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(54) MONOMERS CONTAINING POLYOXYALKYLENES AND POLYMER SUPPORTS THEREFROM

MONOMERE MIT POLYOXYALKYLENGRUPPEN UND POLYMERTRÄGER DARAUS

MONOMERES CONTENANT DES POLYOXYALKYLENES, MONOMERES ET PROCEDES D'UTILISATION DANS LEUR FABRICATION

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(74) Representative: **Atkinson, Peter Birch et al
Marks & Clerk LLP
1 New York Street
Manchester, M1 4HD (GB)**

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US-A- 4 908 405 US-A- 5 466 758**

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- **HIRATANI K ET AL: "PREPARATION AND CATALYTIC BEHAVIOUR OF POLYMERS WITH PENDANT OLIGOETHYLENEOXY-GROUPS (POLYMERS OF NON-CYCLIC CROWN ETHERS)" ISRAEL JOURNAL OF CHEMISTRY, XX, XX, vol. 18, no. 3/4, 1979, pages 208-213, XP000604342 ISSN: 0021-2148**

(73) Proprietor: **NITTO DENKO Avecia Inc.
Milford MA 01757 (US)**

(72) Inventors:

- **MOODY, David John (Dr.)
Fife, KY 15 7AY (GB)**
- **WELLINGS, Donald Alfred
Northwich, Cheshire, CW8 2AU (GB)**

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Description

[0001] The present invention relates to a process for the synthesis of polymers which are useful as supports in solid phase organic synthesis (SPOS) and to intermediates for use therein.

5 [0002] WO 00/02953 discloses a series of novel polymer resin supports which find use as supports in solid phase organic synthesis (SPOS). WO 0126692 discloses certain protected poly(ethylene glycol compounds. Hiratani et al, Israel Journal of Chemistry Vol 18, 1979, pp208-213 discloses certain polyethoxylated quinolyl compounds.

10 [0003] These polymer resins are of commercial importance and there exists a need for improved methods for their synthesis. We have found that certain novel monomers and resins find use in improved routes to these polymers.

15 [0004] According to a first aspect of the present invention there is provided a monomer for use in a polymerization reaction initiated by a free radical initiator, the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with a poly-aryl methane protecting group.

20 [0005] The hydroxypolyC₂₋₄alkyleneoxy chains attached to the monomer according to the present invention are often selected from hydroxypolyethylenoxy (HO(CH₂CH₂O)₂₋₁₀), hydroxypolypropyleneoxy (HO(CH₂CH(CH₃)O)₂₋₁₀) and hydroxypolybutyleneoxy (HO(CH₂CH(C₂H₅)O)₂₋₁₀) chains. In a preferred embodiment of the invention the hydroxypolyC₂₋₄alkyleneoxy chain is hydroxypolyethylenoxy.

25 [0006] The number of C₂₋₄alkyleneoxy groups in the hydroxypolyC₂₋₄alkyleneoxy chain can range from 2 to 10, but is preferably from 2 to 8 and more preferably from 3 to 5. Most preferably, there are four C₂₋₄alkyleneoxy groups in the hydroxypolyC₂₋₄a/kyleneoxy chain.

30 [0007] In a highly preferred embodiment of the invention the hydroxypolyC₂₋₄alkyleneoxy chain is hydroxytetraethylenoxy (HO(CH₂CH₂O)₄-).

35 [0008] The polymerisable unit of the monomer according to the present invention is often selected from optionally substituted styrenes, acrylates and acrylamides. In a preferred embodiment of the invention the polymerisable unit is an optionally substituted styrene, optionally substituted methylstyrene, optionally substituted ethyl (meth)acrylate, optionally substituted propyl (meth)acrylate or optionally substituted N-methyl (meth)acrylamide.

40 [0009] In a highly preferred embodiment of the invention the polymerisable unit is an optionally substituted styrene or optionally substituted methylstyrene.

45 [0010] When the polymerisable unit is an optionally substituted styrene or optionally substituted methylstyrene, the phenyl ring of the styrene is preferably optionally substituted by 1 or 2 substituents often selected from methyl, ethyl, propyl, fluoro, chloro and bromo.

50 [0011] When the polymerisable unit is an optionally substituted styrene or optionally substituted methylstyrene, preferably the protected hydroxypolyC₂₋₄ alkyleneoxy chain is attached to an optionally substituted styrene or optionally substituted methylstyrene via an oxygen atom directly attached to the phenyl ring of the optionally substituted styrene or optionally substituted methylstyrene.

55 [0012] Poly-aryl methane protecting groups include optionally substituted di-aryl methanes and optionally substituted tri-aryl methanes. Optional substituents may reside on one or more of the aryl groups, and each aryl group may carry one or more substituents. Di-aryl methanes may also be optionally substituted on the carbon to which the two aryls are attached, preferably the optional substituent is an alkyl group.

[0013] Aryl refers to aryl groups which may contain 1 ring or 2 or more fused rings, the fused rings optionally may include cycloalkyl, aryl or heterocyclic rings. Examples of aryl groups include phenyl, tolyl, fluorophenyl, chlorophenyl, bromophenyl, trifluoromethylphenyl, anisyl, naphthyl xanthyl, pyridyl, pyrimidyl, thiophenyl, furanyl, indolyl, quinolyl and isoquinolyl groups.

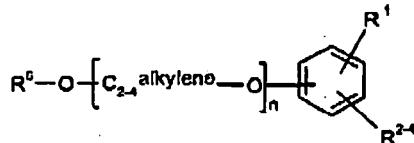
[0014] Preferred aryl groups are optionally substituted phenyl, optionally substituted naphthyl, and optionally substituted xanthyl groups.

[0015] Alkyl groups which may substitute the carbon of a di-aryl methane include linear and branched alkyl groups comprising up to 20 carbon atoms, particularly from 1 to 7 carbon atoms, preferably from 1 to 5 carbon atoms, most preferably 1 or 2 carbon atoms. Examples include methyl, ethyl, propyl, and iso-propyl groups.

[0016] When the poly-aryl methane is substituted, the substituent(s) should be such so as not to adversely affect the stability of the protecting group or the ability to remove the protecting group under acid conditions. Optional substituents include halogen, cyano, nitro, hydrocarbyl, amino, thiol, acyl, hydrocarbyl, perhalogenated hydrocarbyl, heterocyclyl, hydrocarbyloxy, poly(oxyalkylene)oxy, mono or di-hydrocarbyl amino, hydrocarbylthio, esters, carbonates, amides, sulphonyl and sulphonamido groups wherein the hydrocarbyl groups are generally alkyl or aryl groups as defined above. One or more substituents may be present.

[0017] Examples of poly-aryl methane protecting groups include diphenylmethyl, naphthyldiphenylmethyl, phenylxanthyl [pixyl], triphenylmethyl [trityl], di-methoxyphenylphenylmethyl [dimethoxy trityl], methoxyphenyl-di-phenylmethyl [monomethoxy trityl], and 2-chlorophenyldi-phenylmethyl [2-chlorotriptyl] groups

[0018] In a preferred embodiment of the invention, the monomer for use in a polymerisation reaction initiated by a free radical initiator is a compound of formula (1)



10 wherein

R¹ is an optionally substituted ethylene group;
R²⁻⁴ are independently hydrogen, hydrocarbyl, halogen, or hydrocarbyloxy;
R⁵ is a poly-aryl methane protecting group; and
n is 2 to 10.

15 [0019] More preferably R⁵ is a poly-aryl methane protecting group of formula:



wherein:

20 R⁶ is hydrogen, optionally substituted alkyl or optionally substituted aryl group; and
R⁷ and R⁸ are each independently optionally substituted aryl groups, or R⁷ & R⁸ are optionally substituted aryl groups which may be linked to form an optionally substituted ring.

25 [0020] Alkyl groups which may be represented by R⁶ include linear and branched alkyl groups comprising up to 20 carbon atoms, particularly from 1 to 7 carbon atoms, preferably from 1 to 5 carbon atoms, most preferably 1 or 2 carbon atoms. Examples include methyl, ethyl, propyl, and iso-propyl.

30 [0021] Aryl groups which may be represented by R⁶, R⁷ and R⁸ may contain 1 ring or 2 or more fused rings, the fused rings optionally may include cycloalkyl, aryl or heterocyclic rings. Examples of aryl groups include phenyl, tolyl, fluorophenyl, chlorophenyl, bromophenyl, trifluoromethylphenyl, anisyl, naphthyl, pyridyl, pyrimidyl, thiophenyl, furanyl, indolyl, quinolyl and isoquinolyl groups.

[0022] Preferred aryl groups are optionally substituted phenyl.

35 [0023] When R⁷ & R⁸ are optionally substituted aryl groups which are linked in such a way that when taken together with the carbon atom to which they are attached that a ring is formed, it is preferred that the ring is a 5, 6 or 7 membered ring. Examples where R⁷ & R⁸ are optionally substituted aryl groups which are linked to form an optionally substituted ring include xanthyl groups.

40 [0024] When any of R⁶, R⁷ or R⁸ is a substituted alkyl or substituted aryl group, the substituent(s) should be such so as not to adversely affect the stability of the protecting group or the ability to remove the protecting group under acid conditions. Optional substituents include halogen, cyano, nitro, hydrocarbyl, amino, thiol, acyl, hydrocarbyl, perhalogenated hydrocarbyl, heterocycl, hydrocarbyloxy, poly(oxyalkylene)oxy, mono or di-hydrocarbylamino, hydrocarbylthio, esters, carbonates, amides, sulphonyl and sulphonamido groups wherein the hydrocarbyl groups are generally alkyl, aryl, alkaryl and aralkyl groups, the alkyl and aryl groups are as defined above. One or more substituents may be present.

[0025] Most preferably, R⁵ is a poly-aryl methane protecting group of formula:



wherein:

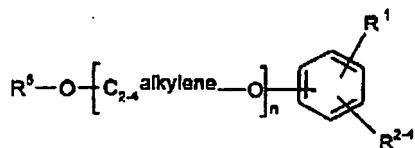
R⁶ is an optionally substituted aryl group; and
R⁷ and R⁸ are each independently optionally substituted aryl groups, or R⁷ & R⁸ are optionally substituted aryl groups which may be linked to form an optionally substituted ring.

50 [0026] In a highly preferred embodiment of the present invention, the poly-aryl methane protecting group is an optionally substituted trityl group.

[0027] According to a second aspect of the present invention there is provided a monomer which comprises a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with an optionally substituted trityl group.

[0028] Optionally substituted trityl groups include triphenylmethyl [trityl], di-methoxyphenylphenylmethyl [dimethoxy trityl], methoxyphonyl-di-phenylmethyl [monomethoxy trityl], and 2-chlorophenyldi-phenylmethyl [2-chlorotriptyl] groups.

[0029] In a most preferred embodiment of the present invention, the monomer is a compound of formula (1a)



wherein

10 R¹ is an optionally substituted ethylene group;

R²-₁ are independently hydrogen, hydrocarbyl, halogen, or hydrocarboxy;

R⁶ is an optionally-substituted triyl group; and

n is 2 to 10.

[0030] Preferably, R¹ is a CH=CH₂, CH=CHCH₃, or C(CH₃)=CH₂ group. Most preferably, R¹ is a CH=CH₂.

[0031] Preferably, the R⁵O-[C₂₋₄alkylene-O]_n group is para to R¹.

[0032] Preferably, [-C₂₋₄alkylene-O]_n is [-CH₂CH₂O]_n, [-CH₂CH(CH₃)O]_n, [-CH₂CH₂CH₂CH₂O]_n or [-CH₂CH(C₂H₅)O]_n, and most preferably [-CH₂CH₂O]_n.

[0033] Preferably n is 2 to 8, more preferably n is 3 to 5. Most preferably n is 4.

[0034] Preferably R²-₁ are all hydrogen.

20 [0035] Hydrocarbyl includes alkyl, aryl, alkaryl and aralkyl groups. Preferably when any of R²-₁ are hydrocarbyl or hydrocarboxy groups the hydrocarbyl is an alkyl group, most preferably a C₁₋₄ alkyl group.

[0036] The monomers according to the first and second aspects of the present invention are useful in polymerisation reactions to form resins from which the polymer supports disclosed in WO 00/02953 can be obtained.

[0037] Accordingly, a third aspect of the present invention provides a process for the preparation of a polymer support comprising polymerisation of a monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with a poly-aryl methane protecting group, under conditions to produce cross-linking and wherein the polymerisation reaction is initiated by a free radical initiator.

[0038] The monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with a poly-aryl methane protecting group can be as described above in the first and second aspects of the present invention.

[0039] The poly-aryl methane protecting group is preferably an optionally substituted triyl group. The preferred poly-aryl methane protecting groups and the optionally substituted triyl groups are as defined above in the first and second aspects of the present invention.

[0040] Optionally, in the process of the present invention the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with a poly-aryl methane protecting group, preferably an optionally substituted triyl group, may comprise a mixture of isomers.

[0041] Preferably, when a mixture of isomers is used in the process of the present invention, the monomer is a compound of formula (1) or (1a). Most preferably, the monomer is a mixture of isomers wherein R^aO-[C₂₋₄alkylene-O]_n group and R¹ occupy isomeric positions on the phenyl ring.

[0042] Preferably, in the process of the present invention, the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit is co-polymerised in the presence of a cross linking monomer.

[0043] The extent of cross linking in the polymers is determined by the concentration of cross linking monomer in the polymerisation reaction. Generally the weight % of cross-linking monomer is in the range of from 0.1 to 70%, commonly from 0.5 to 20%, such as from 1 to 10%, and most preferably no more than 5% by weight. Polymers comprising no more than 20% by weight of cross-linking monomer are generally swellable, whilst polymers comprising greater than 20% of crosslinking monomer are generally not swellable.

[0044] Suitable cross-linking monomers include divinyl benzene (DVB) or multifunctional (meth)acrylates such as di/tri acrylates or di/tri methacrylates such as ethylene glycol diacrylate, ethylene glycol dimethacrylate, trimethylpropane trimethacrylate, trivinylbenzene or N,N'-bis-acryloyl ethylene diamine. Preferably the cross-linking monomer is DVB.

[0045] Preferably 0.5 to 5% by weight of DVB is used. Most preferably 1 to 3% by weight DVB is used.

[0046] In one aspect of the present invention a level of at least 5% crosslinking monomer is used in conjunction with compounds miscible with the organic phase which can act as pore-forming agents or porogens. Typical porogens can include, but are not limited to, organic compounds which are good solvents for the polymer, such as organic aromatic hydrocarbons, chlorinated aliphatic or aromatic hydrocarbons and cyclic aliphatic ethers, organic compounds which are poor solvents for the resulting polymer, such as aliphatic alcohols, ketones, aliphatic hydrocarbons, aliphatic carboxylic

acids and linear polymers. Preferably porogens are selected from toluene, xylene, chlorobenzene, tetrahydrofuran, dioxane, 2-ethyl-1-hexanol, 2-octanol, 1-decanol, 1-dodecanol, acetone, butanone, n-heptane, n-decane, 1-decanoic acid and linear polystyrene of molecular weight 500 to 5000000 g/mol. The resulting polymers have substantially non-swelling behaviour and generally possess a meso- to macro-porous nature, by which mode reagents can access the polymer-bound functionality.

[0047] Optionally, in the process of the present invention, the monomer comprising a protected hydroxypolyC₂₋₄alkyleneoxy chain attached to a polymerisable unit is co-polymerised in the presence of one or more monomers selected from styrenes, for example styrene, hydroxystyrene, methoxystyrene, methylstyrene, hydroxymethylstyrene and chloromethylstyrene, esters of acrylic acid and esters of (meth)acrylic acid, for example methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl acrylate, hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate, and acrylamides, for example N-methyl acrylamide and N-methylol (meth)acrylamide; wherein the phenyl ring in the styrenes is optionally substituted by 1 or 2 substituents often selected from methyl, ethyl, propyl, fluoro, chloro and bromo and wherein hydroxy groups, especially phenolic hydroxy groups, which may be present in the monomers are optionally protected and may subsequently be deprotected.

[0048] In a preferred process of the present invention, the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with an optionally substituted trityl group is co-polymerised in the presence of one or more cross linking monomers, and one or more monomers selected from styrenes, esters of acrylic acid and esters of (meth)acrylic acid, or acrylamides.

[0049] In a highly preferred process of the present invention, the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with an optionally substituted trityl group is co-polymerised in the presence of DVB and styrene.

[0050] When the polymer support is produced by polymerisation of a mixture of monomers comprising the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with a poly-aryl methane protecting group, preferably an optionally substituted trityl group, and one or more monomers selected from styrenes, esters of acrylic acid and esters of (meth)acrylic acid, or acrylamides, the weight percentage of the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit of the total weight of the monomers present is preferably in the range of from 1-99%, more preferably in the range of from 5-80% and most preferably from 15% to 70%.

[0051] The process of the present invention is preferably carried out by aqueous suspension polymerisation. The monomers are suspended as droplets (1-1000μm) in water. Stabilisers are usually added to prevent agglomeration of the droplets, for example polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, polyalkylene oxide, derivatives of cellulose, such as hydroxypropylmethylcellulose or ethylcellulose, barium sulphate, magnesium sulphate or sodium sulphate. The suspension is also normally stirred to maintain the suspension.

[0052] Optionally, organic non-water miscible solvents may be used in the polymerisation process. Organic non-water miscible solvents may assist droplet formation in aqueous suspension polymerisation, or may act as porogens.

[0053] Optionally inorganic salts may be added to the aqueous phase in aqueous suspension polymerisation. Inorganic salts may assist droplet formation by suppressing monomer solubility in the aqueous medium.

[0054] A free radical initiator is used to initiate polymerisation. The type of initiator will generally be selected based on the monomers used. Examples of preferred free radical initiators include benzoyl peroxide, dioctanoyl peroxide, lauroyl peroxide, 2,2'-azobisisobutyronitrile and 2,2'-azobis(2,4-dimethylvaleronitrile).

[0055] Polymerisation is typically assisted by heating the mixture in the range of 15°C to 160°C, preferably 50°C to 90°C. It will be recognised that the temperature to which the mixture can be heated depends upon the type of monomer and initiator employed.

[0056] The resultant polymer may then be washed with suitable solvents such as tetrahydrofuran, methanol and water, dried and bead size classified, for example, by sieving.

[0057] Accordingly a further aspect of the present invention provides a polymer support which comprises protected hydroxypolyC₂₋₄ alkyleneoxy chains attached to a cross-linked polymer wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups, and wherein the hydroxypolyC₂₋₄ alkyleneoxy chains are protected with a poly-aryl methane protecting group and wherein the polymer support has been produced by a polymerisation process initiated by a free radical polymerisation initiator. Preferably the poly-aryl methane group is an optionally substituted trityl group.

[0058] The protected hydroxypolyC₂₋₄ alkyleneoxy chains attached to a cross-linked polymer according to the present invention are often selected from protected hydroxypolyethyleneoxy (protected HO(CH₂CH₂O)₂₋₁₀⁻), protected hydroxypolypropyleneoxy (protected HO(CH₂CH(CH₃)O)₃₋₁₀⁻) and protected hydroxypolybutyleneoxy (protected HO(CH₂CH(C₂H₅)O)₂₋₁₀⁻) chains. In a preferred embodiment of the invention the protected hydroxypolyC₂₋₄ alkyleneoxy chain is

protected hydroxypolyethyleneoxy.

[0059] The number of C₂₋₄alkyleneoxy groups in the protected hydroxypolyC₂₋₄alkyleneoxy chain can range from 2 to 10, but is preferably from 2 to 8 and more preferably from 3 to 5. Most preferably, there are four C₂₋₄alkyleneoxy groups in the protected hydroxypolyC₂₋₄alkyleneoxy chain.

5 [0060] In a highly preferred embodiment of the invention the protected hydroxypolyC₂₋₄alkyleneoxy chain is protected hydroxytetraethyleneoxy (protected HO(CH₂CH₂O)₄-).

[0061] Preferably the protected hydroxypolyC₂₋₄alkyleneoxy chains are attached to a cross-linked polymer via phenoxy other linkages.

[0062] The invention, in its broadest aspect, relates to the particular polymer supports however prepared.

10 [0063] Preferably, the polymer support of the present invention is obtainable by the process of the third aspect of the present invention.

[0064] The poly-aryl methane protecting groups may subsequently be removed to give the cross-linked polymer containing free hydroxy groups.

[0065] Methods appropriate for removal of the optionally substituted trityl group include, for example, acid- hydrolysis.

15 Commonly a mixture of trifluoroacetic acid in methylene chloride can be employed. The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

[0066] Where appropriate, other methods may be also used for the removal of the poly-aryl methane protecting groups, for example the use of iodine under neutral conditions may be used to remove trityl groups, and photolysis may be used 20 to remove pixyl groups.

[0067] Preferably, when the protecting groups are removed the resulting polymer support has from about 0.1 to about 5 meq free hydroxy groups per gram of polymer.

25 [0068] Cross-linked polymers containing a free hydroxy group are usually produced as beads which range in size from 10μm to 2000μm. Preferably the bead size is from 50μm to 1000μm and most preferably from 75μm to 500μm. The cross-linked polymer beads are generally produced by an aqueous suspension polymerisation process, for example see Journal of Applied Polymer Science, 1982, 27, 133-138.

30 [0069] The polymer support obtained when the protecting groups are removed from the support according to the present invention has a hydroxy functionality of from 0.1 to about 5, for example up to 4.8 meq (milliequivalents) of hydroxy per gram of polymer, and often from 0.5 to 3.5, commonly 1.0 to 3.3 meq per gram for example from 1.5 to 3 meq per gram of polymer. In many embodiments, the polymer support obtained when the protecting groups are removed have from 0.5 to 2 meq of hydroxy per gram of polymer.

35 [0070] The polymer supports described above are of use in solid phase organic synthesis, accordingly there is provided the use of a polymer support which comprises protected hydroxypolyC₂₋₄ alkyleneoxy chains attached to a cross-linked polymer wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄alkyleneoxy chains are protected with a poly-aryl methane group in solid phase organic synthesis.

[0071] Preferably, the polymer support is obtained by the process of third aspect of the present invention.

[0072] Preferably, the polymer support is deprotected prior to use.

40 [0073] The invention will now be described, without limitation, by the following examples in which, unless otherwise stated:-

- a) FT-IR spectra were obtained using swollen gels in dichloromethane held between sodium chloride plates, and an ATI Genesis (Matteson)spectrometer.
- b) ¹³C magic angle (MAS) NMR spectra were obtained using solvent swollen gels in the rotor of a Bruker MAS probe on a 400MHz NMR spectrometer.
- c) yields are given for illustration and are not necessarily the maximum attainable.
- d) the following abbreviations have been used: THF = tetrahydrofuran, DMF = N,N-dimethylformamide, Fmoc = fluorenylmethoxycarbonyl, PEG = polyethyleneglycol and THP = tetrahydropyranyl.

50 Examples

EXAMPLE 1 - Preparation of trityl-tetraethyleneglycoxystyrene

STAGE 1

55 [0074] Tetraethyleneglycol (174g, 0.9mol) was placed in a 3 necked round bottom flask fitted with a thermometer and reflux condenser. Pyridine (11cm³, 0.135mol) was added to the mixture stirred. Triphenylmethylchloride (25g, 0.09mol) was dissolved in toluene (30cm³) and this solution was added slowly to the mixture. The mixture was heated to 50°C

and the temperature maintained for 1h.

[0075] The mixture was allowed to cool and toluene (200cm³) was added to the flask. The solution was extracted with water (500cm³). The aqueous phase was back extracted with toluene (2 x 100cm³). The organic layers were combined and washed with water (2 x 100cm³), dried over MgSO₄ and filtered. The toluene was removed by evaporation under reduced pressure to yield a pale yellow oil (yield 38.5g, 98% based on trityl).

5

STAGE 2

[0076] Mono(trityl)tetraethyleneglycol (30g, 0.069mol), 4-toluenesulfonyl chloride (14.4g, 0.076mol) and dry tetrahydrofuran (50cm³) were placed in a 3 necked round bottom flask fitted with a thermometer and reflux condenser. The flask was placed in a dry-ice bath and the mixture allowed to cool to ~ -20°C. A solution of KOH (25.2g, 0.45mol) in water (100cm³) was added drop-wise over a period of 1h whilst maintaining the temperature at <0°C. Following the addition the reaction mixture was stirred for 1h whilst allowing the solution to warm to ambient.

[0077] The solution was extracted with diethylether (3 x 150cm³). The ether layer was dried over MgSO₄, filtered and evaporated under reduced pressure. The solid was washed with MeOH and dried under vacuum (yield 34.3g, 85%).

15

STAGE 3

[0078] NaOMe (0.55g, 10.2mmol) was dissolved in the minimum amount of N,N-dimethylformamide (DMF) and added to 4-acetoxystyrene (1.3cm³, 8.5mmol) contained in a round bottom flask. This solution was stirred at ambient for 45min then a solution of the tosyl derivative of mono(trityl)tetraethyleneglycol (5g, 8.5mmol) in DMF was added. The reaction was allowed to continue overnight at ambient.

[0079] The DMF was removed by evaporation under reduced pressure. The oil remaining was dissolved in isopropylacetate and extracted with water. The organic layers were combined, dried over MgSO₄ and filtered. The solvent was removed by evaporation under reduced pressure to leave a pale yellow oil that crystallised on standing (yield 3.5g, 77%).

25

EXAMPLE 2 - 10 litre scale Preparation of trityl-tetraethyleneglycoxystyrene

STAGE 1

30

[0080] Tetraethylene glycol (4188g, 21.5 mol) was added under a nitrogen atmosphere to a 101 vessel equipped with a mechanical stirrer and stirred at 60 rpm. Pyridine (544g, 6.9 mol) was added to the vessel and the mixture heated to 50°C. Triphenylmethyl chloride (1000g, 3.6 mol) was dissolved in toluene (3000ml) under N₂ atmosphere and added slowly to the glycol keeping the temperature below 60°C. The temperature was held at 50°C for 2 hours and then cooled to room temperature. 2l of toluene were added and the mixture extracted with 6l of deionised water, the water phase extracted with 5l of toluene. The combined organic extracts were washed with 2 x 4l of DI water, dried over 500g sodium sulphate and solvent removed under reduced pressure to yield 1230g (74% based on trityl) of a pale yellow oil, 94.3% purity (by NMR)

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STAGE 2

[0081] Mono(trityl)tetraethyleneglycol (1766.4g, 3.8 mol) was added to a 101 vessel together with 31 THF and cooled under agitation to -12°C. p-Toluenesulphonyl chloride (945g, 5 mol) was added to the glycol/THF mixture. A solution of KOH (880g, 15.7 mol) in deionised water (3l) was added to the solution over 1 hour keeping the temp below -5°C. After completion of the addition the vessel was warmed to 25°C and held for 12 hours. The phases were separated and the lower aqueous layer washed with 2x2.5L THF, the organic layers combined and solvent removed under reduced pressure. The orange/brown oil in 7.5l isopropyl acetate was extracted with 10l water and then 5 x 2l water, dried over magnesium sulphate (500g) and solvent removed to give 1837g (78.0%) of the product as a viscous orange oil, purity 95.3% (by NMR).

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STAGE 3

[0082] Deionised water (1.5l) and THF (2.1l) were added to a 10L vessel and agitation started at 100rpm. The vessel was cooled down to -12°C and potassium hydroxide (535g, 9.5 mol) was added slowly. Acetoxystyrene (575ml, 3.7 mol) in THF (1l), was added to the vessel over about 30 minutes with cooling. The vessel was heated to 30°C and held for 1 hr, then cooled to 20°C. The Stage 2 product (1800g, 2.9 mol) in 1050 ml THF was added to reaction vessel over 15mins, then the mixture heated at 60°C for 40 hrs. The reaction was cooled, the phases separated and the organic layers washed with 2x2l of 8M aqueous potassium hydroxide. The solvent was removed under reduced pressure and the residue dissolved in toluene (5l), washed with 3x2l deionised water, then 2x2l 1M aqueous sodium hydroxide, and

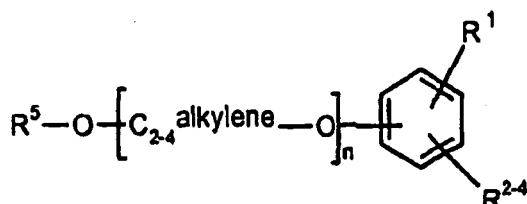
finally 2x3l DI water. The organic layer was dried with sodium sulphate (500g) and solvent removed under reduced pressure to yield 1471 g (75%) of the product as an orange oil, purity 79.7% by NMR.

EXAMPLE 3 - Synthesis of Polymer and subsequent deprotection

[0083] Partially hydrolysed poly(vinyl alcohol) (Airvol 540, 34.9 g of 2.5 wt-% aqueous solution) and sodium chloride (31.2 g) were charged into a 2l cylindrical baffled reactor containing deionised water (1181 ml) and equipped with a mechanical stirrer. A mixture of Stage 3 product (79.7%, 87.2 g), styrene (59.1 g), divinylbenzene (80%, 1.4g) and lauroyl peroxide (5.2 g) were charged to the reactor and agitated at 400 rpm. After 20 minutes the stirrer speed was reduced to 300 rpm and the reaction heated with a water bath to 80°C over 50 minutes. After 16h, the reaction mixture was cooled, transferred to a 50 µm filter cloth bag and washed with deionised water (5x1l). The polymer beads were then washed with THF (4x1l) and dichloromethane (2x1l) and stirred at room temperature under nitrogen in a 5l flange flask/overhead stirrer with a mixture of dichloromethane (1800 ml), trifluoroacetic acid (128 g) and triethylsilane (51.5 g) for 4 hours. The product was then washed with dichloromethane (4x1l) and hexane (5x1l) before drying to constant weight in a vacuum oven, yielding 78g of white polymer beads with a hydroxyl loading of 0.97 mmol/g.

Claims

1. A monomer for use in a polymerisation reaction initiated by a free radical initiator, the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with a poly-aryl methane protecting group.
2. A monomer of formula (1) for use in a polymerisation reaction initiated by a free radical initiator:



wherein

R^1 is an optionally substituted ethylene group;

R^{2-4} are independently hydrogen, hydrocarbyl, halogen, or hydrocarboxy; R^5 is a poly-aryl methane protecting group; and

n is 2 to 10.

3. A monomer according to Claim 2 wherein R^1 is a $\text{CH}=\text{CH}_2$, $\text{CH}=\text{CHCH}_3$, or $\text{C}(\text{CH}_3)=\text{CH}_2$ group.
4. A monomer according to any of Claims 2 or 3 wherein $[-C_{2-4}\text{alkylene}-O-]_n$ is $[-\text{CH}_2\text{CH}_2\text{O}-]_n$, $[-\text{CH}_2\text{CH}(\text{CH}_3)\text{O}-]_n$, $[-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-]_n$ or $[-\text{CH}_2\text{CH}(\text{C}_2\text{H}_5)\text{O}-]_n$.
5. A monomer according to any of Claims 2, 3 or 4 wherein R^{2-4} are hydrogen.
6. A monomer according to any preceding claim wherein R^5 is a poly-aryl methane protecting group of formula:



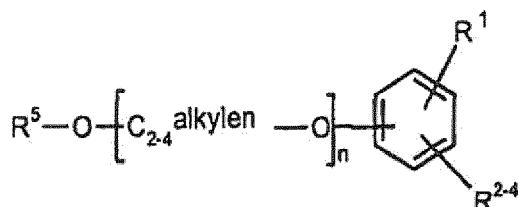
wherein:

R^8 is hydrogen, optionally substituted alkyl or optionally substituted aryl group; and R^7 and R^8 are each independently optionally substituted aryl groups, or R^7 & R^8 are optionally substituted aryl groups which may be linked to form an optionally substituted ring.

7. A monomer according to any preceding claim wherein the poly-aryl methane protecting group is an optionally substituted trityl group.
- 5 8. A process for the preparation of a polymer support comprising polymerisation of a monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups, wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with a poly-aryl methane protecting group, under conditions to produce cross-linking and wherein the polymerisation reaction is initiated by a free radical initiator.
- 10 9. A process according to Claim 8, wherein the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit is copolymerised in the presence of one or more one or more monomers selected from styrenes, for example styrene, hydroxystyrene, methoxystyrene, methylstyrene, hydroxymethylstyrene and chloromethylstyrene, esters of acrylic acid and esters of (meth)acrylate acid, for example methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl acrylate, hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate and acrylamides, for example N-methyl acrylamide and N-methylol (meth)acrylamide.
- 15 10. A process according to Claim 9, wherein the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit is copolymerised in the presence of one or more cross linking monomers, and one or more monomers selected from styrenes, esters of acrylic acid and esters of (meth)acrylic acid, or acrylamides.
- 20 11. A process according to Claim 8, wherein the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit is copolymerised in the presence of divinyl benzene, and styrene.
- 25 12. A process according to any one of Claims 8 to 11, wherein the monomer comprising a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit is a monomer according to any one of Claims 1 to 7.
- 30 13. A polymer support which comprises protected hydroxypolyC₂₋₄ alkyleneoxy chains attached to a cross-linked polymer wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups, wherein the hydroxypolyC₂₋₄ alkyleneoxy chains are protected with a poly-aryl methane protecting group and wherein the polymer support has been produced by a polymerisation process initiated by a free radical polymerisation initiator.
14. A polymer support according to Claim 13 wherein the poly-aryl methane group is an optionally substituted trityl group.
- 35 15. A polymer support obtainable by the process of any one of Claims 8 to 12.
16. Use of a polymer support according to any one of Claims 13 to 15 in solid phase organic synthesis.

Patentansprüche

- 40 1. Monomer zur Verwendung bei einer Polymerisationsreaktion, die durch einen Radikalinitiator initiiert wird, wobei das Monomer eine geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette umfasst, die an eine polymerisierbare Einheit angeknüpft ist, wobei die geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette 2 bis 10 C₂₋₄-Alkylenoxygruppen enthält und wobei die Hydroxypoly-C₂₋₄-Alkylenoxykette mit einer Polyarylmethanschutzgruppe geschützt ist.
- 45 2. Monomer der Formel (1) zur Verwendung bei einer Polymerisationsreaktion, die durch einen Radikalinitiator initiiert wird:



wobei

R¹ eine wahlweise substituierte Ethylengruppe ist;
 R²⁻⁴ unabhängig Wasserstoff, Hydrocarbyl, Halogen oder Hydrocarbyloxy sind; R⁵ eine Polarylmethanschutzgruppe ist; und
 n 2 bis 10 beträgt.

- 5
- 3. Monomer nach Anspruch 2, wobei R¹ eine CH=CH₂--, CH=CHCH₃- oder C(CH₃)=CH₂-Gruppe ist.
 - 4. Monomer nach einem der Ansprüche 2 oder 3, wobei [-C₂₋₄-Alkylen-O-]_n [-CH₂CH₂O-]_n, [-CH₂CH(CH₃)O-]_n, [-CH₂CH₂CH₂O-]_n oder [-CH₂CH(C₂H₅)O-]_n ist.
- 10
- 5. Ein Monomer nach einem der Ansprüche 2, 3 oder 4, wobei R²⁻⁴ Wasserstoff sind.
 - 6. Monomer nach einem der vorhergehenden Ansprüche, wobei R⁵ eine Polarylmethanschutzgruppe der Formel:



ist, wobei:

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R⁸ eine Wasserstoff-, wahlweise substituierte Alkyl- oder wahlweise substituierte Arylgruppe ist; und R⁷ und R⁸ jeweils unabhängig wahlweise substituierte Arylgruppen sind oder R⁷ und R⁸ wahlweise substituierte Arylgruppen sind, die verknüpft sein können, um einen wahlweise substituierten Ring zu bilden.

- 25
- 7. Monomer nach einem der vorhergehenden Ansprüche, wobei die Polarylmethanschutzgruppe eine wahlweise substituierte Tritylgruppe ist.
 - 8. Verfahren zur Herstellung eines Polymerträgers, umfassend die Polymerisation eines Monomers umfassend eine geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette, die an eine polymerisierbare Einheit angeknüpft ist, wobei die geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette 2 bis 10 C₂₋₄-Alkylenoxygruppen enthält, wobei die Hydroxypoly-C₂₋₄-Alkylenoxykette mit einer Polarylmethanschutzgruppe geschützt ist, unter Bedingungen zum Herstellen von Vernetzung und wobei die Polymerisationsreaktion durch einen Radikalinitiator initiiert wird.
- 30
- 9. Verfahren nach Anspruch 8, wobei das Monomer, das eine geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette umfasst, die an eine polymerisierbare Einheit angeknüpft ist, in Gegenwart eines oder mehrerer Monomere ausgewählt unter Styrolen, beispielsweise Styrol, Hydroxystyrol, Methoxystyrol, Methylstyrol, Hydroxymethylstyrol und Chlormethylstyrol, Estern von Acrylsäure und Estern von (Meth)acrylsäure, beispielsweise Methylacrylat, Ethylacrylat, Methylmethacrylat, Ethylacrylat, Hydroxyethyl(meth)acrylat und Hydroxypropyl(meth)acrylat und Acrylamiden, beispielsweise N-Methylacrylamid und N-Methylo(meth)acrylamid, copolymerisiert wird.
- 35
- 10. Verfahren nach Anspruch 9, wobei das Monomer, das eine geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette umfasst, die an eine polymerisierbare Einheit angeknüpft ist, in Gegenwart eines oder mehrerer vernetzender Monomere und eines oder mehrerer Monomere ausgewählt unter Styrolen, Estern von Acrylsäure und Estern von (Meth)acrylsäure oder Acrylamiden copolymerisiert wird.
- 40
- 11. Verfahren nach Anspruch 8, wobei das Monomer, das eine geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette umfasst, die an eine polymerisierbare Einheit angeknüpft ist, in Gegenwart von Divinylbenzol und Styrol copolymerisiert wird.
- 45
- 12. Verfahren nach einem der Ansprüche 8 bis 11, wobei das Monomer, das eine geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette umfasst, die an eine polymerisierbare Einheit angeknüpft ist, ein Monomer nach einem der Ansprüche 1 bis 7 ist.
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- 13. Polymerträger, der geschützte Hydroxypoly-C₂₋₄-Alkylenoxyketten umfasst, die an ein vernetztes Polymer angeknüpft sind, wobei die geschützte Hydroxypoly-C₂₋₄-Alkylenoxykette 2 bis 10 C₂₋₄-Alkylenoxygruppen enthält, wobei die Hydroxypoly-C₂₋₄-Alkylenoxyketten mit einer Polarylmethanschutzgruppe geschützt sind und wobei der Polymerträger durch ein Polymerisationsverfahren hergestellt worden ist, das durch einen Radikalpolymerisationsinitiator initiiert wird.
- 55
- 14. Polymerträger nach Anspruch 13, wbei die Polarylmethangruppe eine wahlweise substituierte Tritylgruppe ist.

15. Polymerträger, der durch das Verfahren nach einem der Ansprüche 8 bis 12 erhältlich ist.

16. Verwendung eines Polymerträgers nach einem der Ansprüche 13 bis 15 bei der organischen Festphasensynthese.

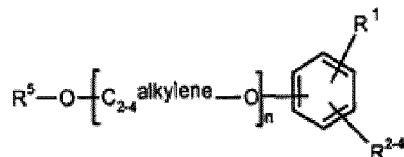
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Revendications

1. Monomère pour l'utilisation dans une réaction de polymérisation initiée par un initiateur de radicaux libres, le monomère comprenant une chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) fixée à un motif polymérisable dans lequel la chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) contient de 2 à 10 groupes alcylèneoxy en C₂₋₄ et dans laquelle la chaîne hydroxypoly(alcylèneoxy en C₂₋₄) est protégée par un groupe protecteur poly-aryl méthane.
2. Monomère de formule (1) pour l'utilisation dans une réaction de polymérisation initiée par un initiateur de radicaux libres:

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dans laquelle

R¹ est un groupe éthylène éventuellement substitué;

R²⁻⁴ sont indépendamment un atome d'hydrogène, un groupe hydrocarbyle, un atome d'halogène, ou un groupe hydrocarbyloxy;

R⁵ est un groupe protecteur poly-aryl méthane; et

n a la valeur de 2 à 10.

- 30 3. Monomère selon la revendication 2, dans lequel R¹ est un groupe CH=CH₂, CH=CHCH₃, ou C(CH₃)=CH₂.
4. Monomère selon l'une quelconque des revendications 2 ou 3, dans lequel $[-(\text{alkylene en C}_{2-4})-\text{O}-]$ _n est $[-\text{CH}_2\text{CH}_2\text{O}-]$ _n, $[-\text{CH}_2\text{CH}(\text{CH}_3)\text{O}-]$ _n, $[-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-]$ _n ou $[-\text{CH}_2\text{CH}(\text{C}_2\text{H}_5)\text{O}-]$ _n.
- 35 5. Monomère selon l'une quelconque des revendications 2, 3 ou 4, dans lequel R²⁻⁴ sont des atomes d'hydrogène.
6. Monomère selon l'une quelconque des revendications précédentes, dans lequel R⁵ est un groupe protecteur poly-aryl méthane de formule:

40



dans lequel:

45 R⁸ est un atome d'hydrogène, un groupe alkyle éventuellement substitué ou un groupe aryle éventuellement substitué; et R⁷ et R⁸ sont chacun indépendamment des groupes aryle éventuellement substitués, ou R⁷ et R⁸ sont des groupes aryle éventuellement substitués qui peuvent être liés pour former un cycle éventuellement substitué.

- 50 7. Monomère selon l'une quelconque des revendications précédentes, dans lequel le groupe protecteur poly-aryl méthane est un groupe trityle éventuellement substitué.
8. Procédé de préparation d'un support polymère comprenant la polymérisation d'un monomère comprenant une chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) fixée à un motif polymérisable dans lequel la chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) contient de 2 à 10 groupes alcylèneoxy en C₂₋₄, dans lequel la chaîne hydroxypoly(alcylèneoxy en C₂₋₄) est protégée par un groupe protecteur poly-aryl méthane, sous des conditions permettant de produire une réticulation et dans lequel la réaction de polymérisation est initiée par un initiateur de radicaux libres.
9. Procédé selon la revendication 8, dans lequel le monomère comprenant une chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) fixée à un motif polymérisable dans lequel la chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) contient de 2 à 10 groupes alcylèneoxy en C₂₋₄, dans lequel la chaîne hydroxypoly(alcylèneoxy en C₂₋₄) est protégée par un groupe protecteur poly-aryl méthane, sous des conditions permettant de produire une réticulation et dans lequel la réaction de polymérisation est initiée par un initiateur de radicaux libres.

5 neoxy en C₂₋₄) fixée à un motif polymérisable est copolymérisé en la présence d'un ou de plus d'un monomère(s) sélectionné(s) parmi les styrènes, par exemple le styrène, l'hydroxystyrène, le méthoxystyrène, le méthylstyrène, l'hydroxyméthylstyrène et le chlorométhylstyrène, les esters de l'acide acrylique et les esters de l'acide (méth)acrylique, par exemple l'acrylate de méthyle, l'acrylate d'éthyle, le méthacrylate de méthyle, l'acrylate d'éthyle, le (méth)acrylate d'hydroxyéthyle et le (méth)acrylate d'hydroxypropyle et les acrylamides, par exemple l'acrylamide de N-méthyle et le (méth)acrylamide de N-méthylol.

- 10 10. Procédé selon la revendication 9, dans lequel le monomère comprenant une chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) fixée à un motif polymérisable est copolymérisé en la présence d'un ou plusieurs monomère(s) de réticulation, et d'un ou plusieurs monomère(s) sélectionné(s) parmi les styrènes, les esters de l'acide acrylique et les esters de l'acide (méth)acrylique, ou les acrylamides.
- 15 11. Procédé selon la revendication 8, dans lequel le monomère comprenant une chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) fixée à un motif polymérisable est copolymérisé en la présence de divinyl benzène, et de styrène.
12. Procédé selon l'une quelconque des revendications 8 à 11, dans lequel le monomère comprenant une chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) fixée à un motif polymérisable est un monomère selon l'une quelconque des revendications 1 à 7.
- 20 13. Support polymère qui comprend les chaînes protégées hydroxypoly(alcylèneoxy en C₂₋₄) fixées à un polymère réticulé dans lequel la chaîne protégée hydroxypoly(alcylèneoxy en C₂₋₄) contient de 2 à 10 groupes alcylèneoxy en C₂₋₄, dans lesquels les chaînes hydroxypoly(alcylèneoxy en C₂₋₄) sont protégées par un groupe protecteur poly-aryl méthane et dans lequel le support polymère a été produit à l'aide d'un procédé de polymérisation initié par un initiateur de polymérisation radicalaire.
- 25 14. Support polymère selon la revendication 13, dans lequel le groupe poly-aryl méthane est un groupe trityle éventuellement substitué.
15. Support polymère pouvant être obtenu par le procédé selon l'une quelconque des revendications 8 à 12.
- 30 16. Utilisation d'un support polymère selon l'une quelconque des revendications 13 à 15 dans la synthèse organique en phase solide.

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REFERENCES CITED IN THE DESCRIPTION

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