Novel Amphiphilic Graft Copolymers Prepared by Ring-Opening Metathesis Polymerization of Poly(ethylene glycol)-Substituted Cyclooctene Macromonomers

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Received July 12, 2002
Revised Manuscript Received October 18, 2002

Poly(ethylene glycol) (PEG) and hybrid “pegylated” materials have wide applicability in both materials science and biotechnology.[1] PEG itself (i.e., α,ω-diols), end-functional PEG of various molecular weight, and PEG-modified polymers are important in materials applications as surfactants and catalysts and in separations.[2−4] In biotechnology, functionalization of polymers and surfaces with PEG is an effective means to enhance biocompatibility, and as such PEG is targeted for a variety of medical applications.[5−7] When pegylated materials are further functionalized with biomolecules such as peptides and nucleic acids, one can explore a wide variety of biological targets that exploit the presence of these multiple functional components.[8−10]

The engineering properties of commodity polymers are potentially useful for biomaterials applications, but most of these polymers lack the necessary biocompatibility. Surface treatment methods are often utilized to address these issues.[11] In the case of polyolefins, such as polyethylene (PE), surface treatment by postpolymerization reactions is limited in scope and precision by the inherent low reactivity of the aliphatic backbone. Direct polymerization methods that afford graft copolymers may be advantageous in this regard. While metallocene-based polyolefin synthesis precludes the use of polar monomers, recent advances in ring-opening metathesis polymerization (ROMP) allow effective polymerization of cyclic olefins even when these contain polar functionalities.[12−15]

Macromonomer polymerization represents a convenient and effective method to access graft copolymers without the need for postpolymerization grafting. For example, the polymerization of norbornene macromonomers containing grafted PEG,[16] PEG-*b*-PS,[17] as well as triglyme and crown ether functionality[18] have been reported. Wagener et al. have synthesized polyolefins from PEG-grafted α,ω-dienes using acyclic diene metathesis (ADMET) polymerization, where the PEG grafts were synthesized by anionic polymerization of ethylene oxide from pendant alkoxides.[19] To our knowledge, polymerization of cyclooctene-based macromonomers has not been reported, probably due in part to the lower strain energy associated with cyclooctene that reduces its polymerizability relative to norbornene. This constraint should be exacerbated by the steric challenge imparted by the large pendant substituents. Nevertheless, graft copolymers from cyclooctene-based macromonomers should be very interesting relative to graft poly(norbornene)s for their inherent physical properties. Furthermore, hydrogenation of the poly(cyclooctene) backbone gives PE, a process that is not applicable to the poly(norbornene) case. Thus, we were intrigued to investigate the synthesis of amphiphilic graft poly(cyclooctene) by the macromonomer approach, where amphiphilicity is provided by pendant PEG chains. Herein we describe copolymerization chemistry of PEG-substituted cyclooctene macromonomers with cyclooctene itself, where the extent of macromonomer present in both the unsaturated polymer and its hydrogenated product can be controlled. This allows controlled manipulation of hydrophilicity, crystallinity, and mechanical properties, all which will contribute to the ultimate biological utility of these materials.

PEG-substituted cyclooctene macromonomers were prepared in two steps from 5-hydroxycyclooctene (**1**),[13] as illustrated in Scheme 1a. Ring-opening of succinic anhydride by **1** in the presence of 4-(dimethylamino)-pyridine (DMAP) gave the corresponding carboxylic acid **2**. This was followed by esterification with PEG−monomethyl ethers under dicyclohexylcarbodiimide (DCC) coupling conditions. Macromonomers **4** and **5** were prepared in this fashion, with PEG molecular weights of ca. 750 and 1000 amu, respectively. We find this pegylation strategy convenient, precluding the need for anionic polymerization of ethylene oxide and providing an ester linkage with possible utility in controlled-release applications.

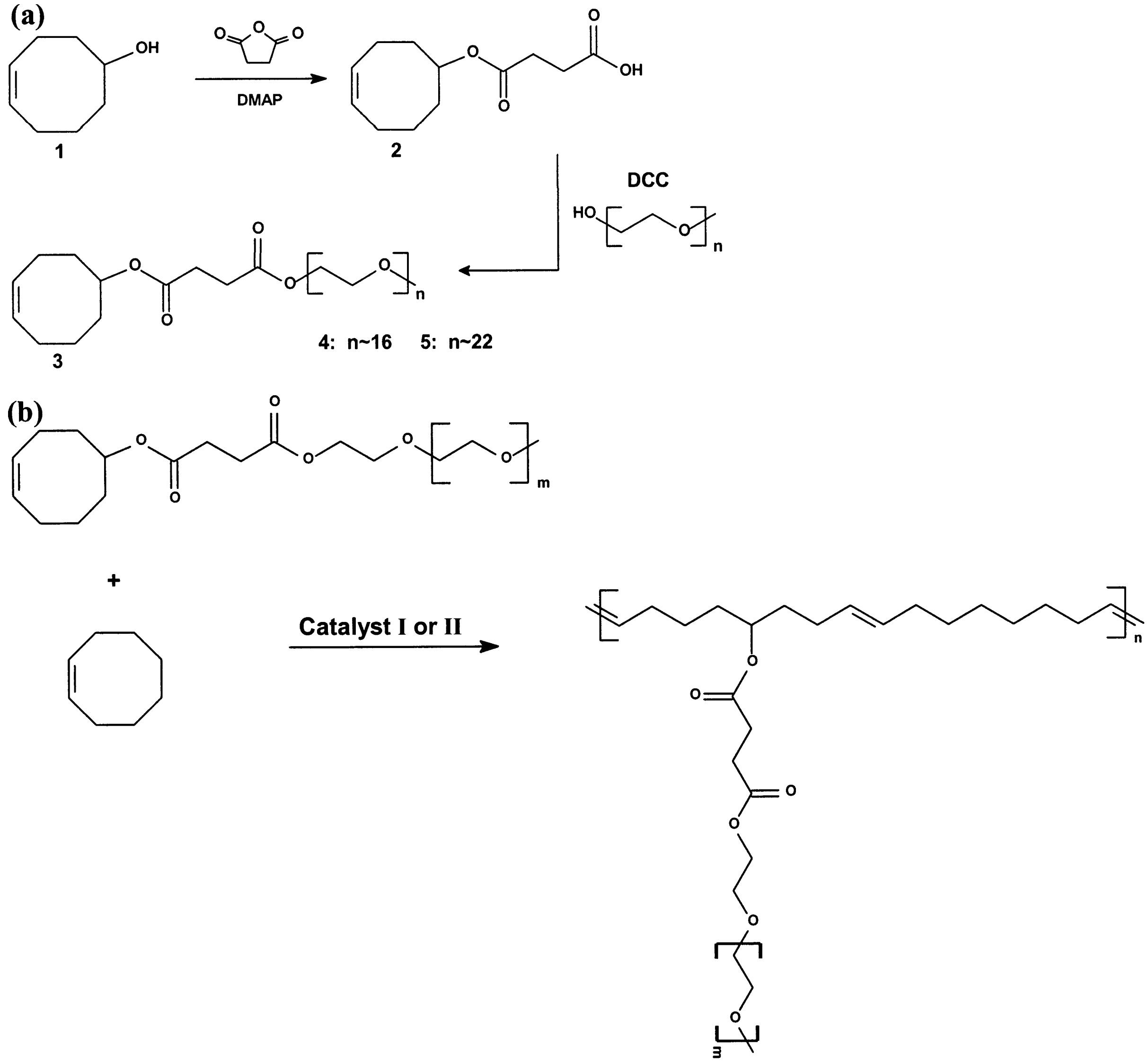
Substituted cyclooctenes **2**, **4**, and **5** are new compounds and have been characterized by a variety of techniques. For example, the ^{1}H NMR spectrum of macromonomer **5** consists of olefinic resonances at δ 5.65 ppm and resonances for the protons of the succinic anhydride linker centered at δ 2.65 ppm. A broad signal centered at δ 3.70 ppm reflects the interior methylene protons of PEG, while a singlet at δ 3.38 ppm reflects the methoxy end group. ^{13}C NMR spectroscopy confirmed the absence of residual mPEG (removed by extraction), which contains a diagnostic methylene signal at δ 61.9 ppm ($H_3CO-PEG-CH_2-OH$). Figure 1a shows gel permeation chromatography (GPC) overlays of **4**, **5**, and mPEG starting materials, where macromonomers **4** and **5** exhibit PDI values (ca. 1.03) in accord with those of the m-PEG starting materials.

Macromonomers **4** and **5** were copolymerized with cyclooctene in the presence of bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (**I**) (Grubbs’ generation I catalyst) and the mono-1,3-dimesitylimidazolidine-2-ylidene derivative (**II**) (Grubbs’ generation II catalyst), as illustrated in Scheme 1b. Typical experiments employed about 0.4 mmol of macromonomer and 0.4−3.8 mmol of cyclooctene. Catalysts were introduced to the macromonomer/cyclooctene mixtures as solutions in dry dichloromethane and then removed after polymerization by termination with ethyl vinyl ether.

As expected, the concentration and temperatures at which these polymerizations were performed dictate the course of the reaction. Our initial polymerization attempts were conducted at room temperature using catalyst **I**; though these achieved considerable molecular weights and conversion (>75%) in about 16 h, a significant presence of low molecular weight cyclics was also observed. In contrast, when polymerizations were carried out at 45 °C and ca. 2.0 M, vitrification occurred

10.1021/ma021094v CCC: $22.00

Scheme 1



within 15−30 min in the case of catalyst **I**, and in seconds using catalyst **II**, with a lower amount of cyclic byproduct.

Copolymers **6**−**11** in Table 1 represent copolymerizations of macromonomer **5** and cyclooctene using catalyst **I**. The extent of macromonomer incorporation into the copolymer was determined by ^{1}H NMR spectroscopy, by integration of olefinic protons of residual macromonomer (δ 5.65 ppm) against the methyne proton of the graft point (i.e., RCH(OR′)R). In all cases, approximately 60−70% of the macromonomer used became incorporated into the polymer product. Molecular weight estimation by GPC in DMF showed a decrease in M_n of the copolymers from approximately 330 000 g/mol (M_n) to 180 000 g/mol upon increasing cyclooctene ratios from 0.5 to 0.9, respectively.[20] The extent of low molecular weight byproducts decreased as well (Figure 1b). While an equilibrium exists between high polymer and cyclic oligomers for metathesis-derived polymers,[21−23] it is clear that the cyclooctene macromonomer is less reactive than unsubstituted cyclooctene in the presence of **I**, thus shifting this equilibrium toward cyclic oligomers.[24] In addition, the unequal reactivity of cyclooctene and macromonomer is believed to further contribute to the multimodality of the polymer peaks observed by GPC when using **I** as catalyst. The increased reactivity of catalyst **II** eliminated this multimodal feature (see below).

Monomer-to-catalyst ratios were investigated for these copolymerizations, as shown for copolymers **10** and **11** of Table 1. As expected, lower monomer-to-catalyst ratios gave lower molecular weight copolymers in a shorter period of time. For example, 50:50 copolymerizations using monomer-to-catalyst ratios of 500:1 (copolymer **6**) and 100:1 (copolymer **11**) gave products with M_n of 330 000 and 140 000 g/mol, respectively (see Supporting Information). Lower monomer-to-catalyst ratios also resulted in a decrease in low molecular weight oligomers, as observed by the more nearly unimodal GPC chromatograms. Similar copolymerization studies using catalyst **II** are shown in copolymers **12**−**14** of Table 1, where nearly complete conversion of macromonomer **4** was obtained in all cases. The increased activity of this catalyst is demonstrated by the fact that excellent macromonomer incorporation can be achieved using lower concentrations (1.0 M). Figure 2 overlays chromatograms of copolymers **6** and **12**, prepared using catalysts **I** and **II**, respectively, and otherwise identical reaction conditions (500:1 monomer-to-catalyst; 2.0 M in monomer). In the case of copolymer

Table 1. Characteristics of PEGylated Poly(cyclooctenamers) Prepared Using Catalysts I and II

entry[a]	copolymer	[M]/[Cat **I**]	[M]/[Cat **II**]	[M]	f_{macro}[b]	F_{macro}[c]	$10^{-3}M_n$[d]	PDI
1	**6**	500		2.0	0.5	0.35	330	1.61
2	**7**	500		2.0	0.4	0.27	310	1.73
3	**8**	500		2.0	0.25	0.15	180	1.78
4	**9**	500		2.0	0.1	0.06	190	1.21
5	**10**	250		2.0	0.5	0.40	220	1.59
6	**11**	100		2.0	0.5	0.46	140	1.54
7	**12**		500	2.0	0.5	0.49	540	2.20
8	**13**		250	1.0	0.5	0.50	330	1.56
9	**14**		100	1.0	0.5	0.50	220	1.60

[a] [M] = 2.0 mol/L, 45 °C in CH_2Cl_2. [b] f_{macro} = feed ratio of macromonomer relative to cyclooctene. [c] F_{macro} = fraction of macromonomer incorporated into polymer, determined by ^1H NMR. [d] Determined by GPC in DMF using linear polystyrene standards.

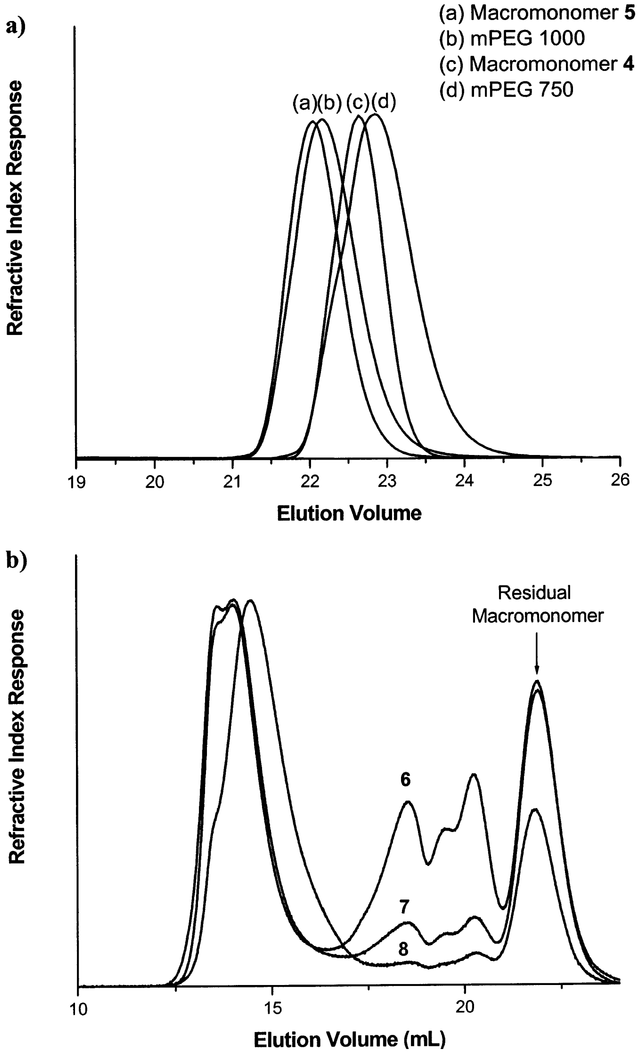


Figure 1. (a) Overlaid GPC chromatograms of macromonomers **4**, **5**, and mPEG starting materials. (b) Overlaid GPC chromatograms in DMF of copolymers **6**−**8** of Table 1 (copolymer **6** = 50:50, **7** = 40:60, **8** = 25:75 macromonomer **5**:cyclooctene).

12, where catalyst **II** was used, the presence of low molecular weight material is reduced dramatically, and reasonably narrow polydispersity is observed. Similar results were obtained when polymerizations were conducted at lower monomer concentrations (copolymers **13** and **14**).

The amphiphilic polycyclooctene−PEG copolymers described above are soluble in a range of organic solvents (MeOH, acetone, CH_2Cl_2, $CHCl_3$, THF, DMF, and toluene) at all percentages of macromonomer incorporation. Hexane proved suitable for precipitation.

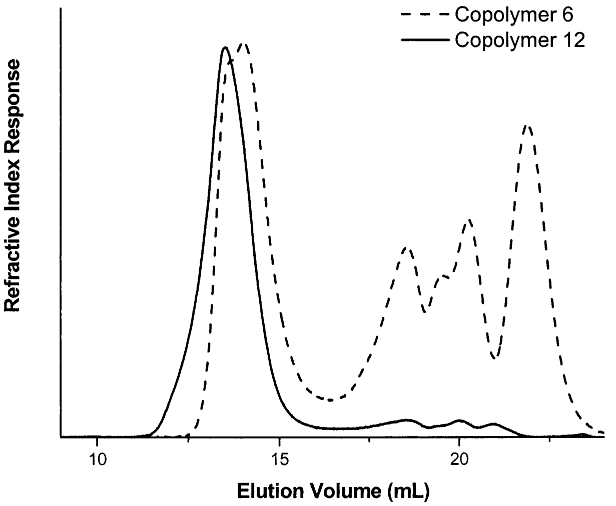


Figure 2. GPC chromatograms in DMF of copolymers **6** and **12** synthesized with catalysts **I** and **II**, respectively.

In addition, except for copolymer **9** in Table 1 all samples readily form aqueous solutions. These amphiphilic copolymers stabilize oil-in-water emulsions for hours to days, depending on macromonomer content. GPC analysis of these copolymers in THF vs DMF highlights their unique solution hydrodynamic volume (see Supporting Information). In THF, a poor solvent for PEG, the copolymer contracts substantially, while in DMF, the PEG grafts are extended, leading to a dramatic increase in hydrodynamic volume.

These unsaturated polycyclooctene copolymers can be hydrogenated using *p*-toluenesulfonhydrazide[14,25] to give the saturated analogues with PE backbones. This chemical transformation resulted in dramatic differences in solubility and crystallinity, with variations depending on macromonomer content. Hydrogenated products with low macromonomer content, such as copolymers **8a** and **9a**, were completely insoluble at room temperature, while copolymer **7a** was soluble in polar solvents. Copolymer **6a**, with the highest macromonomer content studied here, remained water-soluble after hydrogenation. Differential scanning calorimetry (DSC) confirmed the increasing crystallinity of these copolymers with decreasing macromonomer incorporation, and ^1H NMR spectroscopy and GPC analysis were used to further confirm the structure of these hydrogenated products (see Supporting Information). The ^1H NMR spectrum of copolymer **7a**, for example, showed no signals in the olefinic region and showed resonances that reflect the methyne proton of the graft point, the succinic anhydride linker, and the methyl ether end group of the PEG graft, all in accord with the expected structure. GPC analysis (in trichlorobenzene at 135 °C) of copolymer **9a** showed only small changes in molecular weight (using multiple angle laser light scattering detection) from its unsaturated precursor.

In summary, we have synthesized novel PEG-substituted cyclooctene macromonomers and demonstrated their integration into graft copolymers by ring-opening metathesis polymerization. These copolymers display many tunable features based on extent of macromonomer incorporation, including a wide range of organic and aqueous solubility, crystallinity, and ability to function as macromolecular surfactants. The polymerization of cyclooctene-based macromonomers appears to be a viable method to obtain novel, graft polyethylene copolymers, due to the feasibility of backbone hydrogenation. These PEG-functional polyolefins are expected to present many possibilities for the synthesis of novel, biofunctional macromolecules based on polyolefins, with potential in delivery, implant, and biomedical coating applications.

Acknowledgment. The authors acknowledge financial support from the University of Massachusetts, Amherst, a Healey Endowment grant, and a Center for UMASS/Industry Research on Polymers (CUMIRP) Exploratory Award. K.B. acknowledges with thanks the support of a GAANN fellowship. J.S. received an Honors College undergraduate fellowship from UMass, and E.J. acknowledges a Praxis liberal arts fellowship from Smith College, Northampton, MA. Professor E. B. Coughlin is acknowledged for helpful discussions. Bryan Parrish is acknowledged for contribution of early experiments.

Supporting Information Available: Experimental procedures for macromonomer synthesis and copolymerization, GPC chromatograms of copolymers **6** and **11**, copolymer **6** in THF vs DMF, DSC of hydrogenated copolymer **9a**, ^{1}H NMR spectrum of copolymer **7a**, and GPC of copolymer **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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MA021094V