Polycations. II. Chiral Ammonium Dendrimer Synthesis*

Alice Cherestes, Tessie October, and Robert Engel

Department of Chemistry and Biochemistry, Queens College of the City University of New York, 65-30 Kissena Boulevard, Flushing, NY 11367

Received 28 August 1997; revised 10 November 1997

ABSTRACT: The preparation and investigation of chiral cationic dendrimers is described. In these species, cationic sites are provided by quaternary ammonium ion centers derived from the dinitrogen compound 1,4-diazabicyclo[2.2.2]octane (dacbo). Stereogenic sites within the dendrimer structures are provided by derivitization of the readily available (S)-1,2,4-butanetriol. © 1998 John Wiley & Sons, Inc. Heteroatom Chem. 9: 485–494, 1998

INTRODUCTION

In the course of our continuing efforts concerning the synthesis of polycationic organic species [1], both dendrimeric and “stringlike” in nature, we have turned to an investigation of the synthesis and characteristics of chiral ionic dendrimers. Dendrimers are an intriguing class of compounds that incorporate both the repetitive nature of polymers and a regular branching characteristic reminiscent of fractals.

A number of syntheses of chiral dendrimers have previously been reported. While some of these dendrimers have involved chiral components only at relatively late stages of total elaboration or as part of the terminal functionality, some have incorporated chiral units in the focus site and branching sites. These have involved building blocks based on α-amino acids [2a–g], chiral tris(hydroxymethyl)methane) derivatives [2h–j], tetradifferentially substituted pentaerythritol species [2k–l] and the asymmetric dihydroxylation of prochiral alkene monomers [2m]. The present effort is concerned with the synthesis and investigation specifically of chiral ionic dendrimers.

In general, dendrimers involve four structural components: (1) a focus site for the divergent branches, (2) branch points, (3) extension units between the focus sites and branch points and between branch points, and (4) a terminal functionality. This is illustrated schematically in Figure 1.

In the prior reported efforts [1b–j] toward the synthesis of cationic dendrimers, the cationic sites (ammonium or phosphonium) were located at the branch points, and substituents attached to the branch points as they were incorporated into the developing dendrimer constituted the extension units; focus sites, as well as branch points, were alkylated or arylated tertiary amines (or phosphines).

In the present effort, cationic (quaternary am-

Correspondence to: Robert Engel. Fax: (718) 997-5531; E-mail: robert_engel@qc.edu.

*For Part I in this series, see Ref. [1a].

© 1998 John Wiley & Sons, Inc. CCC 1042-7163/98/050485-10

FIGURE 1 Four structural components of dendrimers.
monium) sites are incorporated as components of the extension units using 1,4-diazabicyclo[2.2.2]octane (dabco) that is quaternized at both nitrogen centers. Stereogenic branch points are provided through the use of derivatives of (S)-1,2,4-butane triol, the hydroxyls of the 1- and 2-positions serving as reactive sites for elaboration of new branches. Both monon- and bidirectional focus sites have been used in this effort.

RESULTS AND DISCUSSION

Branch Points

Branching sites for the chiral ionic dendrimers were provided through the use of the readily available (S)-1,2,4-butane triol (1). Initial protection of the vicinal diol portion of 1 by acetonide formation followed by substitution of the remaining hydroxyl group by chloride using known procedures [3,4], after purification by column chromatography, yielded the desired intermediate reagent (S)-2,2-dimethyl-4-(2'-chloroethyl)-1,3-dioxolane (2). Reaction of 2 with dabco produced (S)-2,2-dimethyl-4-(2'-azonia-4'azabicyclo[2.2.2]octyl)ethyl)-1,3-dioxolane chloride (3). The material 3, 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 3, containing the stereogenic site that 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 into the chiral ionic dendrimers described here were derived from 2 in this manner.

Focus Sites

Three focus site units have been used for the construction of the chiral ionic dendrimers reported here. Each of these focus sites were constructed by alkylation of the fundamental building unit 3. These include the following:

a. a monomethylated focus unit: (S)-2,2-dimethyl-4-(2'-azonia-4'-methylazoniabicyclo[2.2.2]octyl)ethyl)-1,3-dioxolane dichloride (4);

b. a monobenzyolated focus unit: benzyl[1-azonia-4-{(S)-3',4'-dihydroxybutyl-1'azaoniabicyclo[2.2.2]octane bromide chloride (5); and

c. a bidirectional focus unit produced by quaternization of two units of 3 with a 1,4-xylylene unit: 1,4-xylylenebis[1'-azonia-4'(S)-3',4'-dihydroxybutyl-1'-azoniabicyclo[2.2.2]octane] dibromide dichloride (6).

The structures of these focus units are shown in Figure 2.

Extension Units

In the present approach toward the construction of chiral ionic dendrimers, 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 that avoids any bond breaking 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 (quaternary) structures, which are extremely susceptible to cleavage [11].

With these difficulties in mind, extension units were devised that would provide sites for attachment of additional building units (by tertiary amine quaternization) 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 α-halocarboxylic acid.

FIGURE 2 Structures of focus site units.
chloride. This avoids breaking any bonds at the stereo
genic site and provides both a reasonably (but not
totally) unreactive linkage for continued elaboration
and reactive sites for alkylation of tertiary amine
units that are relatively distant from each other. The
reagent of choice for extension unit introduction was
4-chlorobutanoyl chloride. Longer alkyl-chain \( \omega\)-
chloroacetyl chlorides would unnecessarily lengthen
the distance between cationic sites, while shorter al-
kalyl-chain systems would result in products that are
exceedingly reactive by extraneous routes (\( \alpha \)-azonia-
and \( \beta \)-azoniaesters). The construction of initially
functionalized focus unit species such as 7 and 8 de-
erived from 3 with chloroacetyl chloride and 2-chlo-
ropropionoyl chloride was successful; however, 7, be-
ing an \( \alpha \)-azoniaester, was overly susceptible to
hydrolysis and 8, being a \( \beta \)-azoniaester, partially un-
derwent elimination upon treatment with the terti-
ary amine reagent 3.

\[
\begin{align*}
ClCH_2C(O)O & \quad H \quad + \quad CH_3 \\
ClCH_2C(O)O & \quad + \quad 2Cl^- \\
ClCH_2CH_2C(O)O & \quad + \quad CH_3 \\
ClCH_2CH_2C(O)O & \quad + \quad 2Cl^- \\
\end{align*}
\]

**Terminal Functionality**

The terminal functionality varies with the stage of
elaboration for all of the species generated in this
investigation. However, the target materials of elab-
oration about each of the focus site units have hy-
droxylic groups as the termini. While all of the mate-
rials synthesized herein exhibit significant solubility
in water, not unexpectedly those with hydroxyl ter-
mini are most soluble, even with extensive elabora-
tion and attendant high molecular mass.

**The Elaboration Process and Dendrimer
Characteristics**

The fundamental building block 3 was converted to
each of the previously noted focus site units 4–6 by
reaction with the appropriate organic halide (iodom-
ethane, benzyl chloride, or 1,4-bis(bromomethyl)-
benzene, respectively). Because of difficulties asso-
ciated with mixed iodide salts, the initial prepara-
tions of 4 were subjected to ion anion exchange us-
ing 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 co-
valent lattice with free-floating counterions, has par-
ticular requirements for the types and conditions of
reactions employed. All reaction conditions must be
relatively mild such that side reactions are virtually
nonexistent; any small amount of cleavage of previ-
ously generated framework bonds is greatly magni-
ﬁed by the production of dendrimer fragments and
the fact that these impurities can be removed only
with the greatest difﬁculty. For example, after the fo-
cus units were generated, and after the incorpora-
tion of higher generations of branching units, re-
moval of the acetonide protecting groups was
accomplished either by treatment with dilute (10\(^{-4}\)
M) hydrochloric acid, or with a standard cation ex-
change resin in the H\(^+\) form. Under these mild con-
ditions, no observable cleavage of ester linkages (or
any other bond) occurred. As noted previously, the
use of shorter extension units produced intermedi-
ate species that underwent degradation even under
the mildest of conditions. Consequently, the vicinal
diols were acylated using an excess of 4-chlorobu-
tanoyl chloride, followed by continued dendrimer
elaboration through reaction with 3. These succes-
sive processes were repeated for the introduction of
a further generation, ending with acetonide hydrol-
ysis to yield the hydroxy-terminal form of the den-
drimer. The process of dendrimer elaboration is il-
ustrated in detail in Scheme 1 for the system based
on focus unit 4 and in Scheme 2 for the system based
on focus unit 6.

In certain instances, not all of the hydrogen chlo-
ride generated in the reaction of hydroxyl groups
with 4-chlorobutanoyl chloride could be removed ef-
ficiently under high vacuum. In such instances, as
the presence of the acid could inhibit quaternization
of the tertiary amine site of 3, removal of remaining
acid by treatment of an aqueous solution of the den-
drimer intermediate with potassium carbonate was
necessary prior to continued dendrimer elaboration.

Caution must also be taken to ensure complete
reaction in a specific manner of all of the terminal
sites of intermediate species in dendrimer elabora-
tion. This is accomplished through the use of a sig-
ificant 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 3 compared to other reagents and dendrimer intermediates is a critical factor. The solubility of 3 in ethyl acetate is quite low, being deposited on the flask walls from ethyl acetate solution as it is formed. (Although preparations of 3 were generally performed using a large excess of dabco, this is not absolutely necessary because of the low solubility of 3 in ethyl acetate and the fact that continued alkylation of 3 with 2 in acetonitrile proceeds only with the greatest difficulty. The reason for the low reactivity of 3 with 2 is not fully understood.) The material 3, 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 3 is
readily removed from elaboration reactions. Similarly, excess of 4-chlorobutanoyl chloride is readily removed by washing with ethyl acetate and diethyl ether, solvents in which the charged dendrimer species are completely insoluble.

Dendrimers based on focus unit 5 were constructed by analogous elaboration procedures as detailed in the Experimental section. The structures of intermediate materials and final dendrimers based on focus unit 5 for which full analytical data and physical characteristics were measured are illustrated in Figure 3.

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 the elaboration progressed. (Optical rotation data are summarized in Table 1.) 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 et al. [1]; 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.

**EXPERIMENTAL**

**General**

All chemicals used in syntheses, purification, and comparison analyses were of commercial reagent quality and were used without purification. 2,2-Dimethyl-4-(2'-chloroethyl)1,3-dioxolane (2) was prepared as previously reported [4]. All NMR spectra were measured using 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 instru-
FIGURE 3 Structures of intermediate materials and final dendrimers based on focus unit 5.

TABLE 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Observed [α]₀</th>
<th>Concentration (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-5.58°</td>
<td>0.003</td>
</tr>
<tr>
<td>4</td>
<td>-3.82°</td>
<td>0.003</td>
</tr>
<tr>
<td>4a</td>
<td>-7.02°</td>
<td>0.003</td>
</tr>
<tr>
<td>4b</td>
<td>+9.48°</td>
<td>0.003</td>
</tr>
<tr>
<td>4c</td>
<td>+6.42°</td>
<td>0.003</td>
</tr>
<tr>
<td>5a</td>
<td>-7.49°</td>
<td>0.0024</td>
</tr>
<tr>
<td>5b</td>
<td>+1.77°</td>
<td>0.011</td>
</tr>
<tr>
<td>5c</td>
<td>-6.33°</td>
<td>0.0029</td>
</tr>
<tr>
<td>6</td>
<td>-5.11°</td>
<td>0.012</td>
</tr>
<tr>
<td>6a</td>
<td>-0.53°</td>
<td>0.003</td>
</tr>
<tr>
<td>6b</td>
<td>+8.7°</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

All measurements were made in aqueous solution using a sodium vapor lamp.

Preparation of (S)-2,2-Dimethyl-4-((2'-1"-azonia-4"-methyazoniabicyclo[2.2.2]octyl)ethyl)-1,3-dioxolane Dichloride (3). In a 1 L flask fitted with a magnetic stirrer were placed dabc (80.0 g, 0.713 mol) and 600 mL ethyl acetate. There was then added 2 (26.55 g, 0.161 mol), and the reaction mixture was allowed to stir at ambient temperature for 2 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 4 additional days, 12.05 g after yet an additional 20 days, and 0.35 g after 1 more day). The material was thus isolated (29.43 g, 65.8% total yield) exhibited spectra and elemental analyses in accord with the proposed structure. 1H NMR (δ D₂O) 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). 13C NMR (D₂O) 111.57, 74.52, 70.85, 63.80, 54.57, 47.29, 28.90, 28.74, 27.23. Anal. C₁₁H₁₉N₂O₂Cl requires: C, 56.41%; H, 9.10%. Found: C, 56.54%; H, 8.96%. [α]₀ (0.003 M, H₂O) = -5.58°.

Preparation of (S)-2,2-Dimethyl-4-((2'-1"-azonia-4"-methyazoniabicyclo[2.2.2]octyl)ethyl)-1,3-dioxolane Dichloride (4). A solution of 3 (1.52 g, 5.49 mmol) in acetonitrile (15 mL) was placed in a reaction flask fitted with a 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 hours, 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) that exhibited spectra and elemental analyses in accord with the pentahydrate of the proposed structure 4. 1H NMR (δ D₂O) 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). 13C NMR (D₂O) 110.69, 72.81, 68.54, 62.56, 53.69, 53.01, 51.76, 26.53, 26.35,
24.71. Anal. C_{16}H_{28}N_{8}O_{2}Cl_{2}·5(H_{2}O) requires: C, 40.28%; H, 19.1%. Found: C, 40.17%; H, 9.23%. [α]_{D}^{25} (0.003 M, H_{2}O) = -3.82°.

Preparation of (S)-1-Methyl-4-(3',4'-dihydroxybutyl)-1,4-diazoniabicyclo[2.2.2]octane Dichloride (4a). The acetonitrile 4 (1.49 g, 4.55 mmol) was added to 10^{-4} M hydrochloric acid (24 mL). The reaction mixture was stirred for 5 hours at ambient temperature after which all volatile materials were removed by freeze drying. White solid residue (dry weight 1.07 g, 81.7% yield), which was extremely hygroscopic, exhibited spectra and elemental analyses in accord with the nonahydrate of the proposed structure 4a. ^{1}H NMR (δ D_{2}O) 1.94 (2H, dm), 3.28 (3H, s), 3.46 (2H, dm), 3.63 (3H, m), 3.93 (12H, br). ^{13}C NMR (D_{2}O) 67.63, 64.15, 61.94, 53.34, 52.36, 51.56, 24.43. Anal. C_{16}H_{28}N_{8}O_{2}Cl_{2}·9(H_{2}O) requires: C, 29.40%; H, 9.42%. Found: C, 29.02%; H, 9.51%. [α]_{D}^{25} (0.003 M, H_{2}O) = -7.02°.

Preparation of (S)-1-Methyl-4-(3',4'-di-[4'-chlorobutanoyloxy]butyl)-1,4-diazoniabicyclo[2.2.2]octane Dichloride (4b). The diol 4a (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 was 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 was washed/washed with ethyl acetate (3 × 50 mL) and diethyl ether (2 × 50 mL). The residue was dried under high vacuum to yield a hygroscopic white solid (dry weight 0.79 g, 48.1% yield) that exhibited spectral and elemental analyses in accord with the dihydrate of the proposed structure 4b. ^{1}H NMR (δ D_{2}O) 2.15 (2H, m), 2.50 (4H, m), 2.36 (3H, s), 3.49-3.74 (7H, m). 3.96 (14H, br). ^{13}C NMR (D_{2}O) 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_{16}H_{28}N_{8}O_{2}Cl_{2}·2(H_{2}O) requires: C, 36.58%; H, 6.14%. Found: C, 36.57%; H, 5.91%. [α]_{D}^{25} (0.003 M, H_{2}O) = +9.48°.

Elaboration of the Modified Focus Site 4b to the First-Generation Dendrimer 4c. In a 100 mL r.b. flask fitted with a magnetic stirrer, heating bath, and reflux condenser were placed 4b (0.145 g, 0.292 mmol) with acetonitrile (50 mL) and an excess of 3 (0.260 g, 0.939 mmol). The reaction mixture was heated at reflux for 15 hours, after which it was cooled, and the supernatant was decanted. The residue was further washed/washed with cool acetonitrile (3 × 50 mL). To the residue was added hydrochloric acid (10^{-4} M, 25 mL) and the mixture stirred for 4 hours. After this time, all volatile materials were evaporated under high vacuum to give a hygroscopic white solid (dry weight 0.163 g, 58.2% yield) that exhibited spectral and elemental analyses in accord with the dodecachloride of the proposed structure 4c. ^{1}H NMR (δ D_{2}O) 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_{2}O) 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_{38}H_{72}N_{12}O_{12}Cl_{12}·12(H_{2}O) requires: C, 39.49%; H, 8.50%. Found: C, 39.44%; H, 8.10%. [α]_{D}^{25} (0.003 M, H_{2}O) = +6.42°.

Elaboration of 4c to Second-Generation Dendrimer 4d. The tetraol 4c (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 reflux condenser. To the reaction system was added 4-chlorobutanoin chloride (1.12 g, 8.0 mmol), the reaction flask was topped with a drying tube, and the reaction mixture was heated at reflux for 2 days. After cooling, the solvent was decanted and the residue washed/washed with cool ethyl acetate (3 × 50 mL). The residue was dried under high vacuum to yield a hygroscopic white solid. To this material was added acetonitrile (50 mL) and 3 (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/washed with cool acetonitrile (3 × 50 mL). To the residue was then added hydrochloric acid (10^{-4} M, 20 mL), and the mixture was stirred for 4 hours at ambient temperature. All volatile materials were then removed by freeze drying to yield a hygroscopic white solid residue (dry weight 0.30 g, 13% yield) that exhibited spectral and elemental analyses in accord with a hydrated form of the proposed structure 4d. ^{1}H NMR (δ D_{2}O) 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_{2}O) 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 4d—186.23, 186.14, 186.02, 185.91, 176.50, 163.27. Anal. C_{38}H_{72}N_{12}O_{12}Cl_{12}·34(H_{2}O) 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-dioxo-
lane Dichloride (5). A solution of 3 (0.500 g, 1.14 mmol) in acetonitrile (50 mL) was placed in a reaction flask fitted with a 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 hours, the resultant precipitate was recovered by suction filtration through sintered glass followed by washing with ethyl acetate (2 × 50 mL) and diethyl ether (2 × 50 mL). After drying under vacuum there was isolated a hydrosopic white solid (dry weight 0.510 g, 74.3% yield) that exhibited spectral and elemental analyses in accord with the monohydrate of the proposed structure 5. 1H NMR (δ D₂O) 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). 13C NMR (D₂O) 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. C₂₀H₂₃N₂O₂Cl₂Br·(H₂O) 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'-aza]bicyclo[2.2.2]octane Bromide Chloride (5a). The ketal 5 (0.500 g, 1.12 mmol) was stirred in aqueous solution (25 mL) with AMBERLYST™-15 in the acid form for 2 hours. After removal of the AMBERLYST™-15 by filtration, the volatile materials were evaporated under high vacuum to give a hydrosopic white solid (dry weight 0.323 g, 70.7% yield) that exhibited spectral and elemental analyses in accord with the pentahydrate of the proposed structure 5a. 1H NMR (δ D₂O) 1.89 (2H, dm), 3.47 (2H, m), 3.69 (3H, s), 3.96 (12H, br), 4.74 (2H, s), 7.55 (5H, m). 13C NMR (D₂O) 133.32, 131.96, 129.99, 125.12, 69.24, 68.81, 65.35, 63.14, 51.63, 51.04, 25.16. Anal. C₂₀H₂₃N₂O₂Cl₂Br·5(H₂O) requires: C, 40.99%; H, 7.69%. Found: C, 40.68%; H, 7.32%. [α]₀ (0.0024 M, H₂O) = -7.49°.

Preparation of Benzyl[1-azonia-4-[(S)-3',4'-di-(4'-chlorobutanoyloxy)butyl-1'-aza]bicyclo-[2.2.2]octane Bromide Chloride (5b). The diol 5a (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 × 50 mL) and diethyl ether (2 × 50 mL). The residue was dried under high vacuum to yield a hydrosopic white solid (dry weight 0.070 g, 56.7% yield) that exhibited spectral and elemental analyses in accord with the octahydrate of the proposed structure 5b. 1H NMR (δ D₂O) 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). 13C NMR (D₂O) 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. C₂₀H₂₃N₂O₂Cl₂Br·8(H₂O) requires: C, 39.46%; H, 7.15%. Found: C, 39.62%; H, 7.02%. [α]₀ (0.011 M, H₂O) = +1.77°.

Elaboration of the Modified Focus Site 5b to the First-Generation Dendrimer 5c. In a 100 mL r.b. flask fitted with a magnetic stirrer, heating bath, and reflux condenser were placed 5b (0.070 g, 0.11 mmol) with acetonitrile (50 mL) and 3 (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 × 50 mL). To the residue was added hydrochloric acid (10–M, 25 mL), and the mixture was stirred for 4 hours. After this time, all volatile materials were evaporated under high vacuum to give a hydrosopic white solid (dry weight 0.030 g, 26.1% yield) that exhibited spectral and elemental analyses in accord with a hydrated form of the proposed structure 5c. 1H NMR (δ D₂O) 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). 13C NMR (D₂O) 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. C₂₀H₂₃N₂O₂Cl₂·13(H₂O) requires: C, 42.22%; H, 8.35%. Found: C, 42.22%; H, 8.03%. [α]₀ (0.0029 M, H₂O) = -6.33°.

Preparation of 1,4-Xylylenebis[1'-azonia-4-[(S)-3',4'-dihydroxybutyl]azaindicyclo[2.2.2]octane Di-bromide Dichloride (6). A solution of 3 (8.57 g, 36.0 mmol) in acetonitrile (25 mL) was placed in a reaction flask fitted with a magnetic stirrer, reflux condenser, and drying tube, and to it was added 1,4-bis(bromomethyl)benzene (4.66 g, 17.8 mmol). After stirring for 4 hours, the resultant precipitate was collected by filtration with suction through sintered glass. The recovered solid was stirred in aqueous solution with AMBERLYST™-15 in the acid form. After removal of the AMBERLYST™-15 by filtration, the volatile materials were evaporated under high vacuum, and the resulting solid was washed with ethyl acetate, cold absolute ethanol, and diethyl ether. There was thus isolated a mildly hydrosopic
white solid (dry weight 7.63 g, 57.5% yield) that exhibited spectra and elemental analyses in accord with the trihydrate of the proposed structure 6. \(^1\)H NMR (\(^{1}D_2O\)) 1.74–2.00 (4H, m), 3.39–4.14 (34H, brm), 4.81 (4H, s), 7.67 (4H, s). \(^{13}\)C NMR (\(^{1}D_2O\)) 134.55, 128.63, 68.83, 68.16, 65.35, 63.21, 51.67, 51.27, 25.55. Anal. C\(_{48}\)H\(_{102}\)N\(_4\)O\(_{18}\)Br\(_{3}\) requires: C, 42.49%; H, 7.13%. Found: C, 42.40%; H, 7.43%. [\(\alpha\)\]D\(_{2}\) (0.012 M, \(H_2O\)) = –5.11°.

**Preparation of 1,4-Xylylenebis-[1'-azonia-4'-[(S)-3',4'-di-4'-chlorotetrahydroxybutyl]azoniabicyclo[2.2.2]octane] Tetrachloride (6a).** The tetral 6 (0.50 g, 0.68 mmol) along with acetonitrile (100 mL) was placed in a 250 mL flask fitted with a magnetic stirrer. To it was added an excess of 4-chlorobutanoyl chloride (1.18 g, 8.33 mmol) and the reaction flask topped with a drying tube. After stirring for 4 days, diethyl ether (50 mL) was added to the clear reaction solution resulting in the formation of an oily precipitate. The supernatant was decanted, and the residue was washed/decanted with ethyl acetate (3 × 50 mL) and diethyl ether (2 × 50 mL). There was thus isolated a solid that was dried under high vacuum to yield a hydrosopic off-white solid (dry weight 0.269 g, 34.2% yield) that exhibited spectral data in accord with the proposed structure 6a. A sample of this material was dissolved in water and passed through a bed of DOWEX 2 in the chloride ion form. After precipitation of the water under vacuum, there was isolated a solid that exhibited elemental analyses in accord with the pentahydrate of the tetrachloride form of the proposed structure 6a. \(^1\)H NMR (\(^{1}D_2O\)) 1.94–2.05 (8H, m), 2.09–2.32 (4H, m), 2.43–2.55 (8H, m), 3.45–4.13 (40H, brm), 4.40 (2H, m), 5.12 (4H, brs), 7.68 (4H, s). \(^{13}\)C NMR (\(^{1}D_2O\)) 173.79, 173.39, 132.84, 126.99, 67.84, 67.76, 63.34, 60.21, 50.03, 49.52, 43.12, 42.50, 29.87, 29.73, 25.79, 25.59, 21.82. Anal. C\(_{48}\)H\(_{102}\)N\(_4\)O\(_{18}\)Br\(_{3}\) requires: C, 45.69%; H, 6.97%. Found: C, 45.96%; H, 7.09%. [\(\alpha\)\]D\(_{2}\) (0.003 M, \(H_2O\)) = –0.53°.

**Elaboration of the Modified Focus Site 6a to the First-Generation Dendrimer 6b.** In a 100 mL r.b. flask fitted with a magnetic stirrer, heating bath, and reflux condenser were placed 6a (dibromide–dichloride form) (0.170 g, 0.147 mmol) with acetonitrile (50 mL) and an excess of 3 (0.184 g, 0.752 mmol). The reaction mixture was stirred for 7 days, after which the supernatant was decanted. The residue was further washed/decanted with cool acetonitrile (3 × 50 mL). To an aqueous solution of the residue was added AMBERLYST\textsuperscript{TM}-15 in the acid form, and the mixture was stirred overnight. After removal of the AMBERLYST\textsuperscript{TM}-15 by filtration, the volatile materials were evaporated under high vacuum, and the resulting solid was washed with ethyl acetate and diethyl ether to give an extremely hydroscopic semisolid (dry weight 0.182 g, 58.0% yield) that exhibited spectral and elemental analyses in accord with a hydrated form of the proposed structure 6b. \(^1\)H NMR (\(^{1}D_2O\)) 1.88–2.56 (28H, complex), 2.36–4.15 (104H, m), 4.35 (6H, m), 5.09 (4H, brs), 7.68 (4H, s). \(^{13}\)C NMR (\(^{1}D_2O\)) 175.74, 175.68, 135.32, 129.41, 71.58, 71.50, 70.30, 70.21, 68.98, 68.90, 67.14, 64.98, 63.68, 62.69, 52.51, 52.01, 46.22, 45.69, 45.68, 45.62, 45.02, 44.54, 32.37, 32.25, 28.31, 28.25, 26.49, 25.28, 24.34. Anal. C\(_{48}\)H\(_{102}\)N\(_4\)O\(_{18}\)Br\(_{3}\) requires: C, 41.57%; H, 7.89%. Found: C, 41.45%; H, 7.62%. [\(\alpha\)\]D\(_{2}\) (0.0014 M, \(H_2O\)) = +8.7°.

**ACKNOWLEDGMENTS**

The authors wish to acknowledge the Howard Hughes Medical Institute, CUNY-AMP, and the PSC-CUNY Research Award Program for financial support of the project, and the National Science Foundation for the purchase of the NMR instrument.

**REFERENCES**


