Ring-Opening Polymerization of 1,4,8-Trioxaspiro[4.6]-9-undecanone: A New Route to Aliphatic Polyesters Bearing Functional Pendent Groups

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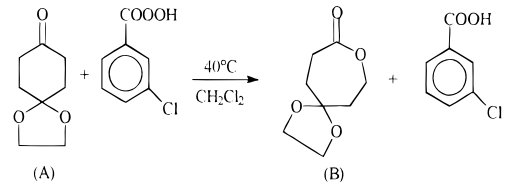
ABSTRACT: A straightforward and very efficient pathway has been reported for the synthesis of a functional derivative of ϵ-caprolactone, i.e. 5-ethylene ketal ϵ-caprolactone. This new monomer has been homopolymerized and copolymerized with ϵ-caprolactone in a well-controlled manner, strongly suggesting absence of any side reactions. Deacetalization of the polyester chains is complete and reduction of the ketone groups into hydroxyl groups as well. No chain scission is observed to occur in the course of these two derivatization reactions. Thus, aliphatic polyesters bearing either ketone pendent groups or hydroxyl pendent groups can be easily prepared, which raises new application prospects. These materials proved to be easily redispersed in an aqueous medium. They form stable colloidal nanodispersions (e.g. 100 nm). These suspensions are stable more than 48 h at room temperature and may be viewed as potential drug colloidal vectors with a core−shell like structure. Different types of reactive groups on the surface of these nanoparticulate vectors are indeed available to the binding of species selected for molecular recognition and drug targeting. For instance, the well-known reactivity of ketones toward primary amines is a direct route to attach peptides onto biodegradable and biocompatible aliphatic polyesters. Poly(ϵ-caprolactone) with hydroxyl groups reactive toward triethylaluminum provides a macroinitiator for lactone and lactide polymerization, so that biodegradable and biocompatible functional comb, graft, and dendritic aliphatic polyesters can now be synthesized.

Over the last 20 years, increasing attention has been paid to synthetic aliphatic polyesters derived from lactones, lactides, and glycolide for applications in medicine and surgery.[1,2] Nevertheless the shortage of polyester chains bearing functional pendent groups is a severe limitation to further progress in the field. Indeed, the availability of functional pendent groups is highly desirable for the fine tuning of properties in view of, e.g., attachment of drugs, improvement of biocompatibility, and promotion of bioadhesion. Examples of polyesters containing functional comonomers are known.[3−16] However, chemistry involved in the synthesis of the functional monomer is most often complex and/or tedious, whereas the subsequent polymerization is generally out of control. For example, Langer et al.[14] have prepared poly(lactic acid-*co*-lysine) copolymers and attached the GRGDY peptide onto the lysine moieties in order to regulate the cell function. The reaction pathway is, however, far from giving complete satisfaction since the synthesis of the protected functional monomer, i.e., 3-(*N*-benzoxycarbonyl-L-lysyl)-6-L-methyl-2,5-morpholinedione, is of a very poor yield (less than 14%), the copolymerization is not "living", and the final content in lysine does not exceed 10 mol %. Furthermore, during the decarbamylation step (75% yield), the polymer molecular weight decreases from 64 000 to 40 000.

The purpose of this paper is to report on (i) the high-yield synthesis of 1,4,8-trioxaspiro[4.6]-9-undecanone (or 5-ethylene ketal ϵ-caprolactone), (ii) the well-controlled homopolymerization of this new ϵ-caprolactone (ϵ-CL), (iii) the random and block copolymerization with ϵ-caprolactone, (iv) the complete deacetalization of the polyester chains with release of ketone pendent groups, which are then quantitatively reduced into hydroxyl pendent groups, and (v) stable colloidal dispersions in water.

Equation 1 schematizes the reaction pathway for the synthesis of 5-ethylene ketal ϵ-caprolactone (B), which relies upon the oxidation of the commercially available



(1)

1,4-cyclohexanedione monoethylene acetal (A) by 3-chloroperoxybenzoic acid. The reaction is complete, and the yield in B is higher than 70%. To our best knowledge, eq 1 is the most straightforward (one step) and efficient (high yield) route to prepare a precursor of functional aliphatic polyester.

Aluminum isopropoxide [$(AlO^iPr)_3$] is a well-known efficient initiator in "living" ring-opening polymerization of ϵ-CL, the mechanism of which involves the selective acyl−oxygen bond cleavage of the cyclic monomer. After the ultimate hydrolytic deactivation of the growing aluminum alkoxide species, the poly(ϵ-caprolactone) chains are end-capped by a hydroxyl function and an isopropyl ester group, respectively. Accordingly, homopolymerization of B and copolymerization of B with ϵ-CL have been initiated by $Al(O^iPr)_3$ in toluene at 25 °C. Representative, although preliminary, results are listed in Table 1.

According to entry 1 in Table 1, homopolymerization of 5-ethylene ketal ϵ-caprolactone is complete at 25 °C within less than 3 h. Actually, the half-polymerization time is ca. 2 min. for $[B]_0 = 1$ M. A kinetics study of the homopolymerization of 5-ethylene ketal ϵ-caprolac-

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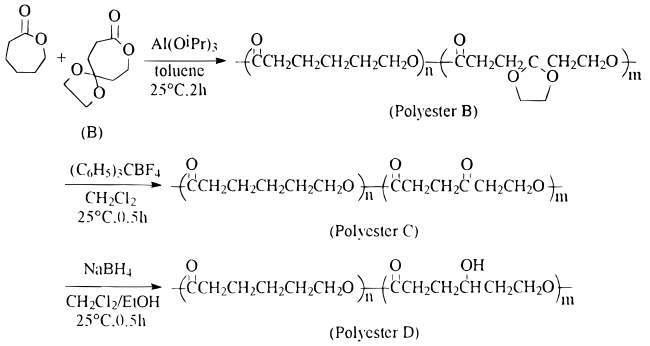
Table 1. Homopolymerization of B and Random Copolymerization of B with ϵ-CL Initiated by Al(O^{i}Pr)$_3$ in Toluene at 25 °C[a]

entries	$[\epsilon\text{-CL}]_0/[I]_0$	$[B]_0/[I]_0$	f_B[b]	time (h)	$\bar{M}_n$(th)[c] x 10^{-3} PCL	$\bar{M}_n$(th)[c] x 10^{-3} PB	$\bar{M}_n$(^{1}H-NMR) x 10^{-3} PCL	$\bar{M}_n$(^{1}H-NMR) x 10^{-3} PB	F_B[d]	$\bar{M}_n$[e] × 10^{-3} (SEC)	$\bar{M}_w/\bar{M}_n$	mean size (nm)[f]
1	0	45.8	1.00	3	0	7.9	0	7.3	1.00	3.8	1.20	64
2	5.6	54.4	0.907	17	0.64	9.4	0.65	8.7	0.90	4.5	1.20	93
3	63.1	9.2	0.127	2	7.2	1.6	7.4	1.5	0.12	7.0	1.15	72

[a] Quantitative conversion ([monomer]$_0$ = 1 M). [b] Molar fraction of B in the comonomer feed. [c] Theoretical molecular weight for a living polymerization. [d] Molar fraction of B in the random copolymer (^{1}H-NMR analysis). [e] $\bar{M}_n$(SEC) based on the universal calibration valid to PCL.[17] [f] Mean size of polymer dispersions (0.01 wt %) in the 10/90 v/v DMSO/water mixture.

Scheme 1



tone will be reported elsewhere.[20] The experimental molecular weight calculated by ^{1}H NMR from the relative intensity of the isopropyl end group coming from the initiator and the methylene protons of the monomeric units is in good agreement with the value calculated from the monomer over initiator molar ratio and the monomer conversion for a "living" polymerization. This observation is a clue for the "livingness" of B polymerization in toluene at 25 °C. The size-exclusion chromatograph shows that the elution peak is symmetrical and narrow; a polydispersity index ($\bar{M}_w/\bar{M}_n$) of 1.20 has been calculated which is in line with a living process and an initiation reaction faster than propagation. Entries 2 and 3 in Table 1 give credit to the very well-controlled copolymerization of mixtures of ϵ-CL and B in toluene at 25 °C. Once again, the experimental molecular weights agree with values calculated from the monomer over initiator molar ratio at complete monomer conversion, and the molecular weight distribution remains narrow. The molar fraction of B (F_B) in the recovered copolymers shows that B is completely incorporated in agreement with a quantitative copolymerization.

ϵ-CL and B have been copolymerized in a sequential way in toluene at 25 °C. Polymerization of ϵ-CL has been first initiated by Al(O^{i}Pr)$_3$, i.e. under conditions known for "livingness".[18] As expected, the PCL molecular weight (M_n = 4100) is in perfect agreement with the value calculated from the initial monomer-to-initiator molar ratio, i.e. 35. The living PCL chains are observed to initiate the 5-ethylene ketal ϵ-caprolactone polymerization in a completely controlled manner, since the experimental molecular weight of the second block (4500) fits the value expected for a living polymerization at complete monomer conversion (4400). The final polydispersity index is 1.21 compared to 1.15 for the first PCL block (M_n = 4100).

The synthesis of aliphatic polyesters bearing functional pendent groups is shown in Scheme 1. The first step, i.e. synthesis of chains bearing acetal pendent groups, has proved the inertness of the acetal groups toward the active initiating and propagating species, at least under the experimental conditions used. Deprotection of the ketone groups has been carried out with triphenylcarbenium tetrafluoroborate,[19] within a 100% yield. Finally, the ketone groups can be completely reduced to hydroxyl groups by sodium borohydride.

^{1}H-NMR analysis of polyester B, C, and D is clear evidence for the completeness of each derivatization reaction. Furthermore, the polyester molecular weight has been calculated from the ^{1}H-NMR spectrum for the hydroxyl groups containing polyester and the ketone-containing precursor, respectively. The calculated values are in agreement within the limits of experimental errors (9.0 × 10^3 ± 10%) and fit the molecular weight of the original ethylene acetal containing polyester. These data strongly support that the ethylene acetal pendent groups have been quantitatively converted into ketones and hydroxyl pendent groups and that the polyester chains have not degraded during this process, in agreement with the narrow molecular weight distribution as determined by size exclusion chromatography ($\bar{M}_w/\bar{M}_n$ = 1.15 before deacetylization, 1.20 after deactalization, and 1.25 after reduction). The elution peak remains rather narrow and symmetrical, which is a good indication for absence of chain scission. Of course, the chemical modification of the copolyester is responsible for changes in the polymer−solvent interactions and thus in the elution volume and apparent molecular weight.

Thus, aliphatic polyesters bearing either ketone pendent groups or hydroxyl pendent groups can be easily prepared, which opens new application prospects. It is worthwhile pointing out that the controlled copolymerization between B and lactides has also been successfully performed.[20] Poly(ϵ-caprolactone) or polylactide with hydroxyl groups highly reactive toward triethylaluminum provides a macroinitiator for lactone and lactide polymerization, so that synthesis of biodegradable and biocompatible functional comb, graft, and dendritic aliphatic polyesters is now an optimistic forecast.[20]

5-Ethylene ketal ϵ-caprolactone copolymerization with ϵ-caprolactone provides easy access to the controlled functionalization of this family of biocompatible and biodegradable polyesters. These materials have proved to be easily redispersed in water. Average sizes of 0.01wt % polymer dispersions are reported in Table 1. Compared to pure PCL in the same molecular weight range that gives a crude precipitate, both 5-ethylene ketal ϵ-caprolactone homopolymer and copolymers with ϵ-caprolactone provide stable dispersions in water of a mean size below 100 nm. Surprisingly enough, even though the functional comonomer is incorporated on a statistical basis at a low content (12 mol %), the copolymer is able to stabilize hydrophobic PCL segments in water. The average size of 0.10 w/w % dispersions of poly(ϵ-caprolactone) containing 12 mol % functional comonomer (sample 3, Table 1) in a 10/90 v/v DMSO/water mixture depends on the functional pendent

groups. The size of the colloidal dispersion decreases from 213 nm in the case of ethylene acetal pendent groups to 72 and 74 nm upon deacetalization into more polar ketone and hydroxyl groups, respectively. An increase in the dispersion concentration of sample 3 from 0.01% to 0.10% results in larger colloidal particles (from 72 to 213 nm). In all the cases, these suspensions are stable more than 48 h at room temperature, as checked by photon correlation spectrometry (PCS). Thus, this novel family of copolymers provides new potentialities for biomedical applications, particularly as tailored drug colloidal vectors with a core−shell like structure. Different types of reactive groups on the surface of these nanoparticulate vectors are indeed available to the binding of species selected for molecular recognition and drug targeting. For instance, the well-known reactivity of ketones toward primary amines is a direct route to attach peptides onto biodegradable and biocompatible aliphatic polyesters. These new opportunities are very promising for further developments in medicine, surgery, and tissues engineering. Work is in progress in this laboratory and will be reported in the near future.

Experimental Section

Materials. 1,4-Cyclohexanedione monoethylene acetal (or 1,4-dioxaspiro[4.5]-8-decanone) (Aldrich), 3-chloroperoxybenzoic acid (Janssen), triphenylcarbenium tetrafluoroborate (Acros), sodium borohydride (Janssen), and ethanol (Riedel-de Haën) were used as received. ϵ-Caprolactone (ϵ-CL; Janssen) was dried over calcium hydride for 48 h at room temperature and distilled under reduced pressure just before use. Toluene (Acros) was dried by refluxing over calcium hydride and distilled under a nitrogen atmosphere. Dichloromethane (Acros) was dried over molecular sieves (Aldrich) and distilled just before use. Aluminum isopropoxide [$Al(O^iPr)_3$] (Aldrich) was twice sublimated and then dissolved in toluene under nitrogen.

Synthesis of 1,4,8-Trioxaspiro[4.6]-9-undecanone (B). B has been synthesized by Baeyer−Villiger oxidation of 1,4-cyclohexanedione monoethylene acetal as previously described.[21] 3-Chloroperoxybenzoic acid (9.02 g, 0.037 mol) was stepwise added to a stirred solution of 1,4-cyclohexanedione monoethylene acetal (A) (5.25 g, 0.034 mol) in CH_2Cl_2 (50 mL) over 30 min (see eq 1). The mixture was refluxed for 15 h. Then workup in the standard manner gave the product B (4.21 g, 72.5%), mp 49−51 °C. ^{1}H-NMR ($CDCl_3$), δ: 1.91 (triplet, 2H, CH_2), 2.01 (triplet, 2H, CH_2), 2.71 (triplet, 2H, CH_2CO), 3.99 (single, 4H, CH_2), 4.29 (triplet, 2H, CH_2OC). IR: 1731 cm^{-1} (KBr). Calculated for $C_8H_{12}O_4$: C, 55.81%; H, 7.02%. Found: C: 56.14; H, 7.20%.

Polymerization Techniques. Homopolymerization and random copolymerization were carried out at 25 °C in toluene. 5-Ethylene ketal ϵ-caprolactone (B) was dried by repeated (three times) azeotropic distillation of toluene just before polymerization. Then solvent, ϵ-caprolactone (for random copolymerization only) and initiator [$Al(O^iPr)_3$ in toluene] were successively added through a rubber septum with a syringe or stainless steel capillary. After polymerization, an excess of 1 N HCl was added and the polymer was recovered by precipitation in cold heptane.

Block copolymerization was carried out as follows. The ϵ-caprolactone polymerization was initiated by $Al(O^iPr)_3$ in toluene at 25 °C. An aliquot of the "living" poly(ϵ-caprolactone) (PCL) solution was picked out, deactivated, and precipitated into cold heptane for analysis by size exclusion chromatography (SEC) and ^{1}H-NMR. A known amount of the solution of 5-ethylene ketal ϵ-caprolactone in toluene was transferred to the "living" PCL solution. After the second monomer conversion was complete, an excess of 1 N HCl was added and the copolymer was precipitated in cold heptane.

Deacetalization of B/ϵ-CL Random Copolymer. The random copolymer of B/ϵ-CL (2.80 g, B content 3.2 mmol) and trityl fluoroborate (1.12 g, 3.4 mmol) were dissolved in 280 mL of dichloromethane under stirring for 30 min at 25 °C. Then polyester (C) was recovered by precipitation in cold methanol.

Reduction of the Ketone Pendent Groups into Hydroxyl Pendent Groups. Polymer C (2.1 g; ketone groups content, 2.4 mmol) and sodium borohydride (0.11 g, 2.9 mmol) were dissolved in 294 mL of a CH_2Cl_2/EtOH (5:2) mixture under stirring for 30 min at 25 °C. Then polyester D was recovered in cold methanol.

Polymer Dispersion in Water. Polymer dispersions have been performed by following the procedure reported in a European Patent Application, EP 95 110 445.4 (Biocompatible and biodegradable nanoparticles designed for proteinaceous drugs absorption and delivery). Briefly, polymer solutions in DMSO (0.10%) are diluted 10 times in water to make a 1/9 v/v DMSO/water dispersion. Mixing is performed by simple manual agitation.

Characterization. ^{1}H-NMR spectra of polyesters were recorded in $CDCl_3$ at 400 MHz in the FT mode with a Bruker AM400 superconducting magnet system. IR spectra were recorded by using a Perkin-Elmer 106 FTIR. Size-exclusion chromatography (SEC) was performed in THF, by using a Hewlett-Packard 1090 liquid chromatograph equipped with a Hewlett-Packard 1037A refractometer index detector and a set of columns (pore size: 10^5, 10^3, 500, and 100 Å). Molecular weights were also calculated by ^{1}H-NMR from the relative intensity of the signals of the methine end group ($(CH_3)_2CH-O-$, coming from the initiator) and the methylene (for PCL) or methine ester groups of the polyester chain. The composition of copolymers was determined by ^{1}H-NMR from the relative intensity of the PCL methylene groups (δ = 4.06 or 1.65 ppm) and the methylene groups of B (δ = 4.16 or 2.00 ppm). Block copolymers were also characterized by SEC. From the overall composition and $\bar{M}_n$ of the first PCL block (SEC and/or ^{1}H-NMR), the molecular weight of the second block was calculated. The distribution size of the colloids are measured by photon correlation spectrometry (PCS) using a Brookhaven linear correlator (BI-2030, Brookhaven Instruments Corp., New York). The autocorrelation function was determined with an argon ion laser (2 W) operating at 488 nm and 20 mW. Time-dependent light scattering fluctuations were measured at 90°, and autocorrelation curves were analyzed with the cumulant software provided by Brookhaven.

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