Ring-opening polymerization of 3,6-dimethyl-2,5-morpholinedione with discrete amino-alkoxy-bis(phenolate) yttrium initiators: mechanistic insights†

Pascal M. Castro, Gang Zhao, Abderramane Amgoune, Christophe M. Thomas and Jean-François Carpentier*

Received (in Cambridge, UK) 31st August 2006, Accepted 20th September 2006
First published as an Advance Article on the web 5th October 2006
DOI: 10.1039/b612580h

Alkoxy-amino-bis(phenolate) yttrium amide and alkoxide complexes promote the ring-opening polymerization of (3*S*,6*S*)-dimethyl-2,5-morpholinedione at 60–100 °C *via* a coordination–insertion polymerization mechanism.

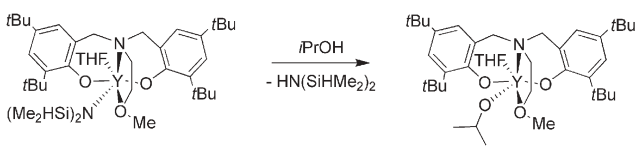
Among the diversity of new biomaterials issued from renewable resources that have emerged in the past few years,[1] polymers synthesized *via* ring-opening polymerization (ROP) of heterocyclic monomers represent a promising category of biodegradable and biocompatible materials.[2,3] ROP of 2,5-morpholinediones—the cyclic dimers of two metabolites found in the human body, α-hydroxy acids and α-amino acids—was first investigated in the mid 80's as an alternative to polycondensation reactions for the synthesis of polydepsipeptides, the alternating copolymers of α-hydroxy acids and α-amino acids.[4,5] Since then, 2,5-morpholinediones with pendant functional groups have been used as comonomers in copolymerization reactions to improve the hydrophilicity of poly(esters) for water-soluble drug encapsulation in controlled drug delivery systems.[6,7] Such copolymers also found applications in the realization of matrix materials used in tissue engineering that requires the presence of specific cell adhesion sites on the polymer surface.[8,9]

In spite of some promising results obtained with enzymatic catalysis,[10–13] the catalyst of choice for the ROP of 2,5-morpholine-diones remains tin(II) octanoate,[4–7,9,13,14] a robust initiator tolerant to oxygen and protic impurities. However, tin(II) octanoate is typically used in melt conditions (above 130 °C), at which temperatures polymerization of 2,5-morpholinediones or its copolymerization with lactide are hampered by a depolymerization process that lowers both the conversion and the molecular mass.[9,13,14] On the other hand, while many efforts have been devoted in the past decade to the rational design of discrete well-characterized metal complexes that act as effective initiators in the controlled ROP of various polar monomers,[15,16] their use in the ROP of 2,5-morpholinediones has scarcely been described.[17]

We have recently reported that yttrium complexes supported by dianionic tetradentate alkoxy-amino-bis(phenolate) ligands are highly active and productive for the controlled ROP of *rac*-lactide[18] and *rac*-β-butyrolactone,[19] exhibiting high stereoselectivities (heterotactic and syndiotactic, respectively). We report herein some preliminary results on the homopolymerization of (3*S*,6*S*)-dimethyl-2,5-morpholinedione (**1**), selected as a model substrate due to its analogy with L-lactide, using alkoxy-amino-bis(phenolate) yttrium amide (**2**) and alkoxide (**3**) complexes as initiators (Scheme 1). Detailed analysis of the resulting polymers by MALDI-TOF-MS and NMR analysis of stoichiometric reactions have also provided mechanistic insights into the ROP of 2,5-morpholinediones with these initiators.

The yttrium bis(dimethylsilyl)amido (**2**) and isopropoxide (**3**) complexes supported by a methoxy-amino-bis(phenolate) ligand that bear bulky *tert*-butyl substituents at the 2 and 6 positions were selected as initiators. Complex **3** was generated *in situ* from **2** by the addition of 3 equiv. of 2-propanol (Scheme 1), according to the reported method.[18] ROP of **1** was first attempted in toluene with **2** and **3** ([**1**]/[Y] = 25) under experimental conditions similar to the ones used in the ROP of lactide,[18] *i.e.* room temperature and [**1**] = 0.44 mol L^{-1}. Representative results are summarized in Table 1. Poor conversions (<5%) were recorded, even after 48 h of reaction (entries 1 and 4, Table 1), while 500 equivalents of lactide are typically polymerized within 1 h under such conditions, confirming that 2,5-morpholinediones do not ring-open as readily as lactides do.[18]‡ An increase of the temperature to 60 °C gave significantly higher conversions: 50% with **2** and up to 85% with **3** after 24 h (entries 2 and 5, Table 1). Noteworthy is that the same experiments carried out in THF at 20–60 °C were unsuccessful with either **2** or **3**. It is assumed that THF, because of the high oxophilicity of Group 3 metals, competes with the 2,5-morpholinedione monomer in coordinating to the metal center. A similar detrimental effect of THF in the rate of ROP reactions promoted by Group 3 metal complexes is often observed, though not systematically.[18,19]

The above results prompted us to examine further the ring-opening ability of **3** by increasing the monomer-to-initiator ratio up to 100 : 1 (entries 3, 6 and 7, Table 1). At 60 °C and after 48 h, a moderate conversion of 55% was observed, which could be enhanced to 74% by increasing the polymerization temperature to



2 **3**

Scheme 1 Yttrium amide (**2**) and alkoxide (**3**) initiators.

Laboratoire Organométalliques et Catalyse, UMR 6226 Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex.
E-mail: jean-francois.carpentier@univ-rennes1.fr;
Fax: +(33)-(0)223 236 939; Tel: +(33)-(0)223 235 950

† Electronic supplementary information (ESI) available: Experimental section and MALDI-TOF-MS spectra of polymers from runs 2 and 6. See DOI: 10.1039/b612580h

Table 1 ROP of (3*S*,6*S*)-dimethyl-2,5-morpholinedione (**1**) by yttrium amide (**2**) and alkoxide (**3**) initiators[a]

Entry	Init.	[**1**]/[Y]	*T*/°C	Time/h	Conv. (%)[b]	$M_{n,\ calc}$[c]	$M_{n,\ exp}$[d]	M_w/M_n[d]
1	**2**	25	20	48	<5	—	—	—
2	**2**	25	60	24	50	1900	438 (495)	1.91 (2.03)
3	**2**	100	100	48	30	4400	5546 (7433)	1.44 (1.32)
4	**3**	25	20	48	<5	—	—	—
5	**3**	25	60	24	85	1100	506 (506)	1.94 (1.94)
6	**3**	100	60	48	55	2700	4042 (5734)	2.20 (2.12)
7	**3**	100	100	48	74	3600	1084 (3214)	2.49 (1.34)

[a] Performed in toluene with [**1**] = 0.44 mol L^{-1}. [b] Determined by ^1H NMR in DMSO-d_6 by integration of the OC*H*CH_3 resonances of **1** and the polymer. [c] Number average molecular weight calculated from the relation = 143.00 × [**1**]/[Y] × conversion, and divided by 3 when *i*PrOH was used. [d] Determined by MALDI-TOF-MS, taking into account all the polymer populations with $M_n = \sum M_i N_i / \sum N_i$ and $M_w = \sum M_i^2 N_i / \sum M_i N_i$; data in parentheses refer to M_n and M_w/M_n values determined by MALDI-TOF-MS, taking into account only the main polymer distribution.

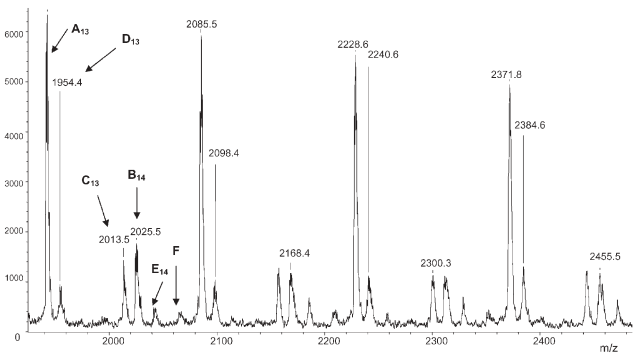


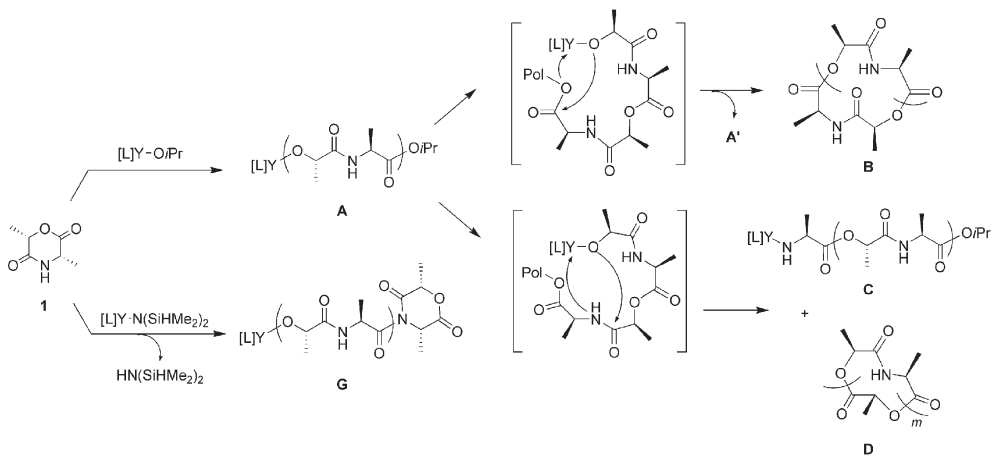
Fig. 1 Detail of the MALDI-TOF-MS spectrum from run 7.

100 °C. ^1H NMR analysis of the polymers in DMSO-d_6 indicated that no racemization of the C*H*-Me chiral centers takes place during the polymerization, even at high temperature.

No relevant SEC analysis could be performed because of the poor solubility of the polymers in the SEC solvent (THF). MALDI-TOF-MS is a more convenient alternative for analyzing the obtained polydepsipeptides.[20] The mass spectra of all the prepared polymers display a major population of polymer chains and some minor distributions (Table 1, Fig. 1; see also ESI†). As a consequence of the heterogeneous polymer population, the molecular weight distributions (M_w/M_n) range between 1.5 and 2.5, and are somewhat narrower when considering only the major polymer population. The experimental number average molecular masses ($M_{n,exp}$) rise up to *ca.* 7400 g mol^{-1}, though the experimental values match only approximately the theoretical ones ($M_{n,calc}$). Increasing the temperature from 60 °C to 100 °C with **3** as the initiator provokes a decrease of the M_n value, whereas the conversion is increased (compare entries 6 and 7, Table 1). This observation contrasts with previous studies on the ROP of 2,5-morpholinediones with tin(II) catalysts in melt conditions, where increasing the temperature diminishes the conversion because of a depolymerization process.[13,14] The decrease of molecular weights is likely indicative of a larger extent of transfer reactions induced by the higher temperature (transamidation, *vide infra*).

Comparison of simulated and experimental MALDI-TOF-MS values shows that the principal polymer population present in the mass spectra obtained from the polydepsipeptides synthesized with **3** can unambiguously be attributed to the sodium adducts of poly(lactic acid–*alt*–alanine) capped with an isopropyl ester and a hydroxyl end group (Fig. 1, Scheme 2). This observation supports the occurrence of a classical coordination-insertion mechanism as it is known in lactide polymerization, with cleavage of the acyl–oxygen bond after the nucleophilic addition of the isopropoxide initiating group on the ester carbonyl carbon.[16]§

The presence of secondary distributions indicates the incidence of side reactions during the polymerization process. Similar to ROP of lactides, inter- and intramolecular transesterification reactions are likely to take place.[16] However, unlike polylactides, intermolecular transesterifications cannot be ascertained by



Scheme 2 Polymerization of **1** and side reactions.

MALDI-TOF-MS experiments, as the resulting chain possesses the same overall structure as the original chain (A, Scheme 2). On the other hand, the presence of cyclic oligomers resulting from intramolecular transesterification can be unequivocally established in both runs 6 and 7 (B, Scheme 2). Two additional peak distributions¶ are observed in the MALDI-TOF-MS spectrum of run 7 (C and D, Fig. 1), which correspond to an intramolecular transamidation reaction leading to a yttrium-amide propagating species (C) and cyclic polymers (D) (Scheme 2). This unique transamidation side-reaction appears to be favored at higher temperature, as the corresponding peaks are not present in the MALDI-TOF-MS spectrum of run 6 (60 °C). This observation is consistent with the above mentioned decrease of molecular weights at high temperature (entry 7, Table 1).

In order to clarify the nature of the initiation process, the 1 : 1 reaction of yttrium alkoxide **3** with **1** was monitored by ^{1}H NMR spectroscopy. The addition of one equivalent of **1** to a C_6D_6 or a toluene-d_8 solution of **3** at room temperature resulted in the rapid disappearance of the white crystals of **1** into the solution indicating that a reaction occurred, **1** being insoluble in either toluene or benzene at room temperature. The resulting ^{1}H NMR spectrum featured mainly broad resonances, suggesting the presence of aggregated species. In addition, a sharp doublet was observed at δ 0.89 ppm, which is consistent with an isopropyl ester end-group,[21] as well as two signals at δ 3.57 and 1.40 ppm assigned to free THF. The latter observation indicates that the THF ligand in **3** has been displaced from the yttrium coordination sphere and suggests intra- or intermolecular coordination of carbonyl oxygens to the yttrium center. After removal of the solvent and other volatiles like excess isopropanol and $HN(SiHMe_2)_2$, a better-quality ^{1}H NMR spectrum was obtained in THF-d_8, showing a signal at δ 1.12 ppm and a septuplet at δ 4.85 ppm, both consistent with an isopropyl ester end-group, thus confirming a coordination-insertion mechanism.

The MALDI-TOF-MS spectra of the polymers obtained with **2** as the initiator exhibit a major population of polymer molecules corresponding to cyclic oligomers B, similar to what was observed in the ring-opening polymerization of lactides with a yttrium bis(dimethylsilyl)amide initiator.[21] The absence of $N(SiHMe_2)_2$ end-capped oligomers in the spectra prompted us to undertake the ^{1}H NMR monitoring of the reaction between **1** and **2**. The addition of 1 equiv. of **1** to a C_6D_6 or toluene-d_8 solution of **2** at room temperature leads to the quantitative release of free THF and $HN(SiHMe_2)_2$. The $Y–N(SiHMe_2)_2$ bond is obviously sensitive to traces of protic impurities that may be present in the monomer, but the release of free amine $HN(SiHMe_2)_2$ would not be quantitative in this case. Rather, $HN(SiHMe_2)_2$ is generated by the aminolysis of $Y–N(SiHMe_2)_2$ by the relatively acidic monomer **1**, creating a new Y–N moiety which is the actual active species (Scheme 2) and produces 2,5-morpholinedione end-capped polymers, consistent with the MALDI-TOF-MS spectra.

In conclusion, we have demonstrated the ability of a single-site yttrium isopropoxide initiator to promote the ring-opening polymerization of (3*S*,6*S*)-dimethyl-2,5-morpholinedione. To our knowledge, this is the first example to date of a well-defined transition metal alkoxide initiator able to polymerize a 2,5-morpholinedione at a temperature below 100 °C.

We gratefully acknowledge the CNRS (post-doctoral position for P. M. C.) and the Région Bretagne (COPOBIO and POLYBIOMAT grants) for financial support, and Clémence Guillaume for her assistance in initial investigations.

Notes and references

‡ A 10% conversion was observed with **2** as initiator, [**1**]/[Y] = 100, in THF, to yield a polymer with M_n = 5000 g mol^{-1} and M_w/M_n = 1.63, as determined by MALDI-TOF-MS. However, analysis of the MS spectrum showed a α,ω-hydroxy terminated polymer, probably because of water contamination.

§ A polymer bearing a benzyloxy and an hydroxyl end group was obtained when **1** was polymerized with Sn(II) octanoate in the presence of benzyl alcohol (**1**–Sn–BnOH = 100 : 1 : 1). See ref. 17.

¶ Two additional, though minor, distributions were also observed in both MALDI-MS spectra (**E**, **F**, Fig. 1). The first one (**E**) was clearly assigned to a α,ω-hydroxy carboxylic acid end-capped polymer.

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