DOI: 10.1002/cjoc.201300638

Synthesis of Novel Glycidol Copolymers with Pendant Alkene and Hydroxyl Groups

Siwei Liu,* Feng Zhang, Yi Zhang, and Jiarui Xu

PCFM Lab, School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou, Guangdong 510275, China

A series of linear poly glycidol copolymers, tethering with both alkene and hydroxyl groups, were prepared by a combination of anionic ring-opening polymerization (ROP) using specific reactions of ethoxy ethyl glycidyl ether (EEGE) and allyl glycidyl ether (AGE) firstly, and subsequently removal of the protection group of glycidol in EEGE to achieve the linear copolymer pendant with both hydroxyl groups and double bonds. The EEGE/AGE monomer reactivity ratio is measured to be 3.30/1.13. The chemical compositions of the as-synthesized polymers were characterized by ^{1}H NMR and GPC, and the glass transition temperatures (T_g) of as-synthesized polymers were determined by DSC. The final copolymers have abundant double bonds and hydroxyl as side groups. Furthermore, the ratio of the double bonds to hydroxyl groups can be controlled by the ratio of the starting materials in a wide range.

Keywords amphiphiles, anions, ring-opening polymerization, glycidol copolymers, biomaterials

Introduction

Poly(ethylene glycol) (PEG) is a kind of bio-functional material with extensive applications in the fields of food, pharmacology and biomedicine.[1-4] It has the following advantages: a good solubility in water and most organic solvents, unique anti-fouling[5-9] and anti-bacteria properties,[10-13] low toxicity which is approved by US FDA, and so on. The PEG, however, only has one or two active chemical group(s) (hydroxyl group) at the end of its backbone, which limits its combining ability with other functional molecules and subsequently limits its practical applications in a variety of application environments. To break through the limitation, PEG has been designed and synthesized with a great number of molecular structures, such as star-shaped, branched, *etc*. Unfortunately, these methods require very complex synthesis process and the number of active groups in the resulting modified PEG is still relatively low. Feng *et al.*[14] reported a series of dendrimer-like poly(ethylene oxide)s with up to 384 external hydroxyl groups; however, due to the steric problem, the number of active hydroxyl groups is far below that number. The star-shaped macromolecules containing polyglycidol and poly(ethylene oxide) as arms synthesized by Lapienis *et al.*[15-18] also have the same steric problem. Probably, in such dendrimer-like or star-shaped structure, due to the folding of the polymer chains (or arms), some of the hydroxyl groups could not be exposed out directly, thus decreasing the reactivity of these hydroxyl groups as a whole for such polymers. To date, besides hydroxyl groups, only amino functionalities are accessible to be introduced in PEG chain via the copolymerization of ethylene oxide. The linear copolymers comprising alkene were synthesized by Holger group through copolymerization of ethylene oxide and allyl glycidyl ether.[19]

To tether multiple (different) functional groups to a single polymer chain (or a single macromolecular) analogous to PEG is one of important ways to widen application of PEG derivatives. In addition, chemical modification of an existing polymer via its active groups is an easy and effective way to incorporate new properties into the original polymer, thus achieving new type of functional material. There are some approaches to attach functional groups onto PEG (or tether PEG to other functional groups conversely). Yao's group grafted PEG onto the anterior surface of hydrophobic acrylic intraocular lens by atmospheric pressure glow discharge treatment to improve their biocompatibility.[20] Due to the improved penetration of PEGylation proteins into tissue, Molly introduced PEG segments onto fibroblast growth factor 2.[21] Su's group modified a rigid porous microsphere [poly(glycidyl methacrylate-divinylbenzene)] with PEG to decrease the irreversible interaction between microsphere and protein, and the results showed that the modified microsphere was expected to become a promising protein purification media.[22]

---

* E-mail: liusiw@mail.sysu.edu.cn
Received August 22, 2013; accepted September 23, 2013; published online October 17, 2013.

In this paper, a series of linear polymer, poly(ethoxy ethyl glycidyl ether-*co*-allyl glycidyl ether) [P(EEGE-*co*-AGE)], were synthesized firstly through anionic ring-opening polymerization (ROP) by using AGE and EEGE with the catalyst of triisobutylaluminum (i-Bu$_3$Al) and tetraoctylammonium bromide (NOct$_4$Br).[23,24] The obtained intermediate product was subsequently hydrolyzed and the linear polymer, P(Gly-*co*-AGE), pendant with both hydroxyl groups and double bonds was generated. The motivation to design and synthesize this kind of polymer is that, for one thing, we desire that the as-synthesized polymers possess active hydroxyl groups (for bio-compatibility and bio-application considerations) as many as possible; for another, the as-synthesized polymers should contain other active functional groups which could be chemically modified further easily (*e.g.*, introduction of DNA, RNA, drug molecules or other bioactive molecules). That is, on a single analog PEG chain, different kind of functional groups are introduced at a time. From the synthetic route it can be expected that the ratio of hydroxyl group to alkene could be adjusted in a wide range to meet the practical application demand.

Experimental

Materials and measurements

Glycidol (2,3-epoxypropan-1-ol, 96%, Aldrich), triisobutylaluminum (i-Bu$_3$Al, 1.0 mol/L in toluene, Aldrich), and tetraoctylammonium bromide (NOct$_4$Br, 98%, Aldrich) were used as received. Allyl glycidyl ether (AGE) purchased from Acros was distilled under vacuum, and treated with triisobutylaluminum for 15 min in a glass flask equipped with PTFE stopcocks to remove traces of impurities. Toluene was purified through distillation over sodium chips under nitrogen atmosphere before use. Other chemical reagents were purchased from local chemical corporations and used as received. FTIR spectra were recorded on a Nexus 670 Fourier transform infrared spectrometer (by Nicolet). The ^{1}H NMR spectroscopies were measured on a Mercury-Plus 300 MHz (by Varian). The molecular weights of the as-synthesized polymers were detected with a Waters Breeze gel chromatography using dimethyl formamide as the solvent and polystyrene as the standard.

Synthesis of 2,3-epoxypropyl-1-ethoxyethyl ether (EEGE)

The protection for the hydroxyl group of glycidol was performed following the procedure reported in the literatures.[25,26] Glycidol (10.00 g) was dissolved into ethyl vinyl ether (40 mL) in a 100 mL flask equipped with a magnetic stirrer; 4-methylbenzenesulfonic acid (0.25 g) was added in batch. In the feeding process, the temperature of the mixture was controlled below 35 ℃ with a constant stirring for 3 h. Then saturated solution of sodium bicarbonate aqueous (100 mL) was added. The obtained organic layer was dried by anhydrous magnesium sulfate for 1 h, and then filtrated. The colorless liquid product (EEGE) was obtained by vacuum distillation (51 ℃/80 Pa) with a yield of 80%.

Copolymerization of EEGE with AGE

The typical procedure used for the copolymerization of EEGE with AGE was as follows: a Schlenk tube (about 20 mL in volume) was vacuumed at 120 ℃ for 1 h and cooled to room temperature and then to 0℃ in argon atmosphere. Toluene (10.0 mL), EEGE (1.0 mL, 6.6 mmol), AGE (0.78 mL, 6.6 mmol), tetraoctylammonium bromide (0.035 g, 0.06 mmol) and triisobutylaluminum (1.0 mol/L in toluene, 1.1 mL) were added into the tube in argon atmosphere and the tube was sealed. Then, the reaction was held at 0 ℃ for 12 h in argon atmosphere. The reaction was terminated by addition of a few drops of ethanol subsequently. After removal of the solvents by rotary evaporation, the residue was dissolved in dichloromethane, dried by anhydrous sodium sulfate and filtered. The final wax-like product was obtained after complete removal of solvents under vacuum at 50 ℃. The yield is near 100%.

Deprotection of the copolymer: P(EEGE-*co*-AGE)

The deprotection procedure was illustrated as follows. P(EEGE-*co*-AGE) (1.2 g) was dissolved into 100 mL ethanol which contained 3% (*V*/*V*) hydrochloric acid (*ca.* 0.054 mol/L). After stirring for 4 h at room temperature, the solution was neutralized by adding 50 mL of 1.0 mol/L sodium carbonate aqueous solution. The reaction mixture was filtered. The filtrate was distilled off the solvent, and then dried at 50 ℃ for 12 h under vacuum. The viscous liquid product was achieved with the yield near 100%.

Results and Discussion

Chemical structure of the as-synthesized copolymers

The synthetic route for P(EEGE-*co*-AGE) and its deprotection form is outlined in Figure 1. The first step, the synthesis of EEGE, was order to protect the hydroxyl group of glycidol to avoid side reaction in the subsequent experiments. Then, EEGE and AGE were copolymerized to generate a linear copolymer, P(EEGE-*co*-AGE), by using tetraoctylammonium bromide as the initiator and triisobutylaluminum as the catalyst. Finally, the polymer was hydrolyzed in ethanol containing hydrochloric acid for 4 h.

Figures 2 and 3 are the ^{1}H NMR spectra of a typical copolymer before (measured in DMSO-d_6) and after (recorded in CD$_3$OD) deprotection. The attribution of each proton in the polymer is labeled in the figures.

After the protection groups of glycidol (in EEGE) were eliminated, some proton peaks, *e.g.*, δ 4.64—4.68 [proton 6 in P(EEGE-*co*-AGE), as shown in Figure 2] disappeared. By comparing Figures 2 and 3, the characteristic peaks of AGE (δ 5.7, 5.3 and 3.9) had no obvious changes during the deprotection procedure. The

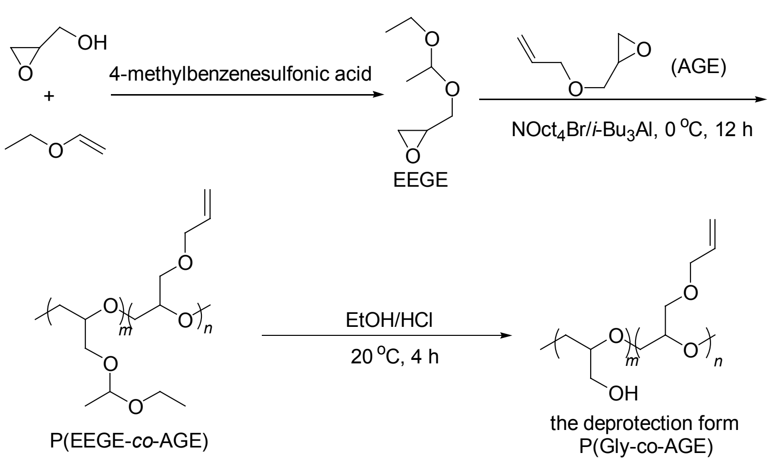

Figure 1 The synthetic route for P(EEGE-*co*-AGE) and its deprotection form, P(Gly-*co*-AGE).

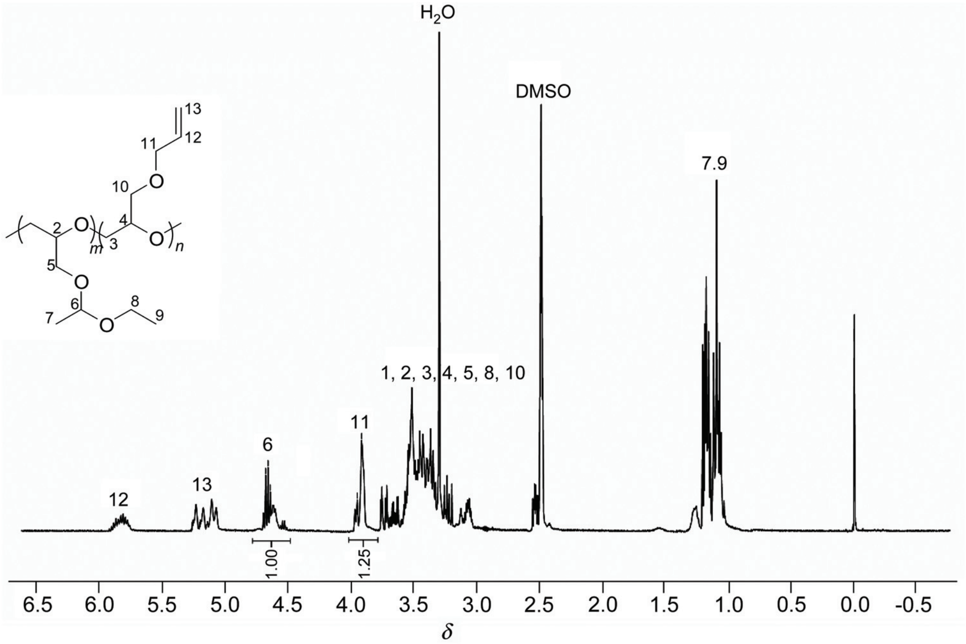

Figure 2 The ^1H NMR spectrum of P(EEGE-*co*-AGE), recorded in DMSO-d_6.

changes in the ^1H NMR spectra indicate that a reaction time of 4 h is suitable for the deprotection procedure of P(EEGE-*co*-AGE).

By varying the feed ratio of EEGE, AGE, initiator and catalyst, a series of P(EEGE-*co*-AGE)s were synthesized, as listed in Table 1. Through the investigation of the self-polymerization of EEGE, Deffieux[23] found that the self-polymerization process of EEGE greatly depended on the ratio of $i\text{-}Bu_3Al/NOct_4Br$. The function of the catalyst $NOct_4Br$ was mainly to initiate the copolymerization, and the other catalyst, $i\text{-}Bu_3Al$, featured prominently not only in initiating stage but also in the copolymerization speed. Only when the ratio was greater than 2, the self-polymerization of EEGE could be carried out. When the ratio was increased up to 4, the polymerization of EEGE could be happened in a quantitative manner. Furthermore, if the ratio was equal to 5, high molecular weight of poly (EEGE) could be generated. As seen in Table 1, the ratio of $i\text{-}Bu_3Al/NOct_4Br$

Table 1 The polymerization parameters and characterization data of P(EEGE-*co*-AGE)

Run	[AGE]/(mol•L^{-1})	AGE/EEGE^a	AGE/EEGE^b
1	0.28	0.14	0.135
2	0.32	0.16	0.145
3	0.42	0.21	0.19
4	0.54	0.27	0.22
5	1	0.5	0.38
6	2	1	0.87
7	3	1.5	1.34

^{a} Molar feed ratio; ^{b} Experimental molar ratio calculated by ^1H NMR. The molar ratio of $i\text{-}Bu_3Al$ to $NOct_4Br$ is 5, the concentration of EEGE is 2 mol/L, and the reaction time is 12 h in each run. The yield is near 100% in all runs (calculated by weight).

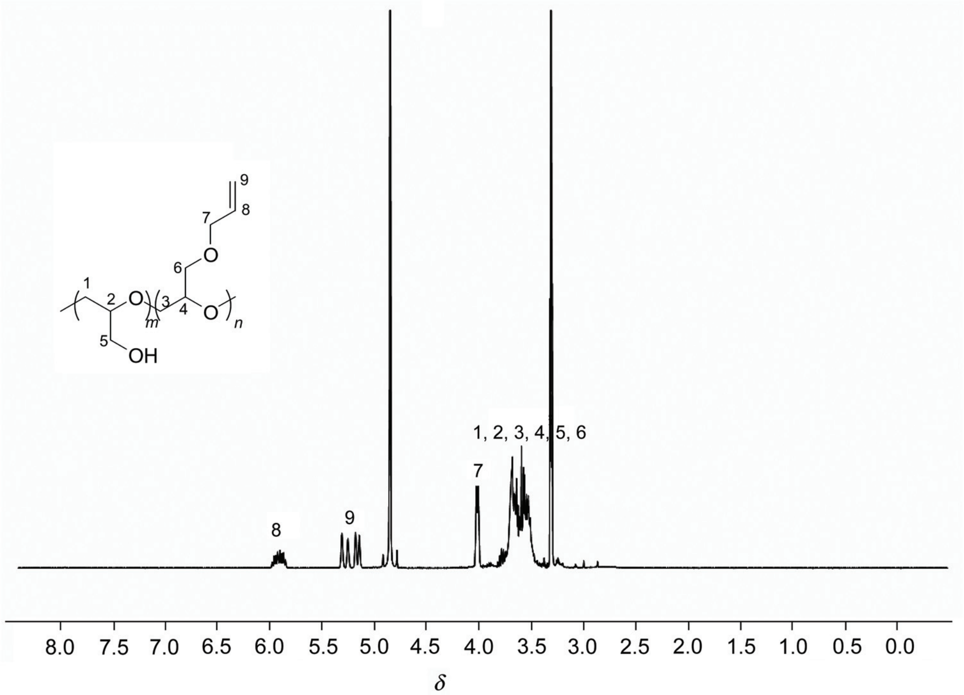

Figure 3 ^{1}H NMR spectrum of the deprotection form of P(EEGE-*co*-AGE), recorded in CD_3OD.

used in all the seven experiments was greater than 4. The yield of each experiment was in all cases near 100%, indicating that the polymerization was carried out in a quantitative manner. The ratio of AGE to EEGE in the P(EEGE-*co*-AGE) increased along with the increase of the feed ratio of AGE to EEGE.

It should be pointed out that the values of AGE to EEGE (molar ratio) in P(EEGE-*co*-AGE) were smaller than their feed ratio. This might be due to the different reactivity of AGE and EEGE in the copolymerization process. To confirm this query, we measured the reactivity ratios of AGE and EEGE in polymerization. In order to accurately calculate the reactivity ratios, each copolymerization was terminated when its conversion rate was less than 10% (Table 2). The reactivity ratios were calculated by the following Eq. (1):[27]

$$\left(\frac{x}{y^{1/2}}\right)r_1-\left(\frac{y^{1/2}}{x}\right)r_2+\left(\frac{1}{y^{1/2}}-y^{1/2}\right)=0 \tag{1}$$

where x is the feed molar ratio (EEGE/AGE) of the copolymerization; y is the molar ratio of (EEGE/AGE) in P(EEGE-*co*-AGE); r_1 is the reactivity ratio of EEGE; r_2 is the reactivity ratio of AGE.

Based on the experimental data, the reactivity ratios for EEGE ($r_1=3.30$) and AGE ($r_2=1.13$) in this copolymerization were calculated. The considerable difference in the reactivity ratios indicates that the reactivity of EEGE is higher than that of AGE while involving such anionic copolymerization. This could be another evidence for the data in Table 1 that the molar ratio of EEGE to AGE in P(EEGE-*co*-AGE) is lower than that in starting materials.

Table 2 Determined EEGE/AGE molar ratio at initial reaction rates

Sample	$R_{\text{feed ratio}}{}^a$	$R_{\text{polymer}}{}^b$	Conversion^c/%
1	1/11.4	1/5.7	8.1
2	1/7.6	1/3.7	7.3
3	1/2.5	1/1.8	6.4
4	1/0.67	1/0.27	5.3
5	1/0.33	1/0.14	4.6

[a] The feed ratio of EEGE to AGE; [b] The molar ratio of EEGE to AGE in P(EEGE-*co*-AGE) is measured by ^{1}H NMR; [c] The data determined by gravimetric method.

After deprotection, there should be lots of hydroxyl groups tethered to the P(EEGE-*co*-AGE) chains. This can be verified from their infrared spectra (Figure 4). In

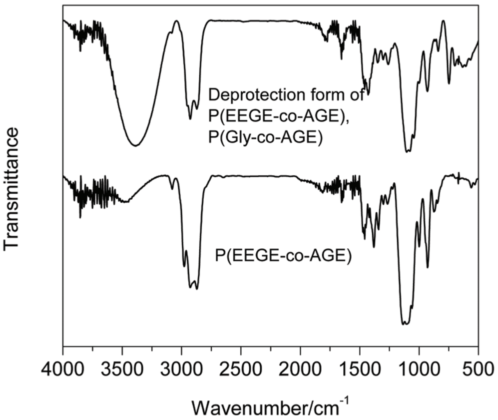

Figure 4 The FT-IR spectra of P(EEGE-*co*-AGE) and the deprotection production of P(EEGE-co-AGE).

Table 3 Molecular weight, monomer composition and T_g of the as-synthesized P(EEGE-*co*-AGE) copolymers

Run	Composition (th^a)	Composition (exp^b)	M_n (th^a, g/mol) (×10^4)	M_n (exp^c, g/mol) (×10^4)	$M_w/M_n{}^c$	T_g/℃
1	AGE_{55}-*co*-$EEGE_{35}$	AGE_{80}-*co*-$EEGE_{117}$	1.1	2.6	1.63	−94.3
2	AGE_{25}-*co*-$EEGE_{118}$	AGE_{15}-*co*-$EEGE_{54}$	2.0	1.0	1.43	−83.8
3	AGE_{59}-*co*-$EEGE_{59}$	AGE_{69}-*co*-$EEGE_{71}$	1.5	1.8	1.68	−83.5
4	AGE_{16}-*co*-$EEGE_{115}$	AGE_{6}-*co*-$EEGE_{41}$	1.9	0.7	1.44	−79.9
5	AGE_{19}-*co*-$EEGE_{118}$	AGE_{6}-*co*-$EEGE_{38}$	1.9	0.6	1.46	−74.7
6	AGE_{32}-*co*-$EEGE_{118}$	AGE_{9}-*co*-$EEGE_{34}$	2.1	0.6	1.50	−74.5
7	AGE_{89}-*co*-$EEGE_{59}$	AGE_{131}-*co*-$EEGE_{91}$	1.9	2.8	1.76	−73.7

^{a} Theoretical values. Experimental data determined by ^{1}H NMR (*b*) and GPC (*c*) in THF using a calibration with polystyrene as standards.

its deprotection form, the peaks around 3400 cm^{-1} become wide and strong, indicating a large number of hydroxyl groups exist in the deprotection form of the copolymer.

Molecular weight of the as-synthesized polymers

The molecular weights of these as-synthesized polymers were determined by gel permeation chromatography (GPC). The data were composited in Table 3 (the experimental run in Table 1 had no relationship to the run in Table 3). There are significant differences between the theoretical values and experimental data. For this kind of polymer, Deffieux[23] proposed that this could be explained by the difference of hydrodynamic volume of P(EEGE) and polyglycidol.

Thermal properties of the as-synthesized polymers

The glass transition temperature (T_g) of these as-synthesized polymers was determined by differential scanning calorimetry (DSC). The T_g values of P(EEGE-*co*-AGE) with different chemical composition are in the range of −73—−95 ℃. However, due to the limitations of the instrument, T_g of the deprotection form of P(EEGE-*co*-AGE), P(Gly-*co*-AGE), was not detected (it might be lower than −100 ℃). From the given data of T_g in Table 3, it can be seen that the variation of T_g seems to be related somewhat with the changes of molecular weight (theoretical values) as well as the chemical composition. The T_g increases with increasing of the molecular weight and the amount of AGE segments in these copolymers. This result is basically the same as the result obtained by Holger.[19] The obvious difference between theoretical M_n and measured M_n is probably due to two reasons: (a) the apparent difference between PEG chain and polystyrene chain in structure (for GPC detection); (b) some of the protons in the PEG chain could not be detected by ^{1}H NMR because of the entanglement of the polymer chains.

Conclusions

In this paper, by using allyl glycidyl ether (AGE) and ethoxyethyl glycidyl ether (EEGE) as the starting materials, triisobutylaluminum and tetraoctylammonium as the catalysts, a series of linear copolymers, P(EEGE-*co*-AGE), were synthesized through anionic polymerization. After deprotection, the resultant polymer was a new type of amphiphilic copolymer pendant with functional side groups with both alkene and hydroxyl group. This method paved a way to synthesize glycidol copolymers with multiple different functional groups at a time. The molar ratio of EEGE to AGE in the copolymer could be controlled by varying the feed ratio of EEGE and AGE as well as the reaction conditions, and subsequently allowing the adjustment of the solubility of the copolymer in water/organic phase. Due to the coexistence of double bonds and hydroxyl groups in the side chain, it provides the reactive sites in the copolymer, just like a chemical reaction platform, for further chemical modification and functionalization.[10,28-30]

Acknowledgement

This study was supported by the National Natural Science Foundation of China (No. 50903096), the Department of Science Technology of Guangdong Province (No. 2008B090500196), and the Fundamental Research Funds for the Central Universities.

References

[1] Duncan, R. *Nat. Rev. Drug Discovery* **2003**, *2*, 347.
[2] Veronese, F. M. *Biomaterials* **2001**, *22*, 405.
[3] Pasut, G.; Veronese, F. M. *Prog. Polym. Sci.* **2007**, *32*, 933.
[4] Lu, Q.; Wei, D.; Zhou, J.; Xu, J.; Cheng, J.; Zhu, J. *Chin. J. Chem.* **2013**, *31*, 401.
[5] Dalsin, J. L.; Hu, B. H.; Lee, B. P.; Messersmith, P. B. *J. Am. Chem. Soc.* **2003**, *125*, 4253.
[6] Nath, N.; Hyun, J.; Ma, H.; Chilkoti, A. *Surf. Sci.* **2004**, *570*, 98.
[7] Dalsin, J. L.; Lin, L.; Tosatti, S.; Vörös, J.; Textor, M.; Messersmith, P. B. *Langmuir* **2005**, *21*, 640.
[8] Nuzzo, R. G. *Nat. Mater.* **2003**, *2*, 207.
[9] Lee, H.; Lee, K. D.; Pyo, K. B.; Park, S. Y.; Lee, H. *Langmuir* **2010**, *26*, 3790.
[10] Mei, Y.; Yao, C.; Fan, K.; Li, X. S. *J. Membrane Sci.* **2012**, *417—418*, 20.
[11] Ding, X.; Yang, C.; Lim, T. P.; Hsu, L. Y.; Engler, A. C.; Hedrick, J. L.; Yang, Y. Y. *Biomaterials* **2012**, *33*, 6593.
[12] Nie, N.; Tu, Q.; Wang, J. C.; Chao, F.; Liu, R.; Zhang, Y. R.; Liu, W. M.; Wang, J. Y. *Colloids Surf. B*: *Biointerfaces* **2012**, *97*, 226.
[13] Zhang, F.; Liu, S. W.; Zhang, Y.; Xu, J. R.; Wei, Y. *Chem. Lett.* **2012**, *41*, 1655.
[14] Feng, X. S.; Taton, D.; Chaikof, E. L.; Gnanou, Y. *J. Am. Chem. Soc.* **2005**, *127*, 10956.

[15] Lapienis, G.; Penczek, S. *Biomacromolecules* **2005**, *6*, 752.
[16] Lapienis, G.; Penczek, S. *Macromol. Symp.* **2003**, *195*, 317.
[17] Xie, C.; Lu, C. F.; Chen, Z. X.; Yang, G. C. *Chin. J. Chem.* **2006**, *24*, 585.
[18] Gong, Y. F.; Fu, X. K.; Zhang, S. P.; Jiang, Q. L. *Chin. J. Chem.* **2007**, *25*, 1743.
[19] Boris, O.; Holger, F. *Bioconjugate Chem.* **2011**, *22*, 436.
[20] Lin, L.; Wang, Y.; Huang, X. D.; Xu, Z. K.; Yao, K. *Appl. Surf. Sci.* **2010**, *256*, 7354.
[21] Catherine, E. K.; Charles, H. T.; Molly, S. S. *J. Controlled Release* **2010**, *144*, 25.
[22] Wang, R. W.; Zhang, Y.; Ma, G. H.; Su, Z. G. *Colloid Surface B* **2006**, *51*, 93.
[23] Gervais, M.; Brocas, A. L.; Cendejas, G.; Deffieux, A.; Carlotti, S. *Macromolecules* **2010**, *43*, 1778.
[24] Yuan, C.; Xu, X.; Zhang, Y.; Ji, S. *Chin. J. Chem.* **2012**, *30*, 1474.
[25] Fitton, A.; Hill, J.; Jane, D.; Miller, R. *Synthesis* **1987**, 1140.
[26] Pang, X. C.; Jing, R. K.; Huang, J. L. *Polymer* **2008**, *49*, 893.
[27] Ezrielev, A. I.; Brokhina, E. L.; Roskin, E. S. *Vysokomol. Soedin., Ser. A* **1969**, *11*, 1670.
[28] Zhang, F.; Liu, S. W.; Zhang, Y.; Xu, J. R.; Wei, Y. *Chin. J. Chem.* **2012**, *30*, 2275.
[29] Zhang, F.; Liu, S. W.; Zhang, Y.; Chi, Z. G.; Xu, J. R.; Wei, Y. *J. Mater. Chem.* **2012**, *22*, 17159.
[30] Gauthier, M. A.; Gibson, M. I.; Klok, H. A. *Angew. Chem., Int. Ed.* **2008**, *48*, 48.

(Zhao, X.)