Functionalized polyesters from organocatalyzed ROP of gluOCA, the *O*-carboxyanhydride derived from glutamic acid†

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Well-controlled poly(α-hydroxyacids) featuring pendant carboxylic acid groups were prepared under mild conditions *via* DMAP-catalyzed ROP of the *O*-carboxyanhydrides derived from glutamic and lactic acids.

Over the last three decades, biodegradable synthetic polyesters, and especially poly(lactic acid) (PLA), have received increasing attention as resorbable biomaterials as well as commodity thermoplastics derived from renewable resources.[1] Concomitantly, various systems, including well-defined metal complexes and organocatalysts, have been developed to promote the efficient ring-opening polymerization (ROP) of lactide (the cyclic dimer of lactic acid) under mild conditions and in a highly controlled fashion.[2] Current efforts in this area are also devoted to the introduction of various pendant groups on the polymer backbone. Indeed, it is necessary to vary and finely tune the physico-chemical properties of poly(α-hydroxyacids) in order to extend their application further. In this regard, *n*-alkyl and phenyl substituents were shown to affect strongly the glass transition temperature (T_g ranging from −40 to 90 °C *vs.* ~45 °C for PLA) and degradation rate of poly(α-hydroxyacids).[3] The introduction of pendant functional groups is also highly desirable in order to impart hydrophilicity and to allow post-polymerization derivatization with biologically relevant compounds.[4–11] However, such modulations are so far complicated by the moderate accessibility[12] and poor reactivity of the required 1,4-dioxane-2,5-diones. Indeed, the homo- and co-polymerization of 1,4-dioxane-2,5-diones **1**–**3**[5–7] derived from aspartic and glutamic acids (Fig. 1) do not systematically proceed to high monomer conversion even under harsh conditions, and the density of pendant carboxyl groups in the resulting polymers does not exceed 50% (so far, **2**, but neither **1** nor **3**, could be efficiently homopolymerized).

In this context, we have recently reported that the ROP of L-lacOCA (the *O*-carboxyanhydride derived from lactic acid) catalyzed by DMAP (4-dimethylaminopyridine) proceeds much faster than that of lactide (typically within a few minutes at room temperature *vs.* a few days at 35 °C), and affords PLA of controlled molecular weights and narrow polydispersities.[13] These promising results prompted us to investigate further the use of *O*-carboxyanhydrides as activated equivalents of 1,4-dioxane-2,5-diones, and we report here the synthesis, characterization and polymerization of L-gluOCA, the *O*-carboxyanhydride derived from glutamic acid. Well-controlled homo- and co-polymers featuring pendant carboxylic acid groups are shown to be accessible under mild conditions *via* DMAP-catalyzed ROP.

The functionalized monomer L-gluOCA was prepared in two steps from γ-benzyl L-glutamic acid (Scheme 1). Diazotization with sodium nitrite in aqueous acetic acid[14] first led to the corresponding α-hydroxy acid, namely γ-benzyl 2-hydroxyglutaric acid. Subsequent treatment with dicyclohexylamine (DCHA) and diphosgene in the presence of polystyrene-supported diisopropylethylamine (PS-DIEA) afforded L-gluOCA in 45% overall yield with an optical purity >95% (as determined by HPLC after derivatization with (+)-α-methylbenzyl amine).[15] L-gluOCA was characterized by elemental analysis, mass spectrometry, NMR spectroscopy and X-ray diffraction analysis.‡ Notably, its five-membered ring adopts a perfectly planar conformation, whereas more or less flattened boat arrangements were found for 1,4-dioxane-2,5-diones.[7,16]

The homopolymerization of L-gluOCA was then investigated with the same organocatalytic system (ROH/DMAP) than that used previously for the ROP of L-lacOCA.[13] Poly(L-glu) with degree of polymerization (DP) up to 100 were prepared under mild conditions (room temperature in dichloromethane) using *n*- or *neo*-pentanol as initiator (Scheme 2, Table 1). The reaction times required to achieve complete conversion of L-gluOCA are similar to those observed for L-lacOCA,[13] meaning that, in marked contrast with that reported for dioxane-diones,[5–7] the lateral functional group does not significantly affect the reactivity of OCAs. Notably, the molecular weights (M_n) of the poly(L-glu) samples increase linearly with the monomer to initiator ratio, and their

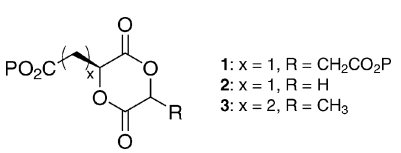

Fig. 1 1,4-Dioxane-2,5-diones featuring pendant carboxyl groups (P = protecting group).

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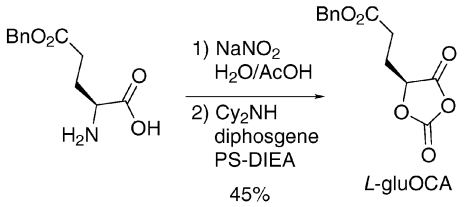


Scheme 1 Synthesis of L-gluOCA from γ-benzyl L-glutamic acid.

Table 1 Polymerization of L-gluOCA with the ROH/DMAP system[a]

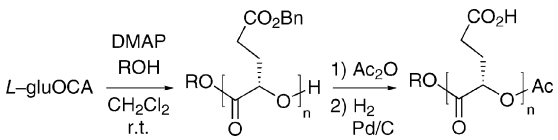
Initiator	M_0/I_0	t/min	DP[b]	M_n[c]	M_w/M_n[c]
Neo-PentOH	15	<5	15	3000	1.16
Neo-PentOH	20	<5	20	3500	1.19
Neo-PentOH	50	5	52	6300	1.18
Neo-PentOH	75	20	74	14 900	1.14
Neo-PentOH	100	90	103	18 300	1.18
n-PentOH	10	<5	9	2260	1.24
n-PentOH	20	<5	21	3290	1.25
n-PenOH	50	5	50	6290	1.18

[a] Polymerizations in CH_2Cl_2 at 25 °C with an initiator to catalyst ratio of 1. In all experiments, conversions were higher than 96%. [b] Calculated by relative integration of the corresponding ^{1}H NMR signals (polymer and ester chain end). [c] Obtained from Size Exclusion Chromatography (in THF) using polystyrene standards.

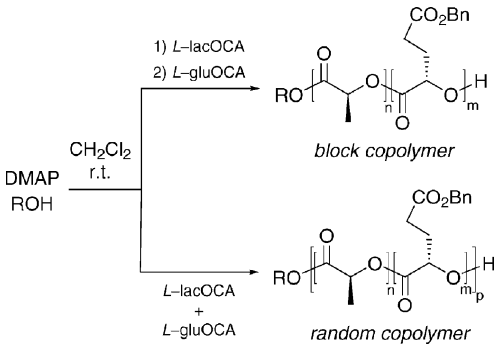
polydispersities are fairly low (M_w/M_n 1.14–1.25) up to high monomer conversion. In addition, quantitative incorporation of the initiator as an ester chain end was demonstrated by ^{1}H NMR spectroscopy and MALDI-MS spectrometry, and the formation of perfectly isotactic polymers was indicated by ^{13}C NMR spectroscopy.[15]

After acetylation of the terminal hydroxyl group with acetic anhydride, the pendant carboxyl groups of poly(L-glu) were deprotected by hydrogenolysis. The complete removal of the benzyl protecting groups was deduced from the disappearance of all of the aromatic signals from the ^{1}H NMR spectrum. In addition, SEC analyses showed that neither the acetylation reaction nor the deprotection step affected the polymer backbone.[15]

The copolymerization of L-gluOCA and L-lacOCA was then investigated (Scheme 3). The access to block copolymers was first studied by successive ROP of both monomers. A PLA macroinitiator with M_n = 1140 g mol^{-1} and M_w/M_n = 1.24 was prepared by the ROP of 20 equiv. of L-lacOCA initiated with *n*-pentanol. Polymerization was then restarted by addition of 10 equiv. of L-gluOCA to afford a copolymer with M_n = 2540 g mol^{-1} and M_w/M_n = 1.23 (Table 2). The formation of the diblock copolymer upon addition of L-gluOCA is accompanied by the disappearance of the quartet signal at 4.34 ppm associated with the terminal PLA-C*H*OH proton in the ^{1}H NMR spectrum.[15]



Scheme 2 ROP of L-gluOCA and deprotection of the pendant carboxyl groups.



Scheme 3 Block and random copolymerization of L-gluOCA and L-lacOCA.

Table 2 Block and random copolymerization of L-gluOCA (M) and L-lacOCA (M') with the ROH/DMAP system[a]

Initiator	$M_0 : M'_0 : I_0$	$M : M'$[b]	M_n[c]	M_w/M_n[c]
n-PentOH[d]	0 : 20 : 1	—	1140	1.24
	10 : 0 : 1	1 : 1.9	2540	1.23
n-PentOH	1 : 10 : 1	1 : 10.9	1130	1.38
n-PentOH	2 : 10 : 1	1 : 5.1	1560	1.33
n-PentOH	10 : 10 : 1	1 : 1	2800	1.38
Neo-PentOH	45 : 55 : 1	1 : 1.1	11 600	1.30

[a] Polymerizations in CH_2Cl_2 at 25 °C with an initiator to catalyst ratio of 1 : 1. In all experiments, conversions were higher than 96%. [b] Calculated by relative integration of the corresponding ^{1}H NMR signals. [c] Obtained from size exclusion chromatography (in THF) using polystyrene standards. [d] Block copolymerisation.

Given their similar reactivities toward homopolymerization, the random copolymerization of L-gluOCA and L-lacOCA was then considered as a promising route to PLA functionalized with pendant carboxyl groups all along the polymer backbone. Accordingly, various random copolymers were synthesised with L-gluOCA : L-lacOCA ratios ranging from 1 : 10 to 1 : 1. In all cases, the monomer composition in the copolymer was in close agreement with the initial feed (Table 2). The random character of the polymer was supported by ^{13}C NMR spectroscopy[15] and the conditions used for the deprotection of the pendant carboxyl groups of the homopolymer also proved effective for the copolymers. In

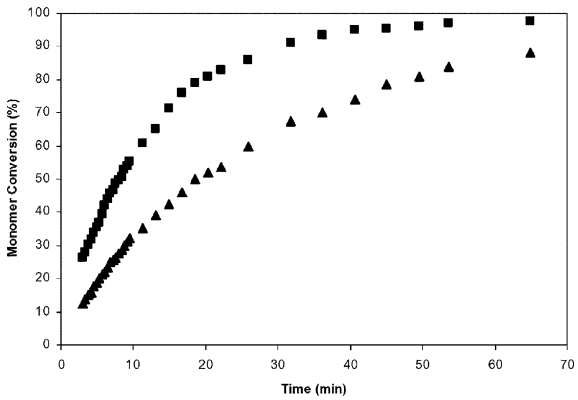


Fig. 2 Conversion of L-gluOCA and L-lacOCA *vs.* time during random copolymerization.

addition, the co-polymerisation of L-gluOCA (45 equiv. relative to *neo*-pentanol used as initiator) and L-lacOCA (55 equiv.) was monitored *in situ* by ^{1}H NMR in order to compare the polymerization rate of both monomers (Fig. 2). Accordingly, the functionalized monomer L-gluOCA proved slightly more reactive than L-lacOCA (50% conversion being reached in approximately 8 and 19 min, respectively). This behavior markedly contrasts with the pronounced deactivation induced by the introduction of pendant functional groups to the 1,4-dioxane-2,5-dione core. Indeed, only moderate monomer conversions (<30%), resulting in low molecular weight polymers (M_n < 3000 g mol^{-1}), have been reported for the ROP of the malic acid dimer **1**.[5] Similar limitations were encountered with the unsymmetrical monomer **3** derived from glutamic acid: homopolymerization proceeds with only 29% conversion, and no more than 14% of the functional monomer is incorporated upon copolymerization with lactide.[7]

In conclusion, the functionalized *O*-carboxyanhydride L-gluOCA exhibits remarkable reactivity compared with related 1,4-dioxane-2,5-diones. Its DMAP-catalyzed ROP proceeds under mild conditions and with a high level of control, giving access to homopolymers as well as block and random copolymers featuring pendant carboxyl groups.[17]

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Notes and references

‡ *Crystal data* for L-gluOCA. $C_{13}H_{12}O_6$, M = 264.23, orthorhombic, space group $P2_12_12_1$, a = 5.6733(14), b = 7.7930(19), c = 27.552(7) Å, V = 1218.1(5) Å^3, T = 173(2) K, Z = 4, 4778 reflections collected (1466 independent, R_{int} = 0.1047), 172 parameters, R_1 [$I > 2\sigma(I)$] = 0.0536, wR_2 (all data) = 0.1012.

1 For general reviews dealing with the applications of PLA, see: (*a*) R. E. Drumright, P. R. Gruber and D. E. Henton, *Adv. Mater.*, 2000, **12**, 1841; (*b*) A.-C. Albertsson and I. K. Varma, *Biomacromolecules*, 2003, **4**, 1466; (*c*) R. Auras, B. Harte and S. Selke, *Macromol. Biosci.*, 2004, **4**, 835; (*d*) S. Mecking, *Angew. Chem., Int. Ed.*, 2004, **43**, 1078.

2 For general reviews dealing with the preparation of PLA, see: (*a*) B. J. O'Keefe, M. A. Hillmyer and W. B. Tolman, *J. Chem. Soc., Dalton Trans.*, 2001, 2215; (*b*) O. Dechy-Cabaret, B. Martin-Vaca and D. Bourissou, *Chem. Rev.*, 2004, **104**, 6147; (*c*) D. Bourissou, S. Moebs-Sanchez and B. Martin-Vaca, *C. R. Chim.*, 2007, **10**, 775; (*d*) N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer and J. L. Hedrick, *Chem. Rev.*, 2007, **107**, 5813.

3 For alkyl- and aralkyl-substituted poly(α-hydroxyacids), see: (*a*) M. Yin and G. L. Baker, *Macromolecules*, 1999, **32**, 7711; (*b*) T. L. Simmons and G. L. Baker, *Biomacromolecules*, 2001, **2**, 658; (*c*) T. Liu, T. L. Simmons, D. A. Bohnsack, M. E. Mackay, M. R. Smith III and G. L. Baker, *Macromolecules*, 2007, **40**, 6040; (*d*) F. Jing, M. R. Smith III and G. L. Baker, *Macromolecules*, 2007, **40**, 9304.

4 (*a*) X. Lou, C. Detrembleur and R. Jérôme, *Macromol. Rapid Commun.*, 2003, **24**, 161; (*b*) C. K. Williams, *Chem. Soc. Rev.*, 2007, **36**, 1573.

5 T. Ouchi and A. Fujino, *Makromol. Chem.*, 1989, **190**, 1523.

6 (*a*) Y. Kimura, K. Shirotani, H. Yamane and T. Kitao, *Macromolecules*, 1988, **21**, 3338; (*b*) Y. Kimura, K. Shirotani, H. Yamane and T. Kitao, *Polymer*, 1993, **34**, 1741; (*c*) T. Yamaoka, Y. Hotta, K. Kobayashi and Y. Kimura, *Int. J. Biol. Macromol.*, 1999, **25**, 265.

7 W. W. Gerhardt, D. E. Noga, K. I. Hardcastle, A. J. Garcia, D. M. Collard and M. Weck, *Biomacromolecules*, 2006, **7**, 1735.

8 For hydroxyl-functionalized poly(α-hydroxyacids), see ref. 7 and (*a*) J. Y. Yang, J. Yu, H. Z. Pan, Z. W. Gu, W. X. Cao and X. D. Feng, *Chin. J. Polym. Sci.*, 2001, **19**, 509; (*b*) M. Leemhuis, J. H. van Steenis, M. J. van Uxem, C. F. van Nostrum and W. E. Hennink, *Eur. J. Org. Chem.*, 2003, 3344; (*c*) M. Leemhuis, C. F. van Nostrum, J. A. W. Kruijtzer, Z. Y. Zhong, M. R. ten Breteler, P. J. Dijkstra, J. Feijen and W. E. Hennink, *Macromolecules*, 2006, **39**, 3500; (*d*) C. A. M. Loontjens, T. Vermonden, M. Leemhuis, M. J. van Steenbergen, C. F. van Nostrum and W. E. Hennink, *Macromolecules*, 2007, **40**, 7208; (*e*) M. Leemhuis, J. A. W. Kruijtzer, C. F. vanNostrum and W. E. Hennink, *Biomacromolecules*, 2007, **8**, 2943.

9 For 1,4-dioxane-2,5-diones featuring pendant oligo(ethylene oxide) groups, see: X. Jiang, M. R. Smith III and G. L. Baker, *Macromolecules*, 2008, **41**, 318.

10 For 1,4-dioxane-2,5-diones derived from D-gluconic acid, see: K. Marcincinova-Benabdillah, M. Boustta, J. Coudane and M. Vert, *Biomacromolecules*, 2001, **2**, 1279.

11 Morpholine-diones have also been used to prepare functionalized poly(ester-amides). For selected references, see: (*a*) P. J. A. in't Veld, P. J. Dijkstra and J. Feijen, *Makromol. Chem.*, 1992, **193**, 2713; (*b*) D. A. Barrera, E. Zylstra, P. T. Lansbury, Jr and R. Langer, *J. Am. Chem. Soc.*, 1993, **115**, 11010; (*c*) P. J. Dijkstra and J. Feijen, *Macromol. Symp.*, 2000, **153**, 67.

12 Self-condensation of α-hydroxyacids is practically limited to symmetrical volatile dioxane-diones. The preparation of unsymmetrically-substituted monomers by step-by-step condensation of an α-hydroxy acid and an α-haloacyl halide usually requires carefully-controlled conditions in order to avoid undesirable oligomerization reactions during the final cyclization step.

13 (*a*) D. Bourissou, O. Thillaye du Boullay, E. Marchal and B. Martin-Vaca, *Int. Pat.*, WO2006037812, April 13, 2006; (*b*) O. Thillaye du Boullay, E. Marchal, B. Martin-Vaca, F. Cossío and D. Bourissou, *J. Am. Chem. Soc.*, 2006, **128**, 16442.

14 S. Deechongkit, S.-L. You and J. W. Kelly, *Org. Lett.*, 2004, **6**, 497.

15 See ESI† for details.

16 (*a*) G. J. Van Hummel, S. Harkema, F. E. Kohn and J. Feijen, *Acta Crystallogr., Sect. B*, 1982, **38**, 1679; (*b*) V. W. Lynch, J. Pojman, J. K. Whitesell and B. E. Davis, *Acta Crystallogr., Sect. C*, 1990, **46**, 1125; (*c*) M. Bolte, H. Beck, M. Nieger and E. Egert, *Acta Crystallogr., Sect. C*, 1994, **50**, 1717; (*d*) M. H. Chisholm, N. W. Eilerts, J. C. Huffman, S. S. Iyer, M. Pacold and K. Phomphrai, *J. Am. Chem. Soc.*, 2000, **122**, 11845; (*e*) H. Kooijman, M. Leemhuis, C. F. van Nostrum, W. E. Hennink and A. L. Spek, *Acta Crystallogr., Sect. E.*, 2005, **61**, o898, o901 and o3480.

17 D. Bourissou, O. Thillaye du Boullay and B. Martin-Vaca, *Int. Pat.*, WO2007113304, October 11, 2007.

