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Synthesis of functional polyesters derived from serine

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SUMMARY

Functional polyesters, bearing lateral amino group, derived from racemic or optically active serine have been prepared by anionic polymerization of N-tritylated serine β-lactones. Polymers with molecular weights up to 30 000 have been obtained. Removal of protective group leads to polyserine-ester.

INTRODUCTION

The presence of functional groups (hydroxyl, thiol, carboxylic acid, ...) in several α-aminoacids offers the opportunity for the preparation of a new class of poly α-amino-acids. In these polymers, the monomeric units are linked by non-amide bonds (ester, thioester, anhydride, ...) and carry in the side-chain an amino group. Such polymers have been named "pseudo polyaminoacids" and a polyester derived from S-hydroxy-proline was obtained by polycondensation method [1]. These materials have potential biomedical applications, e.g. drug delivery systems, since their degradation should lead to non toxic residues. Polyesters seem to be particularly interesting due to their known biodegradability. Moreover, the presence of an asymmetric carbon atom in the repeating unit allows the synthesis of polymers having various distributions of enantiomeric units which may have substantial differences in properties [2]. Parent chiral polyesters belonging to the family of poly-β-hydroxyalkanoates can be synthesized by biotechnological way [3,4,5] or by ring-opening polymerization of β-lactones [6].

The present work describes the synthesis of new polyesters, based on racemic or optically active serine, by ring-opening polymerization of the β-lactone derived from tritylated serine (3-[triphenylmethyl)amino]-2-oxetanone) [7]. The protection of the amino group is required during the polymerization reaction (Scheme 1).

RESULTS AND DISCUSSION

The preparation of the optically active β-lactone derived from S-serine has been reported first by Sheehan et al. [8] with an overall yield of 15 %. However, no details on the experimental conditions were given. More recently, Shanzer et al. [9] used this β-lactone as a precursor for the synthesis of enterobactin, an iron sequestering agent having a cyclic triester skeleton. The yield in β-lactone was of 26 % according to the described experimental

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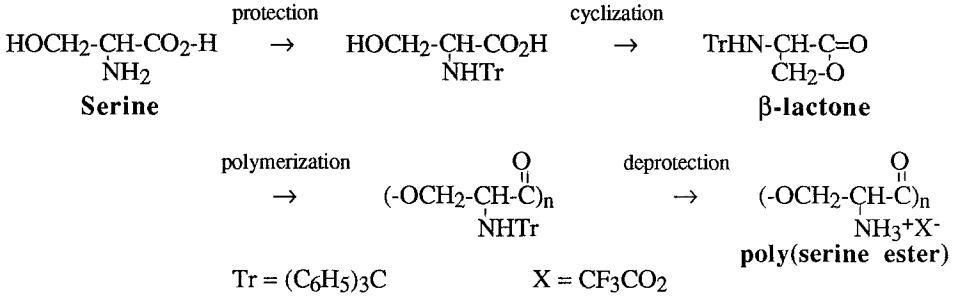
procedure. Using N,N'-diisopropylcarbodiimide [9] as cyclization agent of N-tritylserine [10], we were unable to obtain the desired β-lactone. However, with N,N'-dicyclohexylcarbodiimide, the formation of N-tritylated serine β-lactone is observed.



Scheme 1

The chromatography of the prepared monomer over a column of silica gel, using toluene as eluent (as indicated by Shanzer), leads to an impure material (as evidence by IR). In order to obtain a β-lactone, with a high chemical purity required for polymerization reactions, we have purified it by two column chromatographies on silica gel (Merck 60) : first with toluene, then with the mixture cyclohexane-ethylacetate-dichloromethane (90 : 5 : 5). The overall yield as expected was lower (10 %) as compared to previous results, but our samples of β-lactone were chemically pure (as controlled by analytical and spectroscopic methods). Racemic and optically active monomers have been prepared starting from (R,S) and (S)-serines.

Several anionic initiators usually employed in the polymerization of β-lactones have been tested : triethylamine, betaine, tetraphenylporphinatoaluminium chloride, tetrabutylammonium acetate, potassium acetate/dicyclohexyl-18 crown-6. The best results were obtained with carboxylate salts while triethylamine and betaine were quite inefficient. Results of polymerization of monomers with different enantiomeric enrichment using tetrabutylammonium acetate as initiator are reported in table 1.

The polymerization of β-lactones by tetraalkylammonium carboxylate salts is known to proceed by alkyl-oxygen ring-opening mechanism and can be, in some cases of the living-type [11]. A fairly good agreement between experimental and calculated values of molecular weights is observed for polymerizations carried out at 80°C. Moreover, polymers with narrow molecular weight distribution (M_w/M_n = 1.2 - 1.3) are obtained. This is consistent with a living type character of the polymerization. However, at higher temperatures (130°C), discrepancies between M_n (calc.) and M_n (exp.) are observed indicating the existence of a transfer reaction.

The prepared tritylated polymers have been fully characterized by analytical and spectroscopic methods. They have the expected structure, each monomer carrying a trityl group as indicated by ^1H NMR (250 MHz). All of them are soluble in usual organic solvents (THF, CH_2Cl_2, N-methylpyrrolidone, ...). A preliminary study of microstructure of polymers by ^{13}C NMR (62.89 MHz) indicates that the methine carbon of the main chain is stereosensitive to triad effects.

TABLE 1

Polymerization of tritylated serine β-lactone by tetrabutylammonium acetate in THF solution[a]

Temperature (°C)	E.e. [b] (%)	(C)/(M) (mole %)	Time (h)	Conversion (%)	M_n exp [c] (M_n calc.)	M_w/M_n [d]	Polymer $[\alpha]_D$ ($CHCl_3$,C=0.6)
130	100	1.23	17	80	13000 (21400)	1.30	+ 46.4
130	50	1.09	22	71	13100 (21400)	1.35	+ 15.3
110	0	1.09	113	87	21200 (26300)	1.22	—
80	0	1.10	208	92	30000 (27600)	1.21	—
80	75	0.55	161	63	32000 (37700)	1.29	+ 23.2
80	100	0.73	208	71	28000 (32000)	1.30	+ 47.1

[a] polymerization carried out in sealed ampoules under vacuum

[b] E.e. : enantiomeric excess of initial monomer

[c] by osmometry in toluene ; M_n calc. = (M) / (C) x 329 x conversion

[d] GPC, polystyrene standards

The deprotection from the trityl group in polymers has been carried out according to the method of Barlos et al. [12] using trifluoroacetic acid in anhydrous dichloromethane. The obtained polyaminoesters trifluoroacetates are insoluble in usual organic solvents but can be dissolved in water, methanol and DMSO. The UV-visible spectrum in methanol substantiates that the deprotection is complete (absence of absorption bands corresponding to aromatic moieties).

In order to ascertain that the integrity of the polymeric backbone was preserved during the deprotection reaction, a sample of polyaminoester trifluoroacetate derived from a precursor tritylated polymer having M_n = 27000 (M_w/M_n = 1.18) was retritylated (using trityl chloride and triethylamine in dichloromethane). The regenerated trityl protected polymer had a lower molecular weight M_n = 6500 (M_w/M_n = 1.47) indicating that some cleavages of the polymer chain occur during the deprotection step. The chemical modification of deprotected polymers is presently under investigation.

EXPERIMENTAL PART

Reagents

Synthesis of monomer

8.2 g (0.0236 mol) of N-tritylserine (racemic or optically active, prepared according to Guttmann [10]) are dissolved in 580 ml of anhydrous methylene chloride. To the cooled

to Guttmann [10]) are dissolved in 580 ml of anhydrous methylene chloride. To the cooled solution (0°C) are added 0.57 g (0.0047 mol) of 4-dimethylaminopyridine and 4.87 g (0.0236 mol) of 1,3-dicyclohexylcarbodiimide. The solution is stirred at room temperature during two days. 1,3-Dicyclohexylurea is removed by filtration. The solution is further concentrated by evaporation of solvent under reduced pressure. Purification of monomers is carried out by column chromatography.

The residue obtained after the cyclization reaction is chromatographied first over silica gel (Merck 60) with toluene as eluent. A second chromatography (silica gel, Merck 60) with cyclohexane/ethylacetate/methylene chloride (90/5/5) leads to chemically pure β-lactone (yield ≅ 10 %). The monomer is dried and stored under vacuum.

Monomer

M_p

196°C (S-monomer) 145°C (racemic monomer)

Elemental analysis

	C %	H %	N %	O %
Found	80.42	5.80	4.19	9.59
Calculated	80.24	5.77	4.25	9.73

$[\alpha]^{25}$ (S-monomer) - 68 ± 0.5 (C = 0.5, $CHCl_3$)

IR (KBr)

3334 cm^{-1} (NH), 1825 cm^{-1} (C = O)

^1H NMR

(250 MHz, $CDCl_3$, in ppm from TMS) :
2.74 (d, 1H, H^N), 3.13 and 3.53 (dd, 2H, CH_2O), 4.58 (m, 1H, CHC = O), 7.20 (m, 9H, m and p-ArH), 7.41 (m, 6H, o-ArH).

^{13}C NMR

(62.89 MHz, $CDCl_3$, in ppm from TMS) : 64.69 (CH), 70.67 (CH_2), 70.77 (c-Ar), 127.00 (p-Ar), 128.37 (o-Ar and m-Ar), 145.18 (i-Ar), 171.79 (C = O).

Polymerization

All polymerizations have been carried out under high vacuum is sealed tubes. About 1mg of tetrabutylammonium acetate is dried under vacuum, then anhydrous tetrahydrofuran (1.5ml) and monomer (0.2 g) are introduced under a stream of dry nitrogen. The monomer solution is outgassed by several freeze-pump-thaw cycles under vacuum and the polymerization tube is sealed. Experiments are carried out at 80°C, 110°C or 130°C. At the end of the polymerization, the polymers are precipitated in methanol, recovered by centrifugation and dried under vacuum.

Polymer

Elemental analysis

	C %	H %	N %	O %
Found	80.13	5.93	3.98	9.91
Calculated	80.24	5.77	4.25	9.73

IR (CH_2Cl_2)

3335 cm^{-1} (NH), 1745 cm^{-1} (C = O)

^1H NMR

(250 MHz, $CDCl_3$, in ppm from TMS) :

2.70 (d, 1H, H^N), 3.45 - 4.05 (broad pattern, 3H, CH_2, CH), 7.05 (m, 3H, p-ArH),

7.14 (m, 6H, m-ArH), 7.44 (m, 6H, o-ArH).

^{13}C NMR

(62,89 MHz, $CDCl_3$, in ppm from TMS) :

55.84 (CH), 66.67 (CH_2), 71.08 (c-Ar), 126.63 (p-Ar), 127.96 (m-Ar), 128.75 (o-Ar), 145.51 (i-Ar), 171.19 (C = O).

Measurements

Elemental analyses of the samples were performed by Service Central d'Analyse du C.N.R.S. IR spectra were recorded using a Bruker IRFT IF S45 spectrometer. Molecular weights of the polymers were determined by GPC in THF [Waters apparatus equiped with μ-styragel columns=10^5, 10^4, 10^3, 500, 100 Å ; detection : refractometric and with UV (254nm) ; flow rate: 1 ml/min.]. NMR spectra were recorded for ^1H NMR with a Bruker 250 MHz apparatus and for ^{13}C NMR with a Bruker 62.89 MHz apparatus : $CDCl_3$ was used as solvent. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

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