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(54) Title: BRANCHED POLYOXAALKYL MACROMOLECULES, PROCESS FOR MAKING THEM AND THEIR USES

(57) Abstract

Branched, dendrimeric-type macromolecules composed essentially of a central nucleus and of a series of polyoxaalkyl chains that depart from said nucleus and spread into the surrounding space branching in a cascade fashion useful as carriers of drugs, contrast agents, etc.

BRANCHED POLYOXAALKYL MACROMOLECULES, PROCESS FOR MAKING THEM AND THEIR USES

The present invention concerns a new class of branched, dendrimeric-type macromolecules composed essentially of a central nucleus and of a series of polyoxaalkyl chains that depart from said nucleus and

5   spread into the surrounding space branching in a cascade fashion until the desired size is obtained. The molecules formed in this way do not have excessive functional crowding on their outer surfaces. The invention also includes the synthetic method for

10   obtaining these molecules as well as their uses.

Over the past decade dendrimeric macromolecules have stirred considerable interest because of their intrinsic features which are very different from those of highly polydispersed linear or branched polymers

15   produced by polymerisation processes. On the contrary, dendrimers are obtained through synthetic procedures involving a step-by- step growth which allow for greater control over molecular mass, size and shape. Dendrimeric molecules are characterized by having a

20   central nucleus, termed "core", from which chains originate and branch off to the periphery to occupy all the available space. This leads to a multibranched ordered structure having many functional groups on the external surface. Such a molecule can have a highly

25   congested surface capable of controlling the diffusion of small chemical entities into and out of the dendrimeric structure. Depending on the kind and dimension of their constituents, such macromolecules

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can assume different geometric shapes (spheroidal, cylindrical, mushroom-like, ellipsoidal etc.). Compared with other branched polymers, these macromolecules usually are endowed with a relatively low intrinsic
5   viscosity (limiting viscosity number) even at high molecular masses.

Macromolecules with different denominations, synthesized and patented by different research groups can be included in this class of derivatives. The main
10 classes are shown in Table I.

Table I   Main classes of dendrimeric macromolecules

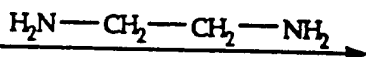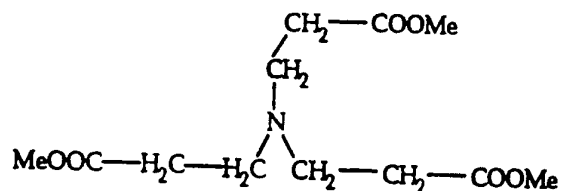| Denomination	Research group	References	Main patents	Chemical structures
Starburst	Tomalia	1-5	US 4,587,329	Starburst dendrimers include: polyamidoamines (PAMAM), polyethyleneimines (PEI), polyethers (PE) polythioethers.
Denkewalter dendrimers	Denkewalter	6	US 4,289,872	Lysine-based branched polymers.
Arborols	Newkome	7-12 29	WO 9321144	Arborols include molecules having either a benzene "core" or a "core" with four saturated hydrocarbon branches.
Dendrimeric poliethers	Fréchet	13-19	US 5,041,516 WO 9208749 WO 9321259	Functionalized benzenes poliethers synthesized through an original synthetic approach (convergent synthesis).
DSM dendrimers	De Brabander-van den Berg	30	WO 9314147	Poly(propylene imine) dendrimers with branches prepared from vinyl cyanide units.

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Starburst dendrimers (Ref. 1-5)

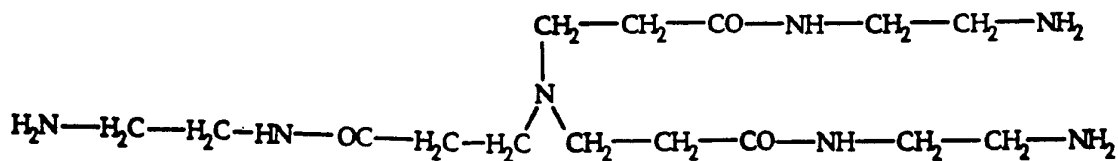Starburst dendrimers synthesized by Tomalia et al. include:

a) Starburst polyamidoamine (PAMAM) dendrimers (Ref. 1-3).

These are compounds with either a nucleophilic or an electrophilic "core". One of the most widely used nucleophilic "core" is ammonia. In this case, the synthesis involves a preliminary reaction with methyl acrylate (Michael's addition) to form a triester which is then amidated with ethylenediamine to form a first generation molecule containing 3 terminal amino groups (Scheme 1).

Scheme 1

$$NH_3 + CH_2\!=\!CH_2\!-\!COOMe \longrightarrow$$

$$
\begin{array}{c}
CH_2\!-\!COOMe\\
|\\
CH_2\\
|\\
MeOOC\!-\!H_2C\!-\!H_2C\!-\!N\!\!\begin{array}{c} \\ CH_2\!-\!CH_2\!-\!COOMe\end{array}
\end{array}
$$

$$\xrightarrow{\ H_2N\!-\!CH_2\!-\!CH_2\!-\!NH_2\ }$$

$$
\begin{array}{c}
CH_2\!-\!CH_2\!-\!CO\!-\!NH\!-\!CH_2\!-\!CH_2\!-\!NH_2\\
|\\
N\\
H_2N\!-\!H_2C\!-\!H_2C\!-\!HN\!-\!OC\!-\!H_2C\!-\!H_2C\!\!\begin{array}{c} \\ CH_2\!-\!CH_2\!-\!CO\!-\!NH\!-\!CH_2\!-\!CH_2\!-\!NH_2\end{array}
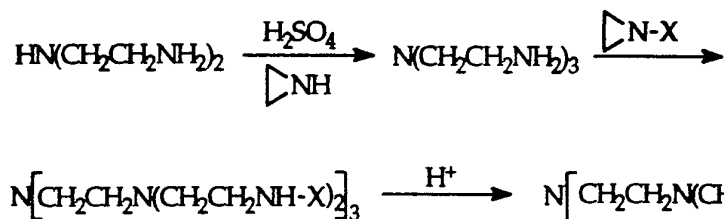\end{array}
$$

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By repeating these synthetic steps the dendrimer
grows in diameter by approximately 10 Å per
generation evolving from an undefined shape for
generations 0-2 to an oblate spheroid for
generations 3-4 and finally to a nearly
symmetrical spheroid for generations 5 and higher.
Another example of "core" is ethylenediamine.

b) Starburst polyethyleneimine (PEI) dendrimers (Ref.
1).

These molecules derive from a symmetrical "core"
comprising 3 amino functions, obtained through
alkylation of diethylenetriamine with aziridine.
The first generation is obtained by reacting this
"core" with N-tosylaziridine or N-mesylaziridine
and by subsequent deprotection (Scheme 2).

Scheme 2

$$HN(CH_2CH_2NH_2)_2 \xrightarrow[\text{[}NH]{H_2SO_4}} N(CH_2CH_2NH_2)_3 \xrightarrow{\text{[}N\text{-}X}$$

$$N[CH_2CH_2N(CH_2CH_2NH\text{-}X)_2]_3 \xrightarrow{H^+} N[CH_2CH_2N(CH_2CH_2NH_2)_2]_3$$

x = tosyl or mesyl

The higher generations are obtained by repeating
these synthetic steps. PEIs differ from PAMAMs
because of their short branch-segment lengths. For
each generation, the diameter increases by only 5
Å compared with the 10 Å of PAMAMs. The CPK®
(Corey Pauling Koltun) models indicate that these
dendrimers are much more compact and congested

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than the starburst PAMAMs. These models show that
the 5th generation is impossible due to the so-
called "dense-packing" phenomenon or excessive
crowding of surface functional groups, phenomenon
which makes impossible or only partially possible
the further growth of the molecule (Ref. 1).
Compared with PAMAMs, PEIs   possess more stable
chemical bonds.

c) Starburst polyether dendrimers (Ref. 1, 4, 5).
These dendrimers are examples of macromolecules
endowed with the maximum packing effect due to the
high   multiplicity of the "core" (4 functional
groups), and of the branching points (3 functional
groups per unit). This gives rise to very compact
molecules having highly   congested microdomains
which possess only very small internal voids. The
starting molecule, pentaerythritol   tetrabromide,
is reacted with pentaerythritol molecules   in
which the 3 hydroxyl functions are protected as
orthoesters. The resulting molecule assumes a
spheroidal shape from the first generation. As a
consequence by the fourth generation, which should
possess 324 hydroxy   groups on the external
surface, a highly constrained and rigid system
with no internal voids or channels should be
formed. Indeed, the fourth generation cannot
itself be obtained because of excessive steric
hindrance on the external surface. Synthetic
studies revealed that branching defects became
progressively higher as one advanced from
generation 2 to generation 3.

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d)   Starburst polythioether dendrimers (Ref. 1).

These are similar to the polyethers except that a mercaptobicyclic orthoester is used for the coupling step instead of the hydroxybicyclic orthoester. In this way, a dendrimer containing thioether bonds and hydroxyl groups on the external surface is obtained. In the case of polythioether dendrimers, the molecules are already hindered by the second generation and attempts to obtain the third generation have so far been unsuccessful. The main difference between PAMAMs and polyether and polythioether dendrimers is that the latter molecules assume a congested structure starting already from the first generation and have almost no internal voids. They are therefore much more compact molecules.

Denkewalter's dendrimers (Ref. 6).

Denkewalter et al. (Ref. 6) reported the synthesis of lysine-based dendrimers obtained by using the classic approach for solid-phase peptide synthesis. The lysine trees were constructed using a benzhydrylamine resin and N-protected tert-butyloxycarbonyl lysine. The branching points, i.e. the lysine amino groups, are located on segments of different length.

Polyamidoalcohol dendrimers (arborols) (Ref. 7-12, 29).

They have been synthesized by Newkome and co-workers. This class of dendrimers is an example of a heterogeneous series of highly branched compounds with a large number of functional groups on the external surface. In the literature, only low-generation

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molecules are described, usually of just first or second generation. The cascadepolymers have been synthesized starting either from a benzene ring, to which three cascade spheres are attached, or from alkyl halides with a single cascade sphere. More recently, arborols with a skeleton consisting of saturated hydrocarbon chains with external hydrophilic groups, have been developed. These macromolecules can host non-polar molecules in their lipophilic cavities and may thus be regarded as unimolecular micelles.

Polyether dendrimers (Ref. 13-19).

These derivatives have been synthesized by Fréchet and co-workers through an original synthetic approach involving two distinct steps:

a) preparing preformed dendrimeric fragments containing a reactive group, termed the "focal point";

b) assembling the dendrimeric molecule through reaction of the fragment focal points with the "core", which consists of a polyfunctional molecule.

However, by this approach the synthesis of dendrimers of fourth and higher generations is difficult because the reactivity of the focal point is reduced due to steric hindrance. The propagation monomers of these molecules are constituted by polyfunctional benzenes and thus these molecules are endowed with a certain degree of rigidity.

The first attempts at synthesizing branched molecules date back to 1978 when Buhleier, Wehner, and Vögtle, (Ref. 20) proposed a synthetic scheme that

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involved the frequent repetition of similar steps which would add successive branches to a starting molecule. In this way, compounds with increasingly growing cavity size were obtained. This process, termed "cascade-like" synthesis, used linear or cyclic mono or diamines as starting molecules which, by reaction with acrylonitrile followed by reduction, give rise to new branching points. Recently, other types of dendrimers have been synthesized. Miller et al. (Ref. 21) prepared a series of dendrimers, containing 4, 10, 22 or 46 benzene rings which possess symmetrical and rigid molecular structures. Such dendrimers are thermally stable and, with the exception of the sparingly soluble first generation, are soluble in organic solvents such as THF, toluene and chloroform. The author suggested the use of these products as standards for size-exclusion chromatography. Uchida et al. (Ref. 22) and Mathias and Carothers (Ref. 23) synthesized silicone-based dendrimers up to the third generation. However, for the dendrimers of Mathias and Carothers, the absolute molecular weight, molecular weight distribution and uniformity of branching are still unknown.

Dendrimers having charges within the cascade structure have been described by Rengan and Engel (Ref 24, 25). These are phosphonium or ammonium sites and only the first three generations have been synthesized. Morikawa et al. (Ref. 26) synthesized starburst dendrimers containing polysiloxane units up to the third generation whose potential applications could be as drug carriers. Nagasaki et al. (Ref. 27) described

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the synthesis of arborols with encapsulated crown ethers in the hope of producing compounds with novel physical properties such as the selectivity towards alkali metal ions, the allosteric effect in the metal-binding process, the conformational change, induced by the metal-binding and the polyelectrolyte-like behaviour of the resulting metal complexes. However, none of these characteristics have so far been demonstrated. These dendrimers were synthesized by the convergent synthetic approach. Because of the insolubility of the first generation and the steric hindrance of functional groups on the molecule, the divergent approach was also examined but failed to give the desired molecules.

To date only the second generation has been obtained.

Polynuclear transition metal complexes of dendrimeric nature have been synthesized by Serroni et al. (Ref. 28).

Building repetition blocks are linked not only through covalent bonds but also through metal chelate bonds.

Brabander-van den Berg et al. (Ref. 30) synthesized poly(propylene imine) dendrimers up to the fifth generation. These dendrimers are obtained through repetitive double Michael addition of acrylonitrile to primary amines, followed by a heterogeneously catalyzed hydrogenation of the nitriles. These kinds of dendrimers are not sensitive to hydrolytic degradation and are stable at high temperature. The process by which they are prepared is suitable for large scale

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productions.

As already mentioned, dendrimers reported in the literature have been obtained by two different synthetic approaches:

a)   divergent synthesis;

b)   convergent synthesis.

The syntheses of most dendrimers have been accomplished using the divergent process. This implies that a polyfunctional molecule is used as a "core" and that, in order to introduce multiplicity, each functional group is bonded to a molecule which also comprises more than one protected reactive site ("propagation monomer"). A first generation dendrimer is thus formed which, by exhaustive addition of polyfunctionalized monomers, gives rise to the next generation and so on. Monomer protection/deprotection systems need to be used in order to perform the selective modification of specific groups at each synthetic step.

Convergent synthesis, as first proposed by Fréchet, differs from the divergent approach in that growth starts at what will become the periphery of the macromolecule.

Such a method results in the formation of large dendrimeric fragments, which ultimately are attached through a reactive group ("focal point") to a polyfunctional "core".

Convergent synthesis has certain advantages over divergent synthesis. With divergent synthesis, the molecule's growth occurs through the simultaneous addition of an increasing number of reactive sites.

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With the convergent approach, on the other hand, size increase involves a limited number of reactive sites. Convergent synthesis makes use of a smaller excess of reagents. Possible side reactions are therefore avoided and the final products more easily purified.

However, one limitation of the convergent approach is that, as the size of the dendrimers increases, there is an increase in the steric hindrance near the functional group, or focal point, which prevents the group from reacting with the "core". This limitation is also common in divergent synthesis since the size of the molecule increases more slowly than the number of external functional groups. This leads to an increase in steric hindrance around the functional groups which are thus prevented from reacting to give the next generation.

There are notable differences among the different types of dendrimers. With regard to the starburst dendrimers, PAMAM and the polyethers possess different multiplicity of the "core" (3 for PAMAM; 4 for the polyethers); as a result PAMAM are much less sterically hindered than the polyethers and show internal cavities. These characteristics allow the synthesis of PAMAM products with higher generation numbers than is possible with polyethers for which the phenomenon of "dense-packing" is already apparent by the third generation. On the other hand, the early generations of PAMAM dendrimers, unlike the polyethers, do not have definite shapes; only the more advanced generations of PAMAM dendrimers have definite shapes. In addition, the large excess of reagents (typically ethylenediamine)

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that are required for the synthesis of PAMAM can cause problems.

In the early generations these reagents are easily removed.

However, as dendrimers grow, the removal of these excesses becomes more difficult. The same is true for certain by-products which may arise from incomplete Michael addition reactions, from intramolecular cyclizations, from fragmentation due to retro-Michael reactions or from intermolecular cyclizations that result in the formation of bridges between two dendrimers. These problems are not seen with starburst polyethers where an excess of reagents is not necessary and where the dendrimers are crystalline.

This makes the purification of polyether dendrimers much easier.

As regards L-lysine-based Denkewalter dendrimers, they have asymmetric "branches" and their structures have not been rigourously established. The different lengths of the "branches" can cause steric hindrance because a few functional groups are buried in the internal part of the molecule and therefore sterically hindered and unreactive.

Newkome et al. (Ref. 8-12, 29) have synthesized less branched, less sterically hindered molecules which have large lipophilic internal cavities capable of accepting hydrophobic molecules and which in solution behave similarly to micelles. The synthesis of such molecules is rather complex, because of the unreactivity of the neopentyl centre ("core") to nucleophilic reactions (Ref. 11). To overcome this

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drawback, the introduction of a "spacer" of at least 3 atoms was necessary.

The dendrimeric macromolecules described above have been synthesized with specific uses in mind. They could, for example, be used as transporters of high quantities of substances and it is for this reason that dendrimers are extensively studied as possible "carriers" for the controlled and targeted release of drugs. It is possible to prepare dendrimers with a lipophilic interior and a hydrophilic surface thus obtaining molecules that can function as micelles. Compared to micelles, such molecules, as a result of their intrinsic characteristics, could show much greater stability. By utilizing suitable monomers in the latter generation, it is theoretically possible to control the porosity of the external sphere of the molecule. In this regard, dendrimers can perhaps be compared with cells. Furthermore, these polymers are characterized by large surface areas which, in combination with high solubility in organic solvents, might facilitate their use as carriers of catalysts that could be recovered at the end of the reaction by simple extraction or filtration.

Compounds that are suitable for association with dendrimers are, in general, molecules that can be used either for therapeutic treatment or for in vivo or in vitro diagnosis. Compounds of this type are for example pharmaceuticals (such as antibiotics, analgesics, antihypertensives, and cardiotonics) used in the treatment of various diseases; radionuclides; signal generators and absorbers; antibodies; metal chelates;

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opacifying diagnostics and hormones. The in vivo and in vitro diagnostic procedures which could benefit from the use of dendrimer derivatives are, for example: radioimmunologic assays, electron microscopy, ELISA, X-ray imaging, magnetic resonance imaging (MRI) and immunoscintigraphy. Dendrimers can also have other uses, for example as "carriers" of chemical substances for agriculture, as adhesives, as absorbents, as oil/water demulsifiers, as thickeners of plastic materials, as calibration standards for ultrafiltration membranes and electron microscopy, as standards for size-exclusion chromatography, and as agents to modify the rheological properties of solutions of dyes and paints. Despite all these possible applications, however, none as yet have been fully realised. This is in part due to the difficulties in synthesizing dendrimers with a large number of generations (because of the "dense-packing" problem), and in part because of the difficulties in the synthesis of three-dimensional structures with adequate internal cavities, in terms of number and dimension, for the intended use.

The objects of the present invention are new, dendrimeric-type macromolecules that comprise the following structural groups:

a)   a central "core", derived from a polyvalent organic molecule from which at least two polyoxaalkyl chains originate,

b)   at least two polyoxaalkyl chains, preferably polyoxyethylene or polyoxypropylene, that are connected to the above-mentioned "core",

c)   at least two polyvalent branched organic residues

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attached to the ends of said chains which function
as branching points for the subsequent growth of
the molecule, because each of these points can be
reacted with two or more reactive groups of other
5   polyoxaalkyl chains,

d)   possibly further polyoxaalkyl chains and branching
points added in succession until the molecule
reaches the desired dimension.

One polyoxaalkyl chain, taken together with its
10   branching point, constitutes a growth, or repetition
unit. The total amount of growth units comprised in the
same shell or growth level represents a generation.

"Core" and branching points are characterized by a
multiplicity number which refers to either the number
15   of functional groups on the "core", that enable growth
of the molecule, or to the degree of branching possible
at each branching point.

The introduction of the first branching point in
the molecule determines the first generation, the
20   introduction of a successive branching point determines
the second generation and so on. The length of the
polyoxaalkyl chain between the "core" and the first
branching point, or between one branching point and the
next one, can vary.

25   Such chain lengths are chosen according to the
structure and the characteristics required for the
macromolecule. For example, the chain length influences
the formation of the internal cavities within the
structure and/or the compactness (density) of the
30   molecule, and in the early generations particularly,
its geometric form as well. The polyoxyethylene chains,

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as a non-limiting example of polyoxaalkyl chains, are characterized by the $-[OCH_2CH_2]n-$ unit where n is a number from 0 to 25 and preferably from 0 to 15. It is therefore possible, when n = 0, to have two branching points next to each other without a polyoxaalkyl chain separating them. Nevertheless, highly preferred compounds are those in which at least one of the generations include polyoxaalkyl chains in which n is different from 0. The distance between the "core" and the first branching point, or between one branching point and next one, is determined by the length of the polyoxaalkyl chain, i.e. by the value of n. This value can be equal in each generations or can vary from generation to generation.

The central nucleus of the compounds of the present invention can derive from any polyvalent, aliphatic organic open chain residue, both branched and not, or from alicyclic residues, or from heterocyclic residues containing N, O and/or S, or from aromatic or heteroaromatic residues. All of them are substituted by at least two reactive groups to which the polyoxaalkyl chains of the first generation are covalently attached. The "core" can also possess one or more reactive groups that do not participate to the growth of the molecule but which are possibly available for the coupling to other structures or as dimerization points. Absolutely non-limiting examples of "core" include, among others, NH3, substituted amines, diamines, suitably functionalized aromatic rings, molecules with neopentyl centres (pentaerythritol, hydroxymethylpropantriol), and triaza- and tetraazamacrocycles. Branching points

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can consist of polyvalent residues with at least two or three reactive functions suitable for introducing multiplicity. In each dendrimer, the branching points can be the same in each generation or may vary from generation to generation.

Multiplicity can also be introduced for example using polyoxaalkyl chains in which the terminal part is already branched. The multiplicity of the "core", the multiplicity of the branching points and the value of n can be chosen according to the characteristics/properties desired in the final macromolecule. In this way it is possible to obtain macromolecules with different distributions of functional groups on the external surface: for example, zonal distribution if the polyoxaalkyl chains connected to the "core" are long and those of the branches short, or uniform distribution if the polyoxaalkyl chains are of equal length. In both cases there will be a different density of terminal groups and/or chains between the peripheral and the central part of the molecule. Increasing the branching multiplicity, with all other parameters equal, results in a notable increase of hindrance at the peripheral part of the structure, relative to the central part. With the degrees of freedom conferred by the length of the polyoxaalkyl chains, by the multiplicity of the "core" and the branching points, one can obtain macromolecules with internal cavities of different dimensions, which are either all equal or which vary from generation to generation.

A further advantage arising from the introduction of

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polyoxaalkyl chains between the "core" and the first branching point, or between one branching point and the next one, is that in this way it is possible to construct molecules that are able to grow further giving structures with a large number of generations. This is the fundamental point of the present invention. Additionally, it is also possible to avoid the phenomenon of "dense-packing", a phenomenon that severely hampers the preparation of the dendrimers of the prior-art by restricting the number of successive generations obtainable. As a general rule, one of the main obstacles to the synthesis of dendrimeric structures is the excessive surface area crowding that inevitably arises with higher numbers of generations. For this reason the growth of the structure becomes progressively more difficult; for example, preparation of molecules of the third generation, in the case of polythioethers, or of the fourth in the case of polyethers, is effectively impossible as reported by Tomalia (Ref. 1).

On the contrary the introduction of polyoxaalkyl chains enables the preparation of molecules with less compact structures. For these macromolecules, problems due to the inclusion of reagents and solvents during the various synthetic steps, phenomenon which can cause significant difficulty during the purification process, are very much reduced.

The external surfaces of the macromolecules of the present invention are well provided with functional groups such as for example hydroxyl, tosyl, mesyl, tresyl, brosyl and similar groups,

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trifluoromethanesulfonyl, phthalimido, amino, thiol, aldehydo, nitrilo, acetyl, pyranyl, cyclic orthoester, carboxyl and amido groups.

As a consequence, the compounds of the present invention may be ideally suited to the transport of drugs and/or molecules for use in diagnostic imaging. Both these classes of compounds can be linked to such macromolecules, either directly or through suitable spacer chains, alternatively they can be included in the macromolecules themselves.

Concerning diagnostic imaging, it is, for example, possible to obtain contrast agents for magnetic resonance (MRI) by linking paramagnetic metal chelates, such as chelates of polyaminopolycarboxylic acids, to these molecules. In this respect they could represent a good solution to the development of new effective blood-pool agents.

Ferromagnetic or superparamagnetic (ferrite, magnetites or derivatives thereof) compounds can also be included in the internal cavities of the macromolecules for diagnostic use in MRI.

The macromolecules of the present invention can also be linked to chelates of radioactive metal ions for use in nuclear medicine, or conjugated to iodinated molecules for use in all roentgenographic diagnostic investigations.

The molecules may also be labelled with isotopes such as ^{13}C, ^{14}C, ^2H, ^3H or ^{125}I and used subsequently in biodistribution studies. Moreover, they may be used in the preparation of pharmaceutical products where controlled release of the active principle is required.

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Moreover, it is even possible to modify the external functional groups with suitable hydrophobic groups to create a molecular structure that behaves as an inverse micelle, i.e. with a hydrophilic internal part and a hydrophobic surface.

Moreover such macromolecules are highly promising as carriers of catalysts, allowing a complete recovery of the same after the reaction. Finally, since the macromolecules of the present invention can be prepared to precise and definite dimensions, they are particularly useful as calibration standards for separation techniques based on molecular shape, such as for example size-exclusion chromatography.

The compounds of the present invention are represented by the following general formula (I)

$$A[G_{1-->p}]_r \qquad (I),$$

where:

A   is a central nucleus, or "core", deriving from a polyvalent organic molecule which can be an aliphatic open chain, branched or not, residue, or an alicyclic, or a heterocyclic residue containing N, O and/or S, or an aromatic or a heteroaromatic residue and which is characterized by the presence of r terminal residues to which the polyoxaalkyl chains of the first generation are attached,

r   is an integer from 2 to 10 representing the multiplicity of the "core" A,

$G_{1-->p}$ represents the branched structure of the macromolecule comprising g levels of generations, from the first one (g_1) to the
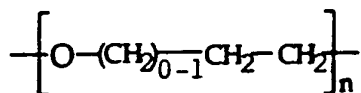
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last one (g_p) in which the total p number of
said generations can range from 1 to 20 and
in which the different generations can
contain the same repetition units or not, and
in which:

a)   each generation g, except for the last, comprises
a number of repetition units, which are
represented by residues of formula

-B-M-

where:

B   is preferably a polyoxyethylene or
polyoxypropylene chain of formula:

$$\left[O-(CH_2)_{0-1}CH_2-CH_2\right]_n$$

in which n can range from 0 to 25 and is different
or not from generation to generation, provided
that, in at least one of the generations of the
macromolecule, n is different from 0,

M   represents a branching point which derives from a
polyvalent aliphatic residue comprising:

-      a single functional group such as OH, NH_2,
SH, COOH, or a derivative thereof, able to
link with the terminal group of chain B,

-      m reactive residues for the linking of the
polyoxaalkyl chains of the next generation,
being

m   an integer ranging from 2 to 5, representing the
branching multiplicity introduced by M and being m
different or not from generation to generation,

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and

being the total number of repetition units -B-M-
in each generation level g equal to the sum of all
the branching multiplicities m of the preceding
generation g_{-1};

b)   the last generation gp comprises residues of
formula:

$$-B_p-M_p[T]_{mp}$$

where B_p, M_p, m_p are defined analogously to B, M,
and m, with the difference that all the m_p
reactive residues of M_p are connected to groups T
in which

T   is a terminal group that can be either H or one of
the following residues: halo, hydroxyl, amino,
thiol, -O-tosyl, -O-mesyl, -O-tresyl, -O-brosyl
and similar groups, trifluoromethanesulfonyl,
aldehydo, carboxy, amido group, such a terminal
group T being free, either dissociated or
undissociated, or protected by suitable
protective groups such as for example, pyranyl,
phthalimido, acetyl, cyclic orthoester group etc.
and

being the total number of the terminal groups T
equal to the sum of all the branching
multiplicities m of the last generation gp, and
with the further condition that

M_p can also be a single bond, in which case m_p is
equal to 1 (i.e., there is no branching) and as a
consequence the last generation g_p comprises
residues of formula:

$$-B_p-T$$

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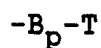
where Bp and T are as above defined;

c) in case p = 1, that is when the macromolecule contains only one generation, g_p corresponds to g_1, i.e. represents the residue:

$$-B_1-M_1[T]_{m1}$$

where B_1, M_1, m_1 and T are defined analogously to B_p, M_p, m_p and T.

As a consequence, in this case the macromolecule is represented by the following formula

$$A[g_1]_r, \text{ i.e.}$$

$$A[B_1-M_1[T]_{m1}]_r$$

in which A, B_1, M_1, T, m_1 and r are defined as above.

Compounds of general formula (I) also comprise those ones which are labelled with isotopes such as ^{13}C, ^{14}C, ^2H, ^3H, and ^{125}I.

For seek of clarity a schematic representation of the structure of the macromolecules of the present invention is sequentially developed according to the following series of formulae:

$$A[G_{1-->p}]_r \hspace{2cm} (I),$$

where:

$G_{1-->p}$ represents $B_1-M_1[G_{2-->p}]_{m1}$, in which B_1-M_1 is g_1 and

$G_{2-->p}$ represents $B_2-M_2[G_{3-->p}]_{m2}$, in which B_2-M_2 is g_2 and

so on until the last generation is reached in which

G_p represents $B_p-M_p[T]_{mp}$,

where the symbols used are as above defined.

The afore-mentioned development can be illustrated in complete form by the following expanded general formula (II)

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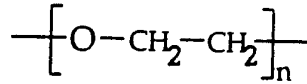$$A[B_1-M_1[B_2-M_2[-->--->--->[B_p-M_p[T]_{mp}]-->--->--->]_{m2}]_{m1}]_r \quad (II)$$
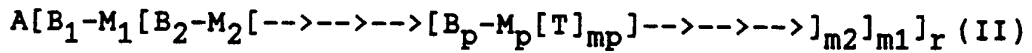
Compounds of the present invention which are particularly preferred are those in which r ranges from 2 to 6, preferably from 2 to 4 and in which the "core" A is a neopentyl residue of formula
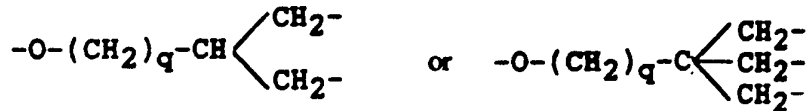
$$C(CH_2-)_4$$

Equally preferred are those in which B is a polyoxyethylene chain of formula

$$-\left[O-CH_2-CH_2\right]_n-$$

in which n is an integer from 0 to 25, preferably from 0 to 15.

Also preferred are those in which M is a bi- or trifunctional branching point represented by a residue of formula:

$$-O-(CH_2)_q-CH\begin{matrix}CH_2-\\CH_2-\end{matrix} \quad or \quad -O-(CH_2)_q-C\begin{matrix}CH_2-\\CH_2-\\CH_2-\end{matrix}$$

in which q is an integer from 0 to 4, preferably from 1 to 2.

Preferred macromolecular compounds are those in which the total number of generations ranges from 1 to 20, preferably from 1 to 15.

As an example of the invention one of the preferred classes of compounds is represented by those having the following general formula (III)

$$C\left[CH_2-(OCH_2CH-)_n-O-CH_2-C\left[CH_2-L\right]_3\right]_4 \quad (III),$$

$$\overset{|}{g_1}$$

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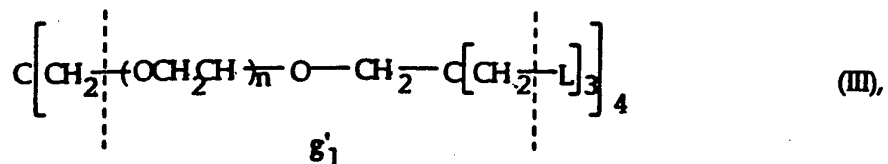
in which:

n   is an integer from 0 to 20, preferably from 0 to
     15, and with the condition that n is different
     from 0 in at least one generation,

g_1' is the first generation having a branching
     multiplicity of 3,

L   represents T, or the sequence of successive
     generations from g_2' to g_p' in which each g', apart
     from g_p', is defined analogously to g_1' and can have
     the same meaning or not whereas g_p' corresponds to
     g_1'-T and T is as above defined; moreover the
     number of generations g can be as high as 20,
     preferably 15.

     The present invention is illustrated particularly
through the preparation of branched macromolecules
having a neopentyl "core" from which four
polyoxyethylene chains depart. The branching is
obtained through the introduction of a residue of
pentaerythritol on the terminal residue of the
polyoxyethylene chains. The synthesis of the compounds
of the present invention can preferably be performed by
two independent synthetic processes:

a)   lengthening of the polyoxyethylene chain,

b)   branching.

     The order of these synthetic pathways can be
modulated at will, in particular with regard to the
type of compound and reaction conditions employed. It
is possible to decide to begin with the central nucleus
and add successively the polyoxaalkyl chains of the
first generation, the branching points, the
polyoxaalkyl chains of the second generation, the new

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branching points and so on until the desired number of generations has been reached.

Alternatively, it is equally possible to prepare already branched polyoxaalkyl chains and then to attach these to either the central nucleus or to a previously formed generation.

Obviously, just as it is possible to utilize one or the other of the two synthetic processes, it is also possible to follow in part the first process and in part the second one according to the synthetic problem to overcome. The reactive functions not involved in a specific reaction are protected with suitable protective groups according to methods well known in chemical syntheses. A consequence of this is that also the process of preparation of these macromolecular compounds forms an embodiment of the present invention.

An illustrative view of the preferred synthetic pathways is given in the experimental part below.

Obviously, the experimental part only has the aim of exemplifying the invention more completely. Consequently, it is not absolutely limiting of the invention itself and any possible change that can be produced in the described examples is immediately evident to the expert technician.

Example 1

Preparation of chlorooxyethylene chains with hydroxyl functions protected by dihydropyran

3,4-Dihydro-2H-pyran (0.6 mol) was slowly added dropwise into the desired chloroalcohol (0.5 mol) of Table II under magnetic stirring. The reaction temperature reached 100- 150°C. After allowing to cool

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to room temperature, the mixture was stirred for 2 h. The mixture was distilled under high vacuum to obtain the desired product as a colourless oil. By this synthetic pathway the following products were obtained:

AI   2-(3-chloroethoxy)oxane $(C_7H_{13}ClO_2)$

AII   2-(3-oxa-5-chloropentyloxy)oxane $(C_9H_{17}ClO_3)$

AIII 2-(3,6-dioxa-8-chlorooctyloxy)oxane $(C_{11}H_{21}ClO_4)$

The reaction yields and starting materials are summarised in Table II. Table III reports the analytical characterizations.

Table II Synthesis of protected oxyethylene chains

Product	Starting chloroalcohol	Reaction yield
AI	$ClCH_2CH_2OH$	85%
AII	$ClCH_2CH_2OCH_2CH_2OH$	91%
AIII	$ClCH_2CH_2OCH_2CH_2OCH_2CH_2OH$	80%

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Table III Analytical characterizationa

Product	b.p. (pressure)	Elemental analysis	
AI	100°C (2676 Pa)	Calculated for $C_7H_{13}ClO_2$:	C 51.11; H 7.96
		found:	C 51.21; H 7.74
AII	85°C (60 Pa)	Calculated for $C_9H_{17}ClO_3$:	C 51.80; H 8.21
		found:	C 51.64; H 8.16
AIII	125°C (60 Pa)	Calculated for $C_{11}H_{21}ClO_4$:	C 51.80; H 8.40
		found:	C 51.49; H 8.44

^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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^{1}H-NMR and ^{13}C-NMR spectra of the described products
are in agreement with the proposed structures.

Similar results were obtained when, in place of
the above-mentioned monofunctional chloroalcohols, the
bifunctional chloroalcohols, $ClCH_2-CH(CH_2OH)_2$ and
$ClCH_2-CH_2-O-CH_2-$ $CH(CH_2OH)_2$, were protected by pyranyl
groups.

Example 2

Alkylation by phase transfer catalysis of neopentyl
"core" molecules with protected oxyethylene chains
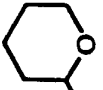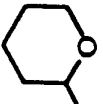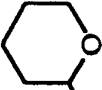
The starting tetraalcohol (0.0156 mol) (Table IV)
was dissolved in 19.06 M NaOH (0.624 mol). The reaction
mixture was than warmed to 65°C under nitrogen and
mechanically stirred. Tetrabutylammonium bromide
(0.0062 mol) and the desired chlorooxyethylenepyranyl
derivative (0.0936 mol) of Table IV, obtained according
to the method of Example 1, were then added to this
solution. The reaction mixture was incubated at 65°C
for 48 h. After this time a freshly prepared 19.06 M
NaOH solution (0.312 mol), the chlorooxyethylenepyranyl
derivative (0.062 mol), tetraoctylammoniumbromide
(0.0062 mol) and NaI (0.0036 mol) were added. The
reaction mixture was stirred for an additional 66 h at
65°C. Tetraethylammonium hydroxyde solution (10 mL; 10%
w/w in water) was then added and the mixture stirred
for 48 h at 80°C. Finally the reaction was cooled to
room temperature, diluted with H_2O and the product
extracted several times with diethylether. The organic
layers were combined and dried over Na_2SO4, filtered
and concentrated under reduced pressure. The crude
product thus obtained was subjected to fractional

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distillation and then chromatographed on a silica gel column (flash chromatography, eluent AcOEt). By this synthetic pathway the following were obtained:

BI   1,4,7,11,14,17-hexaoxa-1,17-bis(oxan-2-yl)-9,9-

5   bis[2,5,8-trioxa-8-oxan-2-yl)octyl]heptadecane

($C_{41}H_{76}O_{16}$);

BII,III   1,4,7,10,14,17,20,23-octaoxa-1,23-bis(oxan-2-yl)-12,12-bis[2,5,8,11-tetraoxa-11-(oxan-2-yl)-undecyl]tricosane ($C_{49}H_{92}O_{20}$);

10   BIV,V   1,4,7,10,13,17,20,23,26,29-decaoxa-1,29-bis(oxan-2-yl)-15,15-bis[2,5,8,11,14-pentaoxa-14-(oxan-2-yl)tetradecyl]nonacosane ($C_{57}H_{108}O_{24}$).
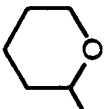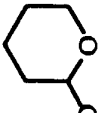
The reaction yields and starting materials are summarised in Table IV. Table V reports the analytical

15   characterizations.

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Table IV   Alkylation reactions by phase transfer catalysis

Product	Starting chlorooxyethylenepyran compound	Starting tetraalcohol	Reaction yield
BI	$ClCH_2CH_2OCH_2CH_2O$ AII	$C(CH_2OH)_4$	54%
BII[a]	$ClCH_2CH_2OCH_2CH_2OCH_2CH_2O$ AIII	$C(CH_2OH)_4$	20%
BIII[a]	$ClCH_2CH_2O$ AI	$C(CH_2OCH_2CH_2OCH_2CH_2OH)_4$ CI	50%

– (continued) –

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Table IV   – (continued)

Product	Starting chlorooxyethylenepyran compound	Starting tetraalcohol	Reaction yield
BIV[b]	 ClCH$_2$CH$_2$O AI	C(CH$_2$OCH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$OH)$_4$ CII	42%
BV[b]	 ClCH$_2$CH$_2$CH$_2$CH$_2$O AII	C(CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OH)$_4$ CI	39%

a)   BII and BIII are the same product but synthetized from different starting materials.

b)   BIV and BV are the same product but synthetized from different starting materials.

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Table V   Analytical characterization[a]

Product	Elemental analysis		
BI	Calculated for $C_{41}H_{76}O_{16}$:	C 59.69;	H 9.29
	found:	C 59.60;	H 9.28
BII	Calculated for $C_{49}H_{92}O_{20} \cdot 0,7$ mol H_2O:	C 58.08;	H 9.23
	found:	C 58.16;	H 9.30
BIII	Calculated for $C_{49}H_{92}O_{20}$:	C 58.78;	H 9.26
	found:	C 58.71;	H 9.30
BIV	Calculated for $C_{57}H_{108}O_{24} \cdot 0,5$ mol H_2O:	C 57.66;	H 9.25
	found:	C 57.29;	H 9.26
BV	Calculated for $C_{57}H_{108}O_{24} \cdot 0,6$ mol H_2O:	C 57.66;	H 9.25
	found:	C 57.49;	H 9.37

[a]   ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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Example 3

Deprotection reaction of the pyranyl derivatives

The desired tetraoxyethylenepyranyl derivative
(0.0024 mol) (Table VI), obtained according to the
5   .method of Example 2, was dissolved in a mixture of
CH_2Cl_2/MeOH 1/1 (v/v) (20 mL). 37% HCl (0.5 ÷ 0.8 mL)
was added and the reaction mixture was stirred for 7 h
at room temperature.

Subsequently, $NaHCO_3$ was added to neutral pH, the
10 inorganic salts were filtered off and the organic layer
dried over Na_2SO4. The solvent was then removed under
vacuum. The crude product was chromatographed on a
silica gel column (eluent CH_2Cl_2/MeOH = 85/15 (v/v)).
By this synthetic pathway the following compounds were
15 obtained:

CI   3,6,10,13-tetraoxa-8,8-bis-(2,5-dioxa-7-
hydroxyheptyl)pentadecan-1,15-diol ($C_{21}H_{44}O_{12}$);

CII   3,6,10,13,16,19-hexaoxa-11,11-bis(2,5,8-trioxa-10-
hydroxydecyl)enicosan-1,21-diol ($C_{29}H_{60}O_{16}$);

20 CIII 14,14-bis(2,5,8,11-tetraoxa-13-hydroxydecyl)-
3,6,9,12,16,19,22,25-octaoxaheptacosan-1,27-diol
($C_{37}H_{76}O_{20}$)

The reaction yields and starting materials are
summarised in Table VI. Table VII reports the
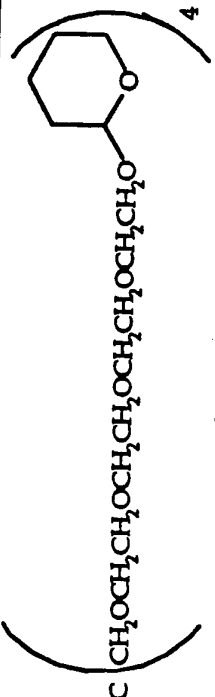25 analytical characterizations.

30

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Table VI   Deprotection reactions

Product	Starting tetraoxyethylenepyranyl	Reaction yield
CI	$C(CH_2OCH_2CH_2OCH_2CH_2O\text{—pyranyl})_4$ BI	92%
CII	$C(CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2O\text{—pyranyl})_4$ BII	90%
CIII	$C(CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2O\text{—pyranyl})_4$ BIV	93%

Table VII Analytical characterization[a]

Product	Elemental analysis	
CI	Calculated for $C_{21}H_{44}O_{12} \cdot 2,25$ mol H_2O:	C 47.67; H 9.24
	found:	C 47.33; H 9.15
CII	Calculated for $C_{29}H_{60}O_{16} \cdot 1$ mol H_2O:	C 51.01; H 9.15
	found:	C 50.76; H 9.31
CIII	Calculated for $C_{37}H_{76}O_{20} \cdot 1.25$ mol H_2O:	C 51.46; H 9.10
	found:	C 51.36; H 9.24

[a] ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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Example 4

Tosylation of the tetraoxyethylenealcohols

The desired tetraoxyethylenealcohol (0.0102 mol)
(Table VIII), obtained according to the method of
Example 3, was dissolved in CH_2Cl_2. Triethylamine
(0.123 mol) was added and the solution cooled to -5°C.
A solution of p-toluenesulfonyl chloride (0.0445 mol)
in CH_2Cl_2 was then added dropwise. The mixture was
stirred for an additional 1 h at 0°C and then left at
room temperature for 24 h. The mixture was washed with
water and the organic layer separated and dried over
Na_2SO_4. The solvent was then removed under vacuum. The
crude product was purified by chromatography on a
silica gel column (eluent $CHCl_3$/AcOEt 1/1 (v/v)). By
this synthetic pathway the following compounds were
obtained:

DI 1,4,7,11,14,17-hexaoxa-1,17-bis(p-toluensulfonyl)-
9,9-bis[2,5,8-trioxa-8-(p-toluenesulfonyl)octyl]-
heptadecane ($C_{49}H_{68}O_{20}S_4$)

DII 1,4,7,10,14,17,20,23-octaoxa-1,23-bis(p-toluene-
sulfonyl)-12,12-bis[2,5,8,11-tetraoxa-11-(p-toluenesul-
fonyl)undecil]tricosane ($C_{57}H_{84}O_{24}S_4$)

DIII 15,15-bis[2,5,8,11,14-pentaoxa-14-(p-toluenesul-
fonyl)tetradecyl]-1,29-bis(p-toluensulfonyl)-
1,4,7,10,13,17,20,23,26,29-decaosanonacosane
($C_{65}H_{100}O_{28}S_4$)

The reaction yields and starting materials are
summarised in Table VIII. Table IX reports the
analytical characterizations.

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Table VIII

Tosylation reactions of the tetraoxyethylenealcohols

Product	Starting tetraoxyethylenealcohol	Reaction yield
DI	$C(CH_2OCH_2CH_2OCH_2CH_2OH)_4$ CI	75%
DII	$C(CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH)_4$ CII	65%
DIII	$C(CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OH)_4$ CIII	60%

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Table IX   Analytical characterization[a]

Product	Elemental analysis
DI	Calculated for $C_{49}H_{68}O_{20}S_4 \cdot 0.5$ mol H_2O: C 58.84; H 6.24; S 11.52
	found: C 52.46; H 6.26; S 11.40
DII	Calculated for $C_{57}H_{84}O_{24}S_4$: C 53.42; H 6.61; S 10
	found: C 53.65; H 7.00; S 10.14
DIII	Calculated for $C_{65}H_{100}O_{28}S_4$: C 53.55; H 6.91; S 8.80
	found: C 53.38; H 6.93; S 8.68

[a] ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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In another tosylation experiment at kg scale, the reaction yield for DI was improved to 90% by inverting the addition order of the reagents and by keeping the reaction temperature at 0°C.

Example 5

Reaction of the tosyl derivatives with potassium phthalimide

The desired tetraoxyethylenetosyl derivative (0.0018 mol) (Table X), obtained according to the method of Example 4, was dissolved in DMF. Potassium phthalimide (0.0072 mol) suspended in DMF was then added to the solution. After 7 h at 140°C the reaction mixture was cooled to room temperature. The DMF was then removed under vacuum and H_2O added to the residue. The reaction mixture was taken up and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under vacuum. The crude product was chromatographed on a silica gel column (flash chromatography; eluent AcOEt/CHCl$_3$ = 7/3 (v/v)). By this synthetic pathway the following compounds were obtained:

EI   3,6,10,13-tetraoxa-1,15-bis(phthalimido)-8,8-bis[2,5-dioxa-7-(phthalimido)heptyl]   pentadecane ($C_{53}H_{56}N_4O_{16}$)

EII 3,6,9,13,16,19-hexaoxa-1,21-bis(phthalimido)-11,11-bis[2,5,8-trioxa-10-(phthalimido) decyl]enicosane ($C_{61}H_{72}N_4O_{20}$)

The reaction yields and starting materials are summarised in Table X. Table XI reports the analytical characterizations.

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Table X Reaction with potassium phthalimide

Product	Starting tetraoxyethylenetosyl derivative	Reaction yield
EI	$C\left(CH_2OCH_2CH_2OCH_2CH_2OSO_2-\bigcirc-CH_3\right)_4$ DI	85%
EII	$C\left(CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OSO_2-\bigcirc-CH_3\right)_4$ DII	65%

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15

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Table XI   Analytical characterization[a]

Product	Elemental analysis		
EI	Calculated for $C_{53}H_{56}N_4O_{16} \cdot 1$ mol H_2O:	C 62.20; H 5.52; N 5.47	
	found:	C 62.55; H 5.71; N 5.44	
EII	Calculated for $C_{61}H_{72}N_4O_{20}$:	C 62.02; H 6.14; N 4.74	
	found:	C 61.65; H 6.22; N 4.6	

a   ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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Example 6

Conversion of the phthalimido derivative into the corresponding tetraoxyethyleneamino derivative

The tetraoxyethylenephthalimido derivative EI (0.00199 mol) (Table XII), obtained according to the method of Example 5, was suspended in absolute ethanol. A solution of hydrazine (0.0119 mol) in absolute ethanol was then added dropwise. The reaction mixture was refluxed for 7 h and then cooled to room temperature. A precipitate was formed and filtered and the solvent removed under vacuum to give the final product. By this synthetic pathway the following compound was obtained:

FI   3,6,10,13-tetraoxa-8,8-bis(2,5-dioxa-7-aminoheptyl)pentadecan-1,15-diamine $(C_{21}H_{48}N_4O_8)$

The reaction yield and the starting material are summarised in Table XII. Table XIII reports the analytical characterizations.

Table XII   Conversion of the phthalimido derivative into the tetraoxyethyleneamino derivative
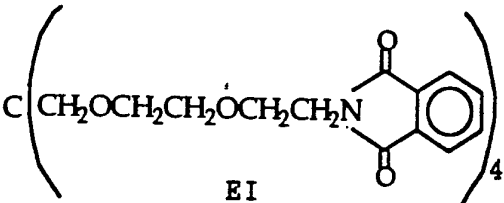
Product	Starting tetraoxyethylenephthalimido derivative	Reaction yield
FI	$C\left(CH_2OCH_2CH_2OCH_2CH_2N\right)_4$ EI	70%

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Table XIII Analytical characterization[a]

Product	Elemental analysis
FI	Calculated for $C_{21}H_{48}N_4O_8 \cdot 3$ mol H_2O: C 46.96; H 10.14; N 10.43
	found: C 46.83; H 9.96; N 10.03

[a] ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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Example 7

Conversion of the tosyl derivative into the corresponding tetraoxyethylenebromide derivative

The tetraoxyethylenetosyl derivative DI (0.00325 mol) (Table XIV), obtained according to the method of Example 4, was dissolved in N,N-dimethylacetamide. NaBr (0.026 mol) was added and the reaction mixture stirred for 1 h at 150°C. The mixture was then cooled to room temperature and the solvent removed under vacuum. The residue was taken up into water and extracted with AcOEt. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under vacuum. The crude product was purified by chromatography on a silica gel column (eluent AcOEt/CHCl$_3$ 1/1 (v/v)). By this synthetic pathway the following compound was obtained:

GI   3,6,10,13-tetraoxa-8,8-bis(2,5-dioxa-7-bromoheptyl)pentadecan-1,15-dibromide ($C_{21}H_{40}O_8Br_4$)

The reaction yield and starting material are summarised in Table XIV. Table XV reports the analytical characterization.

Table XIV   Conversion of the tosylderivative into the tetraoxyethylenebromide derivative

Product	Starting tetraoxyethylenetosyl derivative	Reaction yield
GI	$C\left(CH_2OCH_2CH_2OCH_2CH_2OSO_2-\langle O \rangle - CH_3\right)_4$ DI	60%

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Table XV   Analytical characterization[a]

Product	Elemental analysis
GI	Calculated for $C_{21}H_{40}O_8Br_4 \cdot 3$ mol H_2O: C 34.08; H 5.45; Br 43.18
	found: C 34.20; H 5.47; Br 43.04

[a] ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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Example 8

Branching of the oxyethylene chains by reaction with compounds having further functional groups for subsequent alkylation (example of introduction of a branching point with multiplicity = 3)

4-(Hydroxymethyl)-2,6,7-trioxabicyclo[2.2.2]octane (0.00452 mol), prepared according to the method described by Padias et al. (Ref. 5), was dissolved in diethyleneglycol dimethylether (15 mL) and then added dropwise at 0°C to a solution containing a stoichometric quantity of potassium hydride. The reaction mixture was stirred for 1 h at 0°C and then for 3 h at room temperature. The desired tetraoxyethylenetosyl derivative (0.001808 mol) (Table XVI), obtained according to the method of Example 4, and dissolved in diethyleneglycol dimethylether (25 mL) was then added dropwise to the solution. The reaction mixture was then stirred at 120°C for 14 h. After cooling to room temperature, the solvent was removed under vacuum and the mixture taken up with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under vacuum. The crude product was purified by chromatography on a silica gel column (eluent AcOEt). The fractions containing the product were combined and the solvent removed under vacuum. The residue was dissolved in MeOH and then 37% HCl was added. The mixture was refluxed and the MeOH distilled off very slowly over a period of 2 h. The mixture was cooled to room temperature and the remaining MeOH removed under vacuum. The product was then obtained as a colourless oil. By this

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synthetic   pathway   the   following   compounds   were
obtained:

HI   4,7,10,14,17,20-hexaoxa-2,2,22,22-
tetra(hydroxymethyl)-12,12-bis[2,5,8-trioxa-10,10-
bis(hydroxymethyl)-11-hydroxyundecyl]tricosan-1,23-diol
($C_{41}H_{84}O_{24}$)

HII   18,18-bis[2,5,8,11,14-pentaoxa-16,16-
bis(hydroxymethyl)-17-hydroxyheptadecyl]-2,2,34,34-te-
tra(hydroxymethyl)-4,7,10,13,16,20,23,26,29,32-decaoxa-
pentatriacontan-1,35-diol ($C_{57}H_{116}O_{32}$)

The   reaction   yield   and   starting   material   are
summarised   in   Table   XVI.   Table   XVII   reports   the
analytical characterization.

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Table XVI   Branching reactions

Product	Branching junction	Tetraoxyethylenetosyl derivative	Reaction yield
HI	$C(CH_2OH)_4$	$C\left(CH_2OCH_2CH_2OCH_2CH_2OSO_2\text{—}\bigcirc\text{—}CH_3\right)_4$ **DI**	35%
HII	$C(CH_2OH)_4$	$C\left(CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2OSO_2\text{—}\bigcirc\text{—}CH_3\right)_4$ **DIII**	29%

Table XVII Analytical characterization[a]

Product	Elemental analysis		
HI	Calculated for $C_{41}H_{84}O_{24} \cdot 2.5$ mol H_2O:	C 50.38;	H 8.87
	found:	C 50.25;	H 9.02
HII	Calculated for $C_{57}H_{116}O_{32} \cdot 2.5$ mol H_2O:	C 50.29;	H 8.98
	found:	C 50.37;	H 8.98

a   ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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Example 9

Tosylation reaction of branched alcohols derivatives

The branched alcohol HI (0.00208 mol) (Table XVIII), obtained according to the method of Example 8, was dissolved in pyridine (40 mL) and the solution cooled to -5°C. A solution of p-toluenesulfonyl chloride (0.00583 mol) in pyridine (50 mL) was then added dropwise. The mixture was stirred for 1 h at 0°C and then left at room temperature for 4 days. Water was added and the mixture extracted with CHCl3. The organic layer was dried over Na_2SO_4 and then the solvent was removed under vacuum. The crude product was purified by chromatography on a silica gel column (eluent AcOEt/CHCl$_3$ 1/1 (v/v)). By this synthetic pathway the following compound was obtained:

LI 1,23-di(p-toluenesulfonyloxy)-12,12-bis[11-(p-to-luenesulfonyloxy)-10,10-bis(p-toluenesulfonyloxy-methyl)-2,5,8-trioxaundecyl]-2,2,22,22-tetra(p-toluene-sulfonyloxymethyl)-4,7,10,14,17,20-hexaoxatricosane ($C_{125}H_{156}O_{48}S_{12}$)

The reaction yield and starting material are summarised in Table XVIII. Table XIX reports the analytical characterization.

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Table XVIII   Tosylation of the branched alcohol

Product	Starting branched alcohol	Reaction yield
LI	$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OH)_3\right]_4$	50%

HI

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Table XIX Analytical characterization[a]

Product	Elemental analysis
LI	Calculated for $C_{125}H_{156}O_{48}S_{12} \cdot 1$ mol H_2O: C 53.40; H 5.59; S 13.69
	found: C 53.78; H 5.86; S 13.35

[a] ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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Example 10

Conversion of the branched tosyl derivatives into the corresponding bromo derivatives

The tosyl derivative LI (0.00051 mol) (Table XX), obtained according to the method of Example 9, was dissolved in N,N-dimethylacetamide (50 mL). NaBr (0.01224 mol) was added and the reaction mixture stirred for 1 h at 150°C. The temperature was then cooled to room temperature and the solvent removed under vacuum. The residue was taken up with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent removed under vacuum.

The crude product was purified by chromatography on a silica gel column (eluent AcOEt/CHCl3 1/2 (v/v)). By this synthetic pathway the following compound was obtained:

MI   1,23-dibromo-12,12-bis[11-bromo-10,10-bis(dibromomethyl)-2,5,8-trioxaundecyl]-2,2,22,22-tetrabromomethyl-4,7,10,14,17,20-exaoxatricosane

$(C_{41}H_{72}O_{12}Br_{12})$

The reaction yield and starting material are summarised in Table XX. Table XXI reports the analytical characterization.

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Table XX   Conversion into bromo derivative

Product   Branched tosyl derivative   Reaction
                                                     yield

MI

$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C\left(CH_2OSO_2-\bigcirc-CH_3\right)_3\right]_4 \quad 67\%$$

LI

Table XXI   Analytical characterization[a]

Product	Elemental analysis
MI	Calculated for $C_{41}H_{72}O_{12}Br_{12}$: C 28,7; H 4.23; Br 55.88
	found: C 28,93; H 4.33; Br 55.65

[a] ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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Example 11

Introduction of polyoxyethylene chains on molecules with branched alcohol terminal groups

The branched alcohol HI (0.00104 mol) (Table XXII), obtained according to the method of Example 8, was dissolved in 19.06 M NaOH (0.125 mol) under nitrogen. The reaction mixture was warmed up to 65°C under mechanical stirring. Tetrabutylammonium bromide (0.00042 mol) and the chlorooxyethylenepyranyl derivative (0.00187 mol) were then added. The reaction mixture was incubated at 65°C for 72 h.

Freshly prepared 19.06 M NaOH solution (0.125 mol), the chlorooxyethylenepyranyl derivative (0.0125 mol), tetraoctylammonium bromide (0.000104 mol) and NaI (0.00005 mol) were added and the reaction was stirred for 72 h at 65°C. Tetraethylammonium hydroxide solution (5 mL; 10% w/w in water) was added and the mixture stirred for 96 h at 80°C. Finally the reaction was cooled to room temperature, diluted with water and extracted with CHCl$_3$. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column. The by-products were eluted with AcOEt and the compound of interest was eluted with a mixture of AcOEt/Acetone 7/3 (v/v). By this synthetic pathway the following compound was obtained:

NI   1,35-di(oxan-2-yl-oxy)-18,18-bis[17-(oxan-2-yl-oxy)-10,10-bis(7-(oxan-2-yl-oxy)-2,5-dioxaheptyl)-2,5,8,12,15-pentaoxaheptadecyl]-8,8,28,28-tetra[(7-oxan-2-yl-oxy)-2,5-dioxaheptyl]-3,6,10,13,16,20,23,26,30,33-decaoxapentatricontane

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$(C_{149}H_{276}O_{60})$

The reaction yield and starting material are summarised in Table XXII. Table XXIII reports the analytical characterization.

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Table XXII Introduction of protected oxyethylene chain
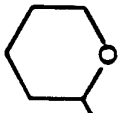
Product	Starting alcohol	Pyranyl derivative	Reaction yield
NI	$C[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OH)_3]_4$ HI	$ClCH_2CH_2OCH_2CH_2O$ AII	40%

Table XXIII   Analytical characterization[a]

Product	Elemental analysis
NI	Calculated for $C_{149}H_{276}O_{60} \cdot 0,5$ mol H_2O: C 58.94; H 9.19; O 31.87
	found: C 58.57; H 9.32; O 32.14

[a]   ^{1}H-NMR and ^{13}C-NMR spectra of the described products are in agreement with the proposed structures.

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The same product was also obtained with a similar synthetic procedure using only tetrabutylammonium hydrogen sulfate as catalyst. Following such a procedure, the reaction yield was improved to 55%. The reaction yield for the introduction of twelve oxyethylene chains was surprisingly high being at least equal or even superior to those observed for the introduction of four oxyethylene chains as described in Example 2. This unexpected feature suggests that these compounds play a role in the phase-transfer catalysis.

Similar results were obtained when the described reaction was carried out on branched molecules with multiplicity = 2, or when monochlorodipyranyl derivatives such as those described in Example 1 were utilized as lengthening units.

Example 12

Introduction of a further branching point (multiplicity = 3)

a) The second generation was obtained according to the method described in Example 8 by reacting the dodecatosyl derivative LI, obtained according to the method described in Example 9, with a stoichometric quantity of the potassium salt of 4-(hydroxymethyl)-2,6,7-trioxabicyclo[2.2.2]octane.

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Reaction scheme:

$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OTs)_3\right]_4 + 12 \ HC\begin{matrix}O—CH_2\\O—CH_2\\O—CH_2\end{matrix}C—CH_2OK \longrightarrow$$

LI

$$\longrightarrow C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OCH_2C(CH_2OH)_3)_3\right]_4$$

PI

$$Ts = \ —SO_2—\bigcirc—CH_3$$
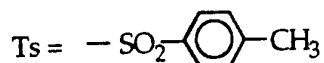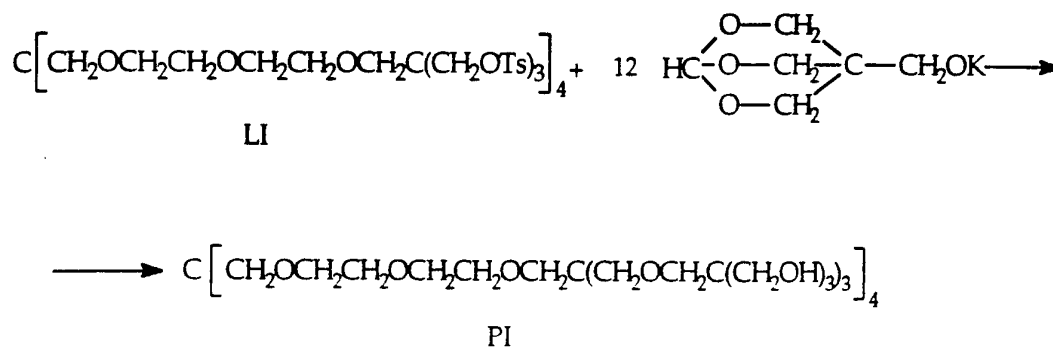
Yield: 19%

^{1}H-NMR, ^{13}C-NMR and mass spectra of all the products described are in agreement with the proposed structure. The same product can be synthesized by starting from the dodecabromo derivative (MI), obtained using the method described in Example 10, by using the same synthetic approach of this example.

b) The compound NI, obtained according to the method described in Example 11, is converted first into the alcohol (QI) and then into the corresponding tosyl derivative (RI) according to the methods described in Examples 3 and 4. Finally, the corresponding second generation derivative (SI) is obtained by introducing a pentaerythritol unit on each chain, according to the method described in Example 8.

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Reaction scheme

$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C\left(CH_2OCH_2CH_2OCH_2CH_2O-\underset{O}{\overset{}{\boxed{}}}\right)_3\right]_4 \xrightarrow{H^+}$$

NI

$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OCH_2CH_2OCH_2CH_2OH)_3\right]_4 \xrightarrow{TsCl}$$

QI

$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OCH_2CH_2OCH_2CH_2OTs)_3\right]_4 \longrightarrow$$

RI

$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OH)_3)_3\right]_4$$

SI

$$Ts = -SO_2-\boxed{\bigcirc}-CH_3$$
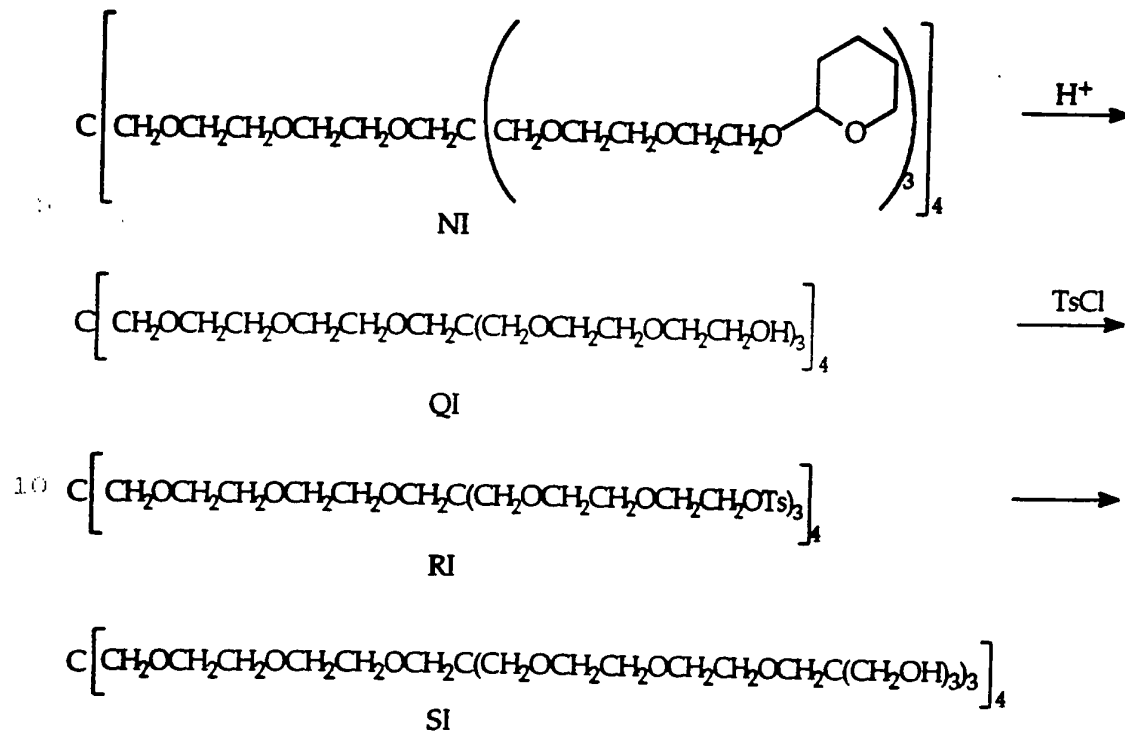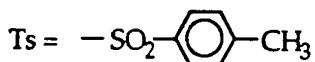
The second generation product

$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OH)_3)_3\right]_4$$

SI
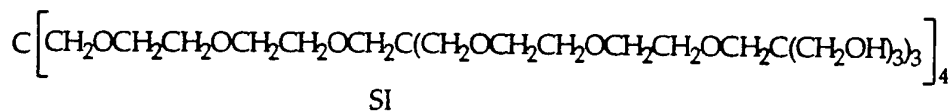
was also obtained, after deprotection of the corresponding orthoester, through the following synthetic pathways:

$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OCH_2CH_2OCH_2CH_2OH)_3\right]_4 +$$

QI

$$Br-CH_2-C\left\langle\begin{array}{c}CH_2O\\CH_2O\\CH_2O\end{array}\right\rangle CH \xrightarrow{\text{phase transfer catalysis}}$$

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$$C\left[CH_2OCH_2CH_2OCH_2CH_2OCH_2C(CH_2OCH_2CH_2OCH_2CH_2OH)_3\right]_4 +$$

QI

$$TsO-CH_2-C\left\langle\begin{array}{c}CH_2O\\CH_2O\\CH_2O\end{array}\right\rangle CH$$
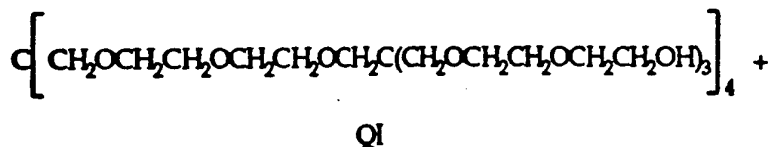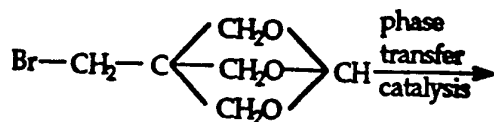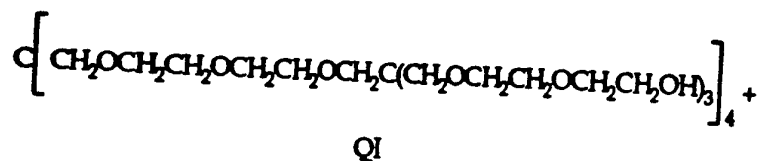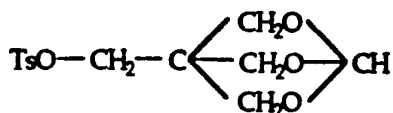
Following similar procedures, products of higher generations were obtained.

Example 13

Determination of limiting viscosity numbers (intrinsic viscosity) and of equivalent viscometric radii

The viscosities of aqueous solutions of compounds of the present invention were determined by measuring the efflux times in an Ubbelohde capillary viscometer controlled by an optical timing detector (AVS, Schott). During the experiments a constant temperature of $37\pm0.005°C$ was maintained. Density measurements were obtained by a Paar precision densimeter. The numerical evaluation of the limiting viscosity number (or intrinsic viscosity) was obtained from the following relationship

$$\frac{\eta-\eta_0}{\eta_0}=\frac{[\eta]c}{1-k[\eta]c}$$

where c corresponds to the concentration of the macromolecule, η is the viscosity of the solution, η_0 is the viscosity of the pure solvent and k is an empirical parameter.

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Numerical evaluations of equivalent viscometric radii
(r) were obtained by the following relationship

$$r = \left(\frac{3[\eta]M}{10\pi N_A} \right)^{1/3}$$

where M is the molar mass of the macromolecule and N_A
is Avogadro's number.

Compounds HI, HII and QI have been compared with
Tomalia's starburst polyether dendrimers of first and
second generation ($C[CH_2OCH_2C(CH_2OH)_3]_4$ and
$C[CH_2OCH_2C(CH_2OCH_2C(CH_2OH)_3)_3]_4$, respectively,
described in Example 11 of US patent 4,587,329) which
do not possess oxyethylene units between the "core" and
the first branching point and between the first and the
second branching points, and which are characterized by
a much more compact structure. Each of these compounds
(except Tomalia's compound of second generation) has
the same number of surface functional groups, i.e. 12
hydroxyl groups. The results are summarized in Table
XXIV.

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Table XXIV Limiting viscosity numbers (intrinsic viscosity) and equivalent viscometric
radii of new polyoxyethylene branched macromolecules

Product	Limiting viscosity number $[\eta]$ mL·g^{-1} (at 37°C)	Equivalent viscometric radius (r) Å
TOMALIA, first generation	2.32 ± 0.06	6.08 ± 0.05
HI	3.38 ± 0.07	8.01 ± 0.06
HII	4.04 ± 0.10	9.44 ± 0.08
QI	4.07 ± 0.04	10.92 ± 0.04
TOMALIA, second generation	2.50 ± 0.03	9.30 ± 0.04

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The data clearly show that the introduction of oxyethylene units gives rise to compounds with radius values which can be even larger than those of higher generation described by Tomalia. With an extremely low,

5   if not absolutely negligeable, "dense-packing" effect there is, as a consequence, the possibility to synthesize molecules up to whatever generation is desired or required for specific uses.

Analogous measurements carried out on

10   macromolecules of successive generations further supported and these statements.

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CLAIMS

1.   Dendrimeric-type macromolecules, being unaffected by functional surface over-crowding and essentially consisting of a central nucleus, or core, and of branched chains, which depart from the same and in a cascade fashion spread into the surrounding space giving rise to a multiplicity of cavities or voids within the structural shape of the molecule, characterized in that:

a)   said core derives from a polyvalent organic molecule,

b)   there are at least two of said branched chains, each one comprising a number of repetition units, which are dendrimerically linked and are equal or different among them, being the structure of every repetition unit further characterized in that it comprises:

    -    a polyoxaalkyl chain of variable length,

    -    a polyvalent branched organic residue attached to one end of said polyoxaalkyl chain, said residue acting as a branching point, on which the polyoxaalkyl chains of the subsequent repetition units are grafted,

c)   the maximum number of subsequent levels of repetition units, or generations, is not more than 20 and the last generation level is characterized by the presence of mono- or polyvalent functional terminal groups.

2.   Macromolecules according to claim 1, of general formula (I)

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$$A[G_{1-->p}]_r \qquad\qquad (I),$$

where:

A   is a central nucleus, or "core", deriving from a
     polyvalent organic molecule which can be an
     aliphatic open chain, branched or not, residue, or
     an alicyclic, or a heterocyclic residue containing
     N, O and/or S, or an aromatic or a heteroaromatic
     residue and which is characterized by the presence
     of r terminal residues to which the polyoxaalkyl
     chains of the first generation are attached,

r   is an integer from 2 to 10 representing the
     multiplicity of the "core" A,

$G_{1-->p}$ represents the branched structure of the
     macromolecule comprising g levels of
     generations, from the first one (g_1) to the
     last one (g_p), in which the total p number
     of said generations can range from 1 to 20
     and in which the different generations can
     contain the same repetition units or not, and
     in which:

a)   each generation g, except for the last, comprises
     a number of repetition units, which are
     represented by residues of formula

-B-M-

where:

B   is a polyoxyethylene or polyoxypropylene chain of
     formula:

$$-\left[O-(CH_2)_{0-1}CH_2-CH_2\right]_n-$$

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in which n can range from 0 to 25 and is different
or not from generation to generation, provided
that, in at least one of the generations of the
macromolecule, n is different from 0,

M   represents a branching point which derives from a
polyvalent aliphatic residue comprising:

-    a single functional group such as OH, NH_2,
     SH, COOH, or a derivative thereof, able to
     link with the terminal group of chain B,

-    m reactive residues for the linking of the
     polyoxaalkyl chains of the next generation,
     being

m   an integer ranging from 2 to 5, representing the
branching multiplicity introduced by M and being m
different or not from generation to generation,
and

being the total number of repetition units -B-M-
in each generation level g equal to the sum of all
the branching multiplicities m of the preceding
generation g_{-1};

b)   the last generation g_p comprises residues of
formula:

$$-B_p-M_p[T]_{mp}$$

where B_p, M_p, m_p are defined analogously to B, M,
and m, with the difference that all the m_p
reactive residues of M_p are connected to groups T
in which

T   is a terminal group that can be either H or one of
the following residues: halo, hydroxyl, amino,
thiol, -O-tosyl, -O-mesyl, -O-tresyl, -O-brosyl,
trifluoromethanesulfonyl, aldehydo, carboxy, amido

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group, such a terminal group T being free, either dissociated or undissociated, or protected by protective groups such as pyranyl, phthalimido, acetyl, cyclic orthoester group and being the total number of the terminal groups T equal to the sum of all the branching multiplicities m of the last generation g_p, and with the further condition that

Mp   can also be a single bond, in which case m_p is equal to 1 (i.e., there is no branching) and as a consequence the last generation g_p comprises residues of formula:

$$-B_p-T$$

where B_p and T are as above defined;

c)   in case p = 1, that is when the macromolecule contains only one generation, g_p corresponds to g_1, i.e. represents the residue:

$$-B_1-M_1[T]_{m1}$$
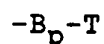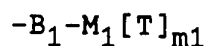
where B_1, M_1, m_1 and T are defined analogously to B_p, M_p, m_p and T, as well as the corresponding derivatives labelled with isotopes such as ^{13}C, ^{14}C, ^{2}H, ^{3}H and ^{125}I.

3.   Macromolecules according to claim 2, in which:

a)   the "core" A is a neopentyl residue of formula:

$$C(CH_2-)_4 \; ;$$
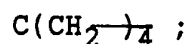
b)   each generation, apart from the last, comprises growth units of formula:

$$-B'-M'-$$
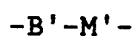
in which

B'   is a polyoxyethylene residue of formula:

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$$-\left[O-CH_2-CH_2\right]_n-$$
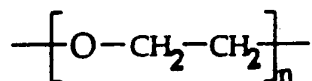
where n is variable from 0 to 15 and is different
or not from generation to generation, with the
condition that it is different from 0 in at least
one generation,

M'   is a branching point with a branching multiplicity
of 2 or 3, of formula:

$$-O-(CH_2)_q-CH\begin{cases}CH_2- \\ CH_2-\end{cases} \quad \text{or} \quad -O-(CH_2)_q-C\begin{cases}CH_2- \\ CH_2- \\ CH_2-\end{cases}$$
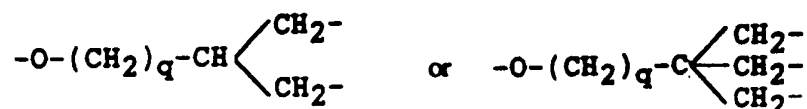
where q is variable from 1 to 2;

c)   the last generation is a residue of the following
formula:

$$-B'_p-M'_p[T]_{2-3}$$
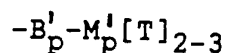
in which B'_p, M'_p are defined analogously to B', M'
and T is as defined in claim 2, or M'_p is a single
bond   and   in   this   case   the   last   generation
corresponds to the residue:

$$-B'_p-T$$
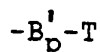
where B'_p and T are as above defined and in which
the total number of generations can range from 1
to 15.

4.   Macromolecules   according   to   claim 3,   of general
formula (III)

$$C\left[CH_2-(OCH_2CH)_n-O-CH_2-C[CH_2-L]_3\right]_4 \qquad \text{(III),}$$

$$B'_1$$
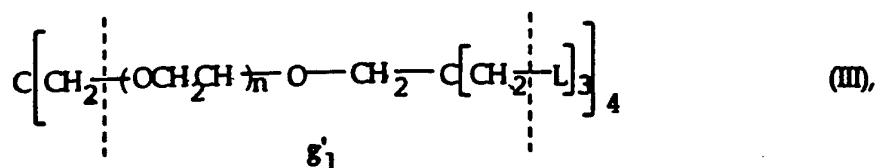
in which:

n   is variable from 0 to 15, and with the condition
      that   n is different from 0 in at least one
      generation,

$g_1^!$ is the first generation having a branching
      multiplicity of 3,

L   represents T, or the sequence of successive
      generations from $g_2^!$ to $g_p^!$ in which each g', apart
      from $g_p^!$, is defined analogously to $g_1^!$ and can have
      the same meaning or not whereas $g_p^!$ corresponds to
      $g_1^!$-T and T is defined as in claim 3, and the
      total number of generations g can be as high as
      15.

5.   Method for the preparation of the dendrimeric-type
molecules according to claim 1, characterized by the
following synthetic steps:

a)   reaction of the reactive terminal functions of the
      central   nucleus   with   the   corresponding
      polyoxaalkyl chains of the first generation, in
      which said polyoxaalkyl chains have an extremity
      functionalized with reactive groups, such as
      halogen groups and have their terminal alcoholic
      group protected with protective agents typical of
      the hydroxy group;

b)   deprotection of the terminal alcoholic groups and
      reaction of the same, either as they are or after
      activation, with a reactive branched group in
      which the terminal functions of the branching are
      protected;

c)   deprotection of these functions and successive
      reaction   with   the   corresponding   polyoxaalkyl

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chains of the second generation, according to the
methodology described for a) above;

d)   repetition of steps a), b) and c) until the
desired number of generations is attained.

6.   Method for the preparation of the dendrimeric-type
molecules according to claim 1, characterized by the
following synthetic steps:

a)   reaction of the terminal alcoholic group of a
polyoxaalkyl chain with a reactive branched group
whose terminal functions are protected;

b)   reaction of the branched polyoxaalkyl chain
obtained in a) with a functionalized central
nucleus to give the already branched first
generation, or,

c)   reaction of the chains resulting from a) with the
terminal functions of the branching point of a
previous generation so as to give a subsequent
generation.

7.   Method for the preparation of the dendrimeric-type
molecules according to claim 1, characterized by the
following synthetic steps:

a)   independent preparation of the single cascade-like
branched chains of the molecule,

b)   reaction of said chains obtained in a) with the
reactive terminal functions of the central
nucleus.

8.   Use of the compounds according to claim 1 as
carriers of drugs, being said drugs either conjugated
or entrapped in said compounds.

9.   Use of the compounds according to claim 1 as
carriers of contrast agents for diagnostic imaging

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being said contrast agents either conjugated or entrapped in said compounds.

10. Use of the compounds according to claim 1 in radiology as vehicles of radioactive species.

11. Use of the compounds according to claim 1 for the preparation of pharmaceutical formulations for the controlled release of active principles.

12. Use of the compounds according to claim 1 as standards for calibrating separation techniques that are based on molecular size.

13. Use of the compounds according to claim 1 as calibration standards for size-exclusion chromatography.

14. Use of the compounds according to claim 1 as carriers of catalysts.

15. Use of the compounds according to claim 1 as catalysts in phase-transfer catalysis reactions.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6　　C08G65/32　　　C08G65/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6　　C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 568 737 (TOMALIA D.A.) 4 February 1986 cited in the application see column 10, line 35 - line 65 ---	1-7
X	J. ORG. CHEM, vol.52, 1987 pages 5305 - 5312 PADIAS A.B. ET AL 'Starburst polyether dendrimers' cited in the application *Reaction scheme III, reaction scheme IV* see page 5309, line 7 - line 10 --- <center>-/--</center>	1,2,5-7, 12,13

[X] Further documents are listed in the continuation of box C.	[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 July 1995	3 1. 07. 95

Name and mailing address of the ISA	Authorized officer
· European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	O'Sullivan, T

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MACROMOLECULES, vol.26, no.21, 1993 pages 5621 - 5627 GITSOV I. ET AL 'Synthesis and properties of novel linear-dendritic block copolymers' *reaction scheme 1a* ---	1
A	US,A,5 041 516 (FRECHET J.M.J.) 20 August 1991 see column 5, line 14 - line 47 -----	1,8,11

1

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		US-A-	4587329	06-05-86
		AT-T-	119177	15-03-95
		AU-B-	560604	09-04-87
		AU-A-	2435484	02-08-84
		CA-A-	1244586	08-11-88
		DE-D-	3486372	06-04-95
		DE-T-	3486372	29-06-95
		DE-T-	608908	14-06-95
		EP-A-	0115771	15-08-84
		EP-A-	0608908	03-08-94
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		JP-B-	7042352	10-05-95
		JP-B-	6070132	07-09-94
		WO-A-	8402705	19-07-84
		US-A-	4558120	10-12-85
		US-A-	4631337	23-12-86
		US-A-	4737550	12-04-88
US-A-5041516	20-08-91	NONE		