systems. G_x cannot be zero for the *n*-hexyl copolymers and homopolymers PNHMA, PCHMA, and PBZMA but G_x is probably very small if not zero for the branched butyl methacrylate polymers. This is probably why the *G* values reported for PIBMA and PTBMA are so close to that of PMMA (i.e., $G_x \simeq 0$ and G_s is primarily determined by the methacrylate structure). There is no apparent effect of a large steric group at the ester R group position and G_x remains small until the alkyl group is greater than C_4. The *G* values obtained form the basis for the concluding prediction that the polymers of this study will be equivalent or less sensitive positive e-beam resists than PMMA.

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Active Esters in the Synthesis of Sequential Polypeptide Models of Collagen. An Improved Synthesis of (Pro-Pro-β-Ala)$_n$

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The synthesis of (Pro-Pro-β-Ala)$_n$ is of special interest as this polymer has similar ORD and CD spectra to (Pro-Pro-Gly)$_n$ suggesting a structural resemblance to collagen.[2a] In the earlier synthesis of the (Pro-Pro-β-Ala)$_n$ via the pentachlorophenyl active ester procedure,[2b] the polymer was obtained in no more than 30% yield and the weight average molecular weight was 6500 ($n \simeq 24$ to 25) or less. Subsequent attempts to synthesize the polymer resulted in variable results, and in some attempts the polymer obtained was of low molecular weight and was completely dialyzed out of the dialysis bag. Similar difficulties were experienced by Urry and Ohnishi[3] and by Bell et al.[4] in the synthesis of H-(Val-Pro-Gly-Gly)$_n$-Val-OMe via the pentachlorophenyl ester procedure. Recently, we reported the synthesis of the above polytetrapeptide in excellent yields (~90%), with $n > 40$ via the *p*-nitrophenyl active ester procedure.[5] As the *p*-nitrophenyl ester procedure proved to be superior in the synthesis of the above polytetrapeptide, the synthesis of (Pro-Pro-β-Ala)$_n$ by this active ester procedure was undertaken.

Experimental Section

(Pro-Pro-Gly)$_n$ was purchased from Miles-Yeda Co. and was purified on a polyacrylamide gel column. Thin layer chromatography was performed on silica gel G plates (Quantum Industries) with the following solvent systems: R_f^1, chloroform/methanol (1:1, v/v); R_f^2, chloroform/methanol (10:1 v/v); R_f^3, chloroform/methanol/acetic acid (95:5:3, v/v); R_f^4, *n*-butyl alcohol acetic acid/water (4:1:1, v/v); R_f^5, *n*-butyl alcohol/pyridine/water (7:3:1, v/v); R_f^6, *n*-butyl alcohol/acetic acid/water/pyridine (30:6:20:24, v/v). The carbon-13 magnetic resonance spectra were obtained on a JEOL PFT-100 pulse spectrometer operating at 25.15 MHz with proton noise spin decoupling and an internal deuterium lock.

The synthetic scheme of the polymer is given below:

Boc-Pro-Pro-β-Ala-OH

$$\xrightarrow{CF_3COOC_6H_4NO_2} \text{Boc-Pro-Pro-β-Ala-ONp} \quad \text{(I)}$$

$$\text{I} + CF_3COOH/CH_2Cl_2 \longrightarrow F_3AcOH\cdot\text{H-Pro-Pro-β-Ala-ONp} \quad \text{(II)}$$

$$\text{II} + NEt_3 \longrightarrow \text{(Pro-Pro-β-Ala)}_n \quad \text{(III)}$$

$$\text{III} + HCOOH/(CH_3CO)_2O \longrightarrow HC(\text{Pro-Pro-β-Ala})_n \quad \text{(IV)}$$

Boc-Pro-Pro-β-Ala-ONp (I). This compound was synthesized from Boc-Pro-Pro-β-Ala-OH (2.3 g, 6 mmol) and *p*-nitrophenyl trifluoroacetate (3.95 g, 16.8 mmol)[6] in pyridine following the procedures described earlier[5] to obtain 2.0 g (66%) of an extremely hygroscopic product: R_f^1, 0.86; R_f^2, 0.89; R_f^3, 0.66. Anal. Calcd for $C_{24}H_{32}N_4O_8\cdot\frac{1}{2}H_2O$: C, 56.13; H, 6.47; N, 10.90. Found: C, 56.12; H, 5.92; N, 10.42.

F_3AcOH·H-Pro-Pro-β-Ala-ONp (II). Compound I (1.8 g, 3.5 mmol) was dissolved in 50% trifluoroacetic acid in dichloromethane (15 mL) and processed as described earlier[5] to obtain an extremely hygroscopic amorphous powder: 1.72 g (95%); R_f^4, 0.25; R_f^5, 0.54; R_f^6, 0.38. The product was used as such in further synthesis.

(Pro-Pro-β-Ala)$_n$ (III). Compound II (403 mg, 0.8 mmol) was dissolved in dimethyl sulfoxide (1.2 mL). Triethylamine (0.22 mL, 0.16 mmol) was added dropwise to the vigorously stirring solution. After 14 days of polymerization, the reaction mixture was diluted with 3 mL of dimethyl sulfoxide and the reaction mixture was dialyzed for 7 days against several changes (14 × 2000) of distilled water and lyophilized to yield 159 mg (75%) of polymer; mp, the compound showed a color change at 75 °C and decomposition at 260 °C; R_f^4, 0.1; R_f^5, 0.88; R_f^6 0.16. Anal. Calcd for $C_{13}H_{19}N_3O_3\cdot\frac{2}{3}H_2O$: C, 56.00; H, 7.41; N, 15.12. Found: C, 55.59; H, 7.02; N, 15.12. Amino acid analysis: Pro, 2.00; β-Ala, 0.96.

Formyl-(Pro-Pro-β-Ala)$_n$ (IV). Compound III (45 mg) was formylated as described earlier[5] to obtain 31 mg of formylated product: R_f^4, 0.16; R_f^6, 0.26. Amino acid analysis: Pro, 2.00; β-Ala, 0.98. The compound was shown to have an average $n > 40$ by NMR analysis of end groups.[3,7,8]

Results and Discussion

The ^{13}C NMR of I is presented in Figure 1A, and it was shown to be of sufficient purity for polymerization, as utilization of pure intermediates is of critical importance to obtain good yields of large molecular weight polymers.[9] The ^{13}C NMR of the polymer, III, is presented in Figure 1B. Utilization of the *p*-nitrophenyl ester procedure in the synthesis of the polymer resulted in good yields (an average yield of 71%) and the polymers were shown to be of large molecular weight ($n > 40$). The *p*-nitrophenyl ester method produced not only good yields of higher molecular weight polymers but was also shown to yield reproducible results in three separate attempts (see Table I).

It is reasonable to consider[5] that the superiority of *p*-nitrophenyl ester to pentachlorophenyl ester be due to the fact that the pentachlorophenyl esters are comparatively more activated, hence more likely to be decomposed by higher concentrations of base, thereby terminating the polymerizing species prematurely. Another reason might be that H-Pro-Pro-β-Ala-OPcp is a more active ester than the corresponding *p*-nitrophenyl ester and that in the former the tendency to form prolylprolyl diketopiperazine with simultaneous

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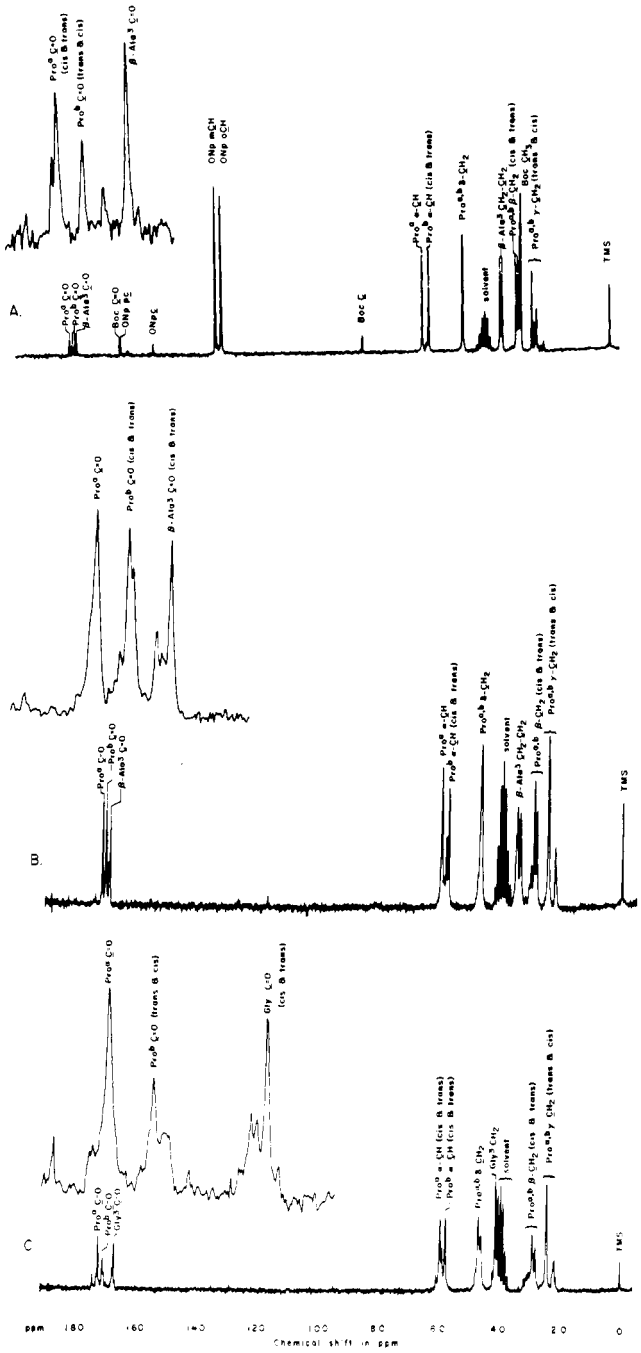

Figure 1. Carbon-13 magnetic resonance at 25 MHz in Me_2SO-d_6 of (A) Boc-Pro_1-Pro_2-β-Ala_3-ONp, (B) $(Pro_1$-Pro_2-β-$Ala_3)_n$, and (C) $(Pro_1$-Pro_2-$Gly_3)_n$. Note that the carbonyl signals are shown in the expanded scale at the top of each spectrum.

elimination of the terminal amino acid might be greater. The facile formation of the diketopiperazine could be the reason for obtaining low molecular weight, dialyzable polymers by the pentachlorophenyl ester method.

In the carbonyl region of the ^{13}C spectrum of Boc-Pro_1-Pro_2-β-Ala_3-ONp (shown also in the expanded scale at the top of each spectrum), the two prolyl carbonyls are not assigned and only referred to as Pro^a C=O and Pro^b C=O, Pro^a C=O being the one that appears at the lowest field of the carbonyl region. Comparison of ^{13}C spectra of $(Pro_1$-Pro_2-$Gly_3)_n$ and $(Pro_1$-Pro_2-β-$Ala_3)_n$ shows that Gly_3 C=O and β-Ala_3 C=O appear farthest upfield in the carbonyl region (Figures 1B and 1C). By decoupling procedures it appears that Pro^a is Pro_2 and Pro_b is Pro_1.

It can be pointed out from Figures 1B and 1C that the cis and trans isomeric behaviors of both $(Pro_1$-Pro_2-β-$Ala_3)_n$ and $(Pro_1$-Pro_2-$Gly_3)_n$ are almost identical. Since $(Pro$-Pro-$Gly)_n$ has been shown by earlier studies to form triple helical structures[10-14] and $(Pro$-Pro-β-$Ala)_n$ was shown to have a similar ORD and CD spectra[2a] to $(Pro$-Pro-$Gly)_n$, it is possible that $(Pro$-Pro-β-$Ala)_n$ forms a similar helical structure. Further work is in progress in the assignment of ^{13}C signals of these compounds by isotopic labeling and in deriving the preferred conformations in solution of peptide analogues of collagen.

Table I

Attempt	Monomer	% yield of polymer	Av mol wt of polymer
1	F_3AcOH·H-Pro-Pro-β-Ala-ONp, 415 mg	159 mg, 75%	$n > 40$
2	F_3AcOH·H-Pro-Pro-β-Ala-ONp, 415 mg	149 mg, 70%	$n > 40$
3	F_3AcOH·H-Pro-Pro-β-Ala-ONp, 415 mg	144 mg, 68%	$n > 40$

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Preferential Adsorption to Poly[N^5-(2-hydroxyethyl)-L-glutamine] in Water/2-Chloroethanol Mixtures

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The helix–coil transition in proteins and synthetic polypeptides is accompanied by changes in preferential adsorption to the polymer in water/organic solvent mixtures.[1] The interactions of proteins with solvent components of mixed water/2-chloroethanol have been extensively studied.[1,2] 2-Chloroethanol was shown to be a structure forming denaturant solvent and capable of interacting with proteins, probably by way of hydrophobic interactions with the aliphatic side chains. In the case of poly[N^5-(3-hydroxypropyl)-L-glutamine] (PHPG), it was shown that, at low 2-chloroethanol concen-

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