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(54) Title: MACROMONOMERS FOR PREPARATION OF DEGRADABLE POLYMERS AND MODEL NETWORKS

(57) Abstract: The present invention relates to methods for preparing degradable model networks from any monomer functionality with any degradation methodology. It is based on the use of Atom-Transfer Radical Polymerization and CLICK chemistry to form the desired product.

MACROMONOMERS FOR PREPARATION OF DEGRADABLE POLYMERS AND MODEL NETWORKS

SPECIFICATION

RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application Serial No. 60/834,501 filed on July 28, 2006 the contents of which are incorporated herein in its entirety.

GRANT INFORMATION

The subject matter of this application was developed, at least in part, using funds from National Science Foundation Grants Nos. DGE-02-21589, DMR-02-13574, DMR-02-14363, and CHE-04-15516, and U.S. Army Research Office Grant No. DAAD19-06-1-0104, so that the United States Government has certain rights herein.

1. INTRODUCTION

The present invention relates to macromonomers suitable for preparing degradable polymers and model networks, methods for their production, and polymers and polymeric articles fabricated therefrom.

2. BACKGROUND OF THE INVENTION

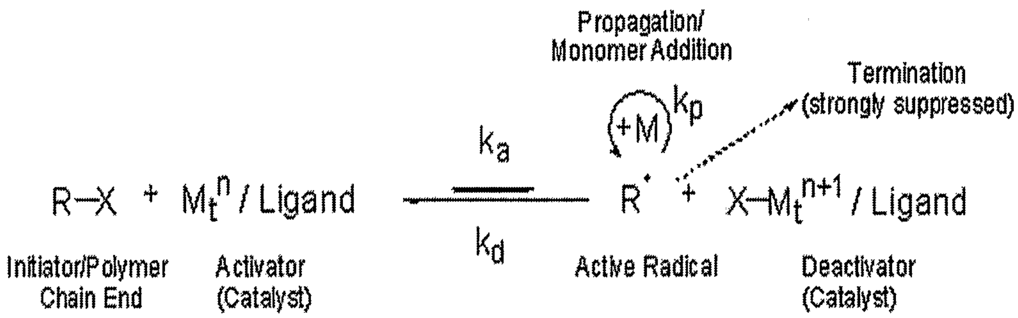
2.1. Polymer Networks

Synthetic polymer networks have been the subject of extensive theoretical, physical, and chemical study over the past century (i,ii), and are still finding new applications. (iii,iv). The structurally simplest polymer networks are termed "model networks" (MNs) and are typically comprised of linear telechelic, or α,ω-functional, polymers, or macromonomers (MAC), covalently crosslinked through their end groups with multi-functional small molecules. Macromonomers are defined as oligomers with a number average molecular weight M_n between about 1,000 and about 10,000 that contain at least one functional group suitable for further polymerizations. MNs are unique because the crosslink functionality is constant and predetermined, so that the molecular weight between crosslinks is defined by that of the MAC, and the material is homogenous with respect to the crosslink density. (v). Well defined-pore sizes are therefore obtained, providing potential advantages for certain applications. (vi). Although MNs have well-defined structure, they are not considered 'ideal' in a theoretical sense, because they unavoidably contain some number of unreacted functionalities, dangling chains, chain entanglements, and inelastic loops. (v).

Due to their insolubility in all solvents, MNs are notoriously difficult to characterize by common chemical techniques. As a consequence, certain network parameters, like the number of dangling chains, are typically estimated from combining macroscopic measurements (swelling, rheology, etc...) with theory. Recent research has utilized a hydrolytically labile crosslinker for the degradation of cross-linked star-polymer model networks (CSPMNs), and size exclusion chromatography (SEC) of the degradation products to verify the parent network structure. (iii). However, such CSPMNs have been prepared successfully only through the use of methyl methacrylate (MMA) monomers. If applied to networks of linear MACs, analysis of degradation products can also, in principle, yield the number of dangling chains after subtracting out the sol portion.

Recently, the development of a controlled/"living" free radical polymerization technique known as Atom Transfer Radical Polymerization (ATRP), described in Wang, J-S. and Matyjaszewski, K., *Journal of the American Chemical Society*, Vol. 117 (1995), p. 5641, has rendered possible the synthesis of a variety of well-defined polymers with low polydispersity indexes ($M_w/M_n < 1.3$, where M_w is the weight average molecular weight) and predetermined molecular weights, defined by the relationship $DP = \Delta[M]/[I]_0$, where DP is the degree of polymerization, [M] is the reacted monomer concentration, and $[I]_0$ is the initial concentration of the initiator. The mechanism of ATRP, shown in Scheme 1 below, is believed to be based on the repetitive addition of a monomer M to growing radicals R• generated from alkyl halides R-X by a reversible redox process. This process is catalyzed by transition metal compounds, especially cuprous (Cu(I)) halides, complexed by suitable ligands such as bipyridines and bi-, tri- and tetradentate amines, as described in Xia, J. Zhang, X. and Matyjaszewski, K., *American Chemical Society Symposium Series*, Vol. 760

(2000), pp. 207-23. The rate of monomer addition is dependent on the equilibrium constant between the activated (Cu(I)) and deactivated (Cu(II)) species. By maintaining a low concentration of active radicals, slow growth of the molecular weight is promoted and the "living" ATRP process is controlled. The degree of polymerization is determined by the ratio of reacted monomer concentration to initiator concentration ($DP_n = \Delta[M]/[R\text{-}X]_0$).



Scheme 1: Mechanism of ATRP

Radical reactions allow for polymerization of a large variety of vinyl monomers and are tolerant to many functional groups. ATRP is applicable to the reactions of hydrophobic monomers such as acrylates, methacrylates and styrene, as shown in Patten, T. E. and Matyjaszewski, K. *Advanced Materials*, Vol. 10 (1998), pp. 901-915, and also of hydrophobic and functional monomers such as 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, 2-(dimethylamino)ethyl methacrylate (DMAEMA) and 4-vinylpyridine. *See* Matyjaszewski, K., Gaynor, S. G., Qiu, J., Beers, K., Coca, S., Davis, K., Muhlebach, A., Xia, J., and Zhang, X., *American Chemical Society Symposium Series*, Vol. 765 (2000), pp. 52-71.

Further, researchers have recently reported the copper (I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction (vii, viii), which has emerged as the best example of "click chemistry," (ix) characterized by extraordinary reliability and functional group tolerance. This ligation process has proven useful for the synthesis of model polymers and materials in many situations.

2.2. Degradable Polymers

A degradable polymer is a polymer that contains a cleavage site, a bond in the chemical structure that will cleave under certain conditions. Degradable polymers have many applications, such as drug delivery, medical devices, environmentally-friendly plastics, and temporary adhesives or coatings. A variety of natural and synthetic polymers are degradable. Generally, a polymer based on a C-C backbone tends to be non-degradable, while heteroatom-containing polymer backbones are degradable. Degradability can therefore be engineered into polymers by the addition of chemical linkages such as anhydride, ester, or amide bonds, among others.

Biodegradable polymers with hydrolyzable chemical bonds have been the subject of extensive research. Polymers based on polylactide (PLA), polyglycolide (PGA), polycaprolactone (PCL) and their copolymers have been extensively employed as biodegradable materials. Degradation of these materials yields the corresponding hydroxyacids, making them safe for *in vivo* use.

Photodegradable polymers can be created by the addition of photosensitive groups (promoters) to the polymer. Two common promoters are carbonyl groups and metal complexes, which cleave when exposed to sufficient ultraviolet radiation, such as that present in sunlight. However, metals left behind by cleavage of these heavy metal complexes can cause environmental problems in sufficient quantities.

Degradable model networks in particular have many potential applications, yet in order to be successfully used, a method of yielding MACs of low polydispersity that possess orthogonal crosslinking and various degradation functionalities is necessary.

3. SUMMARY OF THE INVENTION

The present invention relates to macromonomers suitable for preparing degradable polymers and model networks, methods for their production, and polymers and polymeric articles fabricated therefrom. It is based, at least in part, on the discovery that ATRP can be used to synthesize macromonomers of low polydispersity that possess orthogonal cross-linking and degradation functionalities. Such macromonomers include, in non-limiting embodiments, both α,ω-difunctional and heterobifunctional macromonomers, and star polymer macromonomers, all of which are preferably rendered degradable through the incorporation of various degradation functionalities as taught by the inventive method.

The present invention further provides for a wide variety of articles fabricated from materials comprising the macromonomers of the invention, including polymer model networks, hydrogels, drug delivery vehicles, tissue scaffolding, cosmetics, bags, films, surface modification agents, contrast agents, and nanoparticles.

4. BRIEF DESCRIPTION OF THE FIGURES

5. DETAILED DESCRIPTION OF THE INVENTION

For clarity, and not by way of limitation, the detailed description of the invention is divided into the following subsections:

(5.1) Difunctional Macromonomer Synthesis;

(5.2) Heterobifunctional Macromonomer Synthesis;

(5.3) Star Polymer Macromonomer Synthesis;

(5.4) Uses of the Invention

5.1 α,ω-Difunctional Macromonomer Synthesis

In one set of embodiments, the present invention provides for a method of synthesizing α,ω-difunctional macromonomers with a general structure of C-$(R)_n$-L-$(R)_n$-C and α,ω-difunctional block macromonomers with a general structure of C-$(R')_n$-$(R)_n$-L-$(R)_n$-$(R')_n$-C. "L" is a linker, chosen from the group consisting of non-degradable, photodegradable, ozonolyzable, biodegradable, or hydrolyzable. "R" is a monomer, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids. "R'" is a monomer, different from "R," selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids. "n" is a variable representing the number of monomers in the macromonomer, and is chosen such that the macromonomer has a molecular weight between about 1,000 and 10,000. "C" is a terminal functional group, chosen from the group consisting of hydroxyl, allyl, acrylate, or azide.

As shown in Fig. 1, synthesis begins with a bifunctional polymerization initiator (10) containing a linker "L" (20), represented as a circle. The linker "L" (20) may be non-degradable, but may also include photodegradable, ozonolyzable, biodegradable or hydrolyzable linkages. As examples, an ozonolyzable linker may include an olefin moiety, while a photodegradable linker may include a nitrobenzylcarbonyl moiety. A biodegradable linker may include a peptide bond, while hydrolyzable linkers may include ester linkages.

The initiator (10) is bifunctional, containing terminal halogen groups (120) as initiation sites for polymerization. Bromine is especially suited for such use as an initiation site for ATRP reactions. Specific, non-limiting examples of initiator (10) are 1,2-bis(bromoisobutyryloxy)-2-butene (Compound 4) described in Section 6 below, and the novel bifunctional nitrobenzyloxycarbonyl (NBOC) initiator (**1**) described in Section 7 below.

The initiator (10) is then reacted with a sufficient amount of a chosen monomer "R" (30) through ATRP to form a macromonomer (40), an oligomer with a number average molecular weight M_N between about 1,000 and about 10,000. The monomer "R" (30) can include acrylates, methacrylates, styrenics, and polyacids. However, due to ATRP's sensitivity to the presence of acid functionalities, in order to polymerize polyacid monomers, monomers with protected acid groups must be polymerized followed by a deprotection step to regenerate the desired acid functionality. If an α,ω-difunctional block macromonomer (110 or 105) is desired, the ATRP step is repeated using a different monomer base "R'" (90), such that the resulting oligomer has a M_N between about 1,000 and about 10,000. The resulting macromonomers (100) and (40) are polymeric halides. A specific, non-limiting example of macromonomer (40) is α,ω-bromo-poly(*tert*-butyl acrylate) (Compound 5), described in Section 6 below.

The description will be continued now with respect to synthesis of an α,ω-difunctional macromonomer (50 or 70). Synthesis of an α,ω-difunctional block macromonomer is conducted using similar steps. In order to continue synthesis, the terminal halogen groups of the resulting polymeric halide (40) can be converted via a post-polymerization transformation (PPT) to a hydroxyl, allyl, acrylate, or azide functional group "C" (60), represented as an octagon, forming an α,ω-difunctional macromonomer (50). Hydroxyl groups may be added by treating the halide (40) with 4-aminobutanol in dimethylformamide (DMF), while allyl groups may be added by treating the halide (40) with allyltributyltin. Azide groups are especially suited for the CuAAC "click chemistry" reaction, and may be added by treating the halide (40) with sodium azide in DMF. Following addition of a terminal azide group, further terminal functional groups (80), represented as triangles, may be added, including aldehyde, hydroxy, carboxy, amine, peptide, epoxide, or thiol groups, through click reactions of the resulting terminal azide (60) with functional alkyne, norbornadiene, or cyclooctyne. Use of a functional alkyne requires a copper catalyst, while use of a functional cyclooctyne does not require a copper catalyst and is thus better suited for biomedical applications. The ability to add various terminal functional groups allows the user to choose the cure chemistry that may be utilized later to crosslink the linear macromonomers to form a polymer MN. Specific non-limiting examples of such polymer MNs that may be formed are MNs 1a, 1b, and **3**, described in Sections 6 and

7 below. Specific non-limiting examples of crosslinkers that may be used are **CLa** and **CLb**, described in Section 6 below. If the click chemistry process is chosen for crosslinking, subsequent to crosslinking, unreacted terminal azide groups may also be replaced with similar terminal functional groups. Specific, non-limiting examples of α,ω-difunctional macromonomer (50) are MAC 1, described in Section 6 below, and MAC **2**, described in Section 7 below.

5.2 Heterobifunctional Macromonomer Synthesis

In further non-limiting embodiments, the present invention provides for a method of synthesizing Heterobifunctional Macromonomers with a general structure of E-L-$(R)_n$-C and Heterobifunctional Block Macromonomers with a general structure of E-L-$(R)_n$-$(R')_n$-C. "E" is a terminal functional group, chosen from the group consisting of hydroxyl, allyl, acrylate, or alkyne. "L" is a linker, chosen from the group consisting of non-degradable, photodegradable, ozonolyzable, biodegradable, or hydrolyzable. "R" is a monomer, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids. "R'" is a monomer, different from "R," selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids. "n" is a variable representing the number of monomers in the macromonomer, and is chosen such that the macromonomer has a molecular weight between about 1,000 and 10,000. "C" is a terminal functional group, chosen from the group consisting of hydroxyl, allyl, acrylate, or azide.

As shown in Figure 2, synthesis begins with a heterobifunctional polymerization initiator (230) containing a linker "L" (200), represented as a circle. Linker "L" (200) may be non-degradable, but may also include photodegradable, ozonolyzable, biodegradable, or hydrolyzable linkages. As examples, an ozonolyzable linker may include an olefin moiety, while a photodegradable linker may include a nitrobenzylcarbonyl moiety. A biodegradable linker may include a peptide bond, while hydrolyzable linkers may include ester linkages.

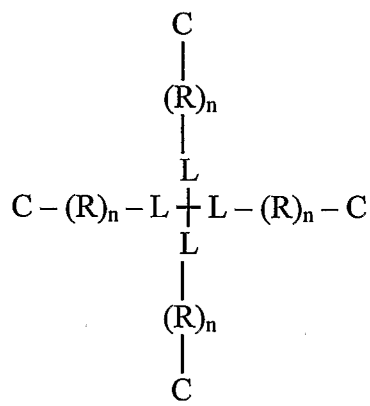
The initiator (230) is heterobifunctional, containing one terminal halogen group (220) as an initiation site for polymerization, and a functional end group "E" (210) that may be a hydroxyl, allyl, acrylate, or alkyne group. Bromine is especially suited for such use as an initiation site for ATRP reactions.

The initiator (230) is then reacted with a chosen monomer "R" (240) through ATRP to form a macromonomer (250), an oligomer with a number average molecular weight M_N between about 1,000 and about 10,000. The monomer "R" (240) can include acrylates, methacrylates, styrenics, and polyacids. However, due to ATRP's sensitivity to the presence of acid functionalities, in order to polymerize polyacid monomers, monomers with protected acid groups must be polymerized followed by a deprotection step to regenerate the desired acid functionality. If a heterobifunctional block macromonomer (295 or 292) is desired, the ATRP step is repeated using a different monomer base, "R'" (265), such that the resulting oligomer has a M_N between about 1,000 and about 10,000. The resulting macromonomers (275) and (250) are polymeric halides that contain terminal halogen groups (255) and (285) at the end of a polymer chain on one end of the linkage (200), and the original functional group (210) on the other end.

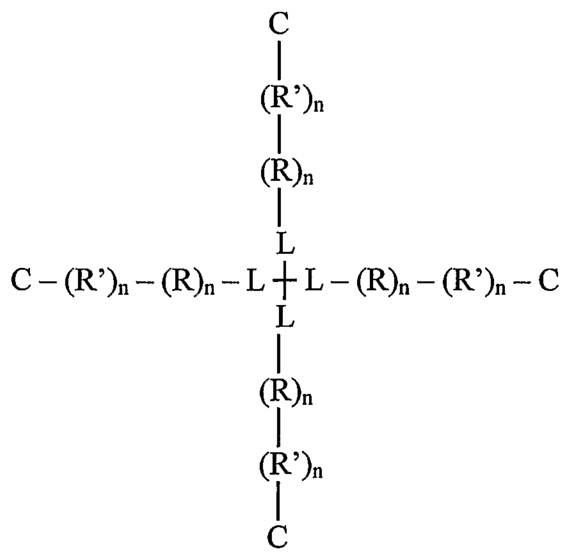
The description will be continued now with respect to synthesis of a heterobifunctional macromonomer (260 or 280). Synthesis of a heterobifunctional block macromonomer is conducted using similar steps. In order to continue synthesis, the terminal halogen group (255) of the resulting polymeric halide (250) can be converted via a post-polymerization transformation (PPT) to a hydroxyl, allyl, acrylate, or azide functional group "C" (270), represented as an octagon, forming a heterobifunctional macromonomer (260). Hydroxyl groups may be added by treating the halide (250) with 4-aminobutanol in DMF, while allyl groups may be added by treating the halide (250) with allyltributyltin. Azide groups are especially suited for the CuAAC "click chemistry" reaction, and may be added by treating the halide (250) with sodium azide in DMF. Following addition of a terminal azide group, a further terminal functional end group (290), represented as a triangle, may be added, including aldehyde, hydroxy, carboxy, amine, peptide, epoxide, or thiol groups through click reactions of the resulting terminal azide with functional alkyne, norbornadiene, or cyclooctyne. Use of a functional alkyne requires a copper catalyst, while use of a functional cyclooctyne does not require a copper catalyst and is thus better suited for biomedical applications. The ability to add various terminal functional groups allows the user to choose the cure chemistry that may be utilized later to crosslink the linear macromonomers to form a polymer MN. Specific non-limiting examples of crosslinkers that may be used are crosslinkers **CLa** and **CLb**, described in Section 6 below. If the click chemistry process is chosen for crosslinking, subsequent to crosslinking, unreacted terminal azide groups may also be replaced with similar terminal functional groups.

5.3 Star Polymer Macromonomer Synthesis

In one set of embodiments, the present invention provides for a method of synthesizing star polymer macromonomers with a general structure of:



and star polymer block macromonomers with a general structure of:



"L" is a linker, chosen from the group consisting of non-degradable, photodegradable, ozonolyzable, biodegradable, or hydrolyzable. "R" is a monomer, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids. "R'" is a monomer, different from "R," selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids. "n" is a variable representing the number of monomers in the macromonomer, and is chosen such that the macromonomer has a molecular weight between about 4,000 and 40,000. "C" is a terminal functional group, chosen from the group consisting of hydroxyl, allyl, acrylate, or azide.

As shown in Fig. 9, synthesis begins with a tetrafunctional polymerization initiator (310) containing a linker "L" (320), represented as a circle, for each initiation site. The linker "L" (320) may be non-degradable, but may also include photodegradable, ozonolyzable, biodegradable or hydrolyzable linkages. As examples, an ozonolyzable linker may include an olefin moiety, while a photodegradable linker may include a nitrobenzylcarbonyl moiety. A biodegradable linker may include a peptide bond, while hydrolyzable linkers may include ester linkages.

The initiator (310) is tetrafunctional, containing four terminal halogen groups (325) as initiation sites for polymerization. Bromine is especially suited for such use as an initiation site for ATRP reactions.

The initiator (310) is then reacted with a sufficient amount of a chosen monomer "R" (330) through ATRP to form a star polymer macromonomer (340), an oligomer with a number average molecular weight M_N between about 1,000 and about 10,000. The monomer "R" (330) can include acrylates, methacrylates, styrenics, and polyacids. However, due to ATRP's sensitivity to the presence of acid functionalities, in order to polymerize polyacid monomers, monomers with protected acid groups must be polymerized followed by a deprotection step to regenerate the desired acid functionality. If a star polymer block macromonomer (355 or 395) is desired, the ATRP step is repeated using a different monomer base "R'" (390), such that the resulting oligomer has a M_N between about 4,000 and about 40,000. The resulting star polymer macromonomers (340) and (345) are polymeric halides. A specific, non-limiting example of macromonomer (340) is ptBA star polymer **15**, described in Section 7b below.

The description will be continued now with respect to synthesis of a star polymer macromonomer (350 or 370). Synthesis of a star polymer block macromonomer is conducted using similar steps. In order to continue synthesis, the terminal halogen groups of the resulting polymeric halide (340) can be converted via a post-polymerization transformation (PPT) to hydroxyl, allyl, acrylate, or azide functional groups "C" (360), represented as octagons, forming a star polymer macromonomer (350). Hydroxyl groups may be added by treating the halide (340) with 4-aminobutanol in dimethylformamide (DMF), while allyl groups may be added by treating the halide (340) with allyltributyltin. Azide groups are especially suited for the CuAAC "click chemistry" reaction, and may be added by treating the halide (340) with sodium azide in DMF. Following addition of a terminal azide group, further terminal functional groups (380), represented as triangles, may be added, including aldehyde, hydroxy, carboxy, amine, peptide, epoxide, or thiol groups, through click reactions of the resulting terminal azide (360) with functional alkyne, norbornadiene, or cyclooctyne. Use of a functional alkyne requires a copper catalyst, while use of a functional cyclooctyne does not require a copper catalyst and is thus better suited for biomedical applications. The ability to add various terminal functional groups allows the user to choose the cure chemistry that may be utilized later to crosslink the star polymer macromonomers to form a polymer MN. A specific non-limiting example of such polymer MNs that may be formed is MN **19**, described in Section 7b below. A specific non-limiting example of a crosslinker that may be used is Compound **18**, described in Section 7b below. If the click chemistry process is chosen for crosslinking, subsequent to crosslinking, unreacted terminal azide groups may also be replaced with similar terminal functional groups. A specific, non-limiting example of star polymer macromonomer (350) is MAC **17**, described in Section 7b below.

5.4 Uses of the Invention

The macromonomers of the present invention may be used to produce cross-linked polymer model networks, gels, and hydrogels. Hydroxy-terminated macromonomers allow use of a polyurethane cure, while amine-terminated macromonomers allow an epoxide/polyurethane cure. Alkene-terminated macromonomers allow a free-radical/hydrosilylation cure, while epoxide-terminated macromonomers allow an amine cure, and thiol-terminated macromonomers allow a disulfide/vulcanization cure. Alkyne-terminated macromonomers allow a hydrosilylation/azide cure, while azide-terminated macromonomers allow an alkyne/Diels-Alder cure. The ability to select the cure chemistry desired allows the user to tailor such macromonomers to their expected environment. Such materials have a broad range of applications, including cosmetics such as nail polish, biomedical products such as degradable hydrogels or tissue scaffolding, consumer products such as degradable bags or films, and pharmaceutical products such as drug delivery vehicles. Macromonomers are also useful as surface modification agents, contrast agents, and nanoparticles.

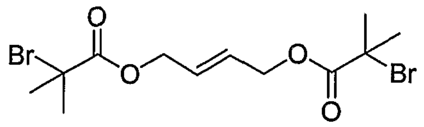
6. Example - Preparation and Degradation of Ozonolyzable Model Network

General

With reference to Fig. 4, this scheme was employed to prepare the first *tert*-butyl acrylate based MNs (**1a**, **1b**) (430) comprised of an α,ω-azido-poly(tBA) MAC (**1**) (400) crosslinked with tri- (410) and tetra- (not shown) acetylene crosslinkers (**a** and **b** respectively). After synthesis, the olefin moiety (420) at the center of the MAC (400) was cleaved through ozonolysis to form tri-armed polymers (440) with aldehyde terminal groups (450).

All reagents were purchased from Aldrich chemical company and were used as supplied unless otherwise noted. *Tert*-butyl acrylate was distilled under reduced pressure over CaH_2 prior to use. Toluene and *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA) were degassed with argon for 20 m prior to use. Crosslinkers 2,2,2-tris(2-propynyloxymethyl)ethanol (**CLa**) and tetrakis(2-propynyloxymethyl)methane (**CLb**) were prepared according to literature procedures. (x,xi,xii). SEC measurements were performed on a Knauer GPC system with a Knauer K-2301 refractive index detector and a Spark Holland Basic Marathon autosampler. Three Polymer Laboratories 5 μm particle size PLgel columns (one 100 Å and two MIXED-D pore types) placed in series were employed for the chromatography. The system was calibrated against linear polystyrene standards ranging in molecular weight from 580-377,400 Da. Experiments were performed at room temperature in THF eluant with a flow rate of 1.0 mL/min. Ozone for degradation studies was generated from an Ozone Lab OL100 Ozone Generator.

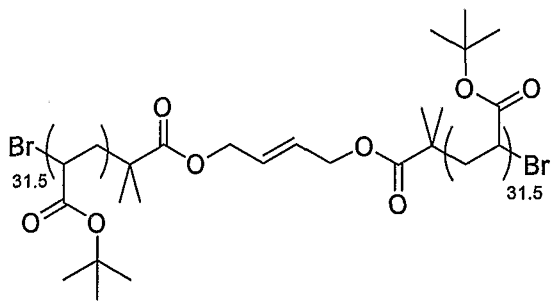
Synthesis of 1,2-bis(bromoisobutyryloxy)-2-butene (Compound 4)



Compound 4

Triethylamine (1.20 g, 11.8 mmol) was added to a round-bottom flask containing 2-butene-1,4-diol (0.454 g, 5.15 mmol) and tetrahydrofuran (THF, 30 mL). This solution was added dropwise to a stirring solution of **α**-bromoisobutyryl bromide (2.60 g, 1.40 mL) in THF (25 mL) at 0 °C. A white precipitate formed immediately. The mixture was stirred for 2 h at 0 °C followed by overnight stirring at room temperature. After this time, the reaction mixture was filtered, condensed on a rotary evaporator, diluted with ethyl acetate (EtOAc, 50 mL), and extracted 4 times with water (50 mL). The organic layer was dried over $MgSO_4$, filtered, condensed on a rotary evaporator, and dried *en vacuo* overnight to yield 1,2-bis(bromoisobutrylyoxy)-2-butene (1.68 g, 85%) as a yellow oil.

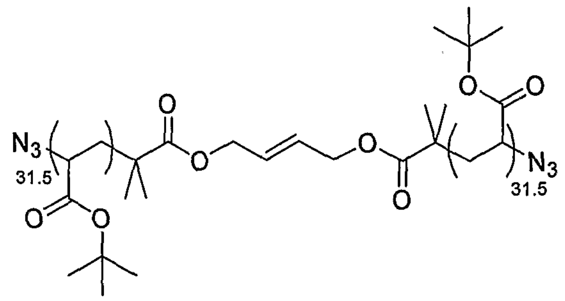
Synthesis of ozonolyzable α,ω-bromo-poly(*tert*-butyl acrylate) (Compound 5)



Compound 5

CuBr (418 mg, 2.91 mmol) and Compound 4 (565 mg, 1.46 mmol) were added to a clean, dry round bottom flask, which was subsequently evacuated for 15 m and back-filled with argon. Freshly distilled *tert*-butyl acrylate (15.0 g, 117 mmol) was added *via* a degassed syringe followed by degassed toluene (7.5 mL), and PMDETA (489 mg, 2.93 mmol). The reaction flask was immediately submerged in liquid N_2 until frozen, evacuated for 15 m, removed from liquid N_2, and backfilled with argon. When the mixture thawed completely, the flask was submerged in a 70 °C oil bath and stirred for 1 h under argon atmosphere. After 1 h, the reaction flask was opened to air, and the viscous, black mixture was diluted with tetrahydrofuran (20 mL) and frozen in liquid N_2. After thawing, the mixture was passed through a column of neutral alumina, concentrated on a rotary evaporator, precipitated in a 10:1 volume of 50-50 methanol-water three times, dissolved in diethyl ether, dried over $MgSO_4$, filtered, concentrated on a rotary evaporator, and dried *in vacuo* for 2 d to yield compound **1** (6.90 g, M_n(NMR): 10,600 Da) as a white solid.

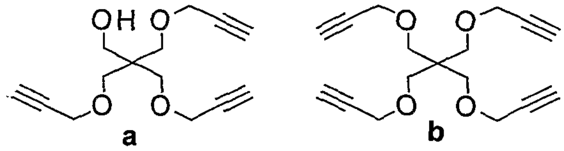
Synthesis of MAC 1



MAC 1

Sodium azide (57.5 mg, 884 mmol) was added to a round-bottom flask containing Compound 5 (3.4 g, 0.402 mmol) dissolved in DMF (100 mL). The reaction mixture was stirred at 50 °C for 1 d after which time it was allowed to cool to room temperature, diluted with ether (50 mL), and extracted 4 times with water (100 mL). The organics were concentrated on a rotary evaporator and precipitated into a 10:1 volume of 50-50 methanol-water. After decanting the methanol-water solution, the remaining solid was dissolved in diethyl ether, dried over $MgSO_4$, filtered, concentrated on a rotary evaporator, and dried for 2 d *in vacuo* to yield MAC 1 (3.06 g, 90%) as a white solid. The success of the substitution reaction was indicated by the shift of the H NMR resonance of the proton next to the end groups, the appearance of a strong absorbance in the IR spectrum characteristic of alkyl azide, and by elemental analysis, the latter showing the transformation to be complete

Typical procedure for the crosslinking MACs with CLs to form MNs 1a and 1b through CLICK Chemistry



Crosslinkers CLa (410 and 510) and CLb (not shown in figures)

MAC 1 (3/2 or 2 equiv. depending on **CLa** or **CLb** respectively) was added to a clean vial followed by the copper catalyst (CuBr, CuI, $CuSO_4$, or $CuBr(PPh_3)_3$, 10 equiv. to alkyne). The vial was evacuated for 5 minutes and backfilled with argon before degassed solvent (DMF or toluene, 0.5 mL / g of MAC) was added. Sodium ascorbate (4 M in H_2O, 20 equiv.) and alkyl amine (PMDETA or DIEA, 10 equiv.) were then added if necessary. The vial was immediately placed in an oven preset to 80 °C and allowed to react for the required time. In most cases) insoluble material formed. However, the appearance of the materials varied from insoluble particulates to stable homogeneous gels depending on the reaction conditions. When the term "homogeneous" is used, it implies that the material was uniform in appearance and that the entire reaction mixture formed a single material. Also, the homogenous materials were mechanically stable, meaning they were able to be handled without breaking apart. When aqueous sodium ascorbate was added to the reaction mixture, a precipitate would form in the region where the water contacted the DMF solution containing MAC 1. These materials are referred to as "slightly more heterogeneous" because at the end of the crosslinking reaction, this region would have a rougher texture. "Heterogeneous" also refers to cases where the reaction mixture formed anything but a single gel (e.g. particulates). In general, the solvent-swollen "heterogeneous" materials would break apart under their own weight. Due to copper catalyst trapped within the networks, all of the materials were colored after the crosslinking reaction, but repeated swelling in fresh acetone yielded colorless materials.

As shown in Fig. 6, the IR spectra of the products (630) closely resembled that of MAC 1 (610) without the azide peak, indicating that the crosslinking proceeded in high yield. For comparison, the spectrum of α,ω-bromo-poly(*tert*-butyl acrylate) is indicated (600). When no copper catalyst was employed (620), the azide remained, and when a 2:1 ratio of azide to alkyne was used (640), the resulting material still possessed azide functionalities, which could presumably be used for post-crosslinking functionalization of the material. The olefin moiety can also be functionalized after crosslinking, providing another means of tailoring the properties of these materials.

Ozonolysis of MAC 1, MNs 1a and 1b

In order to determine the approximate amount of unreacted material left after CuAAC crosslinking and to confirm that the M_n between crosslinks was well-defined, MNs 1a and 1b were ozonolyzed to yield soluble products. The substrate was dissolved (MAC 1) or swollen (MNs 1a and 1b) in CH_2Cl_2 (20 mL) in a glass vial. The vial was submerged in an acetone/dry ice bath at -76 °C and allowed to cool for 5 m. O_3 was bubbled directly into the system *via* a glass Pasteur pipette for 20 m until the solution became blue and there were no insoluble materials. After this time, the solution was allowed to warm to room temperature, dried on a rotary evaporator, dissolved in THF, passed through a short alumina plug, and analyzed by SEC.

As shown in Fig. 5, based on the hypothesized network structure for MN 1a (520) (using tri-functional crosslinks (510)), ozonolysis of the olefin moiety present at the midpoints of each junction can yield only four products (530-560) the major of which is a three-armed star polymer (530) with M_n equaling 1.5 times that of MAC 1 (500).

With reference to the SEC chromatograph shown in Fig. 7, it can be seen that the major degradation product of MN 1a had the expected molecular weight. The ozonolysis product from MAC 1 (730) had a M_n approximately one-half that of MAC 1 (720). Similarly, the major degradation product of MN 1a (710) had an M_n approximately equal to twice that of MAC 1, which would be expected for a tetrafunctional MN. However, both networks also possess a peak corresponding to one-half the M_n of MAC 1 (720). Considering that no extraction of soluble material was performed before ozonolysis, this peak must arise from cases in which only one, or neither, of the MAC azides reacted. The sample from MN 1b (700) showed more of this unreacted material, suggesting that the increased steric hindrance of a tetra-functional network may limit the extent of crosslinking.

7. Examples of Preparation and Degradation of Photodegradable Model Network

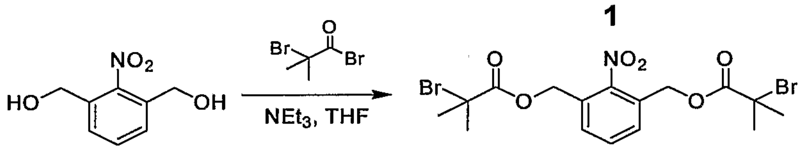
a. Linear Macromonomer

The procedure described in above section 5.1 was adapted for the preparation of photodegradable tBA MNs by ATRP synthesis of a photocleavable tBA macromonomer (MAC) from a novel bifunctional nitrobenzyloxycarbonyl (NBOC) initiator (**1**). SEC characterization of the MN photodegradation products provides evidence that the pore sizes of the parent MN were defined by the number average molecular weight (M_n) of the MAC.

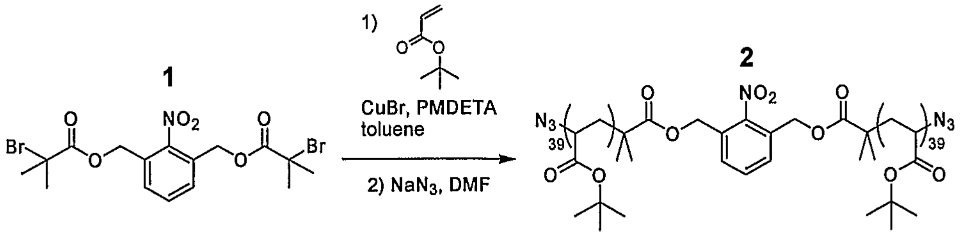
Synthesis of MAC 2

The preparation begins with synthesis of the NBOC-ATRP initiator **1**, which is capable of photocleavage *via* the well-known Norrish type II mechanism. (xiii).

1



ATRP of tBA from **1** proceeded in a controlled fashion to yield α,ω-bromo-poly(tBA) (ptBA, M_n = 10,400, PDI = 1.16). Treatment of this polymer with sodium azide in DMF yielded MAC **2**.



Photocleavage of **2** proceeds quantitatively to yield linear polymers with number average molecular weight (M_n) one-half that of **2**.

Crosslinking of 2 to Form MNs

Crosslinking of **2** with a tetra-functional acetylene *via* CuAAC yielded model network **3**. The most homogeneous materials formed when CuBr was used as the CuAAC catalyst, in the presence of 2,2'-bipyridyl ligand, and DMF solvent under argon atmosphere. Ultrasonication of this mixture for 15 seconds yielded a viscous solution which was subsequently cured overnight at 40 °C. After this time, the materials were repeatedly swollen in fresh 30% H_2O/acetone for 4 d to remove the sol portion and the copper catalyst. The resulting materials were colorless and transparent.

Photodegradation of MNs and SEC of the degradation products

Irradiation of THF-swollen **3** with 350 nm light for 30 min yielded a light yellow liquid. After irradiation for two days to ensure complete degradation the THF solution was analyzed by SEC. As shown in Fig. 8, as expected, the primary degradation product **4** (800) was a four arm star polymer, with M_n equal to twice that of **2** (810), indicating that the pore size of the parent MN was defined by the length of **2**. A small amount of material having M_n equal to half that of **2** was also observed (820), presumably arising from "dangling chains" (MACs that only reacted on one end) within the network. These remaining functionalities may be later utilized for decoration of the material with functional species. With reference to Fig. 9, the hypothesized molecular structure of **3** (900) and degradation product **4** (910) can be seen.

b. Star Polymer Macromonomer

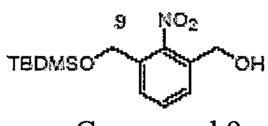
General

Star Polymer Macromonomer **15** was prepared via a one-pot strategy. The conditions for ATRP and CuAAC are essentially identical, with the important catalytic entity being Cu(I) in both cases. Therefore, a one-pot star polymer synthesis using a small, tetrafunctional azide was used. With reference to Fig. 10, the initiator **13** (1010) has an alkyne separated from the initiation site by an NBOC functionality, thus enabling cleavage of the resulting polymer from the alkyne. Treatment of **13** (1010) with 0.25 equivalents of tetraazide **14** and 200 equivalents of tBA with CuBr catalyst, PMDETA ligand, and 50-50 toluene-DMF solvent yielded star polymer **15** (1020) (M_n(SEC) = 37,200, PDI = 1.11), the result of tandem CuAAC coupling and

ATRP (Scheme 6). Conversion of the bromine end groups of **15** (1020) to azides by treatment with NaN_3 in DMF yielded star MAC **17** (1030) (Scheme 6). Fig. 11 shows the ^1H NMR resonances in **17** corresponding to the triazole proton resulting from the CuAAC reaction, the methylene protons from **14** and **13**, the aromatic protons of **13**, the terminal protons adjacent to the azide groups, and the backbone and *tert*-butyl protons of ptBA. With reference to Fig. 12, comparison of the FTIR spectra of **15** and **17** confirms the existence of azide groups in **17**.

Returning to Fig. 10, CuAAC crosslinking of **17** (1030) with bifunctional alkyne **18** (1040) (under the same conditions used for the linear polymers described above yielded insoluble gel materials **19** (1050). Photodegradation of **19** (1050) yielded linear polymer **20** (1060), with M_n approximately one-half that of MAC **17** (1030) as the primary degradation product. Irradiation of the 90:10 THF:water swollen material for 25 minutes yielded a light yellow liquid and no visible trace of the insoluble material. Continued irradiation for 2 d and SEC analysis yielded product **20** which possessed the expected M_n confirming the presence of tetra-functional branching points in the parent MN. As for the case with the linear MACs, there existed a low molecular weight SEC peak (~10,000 Da) corresponding to unreacted arms of the star MACs.

Synthesis of 2-nitro-3-(*tert*-butyldimethylsilyloxymethyl)-hydroxymethylbenzene (Compound 9)

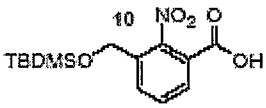


Compound 9

To a clean, dry round-bottom flask was added 2-nitro-1,3-benzenedimethanol (818 mg, 4.47mmol), anhydrous DMF (40 mL), and imidazole (304.2 mg, 4.47 mmol). The solution was maintained at 0 °C while *tert*-butyldimethylsilylchloride (337 mg, 2.24 mmol) was slowly added. The resulting pale yellow solution was allowed to warm to room temperature and stirred overnight under argon before being diluted with ethyl acetate (100 mL), washed with water (5 X 50 mL), dried over $MgSO_4$, filtered, concentrated on a rotary evaporator, and purified by silica gel chromatography (30% EtOAc:hexanes) to yield 3-(*tert*-

butyldimethylsilyloxymethyl)-2-nitro-hydroxymethylbenzene as a yellow oil which crystallized upon further solvent removal *in vacuo*. The excess 2-nitro-1,3-benzenedimethanol was recovered and re-subjected to the reaction conditions to yield Compound **9** in 80% yield after three iterations.

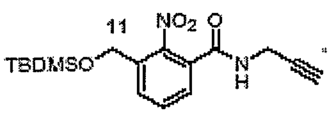
Synthesis of 3-(*tert*-butyldimethylsilyloxymethyl)-2-nitrobenzoic acid (Compound 10)



Compound 10

An aqueous solution of 15% $NaHCO_3$ (18 mL) was added to a stirring solution of Compound **9** (1.80 g, 2.69 mmol) in acetone (60 mL) at 0 °C. NaBr (133 mg, 1.29 mmol) and TEMPO (18.9 mg, 0.121 mmol) were then added followed by the slow addition of trichloroisocyanuric acid (2.81 g, 12.1 mmol). The resulting solution was allowed to warm to room temperature and stirring for 1 d after which time 2-propanol (3.63 mL) was added. The mixture was filtered over Celite, concentrated on a rotary evaporator, dissolved in 18 mL of saturated Na_2CO_3, washed with EtOAc (3 X 10 mL), acidified with 1 M HCl, and extracted with ethyl acetate (3 X 50 mL). The resulting organics were dried over Na_2SO_4, filtered, concentrated on a rotary evaporator and purified by silica gel chromatography (10% MeOH:CH_2Cl_2) to yield Compound **10** (1.05 g, 56%) as a white solid.

Synthesis of 3-(*tert*-butyldimethylsilyloxymethyl)-2-nitro-*N*-propargylbenzamide (Compound 11)

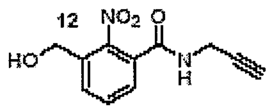


Compound 11

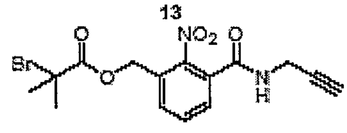
HBTU (183 mg, 0.482 mmol) and HOBt (65.1 mg, 0.482 mmol) were added to a stirring solution of Compound **10** (150 mg, 0.482 mmol) in anhydrous DMF (4.82 mL) followed by *N*,*N*-diisopropylethylamine (187 mg, 1.45 mmol) and propargyl amine (79.6 mg, 1.45 mmol). The resulting solution was stirred for 30 h at room temperature after which time 25 mL of EtOAc were added and the solution was washed with water (3 X 10 mL), aqueous saturated NH_4Cl (1 X 10 mL), and brine (1

X 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The resulting oil was purified by silica gel chromatography (50% EtOAc:hexanes) to yield Compound **11** as a white solid (92.3 mg, 55%).

Synthesis of 3-(2-bromoisobutyryl)methyl-2-nitro-*N*-propargylbenzami de (Compound 13)



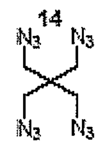
Compound 12



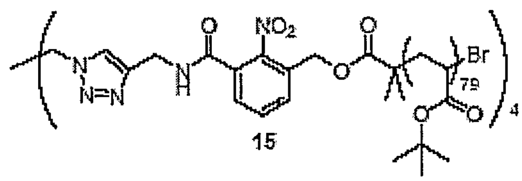
Compound 13

TBAF (4.19 mL of a 1.0 M solution in THF) was added dropwise to a stirring solution of Compound **11** (487 mg, 1.40 mmol) in THF (14 mL). TLC analysis showed complete reaction after 5 minutes, after which time the THF was removed on a rotary evaporator and the resulting oil was dissolved in EtOAc (50 mL), washed with saturated NH_4Cl (2 X 20 mL), water (2 X 50 mL), dried over $MgSO_4$, concentrated *in vacuo*. The resulting white solid (Compound **12**) was dissolved in anhydrous THF (14 mL), triethylamine (184 mg, 1.81 mmol) was added, and the resulting solution was added dropwise to a stirring solution of □-bromoisobutyrylbromide (225 mg, 1.82 mmol) in THF (5 mL) at 0 °C. A white precipitate formed immediately. The mixure was allowed to warm to room temperature and stirred overnight under argon atmosphere after which time the solid salts were filtered, and the solvent was removed on a rotary evaporator. The resulting yellow oil was dissolved in ethyl acetate (50 mL) and washed with water (3 X 20 mL), dried over $MgSO_4$, concentrated *in vacuo*, and purified by silica gel chromatography (50% EtOAc:hexanes) to yield Compound **13** (321 mg, 60%) as a white solid.

Synthesis of 4-arm ptBA star polymer (15)



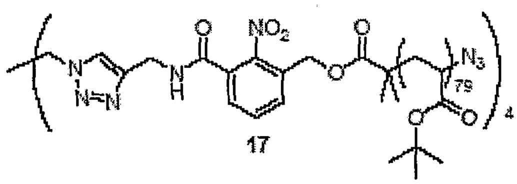
Compound 14



Compound 15

CuBr (115 mg, 0.80 mmol) was added to a clean, dry round bottom flask which was evacuated for 5 minutes before backfilling with argon. Freshly distilled tBA (10.3 g, 80.0 mmol) and a degassed solution of Compound **14** (23.6 mg, 0.100 mmol) in toluene (2.50 mL) were added via a degassed syringe. A solution of Compound **13** (151 mg, 0.400 mmol) in DMF (2.50 mL) was bubbled with argon for 5 minutes and added to the reaction flask via a degassed syringe. The flask was immediately submerged in liquid N_2 until frozen, subjected to vacuum for 10 min, removed from liquid N_2 and backfilled with argon. After completely thawing, the light green reaction mixture was submerged in a preheated oil bath at 70 °C and stirred under argon atmosphere for 3.5 h. Samples were taken via a degassed syringe at various time intervals for kinetic analysis by ^{1}H NMR. When the reaction had reaction ~40% conversion, the flask was opened to air and submerged in liquid nitrogen to quench the reaction. Dilution with THF, passing through a neutral alumina column, concentration on a rotary evaporator, and precipitation (3 X in a 10:1 volume of 50-50 methanol-water three times) yielded star polymer **15** as a white solid.

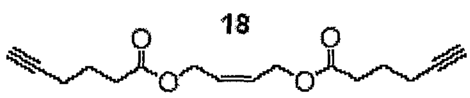
Synthesis of tetra-azido functionalized ptBA star polymer (MAC 17)



MAC 17

Star polymer MAC **17** was prepared in a manner similar to linear MAC **1** using 4-arm ptBA star polymer 15 as the substrate as opposed to Compound 4.

Synthesis of bifunctional alkyne crosslinker (Compound 18)



Compound 18

Hexynoyl chloride (1.74 g, 13.3 mmol) was added dropwise to a stirring solution of butane-1,4-diol (0.901 g, 10.2 mmol) and triethylamine (1.35 g, 13.3 mmol) in methylene chloride (25 mL). A white precipitate formed immediately. The mixture was stirred overnight at room temperature after which time it was filtered and concentrated on a rotary evaporator. The residue was dissolved in EtOAc (50 mL) and washed with water (2 X 25 mL), saturated aqueous Na_2CO_3 (2 X 25 mL), and brine (1 X 25mL). The organic layer was dried over $MgSO_4$, filtered, concentrated on a rotary evaporator, and purified by silica gel chromatography (80% hexanes:EtOAc) using anisaldehyde stain to yield Compound **18** as a colorless oil (2.00 g, 70%).

Preparation of Model Network 19

The MAC precursor **17** and CuBr (10 equiv. per azide) were added to a clean glass vial which was capped with a septum and evacuated for 5 min before backfilling with argon. Anhydrous DMF (30% by weight of MAC) was added via a degassed syringe, followed by crosslinker **18** (1 equiv. of alkyne to azide), and PMDETA (20 equiv. per azide). The vial was placed in an ultrasonication bath for 10 s to homogenize the solution before placing the vial in a preheated oven at 60 °C under argon for overnight reaction to yield insoluble MNs which were deep blue in color due to the presence of trapped copper catalyst.

Photodegradation of Model Network 19

The insoluble MN materials were removed from the vials in which they were prepared, and added to a larger vial containing fresh methylene chloride. For 2 d, the solvent was exchanged approximately every 10 hours until the gel materials became colorless. After this time, the methylene chloride was removed and the MN was swollen in 90% THF:water. Excess THF:water was removed with a Pasteur pipette, and the vial containing the swollen material was capped tightly and placed in a rayonet reactor under UV irradiation at 350 nm peak wavelength. Samples were taken at various times for SEC analysis. Complete degradation of insoluble material was observed after 25 min, but SEC analysis indicated that several days were needed for complete degradation.

8. <u>Example of Substitution of Bromine End Group with Hydroxyl Group</u>

Bromo-terminated p(*t*-BMA)-*b*-p(St) with α-hydroxyl end group (*M*n = 5861, *M*w/*M*n = 1.17, 0.4g, 58 ηmol) and 10 eq. of Na_2CO_3 (0.1 g) were placed into 25mL rbf and degassed and back-filled with argon three times. Degassed DMF (10 mL) was added using a syringe (white suspension - Na_2CO_3 was partly dissolved). Then 30 eq. of 4-aminobutanol (300 ηL) was added drop-wise under argon. After stirring for 48 h at room temperature, the α,ω-hydroxyl terminated p(*t*-BMA)-*b*-p(St) block copolymer was precipitated into a 10-fold excess of a 50/50 v/v mixture of MeOH/D.I. water. H NMR ($CDCl_3$): The peak of CH(Ph)-Br at δ = 4.4-4.6 ppm disappeared and a new peak of -**CH**$_2$-OH at δ = 3.4 -3.6 arised.

9. Example of Substitution of Bromine End Group with Acrylate Group

Bromo-terminated p(*t*-BMA)-*b*-p(St) with α-hydroxyl end group is transformed into α,ω-hydroxyl-terminated p(*t*-BMA)-*b*-p(St) via the procedure outlined in section 7 above. The product was added to a 100 mL rbf, sealed with a rubber septum, degassed and back-filled with argon three times before dissolving in 20 mL of degassed THF. Then 11 molar excess (with regard to the OH groups) of deoxygenated TEA (306 ηL, 2.24 mmol) was added and the solution was cooled in an ice-bath. A 10 molar excess of acryloyl chloride (162 ηL, 2.04 mmol) was introduced drop-wise and white precipitation appeared. After stirring of the solution for 24 h at room temperature, the resulting macromonomer was precipitated into a 10-fold excess of a 50/50 v/v mixture of MeOH/D.I. water. H NMR ($CDCl_3$): The peaks of -**CH**$_2$-OH protons (δ = 3.8 - 3.9 ppm) and -**CH**$_2$-OCO- protons (δ = 4.15 - 4.3 ppm) disappeared and new peaks of acrylate groups raised: 2x **CH**$_2$= protons (δ = 6.43 and 5.80 ppm), 2x -C**H**-COO- (δ = 6.05 ppm), 3x **CH**$_2$-OCO- (δ = 4.27, 4.36, and 4.43 ppm) and C**H**(Ph)-NH proton δ = 3.90 ppm.

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CLAIMS

1. An α,ω-Difunctional Macromonomer having the formula:

$C-(R)_n-L-(R)_n-C$,

wherein

R is a monomer selected from the group consisting of acrylates, styrenics, and polyacids; and

n is the number of monomer groups in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, a hydrolyzable linker, and a non-degradable linker; and

C is a terminal functional group chosen from the group consisting of acrylate, hydroxyl, and azide.

2. An α,ω-Difunctional Macromonomer having the formula:

$C-(R)_n-L-(R)_n-C$,

wherein

R is a monomer selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of monomer groups in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, and a hydrolyzable linker; and

C is a terminal functional group chosen from the group consisting of acrylate, allyl, hydroxyl and azide.

3. An α,ω-Difunctional Block Macromonomer having the formula:

$C-(R')_n-(R)_n-L-(R)_n-(R')_n-C$,

wherein

R is a monomer selected from the group consisting of acrylates, styrenics, and polyacids; and

R' is a monomer, different from R, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of each monomer group in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, a hydrolyzable linker, and a non-degradable linker; and

C is a terminal functional group chosen from the group consisting of acrylate, hydroxyl, and azide.

4. An α,ω-Difunctional Block Macromonomer having the formula:

$C\text{-}(R')_n\text{-}(R)_n\text{-}L\text{-}(R)_n\text{-}(R')_n\text{-}C$,

wherein

R is a monomer selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

R' is a monomer, different from R, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of each monomer group in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, and a hydrolyzable linker; and

C is a terminal functional group chosen from the group consisting of acrylate, allyl, hyrdoxyl and azide.

5. An α,ω-Heterobifunctional Macromonomer having the formula:

$E\text{-}L\text{-}(R)_n\text{-}C$,

wherein

R is a monomer selected from the group consisting of acrylates, styrenics, and polyacids; and

n is the number of monomer groups in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, a hydrolyzable linker, and a non-degradable linker; and

C is a terminal functional group chosen from the group consisting of azide, hydroxyl, and acrylate; and

E is a terminal functional group chosen from the group consisting of azide, acrylate, and alkyne.

6. An α,ω-Heterobifunctional Macromonomer having the formula:

$E\text{-}L\text{-}(R)_n\text{-}C$,

wherein

R is a monomer selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of monomer groups in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, and a hydrolyzable linker; and

C is a terminal functional group chosen from the group consisting of hydroxyl, allyl, azide and acrylate; and

E is a terminal functional group chosen from the group consisting of hydroxyl, allyl, acrylate, and alkyne.

7. An α,ω-Heterobifunctional Block Macromonomer having the formula:

$E\text{-}L\text{-}(R)_n\text{-}(R')_n\text{-}C$,

wherein

R is a monomer selected from the group consisting of acrylates, styrenics, and polyacids; and

R' is a monomer, different from R, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of each monomer group in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, a hydrolyzable linker, and a non-degradable linker; and

C is a terminal functional group chosen from the group consisting of azide, hydroxyl, and acrylate; and

E is a terminal functional group chosen from the group consisting of hydroxyl, allyl acrylate, and alkyne.

8. An α,ω-Heterobifunctional Block Macromonomer having the formula:

$E\text{-}L\text{-}(R)_n\text{-}(R')_n\text{-}C$,

wherein

R is a monomer selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

R' is a monomer, different from R, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of each monomer group in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, and a hydrolyzable linker; and

C is a terminal functional group chosen from the group consisting of hydroxyl, allyl, azide and acrylate; and

E is a terminal functional group chosen from the group consisting of hydroxyl, allyl, acrylate, and alkyne.

9. A method of preparing a linear macromonomer, comprising:

a) preparing an initiator with at least one terminal halogen group;

b) polymerizing the initiator with the chosen monomer functionality through ATRP to form a polymeric halide;

c) modifying the polymeric halide through a post-polymerization transformation to replace the terminal halogen group with a desired functional end group, wherein the desired functional end group is selected from the group consisting of hydroxyl, acrylate, and azide.

10. The method of claim 9, wherein the polymerization initiator contains a degradable linkage.

11. The method of claim 10, wherein the degradable linker is chosen from a group consisting of a photodegradable, ozonolyzable, biodegradable, and hydrolyzable linkages.

12. The method of claim 9, wherein the monomer functionality is selected from the group consisting of acrylates, methacrylates, sytrenics, and polyacids.

13. The method of claim 9, wherein the polymerization step is repeated using a different monomer functionality.

14. The method of claim 9, wherein the post-polymerization transformation to add an azide functional end group comprises treating the polymeric halide with sodium azide in dimethylformamide.

15. The method of claim 9, wherein the post-polymerization transformation is conducted to add an azide functional end group, further comprising the step of modifying the polymeric azide through CLICK chemistry to add a further desired functional end group.

16. The method of claim 15, wherein the further desired functional end group is selected from the group consisting of aldehyde, hydroxy, carboxy, amine, peptide, epoxide, and thiol.

17. A linear macromonomer, prepared by the method comprising:

a) preparing an initiator with at least one terminal halogen group;

b) polymerizing the initiator with the chosen monomer functionality through ATRP to form a polymeric halide;

c) modifying the polymeric halide through a post-polymerization transformation to replace the terminal halogen group with a desired functional end group, wherein the desired functional end group is selected from the group consisting of hydroxyl, acrylate, and azide.

18. The linear macromonomer of claim 17, wherein the polymerization initiator contains a degradable linkage.

19. The linear macromonomer of claim 18, wherein the degradable linkage is chosen from a group consisting of a photodegradable, ozonolyzable, biodegradable, and hydrolyzable linkages.

20. The linear macromonomer of claim 17, wherein the monomer functionality is selected from the group consisting of acrylates, methacrylates, sytrenics, and polyacids.

21. The linear macromonomer of claim 17, wherein the polymerization step is repeated using a different monomer functionality.

22. The linear macromonomer of claim 17, wherein the post-polymerization transformation to add a desired azide functional end group comprises treating the polymeric halide with sodium azide in dimethylformamide.

23. The linear macromonomer of claim 17, wherein the post-polymerization transformation is conducted to add an azide functional end group,

further comprising the step of modifying the polymeric azide through CLICK chemistry to add a further desired functional end group.

24. The linear macromonomer of claim 23, wherein the further desired functional end group is selected from the group consisting of aldehyde, hydroxy, carboxy, amine, peptide, epoxide, and thiol.

25. A method of preparing a degradable allyl-terminated linear macromonomer, comprising:

a) preparing an initiator that contains a degradable linkage and at least one terminal halogen group;

b) polymerizing the initiator with the chosen monomer functionality through ATRP to form a polymeric halide;

c) modifying the polymeric halide through a post-polymerization transformation to replace any terminal halogen groups with allyl groups.

26. The method of claim 25 wherein the post-polymerization transformation is conducted by reacting the polymeric halide with allyltributyltin.

27. The method of claim 25, wherein the degradable linkage is chosen from a group consisting of a photodegradable, ozonolyzable, biodegradable, and hydrolyzable linkages.

28. The method of claim 25, wherein the monomer functionality is selected from the group consisting of acrylates, methacrylates, sytrenics, and polyacids.

29. The method of claim 25, wherein the polymerization step is repeated using a different monomer functionality.

30. A degradable allyl-terminated linear macromonomer, prepared by the method comprising:

a) preparing an initiator comprising a degradable linkage and at least one terminal halogen group;

b) polymerizing the initiator with the chosen monomer functionality through ATRP to form a polymeric halide;

c) modifying the polymeric halide through a post-polymerization transformation to replace any terminal halogen groups with allyl groups.

31. The degradable allyl-terminated linear macromonomer of claim 30 wherein the post-polymerization transformation is conducted by reacting the polymeric halide with allyltributyltin.

32. The degradable allyl-terminated linear macromonomer of claim 30, wherein the degradable linkage is chosen from a group consisting of a photodegradable, ozonolyzable, biodegradable, and hydrolyzable linkages.

33. The degradable allyl-terminated linear macromonomer of claim 30, wherein the monomer functionality is selected from the group consisting of acrylates, methacrylates, sytrenics, and polyacids.

34. The degradable allyl-terminated linear macromonomer of claim 30, wherein the polymerization step is repeated using a different monomer functionality.

35. A method of preparing a degradable polymer model network comprising:

a) forming a mixture containing a plurality of units of a linear or star polymer macromonomer;

b) crosslinking or end-linking the plurality of units of a degradable linear or star polymer macromonomer.

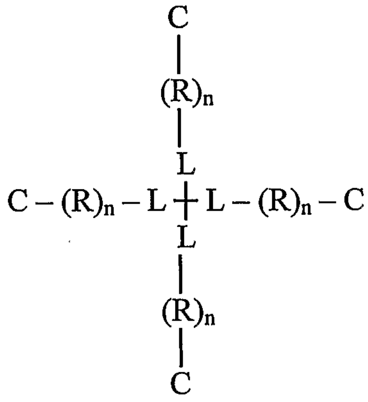
36. A degradable polymer model network, prepared by the method comprising:

a) forming a mixture containing a plurality of units of a degradable linear or star polymer macromonomer;

b) crosslinking or end-linking the plurality of units of a degradable linear or star polymer macromonomer.

37. A degradable polymer network, comprising a plurality of units of a degradable linear macromonomer, wherein the plurality of units of a degradable linear macromonomer are end-linked or crosslinked together.

38. A Star Polymer Macromonomer having the formula:



wherein

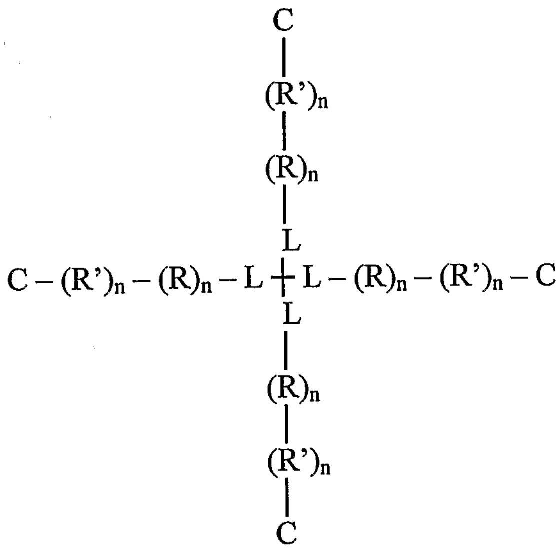
R is a monomer selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of monomer groups in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, and a hydrolyzable linker; and

C is a terminal functional group chosen from the group consisting of acrylate, allyl, hydroxyl and azide.

39. A Star Polymer Block Macromonomer having the formula:



wherein

R is a monomer selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

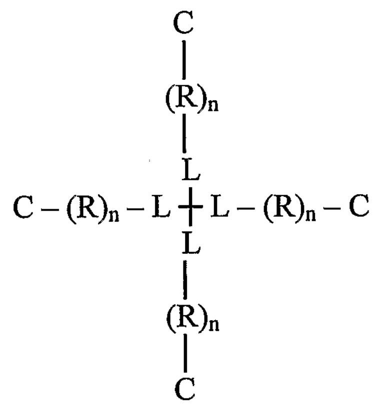
R' is a monomer, different from R, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of each monomer group in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, and a hydrolyzable linker; and

C is a terminal functional group chosen from the group consisting of acrylate, allyl, hyrdoxyl and azide.

40. A Star Polymer Macromonomer having the formula:



wherein

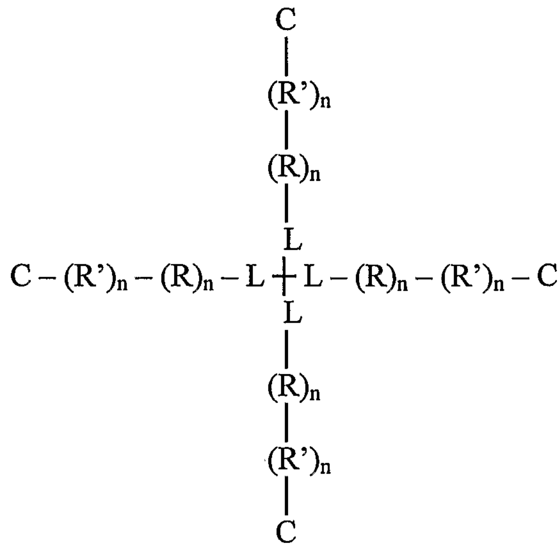
R is a monomer selected from the group consisting of acrylates, styrenics, and polyacids; and

n is the number of monomer groups in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, a hydrolyzable linker, and a non-degradable linker; and

C is a terminal functional group chosen from the group consisting of acrylate, hydroxyl, and azide.

41. A Star Polymer Block Macromonomer having the formula:



wherein

R is a monomer selected from the group consisting of acrylates, styrenics, and polyacids; and

R' is a monomer, different from R, selected from the group consisting of acrylates, methacrylates, styrenics, and polyacids; and

n is the number of each monomer group in the macromonomer; and

L is a linker chosen from the group consisting of a photodegradable linker, an ozonolyzable linker, a biodegradable linker, a hydrolyzable linker, and a non-degradable linker; and

C is a terminal functional group chosen from the group consisting of acrylate, hydroxyl, and azide.

42. A method of preparing a star polymer macromonomer, comprising:

a) preparing a tetrafunctional initiator with terminal halogen groups;

b) polymerizing the initiator with the chosen monomer functionality through ATRP to form a polymeric halide;

c) modifying the polymeric halide through a post-polymerization transformation to replace the terminal halogen groups with desired functional end groups, wherein the desired functional end groups are selected from the group consisting of hydroxyl, acrylate, and azide.

43. The method of claim 42, wherein the polymerization initiator contains a degradable linkage at each initiation site.

44. The method of claim 43, wherein the degradable linker is chosen from a group consisting of a photodegradable, ozonolyzable, biodegradable, and hydrolyzable linkages.

45. The method of claim 42, wherein the monomer functionality is selected from the group consisting of acrylates, methacrylates, sytrenics, and polyacids.

46. The method of claim 42, wherein the polymerization step is repeated using a different monomer functionality.

47. The method of claim 42, wherein the post-polymerization transformation to add an azide functional end group comprises treating the polymeric halide with sodium azide in dimethylformamide.

48. The method of claim 42, wherein the post-polymerization transformation is conducted to add an azide functional end group, further comprising the step of modifying the polymeric azide through CLICK chemistry to add a further desired functional end group.

49. The method of claim 48, wherein the further desired functional end group is selected from the group consisting of aldehyde, hydroxy, carboxy, amine, peptide, epoxide, and thiol.

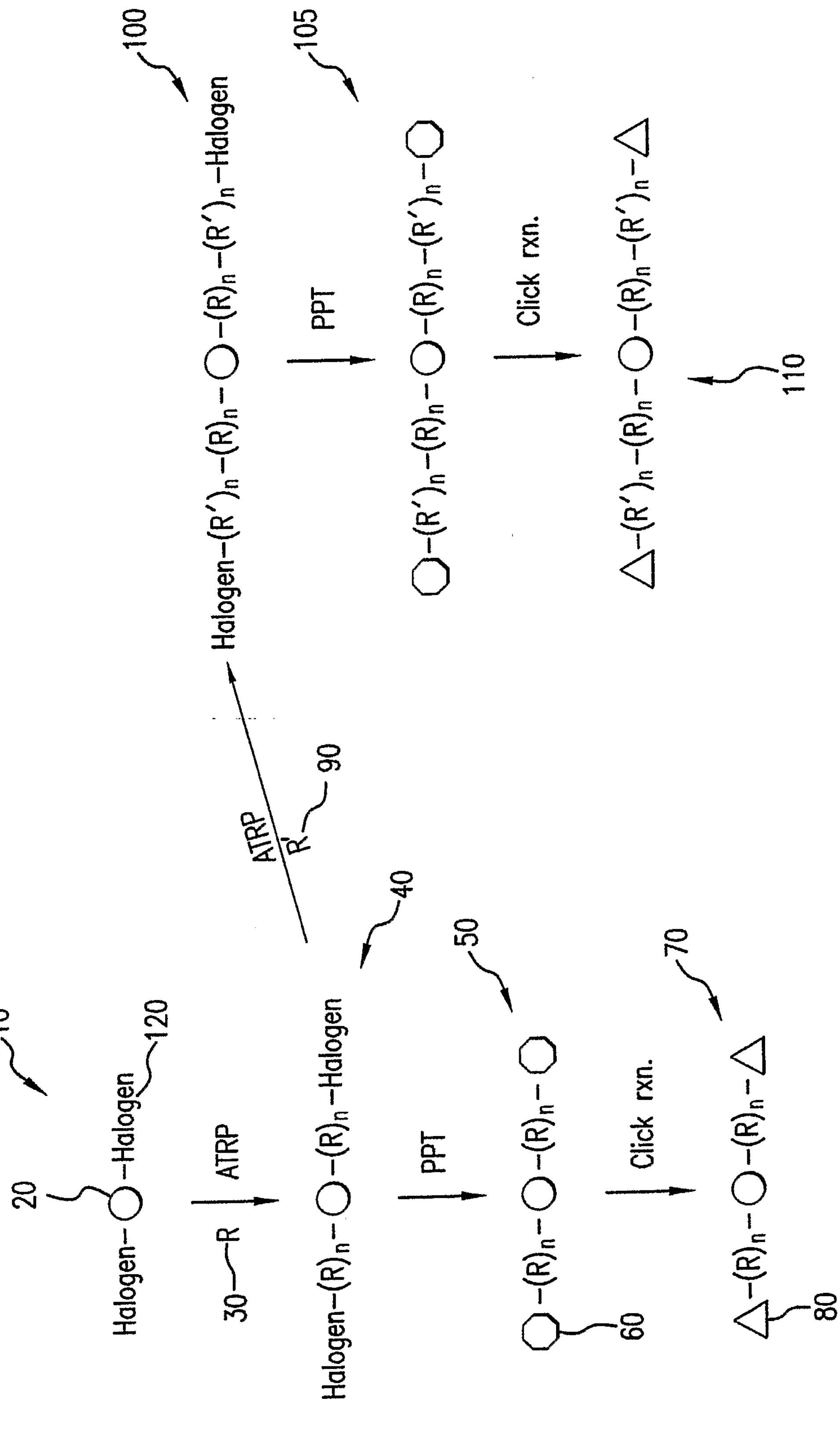

Halogen–○–Halogen
ATRP
R
PPT
Click rxn.
10
20
30
40
50
60
70
80
90
100
105
110
120

FIG. 1

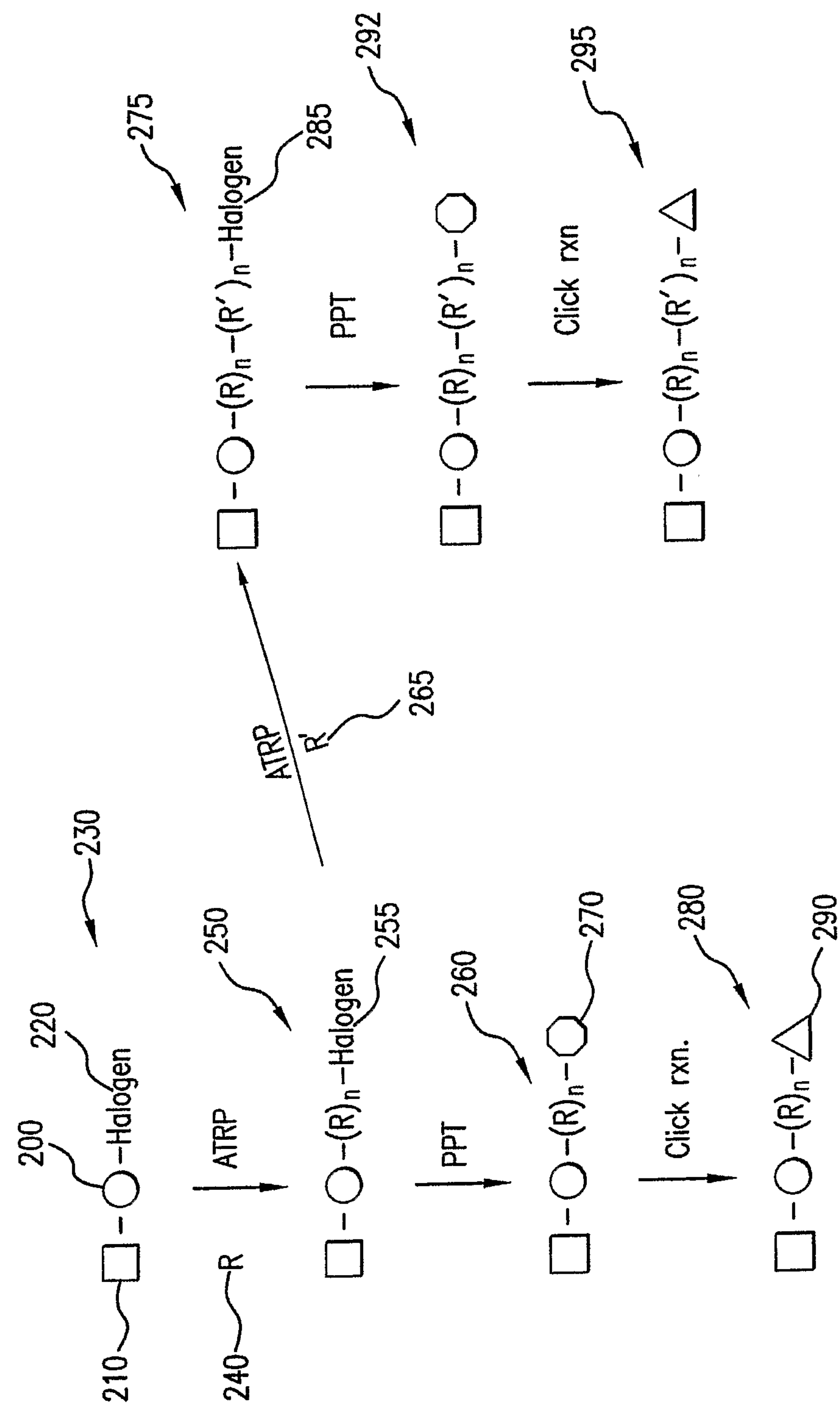

200
210
220
Halogen
230
ATRP
R
240
250
255
(R)n
Halogen
PPT
260
270
Click rxn.
280
290
ATRP
R'
265
275
(R')n
285
PPT
292
Click rxn
295

FIG.2

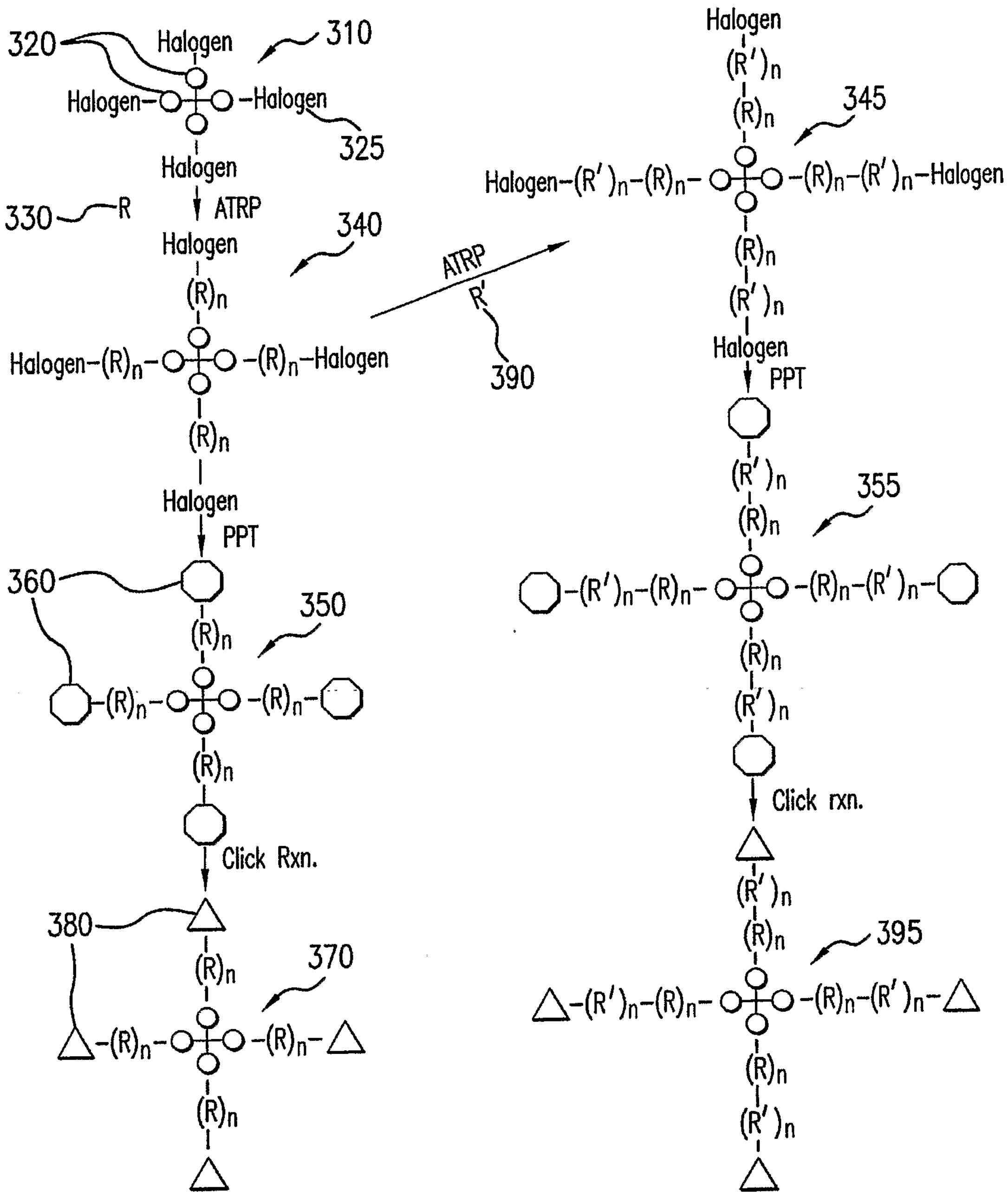

320
Halogen
310
Halogen
Halogen
325
Halogen
330
R
ATRP
Halogen
340
(R)n
Halogen-(R)n-
-(R)n-Halogen
(R)n
Halogen
PPT
360
(R)n
350
-(R)n-
-(R)n-
(R)n
Click Rxn.
380
(R)n
370
-(R)n-
-(R)n-
(R)n
ATRP
R'
390
Halogen
(R')n
(R)n
345
Halogen-(R')n-(R)n-
-(R)n-(R')n-Halogen
(R)n
(R')n
Halogen
PPT
(R')n
(R)n
355
-(R')n-(R)n-
-(R)n-(R')n-
(R)n
(R')n
Click rxn.
(R')n
(R)n
395
-(R')n-(R)n-
-(R)n-(R')n-
(R)n
(R')n

FIG.3

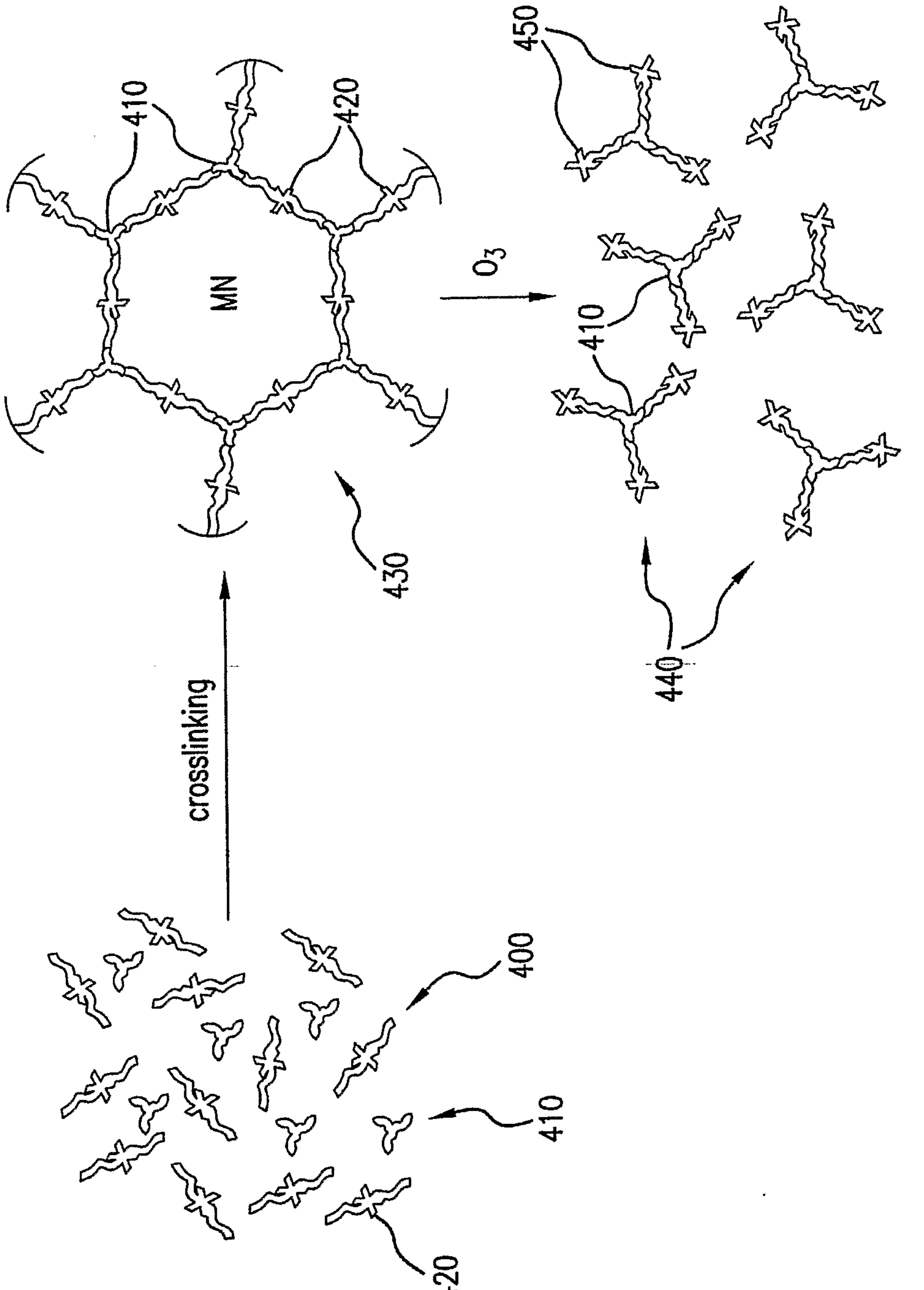


FIG.4

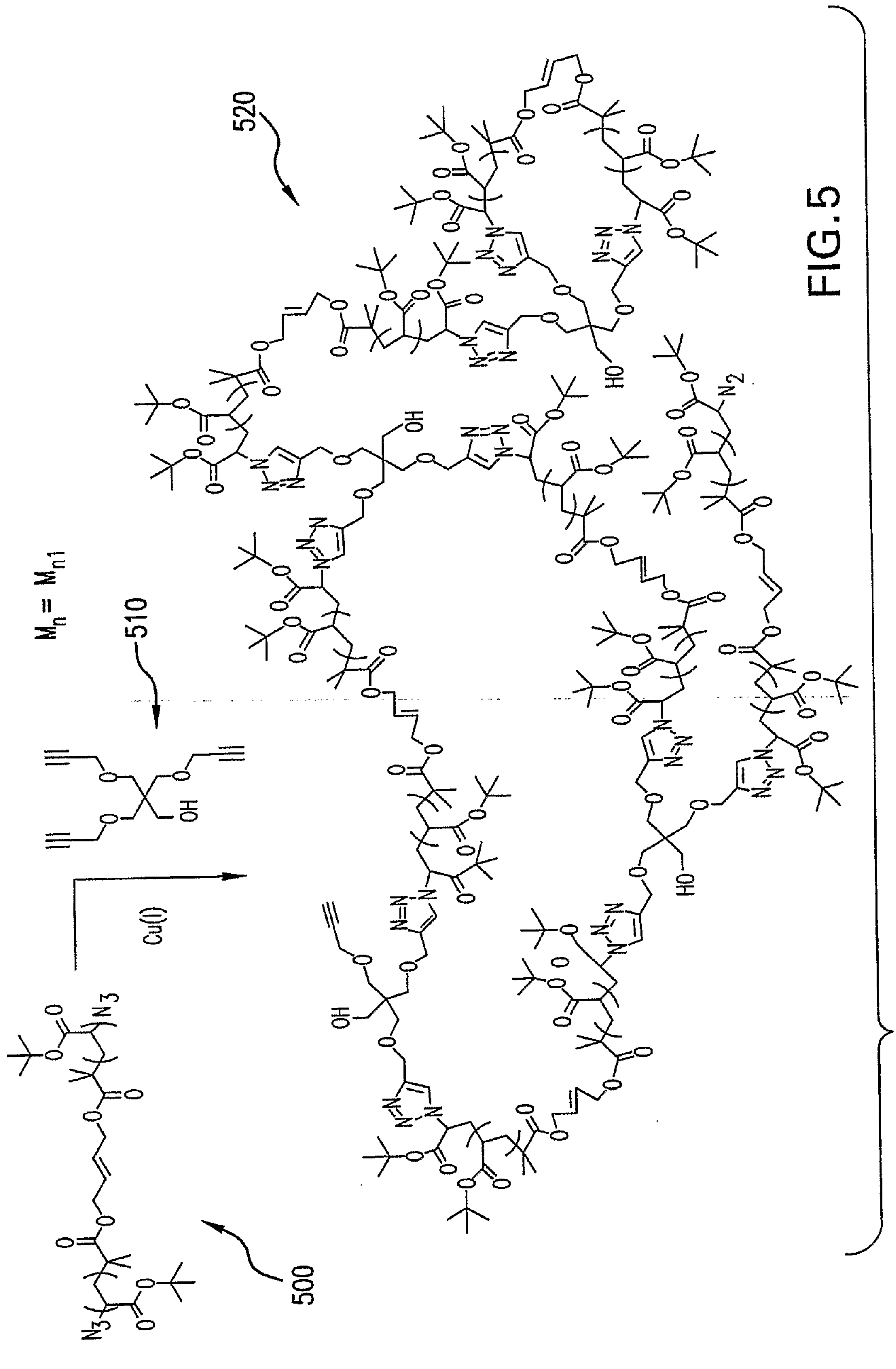


FIG.5

6/12

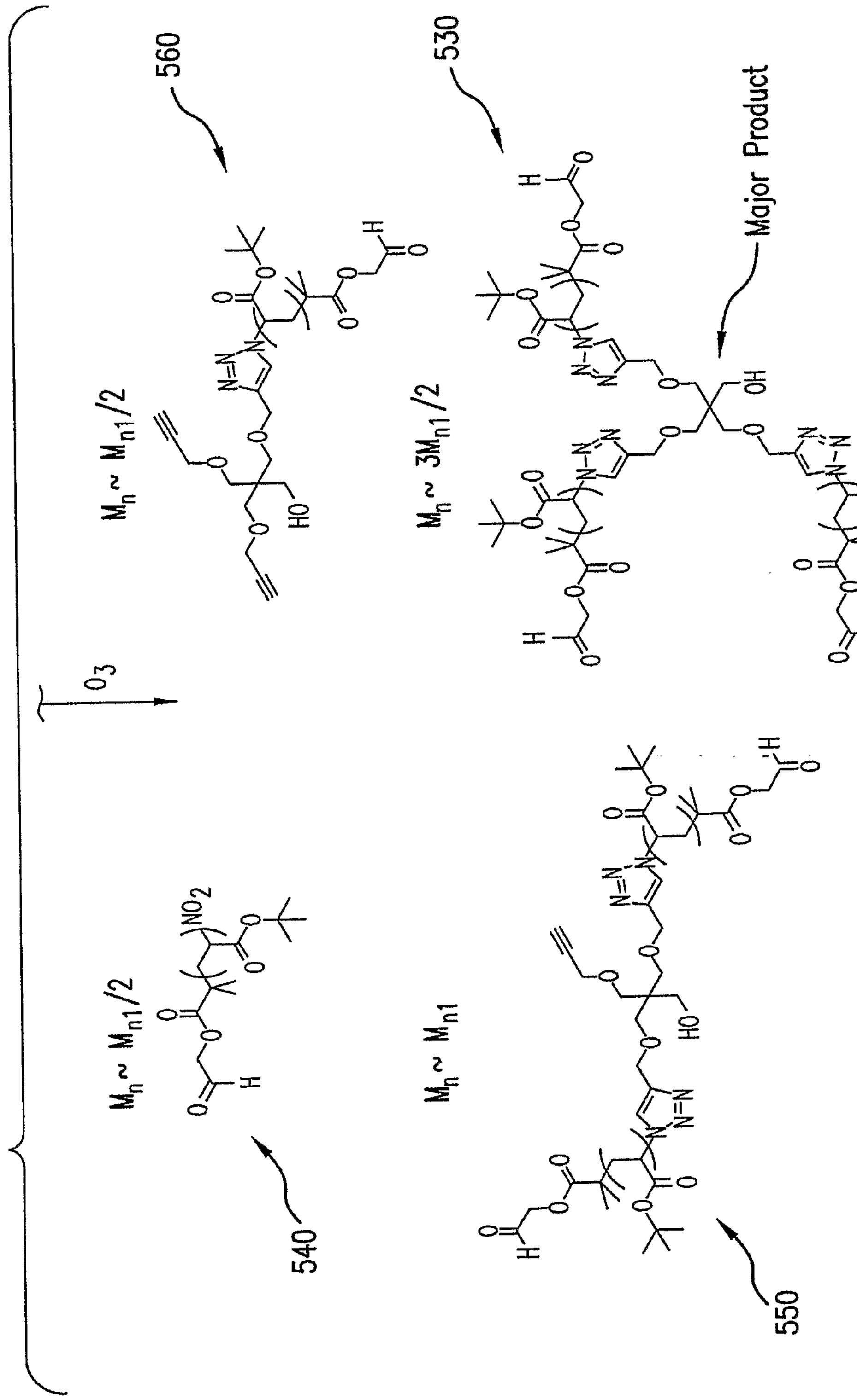


FIG.5 continued

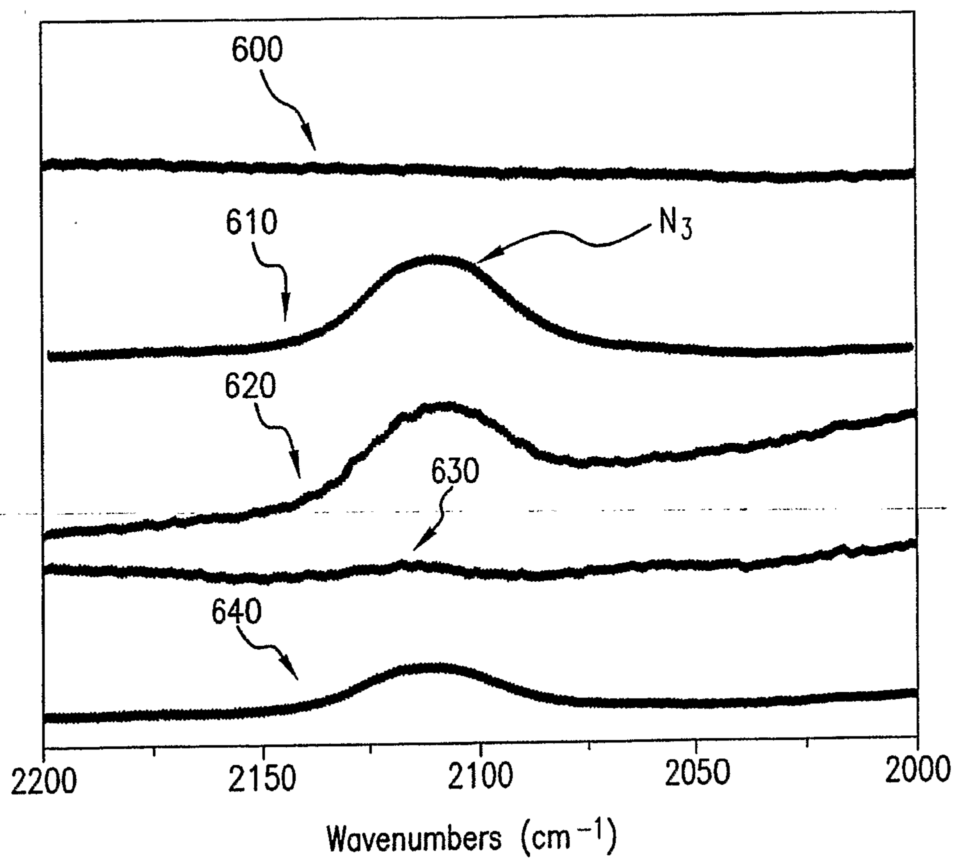
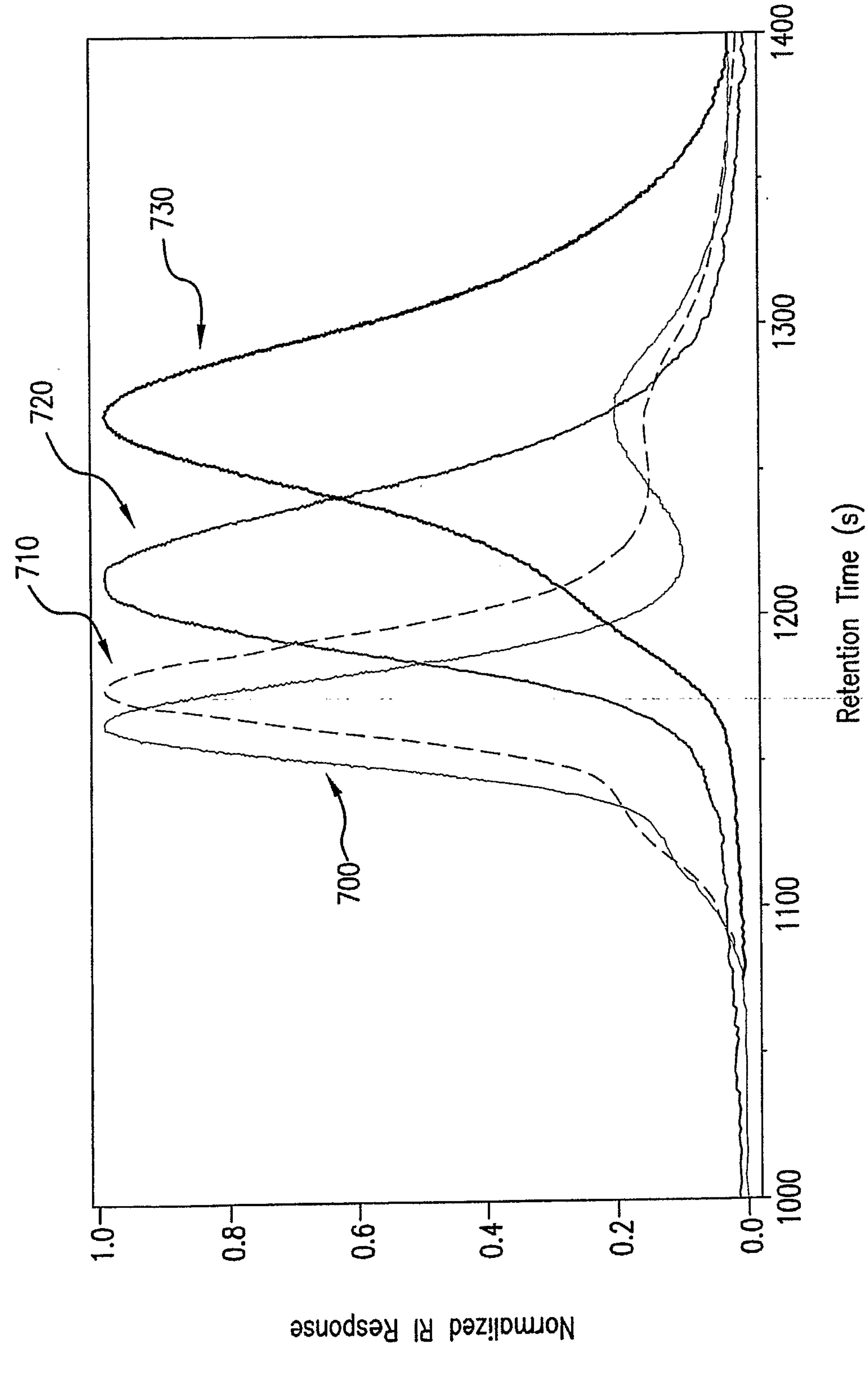

600
610
N3
620
630
640
2200
2150
2100
2050
2000
Wavenumbers (cm -1)

FIG.6



700
710
720
730
Normalized RI Response
0.0
0.2
0.4
0.6
0.8
1.0
1000
1100
1200
1300
1400
Retention Time (s)

FIG. 7

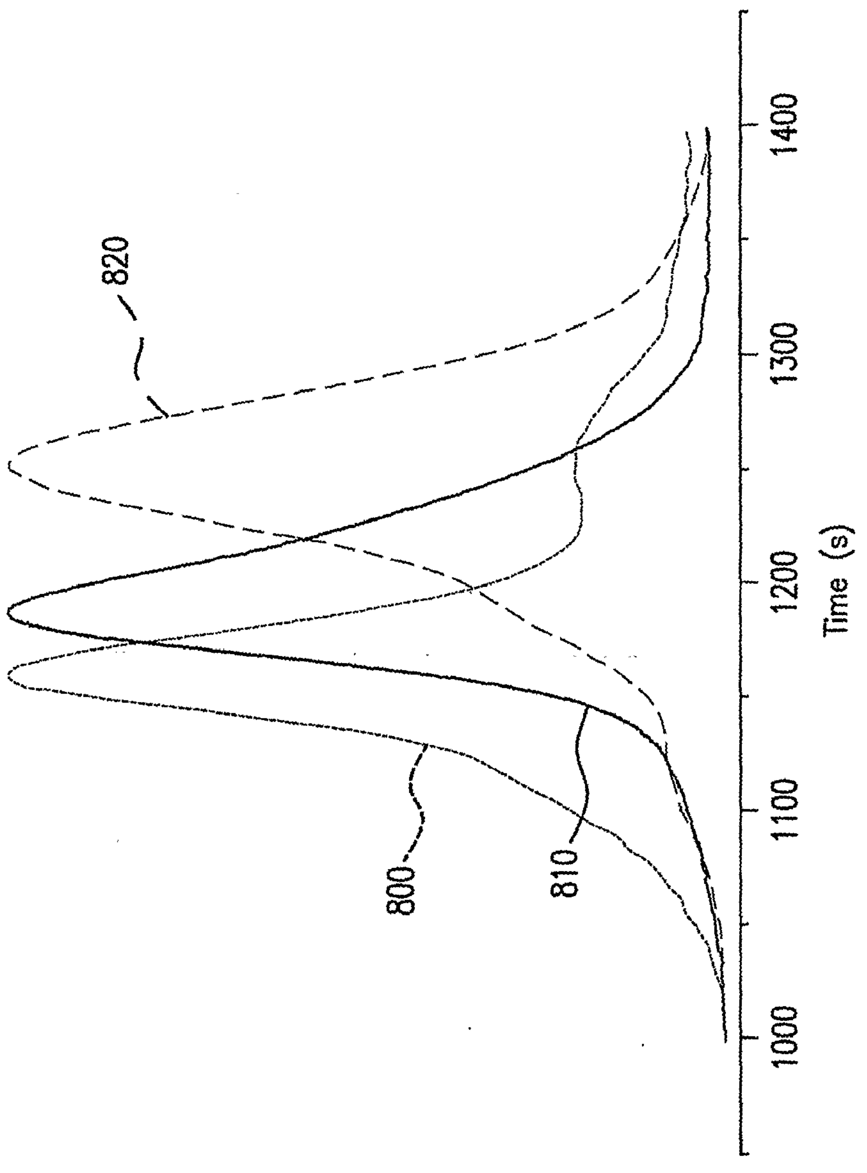


FIG.8

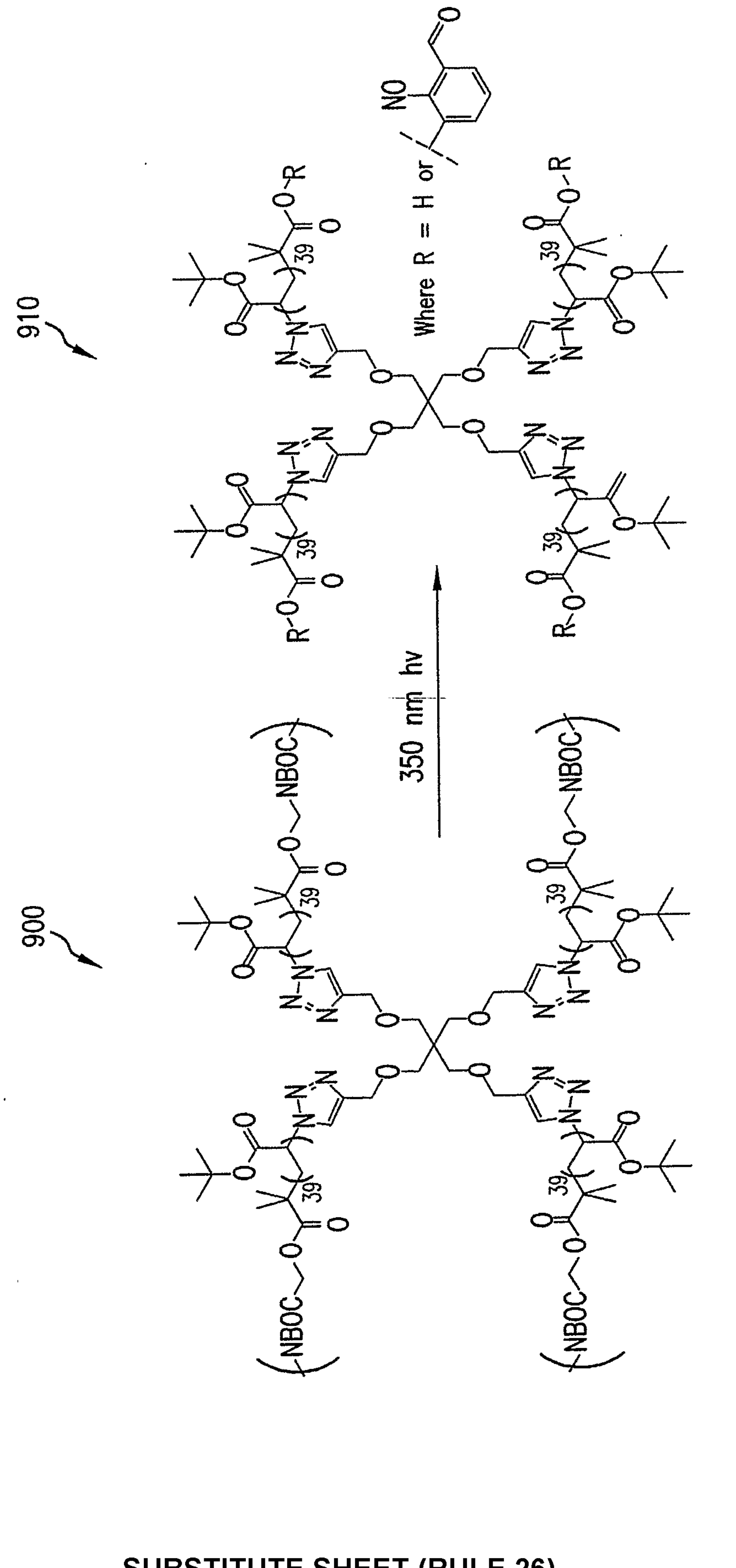


FIG.9

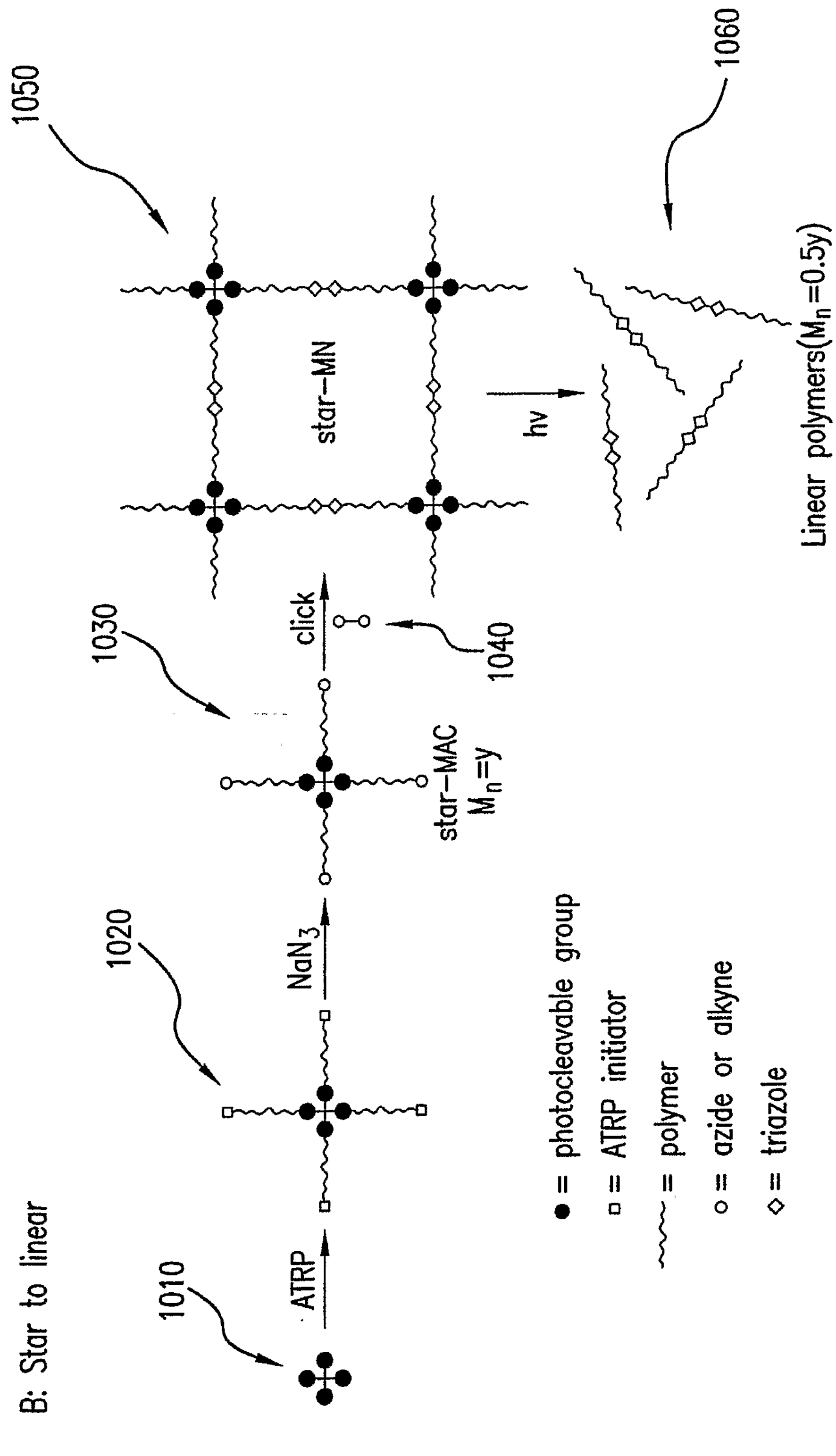

B: Star to linear
1010
ATRP
1020
NaN_3
1030
star–MAC
M_n=y
click
1040
1050
star–MN
hv
1060
Linear polymers(M_n=0.5y)
● = photocleavable group
▫ = ATRP initiator
〰 = polymer
○ = azide or alkyne
◇ = triazole

FIG.10

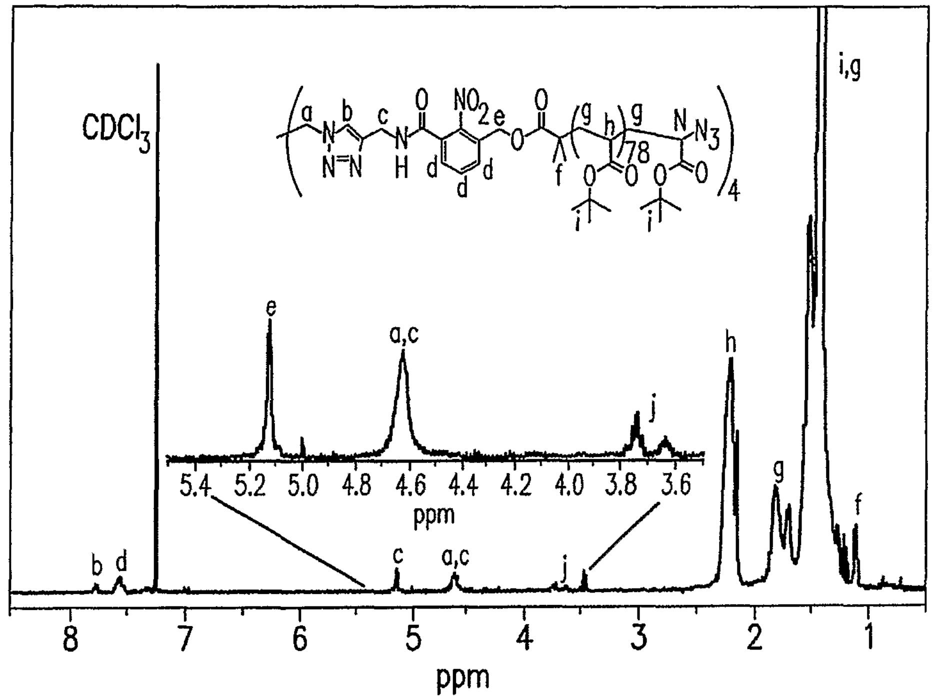

CDCl3
i,g
NO2
N3
78
4
e
a,c
j
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6
ppm
h
g
f
b d
c
8 7 6 5 4 3 2 1
ppm

FIG.11

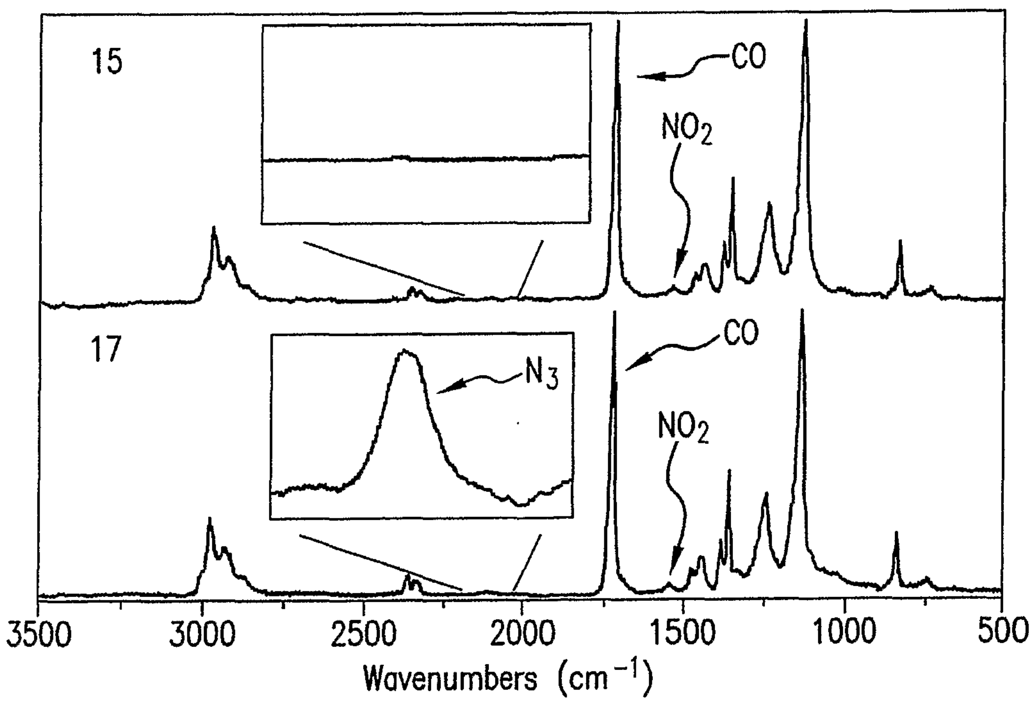

15
CO
NO2
17
N3
CO
NO2
3500 3000 2500 2000 1500 1000 500
Wavenumbers (cm −1)

FIG.12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/41270

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C08F 120/68**(2006.01),**118/02**(2006.01),**4/06**(2006.01),**4/40**(2006.01);**C08G 65/32**(2006.01),**65/04**(2006.01)

USPC: 526/319,318,135,145;525/403,404

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 526/319,318,135,145;525/403,404

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,807,937 (MATYJASZEWSKI et al) 15 September 1998 (15.09.1998), entire document, especially abstract, column 7, lines 1-15, column 8, lines 1-58, column 9, lines 33-50, column 14, lines 45-55, column 17, lines 4-20, column 18, lines 14-55, column 28, lines 47-58, Examples 1-20, 25, claims 1-24	1-16
Y	US 4,722,978 (YU) 02 February 1988 (02.02.1988), abstract, column 4, lines 2-10, 28-45, 48-52, column 6, lines 30-47, column 7, lines 40-64, column 8, lines 5-22, 24-37, column 8, structure 8, column 9, lines 55-65, column 11, lines 10-34, Examples 1-8, claims 1-7	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 April 2007 (16.04.2007)	15 MAY 2007
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer David Wu Telephone No. 571-272-1114 Jean Proctor Paralegal Specialist

INTERNATIONAL SEARCH REPORT	International application No. PCT/US06/41270

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-16

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/41270

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-16, drawn to an α,ω-difunctional macromonomers and a method of preparing of a linear macromonomer.

Group II, claim(s) 17-24, drawn to a linear macromonomer, prepared by the method.

Group III, claim(s) 25-29, drawn to a method of preparing a degradable allyl-terminated linear macromonomer.

Group IV, claim(s) 30-34, drawn to a degradable allyl-terminated linear macromonomer.

Group V, claim(s) 35, drawn to a method of preparing a degradable polymer model network

Group VI, claim(s) 36, drawn to a degradable polymer model network, prepared by the method.

Group VII, claim(s) 37, drawn to a degradable polymer network, comprising a plurality of units.

Group VIII, claim(s) 38-41, drawn to a star polymer macromonomers.

Group IX, claim(s) 42-49, drawn to a method of preparing a star polymer macromonomer.

The inventions listed as Groups I-IX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The special technical feature of Group I claims is the claimed α,ω-difunctional macromonomers and a method of preparing of a linear macromonomer, and this feature is not present in Groups II, VIII and IX.
The only link between the inventions I and III-VII is the claimed α,ω-difunctional macromonomers and a method of preparing of a linear macromonomer, and this link lacks novelty over the teaching of Matyjaszewski et al. (U. S. Patent 5,807,937) and Yu 9U. S. Patent 4,722,978).