Synthesis and Structural Studies of 2,3-Disubstituted Poly(*β*-peptide)s

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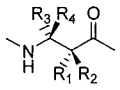
ABSTRACT: The synthesis of 2,3-disubstituted poly(*β*-peptide)s (nylon-3 analogues) bearing the benzyloxy group at position 3 and the diethoxymethyl or the isobutoxycarbonyl group at position 2, is described. Both optically pure and racemic forms were prepared for each case and all them were characterized by standard methods. The structure of these poly(*β*-peptide)s was preliminary examined by X-ray diffraction and infrared spectroscopy. It was concluded that they do not tend to adopt the α-helixlike conformation characteristic of poly(*β*-L-aspartate)s but rather a contracted conformation with amide groups in the nonassociated state.

Introduction

During the last 2 decades, it has been established that poly(*β*-peptide)s are able to adopt regular conformations stabilized by intramolecular hydrogen bonds with features very similar to the α-helix characteristic of poly(α-peptide)s. Most of evidence in support of this significant finding has been obtained in the study of poly(α-*n*-alkyl-*β*-L-aspartate)s.[1] These poly(*β*-peptide)s may be envisaged as nylon-3 derivatives with an alkoxycarbonyl side group attached to position 3 ($R_3 = -COOC_nH_{2n+1}$, $R_1 = R_2 = R_4 = H$). Definitive corroboration to this conclusion has been provided recently by X-ray and NMR spectroscopical data resulting from the study of small oligo(*β*-peptide)s for a variety of substituents.[2] Conversely, poly(*β*-alanine) (unsubstituted nylon-3) is known to crystallize exclusively in the extended conformation[3] with intermolecular hydrogen bonds. On the other hand, pioneering structural studies made on alkyl-substituted nylons-3 had showed that these compounds invariably adopt the layered structure happening in unsubstituted nylons.[4] It has been also shown that the presence of two substituents (R_1, R_2 = alkyl or phenyl and $R_3 = R_4 = H$) attached to the same main chain carbon atom induces the formation of helical arrangements having 2-fold symmetry and displaying features completely dissimilar to those displayed by the α-helix.[5,6] The occurrence of severe clashes between the pendant group and the main chain in the α-helixlike conformation seems to be the reason for such a behavior. It is clear therefore that not only main chain substitution but also the constitution and position of the substituents are determinant for the conformation adopted by poly(*β*-peptide)s and more specifically for the type of helix that they may take up.



Chemical repeating unit of poly(β-peptide)s

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In this paper we wish to describe the synthesis of a set of poly(*β*-peptide)s (**P*β*P**) which distinguish in having the two main chain carbons monosubstituted with large size groups. Both chiral (**c**) and racemic (**r**) compounds with a benzyloxy group at position α and with either a dietoxymethyl (**I**) or an isobutoxycarbonyl group (**II**) at position *β* are prepared and characterized. The conformation and crystalline behavior of these compounds are preliminary examined by X-ray diffraction and infrared spectroscopy. To our knowledge, this is the first time that 2,3-disubstituted poly(*β*-peptide)s have been synthesized and investigated in connection with the formation of regular conformations.

Experimental Section

General Methods. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured at 20 ± 5 °C with a Bellingham & Standley, Ltd., P20 polarimeter (5 cm cell). TLC was performed on silica gel 60F254 (Merck) with detection by UV light or charring with sulfuric acid. Flash column chromatography was performed using Merck silica gel 60 (230−400 mesh). IR spectra (films or KBr disks) were recorded with either a Michelson 100 or a Perkin-Elmer 2000 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded with Bruker 200 AC-P and 500 AMX spectrometers. Chemical shifts are reported as parts per million downfield from tetramethylsilane. The following abbreviations are used to describe the ^{1}H NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad. Mass spectra were obtained using a Kratos MS80RFA instrument. Elemental analyses were determined in the Microanalysis Laboratories at the Universidad Complutense de Madrid. Compounds characterized by exact mass were shown to be pure by TLC and NMR analyses. Gel permeation chromatography (GPC) analyses were carried out in a Waters apparatus fitted with a Waters model 420 RI detector, and a Millenium 2010 computerized data station. Three Waters styragel HR columns were placed in series, and the analysis was performed in chloroform or chloroform-*o*-chlorophenol (95:5 v/v) at a flow rate of 1 mL/min. Molecular weights were estimated against polystyrene standards. Intrinsic viscosity measurements were carried out in chloroform or *m*-cresol with a Cannon-Ubbelohde 100/L30 semimicroviscometer at 25.0 ± 0.1 °C. Calorimetric measurements and thermal treatments were performed under a nitrogen atmosphere on a Perkin-Elmer DSC-7 instrument at a heating rate of 20 °C/min and cooled at different rates depending on the purpose.

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Both powder and films were used for structural studies. Densities were measured by the flotation method using either water−aqueous KBr solution or water−glycerin mixtures. Powder samples were those coming directly from synthesis and films were prepared by casting from chloroform. Oriented films were obtained by uniaxial mechanical stretching at 160 °C. Dichroism infrared studies were made on oriented films using a FTIR Perkin-Elmer 2000 apparatus provided with an external gold polarizer. X-ray diffraction was performed on a modified Statton camera (W. H. Wharus, Willmington, DE) using graphite monochromatized Cu Kα radiation of wavelength of 0.1542 nm. Diffraction patterns were recorded on flat films and calibrated with molybdenum sulfide (d_{200} = 0.647 nm).

Synthesis of Intermediate Compounds and Monomers. The chemical pathway leading to polymers **PβP-I** and **PβP-II** is depicted in Schemes 1−3. The synthesis of stereoregular **PβP-IIc** has been described in detail elsewhere.[7] Compound **4c** was prepared by reaction of commercial benzyloxyacetyl chloride **1** with the Schiff base **2**, which was previously obtained by reaction of D-glyceraldehyde acetonide with *p*-anisidine. Hydrolysis of **4c** followed by oxidation with $NaIO_4$ rendered **6c** in high yields. Oxidation of **6c** to the acid **8c** followed by esterification with isobutanol and dearylation led to the β-lactam **IIc** in moderate yields.

(±)-*cis*-3-Benzyloxy-1-(4-methoxyphenyl)-4-(α-styryl)-azetidin-2-one (5r). A cooled solution (−78 °C) of *N*-(cinnamylidene)-*p*-anisidine **3** (6.39 g, 27 mmol) in dichloromethane (47 mL) was treated with triethylamine (7.56 mL, 54 mmol) under a nitrogen atmosphere, and a solution of benzyloxyacetyl chloride, **1** (5.0 g, 27 mmol), in dichloromethane (30 mL) was then added dropwise under such conditions. The mixture was stirred overnight at room temperature, then water (25 mL) was added, and the organic layer was washed with 0.1 M hydrochloric acid (25 mL), saturated hydrogen carbonate solution (25 mL), and water (25 mL), dried (sodium sulfate), filtered, and concentrated. The resulting solid was recrystallized from ethyl acetate to give the title compound as a yellow solid (5.3 g, 51%), mp 154−155 °C. NMR data ($CDCl_3$): ^{1}H, δ 7.50−7.25 (m, 10H, phenyl), 6.90−6.75 (m, 4H, phenyl), 6.85 (d, 1H, $J_{1',2'}$ = 16.1 Hz, H-2′), 6.37 (dd, 1H, $J_{1',4}$ = 7.7 Hz, H-1′), 4.96 (d, 1H, $J_{3,4}$ = 4.7 Hz, H-3), 4.777 (d, 1H, *J* = 11.2 Hz, OCH_2Ph), 4.770 (dd, 1H, H-4), 4.69 (d, 1H, *J* = 4.7 Hz, CH_2Ph) , 3.58 (s, 3H, OCH_3); ^{13}C, δ 163.6 (C-2), 136.6, 135.8, 131.1, 128.6, 128.4, 128.3, 128.2, 128.1, 126.7, 136.3 (C-2′), 123.8 (C-1′), 82.8 (C-3), 73.0 (CH_2Ph), 61.1 (C-4), 55.4 (OCH_3). Mass spectrum (CI): *m/z* 386 $(M + 1)^+$. Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.77; H, 6.13; N, 3.60.

(±)-*cis*-3-Benzyloxy-4-formyl-1-(4-metoxyphenyl)azetidin-2-one (6r). Ozone was bubbled through a solution of **5r** (1.03 g, 2.67 mmol) in dry dichloromethane (20 mL) at −78 °C until a weak blue color was observed. Oxygen was passed through the solution and a solution of dimethyl sulfide (1 mL) in dichloromethane (2 mL) was added dropwise with stirring at the same temperature. Then, the mixture was left to reach the room temperature, diluted with dichloromethane (30 mL), washed with water (2 × 20 mL) and saturated sodium chloride solution (2 × 20 mL), dried (sodium sulfate), and concentrated to a solid. Recrystallization from ethyl acetate gave a first crop of pure **6r** (0.25 g). The mother liquors were concentrated and the residue was purified by flash column chromatography (1:1 diethyl ether−hexane) affording 0.33 g of the title compound, which raised the yield to 70%, mp 121−122 °C. This compound showed spectroscopic data identical to the corresponding optically pure isomer previously described.[7] HRMS: *m/z* 311.1148 (calculated for $C_{18}H_{17}NO_4$: 311.1170). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.49. Found: C, 68.95; H, 5.62; N, 4.44.

(3*R*,4*R*)-3-Benzyloxy-4-diethoxyformyl-1-(4-methoxyphenyl)-azetidin-2-one (7c). A solution of **6c** (1.44 g, 4.62 mmol) in dichloromethane (18 mL) was stirred with 0.3 nm molecular sieves for 10 min, then triethyl orthoformate (3 mL, 18.5 mmol) and *p*-toluenesulfonic acid monohydrate (8.74 mg, 0.064 mmol) were added and the mixture was stirred at room-temperature overnight. The reaction was diluted with dichloromethane (20 mL), washed with saturated sodium hydrogen carbonate solution (2 × 20 mL) and water (20 mL), dried (sodium sulfate), and concentrated to a syrup, which crystallized on standing. Recrystallization from ethyl acetate−hexane afforded pure **7c** (1.33 g, 75%), mp 57−58 °C (from ethyl acetate−hexane), $[\alpha]_D$ + 49 (*c* 0.8, dichloromethane). IR: ν_{max} 1756 (CO) cm^{-1}. NMR data ($CDCl_3$): ^{1}H, δ 7.60−6.70 (m, 9H, phenyl), 4.83 (d, 1H, *J* 12 Hz, CH_2Ph), 4.775 (d, 1H, CH_2Ph), 4.772 (d, 1H, $J_{3,4}$ = 5.1 Hz, H-3), 4.74 (d, 1H, $J_{1',4}$ 7.3 = Hz, H-1′), 4.26 (dd, 1H, H-4), 3.90−3.30 (m, 4H, 2 CH_2CH$_3$), 3.76 (s, 3H, OCH_3), 1.21 (t, 3H, *J* 7.0 Hz, CH_2CH_3), 0.91 (t, 3H, *J* 7.0 Hz, CH_2CH_3); ^{13}C, δ 165.2 (C-2), 156.3, 137.0, 130.9, 128.4, 127.9, 127.5, 119.7, 113.6 (phenyl), 103.1 (C-1′), 80.4 (C-3), 73.2 (CH_2Ph), 66.3, 63.9 (2 C-2′), 60.0 (C-4), 55.4 (OMe), 15.2, 15.1 (2 C-3′). Mass spectrum (EI): *m/z* 385 $(M)^+$. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.40; H, 6.95; N, 3.61.

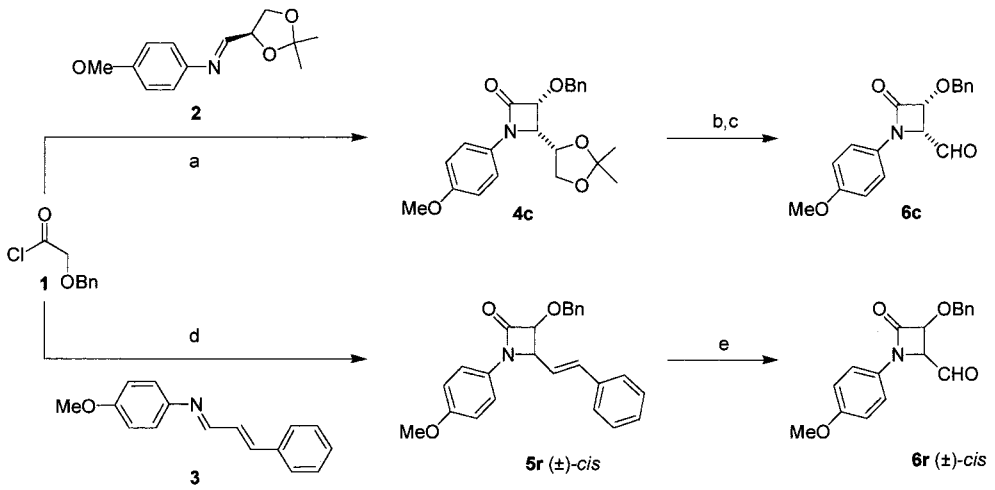
(±)-*cis*-3-Benzyloxy-4-diethoxyformyl-1-(4-metoxyphenyl)azetidin-2-one (7r). The same procedure used for the synthesis of **7c** described above and using compound **6r** (0.68 g, 2.18 mmol) as the starting material led to pure **7r** (0.69 g, 82%), mp 64−65 °C (from hexane). This compound showed spectroscopic data identical to the corresponding optically pure isomer. Mass spectrum (EI): *m/z* 385 $(M)^+$. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.50; H, 6.91; N, 3.61.

(±)-*cis*-3-Benzyloxy-1-(4-methoxyphenyl)-2-oxoazetidin-4-carboxylic acid (8r). To a cooled suspension (0−5 °C) of sodium periodate (1.5 g, 70 mmol) in acetone (60 mL) and water (30 mL) was added ruthenium trichloride hydrate (25 mg), and the mixture was stirred for 30 min. A suspension of **6r** (0. 7 g, 2.29 mmol) in acetone (12 mL) was then added and the mixture vigorously stirred for 2 h at the same temperature. After being stirred at room-temperature overnight, the suspension was diluted with dichloromethane and acetone, filtered through diatomaceous earth, and concentrated and the remaining water solution was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogen carbonate solution and the combined aqueous layers were acidified; after this a white solid precipitated, which was filtered, washed with cold water, and dried (0.5 g, 73.5%), mp 208−210 °C with decomposition. This solid was identified as the title compound, which showed identical spectroscopic data to the corresponding optically pure compound **8c** previously described.[7] HRMS: *m/z* 327.1110 (calculated for $C_{18}H_{17}NO_5$: 327.1107).

(±)-*cis*-Isobutyl 3-Benzyloxy-1-(4-methoxyphenyl)-2-oxoazetidin-4-carboxylate (9r). To a suspension of **8r** (520 mg, 1.59 mmol) in dichloromethane (20 mL) were added *N*,*N*-dicyclohexylcarbodiimide (361 mg, 1.75 mmol), 2-methylpropan-1-ol (0.16 mL, 1.75 mmol), and 4-*N*,*N*-(dimethylamino)-pyridine (17 mg). The mixture was stirred at room-temperature overnight. The *N*,*N*-dicyclohexylurea was filtered off, and the organic solution was washed with water (10 mL), 5% acetic acid solution (15 mL), and again with water (10 mL) and dried (anhydrous sodium sulfate) and the solvent concentrated. Flash column chromatography of the residue (1:2 diethyl ether−hexane) gave pure the title compound (476 mg, 78%), mp 62−64 °C, which showed identical spectroscopic data to the corresponding optically pure compound **9c** previously described.[7] Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.79; H, 6.51; N, 3.81.

Preparation of Monomers I and II. General Procedure for N-Dearylation. To a cooled solution (0−5 °C) of the corresponding β-lactam (1.0 mmol) in acetonitrile (20 mL) was added a solution of cerium (IV) ammonium nitrate (1.64 g, 3.0 mmol) in water (5 mL) during 10 min. The mixture was stirred for 10 min more, diluted with water (30 mL), and extracted with ethyl acetate (4 × 20 mL). The combined extracts were washed with saturated sodium hydrogen carbonate solution (20 mL) and the aqueous phase was again extracted with ethyl acetate (10 mL). The organic solution was washed successively with 40% sodium hydrogen sulfite solution (2 × 20 mL), saturated sodium hydrogen carbonate solution (20 mL), and

Scheme 1



(d) Et_3N, CH_2Cl_2, -78 °C; (e) Ozone, CH_2Cl_2, -78 °C; (a) ; (b) *p*-TsOH·H_2O, TFA-H_2O, reflux (24h); (b) $NaIO_4$, MeOH (2h); (c) $CH(OEt)_3$, p-TsOH·H_2O, CH_2Cl_2, 0.3 nm molecular sieves.

brine (20 mL), dried (sodium sulfate), and concentrated. The crude residue was purified by flash column chromatography (1:1 diethyl ether−hexane or 2:1 ethyl acetate−hexane) and then recrystallized from the appropriate solvent.

(3*R*,4*R*)-3-Benzyloxy-4-diethoxyformylazetidin-2-one (Ic). This compound was purified by recrystallization from hexane to afford 0.172 g (61%), mp 46−47 °C, $[\alpha]_D$ − 20 (*c* 1, dichloromethane). IR: ν_{max} 3265 (NH), 1764 (CO) cm^{-1}. NMR data ($CDCl_3$): ^{1}H, δ 7.30 (m, 5H, phenyl), 6.30 (bs, 1H, H-1), 4.74 (s, 2H, CH_2Ph), 4.70 (dd, 1H, J = 4.7 Hz, J = 2.4 Hz, H-1′), 4.66 (d, 1H, $J_{3,4}$ = 7.7 Hz, H-3), 3.65 (m, 5H, 2 CH_2CH$_3$ and H-4), 1.19, 1.17 (2t, 6H, J = 7.0 Hz, 2CH_2CH_3); ^{13}C, δ 168.2 (C-2), 137.0, 128.3, 127.8, 127.5 (phenyl), 101.9 (C-1′), 82.0 (C-3), 72.8 (CH_2Ph), 63.8, 63.7 (2 C-2′), 55.6 (C-4), 15.5, 15.3 (2 C-3′). Mass spectrum (CI): *m*/*z* 280 $(M+1)^+$. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.57; N, 5.01. Found: C, 64.27; H, 7.41; N, 4.94.

(±)-*cis*-3-Benzyloxy-4-diethoxyformylazetidin-2-one (Ir). The title compound was obtained in 59% yield (0.165 g). This solid was identified as the title compound, mp 86−87 °C, which showed spectroscopic data identical with data for the corresponding optically pure compound (**Ic**) described above. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.57; N, 5.01. Found: C, 64.44; H, 7.41; N, 4.98.

(±)-*cis*-Isobutyl-3-benzyloxy-2-oxoazetidin-4-carboxylate (IIr). This compound was obtained as a syrup (0.21 mg), in 61% yield after purification by flash column chromatography, which showed identical spectroscopic data to the corresponding optically pure compound previously described.[7] HRMS: *m*/*z* 278.1383 (calculated for $C_{15}H_{20}NO_4$: 278.1392).

Preparation of Polymers P*β*P-I and P*β*P-II. General Procedure. To a 0.15 M solution of the corresponding azetindin-2-one monomer in dichloromethane were added 1-*tert*-butoxycarbonyl-4-methyl-4-phenylazetidin-2-one (1/100 mol of monomer) and potassium *tert*-butoxide (5/100 mol of monomer), and the reaction mixture was stirred under nitrogen for 2−3 days at room temperature. The solution was diluted with dichloromethane (8−10 mL) and added dropwise onto ethyl ether (500 mL) with stirring, and a solid precipitated, which was filtered off and washed with diethyl ether, hexane, water, and diethyl ether again. The polymer was dried under vacuum to give 70−80% yields.

Poly[(2*R*,3*R*)-2-benzyloxy-3-diethoxymethyl)-1,3-propanamide] (P*β*P-Ic). White solid, 75% yield; n_{inh} 0.24 dL/g (*m*-cresol). T_m/T_d: 230 °C (DSC), $[\alpha]_D$ − 2.5 (*c* 0.3, *m*-cresol). Anal. Calcd for $(C_{15}H_{21}NO_4 \cdot 0.6\ H_2O)_n$: C, 62.09; H, 7.71; N, 4.82. Found: C, 62.09; H, 6.94; N 4.72.

Poly[(2*R*,3*R* and 2*S*,3*S*)-2-benzyloxy-3-diethoxymethyl-1,3-propanamide] (P*β*P-Ir). White solid, 70% yield; [η] 0.3 dL/g (chloroform). T_m/T_d 267 °C (DSC). M_w 173 000, M_n 30 300 (GPC). NMR data ($CDCl_3$): ^{13}C, δ 169.3 (C-4), 137.1, 128.3, 127.7 (phenyl), 100.5 (C-1′), 78.4 (C-3), 74.0 (CH_2Ph), 62.9 (CH_2-CH$_3$), 50.7 (C-2), 15.1 (CH$_2$CH_3). Anal. Calcd for $(C_{15}H_{21}NO_4 \cdot 0.6\ H_2O)_n$: C, 62.09; H, 7.71; N, 4.82. Found: C, 62.05; H, 7.01; N, 4.71.

Poly[(2*R*,3*R*)-2-benzyloxy-3-isobutoxycarbonyl-1,3-propanamide] (P*β*P-IIc). The synthesis and characterization of this compound are reported in ref 7.

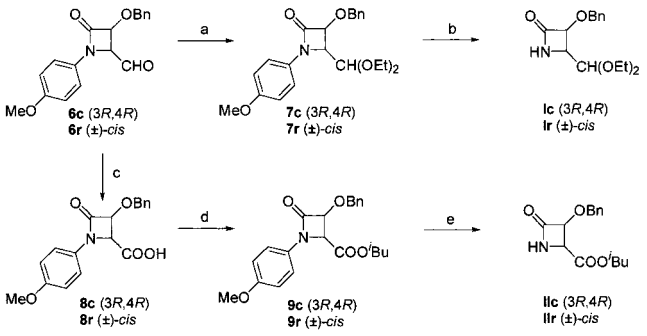
Poly[(2*R*,3*R* and 2*S*,3*S*)-2-bencyloxy-3-isobutoxycarbonyl-1,3-propanamide)] (P*β*P-IIr). White solid, 75% yield; [η] 0.9 dL/g (dichloroacetic acid). T_m/T_d 280 °C (DSC). M_w 153 000, M_n 70 000 (GPC). NMR data ($CDCl_3$): ^{1}H, d 7.40 (d, 1H, $J_{NH,2}$ = 9.9 Hz, NH), 7.15 (m, 5H, phenyl), 5.25 (m, 1H, H-2), 4.55 (m, 2H, CH_2Ph), 3.70 (m, 1H, H-3), 3.55 (m, 1H, H-1′), 1.75 (m, 1H, H-2′), 0.80, 0.78 (2bs, 3H each, 2 CH$_3$); ^{13}C, δ 169.3 (C-1′), 168.2 (C-4), 136.5, 128.5, 128.4, 127.9 (phenyl), 79.1 (C-3), 73.9 (CH_2Ph), 71.7 (C-1′), 53.2 (C-2), 27.4 (C-2′), 19.0 (2 CH$_3$). Anal. Calcd for $(C_{15}H_{19}NO_4 \cdot 0.6H_2O)_n$: C, 62.53; H, 7.06; N, 4.86. Found: C, 62.43; H, 6.80; N, 4.97.

Results and Discussion

Synthesis and Characterization. 4-Formyl-2-azetidinones, **6**, are intermediates in the synthesis of compounds **I** and **II** used as monomers in the preparation of poly(*β*-peptide)s both **P*β*P-I** and **P*β*P-II**. Whereas the synthesis of the chiral enantiomorph **6c** from D-glyceraldehyde acetonide as chiral synton[8] has been described in a preceding paper, the racemic form **6r** is synthesized now for the first time. As it is shown in Scheme 1, the Schiff base **3** was made to react with bencyloxyacetyl chloride to obtain the enantiomeric pair **5r** in the cis configuration, which was then treated with ozone to produce **6r**. This showed spectroscopic data identical to the corresponding optically pure stereoisomer **6c**.[7] The route to monomers **I** (Scheme 2), both the optically pure **Ic** and the racemic mixture **Ir**, involved the acetalation of **6** to compound **7** by reaction with triethyl orthoformate and subsequent removal of the *p*-anisyl N-protecting group with cerium salts. On the other hand, monomer **IIr** was prepared following exactly the same procedure used previously by us in the synthesis of monomer **IIc**.[7]

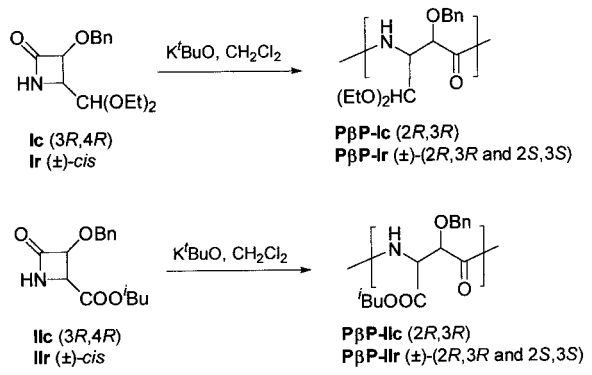
Polyamides **P*β*P-I** and **P*β*P-II** (Scheme 3) were obtained by anionic ring-opening polymerization of the respective monomers **I** and **II** dissolved in dichloromethane with potassium *tert*-butoxide as catalyst. The IR and ^{1}H/^{13}C NMR spectroscopic data were consistent

Scheme 2



(a) $CH(OEt)_3$, *p*-TsOH·H_2O, CH_2Cl_2, 0.3 nm molecular sieves; (b,e) CAN, CH_3CN-H_2O, 0 °C; (c) $RuCl_3$·H_2O, $NaIO_4$, acetone-H_2O, 0 °C; (d) ^{t}BuOH, DCC, 4-DMAP, CH_2Cl_2.

Scheme 3



with the constitution of these polyamides. Elemental analyses were found to be in agreement with values calculated for the expected chemical structure provided that a small amount of water (less than 5%) is assumed to be absorbed by the polymers.

Characteristic data of the polymers are compared in Table 1. Large differences in solubility and melting temperature were found among them depending on their constitution and their optical purity. Whereas polyamides **P*β*P-Ir** and **P*β*P-II** were readily soluble in chloroform, polyamide **P*β*P-Ic** appeared to be only soluble in organic acids and fluorinated solvents like hexafluoro-2-propanol. It was found however that these solvents promoted partial removal of the diethoxy groups of **P*β*P-Ic**. Molecular weights distributions of chloroform soluble polyamides were estimated by GPC in this solvent. Weight-average values ranged between 150 000 and 230 000 with dispersities oscillating between 2 and 5. Estimations based on the viscosity measurements using the viscosimetric equation $[\eta] = 2.78 \times 10^{-5} M_v^{0.87}$ established for poly(γ-benzyl-α-L-glutamate)[9] afforded values between 150 000 and 220 000 perfectly comparable to those obtained by GPC.

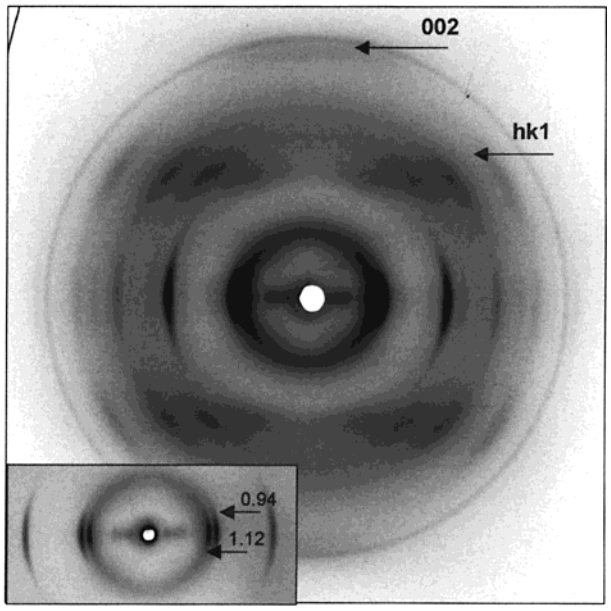
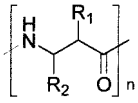


Figure 1. Fiber X-ray diffraction pattern of the nonstereoregular polyamide **P*β*P-Ir**. Inset: Enlargement of the inner region showing the two equatorial reflections indexed as 200 and 020.

The thermal behavior of the synthesized polyamides was examined by differential scanning calorimetry. DSC traces of all these polyamides showed endotherms associated with crystalline melting and decomposition was observed to occur immediately after melting. T_m values were found to range from 230 up to 285 °C with higher values being showed by racemic polymers.

Structural Studies. The high melting temperatures and poor solubility shown by these polyamides have restricted severely their structural analysis and prevented a systematic study to be undertaken. Only **P*β*P-Ir** could be stretched into a fiber showing acceptable orientation, which gave the diffraction pattern shown in Figure 1. The pattern could be indexed on the basis of an orthogonal crystal lattice of parameters $a = 2.240$ nm, $b = 1.894$ nm, and $c = 0.653$ nm. Experimental and calculated spacings are compared in Table 2. The missing of meridional scattering on the first layer line and the presence of the 002 reflection indicates the existence of a 2-fold screw axis parallel to the *c*-axis. The calculated density for this structure (containing four chains per unit cell, i.e. eight monomeric units) is 1.34 g mL^{-1}, which is in acceptable agreement with the experimental value of 1.22 g mL^{-1}.

Table 1. Chemical Structure and Some Properties of Poly(*β*-peptide)s



	substituents							
polyamide	R_2	R_1	configuration	$[\eta]^a$ (dL g^{-1})	$M_w{}^b$	$[\alpha]_D$ (deg)	$T_m{}^c$ (°C)	$d_{hkl}{}^d$ (nm)
P*β*P-Ic	$CH(OEt)_2$	OBn	2*R*, 3*R*			−2.5	230	1.3; 0.51; 0.40; 0.32
P*β*P-Ir	$CH(OEt)_2$	OBn	racemic	0.30[1]	170 000		267	1.1; 0.94; 0.55; 0.40; 0.34
P*β*P-IIc	COO^iBu	OBn	2*R*, 3*R*	1.23[2]	230 000	−10.4	250	1.1; 0.85; 0.66; 0.40; 0.37
P*β*P-IIr	COO^iBu	OBn	racemic	0.90[2]	150 000		280	1.0; 0.63; 0.45

[a] Intrinsic viscosity measured in chloroform[1] or dichloroacetic acid.[2] [b] Weight-average molecular weight measured by GPC. [c] Melting-decomposition temperature measured by DSC. [d] Spacings observed in powder X-ray diffraction patterns; medium to strong intensity signals with $d > 0.3$ nm are only listed.

Table 2. Observed and Calculated Spacings for P*β*P-Ir [(±)-Poly(2-benzyloxy-3-diethoxy-1,3-propanamide)]

d_{obs} (nm)[a]			
powder	fiber	hkl[b]	d_{calc} (nm)[b]
1.118 (s)	1.118 (s)	200	1.120
0.945 (s)	0.945 (s)	020	0.947
0.611 (vw)	0.611 (vw)	130	0.608
0.540 (s)	0.540 (s)	410	0.537
0.485 (vw)	0.485 (vw)	330	0.482
0.428 (vw)	0.433 (vw)	510	0.436
0.405 (m)	0.405 (m)	520	0.405
	0.367 (vw)	530	0.365
0.344 (w)	0.344 (w)	620	0.347
	0.303 (vw)	260	0.304
		(001)	0.653
	0.562 (m)	201	0.564
0.540 (s)	0.540 (m)	021	0.538
0.485 (vw)	0.482 (m)	221	0.485
0.405 (m)	0.414 (m)	411	0.415
0.344 (w)	0.345 (m)	521	0.344
	0.326 (w)	002	0.326

[a] Visual estimation of intensities denoted as s (strong), m (medium), w (weak), and vw (very weak). [b] Indexing and calculated spacings for an orthogonal lattice of parameters $a = 2.240$ nm, $b_0 = 1.894$ nm, and c_0 (chain axis) $= 0.653$ nm.

The infrared spectra of **P*β*P-Ir**, both in the solid state and in solution, show the main amide A band at 3425 cm^{-1}, a position that did not change either with temperature or with dilution. Poly(*β*-L-aspartate)s[10] and poly(α-peptide)s in general[11] are known to show the amide A band in the range 3260−3300 cm^{-1} when they are in the α-helix conformation. On the other side, the amide A band in poly(*β*-alanine), which crystallizes with the chain intermolecular hydrogen bonded, appears at 3250 cm^{-1}. It can be concluded therefore that the amide groups in **P*β*P-Ir** are in the nonassociated state. The polarized infrared spectrum recorded from the same stretched film of **P*β*P-Ir** that was used for X-ray diffraction, displayed perpendicular dichroism for amide A and amide I bands as well as parallel dichroism for amide II band (Figure 2). This can be taken as an unequivocal indication that the amide groups are arranged with the CO and NH groups pointing to a direction not far from the normal to the chain axis.

According to X-ray diffraction and infrared results, a 2_1 helix with two residues per turn and the amide groups in the free state is put forward for **P*β*P-Ir**. This implies a severe distortion of the zigzag conformation with a shortening of about 0.15 nm per amino acid residue. A pleated conformation with a similar contraction has been already observed for α-ethyl-α-phenyl nylon-3.[13] In this case, the amide groups are also in the free state probably due to the steric congestion produced by the bulky side substituents.

Unfortunately, the structural information obtained for **P*β*P** other than **P*β*P-Ir** is restricted to that provided by powder X-ray diffraction and nonpolarized infrared spectroscopy. The crystalline Debye−Sherrer patterns obtained for the four polyamides are shown in Figure 3 and their most characteristic *d*-spacings are compared in Table 1. Although certain analogies are observed for the four polyamides, no structural conclusions can be drawn from these data. The characteristic infrared absorptions of the four studied polyamides are compared in Table 3. Since **P*β*P-IIc** and **P*β*P-IIr** have the amide A band at 3425−3430 cm^{-1} characteristic of a free amide group, the occurrence of α-helixlike conformations can be also discarded in these polypeptides. On the other hand, **P*β*P-Ic** is unique in displaying an infrared pattern compatible with the occurrence of associated amide groups, most likely forming intermolecular hydrogen bonds according to the extremely poor solubility displayed by this compound.

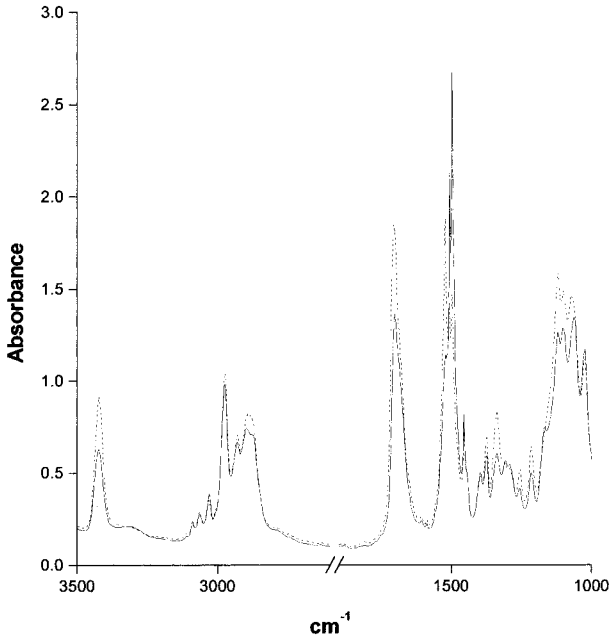


Figure 2. Polarized infrared spectrum of **P*β*P-Ir**. Traces recorded with the stretching axis parallel and perpendicular to the infrared polarization vector are represented by dotted and solid lines, respectively.

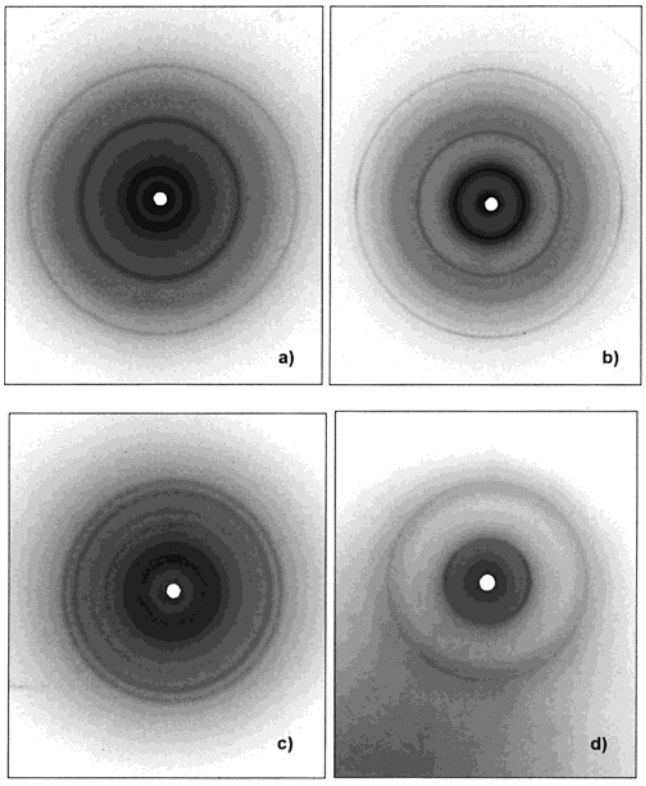


Figure 3. Powder X-ray diffraction patterns of **P*β*P**: (a) **P*β*P-Ic**; (b) **P*β*P-Ir**; (c) **P*β*P-IIc**; (d) **P*β*P-IIr** (after annealing at 125 °C).

A remarkable result of this study is that racemic compounds display a crystallinity degree comparable to their chiral analogues and even higher melting temperatures. The capability of racemic poly(*β*-peptide)s and

Table 3. Infrared Data of Poly(β-peptide)s in cm^{-1}

poly(β-peptide)	amide A	amide I	amide II	ester
PβP-Ic	3420 w 3265 s	1660	1569	
PβP-Ir	3425 vs 3308 w	1680	1506	
PβP-IIc	3428	1675	1500	1745
PβP-IIr	3430	1670	1509	1752
PAIBLA[a]	3292	1660	1548	1751
poly(β-alanine)[b]	3250	1645	1540	

[a] Poly(α-isobutyl-β,L-aspartate) in 13/4 helix conformation.[10] [b] Nylon-3 in the fully extended α-form.[12]

poly(γ-peptide)s to crystallize has been observed before for poly(β-aspartate)s[14] and poly(γ-glutamate)s.[15] This striking behavior has been reasoned by assuming that the racemic polymer is made of homogeneous stereoblocks, which are formed by self-induced stereospecific polymerization. This could be also the case for **PβP**.

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