e-Polymers **2007**, no. 148

http://www.e-polymers.org

ISSN 1618-7229

Synthesis and complete NMR characterization of methacrylateendcapped poly(ortho-esters)

Bert Paesen,[1] *Tom Baekelandt*,[1] *Jorge Heller*,[2] *José C. Martins*,[3] *Etienne H. Schacht*[1]*

[1*] Ghent University, Department of Organic Chemistry, Polymer Materials Research Group, Krijgslaan 281 S4, B-9000 Ghent, Belgium; fax: +32-9-2644972; email: Bert.Paesen@UGent.be, Etienne.Schacht@UGent.be
[2] Advanced Polymer Systems, Inc., 123 Saginaw Dr., Redwood City, California 94063; email: Jorgeheller@aol.com
[3] Ghent University, Department of Organic Chemistry, NMR and Structure Analysis Unit, Krijgslaan 281 S4, B-9000 Ghent, Belgium; fax: +32-9-2644972; email: Jose.Martins@UGent.be

(Received: 28 July, 2007; published: 29 November, 2007)

Abstract: In this paper a synthesis method for low molecular weight poly(ortho-esters) with photo crosslinkable methacrylate endgroups is presented. Using this procedure, the molecular weight could be controlled and the desired endgroup functionality was introduced in a single reaction step. The detailed characterization of the molecular structure of bismethacrylate endcapped poly(ortho-esters) using NMR affords a re-evaluation of previous assignments reported for similar poly(ortho-ester) polymers. In addition, the use of diffusion filtered 1D ^{1}H NMR spectroscopy as a simple but effective analysis tool that allows to distinguish resonance contributions from impurities and low molecular weight compounds, most probably the result of degradation, from those of the full size polymer, is demonstrated.

Introduction

Poly(ortho-esters) are a relatively new class of bio-erodable polymers developed by Heller and co-workers (Heller et al. [1], Ng et al. [2], Heller [3]). The first type of poly(ortho-ester), known as Alzamer, was reported in the patent literature in the late 70's. Twenty-five years later, a number of families have been developed of this type of polymer, mostly for the controlled delivery of drugs. Sustained and controlled release of drugs is an interesting, and very broadly studied domain within the field of biomaterials that aims at providing a longer lasting effect of local drugs compared with conventional administration methods, while minimizing side effects. A few examples of drugs or other active compounds used in poly(ortho-ester) based controlled drug delivery systems are insulin (Heller et al. [4]), 5-fluorouracil (Maa et al. [5], Heller et al. [6]), naltrexone (Maa et al. [7]) and tetracycline (Heller et al. [8]).

Another promising application of poly(ortho-esters) is their use in orthopaedic, plastic and reconstructive surgery. Currently, a significant research effort aims at the development of several polymeric systems for bone tissue engineering applications. The polymers are mixed with several additives and shaped by different fabrication techniques, such as solution processing, melt processing, compression moulding and photo polymerization. The best-known systems are based on copolymers of lactic

acid, glycolic acid and ε-caprolactone (Coombes et al. [9]). Within this context, poly(ortho-esters) can serve as valuable alternatives. These polymers can be solid or semi-solid depending on the chemical structure of the polymer. For instance, Andriano et al. prepared self-catalytic poly(ortho-esters) scaffolds as temporary bone grafts (Andriano et al. [10]). The solid linear biodegradable polymer was mixed with salts and converted into a scaffold by hot-compression molding. A possible disadvantage of hot compression molding is that elevated temperatures are used that can be incompatible with a drug mixed in the system. An alternative approach to obtain solid poly(ortho-ester) scaffolds is the use of photo chemistry, starting from semi-solid precursor materials. These viscous materials can be mixed with several additives and converted at room temperature into solid biodegradable poly(ortho-ester) networks when the polymer chains contain photo polymerizable groups.

Photo polymerizable systems are mostly based on (meth)acrylate containing (macro)monomers (Mizutani et al. [11], Sawhney et al. [12]). These (meth)acrylate functionalities can be grafted onto the polymer chain or be present as endgroups of a polymer. After *in situ* crosslinking, highly crosslinked networks are formed with enhanced mechanical properties compared to the linear derivatives. This concept has been used before to prepare crosslinkable bismethacrylates of biodegradable polyesters e.g. poly-ε-caprolacton, polylactide-co-glycolide (Davis et al. [13]). Until now, no photo polymerizable system involving poly(ortho-esters) has been reported in the literature.

The aim of this work is the synthesis and structural characterization of low molecular weight viscous poly(ortho-esters) with methacrylate end groups. The viscous properties of the system will offer two advantages. First it is possible to mix additives (calcium phosphates, drugs, etc) with the prepolymer before crosslinking into a biodegradable network. Secondly, the viscous consistency of the precursor material makes it possible to fill irregular shaped bone defects. Here, the physical properties (e.g. T_g) of the polymers can be controlled using diols with variable chain flexibility. As the glass transition temperature should be below room temperature to obtain a viscous texture, flexible diols such as 1,12-dodecane diol and tetra ethylene glycol were used. The molecular weight of the polymers, which also contributes to polymer viscosity, was controlled by adding a mono functional monomer, 2-hydroxyethyl methacrylate (HEMA), as a chain stopper at the start of the polymerization. Complete assignment of ^{1}H and ^{13}C resonances are presented and compared with previous reports. The inclusion of diffusion filtered ^{1}H NMR spectroscopy in obtaining full characterization is presented and its benefits are discussed.

Results and discussion

Synthesis

A typical procedure for the synthesis of low molecular weight (meth)acrylate endcapped polymers consists of a two-step reaction. The first step is the synthesis of a polymer with hydroxyl endgroups. In the second step the hydroxyl terminal groups are esterificated using (meth)acryloyl chloride. This two-step route was first used to prepare type II poly(ortho-ester) bismethacrylate polymers in a polyaddition polymerization using DETOSU and one or more diols as monomers. Control of the molecular weight in this type of polymerizations can normally be obtained by varying the stoichiometry of the monomers according to the Flory formula:

$$DP = \frac{1+r}{1+r-2rp} \quad (1)$$

DP is the average degree of polymerization, r is the excess of one monomer to the other and p is the degree of conversion of the polymerization. In our case, the diol monomers should be in excess to obtain hydroxyl endgroups. Unfortunately, it proved impossible to achieve control of the molecular weight in these conditions. For example the synthesis of a polymer with a theoretical molecular mass of 3000 $gmol^{-1}$, resulted in numerical molecular weights of 7000 ± 2000 $gmol^{-1}$. The degree of polymerization was consistently much higher than expected and difficult to reproduce.

To solve this problem Schwach-Abdellaoui *et al.* [15] reported a method to control the molecular weight by adding a monofunctional monomer, i.e. an alcohol instead of a diol, at the beginning of the polymerization. Reaction of such an alcohol with the ketene acetal function of the DETOSU blocks the polymerization at one end of the polymer chain. Incorporation of the alcohol on both sides of the chain will produce a polymer endcapped with this monofunctional monomer. Since we aim at methacrylate endcapped polymers, HEMA was added as monofunctional monomer (Figure 1).

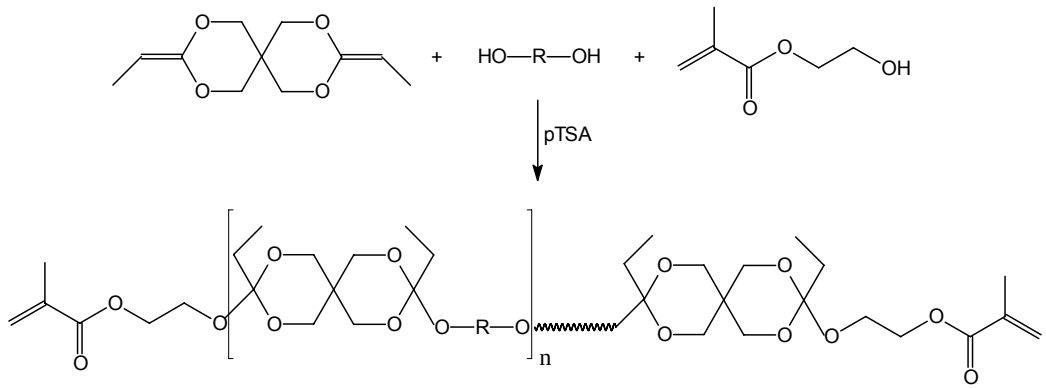


Fig. 1. Synthesis of a poly(ortho-ester) bismethacrylate.

A series of polymers were prepared by adding an increasing quantity of HEMA to the reaction medium. Because the hydroxyl group is the only reactive functionality of HEMA in this polymerization, the probability that a HEMA molecule reacts with a ketene acetal function of the DETOSU should increase when the amount of HEMA increases. Thus, we would expect that the molecular weight is inversely proportional to the HEMA concentration. Figure 2 shows the molecular weight variation as function of the amount of HEMA for a polymer with a theoretical molecular weight of 3000 $gmol^{-1}$.

Addition of HEMA gives an almost linear decrease in molecular weight (r^2 = 0,97). The value with the highest deviation, occurs at 2,5 times excess of HEMA (r^2=0.99 when this data point is not considered). This can be explained by the fact that the molecular weight of the polymer is too low to completely precipitate in MeOH and remains partly dissolved. This phenomenon results in the shift from the molecular weight to higher values. Using this procedure, the molecular weight could be controlled and the desired endgroup functionality was introduced in a single reaction step.

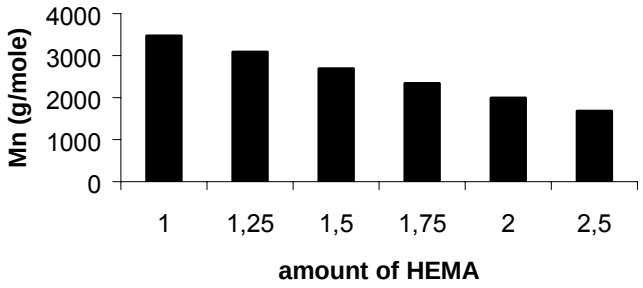


Fig. 2. Molecular weight as function of the amount of HEMA. The value of 1 refers to the stoichiometrical quantity needed for synthesis of a bismethacrylate endcapped polymer.

Detailed NMR-characterization of bismethacrylate polymers

NMR data is available in the literature for poly(ortho-esters). Schwach-Abdellaoui et al have reported an assignment of the ^{1}H and ^{13}C-NMR spectra of poly(ortho-esters), based only on chemical shift arguments and incremental rules (Schwach-Abdellaoui et al [15], Schwach-Abdellaoui et al [16]).

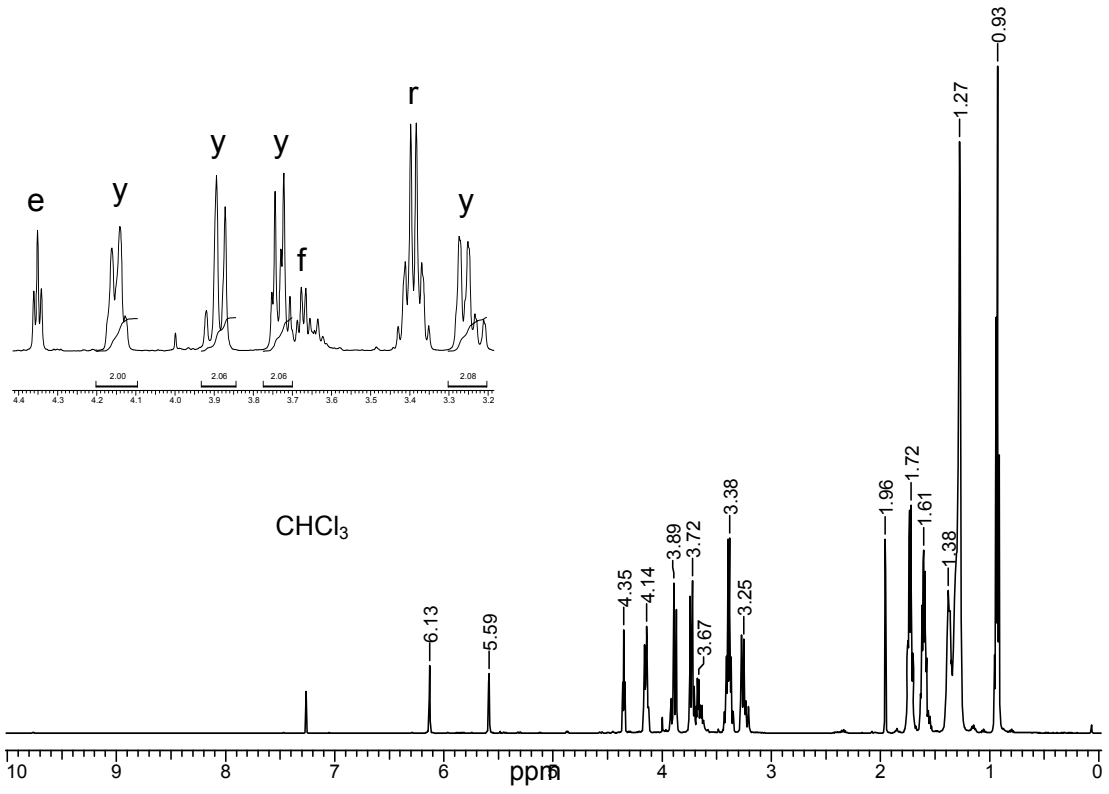
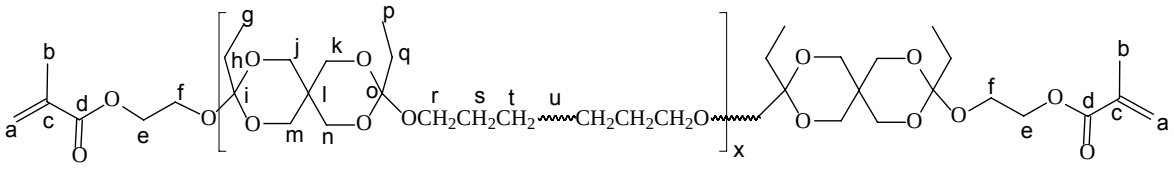


Fig. 3. ^{1}H-NMR spectrum of the POE-DOD100 bismethacrylate polymer. The spectrum displays a sample of the desired polymer with optimal purity (see text). The intensity values for the 4 doublets in the inset, are reported relative to the DETOSU methyl resonance that was calibrated as 6 hydrogens (2 equivalent methyl groups per DETOSU unit).

As these data did not allow us to fully explain our own NMR data, an NMR study using 1D and 2D scalar coupling correlation techniques was undertaken to confirm the general structure of the POE-DOD100 bismethacrylate polymer and to independently generate ^{1}H and ^{13}C resonance assignments. The Important detail for the successful analysis was the discrimination of resonances arising from the polymer, from those of small molecular species using diffusion filtering techniques (*vide infra)*.

Figure 3 shows the ^{1}H-NMR spectrum of the POE-DOD100 bismethacrylate polymer (Scheme 1); the complete ^{1}H and ^{13}C peak assignments are listed in Table 1. It should be noted that the pentaerythritol methylene protons in the DETOSU can be differentiated, as they are not all mutually homotopical. These eight hydrogens are observed in pairs, as a series of 4 resolved resonances at 3.25, 3.72, 3.89 and 4.14 ppm (labeled 'y' in Figure 3), representing each a pair of homotopic hydrogens symmetrically located in opposing rings with respect to the central Spiro carbon. This is supported by the observation that COSY crosspeak identified between the resonances at 3.25 and 3.72 ppm respectively 3.89 and 4.41 ppm, pair protons that, based on the HSQC spectrum, are seen to belong to the same carbon atom (Figure 4).



Scheme 1. Representation of the PEO structure with labels referring to the ^{1}H and ^{13}C chemical shifts collected in Table 1.

Tab. 1. ^{1}H and ^{13}C Resonance assignments of POE-DOD100 bismethacrylate.

Assignment	^{1}H δ in ppm and (multiplicity)	^{13}C δ (ppm) [APT/DEPT]
a_1	5.59 (s)	125.6 [CH_2]
a_2	6.13 (s)	125.6 [CH_2]
b	1.96 (s)	18.2 [CH_3]
c	n.a.	135.9 [C]
d	n.a.	167.0 [C]
e	4.35 (t)	63.4 [CH_2]
f	3.67 (t)	60.4 [CH_2]
g,p	0.93 (t)	7.3 [CH_3]
h,q	1.72 (q)	28.4 [CH_2]
i,o	n.a.	112.3 [C]
[j, k, m, n]*	3.25, 3.72, 3.89, 4.14 (d)	60-66 [CH_2]
l	n.a.	30.4 [C]
r	3.38 (t)	60-66 [CH_2]
s	1.61 (p)	25-30 [CH_2]
t	1.38 (m)	25-30 [CH_2]
u	1.27 (m)	25-30 [CH_2]

*No site specific assignments were obtained, therefore no correlation between the labels and the reported ppm values should be inferred. n.a. Not applicable (no ^{1}H resonance at this position).

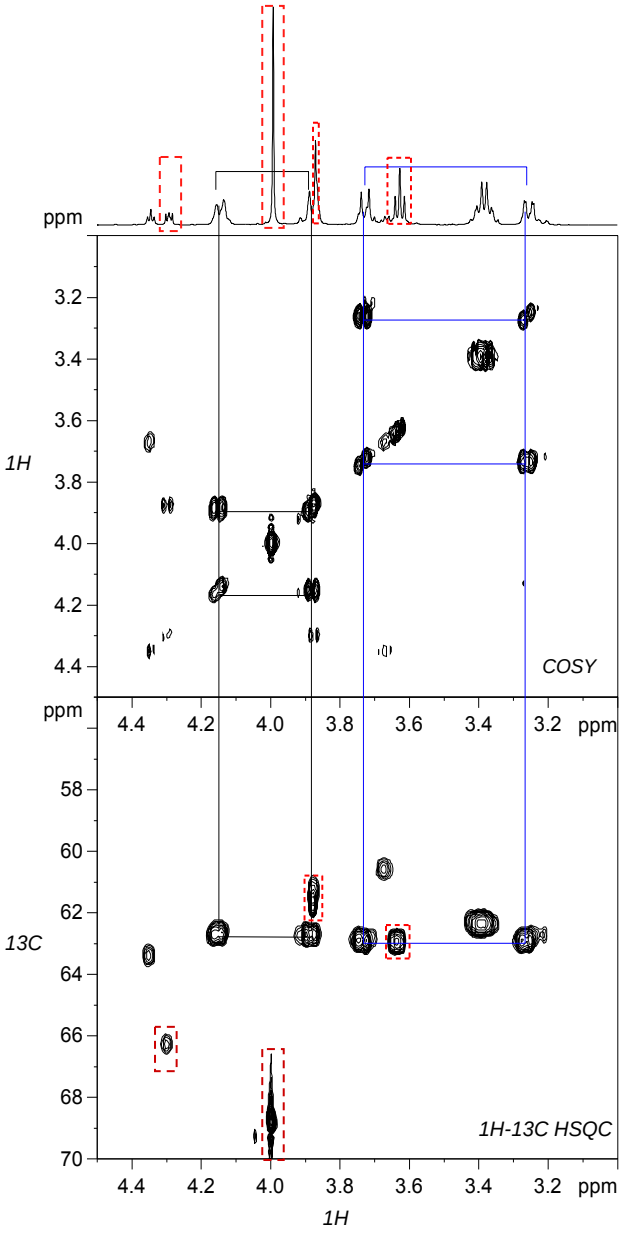


Fig. 4. Combined 1D ^{1}H (top), ^{1}H-^{1}H COSY (middle) and ^{1}H-^{13}C HSQC (bottom) analysis of the methylene resonances from the DETOSU moiety in the POE-DOD100 bismethacrylate polymer. The black and blue lines group together the two diastereotopic methylene ^{1}H resonances coupled via mutual scalar coupling in the COSY, and clearly linked to the same ^{13}C resonance in the HSQC. Each resonance groups two homotopic ^{1}H's on the opposing rings. The red-dashed boxes in the 1D ^{1}H spectrum single out resonances absent in the diffusion filtered ^{1}H spectrum. Thus, the corresponding ^{1}H-^{13}C cross-peaks in red-dashed boxes need not be considered for the structure analysis of the PEO-DOD100 polymer. This facilitates the overall analysis, as described in the text.

The main difference in the ^{1}H NMR data reported here compared to previous reports concerns the non-trivial assignment of the pentaerythritol methylenes. Previously, these eight methylene hydrogens were all attributed to a singlet appearing at 4.0 ppm (Schwach-Abdellaoui et al [15]), or reported as three separate resonances appearing

at 3.2, 3.4 and 3.7 ppm respectively (Schwach-Abdellaoui et al [16]). While such a singlet indeed appeared in our spectra as well, we could attribute this to a different molecular species, as discussed further below.

As can be expected, the methylene resonances in the 1,12-dodecane diol moiety suffer from considerable overlap both in the ^{1}H and ^{13}C dimension. To assist in their assignment, three homopolymers were synthesized with ethylene glycol, butane diol and hexane diols as bifunctional diol monomers. In this fashion, the assignment of the ^{1}H resonance positions of the α-, β- and γ-CH_2 protons could be delineated (r, s, t in Table 1), by monitoring the appearance of their resonances, and establishing mutual scalar couplings in the COSY spectra (data not shown).

Diffusion filtered ^{1}H NMR analysis

Despite achieving complete ^{1}H and ^{13}C resonance assignment of the poly-orthoester, several additional resonances remain unexplained. When this problem, often encountered in polymer synthesis, occurs, it would be extremely helpful to establish in a straightforward manner, whether these remaining resonances are contributed by chemical moieties part of the polymer's structure, or represent distinct chemical species instead. While many of these can often be identified as originating from incompletely removed reagents or solvents used during reaction and purification stages, several resonances often remain unexplained, casting doubt on the polymer's structural identity and integrity. This issue can be addressed in a simple and straightforward fashion using diffusion filtered ^{1}H NMR spectroscopy.

By allowing a spin echo pulse sequence element, that incorporates a free diffusion period Δ between sinusoid pulsed field gradients of duration δ and amplitude *G,* to be inserted between the initial ^{1}H excitation pulse and final signal acquisition, the translational diffusion behavior of each molecular species may be encoded in each of its ^{1}H resonance intensities *I*, according to

$$I = I_0 e^{-K^2 D(\Delta - \delta/4)} \qquad (2)$$

where I_0 is the initial intensity when no gradient is applied (G = 0 $T.m^{-1}$), $K = \gamma_H G \delta$ with γ_H the ^{1}H gyromagnetic ratio and *D* is the molecule's translational diffusion coefficient (Stesjkal et al. [17]). The value of D may be extracted from (2) by applying an appropriate fitting procedure on the intensities *I* obtained in a series of experiments in which either G, δ or Δ is varied. A variety of techniques have been developed for this purpose, and generally G is varied, as this prevents T_2-relaxation induced attenuation to superimpose itself on the signal attenuation (Stillbs, [18], Johnson [19]). These techniques have been widely used to study translational diffusion of molecules, including polymers, to impart virtual separation of mixtures and in some cases study polydispersity (Stillbs, [18], Johnson [19], Chen et al [20], Jerschow and Müller [21]). While these analyses seems interesting, we only aim at taking advantage of the significantly slower translational diffusion of the polymeric species with respect to low molecular weight species, to differentially attenuate or even completely remove the latter's response from the ^{1}H NMR spectrum, as shown in Figure 5. This may be inferred from (2), as explained below.

Consider two molecular species A and B present in the sample, having diffusion properties characterized by their respective translational diffusion coefficients D_A and D_B and contributing at least one ^{1}H resonance with intensity $I_{0,A}$ and $I_{0,B}$. The application of a diffusion pulse sequence element prior to signal acquisition will

attenuate the respective intensities I_A to I_B according to Eq. 2 such, that their ratio R will be given by (3):

$$R = \frac{I_A}{I_B} = R_0 e^{-K^2(D_A - D_B)(\Delta - \delta/4)} \quad (3)$$

R_0 being the initial intensity ratio, obtained when the diffusion pulse sequence is applied, but the gradient amplitude is set to zero (i.e. K=0). This equation may be recast to yield the separation factor S

$$S = \ln\left(\frac{R}{R_0}\right) = -K^2(D_A - D_B)(\Delta - \delta/4) \quad (4)$$

to clearly illustrate that for a given set of K (and thus gradient amplitude G), diffusion delay Δ and gradient pulse duration δ, the ratio S will vary logarithmically as the difference between the diffusion delays D_A and D_B increases. Thus, it suffices to compare the ratio between the intensities of two resonances obtained from diffusion filtered 1D ^{1}H NMR spectra recorded with (filtered) and without (or with minimal amplitude) (control) the application of the pulsed field gradient, to assess whether two resonances belong to the same molecule or not. T_1 and T_2 relaxation induced differences are not an issue, since these will operate equally during the control and filtered experiment.

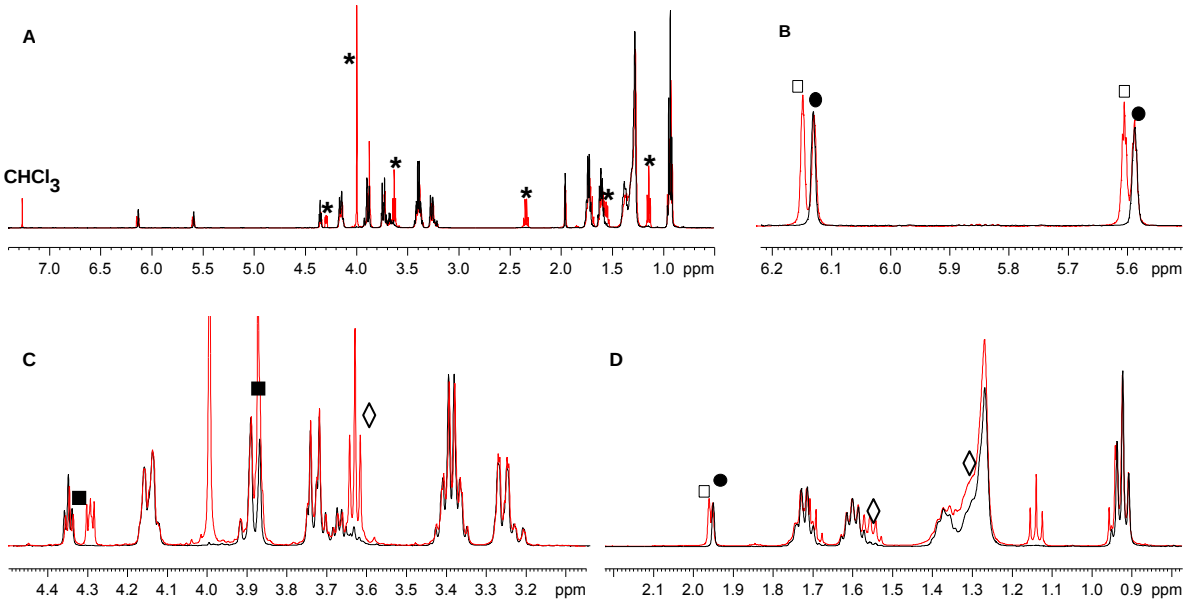


Fig. 5. Overview (A) and details (B-D) of the control (black) and diffusion filtered ^{1}H NMR spectrum of POE-DOD100 bismethacrylate polymer, with less than optimal purity. Signals that clearly disappear upon application of the diffusion filter are indicated in A using *. In B and D, resonances corresponding to monomeric and polymeric bound methacrylate moieties in the HEMA fragment are labeled using • and □ respectively. C illustrates the complete elimination of the singlet at 4.0 ppm, as well as the disappearance of other resonances, labeled ■ and ◊, that arise from the ethylene moiety in a HEMA molecule and the aliphatic chain of the dodecanediol, respectively. The spectra were recorded with the standard BPP-LED sequence using a diffusion delay Δ of 30 ms only, applying a 5 ms bipolar gradient pulse limited to 30% of the maximum gradient amplitude available (diffusion filtered one).

For a given difference in diffusion coefficients, the value of Δ, δ and G may be optimized to increase the differential attenuation thereby fine tuning the discriminating capabilities. Thus, as the diffusion coefficients of two species approach each other, longer diffusion delays combined with higher gradient amplitude and duration are necessary. The latter is generally preferred since S scales quadratically with G as opposed to linearly with Δ. However, in the case of polymeric species in the presence of small(er) molecule impurities addressed here, the intrinsic difference is such that complete removal of the contribution of the small molecular species can readily be achieved.

When comparing the control 1D ^{1}H spectrum with the diffusion filtered one in Figure 5.A, resonances lacking in the filtered one are immediately obvious in various regions of the spectrum. Most evident is the complete removal of the ^{1}H signal of the chloroform solvent used. Application of the diffusion filter also allows to simplify the spectral regions containing signals from methacrylate functionalities. As shown in Figure 5.B and 5.D, application of a diffusion filter allows to discriminate between polymer bound (•) and residual monomeric (□) methacrylate species thus removing any ambiguity. The singlet resonance at 4.0 ppm, previously reported as corresponding to the eight isochronous DETOSU methylene ^{1}H's [15], is also completely removed (Figure 5.C). Other resonances are clearly lacking with respect to the control spectrum indicating additional small molecular species, not chemically linked to the polymer.

Degradation may account for the additional molecular species observed using NMR

The nature and origin of the faster diffusing, and therefore smaller molecular weight compounds, giving rise to the additional resonances when purity is less than optimal, was also investigated. These could be left over monomeric reagents or, in view of the inherent degradable nature of the POE synthesized, more probably arise from some degradation products that arise from hydrolysis as shown in Figure 6. Secondary Ion Mass Spectroscopy (SIMS) was used by Leadley et al. to prove that the preferred pathway for the hydrolysis of poly(ortho-esters) was via the cleavage of the exocyclic alkoxy bond in the DETOSU unit (Leadley et al. [22]). Thus a variety of small molecular species may be expected to contribute to the ^{1}H and ^{13}C NMR spectrum. This initial hydrolysis produces a pentaerythritol dipropionate (**6.1)**, which may be further hydrolyzed to the mono ester **(6.2)** and finally pentaerythritol **(6.3)** and propionic acid **(6.4)**, as described before by Heller et al [23]. In the process, a HEMA molecule **(6.5)** or a diol (**6.6)** can be released.

We find ample evidence for this degradation profile within the ^{1}H and ^{13}C NMR spectra. First, the triplet and quadruplet at respectively 1.15 ppm and 2.34 ppm (Figure 5.A) are shown to couple in the COSY spectrum. Taking into account the ^{1}H and ^{13}C chemical shifts values (8.83, resp. 27.1 ppm), this is consistent with an ethyl moiety group bound to a carbonyl group e.g. a propionic ester. The large singlet at 4 (68.8) ppm as well as a second singlet of lower intensity at 3.88 (61.7) ppm, both being a CH_2 group as seen in the DEPT135 spectrum (data not shown), can be attributed to a pentaerythritol moiety. As this is no longer embedded in a cyclic structure, the CH_2 resonances should be equivalent, explaining the singlet, at least in **6.1** and **6.3**.

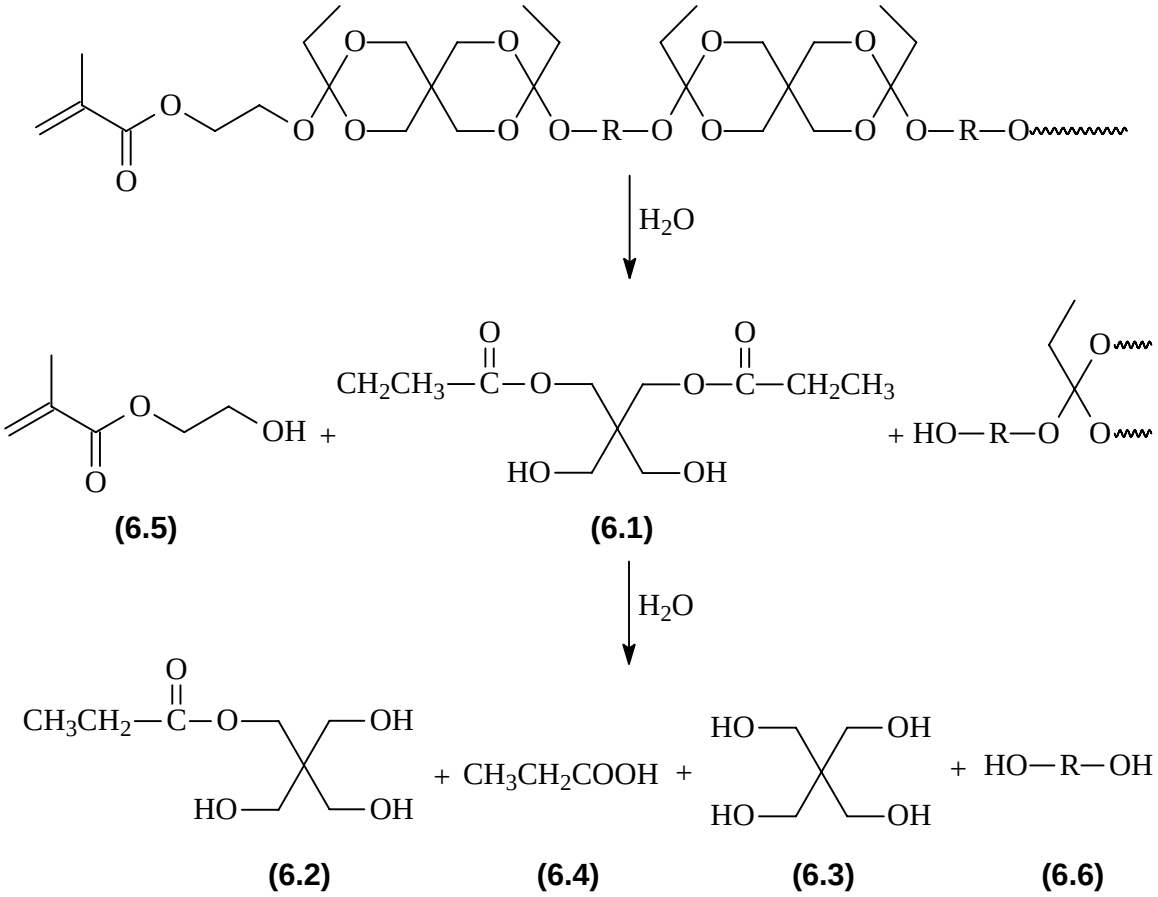


Fig. 6. Degradation mechanism of poly(ortho-ester) functionality with the formation of various small molecular species, further discussed in the text.

In the monoester **6.2**, two singlets can be expected, belonging to the CH_2 proximal to the ester and hydroxyl functionality respectively. We propose the two singlet resonances to represent both of these functionalities as they occur in **6.1**, **6.2** and **6.3** respectively. From Figure 6, the ratio between the sum of the CH_2 and CH_3 resonance intensity of the various ethyl groups and the CH_2 protons in the penta erythritol moieties should be respectively 5:6. Assessment of this ratio in the spectra is difficult due to multiple overlaps; however we estimate it to approximately 9:6 i.e. less propionic acid than expected. A reasonable explanation is the evaporation of propionic acid during the drying process in the vacuum oven. Nevertheless, our analysis provides good evidence to attribute the additional resonances to molecular species arising from degradation prior to NMR measurement.

When the ortho-ester functionality at the end of the polymer chain is hydrolyzed, a HEMA molecule is formed. In Figure 5, the ^1H fingerprint of monomeric HEMA can be recognized from disappearing resonance frequencies at 1.94, 3.67 (overlapped), 4.30, 5.59 and 6.12 ppm in the diffusion filtered ^1H experiment. The peaks at 3.67 and 1.55 ppm can be assigned to respectively the α-CH_2 and the β-CH_2 from free 1,12-dodecane diol, formed during degradation. The disappearance of the remaining intrachain resonances at ~1.3 ppm is clearly evident from Figure 5.D.

FT-IR analysis of the polymers showed an absorption band at 1723 cm^{-1} attributed to the HEMA end group. In view of our NMR data, this peak may not be completely accounted for due to the HEMA end group but can also partially overlap with the

ester group of the degradation product. Tudor and coworkers performed a detailed infrared analysis of poly(ortho-esters), i.e. without a HEMA endgroup (Tudor et al. [24]). They also found a small carbonyl vibration at 1739 cm^{-1} in the FT-IR spectrum, although their polymers did not contain any type of carbonyl group in the polymer chain but provided no explanation. We propose this indicates some level of degradation.

Conclusions

This study has demonstrated a procedure to prepare photo-crosslinkable poly(ortho-ester) bismethacrylates in a single step reaction. An end capping mechanism, where the monofunctional monomer HEMA acts as the chain stopper, was developed to gain control over the molecular weight and introduce the photo-crosslinkable endgroup.

An NMR study using 1D and 2D homonuclear and heteronuclear scalar coupling correlation techniques was undertaken to confirm the molecular structure of a POE-DOD100 bismethacrylate polymer and to generate resonance assignments of ^{1}H and ^{13}C resonances. These have allowed a revision of several critical resonance assignments, previously based on 1D 1H and 13C spectra and chemical shift predictions only (Schwach-Abdellaoui et al [15, 16]).

Application of a diffusion filter was shown to be extremely helpful to establish, in a straightforward manner, whether unexplained resonances in the NMR spectrum are contributed by chemical moieties part of the polymer's structure. This is important information as it determines the further course of action. When part of the polymer, its presence should be explained and if undesirable, reaction conditions should be adapted accordingly. If these originate from distinct and often low-molecular weight molecular species, their presence may hint at incompletely removed reagents or be contributed during the purification stages. In this case, additional application and fine-tuning of the purification protocol needs to be considered. Importantly, the presence of these resonances may also indicate the occurrence of undesirable side reactions during synthesis or chemical breakdown of the polymer into smaller units, as was the case here. Given that the necessary hardware (gradient probe head) as well as pulse sequences and parameters for diffusion filtered 1D ^{1}H NMR are customary to the standard routine NMR equipment, it should be widely and easily applicable.

Experimental part

Materials

3,9-Di-ethylidene-2,4,8,10-tetraoxaspiro[5,5']undecane (DETOSU) was used as received from APPharma. The diols were from Acros Organics except 1,12-dodecanediol (DOD) (Fluka), ethylene glycol (Avocado) and hexanediol (Aldrich). All diols were dried for 2 days over P_2O_5 at 105 °C. P-toluenesulfonic acid (pTSA) (Aldrich) was dried over KOH. 2-hydroxyethylmethacrylate (HEMA) (Acros Organics) was purified before use. MeOH (Merck eurolab) and THF (Acros Organics) and triethylamine (TEA) (Avocado) were distilled before use.

Homopolymerization with DETOSU and 1,12-dodecanediol

In a dry-box, 40 ml dry THF was added to 3.955 g (19.5 mmol) 1,12-dodecane diol. The mixture was stirred and heated until everything dissolved; then 1.565 g (12.0

mmol) HEMA and 5 g (23.6 mmol) DETOSU were added. The polymerization was initiated by the addition of a trace of a 10 mg/ml solution of pTSA in dry THF. The reaction was completed after a few minutes, stirring being continued until room temperature was achieved. The THF was evaporated with a rotavapor and the viscous residue precipitated in MeOH, stabilized with a few drops of triethylamine. The TEA is used to trap the catalyst. Afterwards the MeOH was removed by filtration over a glass filter (pore size P1), and the polymer repeatedly washed with MeOH. Finally, the polymer slurry was dried in a vacuum oven for two days to remove traces of residual solvents.

Copolymerization with DETOSU, 1,12-dodecane diol (80%) and tetra ethylene glycol (20%)

For a copolymer with 80% DOD and 20% TEEG in a dry-box, 3.167 g (15.6 mmol) DOD and 0.762 g (3.9 mmol) tetra ethylene glycol (TEEG) were dissolved in 40 ml dry THF. Again the mixture was stirred and heated until complete dissolution. 5 g (23.6 mmol) DETOSU and 1.557 g (12.0 mmol) HEMA were added. The polymerization and precipitation procedure was completely identical to the one described above for the homopolymer.

Spectroscopic and other characterization methods

Samples were prepared by dissolving 10 mg of compound in $CDCl_3$. All NMR spectra were recorded at 298 K on a Bruker DRX 500 spectrometer equipped with a 5 mm TBI-Z-gradient probe and operating at 500.13 MHz and 125.76 MHz for ^{1}H and ^{13}C respectively. All pulse programs were taken from the standard Bruker library. DEPT135 was compared to APT to distinguish quaternary from methylene carbons. The 2D COSY and 1H-{^{13}C} HSQC spectra were recorded using Z-gradients for coherence selection and optimal artifact suppression. Diffusion filtered 1D 1H NMR spectra were obtained using the standard BPP-LED sequence with sine shaped gradient pulses (Morris et al. [14], Johnson et al. [15]). A diffusion delay Δ of 30 ms was used, preceded and followed by a bipolar pulsed gradient pair of total duration δ of 5 ms. The gradient amplitude was varied for optimal results, which occurred at 30% of the maximum amplitude value (53.5 Gauss·cm^{-1}). For each spectrum, 8 dummy scans were followed by accumulation of 16 scans, representing the minimum phase cycle required to eliminate spurious contributions to the spectrum.

Infrared spectra were measured on a Biorad FT-IR spectrometer FTS 575C. In 1 ml dichloromethane 10 mg polymer was dissolved and transferred onto a KBr plate.

Gel permeation Chromatography was performed on Waters 510 HPLC pump and a Melz RI detector to determine the relative molecular weights. The mobile phase was THF (Acros Organics). Calibration was carried out using polystyrene standards (Polymer Laboratories, Inc.) covering the mass range 1260 to 68900 g·mole^{-1}. The thermal analysis of the different polymers was performed on a TA instruments 2920 modulated DSC. The heating rate was 10° C·min^{-1}. T_g's were read at half height of the change in the heat capacity and were taken from the second heating scan.

Acknowledgements

The authors like to thank the IWT Flanders for the financial support and APPharma for the delivery of DETOSU. J. C. M. thank the Fund for Scientific Research (FWO) Flanders (Belgium) for the research and equipment grant G.0365.03.

References

[1] Heller, J.; Penhale, D.W.H.; Helwing, R.F. *J. Polym. Sci., Polym. Lett.* **1980**, *18*, 82.
[2] Ng, S.Y.; Penhale, D.W.H., Heller, J. *Macromolec. Synth.* **1992**, *11*, 23.
[3] Heller, J. *Adv. Polym. Sci.* **1993**, *107*, 41.
[4] Heller, J. Chang, A.C.; Rodd, G.; Grodsky, G.M. *J. Contr. Rel.* **1990**, *13*, 295.
[5] Maa, Y.F. Heller, J.; *J. Contr. Rel.* **1990**, *13*, 11.
[6] Heller, J. Maa, Y.F.; Wuthrich, P.; Ng, S.Y.; Duncan, R. *J. J. Contr. Rel.* **1991**, *16*, 3.
[7] Maa, Y.F.; Heller, J. *J. Contr. Rel.* **1990**, *14*, 21.
[8] Heller, J. Barr, J.; Ng, S.Y.; Shen, H.-R.; Schwach-Abdellaoui, K.; Gurny, R.; Vivien-Castioni, N.; Loup, P.J.; Baehni, P.; Mombelli, A. *Biomater.* **2002**, *23*, 4397.
[9] Coombes, A.G.A.; Meikle, M.C.; *Clin. Mater.* **1994**, *17*, 35. and Middleton, J.C.; Tipton, A.J. *Biomater.* **2000**, *21*, 2335.
[10] Andriano, K.P.; Tabata, Y.; Ikada, Y.; Heller, J. *J. Biomed. Mater. Res. (Appl. Biomater.)* **1999**, *48*, 602.
[11] Mizutani, M.; Matsuda, T. *J. Biomed. Mater. Res.* **2002**, *62*, 387.
[12] Sawhney, S.A.; Pathak, C.P.; Hubbell, J.A. *Macromol.* **1993**, *26*, 581.
[13] Davis, K.A.; Burdick, J.A.; Anseth, K.S. *Biomater.* **2003**, *24*, 2485.
[14] Morris, K.F., Johnson, C.S. Jr. *J. Am. Chem. Soc.* **1992**, *114*, 3139.
[15] Schwach-Abdellaoui, K.; Gurny, R.; Heller, J.; Barr, J. *Int. J. Polym. Anal. Charact.* **2002**, *7*, 145.
[16] Schwach-Abdellaoui, K.; Heller, J.; Gurny, R. *J. Biomater. Sci. Polym. Edn*. **1999**, *10*, 375.
[17] Stejskal, E. O.; Tanner, J. E. *J. Chem. Phys.* **1965**, *48*, 288.
[18] Johnson, C. S. Jr. *Progr. NMR Spectrosc*. **1999**, *34,* 203-256.
[19] Stilbs, P. *Progr. NMR Spectrosc*. **1999**, *19*, 1-45.
[20] Chen, A.; Wu, D.; Johnson Jr, C.S. *J. Am. Chem. Soc.* 117, **1995**, 7965.
[21] Jerschow, A.; Müller, N. *Macromolecules* **1998**, 31, 6573.
[22] Leadley, S.R.; Shakesheff, K.M.; Davies, M.C.; Heller, J.; Franson, N.M.; Paul, A.J.; Brown, A.M.; Watts, J.F. *Biomater.* **1998**, *19*, 1353.
[23] Heller, J.; Ng, S.Y.; Penhale, D.W.H.; Fritzinger, B.K.; Sanders, L.M.; Burns, R.A.; Gaynon, M.G.; Bhosale, S.S. *J. Contr. Rel.* **1987**, *6*, 217
[24] Tudor, A.M.; Melia, C.D.; Davies, M.C.; Church, S.J.; Heller, J. *Spectrochim. Acta* **1993**, *49A*, 759.