Preparation of α,ω-Telechelic Hexyl Acrylate Polymers with —OH, —COOH, and —NH_2 Functional Groups by RAFT

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ABSTRACT: The design, synthesis, and use of two new, stable, functionalized chain transfer agents (CTA's) containing OH and amine end groups for the RAFT polymerization is reported: 2-hydroxyethoxy-carbonylphenylmethyl dithiobenzoate and 2-(2-(*tert*-butoxycarbonyl)ethylamino)-2-oxo-1-phenylethyl benzodithioate, respectively. The RAFT polymerization of *n*-hexyl acrylate (HA) using those CTA's, were compared to several other functionalized dithiobenzoate esters reported in the literature containing COOH and Ester groups. The performances of the dithiobenzoates were compared in terms of kinetics and molecular weight distribution control. Good control in polymerization of *n*-hexyl acrylate with a linear increase of M_n with conversion mantaining polydispersity indices (PDI) below 1.1 was obtained by use of the new functionalized CTA's developed and also by use of some other CTA's tested, to produce well-defined linear polymers with one specific chain-end functionality: —OH, —COOH or Amine. Using a post-polymerization reaction with functionalized azocompounds in a 5 to 1 ratio, α,ω-telechelic polymers, with —OH or —COOH as functional group at the second end were obtained. By using this synthetic strategy α,ω-homotelechelic and heterotelechelic polymers were readily prepared. The chemical availability of functional end-groups in the telechelics was demonstrated by reaction with methacrylic anhydride. © 2010 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 48: 3033–3051, 2010

KEYWORDS: α,ω-telechelics; acrylates; dithiobenzoates; dithioesters; reversible addition fragmentation chain transfer; synthesis; telechelics

INTRODUCTION Reversible addition-fragmentation chain transfer (RAFT) polymerization has been in the focus of many research groups. Numerous publications have been reported on the mechanism, parameters effecting performance or the application of method of synthesis to the preparation of well-defined macromolecular structures.[1,2] RAFT polymerization has been one of the most promising recent advances in controlled free-radical polymerization because of its compatibility with a wide range of monomers and its versatility; all this makes RAFT polymerization an ideal method for synthesis of polymeric biomaterials, such as drug delivery systems, implants, contact lenses, vascular grafts, dental materials, and parts of artificial organs, which due to strict regulations imposed on all pharmaceuticals and other health related products have to be of well-controlled molecular weight and high purity beside other specific properties.[3–5] As the popularity of the method has grown, more new RAFT agents have been synthesized and used for polymerization of various monomers. As a consequence of the RAFT process, nearly all polymer chains bear a thiocarbonylthio group at one chain end and the R substituent at the other end. An additional feature of this technique is the possibility to design polymeric chains with specific chain-end functionalities. This end-group functionalization enables the subsequent synthesis of complex architectures starting with telechelic polymers (telechelics). Telechelics are polymers containing reactive groups on one end (semitelechelics) or both ends (α,ω-telechelics) and are widely used in colloidal applications, catalysis, drug delivery systems, surface modification, as compatiblizers, for block copolymer synthesis, preparation of polymer networks, as crosslinking agents, in nanotechnology applications and for conjugation with bioactive molecules.[6–9] There are different techniques to prepare telechelic polymers via a variety of reaction mechanisms of different complexity due to functional groups present in reacting compounds and due to inherent steric effects of reactions with macromolecules. Lai et al.[10] prepared α,ω-telechelic polymers in one step using symmetrical trithiocarbonates. One limitation of this technique is the poor results with methacrylic monomers, due to the relatively low stability of the leaving group compared to the one of a methacrylic radical. Haddleton et al.[11] reported the use of molecules bearing a hydroxyl group that can be transformed into initiators for copper mediated ATRP living radical polymerization. This strategy lead to the synthesis of block copolymers including blocks that cannot be formed through conventional free

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radical polymerization; to the synthesis of polymers showing specific functionalities at their chain-ends, to star polymers, etc. Other common pathway to introduce functional groups into polymers is the use of bifunctional initiators in conventional free radical polymerization. A variety of bifunctional initiators with carboxyl, hydroxyl, nitrile, and isocyanate groups have been used for this purposes. However, the number of introduced functional groups is very difficult to control in addition to the fact that polydispersity is normally very high. An alternative strategy has been to introduce by synthesis different functional groups in the leaving/reinitiating R group of chain transfer agents used for RAFT-polymerization. In this way, both polydispersity and the number of functional groups introduced (normally one) are controlled. A variety of end-functionalized semitelechelics can be obtained using this strategy; however for specific applications, the thiocarbonyl-thio moiety introduced by RAFT, needs to be removed. For the removal of the thiocarbonyl-thio moiety several strategies are under investigation, this include: aminolysis,[12–16] thermal treatment,[17–20] reaction with a functionalized azoinitiator in excess,[21] reaction with oxidizing agents[22,23] and very recently, a reaction with a combination of azoinitiator and a peroxide for styrenic and acrylic polymers.[24] A disadvantage of aminolysis and thermal treatment methods is the formation of thermal labile disulfide bonds as side reaction resulting in increasing the molecular weight by chain-chain coupling.[25] To overcome this problem, several groups have reported an approach employing aminolysis of the thiocarbonyl-thio end-group while simultaneously reacting the resulting thiol with other compounds. Theato et al.[26] reports aminolysis in the presence of *S*-3-butynyl methane thiosulfonate leading to acetylene functionalized polymers for further use in "click chemistry." This method is of advantage compared with conjugations with functional maleimides, where isolation of terminal thiols is often required. Other approach is the aminolysis of the thiocarbonyl-thio end-group in the presence of pyridyldisulfide-bearing[27] or ene-bearing compounds,[28–30] leading to simultaneous protection/functionalization of the created thiols. This methodology exploits thiol-ene chemistry with a range of enes and yields successfully conjugates to build macromonomers and more complex polymer architectures.[31] Perrier et al.[21] proposed a reaction that leads simultaneously to the full removal of the thiocarbonyl thio end group from the polymeric chains and introduction of chain-end functionalities on the polymers. The technique allows functionalized polymers to be prepared directly from a difunctional chain transfer agent with only one postpolymerization reaction using an excess of azoinitiator. The strategy involving azoinitiators is reported to result in side reactions including disproportionation of the polymer chains when only a slight excess of azocompound is used, therefore a large excess (20:1) is suggested,[20] which is impractical for several applications. Other method for the conversion of polymers capped by thiocarbonyl thio group into hydroxy terminated polymers was reported by Barner-Kowollik et al.[32] The reaction involves dithioester-capped polymers and azoinitiator in tetrahydrofuran yielding hydroperoxide functionalities that are efficiently reduced to hydroxy end group. Telechelic polymers with primary amine end-groups have the advantage with respect to polymers with other reactive functionality (hydroxy or carboxy) because of their greater reactivity.[2] Therefore there has been a number of previous reports aiming the synthesis of polymers with primary amine end-groups.[33–39] Either the amino group is obtained after reaction of a semitelechelic polymer containing azido[38] or alquene[36] end-groups with amine functionalized reagents; or the amino functionality was introduced during conventional polymerization by use of amine functionalized chain transfer agents[33] or by means of "living" radical polymerization as a phthalimido group by ATRP[35] or by RAFT[39] followed by hydrazinolysis to yield the desired free amino end group. For the present report two new —OH and amine functionalized dithioesters were developed and their ability for the RAFT polymerization of *n*-hexyl acrylate (HA) as a model monomer were tested and compared to other frequently used RAFT agents containing functional groups. The capability of these new dithioesters for controlled polymerization of styrene and methacrylates is currently under investigation in our laboratory and is subject of a future report. In this study, the amine functionality is introduced by RAFT as *t*-BOC protected group which can be easily removed afterward by use of trifluoroacetic acid as reported for ATRP polymerization.[40] Furthermore, an in-depth study on the postpolymerization reaction of semitelechelic polyHA with functionalized azocompounds is reported, aiming to minimize the azoexcess and to demonstrate the chemical availability of the introduced end-groups in α,ω-telechelics for further transformations.

EXPERIMENTAL

Reagents and Methods

Unless otherwise stated, all materials were purchased from commercial sources and used without further purification. All air and moisture sensitive compounds were manipulated using standard Schlenk techniques under a dry nitrogen atmosphere. Solvents (Fermont, México) were distilled prior to use; *n*-hexyl acrylate (HA, Aldrich) was purified by passing through an inhibitor remover column for HQ (Aldrich). 2-Bromoacetic acid, carbon disulfide, phenylmagnesium bromide (3.0 M solution in diethyl ether), α-bromophenyl acetic acid, potassium ferricyanide (III), benzyl chloride, were purchased from Aldrich. Thionyl chloride and sodium thiosulfate were purchased from Aldrich. 4,4′-Azobis(4-cyanovaleric acid) (azo-8, Aldrich, 75%) was recrystallized from methanol, and 4,4′-azobis(4-cyanopentanol) was prepared according to the method described by Clouet et al.[41] 5-Hydroxy-2-pentanone, sodium cyanide, *tert*-butyl 2-aminoethylcarbamate was prepared according to a published procedure.[42] Gel permeation chromatography (GPC) was performed on a Varian 9002 chromatograph equipped with two mixed-bead columns in series (Phenogel 5 linear and Phenolgel 10 linear) and two detectors: refractive index (Varian RI-4) and a triangle light scattering detector (MINI-DAWN, Wyatt). The measurements were performed in THF at 35 °C and monodisperse

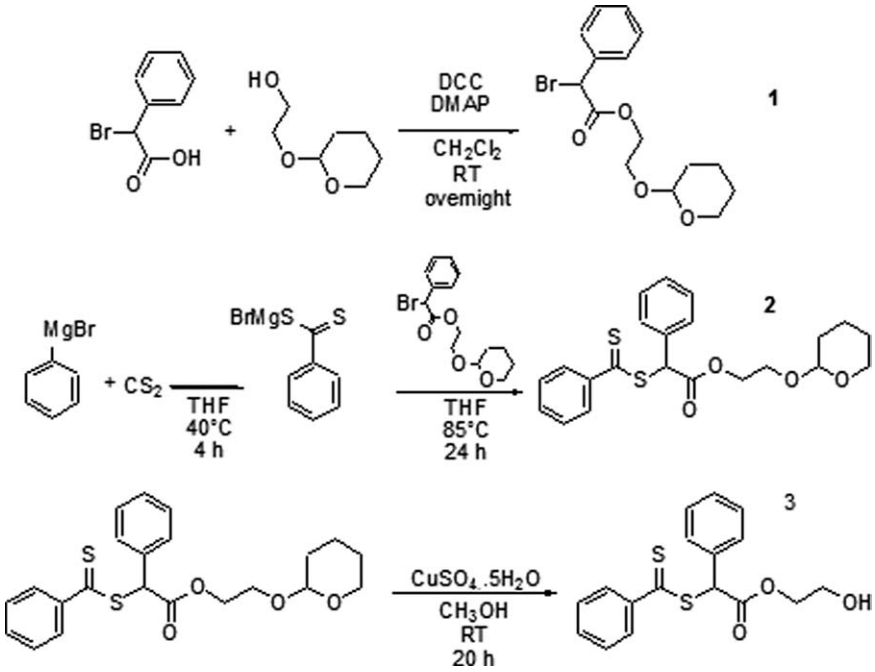


FIGURE 1 Synthetic scheme for the preparation of 2-hydroxyethoxy-carbonylphenylmethyl dithiobenzoate (CTA-2).

polystyrene standards were used for calibration. Reported dn/dc values for poly(n-butylacrylate) in THF[43] were used for the molecular weight evaluations of polyHA. Mass spectroscopy (MS) mode (20 eV) was performed on a Hewlett–Packard 5989A equipment. ^{1}H (500 or 200 MHz) NMR spectra were recorded on a Varian Inova 500 (500 MHz) or on a Varian Gemini (200 MHz) spectrometers and are reported in ppm using TMS as internal standard. Data are reported as: (b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dt, double triplet and combinations like bs, broad singlet, etc.; coupling constant(s) in Hz, integration). ^{13}C (125 or 50 MHz) NMR spectra were recorded on a Varian Inova 500 (125 MHz) or on a Varian Gemini (50 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane (TMS), with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). Fourier transform infrared spectroscopy (FTIR) was performed on a Perking Elmer, 1600 Series FTIR. UV spectroscopy was performed on a Varian CARY 100. Elemental analysis were performed by NuMega Labs in San Diego, CA.

SYNTHESIS OF CTA'S

Seven different functionalized chain transfer agents (CTA's) were synthesized for this investigation: 2-cyano-5-hydroxypentan-2-yl benzodithioate (CTA-1), 2-hydroxyethoxy-carbonylphenylmethyl dithiobenzoate (CTA-2), 4-cyanopentanoic acid dithiobenzoate (CTA-3), 2-phenyl-2-(phenylcarbonothioylthio)acetic acid (CTA-4), 2-(phenylcarbonothioylthio)-acetic acid (CTA-5), 2-(2-(*tert*-butoxycarbonyl)ethylamino)-2-oxo-1-phenylethyl benzodithioate (CTA-6) and 2-phenyl-2-(phenylcarbonothioylthio)acetate (CTA-7). CTA's 2 and 6 are reported for the first time (below) while the synthesis of the other five CTA's is adapted from literature reports and is described in detail with spectroscopic information as Supporting Information:

Synthesis of 2-Hydroxyethoxy-carbonylphenylmethyl Dithiobenzoate

The preparation of this CTA-2 was conceived as a three steps method shown in Figure 1.

Synthesis of 2-(Tetrahydro-2H-pyran-2-yloxy) Ethyl α-Bromophenylacetate

In a 500-mL-round-bottom glass and magnetic stirring, a solution of α-bromophenylacetic acid (10.97 g, 50 mmol) in anhydrous CH_2Cl_2 (100 mL) was added. DMAP (0.61 g, 5 mmol) and 2-(Tetrahydro-2H-pyran-2-yloxy) ethanol (8.05 g, 55 mmol) were added. Then the reaction mixture was cooled down to 0 °C and DCC (11.35 g, 55 mmol) was added dropwise. The solution stirred for 10 min at 0 °C and then overnight at RT. Precipitated urea was then filtered off and the filtrate was concentrated removing the solvent under vacuum. The residue was dissolved in ethyl ether (40 mL) and filtered again. The solvent was removed by evaporating and the ester purified by flash chromatography on silica gel (70–230 mesh), using hexanes/ethyl acetate (9:1)v as eluent. The product was a colorless oil (16.5 g, yield 96%).

FTIR (Film, cm^{-1}): 3064, 3032 (Aromatic C—H stretch), 2944, 2871 (Aliphatic C—H stretch), 1748 (C=O Stretch); 1496 (C=C ring stretch), 1454, 1439, 1384, 1352, 1279, 1258, 1212, 1138, 1128 (Asymmetric C—O—C stretch). ^{1}H NMR (200 MHz, $CDCl_3$, δ in ppm): 7.54–7.6 (m, 2H, Ar-*H*), 7.3–7.40 (m, 3H, Ar-*H*), 5.41 (s, 1H, C*H*), 4.6 (dt, J = 8.4, 3.4 Hz, 1H, O-C*H*-O), 4.37 (m, 2H, —COOCH_2—), 3.91–3.47 (m, 4H, CH_2 of THP), 1.4–1.9 (complex m, 6H, 3 × CH_2 of THP). ^{13}C NMR (50 MHz, $CDCl_3$, δ in ppm): 168.63 (*C*=O), 136.18, 136.16, 129.66, 129.19, 129.09 (*C* of Ar), 99.01 (O—*C*H—O), 65.90 (COO*C*H$_2$), 65.08 (O—*C*H$_2$ of THP), 62.24

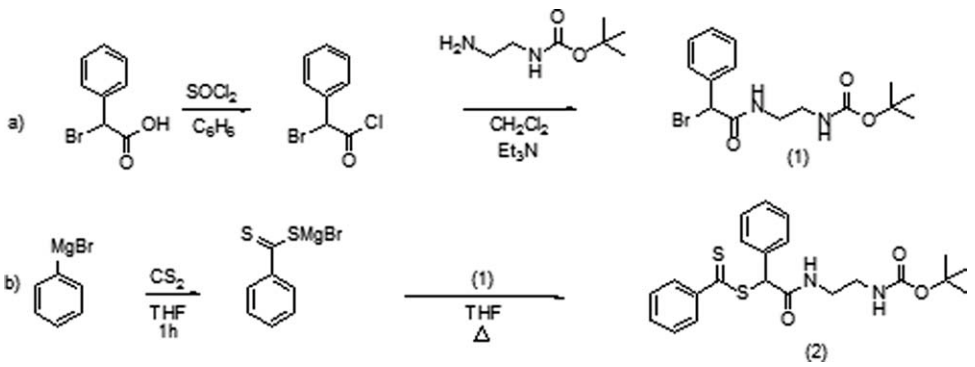


FIGURE 2 Synthetic scheme for the preparation of 2-(2-(*tert*-butoxycarbonyl)ethylamino)-2-oxo-1-phenylethyl benzodithioate (CTA-6).

(CH_2—O—CH), 47.11 (S—*C*H—(C=O)), 30.72, 25.74, 19.45 (3 × *C*H_2 of THP).

Synthesis of 2-(Tetrahydro-2H-pyran-2-yloxy) Ethoxy-carbonylphenylmethyl Dithiobenzoate

In a 250-mL-three-necked round bottom glass equipped with condenser, gas inlet, and magnetic stirring, a solution of phenyl magnesium bromide (13.24 mL, 40 mmol) in THF (3.0 M) was added to a flask containing dry THF (100 mL). The solution was cooled to 0 °C and then carbon disulfide (3.02 g, 40 mmol) was added dropwise. After 4 h, 2-(tetrahydro-2H-pyran-2-yloxy) ethyl α-bromophenylacetate (BrEOTHP) (15 g, 44 mmol) was added to the reaction mixture. The temperature was rise to 85 °C and maintained for 24 h. Then the reaction mixture was cooled down and water (50 mL) was added. The organic product was extracted with ethyl ether (3 × 50 mL) and dried with anhydrous magnesium sulfate, then concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (70–230 mesh) with hexanes:ethyl acetate (7:3)v, obtaining a red oil (14.49 g, 88% yield).

FTIR (Film, cm^{-1}): 3060, 3030 (Aromatic C—H stretch), 2943, 2871 (Aliphatic C—H stretch), 1740 (C=O stretch); 1590, 1496, 1445 (C=C ring stretch), 1384, 1352, 1279, 1232 (C=S stretch), 1202, 1181, 1159 (C—C (=O)—O stretch), 1138, 1127 (Asymmetric C—O—C stretch), 1080, 578 (C—S). ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 8.00–8.06 (dt, J = 8.4, 1.1 Hz, 2H, —SC(Ar-*H*)S—), 7.30–7.60 (m, 8H, Ar-*H*), 5.78 (s, 1H, C*H*), 4.59 (dt, J = 20.4, 3.3 Hz, 1H, O—C*H*—O), 4.2–4.5 (m, 2H, —COOCH_2—), 3.91–3.46 (m, 4H, CH_2 of THP), 1.4–1.9 (complex m, 6H, 3 × CH_2 of THP). ^{13}C NMR (125 MHz, $CDCl_3$, δ in ppm): 226.40 (*C*S_2), 169.20 (*C*=O), 144.31, 133.78, 133.19, 129.59, 129.40, 129.21, 128.86, 127.35 (*C* of Ar), 98.96 (O—*C*H—O), 65.68 (COO*C*H_2), 65.18 (O—*C*H_2 of THP), 62.17 (*C*H_2—O—CH), 59.25 (S—*C*H—(C=O)), 30.74, 25.77, 19.37 (3 × *C*H_2 of THP).

Synthesis of 2-Hydroxyethoxy-carbonylphenylmethyl Dithiobenzoate

In a 250-mL-bottom-glass equipped with condenser, gas inlet and magnetic stirring, a solution of 2-(tetrahydro-2H-pyran-2-yloxy) ethoxy-carbonylphenylmethyl dithiobenzoate (CTA-OTHP; 16.69 g, 40 mmol) in methanol (125 mL) was poured and cupric sulfate pentahydrate (2 g, 8 mmol), was added. The mixture was stirred at room temperature for 12 h. Then the solid cupric sulfate was filtered off and the solid residue was washed with anhydrous ethyl ether (2 × 40 mL). The filtrate was concentrated and then purified by flash column chromatography on sílica gel (70–230 mesh) (hexanes:ethylacetate (9:1)v. The CTA was obtained as a red oil (8.64 g, 65% yield).

FTIR (Film, cm^{-1}): 3446 (O—H stretch); 3060, 3030 (Aromatic C—H stretch), 2953, 2880 (Aliphatic C—H stretch), 1737 (C=O stretch), 1589, 1495, 1446 (C=C ring stretch), 1372, 1280, 1233 (C=S stretch), 1159 (C—C (=O)—O stretch), 1081, 1046, 1027 (C—O stretch), 578 (C—S), 564, 498. ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 8.00–8.06 (dt, J = 8.3, 1.4 Hz, 2H, —SC(Ar-*H*)S—), 7.36–7.60 (m, 8H, Ar-*H*), 5.75 (s, 1H, C*H*), 4.42 (m, 1H, —COOCH_2—), 4.27 (m, 1H, —COOCH_2—), 3.85 (m, 2H, —CH_2—OH), 1.79 (bs, 1H, —O*H*). ^{13}C NMR (125 MHz, $CDCl_3$, δ in ppm): 226.40 (*C*S_2), 169.48 (*C*=O), 144.21, 133.36, 133.28, 129.59, 129.49, 129.20, 128.86, 127.37 (*C* of Ar), 68.12 (COO*C*H_2), 61.40 (*C*H_2—OH), 59.27 (*C*H). Elem. Anal. for $C_{17}H_{16}O_3S_2$ Calc.: C, 61.42; H, 4.85; S, 19.29; Found: C, 61.43; H, 4.95; S, 18.9.

Synthesis of 2-(2-(*tert*-Butoxycarbonyl)ethylamino)-2-oxo-1-phenylethyl benzodithioate

The preparation of this CTA-*6* was conceived as a two steps method shown in Figure 2.

tert-Butyl 2-(2-Bromo-2-phenylacetamido) ethylcarbamate

α-bromophenyl acetic acid (2 g, 9.3 mmol) was dissolved in benzene (20 mL); added thionyl chloride (0.67 mL, 9.3 mmol) and the mixture was heated under reflux to 80 °C for 5 h. The solvent was removed under reduced pressure to yield 2-bromo-2-phenylacetyl chloride (yellowish oil). The resulting product was immediately dissolved in CH_2Cl_2 (30 mL) and the mixture was then cooled to 0 °C and an equimolar amount of triethylamine (0.94 g, 9.3 mmol) was added to the solution; afterward *tert*-butyl 2-aminoethylcarbamate (1.49 g, 9.3 mmol), prepared according to a published procedure,[15] was added slowly. The solution was allowed to warm to room temperature and stirred overnight. The solvent was then removed under reduced pressure and the residue chromatographed on silica gel (70–230 mesh), with ethyl acetate:CH_2Cl_2 (1:9)v to obtain *tert*-butyl 2-(2-bromo-2-phenylacetamido)ethylcarbamate. The product (1.5 g, 4.2 mmol; 45% yield) was a white powder; mp 114–116 °C.

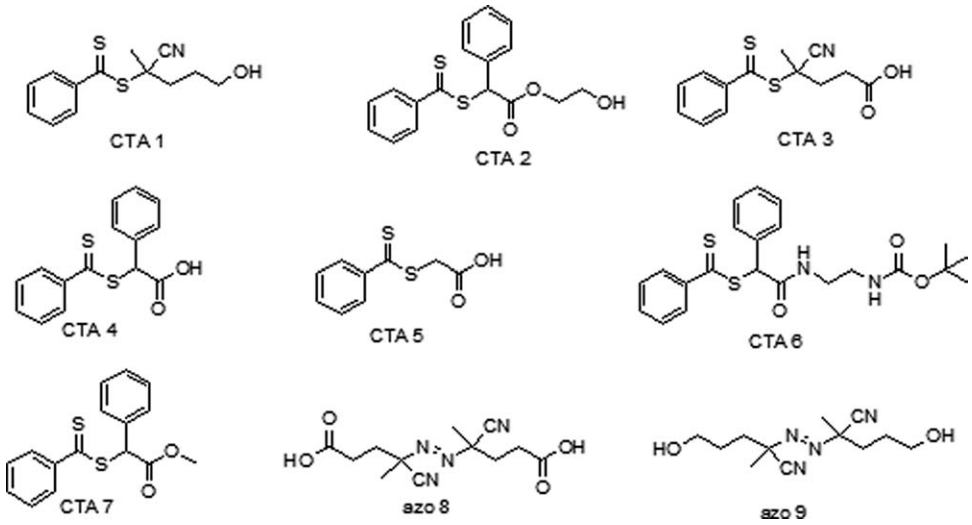


FIGURE 3 Structures of chain transfer agents (CTA's) and azo initiators used in polymerization of HA.

FTIR (KBr, cm^{-1}): 3356, 3317 (*N*—H stretch), 3063 (Aromatic C—H stretch), 2977, 2938 (Aliphatic C—H stretch), 1693 (C=O Stretch), 1646, 1535, 1449 (C=C ring stretch), 1366, 1280, 1250, 1168 (C—O stretching). ^{1}H NMR (200 MHz, $CDCl_3$, δ in ppm): 7.25–7.27 (m, 5H, Ar-*H*), 5.63 (s, 1H, C*H*), 4.9 (br, 1H, *H*NC(O)O), 3.26–3.32 (m, 4H, HNCH_2CH_2NH), 1.35 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ in ppm): 167.61 (—*C*ONH—), 156.54 (—*C*—O—C$(CH_3)_3$), 137.06, 128.72, 128.59, 128.55, 128.05, 127.5 (*C* of Ar), 50.62 (—*C*$(CH_3)_3$), 41.36, 39.5, 28.07. MS-EI *m/z* $[M]^+$ 356 (1), 301 (8), 277 (10), 257 (7), 214 (6), 169 (15), 148 (37), 87 (81), 57 (100).

2-(2-(*tert*-Butoxycarbonyl)ethylamino)-2-oxo-1-phenylethyl Benzodithioate

Phenyl magnesium bromide (1.32 mL, 4.0 mmol) 3.0 M in diethyl ether was pleased in a Schlenk flask equipped with condenser under nitrogen flow. Dry THF (10 mL) were transferred to the flask. The reaction mixture was then cooled to 0 °C and carbon disulfide (0.302 g, 4.0 mmol) introduced dropwise, via a degassed syringe. The addition of de CS_2 led to a color change from green-gray to red. The reaction mixture was allowed to reach room temperature and react for 1 h. After this time *tert*-butyl 2-(2-bromo-2-phenylacetamido)ethylcarbamate (**1**) (1.57 g, 4.4 mmol) was added to this reaction mixture dissolved in the minimum amount of anhydrous tetrahydrofuran (2–3 mL) via degassed syringe. The reaction mixture was stirred at RT for 24 h. Then, water (10 mL) was added, and the organic layer was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with water and dried over magnesium sulfate. The solvent was then evaporated and the obtained product purified by column chromatography on silica gel (70–230 mesh), with a CH_2Cl_2:ethyl acetate (9:1)v mixture as an eluent. The compound obtained was a pink-orange solid (0.85 g, 44% yield); mp 156–158 °C.

FTIR (KBr, cm^{-1}): 3314 (*N*—H stretch), 3065 (Aromatic C—H stretch), 2975, 2932 (Aliphatic C—H stretch), 1682 (C=O Stretch), 1663, 1450 (C=C ring stretch), 1365, 1276, 1249 (C=S stretch), 1167; ^{1}H NMR (200 MHz, $CDCl_3$, δ in ppm): 7.96–7.91 (m, 2H, S = C*Ar-H*), 7.44–7.19 (m, 8H, *Ar-H*), 6.8 (br, 1H, *HN*—C=O), 5.60 (s, 1H, C*H*), 4.8 (br, 1H, *HN*—C(O)O), 3.18–3.38 (m, 4H, HN—CH_2—CH_2—NH), 1.35 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, δ in ppm): 168.61 (—*C*ON—), 144.14, 134.81, 132.86, 129.0, 128.95, 128.69, 128.41, 127.09 (*C* of Ar), 59.82, 41.24 (—CH_2), 40.0 (—CH_2), 28.37 (—C(*C*H_3)$_3$). MS-EI *m/e* $[M]^+$ 398 (1), 374 (1), 341 (1), 297 (1), 270 (37), 253 (7), 209 (13), 178 (4), 149 (8), 121 (100), 57 (60). Elem. Anal. for $C_{22}H_{26}N_3O_3S_2$ Calc.: C, 61.37; H, 6.09; N, 6.51; Found: C, 60.94; H, 6.38; N, 6.51.

POLYMERIZATION PROCEDURE

Preparation of Semitelechelic PolyHA via RAFT Method

All semitelechelic polyHA's were prepared using the same methodology; the only changes were the use of specific CTA's and functional group matching azocompounds. Therefore, CTA-1, CTA-2, and CTA-6 were used with azo 9; while CTA-3, CTA-4, CTA-5, and CTA-7 were used with azo 8 (see Fig. 3 for chemical structures). The reaction conditions, purification and characterization of the products were the same. As an example we describe in detail an experiment using CTA-2 and azo 9.

Hexyl acrylate (HA) (1 g, 6.4 mmol), 4,4′-azobis(4-cyanopentanol) (azo 9) (0.005 g, 0.02 mmol), (2-hydroxyethoxy-carbonylphenylmethyl dithiobenzoate) (CTA-2) (0.033 g, 0.1 mmol) and 1,4-Dioxane (4.0 mL) were mixed in a glass vial. This mixture was transferred to a 20 mL ampoule containing a magnetic stir bar. The oxygen was removed using 5 freeze-thaw evacuation cycles, and the ampoule was sealed with flame under vacuum. The solution was heated to 70 °C in an oil bath with magnetic stirring. At designated time, the polymerization was stopped by cooling to room temperature. The polymerization yield was obtained gravimetrically by adding a fivefold excess of cold methanol, a nonsolvent for polyHA. The polymer product was purified by dissolution in the minimum amount of ethyl ether followed by adding a fivefold excess of cold methanol and decanting. This

procedure was repeated three times to remove residual monomer followed by drying under vacuum to constant weight.

Preparation of Dihydroxy Homotelechelic PolyHA

To a solution of hydroxy semitelechelic PolyHA (0.58 g, 0.0528 mmol of M_n = 10,980 g mol^{-1}) in 1,4-Dioxane (10 mL) in a Schlenk tube; 4,4′-azobis(4-cyanopentanol) (0.066 g, 0.264 mmol) was added in a 5:1 ratio. The solution was purged with argon for 10 min and the temperature was raised to 70 °C. The reaction was performed under argon for 10 h at 70 °C. After cooling down to RT, the solvent was removed in vacuum. Hexane was added to the mixture and the precipitated formed was eliminated. The polymer was purified by dissolution in the minimum amount of ethyl ether followed by adding a fivefold excess of cold methanol and decanting. This procedure was repeated three times to remove CTA residues. Finally, the telechelic polymer was dried under vacuum at RT. The product is a colorless viscous liquid at room temperature (0.5 g, 86.2% yield of M_n = 10,100 g mol^{-1}).

Semitelechelic-OH: ^{1}H NMR (500 MHz, CDCl3, δ in ppm): 7.98–7.82 (bd, SC(Ar-*H*)S, phenyl protons from thiocarbonyl thio ester), 7.55–7.27 (m, other phenyl protons from CTA 2), 4.25–4.15 (m, —COOCH_2— of CTA 2), 3.85–4.20 (bm, —COOCH_2— of the hexyl acrylate polymer), 3.45–3.80 (m, —CH_2—OH of CTA 2), 2.40–1.80 (bm, —CH and CH_2, backbone), 1.20–1.80 (m, —[CH_2]$_4$— of the hexyl acrylate polymer), 0.80–1.0 (bs, —CH_3 of the hexyl acrylate polymer).

Telechelic-OH: ^{1}H NMR (500 MHz, CDCl3, δ in ppm): 7.55–7.27 (m, phenyl protons from CTA 2), 4.18–4.25 (m, —COOCH_2— of the CTA 2),), 3.85–4.20 (m, —COOCH_2— of the hexyl acrylate polymer), 3.45–3.80 (m, —CH_2—OH of CTA 2 and —CH_2OH of AZO), 2.40–1.80 (bm,—CH and CH_2, backbone), 1.20–1.80 (bm, —[CH_2]$_4$— of the hexyl acrylate polymer), 0.80–1.0 (bs, —CH_3 of the hexyl acrylate polymer).

Preparation of Dicarboxylic Acid Homotelechelic PolyHA

To a solution of carboxylic acid semitelechelic polyHA (0.25 g, 0.037 mmol of M_n = 6771 g mol^{-1}) in 1,4-dioxane (10 mL) in a Schlenk tube 4,4′-azobis(4-cyanopentanoic acid) (0.051 g, 0.185 mmol) was added in a 5:1 ratio. The reaction conditions, purification and characterization of the product was the same as for the preparation of dihydroxy telechelic polyHA. The product is a colorless viscous liquid a room temperature (0.24 g, 96% yield of M_n = 6414 g mol^{-1}).

Semitelechelic-COOH: ^{1}H NMR (200 MHz, CDCl3, δ in ppm): 8.05–7.92 (bd, SC(Ar-*H*)S, phenyl protons from thiocarbonyl thio ester), 7.36–7.62 (m, other phenyl protons from thiocarbonyl thio ester), 3.85–4.20 (bm, —COOCH_2— of the hexyl acrylate polymer), 2.62–2.40 (bm, —CH_2CH_2 from CTA 3), 2.40–1.80 (bm, CH and CH_2, backbone), 1.20–1.80 (bm, —[CH_2]$_4$— of the hexyl acrylate polymer), 0.80–1.0 (H bs, —CH_3 of the hexyl acrylate polymer).

Telechelic-COOH: ^{1}H NMR (200 MHz, CDCl3, δ in ppm): 3.85–4.20 (bm, —COOCH_2— of the hexyl acrylate polymer), 2.62–2.40 (bm, —CH_2CH_2 from CTA 3), 2.40–1.80 (bm, CH and CH_2, backbone), 1.20–1.80 (bm, —[CH_2]$_4$— of the hexyl acrylate polymer), 0.80–1.0 (H bs, —CH_3 of the hexyl acrylate polymer).

Preparation of Hydroxy-amine Heterotelechelic PolyHA

The procedure requires two steps, in the first step a *t*-BOC protected amino semitelechelic polyHA (0.3 g, 0.035 mmol, M_n = 8369 g mol^{-1}); prepared using 2-(2-(*tert*-butoxycarbonyl)ethylamino)-2-oxo-1-phenylethyl benzodithioate (CTA-6) was dissolved in 1,4-dioxane (5 mL) and poured into a 10-mL-Schlenk flask equipped with condenser and magnetic stirrer. 4,4′-azobis(4-cyanopentanol) (0.044 g, 0.175 mmol) was added in a 5:1 ratio. The solution was purged with argon and the temperature was raised to 70 °C. The reaction was performed under argon for 10 h at 70 °C. After cooling down to RT the solvent was removed in vacuum. Hexane (5 mL) was added to the mixture and the precipitated formed was eliminated. The polymer was purified by dissolution in the minimum amount of ethyl ether followed by adding a fivefold excess of cold methanol and decanting. This procedure was repeated three times to remove residues from the CTA. Finally, the polymer was dried under vacuum at RT. The product was a colorless viscous liquid at room temperature (0.27 g, M_n = 7939 g mol^{-1}, 90% yield).

Semitelechelic-*t*BOC-amino: ^{1}H NMR (200 MHz, CDCl3, δ in ppm): 8.03–7.84 (bd, SC(Ar-*H*)S, phenyl protons from thiocarbonyl thio ester), 7.58–7.27 (m, other phenyl protons from CTA 6), 3.85–4.20 (bm, —COOCH_2— of the hexyl acrylate polymer), 3.05–3.40 (HN—CH_2—CH_2—NH protons from CTA 6), 2.40–1.80 (bm,—CH and CH_2, backbone), 1.20–1.80 (m, —[CH_2]$_4$— of the hexyl acrylate polymer), 1.41 (bs, —C(CH_3)$_3$ from CTA 6), 0.80–1.0 (bs, —CH_3 of the hexyl acrylate polymer).

Telechelic-OH, *t*BOC-amino: ^{1}H NMR (200 MHz, CDCl3, δ in ppm): 7.34–7.27 (m, other phenyl protons from CTA 6), 3.85–4.20 (bm, —COOCH_2— of the hexyl acrylate polymer), 3.05–3.40 (HN—CH_2—CH_2—NH protons from CTA 6), 2.40–1.80 (bm,—CH and CH_2, backbone), 1.20–1.80 (m, —[CH_2]$_4$— of the hexyl acrylate polymer), 1.41 (bs, —C(CH_3)$_3$ from CTA 6), 0.80–1.0 (bs, —CH_3 of the hexyl acrylate polymer).

Deprotection of *t*-BOC

In the second step, a solution of the previous product (hydroxy *t*-BOC-amine telechelic polyHA, 0.27 g, M_n = 7939 g mol^{-1}) was dissolved in anhydrous CH_2Cl_2 (5 mL), poured into a 20-mL-round bottom flask and cooled down to 0 °C. Trifluoroacetic acid (TFA, 15 equiv, 0.039 mL) was dropped in slowly, and then the mixture was allowed to warm to room temperature and stirred for additional 2 h. The solvent was removed in vacuum to give the hydroxyl-amine telechelic polyHA as its TFA salt in quantitative yield. The product was dissolved in CH_2Cl_2 (5 mL) and sodium hydroxide solution (5 mL, 1 M) was added and vigorously mixed. After separation of the aqueous layer, the product was obtained by removal of solvent in vacuum from organic layer. The final product is a colorless viscous liquid at room temperature (0.15 g, M_n = 7939 g mol^{-1}, 90% yield).

Telechelic-OH, Amine: ^{1}H NMR (200 MHz, CDCl3, δ in ppm): ^{1}H NMR (CDCl3, δ in ppm): 7.34–7.27 (m, other phenyl protons from CTA 6), 3.85–4.20 (bm, —COOCH_2— of the hexyl acrylate polymer), 2.40–1.80 (bm, —CH and CH_2, backbone), 1.20–1.80 (m, —[CH_2]$_4$— of the hexyl acrylate polymer), 0.80–1.0 (bs, —CH_3 of the hexyl acrylate polymer).

Reaction of Dihidroxy Telechelic PolyHA with Methacrylic Anhydride

To a solution of dihydroxy telechelic polyHA (0.25 g, 0.048 mmol of M_n = 5200 g mol^{-1}) in dry dichloromethane (5 mL) methacrylic anhydride (0.018 g, 0.12 mmol) and triethylamine (4 equiv) were added. The reaction was carried out during 7 days at room temperature. After this time the solvent was removed in vacuum. Hexane (5 mL) was added to the mixture and the precipitated formed was eliminated. The polymer was purified by dissolution in the minimum amount of ethyl ether followed by adding a fivefold excess of cold methanol and decanting. This procedure was repeated three times to remove residues. Finally, the polymer was dried under vacuum at RT. The product was a colorless viscous liquid a room temperature (0.18 g, M_n = 5150 g mol^{-1}, 78% yield).

Telechelic-methacrylate: ^{1}H NMR (500 MHz, CDCl3, δ in ppm): 7.35–7.27 (m, phenyl protons from CTA 2), 5.94 (bs, —C=CH$_a$H$_b$), 5.51 (bs, —C=CH$_a$H$_b$), 4.35–4.15 (m, —COOCH_2— of CTA 2 and —CH_2COO— of ester end group), 3.85–4.20 (m, —COOCH_2— of the hexyl acrylate polymer), 3.45–3.80 (m, —CH_2—OH of CTA 2 and —CH_2OH of AZO), 2.40–1.80 (bm, —CH and CH_2, backbone), 1.20–1.80 (bm, —[CH_2]$_4$— of the hexyl acrylate polymer), 1.84 (bs, CH_3 of the methacrylic end group), 0.80–1.0 (bs, —CH_3 of the hexyl acrylate polymer).

RESULTS AND DISCUSSION

Synthesis of New Functionalized CTA's

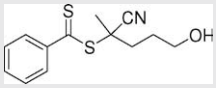
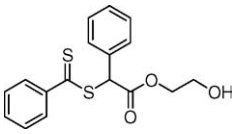
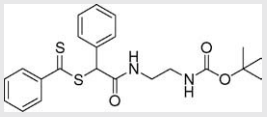
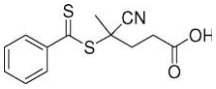
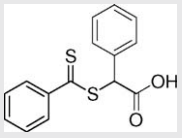
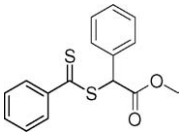
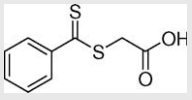
Carboxylic acid containing RAFT chain transfer agents based on dithiobenzoates and trithiocarbonates have been used to prepare a wide variety of polymers containing a carboxylic acid end-group.[1,2,44-46] Perhaps the most widely used is 4-cyanopentanoic acid dithiobenzoate (CTA-3)[47] because of its solubility in a wide variety of polar solvents including water (pH > 8) and the commercial availability of 4,4′ azobis-(cyanovaleric acid) (ACVA), a free radical initiator yielding exactly the same initiating R group than the leaving/re-initiating group contained in the dithiobenzoate (CTA-3). However, the shelf lifetime of this CTA-3 is limited due to hydrolysis and light sensitivity.[47,48] We wish to describe herein, the synthesis of two new functionalized RAFT chain transfer agents (CTA's), containing a leaving/reinitiating group (R, attached to sulfur) yielding a secondary carbon radical by fragmentation in the RAFT-equillibrium containing either a functional OH group (CTA-2) or a *t*-BOC protected amine group (CTA-6), respectively. It is worth to mention that the chemical structure next to dithiobenzoate can make a big difference for stability of a CTA.[12,49] The synthetic schemes are described in Figure 1 for 2-hydroxyethyl 2-phenyl-2-(pahenylcarbonothioylthio)acetate (CTA-2) and in Figure 2 for (2-(2-(*tert*-butoxycarbonyl)ethylamino)-2-oxo-1-phenylethyl benzodithioate (CTA-6), respectively. The synthesis of CTA-2 is based on a Grignard reaction involving the product of phenylmagnesium bromide and carbondisulfide with BrEOTHP, which was obtained in the first step by conventional esterification of α-bromophenylacetic acid (10.97 g, 50 mmol) with 2-(tetrahydro-2H-pyran-2-yloxy) ethanol using DCC; to obtain 2-(tetrahydro-2H-pyran-2-yloxy) ethoxy-carbonylphenylmethyl dithiobenzoate (CTA-OTHP). CTA-2 was obtained as a red semisolid compound by deprotection of CTA-OTHP in methanol with cupric sulfate pentahydrate in a good global yield of 65%. Following an analogous synthetic route CTA-6 was prepared by Grignard reaction involving the product of phenylmagnesium bromide and carbondisulfide with *tert*-butyl 2-(2-bromo-2-phenylacetamido)ethylcarbamate), which was synthesized by acylation of mono-*t*-BOC protected ethylene diamine with 2-bromo-2-phenylacetyl chloride in the first step. The product (2-(2-(*tert*-butoxycarbonyl)ethylamino)-2-oxo-1-phenylethyl benzodithioate (CTA-6) was obtained in acceptable global yield of 44%. For both CTA's the characteristic singlet peaks of *R*-group's are observed at a chemical shift of ~ 5.65 ppm (^{1}H NMR) for methine hydrogen (NMR spectra in Supporting Information).

RAFT Polymerization of n-Hexylacrylate

One important goal in this investigation was to explore the effect of different R substituents in dithiobenzoate esters, on the outcome of polymerizations of HA and to examine the effect of varying the functionality introduced in the leaving group, if any, in the RAFT polymerization of HA. The variety of functional chain transfer agents of the dithiobenzoate family tested (Fig. 3) can produce a variety of semitelechelic polymers with specific functionalities at their chain-ends.

The following RAFT chain transfer agents: CTA-1 (2-cyano-5-hydroxypentan-2-yl benzodithioate),[2,3,11] CTA-3 (4-cyano-4-(phenylcarbonothioylthio)pentanoic acid)[2,49] and CTA-7 (methyl 2-phenyl-2-(phenylcarbonothioylthio)acetate)[3,50] has been proved successful in a number of RAFT polymerization systems. Among these, cyanopentanoic dithiobenzoate CTA-3 was particularly chosen because it is one of the most studied RAFT agents for aqueous polymerization of monomers containing functional groups.[2,44,45] The synthesis of CTA-4 has been reported by Legge et al.,[50] although, it has not being tested as a RAFT chain transfer agent. CTA-5 (2-(phenylcarbonothioylthio)acetic acid) was used by Choe et al.[51,52] for the polymerization of styrene and by Pichot et al.[3] for the polymerization of *N*-acryloylmorpholine and they found that the CTA-5 was not efficient enough to control the polymerization. The new CTA's 2 and 6 have similarities in their structure with CTA-4 and CTA-7 since they generate by the fragmentation of the CTA a secondary radical (·R) with a bulky phenyl group that may add resonance stability to the radical, but they include another functional groups (OH and *t*-BOC protected amine) which are important for the preparation of telechelic polymers, as we will discuss later. Steric hindrance contributes also to the R radical stability and it is reported to play a major role in dithioester efficiency.[53]

TABLE 1 RAFT Polymerization of HA in 1,4-Dioxane in the Presence of CTA's **1**-**7** and Azo Initiators **8** and **9** at 70 °C Using a Molar Ratio $[HA]_0:[CTA]_0:[AZO]_0$ of 320:5 :1

CTA	RAFT Agent	Time, (h)	Initiator	Conv. (%)[a]	$M_{n,\ GPC}$ (g mol^{-1})[b]	M_w/M_n	$M_{n,\ calc.}$[c] (g mol^{-1})
1		12	Azo 9	50	8195	1.021	5257
2		12	Azo 9	25.4	6042	1.094	2868
6		12	Azo 9	56	8225	1.012	6021
3		12	Azo 8	57.4	9698	1.001	6010
4		12	Azo 8	44	7332	1.012	4681
7		12	Azo 8	46	7365	1.049	4895
5		9	Azo 8	14	14,900	1.110	1610

[a] Conversion calculated by mass of isolated polymer using methanol.
[b] Molecular weight and PDI values determined by GPC.
[c] Calculated molecular weights based on eq 1.

A summary of experimental conditions and the molecular characteristics (molecular weights, polydispersities, and percent conversions) of the polymers obtained by RAFT polymerizations of HA in the presence of several functionalized dithioesters under similar reaction conditions are shown in Table 1. The obtained polymers have very low polydispersities (PDI range between 1.00 and 1.10) as determined by GPC (Table 1), and the elution profiles were monomodal and symmetrical (Fig. 4). A comparison with the calculated molecular weights according to the simple eq 1[3] shows that the molecular weights determined by GPC were always higher than the calculated but this may result from inaccuracy in conversion determination gravimetrically using a nonsolvent given the fact that polyHA was difficult to isolate because it is a viscous liquid at room temperature. Therefore, the difference can be attributed to the loss of material during polymer purification.

$$M_n = \left(\frac{[M]_o}{[CTA]_o} \times \text{Conversion} \times M_{mon}\right) + M_{CTA} \qquad (1)$$

In any case, the calculated molecular weight by 100% conversion would be around 10,000 g mol^{-1} an the measured molecular weights by GPC are, with the exception of the experiment using CTA-5, close to that value. The best match is given by using CTA-3; additionally the highest conversion and lowest PDI was obtained using this CTA (see Table 1 and Fig. 4). It is also evident that CTA-5 provided poor control in RAFT polymerization resulting in formation of chains of high molecular weight by low conversion. All functionalized dithioesters were effective in controlling the molecular weight; possess similar reactivities and provided a narrow polydispersity excepting CTA-5. This CTA-5 does not have a good leaving group (carboxymethyl), corresponding to a primary carbon centered radical. CTA's 1 and 3 produce in the fragmentation step of RAFT equilibrium a tertiary carbon radical, stabilized by the cyano group and were evidently very effective in controlling the RAFT polymerization of HA.

The novel CTA's 2 and 6, together with CTA's 4 and 7 produce in RAFT equillibrium a secondary leaving group (radical

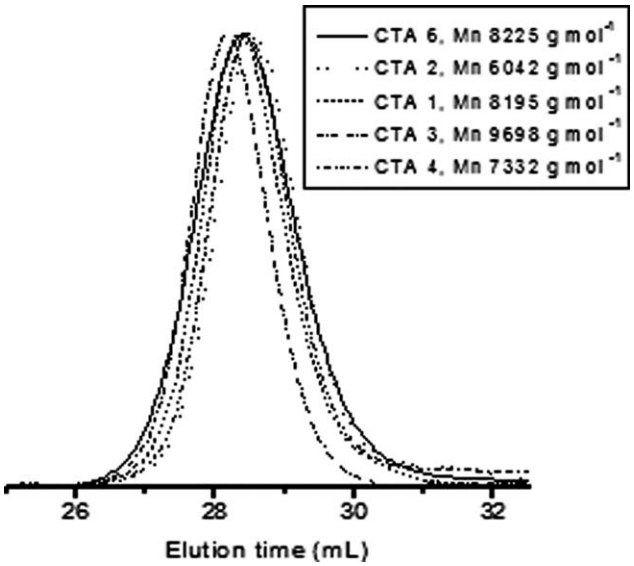


FIGURE 4 Gel permeation chromatograms (GPC-traces) of poly(*n*-hexyl acrylate) prepared by RAFT polymerization using several functionalized CTA's. Experimental conditions in Table 1.

R) containing a bulky phenyl group adjacent to the carbon-radical.

The presence of a phenyl group is anticipated to increase the stability of the generated radical. Their ability to control the polymerization of hexyl acrylate was also good.

We decided to study in detail the kinetics of HA RAFT polymerization using CTA-2. These results are summarized on Table 2 and Figure 5, which show the evolution of M_n and PDI with monomer conversion. The ability of the CTA-2 to control the molecular weight and give narrow polydispersity for poly(HA) is evident as shown by a linear increase of M_n with conversions up to 65% and a low PDI (<1.1) thorough the course of the reaction. The pseudo first order kinetic plot in Figure 6 do not shows a very good linearity thorough the polymerization. It seems that the polymerization rate is slowed down at high conversion and that the molecular weight comes to a limiting value (compare with Fig. 5 at high conversion); however, this downward curvature in kinetic plots of radical polymerization is reported to be common in nearly all controlled free-radical polymerization methods at high conversions.[46,53,54] It is also important to note that the limiting molecular weight value is very close to the theoretical molecular weight at 100% conversion.

The first requirement for an effective CTA is that it should have a high transfer constant relative to the monomers being polymerized, which means a high rate of addition and a suitable leaving group for the propagating radical. The second important quality of an effective CTA is the ability of forming intermediates that fragment rapidly, giving no side reactions. It is expected that the *R*-group structure of the CTA's plays an important role in the RAFT polymerization rate of HA since polymerization rate should decrease with decreasing radical stability of the R group in CTA (leaving/re-initiating radical R): tertiary R> secondary R > primary R (see Scheme 1). Thus, the rate of RAFT polymerization using CTA-1 and CTA-3 is expected to be very similar and faster than using CTA's 2, 4, 6, and 7; while the polymerization rate using CTA-5 is expected to be the slowest for RAFT polymerization among the CTA's tested in this study. Table 3 shows that in fact for polymerization times of 12 h the use of CTA-1 and CTA-3 resulted in higher conversions (50 and 54.4%, respectively) than for the polymerizations using all other CTA's tested with one important exception, the use of CTA-6 resulted in a conversion of around 56% in 12 h. This may result from the bulky structure of the R group in CTA-6 facilitating the rapid fragmentation. The conversions at 12 h obtained by using CTA's 4 and 7 are very similar (44 and 46% respectively), while the polymerization rate using CTA-5 and CTA-2 were the slowest. The polydispersity values reflect the quality of the RAFT process, since a high polydispersity is an indicator of the deviation from a controlled-radical (living) system. It is evident that the use of CTA-2

TABLE 2 RAFT Polymerization of HA in 1,4-Dioxane in the Presence of CTA **2** and Azo Initiator **9** at 70 °C Using a Molar Ratio $[HA]_0:[CTA]_0:[AZO]_0$ of 640:5:1

Entry	Time (h)	Conv. (%)[a]	M_n, GPC (g mol^{-1})[b]	M_w/M_n	M_n, calc. (g mol^{-1})[c]
1	2	8.8	1921	1.007	2089
2	4	22.0	8020	1.004	4725
3	6	33.5	10,830	1.001	7021
4	8	47.6	14,700	1.012	9837
5	10	52.9	17,350	1.069	10,895
6	12	64.1	18,100	1.033	13,131
7	14	62.9	18,830	1.053	12,892
8	16	71.1	19,490	1.060	14,529
9	18	70.5	20,920	1.100	14,409

[a] Conversion calculated by mass of isolated polymer using methanol.
[b] Molecular weight and PDI values determined by GPC.
[c] Calculated molecular weights based on eq 1.

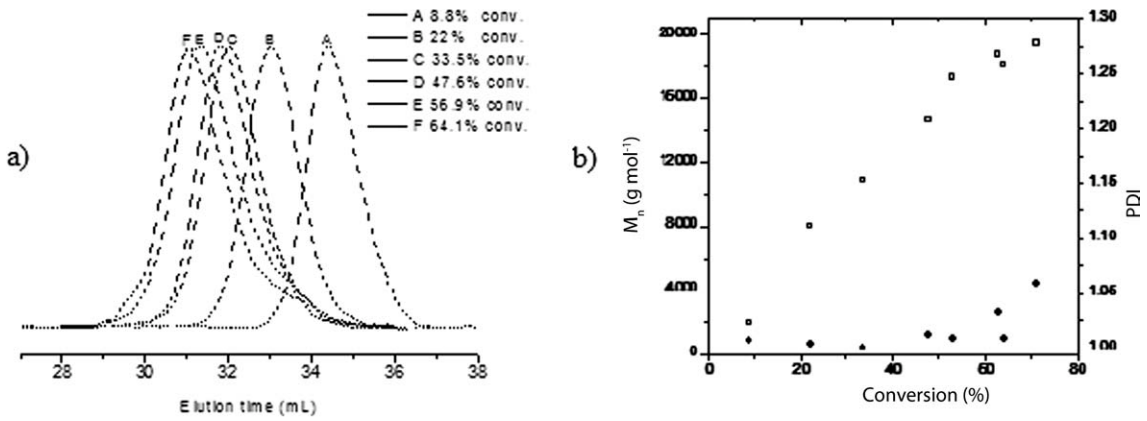


FIGURE 5 Evolution of molecular weight for RAFT polymerization of HA in 1,4-dioxane in the presence of CTA-2 and Azo-9 at 70 °C using a molar ratio $[HA]_0$:$[CTA]_0$:$[AZO]_0$ of 640:5:1. A: GPC chromatograms. B: Evolution of M_n and PDI with conversion.

resulted in a controlled RAFT polymerization although the polymerization rate is as low as for using CTA-5, a noncontrolling dithiobenzoate RAFT agent: Using CTA-2, at 36.4% conversion M_n = 9836 g mol^{-1}with polydispersity 1.00 was obtained; while using CTA-5 at 35% conversion M_n = 23,480 g mol^{-1}, with polydispersity 1.30 (Table 3) was obtained. It should be also mentioned that the secondary carbon radicals that are produced after fragmentation of CTA's 2, 4, 6, and 7 are further stabilized by resonance of the phenyl group, which may allow them to increase their fragmentation rate constant yielding good controlling RAFT agents. In all cases, the expelled radicals (•R) are able to reinitiate the polymerization of HA since no polymerization inhibition was observed.

The synthesized new CTA's 2 and 6 are good RAFT agents for the polymerization of HA, successfully controlling its molecular weights and distribution. The application of these new CTA's to the RAFT polymerization of other classes of monomers like styrene and methylmethacrylate is subject of a separate report.[55]

Stability of chain transfers agents (CTA's) for RAFT polymerization is an important factor that has not been addressed extensively. The most commonly used dithioester compounds are known to be sensitive to hydrolysis. For example, CTA's 1 and 3 are used frequently, but they are unstable even in freeze storage; in our experience CTA 1 is more hydrolytic unstable, after a month of synthesis it starts to decompose under storage conditions. Possibly the electron withdrawing —CN group in α-position to the dithioester bond is responsible for faster hydrolysis. After 2 months in freeze storage degradation of CTA 3 starts, as evidenced by the appearance of a singlet at 1.86 ppm attributed to the methyl group (CH_3—(CCN)—S(C=S)—) in it's ^{1}H NMR spectrum. In contrast CTA's 2, 4, 6, and 7 showed good hydrolytic stability under freeze storage conditions. After 1 year of synthesis CTA's 2, 4, and 6 showed good performance in polymerization of HA both in molecular weight control and in low polydispersity. Table 4 shows polymerization results of HA using CTA's 2, 4, and 6 under exactly the same synthetic conditions and ratios using the freshly synthesized CTA and after 1 year of storage in freezer. It is evident that the results obtained after 1 year of storage are very similar to those originally obtained demonstrating the good stability of these type of CTA's making clear another advantage of their use in RAFT polymerization; among them are CTA 2 and CTA 6, the two new CTA's reported in this study for the first time.

Synthesis of α,ω-Telechelic Polymers

In the literature, numerous reports claiming telechelic polymer synthesis have been published, without thoroughly characterizing the resulting polymer regarding the functional end-groups. Many examples of affirmations based on the theoretical chemistry involved in the synthesis, or nonwell-adapted analytical techniques, can be found. The inherent low concentration of end groups and the possibility of side

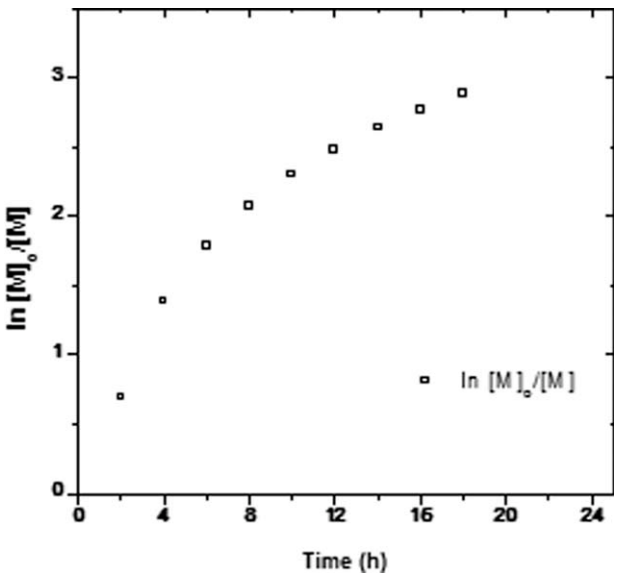
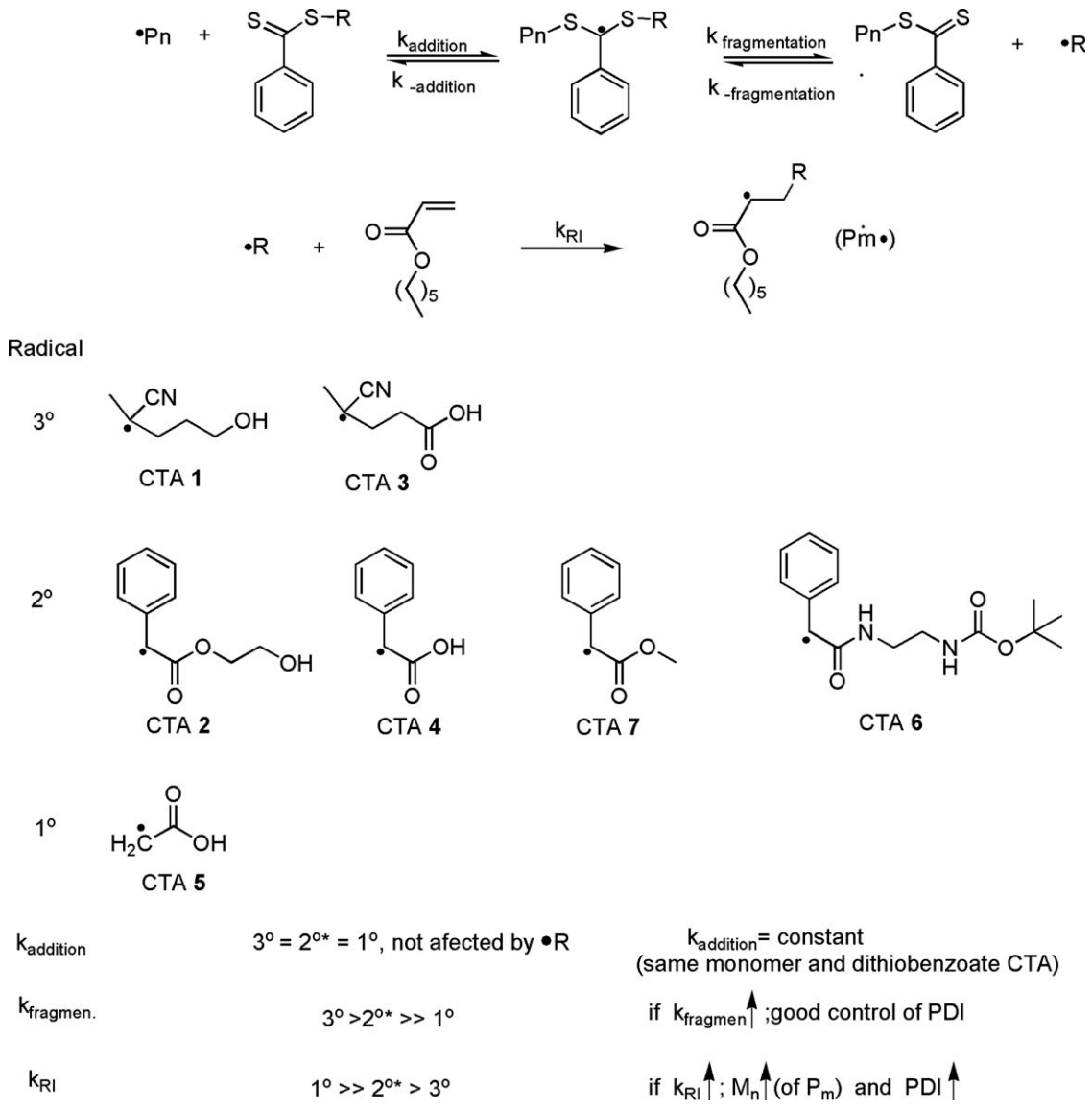


FIGURE 6 Pseudofist-order kinetic plot with time for polymerization of HA ($[HA]_0$ = 1.18 M in 1,4-dioxane) at 70 °C with Azo-9 in the presence of CTA 2. $[HA]_0$:$[CTA]_0$:$[AZO]_0$ of 640:5:1.



SCHEME 1 RAFT equilibrium and analysis of leaving/reinitiating groups from CTA's.

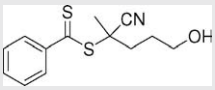
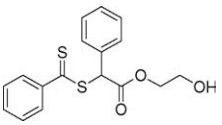
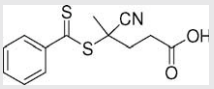
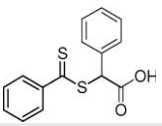
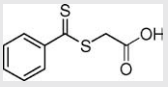
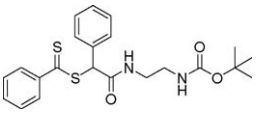
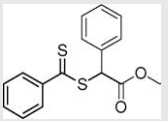
reactions with other functional groups within the polymer, make reactions with high efficiency and selectivity necessary for successful and specific polymer modification.

Telechelic Polymers with Hydroxyl End-Groups

To achieve the synthesis of α,ω-hydroxyl end-functionalized telechelic polymers we followed a two step synthetic path (Scheme 2). In the first step either CTA-1 or CTA-2 in conjunction with azo 9 were used for the polymerization of HA to yield a semitelechelic poly(*n*-hexylacrylate) (PHA) with a terminal —OH group. Use of the azo cyanopentanol free-radical initiator (azo 9) is crucial to guarantee the semitelechelic —OH endgroups in PHA, since the initiator moiety and the R leaving/re-initiating group in CTA-1 and CTA-2 contain both a OH group. In the second step, the second —OH end-group was introduced while simultaneously removing the dithioester functional group following the Perrier et al.[21] radical exchange method but using a ratio of 5:1 (azo:PHA) to minimize the excess of azo compound. The addition of azo-9 to a solution of the semitelechelic PHA was accompanied by a rapid color change from pink to colorless, indicating removal of the dithiobenzoate moiety of the RAFT end group. After purification, the extent of the reaction was monitored by ^{1}H NMR. For lower molecular weight polymers, end group transformations can be conveniently followed by NMR.

The large excess of azo compound used in the Perrier[21] method is reported to be necessary to avoid termination by disproportionation in the case of polystyrene. It should be noted that the accuracy of the analysis of end group signals was limited in some cases by the poor signals obtained in the spectrum. In our experiments, no signals in the olefinic region (between 5 and 6 ppm) of the ^{1}H NMR spectrum, which

TABLE 3 RAFT Polymerization of HA in 1,4-Dioxane in the Presence of CTA's **1–7** and Azo Initiators **8** and **9** at 70 °C Using a Molar Ratio $[HA]_0:[CTA]_0:[AZO]_0$ of 320:5:1

Entry	RAFT Agent	Time (h)	Conv. (%)[a]	$M_{n,\ GPC}$[b]	M_w/M_n	$M_{n,\ Calc.}$[c]
1		4	4	3120	1.33	664
2		7	29.6	6723	1.06	3220
3		12	50	8195	1.021	5257
4		9	12.4	4128	1.29	1570
5		12	25.4	6042	1.094	2868
6		14	36.4	9836	1.00	3966
7		16	54.4	10,730	1.00	5763
8		4	–	5103	1.10	–
9		6	35.3	5687	1.13	3803
10		8	37.3	6915	1.05	4003
11		12	54.4	9698	1.00	5710
12		16	59.3	11,510	1.00	6200
13		12	44	7332	1.012	4681
14		20	60	9425	1.004	6278
15		7	13.6	14,900	1.11	1570
16		9	19	16,950	1.11	2108
17		16	35	23,480	1.30	3712
18		6	16	4988	1.06	2027
19		10	42	8369	1.028	4623
20		12	56	8225	1.012	6021
21		12	46	7365	1.049	4895
22		20	56	8637	1.020	5893

[a] Conversion calculated by mass of isolated polymer using methanol.
[b] Molecular weight and PDI values determined by GPC.
[c] Calculated molecular weights based on eq 1.

would be evidence for termination by disproportionation, could be detected, even if we used a molar excess of azo-9 of only 5:1. (Compare for this the NMR Spectra in Fig. 7).

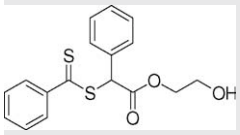
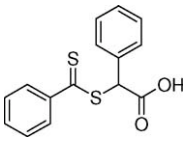
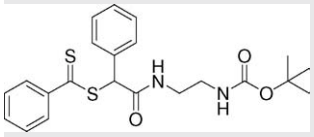
Furthermore, as can be seen in Figure 7 the aromatic signals in the ^1H NMR spectrum of the semitelechelic polyHA between 7.4 and 8.0 ppm, disappeared after reaction with the excess of azo initiator. This proves further the complete removal of the thiocarbonyl thio end moiety from the polymeric chain; while the aromatic protons attributed to the phenyl ring adjacent to the dithioester in the CTA could be clearly identified close to 7.3 ppm [Fig. 7(a,b)] indicating the presence of the RAFT end group.

In addition to NMR, UV–vis spectroscopy was also used as a simple procedure for the characterization of the resulting polymers. The absorbance of the C=S group in visible band is a valuable tool to determine the amount of active dithioester end groups when the semitelechelic polymers are analyzed. The dithioester moiety has a strong absorption band at 346 nm and weak absorption at 500 nm (Fig. 8); which allows one to use UV–vis spectroscopy as a simple procedure for identification of the presence of the dithioester moiety in the resulting polymers. As a result of the radical exchange process used, the absorption due to the dithioester is absent, indicating that the radical exchange was complete and that the second —OH functional group was introduced; compare absorption spectra before and after radical exchange reaction in Figure 8.

Telechelic Polymers with Carboxylic Acid End-Groups

For synthesizing α,ω-carboxylic acid end-functionalized telechelic polymers we followed a two step synthetic path similar to that described in Scheme 2, but using a CTA and an initiator containing the carboxylic acid moiety. In the first step, CTA-3 in conjunction with azo 8 were used for the polymerization of HA to yield a semitelechelic PHA with a terminal —COOH group. Use of CTA-3 in conjunction with the azo cyanopentanoic acid free-radical initiator (azo 8) was

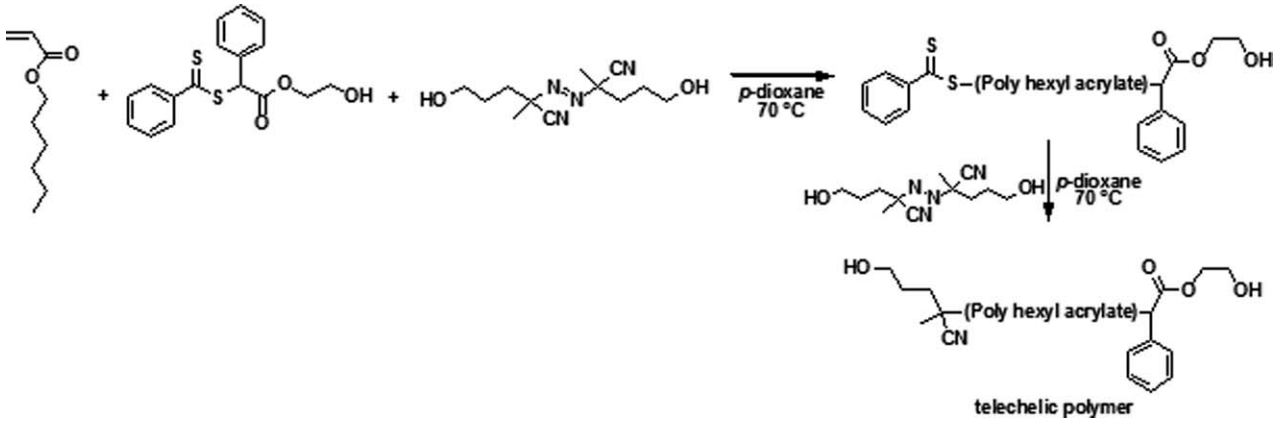
TABLE 4 Outcome of Polymerization of HA Using Freshly Synthesized CTA's **2**, **4** and **6** and After a Year of Storage at 70 °C Using a Molar Ratio $[HA]_0:[CTA]_0:[AZO]_0$ of 320:5:1

CTA	M_n (g mol^{-1})/PDI Freshly Synthesized	M_n (g mol^{-1})/PDI After a Year
	9469/1.001	8465/1.008
	9698/1.007	10030/1.006
	8369/1.020	8607/1.004

chosen to guarantee the same initiating and re-initiating *R*-Group. Using this strategy it is ensured that all polymer chains contain the same end-group with the carboxylic acid moiety independently of RAFT polymerization kinetics. However, when an azoinitiator is used containing a different R-group than the one evolving from the CTA it will results in a minor fraction (depending on kinetics) of polymer chains derived from the initiator and a major fraction of polymer chains derived from the CTA's leaving/re-initiating *R*-group.[56] Figure 9 shows the ^{1}H NMR spectrum of the semitelechelic polymer ("Telechelic Polymers with Hydroxyl End-Groups" section) and of the telechelic polymer after radical exchange reaction ("Telechelic Polymers with Carboxylic Acid End-Groups" section). No signals in the olefinic region (between 5 and 6 ppm) of the ^{1}H NMR spectrum can be observed (see expansion of spectrum) while the aromatic signals of the semitelechelic PHA between 7.4 and 8.0 ppm disappeared after the radical exchange reaction evidencing the removal of thiocarbonyl thio moiety.

Heterotelechelic Polymers with Hydroxyl and Amino End-Groups

To achieve the synthesis of telechelic polymers containing an amino end-group, the functional initiator approach to synthesize amino telechelics causes some complications since amine compounds participate in chain-transfer reactions. Accordingly, the reaction between thiocarbonyl thio groups and primary amines is well known to occur rapidly at ambient temperatures leading irreversibly to thioamides and thiols.[18] Therefore the introduction of amine end-groups to polymers by RAFT is accomplished by using an amine-group protected approach. For the preparation of polystyrene with amine end-group a series of phthalimido-functional RAFT agents (CTA's) were developed and used followed by a reduction of the tritiocarbonate moiety with tributylstannane and hydrazinolysis to obtain amine end-group.[11,39] Despite the fact that the phthalimido strategy was proven to be successful for polystyrene, the application of this method to other type of polymers relies on adapting the kinetics of the phthalimido-CTA to other monomers, which is reported to yield in some cases bimodal distributions of molecular weight as in the case of butyl acrylate.[57] For the investigation reported here, we followed another strategy: the amine group is protected by the well known *t*-BOC group[40] and is located in the CTA-6 (Fig. 3) in the leaving/re-initiating R group of the CTA far apart from the sulfur atom of the dithioester, affecting only slightly the RAFT kinetics. We prepared amine-hydroxy end-functionalized hetero-telechelic polymers of hexyl acrylate using the strategy described in Scheme 3. In the first step CTA-6 in conjunction with azo 9 were used for the polymerization of HA to yield a semitelechelic PHA with a terminal —NH*t*-BOC group. Figure 10(a) shows ^{1}H NMR spectrum of this semitelechelic polymer. It is important to note the presence of the signals of *t*-BOC group (proton 11 at 1.4 ppm) and the aromatic protons 16–18 between 7.2 ppm and 8.0 ppm. In the second step, the —OH



SCHEME 2 Preparation of dihydroxy-terminated homotelechelic poly(*n*-hexyl acrylate).

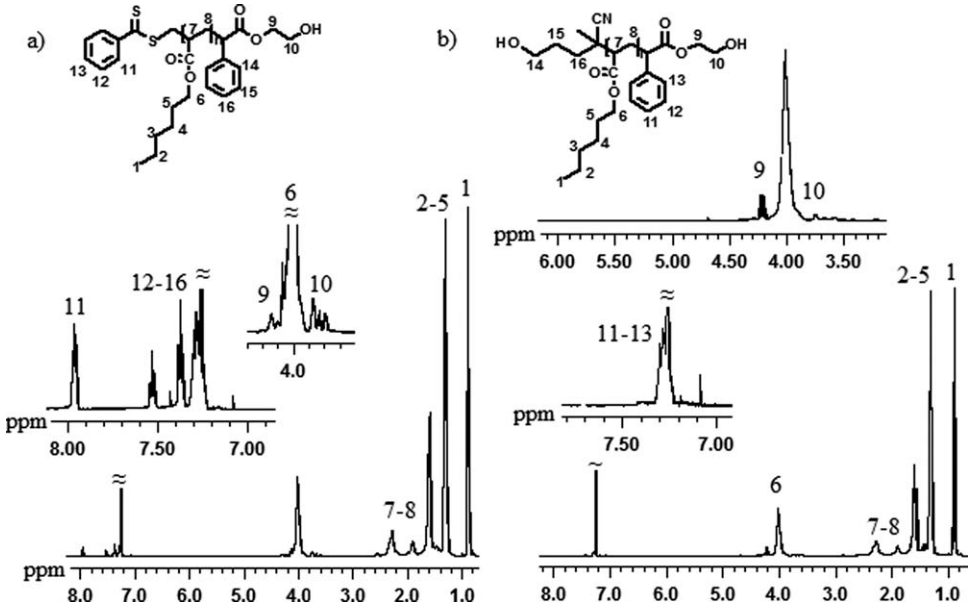


FIGURE 7 (a) ^{1}H NMR spectra (500 MHz) of hydroxy-semitelechelic poly(*n*-hexyl acrylate) and (b) dihydroxy-terminated telechelic poly(*n*-hexyl acrylate).

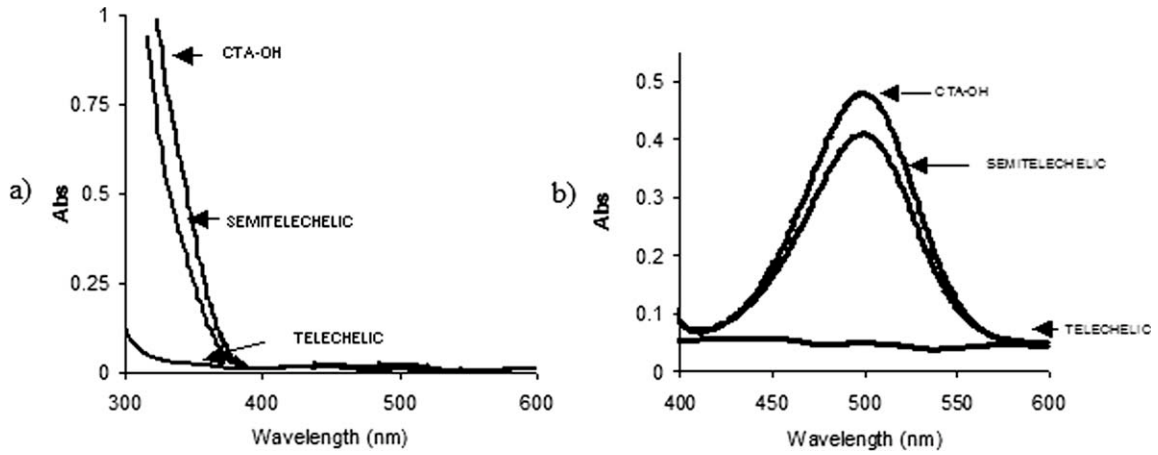


FIGURE 8 UV/vis absorbance spectrum of CTA-2 (OH), semitelechelic polyHA (OH) before and after radical exchange reaction with Azo-9 to yield telechelic polyHA (OH): (a) Region between 300 and 600 nm (in all cases $c = 1.0 \times 10^{-4}$ mol/L). (b) Region between 400 and 600 nm. (in all cases $c = 3.0 \times 10^{-3}$ mol/L).

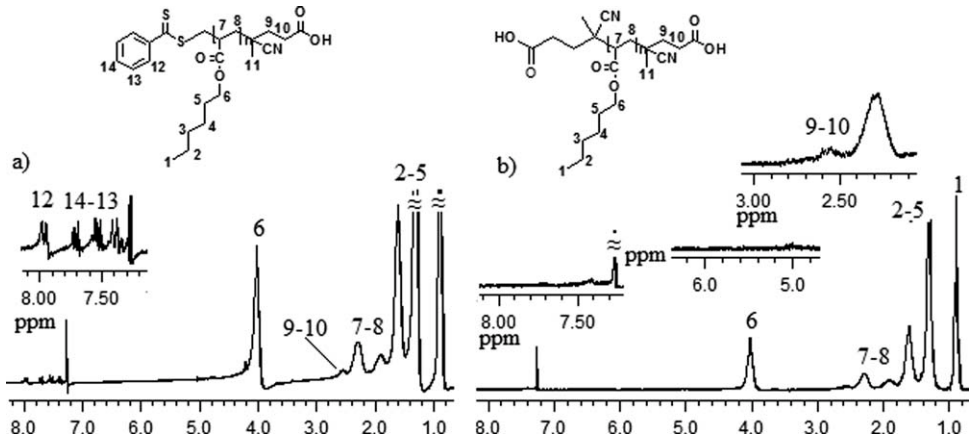
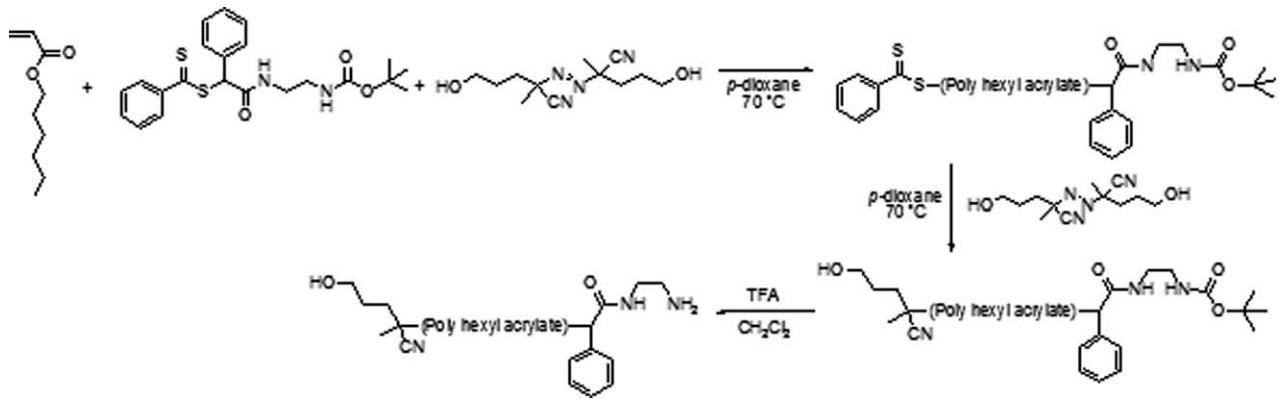


FIGURE 9 ^{1}H NMR spectra (200 MHz) of (a) carboxylic acid-semitelechelic poly(*n*-hexyl acrylate) and (b) dicarboxylic acid-terminated telechelic poly(*n*-hexyl acrylate).



SCHEME 3 Preparation of amine-hydroxy-terminated heterotelechelic poly(*n*-hexyl acrylate).

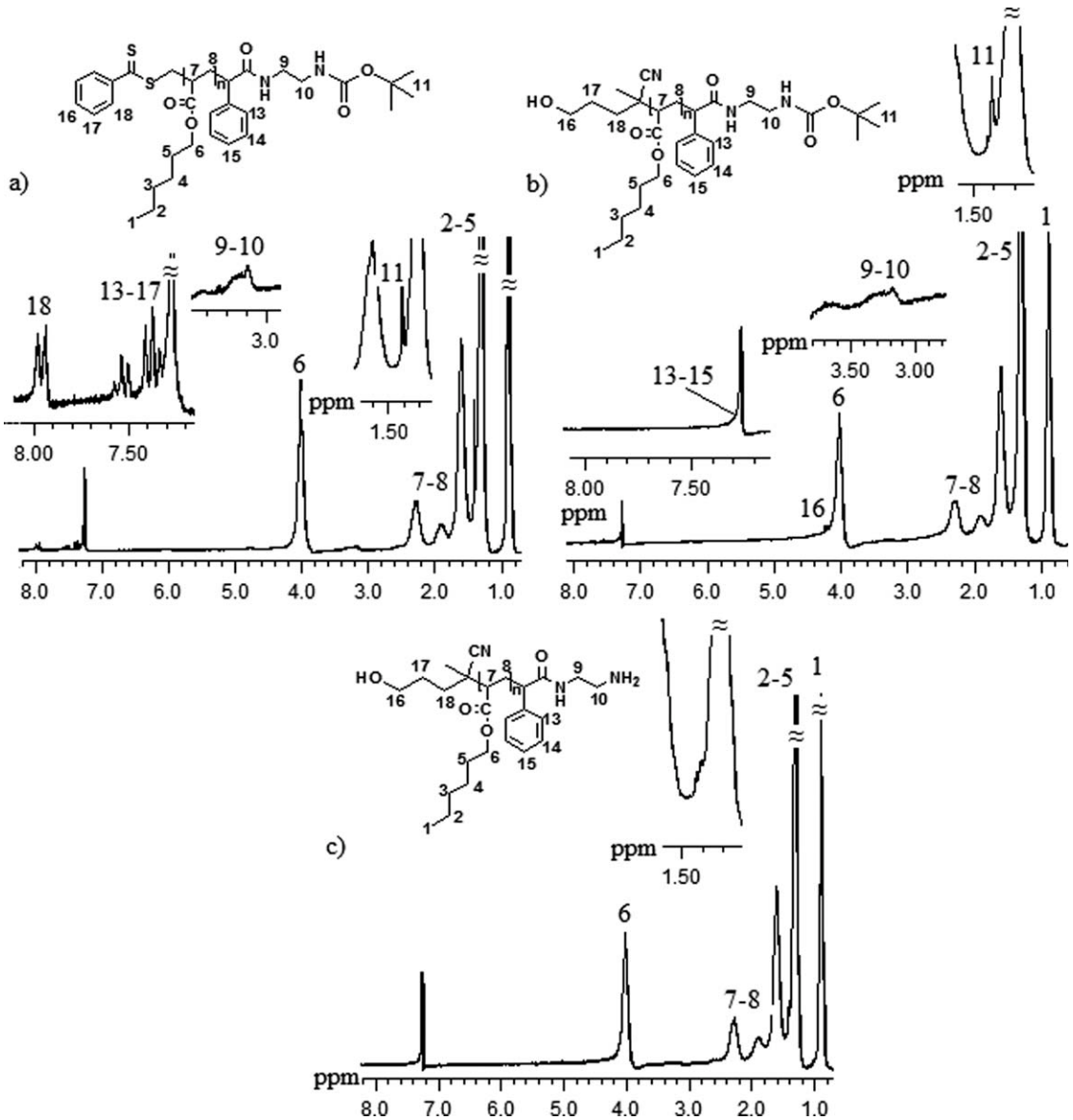
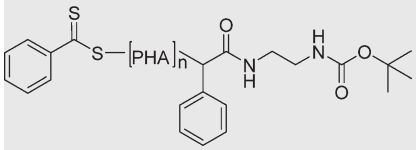
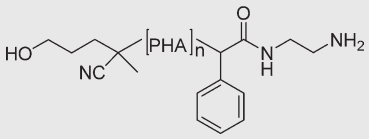
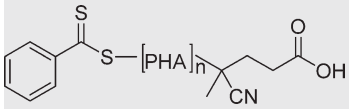
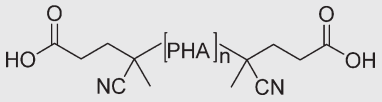
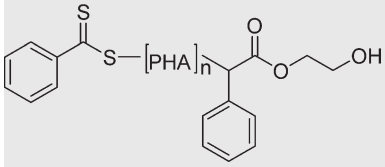
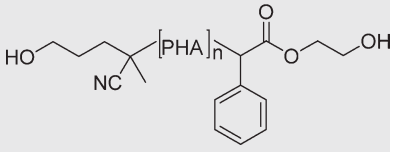
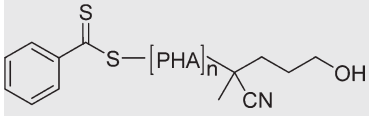
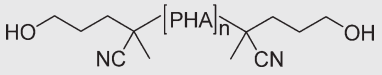


FIGURE 10 (a) ^{1}H NMR spectra (200 MHz) of *t*-BOC protected amine semitelechelic poly(*n*-hexyl acrylate). (b) ^{1}H NMR spectra of *t*-BOC protected amine, hydroxy-telechelic poly(*n*-hexyl acrylate). (c) ^{1}H NMR spectra of amine, hydroxy-terminated telechelic poly(*n*-hexyl acrylate) prepared after *t*-BOC deprotection reaction with TFA.

TABLE 5 Telechelic Polymers with Different Functional End Groups Using Functional Azo Initiators

Semitelechelic Polymer	Telechelic Polymer
	
M_n = 8131, PDI= 1.028	M_n = 7954, PDI= 1.007
	
M_n = 6771, PDI= 1.004	M_n = 6414, PDI= 1.006
	
M_n = 8708, PDI= 1.004	M_n = 7967, PDI= 1.009
	
M_n = 5030, PDI= 1.00	M_n = 4900, PDI= 1.00

end-group was introduced following the radical exchange strategy described for the other telechelics using azo 9 in fivefold excess. Figure 10(b) shows ^{1}H NMR spectrum of the telechelic product evidencing the removal of the dithio moiety as can be seen in the aromatic region between 7.2 and 8.0 ppm. Aromatic protons at 8.0 ppm disappeared and the other two aromatic signals (between 7.3 and 7.6 ppm) became less complex. The final step is the removal of *t*-butyl groups in the polymer (deprotection of amine) this was accomplished by the use of CF_3COOH in CH_2Cl_2. ^{1}H NMR spectrum in Figure 10(c) shows that the signal attributed to *t*-butyl groups disappeared indicating the deprotection of the amine end group.

In addition to the structural evidences by NMR in each step of the synthetic strategy for the preparation of the different telechelic polymers discussed, GPC analysis showed that no significant change in molecular weight or polydispersity resulted from the dithioester group removal through the radical exchange method (Table 5). This is an additional advantage of the radical exchange method for removing the dithioester moiety as compared with other methods like aminolysis[12–16] or thermal treatment[17-20,39] that may result in polymer to polymer coupling increasing the polydispersity and altering the molecular weight. Table 5 show results of molecular weights (M_n) and polydispersity (PDI) of several semitelechelic and telechelic polymers prepared in this work with diverse end group functionalizations using the radical exchange reaction in a 5:1 ratio. In all cases the molecular weight decreases slightly after the radical exchange reaction in accordance with the substitution of the dithiobenzoate moiety with a lower molecular weight radical from the azo compound used. No increase in the PDI was observed.

Chemical Availability of End Groups in Telechelics

The presence of end groups by the synthetic strategy used is demonstrated sufficiently. Further derivations using the α, ω bifunctional polymers can be achieved using classical synthetic organic chemistry. Moreover, the synthetic strategy used could serve as an efficient way to introduce functional moieties to polymers for further bioconjugations or hydrogel preparations.[5,31] In this work, we show an esterification reaction between the hydroxyl end groups of dihydroxy telechelic polymers and methacrylic anhydride. The analysis of the product by ^{1}H NMR spectra allows identifying the signals of alkene protons between 5 and 6 ppm of the methacrylate (Fig. 11). The long reaction at room temperature was needed to avoid methacrylate radical reaction and to allow complete conversion of the hydroxyl groups.

CONCLUSIONS

We have described the synthesis and uses of two new functionalized chain transfer agents (CTA's) containing OH and protected amine groups and demonstrated its usefulness to control the synthesis of telechelic polymers from hexyl acrylate. Good control over molecular weight distributions of the

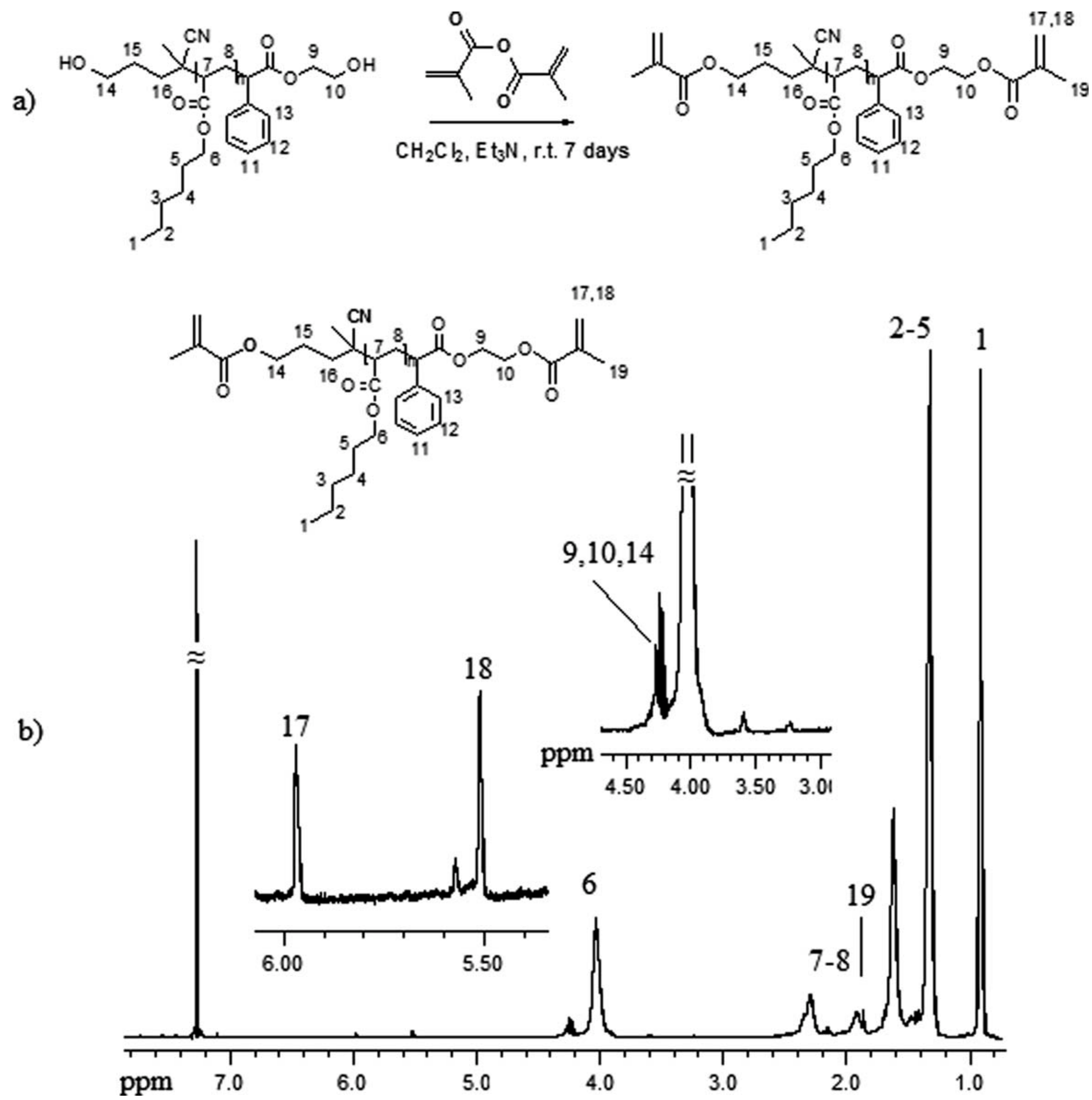


FIGURE 11 Introduction of alkene moieties into dihydroxy-telechelic poly(*n*-hexyl acrylate): (a) Reaction scheme, (b) ^{1}H NMR spectrum (500 MHz) of dimethacrylate-telechelic poly(*n*-hexyl acrylate).

obtained polymers shows that these dithioesters possesses similar reactivities and provided a narrow polydispersity as compared to more known dithioester derivatives of 4-ciano pentanoic acid and analogue CTA's. The developed type of CTA's have the advantage of the longer shelf lifetime because they are not prone to hydrolysis like the other type of CTA's used. Using a postpolymerization reaction with functionalized azocompounds α,ω-telechelic polymers, with —OH or —COOH as functional group at the second end were obtained adapting a methodology proposed initially by Perrier et al. but using only a fivefold excess of azo compounds instead of 20-fold excess as suggested in his report. This is important to save precious functionalized azocompound in this application. It was demonstrated that the strategy using only a fivefold excess of CTA was effective to obtain homotelechelic poly(*n*-hexylacrylate) with end functional OH and COOH groups and also to obtain heterotelechelic poly(*n*-hexylacrylate) with end functional OH and NH_2 groups. It was also demonstrated that the telechelic polymers prepared can be further derivatized to introduce other functionalities, like alkene groups as shown in a reaction of telechelic dihydroxy-poly(*n*-hexylacrylate) with methacrylic anhydride opening the door for the versatile thiol-ene chemistry. The developed CTA's are potentially useful for the preparation of other telechelic polymers that is, other acrylates, methacrylates, and styrenes.

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Science and Technology of Mexico (CONACYT) grant CIAM-2003-41414.

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