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Julien Tailhades, Sébastien Blanquer, Benjamin Nottelet, Jean Coudane, Gilles Subra, et al.. From Polyesters to Polyamides Via O N Acyl Migration: An Original Multi-Transfer Reaction. *Macromolecular Rapid Communications*, 2011, 32 (12), pp.876 - 880. 10.1002/marc.201100235 . hal-01833151

HAL Id: hal-01833151

<https://hal.science/hal-01833151>

Submitted on 27 Aug 2022

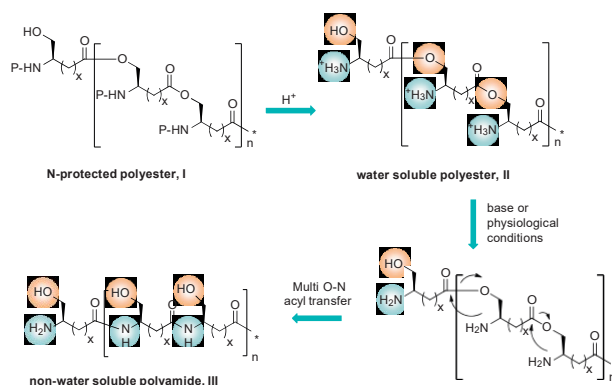
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From Polyesters to Polyamides Via O–N Acyl Migration: An Original Multi-Transfer Reaction^a

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A new strategy for the synthesis of polyamides from polyesters of hydroxyl-containing amino acids using a multi O–N acyl transfer reaction was developed. This original approach allowed the synthesis of three generations of polymers from the same starting monomer. The polymerization of *N*-benzyloxycarbonyl-serine and its *g*-homologated derivative provided the Z-protected polyesters; then the water-soluble polycationic polyesters were obtained by removal of the Z-protecting group; and finally the polyamides were obtained by a base-induced multi O–N acyl transfer, both in aqueous or organic medium. The key step transfer reaction was monitored by the disappearance and appearance of characteristic NMR proton signals and IR bands of polyesters and polyamides.



Introduction

The N–O acyl migration of β -amino alcohols, firstly described by Bergmann,^[1] is a well-known side reaction

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in peptide synthesis.^[2] This reversible, pH-dependent migration occurs in peptides or proteins at serine or threonine residues upon treatment with strong acid, but also in moderately acidic medium.^[3] It has been reported that strong acid treatment of polyserine amide promotes, as a side reaction, a partial N–O acyl shift to produce an amide-ester copolymer.^[4] In the last few years, the O–N acyl transfer reaction, initially developed as an alternative to native chemical ligation,^[5] was extensively used with serine and threonine containing peptides as an aggregate suppressor tool in protein and difficult peptides synthesis,^[6–10] in prodrug design^[11] and for the synthesis of cyclic peptides^[12] or solid supported peptide alcohols.^[13] All these methodologies are based on the O–N acyl shift from O-acylated serine or threonine derivatives that occurs in neutral or basic conditions.

Synthetic biodegradable polymers are under extensive research for a number of years for their use in tissue

^a Supporting Information for this article is available from the Wiley Online Library or from the author.

engineering, regenerative medicine, gene therapy, drug carriers, temporary implants, nanotechnology or for environmental applications.^[14,15] Among the elemental monomers used for the synthesis of polymers, amino acids that are natural building blocks, constitute an attractive starting material. Their polymerization is usually performed from N-carboxyanhydrides that need to be safely produced.^[16] Amino-functionalized lactones as precursors for polymerization of hydroxyl-amino acids such as serine or related compounds have also been described.^[17–21]

The aim of this project was to propose a new methodology for the synthesis of switchable biopolymers. It is based on an original multi O–N acyl transfer reaction for the synthesis of three different generations of polymers from hydroxyl-containing monomeric units. In this study, the methodology was applied to serine derivatives and analogues, for the synthesis of polyamides from polyesters (Figure 1). After polyester (I) formation, the water-soluble polycationic polyester (II) was obtained by removal of the N-protecting group. The simple base-induced O–N acyl transfer, both in aqueous or organic medium, resulted in N-acylation of the free amino functions, and allowed the production of the third corresponding polymer, polyamide (III). Such a methodology could be applied to the development of water injectable biopolymer systems that turn into insoluble biopolymers in physiological conditions. We describe here the multi O–N acyl transfer reaction on polyesters that to our knowledge, has never been reported so far.

Experimental Section

Materials and methods are given in Supporting Information.

Results and Discussion

First Generation of Polymers

As a proof of concept, two poly(hydroxy-amino acid) esters were used as models: polyserine ester and poly-g-homologated serine (ghhSer)^[22] ester. The multi O–N acyl shift leading to polyserine or poly-g-serine was then studied. N-(Benzyloxycarbonyl)-hydroxy-amino acids were used as starting monomeric units (Scheme 1). Several methods have been reported to access to N-protected polyserine. In our study, the N-benzyloxycarbonyl poly(L)serine ester (2a) was obtained in one-step by mesyl chloride activation of Z-

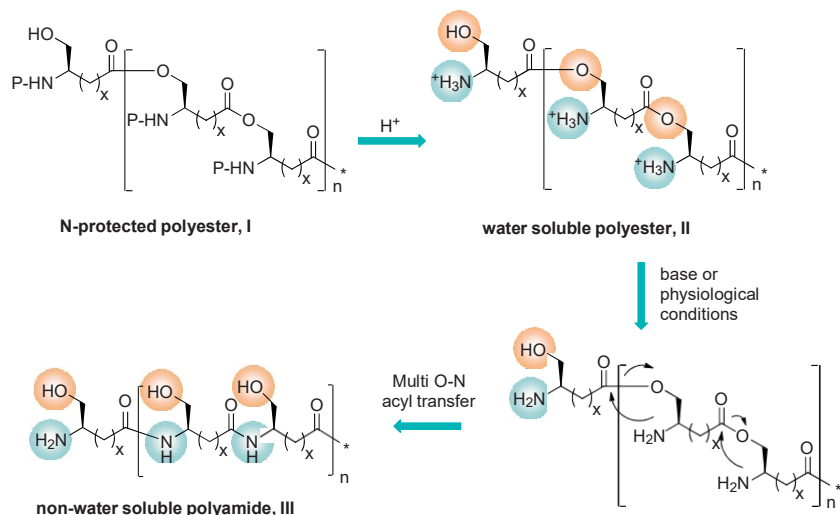


Figure 1. Synthesis of polyamides from polyesters via a multi O–N acyl migration.

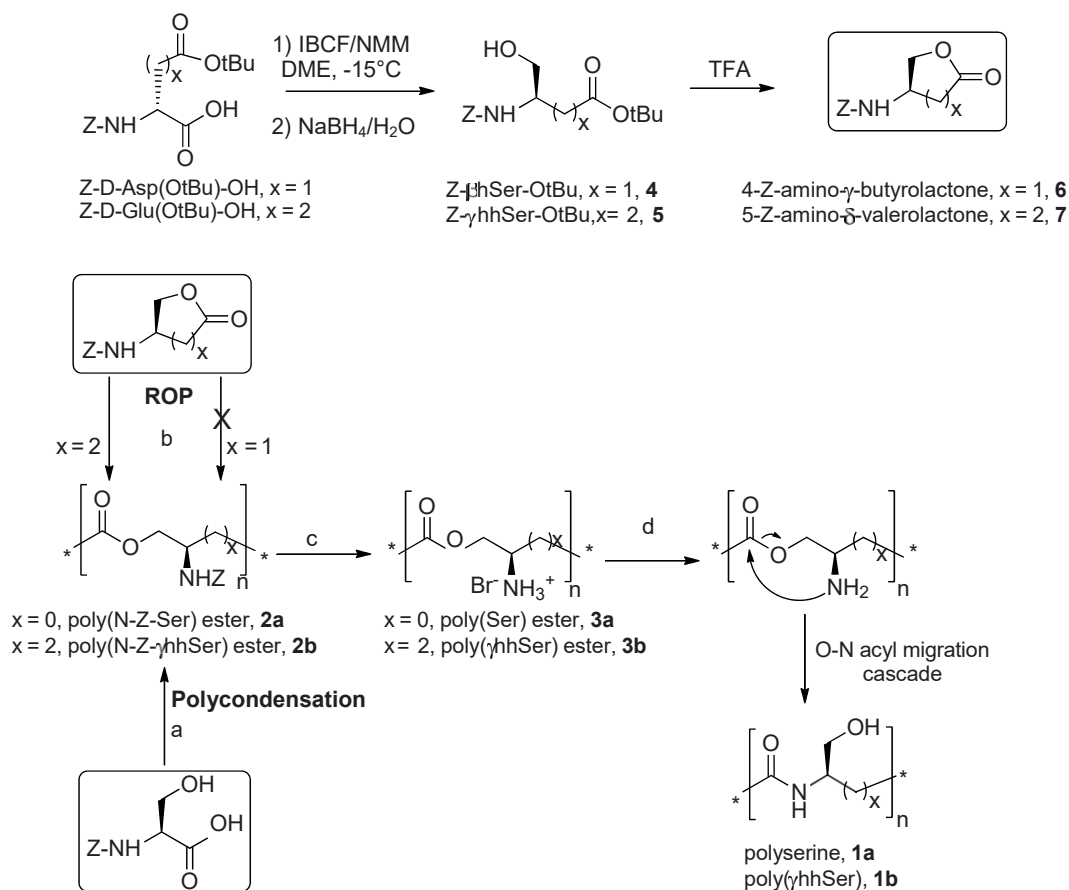
Ser-OH in basic condition as previously described.^[20] We also included in our study the recently described poly(N-Z-ghhSer) (PghhSZ, 2b).^[21]

Z-bhSer-OtBu (4) and Z-ghhSer-OtBu (5) were obtained by sodium borohydride reduction of the mixed anhydride of Z-D-Asp(OtBu)-OH and Z-D-Glu(OtBu)-OH, respectively.^[23] Acidic treatment to remove the tBu protecting group of compounds 4 and 5 led to spontaneous cyclization into the corresponding 4-(benzyloxycarbonyl)amino g-butyrolactone 6 and 5-(benzyloxycarbonyl)amino d-valerolactone 7. Polymerization under standard ring opening polymerization conditions of lactone 7 afforded the poly(N-Z-ghhSer) 2b. Unfortunately, attempts to obtain the poly(N-Z-bhSer) from the lactone 6 under the same experimental conditions failed due to a too high stability of the 5-membered ring lactone.^[24] Poly(N-Z-Ser) 2a was finally obtained by polycondensation of Z-Ser-OH as previously described.^[20]

Second Generation of Polymers

Removal of the Z groups from PSZ 2a and PghhSZ 2b was carried out in a 50/50 (v/v) solution of HBr (33%) in acetic acid/dry DCM at room temperature for 10 and 20 min, respectively, to afford poly(Ser) ester.HBr 3a (PAS) and poly(ghhSer) ester.HBr 3b (PAGhhS). The swelling properties of DCM allowed a drastic reduction of the time of deprotection thus preserving the integrity of the polyester backbone. The level of degradation was controlled as previously described by N-Z re-protection of the amino groups.^[20]

The Z group removal was monitored by the disappearance of its characteristic NMR proton signals and IR bands.



Scheme 1. Synthesis of polyserine and poly- γ hserine from their corresponding polyesters: (a) $\text{CH}_3\text{-SO}_2\text{Cl}$ (1.3 equiv), Na_2CO_3 (4 equiv), anhydrous acetone, RT, 24 h; (b) 2% wt $\text{Sn}[\text{Oct}_2]$ in bulk, 140 $^{\circ}\text{C}$, 10^{-3} bar, 5 d; (c) 33% HBr/AcOH (5 equiv) in anhydrous DCM, RT, 10 min for **2a** and 20 min for **2b**; (d) 10% Et_3N in anhydrous DMF, RT, 1 h or phosphate buffer, RT, 24 h.

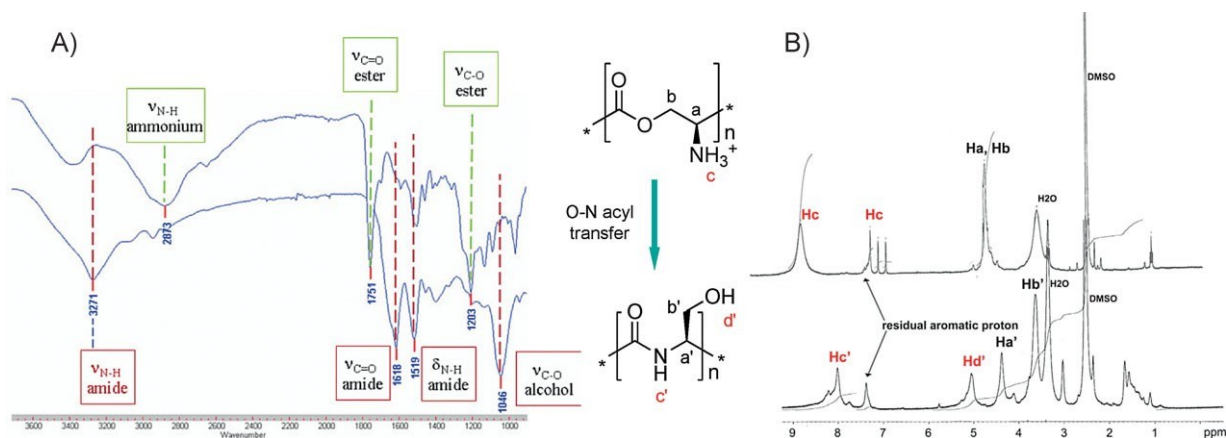
As previously observed, more than 95% of deprotection occurred (see Supporting Information).

Multi O–N Acyl Migration: Third Generation of Polymers

Conversion to the target polyamide **1a** and **1b** was achieved through the multi O–N acyl migration. The reaction was carried out either in aqueous or in organic medium. For that purpose, polyesters **3a** and **3b** were dissolved in aqueous phosphate buffer at pH 7.4 or in a 90/10 DMF/ Et_3N solution. When the reaction was carried out in phosphate buffer, polymers **3a** and **3b** were soluble. After 1 h stirring at room temperature, formation of a white precipitate suggested a structural modification of **3a** and **3b** initiated by the O–N acyl transfer. On the other hand, the polyesters **3a** and **3b** were insoluble in DMF/ Et_3N mixture but after 1 h stirring,

no detectable insoluble material was observed. This also suggested a structural modification of the polymers **3a** and **3b** in the DMF/ Et_3N mixture. The characteristic signals by FT-IR and NMR analyses (Figure 2 and Supporting Information) of polyesters (**3a** and **3b**) and polyamides (**1a** and **1b**) confirmed the complete conversion of the polyesters **3a** and **3b** into the polyamides **1a** and **1b** by the multi transfer reaction.^b Indeed, the disappearance of the ammonium (2873 cm^{-1}), ester carbonyl (1751 cm^{-1}) and C–O (1693 cm^{-1}) bands and the detection of the IR NH stretch (2873 cm^{-1}) identified the conversion of the polyester **3a** into the polyamide **1a** (Figure 2A). ^1H NMR data in DMSO confirmed the structural modification. The characteristic ammonium proton signal at 8.9 ppm and

^b The conversion was assessed according to the limitation of the detection of the spectroscopic methods that we used.



■ Figure 2. (A) FT-IR and (B) NMR data of 3a and 1a.

triplet at 7.2 ppm of the polyester 3a^c disappeared in favour of an amide proton signal at 8.0 ppm for the polyamide 1a (Figure 2B).

GPC Analyses of the Three Generations of Polymers

The molecular weights of the three generations of polymers (2a, 3a and 1a) were determined by gel-permeation chromatography (GPC relative to Pullulan standards) in DMSO (Table 1). Polymerization of Z-Ser-OH lead to the first generation of polymers (2a) with an average molecular weight (\overline{M}_n) of about 7 000 and 72 000 g mol⁻¹, corresponding to sequences varying from 32 to 325 monomeric units. The coexistence of two distinct polymer populations when a polycondensation process is performed with Z-Ser-OH is typically observed.^[20] After Z removal, the second generation of polymer, the polycationic polyester 3a, had a \overline{M}_n of 5 000 and 18 000 corresponding to 57 and 207 monomeric units. The difference in the number average of monomeric units constituting polyesters 2a and 3a is a well-known problem of using GPC relative to standards for polymers with different intrinsic physical properties. This was confirmed by the molecular weight observed after N-Z re-protection of 3a into 2a⁰ (Table 1). The GPC chromatogram of the third generation of polymer 1a showed peaks corresponding to \overline{M}_n of about 28 000, 120 000 and 360 000. The 28 000 molecular weight was in good agreement with a multi O–N acyl transfer of the 320 monomeric units sequence 3a. However, the drastic increase of monomeric units (120 000 and 360 000) could be attributed to aggregation due to b-sheet structuration of polyserine.^[25] This concern was confirmed by dynamic

Table 1. GPC data of polyesters 2a, 2a⁰, 3a and polyamide 1a in DMSO.

Polymer	\overline{M}_n [Da]	Number of monomeric units [DP]	Polydispersity
2a	7 000	32	1.12
	72 000	326	1.28
2a ⁰	7 000	32	1.06
	72 000	326	1.50
3a	5 000	57	1.01
	18 000	207	1.46
1a ^{a)}	28 000	321	1.12
	120 000	Aggregation	–
	360 000	Aggregation	–

^{a)}Low molecular weight polyamides were eliminated during washings.

light scattering highlighting the presence of aggregates (Supporting Information). The results were finally in good agreement with the stability of polymers under deprotection conditions and complete O–N acyl transfer reactions as no smaller peptide fragments were detected in our analyses.

Conclusion

We demonstrated in this study the successful application of a multi O–N intramolecular acyl migration for the synthesis of polyamides from polyesters. The results from

^cThis feature should be the characteristic of a free and blocked conformation of the ammonium.

FT-IR and NMR analyses showed that the O—N shift occurred to completion producing insoluble polyamides from water soluble polyesters. This methodology allowed a simple synthesis of three generations of polymers, two polyesters and a resulting polyamide, from the same starting material. The concept of the methodology applied to serine and g-hhserine was expected to be useful to elaborate protein-like structures and should allow in the future the synthesis of other modified poly(hydroxy-amino acid) and polymer of serine containing peptide sequences.

Acknowledgements: We gratefully acknowledge ABR Development and Stiefel Laboratories for the financial support to Julien Tailhades.

Received: April 8, 2011; Published online: May 20, 2011; DOI: 10.1002/marc.201100235

Keywords: multi O—N acyl migration; polycationic polyester; polypeptide amide; polypeptide ester; switchable biopolymer

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