Dialkylgallium alkoxides – a tool for facile and stereoselective synthesis of PLA–drug conjugates

M. Cybularczyk-Cecotka,a b R. Zaremba,a b A. Hurko,c A. Plichta,c M. Dranka,c and P. Horeglad a,b†

Herein, a method for the synthesis of PLA-(β-blocker) conjugates with a tunable stereostructure of the PLA fragment is demonstrated using stereoselective [R2Ga(μ-β-blocker)]2 catalysts and [R2Ga(μ-OR)]2/H-(β-blocker) catalytic systems for the ring-opening polymerisation (ROP) and immortal ring-opening polymerisation (iROP) of racemic lactide (rac-LA), respectively.

The growing interest in polylactide (PLA) – a biodegradable and biocompatible polymer – is due to its numerous applications, ranging from packaging to medical materials including PLA–drug conjugates and PLA-based drug delivery systems. While PLA–drug conjugates could be synthesized, among others, by the polymerisation of lactide using non-toxic Zn3 and Mg4 complexes, a catalyst was crucial for the modification of the PLA structure and properties of the PLA–drug conjugates.3a However, although the tacticity of PLA can affect its physicochemical properties,5 including the degradation rate of PLA–drug conjugates,6 both the synthesis of PLAs of different stereostructures, including PLA copolymers built of blocks of different tacticity,7 and their use in order to tailor the drug release properties of PLA–drug conjugates or drug delivery systems based on PLA,6,8 are in their infancy. We have shown that dialkylgallium catalysts [R2Ga(μ-OR)]2, which constitute a rare example of gallium catalysts for the polymerisation of lactide or other cyclic esters,9 can catalyse the polymerisation of rac-LA to PLA in a controlled and stereoselective manner,10 leading to a non-cytotoxic PLA.6 Dialkylgallium alkoxides exhibit unique features with regard to the stereoselective polymerisation of rac-lactide (rac-LA). In this case the addition of a Lewis base (LB), such as pyridines or THF, to non-selective [R2Ga(μ-OR)]2 complexes resulted in the formation of heteroselective [R2Ga(μ-OR)]2/LB catalytic systems offering tuneable heterogeneous selectivity in the range of 0.5 < Pl < 0.85 (Pl = probability of racemo linkages in PLA).10,11 On the other hand, the addition of N-heterocyclic carbenes or organosuperbases to [R2GaOR]2 led to isoselective species, resulting in a facile stereoselectivity switch,12,13 which allowed for the synthesis of stereodiblock PLA copolymers.13 Therefore [R2Ga(μ-OR)]2, which exhibits low reactivity towards different functional groups,14 should be considered as an interesting catalyst for the synthesis of PLA–drug conjugates, additionally offering easy modification of the tacticity/stereostructure of PLA. We hereby demonstrate that PLA-(β-blocker) conjugates with a tunable stereostructure of the PLA can be synthesized by the polymerisation of rac-LA with [R2Ga(β-blocker)]2 (Scheme 1a) or stereoselective [R2Ga(β-blocker)]2/LB catalysts. Importantly, we also show that dialkylgallium alkoxides can be applied for the stereoselective immortal ring-opening polymerisation (iROP) of rac-LA. In this case [R2Ga(μ-OR)]2/H-(β-blocker) (Scheme 1b) and [R2Ga(μ-OR)]2/H-(β-blocker)/LB catalytic systems offer a facile and stereoselective synthesis of PLA-(β-blocker) conjugates.15,15

In order to confirm the structure of [R2Ga(β-blocker)]2, active species in the ROP of lactide, we investigated the synthesis, structure and activity of [Me2Ga(μ-OCHRCH2NHr)]2 (R = H, R’ = Me (1); R = H, R’ = iPr (2); R = CH2OPh, R’ = iPr (3)) in the ROP of rac-LA, where HOCHRCH2NHr mimics the main skeleton of β-blockers16 (Scheme 2). For 1–3, which were isolated as colourless crystals, the X-ray analysis revealed the presence of dimers in the solid state (Fig. 1, see the ESI† for the structure of 1 and 2). Although, the dimeric structure of 1–3 is typical for [Me2Ga(OX)]2, where (OX) represents a monoanionic alkoxide bidentate ligand with Lewis base functionality,14 the lack of reactivity of the secondary amine group of A–C towards Ga–Me is noteworthy prior to further synthesis of PLA-(A–C) as well as PLA-atenolol conjugates (see below). Noteworthily, a weak Ga–N bond to the fifth coordinate site of gallium was observed for 1–3, while the Ga–N bond distances increased in the order 1 (2.333(4) Å) < 2 (2.359(1) Å) < 3 (2.548(1) Å) with growing steric hindrances on the R and R’ substituents.
of the growing PLA chain with gallium,\textsuperscript{10} should not affect the insertion of lactide into the Ga–O\textsubscript{alkoxide} bond of 1–3 or any other [Me\textsubscript{2}Ga(\beta-blocker)]\textsubscript{2}, which is advantageous in comparison with e.g. analogous aluminium complexes, which form considerably stronger chelate bonds with both Lewis base functionalities of alkoxide ligands or growing PLA chains.\textsuperscript{17} Furthermore, the weakest Ga–N bond for 3, in which the structure of C mimics a whole main skeleton of \(\beta\)-blockers, indicates that the insertion of lactide into the Ga–O\textsubscript{alkoxide} bond of any [R\textsubscript{2}Ga(\beta-blocker)]\textsubscript{2}, should be facilitated in comparison with model 1 or 2 complexes. Finally, the propagating species in the \textit{rac}-LA polymerisation with 1–3 should be similar to propagating species in the case of [Me\textsubscript{2}Ga(\mu-OCH\textsubscript{2}CH\textsubscript{2}NHiPr)],\textsuperscript{11,13a} and therefore allow for the stereoselective polymerisation. Our reasoning was confirmed by the activity and stereoselectivity of compound 2 in the ROP of \textit{rac}-LA (Table 1).

Compound 2 catalysed polymerisation of \textit{rac}-LA at 40 °C and 70 °C showing similar activities and stereoselectivities to diallylgallium alkoxides already reported by us.\textsuperscript{10,11,13a} Importantly, the interaction of a secondary amine group of OCH\textsubscript{2}CH\textsubscript{2}NHiPr, typical for \(\beta\)-blockers, with gallium neither had an adverse effect on the activity of the investigated catalysts nor affected the insertion of \textit{rac}-LA into the Ga–O\textsubscript{alkoxide} bond. The latter led to the essentially exclusive formation of HO–PLA–OCH\textsubscript{2}CH\textsubscript{2}NHiPr, which was clearly evidenced by MALDI-TOF spectroscopy (see the ESI†). Importantly, the heterostereoselective polymerisation of \textit{rac}-LA with 2/pyridine and 2/DMAP catalytic systems leading to the heterotactically enriched PLA up to \(P_{r}\) of 0.85 (Table 1, entries 3 and 4), as well as isoselective polymerisation using 2/DBU (\(P_{r} = 0.22\), Table 1, entry 5), indicated the facile modification of the tacticity of PLA, in the range of \(P_{r}\) between 0.22 and 0.85, for HO–PLA–OCH\textsubscript{2}CH\textsubscript{2}NHiPr and potentially HO–PLA–(\(\beta\)-blocker) conjugates. Although the approach presented on Scheme 1a and discussed above indicates the possibility of the synthesis of PLA–(\(\beta\)-blocker) conjugates, it would not be the most convenient one, e.g. due to possible reactivity of drugs towards Me\textsubscript{3}Ga. Therefore we focused on the possibility of the synthesis of [R\textsubscript{2}Ga(\beta-blocker)]\textsubscript{2} catalytic centres using the immortal ring-opening polymerisation (iROP) of lactide with [Me\textsubscript{2}Ga(\mu-OR)]\textsubscript{2}/H–(\(\beta\)-blocker) catalytic systems (Scheme 1b).

As the structures of 1–3 were similar, both in the solid state and solution (see the ESI†), to [Me\textsubscript{2}Ga(\mu-OCH(Me)CO\textsubscript{2}Me)]\textsubscript{2}, which mimics active centres in the ROP of lactide,\textsuperscript{10,11} we expected that PLA–drug conjugates could be synthesized due to insertion of lactide into the Ga–O\textsubscript{alkoxide} group of 1–3, moreover, in a stereoselective fashion. In this case, the weak Ga–N chelate bond, as well as Ga–O–C resulting from the interaction

![Scheme 1](https://example.com/scheme1.png)

**Scheme 1** Synthesis of PLA–(\(\beta\)-blocker) conjugates with [Me\textsubscript{2}Ga(\(\beta\)-blocker)]\textsubscript{2} catalytic centres using ROP (a) and iROP (b) of \textit{rac}-LA. H–(\(\beta\)-blocker) represents a skeleton characteristic for \(\beta\)-blockers,\textsuperscript{16} and \(\beta\)-blocker represents a respective alkoxide anion with a deprotonated OH group. OR represents an alkoxide group.

![Scheme 2](https://example.com/scheme2.png)

**Scheme 2** Synthesis of [Me\textsubscript{2}Ga(\mu-OCHR\textsubscript{2}CH\textsubscript{2}NHR')]\textsubscript{2} (1–3).

![Figure 1](https://example.com/figure1.png)

**Fig. 1** Molecular structure of 3 with ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond length (Å) and angles (deg): Ga(1)–O(1) 1.9452(11), Ga(1)–O(1)\textsubscript{i} 2.0717(11), Ga(1)–C(4) 1.9648(18), Ga(1)–C(5) 1.9578(18), Ga(1)–N(1) 2.5478(14), N(1)–Ga(1)–O(1)\textsubscript{i} 152.51(5), O(1)–Ga(1)–O(1)\textsubscript{i} 77.12(5), Ga(1)–O\textsubscript{1}–Ga(1)\textsubscript{i} 101.21(5); i = 1 – x, +y, 3/2 – z.
Although metal complexes have been shown to polymerise rac-LA in an immortial and stereoselective fashion in the presence of aromatics, \[\text{Me}_2\text{Ga(OR)}_2\] /ROH have not been demonstrated so far to catalyse the iROP of heterocyclic monomers. In order to demonstrate the possibility of the synthesis of PLA-[ð-blocker] conjugates using immortal ring-opening polymerisation (iROP) of rac-LA with \[\text{Me}_2\text{Ga(OR)(Me)}_2\]/(H- or B-), we focused on \[\text{Me}_2\text{Ga(OR)(Me)}_2\]/[H/A] or [H/B] as well as \[\text{Me}_2\text{Ga(OR(OMe))}_2]/[H/B], [H/C] or H-atenolol ([ð-blocker]) catalytic systems. Notably, dialkyllgallium alkoxides and aryloxides are not prone to the reaction with alcohols leading to the evolution of alkane and formation of dialkoxide or trialkoxide gallium species.\(^\text{14}\) On the other hand, the exchange of alkoxide groups between dialkyllgallium alkoxides and alcohol added should lead in the case of \[\text{Me}_2\text{Ga(OCH(Me)CO}_2\text{Me)}]/[H/A] or [H/B] as well as \[\text{Me}_2\text{Ga(OCH(OMe))}_2]/[H/B], [H/C] or H-atenolol to the presence of both \[\text{Me}_2\text{Ga(OCH(Me)CO}_2\text{Me)}]/[H/A] or [H/B] complexes, as well as \[\text{Me}_2\text{Ga(OR)}_2]/\text{Me}_2\text{Ga(OR(OMe))}_2/\text{Me}]/[H/A] or [H/B].\(^\text{11}\) The formation of the latter catalytic centres resulted in the formation of PLA-A, PLA-B, PLA-C, as well as PLA-atenolol conjugates (Table 2).

\[\text{Me}_2\text{Ga(OCH(Me)CO}_2\text{Me)}]/[H/B] polymerised rac-LA at 40 °C and 70 °C, which led to the formation of both HO-PLA-[ð-blocker] and HO-PLA-B chains, as evidenced by MALDI-TOF spectroscopy (see the ESI). Moreover, the presence of PLA chains of similar \(M_n\) as shown by GPC, indicated the presence of equilibrium and quick exchange of alkoxide groups OCH(Me)CO\(_2\)Me and H-B at the gallium centre under polymerisation conditions. However, as the molecular weight of the end groups of the resulting HO-PLA-[ð-OCH(Me)CO\(_2\)Me] (104.1 Da) and HO-PLA-B (103.2 Da) chains were almost the same, we confirmed the formation of both HO-PLA-[ð-OCH(Me)CO\(_2\)Me] and HO-PLA-B using \[\text{Me}_2\text{Ga(OCH(Me)CO}_2\text{Me)}]/[H/A] (see Fig. S69 and S70, ESI). On the other hand, the polymerisation of rac-LA with \[\text{Me}_2\text{Ga(OCH(OMe))}_2]/[H/B] led to the formation of essentially only HO-PLA-B chains indicating essentially no insertion of rac-LA into the Ga-ð-aryloxide bond of \[\text{Me}_2\text{Ga(OCH(OMe))}_2]\] under the investigated conditions. The activity of \[\text{Me}_2\text{Ga(OCH(OMe))}_2]/[H/B] was almost the same as in the case of \[\text{Me}_2\text{Ga(OCH(Me)CO}_2\text{Me)}]/[H/B] which was in line with the formation of \[\text{Me}_2\text{Ga(B)}\] species. The formation of dimeric catalytic species allowed for the heterogeneous polymerisation of rac-LA using both \[\text{Me}_2\text{Ga(OCH(OMe))}_2]/[H/B] (pyridines and \[\text{Me}_2\text{Ga(OCH(Me)CO}_2\text{Me)}]/[H/B]/pyridines) (Table 2, entries 3, 4, 6–8), which is in agreement with the mechanism of heterogeneous polymerisation of rac-LA with dialkyllgallium alkoxides recently suggested by us.\(^\text{11}\) The latter suggests an increase in heteroselectivity observed in the case of...
The facile synthesis of PLA–drug conjugates, using as an example entry 13). Importantly, the results discussed above clearly show that heteroselective polymerisation of rac-LA with dialkyllgallium alkoxides in the presence of a Lewis base works also under iROP conditions with [Me₂Ga]₂/[ROH]/LB catalytic systems. Although [Me₂Ga([H]OC₆H₄OMe)]₂/[(H-B)]DBU (1:2:2) led to predominantly isotactic PLA (Pᵣ = 0.22), both GPC and MALDI-TOF were in this case inconclusive for the controlled and immortal nature of rac-LA polymerisation (see the ESIF).

We confirmed also the possibility of the synthesis of PLA-[β-blocker] conjugates using [Me₂Ga([H]OC₆H₄OMe)]₂/(H-C) (Table 2, entries 9 and 10) as well as [Me₂Ga([H]OC₆H₄OMe)]₂/H-atenolol (Table 2, entries 11–13). In both cases the formation of essentially only HO-PLA-C or HO-PLA-atenolol (Fig. 2) under applied polymerisation conditions was evidenced by MALDI-TOF (see the ESIF). Finally, both controlled and heteroselective iROP of rac-LA, as well as facile modification of the stereostructure of PLA, was demonstrated by the synthesis of the HO-(atactic-PLA)-b-(heterotactically enriched-PLA)-atenolol conjugate (Table 2, entry 13).

We showed that dialkyllgallium alkoxides can be applied for the facile synthesis of PLA-drug conjugates, using as an example the synthesis of HO-PLA-[β-blocker] conjugates in the presence of [R₂Ga([β-blocker])₂] catalytic centres. Moreover, the stereostructure of the PLA fragment of HO-PLA-[β-blocker] can be easily tuned by the simple modification of the catalytic system. Importantly, the use of [R₂Ga([OR])₂]/[H-[β-blocker]] for the synthesis of HO-PLA-[β-blocker] demonstrated for the first time that dialkyllgallium alkoxides/aryloxides can be used in the immortal ROP of lactide. The latter opens new synthetic pathways of both PLA-drug conjugates and PLA copolymers of novel architectures. Both are currently being investigated in our research group.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

This work was financially supported by the Foundation for Polish Science, IMPULS competition within SKILLS project, Grant No. 150/UD/SKILLS/2015, cofinanced by the EU European Social Fund.