Direct Synthesis of α-Azido,ω-hydroxypolyethers by Monomer-Activated Anionic Polymerization

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Received September 10, 2008; Revised Manuscript Received January 28, 2009

ABSTRACT: α-Azido,ω-hydroxypolyethers were prepared directly by monomer-activated anionic polymerization. The introduction of the azido function in the α-position of poly(ethylene oxide), poly(propylene oxide), protected polyglycidol and polyepichlorohydrin was carried out by tetrabutylammonium azide used as initiator. A slight excess of triisobutylaluminum with respect to the ammonium salt ($[i\text{-}Bu_3Al]/[NBu_4N_3] = 1.5$ to 5) was added to trigger the polymerization and get polyethers with controlled molar masses up to 30000 g/mol in a few hours. The terminal hydroxyl function was formed by deactivation of the active polymer ends. The successful and direct preparation of these N_3-functionalized polyethers was proven by NMR spectroscopy, size exclusion chromatography and matrix-assisted laser desorption/ionization time-of-flight characterizations as well as "click" reactions.

Introduction

The precise control of chain end functionalization is essential for the preparation of reactive polymers and for their selective conjugation to organic and inorganic substrates as well as to their end coupling to other polymer chains. The conjugation/coupling reaction should be highly chemoselective, fast and quantitative. It should also be able to preserve the active moieties that often possess reactive functions. Among the various conjugation strategies available, the so-called "click chemistry" based on Huisgen's 1,3-dipolar cycloaddition between an azide and an alkyne function in presence of a copper catalyst[1,2] has been very successfully used for such applications.[3−11] This reaction can be carried out in various media including water, and is becoming more and more attractive.[12] Lutz[13] and Binder,[14] in recent reviews on this topic, have shown that click chemistry can be very efficiently applied to the preparation of linear block copolymers, dendrimers, gels, surface functionalization, as well as to cells and virus modifications in biomolecular engineering.

In particular the conjugation of active molecules such as drugs, peptide sequences and ligands of biological interest onto end-functionalized poly(ethylene glycol) (PEG), or poly(ethylene oxide) (PEO), called "PEGylation", is extensively utilized for biomedical applications,[15,16] thanks to the biocompatibility and specific properties of the poly(ethylene glycol) (poly(ethylene oxide)) chain. The use of click chemistry for such applications is extremely attractive since the cyclic triazole linking unit can be viewed as a biocompatible amino-acid linkage,[17,18] opening a versatile route to new therapeutics.[19−22]

Kataoka reported very recently the synthesis of azido-terminated heterobifunctional PEGs in a multistep process involving (i) the ring-opening polymerization of ethylene oxide initiated by allyl alcohol and (ii) the subsequent transformation of α-allyloxy and ω-hydroxy PEG end groups[23] by a series of chemical reactions. The azide group was introduced by mesylation of the hydroxyl terminus followed by its subsequent substitution with sodium azide.[24,25] Indeed, most of the PEG azidation routes reported in the literature involve so far the chemical modification of previously formed hydroxy terminated PEGs.[26−28]

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Here we report the direct synthesis of α-azido,ω-hydroxy-terminated PEO and of various other α-azido,ω-hydroxypolyethers by direct initiation of oxiranes via their controlled/living anionic polymerization with tetrabutylammonium azide in the presence of a catalytic amount of triisobutylaluminum as activating and regulating agent.

Experimental Section

Materials. Ethylene oxide (99.8%, Fluka) was purified under vacuum over *sec*-BuLi for 30 min, distilled under vacuum, and stored at room temperature (RT) in high-pressure graduated glass tubes. Propylene oxide (POx) (99%, Fluka) was purified over CaH_2, distilled under vacuum, and stored for 15 min in a glass flask equipped with PTFE stopcocks in the presence of $i\text{-}Bu_3Al$ to remove traces of impurities. POx was finally distilled under vacuum and stored under vacuum at RT in graduated glass tubes until use. Epichlorohydrin (ECH) (99%, Aldrich) was purified over CaH_2, transferred under vacuum over $i\text{-}Bu_3Al$ for a few hours and then transferred and stored at 4 °C in glass tubes. Ethoxyethyl glycidyl ether (EEGE) was synthesized by the reaction of 2,3-epoxypropan-1-ol with ethyl vinyl ether catalyzed with *p*-toluene sulfonic acid as described elsewhere.[29] 2,3-Epoxypropan-1-ol (96%, Aldrich) and ethyl vinyl ether (99%, Aldrich) were used as received. EEGE was purified by distillation over CaH_2 and stored in glass tubes at 4 °C. Triisobutylaluminum ($i\text{-}Bu_3Al$, 1 mol/L in toluene, Aldrich), N,N-dimethylformamide (HPLC grade, Scharlau) and *N*,*N*,*N*′,*N*′,*N*′-pentamethyldiethylenetriamine (99%, Aldrich) were used without further purification. Copper bromide(I) (Aldrich, 98%) was washed with a water/acetic acid (1:2) solution then filtered and washed again with methanol before use. 1,7-octadiyne (98%, Aldrich) was diluted with butanol and used without further purification. Phenylacetylene (98%, Aldrich) was distilled and stored at low temperature. Toluene (98%, J.T. Baker) was purified with polystyryllithium seeds. It was distilled under vacuum and then stored in graduated glass tubes under vacuum. NBu_4N_3 (97%, Aldrich) was solubilized into dried toluene. The solution was then stored in graduated glass tubes fitted with PTFE stopcocks at 4 °C.

Procedures. All polymerizations were performed between −30 and +20 °C under argon in a glass reactor equipped with a magnetic stirrer and fitted with PTFE stopcocks. The reactor was flame-dried under vacuum and cooled prior to the introduction of the solvent through connected glass tubes. As example, 1 mL of ethylene oxide ($n_{OE} = 0.02$ mol) is added to 12 mL of toluene. Then 0.27 mL of a toluene solution of NBu_4N_3 ($n_{initiator} = 0.09$ mmol) and 0.14 mL of a triisobutylaluminum solution in toluene ($n_{i\text{-}Bu3Al} = 0.14$ mmol)

10.1021/ma802063s CCC: $40.75
Published on Web 03/10/2009

Table 1. Anionic Polymerization of Various Oxiranes Initiated by Tetrabutylammonium Azide in the Presence of Triisobutylaluminum (Toluene, $t = 20$ °C,[a] Time = 3 h, Conversion = 100%)

run	monomer[b]	[i-Bu_3Al]/[NBu_4N_3]	[monomer] (mol/L)	$\bar{M}_n$(th)[c] (g/mol)	$\bar{M}_n$ (exp)[d] (g/mol)	$\bar{M}_w/\bar{M}_n$
1	EO	1.5	1.5	5000	6000	1.23
2	EO	1.5	1.5	11000	14000	1.24
3	POx	1.5	3.0	10000	12200	1.24
4	POx	2.6	3.0	30000	30800	1.18
5	ECH	2.5	2.0	10000	12500	1.23
6	EEGE	5.0	0.6	10000	9900	1.30
7	EEGE	4.0	0.5	10000	11000	1.25
8	EEGE	4.0	0.5	30000	28000	1.09

[a] Initiation of the polymerization was performed at −30 °C and the temperature of the system let to increase to 20 °C. [b] EO = ethylene oxide, POx = propylene oxide, ECH = epichlorohydrin, EEGE = ethoxyethyl glycidyl ether. [c] Number-average molar mass calculated by ([monomer]/[initiator]) × conversion. [d] Number-average molar mass determined by SEC in tetrahydrofuran using a calibration with poly(ethylene oxide) (PEO) standards for PEO or polystyrene standards for other polyethers.

were then added via a syringe under argon at −30 °C. The reaction is stirred for 4 h. Ethanol (1 mL) was used to stop the reaction. The polymer conversions were determined gravimetrically after complete drying of the polymer under vacuum at 50 °C. Conversion: 100%. Theoretical $\bar{M}_n = 10\,000$ g/mol and SEC $\bar{M}_n = 14\,000$ g/mol. $I_p = 1.24$.

For the "click" reaction, 0.94 g of azido-functionalized PEO ($n_{PEO} = 0.067$ mmol) was solubilized into 7 mL of dimethylformamide (DMF). 0.02 g of CuBr ($n_{CuBr} = 0.134$ mmol), 0.028 mL of pentamethyldiethylenetriamine (PMDETA) ($n_{PMDETA} = 0.0134$ mmol) and 0.22 mL of a solution of octadiyne in toluene ($n_{Octadiyne} = 0.033$ mmol) were then added. The reaction was stirred at room temperature for 48 h. The polymer was recovered by drying under vacuum, redissolved in pure toluene and precipitated in pentane several times at low temperature before analysis. $\bar{M}_n =$ 14 000 g/mol and $I_p = 1.24$ before reaction and $\bar{M}_n = 30\,000$ g/mol and $I_p = 1.20$ after reaction.

Analysis. Polymer molar masses were determined by size exclusion chromatography (SEC) at 40 °C using tetrahydrofuran as eluent on a PL GPC50 apparatus with three TSK columns G4000HXL (particles of 5 μm, pore size of 200Å and exclusion limit of 400 000 Da), G3000HXL (particles of 5 μm, pore size of 75 Å and exclusion limit of 60 000 Da), G2000HXL (particles of 5 μm, pore size of 20 Å and exclusion limit of 10 000 Da) at an elution rate of 1 mL/min. Polystyrene or poly(ethylene oxide) were used as standards.

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR measurements of PEO, PPOx, PECH and PEEGE were perfomed on a Brüker Avance 400 spectrometer, in $CDCl_3$ at room temperature.

• N_3−PEO−H.^{1}H: CH_2−O, 3.64 ppm. ^{13}C: −CH_2−O−, 70.55 ppm; CH_2−OH, 61.57 ppm; CH_2−CH_2− OH, 72.84 ppm; CH_2−N_3, 50.72 ppm.

• PhAcetylene−PEO−H. ^{1}H,C_6H_5(1)−C≡CH(2)− N_3−(CH_2-(3)−CH_2(4)−O)$_n$: 1, 7.82−7.80 ppm, 7.42−7.38 and 7.30 ppm; 2, 8.01 ppm; 3 and 4, 3.64 ppm.

• N_3−PPOx−H. ^{1}H: CH_2−O and CH−O, 3.3−3.8 ppm; −CH_3, 1.13 ppm.

• N_3−PEEGE−H. ^{1}H,O−CH_2(1)−CH(2)[CH_2(3)−O−CH(4)−CH_3(5)−O−CH_2(6)−CH_3(7)]−O: 1, 2, 3, 6, 3.35−3.75 ppm; 4, quadruplet, 4.75 ppm; 5, 1.27 ppm; 7, 1.17 ppm.

• N_3−PECH−H. ^{1}H: O−CH_2−CH(CH_2−Cl)−O, between 3.35 and 3.75 ppm.

Matrix-assisted laser desorption/ionization time-of-flight (MALDI−TOF) spectra were performed on a Voyager mass spectrometer (Applied Biosystems). The instrument was equipped with a pulsed N_2 laser (337 nm) and a time-delayed extracted ion source. Spectra were recorded in the positive-ion mode using the reflectron and with an accelerating voltage of 20 kV. Samples were dissolved in CH_2Cl_2 at 10 mg/mL. The DCTB matrix (*trans*-2-(3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene)malononitrile) solution was prepared by dissolving 10 mg in 1 mL of CH_2Cl_2. A MeOH solution of cationization agent (NaI, 10 mg/mL) was also prepared. The solutions were combined in a 10:1:1 volume ratio of matrix to sample to cationization agent. 1−2 μL of the obtained solution was deposited onto the sample target and vacuum-dried.

Results and Discussion

In recent reports we have shown that simple initiating systems obtained by the combination of triisobutylaluminum (i-Bu_3Al) with either alkali metal alkoxides or tetraalkylammonium salts (NR_4X), yield a rapid and well-controlled polymerization of propylene oxide.[30−32] Although alkali metal alkoxides (K, Na) associated to i-Bu_3Al afford a good control of the poly(propylene oxide) (PPOx) molar masses in the low to medium molar mass range, tetralkylammonium halide (Br, Cl) systems yield a better control of the initiation and of the propagation steps with a very limited contribution of side initiation and of transfer reactions.[30−32] This allowed the direct preparation of end-functional polyethers of controlled molar masses, up to 100000 g/mol, with an halide in α-position and, after termination of the polymerization by protonic species (alcohol), an ω-hydroxyl end.

Providing that other tetraalkylammonium based initiating systems associated to trialkylaluminum would also allow selective initiation and propagation reactions of oxiranes, the direct introduction of various functional α-end groups into polyether chains using several tetraalkylammonium salts was further explored. As indicated above, one functional group of particular interest is the azide one. With the aim of introducing directly this function in α-position of PEO and of other polyether chains, the ring opening polymerization of a series of oxiranes initiated by tetrabutylammonium azide (NBu_4N_3) in the presence of triisobutylaluminum as activator was studied.

Some representative polymerization results obtained respectively with ethylene oxide, propylene oxide, epichlorohydrin and ethoxyethyl glycidyl ether an hydroxyl-protected glycidol, are indicated in Table 1. To reduce the initial polymerization rate, initiation was performed at low temperature (−30 °C). Then after a few minutes the temperature of the vessel was allowed to slowly rise up to 20 °C. In these conditions the formation of narrowly dispersed PEO and of other polyethers with experimental molar masses in good agreement with theoretical values, calculated assuming one chain formed per NBu_4N_3 initiator molecule, proceeds readily and quantitatively at room temperature, even in the case of the chlorinated monomer. As previously reported for the polymerization of propylene oxide with $NOct_4Br/i$-Bu_3Al,[32] a monomer activated anionic polymerization can be postulated with NBu_4N_3/i-Bu_3Al. The reaction mechanism involves a complexation of the propagating active species with one equivalent of i-Bu_3Al and a strong nucleophilic activation of the oxirane ring via complexation with the remaining i-Bu_3Al molecules (see Scheme 1). After insertion of the activated monomer in the growing chain, the Lewis acid is released, becoming able again to complex and activate another monomer molecule.

The presence of an azido group at the chain head (α-position) was first checked by ^{13}C NMR spectroscopy in the case of PEO samples. As shown in Figure 1, the carbon bearing the azido function appears at 50.7 ppm, as already indicated by Kataoka,[23]

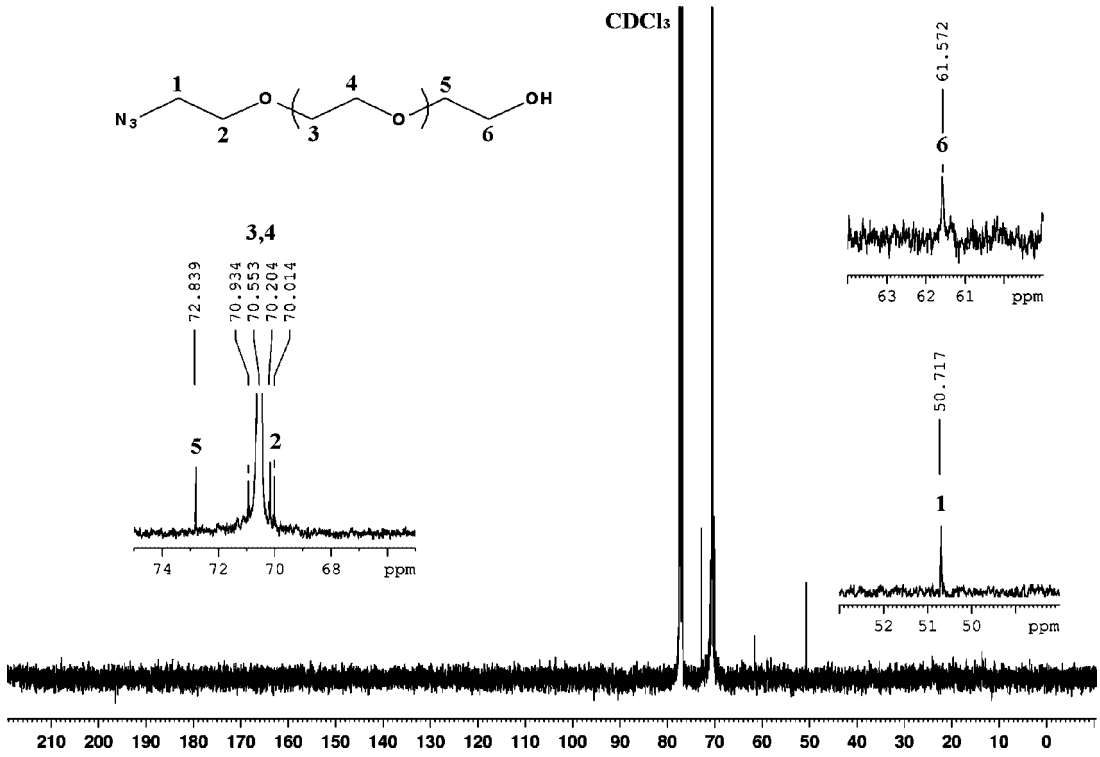
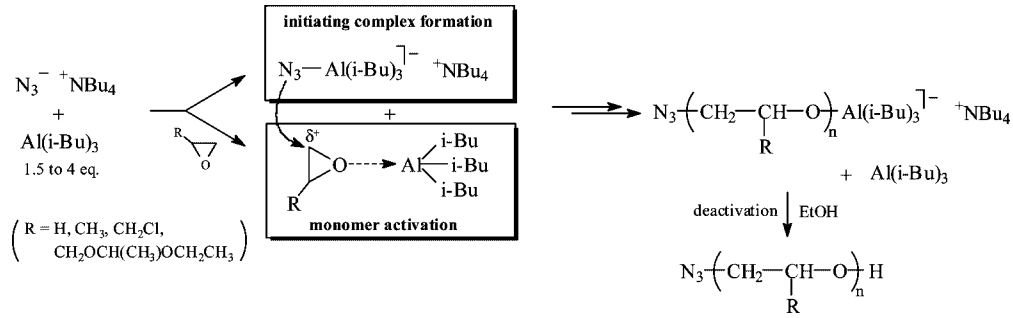


Figure 1. ^{13}C NMR spectrum in $CDCl_3$ of $N_3-PEO-OH$ (run 1, Table 1) obtained in presence of $NBu_4N_3/i\text{-}Bu_3Al$ as initiating system.

Scheme 1. Polymerization Mechanism via a Monomer Activation of Epoxides



whereas the one carrying the terminal hydroxyl is located at 61.6 ppm. The main signal of the PEO methylene groups observed at 70.5 ppm is surrounded by other small peaks at 72.8 ppm and between 70.0−71.0 ppm, which can be attributed to CH_2 groups near the chain end functions, (see Figure 1).

To get complementary information, a $N_3-PEO-OH$ ($\bar{M}_n$ = 6000 g/mol, I_p = 1.23) was analyzed by MALDI−TOF spectrometry to further identify the chain termini and elucidate on the selectivity of the azide initiation reaction and the possible contribution of transfer and termination reactions. Two main PEO populations, P_1 and P_2, are observed, (see Figure 2). The peak molar masses of the main P_1 peak series ($P_1n = M_{Na}^+ + nM_{EO} + M_H + M_N$) ($P_1$ = 2152.5 for n = 48) agrees with the expected $N_3-PEO-OH$ polymer structure taking into account a loss of N_2 due to azide fragmentation under the high laser power used during MALDI−TOF analysis, as already noticed by Kataoka.[23] The P_2 peak series is indeed more complex and apparently composed both by the targeted $N_3-PEO-OH$ chains ($P_{2a}n = M_{Na}^+ + nM_{EO} + M_H + M_{N3}$) ($P_{2a}$ = 2136.5 for n = 47) and by H−PEO−OH chains with an hydrogen at the chain head ($P_{2b}(n+1) = M_{Na}^+ + (n+1)M_{EO} + 2M_H$) ($P_{2b}$ = 2139.5 for n = 48) whose molar masses only very slightly differ and are overlapping on the spectrum. The population with a hydrogen in α-position likely results from a side hydride initiation of the EO polymerization, as already reported for some other initiating systems.[30−32]

In order to get further information on the selectivity of tetralkylammonium azide initiation, a similar MALDI−TOF analysis was performed on a protected azido polyglycidol ($N_3-PEEGE-OH$) synthesized using the same approach. The spectrum (enlarged region around 3000 g/mol) is presented in Figure 3. It shows five different peak series corresponding to distinct X-PEEGE−OH populations, all of them possessing an ω-hydroxyl end but carrying different head groups, i.e., $P_n = M_{Na}^+ + nM_{EEGE} + M_H + M_x$. The two main populations of P_1 ($P_1n = M_{Na}^+ + nM_{EEGE} + M_{N3} + M_H$) ($P_1$ = 2988.16 for n = 20) and P_2 ($P_2n = M_{Na}^+ + nM_{EEGE} + M_H + M_N$) ($P_2$ = 2962.51 for n = 20) exhibit peak molar masses in agreement with the formation of $N_3-PEEGE-OH$ chains, the presence of P_2 being explained again by the fragmentation of N_3 with loss of N_2 during MALDI−TOF analysis. As for P_1 and P_2 populations P_1' and P_2' exhibit peak molar masses which are also consistent with $N_3-PEEGE-OH$ chains (respectively with N_3- and N− on the spectrum), which have lost a side hydroxyl protective group (-$C(CH_3)OCH_2CH_3$, M = 72 g/mol) of one of their EEGE units ($P_1' = P_1 - 72$ and $P_2' = P_2 - 72$). The last population observed P_3 ($P_3n = M_{Na}^+ + nM_{EEGE} + 2M_H$) ($P_3$ = 2947.19 for n = 20) corresponds to chains with a hydrogen in α-position

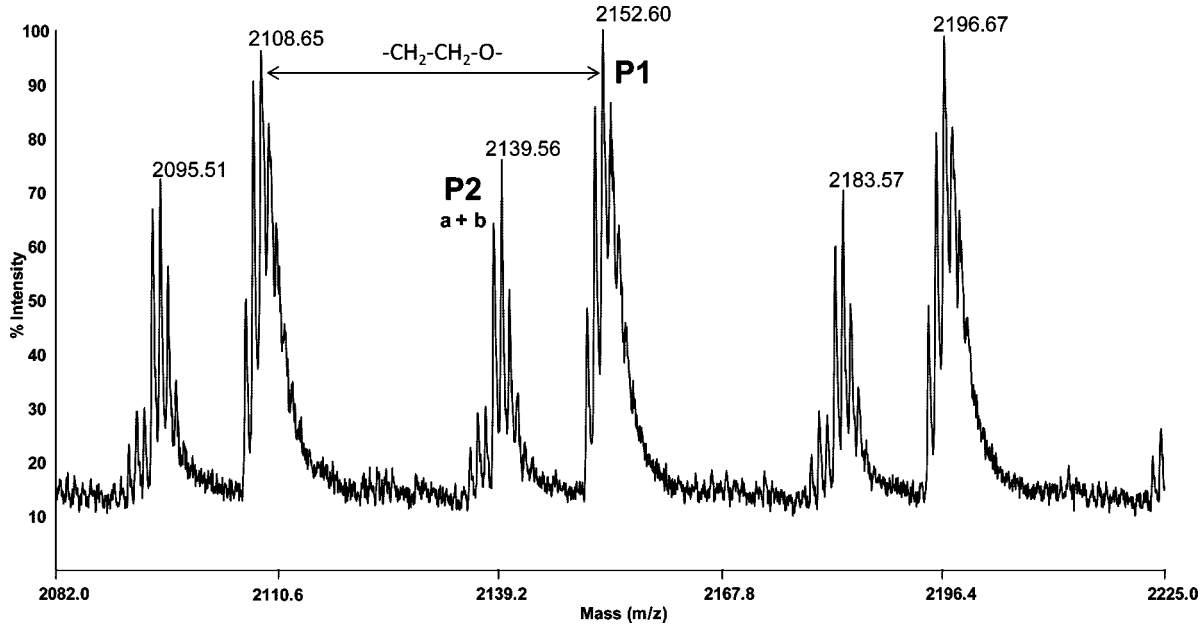


Figure 2. Enlarged region of the matrix-assisted laser desorption/ionization time-of-flight mass spectrum (*trans*-2-(3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene)malononitrile as matrix and NaI as cationisation agent) of $N_3-PEO-OH$ (run 1, Table 1) synthesized with NBu_4N_3/*i*-Bu_3Al.

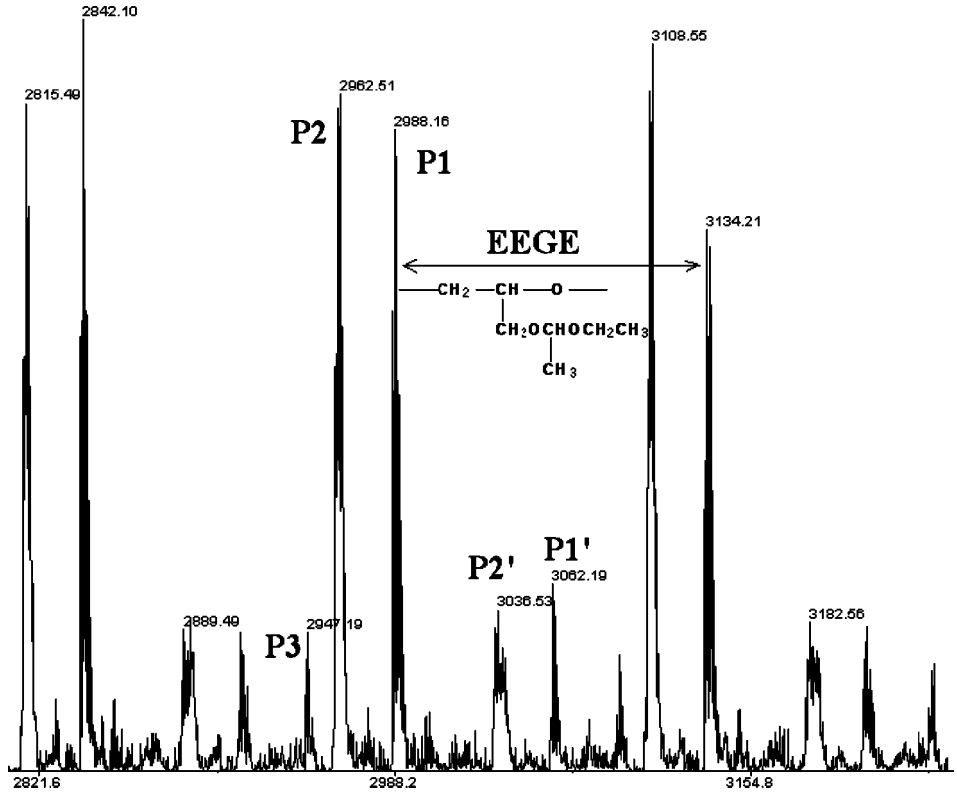


Figure 3. Enlarged region of the matrix-assisted laser desorption/ionization time-of-flight mass spectrum (*trans*-2-(3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene)malononitrile as matrix and NaI as cationisation agent) of poly(ethoxyethyl glycidyl ether) (PEEGE) synthesized with NBu_4N_3/*i*-Bu_3Al (M_n = 9900 g/mol, I_p = 1.30, Table 1).

which result as already indicated for PEO from a side hydride initiation.[30−32] Although it cannot be precisely quantified the amount of H−PEEGE−OH chains resulting from this side initiation process appears almost negligible as compared to the azido-functionalized ones.

To further confirm the almost quantitative formation of azido-polyethers, a series of coupling reactions using the "click chemistry" approach was carried out on various polyethers prepared with NBu_4N_3/*i*-Bu_3Al as initiating system.

As a first example, $N_3-PEO-OH$ was reacted with phenyl acetylene in excess since the aromatic compound anchored to PEO chains can be easily detected using SEC equipped with a UV−visible detector. The observed signal at the polymer elution time confirms the presence of the phenyl group bonded to the polymer. The ^1H NMR analysis of the phenyl acetylene modified PEO (Figure 4) shows specific resonances at 4.6 ppm and 8.1 ppm that can be attributed respectively to $-CH_2-N-$ at the PEO end and to $=CH-N-$ of the imidazole group while

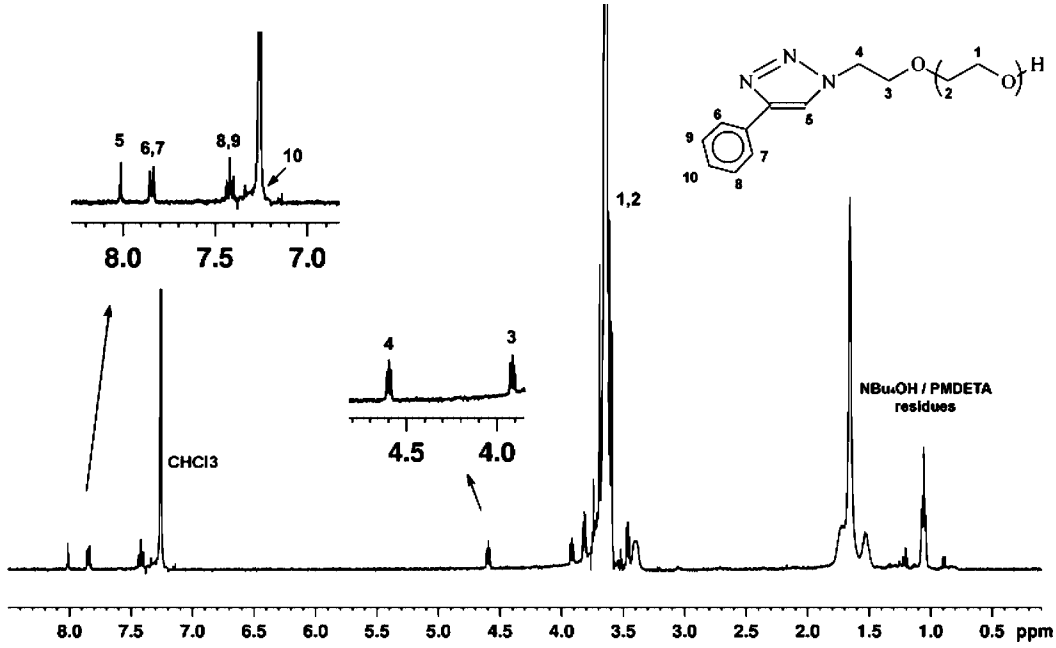


Figure 4. ^{1}H NMR spectrum in $CDCl_3$ of N_3-PEO ($\bar{M}_n$= 7400 g/mol, I_p = 1.24) after reaction with phenylacetylene in presence of CuBr/PMDETA.

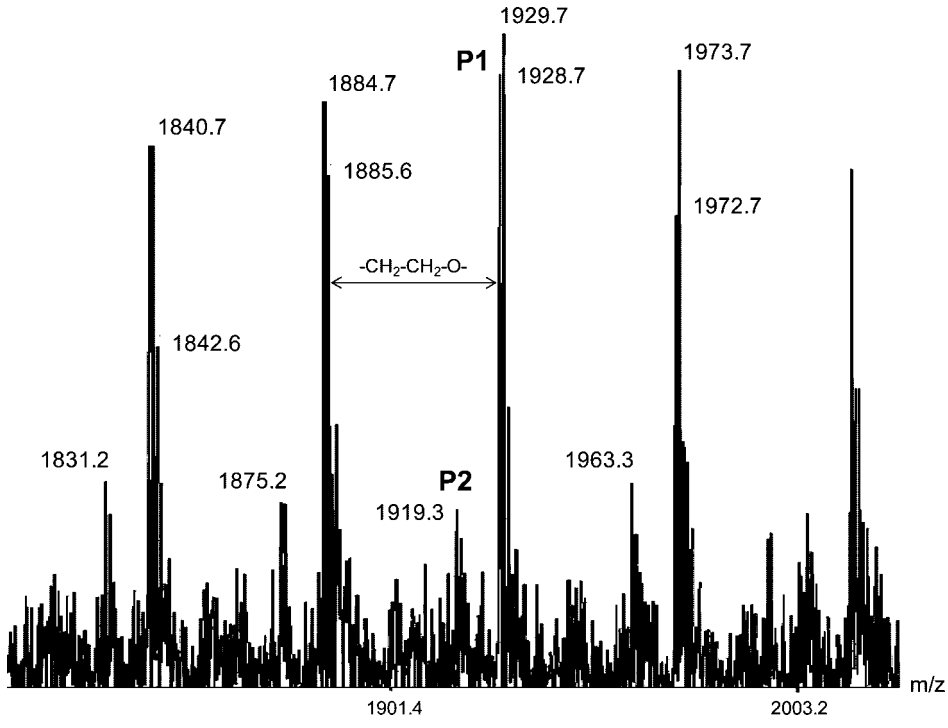


Figure 5. Enlarged region of the matrix-assisted laser desorption/ionization time-of-flight mass spectrum (*trans*-2-(3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene)malononitrile as matrix and NaI as cationisation agent) of a $N_3-PEO-OH$ reacted with phenylacetylene in presence of CuBr/PMDETA.

the aromatic protons of phenyl triazole are located between 7.2 and 8.1 ppm. On the basis of the relative intensity of phenyl protons of the triazole group and PEO methylene groups at 3.6 ppm on one hand and on the PEO molar mass determined by SEC on the other hand, the coupling efficiency can be estimated to about 95%, in agreement with an almost quantitative α-end azide functionalization of PEO−OH chains. A complementary analysis of this phenylacetylene-reacted PEO was also carried out by MALDI−TOF and confirmed the highly azido functionalization by the initiation step (Figure 5). Indeed, it showed one main population P_1 ($P_1n = M_{Na}^+ + nM_{EO} + M_H + M_{C8H6N3}$) ($P_1$ = 1929.7 for n = 40) which agrees with the expected $N_3-PEO-OH$ polymer structure reacted with phenylacetylene. The P_2 peak series, which appear in a low proportion, corresponds to a poly(ethylene oxide) with a hydrogen at the chain head (H−PEO−OH) ($P_2n = M_{Na}^+ + nM_{EO} + 2M_H$) ($P_2$ = 1919.3 for n = 43) coming from the transfer reaction to *i*-Bu_3Al.

Reaction of α-azido polyether chains onto octadiyne that should yield chain-to-chain coupling was also investigated at the 1:1 stoichiometry between alkyne functions and PEO chains to demonstrate the selectivity of our azide functionalization approach. As shown by SEC analysis for $N_3-PEO-OH$ ($\bar{M}_n$ = 14000 g/mol), Figure 6, the "click" reaction leads to an increase of the PEO molar mass by a factor of about two ($\bar{M}_n$

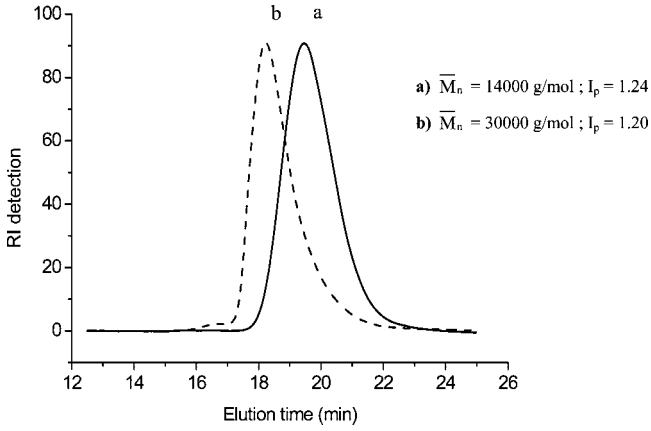


Figure 6. Size exclusion chromatography traces of (a) an α-N_3,ω-OH−PEO (see Table 1) and (b) of the corresponding polymer after reaction with octadiyne in presence of CuBr/PMDETA in dimethylformamide.

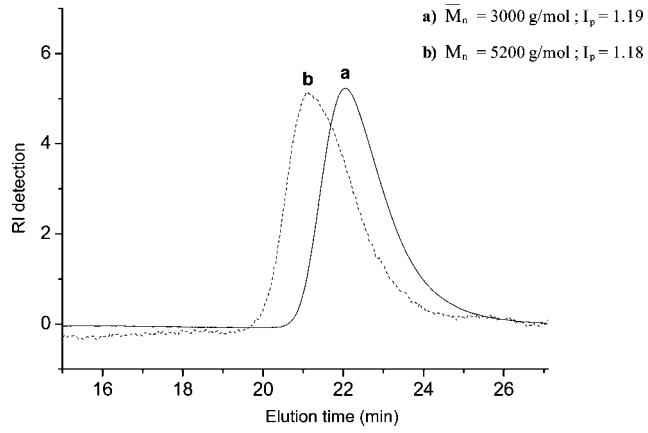


Figure 7. Size exclusion chromatography traces of (a) an α-N_3,ω-OH−PPOx (see Table 2 run 2) and (b) of the corresponding polymer after reaction with octadiyne in presence of CuBr/PMDETA in dimethylformamide.

Table 2. Coupling Reaction of α-N_3 Polyethers with Octadiyne by "Click" Chemistry

polymer	$\bar{M}_n$(exp) precursor (g/mol)	$\bar{M}_w$(exp) final (g/mol)	$\bar{M}_w/\bar{M}_n$
N_3−PEO−OH	14000	30000	1.20
N_3−PPOx−OH	3000	5200	1.18
N_3−PEEGE−OH	11000	20000	1.60
N_3−PECH−OH	12500	22000	1.54

= 30000 g/mol). The absence of any detectable peak or shoulder at lower molar mass tends to confirm the efficiency of the reaction and the high functionality of the PEO chains. Only a slight and low molar mass tail can be observed and explained by a few noncoupled chains due to some residual transfer to a hydride from *i*-Bu_3Al which still remains limited.

Very similar results were obtained with poly(propylene oxide) (N_3−PPOx−OH) (Figure 7), hydroxyl-protected polyglycidol (N_3−PEEGE−OH) and polyepichlorohydrin (N_3−PECH−OH), all the coupled polyethers having terminal hydroxyl functions at each chain end. Typical data are indicated in Table 2. These results show the relatively broad scope of this chain end α-azido functionalization of polyethers through initiation of the anionic polymerization of the corresponding oxirane monomers by tetraalkylammonium azide in the presence of triisobutylaluminum.

Conclusions

The direct synthesis of a broad series of heterofunctional polyethers bearing an azide and an hydroxyl function at the chain termini, including PEO broadly used for PEGylation reactions, have been prepared with a very good functionalization efficiency by direct initiation of the living/controlled polymerization of the corresponding oxirane monomers by tetralkylammonium azide, in the presence of trialkylaluminum as activator. Depending on the nature of the lateral group associated to the polyether chain, these functional polymers may exhibit a large scope of properties, which make them of great interest as polymeric synthons, in particular for "click" chemistry.

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MA802063S