Synthesis of 3,3-Di(ethoxycarbonyl)-1-vinylpyrrolidin-2-one and Determination of Its Reactivity Ratios with 1-Vinylpyrrolidin-2-one

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ABSTRACT: Novel 1-vinylpyrrolidin-2-one (VP) derivatives, namely 3,3-di(ethoxycarbonyl)-1-vinylpyrrolidin-2-one (DEVP) and 3-(ethoxycarbonyl)-1-vinylpyrrolidin-2-one (EVP), were obtained through a two-step synthetic pathway involving the abstraction of a hydrogen atom α to the lactam C=O, followed by condensation with ethyl chloroformate. By properly selecting the reaction conditions, DEVP could be obtained in high yields, through a straightforward purification procedure. Both DEVP and EVP were converted to sodium 1-vinylpyrrolidin-2-one-3-carboxylate (VP-COONa) by saponification of the ester group, followed by decarboxylation reaction in the case of DEVP. All monomers were homo- and copolymerized with VP by radical polymerization, the structure of the polymer obtained was determined by means of ^{1}H and ^{13}C NMR spectroscopy, and molecular weights were analyzed by means of size exclusion chromatography. The resultant DEVP- and EVP-based polymers also underwent hydrolysis with alkali solutions, followed by decarboxylation reaction in the case of DEVP units, which led in all cases to one carboxylate function linked to the lactam ring. The reactivity ratios for the copolymerization of DEVP with VP were determined in methanol solution according to the Kelen−Tüdös procedure, through polymerization experiments performed at different feed, in which compositional drifts were followed by monitoring monomer conversions by means of ^{1}H NMR spectroscopy. The values of the reactivity ratios obtained were $r_{DEVP} = 0.63$ and $r_{VP} = 0.33$. The validity of these parameters was checked by means of the classical Skeist equation.

Introduction

Poly(1-vinylpyrrolidin-2-one) (PVP) is one of the most promising bioactive and biocompatible polymers, characterized by unique properties such as amphiphilicity, physiological acceptability, protective-colloid action, and complexing ability toward different organic and inorganic compounds.[1,2] The functionalization of PVP is a relevant challenge in polymer science, since functionalized PVP can lead to the modification of bioactive molecules[3−7] and to the design of new macromolecular architectures, such as hydrophilic/hydrophobic block[8] and graft[9] copolymers. Our group has extensively investigated the synthesis of PVP oligomers functionalized at one chain end with reactive functions, based on the radical polymerization of 1-vinylpyrrolidin-2-one (VP) in the presence of different chain transfer agents.[7,10−12] These functional oligomers have been used in the modification of bioactive molecules[4] or macromolecules[5−7] and in the synthesis of A−B block copolymers.[8]

A conventional route to the functionalization of PVP is the copolymerization of VP with different functional comonomers, as for instance acrylates or methacrylates. PVP/acrylate or methacrylate copolymers have been widely investigated for uses in pharmacology and biotechnology[3,13−16] and in different technical areas.[17−20]

However, in free radical copolymerization with acrylates and methacrylates, a considerable compositional drift is observed, due to reactivity ratios unfavorable to VP. In fact, by defining VP and the acrylic monomer as M_1 and M_2, respectively, the value of the reactivity ratios r_1/r_2 usually ranges between 10^{-1} and 10^{-3}.[14−16,19−23] More favorable reactivity ratios can be reasonably expected by using as comonomers functionalized VP derivatives containing reactive functional groups directly linked to the lactam ring. Recently, the synthesis and polymerization of a new functional VP derivative, namely 3-(*tert*-butoxycarbonyl)-1-vinylpyrrolidin-2-one, have been reported.[24] The reaction pathway consisted in the abstraction of one hydrogen atom α to the lactam C=O by reaction with lithium diisopropylamide, followed by reaction of the resultant carbanion with di-*tert*-butyl dicarbonate. The raw product, purified by means of column chromatography, led to a 48% reaction yield, and the pure product could be homopolymerized with good yields. The *tert*-butoxy protective group was eventually removed from the homopolymer by thermal treatment or by hydrolysis in the presence of trifluoroacetic acid, and hydrolysis resulted in a PVP-based homopolymer containing a carboxyl group per repeating unit. However, the authors did not report on the 3-(*tert*-butoxycarbonyl)-1-vinylpyrrolidin-2-one copolymerization with VP.

On the basis of this premise, we thought it interesting to investigate the synthesis of a novel functionalized VP derivative, containing ester or carboxylate functions α to the lactam carbonyl function, namely 3,3-di(ethoxycarbonyl)-1-vinylpyrrolidin-2-one (DEVP), 3-(ethoxycarbonyl)-1-vinylpyrrolidin-2-one (EVP), and sodium 1-vinylpyrrolidin-2-one-3-carboxylate (VP-COONa) (Scheme 1).

In particular, DEVP and EVP are characterized by a lower steric hindrance of the C=O ester function, if compared to 3-(*tert*-butoxycarbonyl)-1-vinylpyrrolidin-2-one, and this may improve the reactivity, for instance in nucleophilic substitution reactions. The reactivity ratios of the radical copolymerization of DEVP with VP in methanol solution were determined in purposely

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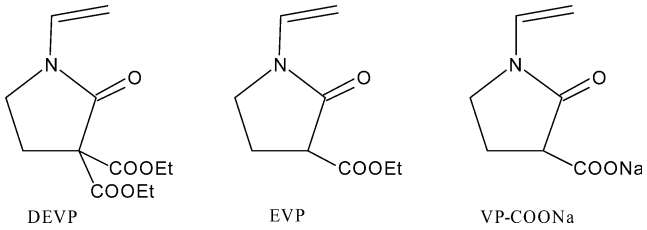
Scheme 1. Structure of DEVP, EVP, and VP-COONa



designed polymerization experiments, in which monomers' consumption was followed by means of ^{1}H NMR spectroscopy. The experimental data were elaborated according to Kelen and Tüdös.[23]

Experimental Part

Instruments and Methods. ^{1}H and ^{13}C NMR spectra were run on a Brüker Advance 400 spectrometer operating at 400.132 MHz (^{1}H) and 100.623 (^{13}C). IR spectra were run on a FT-IR Perkin-Elmer 1725X spectrometer. Polymer IR spectra were obtained on films cast onto NaCl plates from CH_2Cl_2 solution in the case of samples soluble in organic solvents and on KBr pellets in the case of the insoluble polymers. Mass spectra were recorded on a LCQ Advantage Termofinnigan (E.S.I. source).

Size exclusion chromatography (SEC) traces of polymer samples soluble in aqueous solutions were obtained making use of TosoHaas TSK-gel G4000 PW and TSK-gel G3000 PW columns, which were connected in series. The mobile phase was a 0.1 M TRIS buffer solution at pH 8.00 plus 0.2 M NaCl, the sample concentration was 1% w/w, the flow rate was 1 mL/min (Waters model HPLC pump 515), the UV detector was a Waters model 486, operating at 230 nm, and the refractive detector was a Waters model 2410. Molecular weight determinations were based on a calibration curve obtained with pullulan standards. SEC traces of polymer samples soluble in organics solvents were obtained making use of Phenomenex Phenogel 500, 10^3, and 10^4 Å columns, connected in series, with a Knauer model UV detector operating at 254 nm and flow rate 1 mL/min. The mobile phase was a 9/1 dichloromethane/methanol mixture and polymer concentration 1 wt %. Molecular weight determinations were based on a calibration curve obtained with polystyrene standards.

Materials. Absolute ethanol and analytical grade HPLC solvents were purchased from Fluka and used as received. 4,4′-Azobis(4-cyanovaleric acid), CD_3OD (99.8%+), and $CDCl_3$ (99.8%+) stabilized over silver coil were purchased from Aldrich and used as received. Ethyl chloroformate (98%) and 1-vinylpirrolidin-2-one (97%) (VP) were purchased from Fluka and distilled before use. Diisopropylamine, redistilled under nitrogen (99.5%), was purchased from Aldrich and used without further purifications. 2,2′-Azobis(2-methylpropionitrile) (AIBN) (98%) was purchased from Fluka and crystallized from 2-propanol. THF, purchased from Fluka, was dried by distillation over sodium wire/benzophenone. 1.6 and 10 M butyllithium *n*-hexane solutions were obtained from Fluka and used after titration with 1,3-diphenyl-2-propanone tosylhydrazone. Thin-layer chromatography (TLC) was performed using Macherey-Nagel alugram SIL G/UV_{254} for TLC. Column chromatography was performed using Acros Organics silicagel pore (diameters ca. 6 nm). Unless otherwise stated, all operations were performed under an inert atmosphere and using dried glassware. The synthetic apparatus used was a two-necked flask, equipped with magnetic stirrer and nitrogen inlet. In the case of polymer synthesis, this apparatus was also equipped with a condenser.

Synthesis of 3-Ethoxycarbonyl-1-vinylpyrrolidin-2-one (EVP). VP (1.040 g, 9.37 mmol) was added dropwise to a dry 1.2 M THF solution of lithium diisopropyl amide (LDA) (8 mL) at −78 °C. The LDA solution was prepared from diisopropylamine (0.946 g, 9.37 mmol) and 1.6 M *n*-butyllithium hexane solution (9.37 mmol) in dry THF (2 mL). The resultant solution was stirred for 30 min, then allowed to warm to room temperature, and eventually stirred for further 45 min. After this time, the solution of the VP carbanion obtained was cooled to −78 °C and then added dropwise to a 2.34 M THF solution of ethyl chloroformate (4 mL) maintained at −78 °C. After the addition was complete, the solution was stirred for a further 2 h at this temperature. The reaction progress was monitored by means of TLC chromatography (eluent: light petroleum/ethyl acetate 6:4, $R_{f,EVP} = 0.26$). The reaction mixture was quenched with water (10 mL) and then warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the crude material was purified by column chromatography (eluent: light petroleum/ethyl acetate 7:3). Yield = 0.343 g (20%) of product as colorless oil. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.28 (t, 3H, CH_3 ester); 2.42 (m, 2H, ring CH_2); 3.52 (m, 3H, ring CH_2 and CH); 4.21 (q, 2H, ester CH_2); 4.47 (q, 2H, vinyl CH_2); 7.02 (q, 1H, vinyl CH). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.03 (ester CH_3); 21.77 (ring CH_2); 43.13 (ring CH_2); 48.89 (ring CH); 61.59 (ester CH_2); 95.53 (vinyl CH_2); 129.14 (vinyl CH); 168.14 (amide C=O); 169.48 (ester C=O). IR (liquid film) (cm^{-1}): 2976, 2942 (ν C−H), 1738 (ν ester C=O), 1704 (ν amide C=O), 1633 cm^{-1} (ν C=C), 1279 (ν C−O). ESIMS *m/z*: 206.3 (M + 23), 184.2 (M + 1), 170.1, 161.1, 156.1, 145.4.

Synthesis of 3,3-Di(ethoxycarbonyl)-1-vinylpyrrolidin-2-one (DEVP). VP (1.040 g, 9.37 mmol) was added dropwise to a 0.94 M THF solution of lithium diisopropyl amide (LDA) (20 mL) at 0 °C. The LDA solution was prepared from diisopropylamine (2.086 g, 20.61 mmol) and 10 M *n*-butyllithium hexane solution (20.61 mmol) in dry THF (22 mL). The resultant solution was stirred for 80 min at 0 °C, and ethyl chloroformate (4.060 g, 37.48 mmol), maintained at 0 °C, was added dropwise. After the addition was complete, the solution was stirred for 1 h at this temperature. The reaction progress was monitor by TLC (eluent: light petroleum/ethyl acetate 6:4, $R_{f,DEVP} = 0.33$). The reaction mixture was quenched with water (10 mL) and then warmed to room temperature. THF was subsequently removed at reduced pressure, and CH_2Cl_2 (25 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, and then the solvent was evaporated under reduced pressure. The crude product obtained was filtered through silica gel (eluent: light petroleum/ethyl acetate 6:4) affording 2.176 g (8.53 mmol, yield 91%) of product as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.19 (t, 6H, ester CH_3); 2.65 (t, 2H, ring CH_2); 3.43 (t, 2H, ring CH_2); 4.17 (q, 4H, ester OCH_2); 4.43 (q, 2H, vinyl =CH_2); 6.93 (q, 1H, vinyl =CH). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.26 (ester CH_3); 27.88 (ring CH_2); 42.21 (ring CH_2); 62.90 (ester OCH_2); 64.07 (ring C); 96.56 (vinyl = CH_2); 129.65 (vinyl =CH); 165.23 (amide C=O); 167.10 (ester C=O). IR (liquid film) (cm^{-1}): 2977, 2937 (ν C−H), 1733 (ν ester C=O), 1693 (ν amide C=O), 1636 (ν C=C). EIMS *m/z*: 278 (M + 23), 205.8, 159.8.

Synthesis of Sodium 1-Vinylpyrrolidin-2-one-3-carboxylate (VP-COONa). A 6.15 M NaOH aqueous solution (0.45 mL) was added dropwise to a 0.45 M ethanol solution of DEVP (3 mL). After the addition was complete, the solution was maintained under stirring for 1 h at room temperature, while monitoring the progress of the reaction by TLC until total reagent consumption (eluent: light petroleum/ethyl acetate 6:4, $R_{f,DEVP} = 0.33$). Ethanol was then removed at reduced pressure, and the reactive solution diluted with water (10 mL), freeze-dried, and then purified by filtration through silica gel (solvent: methanol), affording 0.234 g (yield 98%) of yellow pale solid. ^{1}H NMR (D_2O): δ (ppm) = 2.30 (m, 2H, ring CH_2), 3.42 (m, 1H, ring CH), 3.63 (m, 2H, ring CH_2), 4.66 (q, 2H, vinyl =CH_2), 6.94 (q, 1H, vinyl =CH). ^{13}C NMR (DMSO): δ (ppm) = 22.72 (ring CH_2), 43.70 (ring CH_2), 51.13 (ring CH), 94.43 (vinyl =CH_2), 129.91 (vinyl =CH), 172.08 (carboxylate C=O), 173.33 (amide C=O). IR (Nujol mull) (cm^{-1}): 2922, 2854 (ν C−H), 1690 (ν amide C=O), 1631 cm^{-1} (ν C=C), 1600 cm^{-1} (ν carboxylate C=O), 1460 (δ CH_2). ESIMS *m/z*: 200.0 (M + 23), 178.0 (M + 1), 158.9, 145.9, 119.0, 101.3, 77.7, 66.0, 62.9.

Synthesis of Poly(3,3-di(ethoxycarbonyl)-1-vinylpyrrolidin-2-one) (PDEVP). DEVP (0.580 g, 1.96 mmol) was dissolved in ethanol (2.5 mL). AIBN (5 mg) was added, and the polymerizing solution was brought under an inert atmosphere by flushing with nitrogen. The reaction was conducted at 70 °C for 21 h under stirring. After this time, the solvent was removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2 (3 mL) and precipitated into diethyl ether (130 mL). The white solid obtained was dried under reduced pressure. Yield = 0.44 g (88%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.22 (ester CH_3), 2.19 (chain CH_2), 2.70 (ring CH_2), 3.30 (ring CH_2), 3.80 (chain CH), 4.19 (ester CH_2). ^{13}C NMR ($CDCl_3$): δ (ppm) = 13.97 (ester CH_3), 28.45 (ring CH_2), 34.07 (chain CH_2), 39.03 (ring CH_2), 45.36 (chain CH), 62.01 (ester CH_2), 63.69 (quaternary C), 167.40 (lactam and ester C=O). IR (cm^{-1}): 2984, 2940 (ν C−H), 1730 (ν ester C=O), 1698 (ν lactam C=O), 1107 (ν C−O). SEC (9:1/CH_2Cl_2: MeOH): $\bar{M}_n$ = 80 500, $\bar{M}_w$ = 467 000, d = 5.80.

Poly(3-(ethoxycarbonyl)-1-vinylpyrrolidin-2-one) (PEVP), poly((3,3-diethoxycarbonyl)-1-vinylpyrrolidin-2-one-*co*-1-vinylpyrrolidin-2-one) (P(DEVP-*co*-VP)), and poly((3-ethoxycarbonyl)-1-vinylpyrrolidin-2-one-*co*-1-vinylpyrrolidin-2-one) (P(EVP-*co*-VP)) were synthesized by following the same procedure adopted in the case of PDEVP and by using the following amounts of reagents:

PEVP: EVP (0.200 g, 1.093 mmol), AIBN (4 mg), ethanol (2 mL). Yield = 0.172 (86%).

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.26 (ester CH_3), 1.59 (chain CH_2), 2.30 (ring CH_2), 3.40 (ring CH_2 and CH ring, and chain CH_2), 4.17 (CH_2 ester). ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.18 (ester CH_3), 22.98 (ring CH_2), 34.24 (chain CH_2), 40.65 (ring CH_2), 45.71 (chain CH), 48.81 (ring CH), 61.17 (ester CH_2), 170.73 (lactam and ester C=O). IR (cm^{-1}): 2983, 2935 (ν C−H), 1734 (ν ester C=O), 1686 (ν lactam C=O), 1178 (ν C−O). SEC (9:1/CH_2Cl_2: MeOH) $\bar{M}_n$ = 118 000, $\bar{M}_w$ = 1 800 000, d = 15.25.

P(DEVP-co-VP). DEVP (0.200 g, 0.784 mmol), VP (0.580, 5.23 mmol), ethanol (2 mL), AIBN (9 mg). Yield: 0.66 g (85%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.22 (ester CH_3), 1.41, 1.68, 1.98 (chain CH_2), 2.22, 2.84, 3.19, 3.69 (chain CH), 4.23 (ester CH_2). ^{13}C NMR ($CDCl_3$): δ = 13.99 (ester CH_3), 18.89 (4 CH_2 ring VP), 27.95 (4 CH_2 ring DEVP), 31.44 (3 CH_2 ring VP), 34.58 (chain CH_2), 41.99 (5 CH_2 ring VP), 44.26 (chain CH), 62.27 (ester CH_2), 166.78 (lactam C=O and ester C=O of DEVP units) and 175.23 (lactam C=O of VP units). IR (cm^{-1}): 2956, 2928 (ν C−H), 1728 (ν ester C=O), 1670 (ν lactam C=O), 1107 (ν C−O). SEC (9:1/CH_2Cl_2: MeOH) $\bar{M}_n$ = 200 000, $\bar{M}_w$ = 1 500 000, d = 7.5.

P(EVP-co-VP): EVP (0.020 g, 0.109 mmol), VP (0.087 g, 0.783 mmol), ethanol (2 mL), AIBN (1 mg). Yield: 0.086 (89%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.28 (ester CH_3), 1.41, 1.68, 1.98 (chain CH_2), 2.02, 2.24, 2.35, 3.22, 3.72 (chain CH and CH_2), 4.18 (ester CH_2). ^{13}C NMR ($CDCl_3$): δ (ppm) = 13.98 (ester CH_3), 18.87 (4 CH_2 ring VP), 22.94 (4 CH_2 ring EVP), 30.12 (3 CH_2 ring VP), 36.83 (chain CH_2), 42.00 (5 CH_2 ring VP), 44.41 (chain CH), 48.82 (ring CH), 61.84 (ester CH_2), 170.40 (lactam and ester C=O of EVP units) and 175.28 (lactam C=O of VP units). IR (cm^{-1}): 2960, 2930 (ν C−H), 1730 (ν ester C=O), 1675 (ν lactam C=O), 1127 (ν C−O). SEC (9:1/CH_2Cl_2: MeOH) $\bar{M}_n$ = 437 000, $\bar{M}_w$ = 2 700 000, d = 6.18.

Synthesis of Sodium Poly(1-vinylpirrolidin-2-one-3-carboxylate) (PVP-COONa). *Method A.* VP-COONa (0.150 g, 0.847 mmol) was dissolved in water (5 mL) and polymerized using 4,4′-azobis(4-cyanovaleric acid) (3 mg). The raw product was purified by ultrafiltration through a membrane with a molecular weight cutoff of 3000 and eventually freeze-dried. Yield = 0.125 g (83%). ^{1}H NMR (D_2O): δ (ppm) = 1.65 (chain CH_2), 2.06, 2.21 (ring CH_2), 3.14, 3.22 (ring CH_2), 3.56 (chain CH). ^{13}C NMR (D_2O): δ (ppm) = 23.28 (ring CH_2), 34.70 (chain CH_2), 41.48, 44.35 (ring CH_2), 45.70 (chain CH), 51.79 (ring CH), 174.32 (carboxylate C=O), 177.45 (lactam C=O). IR (cm^{-1}): 2955 (ν C−H), 1670 (ν lactam C=O), 1588 cm^{-1} (ν carboxylate C=O).

Method B. PDEVP (0.150 g) was dispersed in a 1 M NaOH aqueous solution (2.75 mL), and the dispersion obtained was maintained under stirring for 7 h at 50 °C until complete dissolution. The solution obtained was purified by ultrafiltration through a membrane having a molecular weight cutoff of 3000 and eventually freeze-dried. Yield = 90 mg (86%).

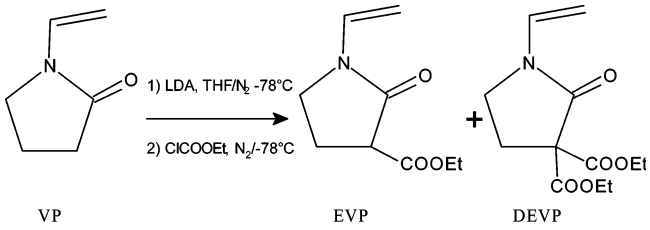
Method C. PEVP was treated as reported in method B, in the case of PDEVP.

Synthesis of Sodium Poly(1-vinylpyrrolidin-2-one-3-carboxylate-*co*-1-vinylpyrrolidin-2-one) (PVP-COONa-*co*-VP)). *Method A.* P(DEVP-*co*-VP) (0.300 g) was dissolved in a 1 M NaOH aqueous solution (10 mL) and maintained under stirring for 48 h at room temperature. After this time, the crude product was diluted with water (10 mL), ultrafiltered through a membrane having a molecular weight cutoff of 3000, and eventually freeze-dried. Yield = 0.258 g (90%). ^{1}H NMR (D_2O): δ (ppm) = 1.57, 1.71, 2.00 (chain CH_2), 2.29, 2.42, 3.29, 3.62, 3.75 (chain CH and CH_2). ^{13}C NMR (D_2O): δ (ppm) = 17.69 (4 CH_2 ring VP), 23.51 (4 CH_2 ring VP−COONa), 31.41, 34.85 (chain CH_2), 42.62 (5 CH_2 ring VP), 44.76, 45.90 (chain CH), 52.40 (3 CH ring VP−COONa), 174.87 (carboxylate C=O), 177.86 (lactam C=O). IR (cm^{-1}): 2957 (ν C−H), 1661 (ν C=O lactam), 1588 cm^{-1} (ν carboxylate C=O).

Method B. P(VP-COONa-*co*-VP) was synthesized from P(EVP-*co*-VP), as described in the case of P(DEVP-*co*-VP) (method A).

Kinetics of the Copolymerization Reaction of VP and DEVP (Standard Experiment). DEVP (28.41 mg, 0.1114 mmol) and VP (26.70 mg, 0.2405 mmol) were dissolved in CD_3-OD (0.75 mL), transferred to an NMR tube, and then flushed with nitrogen. AIBN (1 mg) was added, and the tube was subsequently sealed, placed into the NMR probe, and eventually warmed to 50 °C. The polymerization progress was followed by monitoring the decrease of the area of the diagnostic peaks placed at 4.70, 4.66, 4.64, and 4.62 ppm, relative to the double bond hydrogens of DEVP and of peaks placed at 4.56, 4.51, and 4.49 ppm, relative to the double bond hydrogens of VP. Conversion was experimentally determined through the ratio of the peak integrals of the selected diagnostic peaks with respect to that of the resonance peak placed at 4.28 ppm, relative to OCH_2 ester group, taken as internal standard.

Scheme 2. Synthesis of a Mixture of EVP and DEVP

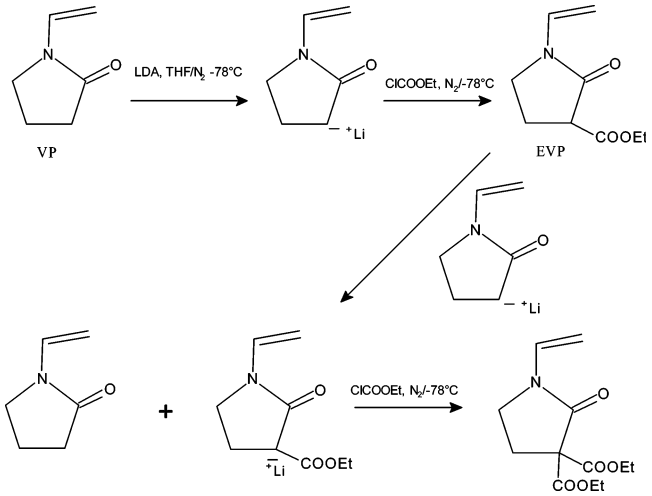


Results and Discussion

Synthesis of Functionalized 1-Vinylpyrrolidin-2-one (VP) Derivatives. The rationale of this work was to obtain a new functional VP derivative containing one ester or carboxylate function linked to the lactam ring, which in radical polymerization exhibited a reactivity very close to that of VP. To this purpose, a first two-step procedure was developed on the basis of literature reports dealing with different modification reactions of lactams.[26,27] According to this procedure, VP was deprotonated in the position α to the C=O lactam function with 1.1 equiv of lithium diisopropylamide (LDA) in dry THF at −78 °C. The VP carbanion obtained was then reacted with 1.1 equiv of ethyl chloroformate at −78 °C (see Scheme 2).

This procedure, which led to an overall 65% VP conversion, resulted in a mixture of products, in which the major component was a difunctional ester derivative, namely 3,3-di(ethoxycarbonyl)-1-vinyl-pyrrolidin-2-one (DEVP) (55% conversion), and the minor one was the desired monofunctional 3-ethoxycarbonyl-1-vinyl-pyrrolidin-2-one (EVP) (10% conversion). This result

Scheme 3. Synthetic Pathway Leading to DEVP



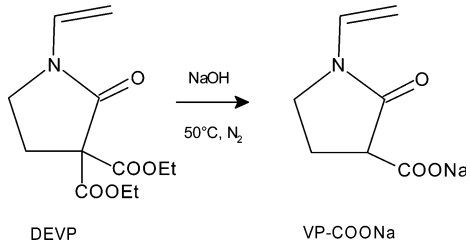
was explained as follows. In EVP, the hydrogen atom α to the ester and amide C=O functions is more acid then the corresponding hydrogen atoms in VP, since it is now placed in between two withdrawing groups. As a consequence, EVP undergoes a rapid acid/base equilibrium exchange with VP carbanion. The EVP carbanion is formed and subsequently reacts with a second molecule of ethyl chloroformate (see Scheme 3).

DEVP and EVP could eventually be separated by means of column chromatography, by using light petroleum/ethyl acetate 6:4 as eluent. To selectively increase VP conversion to the monofunctional EVP monomer, a modified procedure was subsequently attempted, consisting in the dropwise addition of VP carbanion, obtained as described above, to an ethyl chloroformate THF solution at −78 °C. The rationale of this procedure consisted in forcing the VP carbanion to react at all reaction times with excess ethyl chloroformate. The results, however, were not not significantly different. The reaction product was, in fact, a mixture of DEVP and EVP, obtained respectively in 40% and 20% yield (based on VP).

These preliminary results, coupled to the observation that DEVP has the structure of a substituted malonic ester, which normally undergoes decarboxylation reaction under mild basic conditions, led us to the conclusion that from a practical standpoint the best strategy was selectively synthesize DEVP and then use it.

DEVP could be used in different ways. For instance, DEVP could be converted into sodium 1-vinyl-pyrrolidin-2-one-3-carboxylate (VP-COONa) which, in turn, could be copolymerized with VP in aqueous media. Alternatively, DEVP could be copolymerized with VP in organic solvents. The DEVP units present in the resultant copolymer could be converted by a one-step saponification and decarboxylation reaction to VP-COONa units, thus leading to the same product as the previous procedure, or employed as substrate for nucleophilic substitutions, such as transesterification.

Scheme 4. Conversion of DEVP to VP-COONa



Following the above considerations, a modified procedure was designed that proved capable of dramatically improving both conversion and selectivity toward DEVP. In this procedure the ethyl chloroformate/VP carbanion molar ratio was increased to 4:1 and the reaction temperature increased to 0 °C. The VP conversion to DEVP, after a rapid filtration through silica gel in order to separate the inorganic byproducts, was 91%. No unreacted VP or EVP was found in the crude product.

Both DEVP and EVP were characterized by ^{1}H and ^{13}C NMR spectroscopy. The results were in complete agreement with the proposed structures. DEVP was also quantitatively converted to VP-COONa by hydrolytic reaction performed at room temperature in the presence of a 0.8 M NaOH solution in aqueous ethanol (see Scheme 4).

Synthesis of Functionalized PVP−Based Homopolymers and Copolymers. A series of PVP-based homo- and copolymers containing ester or carboxylate functions in their main chain were synthesized by conventional radical polymerization carried out at 70 °C in ethanol or water in the presence of AIBN and 4,4′-azobis(4-cyanovaleric acid), respectively, and using the amounts of reagents reported in Table 1. The chemical structures of the resultant copolymers are reported in Table 2. P(VP-COONa-*co*-VP) copolymers, which are water-soluble, were purified by ultrafiltration through membranes with nominal cutoff 3000, while PDEVP and PEVP homopolymers, which are soluble only in organic solvents, were purified by precipitation from dichloromethane into diethyl ether. The solubility properties of all synthesized polymers are reported in Table 3. The results obtained show that all polymers, with the exception of PDEVP, are soluble in water, and all of them, with the exception of PVP-COONa, are soluble in CH_3OH. Not unexpectedly, P(DEVP-*co*-VP) and P(EVP-*co*-VP) copolymers are soluble both in water and in organic solvents.

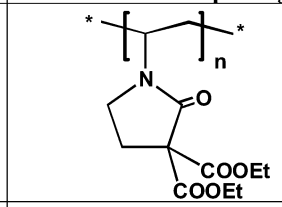
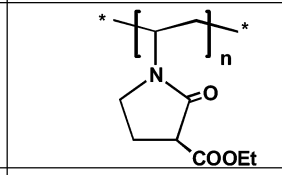
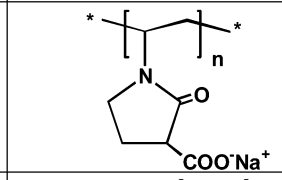
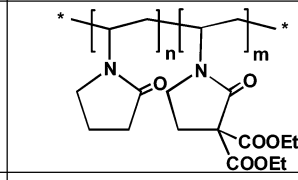
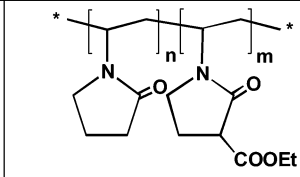
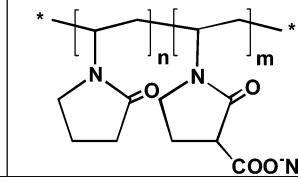
The structure of all polymers was determined by means of ^{1}H and ^{13}C NMR and by FT-IR spectroscopy. The spectroscopic data obtained, reported in the Experimental Part, were in complete agreement with the proposed structures. It may be observed, for instance, that the ^{13}C NMR resonance peaks of the vinylic carbon atoms of monomers, placed in the range 95−130 ppm, were not detected in the spectra of polymers, while the skeleton CH_2 (34 ppm) and CH (44−45 ppm) resonance peaks were invariably shown. Moreover, the chemical

Table 1. Amounts of the Reagents Used in the Polymerization Reactions Leading to PVP-Based Homo- and Copolymers

polymer sample	DEVP (mmol)	EVP (mmol)	VP (mmol)	VP-COONa (mmol)	ethanol[a] (mL)	water[b] (mL)
PDEVP	1.961				2.5	
PEVP		1.093			2	
PVP-COONa				0.847		5
P(DEVP-*co*-VP)	0.7843		5.228		2	
P(EVP-*co*-VP)		0.1093	0.7829		2	

[a] Initiator: AIBN. [b] Initiator: 4,4′-azobis(4-cyanovaleric acid).

Table 2. Structure of the PVP-Based Homo- and Copolymers

Polymer sample	Structure of the repeating unit
PDEVP	
PEVP	
PVP-COONa	
P(DEVP-*co*-VP)	
P(EVP-*co*-VP)	
P(VP-COONa-*co*-VP)	

shifts relative to the carbon atoms of the lactam rings and of ethoxycarbonyl residues remain almost unchanged if compared to those of the starting monomers. For comparison purposes, the ^{13}C NMR spectrum of a P(DEVP-*co*-VP) copolymer with 1:3 DEVP/VP molar ratio is reported in Figure 1, together with assignments.

The molecular weights of the polymers were determined by SEC carried out in 9:1 dichloromethane/methanol phase against polystyrene standards in the case of PDEVP and PEVP and in TRIS buffer pH 8.0 aqueous phase in the case of all the other polymers. The number-average molecular weights of the synthesized products ranged between 80 000 and 437 000. These values are not absolute, since they were determined against SEC standards other than PVP, but provide evidence that the polymers described in this paper were of remarkably high molecular weight.

Hydrolysis Reactions of Pendant Ester Functions of PVP-Based Homopolymers and Copolymers. PDEVP and PEVP homopolymers and P(DEVP-*co*-VP) and P(EVP-*co*-VP) copolymers underwent saponification reactions, for instance in 1 M sodium hydroxide at 50 °C. Initially, the reaction mixture was homogeneous only in the case of P(DEVP-*co*-VP) and P(EVP-*co*-VP) with high VP content, that is, the water-soluble copolymers. Water-insoluble polymers gave initially milky suspensions that, however, rapidly became homogeneous as esterolysis proceeded. In all cases, including PDEVP and PEVP, the reaction went to completion after a few hours. The final products were ultrafiltered through a membrane with molecular weight cutoff 3000 and then analyzed by NMR and FT-IR. It was found that in both EVP-based polymers, PEVP and P(EVP-*co*-VP), all pendant ethyl ester functions had been quantitatively converted into carboxylate groups (see Scheme 5). By contrast, in both DEVP-based polymers, PDEVP and P(DEVP-*co*-VP), the saponification reaction was accompanied by decarboxylation. Therefore, EVP and DEVP-based polymers containing the same number of carboxyl units, when treated by aqueous base, yielded the same polymer PVP−COONa, as inferred from IR and NMR spectra.

Determination of Reactivity Ratios of 3,3-Di(ethoxycarbonyl)-1-vinylpyrrolidin-2-one and 1-Vinylpyrrolidin-2-one. By considering the above results, we concluded that DEVP was the most convenient VP comonomer for obtaining carboxylated PVP-like polymers. This prompted us to study in more detail the radical copolymerization of DEVP with VP to control the overall copolymerization process and to obtain a homogeneous distribution of the functionalized repeating units along the polymer chain. This involved the determination of the reactivity ratios of the two monomers, r_{DEVP} and r_{VP}. These parameters were determined by following the Kelen−Tüdös method, which represents, to date, one of the most popular and widely used linear least-squares determination technique.[25,29−33] According to this procedure, the copolymerization equation

$$y = x\frac{r_1 x + 1}{r_2 + x} \tag{1}$$

where

$$x = \frac{M_1}{M_2} \tag{2}$$

$$y = \frac{\mathrm{d}M_1}{\mathrm{d}M_2} \tag{3}$$

and

$$r_1 = \frac{k_{11}}{k_{12}} \tag{4}$$

$$r_2 = \frac{k_{22}}{k_{21}} \tag{5}$$

where M_1 and M_2 are monomer concentrations, $\mathrm{d}M_1$ and $\mathrm{d}M_2$ the instantaneous polymer compositions, r_1 and r_2 monomer reactivity ratios, and k_{11}, k_{12}, k_{22}, and k_{21} the kinetic constants of the propagation reactions in copolymerization, can be written as

$$\eta_t = \left(r_1 + \frac{r_2}{\alpha}\right)\xi_t - \frac{r_2}{\alpha} \tag{6}$$

where

$$\eta_t = \frac{x\dfrac{y-1}{y}}{\alpha + \dfrac{x^2}{y}} \tag{7}$$

$$\xi_t = \frac{\dfrac{x^2}{y}}{\alpha + \dfrac{x^2}{y}} \tag{8}$$

where α is an arbitrary constant. If the monomers' reactivity ratios are very close to each other, that is, $r_1 \cong r_2$, the choice of $\alpha = 1$ is generally satisfactory. When the two monomers exhibit a different reactivity or if the assumption of $\alpha = 1$ involves a rather asymmetric data distribution along the interval (0,1), a satisfactory α value can be determined from eq 9

$$\alpha = (F_{max}F_{min})^{1/2} \tag{9}$$

where

$$F = \frac{x^2}{y} \tag{10}$$

and F_{max} and F_{min} represent the maximum and minimum values.

The reactivity ratios r_{DEVP} and r_{VP} in methanol solution were experimentally determined by following the decrease of the instantaneous concentrations of DEVP and VP monomers by means of ^{1}H NMR spectroscopy in polymerization experiments carried out in CD_3OD at 50 °C, inside an NMR tube (see the Experimental Part). These experiments were performed by using five different monomer ratios, as reported in Table 4. The instantaneous monomer concentrations in the polymerization solution were determined by calculating the relative decrease of the diagnostic peaks due to the resonance of the vinyl CH_2 hydrogens of DEVP and VP with respect to the resonance peak of ester OCH_2, taken as internal standard. The main advantage of the procedure adopted in this work is that it allows on line monitoring true monomer concentrations and, consequently, calculating instantaneous polymer compositions over a wide conversion range, for instance, in this work, from 1.58 up to 77.2%. By contrast, the conventional procedure, still frequently reported in the literature,[33−37] consists of performing several copolymerization experiments at different starting monomer ratios, then stopping the polymerization reaction at very low yields, to assume monomer concentration and polymer composition constant. This procedure, which allows determining only one monomer ratio (x)/polymer composition (y) datum per experiment, is affected by a relatively high experimental error and requires several

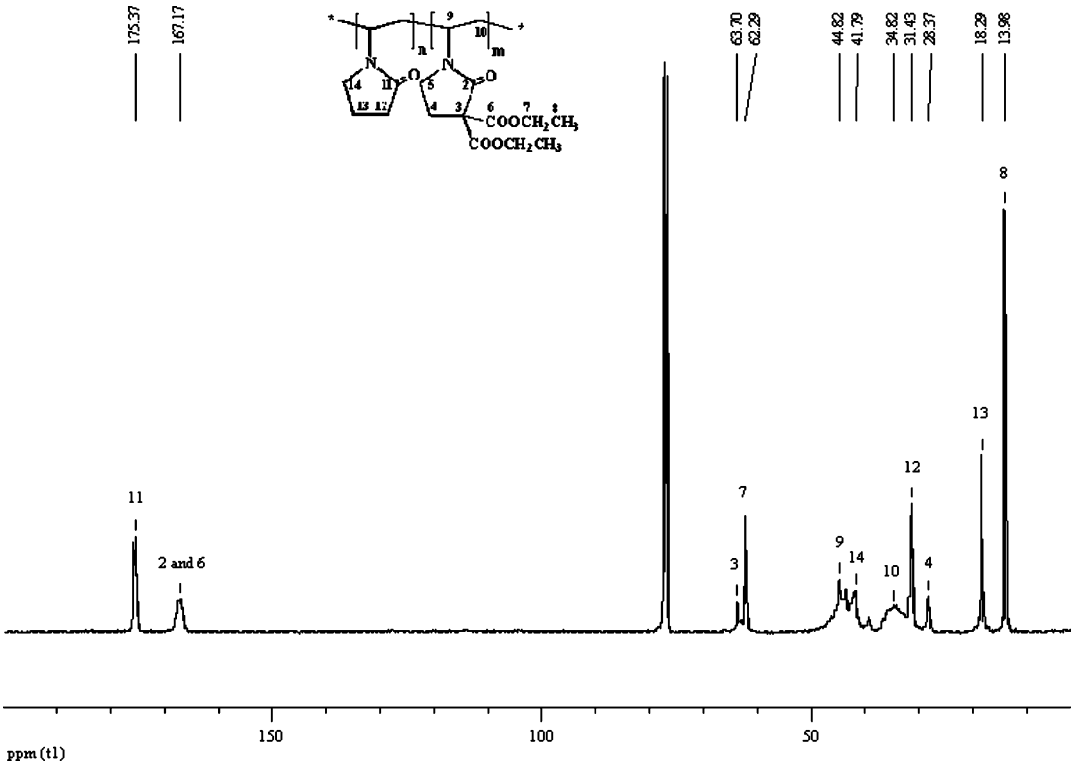


Figure 1. ^{13}C NMR spectrum of a P(DEVP-*co*-VP) copolymer with 30% on a molar basis of DEVP units, in $CDCl_3$.

Table 3. Solubility Properties of PVP-based Homo- and Copolymers

polymer sample	H_2O	CH_2Cl_2	MeOH	ethyl ether	toluene	ethyl acetate	DMSO	DMF
PDEVP	i[a]	s[a]	s	i	s	s	s	s
PEVP	s	s	s	i	s	s	s	s
PVP-COONa	s	i	i	i	i	i	i	i
P(DEVP-*co*-VP)	s	s	s	i	i	s	s	s
P(EVP-*co*-VP)	s	s	s	i	i	s	s	s
P(VP-COONa-*co*-VP)	s	i	s	i	i	i	s	i

[a] s = soluble; i = insoluble.

Scheme 5. Esterolytic Reactions of PVP-Based Homo- and Copolymers

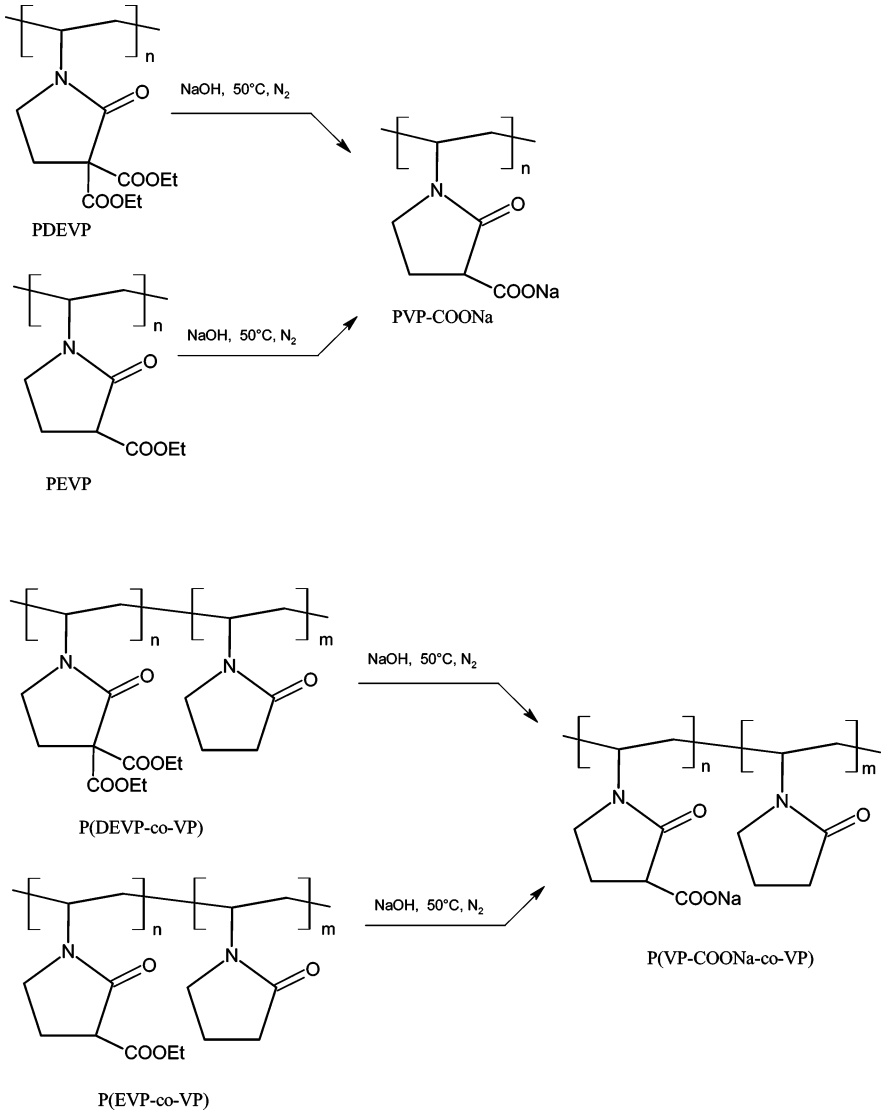


Table 4. Monomer Amounts Used in the Polymerization Kinetics of DEVP with VP[a]

kinetic	DEVP (mmol)	VP (mmol)	DEVP/VP (mol/mol)
1	0.1114	0.2405	0.46
2	0.1165	0.0748	1.56
3	0.1369	0.1514	0.90
4	0.0667	0.1991	0.33
5	0.3569	0.1117	3.20

[a] Initiator = AIBN, 1% (w/w) with respect to monomers; volume = 0.75 mL; temperature = 70 °C.

different experiments to obtain reasonable fitting data. Conversely, our on line method permits to determine different x and y experimental values, in this work from 2 to 4, from the same experimental curve. Typical conversion curves relative to a DEVP/VP copolymerization experiment performed at a 0.183 M DEVP and 0.202 M VP concentration are reported in Figure 2. For the sake of clearness, Table 5 reports the x and y experimental values, as determined by the NMR analyses of five different polymerization kinetics, used to obtain the Kelen−Tüdös (K/N) graph, while Table 6 reports the calculated values of K/N parameters.

Plotting η_t vs ξ_t parameters reported in Table 6, a linear correlation was observed, with a regular distribution through all the useful ξ_t range (0,1), as shown in Figure 3. The elaboration of the experimental data lead to the linear η/ξ relationship shown in eq 4.

$$\eta_t = 0.6426\xi_t - 0.3141 \tag{11}$$

By choosing a 2.02 α value, the following values of the reactivity ratios were obtained: $r_{DEVP} = 0.63$ and $r_{VP} = 0.33$. These values indicate that the intrinsic reactivity of DEVP in the copolymerization with VP allows an easy process control.

We have subsequently checked the validity of the above parameters by means of an independent method based on the use of the classical Skeist equation,[38] whose integrated form is reported in eq 12. This equation correlates the variation in the feed composition with the degree of conversion, defined as $1 - M/M_o$, where M and M_o represent the overall monomer concentration at time t and in the initial feed:

$$1 - \frac{M}{M_o} = 1 - \left[\frac{f_1}{f_{1,0}}\right]^{\alpha}\left[\frac{f_2}{f_{2,0}}\right]^{\beta}\left[\frac{f_{1,0} - \delta}{f_1 - \delta}\right]^{\gamma} \tag{12}$$

where f_1 and f_2 are the molar fractions of monomers in

Table 5. Results of ^{1}H NMR Spectral Analysis in the Evaluation of DEVP/VP Copolymerization Kinetics

expt	time (min)	VP/Ref[a] (mol/mol)	DEVP/Ref[a] (mol/mol)	M_{VP}[b] (mmol)	M_{DEVP}[b] (mmol)	dM_{VP}[c] (mmol)	dM_{DEVP}[c] (mmol)
1	60	0.9025	0.4529	0.2168	0.0944	0.023720	0.016960
1	240	0.3736	0.1265	0.0898	0.0264	0.009425	0.005856
2	90	0.2855	0.4586	0.0707	0.1054	0.003718	0.006504
2	180	0.1867	0.2687	0.0462	0.0617	0.007836	0.010610
3	40	0.5965	0.5368	0.1494	0.1346	0.001988	0.002344
3	60	0.5677	0.5049	0.1422	0.1266	0.007209	0.007992
3	240	0.2282	0.1467	0.0571	0.0368	0.005068	0.004909
3	300	0.1819	0.1052	0.0455	0.0264	0.011580	0.010480
4	240	0.9202	0.1352	0.1276	0.0198	0.012860	0.004220
4	300	0.7436	0.0882	0.1031	0.0129	0.024490	0.006881
5	30	0.1220	0.3438	0.0920	0.3011	0.019720	0.055770
5	45	0.0857	0.2571	0.0646	0.2253	0.027360	0.075870

[a] Relative monomer amount, calculated with respect to the internal standard. [b] Composition of the polymerization solution: data obtained from those reported in the second and third columns and from the knowledge of the starting monomer concentrations. [c] Instantaneous polymer composition: data obtained by calculating the decrease of monomer amount in solution in the time interval considered.

Table 6. Determination of Kelen–Tüdös Parameters[a]

expt	time (min)	X	Y	F	$\alpha + F$[b]	A[c]	ξ_t	η_t	yield (%)
1	60	2.2966	1.3983	3.7721	5.7921	0.6542	0.6512	0.1129	12.63
1	240	3.4042	1.6094	7.2005	9.2205	1.2890	0.7809	0.1398	69.72
2	90	0.6706	0.5716	0.7868	2.8068	−0.5026	0.2803	−0.1790	8.63
2	180	0.7486	0.7386	0.7587	2.7787	−0.2650	0.2730	−0.0953	45.06
3	40	1.1100	0.8481	1.4528	3.4728	−0.1988	0.4183	−0.0572	1.58
3	60	1.1232	0.9020	1.3986	3.4186	−0.1220	0.4091	−0.0357	7.07
3	240	1.5510	1.0324	2.3301	4.3501	0.0487	0.5356	0.0112	69.57
3	300	1.7281	1.1055	2.7013	4.7213	0.1649	0.5721	0.0349	77.22

[a] Where not otherwise stated, the definition of the variable reported in the table is given in the text. [b] $\alpha = 2.02$. [c] $A = x[(y - 1)/y]$.

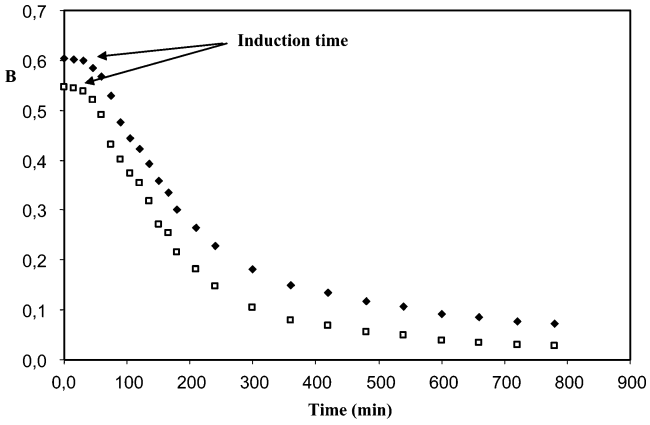


Figure 2. Copolymerization kinetics of DEVP with VP in CD_3OD solution at 50 °C. Experimental conditions: DEVP = 0.1369 mmol, VP = 0.1514 mmol. B = monomers integral value of vinyl CH_2 peak/integral value reference peak; ◆ = VP/reference peak (molar ratio), □ = DEVP/Reference peak (molar ratio).

the feed and the zero subscribe refers to the initial quantities, while the other symbols are given by

$$\alpha = \frac{r_2}{1 - r_2} \tag{13}$$

$$\beta = \frac{r_1}{1 - r_1} \tag{14}$$

and

$$\delta = \frac{1 - r_2}{2 - r_1 - r_2} \tag{15}$$

$$\gamma = \frac{1 - r_1 r_2}{(1 - r_1)(1 - r_2)} \tag{16}$$

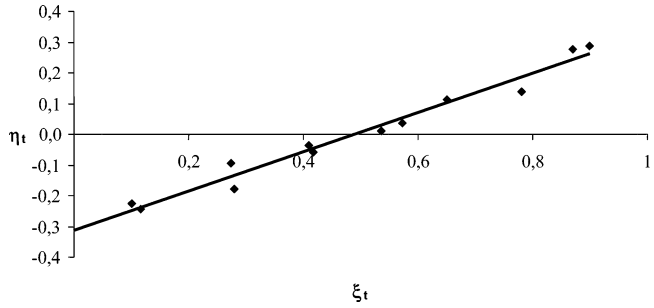


Figure 3. Kelen and Tüdös plot for the copolymerization of DEVP with VP in CD_3OD solution at 50 °C.

The experimental feed/conversion curves, obtained by NMR data, were compared with the theoretical ones, obtained by means of eq 12, in which the values of the r_1 and r_2 parameters were those determined according to the K/T method, that is, $r_{DEVP} = 0.63$ and $r_{VP} = 0.33$. The results obtained for the kinetic experiment of Figure 2 are reported in Figure 4, in which the continuous lines refer to the theoretical feed/conversion values obtained by using eq 12, and the dots represent the experimental values obtained from NMR data. The agreement among the experimental and calculated values is apparent.

Conclusions

The results obtained in this paper lead to the following conclusions:

1. New functionalized VP derivatives namely EVP, DEVP, and VP-COONa, were obtained by means of purposely designed synthetic procedures, developed by modification of previously reported functionalization methods of lactams. All these derivatives can be used for preparing PVP derivatives carrying reactive functions because they act as VP comonomers in radical polymerization. Out of them, DEVP can be obtained in the highest yield and by the simplest procedure.

2. In particular, the synthesis of DEVP was carried out in 91% yield, after a simple purification procedure

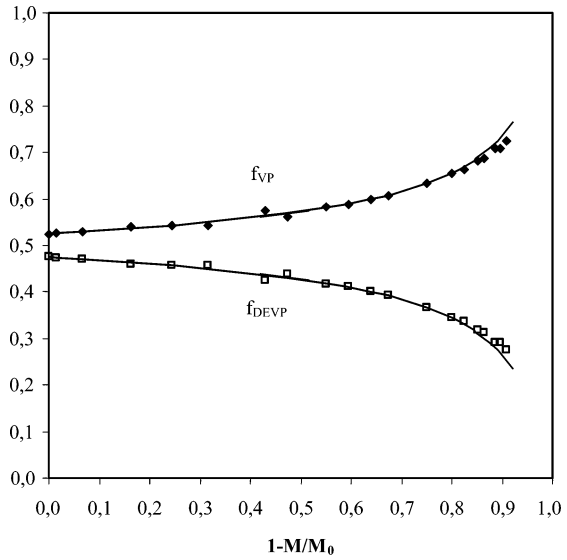


Figure 4. Comparison between the experimental and theoretical feed/conversion curves for the copolymerization kinetics of Figure 2. Experimental conditions: DEVP = 0.183 M, VP = 0.202 M in CD_3OD at 50 °C. f_{VP}, f_{DEVP} = monomer molar ratios, $1 - M/M_o$ = overall monomer conversion. Continuos lines = theoretical values according to eq 12; dots = experimental values from NMR data.

consisting of a filtration through silica gel. DEVP was therefore selected as the monomer of choice for VP copolymerization.

3. DEVP can be easily copolymerized with VP and the reactivity ratios, determined in methanol solution were $r_{DEVP} = 0.63$ and $r_{VP} = 0.33$. The intrinsic reactivity of DEVP in the copolymerization with VP allows, therefore, an easy process control.

4. The diethoxycarbonyl units in PDEVP, as well as in P(DEVP-*co*-VP), by treatment with aqueous alkali undergo both esterolysis and decarboxylation reactions, giving VP-COONa units, the same that can be obtained starting from EVP-based polymers.

5. From the results obtained in this paper we think that the copolymerization of VP with DEVP is to date the best available procedure for VP functionalization.

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