# Synthesis of Poly(glycolic acid-*alt*-L-aspartic acid) from a Morpholine-2,5-dione Derivative

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ABSTRACT: For the purpose of increasing the hydrophilicity of a polylactide, a new monomer, (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione, was successfully polymerized. The benzyl protective group of the polymer was completely removed to give poly(glycolic acid-*alt*-L-aspartic acid). The structures and properties of both protected and deprotected polymers were carefully studied by NMR, GPC, and DCA. It is found that the morpholine-2,5-dione derivatives with side functional groups which have no substituent on the 6 position of the morpholine ring are much more reactive than those monomers with a substituent on the 6 position of the ring in polymerization. The resulting polymer shows promising hydrophilicity, as can be seen from the DCA result.

## Introduction

Poly(α-hydroxy acid)s are a group of synthetic, biodegradable polymers that have received great interest for many years.[1−4] Due to their well-known safety in vivo, they are widely used in the biomedical fields, e.g., as sutures, implant materials, and drug delivery systems.

Recently, with the development of pharmaceutical chemistry, many water-soluble drugs, such as peptides and proteins, have appeared, with an urgent need for a suitable delivery system which would protect the unstable molecules against degradation.[5,6] The existing system based on poly(α-hydroxy acid)s and their copolymers was proved to be unsuitable, because the hydrophobic nature led to lower drug loading in the system and limited the method of microencapsulation.[7,8]

Several investigations on the introduction of functional groups into polyesters have been reported.[9−14] The matrices made of these materials may have better affinity with the water-soluble drugs. Among these attempts is the synthesis of polyesteramides with pendant functional groups from morpholine-2,5-dione derivatives.[14,15] Unfortunately, the homopolymerization of morpholine-2,5-dione derivatives with side functional groups failed, and only a small amount of the monomer can be copolymerized with d,l-lactide and ε-caprolactone. The lysine ε-amino groups in linear poly(L-lactic acid-*co*-L-lysine) copolymers with about 1% lysine content were utilized to initiate the ring-opening polymerization of the amino acid *N*-carboxyanhydrides to yield the comblike graft copolymer.[16] Unfortunately, the process is very complicated.

In the present paper, we report the synthesis of (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione as a new monomer and its successful homopolymerization, which indicate the higher reactivity of the monomer and the possibility of its copolymerization with lactide or lactone. The protective group of the side carboxy group can be easily removed by catalytic hydrogenation with Pd/C, which leads to the formation of a new polymer, poly(glycolic acid-*alt*-L-aspartic acid). The structures and properties of both protected and deprotected polymers are also given in detail.

## Experimental Section

**Materials.** Stannous octoate was purchased from Aldrich and was used as received. Tetrahydrofuran (THF) was distilled from $CaH_2$. 1,4-Dioxane was distilled from sodium powder. All the other reagents were purchased from Beijing Chemical Reagent Co. and used without further purification.

**Methods.** Melting points were measured with the Thiele apparatus.

Elemental analyses were carried out by the Center of Analysis & Testing of Peking University.

$^1$H NMR and $^{13}$C NMR spectroscopy was performed on a Bruker ARX-400 spectrometer. $CDCl_3$ and DMSO-$d_6$ were used as solvents. Tetramethylsilane was used as an internal standard.

Mass spectra were obtained with a VG ZAB-HS mass spectrometer (EI).

FTIR results were obtained from a Nicolet Magna-IR 750 spectrometer.

The $\bar{M}_n$ and $\bar{M}_w$ of polymer were determined by gel permeation chromatography (GPC). The GPC measurements were carried out with THF as eluent (1.0 mL/min) using a Waters 510 pump, a Waters U6K injector, three Waters μStyragel columns ($10^5$, $10^4$, 500 Å) in series, and a Waters 401 differential refractomer. The columns were calibrated with polystyrene standards having a narrow molecular weight distribution.

Dynamic contact angles of the polymers were tested by a CAHN dynamic contact angle analyzer (DCA-322).

**Monomer Synthesis. (i) Bromoacetyl Bromide.** Red phosphorus (24 g, dried at 110 °C for 4 h) and acetic anhydride (2 mL) were added to 115 mL of acetic acid. With vigorous stirring, dry bromine (200 mL) was added to the suspension gradually. Heating of the mixture was started when half of the bromine was added, and the mixture was kept at 140 °C for another 2 h after the addition. When the distillation was carried out, the resulting product was collected at a temperature ranging from 146 to 151 °C. The yield was 40.2% (70 mL). Because of its great sensitivity to moisture, the resulting bromoacetyl bromide was not rectified.

**(ii) β-Benzyl-L-aspartate.** With vigorous stirring, 45 mL of concentrated hydrochloride solution was added to the suspension of L-aspartate (26.6 g) in benzyl alcohol (300 mL). A clear solution was obtained after 5 min of heating over a boiling water bath, and it was heated for another 25 min to complete the reaction. The solution was cooled to room temperature quickly, followed by immediate addition of triethylamine (56 mL). White crystals appeared, and the mixture was stored in a refrigerator overnight to complete the crystallization. The crystal was filtered and washed with alcohol and acetone. The yield was 57.2% (25 g). The crude product was dissolved in 270 mL of hot water. After addition of 2 mL of triethylamine, the solution was cooled to recrystallize the product. The final yield was 42.6% (19 g): mp 214−215 °C.

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Anal. Calcd for $C_{11}H_{13}O_4N$: C, 59.17; H, 5.87; N, 6.3. Found: C, 58.74; H, 5.89; N, 6.17.

**(iii) *β*-Benzyl-*N*-(bromoacetyl)-L-aspartate.** With the addition of 30 mL of a 4 N aqueous NaOH solution, 26.8 g of *β*-benzyl-L-aspartate was dissolved in 250 mL of 1,4-dioxane/water (1/1 v/v), which was cooled with an ice/water bath (5−10 °C). And it was further cooled with a salt/ice bath to −5 to 0 °C. To the resulting solution was slowly added 50 mL of 4 N aqueous NaOH solution; simultaneously, 11 mL of bromoacetyl bromide (in 40 mL of dry 1,4-dioxane) was added to the solution at the same speed. The solution was stirred vigorously during the whole process. After the addition was completed, stirring was continued for another 5 min. The resulting solution turned opaque when its pH value was lowered to 2. It was then extracted with two 200 mL portions of diethyl ether. The diethyl ether layer was combined and washed with saturated NaCl solution five times. It was dried over $MgSO_4$ and concentrated in vacuo to yield a sticky yellow oil. A small amount of the crude product was purified by silica gel chromatography. The resulting pure sample was recrystallized from acetone/petroleum ether (30−60 °C) to give an excellent crystal. It was used as seed in the recrystallization of a large amount of crude product. The yield was 30% (12.4g): mp 100−102 °C. $^1$H NMR ($CDCl_3$) $\delta = 2.9284{-}3.1987$ (m, 2H, $CH_2COOBz$), 3.8628−3.9466 (q, 2H, $BrCH_2$), 4.8850−4.9270 (m, 1H, NHC*H*), 5.1757 (s, 2H, $CH_2Ph$), 7.3348−7.4109 (m, 5H, Ph), 7.5288 and 7.5488 (two s, 1H, NH), 8.5083 (br s, 1H, COOH). Anal. Calcd for $C_{13}H_{14}O_5NBr$: C, 45.37; H, 4.10; N, 4.07. Found: C, 45.30; H, 4.39; N, 3.88.

**(iv) (3*S*)-3-[(Benzyloxycarbonyl)methyl]morpholine-2,5-dione.** *β*-Benzyl-*N*-(bromoacetyl)-L-aspartate (17.2 g) was dissolved in 150 mL of *N*,*N*-dimethylformamide (DMF). To the resulting solution was added 6.96 mL of TEA, and the solution was kept at 100 °C for 3 h to complete the reaction. After removal of DMF and TEA in vacuo, a small amount of ethyl acetate was added to the residue. The resulting white precipitate was filtered and washed with water and cold ethyl acetate. After four recrystallizations, the product was suspended in water and stirred for 10 min, filtered, and dried in vacuo for another 24 h. Then it was recrystallized once more. Finally, 5.2 g of pure product was obtained, and the yield was 51.7%: $^1$H NMR ($CDCl_3$) $\delta = 3.0301{-}3.0515$ (q, 2H, $CH_2COOBz$), 4.5106−4.5423 (m, 1H, NHC*H*), 4.7617−4.8895 (q, 2H, $COCH_2O$), 5.1787 (s, 2H, $CH_2Ph$), 6.8676 (s, 1H, NH), 7.2651−7.3980 (m, 5H, Ph); FTIR (KBr) spectrum (cm$^{-1}$) 3196 ($\nu$ NH), 3125, 3031 ($\nu$ CH of aromatic ring), 2942 ($\nu$ as $CH_2$), 2896 ($\nu$ s$CH_2$), 1766 ($\nu$ C=O of lactone), 1733 ($\nu$ C=O of $CH_2COOBz$), 1690 ($\nu$ C=O of amide; $\delta$ NH, $\nu$ C−N coupling peak; overlap); MS(EI) *m*/*z* (relative intensity) 263 (13.30, M$^+$), 235 (2.11), 172 (2.11), 156 (8.69), 129 (9.78), 115 (8.25), 107 (31.16), 91 (100), 79 (6.14), 65 (9.32), 43 (6.83); mp 150−150.2 °C.

**Polymerization.** The polymerization tubes were silanized and kept at 110 °C for 24 h. About 3.4 mmol of monomer and a dry stirring bar were put into the warm tube quickly. The tube was then dried in vacuo for 8 h at 56 °C and sealed with a dry rubber septum. The tube was connected to a Schlenk line, where an exhausting−refilling process was repeated three times. The monomer in the tube melted completely after the tube was put into an oil bath (155 °C). With vigorous stirring, a certain amount of stannous octoate in dry toluene (0.2 M) was added to the melt. Five minutes later, the exhausting−refilling process was carried out again to remove the toluene. After the addition of initiator, the temperature of the oil bath was lowered to 152 ± 1 °C. When the polymerization was finished, the reaction was stopped by putting the tube into the freezer. The tube was broken, and the resulting product was dissolved in THF and dropped into an excess of petroleum ether (30−60 °C). The precipitate was filtered and dried in vacuo at 56 °C for 6 h. After a small amount of the solid was saved for the NMR study, the remaining product was dissolved in THF again and precipitated with excess methanol to remove the monomer: $^1$H NMR ($CDCl_3$) $\delta = 2.980{-}3.021$ (m, $CH_2COOBz$), 4.575−4.599 (m, $COCH_2O$), 4.725 (s, NHC*H*), 5.084 (s, $CH_2Ph$), 7.248−7.321 (m, Ph), 8.026 (s, NH).

**Deprotection of the Polymer.** The polymer precipitated from methanol was dried and dissolved in 20 mL of THF. Then, 6 mL of methanol and a small amount of Pd/C (5%) were added to the solution. With vigorous stirring, hydrogen was bubbled through the suspension for 36 h. After removal of the Pd/C powder, the solution was dropped into an excess of petroleum ether (30−60 °C). The precipitate was dried in vacuo at 56 °C for 6 h: $^1$H NMR (DMSO-$d_6$) $\delta = 2.67891{-}2.86829$ (m, C*H*$_2$COOH), 4.52410−4.57251 (m, $COCH_2O$), 4.74555−4.77742 (m, NHC*H*), 8.33804−8.35369 (m, NH), 12.6 (very broad, s, COOH).

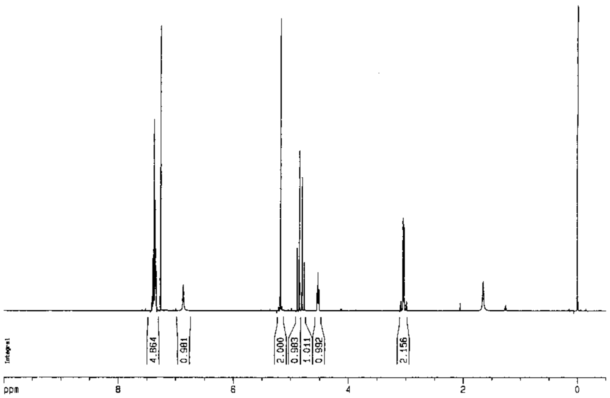
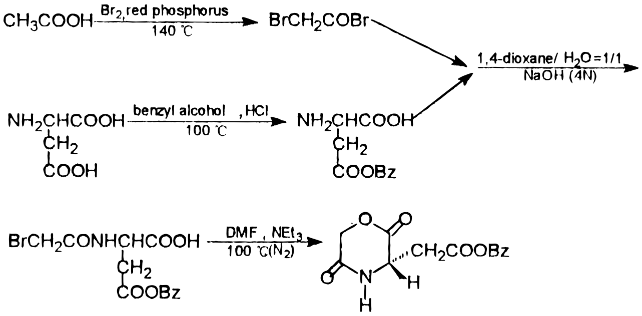


**Figure 1.** $^1$H NMR ($CDCl_3$) spectrum of (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione. $\delta = 3.0301{-}3.0515$ (q, 2H, $CH_2COOBz$), 4.5106−4.5423 (m, 1H, NHC*H*), 4.7617−4.8895 (q, 2H, $COCH_2O$), 5.1787 (s, 2H, $CH_2Ph$), 6.8676 (s, 1H, NH), 7.2651−7.3980 (m, 5H, Ph).

**Scheme 1. Synthesis of (3*S*)-3-[(Benzyloxycarbonyl)methyl]morpholine-2,5-dione**



## Results and Discussion

**Monomer Synthesis.** Several syntheses of morpholine-2,5-dione derivatives, including those with functional groups, have been reported. We follow Feijen's method[14] with some modification as necessary (Scheme 1). The initial yield of *β*-benzyl-*N*-(bromoacetyl)-L-aspartate is low (17.1%), but this does not include that existing in the mother liquor of recrystallization. When the loss was recycled, the overall yield reached 30%.

The $^1$H NMR ($CDCl_3$) and FTIR (KBr) spectra of the monomer are shown in Figures 1 and 2, respectively.

**Homopolymerization.** The ring-opening polymerization of morpholine-2,5-dione derivatives with side functional groups was studied in several papers.[14,15] All of them, however, failed to give homopolymers of the corresponding monomers. In fact, it was proved that substituents on the 3 or 6 position of the monomer would reduce the reactivity of polymerization.[14,17] With this in mind, we decided to keep our monomer free from any substituent on the 6 position of the morpholine ring.

The FTIR spectrum of our monomer is shown in Figure 2. The N−H stretch comes at 3196 cm$^{-1}$ not at 3420 cm$^{-1}$ as expected. This can only be attributed to the formation of a hydrogen bond in the sample.[19] But without data from a single crystal, we cannot decide

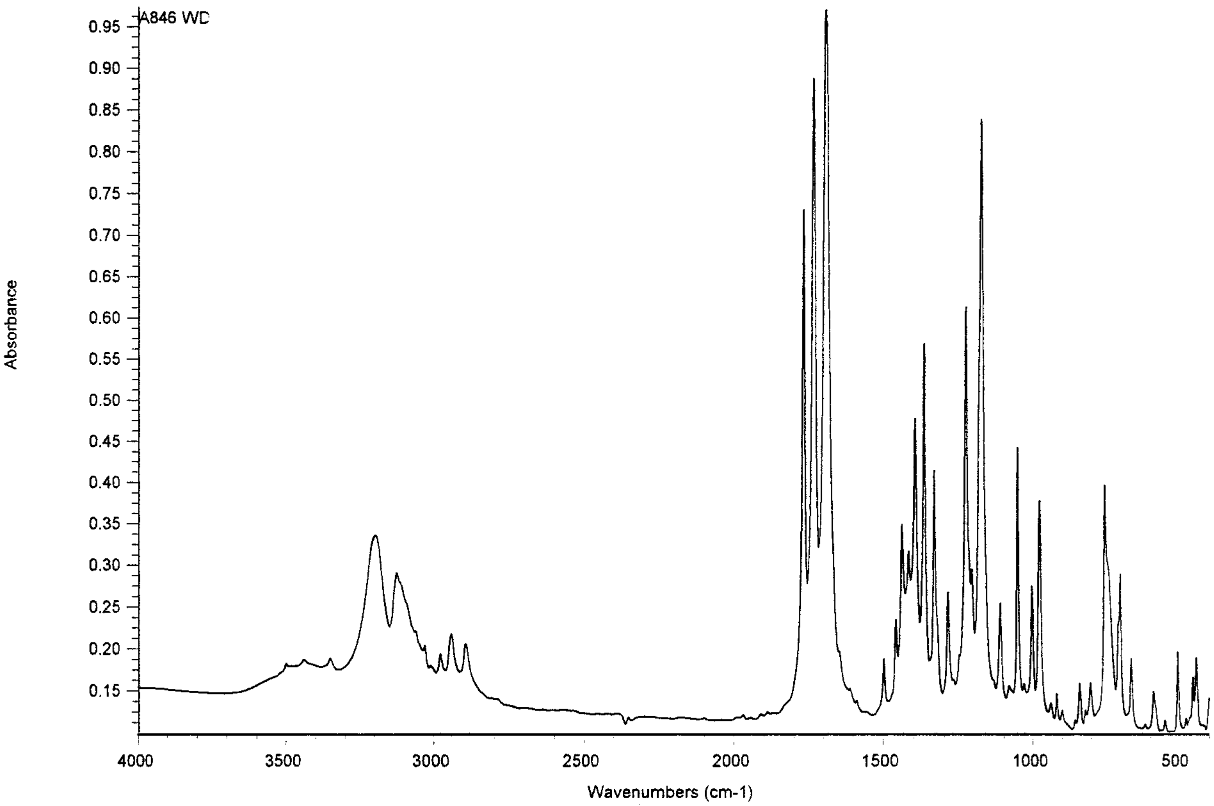


**Figure 2.** FTIR (KBr) spectrum of (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione. Peak assignment ($cm^{-1}$): 3196 ($\nu$ NH), 3125, 3031 ($\nu$ CH of aromatic ring), 2942 ($\nu$ as$CH_2$), 2896 ($\nu$ s$CH_2$), 1766 ($\nu$ C=O of lactone), 1733 ($\nu$ C=O of $CH_2COOBz$), 1690 ($\nu$ C=O of amide; $\delta$ NH, $\nu$ C−N coupling peak; overlap).

**Table 1. Result of the Homopolymerization of (3*S*)-3-[(Benzyloxycarbonyl)methyl]morpholine-2,5-dione**[a]

| no. | M/I | conversion (%) | yield (%) | time (min) | $10^{-4}\bar{M}_n$ | $10^{-4}\bar{M}_w$ | $\bar{M}_w/\bar{M}_n$ |
|---|---|---|---|---|---|---|---|
| 1 | 1000/1 | 64.90 | 60.84 | 90 | 1.06 | 2.77 | 2.59 |
| 2 | 1000/1 | 75.50 | 71.25 | 180 | 1.28 | 3.14 | 2.45 |
| 3 | 1000/1 | 75.86 | 68.74 | 290 | 0.88 | 2.57 | 3.18 |
| 4[b] | 500/1 | 55.31 | 54.10 | 40 | 1.22 | 3.99 | 3.27 |
| 5 | 500/1 | 68.75 | 65.62 | 40 | 1.35 | 3.20 | 2.37 |
| 6 | 500/1 | 79.10 | 73.63 | 120 | 1.13 | 3.26 | 2.89 |
| 7 | 500/1 | 81.13 | 75.16 | 240 | 0.74 | 1.89 | 2.56 |
| 8 | 250/1 | 70.72 | 66.40 | 20 | 0.88 | 2.83 | 2.92 |
| 9 | 250/1 | 78.06 | 62.86 | 60 | 0.88 | 2.55 | 2.88 |
| 10 | 250/1 | 82.56 | 71.59 | 100 | 0.58 | 1.79 | 3.06 |

[a] Polymerization was carried out in bulk at 152 ± 1 °C. Conversion (%) was calculated from $^1H$ NMR. [b] Corresponds to the polymerization in which initiator was added before the monomer was melted.

whether it was caused by an intermolecular or intramolecular effect. No matter what kind of effect it was, the hydrogen bond may, to a certain extent, prevent -NH- from contacting with stannous octoate, which can slow down the polymerization.

It is shown in Table 1 that (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione was successfully polymerized. All the selected conditions gave relatively good yield and conversion. But an exception was made in no. 4, because of its relatively lower conversion compared with that of no. 5. Traditionally, initiator was always added into the monomer before it was melted. Our observation revealed that this would lead to uneven polymerization ($\bar{M}_w/\bar{M}_n = 3.27$). In this case, when the loaded tube was placed into a hot oil bath, the monomer inside which the initiator was trapped would polymerize first. After all the other monomer was melted, the polymerization region had become so sticky that both the monomer and the initiator were quite difficult to transmit to each other. Temperature is another important factor that controls the mass transfer. Raising the temperature may prompt the mass transfer process. But when the temperature was raised to >160 °C, the monomer would quickly turn deep brown, which indicated severe degradation. Thus, 152 °C (2 °C higher than the melting point of the monomer) was set as the temperature for the polymerization.

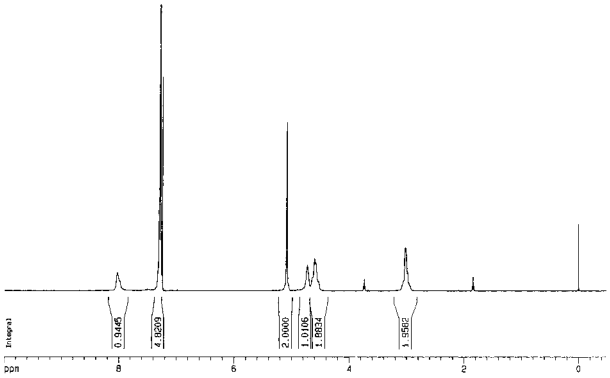


**Figure 3.** $^1H$ NMR ($CDCl_3$) spectrum of poly(glycolic acid-*alt*-L-aspartic acid). $\delta = 2.980-3.021$ (m, $CH_2COOBz$), 4.575−4.599 (m, $COCH_2O$), 4.725 (s, NHC*H*), 5.084 (s, $CH_2Ph$), 7.248−7.321 (m, Ph), 8.026 (s, NH).

Compared with the $^1H$ NMR ($CDCl_3$) spectrum of the monomer (Figure 1), the chemical shifts in the $^1H$ NMR ($CDCl_3$) spectrum of the corresponding polymer (Figure 3) do not change greatly, except for the down-field shift of -NH- signal from 6.8676 to 8.026 ppm. The signals of -NHC*H*- and -$COCH_2O$- of the monomer move slightly and exchange their positions in the spectrum of the polymer. It was also shown in these two figures that the sharp, well-distinguished peaks of the monomer changed into broad peaks after polymerization.

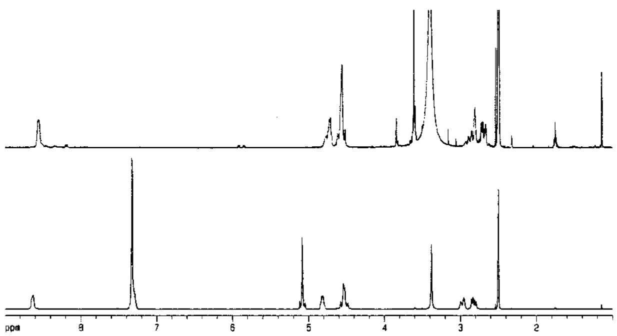
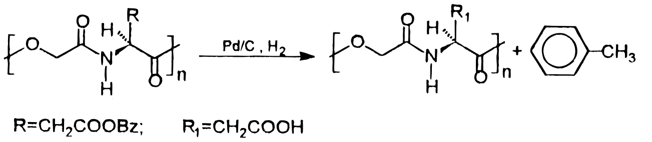


**Figure 4.** $^1$H NMR (DMSO-$d_6$) of protected (lower) and deprotected (upper) polymer.

**Scheme 2. Deprotection of the Benzyl Protective Group of the Polymer**



In order to optimize the polymerization condition, three monomer−initiator ratios (M/I) were tested. It was found that, as more initiator was added, higher conversion resulted, but the molecular weight distribution (MWD) was broadened during this process. This result could be attributed to the involvement of initiator in both polymerization and depolymerization processes. Although stannous octoate is a good initiator for ring-opening polymerization of morpholine-2,5-dione derivatives, its actual reaction mechanism is still unclear. It was suggested that the polymerization might proceed via a coordinated insertion mechanism.[14] Presumably, this mechanism also applies for the depolymerization process, which involves the interaction between the ester bond in the polymer chain and the initiator. When the polymerization lasted for a longer time, the depolymerization effect became remarkable. The $\bar{M}_n$ was reduced and the MWD was broadened to about 3, just like what was demonstrated in Table 1. It may be reasonable to assume that some interaction between the benzyl protective group and the initiator would lead to branching in the polymer chain, but the $^{13}$C NMR spectra of our polymer shows no sign of branching carbon.

**Deprotection.** It is well known that the benzyl protective group of the polymer can be removed by catalytic hydrogenation with the use of Pd/C (5%) as a catalyst (Scheme 2).[18] The $^1$H NMR result (DMSO-$d_6$) for the protected and deprotected polymer indicated complete removal of the protective group (Figure 4), as can be seen from the disappearance of the proton signals of the benzyl group at $\delta = 5.0822$, 7.2844−7.3323. The little small peaks at $\delta = 1.1424$, 1.7558, 3.6094, and 3.8450 were from the protons of THF and methanol, which could hardly be removed because of the strong hydrogen bond between the deprotected polymer and the solvent.

The dynamic contact angle (DCA) results of both protected and deprotected polymer are shown in Figure 5. Compared with the cycle of the protected polymer, the deprotected one gave much higher force in the advancing half-cycle. In the retreating half-cycle, the curves of both polymers are not far from each other. The advancing and retreating angles of the polymers calculated from the figure are shown in Table 2.

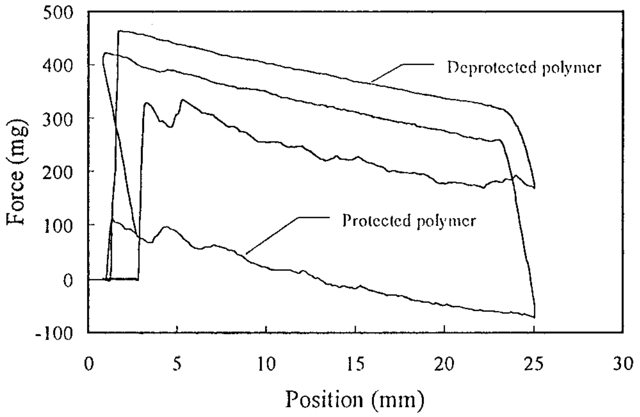


**Figure 5.** Dynamic contact angle (DCA) of protected and deprotected polymer.

**Table 2. Data of Advancing and Retreating Angles Obtained from Figure 5**

| | advancing angle ($\theta$) | retreating angle (cos $\theta$) |
|---|---|---|
| protected polymer | 76.864° | 1.16 |
| deprotected polymer | 24.65° | 1.29 |

These data clearly demonstrate the promising hydrophilicity of poly(glycolic acid-*alt*-L-aspartic acid) (the deprotected polymer) compared with that of the protected polymer, which is absolutely insoluble in water. In fact, poly(glycolic acid-*alt*-L-aspartic acid) became sticky immediately after it was submerged in water, and it would take several hours of stirring to dissolve the polymer. Obviously, this change in property was due to the abundant carboxy group in the deprotected polymer.

## Conclusions

As a new monomer, (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione has been successfully synthesized via a modified traditional route. The ring-opening homopolymerization initiated by stannous octoate was very successful. It is found that (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione was different from other morpholine-2,5-dione derivatives with side functional groups. It has better reactivity, which leads to higher conversion and yield. The selective removal of the benzyl group from the polymer was carried out by catalytic hydrogenation. The resulting poly(glycolic acid-*alt*-L-aspartic acid) was showed promising hydrophilicity.

It is predicted that this monomer will easily copolymerize with $\epsilon$-caprolactone and lactides in different monomer ratios. After deprotection, the copolymer will give a series of materials with different hydrophilicities. It can be expected that they will serve as candidate materials with many excellent properties for use in the delivery of water-soluble drugs.

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