Degradable Elastomers

DOI: 10.1002/ange.200602096

Main-Chain Bile Acid Based Degradable Elastomers Synthesized by Entropy-Driven Ring-Opening Metathesis Polymerization**

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Despite the tremendous progress made in the field of biomedical engineering, many challenges still remain to be addressed—especially in the design of new materials. The biodegradable synthetic polymers currently used for biomedical applications are almost exclusively based on short aliphatic moieties, such as lactides, glycolides, ε-caprolactone, and sebacic acid, which all display relatively "hard" mechanical properties that adjust poorly to those of tissues, and therefore cause considerable stress mismatches at the interface responsible for necrosis or abnormal regeneration.[1]

Materials based on bile acids show great promise for drug delivery[2] and controlled release[3] applications, and their rigid steroidal backbone and amphiphilicity appear to make them candidates of choice for fine-tuning the mechanical and interfacial properties of synthetic degradable polymers. However, reports on main-chain bile acid based polyesters, polyamides, and polyurethanes are still scarce in the literature, and their synthesis constitutes a real challenge, especially when higher molecular weights are required. Most techniques used to date rely on the use of toxic coupling agents.

Ring-opening polymerization (ROP) is a very versatile technique that has been applied to the synthesis of polyesters with a controlled molecular weight. In virtually all cases, small strained cycles (3–8-membered rings) are used and enthalpy drives the polymerization. However, macrocycles, including those based on esters and alkenes, could be polymerized, and afforded appreciably high molecular weights, depending on the conditions.[4] In these cases, polymerization is driven by entropy, as described by the Jacobson–Stockmayer theory for ring-chain equilibria.[5]

Entropy-driven ring-opening polymerization (ED-ROP) therefore appears to be a method of choice for the synthesis of high-molecular-weight polyesters based on bile acids. Furthermore, the use of this technique means that the use of large amounts of coupling agents often required in polycondensations can be avoided, thus considerably lowering the toxicity of the material. Furthermore, metathesis chemistry has proved to be a powerful tool for both the preparation of macrocycles[6] and the polymerization of alkenes.[3a,7] We describe here the synthesis of novel macrocycles by the simple ring-closure metathesis (RCM) of two flexible chains attached to a bile acid core through ester bonds, and their entropy-driven ring-opening metathesis polymerization (ED-ROMP) using ruthenium-based Grubbs catalysts. The polymers obtained show typical rubberlike elasticity, with elongation moduli that favorably compare to those of soft tissues and elastin[1c,8] (Figure 1) and constitute, to the best of our knowledge, the first example of degradable thermoplastic amorphous elastomers.

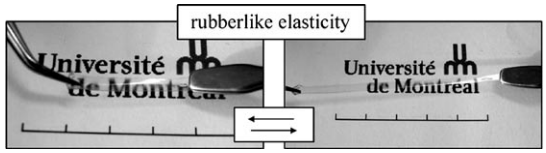

Figure 1. Elongation of a film of polymer **3** (0.1 mm thick) displaying rubberlike elasticity.

Cyclic bile acids **1** (38-membered ring) and **2** (35-membered ring) were synthesized (Scheme 1) in relatively high yields (73 and 59%, respectively) from their corresponding dienes, at high dilution.[9] Cyclic oligomers were also formed during the reaction (which is in agreement with the Jacobson–Stockmayer theory[5a]) as evidenced by MALDI-TOF mass spectrometric analysis.[9] Such high yields in cyclic monomers from an equilibrium reaction are clear indication of the flexibility introduced through the aliphatic chains and the extremely low strain of the macrocycles formed.

ED-ROMP of **1** and **2** at high concentrations using the highly efficient and stable second generation Grubbs catalyst afforded high-molecular-weight polymers in high yields after precipitation from methanol/hexane mixtures (Table 1). In comparison, the acyclic diene metathesis (ADMET) polymerization of the diene precursor of **1** only afforded low-molecular-weight materials with a typical M_n value of 22300.[10] It is thus clear that ED-ROMP, in which only end groups arising from the reaction with the catalyst are present, affords much higher molecular weights than ADMET polycondensation, in which "end groups" must be eliminated from the reaction mixture under vacuum.

The fact that ED-ROMP is a ring-chain equilibrium is perfectly depicted by the increase in the degree of conversion and cyclic oligomer-to-polymer ratio with an increase in the initial concentration of the monomer (Table 1). Higher conversions and lower total amounts of cyclic oligomers are observed at higher concentrations, which are again consistent with the predictions from Jacobson–Stockmayer theory.

Polymers **3** and **4** both display a glass transition temperature T_g below room temperature ($T_g = 2.3 \pm 0.2$ and 14.6 ± 1.0 °C for **3** and **4**, respectively) without any evidence of

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[**] The financial support from the NSERC of Canada, FQRNT of Quebec, and the Canada Research Chair program is gratefully acknowledged. The authors also thank Marc Gauthier for his help and comments on dynamic mechanical analysis measurements.

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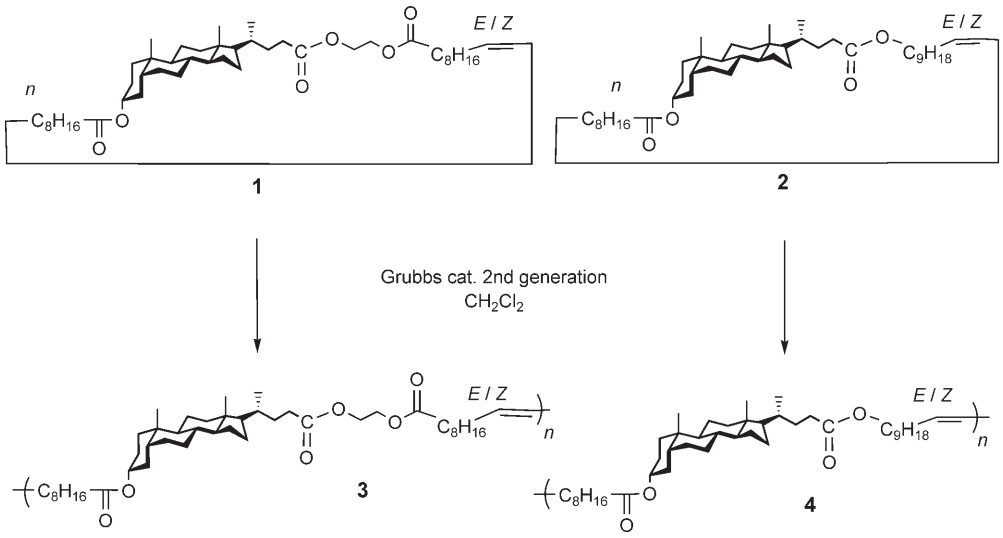

Scheme 1. ED-ROMP of macrocycles **1** and **2** based on bile acids.

Table 1: ED-ROMP of macrocycles **1** and **2** based on bile acids with the 2nd generation Grubbs catalyst (1 mol%) at room temperature.

Monomer	[Monomer] [M]	Conv. [%]	Cycl. olig./ poly.[a]	M_n ($\times 10^3$)[b]	M_w ($\times 10^3$)[b]
1	1.07	98.2	2.4/97.6	151.5	266.5
1	0.23	95.9	5.8/94.2	73.1	121.7
1	0.12	94.3	8.5/91.5	63.8	112.0
2	0.77	98.6	1.4/98.6	146.0	273.5
2	0.13	95.2	9.1/90.9	58.7	106.7

[a] Total cyclic oligomers/polymer ratio determined by GPC.[9] [b] Molecular weights determined by GPC.[10]

melting before decomposition starts to occur, as evidenced by differential scanning calorimetry (DSC). This fact, together with the transparency of films made from these polymers, suggests that these materials are amorphous. The glass transition of the polymer films was also measured by dynamic mechanical analysis (DMA) in the multifrequency mode ($T_g = 12.4 \pm 0.4$ and 19.9 ± 0.6 °C for **3** and **4**, respectively) (Figure 2). Below these temperatures, the materials are relatively hard and brittle ($E = 531 \pm 107$ and 672 ± 150 MPa for **3** and **4**, respectively, at -10 °C), whereas above these temperatures, they display typical rubberlike elasticity ($E = 1.23 \pm 0.06$ and 2.09 ± 0.32 MPa for **3** and **4**, respectively, at 37 °C), with maximum elongations higher than 400% (geometrical limit of the equipment). It is important to stress that **3** and **4** are thermoplastics and that their elasticity behavior is solely due to chain entanglement and weak physical cross-links, as demonstrated by stress-relaxation experiments, which clearly show that stress relaxes to zero over several hours.[9] This property constitutes an important advantage over other thermoplastic degradable materials, since crystalline and amorphous domains are known to degrade at very different rates.[11]

In conclusion, ED-ROMP of macrocycles based on bile acids affords high-molecular-weight polyesters in high yields. The polymers obtained showed typical rubberlike elasticity

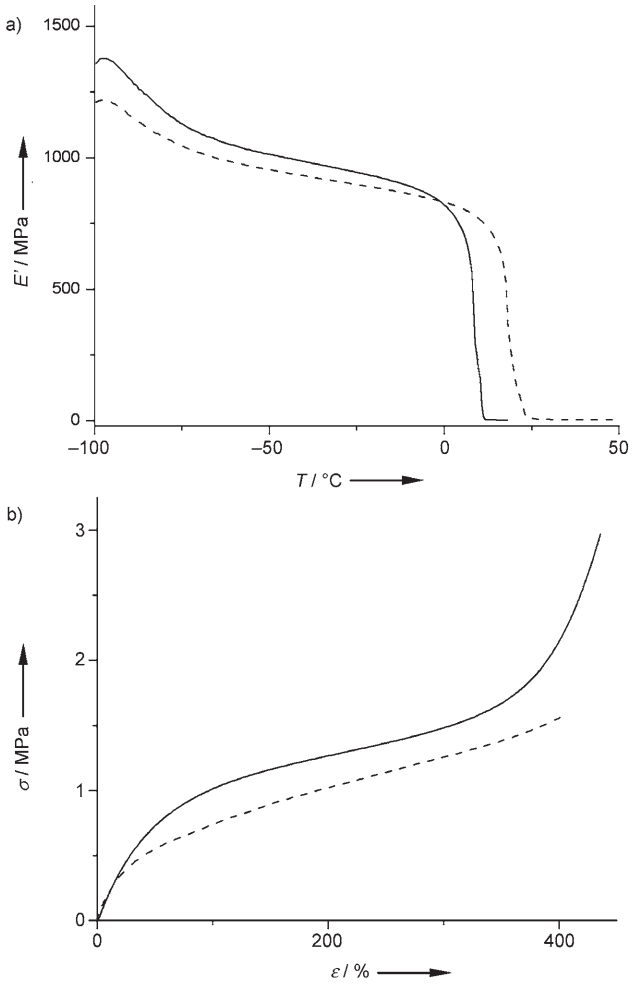

Figure 2. DMA results obtained for films of polymers **3** (solid line) and **4** (dashed line) prepared by evaporation of a CH_2Cl_2 solution (100 mg mL^{-1}) in a mold and subsequent drying in vacuo. a) Multifrequency experiments at 1 Hz; b) stress–strain curves obtained at 37 °C (maximal elongations correspond to travel limits of the equipment geometry rather than elongations at break).

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and constitute the first family of degradable amorphous thermoplastics, with elongation moduli closely matching those of many soft tissues, such as elastic cartilage, aortic heart valves, and aorta.[1c] Moreover, the use of bile acids as rigid moieties should provide low systemic toxicity. The high pK_a value[12] of the ultimate degradation products released after complete hydrolysis of the two polymers synthesized, together with their high molar mass, also ensures low inflammation response arising from a local decrease in the pH value, in contrast to the case observed for smaller acids such as lactic acid.[13] Preliminary results show that polymers **3** and **4** degrade slowly over a period of several months at 37 °C in phosphate-buffered saline solutions, as evidenced by weight loss and a decrease in the molecular weight.

More generally, ED-ROP could prove extremely useful for the synthesis of polyesters, polyamides, or polyurethanes bearing large moieties within the polymer backbone, while avoiding the use of large quantities of toxic coupling agents incompatible with biomedical applications. From an industrial point of view, ED-ROP offers the advantage of releasing no heat, unlike enthalpy-driven polymerizations,[4b] and no volatiles, which allows in situ polymerizations to be carried out in biosystems with, for example, transesterification enzymes. Furthermore, the lower viscosity typical of macrocycles, relative to high-molecular-weight polymers, makes ED-ROP a promising technique for micromolding, a topic of importance for the design of a new generation of biomedical devices.

Received: May 25, 2006
Published online: September 26, 2006

Keywords: bile acids · elastomers · metathesis · polyesters · ring-opening polymerization

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[9] See Supporting Information for experimental procedures, MALDI-TOF, GPC, stress-relaxation data, and ^1H and ^{13}C NMR spectra of polymer **4**.

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