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Polymers of malic acid conjugated with the 1-adamantyl moiety as lipophilic pendant group

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Ethyladamantyl malolactonate and butyladamantanamide malolactonate were prepared, starting from malic acid, following the usual synthesis route described for different malolactonic acid esters. Despite the steric hindrance of both adamantyl groups, the three-step synthesis led to the corresponding lactones with a quite good yield and high purity. Otherwise, ethyladamantyl malolactonate has been obtained by chemical modification of the lateral carboxylic acid function of malolactonic acid. Both ethyladamantyl malolactonate and butyladamantanamide malolactonate were homopolymerized by anionic ring opening polymerization using tetramethylammonium benzoate as initiator. Expected high molecular weight homopolymers were obtained and characterized by ^{1}H nuclear magnetic resonance (n.m.r.) and size exclusion chromatography (s.e.c.). Furthermore, ethyladamantyl malolactonate was copolymerized with benzyl malolactonate in the molar ratio 5/95. The resulting copolymer was studied by ^{1}H and ^{13}C n.m.r., s.e.c. and differential scanning calorimetry. After deprotection of the benzyl protecting groups by catalytic hydrogenolysis, the corresponding poly(β-malic acid-*co*-ethyladamantyl β-malate) displayed a water solubility. © 1997 Elsevier Science Ltd.

(Keywords: alkyladamantyl malolactonates; poly(alkyladamantyl β-malate); poly(β-malic acid-*co*-alkyladamantyl β-malate)

Introduction

Adamantane (tricyclo[3.3.1.1^{3,7}]decane) is a highly symmetrical tricyclic hydrocarbon which consists of fused chair-form cyclohexane rings[1]. The unique structure of this substance is reflected in highly unusual physical and chemical properties such as thermal and oxidation stabilities, low surface energy, high density and hydrophobicity. These particular characteristics are conducive to the incorporation of adamantyl groups either into polymers to improve thermal properties[2] or into bioactive molecules as a tool for drug delivery[3] or in the preparation of host–guest complexes by association with β-cyclodextrin derivatives[4].

The improvement of thermal properties of adamantyl containing polymers results from the rigidity and the bulkiness of the adamantyl moiety, which greatly reduce the chain mobility and inhibit chain packing[2]. Consequently, the thermal stability and the glass transition temperatures of the adamantyl containing polymers are increased and solubility in organic solvents is enhanced[5,6]. Bioactive compounds such as AZT[3], which cannot cross the blood–brain barrier, have been conjugated with adamantane derivatives via an ester or amide bond in the goal to improve their transport into the central nervous system[7]. The pronounced lipophilic nature associated with the compact highly symmetrical architecture of the adamantane molecule are of great interest in reaching particular biological targets.

The necessary adjustment of the material properties for a specific therapeutic device is conducive to the tailor-making of multimeric polymers with a degradable backbone and a wide spectrum of variable pendant functional groups. Therefore, suitable material properties, such as hydrophilic/hydrophobic balance, morphology, degradation rate, bioactive or targeting molecules attachment, can be achieved by copolymerization or chemical modification. Poly(β-malic acid) derivatives can be used as smart polymers for temporary therapeutic applications due to carboxylic acid lateral groups, besides the presence of one stereogenic centre and one ester cleavable bond in the repeating unit. A large family of different compounds bearing specific neutral, bioactive, chiral or mesogenic pendant groups have been prepared[8–10]. The limitation for obtaining such functional macromolecules is in the possibility of synthesizing the corresponding monomers, e.g. β-substituted β-lactones.

The present paper describes the possibility of introducing the adamantyl moiety into the 4-[(substituted)-oxycarbonyl]-2-oxetanone by two different routes and with varied spacer groups. We will present the possibilities of obtaining polymers containing one type of repeating unit bearing adamantyl groups. Last, but not least, we will describe the preparation and characterization of poly(β-malic acid-*co*-adamantyl β-malate) containing well defined proportions of the adamantyl group.

Experimental

Melting points (m.p.) were measured by using a Kofler hot bench. Infra-red (i.r.) spectra were recorded on a Perkin-Elmer 283B spectrometer and are given in cm^{-1}. The i.r. spectra of oils were recorded as a thin film of the product held in the i.r. beam between cell windows of KBr. Solids were solubilized in acetone and applied as a thin film between cell windows of KBr. The nuclear magnetic resonance (n.m.r.) ^{1}H spectra were recorded on a Bruker A2000 (200 MHz) spectrometer. The ^{1}H

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chemical shifts are reported in ppm with the solvent as the internal reference. Glass transition temperatures (T_g) of polymers were measured by differential scanning calorimetry (d.s.c.) using a Setaram 92-DSC apparatus under normal atmosphere (air) at a heating rate of $10°C\,min^{-1}$. The molecular weight distributions of polymers were determined by size exclusion chromatography (s.e.c.) using a Spectra Physics P100 equipped with three columns of PL-gel (100, 500 and 10^4 Å) and a Shodex RI-71 refractive index detector, in tetrahydrofuran (THF) with a rate flow of $1\,ml\,min^{-1}$.

Trifluoroacetate of malic acid anhydride (**2**). DL-Malic acid (2 g, 1.5×10^{-2} mol) was placed in a 50 ml round-bottomed flask and cooled in an ice bath. Trifluoroacetic anhydride (TFAA) (2 eq., 3×10^{-2} mol) was added and the suspension was stirred magnetically at 0°C for 1 h and at room temperature for 3 h. The trifluoroacetic acid formed and the excess of TFAA were removed by vacuum distillation at 35°C to give the trifluoroacetate of malic acid anhydride (**2**) as a white solid with a quantitative yield[11].

3-Ethyladamantyloxycarbonyl-3-hydroxypropanoic acid (**3a**). Compound **2** was dissolved in 1 ml of anhydrous THF. 1-Adamantylethanol (**5a**) (2.7 g, 1.5×10^{-2} mol; Fluka), dissolved in 2 ml of anhydrous THF, was added and the mixture was stirred for 48 h at room temperature. THF was removed by vacuum distillation. The resulting oil was dissolved in ethyl acetate (50 ml) and extracted with three portions of aqueous 1 M $NaHCO_3$. The combined aqueous solutions were washed with ethyl acetate and then acidified to pH 2 with 1.2 N HCl. The aqueous layer was extracted with several portions of ethyl acetate. These latter organic extracts were combined, dried over $MgSO_4$ and evaporated to give crude **3a** as a white solid (yield 80%).

M.p. = 50°C. ^{1}H n.m.r. (200 MHz, CD_3COCD_3, δ ppm): 1.4–1.7(*m*, 17H, Ad–CH_2), 2.6–2.8(*m*, 2H, CH_2), 4.2(*t*, 2H, $C\underline{H}_2$–CH_2–Ad), 4.5(*m*, 1H, CH).

3-Butyladamantanamideoxycarbonyl-3-hydroxypropanoic acid (**3b**). Compound **3b** was prepared following the same procedure as that described for the preparation of **3a**, using *N*-2-hydroxybutyl-1-adamantylformamide (**5b**) synthesized as described below.

A solution of butanolamine (3.2 ml, 3.6×10^{-2} mol) in CH_2Cl_2 (16 ml) was stirred magnetically in a 250 ml Erlenmeyer flask and cooled to 0°C with an ice/water bath. 1-Adamantylcarboxylic acid chloride (3.5 g, 1.8×10^{-2} mol; Janssen Chemica), in CH_2Cl_2 (10 ml), was then added to this solution through an addition funnel at a moderate rate without causing violent reaction. After complete addition, the white precipitate [HO-$(CH_2)_4$-$NH_3^+Cl^-$] formed during the addition was filtered off. Pure **5b** was obtained by evaporation of CH_2Cl_2, followed by recrystallization from toluene/cyclohexane (yield 75%).

M.p. = 120°C. ^{1}H n.m.r. (200 MHz, $CDCl_3$, δ ppm): 1.5–2.0(*m*, 19H, Ad–CONH–CH_2–$C\underline{H}_2$–$C\underline{H}_2$–CH_2–), 3.3(*m*, 2H, $C\underline{H}_2$–NH), 3.7(*t*, 2H, $C\underline{H}_2$–OH).

The reaction between the trifluoroacetate of malic acid anhydride (**2**) and *N*-2-hydroxybutyl-1-adamantylformamide (**5b**), as described for (**3a**), led to crude **3b** as a white oil (yield 80%).

^{1}H n.m.r. (200 MHz, $CDCl_3$, δppm): 1.3–2.1(*m*, 19H, Ad–CONH–CH_2–$C\underline{H}_2$–$C\underline{H}_2$–CH_2–); 2.7–2.9(*m*, 2H, CH_2), 3.3(*m*, 2H, $C\underline{H}_2$–NH), 4.2(*t*, 2H, $C\underline{H}_2$–CO), 4.6(*t*, 1H, CH).

Ethyladamantyl malolactonate (**4a**). The ethyladamantyl malolactonate **4a** was prepared as previously described for alkyl malolactonates[11]. The crude lactone was purified by three chromatographic runs on silica gel. Eluents were, successively, petroleum ether/diethyl ether (3/2), ethyl acetate/cyclohexane (1/4) and dichloromethane/petroleum ether (3/2). Compound **4a** was obtained as a white solid (yield 21%).

M.p. < 30°C. ^{1}H n.m.r. (200 MHz, $CDCl_3$, δ ppm): 1.4–1.9(*m*, 17H, Ad–CH_2); 3.5–3.8(*m*, 2H, CH_2 lactone); 4.3(*t*, 2H, $C\underline{H}_2$–CH_2–Ad); 4.8(*m*, 1H, CH lactone).

Butyladamantanamide malolactonate (**4b**). The butyladamantanamide malolactonate **4b** was prepared from **3b** according to the same procedure as for **4a**. The crude lactone was purified by two chromatographic runs on silica gel. Eluents were, successively, ethyl acetate and ethyl acetate/petroleum ether (4/1). Compound **4b** was obtained as a transparent oil (yield 25%).

^{1}H n.m.r. (200 MHz, $CDCl_3$, δ ppm): 1.6–1.9(*m*, 19H, Ad–CONH–CH_2–$C\underline{H}_2$–$C\underline{H}_2$–CH_2–); 3.3(*m*, 2H, $C\underline{H}_2$–NH); 3.7(*m*, 2H, CH_2 lactone); 4.3(*t*, 2H, $C\underline{H}_2$–CO); 4.9(*m*, 1H, CH lactone).

Ethyladamantyl malolactonate (**8**). The ethyladamantyl malolactonate **8** was prepared from malolactonic acid (**7**) and 1-adamantylethanol (**5a**) as described elsewhere[8]. Compound **7** was obtained by catalytic hydrogenolysis[8] of benzylmalolactonate, which was synthesized as previously described[12,13].

The crude lactone **8** was purified by chromatography on silica gel with the mixture petroleum ether/diethyl ether (3/2) as eluent, leading to pure **8** (yield 40%). M.p. < 30°C. ^{1}H n.m.r. (200 MHz, $CDCl_3$, δ ppm): see spectrum of **4a**.

Poly(ethyladamantyl β-malate) (**9**). Poly(ethyladamantyl β-malate) (**9**) was synthesized by polymerizing 300 mg of **4a** in the presence of tetramethylammonium benzoate as initiator (10^{-3} mol per mol of monomer) under nitrogen at 40°C during seven days. The end of polymerization was controlled by i.r. The crude polymer was dissolved in CH_2Cl_2 and precipitated in ethanol. After separation, the homopolymer was dried *in vacuo* at 40°C.

T_g = 70°C. S.e.c. (THF, standard polystyrene): $\overline{M}_n$ = 17 300, $\overline{M}_w$ = 27 200, I_p = 1.6. ^{1}H n.m.r. (400 MHz, $CDCl_3$, δ ppm): 1.5–1.7(*m*, 17H, Ad–CH_2), 3.0(*s*, 2H, CH_2 main chain), 4.2(*s*, 2H, $C\underline{H}_2$–CH_2–Ad), 5.5(*s*, 1H, CH main chain); ^{13}C n.m.r. (100 MHz, $CDCl_3$, δ ppm): 17.5(Ad–CH_2), 28.4(Ad–CH_2), 31.6(Ad–CH_2), 35.5(CH_2 main chain), 36.9(Ad–CH_2), 42.0(Ad–CH_2), 42.3 (Ad–CH_2), 49.5(Ad–CH_2), 62.5($C\underline{H}_2$–CH_2–Ad), 68.5(CH main chain), 168.0(CO).

Poly(benzyl β-malate-co-ethyladamantyl β-malate) (95/5) (**10**). The copolymer was synthesized by polymerizing 400 mg (0.5 eq) of **4a** 7.6 g (0.95 eq) of racemic benzyl malolactonate (**6**) in the presence of initiator (10^{-3} mol per mol of monomer) under nitrogen at 40°C during seven days. Polymerization was controlled by i.r. The crude

polymer was dissolved in acetone and precipitated in ethanol. The copolymer was dried *in vacuo* at 40°C.

T_g = 20°C. S.e.c. (THF, standard polystyrene): $\overline{M_n}$ = 26 200, $\overline{M_w}$ = 45 500, I_p = 1.7. ^{1}H n.m.r. (400 MHz, CD_3COCD_3, δ ppm): 1.2–1.9(*m*, 0.85H, Ad–CH_2), 2.95 (*s*, 2H, CH_2 main chain), 4.15(*s*, 0.1H, $C\underline{H}_2$–CH_2–Ad), 5.15(*s* 1.9H, $C\underline{H}_2$Ph), 5.55(*s*, 1H, CH main chain), 7.4(*m*, 4.75H, $CH_2\underline{Ph}$); ^{13}C n.m.r. (100 MHz, CD_3COCD_3, δ ppm): 18.3(Ad–CH_2), 29.0(Ad-CH_2), 32.0(Ad–CH_2), 36.0(CH_2 main chain), 37.5(Ad–CH_2), 42.8(Ad–CH_2), 42.9(Ad–CH_2); 62.7($C\underline{H}_2$–CH_2–Ad), 67.8($C\underline{H}_2$Ph), 69.4(CH main chain), 128.0–129.0 and 136.0($CH_2\underline{Ph}$), 168.0–169.0(CO).

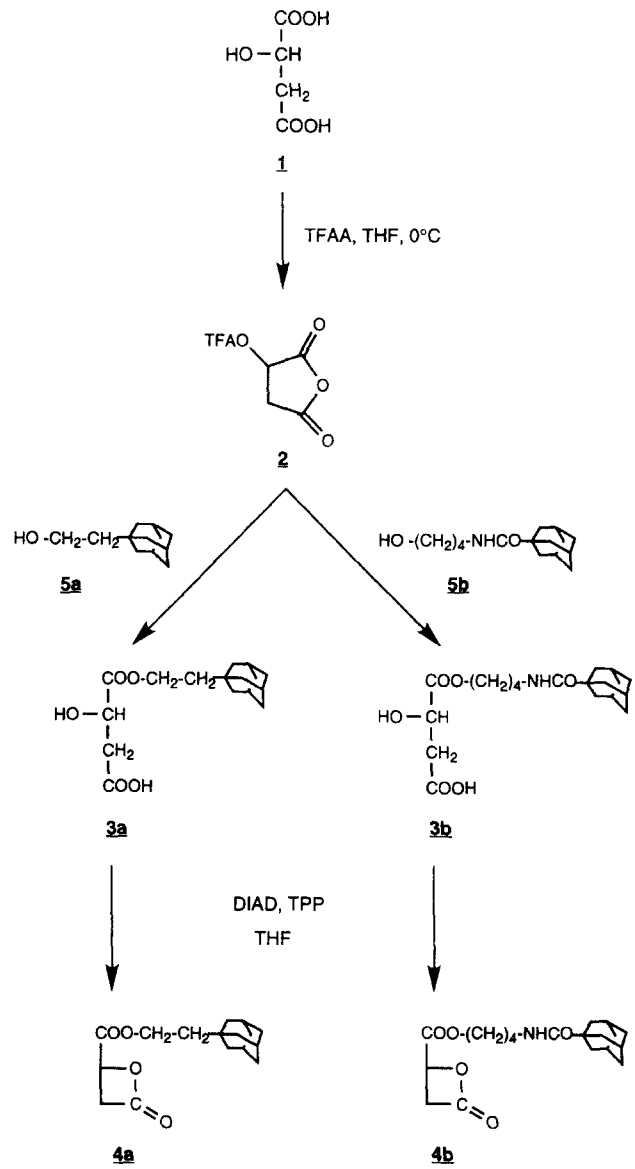
*Poly(β-malic acid-*co*-ethyladamantyl β-malate) (95/5)* (**11**). Compound **11** was obtained by catalytic hydrogenolysis of **10**. After dissolution of the polymer in dioxane in the presence of 20 wt% of palladium[14] (Janssen Chemica) the hydrogenolysis was conducted at room temperature during one night. After filtration over celite, dioxane was eliminated and the resulting copolymer **11** was dried *in vacuo* at room temperature.

^{1}H n.m.r. (400 MHz, CD_3COCD_3, δ ppm): 1.2–1.9(*m*, 0.85H, Ad–CH_2), 3.0(*s*, 2H, CH_2 main chain), 4.2(*s*, 0.1H, $C\underline{H}_2$–CH_2–Ad), 5.4(*s*, 1H, CH main chain); ^{1}H n.m.r. (200 MHz, D_2O, δ ppm): 1.2–1.9(*m*, 0.85H, Ad–CH_2), 2.95(*s*, 2H, CH_2 main chain), 4.2(*s*, 0.1H, $C\underline{H}_2$–CH_2–Ad), 5.5(*s*, 1H, CH main chain); ^{13}C n.m.r. (100 MHz, CD_3COCD_3, δ ppm): 18.2(Ad–CH_2), 29.4(Ad–CH_2), 32.3(Ad–CH_2), 36.2(CH_2 main chain), 37.5(Ad–CH_2), 42.8(Ad–CH_2), 42.9(Ad–CH_2); 62.7($C\underline{H}_2$–CH_2–Ad), 69.4(CH main chain), 169.0(CO ester), 170.0 (CO acid).

Results and discussion

The preparation of racemic 4-ethyladamantyloxycarbonyl-2-oxetanone (ethyladamantyl malolactonate) (**4a**), as well as racemic 4-butyladamantanamidoxycarbonyl-2-oxetanone (4-butyladamantanamide malolactonate) (**4b**) was based on the chemical synthesis route established for benzyl and alkyl malolactonates starting from malic acid[11]. As shown by *Scheme 1*, racemic malic acid was reacted with TFAA to lead to the corresponding cyclic anhydride **2**. This anhydride was usually opened with a none too bulky alcohol such as benzyl alcohol, methanol, ethanol or 2-methyl-1-butanol[11,15].

Despite the steric hindrance of both adamantyl alcohols studied (**5a** and **5b**), the trifluoroacetate of malic acid anhydride **2** was successfully transformed into its corresponding monoester **3a** or **3b** with quite good yields (75 and 80%, respectively). The monoester **3a** or **3b** was then intramolecularly dehydrated using diisopropylazodicarboxylate and triphenylphosphine to lead to the corresponding lactone **4a** or **4b**. In both cases, the formation of the lactone was demonstrated by i.r. spectroscopy. Indeed, the presence of the lactone ring was characterized by two bands at 1850 and 1740 cm^{-1} corresponding to the carbonyl groups of the lactone. After purifications by chromatography on silica gel, **4a** and **4b** were studied by ^{1}H n.m.r. in $CDCl_3$. As shown on *Figure 1*, signals corresponding to the lactone cycles (3.5–3.8 ppm $C\underline{H}_2$ and 4.9 ppm $C\underline{H}$) were present in both spectra. Peaks of ethyladamantyl and butyladamantanamide groups were also assigned. Moreover, the absence of additional signals showed that the purity of both prepared lactones was high.



Scheme 1 Synthesis of ethyladamantyl malolactonate (**4a**) and butyladamantanamide malolactonate (**4b**) from DL-malic acid

Recently, we have shown that malolactonic acid, which was considered as totally unstable because of the presence of a lateral carboxylic group, could be prepared in large quantities by catalytic hydrogenolysis of benzyl malolactonate[8]. The free carboxylic function of malolactonic acid can be used for attachment of neutral groups, bioactive molecules or targeting moieties using dicyclohexyldicarbodiimide (DCC) as coupling reagent[8]. As shown by *Scheme 2*, ethyladamantyl malolactonate (**8**) was obtained by reaction of ethyladamantyl alcohol with malolactonic acid in the presence of DCC as coupling reagent. In this case also, the presence of **8** was demonstrated by i.r. spectroscopy (bands at 1850 and 1740 cm^{-1}). The ^{1}H n.m.r. spectrum of this lactone was identical to the one of **4a** obtained from malic acid.

It is worth noting that ethyladamantyl malolactonate can be prepared by two different routes despite the bulky adamantyl group. The second synthesis route is of great interest because it allows ethyladamantyl malolactonate to be obtained in quite large quantities. Indeed, benzyl malolactonate is easily synthesized from aspartic acid[12,13] and deprotection of the carboxylic function by

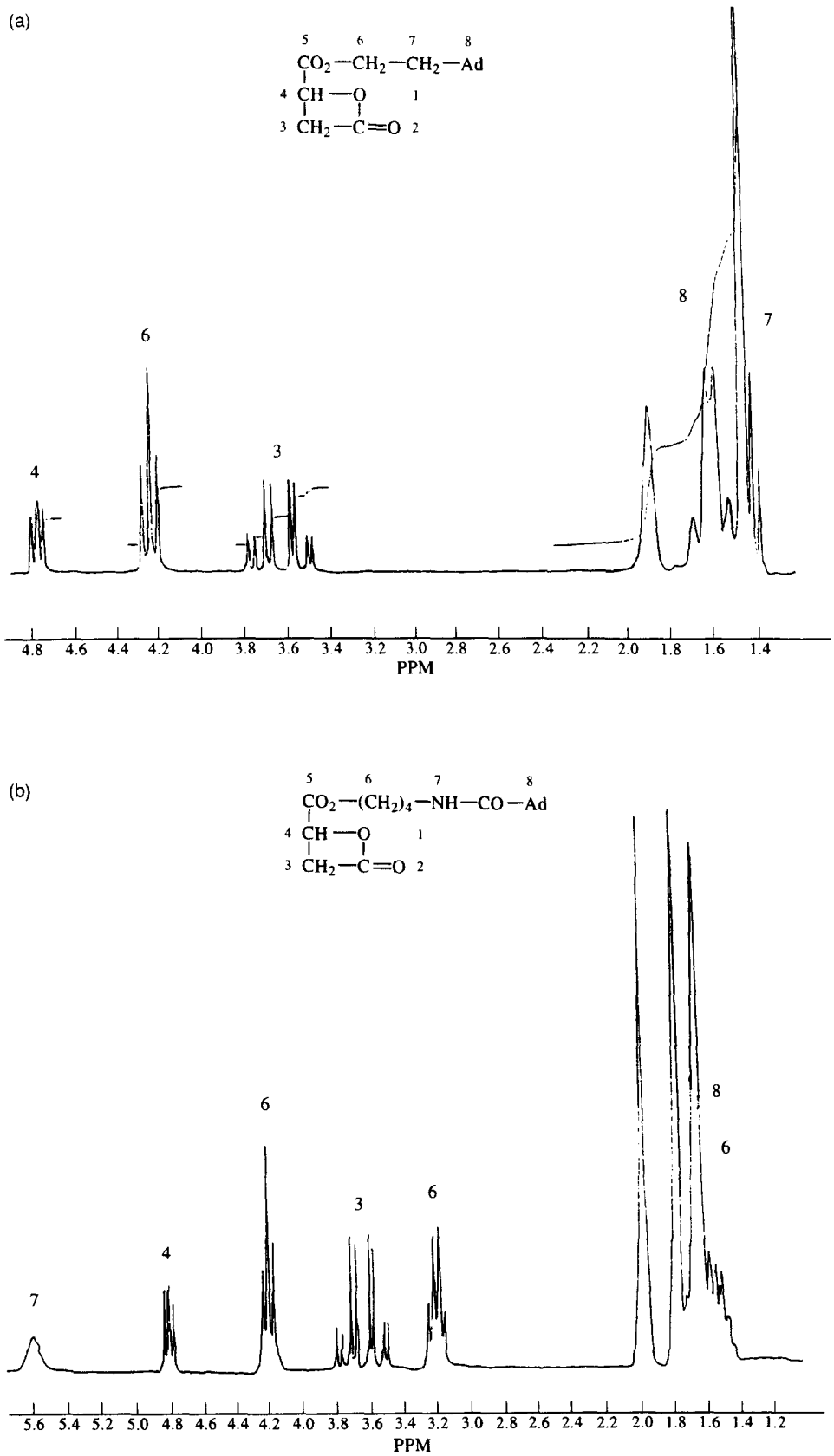
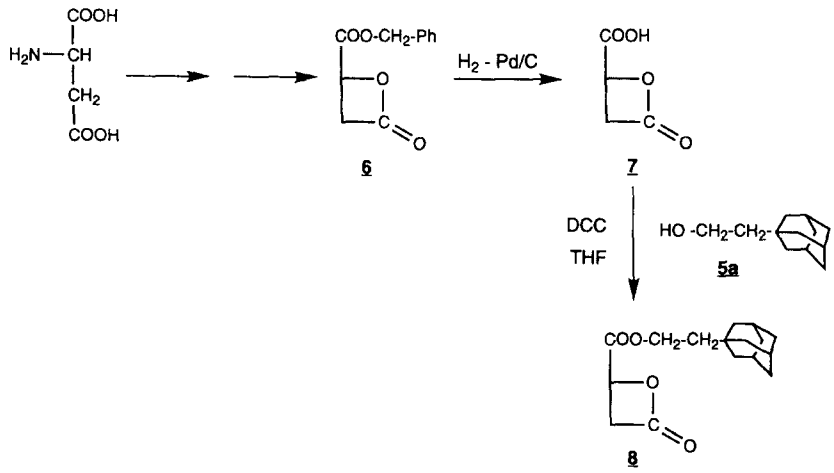


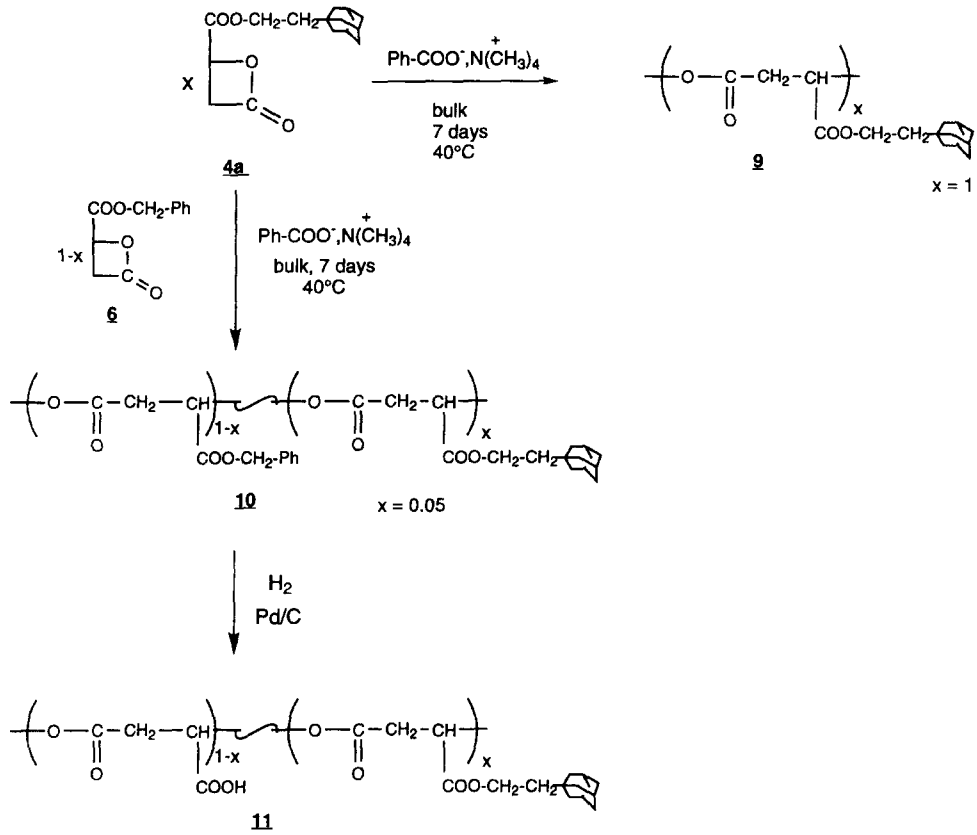
Figure 1 ^{1}H n.m.r. spectra (200 MHz) in $CDCl_3$ of: (a) ethyladamantyl malolactonate (**4a**) and (**8**); (b) butyladamantanamide malolactonate (**4b**)

catalytic hydrogenolysis can be conducted on a large scale. This technique is under extension to other adamantyl malolactonic acid esters.

The ethyladamantyl malolactonate (**4a** or **8**) was polymerized according to the usual conditions and has led to the corresponding homopolymer **9** (*Scheme 3*). I.r. spectroscopy has shown the complete disappearance of ethyladamantyl malolactonate. Formation of poly-(ethyladamantyl β-malate) was not evident because of the steric hindrance of the adamantyl group, which could lead to a difficult or impossible polymerization of this lactone. This new functionalized polyester was



Scheme 2 Synthesis of ethyladamantyl malolactonate (**8**) from benzyl malolactonate



Scheme 3 Synthesis of poly(ethyladamantyl β-malate) (**9**) and poly(β-malic acid-*co*-ethyladamantyl β-malate) (**11**)

soluble in chloroform and THF and insoluble in acetone and carbon tetrachloride.

Introduction of an adamantyl moiety into acrylate polymers[16] leads to an increase in the glass transition temperature (T_g = 153°C). Indeed, this rigid pendant group restricts mobility significantly, resulting in an increase in T_g of more than 100°C compared to poly(benzyl acrylate) (T_g = 6°C). Introduction of adamantyl groups into poly(benzyl β-malate) leads to a weaker improvement of thermal properties compared to acrylate polymers. Indeed, poly(benzyl β-malate) presents a T_g at 37°C compared to a T_g of 70°C for poly(ethyladamantyl β-malate). Chains of polyesters are more flexible than those of acrylates.

Besides the possibility of homopolymerizing ethyladamantyl malolactonate, which could be used in the preparation of highly hydrophobic blocks in the building of particular polymeric drug carriers, it is important to have at one's disposal water soluble derivatives. Consequently, ethyladamantyl malolactonate (0.5 eq) was copolymerized with benzyl malolactonate (0.95 eq) under usual conditions (*Scheme 3*). As shown by the ^{1}H n.m.r. spectrum (*Figure 2a*), the composition of poly(benzyl β-malate-*co*-ethyladamantyl β-malate) (**10**) is equivalent to the initial composition in lactones. The glass transition temperature of this copolymer has been determined to be at 20°C by d.s.c. Compound **10** was soluble in acetone, carbon tetrachloride, dioxan, chloroform and THF.

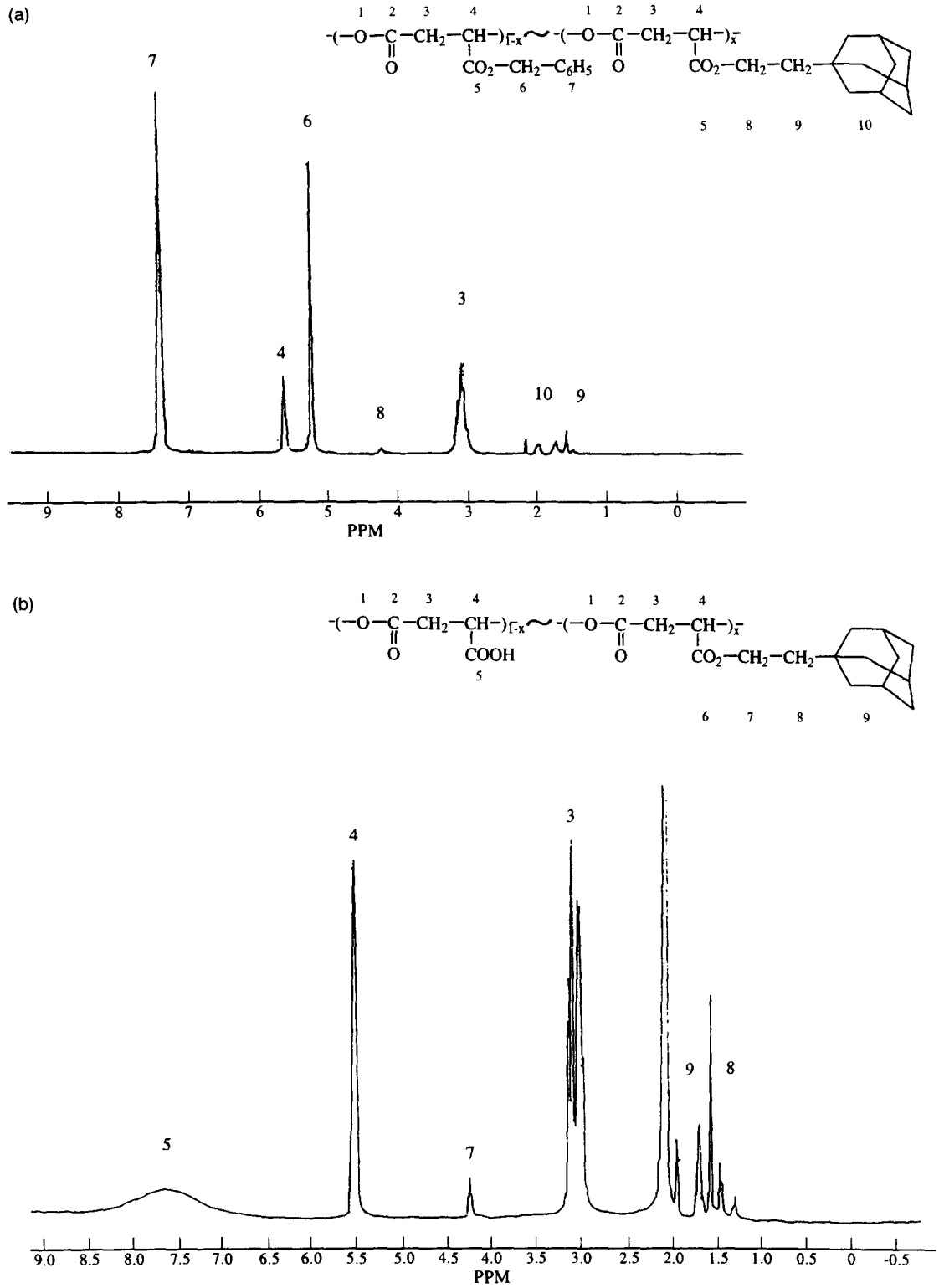


Figure 2 ^{1}H n.m.r. spectra (200 MHz) in CD_3COCD_3 of: (a) poly(benzyl β-malate-*co*-ethyladamantyl β-malate) (**10**); (b) poly(β-malic acid-*co*-ethyladamantyl β-malate) (**11**)

The last stage was the obtaining of poly(β-malic acid-*co*-ethyladamantyl β-malate) **11** by catalytic hydrogenolysis[14] of **10** (*Scheme 3*). As shown by *Figure 2b*, peaks corresponding to the lateral benzyl groups (5.15 and 7.4 ppm) have completely disappeared, thus demonstrating that the deprotection was total. This copolymer was shown to be soluble in water. Moreover, lateral carboxylic acid functions can be used for attachment of biologically active molecules for targeting.

The butyladamantanamide malolactonate **4b** was also homopolymerized and copolymerized with benzyl malolactonate in different proportions. Characterizations of these corresponding polymers are under investigation.

Conclusion

We have shown that alkyladamantyl malolactonates can be synthesized using usual synthesis routes. Moreover, the corresponding homopolymer can be prepared

and characterized. Worth noticing is that a copolymer of ethyladamantyl malolactonate and benzyl malolactonate was obtained and deprotected by catalytic hydrogenolysis to lead to a poly(β-malic acid-*co*-ethyladamantyl β-malate). This polymer is of interest due to its water solubility and to the simultaneous presence of lateral adamantyl groups and carboxylic acid functions.

The preparation and the study of water soluble copolymers containing different proportions of adamantyl groups are under investigation. These copolymers are very important with regard to the control of their degradation rate in relation to the pH of the solution and for introducing hydrophobic interactions with the aim of forming pH dependent hydrogels, therefore leading to intelligent polymeric systems.

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