# Synthesis of Novel Pseudo Amino Acid/Functional $\varepsilon$-Caprolactone Polyesters and Photo-Cross-Linked Networks

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ABSTRACT: Novel copolymers of *trans*-4-hydroxy-L-proline (Hpr) and $\varepsilon$-caprolactones bearing protected functional groups (4-henzyloxy and 4-acryloyloxy) were synthesized *via* direct melt copolymerization with 1.5 wt% stannous octoate as catalyst at 140°C for 24 h. The synthesized copolymers were characterized by IR spectroscopy, proton nuclear magnetic resonance, differential scanning calormietry and viscometry using Übbelohde type viscometer. The glass transition temperature ($T_g$) of the copolymers shifted to lower with increasing molar ratio of $\varepsilon$-caprolactone derivatives. The poly($N$-benzyloxycarbonyl-Hpr-*co*-4-acryloyloxy-$\varepsilon$-caprolactone) bearing a pendant acrylate groups can be cross-linked by ultraviolet light irradiation in the presence of benzyl diethyl ketal, giving a new biodegradable network.
KEY WORDS Pseudo Hydroxyproline / 4-Functional-$\varepsilon$-caprolactone / Crosslinked Network /

The past two decades have seen increasing attention to synthetic polyesters for biomedical applications including surgery and medicine.[1] Many of these polymers are readily hydrolyzed to their constituent hydroxy acids which are assimilated by general metabolic pathways.[2] However, the biodegradation rates of these polyesters are difficult to control due to hydrophobicity and semicrystalline morphology.[3] The impetus for research in this area has focused on the need for functional polyesters. There are numerous reports of functional polyesters prepared from protected monomers by condensation and ring-opening polymerization (ROP) techniques.[4] Kimura *et al.*[4c,d] reported the synthesis of pendant carboxyl functional polyesters through ring-opening polymerization of 3-($S$)-[(benzyloxycarbonyl)methyl]-l,4-dioxane-2,5-dione with lactide in the presence of stannous 2-ethylhexanoate (Sn(Oct)$_2$). The benzyl protecting groups were readily removed by catalytic hydrogenolysis to give the highly functionalized bioresorbable polyester. Langer *et al.*[4e] reported the synthesis of poly(lactic acid-*co*-lysine) copolymers from the protected functional monomer, 3-($N$-benzyloxycarbonyl-L-lysyl)-6-L-methyl-2,5-morpholinedione, and attached a peptide to the pendant lysine amino group for tissue engineering application. Hedrick *et al.*[5] described a most exquisite route to functional polyester from protected functional $\varepsilon$-caprolactone (hydroxyl-, amino-, and carboxyl- substituted), using either Al(O$^i$Pr)$_3$ or Sn(Oct)$_2$ as catalyst. Previous articles report the synthesis of polyesters and poly(ester-

urethane) bearing pendant amino functional groups on the backbone from pseudo amino acid.[6]

The phtopolymerization of unsaturated polyester to produce cross-linked networks shows great potential for the fabrication of bioabsorbable composites.[7] This paper investigates the polycondensability of *trans*-4-hydroxy-$N$-benzyloxycarbonyl-L-proline ($N$-CBz-Hpr) with bifunctional $\varepsilon$-lactone ($\varepsilon$-CL) bearing a pendant benzyloxy (or acryloyloxy) group and photopolymerization to form cross-linked network from acrylaled poly($N-$CBz-Hpr-*co*-4-acryloyloxy-$\varepsilon$-CL). These new copolymers were identified by ^{1}H NMR, IR and differential scanning calorimetry (DSC). The effects of comonomers on the inherent viscosity ($\eta_{inh}$) and glass-transition temperature ($T_g$) were also examined.

## EXPERIMENTAL

### Materials

Hpr, benzyloxychloroformate, 1,4-cyclohexanediol, pyridinium chlorochromate (PCC), *m*-chloroperoxybenzoic acid (*m*-CPBA), benzyl bromide, acrylic chloride, and triethyl amine were obtained from Aldrich Chemical Co. Stannous 2-ethylhexanoate (Sn(Oct)$_2$) was used as obtained from Strem Chemical Co, and 2,2-diethoxy-2-phenyl acetophenone (benzyl diethyl ketal, BDEK) was obtained from Wako Chemical Co. Organic solvents (*e.g.*, tetrahydrofuran, methanol, chloroform, diethyl ether, and ethyl acetate) and inorganic compounds (*e.g.*, magnesium sulfate and sodium bicarbonate) were reagent-grade.
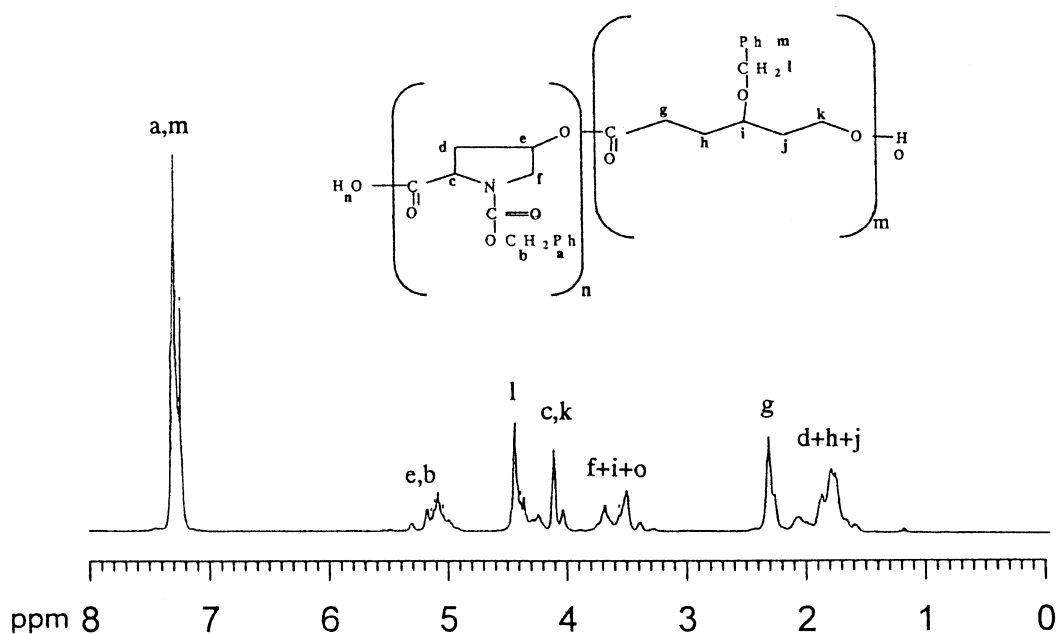
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**Figure 1.** ^{1}H NMR spectrum of poly(N-CBz-Hpr-co-4-BzO-ε-CL) **3F**.

## Characterization

IR spectra were measured on a Jasco IR Report-100 IR spectrophotometer. Samples were either neat onto NaCl plates or pressed into KBr pellets. ^{1}H NMR spectra were recorded at 500 MHz (Brucker WB/DMX-500 spectrometer) with tetramethylsilane as internal standard. Elemental analyses were run on a Perkin–Elmer model 2400 CHN analyzer. Inherent viscosities were measured with an Übbelohde viscometer at 30°C. Thermal analysis of the polymer was performed on a DuPont 9900 system that consisted of a differential scanning calorimeter. The heating rate was 20°C min$^{-1}$. $T_g$s were read at the middle of the change in the heat capacity and taken from the second heating scan after quick cooling.

## Monomer Synthesis

Trans-4-hydroxy-N-benzyloxycarbonyl-L-proline (N-CBz-Hpr-OH; **1a**) and its methyl ester (N-CBz-Hpr-OCH$_3$; **1b**) were prepared according to the process in our previous study.[6a] 4-Benzyloxy-ε-caprolactone (4-BzO-ε-CL; **2a**) and 4-acryloyloxy-ε-caprolactone (4-AcrO-ε-CL; **2b**) were synthesized following the method of Hedrick.[5]

## Synthesis of Copolymers 3

In general, polymerization was conducted in a round flask with a sidearm. The flask was charged with purified monomer N-CBz-Hpr (**1**; 1.93 mmol) and 4-functional-ε-CL (**2**; 1.93 mmol). The catalyst Sn(II) octoate (1.5 wt%) was added. The flask was purged with nitrogen and ROP was carried out under vacuum

at 140°C for 24 h. The crude polymer was dissolved in tetrahydrofuran and precipitated into n-hexane with stirring. After purification, the polymer was dried in vacuo for 24 h and analyzed. Representative ^{1}H NMR and IR spectra of the **3** copolymers are shown in Figures 1, 2, 3A, and 3B, respectively. Elemental analyses of the representative **3** copolymers indicated that experimental and calculated to closely match (Table I).

## UV Polymerization

Acrylated copolymer **3K** was photopolymerized by UV irradiation. A 10% w/v solution of **3k** (0.34 g) and BDEK (1 wt% on the basis of **3K**) as initiator dissolved in dichloromethane was prepared. The solution was irradiated with light of wavelength 365 nm for 50 min. The resulting cross-linked polymer was filtered, washed with dichloromethane, and dried in a vacuum for 24 h. IR and ^{1}H NMR spectra of the cross-linked network **4** are shown in Figures 3C and 4, respectively.

## RESULTS AND DISCUSSION

### Polymerization

Stannous(II) salt especially, stannous(II) octoate, is widely used as initiator for the ring-opening polymerization of lactones. The copolymerization of Hpr **1** and lactones with Sn(II) octoate is usually conducted in bulk, because this initiator is rather inactive at low temperature. The temperature range from 100–180°C is suitable for the ring-opening polymerization of lactones.[8] Therefore 140°C was selected for the present
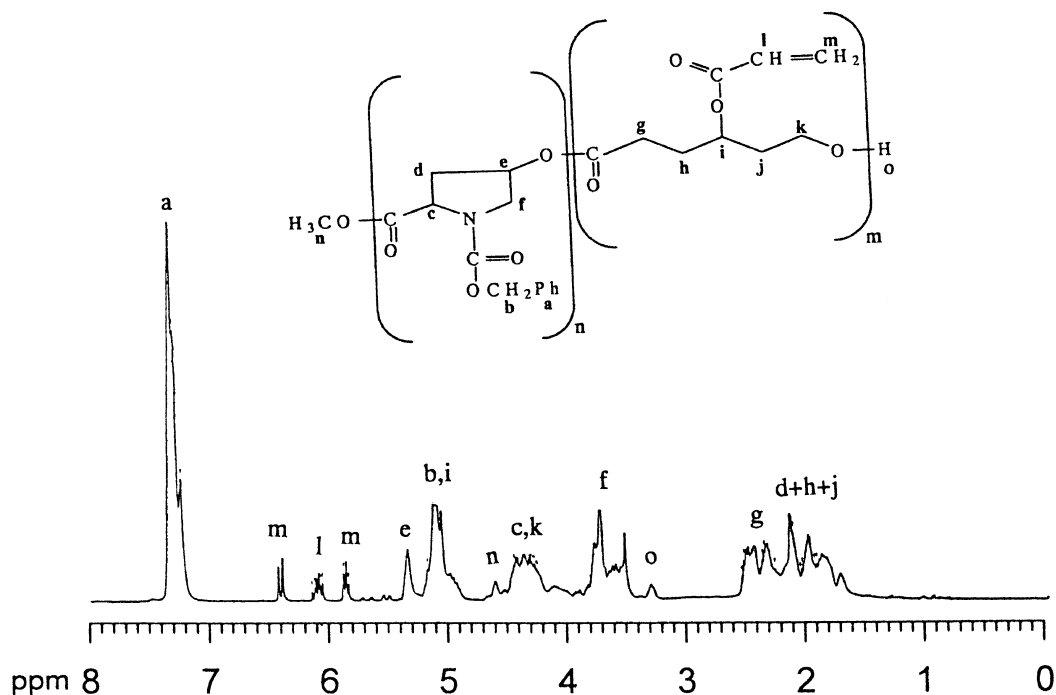
**Figure 2.** $^1$H NMR spectrum of poly($N$-CBz-Hpr-$co$-4-AcrO-$\varepsilon$-CL) **3K**.

study. Hpr **1** were copolymerized with 4-functional-$\varepsilon$-CL **2** at different ratios, in presence of the Sn(II) octoate (1.5 wt%) as initiator at 140°C for 24 h as shown in Scheme 1 and the results are summarized in Table I.

$N$-CBz-Hpr-OH **la** and $N$-CBz-Hpr-OCH$_3$ **lb** can copolymerize with $\varepsilon$-caprolactone bearing a pendant benzyloxy functional group (4-BzO-$\varepsilon$-CL, **2a**). But the $\eta_{\text{inh}}$ of poly($N$-CBz-Hpr-OH-$co$-4-BzO-$\varepsilon$-CL) (**3E**, $\eta_{\text{inh}}$ = 1.92 dLg$^{-1}$) is higher than that of the poly($N$-CBz-Hpr-OCH$_3$-$co$-4-BzO-$\varepsilon$-CL) (**3J**, $\eta_{\text{inh}}$ = 0.88 dLg$^{-1}$). This is due to the carboxylic acid ($N$-CBz-Hpr-OH, **la**) more reactive than the carboxylic ester ($N$-CBz-Hpr-OCH$_3$, **lb**) in polycondensation. So, in the following, we focus on the copolymerization of $N$-CBz-Hpr-OH **la** with 4-BzO-$\varepsilon$-CL **2a**.

To study the effects of the monomer feed ratio on the yield and $\eta_{\text{inh}}$, the copolymerization of $N$-CBz-Hpr **la** with 4-BzO-$\varepsilon$-CL **2a** were investigated over a wide range of composition (10–90 mol%). Yield were high in every polymerization (> 89%) and $\eta_{\text{inh}}$ increased from 1.09 to 2.39 dLg$^{-1}$ when 4-BzO-$\varepsilon$-CL **2a** increased from 18 to 90 mol% (copolymers **3A-3I**). This due to the forming primary hydroxy group which the acyl-oxygen of the lactone ring cleavage, more reactive than the secondary hydroxy group of $N$-CBz-Hpr. $\eta_{\text{inh}}$ of the copolymer increases when incorporated 4-BzO-$\varepsilon$-CL.

### Determination of the Compositions

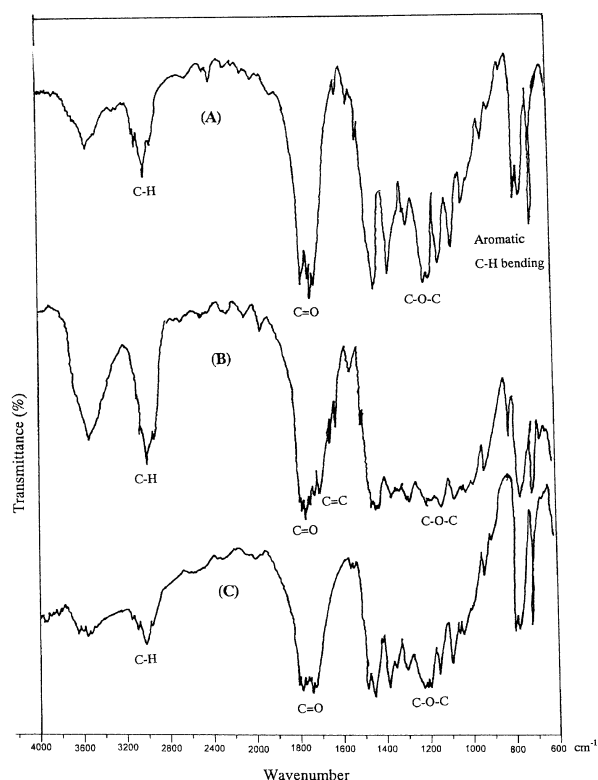To investigate whether compositions of the copolymers are in agreement with the feed ratios. Compo-



**Figure 3.** Representative IR spectra of (A) poly($N$-CBz-Hpr-$co$-4-BzO-$\varepsilon$-CL) **3B**, (B) poly($N$-CBz-Hpr-$co$-4-AcrO-$\varepsilon$-CL) **3K**, and (C) cross-linked network **4**.

sitions in the copolymers were analyzed by $^1$H NMR spectra. Monomer incorporated into the copolymer could be calculated from a comparison of the integral area of the absorption peaks ($\delta$ 5.15 ppm) of the methine proton (C$_4$–H) of the proline with those

**Table I.** Results of the melt copolymerization of *N*-CBz-Hpr (**1**) and 4-functional-*ε*-caprolactone (**2**)[a]

| Copolymer (3) | Monomer Composition in the Copolymer (mol%)[b] | ¹H NMR Coposition in the Copolymer (mol%) | $\eta_{inh}$ | $T_g$ | Yield | Elemental Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *N*-CBz-Hpr /*ε*-CL | *N*-CBz-Hpr / *ε*-CL | dLg⁻¹[c] | °C | % | C (%) | | H (%) | | N (%) | |
| | | | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| *N*-CBz-Hpr-OH/ 4-BzO-*ε*-CL | | | | | | | | | | | |
| A | 90/10 | 82/18 | 1.09 | 62 | 99 | 64.42 | 63.89 | 5.63 | 5.32 | 4.74 | 4.72 |
| B | 80/20 | 77/23 | 1.46 | 53 | 98 | 64.78 | 64.47 | 5.72 | 5.66 | 4.47 | 4.32 |
| C | 70/30 | 69/31 | 1.44 | 44 | 96 | 65.36 | 65.01 | 5.88 | 5.86 | 4.05 | 3.96 |
| D | 60/40 | 54/46 | 1.45 | 32 | 89 | 66.49 | 65.74 | 6.17 | 6.14 | 3.22 | 3.38 |
| E | 50/50 | 44/56 | 1.92 | 22 | 90 | 67.26 | 66.44 | 6.37 | 6.57 | 2.65 | 2.66 |
| F | 40/60 | 38/62 | 1.38 | 13 | 98 | 67.76 | 67.35 | 6.50 | 6.51 | 2.29 | 2.14 |
| G | 30/70 | 29/71 | 1.55 | 6 | 96 | 68.42 | 68.14 | 6.68 | 6.64 | 1.81 | 1.73 |
| H | 20/80 | 20/80 | 1.86 | −1 | 99 | 69.17 | 68.67 | 6.87 | 6.98 | 1.26 | 1.27 |
| I | 10/90 | 10/90 | 2.39 | −15 | 91 | 70.06 | 69.57 | 7.11 | 7.22 | 0.60 | 0.59 |
| *N*-CBz-Hpr-OCH₃/ 4-BzO-*ε*-CL | | | | | | | | | | | |
| J | 50/50 | 45/55 | 0.88 | 15 | 80 | 67.18 | 66.24 | 6.35 | 6.69 | 2.71 | 2.74 |
| *N*-CBz-Hpr-OCH₃/ 4-AcrO-*ε*-CL | | | | | | | | | | | |
| K | 50/50 | 84/16 | 0.82 | 13 | 63 | 62.58 | 62.24 | 5.46 | 5.63 | 4.94 | 4.14 |

[a]Reaction performed using 1.5 wt% stannous octoate as catalyst at 140°C for 24 h. [b]Molar ratio percentage of the *N*-CBz-Hpr (**1**) over the comonomer *ε*-CL (**2**) was fed in the polymerization. [c]Measured at 0.1 gdL⁻¹ in CHCl₃ at 30°C.
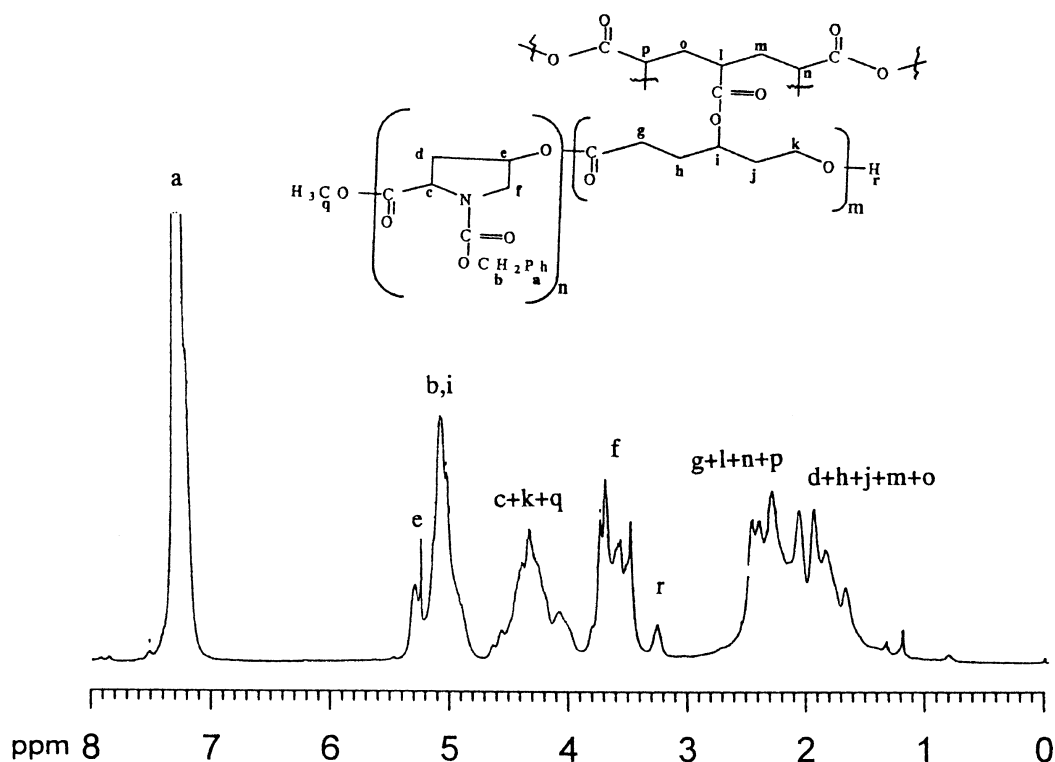


**Figure 4.** ¹H NMR spectrum of cross-linked network **4**.

($\delta$ 1.62–1.90 ppm) of the methylene protons (C₃ and C₅) of the 4-BzO-*ε*-CL. Molar ratio percentages of the comonomers incorporated into the copolymers are shown in Table I. In the copolymerization of *N*-CBz-Hpr **1** with 4-BzO-*ε*-CL **2a**, the composition ratio in poly(*N*-CBz-Hpr-*co*-4-BzO-*ε*-CL) was in agreement with the feed ratio (copolymers **3A-3J**). But in the case of *N*-CBz-Hpr **la** with 4-AcrO-*ε*-CL **2b**, irrespectively of the monomer feed ratio, the content of 4-AcrO-*ε*-CL in the copolymer was less than that in the monomer

feed (copolymer **3K**). This may be that the 4-AcrO-*ε*-CL is unstable in the polymerization condition.

*Thermal Analysis*

Thermoanalytic measurements were made with DSC equipment. $T_g$s of the copolymers with different compositions are shown in Table I. According to DSC, *N*-CBz-Hpr/4-functional-*ε*-CL copolymers exhibited only $T_g$. So, all the copolymers were amorphous. With increasing content of 4-functional-*ε*-CL in the copoly-

Z = CO₂CH₂Ph

1a R= H
1b R=CH₃

2a R¹ = CH₂Ph
2b R¹ = CO(CH=CH₂)

**3**
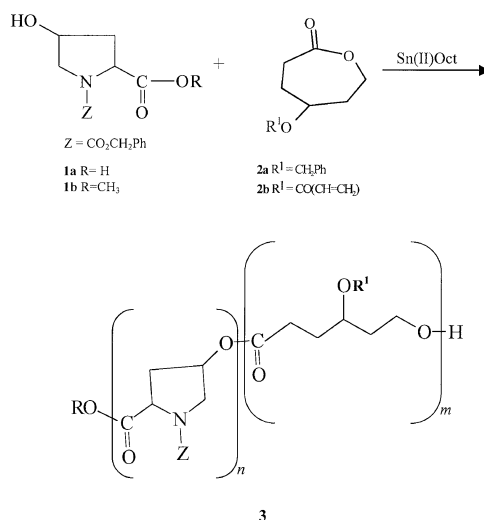
**Scheme 1.**  Condenstion copolymerization of Hpr **(1)** and 4-functional-ε-caprolactone **(2)**.

mer, decrease in $T_g$ was observed.  For *N*-CBz-Hpr/4-BzO-ε-CL type copolymers, $T_g$ decreased from 62 to −15°C when the molar ratio percentage of 4-BzO-ε-CL increased from 18 to 90 mol% (copolymers **3A-3I**). This is due to the fact that ε-CL can be considered a soft component in comparison with *N*-CBz-Hpr.  Therefore, when a larger amount of flexible linkages, such as methylene groups, incorporated into the macromolecular backbone, there was a decrease in $T_g$.

*Cross-Linked Network*

Acrylate pendant groups in polymers serve as cross-linking sites using radical reaction.  This feature of aliphatic polyesters is of great interest for the design of biomaterials.  Poly(*N*-CBz-Hpr-OMe-*co*-(4-acryloyloxy-ε-CL) **3k** was dissolved in dichloromethane and BDEK was added as radical photoinitiator (Scheme 2). The solution was irradiated with 365 nm UV light at room temperature and after 50 min a gel was obtained. The obtained cross-linked network **4** was glassy and transparent. $\eta_{inh}$ the network **4** ($\eta_{inh}$ = 2.15 dLg⁻¹) was higher than the original copolymer **3K** ($\eta_{inh}$ = 0.82 dLg⁻¹).  In agreement with the proposed radical cross-linking, analysis of the cross-linked network by ¹H NMR and IR spectroscopy showed the disappearance of the absorption peaks present in the original copolymer at $\delta$ 5.84–6.42 ppm (Figure 4) and 1620 cm⁻¹ (Figure 3C), characteristic of the acryloyloxy substituents.

The thermal behavior of the cross-linked network was examined by DSC. $T_g$ of the cross-linked network **4** ($T_g$ = 52°C) was higher compared to the original copolymer **3K** ($T_g$ = 13°C), as expected due to the increase in molecular weight during cross-linking.

## CONCLUSIONS

New biodegradation copolymers of pseudo amino acid with pendant amino and hydroxyl functional groups were synthesized by melt polycondensation of Hpr and bifunctional lactone (4-functional-ε-caprolactone).  $\eta_{inh}$ and $T_g$ of the copolymers could be controlled by amounts of monomers.  The copolymer bearing a pendant acrylate group could be cross-linked by ultraviolet light irradiation giving rise to new biodegradable networks. Further studies are in progress to evaluate the biodegradability and biocompatibility of the obtained networks.

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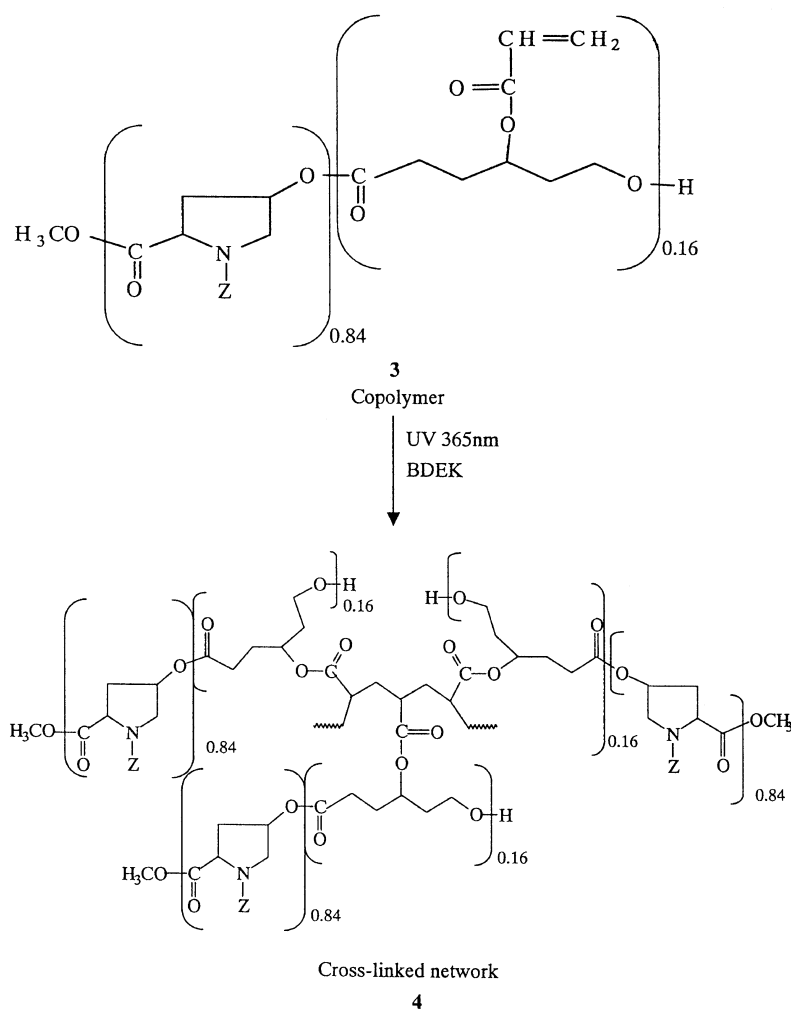
**Scheme 2.** Synthesis of cross-linked network **4**.

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