



(22) Date de dépôt/Filing Date: 2004/08/04

(41) Mise à la disp. pub./Open to Public Insp.: 2005/02/10

(45) Date de délivrance/Issue Date: 2014/01/14

(62) Demande originale/Original Application: 2 534 616

(30) Priorité/Priority: 2003/08/04 (US60/491,969)

(51) Cl.Int./Int.Cl. *C08G 65/02* (2006.01),
C07C 21/073 (2006.01), *C07C 69/653* (2006.01),
C08F 283/06 (2006.01), *C08F 290/06* (2006.01),
C08J 3/24 (2006.01)

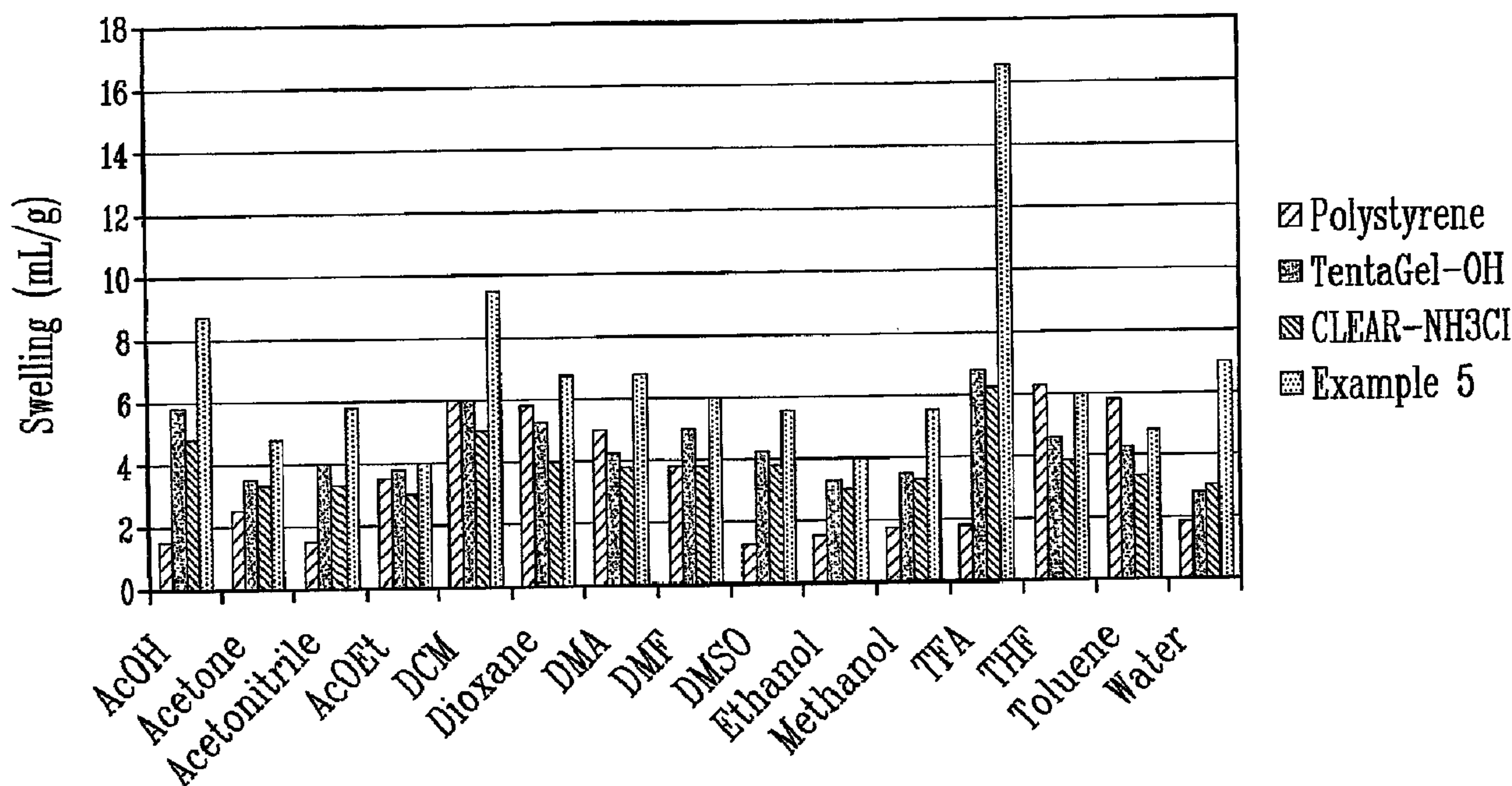
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(54) Titre : NOUVEAUX MONOMERES A BASE DE POLYETHER ET RESINES AMPHIPHILES FORTEMENT
RETICULEES

(54) Title: NEW POLYETHER BASED MONOMERS AND HIGHLY CROSS-LINKED AMPHIPHILE RESINS



(57) Abrégé/Abstract:

The present invention relates to a cross-linked polyether which is obtained by polymerization of at least one monomer selected from the group consisting of (a) (α -X-methyl) vinyl-EWG, (α -X-methyl) vinyl-ERG, or (α -X-methyl) vinyl-aryl, where X is oxygen, sulfur, PEG, PPG or poly (THF); (b) a monomer which is polymerizable with a PEG, PPG or poly (THF) cross-linker having at least one (α -X-methyl) vinyl-EWG, (α -X-methyl) vinyl-ERG or (α -X-methyl) vinyl-aryl, where X is oxygen, sulfur, PEG, PPG, or poly (THF); (c) a PEG, PPG, or poly (THF) cross-linker having at least an acrylamide or a methacrylamide end group; and (d) mixtures thereof. Various monomers, resins and methods for preparing such cross-linked polyethers are also disclosed.

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NEW POLYETHER BASED MONOMERS AND HIGHLY CROSS- LINKED AMPHIPHILE RESINS ✓

TECHNICAL FIELD

The invention relates to cross-linked polyethers and methods for preparing these polymers. These polyethers can be used as polymeric support in bioorganic or organic chemistry.

BACKGROUND OF THE INVENTION

The search for more stable amphiphilic resins is nowadays needed. Most of the presently known resins of this kind are based on polystyrene-PEG, polyamide, polyester or any kind of polymerized vinylic core. Their main drawback is their low chemical stability. CLEAR[®] (Kempe *et al.*, (1996), J. Am. Chem. Soc., 118, 7083-7093 and (1999), US Pat. 5,910,554) and PEGA[®] (Meldal, (1992), Tetrahedron Lett., 33, 3077-3080 and (1993), WO 93/16118) resins are cleaved in nucleophilic conditions (e.g. hydrolytic) as TENTAGEL[®] (Bayer, (1990), US Pat. 4,908,405 and (1991), Angew. Chem. Int. Ed. Engl. 30, 113-129) in acidic media.

Resins based on primary ether bound can be used to solve some problems, however other problems remain. The presence of the polystyrene core limits the ability of the final resin to perform for example the standard Friedel-Crafts reaction and generally have low loading capacity (e.g. between 0.2 and 0.5mmol/g to ARGOGEL[®]) (Labadie *et al.*, (1997), WO 97/27226 and Gooding *et al.*, (1999), J. Comb. Chem., 1, 113-123). Reaching higher loadings lowers the final amphiphilicity of the resin because the PEG content is decreasing proportionally (e.g. Rapp Polymere's HYPOGEL[®]).

Few examples of non-polystyrene-PEG based resins are known. Meldal showed the usefulness of the POEPOP resin (Renil *et al.*, (1996), Tetrahedron

Lett., 37, 6185-6188) based on PEG epoxide, and the SPOCC (Rademann *et al.*, (1999), J. Am. Chem. Soc., 121, 5459-5466 and Meldal *et al.*, (2000), WO 00/18823) based on PEG oxetane. Unfortunately, the use of non-conventional polymerization conditions with silicone oil and an appropriate surfactant gives a high cost manufacturing process (Grøtli *et al.*, (2001), J. Comb. Chem., 3, 28-33). Furthermore, low loadings are obtained when higher cross-linker (CL) content is used to give better mechanical stability. EXPO₃₀₀₀ (Tornøe *et al.*, (2002), Tetrahedron Lett., 43, 6409-6411) is a derivative of the former SPOCC resin based on PEG dioxetane with a silylated CL that gives a high amphiphilic resin employed in synthesis and enzymatic assays.

Recently, Oishi (Miwa *et al.*, (2001), Polymer Journal, Vol.33, No.12, 927-933) showed the use of a similar oxetane based on POE as a new polymer electrolyte for lithium batteries. The polymerization process is induced by LiBF₄ (or LiPF₆ as further electrolyte). The final polymer is nevertheless not in a beaded form and not employed for any organic chemistry reaction. The difference between the Meldal's monomers (used for the SPOCC synthesis) and the ones presented in Oishi's article is the nature of the methyl group replaced by a ethyl one.

The use of divinylether as CL gives secondary ethers that are more susceptible to hydrolysis such as the Meldal's POEPOP. Finally, PEG diallylethers (known to give low molecular weight polymers) would give low mechanical stability polymers containing only primary ethers. The PEG vinyl ketone (that will be later reduced) offers an interesting alternative to polyether with primary ether having the right specifications.

Dörwald (Dörwald, (2000), Organic Synthesis on Solid Phase, Chap. 2. Wiley-VCH Verlag, Weinheim, Federal Republic of Germany), Meldal (Meldal, (1997), Methods in enzymology, 289, 83-104, Academic Press, N.Y.) and Côté (Côté, (2002), WO 02/40559) offer more exhaustive reviews on amphiphilic resins.

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The following specifications are required for a new and low-cost amphiphilic resin:

PEG based;

Primary ethers only (chemical stability);

High loadings available;

Solid to waxy state (non-sticky);

Mechanical stability;

Normal suspension polymerization (in water);

Low manufacturing cost (commercial products).

PEG macromonomers had been investigated in the early 90' until today by several groups. Ito (Chao *et al.*, (1991), Polym. J., Vol.23, 1045-1052) reported the synthesis and the polymerization behavior of several styrenic and standard methacrylic PEG monomers covering most of the amphiphilic resins found today.

Yamada (Yamada *et al.*, (1991), Makromol. Chem., 192, 2713-2722; and (1993), J. Polym. Sci. Part A: Polym. Chem., Vol.31, 3433-3438) took another approach: the (α -PEG-methyl) acrylates. New amphiphilic monomers were synthesized and studied in copolymerization with methyl methacrylate and styrene. Unfortunately, very short methoxy-PEG chains of 1 to 3 EO were used, thus limiting the real amphiphilic potential of the final polymer. Moreover, only soluble linear polymers were reported and furthermore without any commercial uses.

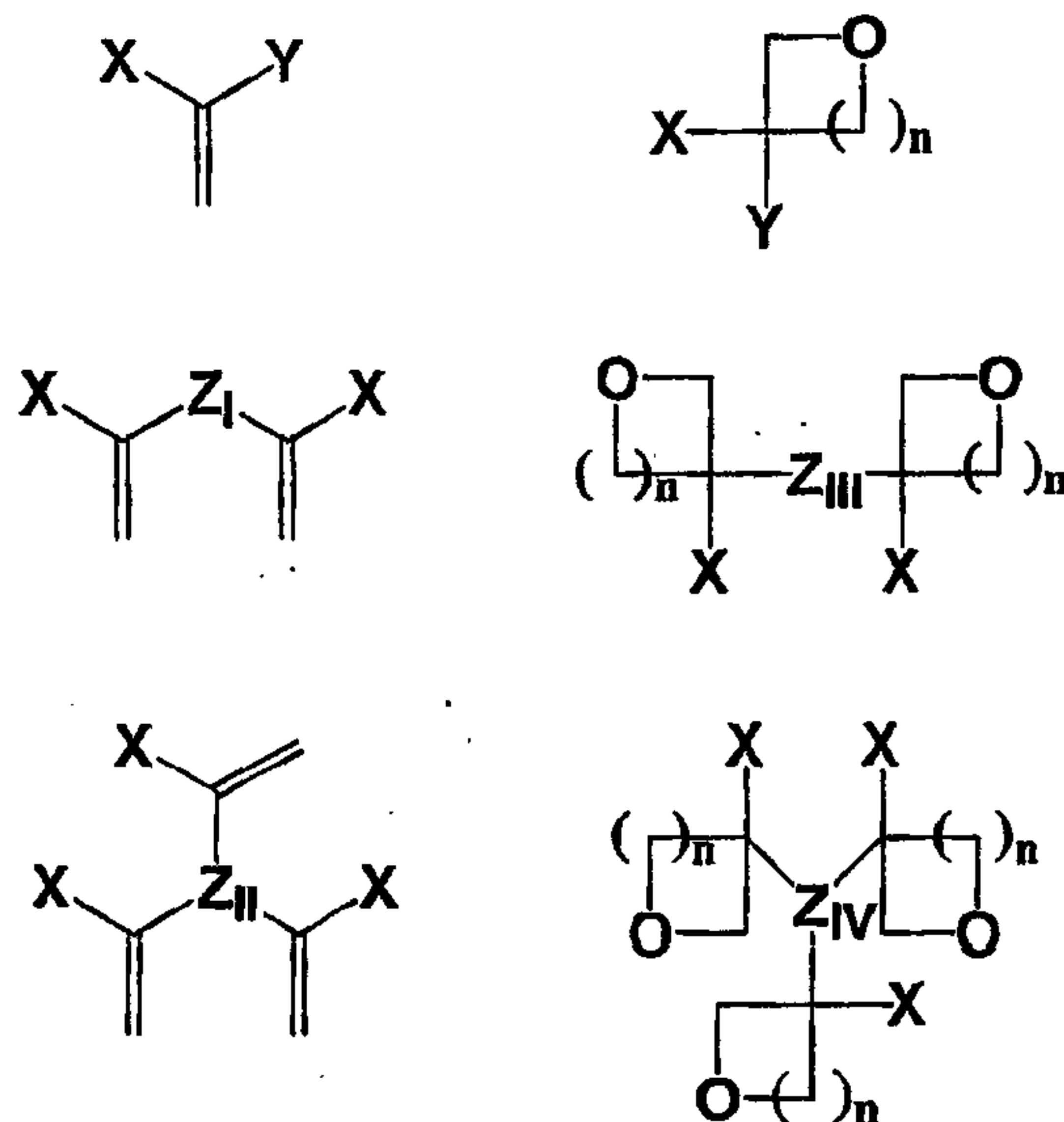
Mathias reported new types of CL based on (α -Y-methyl) acrylates (where Y = malonitrile) (Tsuda, T. *et al.*, (1993), Macromol., Vol.26, 6359-6363); and tetraethylene glycol di(α -fluoroalkoxy-methyl) acrylate (Jariwala, C.P. *et al.*,

(1993), Macromol. Vol.26, 5129-5136). Moreover, Mathias showed how these short CL have the tendency to cyclopolymerize instead of "really" cross-link.

Maillard (Philippon *et al.*, (1997) brings new approaches to synthesize macrocycles (mainly crown ethers). By the use of short PEG-acrylate and (α -PEG-methyl) acrylate (3 EO units only) that are submitted to radical reductive conditions (with Bu_3SnH), several crown ethers were obtained.

Finally, no example of monomers, CL and beaded insoluble polymers based on (α -PEG-methyl) acrylates has been published (review of Yamada *et al.*, (1994), Progr. Polym. Sci., Vol.19, 1089-1131).

It is an object of the present invention to provide a simple monomer design to give maximum loading on the final polymerized material versus known monomers and CL (cross-linker). Usual solid supports are synthesized by the mean of monomers and CL that contain:



where:

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$X = H$ and/or CH_3 ;

$Y = \text{EWG}$ (electron withdrawing group) and/or aryls with anything linked to it;

Z , Z_{III} and $Z_{IV} = \text{anything}$;

$Z_I = \text{EWG} - \text{spacer} - \text{EWG}$;

$Z_{II} = (\text{EWG})_2 - \text{spacer} - \text{EWG}$;

$n = 0$ or 1 .

It is an object of the present invention to provide the use of high percentage of CL without affecting the final loading of the resulting polymer contrary to what is presently found in the literature. As mentioned above, amphiphilic resins are using standard acrylates, methacrylates, acrylamides and/or methacrylamides where high CL content is needed to obtain a non-sticky polymer. This problem occurs also in the case of epoxide and/or oxetane based polymers.

It is an object of the present invention to provide high functionalized monomers, cross-linkers, and polymers. Bifunctional monomers or CL are known (e.g. fumaric, maleic and itaconic acid based) but each is susceptible to hydrolysis and/or nucleophilic attack. Divinylbenzene is also a bifunctional CL but no chemical function is still available once polymerized.

It is an object of the present invention to provide a stable polymer which can be used further as handle, linker and/or spacer for SPPS (Solid Phase Peptide Synthesis) and SPOS (Solid Phase Organic Synthesis).

It is an object of the present invention to provide highly functionalized non hydrolysable CL.

It is another object of the present invention to provide a new type of monomer based on the use of epoxides or oxetane groups. These groups could

be lately derivatized in other CF and/or linkers found in SPPS and/or SPOS before and/or after polymerization.

It is another object of the present invention to provide polymeric solid supports that can be used for the solid phase synthesis of peptides, oligonucleotides, oligosaccharides and in combinational and traditional organic chemistry.

It is another object of the present invention to provide resins that can be used in liquid phase synthesis, chromatography, for scavenging purposes, and for protein and reagents immobilisation.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a cross-linked polyether which is obtained by polymerization of at least one monomer selected from the group consisting of

a) (α -X-methyl) vinyl-EWG, (α -X-methyl) vinyl-ERG, or (α -X-methyl) vinyl-aryl, where X is oxygen, sulfur, PEG, PPG or poly (THF);

b) a monomer which is polymerizable (preferably monomers such as styrenes, divinylbenzenes, acrylates, methacrylates, acrylamides, methacrylamides, styrenes, acroleins, vinyl ketones, maleimides, etc.) with a PEG, PPG or poly (THF) cross-linker having at least one (α -X-methyl) vinyl-EWG, (α -X-methyl) vinyl-ERG or (α -X-methyl) vinyl-aryl, where X is oxygen, sulfur, PEG, PPG, or poly (THF);

c) a PEG, PPG, or poly (THF) cross-linker having at least an acrylamide or a methacrylamide end group; and

d) mixtures thereof.

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In (c), the acrylamide or a methacrylamide can eventually be reduced, once polymerized, to a polyamine. Alternatively, at least two and preferably at least three of these monomers can be copolymerized.

According to a second aspect of the invention, there is provided a cross-linked polyether which is obtained by polymerization of at least one monomer selected from the group consisting of

a) an α,α' -X-Y-epoxide, or an α,α' -X-Y-oxetane, where X is oxygen, sulfur, PEG, PPG, or poly (THF) and Y is selected from the group consisting of C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched alkanes, C₁ to C₅₀ (preferably C₁ to C₁₂) substituted linear or branched alkanes, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched arylalkanes, C₂ to C₅₀ (preferably C₂ to C₁₂) substituted linear or branched arylalkanes, C₁ to C₃₀ (preferably C₄ to C₁₂) substituted or unsubstituted aryls; and

b) a monomer which is polymerizable (preferably monomers such as styrenes, divinylbenzenes, acrylates, methacrylates, acrylamides, methacrylamides, styrenes, acroleins, vinyl ketones, maleimides, etc.) with a PEG, PPG or poly (THF) cross-linker having at least one α,α' -X-Y-epoxide or α,α' -X-Y-oxetane, where X is oxygen, sulfur, PEG, PPG or poly (THF), and Y is selected from the group consisting of C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched alkanes, C₁ to C₅₀ (preferably C₁ to C₁₂) substituted linear or branched alkanes, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched arylalkanes, C₂ to C₅₀ (preferably C₂ to C₁₂) substituted linear or branched arylalkanes, C₁ to C₃₀ (preferably C₄ to C₁₂) substituted or unsubstituted aryls, and

c) mixtures thereof.

Applicant has found that the cross-linked polyethers of the present invention can be used to prepare resins which are amphiphilic and have high

loadings. Moreover, these cross-linked polyethers are compatible with several reaction mediums easy to prepare. Moreover, these polyethers are chemically stable and non-sticky.

According to a third aspect of the invention, there is provided a method for the preparation of a cross-linked polyether, said method comprising the step of polymerizing of at least one monomer selected from the group consisting of

- a) (α -X-methyl) vinyl-EWG, (α -X-methyl) vinyl-ERG, or (α -X-methyl) vinyl-aryl, where X is oxygen, sulfur, PEG, PPG or poly (THF);
- b) a monomer which is polymerizable (preferably monomers such as styrenes, divinylbenzenes, acrylates, methacrylates, acrylamides, methacrylamides, styrenes, acroleins, vinyl ketones, maleimides, etc.) with a PEG, PPG or poly (THF) cross-linker having at least one (α -X-methyl) vinyl-EWG, (α -X-methyl) vinyl-ERG or (α -X-methyl) vinyl-aryl, where X is oxygen, sulfur, PEG, PPG, or poly (THF);
- c) a PEG, PPG, or poly (THF) cross-linker having at least an acrylamide or a methacrylamide end group; and
- d) mixtures thereof.

In (c), the acrylamide or a methacrylamide can eventually be reduced, once polymerized, to a polyamine. Alternatively, at least two and preferably at least three of these monomers can be copolymerized.

According to a fourth aspect of the invention, there is provided a method for the preparation of a cross-linked polyether, said method comprising the step of polymerizing of at least one monomer selected from the group consisting of

- a) an α,α' -X-Y-epoxide, or an α,α' -X-Y-oxetane, where X is oxygen, sulfur, PEG, PPG, or poly (THF) and Y is selected from the group consisting of C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched

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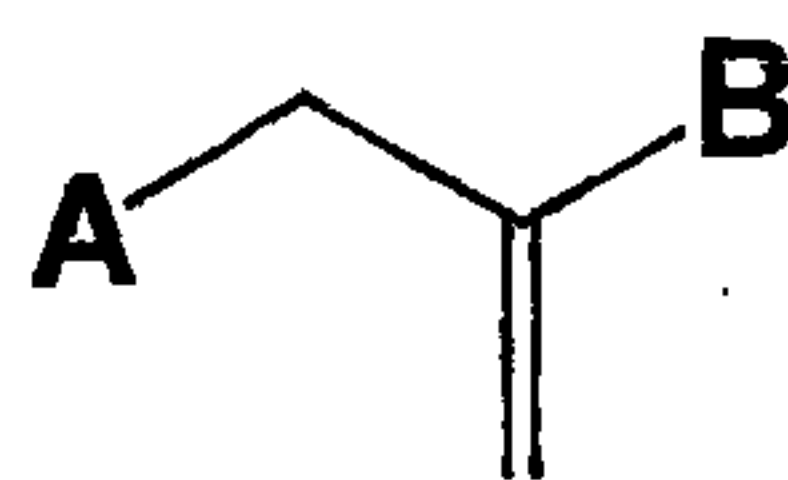
alkanes, C₁ to C₅₀ (preferably C₁ to C₁₂) substituted linear or branched alkanes, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched arylalkanes, C₂ to C₅₀ (preferably C₂ to C₁₂) substituted linear or branched arylalkanes, C₁ to C₃₀ (preferably C₄ to C₁₂) substituted or unsubstituted aryls, and

b) a monomer which is polymerizable (preferably monomers such as styrenes, divinylbenzenes, acrylates, methacrylates, acrylamides, methacrylamides, styrenes, acroleins, vinyl ketones, maleimides, etc.) with a PEG, PPG or poly (THF) cross-linker having at least one α,α' -X-Y-epoxide or α,α' -X-Y-oxetane, where X is oxygen, sulfur, PEG, PPG or poly (THF), and Y is selected from the group consisting of C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched alkanes, C₁ to C₅₀ (preferably C₁ to C₁₂) substituted linear or branched alkanes, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched arylalkanes, C₂ to C₅₀ (preferably C₂ to C₁₂) substituted linear or branched arylalkanes, C₁ to C₃₀ (preferably C₄ to C₁₂) substituted or unsubstituted aryls, and

c) mixtures thereof.

Applicants have found that the methods of the invention are simple and permit to prepare cross-linked polyethers which allow high loadings, and which have an interesting mechanical stability. These cross-linked polyethers also have very interesting swelling properties.

According to a fifth aspect of the invention, there is provided a compound of formula



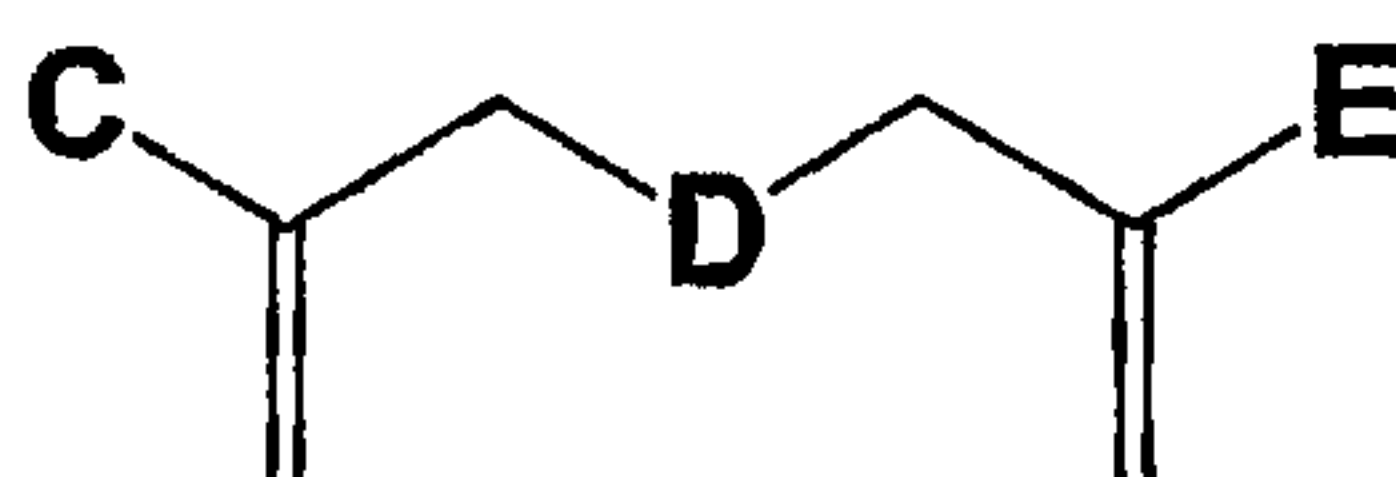
wherein

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A is PEG, PPG, poly (THF), hydroxyl, C₁-C₃₀ (preferably C₁ to C₁₂) alkyloxy, C₁-C₃₀ (preferably C₁ to C₁₂) hydroxyalkyl, amino, C₁-C₃₀ (preferably C₁ to C₁₂) alkylamine, C₁-C₃₀ (preferably C₁ to C₁₂) aminoalkyl, formyl, C₁-C₃₀ (preferably C₁ to C₁₂) alkylaldehyde, thiol, C₁-C₃₀ (preferably C₁ to C₁₂) alkylthiol, halogen or C₁-C₃₀ (preferably C₁ to C₁₂) halogenoalkyl; and

B represents an electron withdrawing group, an electron releasing group or a C₁-C₃₀ (preferably C₄ to C₁₂) aryl.

According to a sixth aspect of the invention, there is provided a compound of formula

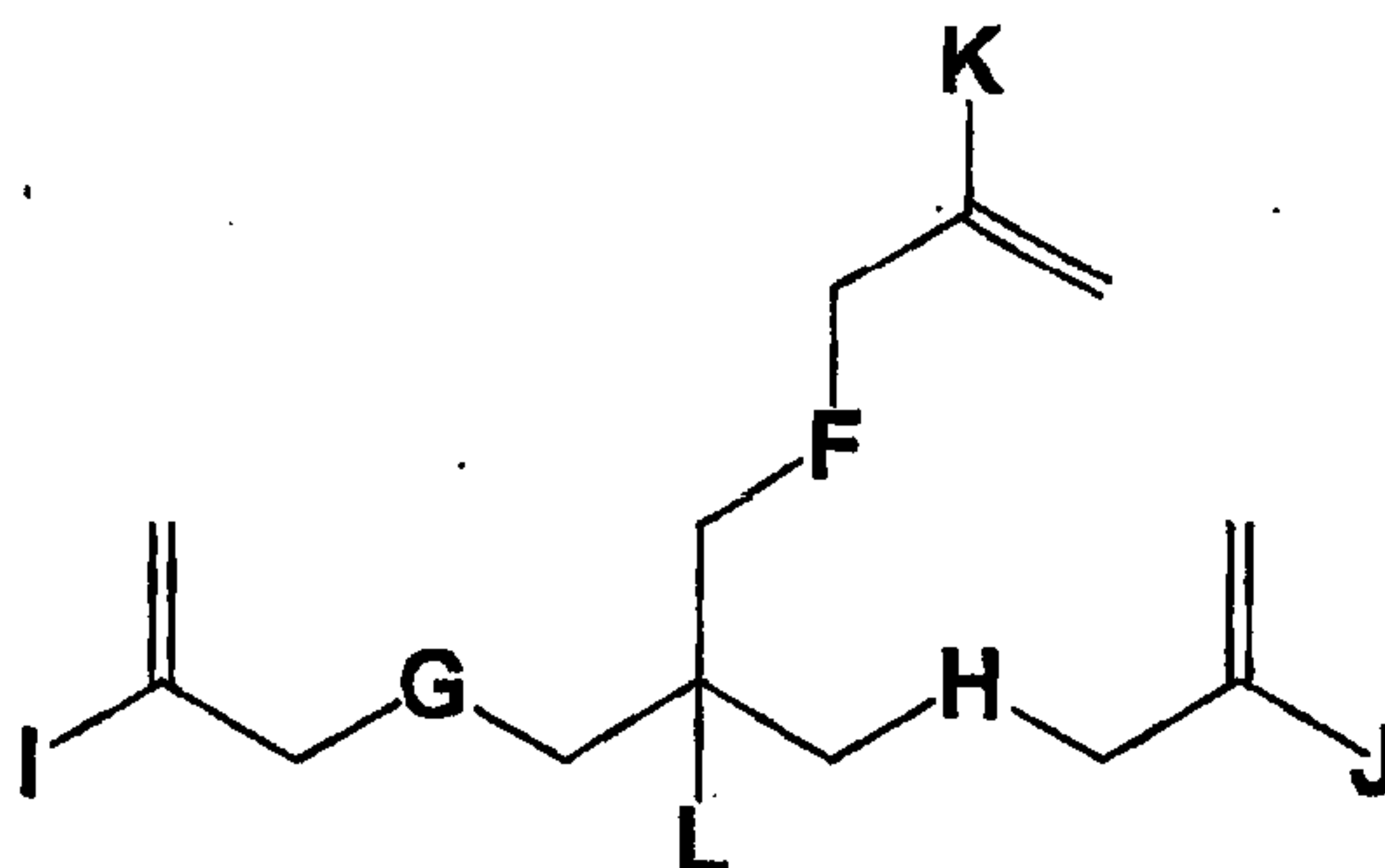


wherein

D is PEG, PPG or poly (THF); and

C and E represent independently an electron withdrawing group, an electron releasing group or a C₁-C₃₀ (preferably C₄ to C₁₂) aryl.

According to a seventh aspect of the invention, there is provided a compound of formula



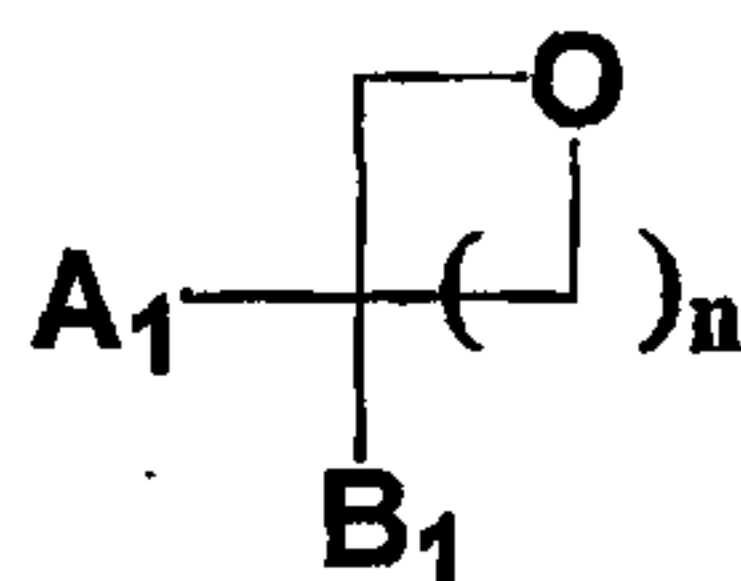
wherein

F, G and H represent independently PEG, PPG or poly (THF);

I, J and K represent independently an electron withdrawing group, an electron releasing group or a C₁-C₃₀ (preferably C₄ to C₁₂) aryl; and

L represents H, C₁-C₃₀ (preferably C₁ to C₁₂) alkyl, C₁-C₃₀ (preferably C₄ to C₁₂) aryl, C₃-C₃₀ (preferably C₃ to C₁₂) aralkyl, glycidyl, C₁-C₃₀ (preferably C₄ to C₁₂) alkylglycidyl, hydroxyl or an alcohol protecting group.

According to an eighth aspect of the invention, there is provided a compound of formula



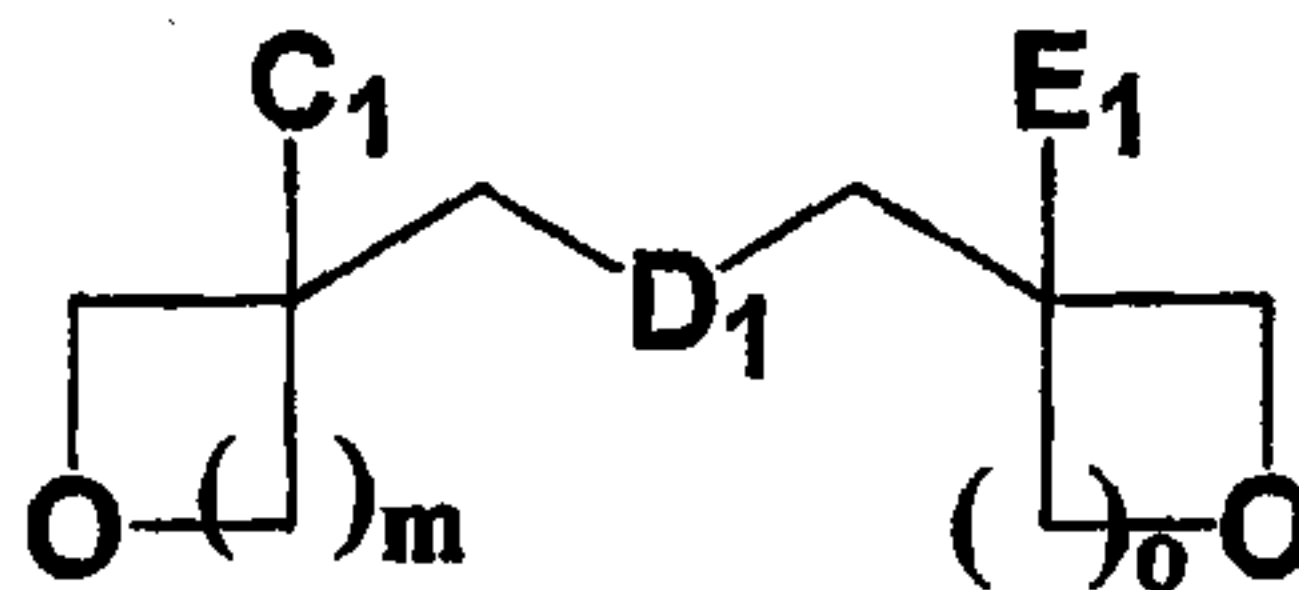
wherein

n = 0 or 1

A₁ represents PEG, PPG, poly (THF); and

B₁ is selected from the group consisting of electron withdrawing groups, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched alkanes, C₁ to C₅₀ (preferably C₁ to C₁₂) substituted linear or branched alkanes, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched arylalkanes, C₂ to C₅₀ (preferably C₂ to C₁₂) substituted linear or branched arylalkanes, and C₁ to C₃₀ (preferably C₁ to C₁₂) substituted or unsubstituted aryls.

According to a ninth aspect of the invention, there is provided a compound of formula



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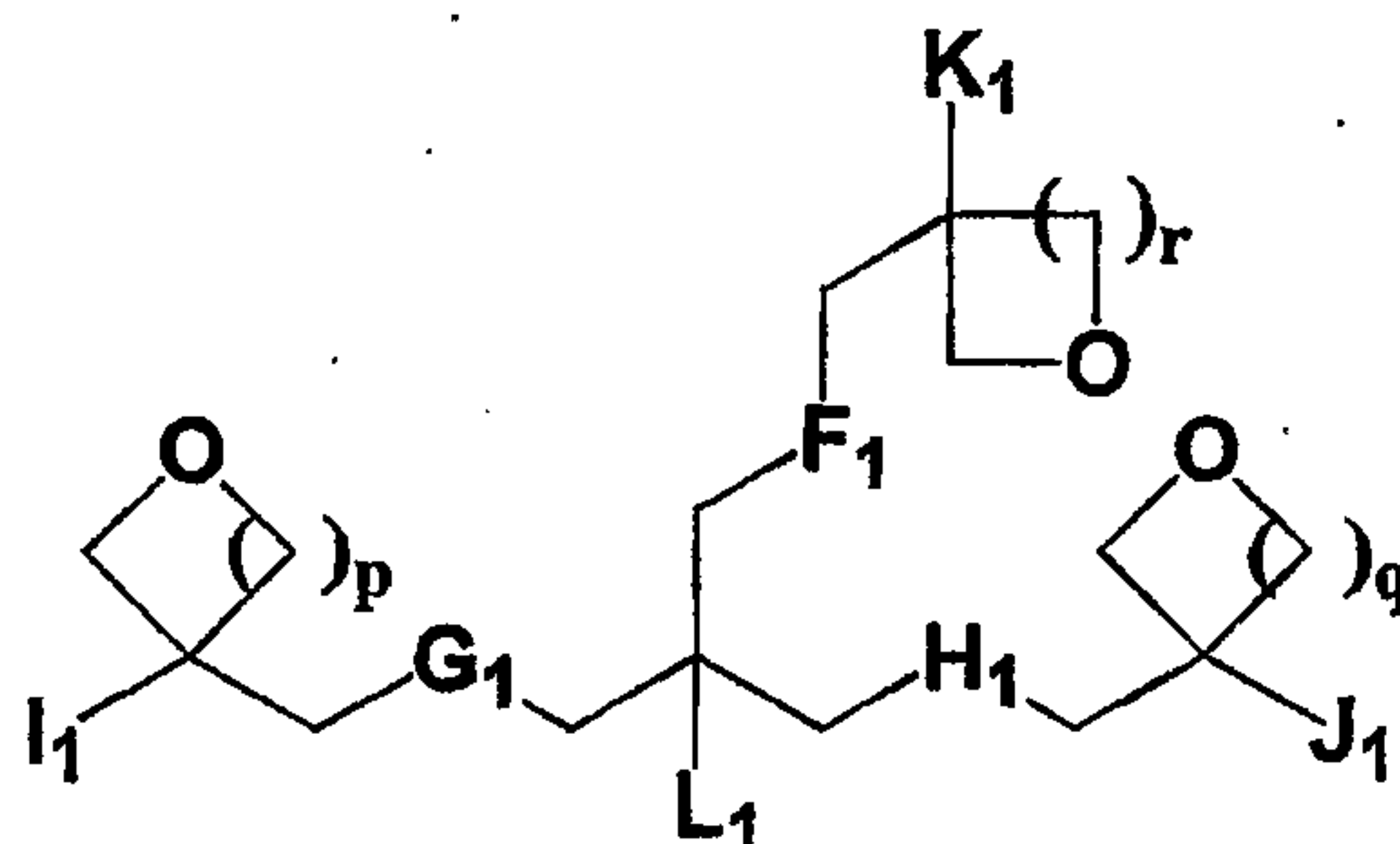
wherein

m and **o** are independently 0 or 1;

D₁ represents PEG, PPG or poly (THF); and

C₁ and **E₁** are independently selected from the group consisting of electron withdrawing groups, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched alkanes, C₁ to C₅₀ (preferably C₁ to C₁₂) substituted linear or branched alkanes, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched arylalkanes, C₂ to C₅₀ (preferably C₂ to C₁₂) substituted linear or branched arylalkanes, and C₁ to C₃₀ (preferably C₄ to C₁₂) substituted or unsubstituted aryls.

According to a tenth aspect of the invention, there is provided a compound of formula



wherein

p, **q** and **r** are independently 0 or 1;

F₁, **G₁** and **H₁** represent independently PEG, PPG or poly(THF);

I₁, **J₁** and **K₁** are independently selected from the group consisting of electron withdrawing groups, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched alkanes, C₁ to C₅₀ (preferably C₁ to C₁₂) substituted linear or branched alkanes, C₃ to C₅₀ (preferably C₃ to C₁₂) unsubstituted linear or branched arylalkanes, C₂ to C₅₀ (preferably C₃ to C₁₂) substituted linear or

branched arylalkanes, and C₁ to C₃₀ (preferably C₄ to C₁₂) substituted or unsubstituted aryls; and

L₁ represents H, C₁-C₃₀ (preferably C₁ to C₁₂) alkyl, C₁-C₃₀ (preferably C₄ to C₁₂) aryl, C₃-C₃₀ (preferably C₃ to C₁₂) aralkyl, glycidyl, C₁-C₃₀ (preferably C₃ to C₁₂) alkylglycidyl, hydroxyl or an alcohol protecting group.

According to an eleventh aspect of the invention, there is provided monomers and cross-linkers which are as defined in the previous aspect of the invention.

According to a twelfth aspect of the invention, there is provided the use of PEG, PPG or poly (THF) based polymer for preparing a cross-linked polyether or for preparing a polymeric support for use in bioorganic or organic chemistry.

The compounds according to any aspect the present invention can be used for preparing the polyether polymers previously defined. Alternatively, they can be used for preparing a cross-linked polyether resin or for preparing a polymeric support for use in bioorganic or organic chemistry. These compounds can also be used in the methods of the present invention. The compounds of the sixth, seventh, eighth, ninth or tenth aspect of the invention can be used as cross-linkers.

The expression "electron withdrawing group"(EWG) has used herein refers to a group bearing an electron deficient group and/or having an electronegativity less than the hydrogen atom. Preferably, the electron withdrawing group is halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate, nitrile, aldehyde, or ketone.

The expression "electron releasing group" (ERG) has used herein refers to a group bearing an electron rich group and/or having an electronegativity more than the hydrogen atom. Preferably, the electron releasing group is selected from the group consisting of C₁ to C₃₀ linear or branched alkyls, C₂ to C₃₀ linear or

branched aralkyls or C₁ to C₃₀ aryls, oxygen, sulphur, ethers, and amines (preferably secondary amines) etc.

The expression "substituted linear or branched alkanes" has used herein refers to alkanes which are substituted. These alkanes can be substituted by alkyls, halogens, amines, amides, alcohols, ethers, esters, aldehydes, carboxylic acids, nitro, cyano, sulphonates, phosphates derivatives etc.

The expression "substituted linear or branched arylalkanes" has used herein refers to arylalkanes which are substituted. These arylalkanes can be substituted by alkyls, halogens, amines, amides, alcohols, ethers, esters, aldehydes, carboxylic acids, nitro, cyano, sulphonates, phosphates derivatives etc.

The expression "substituted linear or branched alkyls" has used herein refers to alkyls which are substituted. These alkyls can be substituted by alkyls, halogens, amines, amides, alcohols, ethers, esters, aldehydes, carboxylic acids, nitro, cyano, sulphonates, phosphates derivatives etc.

The expression "substituted linear or branched arylalkyls" has used herein refers to arylalkyls which are substituted. These arylalkyls can be substituted by alkyls, halogens, amines, amides, alcohols, ethers, esters, aldehydes, carboxylic acids, nitro, cyano, sulphonates, phosphates derivatives etc.

The expression "substituted or unsubstituted aryls" has used herein refers to aryls which are optionally substituted. These aryls can be substituted by alkyls, halogens, amines, amides, alcohols, ethers, esters, aldehydes, carboxylic acids, nitro, cyano, sulphonates, phosphates derivatives etc.

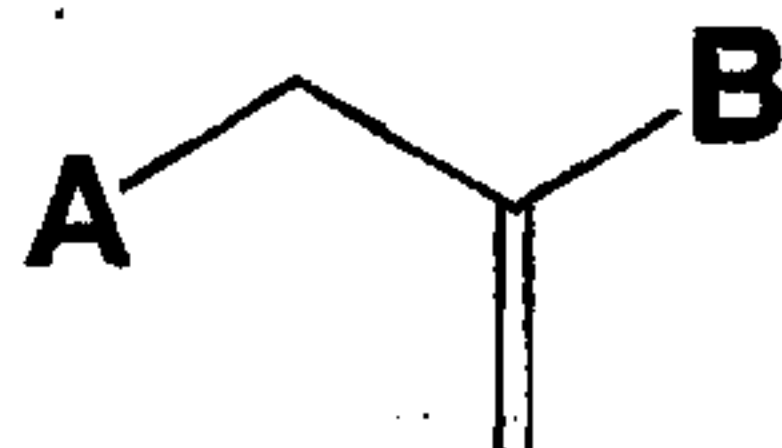
The term "aryls" has used herein can refer to aryls such as phenyls, naphtyls, anthracenyls, etc., or to heteroaryls such as uryl, thienyl, pyridyl, anisoyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl,

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pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl etc.

In the cross-linked polyether according to the first aspect of the invention, the monomer can be copolymerized with styrene, which can be in an amount of about 0.01 to about 99.99 %, and preferably about 10 to about 90 %. Alternatively, the monomer can be copolymerized with cross-linker. The cross-linker can be divinylbenzene, which can be in an amount of about 0.01 to about 99.99 %, and preferably about 0.2 to about 50 %.

In another preferred embodiment, the monomer, in the polyether of the first aspect, can be a polymerizable compound having the general formula



wherein

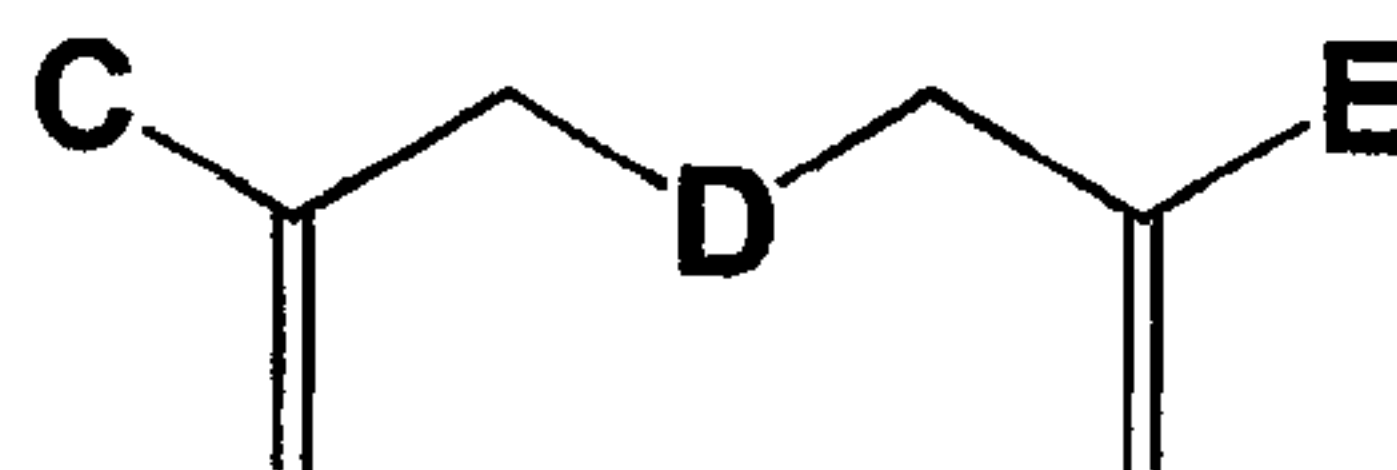
A represents H, C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, PEG, PPG, poly (THF), hydroxyl, C₁-C₃₀ alkyloxy, C₁-C₃₀ hydroxyalkyl, amino, C₁-C₃₀, alkylamine, C₁-C₃₀ aminoalkyl, formyl, C₁-C₃₀ alkylaldehyde, thiol, C₁-C₃₀ alkylthiol, halogen or an C₁-C₃₀ halogenoalkyl; and

B represents an electron withdrawing group, an electron releasing group or a C₁-C₃₀ aryl.

In another preferred embodiment, the monomer of the first or second aspect can be copolymerized with a PEG, PPG, or a poly (THF) based cross-linker.

In another preferred embodiment, the monomer of the first aspect can be copolymerized with a secondary cross-linker of the general formula

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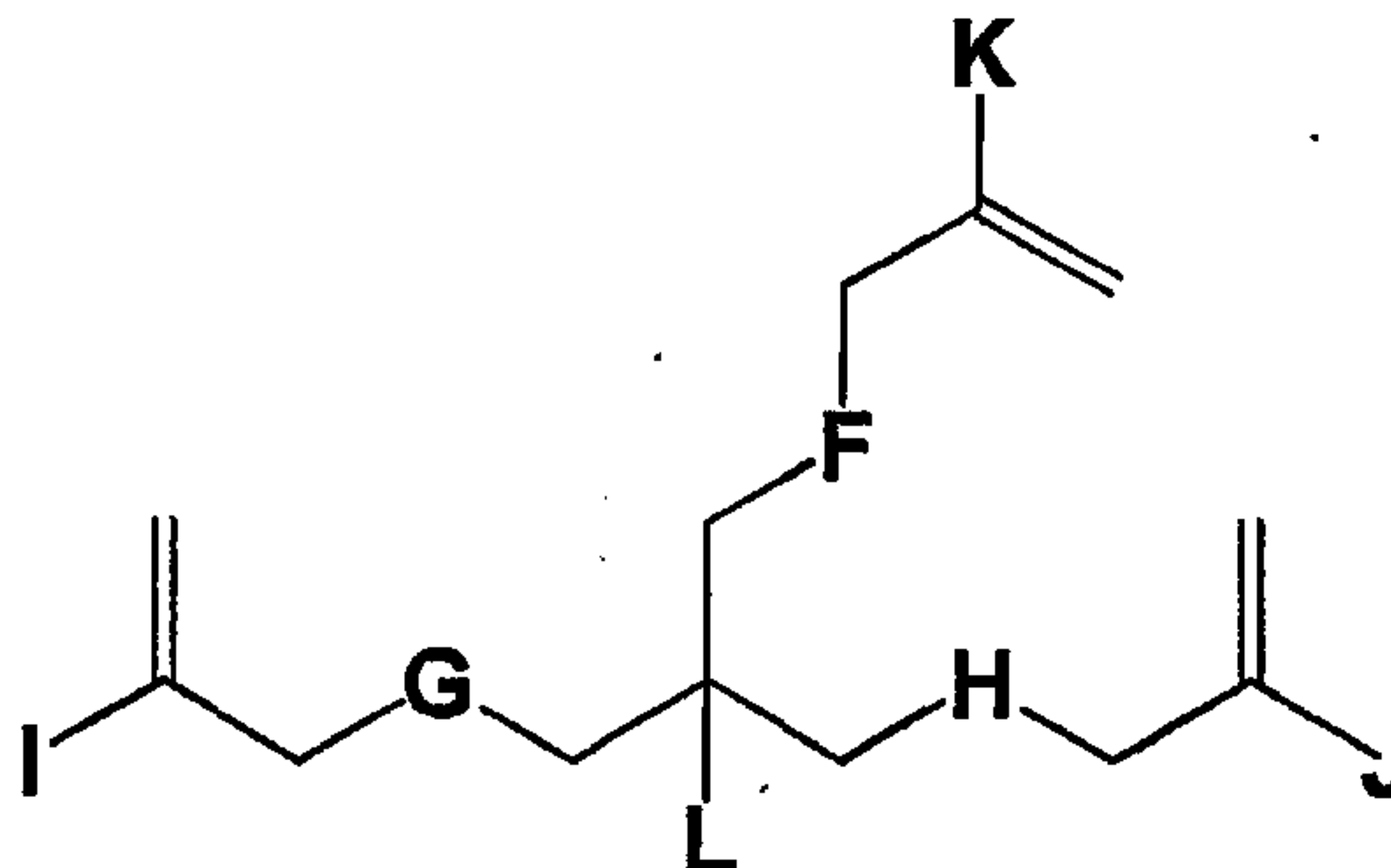
wherein

D represents a C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, oxygen, sulphur, PEG, PPG or poly (THF);

C and **E** represent independently an electron withdrawing group, an electron releasing group or a C₁-C₃₀ aryl.

In another preferred embodiment, the monomer of the first aspect can be copolymerized with a secondary cross-linker selected from the group consisting of a PEG, PPG, poly (THF) or a secondary cross-linker having at least an acrylamide or an methacrylamide) end group.

In another preferred embodiment, the monomer of the first aspect can be copolymerized with a tertiary cross-linker of the general formula



wherein

F, **G** and **H** represent independently a C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, oxygen, sulphur, PEG, PPG or poly (THF);

I, **J** and **K** represent independently an electron withdrawing group, an electron releasing group or a C₁-C₃₀ aryl.

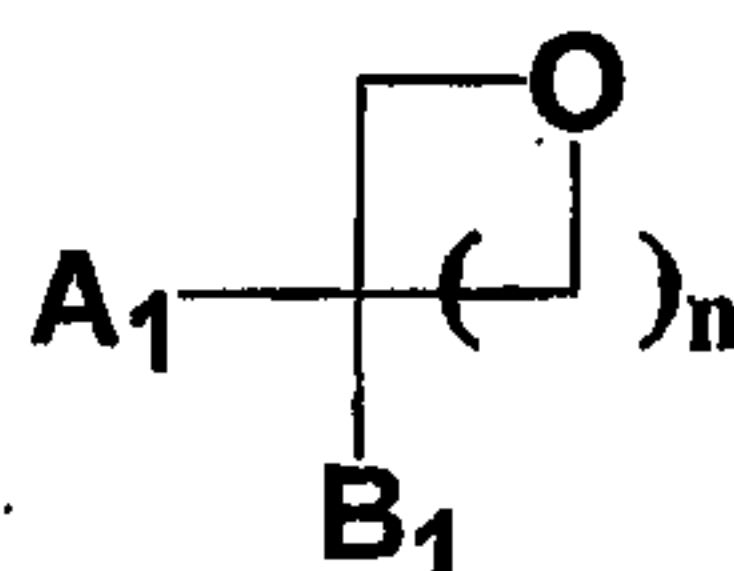
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L represents H, C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, glycidyl, C₁-C₃₀ alkylglycidyl, hydroxyl or an alcohol protecting group.

In another preferred embodiment, the monomer of the first aspect, can be copolymerized with a comb-like or a star-shaped cross-linker derivatized with a (α-X-methyl) vinyl-EWG, (α-X-methyl) vinyl-ERG or (α-X-methyl) vinyl-aryl, where X is oxygen, sulfur, PEG, PPG, or poly (THF); derivatives selected from the group consisting of acrylates, acrylamides, acrylonitriles, acroleins, vinyl ketones, vinyl chlorides, vinyl bromides, and styrenes; or a PEG, PPG, or poly (THF) having at least an acrylamide or a methacrylamide end group.

In another preferred embodiment, the monomer in the cross-linked polyether of the first aspect, can be produced by the Baylis-Hillman reaction or by an acid catalysis from an alcohol and a vinyl derivative, in a dehydration process. Preferably, the vinyl derivative is vinyl-EWG, vinyl-ERG or vinyl-aryl.

In another preferred embodiment, the monomer, in the polyether of the second aspect, can be a polymerizable compound having the general formula



wherein

$n = 0$ or 1

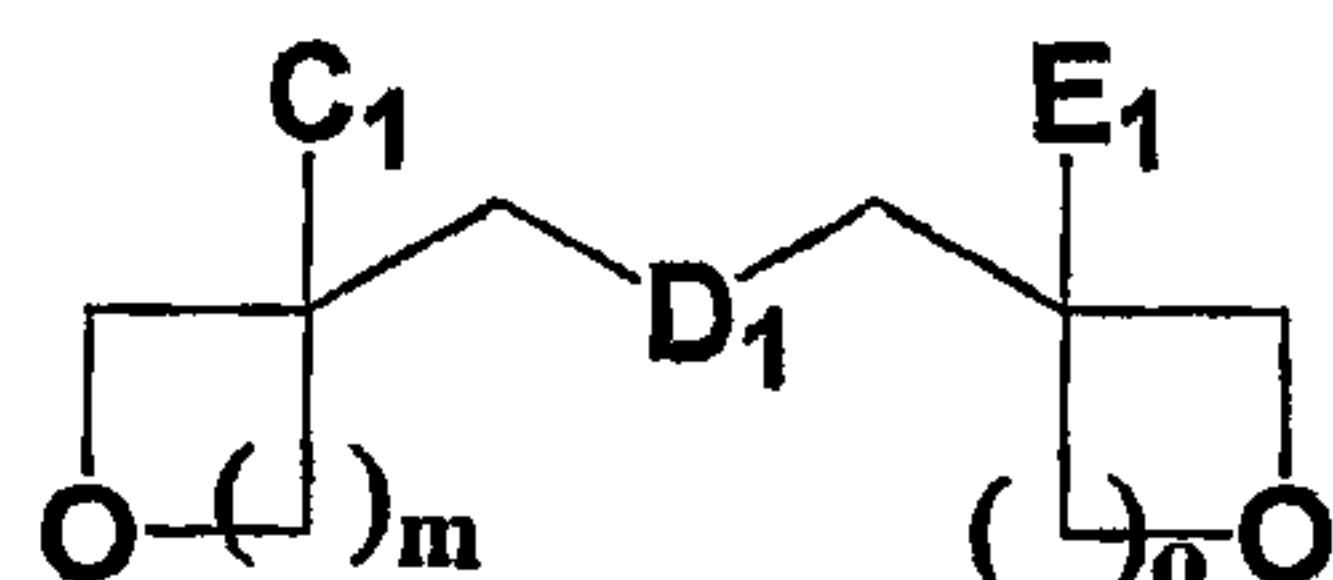
A₁, H, C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, PEG, PPG, poly (THF), hydroxyl, C₁-C₃₀ alkyloxy, C₁-C₃₀ hydroxyalkyl, amino, C₁-C₃₀ alkylamine, C₁-C₃₀ aminoalkyl, formyl, C₁-C₃₀ alkylaldehyde, thiol, C₁-C₃₀ alkylthiol, halogen or an C₁-C₃₀ halogenoalkyl; and

B₁ is selected from the group consisting of electron withdrawing groups, C₃ to C₅₀ unsubstituted linear or branched alkanes, C₁ to C₅₀ substituted linear or

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branched alkanes, C_3 to C_{50} unsubstituted linear or branched arylalkanes, C_2 to C_{50} substituted linear or branched arylalkanes, and C_1 to C_{30} substituted or unsubstituted aryls.

In another preferred embodiment, the monomer of the second aspect can be copolymerized with a secondary cross-linker of the general formula



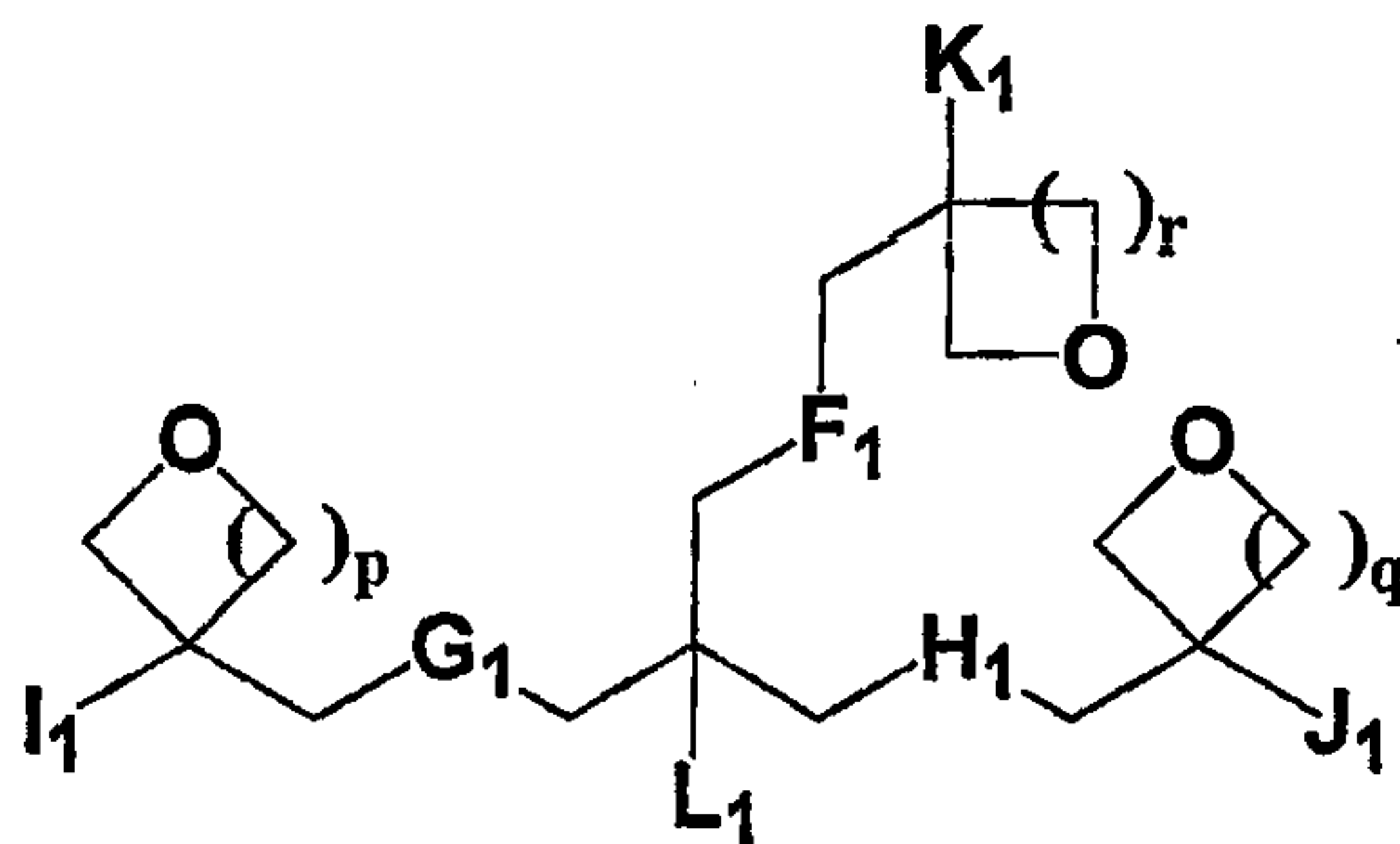
wherein

m and o are independently 0 or 1;

D_1 represents a C_1 - C_{30} alkyl, C_1 - C_{30} aryl, C_3 - C_{30} aralkyl, oxygen, sulphur, PEG, PPG or poly (THF); and

C_1 and E_1 are independently selected from the group consisting of electron withdrawing groups, C_3 to C_{50} unsubstituted linear or branched alkanes, C_1 to C_{50} substituted linear or branched alkanes, C_3 to C_{50} unsubstituted linear or branched arylalkanes, C_2 to C_{50} substituted linear or branched arylalkanes, and C_1 to C_{30} substituted or unsubstituted aryls.

In another preferred embodiment, the monomer of the second aspect can be copolymerized with a tertiary cross-linker of the general formula



wherein

p, **q** and **r** are independently 0 or 1;

F₁, **G₁** and **H₁** represent independently a C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, oxygen, sulphur, PEG, PPG or poly (THF);

I₁, **J₁** and **K₁** are independently selected from the group consisting of electron withdrawing groups, C₃ to C₅₀ unsubstituted linear or branched alkanes, C₁ to C₅₀ substituted linear or branched alkanes, C₃ to C₅₀ unsubstituted linear or branched arylalkanes, C₂ to C₅₀ substituted linear or branched arylalkanes, and C₁ to C₃₀ substituted or unsubstituted aryls; and

L₁ represents H, C₁-C₃₀ alkyl, C₂-C₃₀ aryl, C₃-C₃₀ aralkyl, glycidyl, C₁-C₃₀ alkylglycidyl, hydroxyl or an alcohol protecting group.

In another preferred embodiment, the monomer of the second aspect can be copolymerized with a comb-like or a star-shaped cross-linker derivatized with an α,α' -X-Y-epoxide or an α,α' -X-Y-oxetane, where X is selected from the group consisting of oxygen, sulfur, PEG, PPG and poly (THF)); and Y is selected from the group consisting of C₃ to C₅₀ unsubstituted linear or branched alkanes, C₁ to C₅₀ substituted linear or branched alkanes, C₃ to C₅₀ unsubstituted linear or branched arylalkanes, C₂ to C₅₀ substituted linear or branched arylalkanes, and C₁ to C₃₀ substituted or unsubstituted aryls.

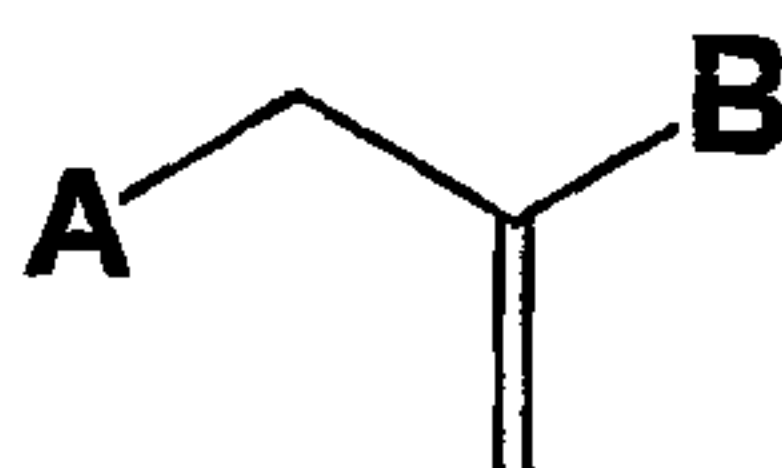
In the polyether of the first and second aspects, and the compounds of any aspect of the invention, the functional groups **A**, **A₁**, **B**, **B₁**, **C**, **C₁**, **E**, **E₁**, **I**, **I₁**, **J**, **J₁**, **K**, **K₁** and **L**, **L₁** can be chemically modified to provide linkers for organic, peptide, protein, nucleotide and saccharide synthesis, for the immobilisation of proteins and reagents, for chromatographic and scavenging purposes, as reverse phase packing and chromatographic devices, in ion exchange and normal phase chromatography. Preferably the linkers are selected from alcohol, C₁-C₃₀ alkylalcohols, halogens, C₁-C₃₀ halogenoalkyls, C₁-C₃₀ hydroxyalkyls, amines, C₁-C₃₀ alkylamines, C₁-C₃₀ alkylaminoalkyls, C₁-C₃₀ aryls, C₁-C₃₀ alkyls, C₃-C₃₀

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aralkyls, nitrile, C₁-C₃₀ alkylnitriles, carboxylic acids, C₁-C₃₀ carboxyalkyls, esters, C₁-C₃₀ alkylesters, thiols, C₁-C₃₀ alkylthiols, sulfos, C₁-C₃₀ alkylsulfos, sulfinos, C₁-C₃₀ alkylsulfinos, sulfenos, C₁-C₃₀ alkylsulfenos, and derivatives thereof. Comb-like (Ito *et al.*, (1992), *Macromol.* Vol.25, 1534-1538) and star-shaped CL are also covered by the present invention. These CL are functionalized with PEG, PPG and/or poly (THF) with the aforementioned (α -methyl) vinyl-EWG and/or α,α' -X-Y-(epoxide and/or oxetane) and/or derivatives and/or having at least one acrylamide (and/or methacrylamide) end group (that will later be reduced once polymerized to a polyamine) at the end of each "tentacles".

The method according to the third aspect of the invention can comprise

a) copolymerizing a polymerizable monomer having the general formula



wherein

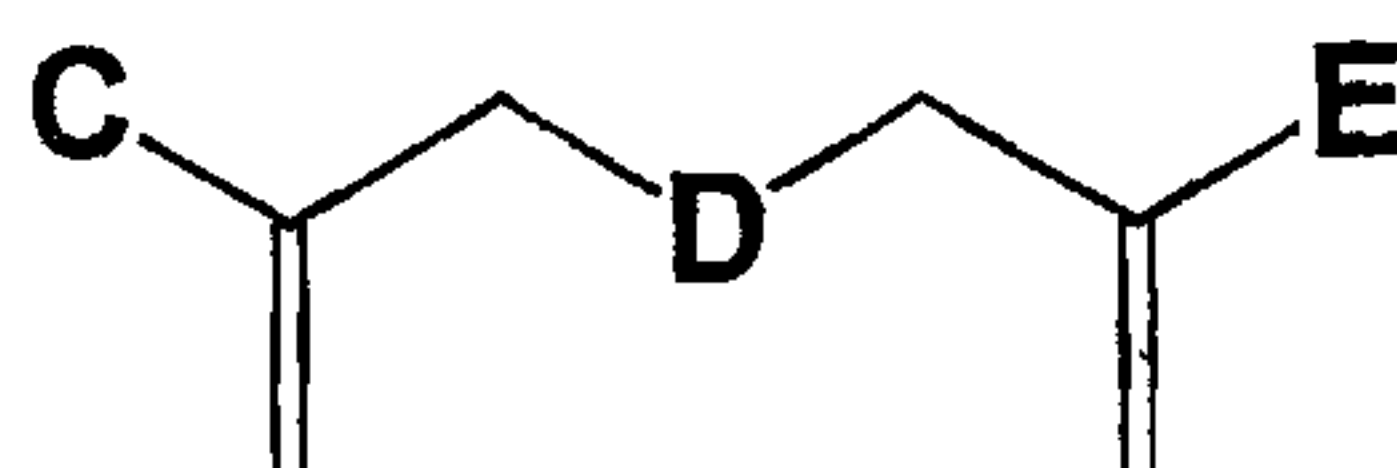
A represents H, C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, PEG, PPG, poly (THF), hydroxyl, C₁-C₃₀ alkyloxy, C₁-C₃₀ hydroxyalkyl, amino, C₁-C₃₀, alkylamine, C₁-C₃₀ aminoalkyl, formyl, C₁-C₃₀ alkylaldehyde, thiol, C₁-C₃₀ alkylthiol, halogen or an C₁-C₃₀ halogenoalkyl; and

B represents an electron withdrawing group, an electron releasing group or an aryl

together with

i) a secondary cross-linker of the general formula

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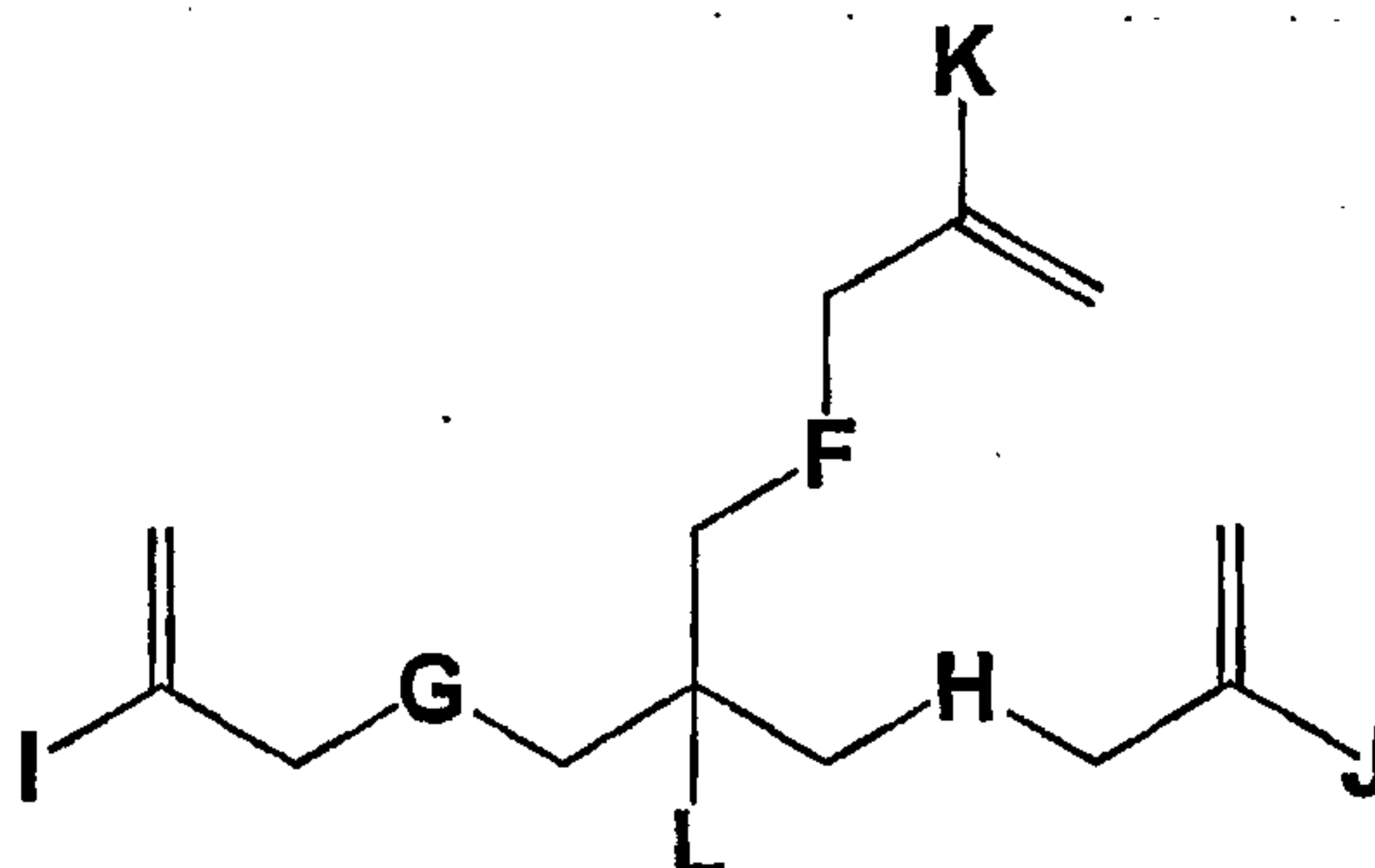
wherein

D represents a C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, oxygen, sulphur, PEG, PPG or poly (THF);

C and E represent independently an electron withdrawing group, an electron releasing group or a C₁-C₃₀ aryl;

ii) a PEG, PPG, or poly (THF) cross-linker having at least an acrylamide or a methacrylamide end group;

iii) a tertiary cross-linker of the general formula



wherein

F, G and H represent independently a C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, oxygen, sulphur, PEG, PPG or poly (THF);

I, J and K represent independently an electron withdrawing group, an electron releasing group or a C₁-C₃₀ aryl;

L represents H, C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, glycidyl, C₁-C₃₀ alkylglycidyl, hydroxyl or an alcohol protecting group;

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iv) a comb-like or a star-shaped cross-linker derivatized with a (α -X-methyl) vinyl-EWG, (α -X-methyl) vinyl-ERG or (α -X-methyl) vinyl-aryl, where X is oxygen, sulfur, PEG, PPG, or poly (THF); derivatives selected from the group consisting of acrylates, acrylamides, acrylonitriles, acroleins, vinyl ketones, vinyl chlorides, vinyl bromides, and styrenes; or a PEG, PPG, or poly (THF) having at least an acrylamide or a methacrylamide end group; or

v) divinylbenzene,

so as to obtain said polyether; and

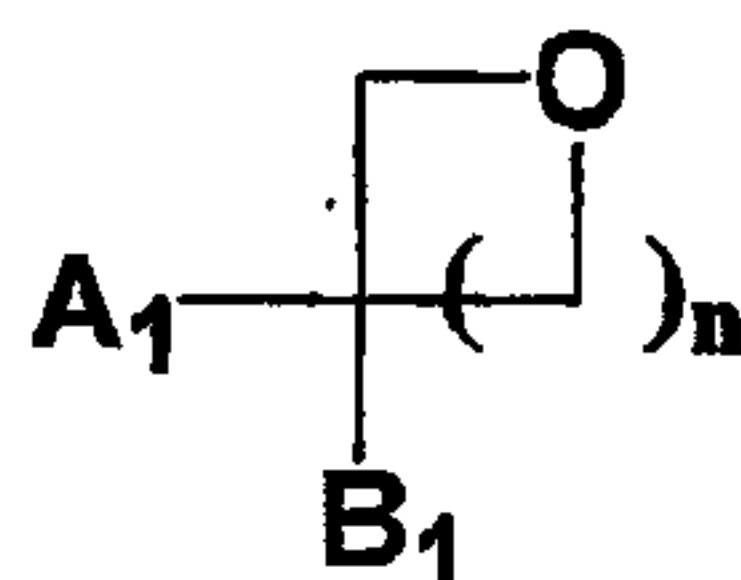
b) chemically modifying said polyether so as to obtain a polyether derivative selected from the group consisting of aldehyde, amine, ketone, halogen, carboxylic acid, thiol, amide and or ester resin.

Preferably, the cross-linked polyether is obtained by suspension radical polymerization. Alternatively, the method comprises carrying said copolymerization in the presence of additional polymerizable monomers selected from the group consisting of styrene, acrylates, acrylamides, acrylonitriles, acroleins (and their methacrylic derivatives), vinyl ketones, vinyl chlorides or vinyl bromides. The method can also comprise functionalizing said monomer with groups capable of anchoring linkers. Alternatively, the method can comprise functionalizing said acrylamide or methacrylamide monomer with groups capable of anchoring linkers.

In accordance with a preferred embodiment, the method of the third aspect comprises (a) copolymerizing the above vinylic polymerizable compound with a compound selected from the above vinylic secondary, tertiary, comb-like, star-shaped and/or divinylbenzene CL to give the above polymer, (b) reacting the polymer to give a polyester (by transesterification or not), polyol, polyaldehyde, polycarboxylic acid, polythiol and/or polyamine (from acrylamide and/or methacrylamide or not) resin that will be later derivatized.

The method according to the fourth aspect of the invention can comprise

a) copolymerizing a polymerizable monomer having the general formula



wherein

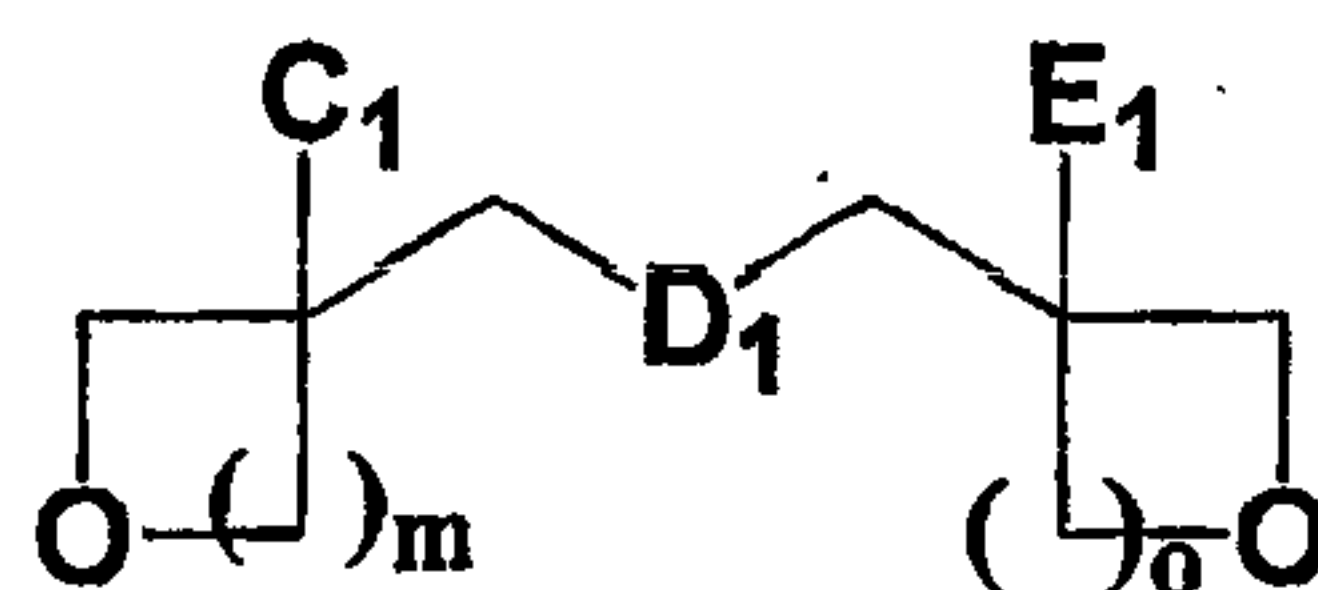
$n = 0$ or 1

A_1 H, C_1 - C_{30} alkyl, C_1 - C_{30} aryl, C_3 - C_{30} aralkyl, PEG, PPG, poly (THF), hydroxyl, C_1 - C_{30} alkyloxy, C_1 - C_{30} hydroxyalkyl, amino, C_1 - C_{30} alkylamine, C_1 - C_{30} aminoalkyl, formyl, C_1 - C_{30} alkylaldehyde, thiol, C_1 - C_{30} alkylthiol, halogen or an C_1 - C_{30} halogenoalkyl; and

B_1 is selected from the group consisting of electron withdrawing groups, C_3 to C_{50} unsubstituted linear or branched alkanes, C_1 to C_{50} substituted linear or branched alkanes, C_3 to C_{50} unsubstituted linear or branched arylalkanes, C_2 to C_{50} substituted linear or branched arylalkanes, and C_1 to C_{30} substituted or unsubstituted aryls,

together with

i) a secondary cross-linker of the general formula



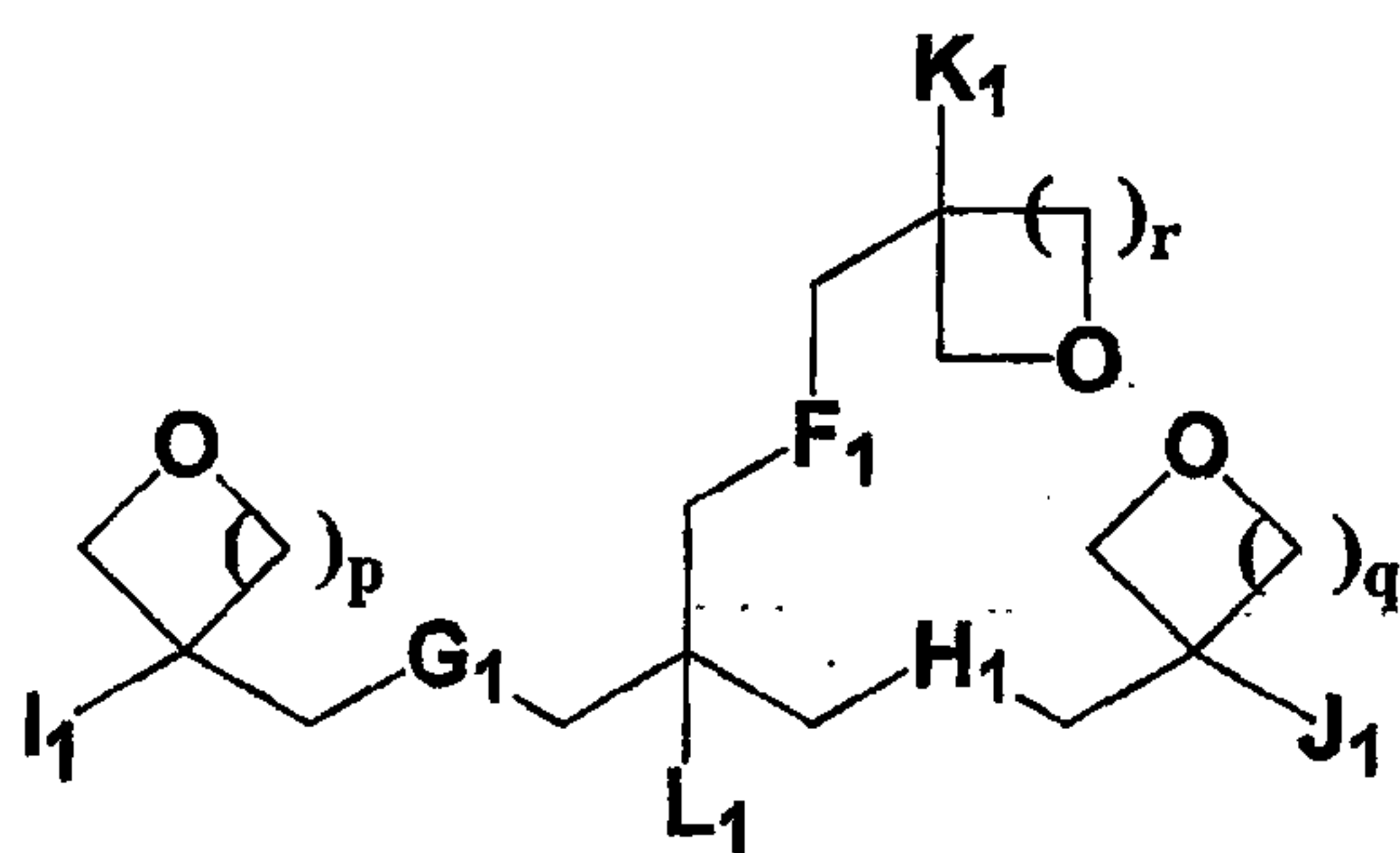
wherein

m and o are independently 0 or 1;

D₁ represents a C₁-C₃₀ alkyl, C₁-C₃₀ aryl, C₃-C₃₀ aralkyl, oxygen, sulphur, PEG, PPG or poly (THF); and

C₁ and **E**₁ are independently selected from the group consisting of electron withdrawing groups, C₃ to C₅₀ unsubstituted linear or branched alkanes, C₁ to C₅₀ substituted linear or branched alkanes, C₃ to C₅₀ unsubstituted linear or branched arylalkanes, C₂ to C₅₀ substituted linear or branched arylalkanes, and C₁ to C₃₀ substituted or unsubstituted aryls;

ii) a tertiary cross-linker of the general formula



wherein

p, **q** and **r** are independently 0 or 1;

F₁, **G**₁ and **H**₁ represent independently a C₁-C₃₀ alkyl, C₂-C₃₀ aryl, C₃-C₃₀ aralkyl, oxygen, sulphur, PEG, PPG or poly (THF);

I₁, **J**₁ and **K**₁ are independently selected from the group consisting of electron withdrawing groups, C₃ to C₅₀ unsubstituted linear or branched alkanes, C₁ to C₅₀ substituted linear or branched alkanes, C₃ to C₅₀ unsubstituted linear or branched arylalkanes, C₂ to C₅₀ substituted linear or branched arylalkanes, and C₁ to C₃₀ substituted or unsubstituted aryls; and

L₁ represents H, C₁-C₃₀ alkyl, C₂-C₃₀ aryl, C₃-C₃₀ aralkyl, glycidyl, C₁-C₃₀ alkylglycidyl, hydroxyl or an C₁-C₃₀ alkylol protecting group; or

iii) a comb-like or a star-shaped cross-linker derivatized with an α,α' -X-Y-epoxide or an α,α' -X-Y-oxetane, where X is selected from the group consisting of oxygen, sulfur, PEG, PPG and poly (THF)), and Y is selected from the group consisting of C₃ to C₅₀ unsubstituted linear or branched alkanes, C₁ to C₅₀ substituted linear or branched alkanes, C₃ to C₅₀ unsubstituted linear or branched arylalkanes, C₂ to C₅₀ substituted linear or branched arylalkanes, and C₁ to C₃₀ substituted or unsubstituted aryls; and

b) chemically modifying said polyether so as to obtain a polyether derivative selected from the group consisting of aldehyde, amine, ketone, halogen, carboxylic acid, thiol, amide and or ester resin.

Preferably, the cross-linked polyether is obtained by suspension cationic polymerization. Alternatively, the method can comprise carrying said copolymerization in the presence of additional polymerizable monomers selected from the group consisting of epoxides, oxetanes, vinyl and allyl ethers. Also, the method can comprise functionalizing said α,α' -X-Y-epoxide or α,α' -X-Y-oxetane monomer with groups capable of anchoring linkers.

In accordance with a preferred embodiment, the method defined in the fourth aspect comprises (a) copolymerizing the above epoxide and/or oxetane polymerizable compound with a compound selected from the above epoxide and/or oxetane secondary, tertiary, comb-like, star-shaped CL to give the above polymer, (b) reacting the polymer to give a polyester (by transesterification or not), polyol, polyaldehyde, polycarboxylic acid, polythiol and/or polyamine (from acrylamide and/or methacrylamide or not) resin that will be later derivatized.

Preferably, the methods of the third and the fourth aspects comprise synthesizing the cross-linked polyether into beaded form. The beads can be formed by normal or inverse suspension. Preferably, the groups capable of

anchoring linkers are selected from aldehydes, alcohols, halogens, ketones, amino, and phenyl groups which can be derivatized into said anchoring linkers.

According to the present invention, any of the new monomers and CL ester bond can be reacted to functionality useful for anchoring linkers used in SPPS and SPOS. The end groups of the monomers and/or CL may also contain alcohol, halogen, aldehyde, amino, carboxylic acid, thiol and/or phenyl groups that can be later derivatized in (or with) useful linkers for peptide synthesis or bioorganic and organic chemistry.

The resins, polymers and compounds of the invention can be used in solid and liquid phase synthesis, chromatography, for scavenging purposes and immobilisation of proteins and reagents.

Monomers and/or CL can be functionalized before or after the polymerization with different linkers useful for peptide, bioorganic and organic chemistry, and the like.

Examples of derivatization of the final polymer:

Chemical function	Reducing	Nucleophilic	Hydrolytic
Ester	Alcohol or aldehyde	Alcohol, ester and amide	Carboxylic acid
Amide	Amine	Alcohol	Carboxylic acid
Nitrile	Amine	Alcohol	Carboxylic acid
Aldehyde	Alcohol	Alcohol	-----
Ketone	Alcohol	Alcohol	-----
Nitro	Amine	-----	-----
Sulfoxide	Thiol	-----	-----
Sulfonate	Thiol	-----	-----

The cross-linked polymer according to the invention is designed in such a way that it is possible to modify its properties by an appropriate choice of monomers (including single monomer, secondary, tertiary, comb-like and/or star-shaped CL). Indeed, the length of each monomer and/or CL will affect the swelling of the final resin. That way, it is possible to obtain a resin with several mechanical and swelling behaviours. That feature is greatly helpful for the design of resins for continuous flow to batchwise synthesis. By using a longer monomer and/or CL, the polymer is a more porous polymer enabling high molecular weight molecule penetration, which is effective for peptide, oligonucleotide, oligosaccharide synthesis and protein immobilisation. Shorter monomers give a resin adapted for small molecule synthesis as found in current organic chemistry.

Furthermore, that physical aspect can be used for permeation chromatography where a porous matrix is essential. A harder resin will be useful for low to high pressure chromatography where a very small to no change in volume of the matrix is needed.

The chemical nature of the PEG, PPG and/or poly (THF) gives to the polymer an exceptional versatility in most of organic and aqueous solvents. In organic synthesis and chromatography, low to high polarity solvents are often used in the same experiment. The amphiphilic nature of the glycol derivatives according to the invention gives extraordinary swelling in solvents such as water, *N,N*-dimethylformamide, methanol, methylene chloride, tetrahydrofuran, acetone, toluene and chemical families associated therewith.

The cross-linked polymer according to the first aspect can be obtained by suspension radical copolymerization of a mixture (or not) of the aforementioned acrylic, acrylonitriles, acrylamides, acroleins, vinyl ketones, vinyl chloride and/or bromide derivative monomers (and/or styrene) with the aforementioned secondary, tertiary, comb-like and/or star-shaped CL and/or divinylbenzene.

The cross-linked polymer according to the second aspect can be obtained by suspension cationic copolymerization of a mixture (or not) of the aforementioned epoxides and/or oxetanes monomers with the aforementioned secondary, tertiary, comb-like and/or star-shaped CL (for examples of such processes, see Renil *et al.* (1996), Tetrahedron Lett., 37, 6185-6188) and Rademann *et al.*, ((1999), J. Am. Chem. Soc., 121, 5459-5466.)

According to the invention, the functional groups L and L₁ can be modified chemically before or after the copolymerization, into several types of linkers such as alcohol, alkylalcohol, amino, alkylamino, aryl, alkyl, aralkyl, cyano, carboxyl, ester, mercapto, sulfo, sulfinio, sulfeno in any derivatives thereof or in any protected form. Furthermore, any already designed linker for organic, peptide, nucleotide and saccharide synthesis can be attached to the monomer (as L and/or L₁) or by any functionality described above as a spacer.

Theses linkers can be used for organic, peptide, protein, nucleotide and saccharide synthesis. They can also be used also for the immobilisation of protein and reagents or for chromatographic and scavenging purposes. End-capped monomers (such as alkyl and aryl in place of L and/or L₁) can be used as chromatographic devices as reversed-phase packing. Other polar functionality for L and/or L₁ such as SO₃H and NH₂ can be used in ion exchange and normal phase chromatography.

According to the present invention, it is possible to use other polymerizable monomers (such as styrene or divinylbenzene) leading to the polymer according to the present invention.

The polymer can be generated into a preferred beaded (spherical) form by processes such as normal and inverse suspension, emulsion, dispersion, seeded or precipitation polymerizations. Normal and/or inverse suspension polymerization is the preferred method for the production of beads according to the present invention.

Bulk and solution polymerization should normally be avoided because no beads are thus formed. Nevertheless, powders obtained directly or by grinding and sieving of the bulk polymer and/or any other solid form of polymer can be obtained by these two processes and can be employed as solid support in the applications listed above.

Radical initiated polymerisation is the standard way by which vinyl monomers are polymerized although other methods can be used according to the present invention.

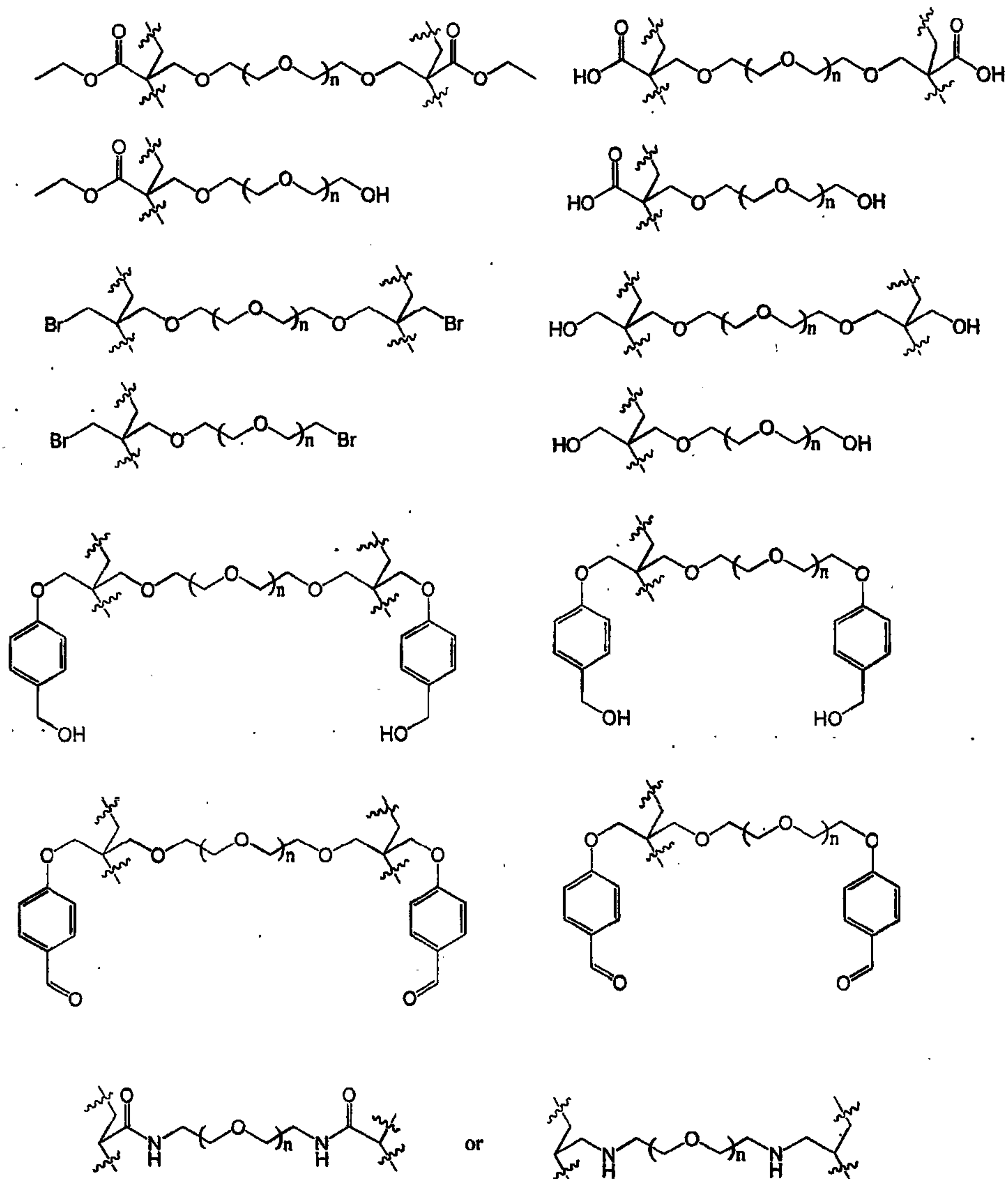
According to the present invention, the aforementioned "(α -methyl) vinyl-EWG" and/or acrylamide and/or methacrylamide monomers and/or CL may for example be copolymerized by radical polymerization with vinyl ether and allyl compounds that are known to copolymerize easily in the presence of other vinyl compounds such as acrylic, methacrylic acids and/or esters and/or derivatives.

The polymerization is normally initiated by products that upon heating, ultraviolet and/or gamma radiation give free radicals. In the present invention organic peroxides such as benzoyl and lauroyl peroxides are preferred. Heating the reaction mixture is the preferred way to form these free radicals.

In a same approach, vinyl and/or allyl ethers can be copolymerized with the aforementioned epoxides and/or oxetanes monomers and/or CL by cationic and/or anionic polymerization processes.

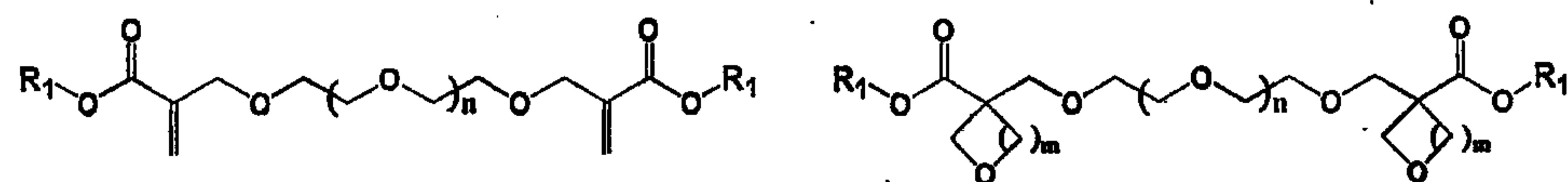
Particularly preferred resins of the present invention are cross-linked polyether resins which comprise a unit of formula

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wherein n has a value of 1 to 100.

Other interesting compounds of the invention are of formula



wherein R_1 is a C_1 - C_{10} alkyl which is linear or branched. R_1 can also be substituted as previously defined.

BRIEF DESCRIPTION OF DRAWINGS

Further features and advantages of the invention will become more readily apparent from the following description of preferred embodiments as illustrated by way of examples in the appended drawings wherein:

Fig. 1 is a diagram comparing the swelling of commercial resins and with the swelling of a resin according to a preferred embodiment of the invention;

Fig. 2 is a chromatogram showing the purity obtained during a synthesis of a compound when using a commercial resin;

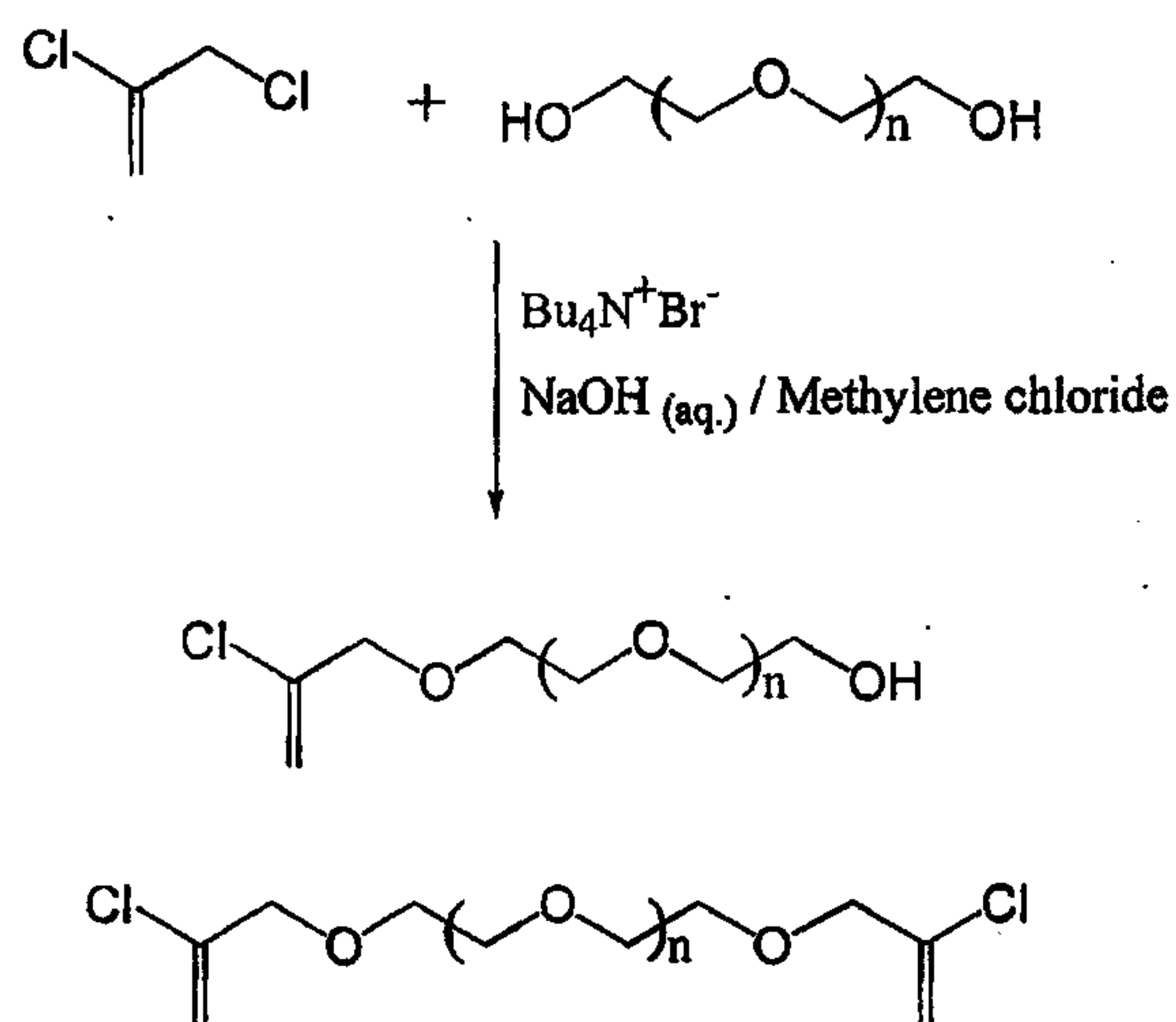
Fig. 3 is a chromatogram showing the purity obtained during a synthesis of a compound when using another commercial resin;

Fig. 4 is a chromatogram showing the purity obtained during a synthesis of a compound when using still another commercial resin; and

Fig. 5 is a chromatogram showing the purity obtained during a synthesis of a compound when using a resin according to a preferred embodiment of the invention.

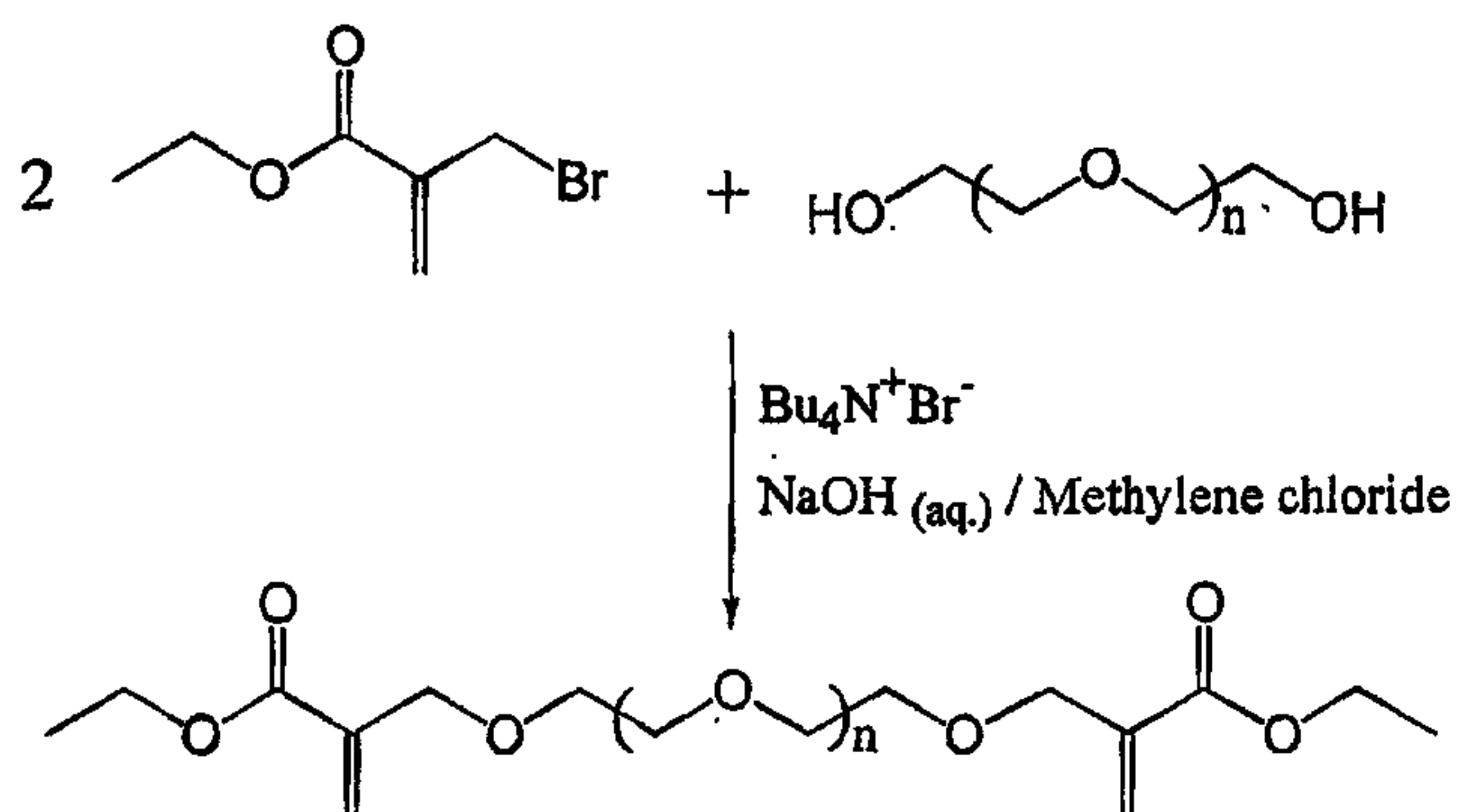
The invention will now be illustrated by means of the following non limiting examples.

Example 1: Synthesis of PEG400 bis ((α -methyl) vinyl chloride) under PTC conditions:



In a round bottom flask of 250mL, PEG 400 (24g; 60mmoles) is dissolved in 75mL of methylene chloride under mechanical agitation. A solution of sodium hydroxide 33% (150mL; 50g; 1250mmoles) with tetrabutylammonium bromide (TBAB) (19.34g; 60mmoles) is added to the organic phase. 2,3-dichloropropene (13.32g; 120mmoles) is gently introduced to the biphasic mixture. After 48h of stirring at room temperature, the organic phase is extracted then dried with Na_2SO_4 . The purification step is accomplished by means of a silica gel pad (hexanes/acetone: 1/1). The solvent is evaporated to dryness under vacuum. The final product is then dried under vacuum at 40°C overnight. Yield: 26.78g. The NMR spectrum shows a ratio between the vinylic protons and the PEG's methylene protons of 50% of mono and bis functionalized PEG 400.

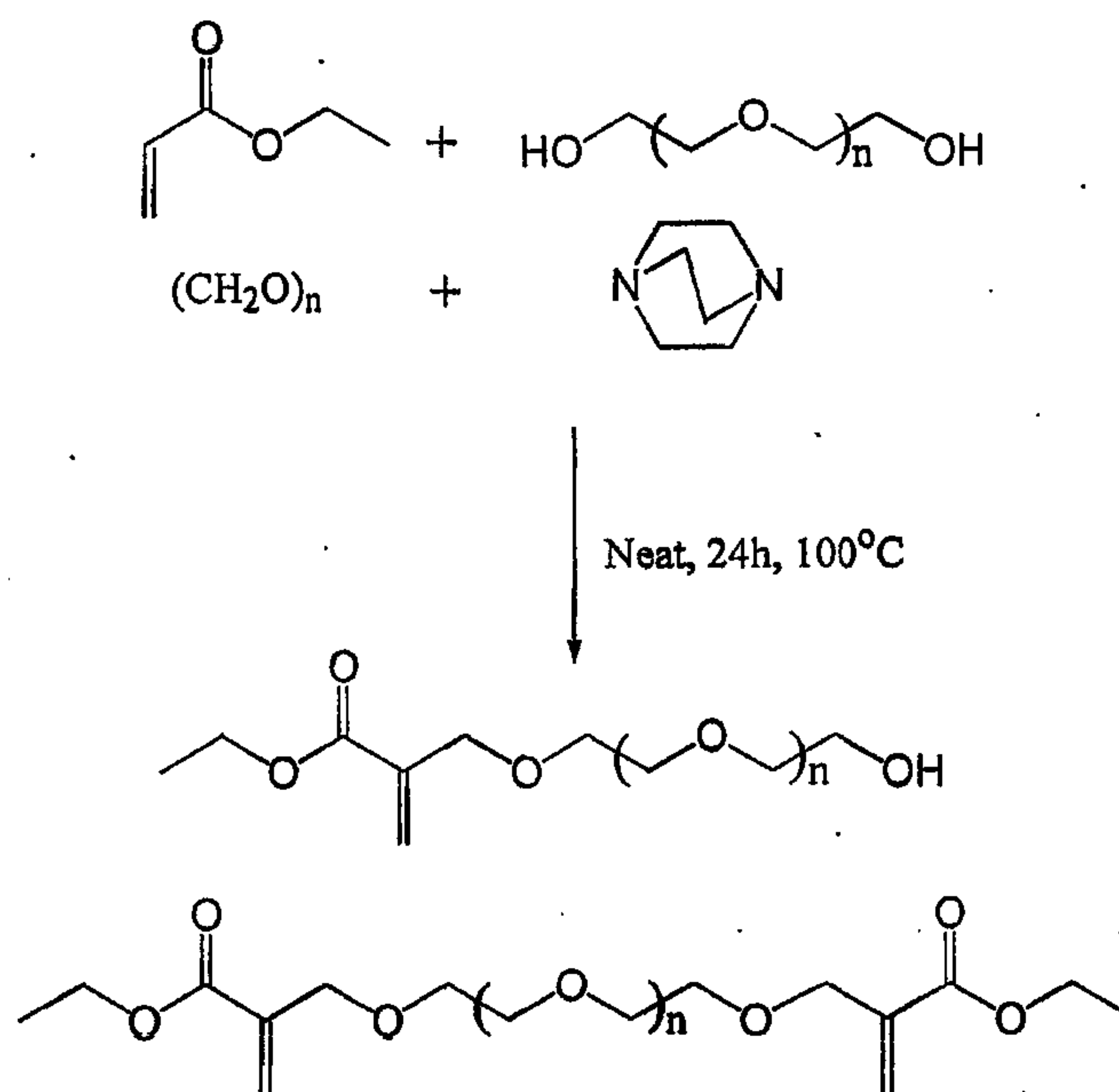
Example 2: Synthesis of PEG2000 bis (ethyl (α -methyl)acrylate) under PTC conditions:



In a round bottom flask of 1L, PEG 2000 (20.0g; 10mmoles) are dissolved in 400mL of methylene chloride under mechanical agitation. A solution of sodium hydroxide 33% (200mL; 67.5g; 1675mmoles) with tetrabutylammonium bromide (TBAB) (0.645g; 2mmoles) is added to the organic phase. Ethyl (bromomethyl) acrylate (7.72g; 40mmoles) is gently introduced to the biphasic mixture. After 24-48h of stirring at room temperature, the organic phase is extracted then dried with Na_2SO_4 . The solvent is evaporated under vacuum to dryness.

In a round bottom flask of 1L, under high-speed mechanical agitation, cold diethyl ether (300mL) is added to the insoluble product and then settled to remove ether by suction. This purification step is repeated three times. The final product is then dried under vacuum at 40°C overnight. Yield: 20.46g (92%) The NMR spectrum shows the right ratio between the vinylic protons and the PEG's methylene protons.

Example 3: Synthesis of PEG1500 mono & bis (ethyl (α -methyl)acrylate) under Baylis-Hillman conditions:



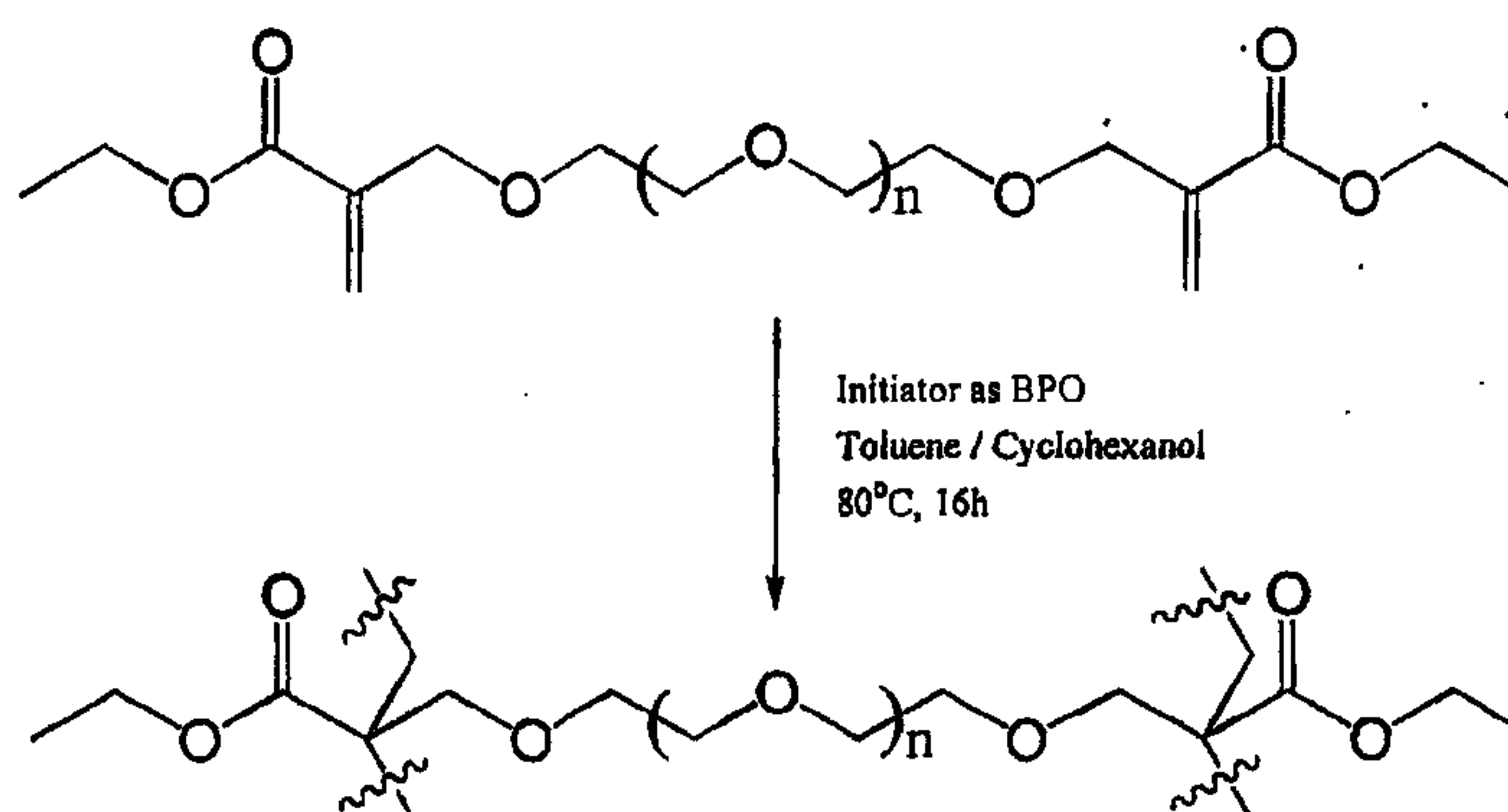
In a round bottom flask of 100mL, PEG 1500 (15,0g; 10mmoles) and DABCO (3,96g; 35mmoles) are dissolved in ethyl acrylate (25mL; 23,1g; 230mmoles) under mechanical agitation. At 100°C, paraformaldehyde (3,6g; 120mmoles) is added to the organic phase in several portions during 2 hours. After 24h of stirring at 100°C, the organic phase is cooled to the room temperature. The flask's content is dissolved in 200mL of acetone. Insoluble matter is filtered and the solvent is evaporated under vacuum to dryness.

The crude product is dissolved with a minimum of methylene chloride (circa 10-20mL) in a round bottom flask of 500mL. Under high-speed mechanical agitation, MTBE (300mL) is added to precipitate the product(s). After 2 hours at 4°C, the precipitate is filtered (MBTE solution is containing impurities) and washed with more MTBE (2x50mL) and finally with hexanes (3x50mL). This purification step is repeated twice. The final product is then dried

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under vacuum at 40°C overnight. Yield: 14,19g (82%) The NMR spectrum shows the presence of a mixture of 50% of PEG1500 mono & bis (ethyl (α -methyl)acrylate).

Example 4: Synthesis of poly(di(ethyl (PEG2000methyl)ester)):



Monomer phase:

Di(ethyl (PEG2000methyl)acrylate) 22.24 g; 10 mmol)

10.85mL of cyclohexanol

10.85mL of toluene

BPO 75% (Benzoyl peroxide) (0.643g ; 2 mmol)

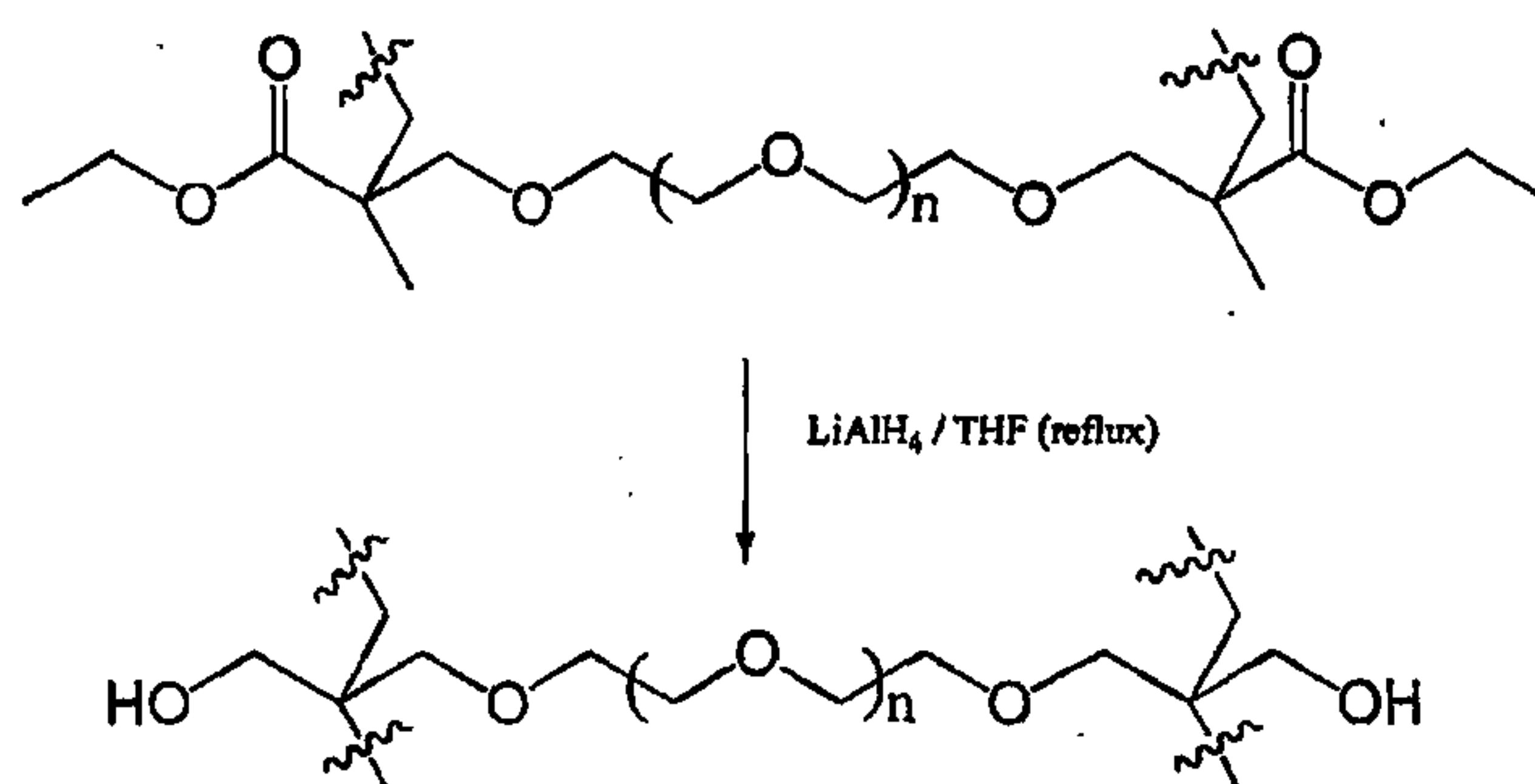
In a 500 mL tri-neck flask, under nitrogen, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (35.11g) and 227mg of sodium dodecylbenzenesulfonate are dissolved in 210 mL of distilled water at 300 r.p.m. at 25°C. A solution of NaOH 50% (15.3mL) is added slowly to the previous aqueous solution to form the final suspension of $\text{Mg}(\text{OH})_2$ media.

In a separate 100 mL Erlenmeyer flask, the monomer phase is prepared by mixing the monomer, porogens (Kita *et al.*, 2001) and initiator. The monomer phase is then poured into the aqueous phase containing the suspending agents and equilibrates for 60 minutes. The polymerization is realized by heating the suspension during 16h at 80°C. The suspension is cooled and treated with HCl

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4N (125mL; 500mmoles) then filtered on a Büchner funnel. The resin is then washed with hot distilled water (4x500mL), acetone (2x250 mL), methanol (2x250 mL) and acetone (2x100 mL). The resin is dried at 40°C under vacuum overnight. Obtained weight: 20.2g. Yield: 90%.

Example 5: Reduction of the polymethacrylate from example 4 to the polyol resin



In a 1L round bottom flask, under dry nitrogen, the polymethacrylate resin from example 4 was swelled in 500mL of THF with vigorous mechanical agitation. LiAlH_4 1M (50mL; 50mmoles) was added carefully. After refluxing during 16 h, the suspension is cooled and n-butanol (100mL) is slowly added to quench the reaction. The final mixture is filtered on a Büchner funnel. The resin is rinsed with THF, distilled water, HCl 6N, distilled water, acetone and methylene chloride (3 x 500mL each). The resin is dried at 40°C under vacuum overnight. The IR spectrum shows the disappearance of the ester (at 1734cm^{-1}) to give strong absorbance of the OH at 3550cm^{-1} . The loading of the final resin is 0.8 mmol/g (by nitrogen elemental analysis), based on the phenyl carbamate derivative (Lee *et al.*, (1995) US Pat. 5,466,758 and Park *et al.*, (1997), Tetrahedron Lett., 38, 591-594) from the reaction of phenyl isocyanate (5 equivalents of the expected value) with the polyol in methylene chloride during 16 hours.

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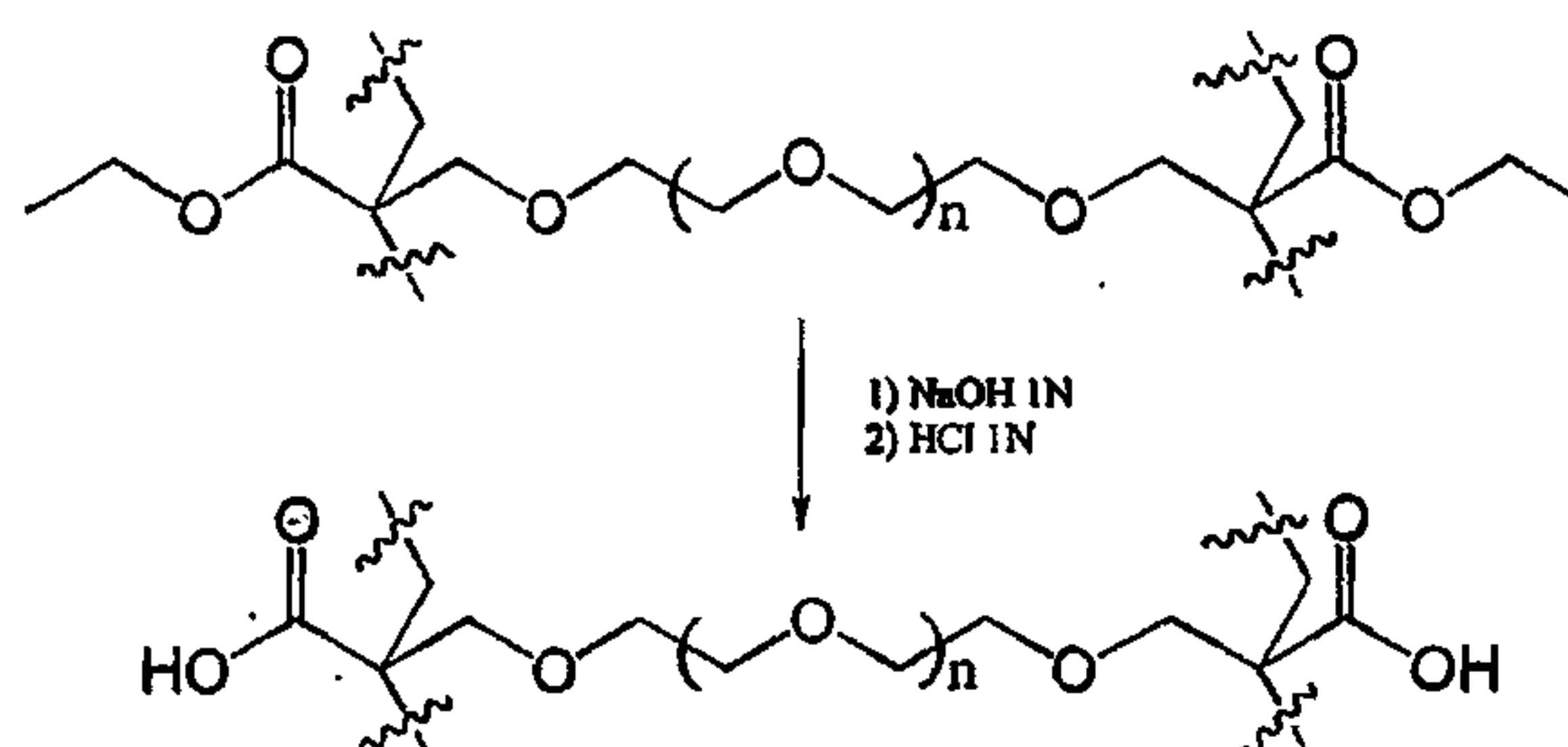
The resin was tested for its ability to swell in several solvents in comparison with other commercial resins. The results are shown in Fig. 1. The resin (200mg) was placed in a syringe of 3,5mL equipped with a 0,45um PTFE frit. A chosen solvent (3mL) was added and the resin was allowed to swell in during 2 minutes before the exhaust of the excess of solvent with the syringe's piston. Once the resin is pressed, the piston is released carefully. The volume occupied by the resin is noted and corrected with the void volume of the PTFE (PTFE = polytetrafluoroethylene) frit (0.15mL). Therefore, the swelling of the resin is calculated by the mean of the following equation:

Swelling (mL/g): (volume of resin + void volume of frit) / weight of resin.

The diagram of Fig. 1 shows how the resin of the present invention is superior to the previous commercial resins in almost any solvents. From non polar to polar solvents, the resin swells more than any other on the market (with the exception of toluene for polystyrene which's of similar chemical nature and almost the same for THF). The major advantage of the present invention is possibility to use many solvents known to be "bad solvents" for polystyrene (acetic acid, acetonitrile, dimethylsulfoxide (DMSO), ethanol, methanol, trifluoroacetic acid (TFA) and water. The present resin swells more in water than any other resins. This shows how the resin is versatile for many fields such as biology, chromatography and "green chemistry". This feature allows the use of the resin in aqueous solutions for organic chemistry where inorganic salts are involved.

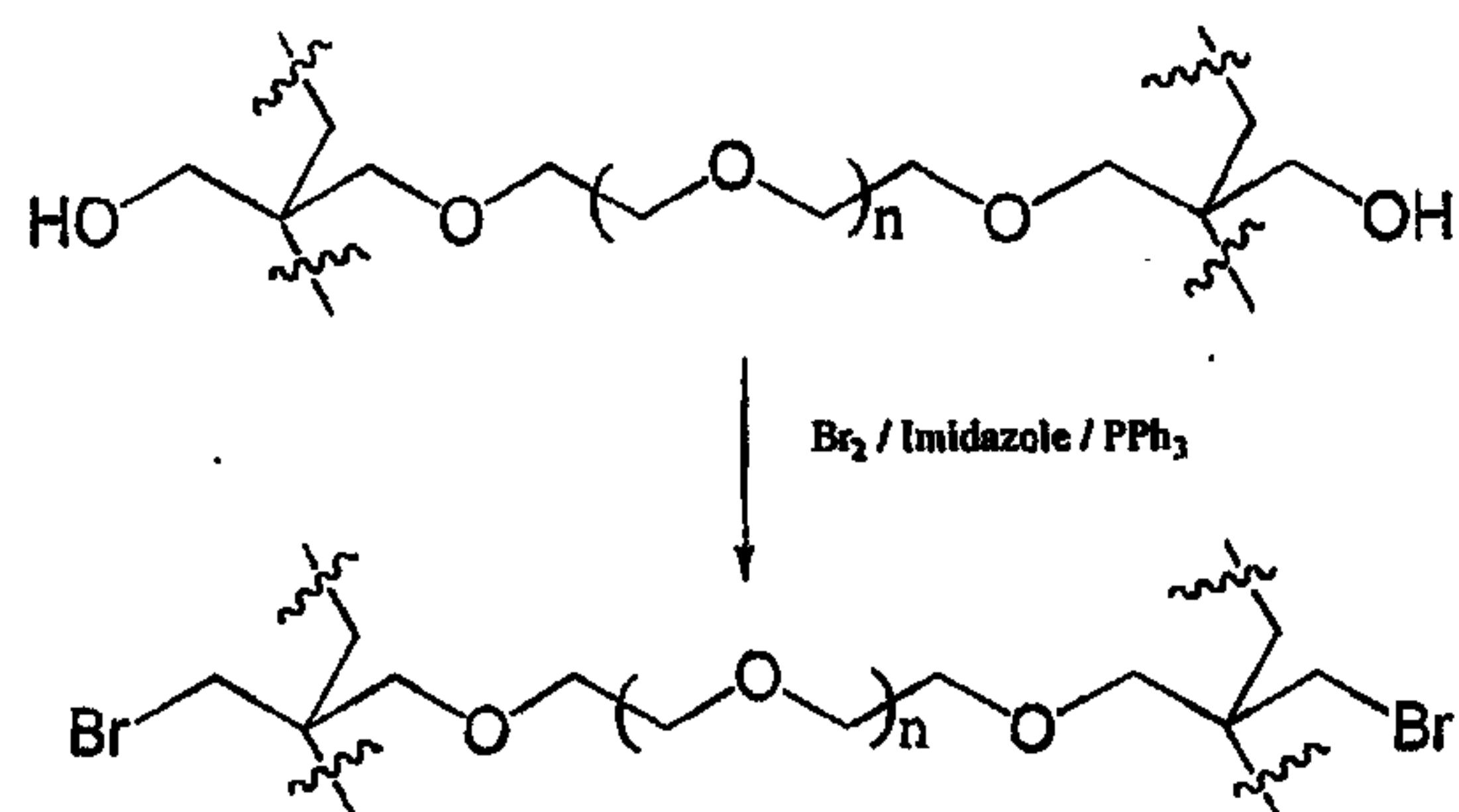
Example 6: Hydrolysis of the polymethacrylate from example 3 to the poly(carboxylic acid) resin

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In a 250mL round bottom flask, 5g of the polymethacrylate resin from example 3 was hydrolyzed in 100mL of NaOH 1N with vigorous mechanical agitation during 3 hours at 25°C. The final mixture is filtered on a Büchner funnel. The resin is rinsed with HCl 1N, distilled water, acetone and methylene chloride (3 x 100mL each). The resin is dried at 40°C under vacuum overnight. The IR spectrum shows a strong absorbance of the OH at 3550cm⁻¹. The loading of the final resin is 0.91mmol/g (by nitrogen elemental analysis), based on the phenyl carbamate derivative from the reaction of phenyl isocyanate (5 equivalents of the expected value) with the poly(carboxylic acid) in methylene chloride during 16 hours.

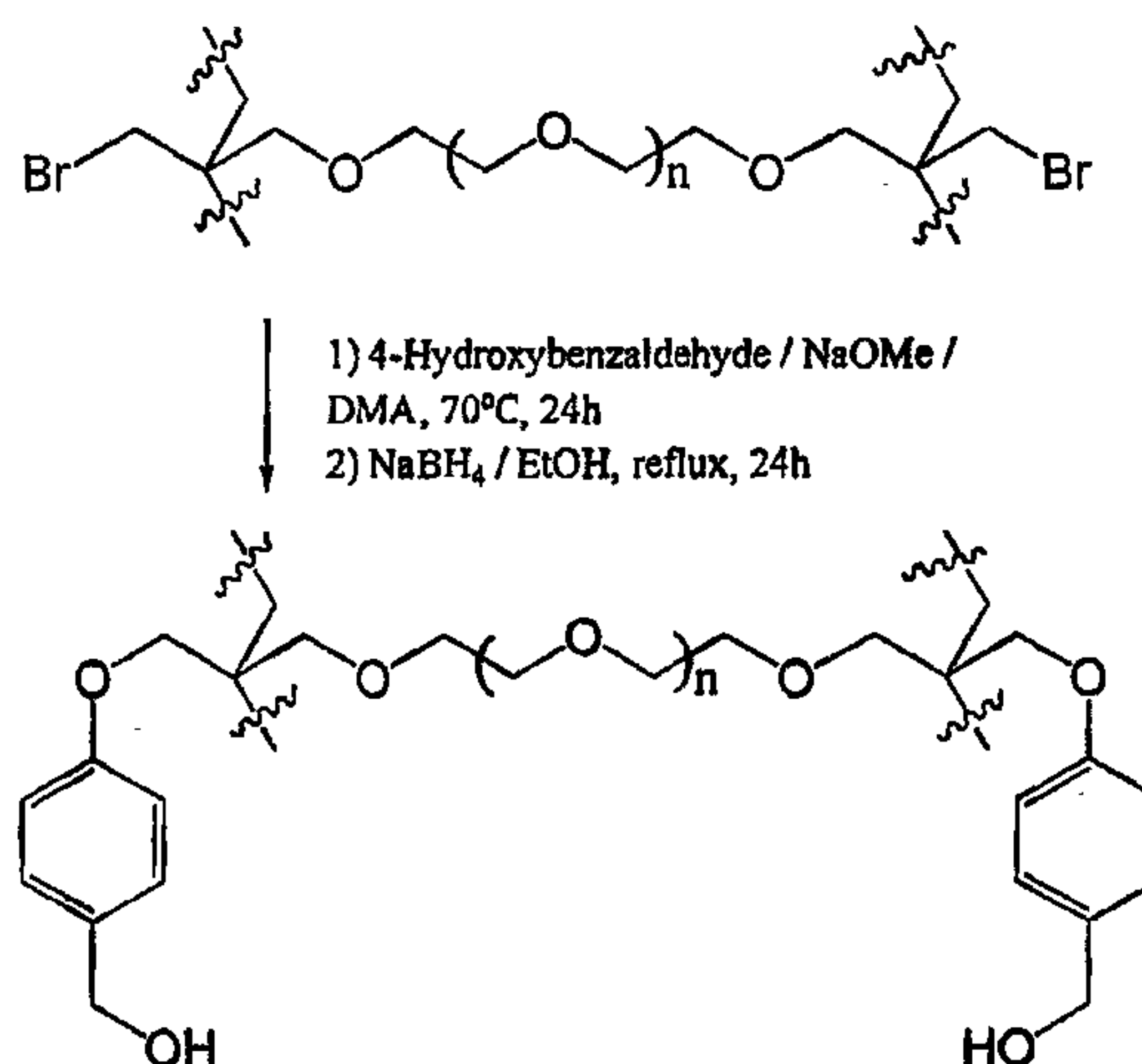
Example 7: Bromination of the polyol from example 5 to the brominated resin



In a 500mL round bottom flask, under dry nitrogen, the polyol resin (20,3g; 16.24mmoles) from example 3 was swelled in 300mL of methylene chloride with vigorous mechanical agitation. PPh_3 (25,02g; 95,4 mmoles) and imidazole (6,50g; 95,4mmoles) were added. At 0°C, bromine (Br_2) (15,25g; 4,89mL; 95,4mmoles) was added drop-wise while keeping the temperature below 5°C. Once the addition is completed, the reaction is allowed to stir overnight at 25°C. The final mixture is filtered on a Büchner funnel. The resin is rinsed with methylene chloride, *N,N*-dimethylformamide, water, Na_2SO_3 1M, water, acetone and methylene chloride (3 x 500mL each). The resin is dried at 40°C under vacuum overnight.

The loading of the final resin is 0.5mmol/g (by nitrogen elemental analysis), based on the reaction of the resin with trimethylamine 40%/water at reflux overnight.

Example 8: Wang type resin obtained from the brominated resin of the example 7.



In a 500mL round bottom flask, under dry nitrogen, the brominated resin (20g; 10mmoles) from example 7 was swelled in 400mL of *N,N*-dimethylacetamide with vigorous mechanical agitation. 4-Alkoxybenzaldehyde (6.1g; 50 mmoles) and sodium methoxide (2.7g; 50 mmoles) were added. The reaction is allowed to stir during 24 hours at 70°C. The final mixture is filtered on a Büchner funnel. The resin is rinsed with *N,N*-dimethylacetamide, water, HCl 1N, water, acetone and ethanol (3 x 200mL each).

The swelled resin in ethanol is directly used as is for its reduction giving the Wang linker. In a 1L round bottom flask, under dry nitrogen, the 4-Alkoxybenzaldehyde resin (20g; *circa* 10mmoles) was swelled in 500mL of ethanol with vigorous mechanical agitation. Sodium borohydride (3.78g; 100 mmoles) were added. The reaction is allowed to stir during 24 hours at reflux. The final mixture is filtered on a Büchner funnel. The resin is rinsed with ethanol, water, HCl 1N, water, acetone and methylene chloride (3 x 500mL each).

The loading of the final resin is 0.6mmol/g (by nitrogen elemental analysis), based on the phenyl carbamate derivative.

Example 9: Loading of the Wang type resin of example 8 with Fmoc-Val-OH

In a 25mL round bottom flask, Fmoc-Val-OH (0,438g; 1.29mmol; 2,15 eq.) and anhydrous 1-Hydroxybenzotriazole (HOBt) (0,174g; 1,29mmol; 2,15 eq.) are dissolved in 4mL of degassed *N,N*-dimethylformamide (DMF). In a separate 50mL round bottom flask, equipped with a magnetic agitator, Wang resin (from example 8) (1.0g; 0.6mmol; 1 eq.) is swelled in 20mL of degassed DMF at 0°C. The solution of Fmoc-Val-OH/HOBt, then *N,N'*-diisopropylcarbodiimide (DIC) (0,163g; 0,202mL; 1,29mmol; 2,15 eq.) are added the suspension of resin at 0°C. A solution of *N,N*-dimethylaminopyridine (DMAP) (0.011g; 0.086mmol; 0.067 eq.) in 1mL of DMF in then added to the suspension. The reaction is allowed to stir during 3 hours at 25°C. A mixture of 1mL of pyridine with 0,75mL of acetic anhydride is added to the suspension for the capping of residual hydroxyl groups of the resin. The reaction is allowed to stir for another additional hour at 25°C. The final suspension is filtered on a Büchner funnel. The resin is rinsed with DMF, methanol, methylene chloride (3 x 20mL each). The resin is dried at 30°C overnight under vacuum.

The substitution of the resulting resin is 0.15mmol/g (measured by the UV spectrophotometric analysis of the fulvene-piperidine adduct.) It should be noted that the example 9 could be further optimized. In particular, the loading of such a resin can be further improved.

Example 10: Synthesis of the retroacyl carrier (74-65) (GNIYDIAAQV) with the resin of example 9 and other commercial resins (see Figs 2 to 5).

The parallel synthesis of the peptide is performed on the following resins on a 0.1 mmol scale using the FASTMOC[®] methodology on an Applied BIOSYSTEMS[®] 433A Peptide Synthesizer using 10 equivalents of the reagents and amino acids in NMP during 45 minutes. Only single couplings were performed. The resins employed in this test were: resin of example 9: 0.15 mmol/g; Wang-Polystyrene-Val-Fmoc: 0.27 mmol/g; TentaGel S PHB-Val-Fmoc (FLUKA (trade-mark); lot: WA10225): 0.22 mmol/g; CLEAR[®]-Val-Fmoc (PEPTIDES INTERNATIONAL (trade-mark); lot 215531): 0.49 mmol/g.

FASTMOC cycles were used with HBTU/HOBt as the coupling reagents. All Fmoc amino acids were commercially available. Deprotection steps were done with piperidine 20%/ NMP (3 x 2 minutes minimum). The peptides were cleaved from the resin using 5 mL of 95% trifluoroacetic acid, 2.5% thioanisole, 1.25% ethanedithiol, and 1.25% water for 2 hours. The crude peptides in solution were precipitated with cold diethyl ether (5 times) and then centrifugated. The solids were dissolved in TFA 0.1% / water and lyophilized for 48 hours.

The HPLC runs were performed on a AQUAPORE (trade-mark) RP-300 C₁₈ reversed-phase column (1x50mm) at 50µL/min using the following pattern:

Mobile phase A: 0.1% TFA in water

Mobile phase B: 80% acetonitrile, 19.92% water, and 0.08% TFA

0-5minutes: 100% A;

5-30 minutes: 100% A to 100% B in 25 minutes;

30-40 minutes: 100% B.

The samples were previously dissolved in TFA 0.1% / water before injection. The volume injected for each run was 3µL. The detection of the peptides was made at 215 nm.

The obtained results are shown in Figs. 2 to 5 and are resumed in Table 1.

Table 1.

Resins	Purity of the crude peptide
Polystyrene (Fig. 2)	9%
TENTAGEL (Fig. 3)	61%
CLEAR (Fig. 4)	62%
Example 9 (Fig. 5)	92%

The chromatograms of Figs. 2 to 5 show the effectiveness of the present invention as compared to commercial resins. For the peptide chemistry, this allows the synthesis of difficult peptide sequence as the one here presented. Moreover, only single couplings were performed instead of double (to triple!) couplings for many synthesis of the same peptide with different resins in the past. This fact is a tremendous advantage for this type of chemistry because it gives higher purity products and then diminishes the need of tedious and costly purifications on analytical and/or preparative columns. Furthermore, the chromatogram of the crude peptide (of the resin of example 9) is showing the absence of "little shoulders" found with other resins herein presented. This is the main problem encountered during the purification step of the crude peptide in peptide chemistry because the separation is often "impossible".

The mass spectra (MALDI-TOF, VOYAGER DE PRO (trade-marks)) of each peptide were performed showed the presence of the desired peptide (in its ionized form).

Polystyrene: $[M + Na]^+$: 1085.4659 (only)

TENTAGEL: $[M + H]^+$: 1063.3026; $[M + Na]^+$: 1085.3520.

CLEAR: $[M + H]^+$: 1063.3374; $[M + Na]^+$: 1085.3204.

Example 9: $[M + H]^+$: 1063.5607; $[M + Na]^+$: 1085.5569.

It has thus been demonstrated that the polyethers of the present invention are very useful and have interesting properties. Indeed, theses polyethers of the

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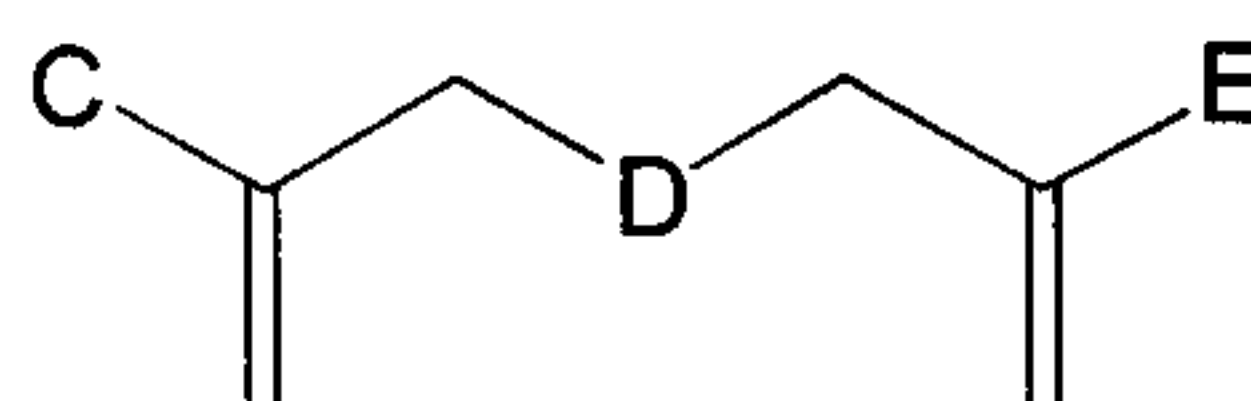
present invention, and particularly the ones based on vinyl monomers and crosslinkers, can be easily prepared through radical polymerisation in suspension polymerization or not. They can also easily prepared on a large scale such as polystyrenes. This feature is very interesting because it allows the industrial manufacture of theses polyethers. The polyethers of the prior art based on standard polyacrylates are not chemically stable as the ones of the present invention.

These cross-linked polyethers also have very good swelling properties. This feature is very interesting because it allows the use of theses polyethers in almost any organic to aqueous medium. This is not encountered with commercial polystyrenes and for a few other commercial "amphiphiles" resins (which are not swelling as far as the polyethers of the present invention.) Moreover, the ability of the present polyethers to swell in water enable its use in biology, "green chemistry", and chemistry based on supported enzymes. The latter needs a highly porous resin to accommodate the three dimensional structure of the enzyme without affecting its activity.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications, uses, and adaptations.

CLAIMS:

1. A cross-linked polyether which is obtained by polymerizing a monomer of the general formula:

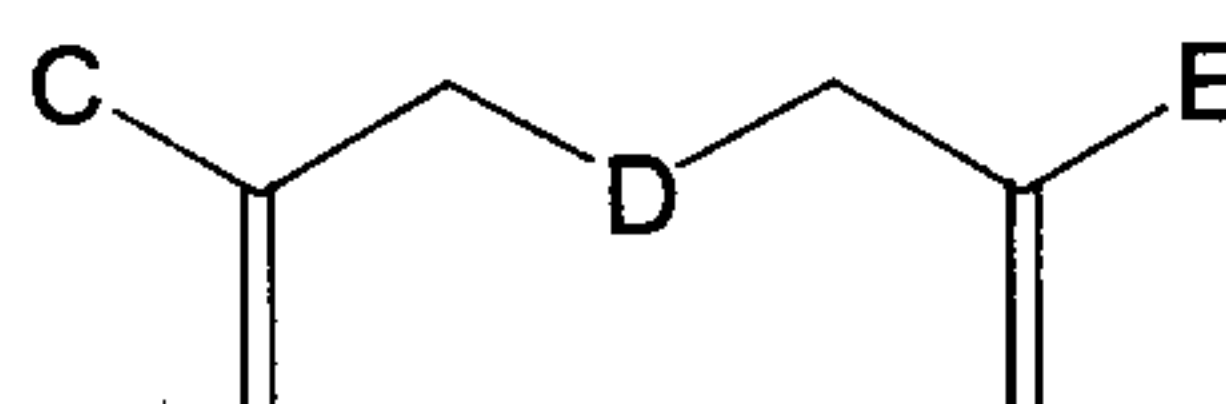


wherein

D is PEG, PPG, or poly(THF), and

C and E independently represent an electron withdrawing group selected from the group consisting of halogen, formyl, amide, ketone, nitro, sulfoxide and sulfonate.

2. A method for preparing a cross-linked polyether, comprising the step of polymerizing a monomer of the general formula:



wherein

D is PEG, PPG, or poly(THF), and

C and E independently represent an electron withdrawing group selected from the group consisting of halogen, formyl, amide, ketone, nitro, sulfoxide and sulfonate.

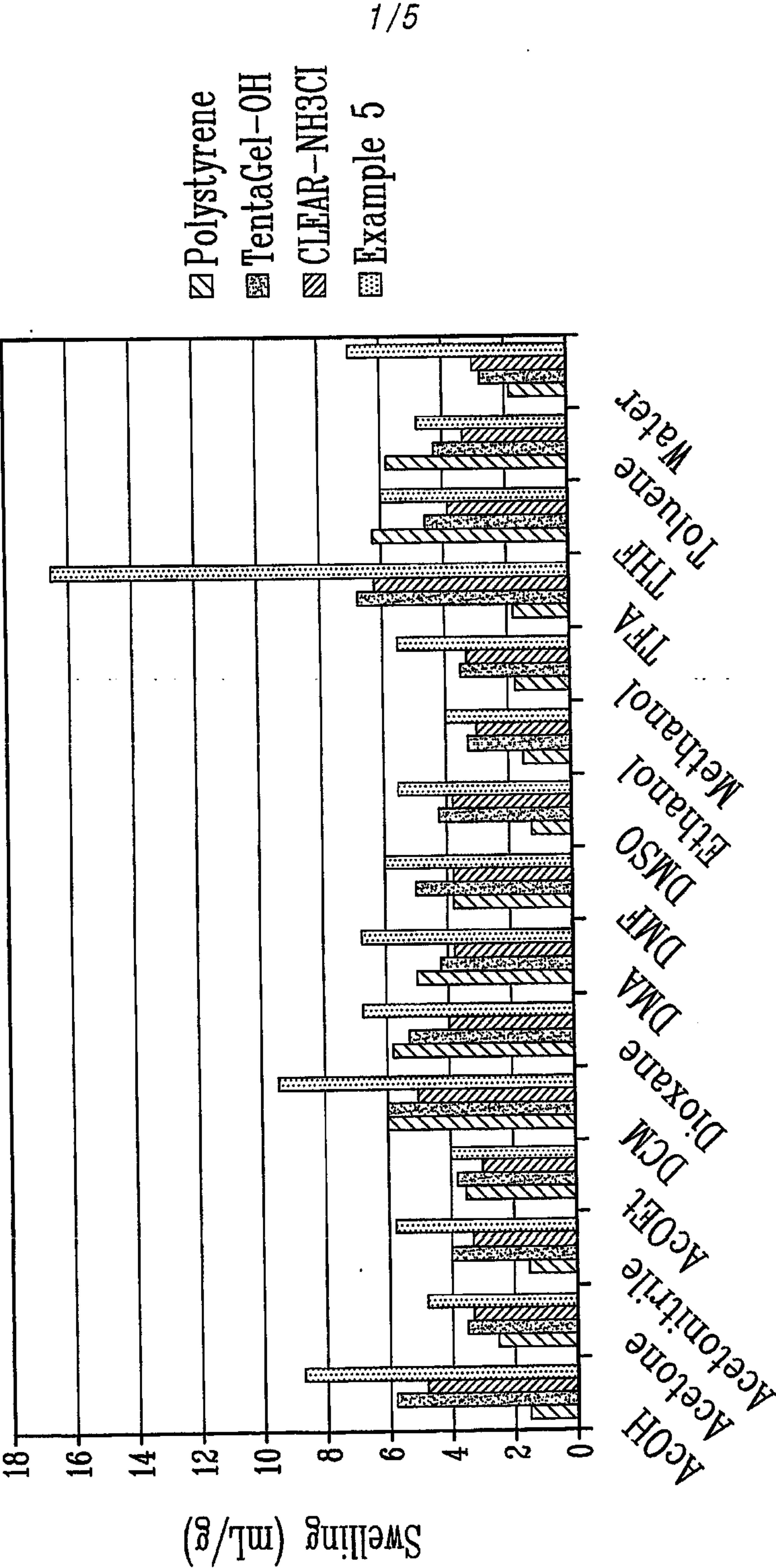
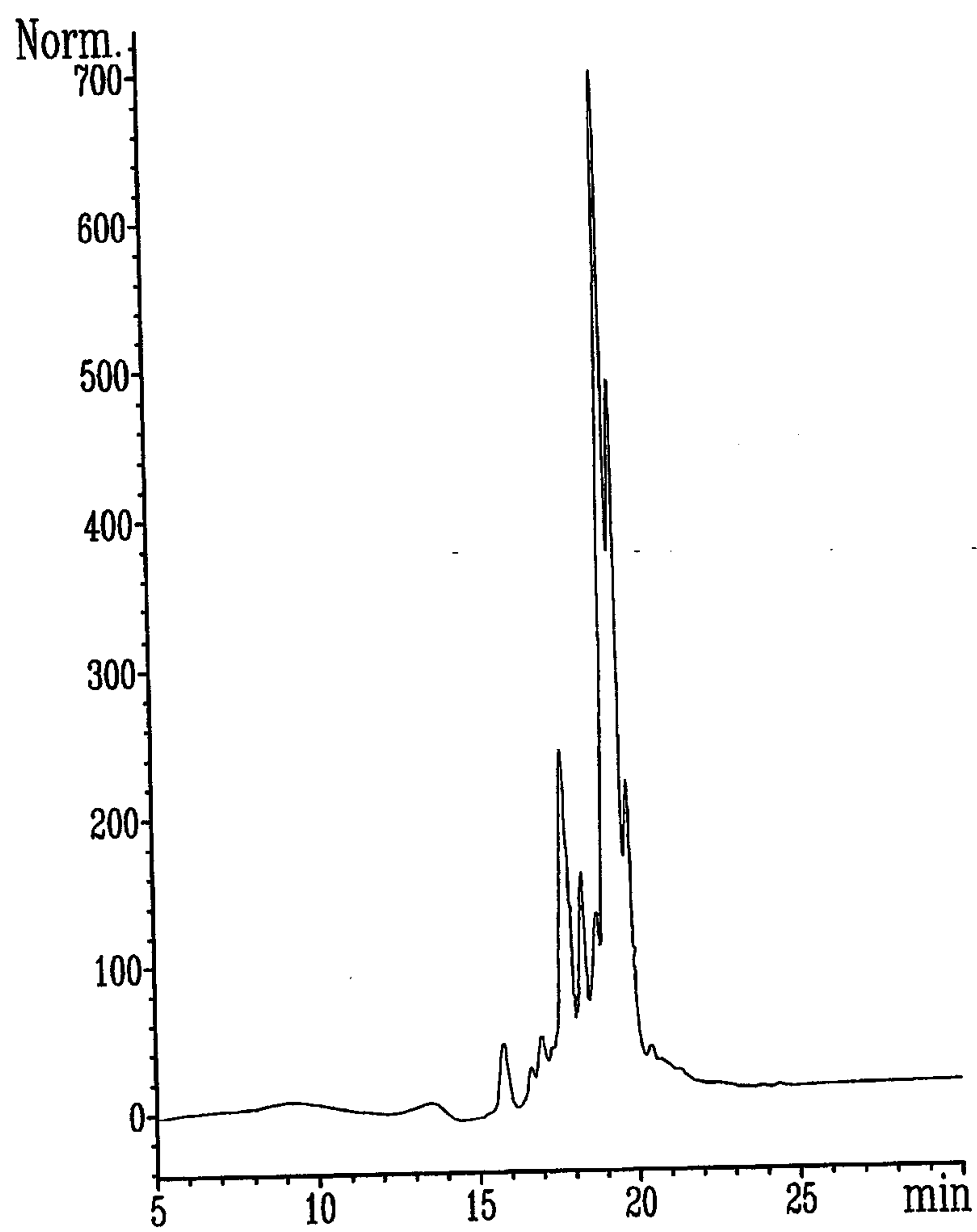
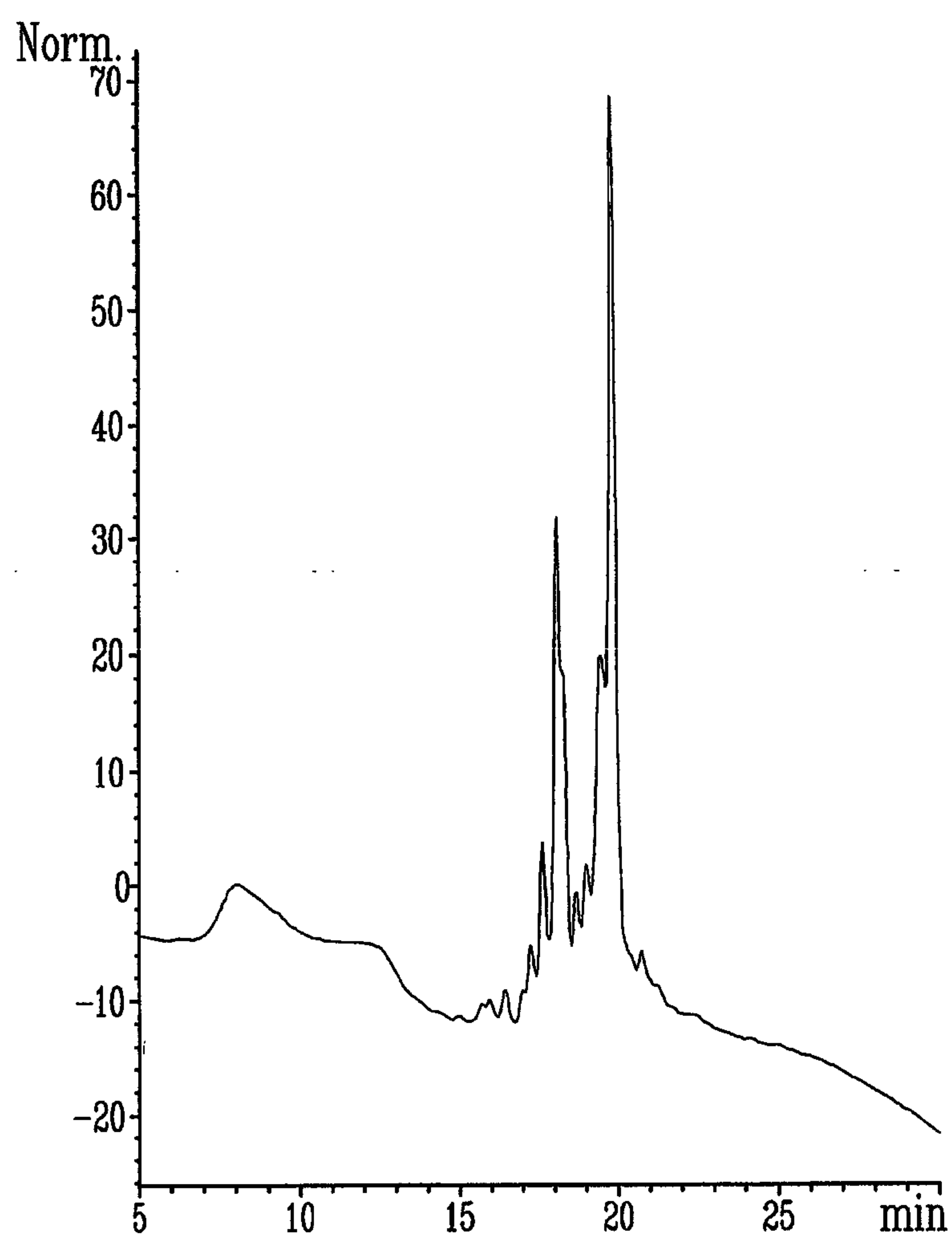


FIG-1

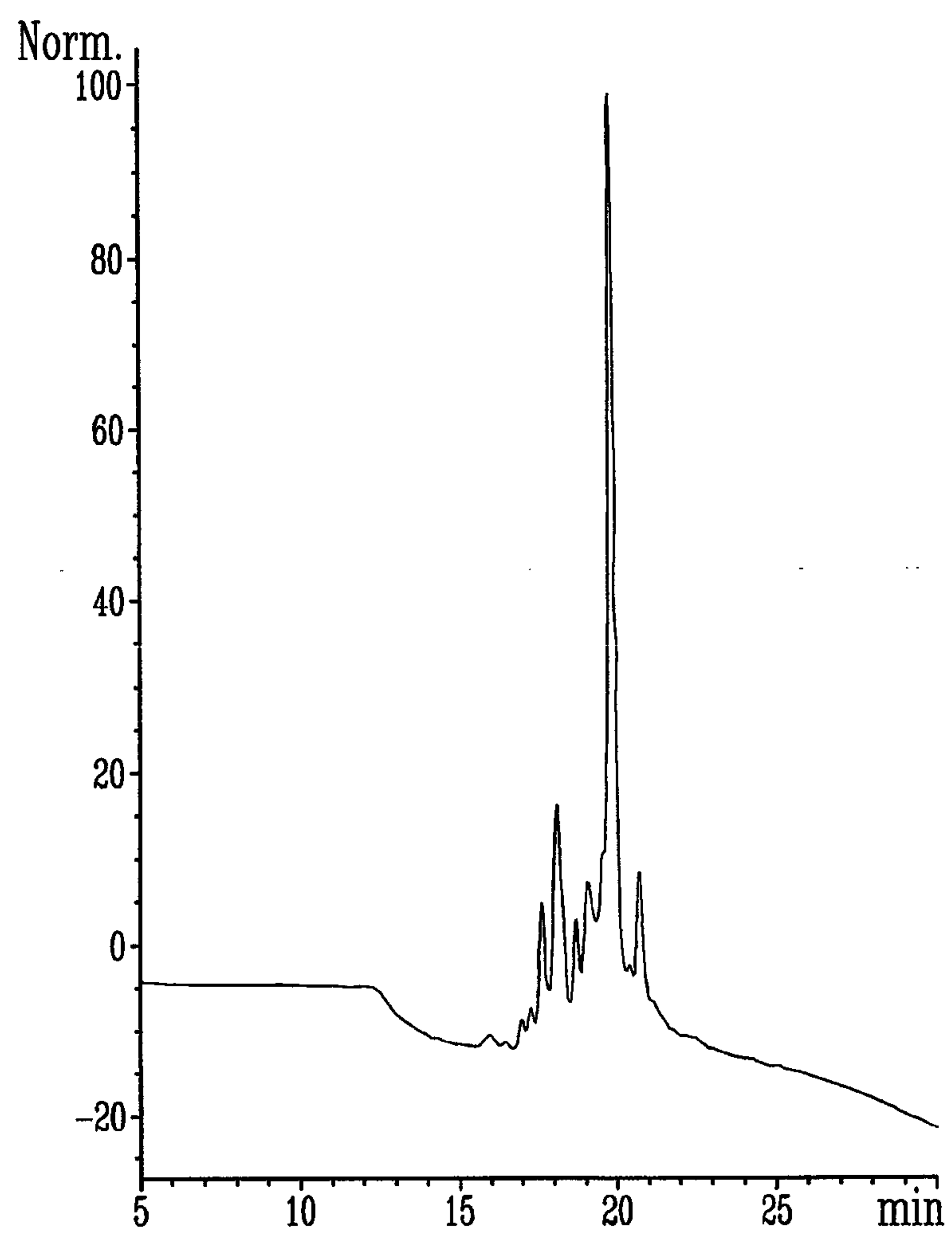
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Fig-2

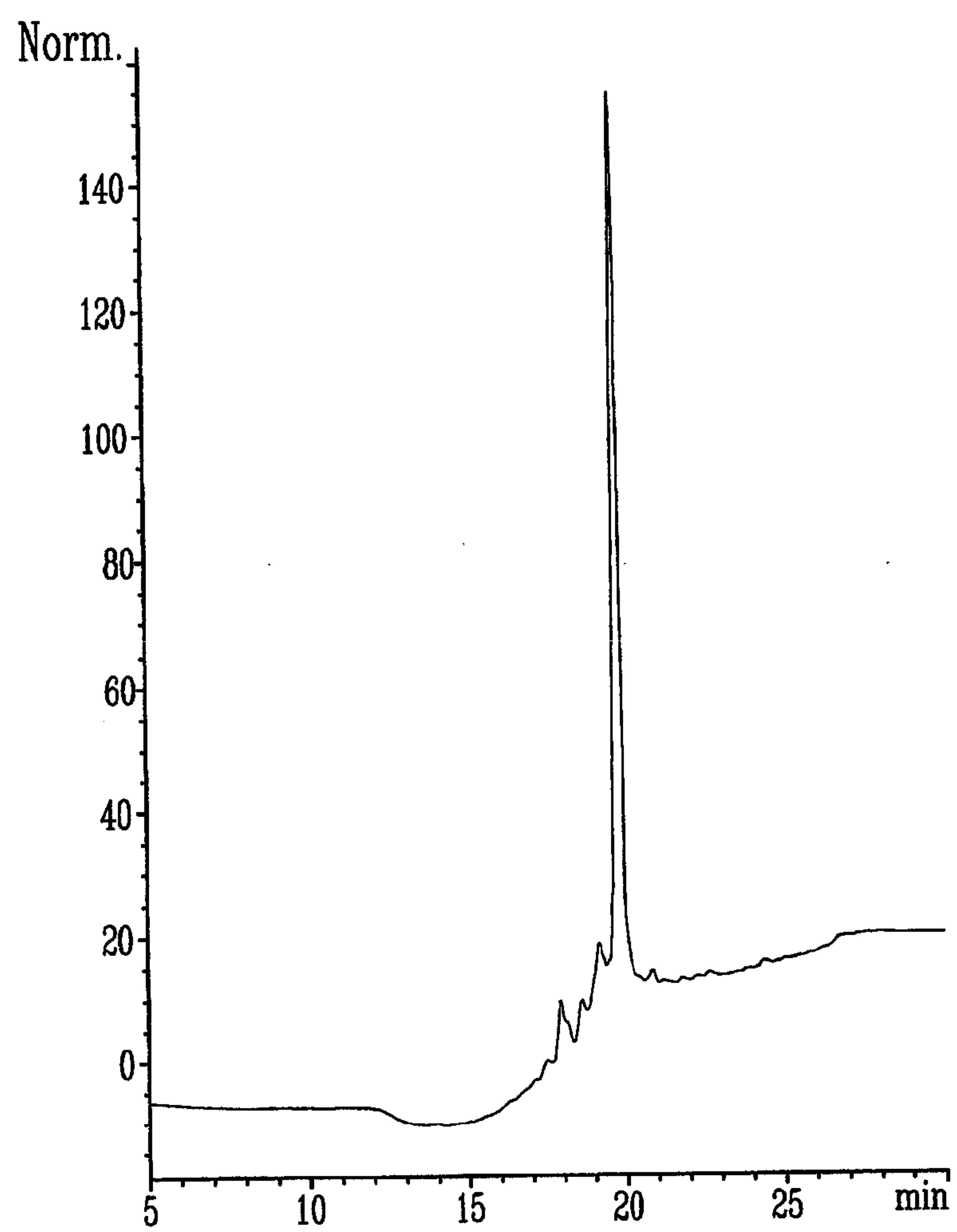
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Fig-3

4/5

Fig-4

5/5

Fig-5

Swelling (mL/g)

