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IONIC DENDRIMERS

by

ALICE D. CHERESTES

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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ABSTRACT

Ionic Dendrimers

by

Alice D. Cherestes

Advisor: Professor Robert Engel

The synthesis of several ionic and chiral ionic dendrimers has been achieved. The first target consisted in the synthesis of cationic dendrimers anchored to an insoluble core and investigation of their applications and properties. The cationic sites were located at the branch points. Anionic dendrimers were also synthesized and investigated. Chiral ionic dendrimers with cationic sites incorporated as components of the extension units and chiral sites at the branch points were also synthesized.

Dedicated to my parents Dr.Ioan Cherestes and Dr.Irma Cherestes.

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INTRODUCTION

HISTORICAL

From a historical point of view, progress toward the synthesis of macromolecules with branched architecture took place in three phases. The first stage occurred roughly from 1860 to 1940, when branched structures were considered to be responsible for the insoluble materials formed in polymerization reactions. Synthetic control, isolation of materials and proof of structure were impossible at that time with these materials.

The early 1940's to the late 1970's marks the second period in which branched structures were studied mainly from a theoretical point of view, but initial attempts were also made at specific preparations of branched structures via classical or single pot polymerization of monomers. In 1943 Flory introduced the idea of a network cell as the most fundamental unit in a molecular network structure.[1-5] He noted:" The breadth of the distribution coupled with the impossibility of selectivity fractionating branching and molecular weight separately make this approach impractical. Attempts to investigate branching by such means consequently have been notable fruitless."

Graessley[6,7] took the notion one step further by describing assembles of these network cells as micronetworks. In the context of the statistical treatment of Gaussian coil networks, analogues species that are part of an open, branched organization have been coined branch cells and branch cell assemblies, respectively. Statistical modeling by Gordon et al.[8-12] reduced such branched species using graph theory designed to mimic the morphological branching of trees. These dendritic models were combined with "cascade theory"[13,14] mathematics to give a reasonable statistical treatment for network forming events. These species were conceptual, and there were no well characterized synthetic examples of such architecture.

The late 1970's and early 1980's recorded the initial successful progress toward macromolecular assembly based on iterative methods that became the cornerstone of dendritic chemistry. In this stage the control over the molecular construction was better established. Isolation, purification and characterization of the newly designed molecules had also reached new necessary levels.

The modern era of dendrimers (or cascade molecules) came to life when Vogtle et al.[15] wrote the following introductory sentence in one of his papers in 1978:

"For the construction of large molecular cavities and pseudocavities that are capable of binding ionic guests and molecules in a host-guest interaction, synthetic pathways allowing a frequent repetition of similar steps would be advantageous." He reported a single isolated example of a protection/ deprotection scheme involving the idea of assembling branches upon branches. The scheme consisted of a series of reactions involving Michael type additions of an amine to acrylonitrile, followed by the reduction of the nitrile group to an amino group. Perhaps due to difficulties in the reduction step and disappointing yields, no subsequent reports could be found of this work. In any case, the idea of a "cascade synthesis" was first introduced in the literature at this time, and it referred to reaction sequences that could be carried out repeatedly, whereby a functional group is made to react in such a way as to appear twice in the subsequent molecule. Repetition of similar and complimentary synthetic steps has since been used for the preparation of many new and exciting materials.

After the initial disclosure of a viable iterative synthetic method for the construction of polyfunctional macromolecules a small number of articles explored the use of repetitive chemistry for the preparation of dendritic materials.

Early divergent branched architectures were constructed mainly employing protection-deprotection schemes. Initial work in this regard was done by Denkelwater, Kolc, Lukasavage[16] in the synthesis of polylysine based dendrimers. These dendritic polymers present the interesting feature of an asymmetric branching pattern and the incorporation of multiple chiral centers at each tier. Next Kricheldorf, Zang and Schwarz[17] demonstrated a renewed interest in branched topologies prepared via single pot procedure and they are currently referred to as hyperbranched polymers. In the late seventies and early eighties the research group of Newkome constructed polyols possessing Carbon based branching[18]. These macromolecules are highly branched dendrimers which are not amenable to size control as a function of generation in that reiterative chemistry for advancing concentric growth has not been reported. These prototypes have been used successfully for controlling molecular shape and in some cases surface moieties. To date examples of uni-, bi-, and tri- directional arborols have been reported. At the same time Tomalia reported the preparation of an entire series of dendrimers possessing trigonal N-based branching centers[19]. Bidd and Whitind described the iterative based synthesis of pure linear, alkyl hydrocarbons[20]. The preparative methodology involved the use of repetitive Wittig coupling and cyclic acetal hydrolysis reactions.

In 1990 the first convergent preparation of dendrimers resulted in poly(aryl ether) architecture as reported by Frechet and Haroker[21]. They used a phenoxide based, benzylic bromide displacement sequence. The same year Miller and Neeman published the convergent preparation of the first series of aromatic based all hydrocarbon dendrimers.[22] These efforts were complemented by theoretical work by Maciejewski[23] who examined "topological trapping by shell molecules." This author alludes to numerous dendritic properties such as the concept of dense packing whereby building block connectivity is precluded due to steric hindrance and void volume entrapment of solvent molecules.

Buchard, Kajiwara and Nerger[24] examined dynamic and static light scattering of regularly branched chain molecules. De Gennes and Hervet[25] published a statistical treatment of starburst dendrimers and they concluded from a mathematical growth model that steric hindrance limiting continued tier addition was dictated by the length of the spacer units that connect the branching centers. This idea reinforced the earlier concept of dense packing.

To understand dendritic macromolecular geometry one has to use concepts of fractal geometry. Fractal geometry was introduced in the mid 1970's by Mandelbrot[26,27] and it provides a rational explanation of complicated structures. A few simple definitions from fractal geometry need to be mentioned in order to understand better the fractal geometry of dendrimers.

Self-similarity is a characteristic of basic fractal objects. As described by Mandelbrot: "when each piece of shape is geometrically similar to the whole, both the shape and the cascade that generate it are called self-similar." Scale-invariance describes the shapes that remain constant regardless of the scale of observation. Thus self-similar or self-invariant macromolecular assembly possesses the same topology or pattern of atomic connectivity in small as well in large segments.[28]

The self similarity of a dendrimer is readily apparent when each generation is viewed consecutively. The appearance of each generation is strikingly similar to the next with respect to such features as 1-3 branching, distance between branching centers and nuclei connectivity. The requirement of self-similarity does not necessitate the strict use of similar monomers at each generation.[29] With respect to dendritic chemistry fractal geometry affords a novel method of comparison of branched architecture as well as, and perhaps more importantly a new way to envision these unique new macromolecules and their properties. Dendritic surface complexity is derived from the features of the supporting superstructure which is in turn derived from the inherent nature of the building blocks used for its construction[30].

DENDRIMER TYPES

The structures of dendrimers can be envisioned easily, but are nearly impossible to name based on current nomenclature systems. Researchers in the field resorted to naming their materials with trivial names such as: arborols, cascadols, cauliflower polymers, crowned arborols, dendrimers, molecular fractals, polycules, silvanols and starburst dendrimers.[18,19,25,31-35]

A cascade polymer at the n-th generation has the general formula:

$$C[R_1(R_2(\ldots R_i(\ldots R_n(T)N_{bn}\ldots)N_{bi}\ldots)N_{b2})N_{b1}]N_c$$

where C is the formula for the core moiety

R_i is the formula for the repeat or the branch unit

T is the formula for the terminal moiety

N_{bi} is the branch multiplicity of the i-th repeat unit or generation

N_c is the multiplicity of he branching from the central core.

Dendrimers can have the following general patterns:

a. Similar internal units[36]

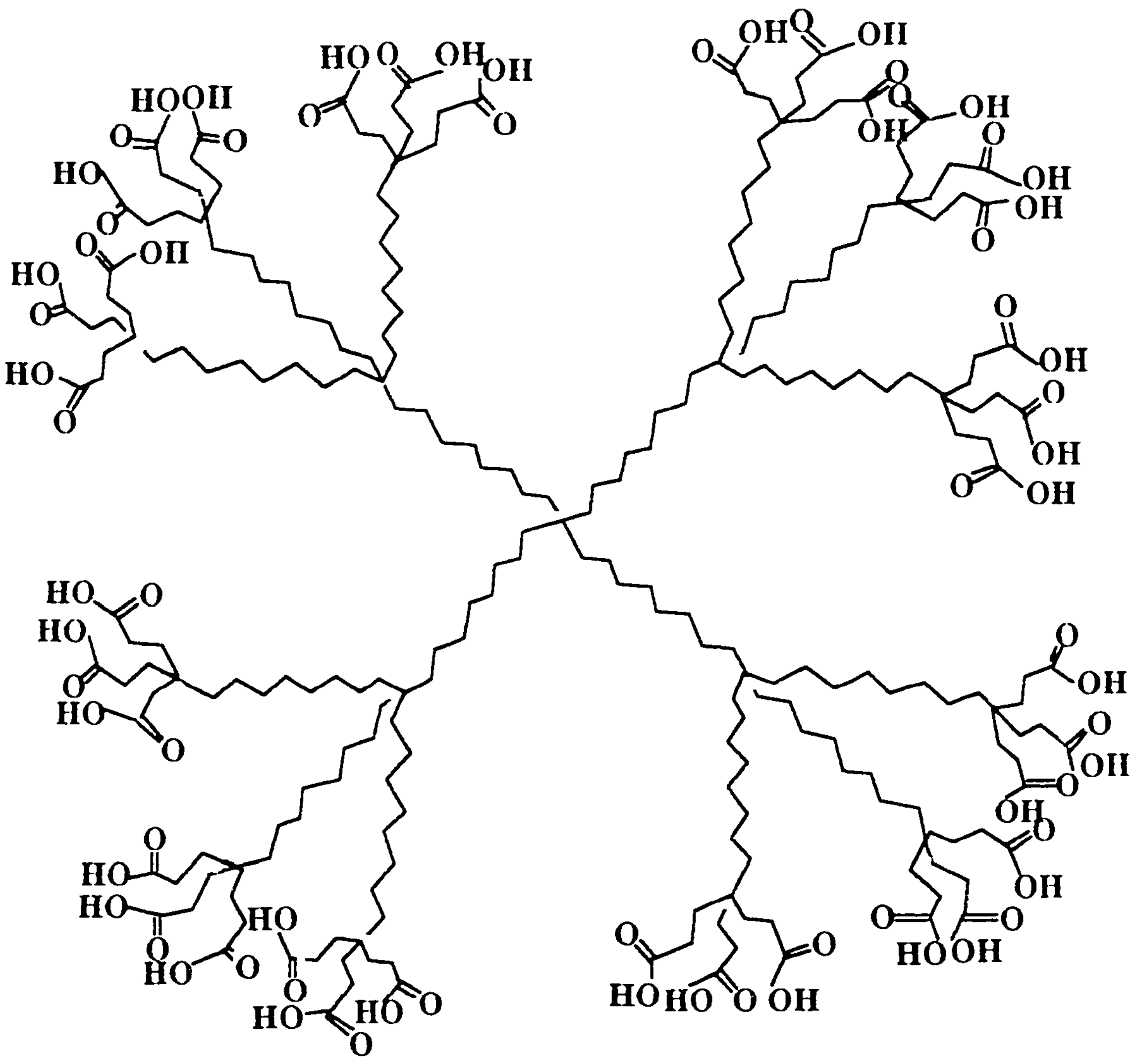


FIGURE 1

b. Similar arms with dissimilar internal units[37]

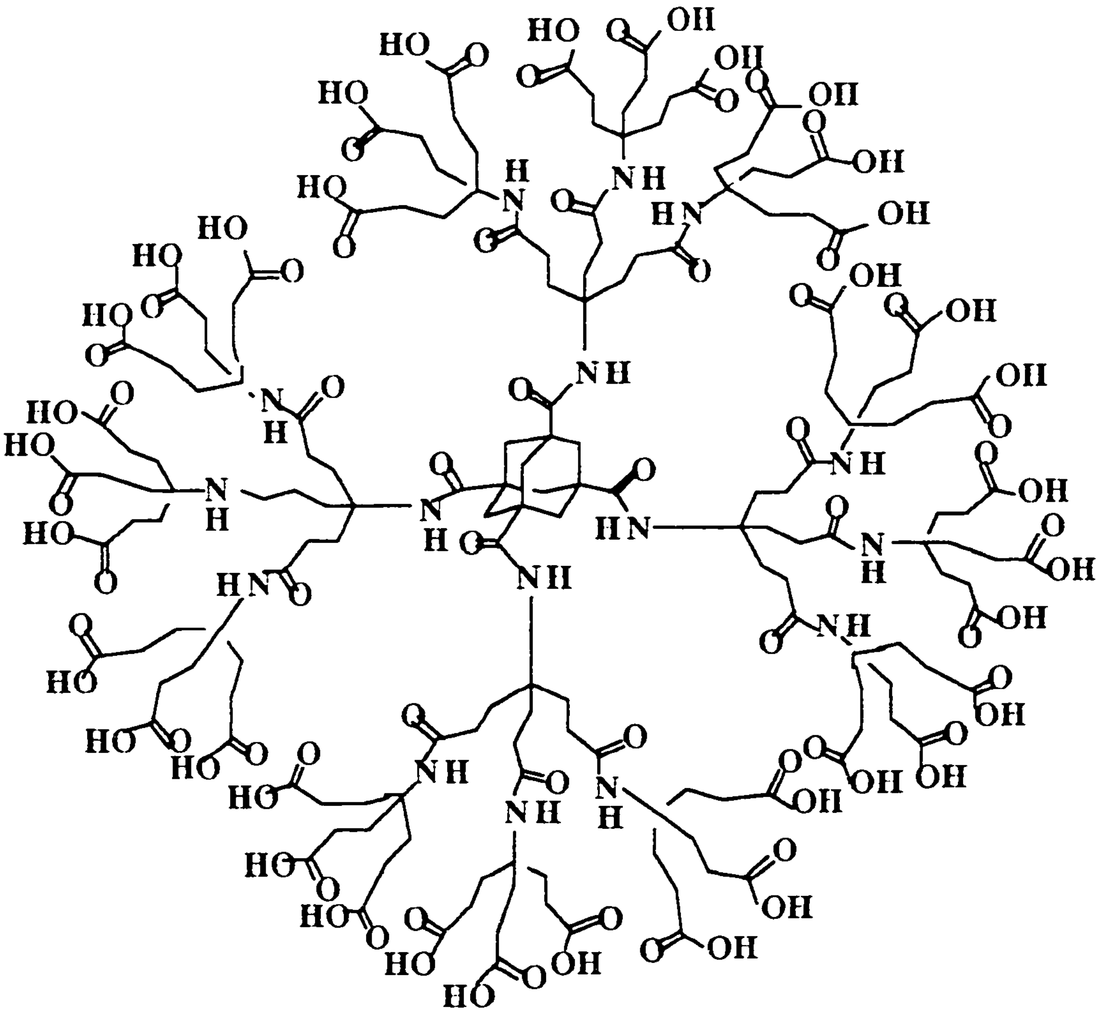


FIGURE 2

c. Dissimilar arms with similar internal branches[38]

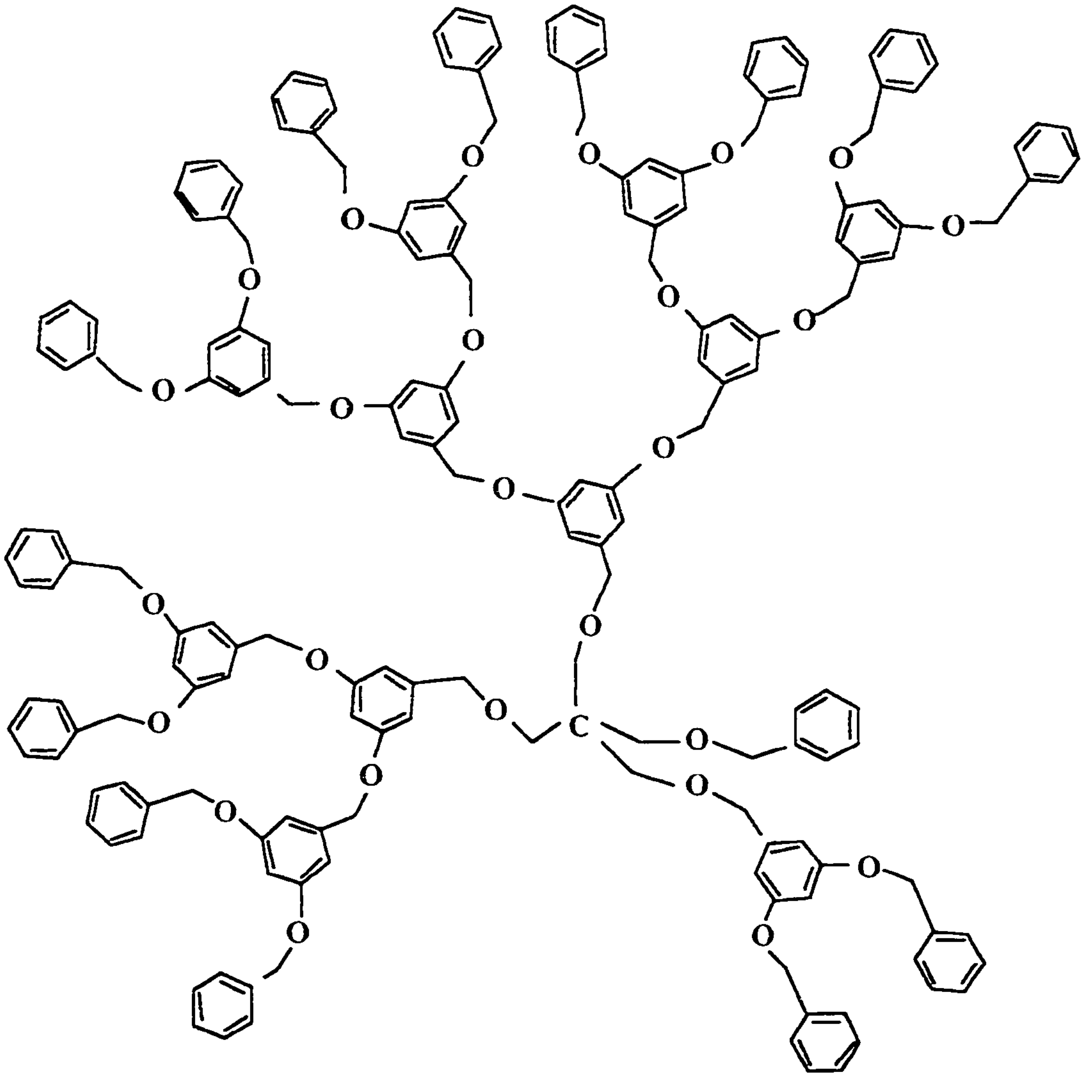


FIGURE 3

d. Dissimilar arms with dissimilar internal branches or terminal groups[39]

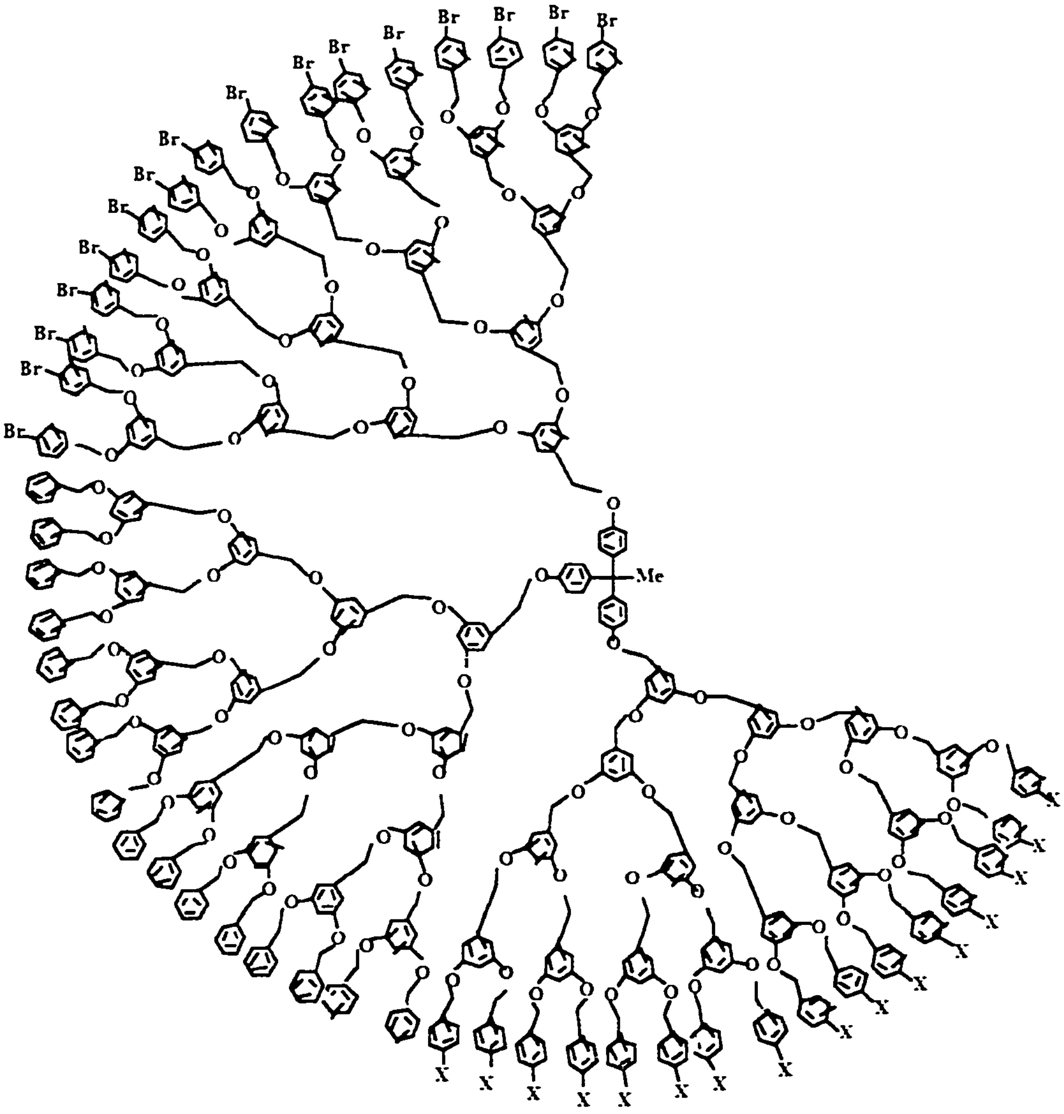


FIGURE 4

e. Unsymmetrically branched cascades[40]

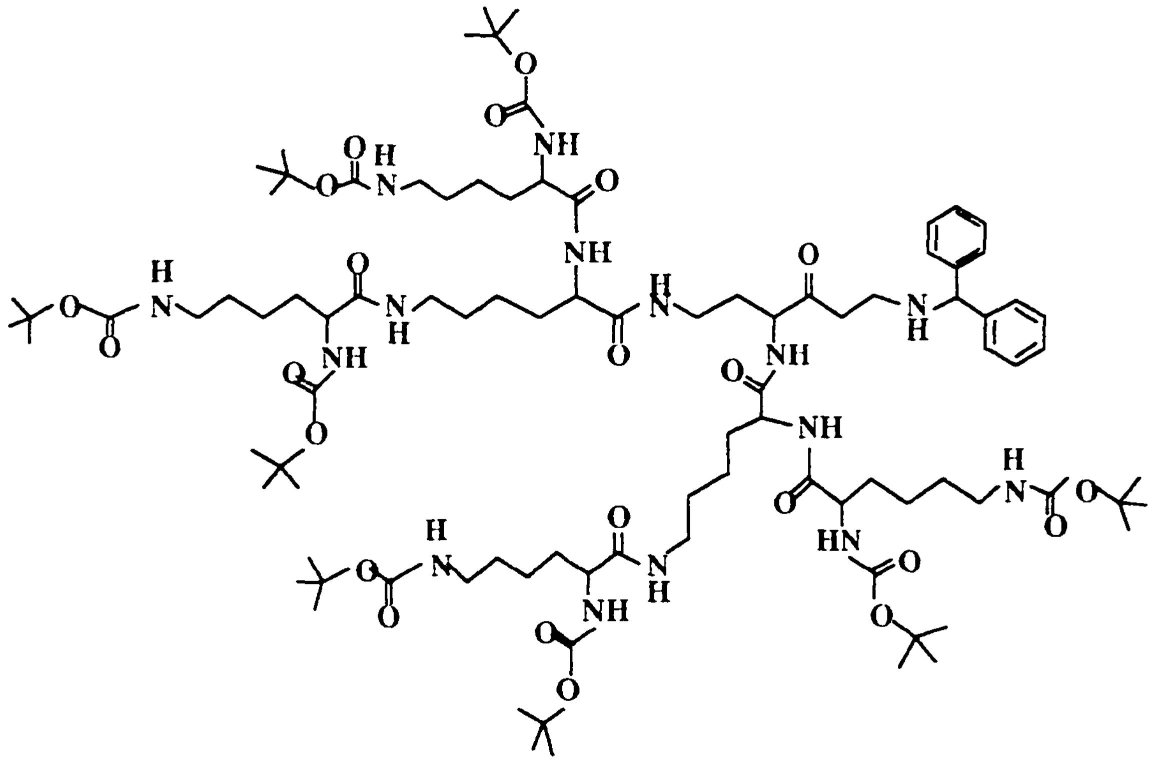


FIGURE 5

DENDRIMER CONSTRUCTION

Dendrimers differ from classical random coil macromolecules in that they possess three distinguished architectural components: 1) an initiator core, 2) interior layers or generations, composed of repeating units, radially attached to the initiator core, and 3) exterior or surface groups of terminal functionality attached to the outermost interior generation. The general diagram of a dendrimer is shown in figure 6 below.

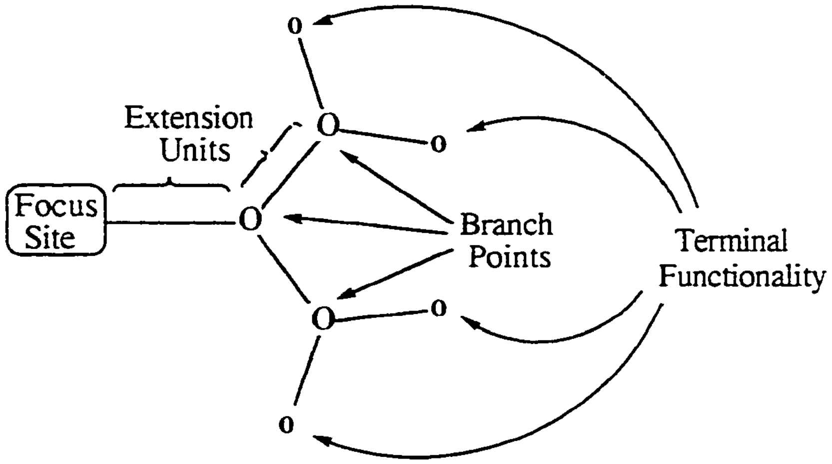


FIGURE 6

The initiator core type can affect the dendrimer shape. Advancement of generations determines the dimensions whereas the surface chemistry can be varied widely. Even in an ideal, homologous dendrimer series there exists a hierarchy of branch cells that are differentiated not only by their topological position but also by structural features.

The initiator core can be as small as an atom or as large as a molecule. It may be homogeneous with the other dendrimer components or it may contain special features which make it heterogeneous. Synthetic elaboration to create the first tier of terminal functionality or branch junctures defines a microdomain referred to as the core cell. In situ construction of branch junctures or coupling branch cell reagents, gives the first three surface cells, each of which possesses two reactive surface groups. On progressing to the next generation the three surface cells become initiator cells and six new surface cells are added. Advancement to the next generation completes the development of cell hierarchy, and it consists of one initiator core cell, three initiator cells, six interior cells, and twelve surface cells.

The selection or synthesis of the unit that will serve as the core is of great importance. Its size, shape, multiplicity and specialized function will influence the dendrimer throughout its construction. Core cell design can range from the simple attachment of only one dendron to the use of multibranched functionalized entities or even to the use of polymeric substrates. Introduction of branch junctures may involve either "in situ" construction, coupling of presynthetized branch cells, or chain propagation of branched monomers to produce the first tier of branch cells. Introduction of a specific function in the initiator core represents stored information which will become buried by subsequent generations. In contrast parameters such as size, shape and multiplicity will be transcribed and displayed throughout the dendrimer development. These variables will have dramatic effects on ultimate shape, interior topology, and the exterior surface properties of the developing dendrimer. The interior of a dendrimer can also be characterized by branch cell differentiation, topology and the evolution of a branch cell hierarchy.

Dendrimer construction which involves the " in situ " synthesis of branch cells requires very high yield conversion syntheses as well as efficient workup procedures for the separation of dendrimers from the reagents. A variety of methods were successful in this regard: protection/deprotection methods, solid phase synthesis, and excess reagent method. The use of protection/deprotection methods allows selective coupling without bridging or looping side reactions.

Dendrimer construction which involves chain propagation methods was first introduced in the synthesis of "hyperbranched polymers." This type of polymerization is based on a monomer of the form $A\text{-}R\text{-}B_n$, where n is greater than one and functional group A can react with functional group B.

The symmetry properties of the interior branch cells can affect the physical and chemical properties of a dendrimer. Symmetrical interior and surface cells exhibit identical connectivity paths from the initial core to the termini. The equal radii place the terminal groups on a sphere or on a segment of a sphere thus making dendrimers ideal models for functionalized submicron spheres. Symmetrical branch junctures appear to favor "shell topology" formation, whereas asymmetrical branch junctures exhibit a more classical relationship between density and molecular mass, due to more effective interior packing of the asymmetrical branch cells.

In contrast, certain dendrimers-polylysine-have unsymmetrical branch cells with either three or seven bonds between branch points. If one considers the path of connectivity from initiator core to termini of a single dendritic branch, it can be seen that no two paths are identical. The different path lengths require that some terminal groups will be closer to the branched assembly than others and be subject to more steric interaction. This suggests that this dendrimer class has surfaces with high fractal geometry and interior branching zones which are less ordered than those of the starburst dendrimer.

Classical random coil macromolecules are substrates on which is difficult to perform high yield reactions because of the inaccessibility of the buried functionalities. Unlike this situation, dendrimer topology presents the terminal functionality in a very favorable fashion, accessible to incoming reagents. Therefore any reaction that proceeds well on a point like organic molecule is expected to occur equally well on a dendrimer surface, at least for the first generations. As generations progress and surface congestion increases, reaction kinetics and stoichiometry are expected to change dramatically.

Considering the intricacies of dendrimer synthesis, one can conceive a variety of defects that would lead to divergence from ideality. The two most important ones are: those involving intra-dendrimer events and those leading to inter-dendrimer bridging or looping. The first type of defects decrease branching ideality, whereas the second type leads to more polydisperse systems. The causes for intradendrimeric events can be as follow: incomplete reactions resulting from surface group deactivation or inappropriate reaction conditions, branch-juncture fragmentation, abnormal branch-juncture development, or sterically induced stoichiometry. Factors that could cause polydispersity include: incomplete removal of reagents (which may function as initiator cores) and dendrimer fragmentation (to produce molecular species which may become initiator species).

In general synthetic strategies which lead to successful syntheses of dendrimers involved the following steps:

1. Selection of a suitable initiator that can be converted in high yield into a reactive initiator core cell.

2. Definition of an iterative reaction sequence that results in high yield conversions to a branched species with a specific molecular surface.

3. Reiteration of these step-growth or chain-growth sequences to produce dendrimers possessing concentric generations of repeating units and branch junctures.

RECENT WORK

Considerable interest has been focused recently on synthesis, characterization and theoretical studies of a new class of topological macromolecules possessing regular dendritic branching with radial symmetry which were referred as "starburst polymers". The self-replicating, symmetrical branching with multiplicity inherent in their architecture provides prototypes of considerable theoretical interest for the study of molecular level fractals, topology of uniform network polymers, molecular self-organization and steric control of microenvironment.

Starburst topology consists of construction of concentric, dendritic tiers around an initiator core. The fundamental building blocks to this new polymer class are referred to as "dendrimers". These dendrimers differ from classical oligomers by their extraordinary symmetry, high branching and maximized terminal functionality density. The dendrimers possess "reactive end groups" which allow controlled molecular weight building, controlled branching, and versatility in design and modification of the terminal end groups. Starburst topology is achieved by introducing both multiplication and self-replication in a geometrically progressive fashion. Dendrimer synthesis is accomplished by a variety of strategies involving " time sequenced propagation techniques". The resulting dendrimers grow in a geometrically progressive fashion[42].

Chemically bridging these dendrimers leads to the new class of macromolecules called "starburst polymers". These highly functionalized, dendritic molecules have been called dendrimers in deference to their branched (Greek=dendritic;tree like) as well as their oligomeric nature. The successful synthesis and characterization of dendrimers helped to demonstrate the controlled occupation of space in three dimensions as a function of size shape and disposition of organic functionality.

Topologically starburst dendrimers can be viewed as analogues of surfaces of biological particles. The dendrimer surface cells would have not only to provide steric protection to the interior of the dendrimer , but also function in primary molecular recognition of external reagents and solvents. Dendrimer solubilities are determined by the hydrophilic-hydrophobic characteristics of the surface cells. For example dendrimers with very hydrophobic interiors and hydrophilic exteriors are water soluble, and those with hydrophobic exteriors are hydrocarbon soluble.

Starburst dendrimers may be functionalized with either reactive or passive surface cells. It is self understood that all dendrimers with starburst growth scheme will possess reactive surface groups, but the reactivity of these groups will be enhanced or suppressed depending on need.

Synthetic methodologies consist of divergent and convergent procedures. Divergent dendritic construction results from sequential monomer addition beginning from a core and proceeding towards the molecular surface. A key feature of the divergent method is the exponentially increasing number of reactions that are required for the attachment of each subsequent tier.

Branching is dependent on building block valency- this also including the valency of the core. A core having one reactive moiety such as a primary amine, is bivalent and will accommodate two monomers assuming a neutral product, or three monomers assuming a quaternary ammonium salt as the product. In the first case branching proceeds in a 1-2 manner and in the second product branching proceeds in a 1-3 manner. For the neutral amine product repetition of monomer addition procedure results in a general 1-2-4-8-16-32.... branching pattern. A tetravalent core that reacts with four equivalents of a 1-2 branching monomer will result in a progression of the form 4-8-16-32-64-128; whereas the same core with a 1-3 branching reagent will give a dendrimer with a progression series with the following multiplicity 4-12-36-108-324-972.[43]

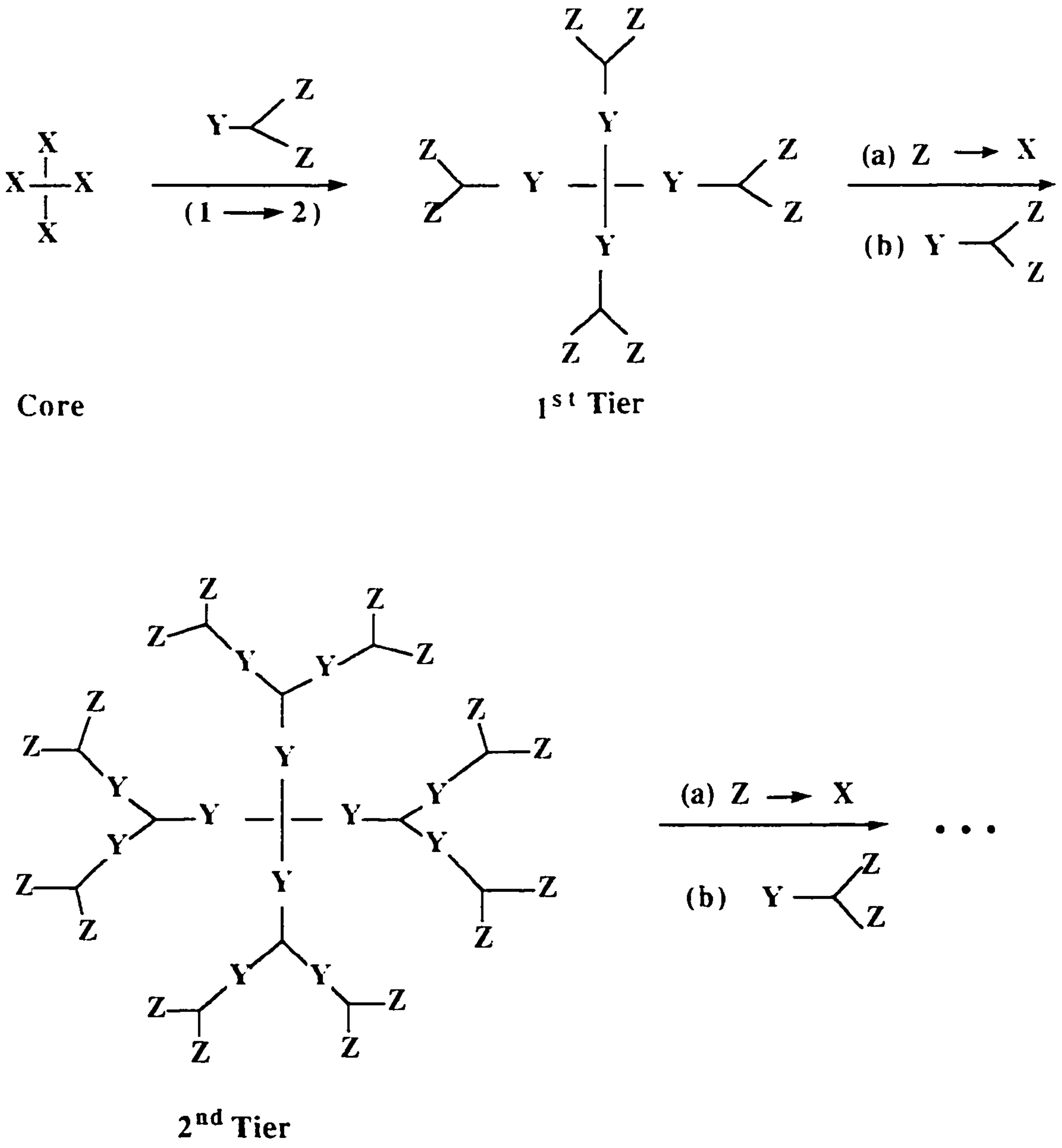


FIGURE 7

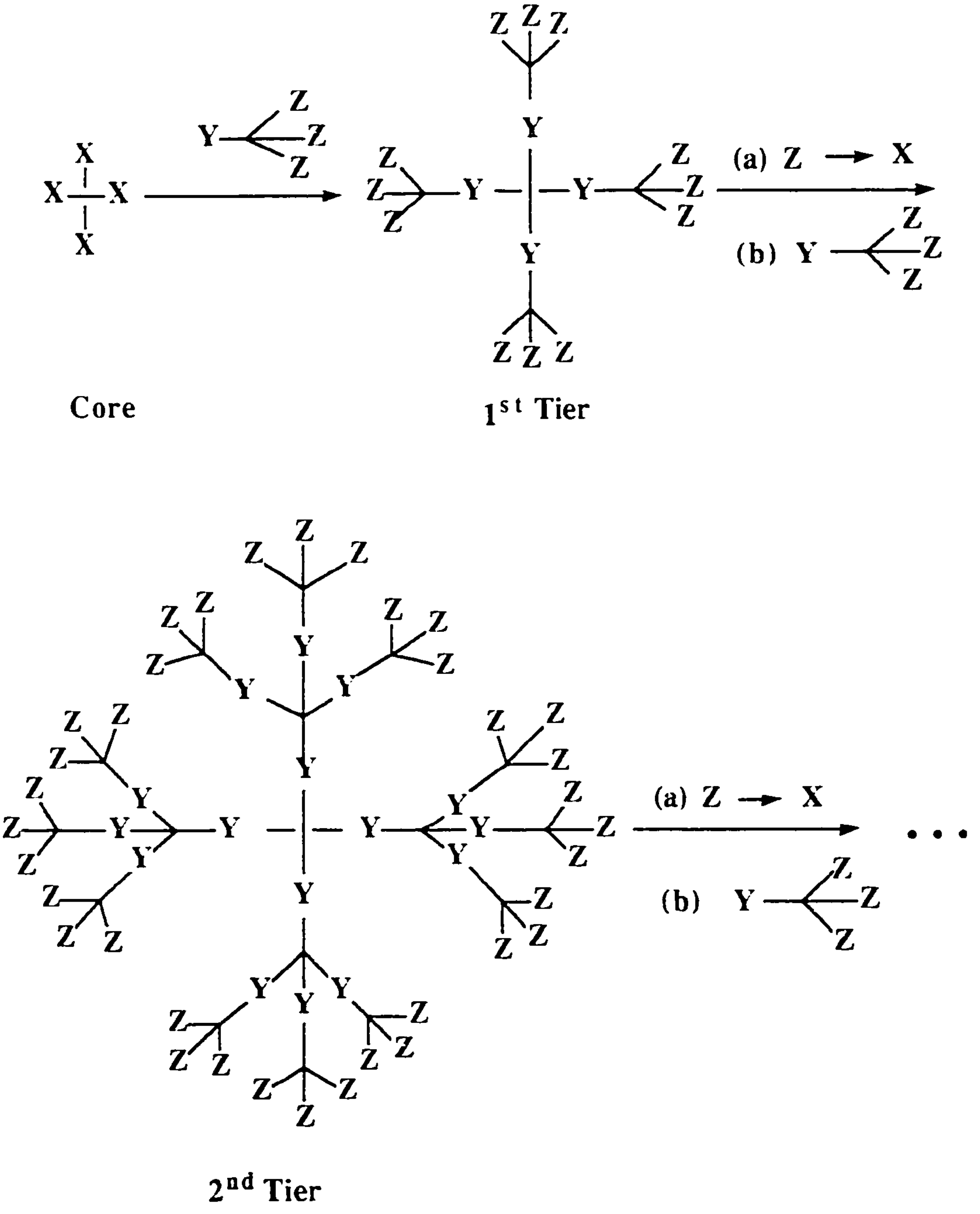


FIGURE 8

The convergent method of dendrimer construction differs from the divergent one by the fact that the branching arms are constructed from the "outside in." This concept can be best illustrated by the following[44-48]: consider two molecules with terminal units containing reactive groups X and a monomer possessing protected functionality Z. Attachment of two moles of the first described molecule to one mole of the second will give the first generation dendrimer. Deprotection of the Z site and then treatment of the first generation with 0.5 moles of monomer gives the next generation. The major advantage of this method is the minimal number of transformations required for dendrimer construction. Using a three directional building block, only two collisions are needed to attach the next generation. The active site of attachment becomes more and more crowded into the structure as the generations progress, therefore chemical connectivity can become difficult as a result of steric interference.

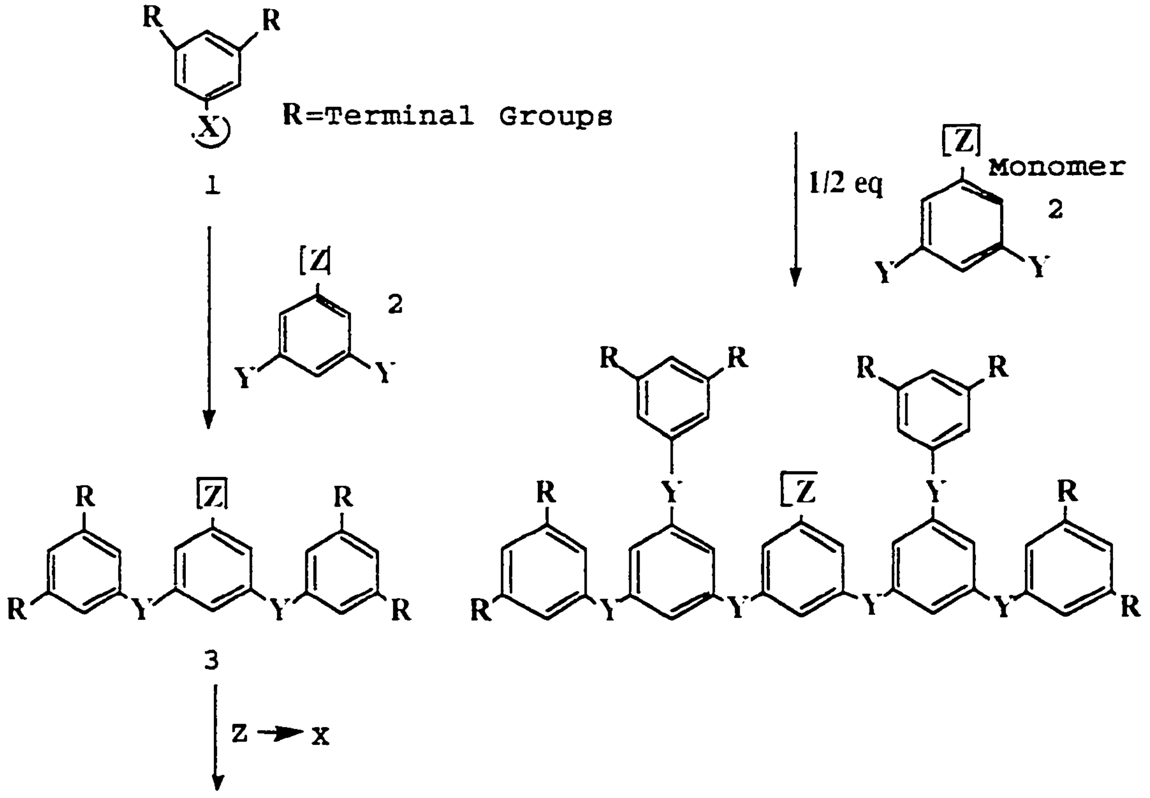


FIGURE 9

Another important synthetic method is the one consisting of one step polycondensations which give rise to hyperbranched polymers. These have a high degree of branching but they are not as perfected as the polymers obtained through step wise procedures. This method presents the advantage of being simpler and more economical but it also has the disadvantage of lack of control of branching and other synthetic aspects.[49-51]

Over the years the concept of dendrimers was developed more and in recently different research groups expended in the synthesis of chiral and ionic dendrimers. The first synthesis of chiral dendrimers was reported using a chiral carboxylic acid as the core of the dendrimer.[52-65] All the references citing dendrimer chirality after the one listed above use the chiral moiety as the core or as the terminal functionality.

In the field of ionic dendrimers the work done was limited to functionalizing the surface of dendrimers with positively or negatively charged ions.

The work done in this laboratory mainly consists in building ionic and chiral ionic dendrimers, which have the ionic sites incorporated in the structure of the dendrimer- at branching points- as well as at the surface, and which have the chiral centers all through the molecule as part of the branching arms.

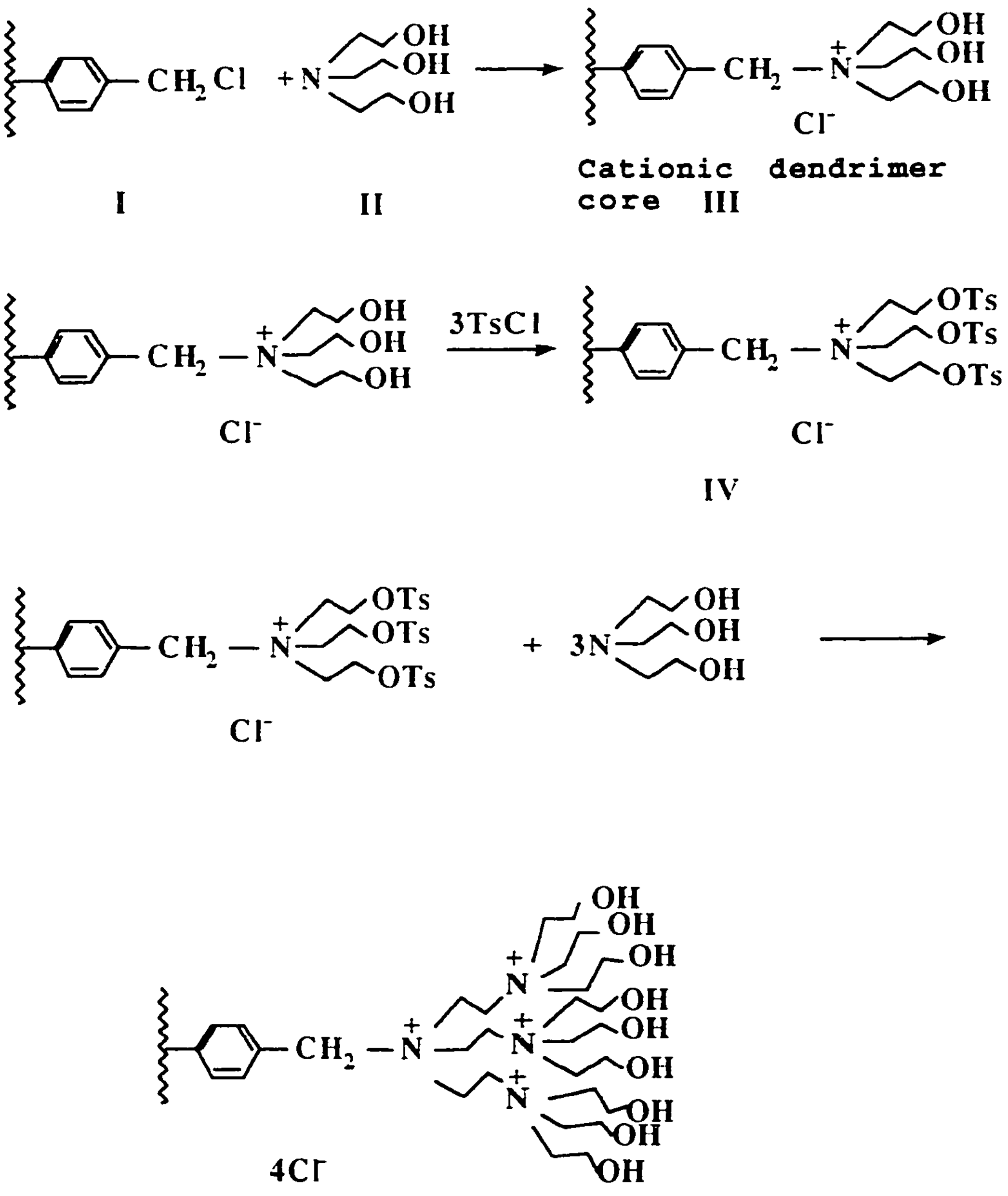
RESULTS AND DISCUSSION

INSOLUBLE IONIC DENDRIMERS

The original target of this project was the synthesis of ionic dendrimeric species which would be anchored to an insoluble polymer chain rendering the entire covalent structural unit insoluble in aqueous and organic solvents. This was done in an attempt to produce insoluble materials bearing a high density of ionic sites with "free-floating" counterions which should be capable of exchanging anions with the surrounding solution.

There were two fundamental types of structures developed: anion exchangers and cation exchangers. The anion exchangers incorporate multiple cationic sites covalently bound to a single structural unit with loosely associated anions. They are prepared by using Merrifield resin as the core, and treating it with a tertiary amine. The choices for the amines were triethanol amine and 1,4-diazobicyclo[2.2.2]octane (DABCO).

In the first instance initial attachment of the amine to the resin, the triethanolamine dendrimer was developed by a two step iterative process involving (1) reaction with p-toluensulfonyl chloride in pyridine, followed by (2) reaction with excess triethanolamine in 1:1 methylene chloride and acetonitrile. This sequence was performed four times. The process is illustrated below in Scheme 1



I

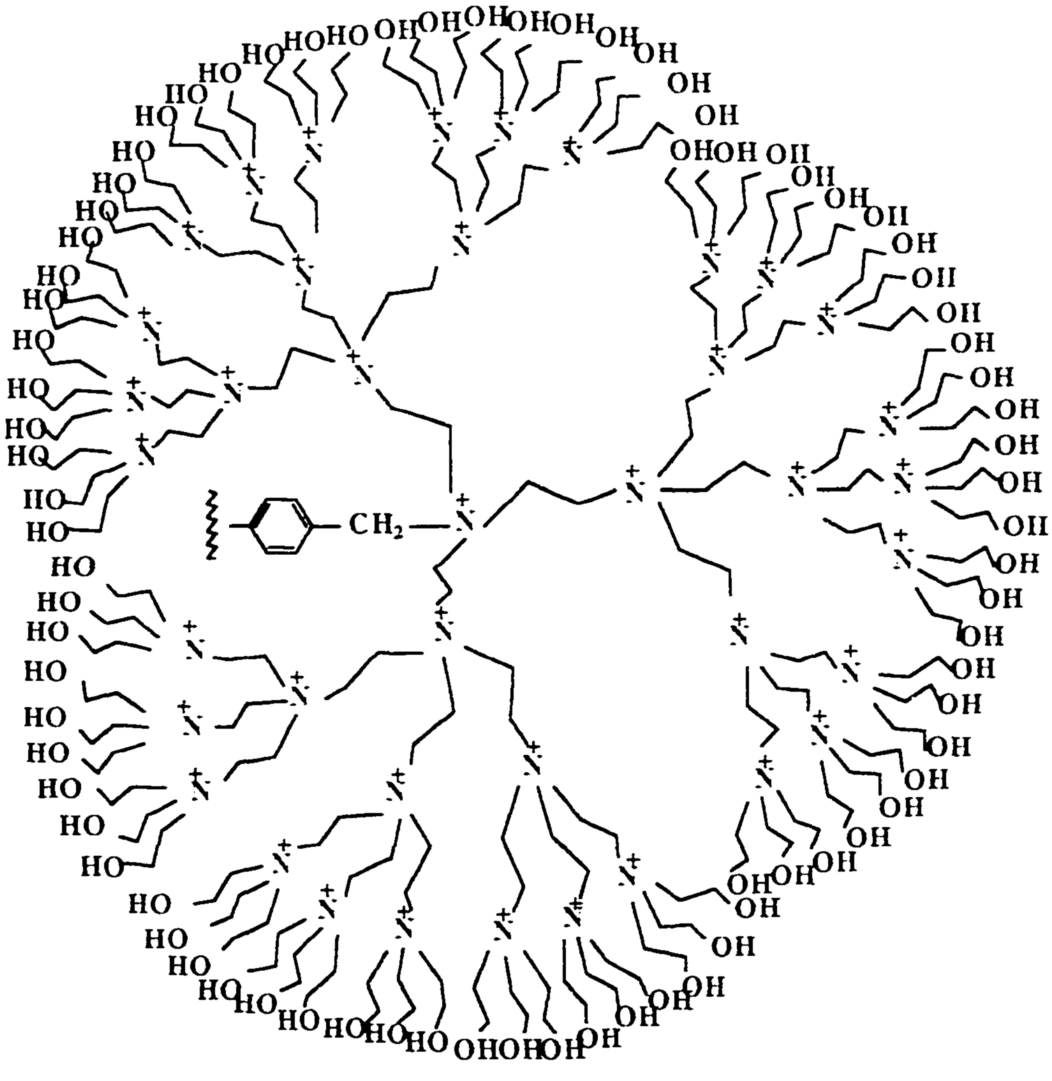
II

Cationic dendrimer core III

IV

First generation cationic dendrimer V

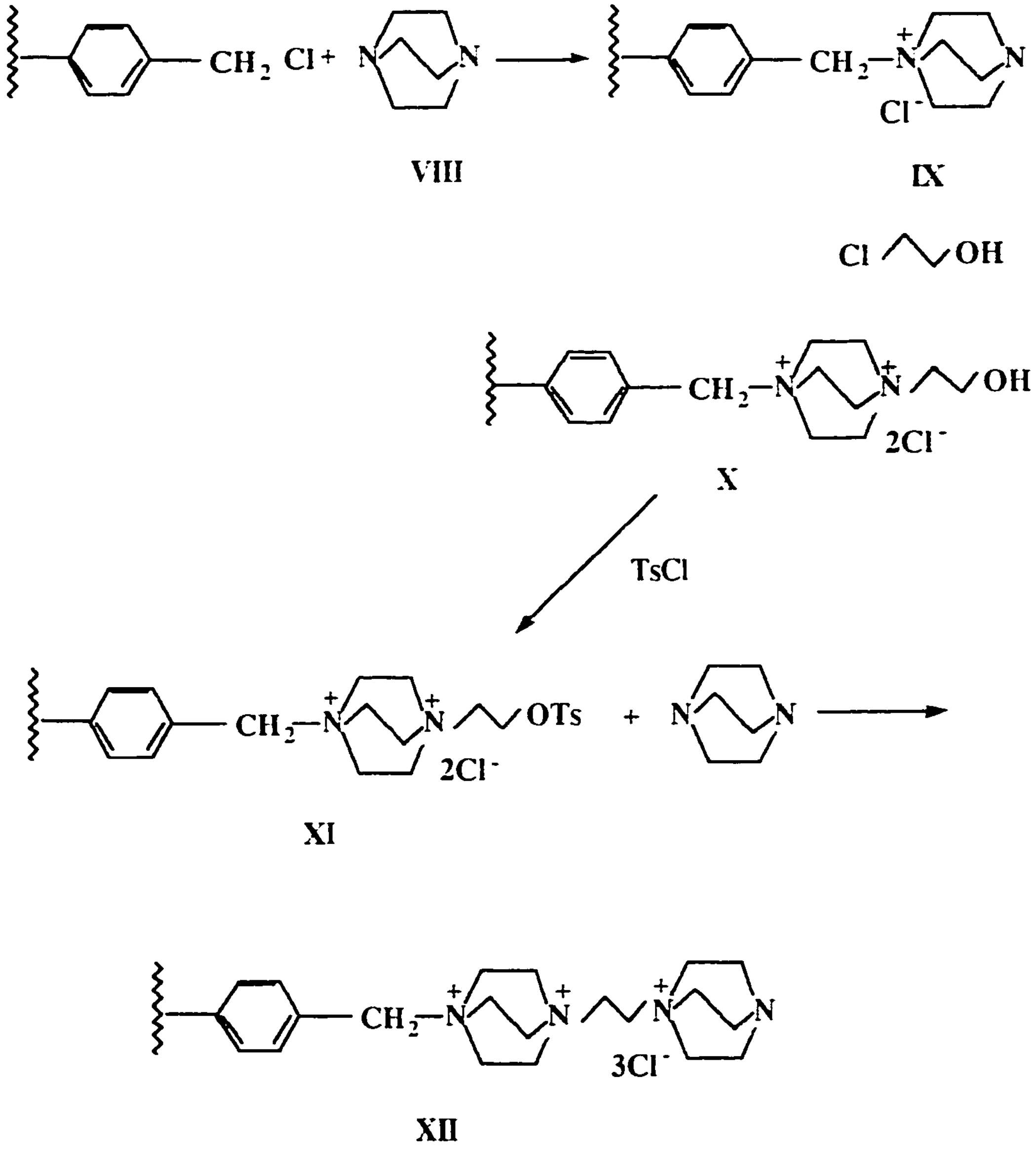
SCHEME 1



40 Cl

FIGURE 10

Using DABCO as the tertiary amine, the dendrimer was synthesized by a three-step iterative procedure involving first reaction with 2-chloroethanol in acetonitrile, followed by a tosylation reaction in pyridine, and then reaction with excess DABCO. The process was repeated twice, and is illustrated in scheme 2.

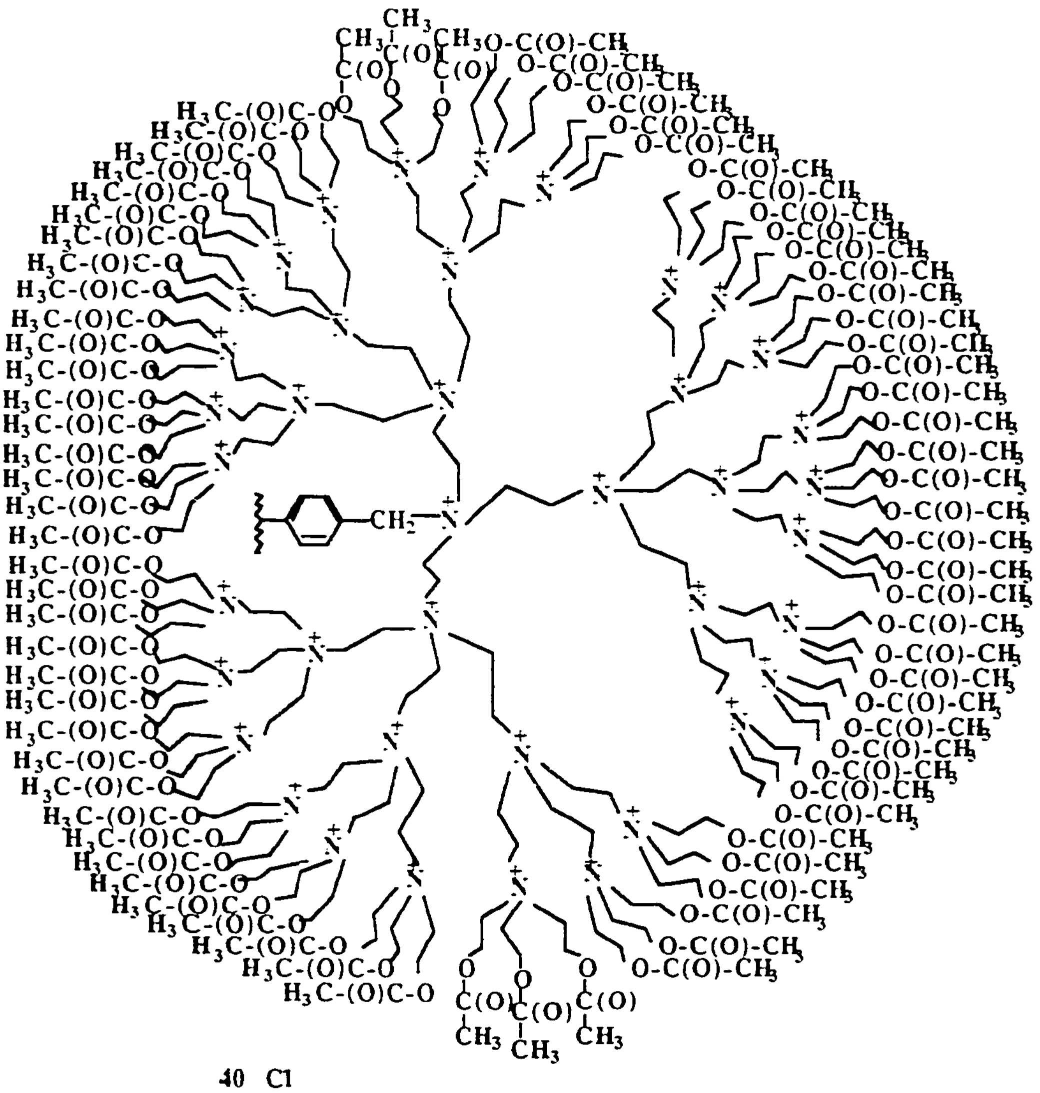


SCHEME 2

Both above mentioned resins had the potential of acting as high capacity anion exchangers due to the presence of multiple positive charges.

This property was tested and indeed both materials exhibited anion exchange properties. The qualitative studies were done by testing for the exchange of different types of ions such as: chloride, bromide, iodide, sulfate. from qualitative studies I concluded that anions originated from strong acids exchange readily. The quantitative studies were mainly done using precipitation techniques. For the case of the triethanol amine system the resin was converted into the sulfate ion form, using a measured excess of sodium sulfate.The excess was then precipitated as barium sulfate, dried and weighed and the exchange capacity of the resin was found to be 14.4 meq/g. For the DABCO system the exchange capacity was determined using spectrophotometric techniques. The resin was converted into the phenylacetate form, which was then displaced by chloride; the amount displaced was determined by its UV absorbance. Using Beer's law the exchange capacity of this particular system was determined to be 11.25 meq/g. Such high exchange capacities were unprecedented.

After initial studies were done to determine the exchange capacity of the triethanolamine system, investigations were performed to determine its ability to remove different types of ions from solutions. For this purpose the final product in scheme 1 was treated with acetic anhydride to protect the terminal hydroxyl groups from potential oxidation. The structure of the product obtained from this reaction is shown below.(Figure 11)



40 Cl

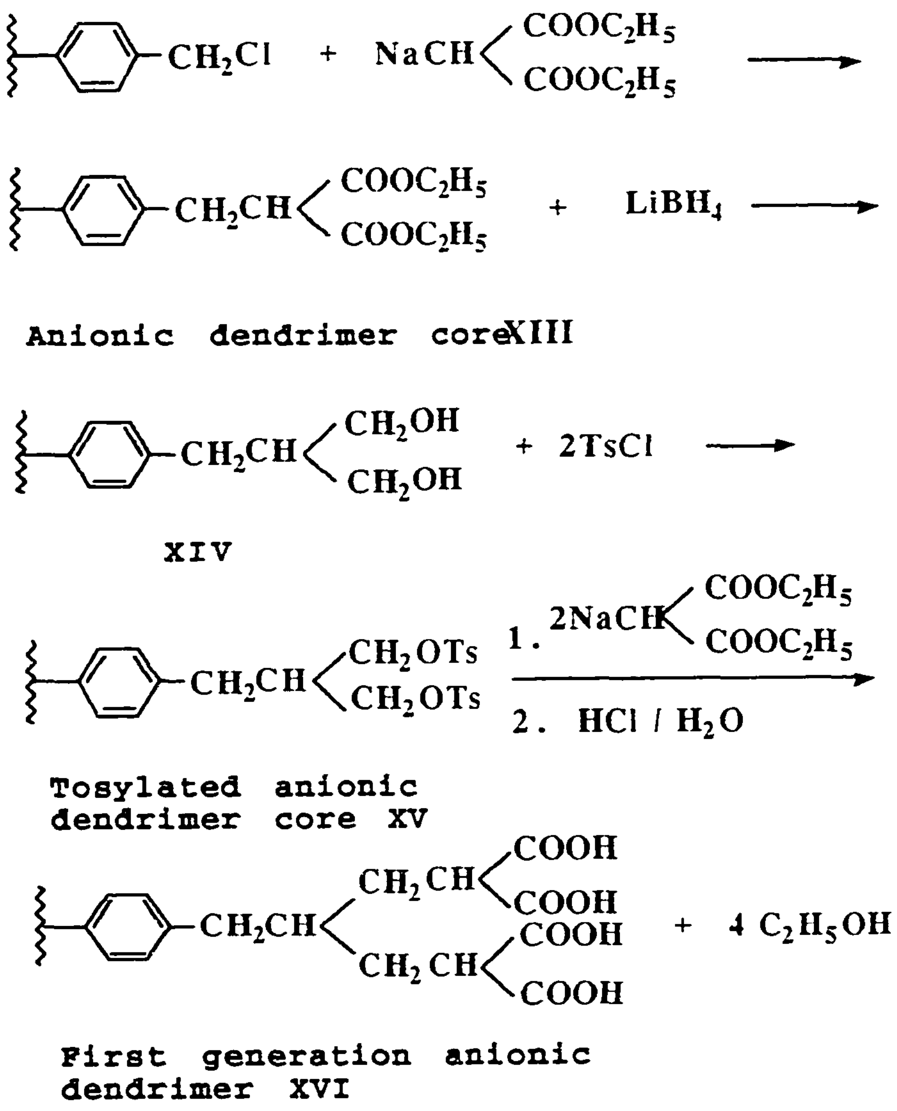
VII

FIGURE 11

The most important study done with this system was the removal of chromate ion from solution. A solution of chromate ion of a known concentration was passed through the resin, it was determined that the resin retained 90% of the chromate present in the original solution. The initial concentration of the chromate ion was varied, using an amount of chromate which equaled 5%, 12% and 25% of the total exchange capacity of the resin. The retention capacity of the resin did not vary significantly with these changes. Finally I attempted to remove the chromate ion from the resin and for all the solutions approximately 30% of the material that was initially retained was then available for further exchange. I made several attempts to remove more than the 30% of the retained chromium. These consisted of stirring the resin in ethanol and washing the resin with a low pH solution anticipating that conversion of chromium ion to chromate would allow it to come off the resin with more ease. The attempts proved futile; the chromate ion initially retained was not further removed in substantial quantities.

The next study performed with this particular system was one in which I varied the size of the ions exchanged. The hypothesis tested was that the larger ions would be attached more strongly to the resin because they would become embedded further in towards the core of the molecule. The ions tested were tosylate anion and chloroacetate anion. The presence of tosylate anion was determined by UV-VIS spectrometry and that of the chloroacetate by the use of NMR. I concluded that the tosylate anion was much more highly retained by the resin than the choloroacetate anion which was easily removed.

The systems described above were all anion exchangers. The cation exchangers synthesized were species which include hydrocarbon arms with carboxylate termini. They were prepared using Merrifield resin as the core and sodium diethyl malonate or sodium tricarboethoxymethane to generate the branching arms. For the system using sodium diethyl malonate the following reactions were repeated: treatment with sodium diethyl malonate, reduction with lithium borohydride and tosylation with tosyl chloride in pyridine. This sequence was repeated four times, as shown in figure 12. Scheme 3



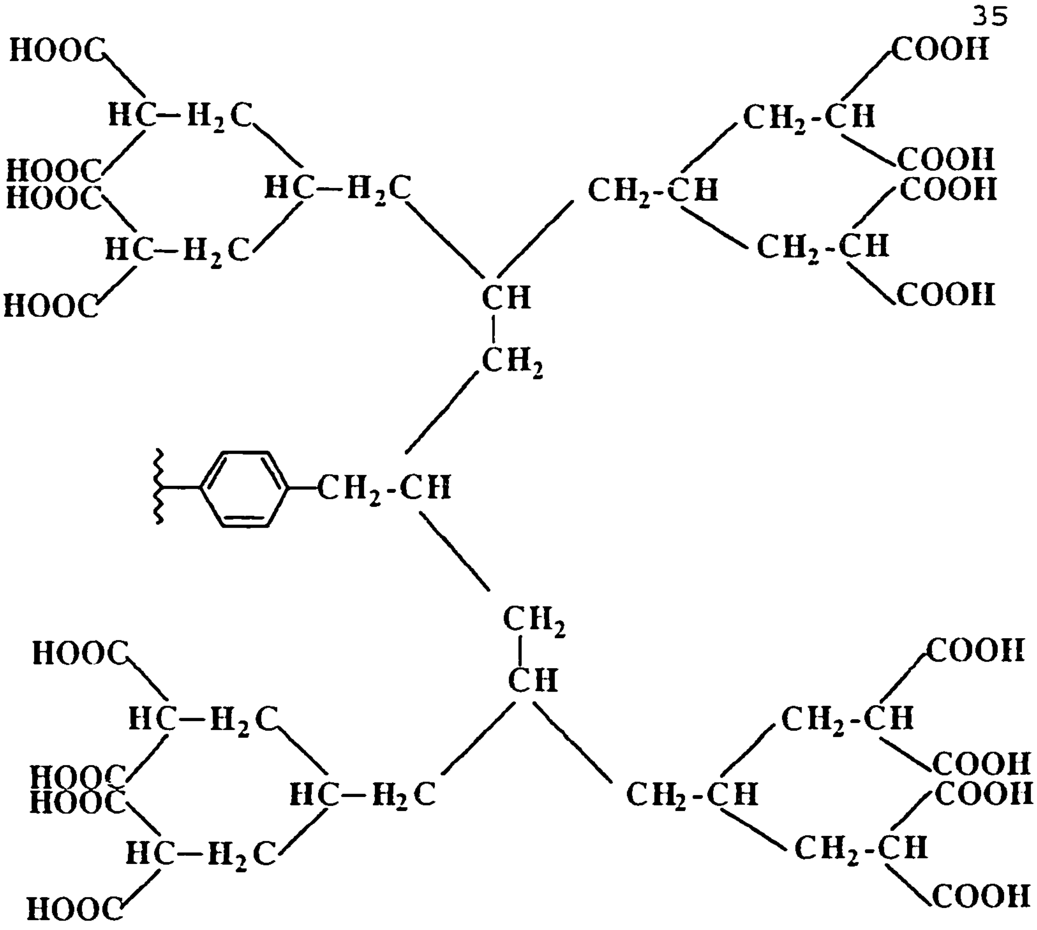
Anionic dendrimer core XIII

XIV

Tosylated anionic dendrimer core XV

First generation anionic dendrimer XVI

SCHEME 3

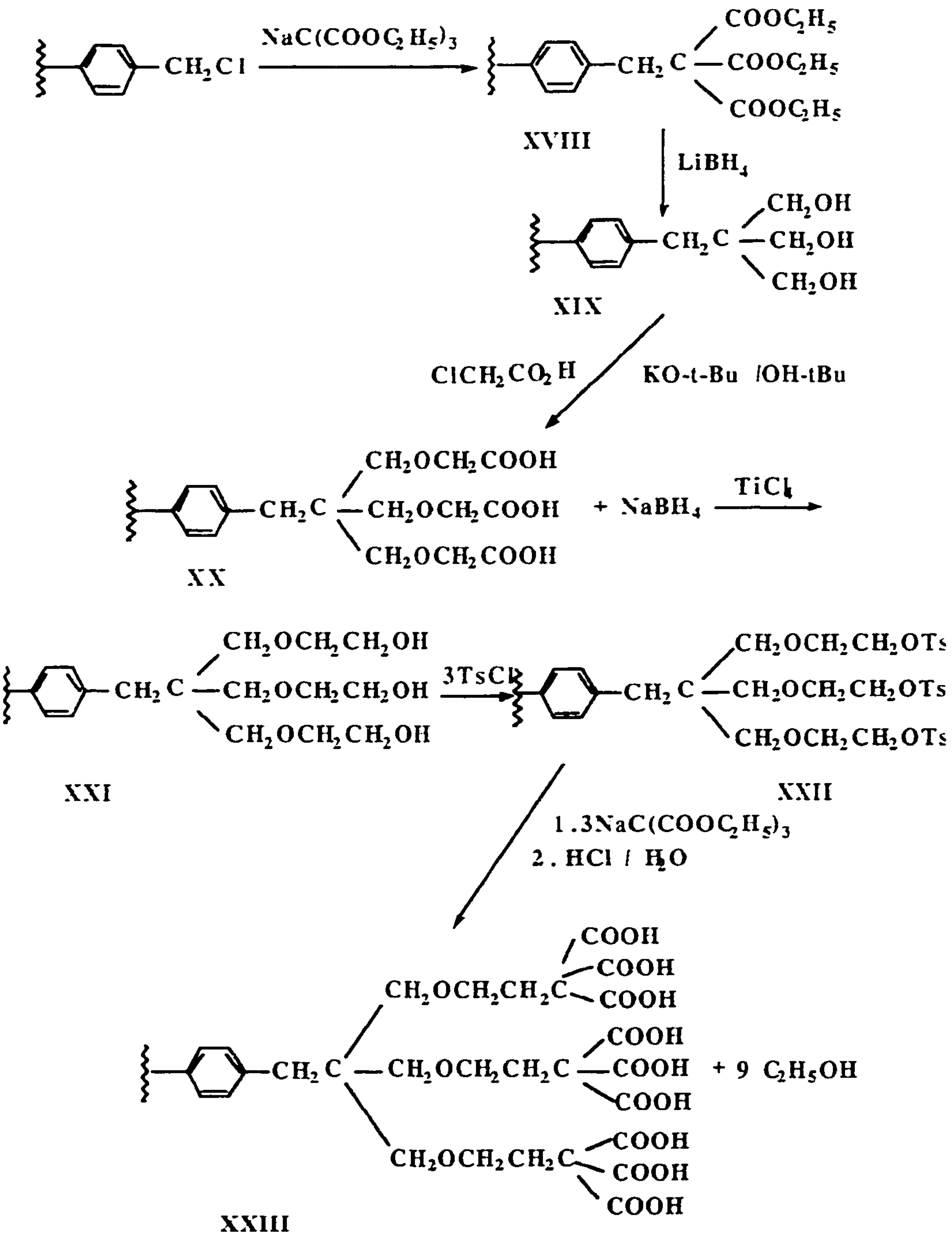


Third generation anionic dendrimer XVII

FIGURE 12

For the system using tricarboethoxymethane, the steps used were the following: treatment with tricarboethoxymethane, reduction with lithium borohydride, extension of the chain with chloroacetic acid, reduction of the carboxylate end with sodium borohydride and titanium tetrachloride and tosylation with tosyl chloride in pyridine. This process was also repeated four times.

Scheme 4



SCHEME 4

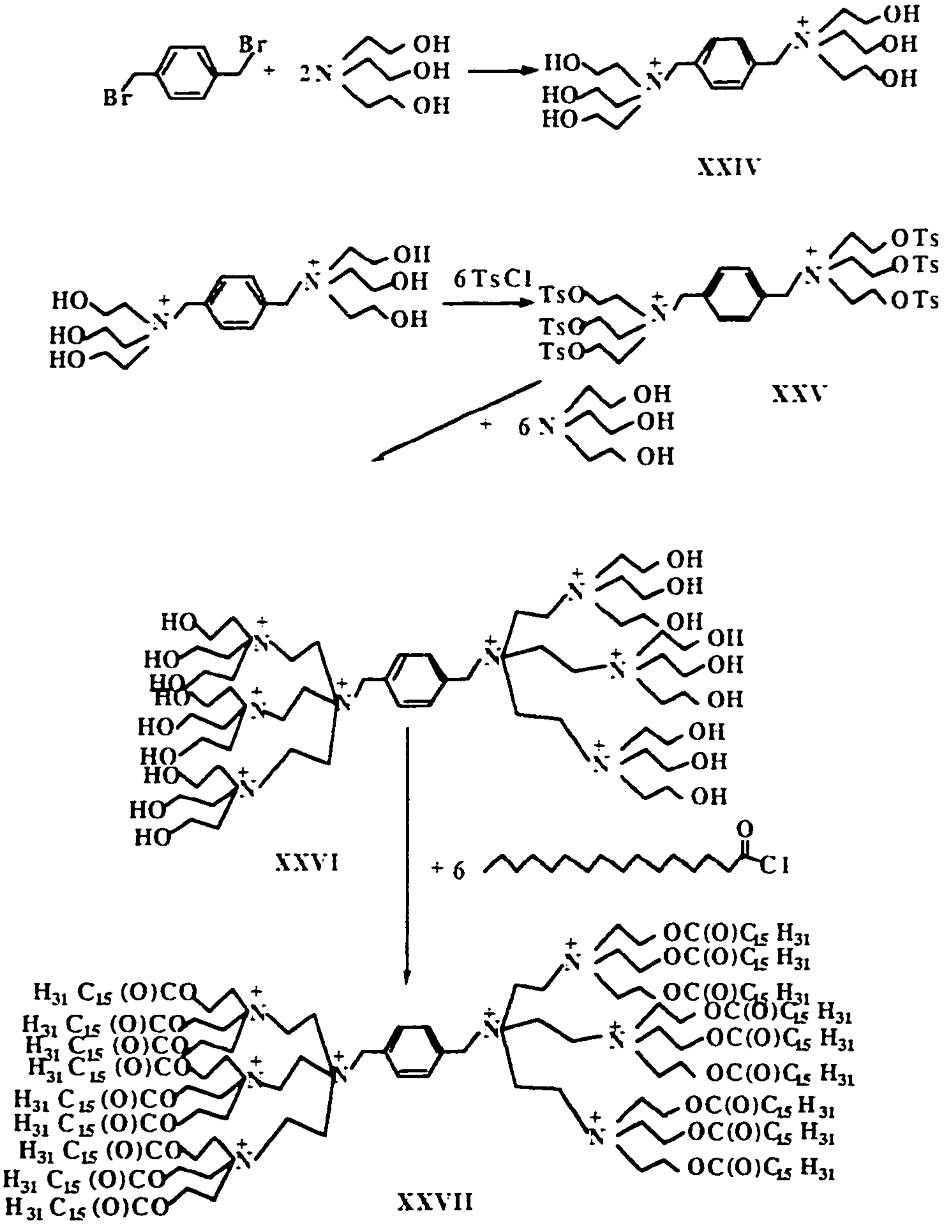
Both systems were tested qualitatively for ion exchange capability and tested positive for the exchange of silver. For quantitative studies, the tricarboethoxymethane system was studied be the removal of lead from aqueous solutions. The problems encountered at this stage involved the quantitation method for the lead ion. Attempts to precipitate the lead as its sulfate resulted in a precipitate which was impossible to separate and weigh. The second method tried was an EDTA titration of lead, but problems were encountered with pH regulation needed for titration. The method of choice was a spectrophotometric one which consisted of extraction of lead into solutions of dithizone in carbon tetrachloride [66]. The amount of lead that the resin retained was equal to 40% of the initial amount of lead present in solution. As with the other systems described earlier the removal of lead from the resin was problematic. Even after several washings the lead was not exchanged from the resin.

This concluded the part of the project which consisted in the synthesis of insoluble dendrimeric exchange materials.

SOLUBLE IONIC DENDRIMERS

Systems which are water soluble were synthesized and studied. The core in these systems was not a polymeric material but other compounds with one or two dimensional capabilities for branching. The main problems that these systems posed consisted in partial reaction and cleavage of branching arms. This made the final compound a mixture of products which could not be separated because of very similar properties and solubilities of its components.

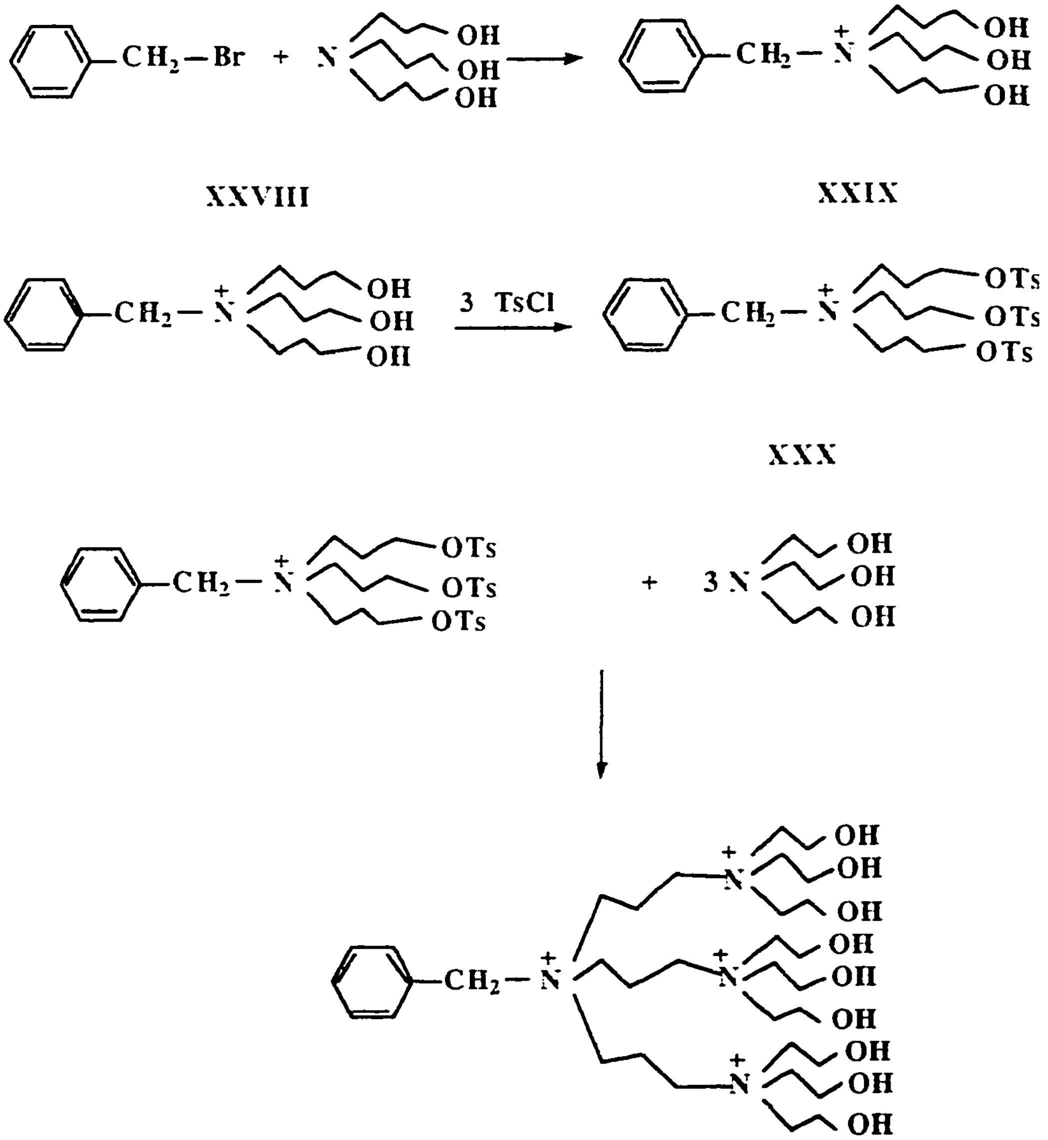
The first soluble dendrimer was constructed according to the following scheme: Scheme 5



SCHEME 5

This particular system was not further pursued because of solubility problems with the final product. It spite of its solubility in chloroform the NMR spectrum was not conclusive even at very high concentration. Development of subsequent generations would be futile since NMR identification was not possible.

The next soluble dendrimer constructed was based on the following core and sequence of reactions:Scheme 6



XXVIII

XXIX

XXX

XXXI

SCHEME 6

The dendrimer described in Scheme 6 also exhibited reactivity problems. Total reaction at all the functional ends was never achieved and cleavage of branching arms occurred. It was decided to investigate these problems and to try to improve reactivity of the system. To ensure total reaction at all the sites, a large excess of reactants was used. To solve the cleavage problem molecular modeling studies were performed which suggested that the molecules would be quite sensitive toward decomposition because of the proximity of the positive charges (two atoms apart). With this in mind increasing the distance between the positive charges was considered. This would involve introduction of a chain extension before the introduction of the next branching unit. Solution of both problems at the same time was attempted since they are closely related. The reactions were performed in the presence of a large excess of reactant and the procedure for introduction of the chain extension was modified but again it was unsuccessful; the products of reactions were still mixtures of partially reacted and partially cleaved compounds. The project was abandoned at this point.

CHIRAL IONIC DENDRIMERS

Next in this project I have turned to an investigation of the synthesis and characteristics of chiral ionic dendrimers. In an effort to generate chiral ionic dendrimers, cationic quaternary ammonium sites were incorporated as components of the extension units using

1,4-diazobicyclo[2.2.2]octane which is quaternized at both nitrogen centers. Stereogenic branch points were provided through use of derivatives of (S)-1,2,4-butanetriol, the hydroxyl of the 1- and 2- positions serving as reactive sites for elaboration of new branches. Mono directional focus sites have been used.

Two different focus sites have been used for the synthesis of the chiral ionic dendrimers: the monomethylated focus site (S)-2,2-dimethyl-4-(2′-{1′′-azonia-4′′-methylazoniabicyclo[2.2.2]octyl}ethyl)-1,3-dioxolane dichloride and a monobenzylated focus site benzyl[1-azonia-4-{(S)-3′,4′-dihydroxybutyl-1′}azoniabicyclo[2.2.2]octane bromide chloride. The structures of these are shown below.

Branching sites for the chiral ionic dendrimers were provided through the use of the readily available (S)-1,2,4 butanetriol. Initial protection of the vicinal diol portion of the triol by acetonide formation followed by substitution of the remaining hydroxyl group by chloride using known procedures,[67,68] after purification, yielded the desired intermediate reagent (S)-2,2-dimethyl-4-(2′-chloroethyl)-1,3-dioxolane. Reaction of this intermediate with DABCO produced (S)-2,2-dimethyl-4-(2′-{1′′-azonia-4′′azabicyclo[2.2.2]octyl}ethyl)-1,3-dioxolane chloride. This material, which served as the fundamental building block for the chiral ionic dendrimers, was slowly formed as a gummy solid deposited on the flask walls from the ethyl acetate reaction solvent. The material, containing the stereogenic site which would serve as the branch point for dendrimer elaboration, could be harvested before completion of the reaction by decanting the reaction solution and washing the residual deposit with diethyl ether to remove any retained reactants. All stereogenic sites incorporated in the chiral ionic dendrimers were derived in the manner described above.

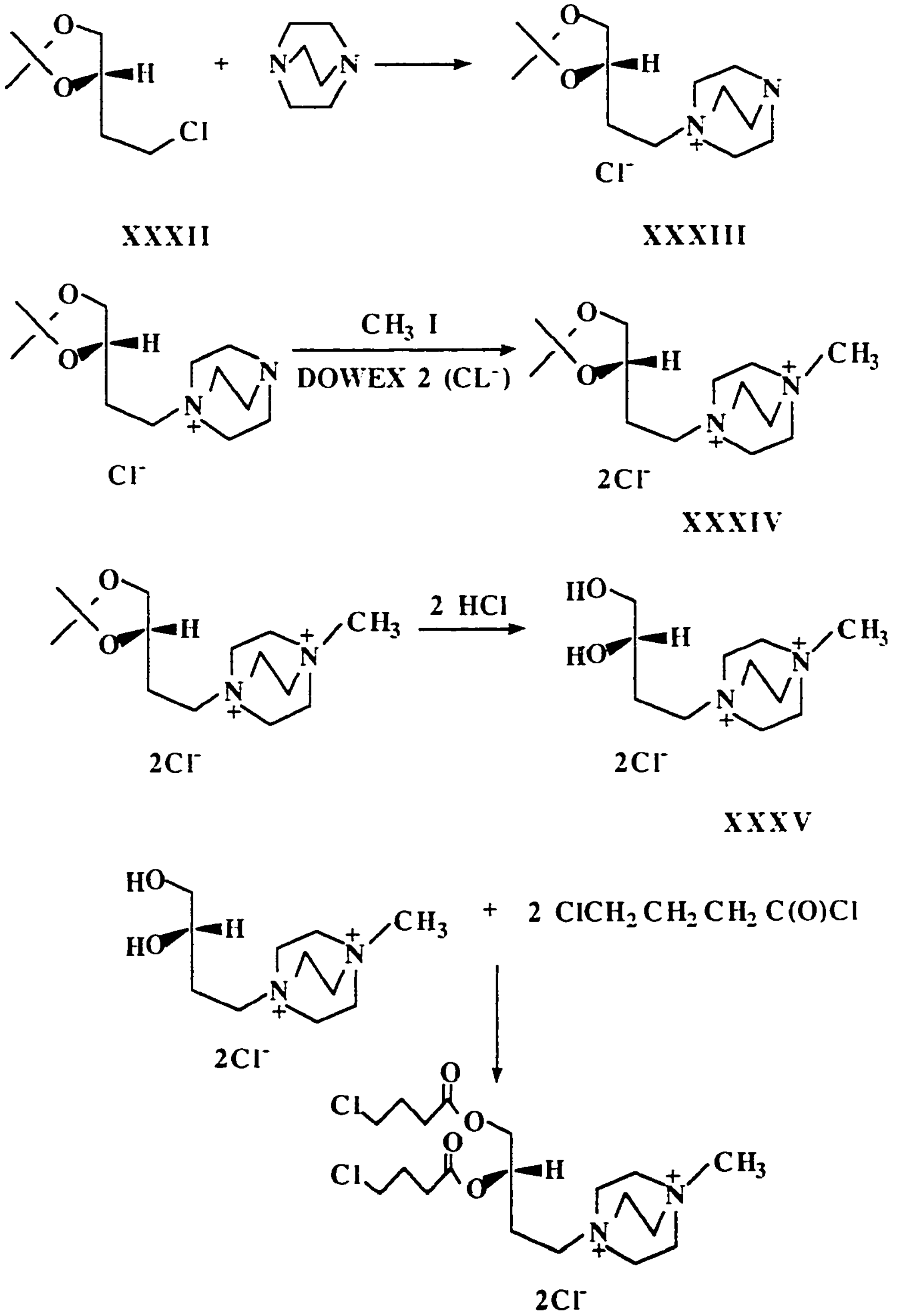
Two significant difficulties are associated with direct introduction of successive branching units without an intervening extension unit. First, all of the core units would first require removal of the acetonide protecting group and conversion of the resultant alcohol functionalities to haloalkyl functionalities to accomplish direct attachment of new building block units. This overall procedure involves two bond breaking processes at the stereogenic carbon site with the attendant possibility of incomplete retention or inversion of configuration in each step. An approach which avoids any bond braking at the stereogenic site is thereby preferable. Second, direct attachment of building block units through tertiary amine quaternization results in the generation of vicinal diammonium structures, which are extremely susceptible to cleavage.[69]

With these difficulties in mind, extension units were devised which would provide sites for attachment of additional building units without breaking bonds at the stereogenic carbon sites. After hydrolytic removal of the acetonide linkage of a focus site unit, the resultant vicinal diol is acylated with an ω-halocarboxylic acid chloride. This avoids breaking any bonds at the stereogenic site and provides both a reasonably inert linkage for continued elaboration and reactive sites for alkylation of tertiary amine units which are relatively distant from each other. The reagent of choice for extension unit introduction was 4-chlorobutanoyl chloride. Longer alkyl chain chlorides would unnecessarily lengthen the distance between cationic sites, while shorter alkyl-chain systems would result in products which are exceedingly reactive by extraneous routes.

The terminal functionality varies with the stage of elaboration for all of the species generated. However, the target materials of elaboration about each of the focus site units have hydroxyl groups as termini. While all of the materials synthesized herein exhibit significant solubility in water, not unexpectedly, those with hydroxyl termini are most soluble, even with extensive elaboration and attendant high molecular mass.

For the elaboration process the fundamental building block mentioned before was converted to each of the previously noted focus sites by reaction with the appropriate organic halide (iodomethane or benzyl chloride). Owing to difficulties associated with mixed iodide salts the initial focus site involving methyl iodide was subjected to ion exchange using DOWEX 2 to generate the species with only chloride as the counterion.

The elaboration of dendrimers, particularly those wherein ionic sites are present within the covalent lattice with free-floating counterions, has particular requirements for the types and conditions of reactions employed. All reaction conditions must be relatively mild such that side reactions are virtually non-existent; any small amount of cleavage of previously generated framework bonds is greatly magnified by the production of dendrimer fragments and the fact that these impurities can be removed only with the greatest difficulty. For example, after the focus units were generated, and after the incorporation of higher generations of branching units, removal of the acetonide protecting groups was accomplished either by treatment with dilute hydrochloric acid, or with a standard cation exchange resin in the H^+ form. Under these mild conditions no observable cleavage of ester linkages or any other bond occurred. As noted previously, the use of shorter extension units produced intermediate species which underwent degradation even under the mildest of conditions. Consequently, the vicinal diols were acylated using an excess of 4-chlorobutanoyl chloride, followed by continued dendrimer elaboration through reaction with the fundamental building block. These successive processes were repeated for the introduction of further generations, ending with acetonide hydrolysis to yield the hydroxy-terminal form of the dendrimer. The process of dendrimer elaboration is illustrated in the following schemes.

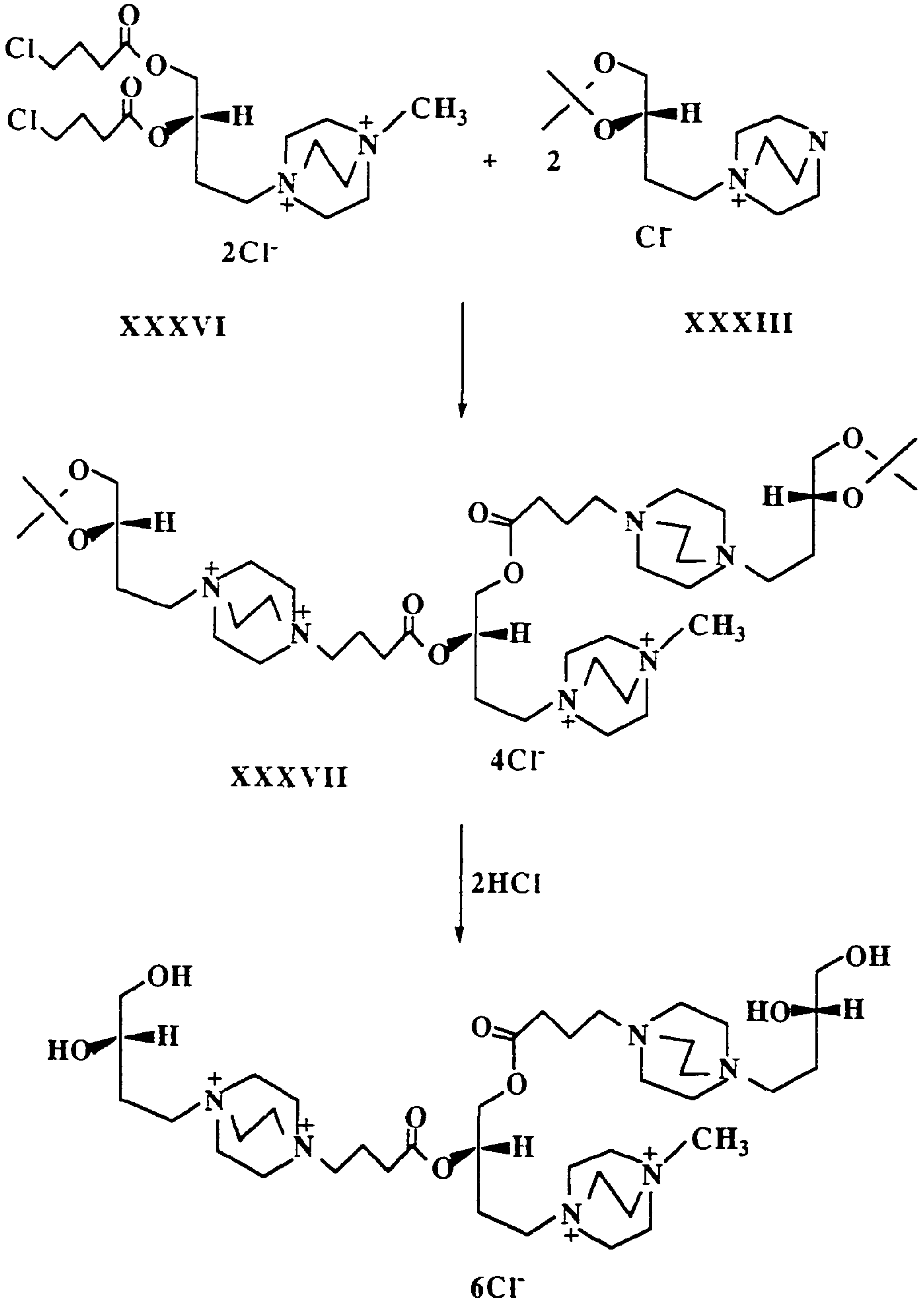

XXXII

XXXIII

XXXIV

XXXV

XXXVI

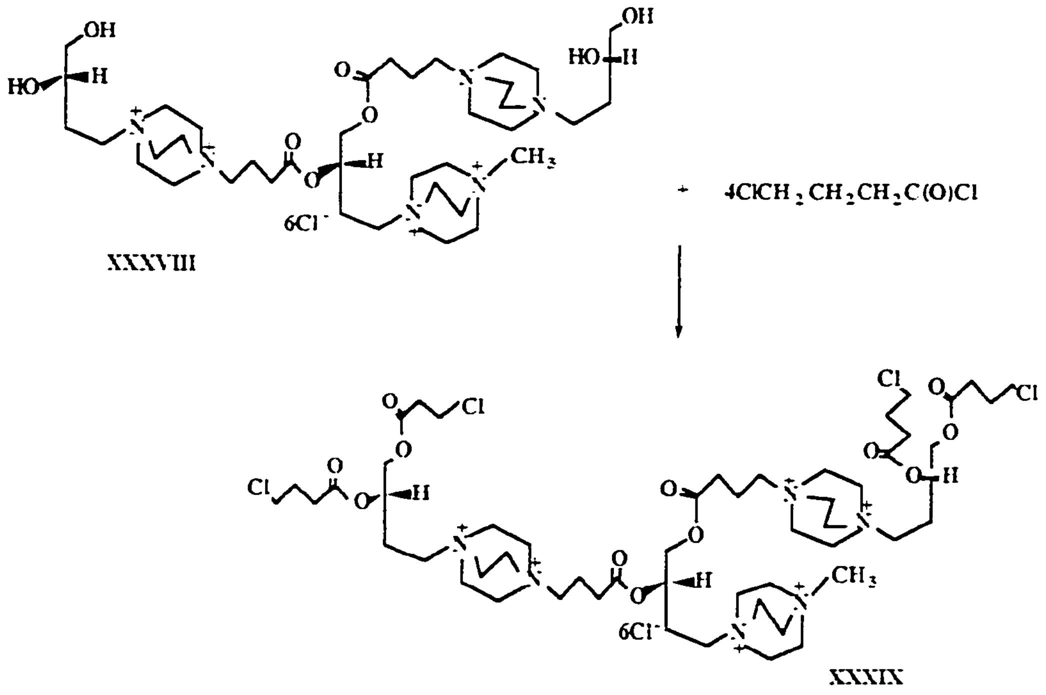


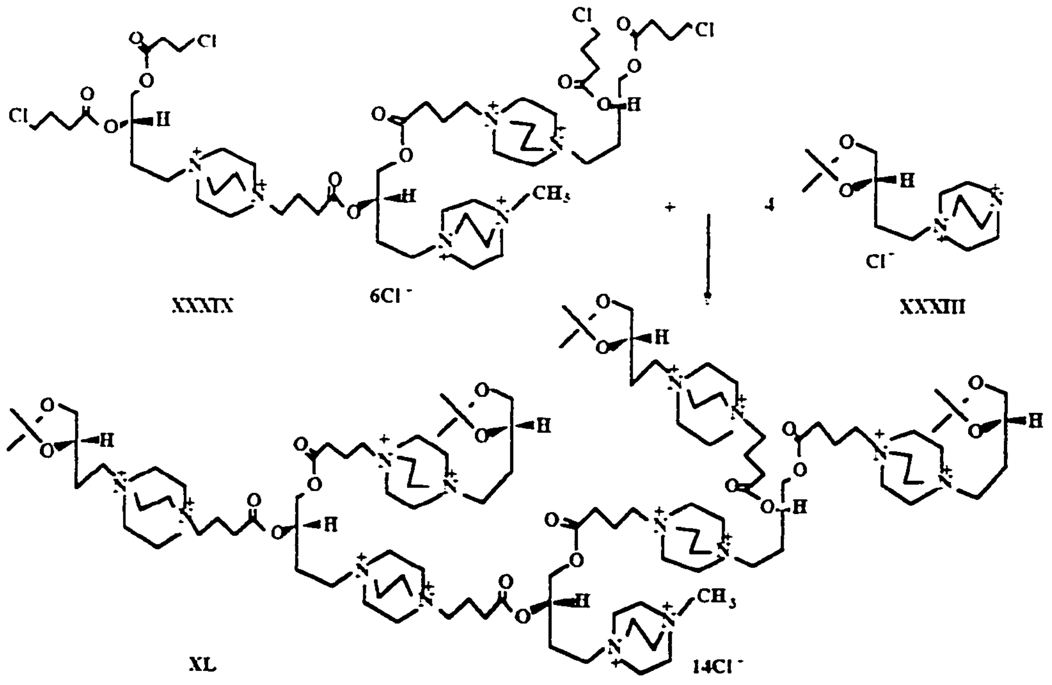
XXXVI

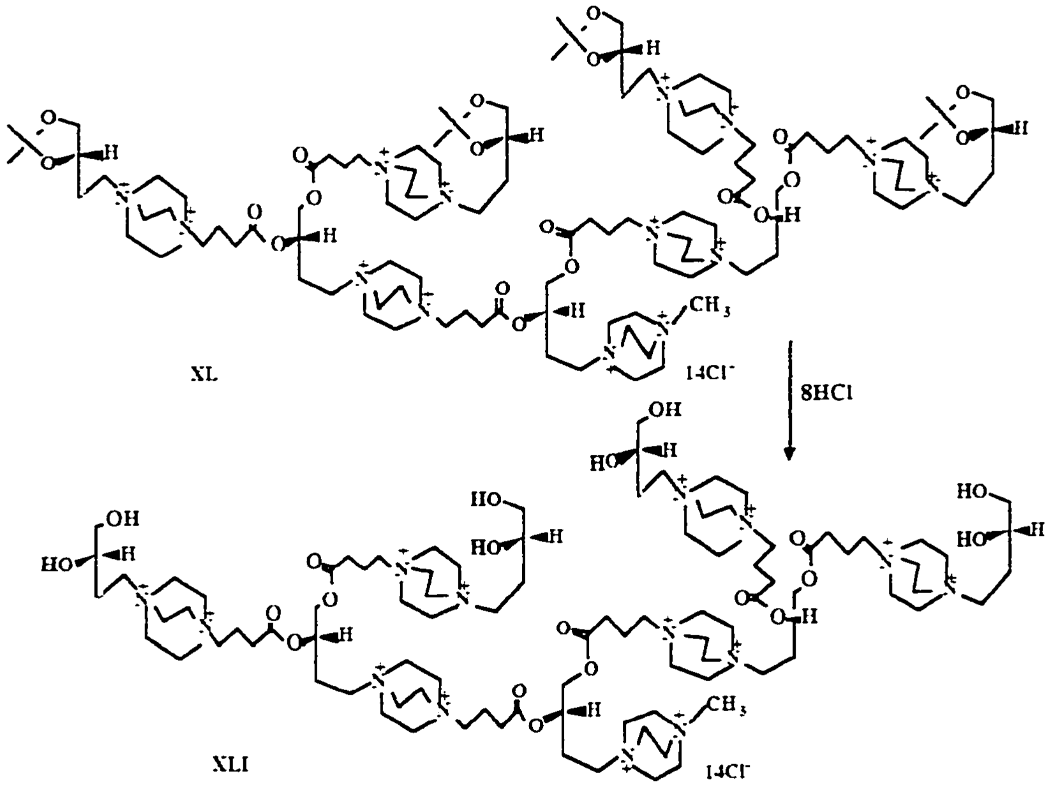
XXXIII

XXXVII

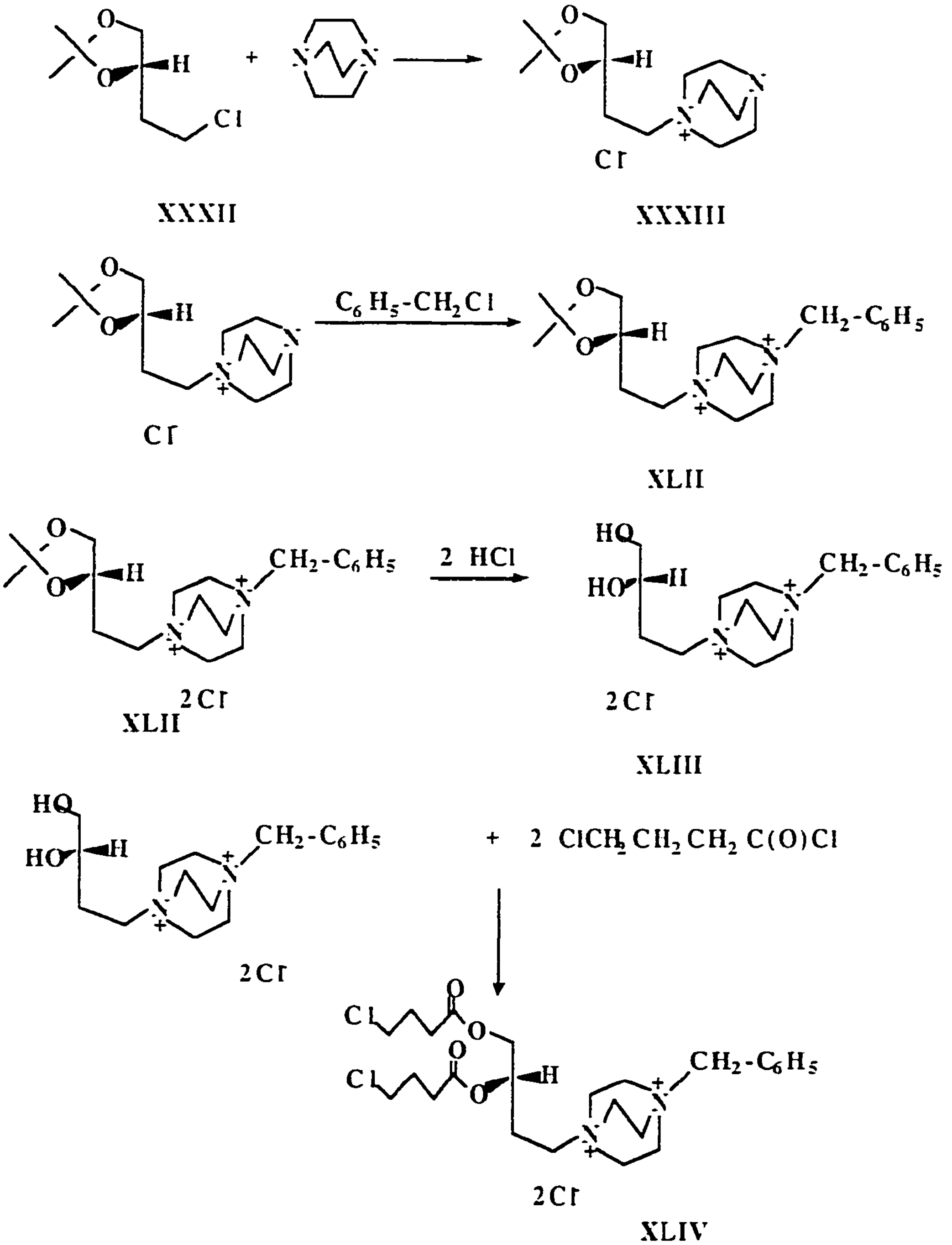
XXXVIII


XXXVIII
6Cl⁻
+ 4ClCH₂CH₂CH₂C(O)Cl
6Cl⁻
XXXIX


XXXIX
6Cl⁻
+ 4
Cl⁻
XXXIII
XL
14Cl⁻



SCHEME 7



XXXII

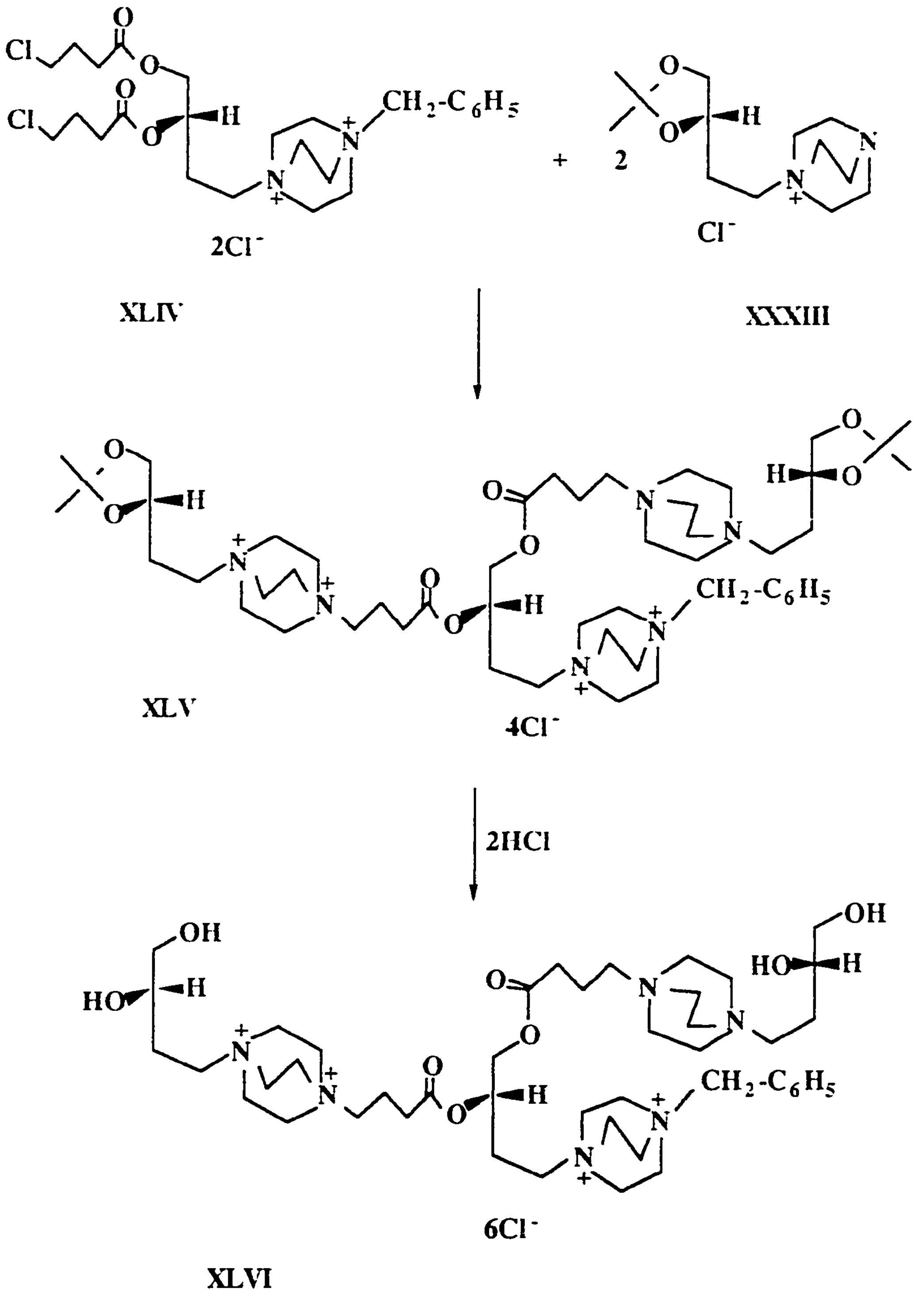
XXXIII

XLII

XLII

XLIII

XLIV

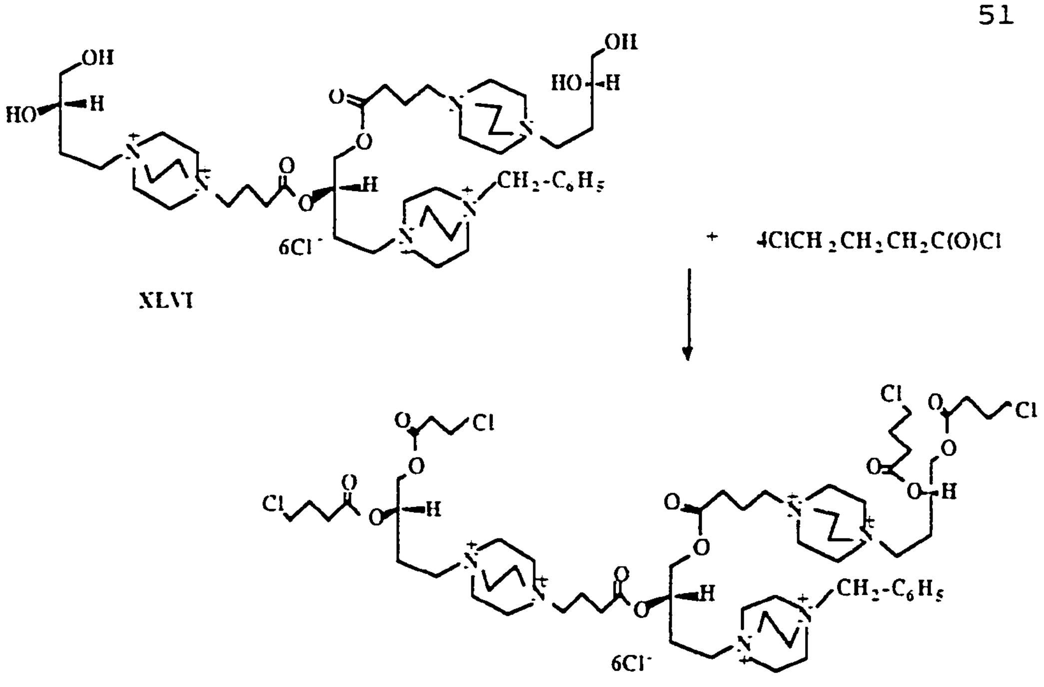


XLIV

XXXIII

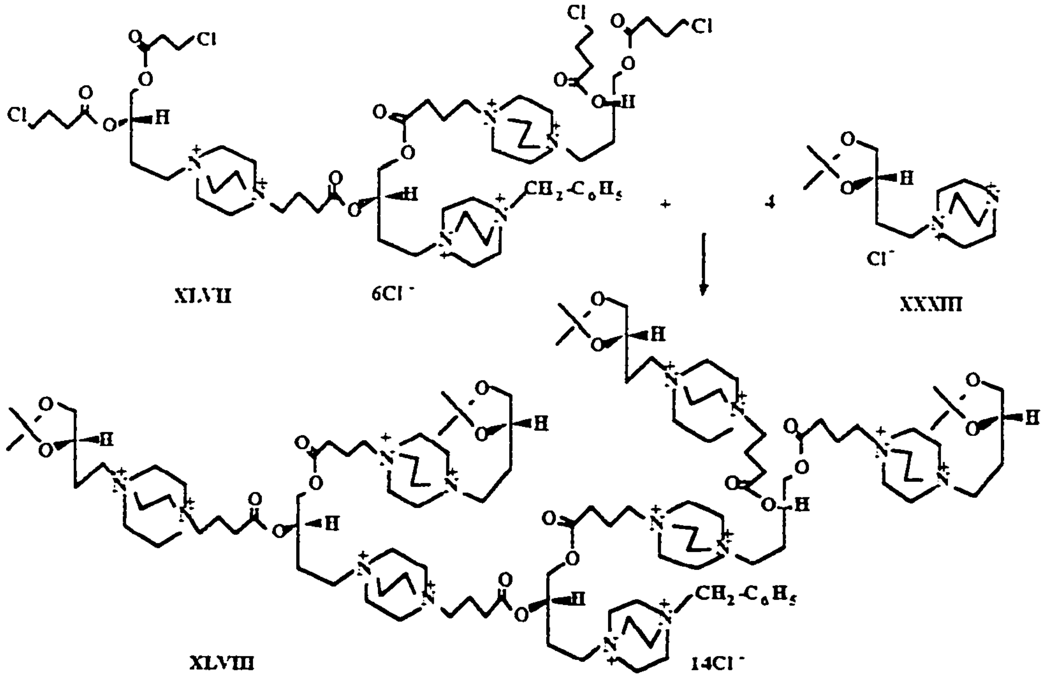
XLV

XLVI



XLVI

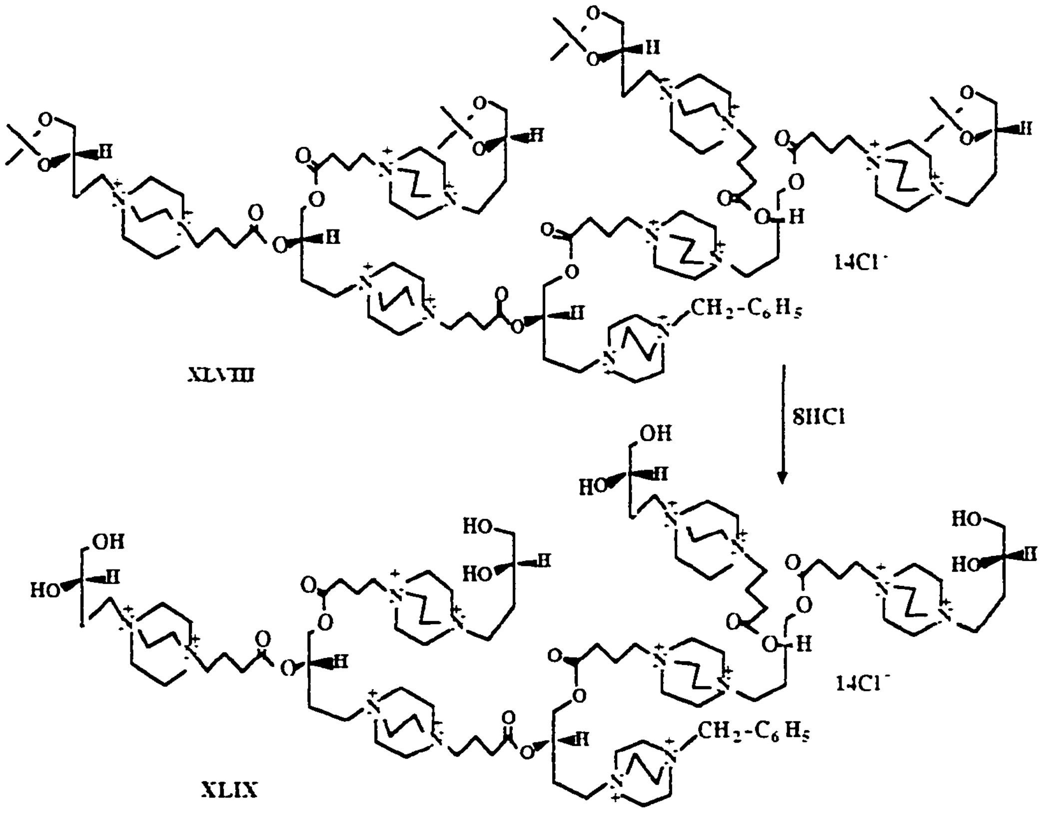
XLVII



XLVII

XXXIII

XLVIII



SCHEME 8

In certain instances not all of the hydrogen chloride generated in the reaction of hydroxyl groups with 4-chlorobutanoyl chloride could be removed efficiently under high vacuum. In such instances, as the presence of the acid could inhibit quaternization of the tertiary amine site of the fundamental building block (elaboration unit), removal of remaining acid by treatment of an aqueous solution of the dendrimer intermediate with potassium carbonate was necessary prior to continued dendrimer elaboration.

Caution must be also taken to ensure complete reaction in a specific manner of all of the terminal sites of intermediate species in dendrimer elaboration. This is accomplished through the use of significant excess of modifying reagent compared to the dendrimer upon which the operation is performed, keeping in mind the requirement for the complete removal of excess reagent. With the elaboration of ionic dendrimers as being performed here, much use is made of differential solubilities for this purpose.

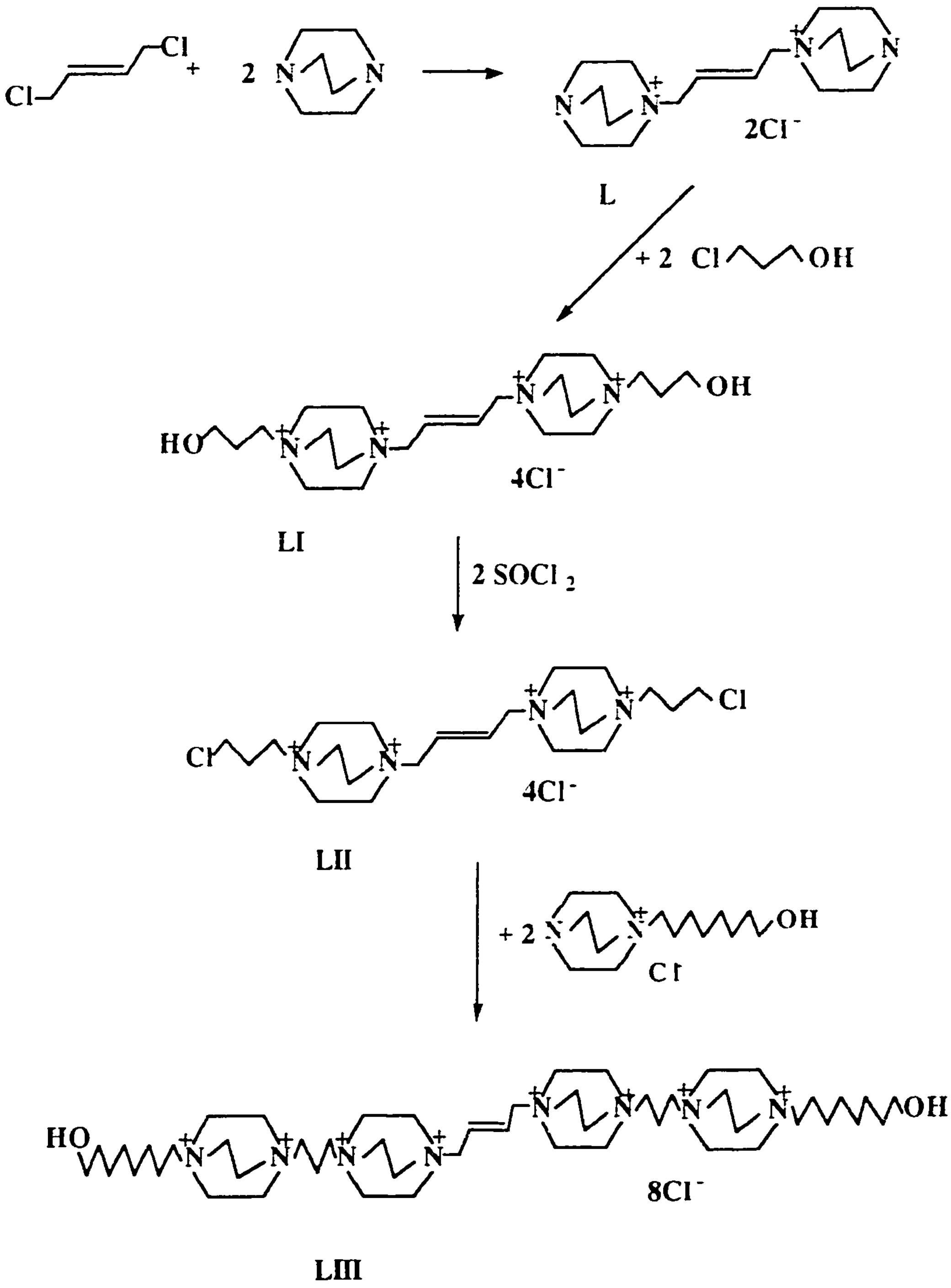
For example, the solubility of the building block compared to other reagents and dendrimer intermediates is a critical factor. The solubility of the building block in ethylacetate is quite low, being deposited on the flask walls from ethylacetate solution as it is formed. The above mentioned material, however, is readily soluble in acetonitrile, a solvent in which more highly charged dendrimer construction intermediates exhibit only limited solubility at elevated temperatures. With these characteristics excess building block is readily removed form elaboration reactions. Similarly, excess of 4-chlorobutanoyl chloride is removed by washing with ethyl acetate and diethyl ether, solvents in which the charged dendrimer species are completely insoluble.

It might have been expected that optical rotation would have increased progressively with elaboration and introduction of additional stereogenic centers. However the observed optical rotation using a standard sodium vapor lamp remained low, and actually decreased as elaboration progressed. Moreover, the species synthesized were inactive in CD measurements, even with UV absorbing chromophores present. Both of these observations are in accord with the observations on uncharged dendrimers as discussed by Seebach;[70] the introduction of new stereogenic centers is "diluted" by the simultaneous addition of mass to the species and, at least at the level of elaboration performed, no conformational chirality is present. Elaboration of the benzyl core chiral dendrimer from its first generation to the second generation as shown by structures XLVII, XLVIII, XLIX was not performed experimentally because of reactivity problems and irrelevant NMR spectra.

Last efforts in this project were directed toward the synthesis and investigation of polycationic dendrimers (branching) and structurally related non-branching species. Polycationic "strings" (non-branching compounds in which the cationic sites are located at regular intervals along a linear chain of defined length) have been found to exhibit significant antibacterial activity, and represent an intriguing structural category for other applications.

It was with a view towards such applications that a particular string was synthesized which bore possibilities for interaction with double-stranded DNA. It is well known that particular cationic metal complexes, such as Ruthenium in an octahedral coordination sphere with three bidentate diimine type ligands bind to double stranded DNA stereoselectively. Preliminary molecular modeling of double stranded DNA associated with polycationic strings based on quaternized DABCO indicate that such strings could be expected to bind easily in the major groove of the B-form helix. In this light the synthesis of polycationic strings was undertaken. In fact, the resultant string do bind to DNA as evidenced by their quite significant effects on the circular dichroism spectra of DNA.

The polycationic strings have been constructed based upon the diamine reagent 1,4-diazobicyclo[2.2.2]octane (DABCO). Sequential quaternization of the two tertiary amine sites of DABCO can be accomplished through judicious choice of the reaction solvent, leading to the controlled assembly of polyquarternaryammonium species wherein the dicationic DABCO species are separated by selected distances. Synthesis was begun by reaction of an α,ω-bis azonia compound which could be further alkylated at each end. Alkylation of the remaining tertiary amine sites could be accomplished with a monofunctional haloalkane, which would terminate chain lengthening, with an ω-halo-alcohol,which would allow sequential incorporation of additional cationic sites, or with an α,ω-dihaloalkane in an oligomerization reaction. The synthetic approach for the preparation of this structurally defined centrosymmetric series of polycations of (4n+2) cationic sites is summarized in the following scheme.


Cl
Cl
+
2
N
N
N
N
N
N
2Cl⁻
L
+ 2 Cl OH
HO
N
N
N
N
OH
4Cl⁻
LI
2 SOCl₂
Cl
N
N
N
N
Cl
4Cl⁻
LII
+ 2
N
N
OH
Cl⁻
HO
N
N
N
N
N
N
N
N
OH
8Cl⁻
LIII

SCHEME 9

SUMMARY

This project accomplished the synthesis of insoluble cationic dendrimers and investigation of their applications, exchange properties and capabilities. The cationic sites were located at the branch points. Anionic dendrimers with the anionic sites on the dendrimeric surface were also synthesized and their properties were analyzed.

Different types of chiral ionic dendrimers with cationic sites incorporated as components of the extension units and chiral sites at the branch points were as well synthesized and elaborated to the second generation.

Finally cationic strings with certain biological activity were synthesized.

SUGGESTED RESEARCH

The first priority for future research would be analysis of the different properties of the chiral ionic dendrimers and their ability to perform chiral separations. For this purpose simple ions such as tartrate ions should be used. The effect of steric hindrance on further elaboration of generations should also be studied.

Different cationic strings with different size and type of linkers between the positive charges should also be synthesized and their antibacterial activity should be studied. Also the correlation between the proximity of the positive charges and the antibacterial strength should be investigated.

EXPERIMENTAL SECTION

REAGENTS AND INSTRUMENTATION

All chemicals used in syntheses, purification and comparison analyses were of commercial reagent quality and were used without purification. NMR spectra were measured using either a Varian EM360 (60 MHz) or a Bruker 400 MHz DPX400 instrument. All optical rotations were measured using a Jasco DIP-140 instrument (1 dm cell, aqueous solution with a sodium vapor lamp), and all CD spectra were measured using a Jasco 500C CD/ORD instrument. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

SYNTHESES

Preparation of cationic dendrimer core **(III)**

In a 250 ml. round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser was placed 10 g. of Merrifield Resin and triethanol amine (14.92 g,0.1 mol). To it was added a 200 ml. mixture 1:1 of acetonitrile and methylene chloride. It was left to reflux for 2 hours, then the product was filtered and washed with 50 mL absolute ethanol, 50 mL water and 50 mL absolute ethanol. The product was dried and weighed (11.00g).

Preparation of tosylated cationic dendrimer core **(IV)**

The product **(III)** was placed in a 200 mL round bottom flask adapted with magnetic stirrer and reflux condenser. To it was added p-toluensulfonylchloride (9.53 g, 5 mmol.) and 100 mL of pyridine. It was left to react overnight. Afterwards it was filtered and washed with 50 mL cold water and 50 mL cold absolute ethanol. It was dried under vacuum and weighed (12.78 g).

Preparation of first generation cationic dendrimer **(V)**

The product **(IV)** was placed in a 250 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser. To it was added triethanol amine (18.65 g,0,125 mol.) and 200 mL mixture of 1:1 acetonitrile and methylene chloride. It was left to reflux for 4 hours. Afterwards it was filtered and washed with 50 mL absolute ethanol, 50 mL water and 50 mL absolute ethanol. It was dried under vacuum and weighed (11,04 g.)

Preparation of tosylated first generation cationic dendrimer

The entire product **(V)** was placed in a 200 mL round bottom flask adapted with magnetic stirrer and reflux condenser. To it was added p-toluensulfonylchloride (11.91 g) and 100 mL of pyridine. It was left to reflux and stir over night. Afterwards it was filtered and washed with 50 mL cold absolute ethanol and 50 mL cold water. It was dried under vacuum and weighed(11.08 g)

Preparation of second generation cationic dendrimer

The entire amount of tosylated first generation dendrimer was placed in a 200 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser. To it was added triethanol amine (23.31 g,0,156 mol.) and 200 mL mixture 1:1 of acetonitrile and methylene chloride. It was left to reflux for 5 hours. Afterwards it was filtered and washed with 50 mL absolute ethanol, 50 mL water and 50 mL absolute ethanol.The product was dried and weighed (11.28 g).

Preparation of tosylated second generation cationic dendrimer

The second generation dendrimer was placed in a 200 mL round bottom flask adapted with magnetic stirrer and reflux condenser. To it was added p-toluensulfonylchloride (14.88 g, 0,078 moles) and 100 mL of pyridine. It was left to react over night. It was filtered and washed with 50 mL cold absolute ethanol and 50 mL cold water. It was dried under vacuum and weighed (11.67 g).

Preparation of third generation cationic dendrimer **(VI)**

The tosylated second generation dendrimer was placed in a 200 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser. To it was added triethanol amine (29.13 g,0.195 mol) and 200 mL mixture 1:1 of acetonitrile and methylene chloride. It was left to reflux for 4 hours. It was filtered and washed with 50 mL absolute ethanol and 50 mL water. It was dried under vacuum and weighed (10.45 g).

Preparation of **(IX)**

In a 200 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser was put 10 g of Merrifield Resin and DABCO (11.33 g, 0.1 mol). To it was added a 200 mL mixture 1:1 of acetonitrile and methylene chloride. It was left to reflux over night. In the morning the reaction was stopped and the product was washed with 100 mL of absolute ethanol, 100 mL of water and 100 mL of absolute ethanol. The product was then left to dry under air and was weighed. (12.06 g).

Preparation of **(X)**

In a 200 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser was put the product **(IX)** and 2-chloroethanol (11.84 g, 0.147 mol). To it was added a 200 mL mixture 1:1 of methylene chloride and chloroform. The reaction was left to reflux over night. In the morning the reaction was stopped and the product was filtered through the sintered glass funnel and it was washed with 100 mL of water and 100 mL absolute ethanol. Then it was left to dry under air and was weighed (11.66 g).

Preparation of **(XI)**

In a 200 mL round bottom flask adapted with magnetic stirrer and reflux condenser was put the product **(X)** and p-toluensulfonylchloride (10.00 g,0.054 mol). To it was added 80 mL pyridine. It was left to stir over night. The reaction was stopped in the morning and the product was filtered through the sintered glass funnel and it was washed with 100 mL ethanol (95%), 100 mL water and 100 mL ethanol. The product was left to dry under air and weighed (12.07 g).

Preparation of **(XII)**

In a 200 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser was put the product **(XI)** and DABCO (14.33 g, 0.128 mol). To it was added 200 mL mixture 1:1 of methylene chloride and acetonitrile. It was left to reflux over night. In the morning the reaction was stopped and the product was washed 100 mL absolute ethanol, 100 mL water and 100 mL ethanol. The product was left to dry under air and weighed (10.35 g).

Preparation of anionic dendrimer core **(XIII)**

In a 100 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser was put 50 mL of toluene and diethyl malonate (2 g,0.01 mol). To it was added sodium hydride (0.2616 g,0.01 mol). It was left to stir for 20 minutes and afterwards 25 mL of dimethylformamide was added to it. It was left again to stir for 20 minutes.

In a separate 250 mL three way round bottom flask adapted with an oil bath, magnetic stirrer, reflux condenser and nitrogen atmosphere and dropping funnel was put 3 g Merrifield Resin and 50 mL of toluene. The sodium diethyl malonate prepared above was added dropwise to the solution. It was left to stir over night. In the morning the reaction was stopped and the product was filtered. Then it was washed with 50 mL absolute ethanol and 100 mL ethyl acetate, dried under vacuum and weighed (3.85 g).

Preparation of **(XIV)** *- reduction of anionic dendrimer core*

The anionic dendrimer core **(XIII)** was placed in a 250 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser. To it was added 100 mL of anhydrous ether and lithium borohydride (0.10 g,0.0045 mol). It was left to stir over night and afterwards saturated ether was added with a dropping funnel. Then it was separated through filtration and it was washed with 50 mL ethyl acetate, 50 mL absolute ethanol, 25 mL water and 50 mL ethyl acetate. It was dried under vacuum and weighed (3.05 g).

Preparation of tosylated anionic dendrimer core **(XV)**

The product **(XIV)** was placed in a 100 mL round bottom flask adapted with magnetic stirrer, oil bath, reflux condenser and nitrogen atmosphere. To it was added p-toluensulfonylchloride (3 g, 0.015 mol) and 50 mL of pyridine. It was left to stir for a day. Then the product was filtered, washed with 50 mL ethyl acetate, 50 mL of absolute ethanol, 50 mL of ethyl acetate and weighed (3.50 g).

Preparation of first generation anionic dendrimer core **(XVI)**

In a 100 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser was put 50 mL of toluene and diethyl malonate (4 g,0.02 mol). To it was added sodium hydride (0.6 g,0.025 mol), which is the equivalent amount. It was left to stir for 20 minutes and afterwards 25 mL of dimethylformamide was added to it. It was left again to stir for 20 minutes.

In another 250 mL round bottom flask adapted with magnetic stirrer, oil bath, reflux condenser, nitrogen atmosphere and dropping funnel was put the tosylated anionic dendrimer core (**XV**). To it was added 50 mL toluene and sodium diethyl malonate prepared above. It was left to stir one day. Then the product was filtered, washed with 75 mL of ethyl acetate, 50 mL of absolute ethanol and 75 mL of ethyl acetate.

Part of the product was placed in a 100 mL round bottom flask adapted with magnetic stirrer, oil bath, reflux condenser and nitrogen atmosphere. To it was added 75 mL of 10% HCl and it was left to stir over night. Then the product was filtered and washed with 75 mL of water and 50 mL of ethanol. It was left to dry under vacuum.

Preparation of second generation anionic dendrimer

The sodium diethyl malonate was prepared as described above.

In a 250 mL round bottom flask adapted with a magnetic stirrer, oil bath, reflux condenser,nitrogen atmosphere was placed the tosylated anionic dendrimer core. To it was added dropwise the sodium diethyl malonate. The reaction was left to stir overnight. Then the product was filtered, washed with 75 mL of ethylacetate, 50 mL of absolute ethanol and 75 mL of ethylacetate. The product was then left to dry under vacuum.

The product was placed in a 250 ml round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser. To it was added 100 mL of anhydrous ether and lithium borohydride (0.20 g, 0.009 mol). It was left to stir over night and afterwards saturated ether was added with a dropping funnel. Then it was separated through filtration and it was washed with 50 mL ethyl acetate, 50 mL absolute ethanol, 25 mL water and 50 mL ethyl acetate. The product obtained was placed in a 100 mL round bottom flask adapted with magnetic stirrer, oil bath, reflux condenser and nitrogen atmosphere. To it was added p-toluensulfonylchloride (6 g,0.031 mol) and 50 mL of pyridine. It was left to stir one day. Then the product was filtered, washed with 50 mL ethyl acetate, 50 mL of absolute ethanol, 50 mL of ethyl acetate and weighed.

Preparation of third generation anionic dendrimer **(XVII)**
The sodium diethyl malonate was prepared as described above.
In a 250 mL round bottom flask adapted with a magnetic stirrer, oil bath, reflux condenser,nitrogen atmosphere was placed the tosylated second generation anionic dendrimer. To it was added dropwise the sodium diethyl malonate. The reaction was left to stir overnight. Then the product was filtered, washed with 75 mL of ethylacetate, 50 mL of absolute ethanol and 75 mL of ethylacetate. The product was then left to dry under vacuum.
The product was placed in a 250 mL round bottom flask adapted with magnetic stirrer, oil bath and reflux condenser. To it was added 100 mL of anhydrous ether and lithium borohydride (0.20 g,0.009 mol). It was left to stir

over night and afterwards ether saturated with water was added with a dropping funnel. Then it was separated through filtration and it was washed with 50 mL ethyl acetate, 50 mL absolute ethanol, 25 mL water and 50 mL ethyl acetate. The product obtained was placed in a 100 mL round bottom flask adapted with magnetic stirrer, oil bath, reflux condenser and nitrogen atmosphere. To it was added p-toluensulfonylchloride (6 g, 0.031 mol) and 50 mL of pyridine. It was left to stir one day. Then the product was filtered, washed with 50 mL ethyl acetate, 50 mL of absolute ethanol, 50 mL of ethyl acetate, dried and weighed.

Preparation of **(XVIII)**

Preparation of the sodium tricarboethoxymethane

In a 250 mL round bottom three way flask, with a reflux condenser and two stoppers, was placed 50 mL of toluene, (2.0g, 0.0086 mol) of tricarboethoxymethane and (0.2 g,0.0083 mol) of sodium hydride. It was left to stir and after 20 minutes 25 mL of dimethylformamide was added. It was left to stir for another 20 minutes.

In another 250 mL round bottom flask with magnetic stirrer, oil bath, nitrogen atmosphere and dropping funnel, was placed 50 mL of toluene and 3.0 g of Merrifield resin. To this was added dropwise the solution prepared above. It was left to stir overnight.

The product was filtered and washed with 50 mL of ethylacetate, 50 mL of absolute ethanol and 50 mL of ethylacetate. Then the product was dried under vacuum. The weight of the product was (3.40 g).

Preparation of **(XIX)**

The product **(XVIII)** was placed in a 200 mL round bottom flask with 100 mL of anhydrous ether and (0.675g, 0.031 mol) of lithium borohydride. The reaction was left to stir at room temperature overnight. The product was then filtered through sintered glass funnel. It was washed with 50 mL of ethylacetate, 50 mL of absolute ethanol, 50 mL of water and 50 mL of ethylacetate. The product was dried under vacuum and it weighed (2.70 g).

Preparation of **(XX)**

The product **(XIX)** was placed in a three way 200 mL round bottom flask adapted with a reflux condenser, magnetic stirrer, oil bath and nitrogen atmosphere. To it was added 10 mL of t-butyl alcohol and then it was treated with 1.344 g (0.012 moles) of potassium t-butoxide under nitrogen. To this was added 0.472 g (0.005 moles) of chloroacetic acid in 3.0 mL of t-butyl alcohol and it was left to reflux overnight. After the reflux was stopped the mixture was left to sit for a half an hour and then 3 mL of HCl were added to the mixture. Then the product was filtered, washed with 50 mL of ethylacetate, 50mL of absolute ethanol and 50 mL of ethylacetate. The material obtained was then dried under vacuum. The weight of the product was (3.02 g).

Preparation of **(XXI)**

In a three way 200 mL round bottom flask adapted with a magnetic stirrer was put 50 mL of tetrahydrofuran. To it was added with a syringe (1.2 mL, 0.01 mol) of titanium tetrachloride. It was left to stir for a couple of minutes and then (1.13 g, 0.029 mol) of sodium borohydride was added to the mixture. Finally the product **(XX)** was mixed in 30 mL dry tetrahydrofuran and it was added to the above mentioned mixture with a pipette. The round bottom flask was placed in a mixture of ice and water and it was left to stir.

The mixture was quenched with 100 mL of water. At the beginning the water was added dropwise because of the violent reaction that was causing. Afterwards ammonium hydroxide was added to the solution until it turned the solution basic. Then the solution was filtered through sintered glass funnel, it was washed with ammonium hydroxide to remove all of the titanium oxide and then washed with 50 mL of ethylacetate, 50 mL of absolute ethanol and 50 ml of ethylacetate. The product was left to dry under vacuum and it weighed (2.98g).

Preparation of **(XXII)**

The product **(XXI)** was placed in a 100 mL round bottom flask adapted with a magnetic stirrer, reflux condenser and a nitrogen atmosphere. To it was added (3.0 g,0.015 mol) of tosyl chloride and 50 mL of pyridine. The reaction was left to stir overnight. The product was then washed with 50 mL of ethylacetate, 50 mL of absolute ethanol and 50 mL of ethylacetate. It was left to dry under vacuum and its weight was (3.35 g).

Preparation of **(XXIII)**

In a 200 mL three way round bottom flask adapted with a magnetic stirrer, oil bath, reflux condenser and nitrogen atmosphere was put (4.0 g,0.017 mol) of tricarboethoxymethane, (0.41 g,0.017 mol) of sodium hydride and 50 mL of toluene. The mixture was left to stir for 20 minutes and then 25 mL of dimethyl formamide was added to the reaction mixture. It was left to stir again for 20 minutes.

In another 200 mL three way round bottom flask, adapted with an oil bath, reflux condenser, magnetic stirrer, nitrogen atmosphere and a dropping funnel was placed the material **(XXII)**, 50 mL of toluene and the sodium tricarboethoxymethane prepared above was dropped in through the dropping funnel. The reaction was left to stir overnight. The product was filtered and it was washed with 50 mL of ethylacetate, 50 mL of absolute ethanol and 50 mL of ethylacetate. The product was dried under vacuum. Its weight was (3.43 g).

The product was then placed in a 200 mL round bottom flask adapted with an oil bath, reflux condenser, magnetic stirrer and nitrogen atmosphere and to it was added 100 mL of 10% HCl. The reaction was left to stir and heat overnight. The product was then washed with 50 mL of water and 50 ml of absolute ethanol. It was left to dry under vacuum and its weight was (2.70 g).

Preparation of **(XXV)**

In a 250 mL round bottom flask adapted with a magnetic stirrer was placed (1.0 g , 0.0024 moles) of the compound **(XXIV)** which was previously prepared by other members of the group. To it was added the equivalent amount of tosyl chloride (2.745 g, 0.0144 moles) and 100 mL of pyridine. The reaction was left to stir at room temperature overnight. The pyridine was then evaporated off on the rotary evaporator and the dry product was weighed (7.28 g). It was a dark brown creamy material

Preparation of **(XXVI)**

In a 200 ml round bottom flask adapted with a magnetic stirrer, oil bath and nitrogen atmosphere was placed the material XXV. To it was added (4.91 g, 0.0329 moles) of triethanol amine and 150 mL of acetonitrile. The reaction was left to stir heating overnight. The product had precipitated out of solution. The product was filtered through sintered glass filter, and it was washed with 50 mL of acetonitrile and 50 mL of ethylacetate. The product was a white powdery material and it weighed (3.25 g).

Preparation of **(XXVII)**

In a 250 mL round bottom flask adapted with a magnetic stirrer, oil bath and a reflux condenser was placed (0.25 g, 0.0002 moles) of **(XXVI)** and to it was added (1.119 g, 0.0037 moles) of palmitoyl chloride. To it was added 150 mL of 1:1 mixture acetonitrile:pyridine. The reaction was left to stir and reflux overnight. The product was filtered and washed with 50 mL of acetonitrile and 50 mL of ethylacetate. The product was a white waxy material and it weighed (0.67 g). The yield of the reaction was 67%.

Preparation of **(XXVIII)**

In a 250 mL round bottom flask adapted with a magnetic stirrer and a reflux condenser was placed (10 g, 0.133 moles) of 3-hydroxyl propylamine and (25.06 g, 0.2666 moles) of 3-chloropropanol. To it was added (27.6 g, 0.2 moles) of potassium carbonate in 300 mL of ethanol. The mixture was left to reflux for 12 hours. Then the reaction was stopped and the reaction mixture was filtered and the filtrate was evaporated on the rotary evaporator and the product was a viscous material.

Preparation of **(XXIX)**

In a 250 mL round bottom flask adapted with a magnetic stirrer was placed (1.0 g, 0.005 moles) of **(XXVIII)**. To it was added an equivalent amount of benzyl bromide (0.895g, 0.005 moles) and 200 mL of acetonitrile. The reaction was left to stir at room temperature. The quaternary salt was expected to precipitate out of solution but the reaction was left on for three days and no precipitate formed. The reaction was stopped and the solvent was evaporated and a viscous brownish material was left behind.

Preparation of **(XXX)**

In a 100 mL round bottom flask adapted with a magnetic stirrer was placed (0.4 g, 0.0016 moles) of **(XXIX)** and to it was added excess p-toluensulfonyl chloride (0.3813g, 0.002 moles) and 50 mL of pyridine. The reaction was left to stir overnight. Then the pyridine was evaporated on the rotary evaporator and the product was isolated. The weight of the product was (1.52 g).

Preparation of **(XXXI)**

In a 100 mL round bottom flask adapted with a magnetic stirrer, oil bath and a reflux condenser was placed (0.8 g, 0.00092 moles) of **(XXX)** and it was reacted with (0.4112 g, 0.00276 moles) of triethanol amine. To the mixture was added 50 mL of 1:1 mixture dichloromethane:acetonitrile. The reaction was left to stir and reflux overnight. Before addition of the solvent and upon addition of the triethanol amine a white precipitate started forming. Upon reflux of the reaction the precipitate increased in amount. The reaction was stopped and the precipitate was filtered. We worked only with the filtrate, which was evaporated and the product a thick brown liquid was left behind.

Preparation of (S)-2,2-dimethyl-4-(2'-chloroethyl)-1,3-dioxolane **(XXXII)**

In a 500 mL round bottom flask adapted with a magnetic stirrer was placed (25.0 g, 0.235 moles) of butanetriol and to it was added 400 mL of acetone and (3.00 g, 0.015 mol) of p-toluensulfonic acid. The solution was left to stir overnight. Then (12.00 g, 0.087 moles) of potassium carbonate was added to neutralize the toluensulfonic acid. It was left to stir for an hour with the potassium carbonate. Then the solution was filtered through sintered glass funnel and the filtrate was evaporated on the rotary evaporator.

The material isolated from the evaporation (24.18 g, 0.165 moles) was then placed in a 500 ml round bottom flask adapted with a magnetic stirrer and a dropping funnel. To it was added (25.41 g, 0.165 moles) of carbon tetrachloride and 50 mL of dichloromethane. The equivalent amount of triphenylphosphine (43.23 g, 0.165 moles) was dissolved in 70 mL dichloromethane and it was added to the mixture through the dropping funnel over a period of forty minutes. Then the mixture was left to stir at room temperature overnight. The reaction was stopped and the mixture was added to 600 mL of hexane and it was left to stir for half an hour for the precipitate to digest. The solution was then filtered through sintered glass funnel and the filtrate was evaporated. The product was a transparent liquid.

This product was purified by column chromatography on neutral alumina and with dichloromethane as the solvent. Weight of product after column chromatography was (26.55 g).

Preparation of (S)-2,2-dimethyl-4-(2′-{1″-azonia-4″-azabicyclo[2.2.2]octyl}ethyl)-1,3-dioxolane chloride **(XXXIII)**

In a 1 L flask fitted with a magnetic stirrer were placed DABCO (80.0 g, 0.713 mol) and 600 mL ethyl acetate. There was then added **(XXXII)** (26.55 g, 0.161 mol) and the reaction mixture was allowed to stir at ambient temperature for two days. A gummy precipitate formed, clinging to the flask walls as well as the bottom, and the first crop of product was isolated by decanting the reaction solution and washing the gummy solid with ethyl acetate followed by diethyl ether and drying under vacuum (dry yield, 6.21 g). (The gummy solid product could be transferred by dissolution in ethanol and evaporation of the solvent.) From the decanted supernatant could be isolated additional crops of product (10.82 g after four additional days, 12.05 g after yet an additional 20 days, and 0.35 g after one further day). The material **(XXXIII)** thus isolated (29.43 g, 65.8 % total yield) exhibited spectra and elemental analyses in accord with the proposed structure. ^{1}H NMR (d D_2O) 1.36 (3H, s); 1.43 (3H, s); 1.99 (2H, m); 3.11 (6H, m); 3.22 (8H, m); 3.67 (1H, m); 4.09 (1H, m); 4.19 (1H, m). ^{13}C NMR (D_2O) 111.57, 74.52, 70.85, 63.80, 54.57, 47.29, 28.90, 28.74, 27.23. Anal: $C_{13}H_{25}N_2O_2Cl$ requires: C, 56.41

%; H, 9.10 %. Found: C, 56.54 %; H, 8.96 %. $[\alpha]_D$ (0.003 *M*, H_2O) = -5.58°.

Preparation of (S)-2,2-dimethyl-4-(2′-{1″-azonia-4″-methylazoniabicyclo[2.2.2]octyl}ethyl)-1,3-dioxolane dichloride **(XXXIV)**

A solution of **(XXXIII)** (1.52 g, 5.49 mmol) in acetonitrile (15 mL) was placed in a reaction flask fitted with magnetic stirrer, reflux condenser and drying tube, and to it was added an excess (2.5 g, 17.6 mmol) of iodomethane. After stirring for 2 hr., the resultant precipitate was collected by filtration with suction through sintered glass and washed with ethyl acetate and diethyl ether. The precipitate was dissolved in water and passed through a bed of DOWEX 2 in the chloride ion form. After evaporation of the water under vacuum there was isolated an extremely hydroscopic white solid (dry weight 1.13 g, 62.8 % yield) which exhibited spectra and elemental analyses in accord with the pentahydrate of the proposed structure **(XXXIV)**. ^{1}H NMR (d D_2O) 1.31 (3H, s); 1.40 (3H, s); 2.14 (2H, m); 3.36 (3H, s); 3.72 (3H, m); 4.02 (12H, br); 4.17 (1H, m); 4.27 (1H, m). ^{13}C NMR (D_2O) 110.69, 72.81, 68.54, 62.56, 53.69, 53.01, 51.76, 26.53, 26.35, 24.71. Anal: $C_{14}H_{28}N_2O_2Cl_2 \cdot 5(H_2O)$ requires: C, 40.28 %; H, 9.18 %. Found: C, 40.17 %; H, 9.23 %. $[\alpha]_D$ (0.003 *M*, H_2O) = -3.82°.

Preparation of (S)-1-methyl-4-(3′,4′-dihydroxybutyl)-1,4-

diazoniabicyclo[2.2.2]octane dichloride **(XXXV)**

The dry acetonide **(XXXIV)** (1.49 g, 4.55 mmol) was added to 10^{-4} *M* hydrochloric acid (24 mL). The reaction mixture was stirred for five hr. at ambient temperature after which all volatile materials were removed by freeze drying. The white solid residue (dry weight 1.07 g, 81.7 % yield), which was extremely hydroscopic, exhibited spectra and elemental analyses in accord with the nonahydrate of the proposed structure **(XXXV)**. ^1H NMR (d D_2O) 1.94 (2H, dm); 3.28 (3H, s); 3.46 (2H, dm); 3.63 (3H, m); 3.93 (12H, br). ^{13}C NMR (D_2O) 67.63, 64.15, 61.94, 53.34, 52.36, 51.56, 24.43. Anal: $C_{11}H_{24}N_2O_2Cl_2 \cdot 9(H_2O)$ requires: C, 29.40 %; H, 9.42 %. Found: C, 29.02 %; H, 9.51 %. $[\alpha]_D$ (0.003 *M*, H_2O) = -7.02°.

Preparation of (S)-1-methyl-4-(3′,4′-di-{4″-chlorobutanoyloxy}butyl)-1,4-diazoniabicyclo[2.2.2]octane dichloride **(XXXVI)**.

The diol **(XXXV)** (0.95 g, 3.31 mmol) along with acetonitrile (25 mL) was placed in a 100 mL flask fitted with a magnetic stirrer. To it was added an excess of 4-chlorobutanoyl chloride (2.5 g, 17.7 mmol) and the reaction flask topped with a drying tube. After stirring for 7 days diethyl ether (50 mL) was added to the clear reaction solution resulting in the formation of an oily white precipitate. The supernatant was decanted and the residue washed/decanted with ethyl acetate (3 x 50 mL) and diethyl ether (2 x 50 mL). The residue was dried under high vacuum to yield a hydroscopic white solid (dry weight 0.79 g, 48.1 % yield) which exhibited spectral and elemental analyses in accord with the dihydrate of the proposed structure **(XXXVI)**. ^{1}H NMR (d D_2O) 1.95 (4H, m); 2.15 (2H, m); 2.50 (4H, m); 3.26 (3H, s); 3.49-3.74 (7H, m); 3.96 (14H, br). ^{13}C NMR (D_2O) 172.33, 171.93, 66.31, 61.86, 58.74, 50.38, 49.64, 48.46, 42.14, 41.64, 28.37, 28.23, 24.23, 24.11, 20.34. Anal: $C_{19}H_{34}N_2O_4Cl_4 \cdot 2(H_2O)$ requires: C, 36.58 %; H, 6.14 %. Found: C, 36.57 %; H, 5.91 %. $[\alpha]_D$ (0.003 *M*, H_2O) = +9.48°.

Elaboration of the modified focus site **(XXXVI)** *to the first generation dendrimer* **(XXXVIII)**

In a 100 mL r.b. flask fitted with magnetic stirrer, heating bath and reflux condenser were placed **(XXXVI)** (0.145 g, 0.292 mmol) with acetonitrile (50 mL) and an excess of **(XXXIII)** (0.260 g, 0.939 mmol). The reaction mixture was heated at reflux for 15 hr. after which it was cooled and the supernatant was decanted. The residue was further washed/decanted with cool acetonitrile (3 x 50 mL). To the residue was added hydrochloric acid (10^{-4} *M*, 25 mL) and the mixture stirred for 4 hr. After this time all volatile materials were evaporated under high vacuum to give a hydroscopic white solid (dry weight 0.163 g, 58.2 % yield) which exhibited spectral and elemental analyses in accord with the dodecahydrate of the proposed structure **(XXXVIII)**.

^1H NMR (d D_2O) 1.87 (2H, m); 1.98 (4H, m); 2.02 (2H, m); 2.33 (2H, m); 2.55 (4H, m); 3.33 (3H, s); 3.46-3.99 (19H, m); 4.14 (36H, br). ^{13}C NMR (D_2O) 173.69, 172.06, 67.57, 62.72, 61.73, 61.54, 60.55, 60.43, 52.21, 51.51, 50.28, 50.22, 50.19, 50.17, 49.83, 44.17, 44.07, 43.57, 43.52, 42.92, 30.27, 30.24, 26.11, 25.99, 24.26, 23.15, 22.22. Anal: $C_{39}H_{76}N_6O_8Cl_6 \cdot 12(H_2O)$ requires: C, 39.49 %; H, 8.50 %. Found: C, 39.44 %; H, 8.10 %. $[\alpha]_D$ (0.003 *M*, H_2O) = +6.42°.

Elaboration of **(XXXVIII)** *to second generation dendrimer* **(XLI)**

The tetraol **(XXXVIII)** (0.97 g, 1.0 mmol) along with acetonitrile (50 mL) was placed in a 100 mL flask fitted with a magnetic stirrer, heating bath and a reflux condenser. To the reaction system was added 4-chlorobutanoyl chloride (1.12 g, 8.0 mmol), the reaction flask was topped with a drying tube and the reaction mixture heated at reflux for 2 days. After cooling, the solvent was decanted and the residue washed/decanted with cool ethyl acetate (3 x 50 mL). The residue was dried under high vacuum to yield a hydroscopic white solid. To this material was added acetonitrile (50 mL) and **(XXXIII)** (2.22 g, 8.02 mmol), and the resultant reaction mixture was stirred while heating at reflux for 3 days. After cooling, the supernatant liquid was decanted and the residue was washed/decanted with cool acetonitrile (3 x 50 mL). To the residue was then added hydrochloric acid (10^{-4} *M*, 20 mL) and the mixture stirred for 4 hr. at ambient temperature. All volatile materials were then removed by freeze drying to yield a hydroscopic white solid residue (dry weight 0.30g, 13 % yield) which exhibited spectral and elemental analyses in accord with a hydrated form of the proposed structure **(XLI)**. ^{1}H NMR (d D_2O) 1.78-2.58 (14H, brm); 2.70-3.23 (12H, brm); 3.28 (3H, s); 3.38-4.22 (143H, br). ^{13}C NMR (D_2O) Full resolution of signals in the range δ 75-0 could not be attained. However, six signals were present and resolved in the "carboxylate ester" region in accord with the presence of six unique carboxylate carbon sites in **(XLI)** - 186.23, 186.14, 186.02, 185.91, 176.50, 163.27. Anal: $C_{95}H_{180}N_{14}O_{20}Cl_{14} \bullet 34(H_2O)$ requires: C, 38.55 %; H, 8.36 %. Found: C, 38.71 %; H, 8.48 %.

Preparation of (S)-2,2-dimethyl-4-(2′-{1″-azonia-4″-benzylazoniabicyclo[2.2.2]octyl}ethyl)-1,3-dioxolane dichloride **(XLII)**

A solution of **(XXXIII)** (0.500 g, 1.14 mmol) in acetonitrile (50 mL) was placed in a reaction flask fitted with magnetic stirrer, reflux condenser and drying tube, and to it was added an excess (0.308 g, 2.21 mmol) of benzyl bromide. After stirring for 12 hr. the resultant precipitate was recovered by suction filtration through sintered glass followed by washing with ethyl acetate (2 x 50 mL) and diethyl ether (2 x 50 mL). After drying under vacuum there was isolated a hydroscopic white solid (dry weight 0.510 g, 74.3 % yield) which exhibited spectra and elemental analyses in accord with the monohydrate of the proposed structure **(XLII)**. ^{1}H NMR (d D_2O) 1.31 (3H, s); 1.40 (3H, s); 1.97 (2H, m); 3.45-3.71 (3H, m); 3.98 (12H, br); 4.12 (1H, m); 4.24 (1H, m); 4.74 (2H, s); 7.54 (5H, m). ^{13}C NMR (D_2O) 132.78, 131.53, 129.55, 124.66, 112.45, 68.83, 68.37, 64.90, 62.75, 51.19, 50.60, 25.12, 25.08, 23.96. Anal: $C_{20}H_{32}N_2O_2ClBr \cdot (H_2O)$ requires: C, 51.56 %; H, 7.36 %. Found: C, 51.19 %; H, 7.74 %.

Preparation of benzyl[1-azonia-4-{(S)-3',4'-dihydroxybutyl-1'-}azoniabicyclo[2.2.2]octane bromide chloride **(XLIII)**

The ketal **(XLII)** (0.500 g, 1.12 mmol) was stirred in aqueous solution (25 mL) with AMBERLYST™-15 in the acid form for 2 hr. After removal of the AMBERLYST™-15 by filtration, the volatile materials were evaporated under high vacuum to give a hydroscopic white solid (dry weight 0.323 g, 70.7% yield which exhibited spectra and elemental analyses in accord with the pentahydrate of the proposed structure **(XLIII)**. ^{1}H NMR (d D_2O) 1.89 (2H, dm); 3.47 (2H, m); 3.69 (3H, m); 3.96 (12H, br) 4.74 (2H, s); 7.55 (5H, m). ^{13}C NMR (D_2O) 133.32, 131.96, 129.99, 125.12, 69.24, 68.81, 65.35, 63.14, 51.63, 51.04, 25.16. Anal: $C_{17}H_{28}N_2O_2BrCl \cdot 5(H_2O)$ requires: C, 40.99 %; H, 7.69 %. Found: C, 40.68 %; H, 7.32 %.

$[\alpha]_D$ (0.0024 *M*, H_2O) = -7.49°.

Preparation of benzyl[1-azonia-4-{(S)-3',4'-di-(4"-chlorobutanoyloxy)butyl-1'-}azoniabicyclo[2.2.2]octane bromide chloride **(XLIV)**

The diol **(XLIII)** (0.080 g, 0.20 mmol) along with acetonitrile (30 mL) was placed in a 50 mL flask fitted with a magnetic stirrer. To it was added an excess of 4-chlorobutanoyl chloride (0.050 g, 0.71 mmol) and the reaction flask topped with a drying tube. After stirring for 2 days diethyl ether (50 mL) was added to the clear reaction solution resulting in the formation of an oily white precipitate. The supernatant was decanted and the residue washed/decanted with ethyl acetate (3 x 50 mL) and diethyl ether (2 x 50 mL). The residue was dried under high vacuum to yield a hydroscopic white solid (dry weight 0.070 g, 56.7 % yield) which exhibited spectral and elemental analyses in accord with the octahydrate of the proposed structure **(XLIV)**. ^1H NMR (d D_2O) 1.98 (4H, m); 2.19 (2H, m); 2.52 (4H, m); 3.50-3.82 (7H, m); 3.94 (14H, br), 4.73 (2H, s), 7.52 (5H, m). ^{13}C NMR (D_2O) 175.50, 175.08, 133.28, 131.99, 130.03, 125.14, 69.62, 69.27, 65.04, 61.78, 51.73, 51.02, 31.60, 31.45, 27.44, 27.31, 25.67, 23.56, 23.50. Anal: $C_{25}H_{38}N_2O_4BrCl_3 \cdot 8(H_2O)$ requires: C, 39.46 %; H, 7.15 %. Found: C, 39.62 %; H, 7.02 %. $[\alpha]_D$ (0.011 *M*, H_2O) = +1.77°.

Elaboration of the modified focus site **(XLIV)** *to the first generation dendrimer* **(XLVI)**

In a 100 mL r.b. flask fitted with magnetic stirrer, heating bath and reflux condenser were placed **(XLIV)** (0.070 g, 0.11 mmol) with acetonitrile (50 mL) and **(XXXIII)** (0.124 g, 0.44 mmol). The reaction mixture was stirred at ambient temperature for 3 days after which the supernatant was decanted. The residue was further washed/decanted with cool acetonitrile (3 x 50 mL). To the residue was added hydrochloric acid (10^{-4} *M*, 25 mL) and the mixture stirred for 4 hr. After this time all volatile materials were evaporated under high vacuum to give a hydroscopic white solid (dry weight 0.030 g, 26.1 % yield) which exhibited spectral and elemental analyses in accord with a hydrated form of the proposed structure **(XLVI)**. H NMR (d D_2O) 1.77 (2H, m); 1.87 (4H, m); 2.00 (2H, m); 2.31-2.58 (6H, brm); 3.36-3.89 (19H, m); 4.10 (36H, br), 4.53 (2H, s), 7.30 (5H, brm). ^{13}C NMR (D_2O) 173.52, 172.44, 131.28, 129.99, 128.02, 124.28, 67.49, 67.26, 66.74, 64.37, 63.04, 62.08, 61.85, 60.89, 59.88, 57.78, 50.07, 49.72, 49.65, 49.51, 49.04, 42.84, 42.32, 41.83, 29.60, 29.46, 28.00, 25.44, 25.32, 23.61, 21.60. Anal: $C_{45}H_{80}N_6O_8Cl_6 \cdot 13(H_2O)$ requires: C, 42.22 %; H, 8.35 %. Found: C, 42.22 %; H, 8.03 %. $[\alpha]_D$ (0.0029 *M*, H_2O) = -6.33°.

*Preparation of (*E*)-1,4-bis-{1'azonia-4'-*

azabicyclo[2.2.2]octyl}-2-butene dichloride (**L**)

To a stirred solution of 1,4-dichloro-trans-2-butene (3.125g, 0.025 mol) in 25mL of acetonitrile was added dropwise a solution containing an eight fold amount of DABCO (22.43 g, 0.02 mol) in 75 mL of acetonitrile. After stirring for 2 hours, the white solid formed was collected by suction filtration, washed with 100 mL of diethylether and dried under vacuum. The resultant material exhibited the following ^1H and ^{13}C NMR spectra:(D_2O) ^1H: 3.12(12H,t); 3.34(12H,t); 3.97(4H,d); 6.23(2H,t). ^{13}C NMR: 44.52, 52.69, 65.04, 129.50.

Preparation of (E)-1,4-bis-{1'-azonia-4'-(3-hydroxypropyl)azoniabicyclo[2.2.2]octyl}-2-butene) tetrachloride (**LI**)

To a stirred mixture of (**L**) (3.49 g, 0.01 mol) in 25mL of acetonitrile was added an excess of 1-chloropropanol (3.78 g, 0.04 mol). The heterogeneous mixture was heated at reflux for two days after which the mixture was cooled and the solid was recovered by suction filtration, washed with 100 mL of diethyl ether and dried under vacuum. The resultant material (LI) had the following spectra:^1H: 1.99(4H,br); 3.13-3.34(4H,br); 3.63(8H,br);3.97(24H,s); 4.34-4.46(2H,br).

^{13}C:26.27, 53.09, 53.17, 59.52, 64.85, 66.81, 131.60

Preparation of (E)-1.4-bis-{1'-azonia-4'-(3-chloropropyl)azoniabicyclo[2.2.2]octyl}-2-butene tetrachloride **(LII)**

In a flask fitted with a heating oil bath, magnetic stirrer and reflux condenser was placed (LI) 92.69 g, 0.005 mol) and distilled chloroform solvent (25x the mass of LI used). To the rapidly stirred mixture was added an excess (6 equivalent amounts) of thionyl chloride. The reaction mixture was heated at reflux for 16 hours, after which time excess thionyl chloride was destroyed by the addition of an excess of anhydrous ethanol. The solid product was collected by suction filtration through sintered glass, washed with 100 mL of anhydrous ether and dried under vacuum. The resultant material **(LII)** had the following spectra: ^{1}H 1.89(4H,br); 3.11-3.42(4H,br); 3.57(8H,br); 3.88(24H,s); 4.31-4.42(2H,br)

^{13}C: 24.90, 40.95, 51.68, 51.72, 63.60, 65.34, 130.02.

Preparation of (E)-1,4 bis-{1'-azonia-4'-(3-{1''-azonia-4''-(8-(hydroxyoctyl)azoniabicyclo[2.2.2]octyl} propyl)azoniabicyclo[2.2.2]octyl}-2-butene octachloride **(LIII)**

To a stirred mixture of **(LII)** (4.6 g, 0.008 mol) in 60 mL of acetonitrile was added an excess of 1-(8-hydroxyoctyl)azonia-4-azabicyclo[2.2.2]octane chloride (3.856 g, 0.016 mol). The heterogeneous mixture was heated at reflux with stirring for five days after which the mixture was cooled and the solid recovered by suction filtration, washed with 100 mL diethyl ether and dried under vacuum. No relevant NMR information was obtained on this product.

ION EXCHANGE STUDIES

Qualitative studies done on the third generation cationic dendrimer **(VI)**

The material **(VI)** was washed with 250 mL of water, 250 mL of 0.5M sodium chloride and then again with 250 mL of water. Afterwards the material was washed with 100 mL of 0.5M sodium nitrate. The eluent was tested for the presence of chloride ion with silver nitrate solution. White precipitate of silver chloride was formed.

Quantitative studies done on third generation cationic dendrimer **(VI)**

The material **(VI)** was washed with 250 mL 1M sodium sulfate, 100 mL of water,50 mL of 1M sodium fluoride solution. The eluent was collected and to it was added 15 mL of barium chloride. The solution was then filtered and the white precipitate was collected. The precipitate was then dried and weighed (1.69 g) which corresponds to 0.0072 moles of barium sulfate. From this we concluded that the exchange capacity of the resin was 14.4 meq/g.

Further qualitative studies done on the third generation cationic dendrimer **(VI)**

The material **(VI)** was washed with 250 mL of 0.1M sodium iodide solution, 250 mL of water and then with 250 mL of 0.1M of sodium nitrate solution. The eluent was then tested for the presence of iodide ions with silver nitrate solution. A yellowish precipitate formed upon the addition of the silver nitrate solution.

The material **(VI)** was washed with 250 mL of 0.1M sodium bromide solution, 250 mL of water and then with 250 mL of 0.1M of sodium nitrate solution. The eluent was then tested for the presence of bromide ions with silver nitrate solution. An off-white precipitate formed upon the addition of the silver nitrate solution.

Preparation of **(VII)**

In a 50 mL round bottom flask adapted with a magnetic stirrer and a reflux condenser was placed the material (VI) and to it was added 20 mL of acetic anhydride. It was left to stir and reflux overnight. The product was filtered and washed with 50 mL of absolute ethanol, 50 mL of water and then 50 mL of absolute ethanol. The material was dried under vacuum.

A solution of 0.1508 g of sodium chromate in 20 mL of water was made up and the material **(VI)** was washed with it. Then the resin was washed with another 20 mL of water and the eluent was dissolved in a volumetric flask to a volume of 100 mL. Spectrophotometric measurements were made on the eluent. Previously the molar absorptivity of the chromate ion was determined to be $\varepsilon=6550\ M^{-1}cm^{-1}$. From

Beer's law calculations we determined that 90% of the chromate ion available in solution was retained by the resin.

Following the resin was washed with 50 mL of 1M sodium chloride and the absorbance of the eluent was measured. From Beer's law calculations we concluded that out of the 0.1508 g of chromate ion that were originally retained by the resin only 0.0041 g were exchanged for chloride ion. After several washings the total amount of chromate ion that was removed equaled 30% of the initial amount retained.

The above procedure was repeated for the following amounts of chromate ion: 0.377g and 0.754g. The amount of chromate ion that was retained by the resin did not vary with the initial concentration of chromate ion in solution.

Qualitative and quantitative studies done on **(XII)**

In a 250 mL Erlenmayer flask was put 1.36g of phenyl acetic acid and 100 mL of water. To this was added 0.4 g of sodium hydroxide and the sodium phenylacetate was formed. The solution of sodium phenylacetate above prepared was then used to determine the molar absorptivity value of the phenyl acetate ion (ε=2068).

The material (XII) was washed with 100 mL of the 0.1M phenylacetate solution prepared above. Spectrophotometric measurements were made on the eluent. From Beer's law calculations we determined that the exchange capacity of the resin was 11.25 meq/g.

Qualitative studies done on the third generation anionic dendrimer **(XVII)**

The material **(XVII)** was washed with 50 mL of 0.1M silver nitrate solution, 100 mL of water and then 50 mL of 0.1M sodium nitrate solution. The eluent was then tested for the presence of silver ions by adding sodium chloride solution and the white precipitate of silver chloride was formed, fact which indicated that exchange took place.

Quantitative studies done on third generation anionic dendrimer **(XVII)**

Preparation of the dithizone solution

In a 1L brown bottle were mixed 10mg of dithizone and 1L of carbon tetrachloride.

Preparation of buffer solution

To 500 mL of 2.8M ammonium hydroxide solution was added 3.20g of ammonium nitrate and 0.37g of sodium sulfite. Once the buffer solution was prepared the material (XVIII) was washed with 200 mL of 0.001M lead acetate tetrahydrate. the eluent after this wash was tested for the presence of lead. Spectrophotometric methods were used. The eluent was diluted 1mL to 500 mL of water. The molar absorptivity of the standard solution was obtained to be $\varepsilon=62083.1M^{-1}cm^{-1}$.

From the measurements obtained on the eluent and from Beer's law calculation we determined that approximately 40%

of the lead initially present in solution was retained by the resin.

SPECTROPHOTOMETRIC MEASUREMENTS

For all the spectrophotometric studies, absorbency measurements were made and the maximum absorbency values were noted. In case the absorbency values were large the necessary dilutions were made to bring the absorbency values in the range of 0.5-0.8. I used standard solutions of known concentrations to find out the molar absorptivity values and then from Beer's Law calculations the concentrations of the different unknown solutions could be found.

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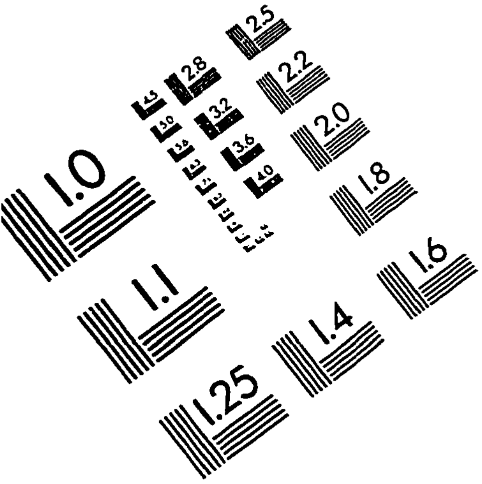
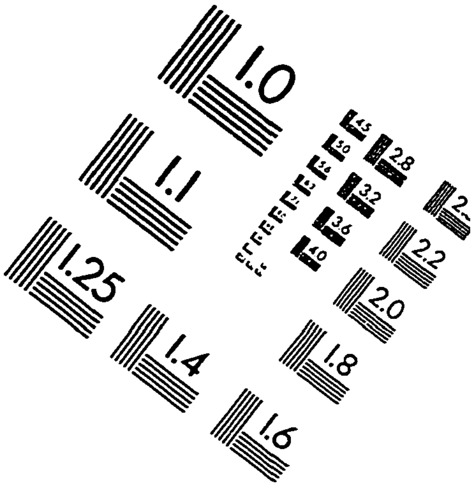
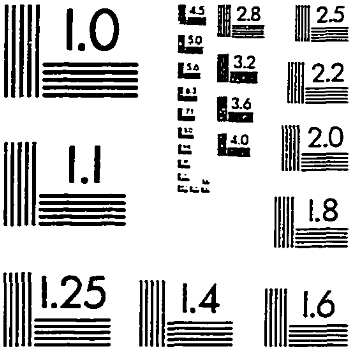
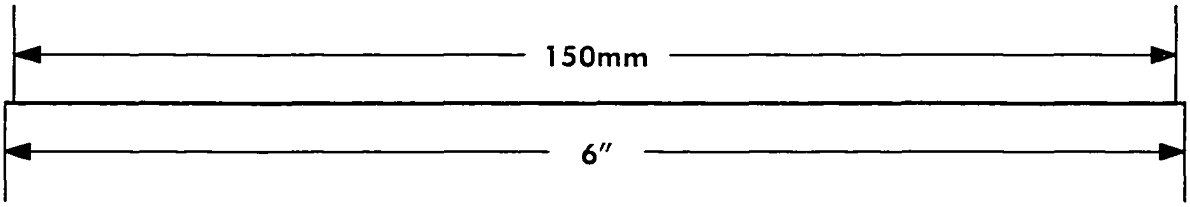
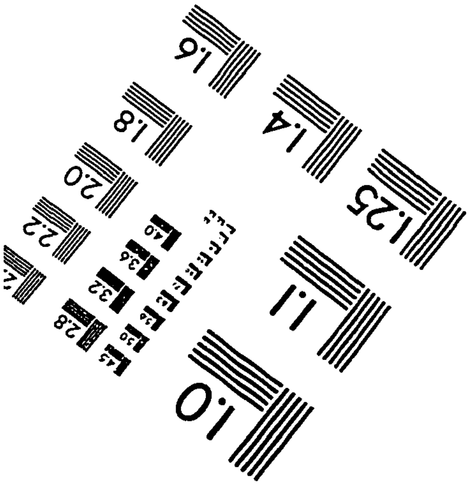
IMAGE EVALUATION TEST TARGET (QA-3)

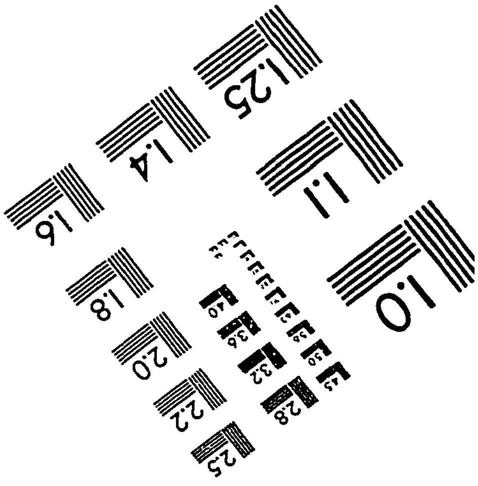












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