior surface make them capable of encapsulating hydrophobic drug molecules and ensure their applications as solubility enhancers of these hydrophobic agents [27,28]. Large numbers of functional groups such as amine, carboxyl and hydroxyl groups on the outer shell of PAMAM dendrimers are responsible for high reactivity and expected to conjugate with a series of biomolecules such as DNA and proteins or bioactive molecules such as drugs. These guest molecules can be loaded either in the functional groups on the surface or can be attached to the hydrophobic cavities. These specific features of dendrimers provide the availability of dendrimers to deliver bioactive agents to specific diseased sites, consequently enhancing bioactivity properties and possibility of minimizing drug systemic toxicity [29,30].

1.2 SYNTHETIC METHODS FOR DENDRIMER SYNTHESIS

1.2.1 CONVENTIONAL METHODS

In order to synthesize dendrimers, there have been used lots of different conventional methods by benefiting from the functional groups of core and branched molecules [31,32]. Chemical reactions driven by conventional heating are more likely to perform under kinetic control. These reactions usually require only mild conditions. A resonance-stabilized intermediate will take the easiest path-one with the lowest activation energy-to its products. Chemical synthesis has been achieved through conductive heating with an external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and reactants. This is a slow and inefficient method for transferring energy into the system because it depends on the thermal conductivity of the various materials that must be penetrated. It results in the temperature of the vessel being higher than that of the reaction mixture inside until sufficient time has elapsed to allow the container and contents to attain thermal equilibrium. This process can take hours or even days.

1.2.2 MICROWAVE METHOD

As an alternative way to conventional methods is microwave irradiation method. In microwave driven reactions, the molecules are provided powerful instantaneous energy, which allows them to reach higher activation energy levels and leads to the thermodynamic product. Clearly, microwave (MW) heating system is extremely useful in slower reactions where high activation energies are required to do various transformations. In microwave system the microwaves directly couple with the molecules that are present in the reaction mixture, leading to a rapid rise in temperature that is necessary in order to reach higher activation energies. With the elevated molecular energy generated by the transfer of microwave energy, reactions that required many hours or even days to complete have been accomplished in minutes [33].

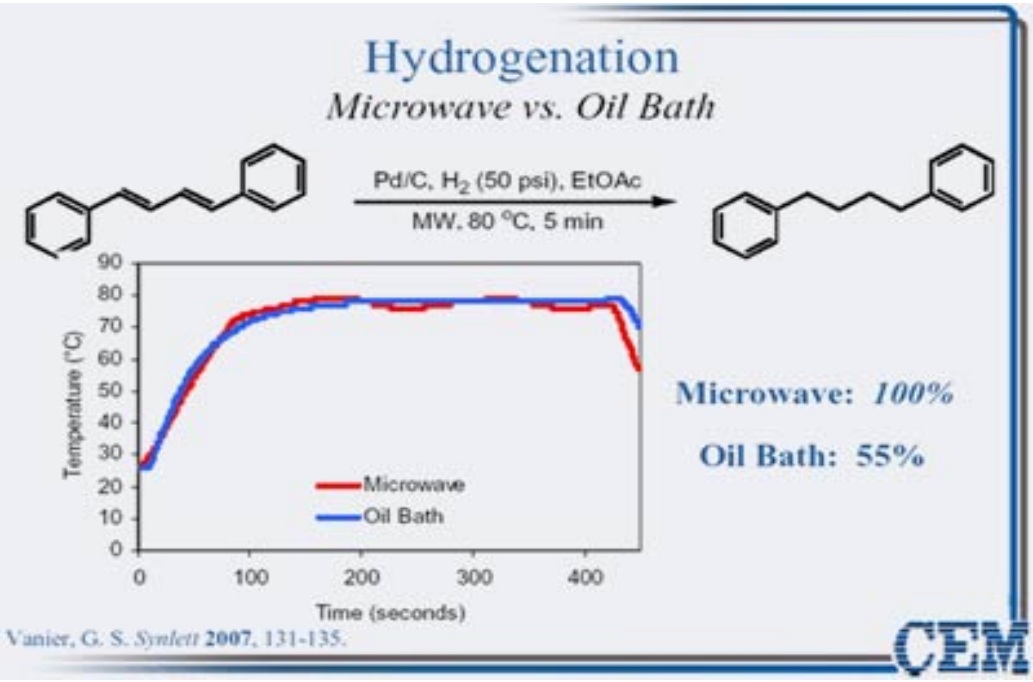


Figure 1.4 Comparison of microwave versus conventional method [34].

Microwave assisted synthesis of organic molecules have been achieved great attention for a decade by many scientists. Instead of time-consuming conventional methods this method provides easiness for the formation of organic molecules in a few minutes. Higher yields and purer compounds can be obtained as seen in Figure 1.4 [34].

The choice of the solvents that are used in the microwave system is an important factor for the outcome of the reaction. The most important characteristic of a solvent is its polarity. The more polar reaction mixture is, the greater its ability to couple with the microwave energy. The microwave irradiation generally gives necessary energy for the complete reaction. Therefore some reactions do not need any solvents that are expensive and harmful for the environment. As a conclusion microwave assisted synthesis can be suggested for a lot of reasons such as easiness, shorter-time reactions, higher yields and clean environment [35,36].

1.3 ANALYTICAL APPLICATIONS

Because of the above mentioned special features (nanoscopic size, spherical shape, controllable reactivity of the surface, and voids and cavities inside the molecule) of the dendrimers there have been lots of different applications, such as drug delivery, gene carrier, DNA binding, catalysis, imaging agent, anti-microbial, and dye … etc. Metal complexation is one of the applications of the dendrimers. Incorporation of metal ions with the dendrimers was initiated by Balzani's and Newkome's research groups in the early 1990s. either by the use of metal branching centers or by internal metal complexation or encapsulation at specific binding site(s), respectively. Commonly, metals have served as branching centers, building blocks connectors, which include core as well as monomer connection, terminal groups and structural auxiliaries, whereby metals are introduced to a framework after dendritic construction (Figure 1.5). Metallodendrimers are suprasuper molecular species possessing novel physical, optical, electrochemical, photochemical, biological, and catalytic properties [37].

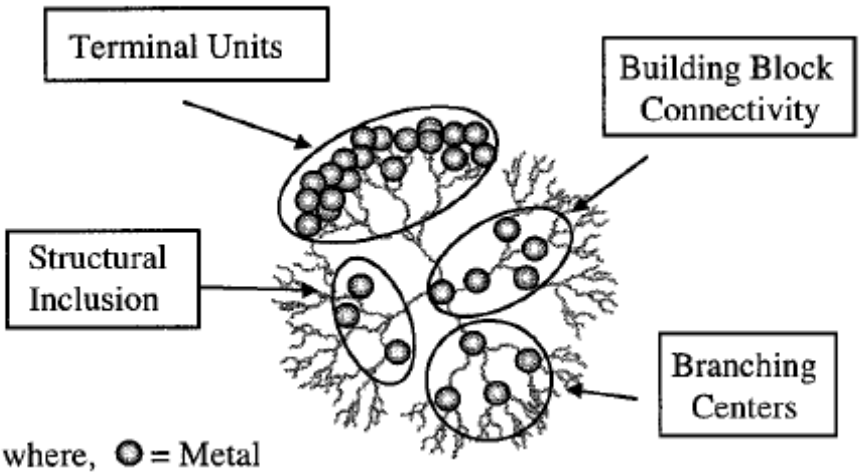


Figure 1.5 Potential uses and positioning of metals within dendritic architectures [37].

The separation of metal ions in aqueous solutions plays an important role for their industrial waste water. Among many separation techniques membrane separation is an efficient process compared to the other separation techniques in terms of technical and economical feasibility [38]. General principle of this technique, Liquid-Phase Polymer Based Retention (LPR), is to add water-soluble polymeric binding agents to a multicomponent solution, so that these agents will form macromolecular compounds with the target ions only. If such a solution is then passed through an ultra filtration membrane, the membrane would separate the target metal ions from the non-target species [39, 40]. This concentration method is designed to recover metals ions from dilute technological solutions and for absolute preconcentraton of elements in analytical chemistry.

In the LPR method, the retention of metal ions in solution by polymeric reagents can be calculated as follows $R\ (\%) = C_r * C_0^{-1} * 100$, where C_r is the metal concentration in the retentate after a filtrate volume of V_f has been passed, and c_o is the initial metal concentration. The filtration factor Z is defined as the ratio of the volume of filtrate V_f and the volume of cell solution V_o: $Z = V_f * V_0^{-1}$.

CHAPTER 2

AIM OF THE STUDY

In this study, the aim is to synthesize different PAMAM-type dendrimers with different functional groups on their peripheries by using Newkome and Tomalia repeating units and make their analytical applications. Both conventional and microwave methods sometimes have been alternatively used for the addition of branched molecules to the corresponding cores and sometimes to change the functional groups. Poly (ethylene glycol) diacid 600, Jeffamine® (polyoxypropylene triamine), Trimesic acid, and TREN (tris (2-aminoethyl) amine) have been chosen as the cores. In order to make a reaction between amines and acids, Dicyclohexyl-Carbodiimide (DCC) coupling reaction was preferred. All amidation reactions related to Behera's amine [41] have been done under normal pressure and at room temperature because of the formation of unwanted lactams at higher temperatures. Acryl groups have been added to the corresponding amines by Michael addition reaction under microwave conditions.

First and second generation dendrimers of corresponding cores have been successfully obtained. After synthesis and characterization of the dendrimers, the metal complexing properties of the dendrimers were studied for Cr(III), Co(II), Ni(II), Cu(II),Zn(II), Cd(II), Pb(II) and Ag(I) ions in aqueous solution using the Liquid-Phase Polymer-Based Retention (LPR) method.

CHAPTER 3

EXPERIMENTAL PART

3.1 CHEMICALS AND APPARATUS

Raney Nickel catalyst (Al-Ni alloy 50 % w/w), Triton B in Methanol 40 % solution, methylacrylate, ethylenediamine, tetrahydrofuran and methanol were obtained from the Merck. Nitromethane, nitroethane and tert-butylacrylate were from the Fluka. Poly(ethylene glycol)600 diacid (acid number 175, 96-98 %, from Fluka) was dried over Na_2SO_4. Jeffamine®T-3000 was obtained from Texaco Chemical Company. Other chemicals were used as obtained from the Fluka without further purification unless otherwise noted. Solvents were dried and distilled according to literature procedures prior to use. Reactions were controlled by thin layer chromatography (TLC) on silica gel 60 F254 and spots were detected either by UV-visible light or by charging with I_2 vapor or cobalt chloride and ammonium thiocyanate solution that is very useful especially in order to see amines on the TLC plate.

3.2 INSTRUMENTATIONS

^{1}H NMR and ^{13}C NMR spectra were recorded on a NMR using an Inova 500 MHz Varian system spectrometer for solutions in $CDCl_3$ and DMSO. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad. Chemical shifts (δ) are expressed in units of ppm relative to TMS. FT-IR spectra were recorded on Perkin Elmer spectrophotometer in the range of 400-4000 cm^{-1} (abbreviations: m, s, br and w). Some of the prominent spectra were given behind the procedure as a numeric value. The microwave assisted reactions have been done via CEM Discovery Microwave tool.

3.3 CHEMICAL SYNTHESIS AND PREPARATION

3.3.1 GENERAL STRATEGIES FOR THE SYNTHESIS OF MONOMERS, DENDRONS AND DENDRIMERS

In this study, mainly five types of reactions were used repeatingly and they are summarized as general procedure.

General Procedure A (Conversion of ester group to an acid): A mixture of ester functionalized compound in formic acid was stirred at 25 ^{o}C for 5 min. Then, the mixture was irradiated by microwave for several minutes under open vessel condition. After concentrated in vacuo, toluene was added and the solution was again evaporated in vacuo to remove azeotropically any residual formic acid.

General Procedure B (Reduction of nitro group to an amine): The nitro reductions were done according to the following T-1 Raney nickel catalyst preparation and general experimental procedure: NaOH (1 part by weight) was dissolved in 10 parts deionized water and then 1.4 parts Raney R type Al-Ni alloy was added in portions within a 1-2 min period. **Caution: Be careful while alloy is added. An explosion can be resulted if the amount of the portions is greater than sufficient amount. There was a violent evolution of H_2, and the temperature rose rapidly. If the amount of H_2 reaches too much it can catch a fire reacting with the oxygen in the air.** Allowing the temperature to reach 85-90 ^{o}C ensures a high activity of the catalyst. Considerable foaming occurs during this period. After the addition of the alloy, stirring was continued for an additional hour. Then, the supernatant, alkaline solution was carefully decanted from the black metal catalyst, being allowed to settle, and rinsed with about one-third the previous volume of distilled/deionized water. After the alloy settled again, the process was repeated several times. Then the alloy was rinsed consecutively, in the same manner with absolute EtOH. Care should be taken to ensure the settling of the catalyst prior to decanting and the catalyst should never become dry as it is highly flammable/combustible. The catalyst should remain in the last portion of EtOH and be used for the hydrogenation immediately. A solution of nitro ester in absolute

EtOH with T-1 Raney Ni was hydrogenated at 90 psi and 25 ^{o}C. The catalyst was cautiously filtered through Celite and the solvent was removed in vacuo.

General Procedure C (Reaction of amines with the acids): A mixture of equivalent amounts of carboxylic acid, amine, dicyclohexylcarbodiimide (DCC), and 4-(dimethylamino) pyridine (DMAP) or 1-Hydroxybenzotriazole (1-HOBT) in THF or in DMF was stirred at room temperature for 24 h. The clear solution becomes turbid. The solid (dicyclohexyl urea) precipitated was filtered off and THF was evaporated in vacuo. The residue was dissolved in EtOAc and washed with water and then saturated brine. The organic phase was dried (Na_2SO_4) and then purified by column chromatography (SiO_2) by using ethyl acetate/hexane as eluents.

General Procedure D (Reaction of acrylates with the amines): Amines was mixed with methylacrylate and then Cerium (IV) sulphate tetrahydrate was added as a catalyst. The mixture was transferred into a sealed vial provided by CEM Company. MW power was applied for several minutes by selecting closed or open vessel mode. The mixture was dissolved in THF and solid catalyst was filtered from the solution. The solvent and any released water were then removed under vacuum.

General Procedure E (Reaction of esters with the amines): Amines was mixed with esters in methanol and calcium carbonate (K_2CO_3) was added as a catalyst. The mixture was mixed for about 5 minutes. Then, microwave power was applied for several minutes by selecting closed or open vessel mode. The mixture was filtered in order to remove the catalyst. The methanol was evaporated in vacuo. The residue was dissolved in EtOAc and washed with water and then saturated brine. The organic phase was dried (Na_2SO_4) and then purified by column chromatography (SiO_2) by using ethyl acetate/hexane as eluents.

3.3.2 THE SYNTHESIS OF DENDRONS

3.3.2.1 Synthesis of Nitro-2 ester, (AB_2), [di-tert-butyl 4-methyl-4-nitroheptanedioate], (1)

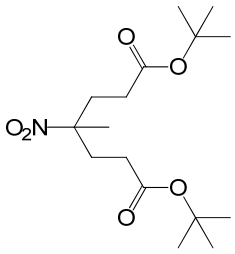


Figure 3.1 Structure of Nitro-2 ester, (AB_2, 1. generation).

Nitro ethane (0.75 g, 0.01 mol) and tert-Butyl acrylate (2.82 g, 0.022 mol) were mixed. Two drops of Triton B (benzyltrimethylammonium hydroxide, 40 % in MeOH) was added into the mixture. Then the mixture was irradiated by microwave (150 W) for a minute under open vessel condition. After concentration in vacuo, the residue was dissolved in $CHCl_3$ and washed with water, then saturated brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the desired diester (1), as a white solid: (3.25 g, 98 %). m.p. 46-48 ºC; IR (KBr) cm^{-1}: 1731 (ester C=O), 1541 (nitro NO_2) 1155 (ester C-O). ^1H NMR δ 1.39 (s, CCH_3, 18H), 1.48 (s, NO_2CCH_3, 3H), 2.25 (m, $CH2CH_2COO$, 4H and CH_2COO, 4H); 13C NMR δ 21.71 (NO_2CCH_3), 28.03 (CCH_3), 30.14 (CH_2CH_2COO), 34.28 (CH_2COO), 80.99 (CCH_3), 89.91 (NO_2CCH_3), 171 (COO) ppm.

3.3.2.2 Synthesis of Nitro-3 ester, (AB_3), [di-tert-butyl 4-(2-(tert-butoxycarbonyl) ethyl)-4-nitroheptanedioate], (2)

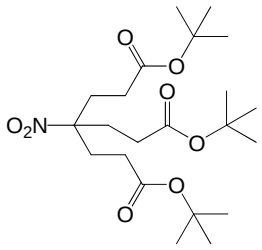


Figure 3.2 Structure of Nitro-3 ester, (AB_3, 1. generation).

Nitro methane (0.61 g, 0.01 mol) and tert-Butyl acrylate (3.97 g, 0.031 mol) was mixed. Triton B (benzyltrimethylammonium hydroxide, 40 % in MeOH; 2 drops) was added into the mixture. Then the mixture was irradiated by microwave (150 W) for a minute under open vessel condition. After concentration in vacuo, the residue was dissolved in hot hexane and filtered off into the 100 mL of ice water. The white crystals were obtained by filtration without any purification and dried in vacuo (4.25 g, 95 %). IR (KBr) cm^{-1}: 1723 (ester C=O), 1534 (nitro NO_2), 1152 (ester C-O). ^1H NMR δ 1.43 (s, CCH_3, 27H), 2.19 (t, CH_2CH_2COO, 6H and t, CH_2COO, 6H); ^{13}C NMR δ 28 (CCH_3), 30.1 (CH_2CH_2COO), 31.4 (CH_2COO), 77-78 (CCH_3), 81.4 (NO_2CCH_2), 171.6 (COO) ppm.

3.3.2.3 Synthesis of Nitro-2 acid, (AB_2), [4-methyl-4-nitroheptanedioic acid], (3)

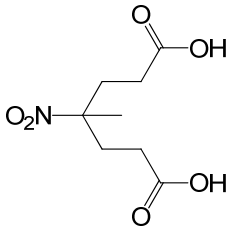


Figure 3. 3 Structure of Nitro-2 acid, (AB_2, 1. generation).

A solution of nitro diester (2.0 g, 6.04 mmol) in formic acid (20 ml) was irradiated by microwave (300 W) for 10 minutes under open vessel condition. After removing unreacted formic acids and tert-butanol in vacuo, the white crystals were obtained (1.24 g, 93.7 %).m.p. 108 ºC; IR (KBr) cm^{-1}: 3360 (br, acid OH), 1713 (acid C=O), 1531 (nitro NO_2). ^1H NMR δ 1.56 (s, NO_2CCH_3, 3H), 2.36 (t, CH_2CH_2COO, 4H), 3.72 (t, CH_2COO, 4H), 9.50 (br, CO_2H, 2H); ^{13}C NMR δ 21.7 (NO_2CCH_3), 28.6 (CH_2CH_2COO), 33.7 (CH_2COO), 89.5(NO_2CCH_3), 172.4 ($COOH$) ppm.

3.3.2.4 Synthesis of Nitro-3 acid, (AB_3), [4-(2-carboxyethyl)-4-nitroheptanedioic acid], (4)

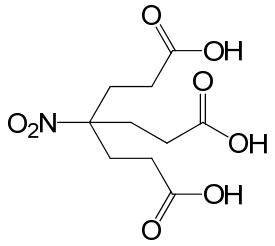


Figure 3. 4 Structure of Nitro-3 acid, (AB_3, 1. generation).

A solution of nitro triester (4.45 g, 0.01 mol) in formic acid (20 ml) was irradiated by microwave (150 W) for 10 minutes under open vessel condition. After removing unreacted formic acids and tert-butanol in vacuo, the white crystals were obtained (2.51 g, 90.6 %). IR (KBr) cm^{-1}: 3365 (br, acid OH), 1710 (acid C=O). ^{1}H NMR δ 1.55 (t, CH_2CH_2COO, 6H and t, CH_2COO, 6H), 7.28 (br, CO_2H, 2H); ^{13}C NMR δ 28 (CH_2CH_2COO), 33 (CH_2COO), 89 (NO_2CCH_2), 172 (*C*OOH) ppm.

3.3.2.5 Synthesis of Amino-2 ester, (AB_2), Di-tert-butyl 4-Amino-4-ethylheptanedioate, (5).

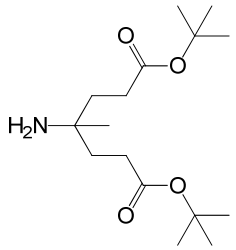


Figure 3. 5 Structure of Amino-2 ester, (AB_2, 1. generation).

A solution of nitro diester (5 g, 15.1 mmol) in absolute EtOH (100 mL) was added to the freshly prepared T-1 Raney Ni, and then hydrogenated (90 p.s.i) at 25 ° C for 5 hours. After the solution was cautiously filtered through Celite, the solvent was removed in vacuo to afford (90.2 %) the desired amine, as a yellowish viscous liquid: 4.1 g; IR (neat) cm^{-1}: 3364 (NH_2), 3310 (NH_2), 1725 (ester C=O), 1151 (ester C-O). ^{1}H NMR δ 1.28 (s, NH_2CCH_3, 3H), 1.44 (s, CH_3, 18H) 1.67 (t, CH_2CH_2COO, 4H), 2.28 (t, CH_2COO, 4H),

5.95 (s, N*H*$_2$, 2H); ^{13}C NMR δ 26.9 (NH$_2$C*C*H$_3$), 28.1 (C*C*H$_3$), 30.3(*C*H$_2$CH$_2$COO), 37.1 (*C*H$_2$COO), 76.4-77.6 (*C*CH$_3$) 80.3 (NH$_2$*C*CH$_3$), 173.2 (*C*OO) ppm.

3.3.2.6 Synthesis of Amino-3 ester, (AB$_3$), 4-Amino-4-[2-(tert-butoxycarbonyl) ethyl)]-heptanedioate, (6)

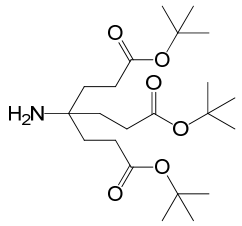


Figure 3. 6 Structure of Amino-3 ester, (AB$_3$, 1. Generation).

A solution of nitro triester (5 g, 11.2 mmol) in EtOH (100 mL) was added to the freshly prepared T-1 Raney Ni, and then hydrogenated (90 p.s.i) at 25 ° C for 5 hours. After the solution was cautiously filtered through Celite, the solvent was removed in *vacuo* to afford (92.2 %) the desired amine, as a white crystalline solid: 4.3 g; IR (KBr) cm^{-1}: 3378, 3320 (NH$_2$), 1724 (ester C=O), 1152 (ester C-O). ^{1}H NMR δ 1.45 (s, C*H*$_3$, 27H), 1.88 (t, C*H*$_2$CH$_2$COO, 6H), 2.25 (t, C*H*$_2$COO, 6H), 6.42 (s, N*H*$_2$, 2H); ^{13}C NMR δ 28.4 (C*C*H$_3$), 30.6 (*C*H$_2$CH$_2$COO), 35.1(*C*H$_2$COO), 77-78 (*C*CH$_3$) 81.1 (NH$_2$*C*CH$_2$), 172.4 (*C*OO) ppm.

3.3.2.7 Synthesis of Nitro-4 ester (AB$_2$, 2. generation), (7)

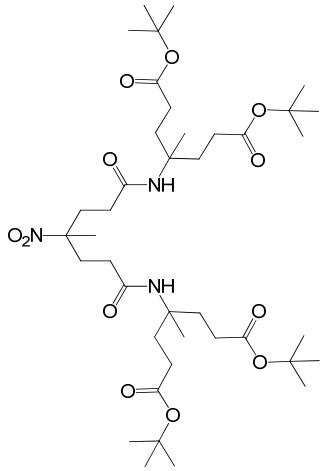


Figure 3. 7 Structure of Nitro-4 ester (AB$_2$, 2. generation).

To a stirred solution of 4-methyl-4-nitroheptanedioic acid (0.5 g, 2.28 mmol) in dry THF (50 mL), was added DCC (0.94 g, 4.56 mmol) and 1-HOBT (0.62 g, 4.56 mmol) at 25 °C. After 30 min, amino diester (1.50 g, 4.98 mmol) was added. The mixture was stirred for an additional 24 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was column chromatographed (SiO_2) eluting with $CHCl_3$ to afford (64.9 %) the 2nd generation dendron , as a white solid: 0.77 g; mp 155-157 ºC; IR (KBr) cm^{-1}: 3365 (amide NH), 1731 (ester C=O), 1682, 1540 (amide C=O) 1152 (ester C-O). ^1H NMR δ 1.28 (s, 6H,CCH_3), 1.52 (s, 3H, CH_3), 1.63 (t, 8H, CH_2CO, J = 4.2 Hz), 1.90 (t, 8H, CH_2CH_2CO, J = 4.2 Hz), 2.04 (t, 4H, CH_2CH_2CO, J = 7.2 Hz), 2.24 (t, 4H, CH_2CH_2CO, J = 7.2 Hz), 5.94(s, 2H, NH); ^{13}C NMR δ 21.7 (CH_3), 23.6 (CH_3), 28.1 (CH_3), 30.3 (CH_2CH_2CO), 31.5CH_2CO), 80.6 (CMe_3), 90.5 (O_2NC), 170.4 (CONH), 173.2 (CO_2).

3.3.2.8 Synthesis of Amino-4 ester (AB_2, 2. generation), (8)

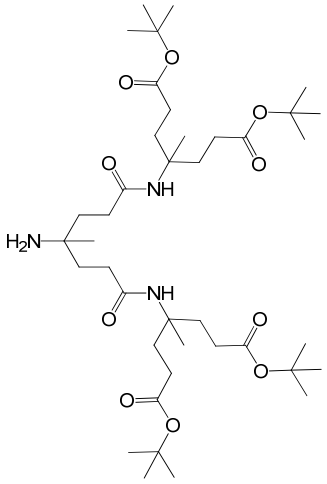


Figure 3. 8 Structure of Amino-4 ester (AB_2, 2. generation).

A solution of Nitro-4ester, (AB2, 2. generation) (0.5 g, 0.64 mmol) in EtOH (100 mL) was added to the freshly prepared T-1 Raney Ni, and then hydrogenated (90 p.s.i) at 25 ° C for 5 hours. After the solution was cautiously filtered through Celite, the solvent was removed in *vacuo* to afford (72.8 %) the desired amine, as a white crystalline solid: 0.35 g;; mp 143 ºC; IR (KBr) cm^{-1}: 3365 (amine, br, NH_2), 1730 (ester C=O), 1681,

1541 (amide C=O), 1155 (ester C-O). ^{1}H NMR δ 1.05 (s, 6H, CH_3), 1.24 (t, 8H, CH_2CH_2CO, J = 6.0 Hz), 1.43 (s, 36H, CH_3), 1.45 (s, 3H, CH_3), 1.66 (t, 8H, CH_2CO, J = 6.0 Hz), 1.96 (t, 4H, CH_2CH_2CO, J = 6.3 Hz), 2.22 (t, 4H, CH_2CO, J = 6.4 Hz), 6.10 (s, 1H, NH), 6.12 (s, 2H, NH_2); ^{13}C NMR δ 23.6 (CH_3), 27.5 (CH_3), 28.0 (CMe_3), 30.2 (CH_2CH_2CO), 32.1 (CH_2CO), 33.2 (CH_2CH_2CO), 37.9 (CH_2CO), 50.9 (HNC), 55.8 (H_2NC), 80.3 (CMe_3), 172.7 (CONH), 173.0 (CO_2).

3.3.2.9 Synthesis of Nitro-6 ester (AB_2, 2. generation), (9)

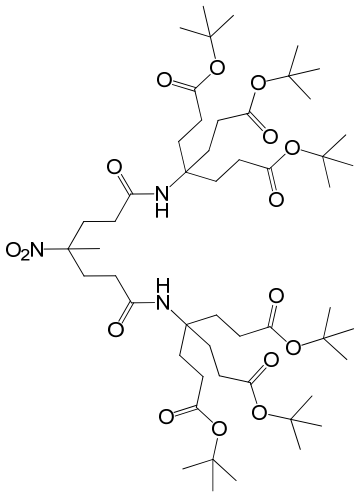


Figure 3. 9 Structure of Nitro-6 ester (AB_2, 2. generation).

To a stirred solution of 4-methyl-4-nitroheptanedioic acid (0.5 g, 2.28 mmol) in dry THF (100 mL) was added DCC (0.94 g, 4.56 mmol) then 1-HOBT (0.62 g, 4.56 mmol) at 25 °C. After 30 min, Behera's amine (amino triester) (2.1 g, 5.05 mmol) was added. The mixture was stirred for an additional 24 h, and then the precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was column chromatographed (SiO_2) eluting with a 10% EtOAc in $CHCl_3$ solvent mixture to afford (58.3 %) the 2nd generation nitro (2-6) ester, as a white solid: 1.35 g; mp 185 ºC; IR (KBr) cm^{-1}: 3358 (amide NH), 1728 (ester C=O), 1680, 1538 (amide C=O),1153 (ester C-O). ^{1}H NMR δ 1.44 (s, 54H, CH_3), 1.52 (s, 3H, CH_3), 1.96 (t, 16H, CH_2CH_2CO, CH_2CO, J = 7.5 Hz), 2.21 (t, 16H, CH_2CO, CH_2CH_2CO, J = 7.5 Hz), 6.16 (s, 1H, NH); ^{13}C NMR δ 21.8 (CH_3), 28.2 (CH_3),

30.0 (CH_2CH_2CO), 31.7 (CH_2CO), 35.1 (CH_2CH_2CO), 57.7 (HNC), 80.9 (CMe_3), 90.5 (CNO_2), 170.5 (CONH), 173.0 (CO_2).

3.3.2.10 Synthesis of Amino-6 ester (AB_2, 2. generation), (10)

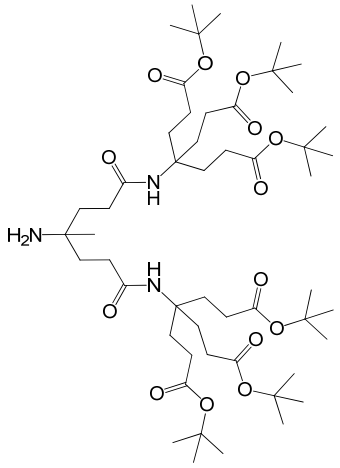


Figure 3. 10 Structure of Amino-6 ester (AB_2, 2. generation).

A solution of nitro triester (0.5 g, 0.49 mmol) in EtOH (100 mL) was added to the freshly prepared T-1 Raney Ni, and then hydrogenated (90 p.s.i) at 25 ° C for 5 hours. After the solution was cautiously filtered through Celite, the solvent was removed in *vacuo* to afford (65.9 %) the desired amine, as a white crystalline solid: 0.32 g; mp 165 ºC; IR (KBr) cm^{-1}: 3359 (amine, br, NH_2), 1731 (ester C=O), 1678, 1542 (amide C=O), 1152 (ester C-O). ^1H NMR δ 1.05 (s, 3H, CH_3), 1.25 (t, 4H, CH_2CH_2CO, J = 6.0 Hz), 1.44 (s, 54H, CH_3), 1.67 (t, 4H, CH_2CO, J = 6.0 Hz), 1.96 (t, 12H, CH_2CH_2CO, J = 7.8 Hz), 2.22 (t, 4H, CH_2CO, J = 7.8 Hz), 6.11 (s, 3H, NH, NH_2); ^{13}C NMR δ 27.2 (CH_3), 28.1 (CH_3), 29.9 (CH_2CH_2CO), 30.0 (CH_2CO), 32.2 (CH_2CH_2CO), 37.9 (CH_2CO), 51.5 (H_2NC), 57.4 (HNC), 80.6 (CMe_3), 172.6 (CONH), 172.9 (CO_2).

3.3.2.11 Synthesis of Nitro-6 ester (AB_3, 2. generation), (11)

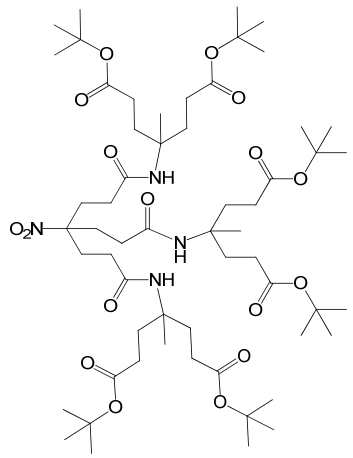


Figure 3. 11 Structure of Nitro-6 ester (AB_3, 2. generation).

To a stirred solution of nitro triacid (0.5 g, 1.80 mmol) in dry THF (100 mL) was added DCC (1.12 g, 5.41 mmol) then DMAP (0.66 g, 5.41 mmol) at 25 °C. After 30 min, amino diester (1.69 g, 5.59 mmol) was added. The mixture was stirred for an additional 24 h, and then the precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was column chromatographed (SiO_2) eluting with a 10% EtOAc in $CHCl_3$ solvent mixture to afford (64.9 %) the 2nd generation nitro predendron, as a white solid: 1.32 g; mp 185 ºC; IR (KBr) cm^{-1}: 3355 (amide NH), 1731 (ester C=O), 1679, 1543 (amide C=O), 1154 (ester C-O). ^1H NMR δ 1.44 (s, 54H, CH_3), 1.52 (s, 3H, CH_3), 1.96 (t, 16H, CH_2CH_2CO, CH2CO, J = 7.5 Hz), 2.21 (t, 16H, CH_2CO, CH_2CH_2CO, J = 7.5 Hz), 6.16 (s, 1H, NH); ^{13}C NMR δ 21.8 (CH_3), 28.2 (CH_3), 30.0 (CH_2CH_2CO), 31.7 (CH_2CO), 35.1 (CH_2CH_2CO), 57.7 (HNC), 80.9 (CMe_3), 90.5 (CNO_2), 170.5 (CONH), 173.0 (CO_2).

3.3.2.12 Synthesis of Amino-6 ester (AB_3, 2. generation), (12)

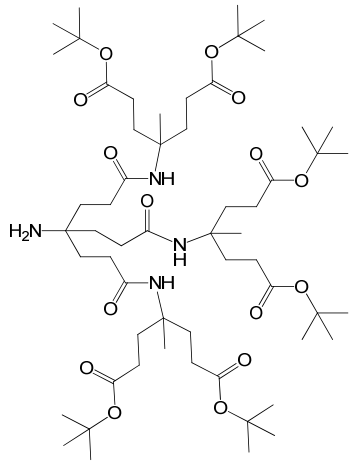


Figure 3. 12 Structure of Amino-6 ester (AB_3, 2. generation).

A solution of nitro (3-6) diester (0.5 g, 0.44 mmol) in EtOH (100 mL) was added to the freshly prepared T-1 Raney Ni, and then hydrogenated (90 p.s.i) at 25 ° C for 5 hours. After the solution was cautiously filtered through Celite, the solvent was removed in *vacuo* to afford (67.8 %) the desired amine, as a white crystalline solid: 0.33 g; mp 152 ºC; IR (KBr) cm^{-1}: 3364 (amine NH_2), 1730 (ester C=O), 1681, 1540 (amide C=O), 1152 (ester C-O). ^1H NMR δ 1.05 (s, 3H, CH_3), 1.25 (t, 4H, CH_2CH_2CO, J = 6.0 Hz), 1.44 (s, 54H, CH_3), 1.67 (t, 4H, CH_2CO, J = 6.0 Hz), 1.96 (t, 12H, CH_2CH_2CO, J = 7.8 Hz), 2.22 (t, 4H, CH_2CO, J = 7.8 Hz), 6.11 (s, 3H, NH, NH_2); ^{13}C NMR δ 27.2 (CH_3), 28.1 (CH_3), 29.9 (CH_2CH_2CO), 30.0 (CH_2CO), 32.2 (CH_2CH_2CO), 37.9 (CH_2CO), 51.5 (H_2NC), 57.4 (HNC), 80.6 (CMe_3), 172.6 (CONH), 172.9 (CO_2).

3.3.2.13 Synthesis of Nitro-9 ester (AB_3, 2. generation), (13)

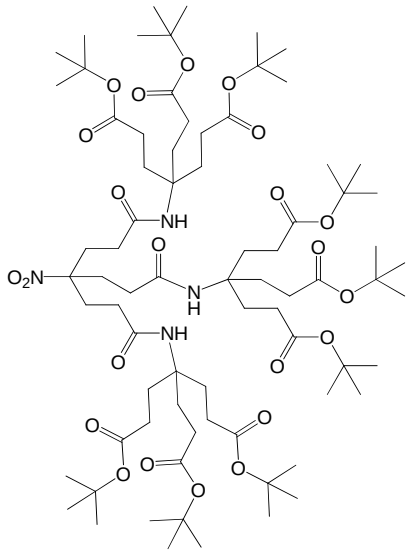


Figure 3. 13 Structure of Nitro-9 ester (AB_3, 2. generation).

To a stirred solution of nitro triacid (0.5 g, 1.80 mmol) in dry THF (100 mL) was added DCC (1.12 g, 5.41 mmol) then DMAP (0.66 g, 5.41 mmol) at 25 °C. After 30 min, amino triester (2.33 g, 5.59 mmol) was added. The mixture was stirred for an additional 24 h. The white precipitate was filtered and THF was removed in vacuum. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by column chromatography (cyclohexane: ethyl acetate 2: 1) to give 1.62 g (61.1 %) of nitro (3-9) ester. IR (KBr) cm^{-1}: 3370 (amide NH, br), 1731 (ester C=O), 1663 (amide C=O), 1540 (nitro NO_2). ^1H NMR δ 1.42 (s, CH_3, 81H), 1.76, 2.37 (m, CH_2, 48H), 5.84 (br, N*H*, 3H). ^{13}C NMR δ 28 (*C*H_3), 30.1 (NHC*C*H_2*C*H_2COO), 34.7 (NO_2C*C*H_2*C*H_2CONH), 60.5 (N*C*CH_2CH_2CO), 80.9 (*C*CH_3), 172.4 (COO), 176.9 (CONH).

3.3.2.14 Synthesis of Amino-9 ester, (AB_3, 2. generation), (14)

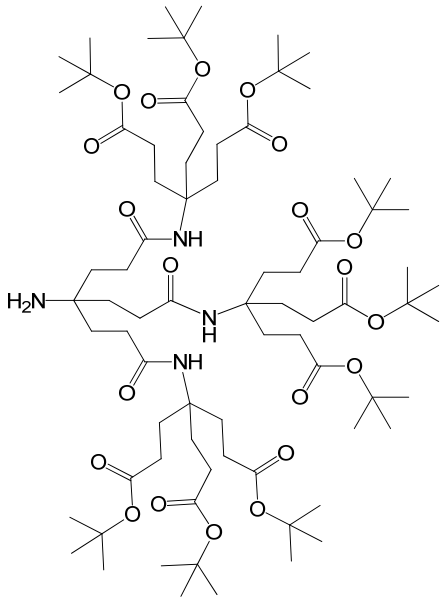


Figure 3. 14 Structure of Amino-9 ester (AB_3, 2. generation).

A solution of nitro (3-9) ester (0.5 g, 3.41 mmol) in EtOH (100 mL) was added to the freshly prepared T-1 Raney Ni, and then hydrogenated (90 p.s.i) at 25 ° C for 5 hours. After the solution was cautiously filtered through Celite, the solvent was removed in *vacuo* to afford (83.7 %) the desired amine, as a white crystalline solid: 0.41 g; IR (KBr) cm^{-1}: 3378, 3320 (NH_2), 1728 (ester C=O), 1680, 1538 (amide C=O), 1152 (ester C-O). ^1H NMR δ 1.05 (s, 3H, CH_3), 1.25 (t, 4H, CH_2CH_2CO, J = 6.0 Hz), 1.44 (s, 54H, CH_3), 1.67 (t, 4H, CH_2CO, J = 6.0 Hz), 1.96 (t, 12H, CH_2CH_2CO, J = 7.8 Hz), 2.22 (t, 4H, CH_2CO, J = 7.8 Hz), 6.11 (s, 3H, NH, NH_2); ^{13}C NMR δ 27.2 (CH_3), 28.1 (CH_3), 29.9 (CH_2CH_2CO), 30.0 (CH_2CO), 32.2 (CH_2CH_2CO), 37.9 (CH_2CO), 51.5 (H_2NC), 57.4 (HNC), 80.6 (CMe_3), 172.6 (CONH), 172.9 (CO_2).

3.3.2.15 Synthesis of nitro-6 alcohol (AB_2, 2. generation), (15)

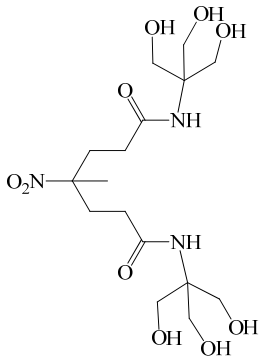


Figure 3. 15 Structure of nitro-6 alcohol (AB_2, 2. generation).

Methanolic solution (100 mL) of nitro diester (0.5 g, 1.51 mmol) was added dropwise to a stirred methanolic solution (5 mL) of TRIS (tris (hydroxymethyl) aminomethane) (0.37 g, 3.02 mmol). K_2CO_3 (0.042 g, 0.3 mmol) was added as the catalyst. The resulting solution was stirred at room temperature for 5 minutes. Then, microwave irradiation (150 W) was applied for 10 minutes under open vessel condition. K_2CO_3 was filtered and solvents were removed by rotary evaporator. The product was purified by column chromatography eluting with ethyl acetate to give 0.45 g (70.1 %) of nitro (2-6) alcohol. IR (neat) cm^{-1}: 3400 (br, OH), 1639 and 1567(amide C=O).

3.3.2.16 Synthesis of nitro-9 alcohol (AB_3, 2. generation), (16)

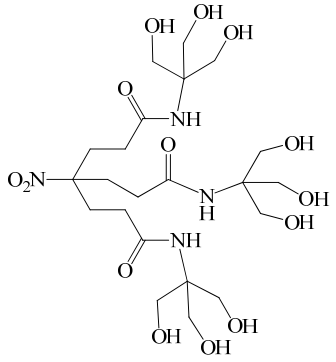


Figure 3. 16 Structure of nitro-9 alcohol (AB_3, 2. generation).

Methanolic solution (100 mL) of nitro triester (0.5 g, 1.12 mmol) was added dropwise to a stirred methanolic solution (5 mL) of TRIS (tris (hydroxymethyl) aminomethane) (0.41 g, 3.37 mmol). K_2CO_3 (0.042 g, 0.3 mmol) was added as the catalyst. The resulting solution was stirred at room temperature for 5 minutes. Then, microwave irradiation (150 W) was applied for 10 minutes under open vessel condition. K_2CO_3 was filtered and solvents were removed by rotary evaporator. The product was purified by column chromatography eluting with ethyl acetate to give 0.48 g (72.9 %) of nitro (3-9) alcohol. IR (neat) cm-1: 3400 (br, OH), 1645 and 1567(amide C=O).

3.3.3 SYNTHESIS OF DENDRIMERS

3.3.3.1 SYNTHESIS OF TRIS (2-AMINOETHYL) AMINE (TREN) CORED PAMAM TYPE DENDRIMERS

3.3.3.1.1 Synthesis of TREN-6 Ester, (17)

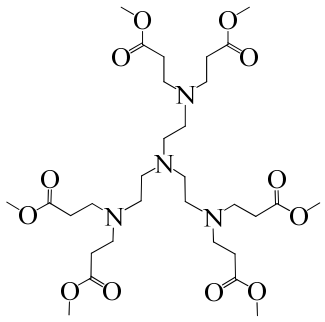


Figure 3. 17 Structure of TREN-6-ester.

A methanolic solution of methyl acrylate (3.59 g, 41.7 mmol) was added dropwise into the methanolic solution of TREN (1 g, 6.84 mmol). Ce (IV) sulphate (0.23 g, 4.17 mmol) was added into the mixture as a catalyst. Then, microwave irradiation (150 W) was applied for 3 minutes under open vessel condition. Cerium (IV) sulphate was filtered. Methanol and excess methyl acrylate was removed in vacuo. A pale yellow, viscous, oily product was obtained. (4.04 g, 89.1 %). IR (KBr) cm-1: 1738 (ester C=O), 1175 (ester C-O).

3.3.3.1.2 Synthesis of TREN-6 Acid, (18)

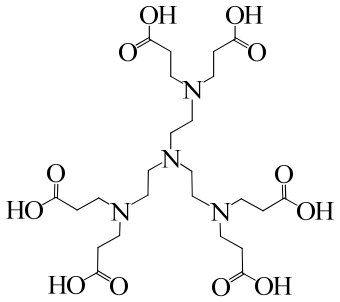


Figure 3. 18 Structure of TREN-6-acid.

It was synthesized according to general procedure A, a solution of TREN-6-ester (1.0 g, 1.51 mmol) in formic acid (20 ml) was stirred for 5 minutes. Then, microwave irradiation (300 W) was applied for 2 hours under open vessel condition. After removing formic acid and methanol by rotary evaporator a reddish oily product was obtained (0.75 g, 84.6 %).IR (neat) cm^{-1}: 3432 (br, OH), 1662 (acid C=O).

3.3.3.1.3 Synthesis of TREN-6 Amine, (19)

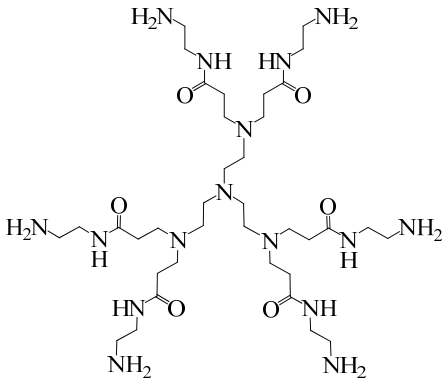


Figure 3. 19 Structure of TREN-6-amine.

Methanolic solution (100 mL) of TREN-6-ester (1.0 g, 1.51 mmol) was added dropwise to a stirred methanolic solution (5 mL) of ethylenediamine (0.6 g, 9.98 mmol). The resulting solution was stirred at room temperature for 5 minutes. Then, microwave irradiation (150 W) was applied for 5 minutes under open vessel condition. The excess

ethylenediamine and solvent were removed under vacuum. Final traces of ethylenediamine was removed by dissolving the residue in 50 mL of n-butanol (a competitive hydrogen bonding solvent), the butanol was then removed under vacuum. The yellow oily product was obtained (1.20 g, 96 %).IR (neat) cm^{-1}: 3400 (br, NH_2), 1639 and 1560 (amide C=O).

3.3.3.1.4 Synthesis of TREN-12 ester, (20)

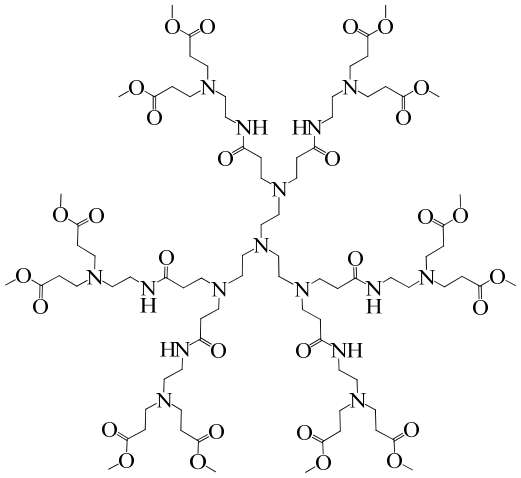


Figure 3. 20 Structure of TREN-12 ester.

A methanolic solution of methyl acrylate (1.00 g, 11.6 mmol) was added dropwise into the methanolic solution of TREN-6-amine (0.50 g, 0.60 mmol). Ce (IV) sulphate (0.02 g, 0.06 mmol) was added into the mixture as a catalyst. Then, microwave irradiation (150 W) was applied for 3 minutes under open vessel condition. Cerium (IV) sulphate was filtered. Methanol and excess methyl acrylate was removed in vacuo. A pale yellow, viscous, oily product was obtained. (1.04 g, 93 %). IR (KBr) cm^{-1}: 3384(amide -CONH), 1735 (ester C=O), 1647 and 1545 (amide C=O), 1177 (ester C-O).

3.3.3.1.5 Synthesis of TREN-18 ol, (21)

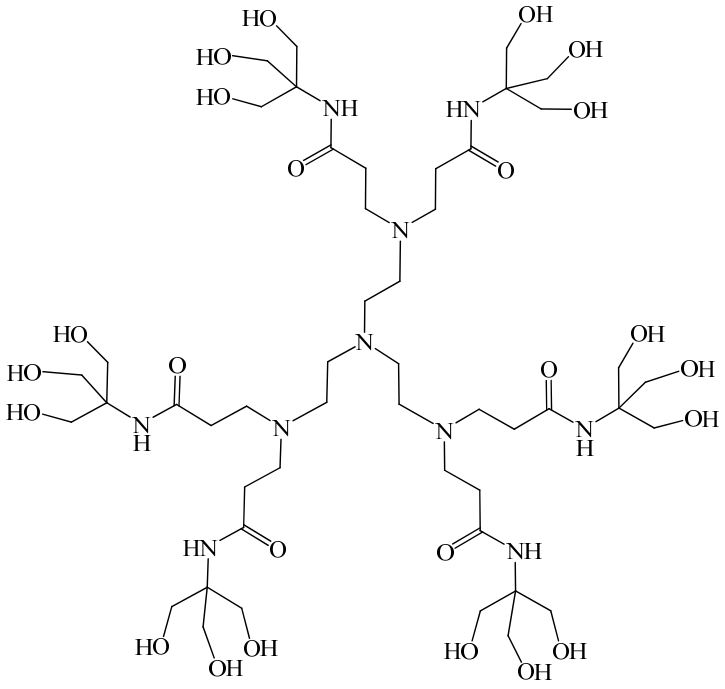


Figure 3. 21 Structure of TREN-18 ol.

Methanolic solution (100 mL) of TREN-6-ester (1.0 g, 1.51 mmol) was added dropwise to a stirred methanolic solution (5 mL) of TRIS (tris (hydroxymethyl) aminomethane) (1.1 g, 7.52 mmol). K_2CO_3 (1.3 g, 9.41 mmol) was added as the catalyst. The resulting solution was stirred at room temperature for 5 minutes. Then, microwave irradiation (150 W) was applied for 10 minutes under open vessel condition. K_2CO_3 was filtered and solvents were removed by rotary evaporator. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by column chromatography eluting with ethyl acetate to give 1.52 g (84.1 %) of desired alcohol. IR (neat) cm^{-1}: 3369 (amide br, NH), 1645 and 1567 (amide C=O).

3.3.3.1.6 Synthesis of TREN-36 ol, (22)

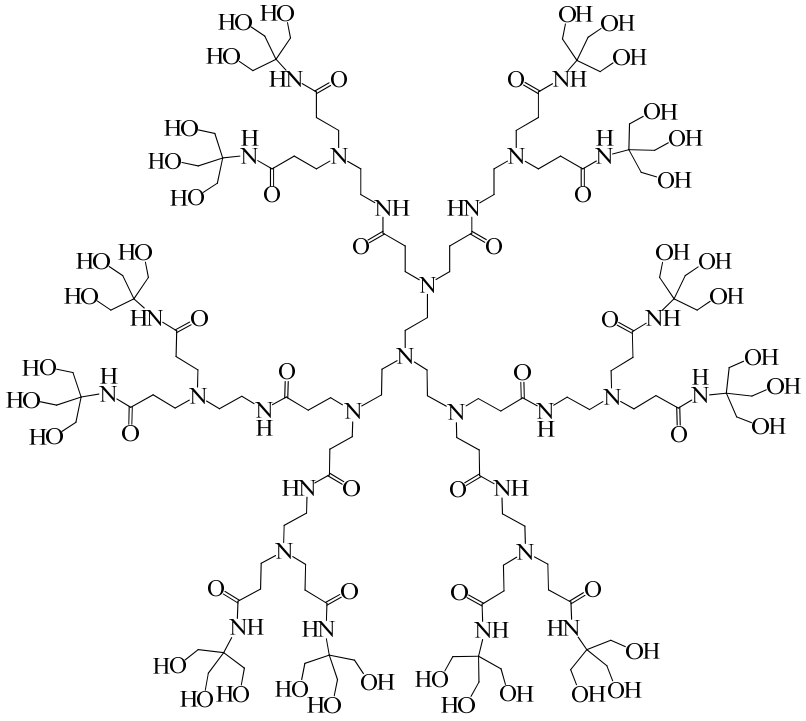


Figure 3. 22 Structure of TREN-36ol.

Methanolic solution (100 mL) of TREN-6-ester (0.337 g, 0.18 mmol) was added dropwise to a stirred methanolic solution (5 mL) of TRIS (tris (hydroxymethyl) aminomethane) (0.167 g, 1.38 mmol). K_2CO_3 (0.015 g, 1.38 mmol) was added as the catalyst. The resulting solution was stirred at room temperature for 5 minutes. Then, microwave irradiation (150 W) was applied for 10 minutes under open vessel condition. K_2CO_3 was filtered and solvents were removed by rotary evaporator. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by column chromatography eluting with ethyl acetate to give 0.35 g (66.0 %) of desired alcohol. IR (neat) cm^{-1}: 3351 (amide br, NH), 1638 and 1560 (amide C=O).

3.3.3.2 SYNTHESIS OF TRIMESIC ACID (TMA) CORED PAMAM TYPE DENDRIMERS

3.3.3.2.1 Synthesis of Trimesic-6 ester, (23)

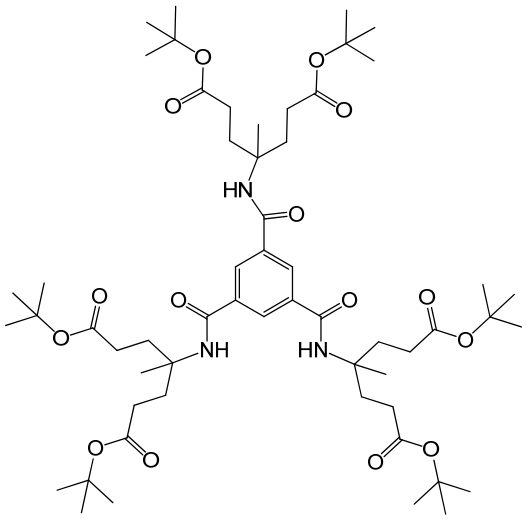


Figure 3. 23 Structure of Trimesic-6ester.

A solution of 0.5 g (2.38 mmol) Trimesic acid dissolved in dry DMF was mixed with 1.57 g (7.61 mmol) DCC, and 1.03 g (7.61 mmol) DMAP. After stirring about 30 minutes, 2.3 g (7.63 mmol) amino diester was added into the mixture. The mixture was stirred for 24 hours at room temperature. The white precipitate was filtered and DMF was removed in vacuo. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by column chromatography eluting with ethyl acetate to give 1.61 g (63.9 %) of TMA-6-ester. IR (KBr) cm^{-1}: 3339 (amide NH, br), 1730 (ester C=O), 1651 (amide C=O), 1537 (amide C=O) and 1152 (ester C-O).

3.3.3.2.2 Synthesis of Trimesic-9 ester, (24)

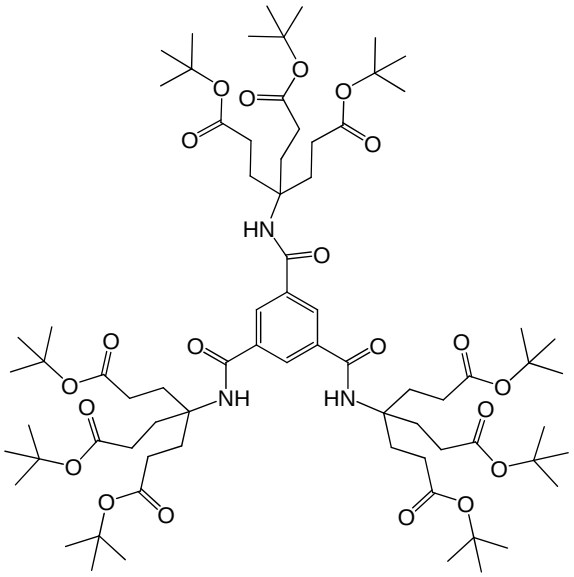


Figure 3. 24 Structure of Trimesic-9 ester.

A solution of 0.5 g (2.38 mmol) Trimesic acid dissolved in dry DMF was mixed with 1.57 g (7.61 mmol) DCC, and 1.03 g (7.61 mmol) DMAP. After stirring about 30 minutes, 3.0 g (7.14 mmol) amino triester (Behera's amine) was added into the mixture. The mixture was stirred for 24 hours at room temperature. The white precipitate was filtered and DMF was removed in vacuo. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by dialysis (MWCO 1000) in methanol. 1.51 g (45.2 %) of TMA-9-ester.m.p.193 ^{0}C; IR (KBr) cm^{-1}: 3354 (amide NH, br), 1731 (ester C=O), 1667 (amide C=O), 1537 (amide C=O) and 1155 (ester C-O).

3.3.3.2.3 Synthesis of Trimesic-9 acid, (25)

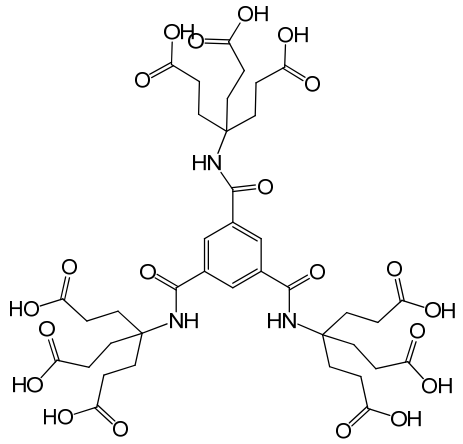


Figure 3. 25 Structure of Trimesic-9 acid.

A solution of TMA-9-ester (1.0 g, 0.71 mmol) in formic acid (20 ml) was stirred for 5 minutes. Then, microwave irradiation (300 W) was applied for 2 hours under open vessel condition. After removing formic acid and methanol by rotary evaporator a reddish oily product was obtained (0.52 g, 81.2 %).IR (neat) cm^{-1}: 3393 (acid br, OH), 1724 (acid C=O).

3.3.3.2.4 Synthesis of Trimesic-12 ester, (26)

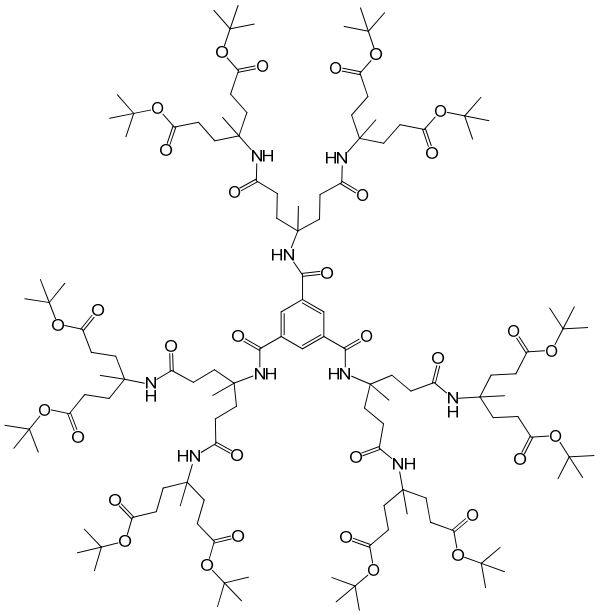


Figure 3. 26 Structure of Trimesic-12 ester.

1, 3, 5-benzenetricarbonyl chloride was prepared from Trimesic acid by using thionyl chloride. Then freshly prepared compound (0.015g, 0.056 mmol) was mixed with the amino (2-6) ester.(0.13 g, 0.17 mmol) in the presence of Et_3N (1 ml) in THF (25 ml) and stirred for 12 h at room temperature and then the mixture was filtered and solvent was evaporated under vacuum. Final product was purified by using membrane filtration system (Spectra/Por MWCO1000) in methanol. After dialysis methanol was removed under vacuum (0.10 g, 73 %). IR (KBr) cm^{-1}: 3314 (amide NH, br), 1731 (ester C=O), 1654 (amide C=O), 1546 (amide C=O) and 1153 (ester C-O)

3.3.3.2.5 Synthesis of Trimesic-27 ester, (27)

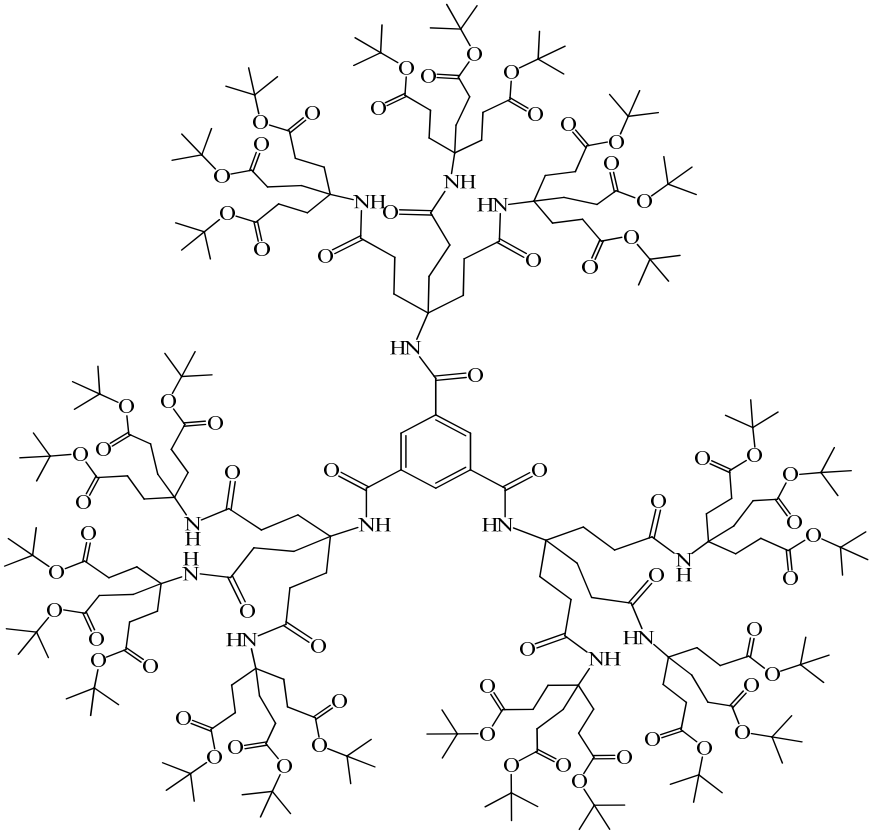


Figure 3. 27 Structure of Trimesic-27 ester.

A solution of 0.5 g (2.38 mmol) Trimesic acid dissolved in dry THF was mixed with 1.57 g (7.61 mmol) DCC, and 1.03 g (7.61 mmol) DMAP. After stirring about 30

minutes, 3.0 g (7.14 mmol) amino triester (Behera's amine) was added into the mixture. The mixture was stirred for 24 hours at room temperature. The white precipitate was filtered and THF was removed in vacuo. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by dialysis (MWCO 1000) in methanol. 1.51 g (45.2 %) of TMA-9-ester.m.p.193 ^{0}C; IR (KBr) cm^{-1}: 3327 (amide NH, br), 1731 (ester C=O), 1686 (amide C=O), 1537 (amide C=O) and 1154 (ester C-O).

3.3.3.3 PEG BASED DENDRIMERS

3.3.3.3.1 Synthesis of PEG-4 ester, (28)

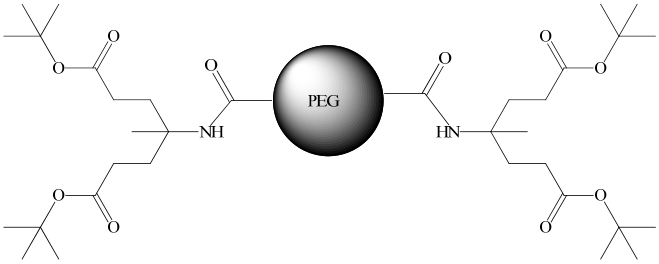


Figure 3. 28 Structure of PEG-4 ester.

A solution of 3.024 g (5.00 mmol) PEG diacid, 3.63 g (12.04 mmol) amino diester, 1.35 g (10.00 mmol) HOBT and 2.06 g (10.0 mmol) DCC in 15 ml DMF was stirred for 48 hours at room temperature. The white precipitate was filtered and DMF was removed in vacuum. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by column chromatography eluting with ethyl acetate to give 4.35 g (74 %) ester. IR (KBr) cm^{-1}: 3357 (amide NH, br), 1728 (ester C=O), 1678(amide C=O) and 1540(amide C=O). ^{1}H NMR δ 1.33 (s, NHCC*H*$_3$, 6H), 1.41 (s, C*H*$_3$, 36H) 1.50 (t, C*H*$_2$CH$_2$COO, 8H), 2.20 (t, C*H*$_2$COO, 8H), 3.15 (q, OC*H*$_2$C*H*$_2$O), 5.38 (s, N*H*, 2H); ^{13}C NMR δ 27.7 (NHC*C*H$_3$), 27.9 (C*C*H$_3$), 30.1 (*C*H$_2$CH$_2$COO), 33.1 (*C*H$_2$COO), 70.3 (*C*CH$_3$) 80.2 (NH*C*CH$_3$), 172.6 (*C*OO), 176.9 (CONH) ppm.

3.3.3.3.2 Synthesis of PEG-4 acid, (29)

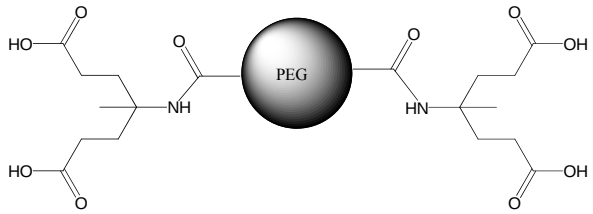


Figure 3. 29 Structure of PEG-4 acid.

A solution of PEG-diester (28) (1.00 g, 0.86 mmol) in formic acid (20 ml) was irradiated by microwave (150 W) for 10 minutes under open vessel condition. After evaporating excess formic acid and hydrolyzed tert-butanol in vacuo, light brown oily product was obtained (0.75 g, 92.9 %). IR (KBr) cm^{-1}: 3434 (br, acid OH), 1723 (acid C=O), 1654 (amide C=O) and 1540(amide C=O). ^{1}H NMR δ 1.35, 1.37 (s, NHCCH_3, 6H), 1.96 (t, C*H*2CH_2COO, 8H), 2.38 (t, CH_2COO, 8H), 3.63 (q, OCH_2CH_2O), 5.29 (s, N*H*, 2H), 9.53 (br, CO_2H, 2H); ^{13}C NMR δ 28.7 (NHC*C*H_3), 30.2 (*C*H_2CH_2COO), 32.9 (*C*H_2COO), 69.9 (NH*C*CH_3), 164.1 (*C*OOH), 179.5 (CONH) ppm.

3.3.3.3.3 Synthesis of PEG-12 ester, (30)

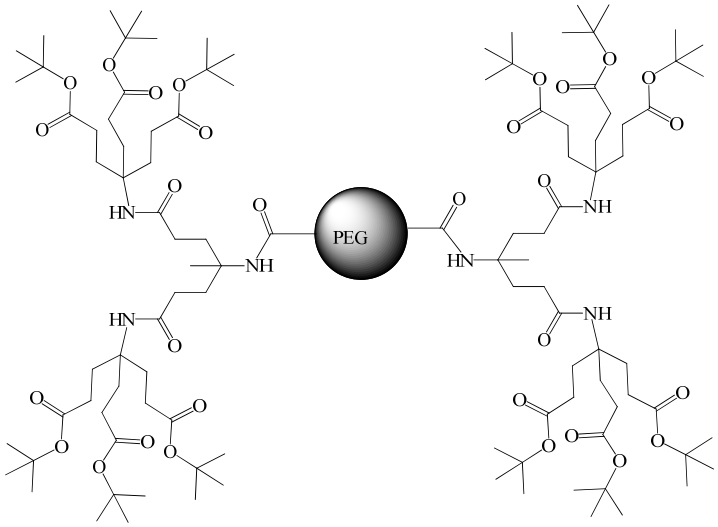


Figure 3. 30 Structure of PEG-12 ester.

A solution of 0.348 g (0.37 mmol) PEG diacid (29), 1.81 g (1.51 mmol) amino triester, 0.20 g (1.48 mmol) HOBT and 0.305 g (1.48 mmol) DCC in 15 ml DMF was stirred for 48 hours at room temperature. The white precipitate was filtered and DMF was removed in vacuum. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by using membrane filtration system (Spectra/Por MWCO1000) in methanol. After dialysis methanol was removed under vacuum (0.65 g, 69.5 %). IR (KBr) cm^{-1}: 3327 (NH), 1731 (ester C=O), 1683 (amide C=O), 1154 (ester C-O). ^1H NMR δ 1.44 (s, CH_3, 72H), 2.17 (t, CH_2, 48H), 4.09 (br, NH, 6H). ^{13}C NMR δ 23.92 (NHC*C*H_3), 28.5 (CH_3), 30.86 (NHC*C*H_2*C*H_2CO), 55-57 (NH*C*CH_2CH_2CO), 80.97 (*C*CH_3), 172 (COO), 173 (CONH).

3.3.3.3.4 Synthesis of PEG-6 ester, (31)

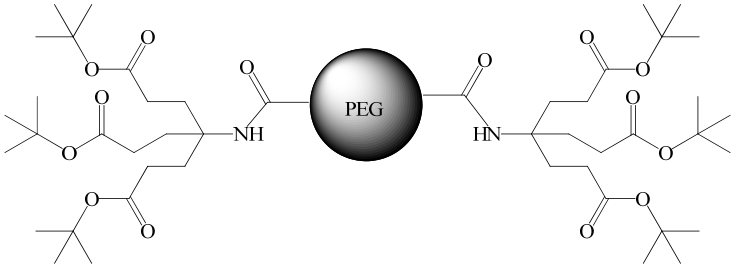


Figure 3. 31 Structure of PEG-6 ester.

A solution of 0.5 g (0.83 mmol) PEG diacid, 0.76 g (1.83 mmol) amino triester, 0.25 g (1.84 mmol) HOBT and 0.38 g (1.84 mmol) DCC in 15 ml DMF was stirred for 48 hours at room temperature. The white precipitate was filtered and DMF was removed in vacuum. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by column chromatography eluting with ethyl acetate to give 0.56 g (48.2 %) ester. IR (KBr) cm^{-1}: 3339 (amide NH, br), 1730 (ester C=O), 1682(amide C=O) and 1531(amide C=O). ^1H NMR δ 1.44 (s, C*H*$_3$, 54H) 1.90 (t, C*H*2CH_2COO, 8H), 2.25 (t, C*H*$_2$COO, 8H), 3.64 (q,

OC*H*$_2$C*H*$_2$O), 5.70 (s, N*H*, 2H); ^{13}C NMR δ 28.2 (C*C*H$_3$), 30.1 (*C*H$_2$CH$_2$COO), 34.7 (*C*H$_2$COO), 80.8 (NH*C*CH$_2$), 172.4 (*C*OO), 176.9 (CONH) ppm.

3.3.3.3.5 Synthesis of PEG-6 acid, (32)

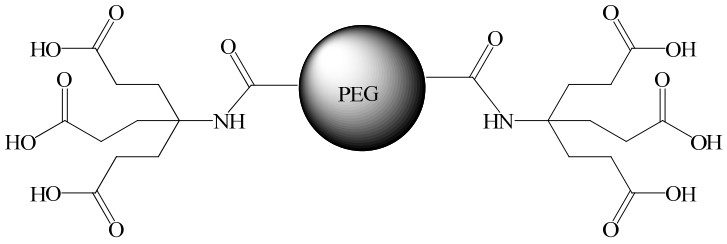


Figure 3. 32 Structure of PEG-6 acid.

A solution of PEG-triester (31) (1.00 g, 0.72 mmol) in formic acid (20 ml) was irradiated by microwave (300 W) for 10 minutes under open vessel condition. After evaporating excess formic acid and hydrolyzed tert-butanol in vacuo, pale yellow oily product was obtained (0.65 g, 85.7 %). IR (KBr) cm^{-1}: 3433 (br, acid OH), 1723 (acid C=O), 1655 (amide C=O) and 1539(amide C=O). ^{1}H NMR δ 2.19 (t, C*H*$_2$CH$_2$COO, 8H and t, C*H*$_2$COO, 8H), 3.66 (q, OC*H*$_2$C*H*$_2$O), 5.70 (s, N*H*, 2H), 8.02 (br, COOH, 8H); ^{13}C NMR δ 30 (*C*H$_2$CH$_2$COO), 34 (*C*H$_2$CO), 80.8 (NH*C*CH$_2$), 170 (*C*OO), 177 (CONH) ppm.

3.3.3.3.6 Synthesis of PEG-18 ester, (33)

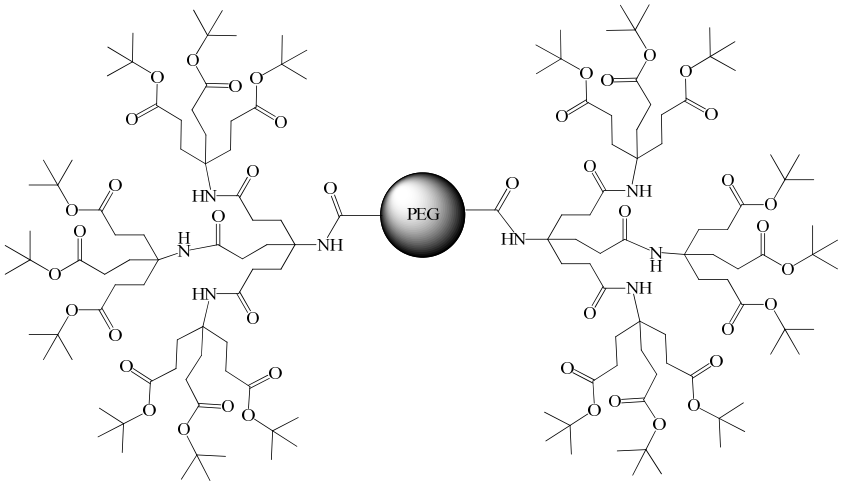


Figure 3. 33 Structure of PEG-18 ester.

A solution of 0.20 g (0.19 mmol) PEG-6-acid (32), 0.48 g (1.15 mmol) amino triester, 0.16 g (1.15 mmol) HOBT and 0.24 g (1.15 mmol) DCC in 15 ml dry DMF was stirred for 24 hours at room temperature. The white precipitate was filtered and DMF was removed in vacuum. The residue was dissolved in 25 ml ethyl acetate and this solution was washed with 10 % HCl, water, saturated aqueous $NaHCO_3$ and brine solutions. After drying the organic phase over $MgSO_4$ and concentration in vacuum the product was purified by using membrane filtration system (Spectra/Por MWCO1000) in methanol. After dialysis methanol was removed under vacuum (0.37 g, 56.9 %). IR (KBr) cm^{-1}: 3338 (NH), 1733 (ester C=O), 1683 (amide C=O), 1541(amide C=O), and 1154 (ester C-O). ^1H NMR δ 1.45 (s, CH3, 162H), 1.63, 1.80 (m, CH_2, 96H), 3.66 (q, OCH_2CH_2O), 6.68 (br, NH, 8H). ^{13}C NMR δ 28.43 (CH_3), 30 ($NHCCH_2CH_2COO$), 35 ($NHCCH_2CH_2CONH$), 61 ($NHCCH_2CH_2CONH$), 81 (CCH_3), 172.7 (COO), 177 (CONH).

3.3.3.4 JEFF AMINE BASED DENDRIMER

3.3.3.4.1 Synthesis of EDTA dianhydride [42], (34)

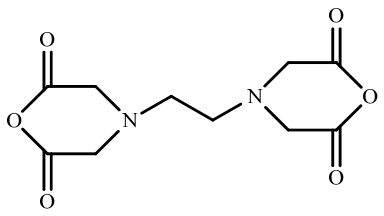


Figure 3. 34 Structure of ETDA dianhydride.

10.0 g of EDTA (34mmol) was suspended in 16ml of pyridine; then 14.0g of acetic anhydride (0.14mmol) was added and the mixture was stirred at 65°C for 24h under nitrogen atmosphere. The product was filtered, washed with acetic anhydride and diethyl

ether, and dried in vacuo for 24h. A pale brown compound was obtained. Yield 90%, mp 195°C. IR (cm^{-1}) 1808, 1760 (-C-O-C-).

3.3.3.4.2 Synthesis of EDTA monoanhydride [42], (35*)*

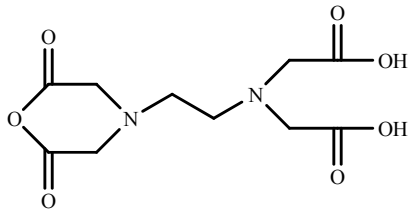


Figure 3. 35 Structure of EDTA monoanhydride.

5.0 g of EDTA dianhydride (19.5 mmol) was mixed with 0.35 mL H_2O (19.5 mmol) in 31 ml dry DMF under nitrogen atmosphere. Then the mixture was stirred at 65°C for 24h. The precipitate was filtered, washed with diethyl ether, and dried in vacuo for 24h. A white crystalline product was obtained. Yield 85%, mp 193°C. IR (cm^{-1}) 1812, 1758 (-C-O-C-), 1691 (-COOH).

3.3.3.4.3 Synthesis of Jeff-EDTA-9 acid, (36)

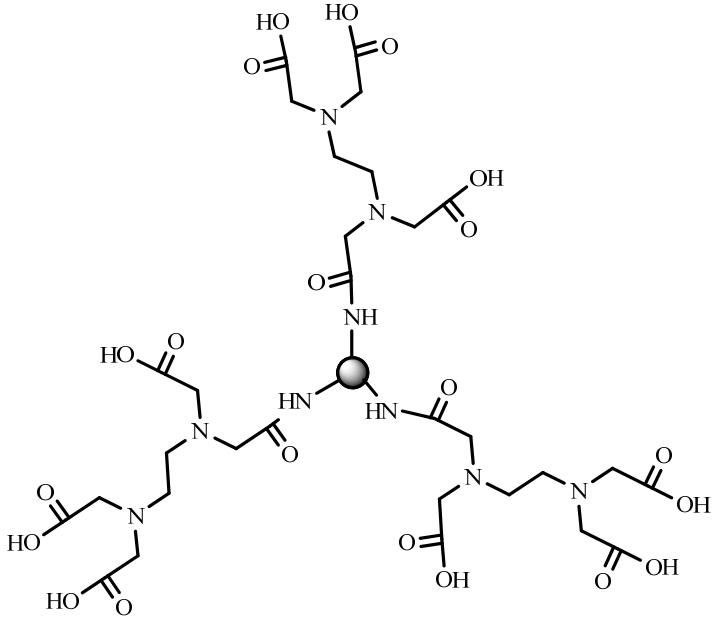


Figure 3. 36 Structure of Jeff-9 acid.

0.5 g of EDTA-MA was added into a solution of Jeff amine dissolved in 10 ml dry DMF. The microwave power (300 W) was applied for 30 minutes under open vessel conditions. After that the solvent was removed in vacuo. Then 1 ml of water was added to the crude product to convert unreacted EDTA-MA to EDTA. Excess amount of EDTA-MA was converted to EDTA that is soluble in water and insoluble parts were removed by filtration. Final product was purified by using membrane filtration system (Spectra/Por MWCO1000) in methanol. A pale yellow Jeff-EDTA-9-Acid as a liquid was obtained. Yield 45%. IR (cm^{-1}); 1728(-COOH), 1668 (-CONH-), 1532 (-CONH).

3.4 METAL ION BINDING CAPACITY

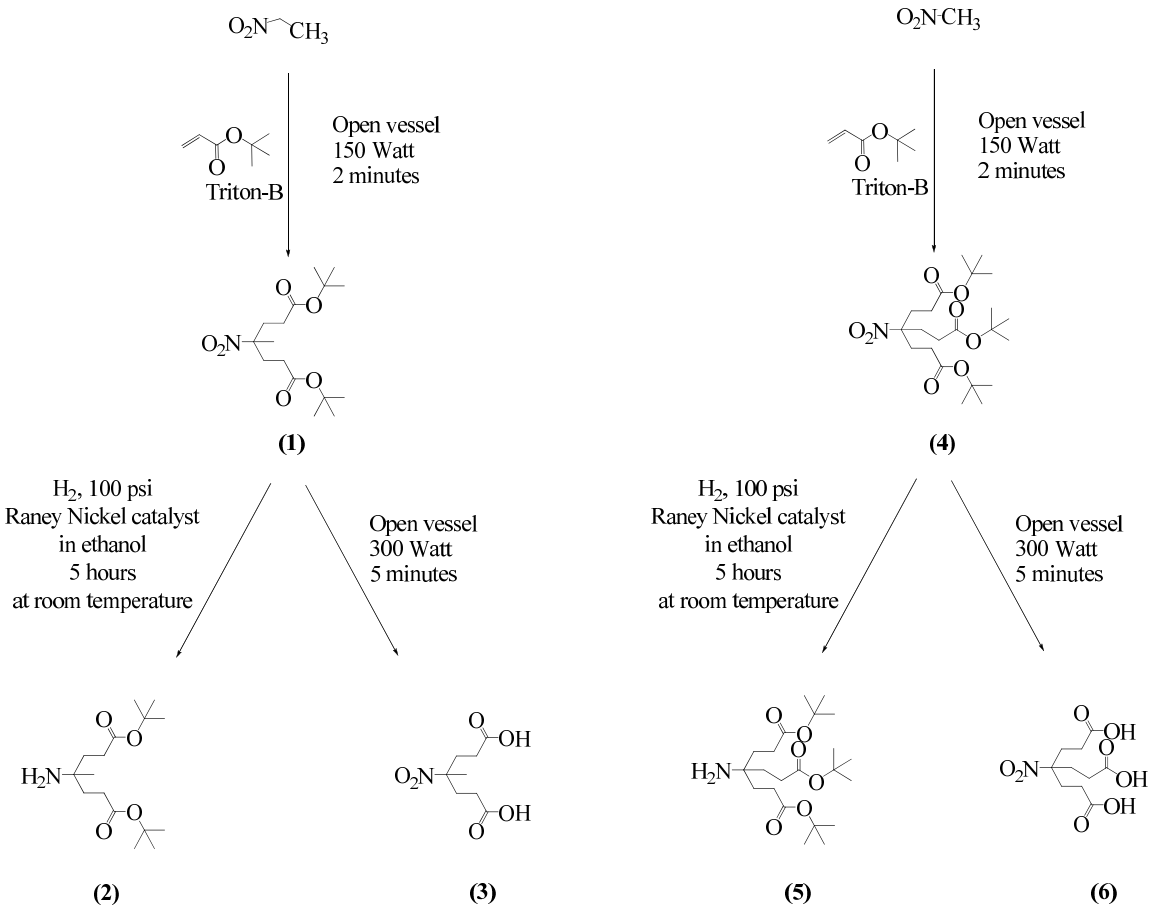
In order to determine the metal selectivity of some water soluble dendrimers, 20 mg of **(29)** and **(32)** were dissolved in 15 ml ultra pure water separately. Each solutions were divided into three part and each part was adjusted to the desired pH (1, 3, 5) by adding 0,01 N HNO_3 or NaOH. 0,08 mM of standard metal solutions containing Cr(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Pb(II) and Ag(I) ions were added to each solutions and transferred into the LPR system. The total volume of the LPR cell was kept constant at 20 mL. A Teflon membrane with an exclusion rate of 1 $kDmol^{-1}$ was used. The filtration fractions (Z = 1-10) were collected, and the concentration of metal ions in the filtrate were determined by using ICP. All results are discussed and showed in the results and discussion part.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 DESIGNING DENDRONS

AB_2 and AB_3 Newkome type nitro esters that have been used as monomeric building blocks for the construction of dendrons and dendrimers were synthesized by Michael addition reaction using microwave irradiation in solvent-free conditions. Nitro ethane and nitro methane were used as starting materials and the addition of excess amount of tert-butyl acrylate and catalytic amount of Triton-B under open vessel conditions in microwave resulted the nitro diester **(1)** and nitro triester **(4)**, respectively. The chemical shifts at δ 89.1 and δ 170.9 for the quaternary and carbonyl carbons in the ^{13}C NMR spectrum, respectively proves the existence of the monomers. The peak at δ 21.1 is assigned to the hydrogens at the methyl group in the nitro diester. A singlet at 1.45 ppm is assigned to the hydrogens at the tert-butyl groups and the multiplet at 2.2 ppm is for the hydrogens in the methylenes in the ^1H NMR spectrum. The peak near 1540 cm^{-1} in the IR spectrum shows the existence of the NO_2 groups.



Scheme 4. 1 Synthesis of first generation dendrons (I).

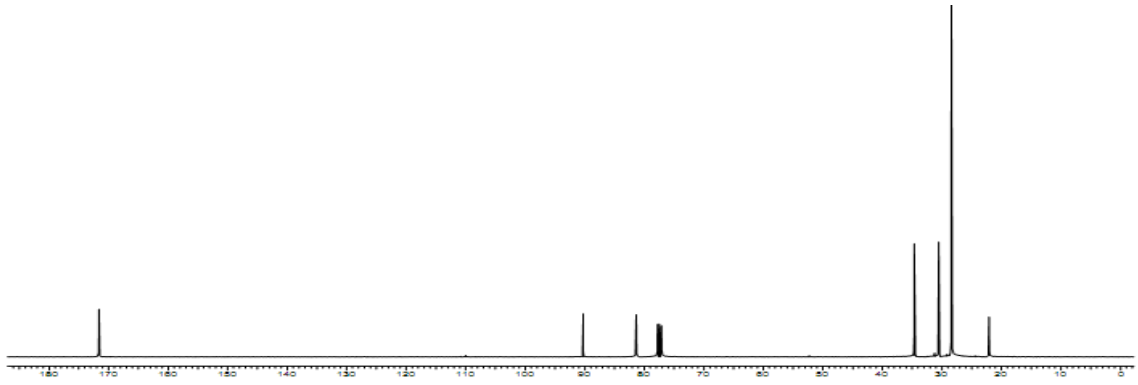


Figure 4. 1 ^{13}C NMR spectrum of nitro-2 ester, **(1).**

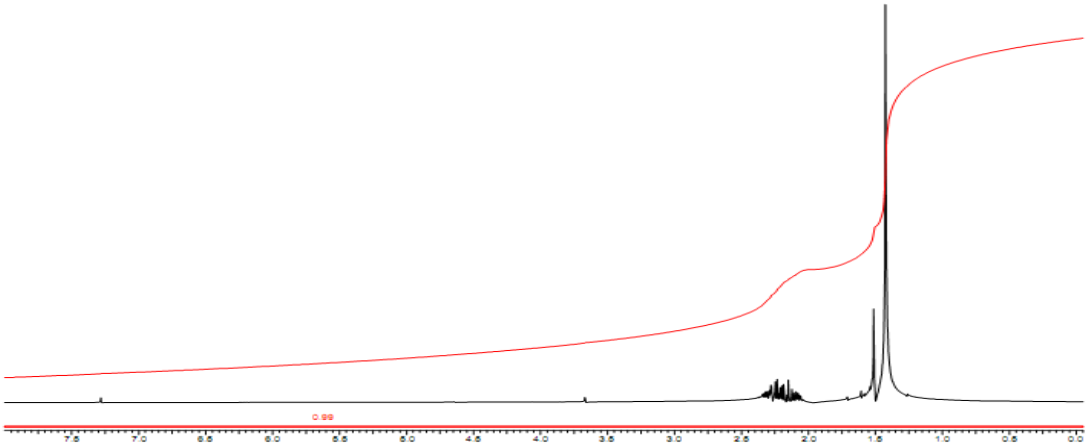


Figure 4. 2 ^{1}H NMR spectrum of nitro-2 ester, **(1).**

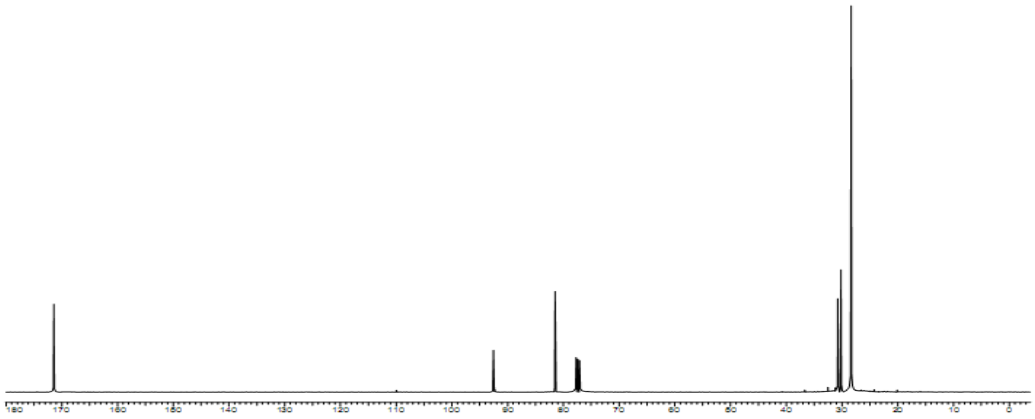


Figure 4. 3 ^{13}C NMR spectrum of nitro-3 ester, **(4)**

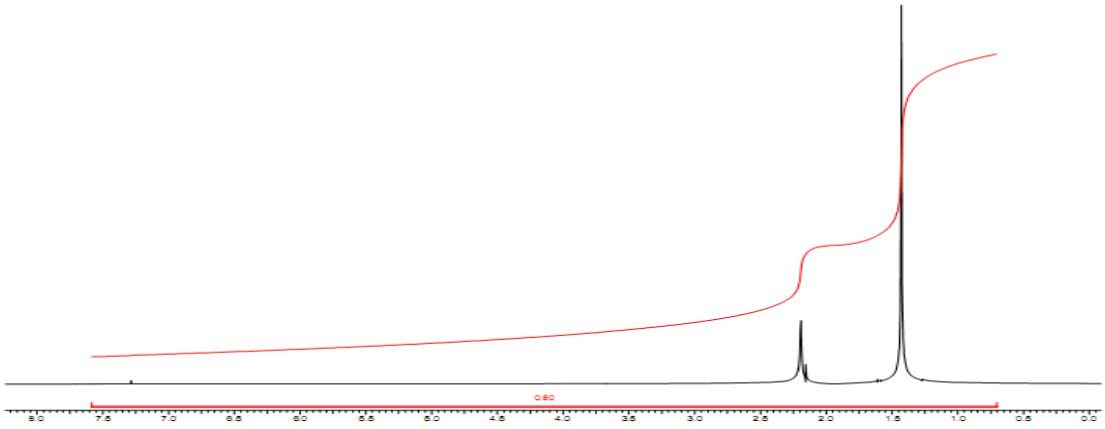


Figure 4. 4 ^{1}H NMR spectrum of nitro-3 ester, **(4).**

Amino-2 ester **(2)** and amino-3 ester **(5)** were synthesized by hydrogenating the nitro groups using Raney Nickel catalyst in ethanol under 100 psi pressures and at room temperature. The disappearance of the peak for the nitro groups at 1540 cm^{-1} and existence of new peaks around 3378 and 3316 cm^{-1} show the complete reduction of the nitro groups and formation of amines. The reduction was confirmed by the upfield shift for the quaternary carbon at 52.2 ppm in the ^{13}C NMR spectrum. The broad singlet at 5.42 is assigned to the amino group.

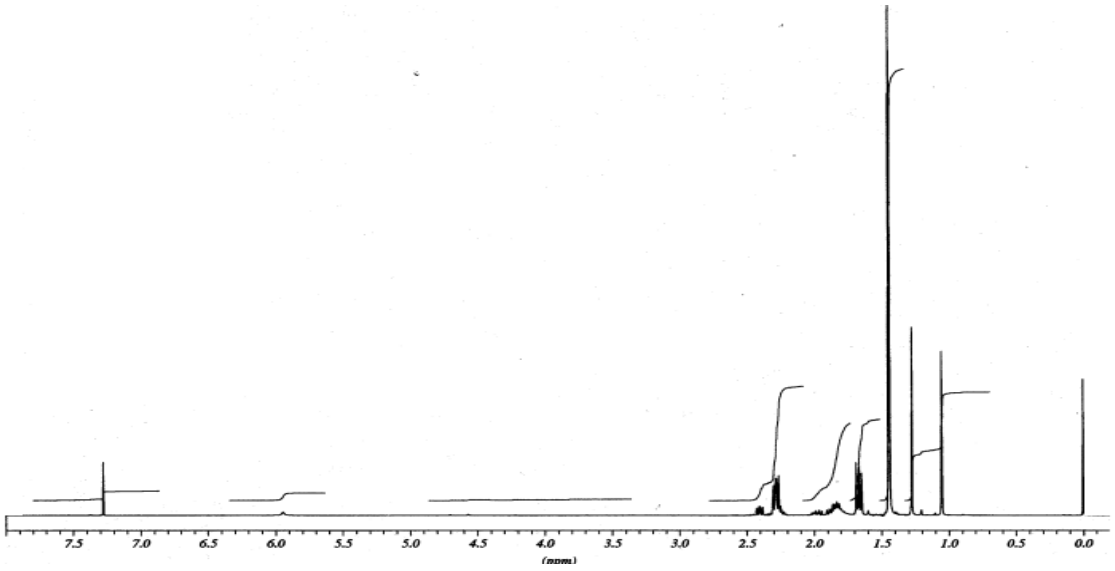


Figure 4. 5 ^{1}H NMR spectrum of amino-2 ester, **(2)**

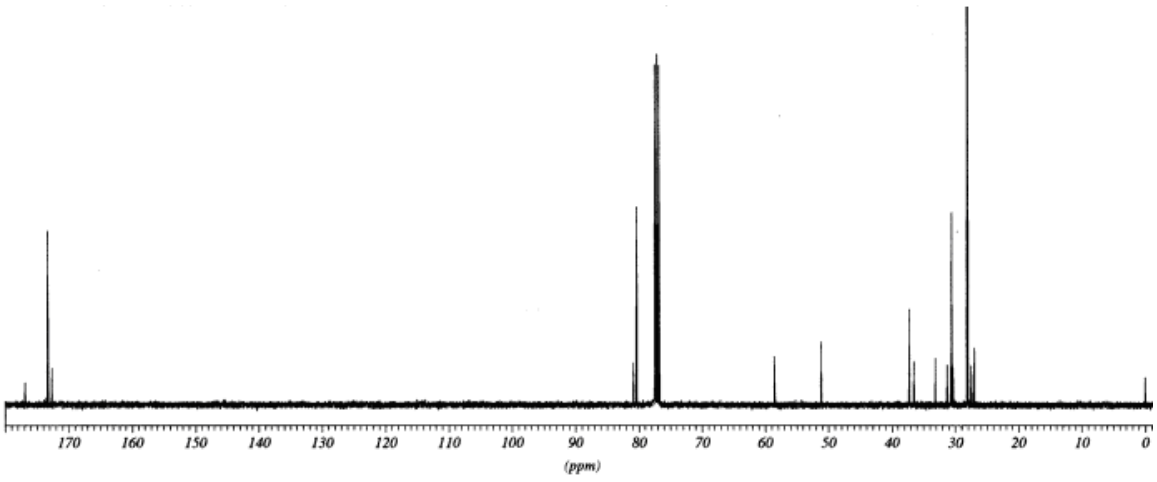


Figure 4. 6 ^{13}C NMR spectrum of amino-3 ester, **(2).**

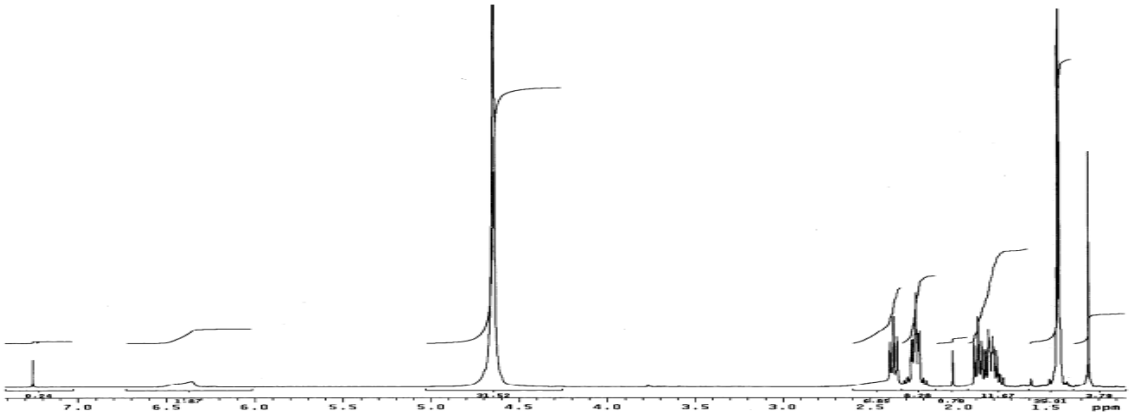


Figure 4. 7 ^{1}H NMR spectrum of amino-3 ester, **(5).**

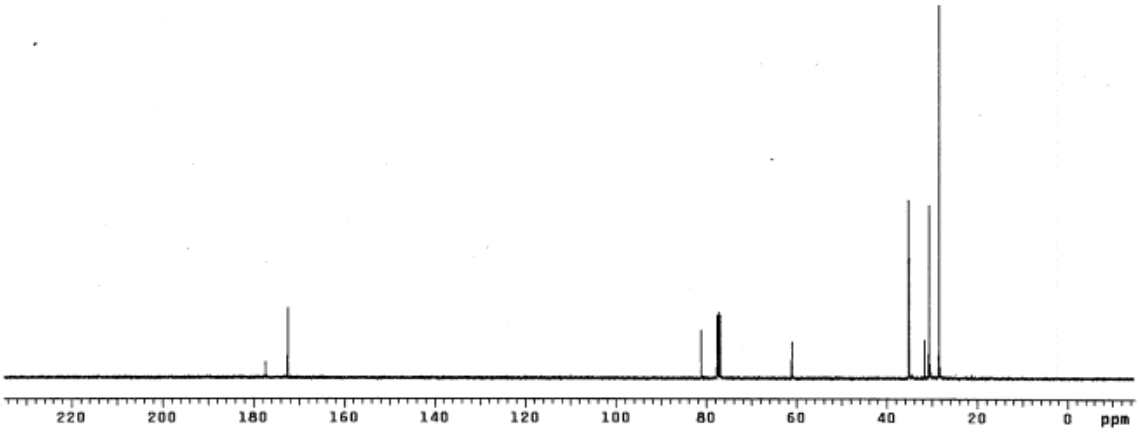


Figure 4. 8 ^{13}C NMR spectrum of amino-3 ester, **(5).**

Nitro-2 acid **(3)** and nitro-3 acid **(6)** syntheses were accomplished quantitatively by hydrolysis with formic acid. The downfield shift from δ 170.9 to δ 178.2 for the carbonyl groups supports the formation of the acid. The loss of the singlet at 1.42 ppm shows that the tert-butyl groups have been completely removed. In the IR spectrum, the shift from 1728 to 1721 cm^{-1} indicates the existence of the acid carbonyls and removal of ester carbonyls. Disappearance of the peak related to carbon and oxygen bond on the tert-butyl groups at 1153 proves the loss of the butyl groups. Also the broad peak between 2500 and 3400 cm^{-1} proves the complete conversion of esters to the acids.

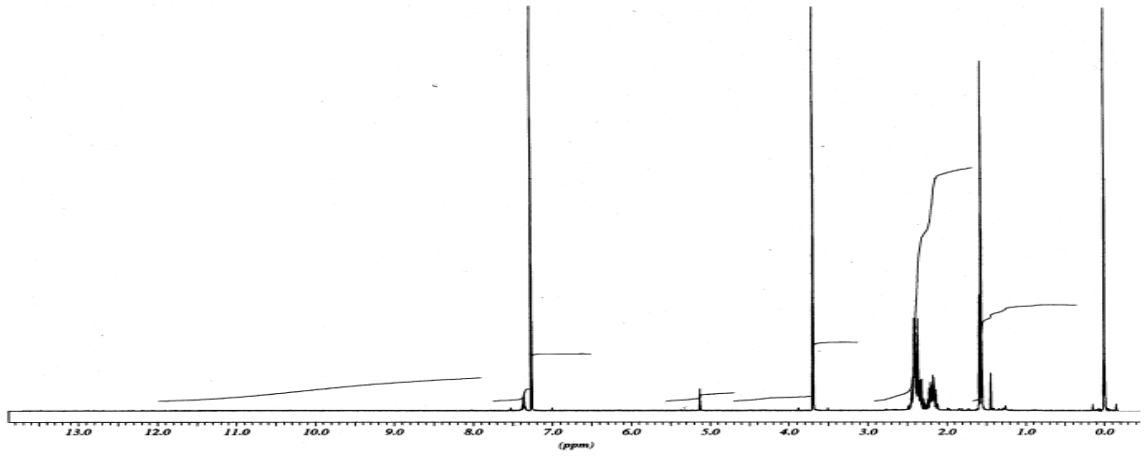


Figure 4. 9 ^{1}H NMR spectrum of nitro-2 acid, **(3).**

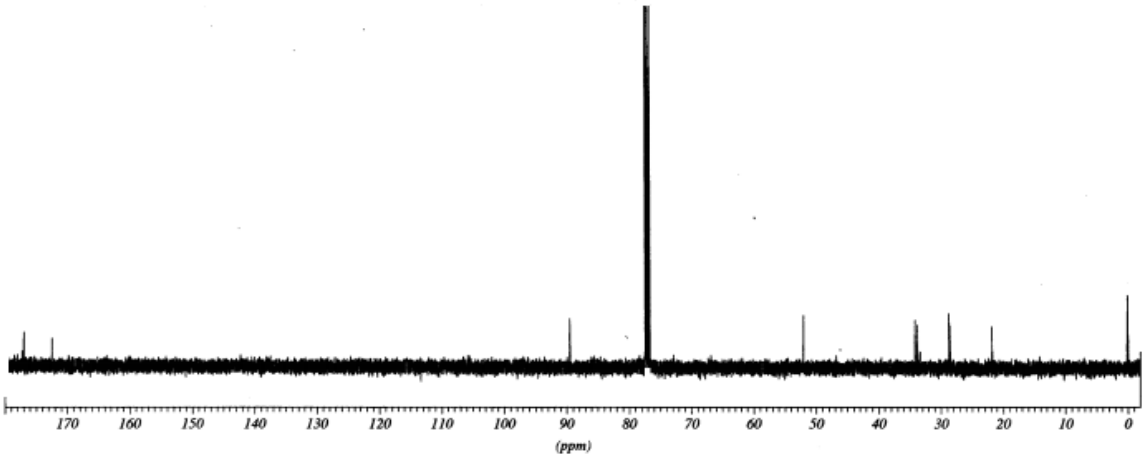


Figure 4. 10 ^{13}C NMR spectrum of nitro-2 acid, **(3).**

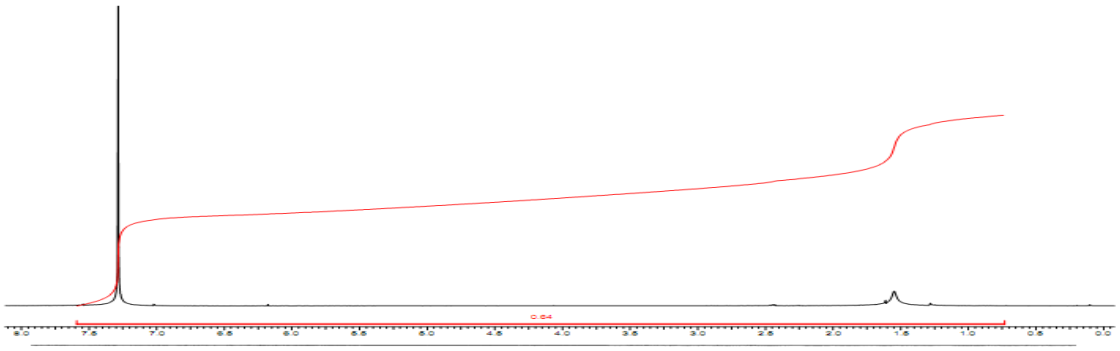


Figure 4. 11 ^{1}H NMR spectrum of nitro-3 acid, **(6).**

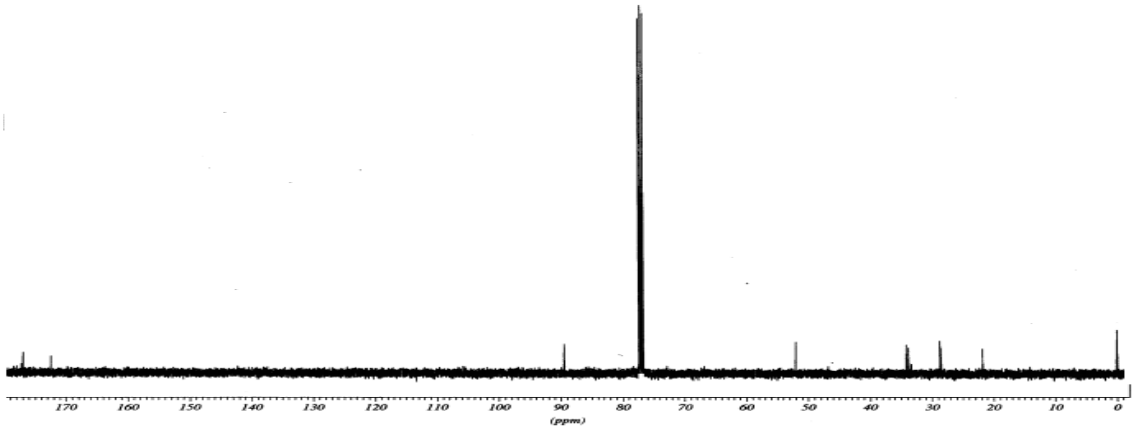


Figure 4. 12 ^{13}C NMR spectrum of amino-3 acid, **(6).**

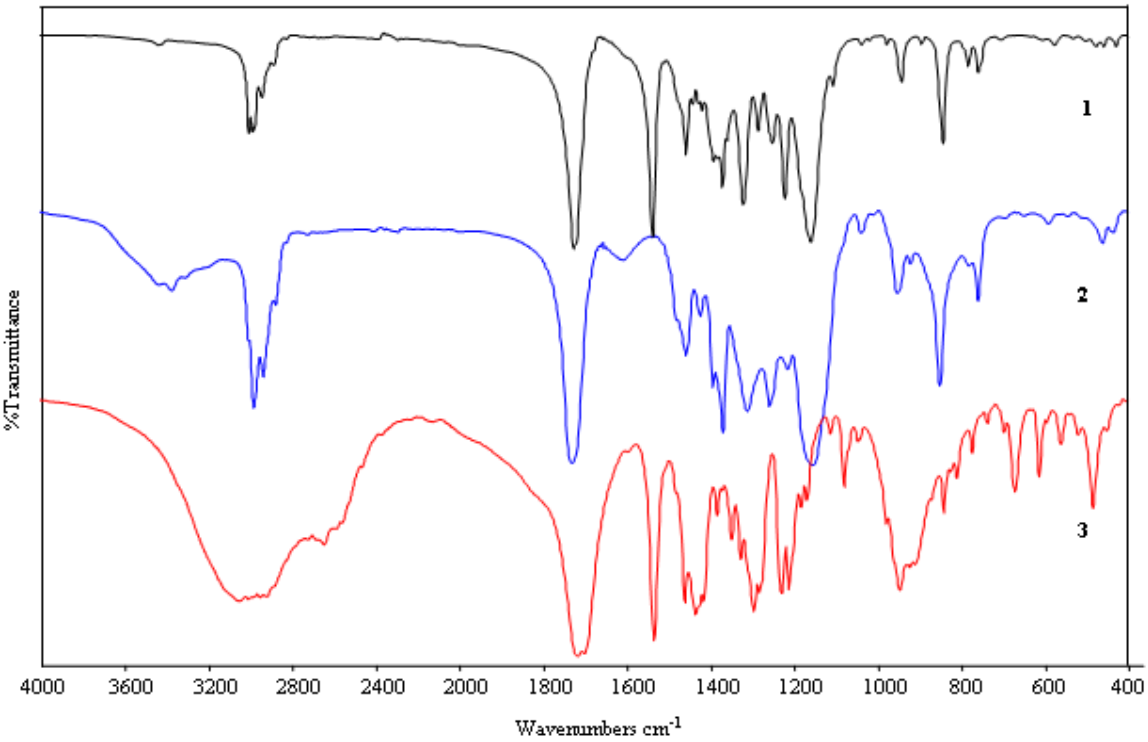


Figure 4. 13 IR spectrum of nitro-2 ester (1), amino-2 ester (2) and nitro-2 acid (3).

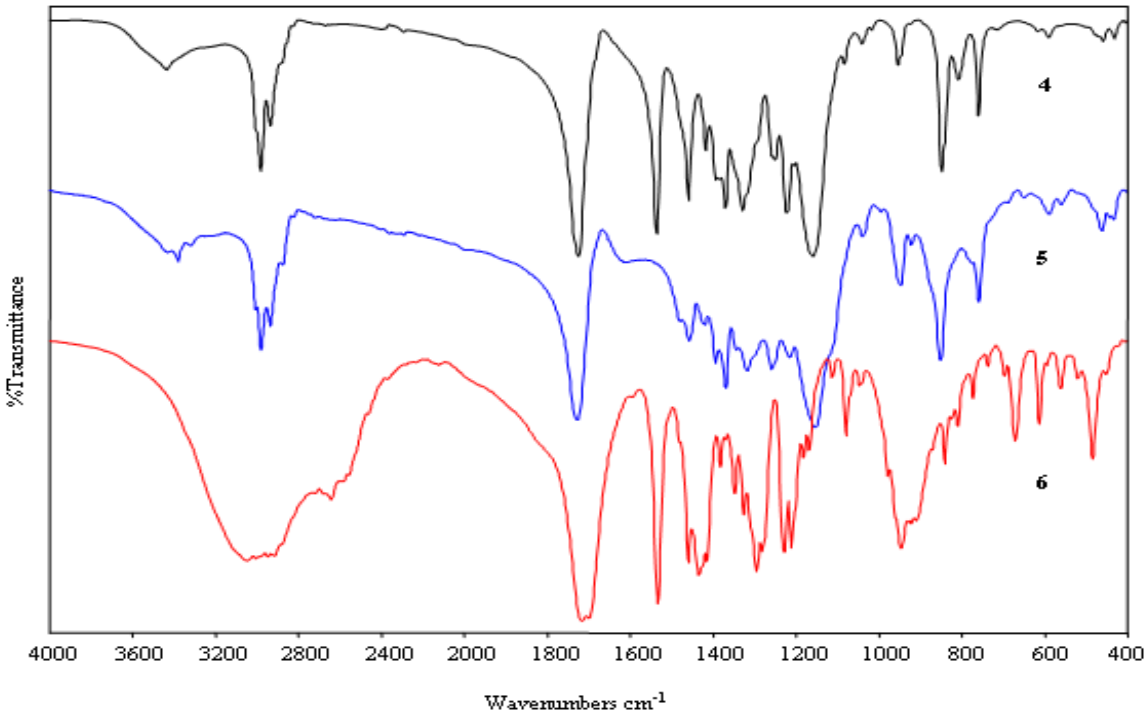
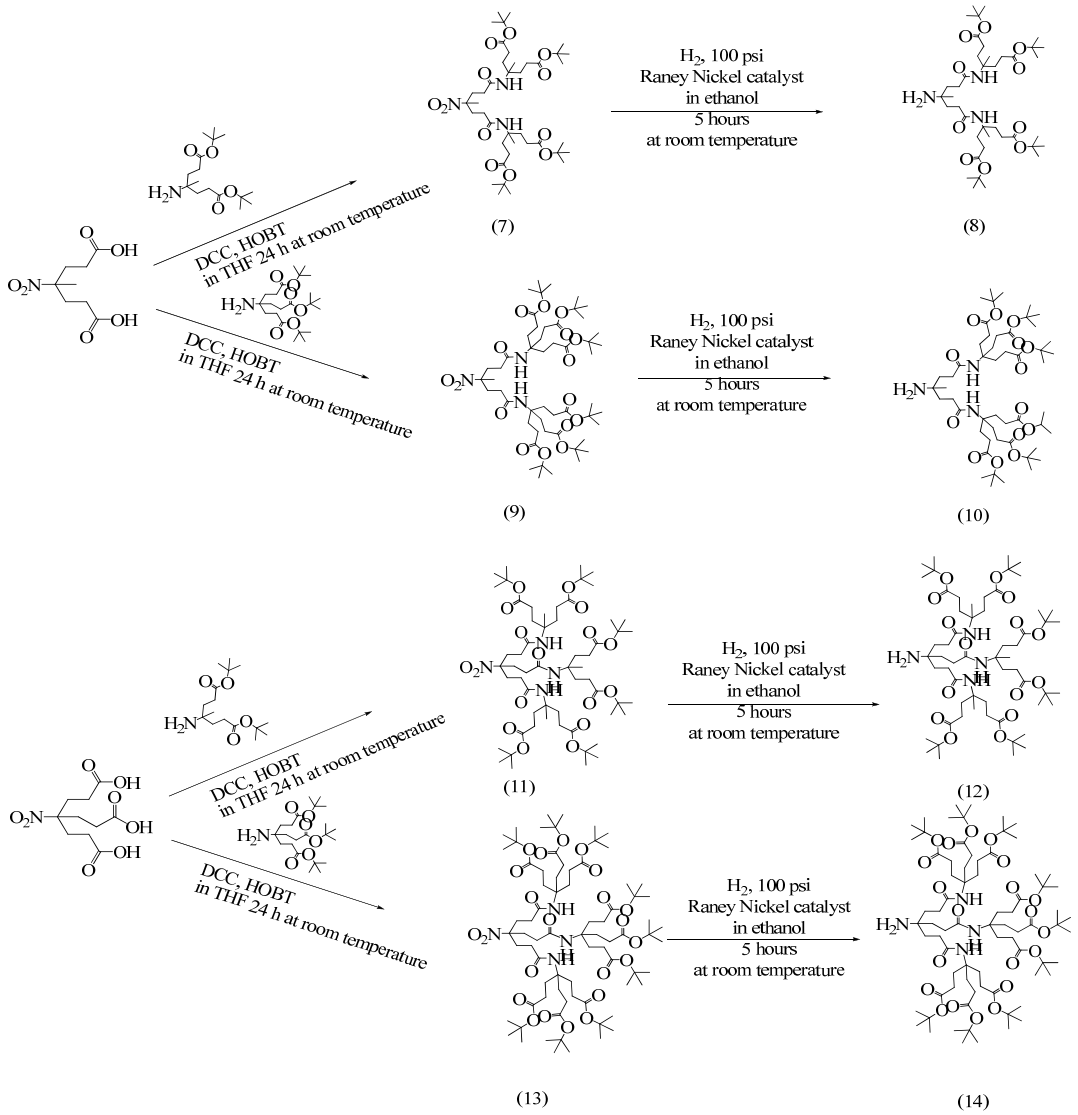


Figure 4. 14 IR spectrums of nitro-3 ester (4), amino-3 ester (5) and nitro-3 acid (6).



Scheme 4. 2 Synthesis of second generation dendrons (II).

The dendrons **(7)**, **(9)**, **(11)**, and **(13)** were synthesized by DCC coupling reaction. Previously synthesized nitro-2 ester and nitro-3 ester were coupled with amino diester and amino triester in order to obtain these products (Scheme 4.2). In the FT-IR spectra the new peaks around 1680 and 1540 cm^{-1} proves the existence of the amides. Also the disappearance of the carbonyl peaks at 1710 cm^{-1} of the acid and existence of the esters around 1730 cm^{-1} show the amide formation. Also in the ^{13}C NMR spectra the downfield shift from δ 178 to δ 173 proves the loss of the acid carbonyl and formation of the amide carbonyls. The chemical shift at δ 170 is responsible for the related esters.

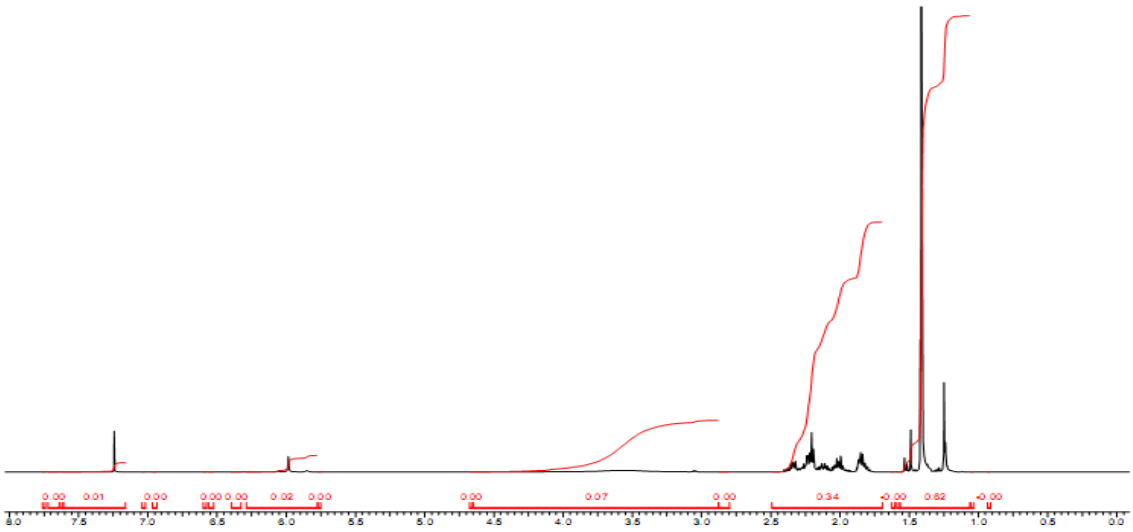


Figure 4. 15 ^{1}H NMR spectrum of Nitro-4 ester, (AB_2, 2. generation), **(7).**

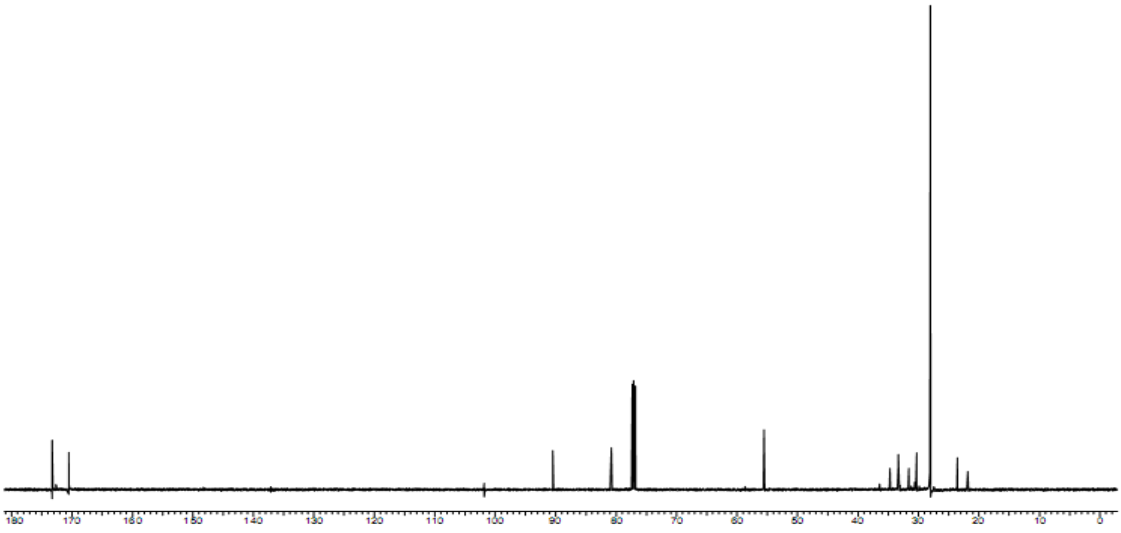


Figure 4. 16 ^{13}C NMR spectrum of Nitro-4 ester, (AB_2, 2. generation), **(7).**

Reduction of the **(7)**, **(9)**, **(11)**, and **(13)** predendrons with Raney-Ni in absolute EtOH at room temperature afforded the desired amino-ester predendrons (**8**, **10**, **12**, and **14**), which was supported by the chemical shifts (^{13}C NMR, Figure 4.18) for the quaternary carbon from 92.5 to 53.1 ppm (O_2NC- and NH_2C-, respectively).

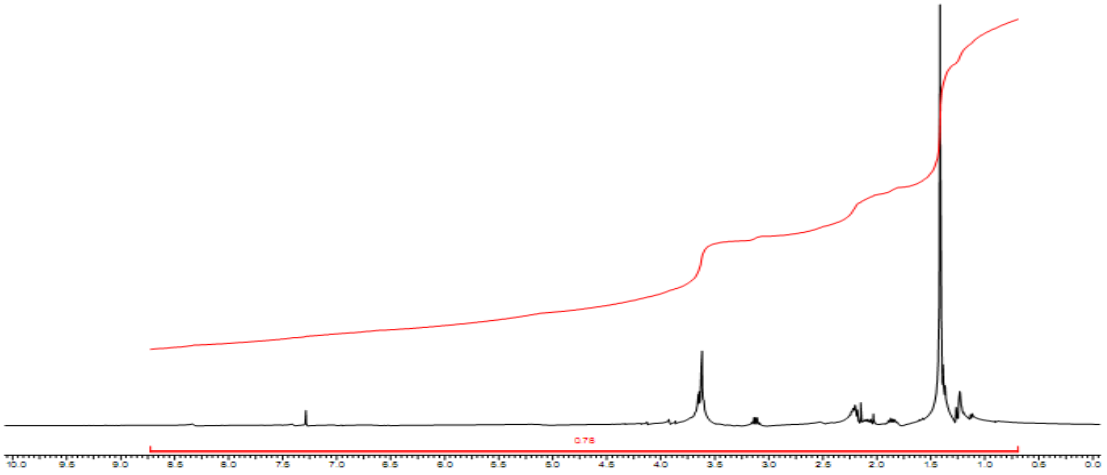


Figure 4. 17 ^{1}H NMR spectrum of amino-4 ester, **(8).**

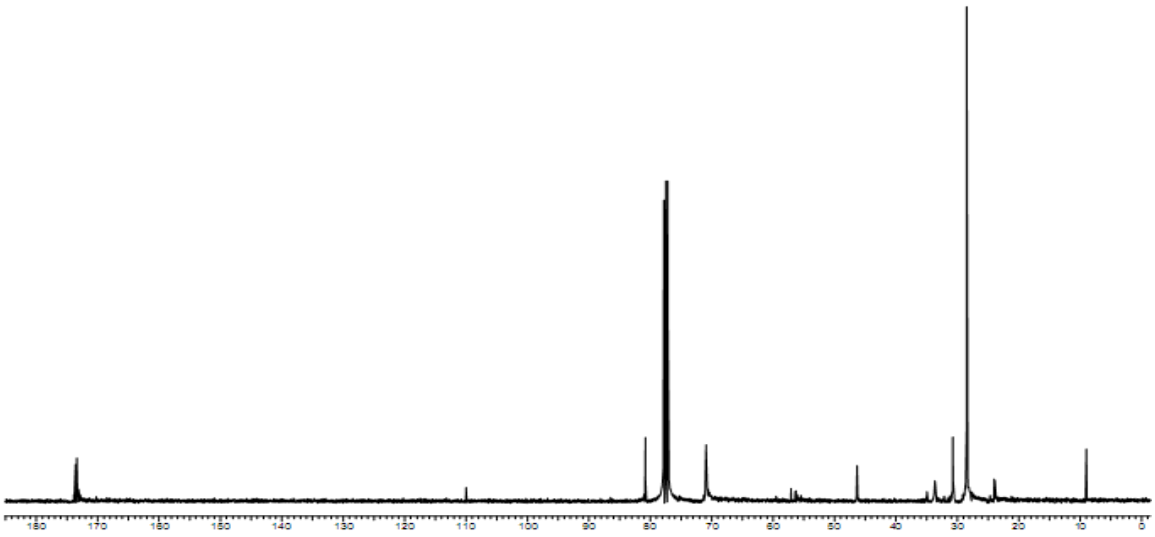


Figure 4. 18 ^{13}C NMR spectrum of amino-4 ester, **(8).**

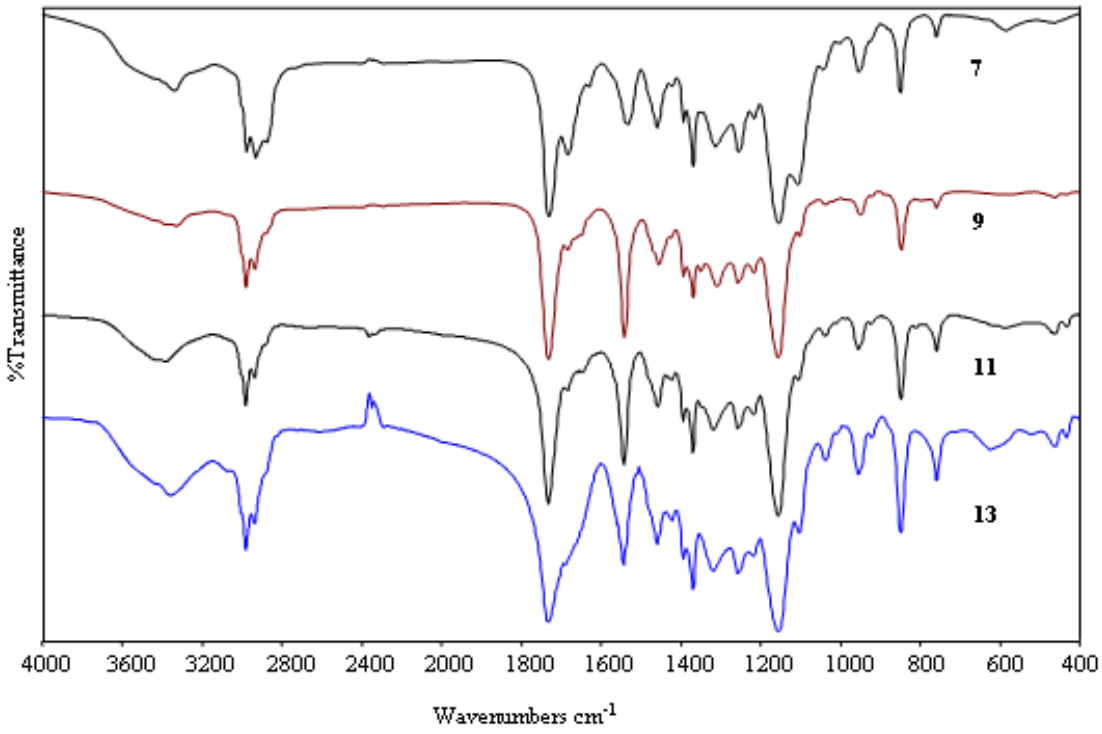
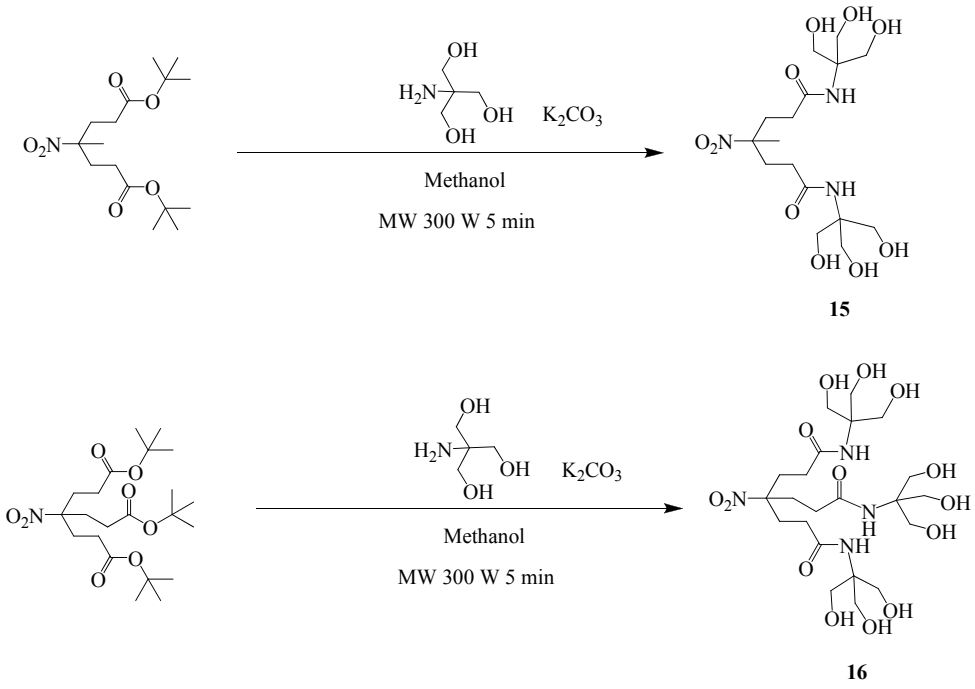


Figure 4. 19 IR spectra of nitro predendrons (7, 9, 11, and 13).

Nitro alcohols **(15)** and **(16)** were produced by the reaction of nitro diester and nitro triester with TRIS, respectively. In the IR spectra existence of the new peaks at 1645 and 1567 cm^{-1} and disappearance of the peak related to the esters at 1730 cm^{-1} proves the formation of the amide bonds (Figure 4.20). Also the broad peak around 3400 cm^{-1} shows the existence of the alcohol groups.



Scheme 4. 3 Synthesis of predendrons (III).

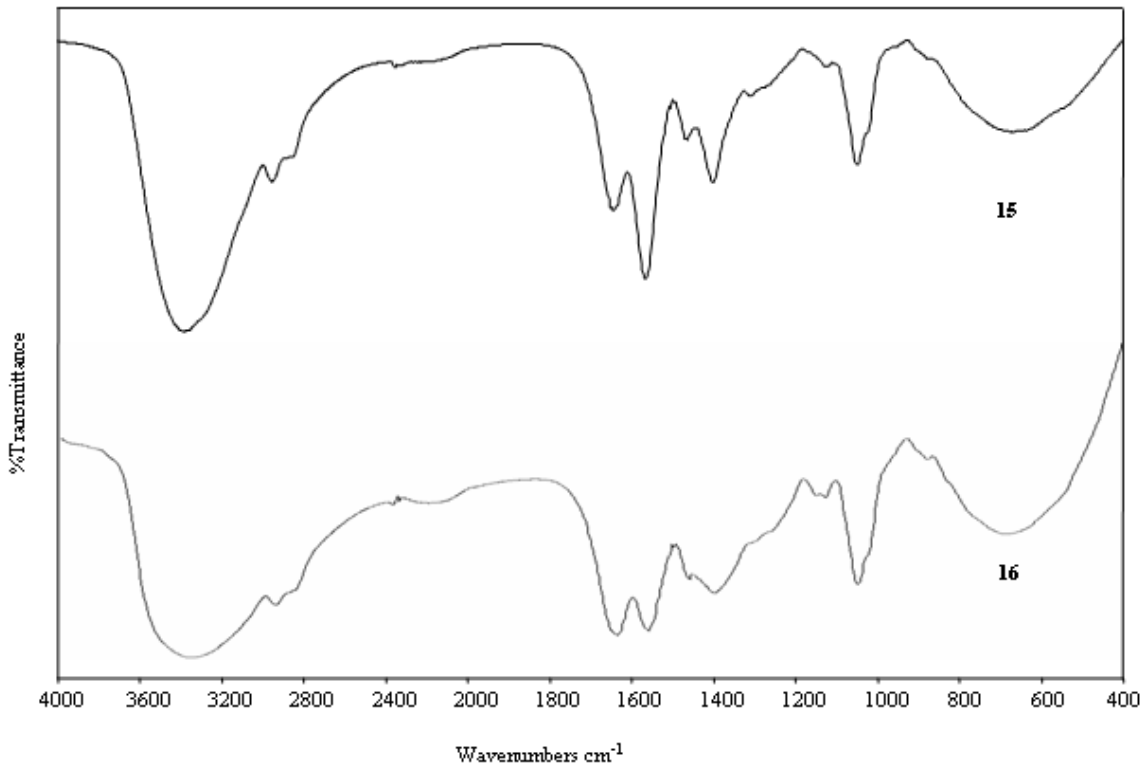


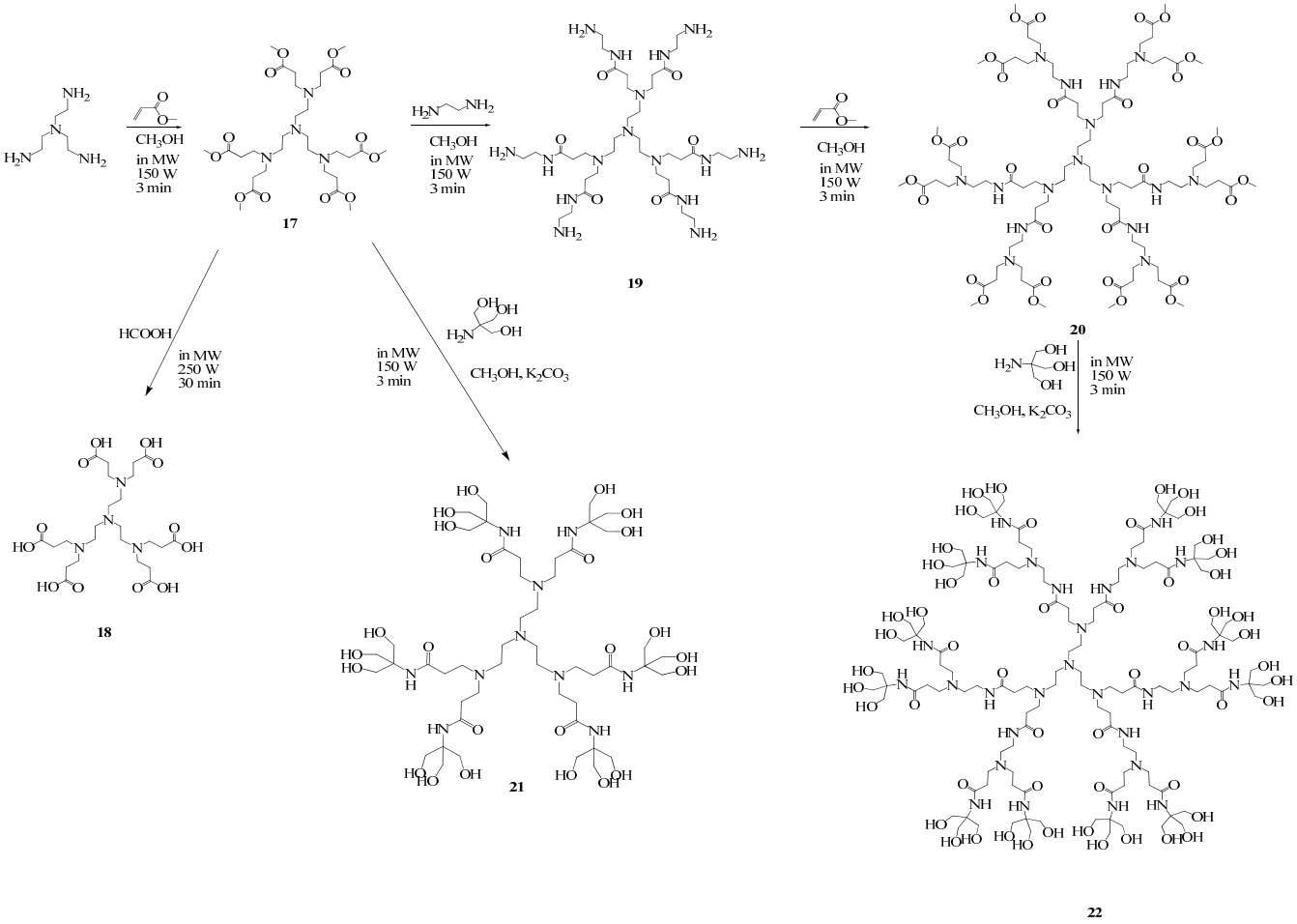
Figure 4. 20 IR spectra of nitro predendrons (15, and 16).

4.2 DESIGNING DENDRIMERS

In the dendrimer synthesis both convergent and divergent synthesis methodologies have been applied successfully. Both methods are suitable for the formation of the first and second generation dendrimers. Because of the versatility in the purification steps the convergent technique was generally used. Consequently TREN, TMA, and PEG cored PAMAM dendrimers have been successfully synthesized.

4.2.1 TRIS (2-AMINOETHYL) AMINE (TREN) CORED DENDRIMERS

TREN based PAMAM type dendrimers have been synthesized by the help of microwave power. All reaction conditions have been shown in the Scheme 4.4.



Scheme 4. 4 Synthesis of TREN-Cored Dendrimers.

By the Michael addition of methyl acrylate into the Tris (2-aminoethyl) amine (TREN), TREN-6 ester **(17)** was obtained. TLC monitoring and IR spectroscopy have been used for the analysis. In the IR spectrum the peak at 1738 and 1175 cm^{-1} shows the presence of esters. The disappearance of the peaks at 1594, 3278 and 3366 cm^{-1} related to the amines show the complete formation of the ester. The ester was hydrolyzed by formic acid using microwave power (Figure 4.21). The new peak at 1662 cm^{-1} and disappearance of the ester peak at 1738 cm^{-1} proves the formation of the ester to the acid.

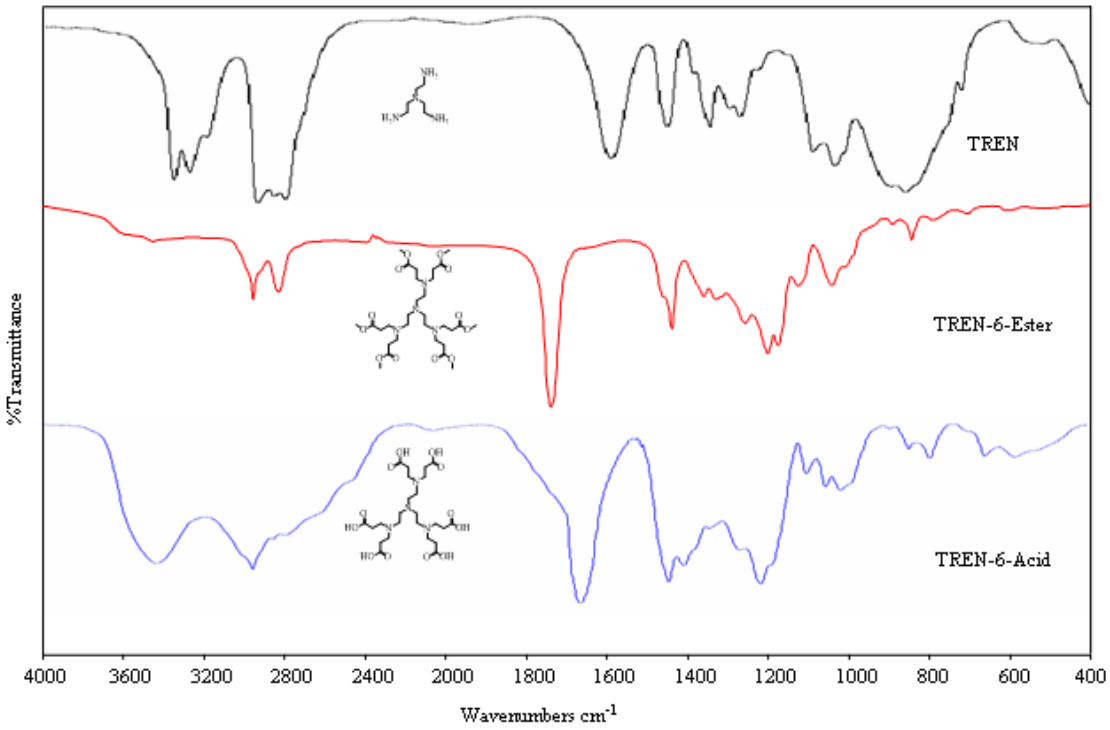


Figure 4. 21 IR spectra of TREN-6-ester and TREN-6-acid (17, and 18).

To obtain **(19)** and **(20)** ethylene diamine (EDA) was added to the TREN-6 ester **(17)** by the help potassium carbonate as the catalyst in methanol. The disappearance of the peak at 1738 and 1175 cm^{-1} related to the esters is the indicator of the complete removal of the esters. Formation of the new peaks at 1639 and 1560 cm^{-1} shows the amide bond formation. The broad peak around 3400 is related to the amines and amides –NH. Michael addition of the newly formed amines with the methyl acrylates gives the second generation ester dendrimers. The new peaks at 1735 and 1175 cm^{-1} prove the addition of ester groups (Figure 4.22).

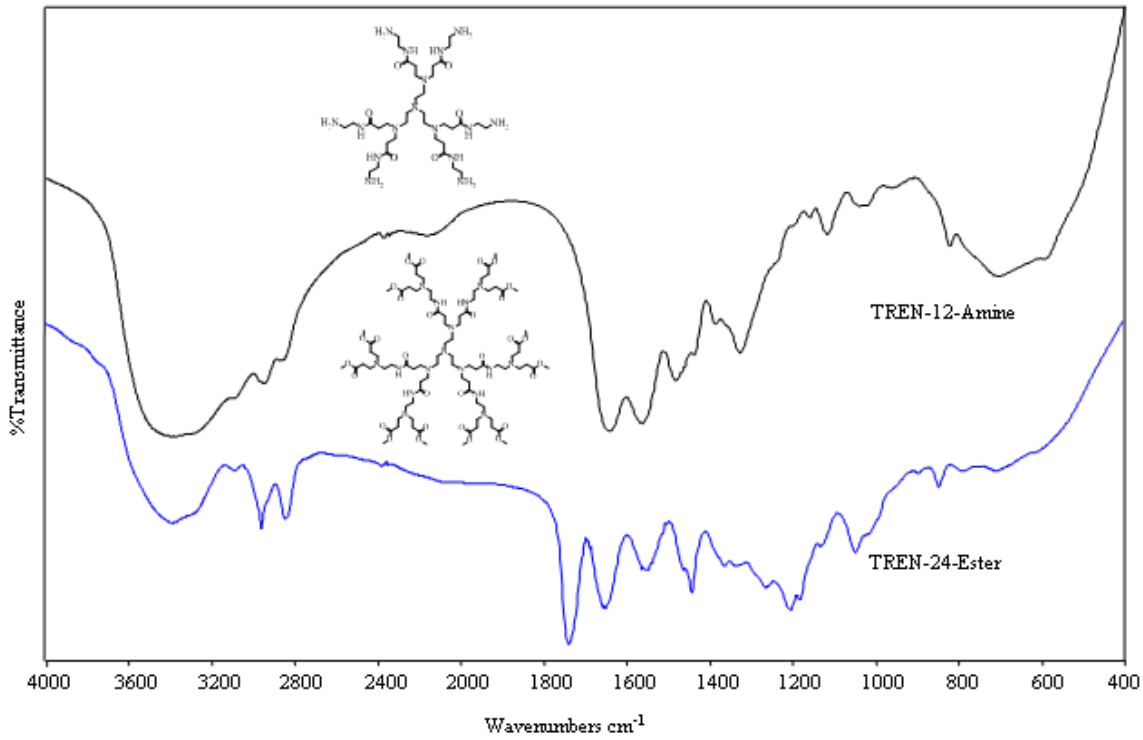


Figure 4. 22 IR spectra of TREN-6 amine and TREN-12 ester, (19 and 20).

First and second generation esters are modified with the –OH groups in order to obtain more functional dendrimers **(21)** and **(22)**. TRIS was added to the related esters **(17)** and **(20)**, respectively. In IR spectra, the disappearance of the ester peak at 1735 (ester carbonyl) and 1175 cm^{-1} (C-O) and the formation of the alcohol peaks near the 3400 cm^{-1} prove the addition of the TRIS to the corresponding esters (Figure 4.23).

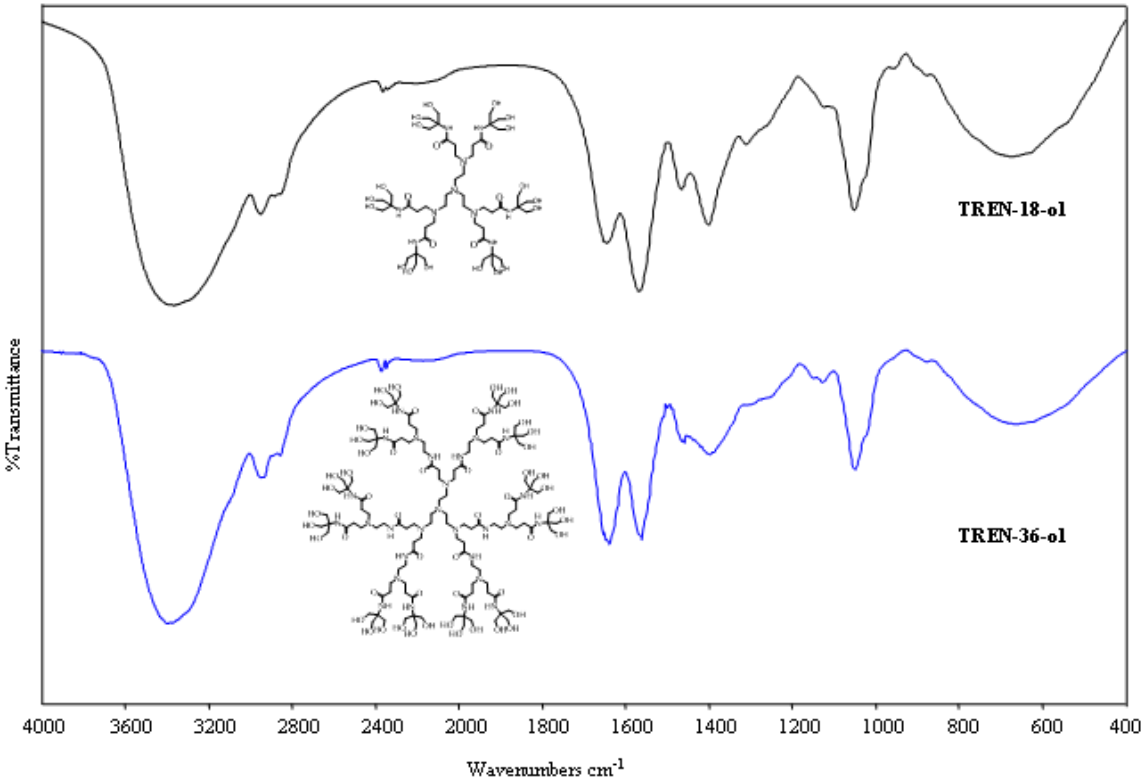
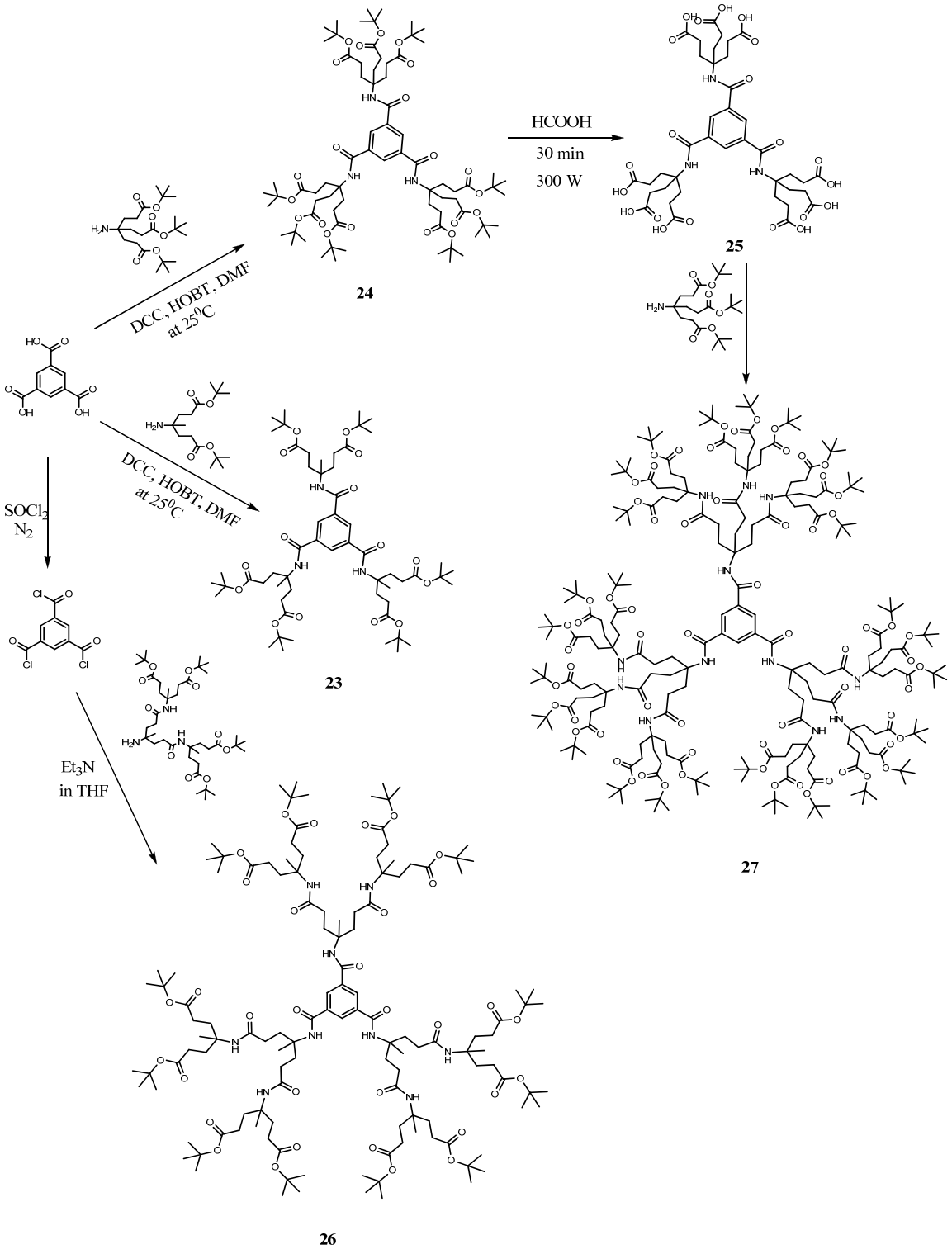


Figure 4. 23 IR spectra of TREN-18 ol and TREN-36 ol, (21 and 22).

4.2.2 TRIMESIC ACID (TMA) CORED DENDRIMERS



Scheme 4. 5 Synthesis of TMA-Cored Dendrimers.

As shown in the Scheme 4.5, TMA-cored dendrimers have been synthesized by convergent or divergent methods, alternatively. Trimesic acid reacted with the amino diester and triester in order to produce the products **(23)** and **(24)**, respectively. In the IR spectra the new peaks around 1680 and 1540 cm^{-1} responsible for the amide bonds and 1155 cm^{-1}(ester C-O) show the formation of the products. The ester **(24)** has been converted to the corresponding acid **(25)** (Figure 4.24).

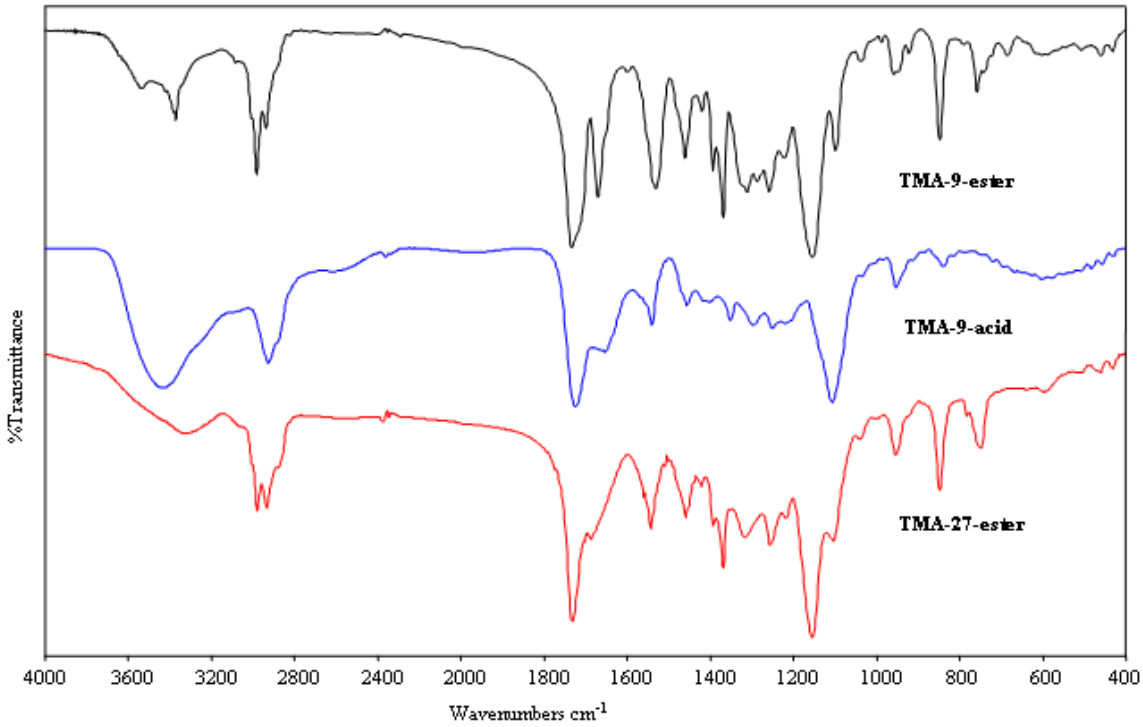


Figure 4. 24 IR spectra of TMA-9 ester, TMA-9 acid and TMA-27 ester (24, 25 and 27).

The conversion is supported by the disappearance of the ester (C-O) peak at 1155 cm^{-1}. The downfield shift of the ester carbonyl also shows the formation of the acid carbonyls. The product **(27)** was synthesized by using the same strategy while synthesizing the products **(23)** and **(24)**. The previously synthesized dendron **(8)** was added to the chlorinated Trimesic acid in THF to obtain the product **(26) (**Figure 4.25).

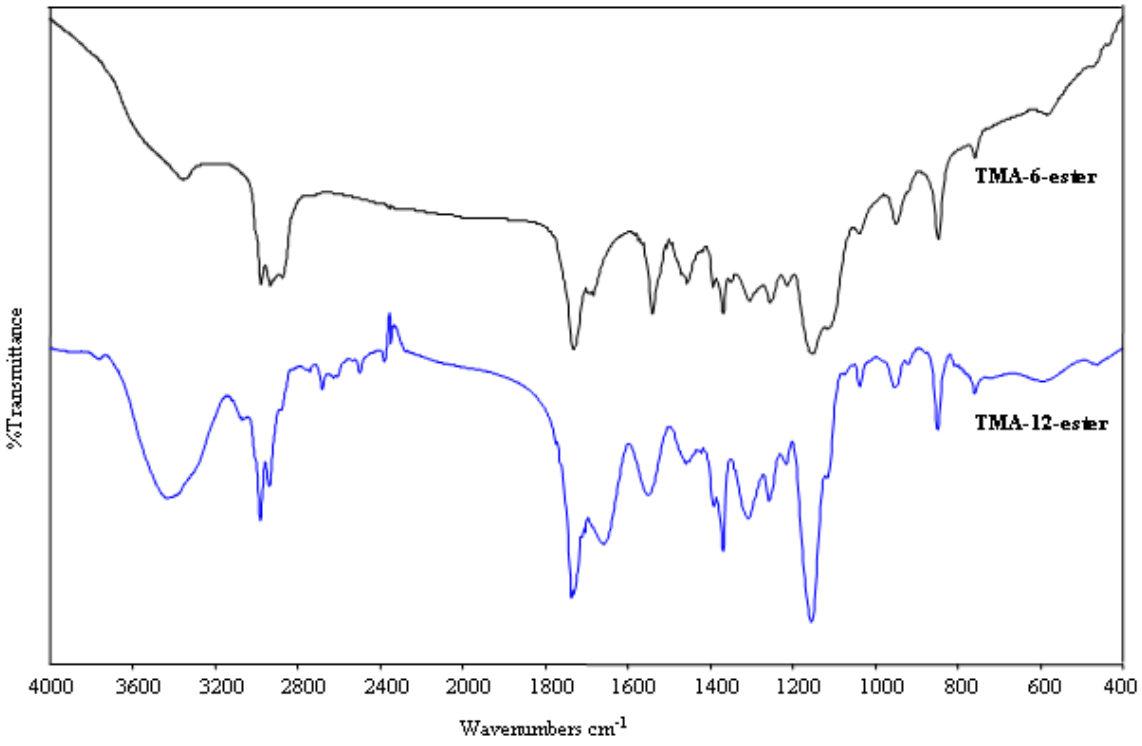


Figure 4. 25 IR spectra of TMA-6 ester and TMA-12 ester, (23 and 26).

4.2.3 POLYETHYLENE GLYCOL (PEG) BASED DENDRIMERS

PEG based dendrimers have been synthesized with DCC coupling reaction. Hydrolysis was achieved by formic acid in microwave (Scheme 4.6). First generation esters **(28)** and **(31)** have been generated from the PEG diacid by the addition of amino-2 ester and amino-3 ester, respectively. In the IR spectra the existence of the new peaks around 3340(amide -NH), 1730 (ester C=O), 1680(amide C=O), and (1540 amide C=O), and 1154 (C-O).

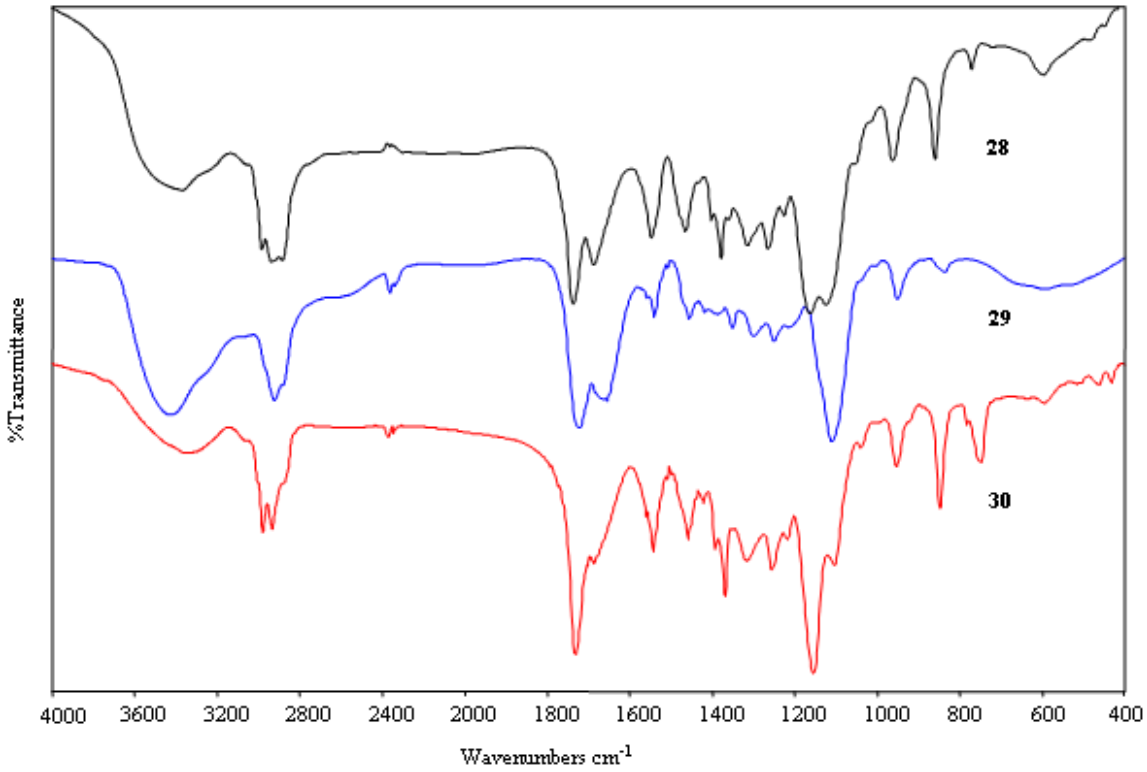
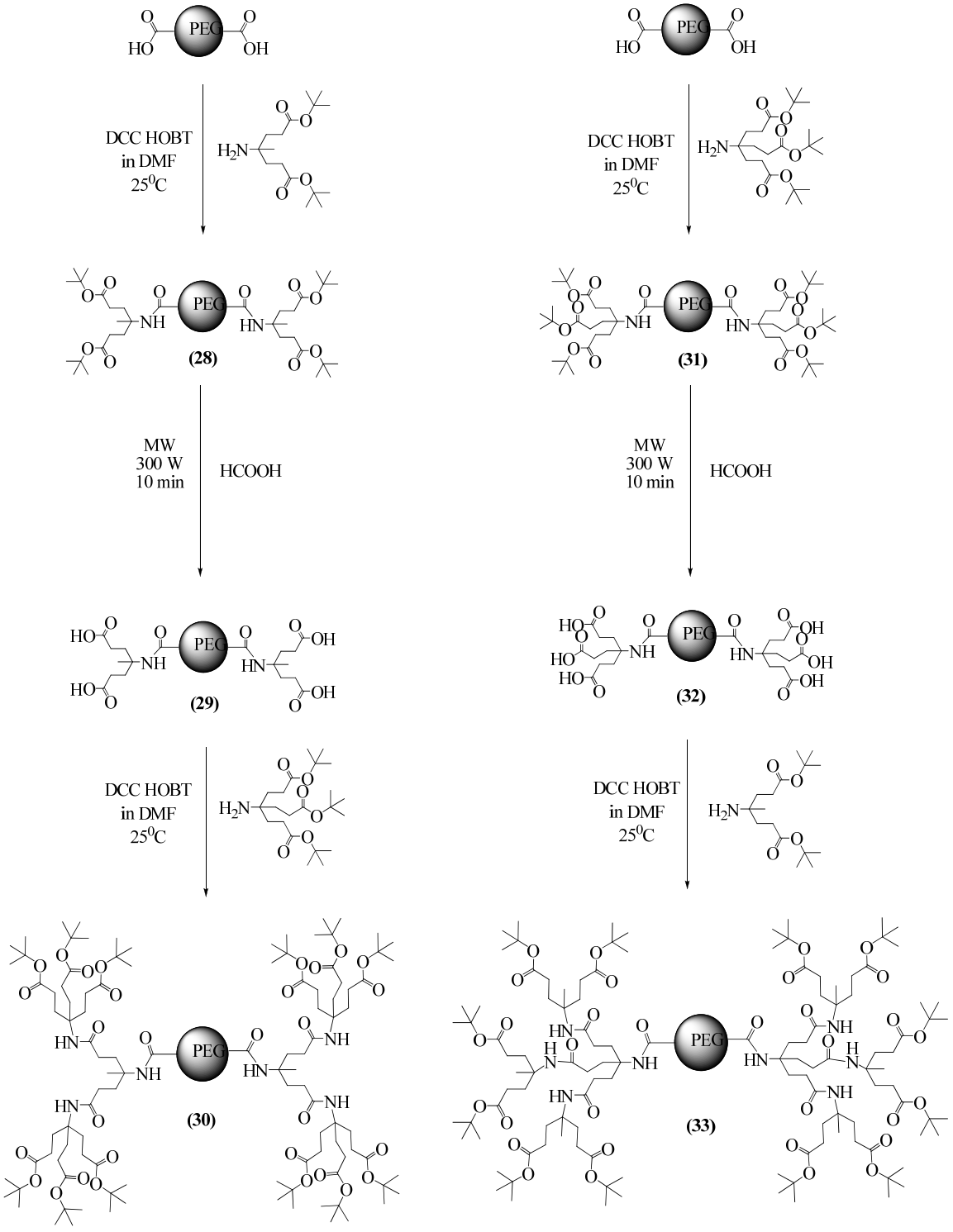


Figure 4. 26 IR spectra of PEG-4 ester, PEG-4 acid and PEG-12 ester (28, 29 and 30).

In the ^{13}C the appearance of the new amido carbonyl group at ~ 172 ppm (C=O) and the ethylene group peaks at 3.1 ppm suggested the dendrimer formation. Deprotection of *tert*-butyl esters groups of 28 and 31 dendrimers with formic acid at 25 ^{o}C quantitatively generated the corresponding acids **(29)** and **(32)**. In the ^{1}H NMR disappearance of the tert-butyl groups resonances and appearance of the peak at ~ 9.6 ppm prove the formation of the acid deprotection (Figure 4.27). In the FT-IR spectra the formation of acid groups is also confirmed by disappearance of the (C-O) ether peaks around 1150 cm^{-1} and existence of the broad peak at ~ 3400 cm^{-1} (Figure 4.26).



Scheme 4. 6 Synthesis of PEG Cored Dendrimers.

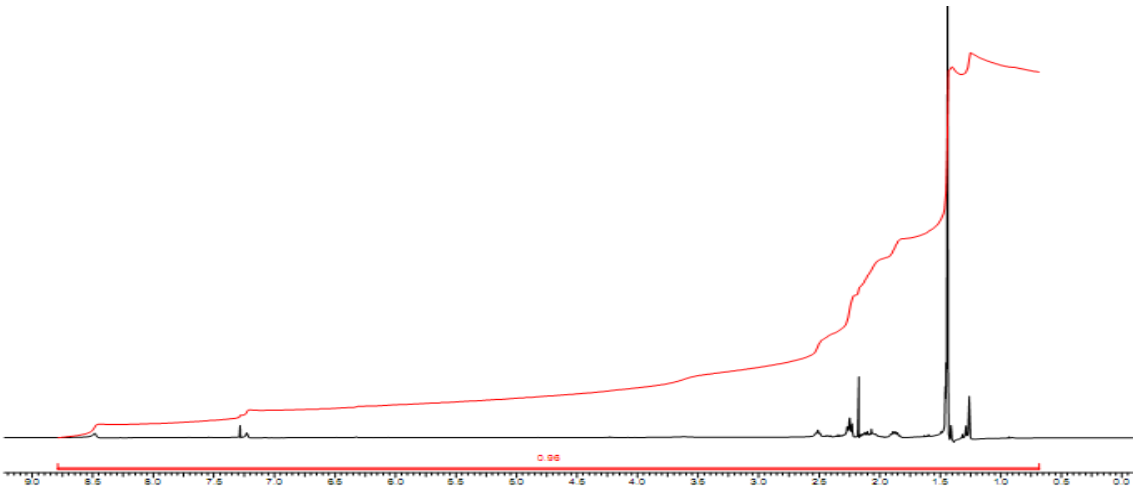


Figure 4. 27 ^{1}H NMR spectrum of PEG-4 acid **(29).**

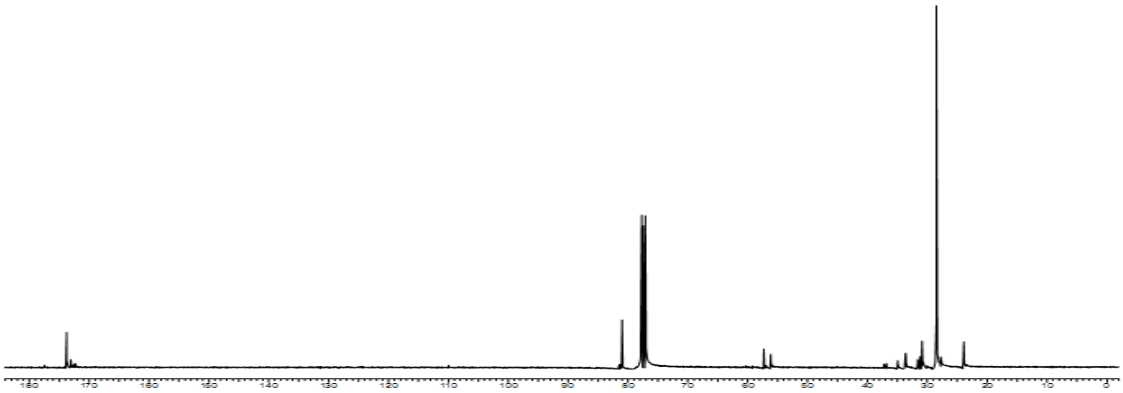


Figure 4. 28 ^{13}C NMR spectrum of PEG-4 acid, **(29).**

By the addition of amino triesters to the PEG-4 acid and PEG-6 acid by DCC coupling reaction, the compounds **(30)** and **(33)** have been obtained. Ester formation can be proven by the existence of the ester C-O at 1150 cm^{-1} and upfield shift of the carbonyl peaks from 1723 to 1731 cm^{-1}(Figure 4.29).

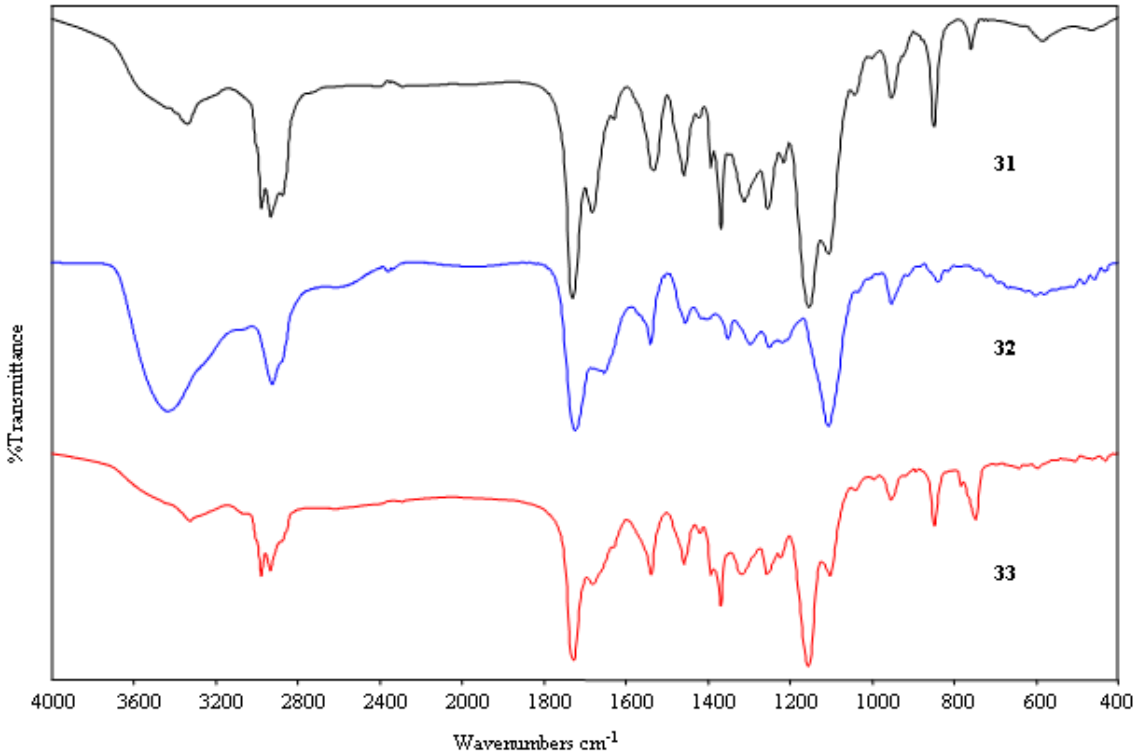
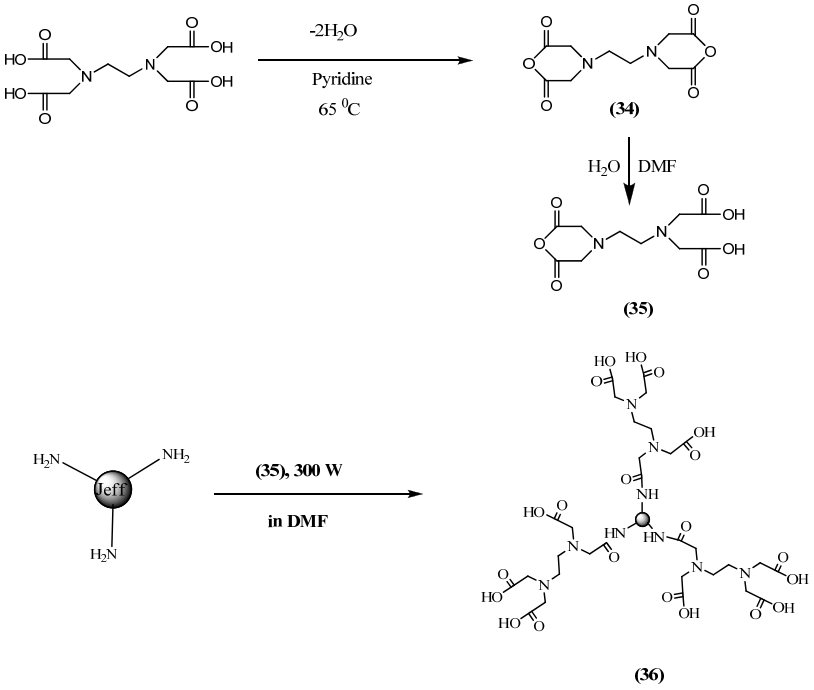


Figure 4. 29 IR spectra of PEG-6 ester, PEG-6 acid and PEG-18 ester, (31, 32 and 33).

4.2.4 JEFF AMINE CORED DENDRIMER



Scheme 4. 7 Synthesis of Jeffamine Cored Dendrimer.

Jeff amine was reacted with the EDTA monoanhydride [43] in order to give Jeff-9 acid. In the IR spectra the new peaks at 1668 and 1530 cm^{-1} confirms the amide bond formation (Figure 4.30).

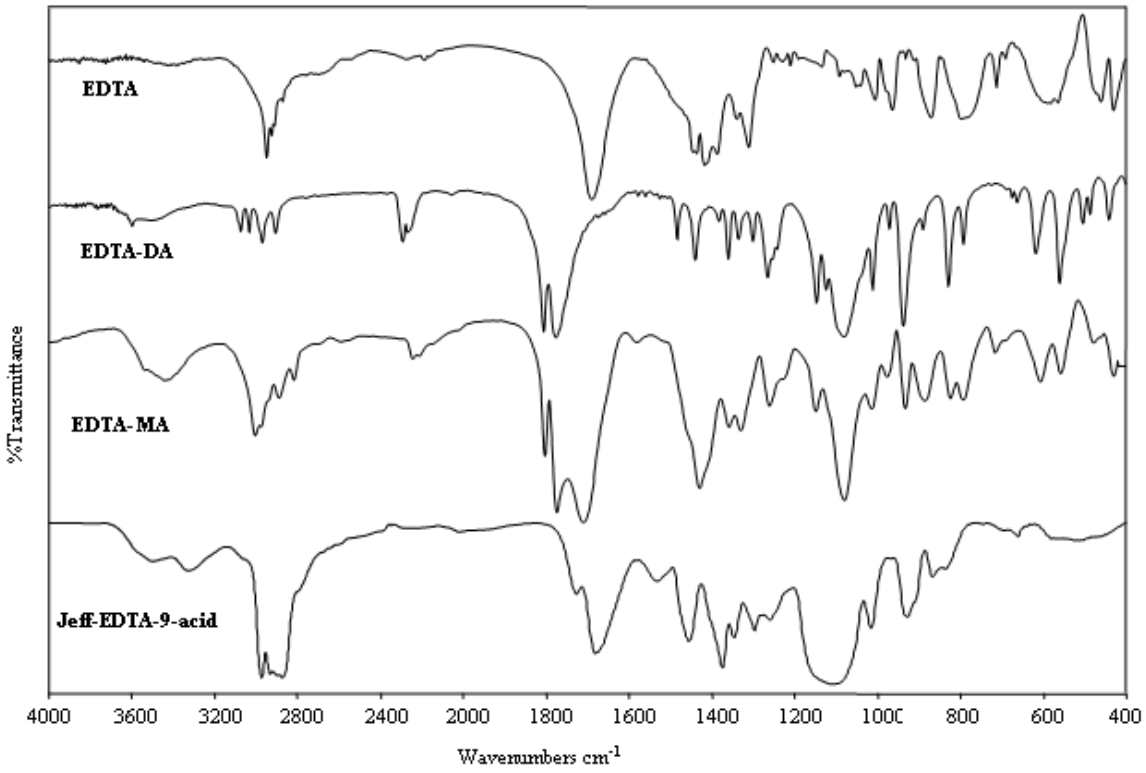


Figure 4. 30 IR spectra of EDTA monoanhydride, EDTA dianhydride and Jeff-9 acid (34, 35 and 36).

4.3 METAL COMPLEXATION STUDIES

Metal complexing ability of the (29) and (32) were studied by using Liquid-Phase Polymer-Based Retention (LPR) technique conjunction with inductively-coupled plasma spectrometry (ICP). The general principle of liquid-phase retention is to add water-soluble polymeric binding agents to a multi component solution, so that these agents will form macromolecular compounds with the target ions only. Thus, the size of the metal ion would be increased significantly whereas the size of the nontarget species would remain unchanged. If such a solution is then passed through an ultra filtration membrane, the membrane would separate the target metal ions from the nontarget species. The retention of metal ions by membranes is influenced by many parameters, depending on their type, solution composition, pH, temperature, membrane material, pore size, hydrodynamics, etc.

However, mostly the size of a dissolved species (hydrated ions, hydrated molecules, colloidal particles, etc.) is essential for the retention by membranes. Generally, low-molecular substances can be bound to macromolecules by all intermolecular forces, predominantly by ionic or complex bonds or the combination of both. Complex bonds are significantly more selective than ionic interactions. The formation of complexes with water-soluble polymers occurs as in the case of chelating resins. For example, it is well known that resins containing amino and imino groups form stable complexes with copper, nickel, and other transition metals. Evidently, a number of factors influence the interactions and binding conditions: Binding degree, pH value, solution composition, and synergism.

Membrane separation processes are based on semi permeable membranes, which separate certain solution components by passing them through the membrane, forming the permeate or filtrate, and retaining others, forming the retentate or concentrate. The most important parameter of membrane separation is the retention R of a component [44].

The soluble, non-crosslinked, hydrophilic polymers with complex-forming moieties, capable to bind, enrich, and separate metal ions from aqueous solutions, were termed “polychelatogens”. The selectivity of the polychelatogens can be significantly enhanced by introducing special ligands such as EDTA, DTPA or Beheras acid, etc. In this study polychelatogens with high molecular weight have been prepared (pore size of the membrane is 1 kilodalton) and investigated in conjunction with LPR technique. Their retention profiles have been shown in the Figure 4.31. It was found that dendrimers form stable complexes through the freely branched carboxylic acids combining with the lone pair of amide bound. According to the results at the pHs of 1, 3, and 5 the acidic groups deprotonates and resulting carboxylates become strong nucleophile towards to the metal ions. When the pH was smaller than 1, all the metal ions released the ligand and only Cr (III) showed a retention more than 30 % at Z=10. At pH 3, the retentions were higher than 50 % for all the metals used, but only Cr (III) showed 100%. The best complexations were observed at pH 5 for Co (II), Ni (II), Zn (II), Cd (II) and Pb (II) with retention values closer to 85 % (Figure 4.32). Only Ag (I) showed lower retention about 30% at Z=10, this was attributed to the monovalency of this metal ion [45, 46].

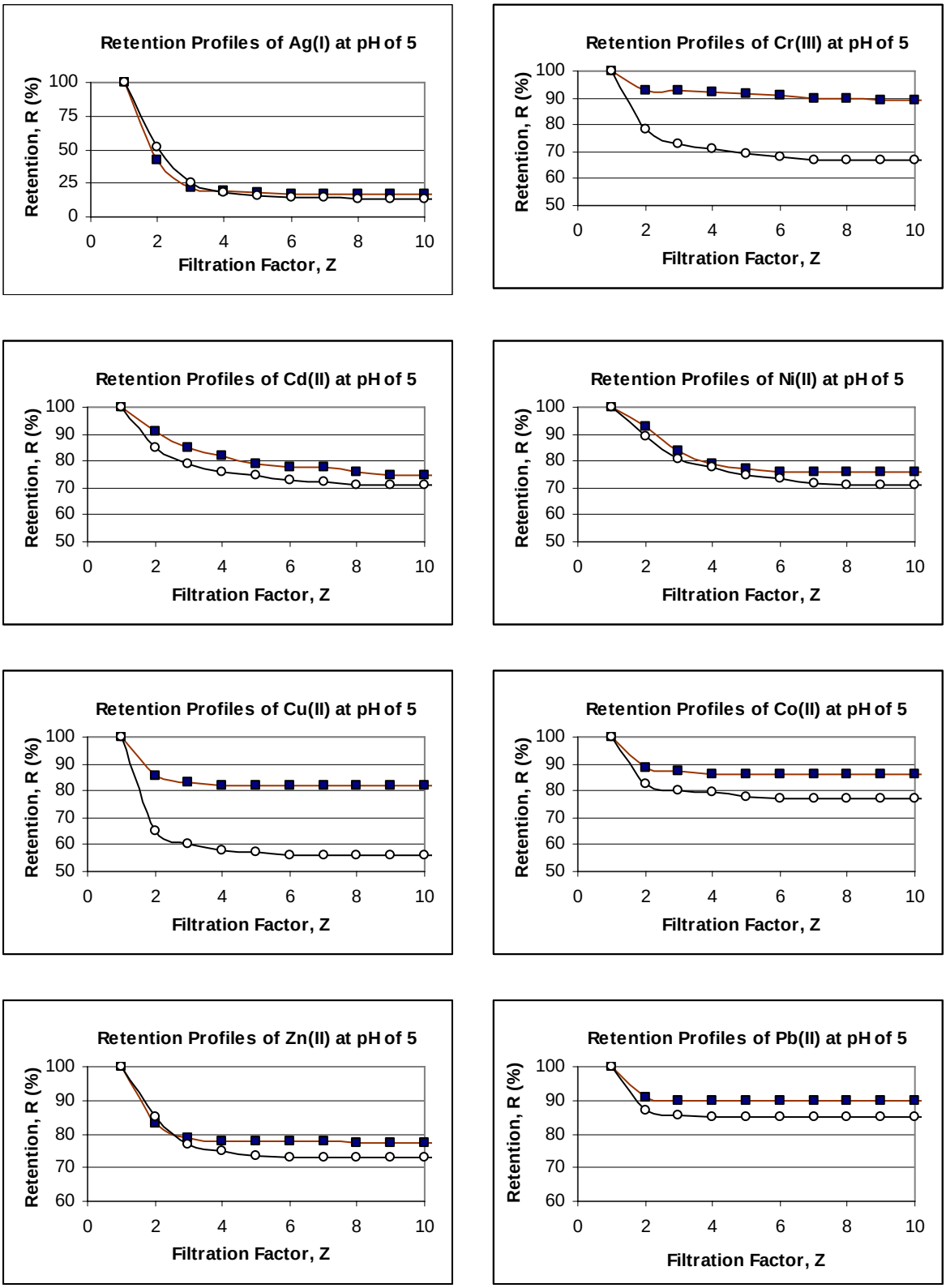


Figure 4. 31 Retention profiles of the dendrimers (29) and (32) with the standard metal ions at the pH value of 5.

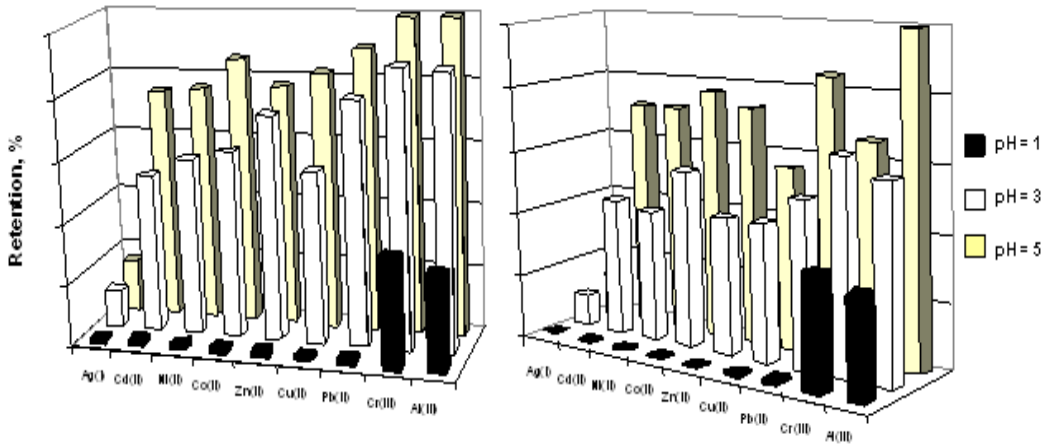


Figure 4. 32 Retention profiles of the dendrimers (29) and (32), respectively, with the standard metal ions at the pH of 1, 3, and 5.

The complexation of the metal ions to the dendrimers (29 and 32) showed that the metals are well-coordinated with the dendrimer (29) compared to the dendrimer (32) that have more carboxyl groups on it. This can be attributed to the steric effect of carboxylic groups. Because of the dendrimer (29) has more voids between the carboxylic groups the metals can place to these places and showed good coordination with the metals.

CHAPTER 5

CONCLUSION

In this thesis, the synthesis, characterization, and metal ion complexation of some dendrons and dendrimers have been investigated. Newkome and Tomalia methodologies have been combined in order to obtain mixed branched dendrimers. Newkome AB_2 type and AB_3 type nitro esters and different molecules with different functionalities such as tris (hydroxymethyl) aminomethane (TRIS) were used as monomeric building blocks for the synthesis of dendrons and dendrimers that have different functional groups on their termini. As the cores, PEG-600 diacid, Jeffamine® T-3000, Trimesic acid and tris (aminoethyl) amine (TREN) have been used. By the addition of different dendrons or monomeric units to the corresponding cores, first and second generation dendrimer synthesis have been successfully achieved. The microwave method and conventional methods have been applied for the synthesis. The positive effect of microwave power on the yield and the reaction time has been observed by comparing the results obtained by the conventional methods. In some reactions microwave irradiation has not been applied because of the deformation of the monomeric blocks at higher temperatures. Therefore, the conventional methods such as DCC coupling have been chosen for the reactions that must be carried out at room temperature.

After the synthesis of dendrimers, the metal complexing properties of the some Dendrimers (**29** and **32**) were studied for Cr(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Pb(II) and Ag(I) ions in aqueous solution using the Liquid-Phase Polymer-Based Retention (LPR) method. According to the retention profiles determined as a function of filtration factor using LPR in conjunction with ICP, two and trivalent metal ions showed a strong interaction with these dendrimers.

Because of the time-dependency and continuing study on the metal complexation of the other synthesized dendrimers with the metals, rest of works will be published in the next manuscript.

REFERENCES

[1] Klajnert, B. and Bryszewska, M. Dendrimers: properties and applications, Acta Biochimica Polonica, Vol. 48 No. 1, 2001.

[2] Tomalia, D.A. et al. (1985) A new class of polymers: Starburst-dendritic Macromolecules. Polym. J. 17, 117–132

[3] Newkome, G.R. et al. (1985) Cascade molecules: a new approach to micelles. A [27]- Arborol. J. Org. Chem. 50, 2003–2004.

[4] D.A. Tomalia, Birth of a New Macromolecular Architecture: Dendrimers as Quantized Building Blocks for Nanoscale Synthetic Organic Chemistry, Aldrichimica Acta, Vol. 37, No. 2 (2004)

[5] R. M. Crooks, H. Tokuhisa, A. J. Ricco, G. C. Osbourn, M.,Kaiser, and R.Spindler,Chemical Sensors Based on Surface-Confined Dendrimers, Proc. Symp. Chem. and Biol. Sensors and Anal. Electrochem. Methods 97-19, The Electrochemical Society: Pennington, NJ (1997); pp. 134-40.

[6] G.M. Dykes, Dendrimers: a review of their appeal and applications. J Chem Technol Biotechnol 76 (2001), pp. 903–918.

[7] "Cascade"- and "Nonskid-Chain-like" Syntheses of Molecular Cavity Topologies Egon Buhleier, Winfried Wehner, Fritz Vögtle Synthesis; 1978: 155-158

[8] Fre´chet J.M.J, Tomalia D.A. Dendrimers and other dendritic polymers. Chichester: Wiley; 2001

[9] Micelles. Part 1. Cascade molecules: a new approach to micelles. A [27]-arborol George R. Newkome, Zhongqi Yao, Gregory R. Baker, Vinod K. Grupta, J. Org. Chem; 1985, 50(11), 2003-2004.

[10] Buhleier, E., Wehner, W. and Vogtle, F., Synthesis, 1978, 155-l 58.

[11] Tomalia, D. A.. Baker, H., Dewald, J., Hall, M., Kallos, G., Martin, S., Roeck, J., Ryder, J. and Smith, P., Polym. J., 1985, 17, 117-132.

[12] Hawker, C. J. and Frechet, J. M. J., J. Am. Chem. Sot., 1990,112,7638-7647.

[13] Miller, T. M., Neenan, T. X., Zayas, R. and Bair, H. E., J. Am. Chem. Soc., 1992,114, 1018- 1025.

[14] Newkome, G. R., Yao, Z., Baker, G. R. and Gupta, V. K., J. Org. Chem., 1985,50,2004-2006.

[15] Uhrich, K. E. and Frechet, J. M. J., J. Chem. Sot. Perkin Trans. I, 1992, 1623-1630.

[16] O.A. Matthews, A.N. Shipway, and J.F. Stoddard, "Dendrimers - Branching Out From Curiosities into New Technologies", Prog. Polym. Sci., Vol. 23, 1998, 1-56.

[17] Andrew N. Shipway, "Dendrimers - A Review", School of Chemistry, University of Birmingham

[18] G. R. Newkome, C. N. Moorefield and F. Vögtle, Dendritic Molecules: Concepts, Synthesis, Perspectives, VCH-Verlag, Weinheim, 1996

[19] S.M. Grayson and J.M.J. Frechet, Convergent dendrons and dendrimers: from synthesis to applications,Chem. Rev. 101 (2001), pp. 3819–3868.

[20] N. Fischer-Durand, M. Salmain, B. Rudolf, L. Jugé, V. Guérineau, O. Laprévote, A. Vessières , G. Jaouen. (2007). Design of a new multi-functionalized PAMAM dendrimer with hydrazide-terminated spacer arm suitable for metal carbonyl multi-labeling of aldehyde-containing molecules. Macromolecules, 40, 8568-8575.

[21] M. F. Ottaviani, R. Valluzzi, L. Balogh. “Internal Structure of Silver-Poly(Amidoamino)-Dendrimer Complexes and Nanocomposites” Macromolecules 35(13), 5105-5115 (2002)

[22] M. Diallo, L. Balogh, A. Shafagati, J. H. Johnson, Jr., W. A. Goddard III and D. A. Tomalia. "Poly(amidoamine) Dendrimers: A New Class of High Capacity Chelating Agents for Cu (II) Ions" Environ. Sci. and Technol. 33(5), 820-824 (1999)

[23] L. Balogh and Donald A. Tomalia. "Poly(Amidoamine) Dendrimer-Templated Nanocomposites I. Synthesis of Zero-Valent Copper Nanoclusters" Journal of Am. Chem. Soc. 120, 7355-7356 (1998)

[24] R. Esfand and D.A. Tomalia, Poly(amidoamine) (PAMAM) dendrimer: from biomimicry to drug delivery and biomedical applications, Drug Discov. Today 6 (2001), pp. 427–436.

[25] M.K. Calabretta, A. Kumar, A.M. McDermott and C. Cai, Antibacterial activities of poly(amidoamine) dendrimers terminated with amino and poly(ethylene glycol) groups, Biomacromolecules 8 (2007), pp. 1807–1811

[26] X. Zhang, X. Wang, S. Huang, R. Zhuo, Z. Liu, H. Mao, and K.W. Leong, "In Vitro Gene Delivery Using Polyamidoamine Dendrimers with a Trimesyl Core", Biomacromolecules 2005, vol. 6, pp. 341-350.

[27] Y. Cheng, J. Wang, T. Rao, X. He, T. Xu, Frontiers Bioscience 13 (2008) 1447.

[28] D.A. Tomalia, Prog. Polym. Sci. 30 (2005) 294.

[29] E.R. Gillies, J.M.J. Frechet, Drug Disc. Today 10 (2005) 35.

[30] M.J. Cloninger, Curr. Opin. Chem. Biol. 6 (2002) 742.

[31] "Poly(amidoamine), Poly(propylenimine), and Related Dendrimers and Dendrons Possessing Different 1→ 2 Branching Motifs: An Overview of Divergent Procedures", Newkome, G. R.; Shreiner, C. D., Polymer, 2008, 49, 1-173.

[32] Dendrimers and Other Dendritic Polymers Fre´chet, J. M. J., Tomalia, D. A., Eds.; John Wiley & Sons: West Sussex, UK, 2001.

[33] L. Hayes Brittany , Microwave Synthesis (Chemistry at the Speed of Light), CEM, Matthews, PO Box, p: 25, 2002

[34] G. S. Vanier, Synlett, 2007, 131-135.

[35] Kumar, K. H.; Perumal, P. T. Can. J. Chem. 2006, 84, 1079-1083.

[36] Loupy A. Microwaves in organic synthesis. Weinheim: Wiley-VCH; 2002.

[37] G.R. Newkome, E.F. He and C.N. Moorefield, Suprasupermolecules with novel properties: Metallodendrimers, Chem. Rev. 99 (1999), pp. 1689–1746.

[38] Geckeler, K. E. Pure Appl. Chem. 2001,73,129.

[39] Geckeler, K. E.; Bayer, E.; Spivakov, B. Y.; Shkinev, V. M.; Vor-obeva, G. A. Anal Chim Acta 1986, 189, 285.

[40] Geckeler, K. E.; Zhou, R.; Rivas, B. L. Angew. Makromol. Chem, 1992, 197, 107.

[41] Newkome, G. R.; Weis, C. D. Org. Prep. Proc. Int. 1996, 28, 485.

[42] Eckelman W.C., J Pharm Sci 64:704 (1975).

[43] Takeshita T.I, Shimohara, T., Maeda, S., Synthesis of EDTA-Monoalkylamide Chelates and Evaluation of the Surface-Active Properties. J. Am. Oil. Chem. Soc. 1982; 59:90.

[44] K.E. Geckeler, Polymer metal complexes for environmental protection. Chemoremediation in the aqueous homogeneous phase, Pure Appl. Chem 73 (2001), p. 129.

[45] Senel, M., *Synthesis and characterization of water soluble dendritic macromolecules*, M. S. Thesis, Fatih University, 2007.

[46] Tulu, M., Senel, M., Dendritic Polychelatogens: Synthesis, Characterization, and Metal Ion Binding Properties, Journal of Applied Polymer Science, No. 109, May. 2008, pp. 2808–2814.