Sustainable synthesis of zwitterionic galactaric acid monoamides as monomers of hydroxylated polyamides

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ABSTRACT
A new and sustainable preparation of zwitterionic monoamides of galactaric acid is reported. The protocol consists of an efficient conversion of aldaric acid into the corresponding lactone and its further reaction in the presence of diamines, leading to the formation of the corresponding zwitterionic monoamides in high yields and selectivity. The zwitterions have been used as monomers to obtain the corresponding polyhydroxyamides. The overall protocol has shown a high atom economy, and all the carbon atoms present in the reagents are preserved.

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Introduction
Nowadays, green and sustainable chemistry has become an area of major interest for the scientific community.\(^1,2\) In this context, the use of waste biomass from agriculture represents a great opportunity to obtain biosourced chemicals and materials.\(^3-6\)

Aldaric acids are dicarboxylic acids derived from the oxidation of aldoses. Due to their chemical nature and renewable origin, aldaric acids exhibit a great potential as monomers or building blocks for the synthesis of bio-based polymers, especially hydroxylated polyesters and polyamides.\(^7,8\) Recently, cationic copolymers based on galactaric acid diamide were also prepared as delivery systems for small interfering RNA.\(^9\)

The products of the polycondensation between aldaric acids and diamines are known as polyhydroxypolyamides (PHPAs) or “Hydroxylated Nylons."\(^10\) In terms of environmental concern, those compounds have gained much attention due to the renewable nature of the carbohydrate backbone of the monomer unit and to their high degradability in soil,
when compared with the classic nylon or with poly(ethylene terephthalate).[11,12]

Some examples of PHPAs prepared from aldric acid derivatives and diamines were first reported by Wolform et al.[13] via the reaction of fully acetylated galactaroyl chlorides and diamines, followed by deprotection of the hydroxyl groups. Later on, Ogata found that the esters of aldric acids readily reacted with a diamine to give the corresponding polyhydroxypolyamide under mild condition in polar solvents without the need of using protecting groups.[14–17] Much is now known about PHPAs also due to the effort of Kiely et al. who had prepared a great variety of those compounds and deeply investigated both the effects of the reaction conditions on the resulting degree of polymerization (DP) and their physical and chemical properties. From a synthetic point of view, PHPAs are obtained by using derivatives of glucaric, mannaric, and xylaric acid lactones, whereas in the case of galactaric acid only its diesters were used as building blocks (Figs. 1a,b).[10,18–22]

It is well known that the critical factor for a polymerization reaction is to achieve a perfect 1:1 ratio between the two monomers. To meet this requirement, galactaric ester diammmonium salts[23] or mono glucararamide sodium salts were used to prepare PHPAs.[18]

Here we report a new, selective and efficient protocol to prepare galactaric acid monoamides, present in zwitterion form, bearing both a carboxylic group and an amino group, that can be directly used as bifunctional monomers in the preparation of PHPAs (Fig. 1c), allowing a perfect and easy control of the 1:1 ratio between the carboxylic and amine functions. The proposed protocol does not require the protection/activation of the
substrates, neither the use of catalysts, and only water is released during the process and all the carbon atoms present in the starting reagents are preserved in the final polymers. Moreover, the overall process shows a high atom economy ranging from 87% to 90% depending on the polymer obtained.

It is reported that galactaric acid, also known as mucic acid, undergoes cyclization in aqueous solution,\(^{[24,25]}\) giving only the corresponding \(\gamma\)-lactone. To the best of our knowledge, only one article in 1956 reported the isolation of galactarolactone in a solid form.\(^{[26]}\) The lactone should be more reactive with respect to the open chain dicarboxylic acid form, but this reactivity was not fully investigated. For this purpose, a simple and easy synthesis of galactaro-1,4-lactone (Fig. 1c) was developed first.

**Results and discussion**

\(\gamma\)-Galactarolactone 2 was prepared in quantitative yield by heating galactaric acid 1 in DMSO at 140 \(^\circ\)C for 30 min (Sch. 1). Their \(^1\)H and \(^{13}\)C NMR spectra in DMSO-d\(_6\) are reported in Supplementary Information (Figs. S3 and S4). The stability of the \(\gamma\)-galactarolactone solution was measured over time and it showed a good stability, giving about 3% of hydrolysis within 4 months (see Supplementary Information, Fig. S34). Heating the DMSO solution of \(\gamma\)-lactone 2 and diamines with stirring at 30–60 \(^\circ\)C provided the corresponding zwitterionic galactaric acid monoamides 3a–d in high yields (Sch. 1).

This procedure represented an advantage because the purification of the intermediate lactone was not required, and the two steps could be performed as a telescoped process starting from mucic acid. Thus, zwitterions 3a–d (Table 1) were obtained by this protocol and were stored under an inert atmosphere. Generally, during the reactions, there was the formation of precipitates, and all the experiments were stopped when the precipitation appeared to be complete.

The reaction in the presence of ethylenediamine was performed at 30 \(^\circ\)C (Table 1, entry 1) and gave a high yield within 2 h, whereas the yields obtained with 1,6-diaminohexane both at 30 and 40 \(^\circ\)C (entries 2 and 3) were still not complete after overnight, as about of 10% of reagents were
still present. The best yield in isolated 3b was achieved within 18 h of the experiment performed at 60 °C (entry 4). The reactions of 1,8-diaminooctane (entry 5) and 2,2′-(ethylenedioxy)bis(ethylamine) (entry 6) gave very good yields at 40 and 30 °C, respectively.

Zwitterions 3a–d were isolated and then characterized by NMR, FT-IR, MS, and TGA-DTA analyses. The 1H NMR spectrum of 3a and assignments of its protons are reported in Supplementary Information (Fig. S1 and Table S1). The three signals at 4.47, 4.23, and 3.99 ppm, respectively, corresponding to the four protons of the galactaric moiety appear as broad singlets, and the chemical shifts of the proton H-2, H-3, and H-4 are very similar to the corresponding protons of galactaric acid salt (Fig. S35). In particular, the signals of the protons on both carboxylic \( \alpha \)-C’s show the same chemical shift. The signal of the methylene protons in \( \alpha \) position to the ammonium group is at a higher frequency compared with that of the pure ethylenediamine as expected for a protonated amine, while the signal of methylene protons in \( \alpha \) position to the nitrogen of the amide group is at 3.59 ppm. The 1H NMR spectrum of 3a, acquired in the presence of a base, showed that both signals of the diamine moiety were shifted to a lower frequency (Supplementary Information, Fig. S36) confirming the presence of the monoamide as a zwitterionic form. Based on these data, the protons of zwitterions 3b-d were assigned (Supplementary Information, Table S1). The chemical shifts of alkyl chain protons of the amine moiety are very similar to those reported in the literature for aminohexyl glucaramide.\(^{27}\)

The TGA-DTA analyses of the four zwitterions (Supplementary Information, Figs. S30–S33) have shown that, except for highly pure 3a, the degradation of the zwitterions takes place generally at a temperature above 130 °C. For this reason, subsequent polymerizations were performed at 125 °C (measured inside the reaction mixture).

The zwitterion 3a prepared from galactaric acid and ethylenediamine was then suspended in DMSO (0.9 mol/L) and heated at 125 °C under

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**Table 1. Synthesis of zwitterions 3a–d in DMSO.**

| Entry | Diamine | \( T (\degree C) \) | \( t (h) \) | Product (isolated yield) |
|-------|---------|---------------------|-----------|-------------------------|
| 1     | H₂N—NH₂ | 30                  | 2         | 3a (92%) |
| 2     | H₂N—NH₂ | 30                  | 18        | 3b (70%)\(^a\) |
| 3     | H₂N—NH₂ | 40                  | 18        | 3b (80%)\(^a\) |
| 4     | H₂N—NH₂ | 60                  | 18        | 3b (85%) |
| 5     | H₂N—O—O—NH₂ | 40      | 7         | 3c (97%) |
| 6     | H₂N—O—O—NH₂ | 30      | 6         | 3d (90%) |

\(^a\)Presence of unreacted lactone 2 and diamine.
vigorous stirring. The system was heterogeneous due to the low solubility of the monomer in the solvent. After 16 h, a sticky solid was formed. Acetonitrile was added to the mixture and the resulting suspension was stirred at room temperature overnight. The solid was then filtered off, washed, and analyzed to confirm the formation of the corresponding polymer 4a. The same protocol was applied to preparing polyamides 4b-d from zwitterions 3b-d (Fig. 2).

It is noteworthy that 3a, when isolated in high purity (absence of traces of solvent), became nonsoluble in the solvent used for polymerization and the reaction did not take place. A possible explanation of this behavior could be related to the strong hydrogen bonds present in the highly pure solid as observed for pure galactaric acid and its polymers. To overcome this problem, we decided to use the 3a–d directly obtained from the filtration. In this way, the residual DMSO present in the solid has the effect to reduce the attitude of the zwitterionic molecules to form strong interactions.

Polymers 4 were characterized by NMR and FT-IR. The spectra of polymers 4b,c were acquired using TFA-d as a solvent and compared with those reported in the literature. The spectra of polymers 4a,d were acquired in D2O and compared with those of the corresponding zwitterions to identify the terminal groups (Fig. 3). 1H NMR data of all polymers and signal assignments are reported in Supplementary Information (Table S2).

In particular, regarding 4a, the three signals of the polymer chain protons appear as broad singlets in the spectrum (Fig. 3a). The small signals at 3.19 and 3.59 ppm have been assigned to the protons of –CH2NH3+ and –CONHCH2– of the ending groups, respectively, since they show the same chemical shifts of the corresponding protons of zwitterion 3a. 1H NMR signal assignment of 4a is described in detail in Supplementary Information (Fig. S2).

The DP’s values of 4a–d were calculated by means of 1H NMR analysis of the isolated polymer (Figs. S25–S28) using the formula $\text{DP} = (R + 1)/2$ reported in the literature, where R is the ratio between the integral of the methylene protons in $\alpha$ to the internal amide and the integral of the methylene protons in $\alpha$ to the terminal nitrogen atom. All the data (yields, DP, $M_n$) for polymers obtained at 125 °C are summarized in Table 2.
The polymer 4a was prepared using two different concentrations 0.9 mol/L (entry 1) and 0.2 mol/L (entry 2), respectively, of monomer 3a, which gave substantially similar results. The polymerization of zwitterions 3b–d

Figure 3. Comparison of the $^1$H NMR spectra of (a) 4a vs. 3a and (b) 4d vs. 3d.
The propensity of aldaric acids to form the corresponding lactones plays a key role in the overall protocol, as the formation of \( \gamma \)-galactarolactone \( 2 \) allows to obtain selectively the corresponding monoamide in the presence of one equivalent of diamine. Under these conditions, the reaction would proceed through the formation of an intermediate lactone salt, which undergoes ring opening by the free amino group, to achieve the desired monoamide as zwitterion. The mechanism was investigated for the reaction between \( 2 \) and 1,6-diaminohexane (Sch. 2).

As expected, the \(^1\)H NMR analysis of a sample withdrawn during the reaction showed the presence of signals due to the presence of an intermediate compatible with the structure of \( 5b \) (Sch. 2), which evolved to zwitterion \( 3b \). To isolate and identify \( 5b \), an experiment in more diluted conditions and in the presence of only 0.5 equivalents of diamine at 30 °C was performed and a small amount of that intermediate was isolated. The \(^1\)H NMR spectrum of this product in D\(_2\)O showed a pattern of signals whose coupling constants were substantially the same with respect to those reported for \( \gamma \)-galactarolactone DABCO salt,\(^{28}\) confirming the structure of \( 5b \) (Fig. S24 in Supplementary Information). Thus, under more diluted conditions the reaction results are slower and, at the same time, in the presence of 0.5 eq. of diamine both nitrogen atoms are in major part protonated; therefore, the attack of the free amine on the lactone salt \( 5b \) and its conversion to the final zwitterion \( 3b \) is inhibited.

### Table 2. Polymerization of 3a–d at 125 °C in DMSO.

| Entry | Monomer | Polymer | Yield | DP | \( M_n \) |
|-------|---------|---------|-------|----|---------|
| 1     | 3a      | 4a      | 40%   | 13.2 | 3,107   |
| 2     | 3a      | 4a      | 47%   | 11.6 | 2,732   |
| 3     | 3b      | 4b      | 53%   | 11.5 | 3,353   |
| 4     | 3c      | 4c      | 58%   | 10.9 | 3,484   |
| 5     | 3d      | 4d      | 74%   | 12.7 | 4,107   |

*Calculated by NMR analysis; \(^1\)H NMR spectra in Supplementary Information.

**Scheme 2.** Proposed pathway for the formation of zwitterion \( 3b \) (structures present as racemic mixture).
The polymerization step required a higher temperature to occur. It is known that the polymerization of galactarate ester with ethylenediamine proceeds through a lactone intermediate.\textsuperscript{[22]} Based on the literature, similarly, in our case, the reaction could proceed through the formation of the corresponding lactone amide intermediate (I) formed by the lactonization of the neutral form 3 (Sch. 3). Notice that the formation of the intermediate lactone I was not observed at lower temperatures used for the preparation of all the zwitterions 3a–d.

**Conclusions**

Zwitterionic monoamides of bio-sourced galactaric acid have been easily prepared. For this purpose, an efficient preparation of galactaro-1,4-lactone has been developed and its reaction with a stoichiometric amount of diamines led to the selective formation of the corresponding monoamides. The procedure can be performed through a telescoped reaction without the need to isolate the lactone since the two steps are performed in the same solvent. The monoamides were then submitted to polymerization in DMSO. The use of zwitterions as monomers avoided the control of the 1:1 ratio between the diacid and the diamine. To the best of our knowledge, this is the first time that aldaric acid zwitterionic monoamides are used as monomers in the preparation of polymers. The overall protocol, from galactaric acid to the final polymer, does not require the use of catalysts, neither the activation of the carboxylic function. All the carbon atoms present in the reagents are preserved and water released in the three steps is the only by-product obtained in the overall process, resulting in a very high atom economy. All these features make the synthetic procedure particularly advantageous from a green and sustainable point of view.

**Experimental**

A Bruker AV 400 MHz instrument equipped with a 5 mm multinuclear probe with reverse detection was used to record $^1$H NMR spectra
(400 MHz) and $^{13}$C NMR (100.6 MHz). Sixteen scans were acquired with an acquiring time of 3 s for $^1$H and 512 scans were acquired with an acquiring time of 5 s for $^{13}$C. $^1$H and $^{13}$C chemical shifts ($\delta$) in DMSO-$d_6$ and TFA-$d$ are referred their residual signals (2.50 and 39.4 ppm, respectively, for $^1$H and $^{13}$C spectra in DMSO-$d_6$; 11.50 and 116.6/164.2 ppm, respectively, for $^1$H and $^{13}$C spectra in TFA-$d$). Regarding the spectra acquired in D$_2$O, the references for $^1$H and $^{13}$C chemical shifts ($\delta$) are specified in the experimental data and in the spectra captions. Infrared spectra were acquired in KBr disks; those of zwitterions were recorded with an FT-IR Varian 640 and those of polymers with an FT-IR Bruker Alpha spectrometer. ESI-MS analyses were performed with an Esquire 3000 plus ion-trap mass spectrometer equipped with an ESI source. Thermo gravimetric analyses and DTA curves have been acquired with a Perkin Elmer SDA6000 Simultaneous Thermal Analyzer (30–900°C, air flow = 40 mL/min). All reagents and solvents were purchased from Aldrich and used without any further purification.

**Preparation of the DMSO solution of galactaro-1,4-lactone (2)**

Galactaric acid (50 g, 0.24 mol) and 100 mL of DMSO were placed in a four necked round bottom flask equipped with a mechanical stirrer and a thermometer. The resulting suspension was heated at 140°C under vigorous stirring for 30 min, bubbling N$_2$ in the reaction mixture. Then the mixture was cooled at room temperature, obtaining a slightly brown solution containing the lactone. The concentration was determined as follows: 100 µL of solution were withdrawn, diluted in 0.5 mL of DMSO-$d_6$ and terephthalic acid was added as an internal standard. The solution was analyzed by $^1$H NMR. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.15 (t, 1H, $J=8.7$ Hz), 4.19 (d, 1H, $J=1.7$ Hz), 4.28–4.35 (m, 2H) ppm; $^{13}$C NMR (100.6 MHz, DMSO-$d_6$): $\delta$ 67.0, 72.4, 73.7, 80.6, 173.1 174.2 ppm. ESI-MS (anions, DMSO solution) m/z 190.8 [M – H].

**Synthesis and purification of zwitterions 3a–d**

All the fresh prepared zwitterions were stored under an inert atmosphere.

**6-[N-(2′aminoethyl)]-γ-galactaramide (as zwitter) (3a)**

Lactone 2 (59 mmol, 27 mL of a 2.2 M solution in DMSO) was placed in a round bottom flask and heated to 30°C under stirring. Ethylenediamine (3.97 mL, 59 mmol) was then slowly added by means of a syringe pump, under stirring keeping the temperature below 45°C. At the end of the addition, a sticky solid was formed, and the mixture was kept at 30°C for 2 h.
Then, 80 mL of acetonitrile were added, and the resulting suspension was stirred at room temperature overnight. The beige solid was then filtered, washed with acetonitrile and acetone, and then dried under vacuum obtaining a solid (yield 92%, purity 70% due to presence of solvents). To obtain highly pure 3a, half of the solid was dispersed in 60 mL of water and the resulting suspension was stirred at room temperature overnight. Then, the solid was recovered by centrifugation and washed with 3 × 10 mL of acetone, removing each time the solvent after centrifugation. The resulting white solid was dried under reduced pressure obtaining 5.3 g (21 mmol) of 3a. $^1$H NMR (400 MHz, D$_2$O, reference DMSO 2.71 ppm): δ 3.19 (t, $J = 5.9$ Hz, 2H, H-2'), 3.59 (m, 2H, H-1'), 3.99 (bs, 2H, H-3, and H-4), 4.23 (bs, 1H, H-2), 4.47 (bs, 1H, H-5) ppm; $^{13}$C NMR (100.6 MHz, D$_2$O): 35.6, 38.2, 69.9, 70.1, 70.2, 70.2, 175.6, 178.1; ESI-MS $m/z$ 235.1 [M − H$_2$O], 253.1 [M + H], 275.1 [M + Na]. IR (KBr): 3,300, 3,220, 3,065, 1,661, 1,618, 1,589, and 1,543 cm$^{-1}$.

6-[N-(6'-aminohexyl)]-$
\text{-}$-galactaramide (as zwitterion) (3b)

Lactone 2 (3.30 mmol, 1.50 mL of a 2.2 M solution in DMSO) was placed in a round bottom flask and heated to 60°C under stirring. Hexamethylenediamine (376 mg, 3.24 mmol) was dissolved in 1.0 mL of DMSO and then slowly added to the lactone solution and the resulting mixture was kept at 60°C for 18 h. The obtained precipitate was filtered, washed with acetonitrile (10 mL), methanol (5 mL), and dried under reduced pressure to give 3b as a white solid (856 mg, 2.78 mmol, 85% yield). $^1$H NMR (400 MHz, D$_2$O, reference DMSO 2.71 ppm): δ 1.30–1.45 (m, 4H, CH$_2$CH$_2$), 1.50–1.58 (m, 2H, CONH$_2$CH$_2$CH$_2$), 1.60–1.70 (m, 2H, −CH$_2$−CH$_2$−NH$_3$$^+$), 2.98 (m, 2H, −CH$_2$−NH$_3$$^+$), 3.18–3.36 (m, 2H, H-1'), 3.92–4.02 (m, 2H, H-3, and H-4), 4.23 (bs, 1H, H-2), 4.41 (bs, 1H, H-5) ppm; $^{13}$C NMR (100.6 MHz, D$_2$O, reference DMSO-d$_6$ 39.4 ppm): 24.0, 24.2, 24.5, 25.5, 25.5, 27.0, 27.2, 37.8, 37.9, 38.3, 38.3, 69.7, 70.0, 70.1, 70.2, 70.3, 70.4, 70.6, 74.1, 174.2, 178.2, 178.3, 178.4; ESI MS $m/z$ 309.1 [M + H]. IR (KBr): 3,368, 3,308, 2,937, 2,866, 1,658, 1,618, 1,595, and 1,543 cm$^{-1}$.

6-[N-(6'-aminohexyl)]-$
\text{-}$-galactaramide (as zwitterion) (3b)

The same experiment reported above was repeated at 30 and 40°C, obtaining, respectively, 70% and 80% yield, and both the solid recovered included about 10% of reagents.
6-[N-(2’aminooctyl)]-β-galactaramide (as zwitterion) (3c)

Lactone 2 (1.8 mmol, 0.82 mL of a 2.2 M solution in DMSO) was placed in a round bottom flask and heated to 40 °C under stirring. 1,8-Diaminoctane (260 mg, 1.8 mmol) was dissolved in 1.0 mL of DMSO and then slowly added to the lactone solution and the resulting mixture was kept at 40 °C and left under stirring. A precipitate was formed during the reaction. After 7 h, 25 mL of acetonitrile were added and the mixture was kept under stirring overnight. The solid was filtered, washed with 5 mL of cold ethanol, and dried under reduced pressure obtaining 3c as a white solid (587 mg, 1.75 mmol, 97% yield).

H NMR (400 MHz, D2O, reference DMSO 2.71 ppm): δ 1.28–1.38 (m, 8H, CH2CH2), 1.48–1.57 (m, 2H, CONH2CH2CH2), 1.59–1.69 (m, 2H, –CH2–CH2–NH3+), 2.98 (m, 2H, –CH2–NH3+), 3.18–3.34 (m, 2H, H-1'), 3.92–4.00 (m, 2H, H-3, and H-4), 4.23 (m, 1H, H-2), 4.40 (bs, 1H, H-5) ppm. 13C NMR (100.6 MHz, D2O, reference DMSO 39.4 ppm): 25.9, 26.0, 26.3, 26.5, 27.2, 27.3, 28.5, 28.6, 28.8, 28.9, 29.0, 39.6, 39.7, 40.1, 40.1, 71.3, 71.7, 71.8, 71.9, 72.0, 72.3, 175.7, 175.7, 179.7, 179.8; ESI-MS m/z 337.1 [M + H], IR (KBr): 3,319, 2,932, 2,854, 1,661, 1,620, 1,595, and 1,544 cm−1.

6-[N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)]-β-galactaramide (as zwitterion) (3d)

Lactone 2 (2.94 mmol, 1.34 mL of a 2.2 M solution in DMSO) was placed in a round bottom flask and heated to 30 °C under stirring. 2,2’-(Ethylenedioxy)bis(ethylamine) (435 mg, 2.94 mmol) was then added to the lactone solution. A precipitate was formed during the reaction. After 6 h, 25 mL of acetonitrile were added to the reaction, and the mixture was left under stirring overnight. The solid was filtered and dried under reduced pressure obtaining 3d as a white solid (885 mg, 2.60 mmol, 90% yield).

H NMR (400 MHz, D2O, reference DMSO 2.71 ppm): δ 3.18–3.24 (m, 2H, –CH2–NH3+), 3.40–3.56 (m, 2H, H-1'), 3.61–3.79 (m, 8H, –CH2–O), 3.92–4.04 (m, 2H, H-3, and H-4), 4.23 (bs, 1H, H2), 4.44 (bs, 1H, H-5) ppm. 13C NMR (100.6 MHz, D2O, reference DMSO-d6 39.4 ppm): 37.7, 38.0, 38.1, 65.4, 65.5, 67.9, 68.5, 68.5, 68.6, 69.5, 70.1, 70.2, 70.3, 174.7, 178.3, 178.3 ppm. ESI-MS m/z 341.1 [M + H], IR (KBr): 3,418, 2,920, 1,670, 1,645, 1,596, and 1,524 cm−1.

Reaction of lactone 2 in the presence of 0.5 equivalent of hexamethylene diamine

To a 1.0 M solution of lactone 2 (4.0 mL, 4.0 mmol) kept under stirring at 30 °C, 1.5 mL of a solution containing 232 mg (2 mmol) of hexamethylene diamine in DMSO was added and the reaction mixture was stirred at this
temperature overnight. Acetonitrile (10 mL) was added and the resulting suspension was kept under stirring for 45' and then filtered obtaining 5b (61% yield). The solid was not further purified. $^1$H NMR (400 MHz, D$_2$O, reference DMSO 2.71 ppm): δ 1.41 (m), 1.67 (m), 3.00 (m), 4.22 (d, J = 2.0 Hz), 4.39 (dd, J = 8.4 and 9.2 Hz), 4.58 (dd, J = 2.0 and 8.4 Hz), 4.62 (d, J = 9.2 Hz) ppm.

**Synthesis of poly(ethylene $\beta$-galactaramide) (4a)**

In a closed round bottom flask, 290 mg of 3a was suspended in 1.2 mL of DMSO. The mixture was heated at 125 °C (reaction mixture) and kept at this temperature under stirring for 18 h. Then the reaction was cooled to room temperature and 5 mL of CH$_3$CN were added. The resulting suspension was stirred overnight, and the formed solid was filtered, washed with acetonitrile, acetone, and dried under reduced pressure to obtain 108 mg (40% yield) of 4a. $^1$H NMR (400 MHz, D$_2$O, reference DMSO 2.71 ppm): δ 3.19 (m, ending group H$_d$), 3.44 (m, 4H, H$_a$), 3.59 (m, ending group amide H$_c$), 4.01 (m, 2H, H$_c$), 4.41 (m, 2H, H$_b$) ppm. $^{13}$C NMR (100.6 MHz, TFA-d): δ 41.2, 41.6, 72.9, 73.6, 75.8, 76.5, 178.3 ppm. IR (KBr): 3,343, 2,945, 1,647, and 1,540 cm$^{-1}$.

**Synthesis of poly(ethylene $\beta$-galactaramide) (4a) in diluted conditions**

In a closed round bottom flask, 290 mg (1.13 mmol) of 3a was suspended in 5.6 mL of DMSO. The mixture was heated at 125 °C (reaction mixture) and kept at this temperature under stirring for 18 h. Then the reaction was cooled to room temperature and 5 mL of CH$_3$CN were added. The resulting suspension was stirred overnight, and the formed solid was filtered, washed with acetonitrile, acetone, and dried under reduced pressure to obtain 127 mg (47% yield) of 4a.

**Synthesis of poly(hexamethylene $\beta$-galactaramide (4b)**

In a closed round bottom flask, 200 mg (0.65 mmol) of 3b was suspended in 1.0 mL of DMSO. The mixture was heated at 125 °C (reaction mixture) and kept at this temperature under stirring for 12 h. Then the reaction was cooled to room temperature and 10 mL of acetonitrile were added. The resulting suspension was stirred overnight, and the white solid formed was filtered, washed with 10 mL of ethanol, and dried under reduced pressure obtaining 100 mg (53% yield) of 4b. $^1$H NMR (400 MHz, TFA-d): δ 1.60 (m, 4H), 1.85 (m, 4H), 3.40 (m, ending group H$_d$), 3.64 (m, 4H, H$_d$), 4.73 (m, 2H, H$_c$), 5.17 (m, 2H, H$_b$) ppm. $^{13}$C NMR (100.6 MHz, TFA-d): δ 28.1,
30.3, 43.0, 72.2, 73.6, 177.6 ppm. IR (KBr): 3,345, 2,931, 2,857, 1,636, and 1,542 cm$^{-1}$.

**Synthesis of poly(octamethylene $\delta$-galactaramide) (4c)**

In a closed round bottom flask, 352 mg (0.9 mmol) of 3c was suspended in 2.0 mL of DMSO. The mixture was heated at 125°C (reaction mixture) and kept at this temperature under stirring for 7 h. Then the reaction was cooled to room temperature and a mixture of acetonitrile/water (2:3) was added until a precipitate was formed. The resulting solid was washed with acetone and dried under reduced pressure obtaining 193 mg of 4c (58% yield). $^1$H NMR (400 MHz, TFA-d): $\delta$ 1.45 (m, 8H), 1.73 (m, 4H), 3.30 (m, ending group $H_d$), 3.53 (m, 4H, $H_b$), 4.64 (m, 2H, $H_d$), 5.08 (m, 2H, $H_c$) ppm. $^{13}$C NMR (100.6 MHz, TFA-d): $\delta$ 28.5, 30.4, 30.8, 43.4, 72.1, 73.6, 177.6 ppm. IR (KBr): 3,404, 2,925, 2,853, 1,645, and 1,542 cm$^{-1}$.

**Synthesis of poly(3’,6’-dioxaoctamethylene $\delta$-galactaramide (4d)**

In a closed round bottom flask, 320 mg of 3d (0.9 mmol) was suspended in 1.0 mL of DMSO. The mixture was heated at 125°C (reaction mixture) and kept at this temperature under stirring for 12 h. Then the reaction was cooled to room temperature and to the solution 3 mL of acetonitrile and 2 mL of diethyl ether were added until a precipitate was formed. The solid was filtered under a nitrogen atmosphere obtaining 224 mg of 4d (74% yield). $^1$H NMR (400 MHz, D$_2$O, reference DMSO 2.71 ppm): $\delta$ 3.21 (m, ending group $H_d$), 3.43–3.53 (m, 4H, $H_a$), 3.60–3.72 (m, 8H), 3.96–4.04 (m, 2H, $H_c$), 4.37–4.46 (m, 2H, $H_b$) ppm. $^{13}$C NMR (100.6 MHz, D$_2$O, reference DMSO 39.4 ppm): $\delta$ 69.5, 70.1, 71.3, 71.4, 176.2 ppm. IR (KBr): 3,399, 2,922, 2,872, 1,645, and 1,541 cm$^{-1}$.

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