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Coupling reactions of activated oligo(ε-caprolactone)s

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Summary
Oligo(ε-caprolactone)s functionalised with acid groups were prepared by reacting hydroxyl terminated oligo(ε-caprolactone)s with succinic anhydride, maleic anhydride or glutaric anhydride. Quantitative conversion of the hydroxyl functionality was achieved in the melt at 130 °C. The resulting acid terminated oligo(ε-caprolactone)s were characterised by ^{1}H and ^{13}C NMR spectroscopy. The reactivity of these oligomers was enhanced by conversion of the acid functionality in an acid chloride functionality using thionyl chloride or an anhydride functionality using acetic anhydride. It was shown that these activated oligo(ε-caprolactone)s can be used for coupling reactions with compounds containing alcohol- or amino functionalities.

Introduction

Telechelic poly(ε-caprolactone)s are commonly prepared by initiating ring-opening polymerization of ε-caprolactone from a compound containing a hydroxyl group, activated by tin(1,2), aluminium (3) or yttrium catalysts (4), and another functionality. This second functionality can then be used for further reactions. Examples include hydroxyl functionalised alkoxy amines (5), suitable for the preparation of block copolymers and hydroxyl functionalised methacrylates (6), suitable for the preparation of comb-like copolymers.

It could also be interesting to prepare telechelic oligo(ε-caprolactone)s, which can be directly applied in product formulations, instead of incorporating the functionalised oligo(ε-caprolactone) in some macromolecular structure. Amphiphilic derivatives of fatty acids and sugars (alkyl polyglucosides) or amino acids (N-acyl alkyl amino acids) have commercial importance as surfactants. It could therefore be interesting to prepare amphiphilic molecules, in which a oligo(ester) moiety functions as a hydrophobic tail.

However, it is not straightforward to prepare well defined oligoester derivatives of compounds containing multiple hydroxyl groups, such as sugars, of which only a limited number are to be functionalised with oligo(ε-caprolactone) chains. Using ring-opening polymerization, the degree of substitution and the chain length can not be varied independently in this case (7).

Therefore, oligo(ε-caprolactone)s with anhydride and acid chloride functionalities were prepared for the modification of polar molecules at ambient temperatures. Acid terminated

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oligomers were used as a precursor to these reactive functionalities. The precursors can be prepared by polycondensating hydroxycaproic acid in the presence of a small excess of acid, or by derivatising a hydroxyl terminated oligomer, prepared by ring-opening polymerization, with a cyclic anhydride. The latter method was preferred as it provides better control over the molecular weight distribution and is easier to perform.

Experimental

Materials: ε-Caprolactone, succinic anhydride, glutaric anhydride, maleic anhydride and methylglucoside were obtained from Merck (Darmstadt, Germany). Ethanol was dried over anhydrous magnesium sulphate and dimethylformamide over calcium hydride, filtered, and distilled prior to use. Stannous octoate was obtained from Sigma-Aldrich Chemie (Steinheim, Germany). The benzylester of glycine was prepared from glycine and benzylalcohol using HCl as a catalyst (8).

Analytical methods: ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer operating at 300 MHz for ^{1}H NMR spectroscopy and 75 MHz for ^{13}C NMR spectroscopy. Spectra were recorded in deuterated chloroform unless reported otherwise. The emulsifying capacity was determined by adding water of pH 9 in small increments, under continous agitation of the emulsion using an ultraturrax device operating at 9500 rpm, to a 2 wt. % solution of oligomer in sunflower oil until the formation of separate water layer. The weight percentage of oil at which fase separation occurred was defined as the emulsifying capacity.

Synthesis of hydroxyl functionalised oligomers: Melt polymerization of ε-caprolactone was carried out in the presence of ethanol and stannous octoate (1 wt. %) as previously described (2). The number average molecular weight was controlled by varying the molar ratio of monomer to alcohol. Number average degrees of polymerization were estimated from integration of the ^{1}H NMR spectra. Oligo(ε-caprolactone)s with degrees of polymerization of 5 and 15 were obtained.

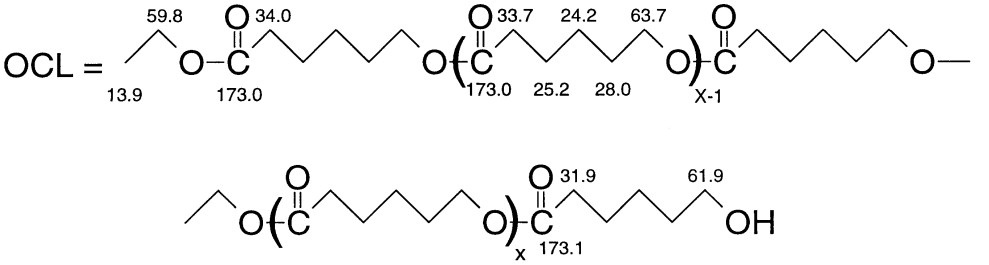
Synthesis of acid functionalised oligomers: A hydroxyl terminated oligo(ε-caprolactone) was contacted in the melt for 24 hours at 130 °C with one equivalent of one of the three cyclic anhydrides used. The product was characterized and used without further work-up.

Synthesis of acid chloride functionalised oligomers

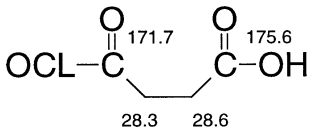
One equivalent of thionyl chloride was added to a molten solution of an acid terminated oligo(ε-caprolactone) at 60 °C with nitrogen bubbling. After one hour, the product was directly used for further reactions without addition of solvent (ethanol), or after dissolution of the reaction product in dimethylformamide (methylglucoside, benzylester of glycine).

Results and discussion

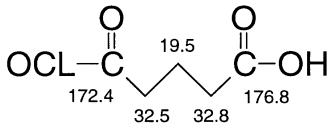
Hydroxyl terminated oligomers of ε-caprolactone (**1**) were prepared by ring-opening polymerization of ε-caprolactone in the presence of ethanol and stannous octoate as previously described (2). The average degree of polymerization is determined by the molar ratio of monomer to alcohol. The conversion of hydroxyl functionalities to acid functionalities was achieved by reacting cyclic anhydrides in stoichiometric amounts with these oligomers at 130 °C.



(1, OCL-H)



(2)



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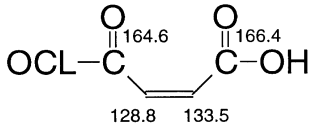

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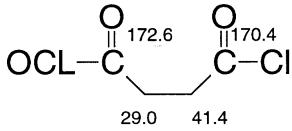
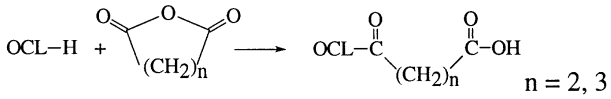


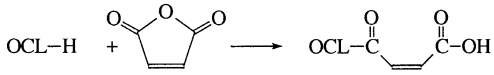
(5)

Scheme 1. Assignments of the signals in the ^{13}C NMR spectra of the oligocaprolactone (OCL) derivatives synthesized.

Hydroxyl terminated oligo(ε-caprolactone)s were reacted with succinic anhydride and glutaric anhydride according to Eq. 1 to give products **2** and **3** and maleic anhydride according to Eq. 2 to give product **4**.



(1)



(2)

The resulting oligomers were characterised by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectra, the signal characteristic for the methylene group adjacent to the hydroxyl functionality (δ = 3.61 ppm) disappeared and new signals for the ring-opened cyclic anhydride appear at chemical shifts according to their structure, e.g. a somewhat broad signal at 2.61 ppm can be discerned for the two methylene groups originating from the succinic anhydride. Integration of the signals in the ^{1}H spectra reveal a quantitative conversion of the hydroxyl functionalities to the corresponding acids.

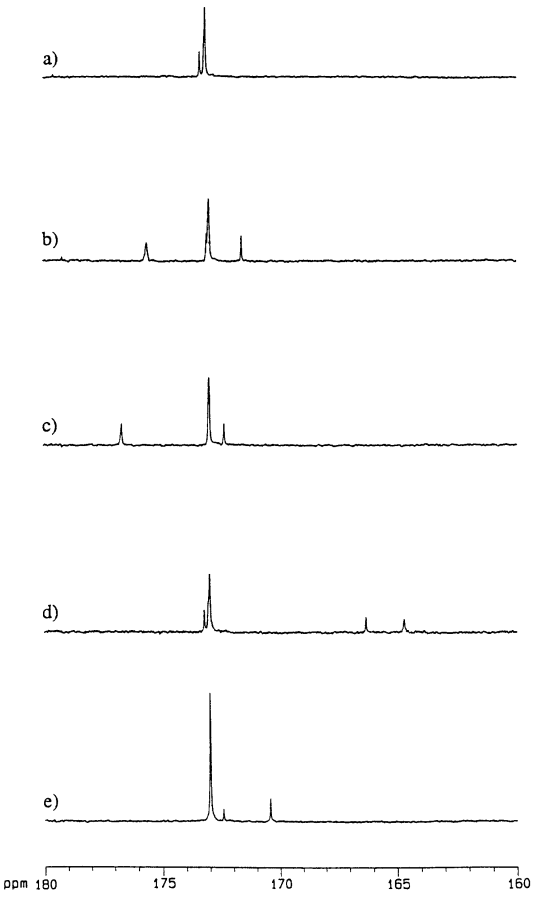
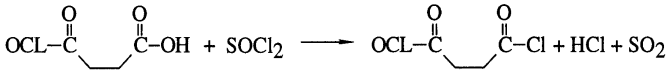


*Figure 1. Detail (carbonyl region) of the ^{13}C NMR spectra of oligomers a) **1**, b), **2**, c) **3**, d) **4**, e) **5**.*

The ^{13}C NMR spectra are even more informative with respect to the chemical structure, as all the different carbon atoms in the end groups can be observed separately. These chemical shifts are summarised in scheme 1. A characteristic region of the ^{13}C NMR spectra is shown in figure 1 (carbonyl region). Corresponding changes are observed in the α-oxygen and α-carbonyl region. During derivatization, the characteristic signals for the hydroxyl terminated oligo(ε-caprolactone) sequence at δ = 31.9 (terminal α-ester), 61.9 (carbon attached to hydroxyl group) and 173.1 (terminal ester carbonyl) disappear. At the same time, the signals of the derivatized oligomers appear, e.g. in the carbonyl region two new signals appear for every derivative. One of these is clearly shifted upfield corresponding to the formation of acid carbonyl carbon atoms, whereas the other signal is obtained from the penultimate carbonyl carbon atom. A complete assignment of the ^{13}C NMR spectra is given in scheme 1.

The resulting prepolymers **2** were converted to their acid chloride analogues (5) by adding one equivalent of thionyl chloride at 60 °C in the melt with nitrogen bubbling to remove gaseous HCl and SO_2 according to Eq. 3.



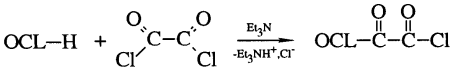
(3)

Attempts to use bases such as triethylamine or pyridine to trap the hydrochloric acid formed, resulted in the formation of strongly coloured products, even in solution at 0 °C, in contrast to the findings of Storey *et al.* using diphenyl chlorophosphate as a chlorine donor in a similar procedure (9).-

Pronounced changes in the ^{1}H and ^{13}C NMR spectra occur during reaction. The acid carbonyl atom shifts from δ = 175.6 to 170.4 ppm upon derivatization, and the methylene carbon next to the acid from δ = 28.6 to 41.4 ppm. It was concluded that the product of the melt reaction is the acid chloride terminated oligomer. The characteristic carbonyl region of the ^{13}C NMR spectrum of **5** is shown in figure 1. The complete assignment of the ^{13}C NMR spectrum is given in scheme 1.

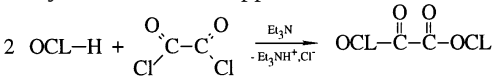
A preliminary experiment showed that **3** could be converted in an analogous manner to an acid chloride derivative, with characteristic ^{13}C NMR signals at δ = 171.9, 45.7, 31.9 and 19.9 ppm. However, derivatization of **4** was not possible in this way, because hydrochlorination of the terminal double bond occurred.

A different approach for the preparation of acid chloride terminated oligo(ε-caprolactone)s was also evaluated. Hydroxyl terminated prepolymers **1** were reacted with an excess of oxalylchloride at room temperature in tetrahydrofuran in the presence of triethylamine according to Eq. 4.



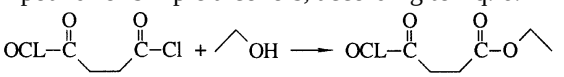
(4)

However, the reaction failed due to the preferential formation of an oxalic acid bridged dimer according to Eq. 5, as evidenced by the characteristics chemical shifts of the central carbonyl atoms at 157.3 ppm.



(5)

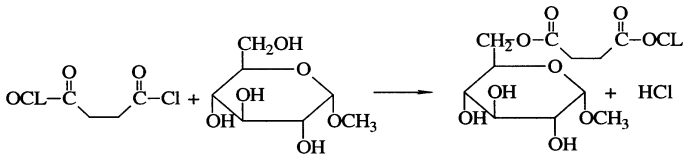
Although other methods for the preparation of acid chloride terminated oligo(ε-caprolactone)s could be envisioned, the reactivity of the conveniently prepared acid chloride 5 was evaluated first. The reactivity of 5 was probed by reacting it with ethanol as a model compound for simple alcohols, according to Eq. 6.



(6)

Instant formation of the ethyl ester derivative was apparent from the disappearance of the signals characteristic for **5**, and the appearance of signals in the ^{13}C spectrum at δ = 174.0 ppm (terminal carbonyl), 60.3 ppm (methylene) and 13.8 ppm methyl for the ethyl ester group (scheme 2). Integration of the signals for the ethyl ester group in the ^{1}H NMR spectrum indicated quantitative formation of this group.

Consequently, **5** was reacted with methylglucoside as a model carbohydrate according to Eq. 7, to give derivative **6**.

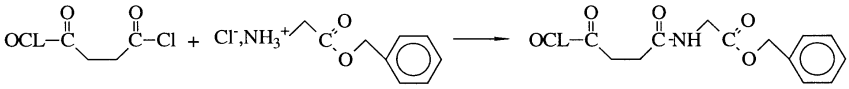


(7)

Methylglucoside was chosen for its favourable solubility characteristics and its occurrence in a single conformation, whereas many other sugars can have multiple conformations, which complicates analysis. In general, amphiphilic sugar derivatives are used as e.g. surfactants and glues, and therefore the modification of sugars with hydrofobic ester chains is of great practical interest. Analysis by ^{13}C NMR spectroscopy of the reaction product revealed that the primary hydroxyl functionality (6-position) of the sugar had reacted preferentially with **5** (scheme 2). However, it also showed the presence of a small amount of the hydrolysis product of **5** (< 5 %), acid **2**, apparently because the solvent or reagent used was insufficiently dry.

As an example of the properties of oligomers **2-4** and **6**, the emulsifying capacity of these oligomers was determined in a water/oil mixture. The results are listed in table 1. Clearly, ionic derivatives **2-4** are far more effective in stabilising a dispersed water phase than is nonionic derivative **6**.

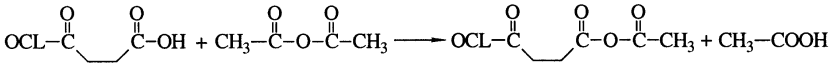
To prepare another class of potentially interesting compounds 5 was reacted with benzylester of glycine according to Eq. 8.



(8)

Deprotection of the amino acid by hydrogenation of this compound yields a product similar to N-acyl derivatives of fatty acids and amines, which are used as surfactants. Under dry conditions, the reaction product of Eq. 8 was formed (Scheme 2) and recovered from DMF by precipitation in methanol.

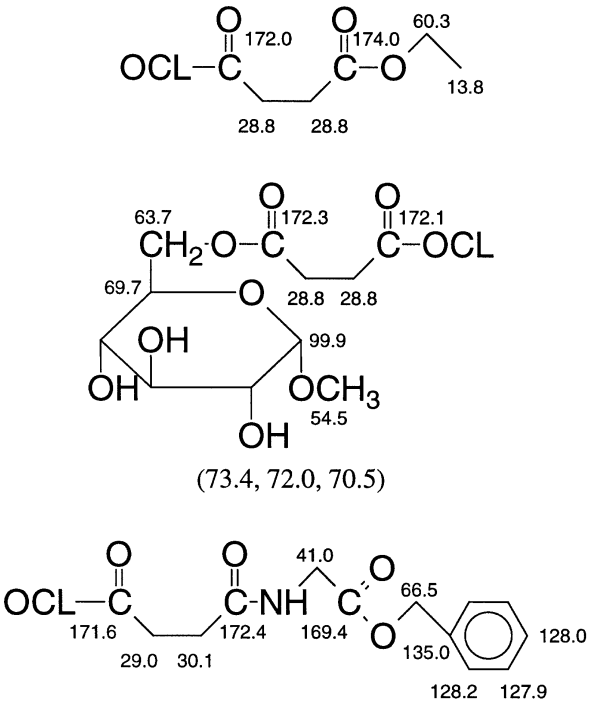
As an alternative to the acid chlorides **5**, it was explored if the acid functionality of **2** could be converted to an anhydride functionality for further reactivity and to broaden the scope of transformations. Therefore, **2** was reacted with acetic acid anhydride according to Eq. 9.



(9)

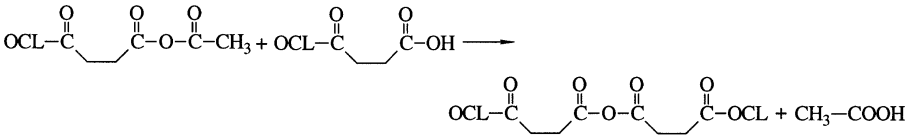
Table 1.

Compound	Emulsifying Capacity
	(%)
2	27
3	33
4	27
6	67



*Scheme 2. Assignments of the signals in the ^{13}C NMR spectra coupling products of **2** and a) ethanol, b) methylglucoside (the numbers between parentheses indicate the chemical shifts of the three remaining ring carbon atoms, which could not be unequivocally assigned by the present technique, DMSO-d_6), c) benzylester of glycine.*

Although the mixed anhydride product (characterized by distinct anhydride carbonyl signals at δ = 165.7 and 167.9 ppm) was readily prepared in the presence of an excess of acetic acid anhydride, the removal of acetic acid and acetic acid anhydride turned out to be problematic. Invariable, a symmetric anhydride (single anhydride carbonyl signal at δ = 167.5 ppm) was formed from the mixed anhydride product according to equation 10.



(10)

This symmetric anhydride displayed no interesting reactivity towards interesting target molecules anymore. It should be noted that polymers with very defined two-stage degradation profiles can be prepared in this way (9).

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