e-Polymers **2007**, no. 104

http://www.e-polymers.org

ISSN 1618-7229

Synthesis and characterization of carboxyl end-functionalized poly(methylidene malonate 2.1.2)

Peggy Studer,[1 2 3] *Gérard Riess*[1*]

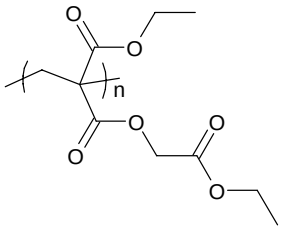
[1] Laboratoire de Chimie Macromoléculaire, Ecole Nationale Supérieure de Chimie de Mulhouse / Institut de Chimie des Surfaces et Interfaces, 3 Rue Alfred Werner, 68200 Mulhouse, France; Fax: +33389336854; email: gerard.riess@uha.fr.
[2] VIRSOL, 46 Rue Boissière, 75116 Paris, France
[3] Current address: ROLIC Technologies Ltd., Gewerbestrasse 18, 4123 Allschwil, Switzerland.

(Received: 1 January, 2007; published: 2007)

Abstract: α-Carboxyl end-functionalized poly(methylidene malonates 2.1.2) were prepared by free-radical polymerization in the molecular weight range 5 000 – 10 000 by using 4,4'-azobis(4-cyanopentanoic acid) as a functional initiator. A functionality of one carboxyl group per chain could be obtained. On the contrary, it was demonstrated that chain transfer functionalization with mercaptans is not applicable in this case. A Michael addition reaction between the mercaptan and the monomer becomes the predominant side-reaction. The corresponding mercaptan-monomer adduct was characterized in detail by ^{1}H and ^{13}C NMR.

Introduction

Poly(methylidene malonates) and in particular poly(methylidene malonate 2.1.2) (PMM 2.1.2) (Scheme 1) developed in the last decade appeared to have attractive properties for biomedical applications [1].



Scheme 1. Structure of poly(methylidene malonate 2.1.2) (PMM 2.1.2).

In fact, PMM 2.1.2 is a hydrophobic bioerodible polymer that becomes hydrophilic by hydrolysis of the lateral ester groups, which can be an enzymatic hydrolysis process as shown by Lescure and co-workers [2]. Moreover, the degradation products, ethanol and glycolic acid, are non-toxic in contrast to those derived from certain poly(alkyl cyanoacrylates) [3]. Amphiphilic PM 2.1.2 block copolymers, leading to biocompatible and biodegradable micellar systems in aqueous medium are of special interest for the preparation of controlled drug delivery systems [4]. These authors have shown that PMM 2.1.2-b-PEO block copolymers can for instance be prepared by sequential anionic polymerization.

An alternative and quite general technique for the preparation of diblock copolymers is the chemical coupling of the two end-functionalized precursor blocks, such as the esterification reaction between precursor blocks with carboxyl and hydroxyl end-groups [5] or the amidation reaction between carboxyl and amino end-functionalized polymers [6].

The aim of this study was to prepare carboxyl end-functionalized PMM 2.1.2 in the molecular weight range of about 5 000 – 10 000. Two preparation strategies of free-radical polymerization were considered by using either functional chain-transfer agents or functional initiators. In fact, chain transfer functionalization, in particular with mercaptans, such as mercaptoacetic acid, is well-documented for the preparation of carboxyl-terminated vinyl polymers [7]. An alternative to this method consists in functionalizing the polymer end during the initiation step as described by different authors [8, 9]. Carboxyl-functional azo initiators such as 4,4'-azobis(4-cyanopentanoic acid) are known as efficient compounds for chain-end functionalization [9,10]. These two possibilities will be examined in the following for the preparation of carboxyl-terminated PMM 2.1.2.

Results and discussion

The use of functional chain transfer agents in radical polymerization is an effective and convenient means for chain-end functionalization of polymers. Mercaptans are well known for their excellent chain transfer properties and are widely used in the literature [11-13]. For the preparation of carboxyl-terminated PMM 2.1.2, the use of mercaptoacetic acid as chain transfer agent will be considered at first and the occurrence of side reactions between the thiol component and MM 2.1.2 will be demonstrated. This section will be followed by the preparation and characterization of carboxyl-terminated PMM 2.1.2 of different molecular weights by using 4,4'-azobis(4-cyanopentanoic acid) as a functional initiator.

Polymerization of MM 2.1.2 in the presence of mercaptoacetic acid

The polymerizations were carried out in the presence of cyclohexyl percarbonate as a free-radical initiator and of various amounts of mercaptoacetic acid as a chain transfer agent. However, almost no polymer but only low molecular weight components were formed when the polymerization are performed in the presence of increasing amounts of mercaptoacetic acid. These results provide evidence that a side-reaction occurs between the thiol and the monomer which most probably might not be influenced by the free-radical character of the polymerization. This observation prompted us to examine in more detail the interaction of MM 2.1.2 with mercaptoacetic acid in the absence of free-radical initiator.

Reaction between MM 2.1.2 and mercaptoacetic acid

From the Size Exclusion Chromatography (SEC) traces shown in Figure 1, it appears that the simple mixture of MM 2.1.2 and mercaptoacetic acid in different ratios, heated at 45 °C for 15 min, leads to the formation of low molecular weight species with a peak maximum at 25.1 min.

The ^{1}H NMR (Figure 2) and ^{13}C NMR revealed that the major product results from a Michael addition between the mercaptoacetic acid and the MM 2.1.2 according to the reaction given in Scheme 2.

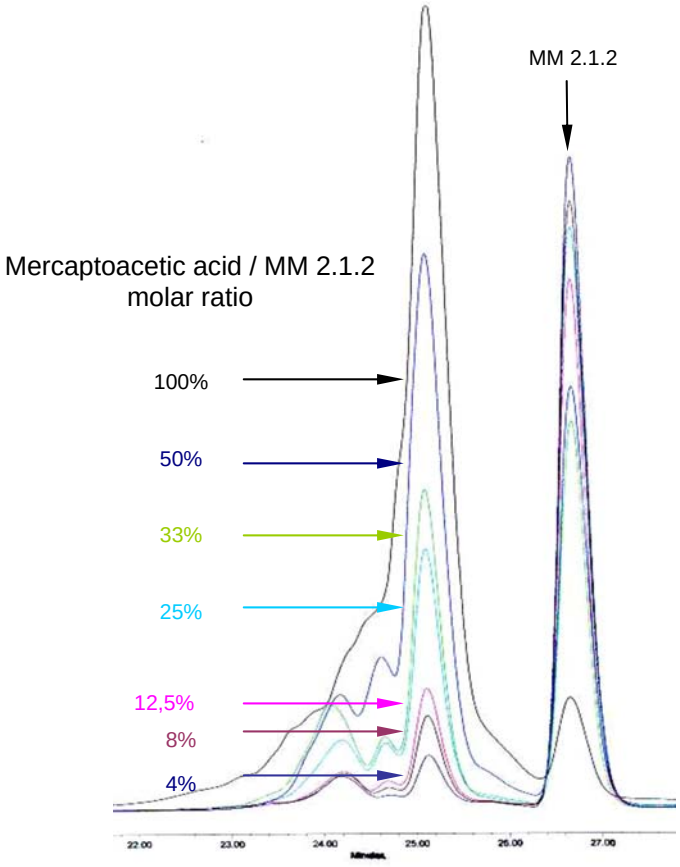
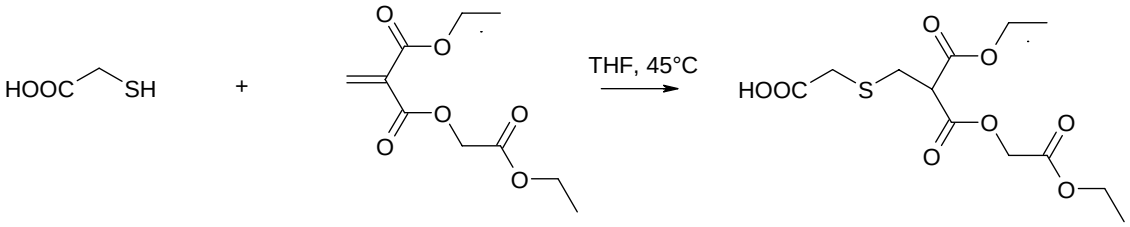


Fig. 1. SEC profiles revealing the formation of the Michael mono-adduct as a function of the mercaptoacetic acid/MM 2.1.2 molar ratio.



Scheme 2. Michael addition reaction between mercaptoacetic acid and MM 2.1.2.

Even if the mono-adduct was shown to be the major reaction product, the tailing of the SEC peak might be attributed to the presence of minor amounts of oligomers, such as for instance cyclic trimers resulting from a nucleophilic back-biting reaction, as demonstrated by Larras [14] in the case of the anionic polymerization of MM 2.1.2.

Thus the use of mercaptoacetic acid as a chain transfer agent for the preparation of carboxyl functionalized PMM 2.1.2 was shown to be inappropriate. More generally, the electrophilic character of methylidene malonate monomers was demonstrated and thus the use of thiols as chain transfer agent for the polymerization of MM 2.1.2 is not applicable.

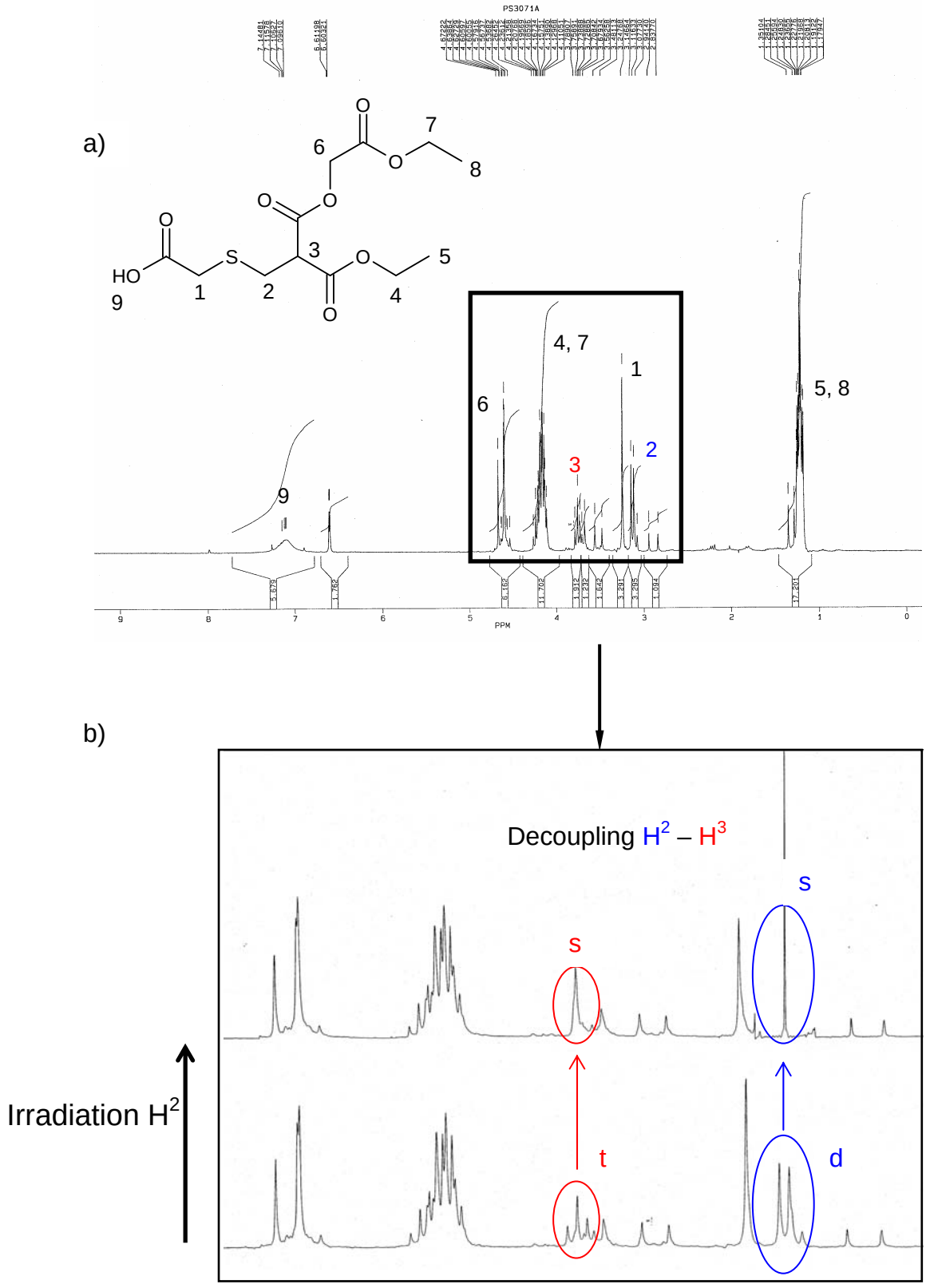
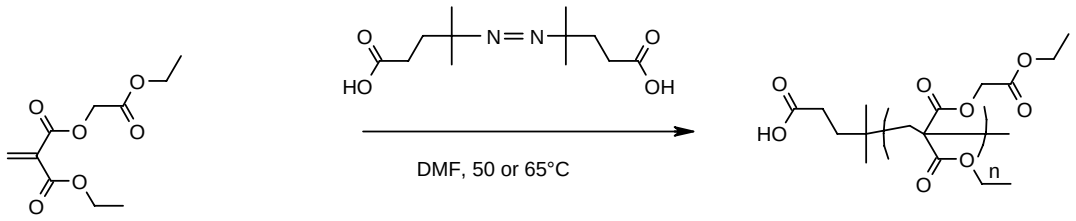


Fig. 2.a) ^{1}H NMR spectrum of Michaels' monoadduct in $CDCl_3$, 250 MHz. b) Decoupling experiment on H^2 (See Experimental part).

Synthesis of α- functionalized PMM 2.1.2 homopolymers

Functionalized azo-initiators such as 2,2'-azobis-iso-butyramidine and 4,4'-azobis(4-cyanopentanoic acid) were successfully used in the literature for the synthesis of functionalized prepolymers but their use is much less described in the literature compared to thiols [15,16]. As an alternative to chain transfer agents, we investigated the use of 4,4'-azobis(4-cyanopentanoic acid) for the functionalization of PMM 2.1.2 in the initiation step (Scheme 3).



Scheme 3. Synthesis route for the preparation of α-carboxyl functionalized PMM 2.1.2 polymers.

This type of initiator was described by Chujo [17] for the synthesis of dicarboxyl-terminated polystyrene. If no chain transfer reactions occur during the polymerization, each chain will be started by a carboxyl-functionalized free-radical. Thus, the functionality will be comprised between 1 and 2 depending on the termination mechanism, either by coupling or by disproportionation. Our aim being mainly a preparative one, rather than a kinetic study, at high polymerization conversions the influence of the polymerization temperature (50° and 65°C) and of the initiator/monomer molar ratio on the number-average molecular weight (M_n) of the polymer was investigated. At 50 °C and 65 °C, the polymerizations were carried out during 48 h and 12 h respectively, these durations being below the half life times of the azo initiator, e.g. the time at which 50% of the initiator is decomposed at a given temperature. At 50 °C and 65 °C, these values are 267 h and 16.6 h respectively [18].

Tab. 1. Synthesis of carboxyl functionalized PMM 2.1.2: reaction conditions and results.

[I]/[MM 2.1.2] in %[a]		0,5	1	2	5	8	10	16
T=65 °C[b] t=12 h[c]	M_n [d]	6 540	5 970	5 355	4 530	4 200	4 125	3 980
	Actual M_n [e]	9 150	8 240	7 280	6 010	5 520	5 400	5 190
	Ip[d]	1,98	1,99	2,21	2,23	2,18	2,13	2,14
T=50 °C[b] t=48 h[c]	M_n [d]	12 025	10 280	7 870	-	6 925	-	-
	Actual M_n [e]	18 350	15 340	11 300	-	9 770	-	-
	Ip[d]	1,89	1,79	2,20	-	2,16	-	-

[a] Molar ratio between the initiator 4,4'-azobis(4-cyanopentanoic acid) and the monomer MM 2.1.2 concentrations
[b] Polymerization temperature (°C)
[c] Polymerization time (h)
[d] M_n and *Ip* were measured by Size Exclusion Chromatography using a polystyrene (PS) calibration
[e] Actual M_n were calculated using Mark-Houwink equation

With the initiator/monomer molar ratio from 0.5 to 16%, our target was to synthesize functionalized prepolymers in the M_n range of 5 000 – 10 000 which can be used for further coupling reactions. The results are shown in Table 1. The table shows, not only the M_n values determined by SEC with polystyrene standards, but also the actual M_n of the PMM 2.1.2 samples $M_{n\ PMM\ 2.1.2}$, calculated according to the "universal calibration technique" developed by Benoît [19]. This technique, widely applied in SEC studies, is based on the fact that, at a given elution time, the hydrodynamic volumes of PS and PMM 2.1.2 are identical. It is furthermore well-known that the hydrodynamic volume is directly related to the molecular weight and to the intrinsic viscosity such as:

$$[\eta]_{PS}\, M_{n\ PS} = [\eta]_{PMM\ 2.1.2}\, M_{n\ PMM\ 2.1.2} \quad (1)$$

with $[\eta] = KM^{\alpha}$ according to the classical Mark-Houwink equation, K and α being the characteristic constants for a polymer in a given solvent at a fixed temperature.

For PS and PMM 2.1.2 in tetrahydrofuran (THF) at 25 °C, which are the experimental conditions of the SEC experiments, the Mark-Houwink equations are as follows:

$$[\eta]_{PMM\ 2.1.2} = 0{,}054\ M_{n\ PMM\ 2.1.2}^{0,5} \text{ [14]} \quad (2)$$

$$[\eta]_{PS} = 13{,}63\ 10^{-3}\ M_{n\ PS}^{0,714} \text{ [20]} \quad (3)$$

Consequently, the actual molecular weight of PMM 2.1.2 is given by the following relationship: $M_{n\ PMM\ 2.1.2} = (13{,}63 / 54)^{1/1.5}\ M_{n\ PS}^{1,714/1,5}$ (4)

Figure 3 gives the PMM 2.1.2 actual number-average molecular weight as a function of the molar ratio between the initiator and the monomer concentrations, the polymerization being carried out at 65 °C for 12 h. As shown from Table 1, the molecular weight decreases exponentially with the initiator concentration and M_n values below 10 000 are easily reached for initiator/monomer ratios above 0.5% mol/mol.

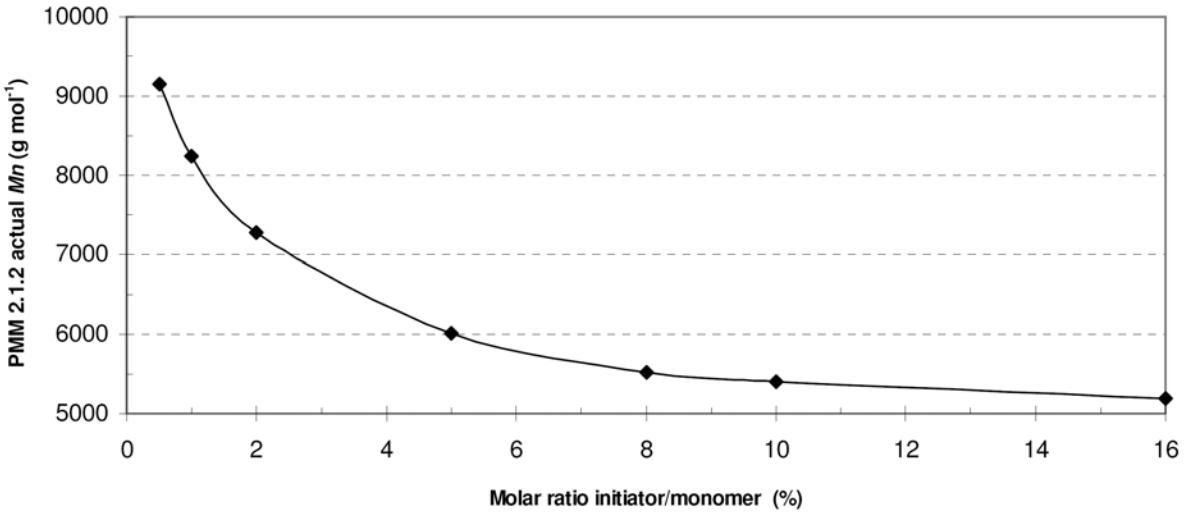


Fig. 3. Variation of the PMM 2.1.2 actual number-average molecular weight as a function of the molar ratio initiator/monomer (T=65 °C, 12 h).

Titration of the carboxyl end groups

As shown previously [21, 22], ^{1}H NMR cannot be used for the determination of the carboxylic functionality. Thus, the carboxylic acid end groups of the polymer dissolved in THF were titrated using a pH metry method developed by Llauro-Darricadès [23] for the titration of carboxylic acid groups from a butadiene-methacrylic acid copolymer with low methacrylic acid content.

As shown in Table 2, the functionality is between 1,1 and 1,2 for all the polymers which we evaluated, whatever the polymerization conditions. According to these results, and within the experimental error limits, it turns out that disproportionation is the major termination mechanism as expected for the polymerization of monomers with bulky substituants. As each macromolecule statistically bears practically one end-group, these functional polymers fulfill the prerequisite conditions for their use in coupling reactions with other functional polymers or with organic molecules.

Tab. 2. Determination of the PMM 2.1.2 functionality by titration.

Experimental conditions			Actual M_n (PMM 2.1.2)[b]	f[c]
Temperature (°C)	Polymerization time (h)	[I]/[MM 2.1.2] (%)[a]		
65	12	5	6010	1,1
65	12	8	5520	1,1
65	12	16	5190	1,15
50	48	2	11300	1,2

[a] Molar ratio between the initiator 4,4'-azobis(4-cyanopentanoic acid) and the monomer MM 2.1.2 concentrations
[b] Calculated using Mark-Houwink's equation
[c] Average number of carboxyl groups for a macromolecule calculated from equation (5) (See Experimental part)

Conclusions

Carboxyl end-functionalized PMM 2.1.2 in the molecular weight range of about 5 000 – 10 000 were successfully synthesized by using 4,4'-azobis(4-cyanopentanoic acid) as a functional azo initiator. The functionality of these polymers comprised between 1,1 and 1,2 which indicates that the termination reaction of the MM 2.1.2 free radical polymerization mainly occurs by disproportionation. Each macromolecule statistically bearing practically one end-group, these functional polymers fulfills the prerequisite conditions for their use in coupling reactions with other functional polymers or with organic molecules. Furthermore, it was demonstrated that the use of mercaptans as chain transfer agents is not applicable for the preparation of PMM 2.1.2 polymers. A Michael addition reaction between the mercaptan and the monomer becomes the predominant side-reaction.

Experimental part

Materials

All the reagents and chemicals used in this study were purchased from Aldrich and used as received unless otherwise noted. Methylidene malonate 2.1.2 (MM 2.1.2), prepared according to Bru-Magniez et al. procedure [1], was kept under sulfur

dioxide at -20 °C. Tetrahydrofuran, THF (>99%, Acros) was purified from CaH_2 prior to use. The 10^{-3} M NaOH solution used for the titration was prepared from Normax dosis (Carlo Erba).

Polymerization of MM 2.1.2 in the presence of mercaptoacetic acid

200 mg de MM 2.1.2 (0,87 mmol) were dissolved in 1 mL of a mercaptoacetic acid solution in THF (11; 22; 65; 109; 174 mmol/L). The solution was degassed for 10 min with nitrogen, heated at 45 °C and 1 mL of a cyclohexyl percarbonate solution in THF (8,7 10^{-3} mmol/L) was added under magnetic stirring. In order to determine the chain transfer constant for the polymerization system MM 2.1.2/mercaptoacetic acid, the polymerization was inhibited after 15 min heating at 45 °C with a hydroquinone solution. The products were analyzed by SEC.

Reaction between MM 2.1.2 and mercaptoacetic acid

200 mg de MM 2.1.2 (0,87 mmol) were dissolved in 1 mL of an mercaptoacetic acid solution in THF (35; 70; 110; 220; 290; 430; 870 mmol/L). The solutions were heated at 45 °C for 15 min and were analyzed by SEC. The product of the reaction was recovered by evaporation of the solvent, dried and analyzed by ^{1}H NMR.

NMR ^{1}H (ppm): 1.23 (t, H^5 and H^8, 6H); 3.13 (d, J=7.6 Hz, H^2, 2H); 3.25 (s, H^1, 2H); 3.76 (t, J=7.6 Hz, H^3, 1H); 4.16 (m, H^4 and H7, 4H); 4.60 (s, H^6, 2H). Additionally, decoupling experiments were run on H^2 to assign the proton resonances H^2- H^3: the resonance at 3.76 ppm (s; t without decoupling) is assigned to H^3, and to H^2 for the resonance at 3.13 ppm (s; d without decoupling) (Figure 2).

NMR ^{13}C (ppm): 13.8 (C^5 and C^8); 30.1 (C^2); 33,5 (C^1); 51.8 (C^3); 61,4-61,7(C^4, C^6 and C^7); 167,0-167,3 (C^9, C^{10} and C^{11}); 174,09 (C^9).

Chemical shifts are given in ppm, multiplicities are defined as follows: s, singulet; d, doublet; t, triplet; m, multiplet.

Synthesis of α- functionalized PMM 2.1.2 homopolymers

In a typical experiment, freshly degassed MM 2.1.2 (4,3 mmol; 1.0 g) was dissolved in 2 mL N,N-dimethylformamide (DMF) to which 1 mL of a 4,4'-azobis(4-cyanopentanoic acid) solution in DMF (21; 43; 86; 215; 344; 430; 688 mmol/L) was added. The glass tube containing the solution was sealed under vacuum. The polymerization was carried out by heating the contents at 50 °C and at 65 °C in a thermostatic water bath for respectively 48 h and 12 h. After polymerization, the solutions were diluted with 2 mL of THF and the polymer was isolated by precipitating the solution into 250 mL of water and finally lyophilized. Yield=95%.

^{1}H-NMR (250 MHz, $CDCl_3$, δ in ppm): 1.30 (m, CH_3 of PMM 2.1.2, 6H), 2.80 (m, CH_2 of the main chain of PMM 2.1.2, 2H), 3.60 (m, CH_2 of PEO, 4H), 4.10 (m, CH_2 of CH_2-CH_3 of PMM 2.1.2, 4H), 4.50 (m, CH_2 of PMM 2.1.2, 2H).

Number-average molecular weight (M_n), weight-average molecular weight (M_w) and polydispersity index (Ip) measured by SEC are given in the Results and Discussion part.

Characterization

Polymer characterization

^{1}H- and ^{13}C-NMR were recorded in $CDCl_3$ using a Bruker AC 250F spectrometer, respectively at 250 and 62.9 MHz. Gel Permeation Chromatography measurements were performed by using a Waters 2690 Alliance system equipped with a sequence of Waters Styragel HR4, HR1 and HR0.5 columns and an internal RI Waters 410 detector (flow rate=1 mL/min). THF was used as an eluant and standards were PS.

Titration of the carboxyl end groups

For the determination of the carboxyl functionality, a pH titration of a polymer solution was conducted using a Mettler Toledo MP220 pH meter equipped with a combination electrode. A titration method developed by Llauro-Darricadès [23] was used which consists in dissolving m_0 mg of polymer in 44 mL of a solution THF/water 10:1. The solution was titrated using a 10^{-3}M NaOH solution. Preliminary tests showed that the ester groups did not hydrolyze during the analysis for a titration duration kept below 10 min. From the acidity corresponding to a given weight m_0 of polymer and its number-average molecular weight given from Mark-Houwink's equation, the functionality of the polymer f could be calculated using the following equation:

$$f = (x\, M_n) / m_0 \qquad (5)$$

where f is the average number of carboxyl groups per polymer chain, *x* is the number of NaOH mol required for the neutralization of the acidic groups contained in m_0 of PMM 2.1.2, m_0 is the weight of PMM 2.1.2 which was dissolved in the solution (g) and M_n is the PMM 2.1.2 actual number-average molecular weight.

Acknowledgements

The authors gratefully acknowledge the financial support by Dr. Nicole Bru. The authors would like to thank Drs. Virginie Larras, David Limal and Serge Sagodira for their helpful discussions.

References

[1] Bru-Magniez, N.; De Cock, C.; Poupaert, J.; De Keyser, J.L., Dumont, P. *EP 0283364*, **1988**.
[2] Lescure, F.; Seguin, C.; Breton, P.; Bourrinet, P.; Roy, D.; Couvreur, P. *Pharm. Res.* **1994**, *11*, 1270.
[3] Couvreur, P. *Crit. Rev. Ther. Drug Carrier Syst.* **1988**, *5*, 1.
[4] Larras, V.; Bru, N.; Breton, P.; Riess, G. *Macromol. Rapid Commun.* **2000**, *21*, 1089.
[5] Francke, V.; Räder, H.J.; Geerts, Y.; Müllen, K.; *Macromol. Rapid Commun.* **1998**, *19*, 275.
[6] Oupicky, D.; Konak, C.; Ulbrich, K.; Wolfert, M.A.; Seymour, L.W. *J. Control. Rel.* **2000**, *65*, 149.
[7] Wu, W.W.L.; Piirma, I. *Polymer Bull.* **1993**, *31*, 531.
[8] Goethals, E.J. *Telechelic Polymers: Synthesis and Applications*, CRC Press, Inc., Boca Raton, Florida, **1989**, 85.
[9] Bamford, C.H.; Jenkins, A.D.; Wayne, R.P. *Trans Faraday Soc.* **1960,** *56*, 932.
[10] Reed, S.F. *J. Polymer Sci., Part A1* **1971**, *9*, 2147.

[11] Cammas, S.; Suzuki, K.; Sone, C.; Sakuraï, Y.; Kataoka, K.; Okano, T. *J. Control. Rel.* **1997,** *48*, 157.
[12] Chung, J.E.; Yokoyama, M.; Aoyagi, T.; Sakurai, Y.; Okano, T. *J. Control. Rel.* **1998**, *53*, 119.
[13] Cheon, J.B.; Jeong, Y.I.; Cho, C.S. *Polymer* **1999**, *40*, 2041.
[14] Larras, V. Ph.D. Thesis, University of Haute-Alsace (France), S*ynthesis of bioerodible polymers and copolymers based on methylidene malonate. Vectorization of active components (Synthèse de polymères et de copolymères biodégradables à base d'un méthylidène malonate. Application à la préparation de vecteurs colloïdaux pour la libération contrôlée de principes actifs)*, **1997**.
[15] Wang, D.; Kopeckova, P.; Minko, T.; Nanayakkara, V.; Kopecek, J. *ACS Polym. Prep.* **2000**, *41*, 994.
[16] Ouchi, T.; Hirano, T.; Maruhashi, S.; Nishizawa, H.; Shizuno, K.; Ohya, Y. *ACS Polym. Prep.* **2000**, *41*, 1548.
[17] Chujo, Y.; Hiraiwa, A.; Yamoshita, Y. *Makromol. Chem.* **1984**, *185*, 2077.
[18] Technical data brochure, Wako Chemical GmbH.
[19] Benoît, H.; Grubisic, Z.; Rempp, P. *Polymer Lett.* **1967**, *B5*, 753.
[20] Brandrup, J.; Immergut, E.H. *Polymer Handbook*, 3rd Ed, John Wiley, New-York, **1989**, VII/16.
[21] Studer, P. Ph.D. Thesis, University of Haute-Alsace (France), *Synthesis and characterization of methylidene malonate 2.1.2-based functionalized homo- and copolymers. Vectorization of active components (Synthèse et caractérisation de polymères fonctionnalisés à base de méthylidène malonate 2.1.2. Application à la vectorisation de principes actifs)*, **2001**.
[22] Studer, P.; Breton, P.; Riess, G. *Macromol. Chem. Phys.* **2005**, *206*, 2461.
[23] Llauro-Darricadès, M.F. PhD Thesis, University of Strasbourg (France), *Separation of grafted copolymer from the homopolymer corresponding to the grafts based on the formation of reversible gels, Application to ABS resins (Séparation d'un copolymère greffé de l'homopolymère correspondant aux greffons par gel réversible, Application aux résines ABS),* **1970**.