

# Synthesis of Prepolymers of Poly(glycerol-co-diacids) Based on Sebacic and Succinic Acid Mixtures

Bruno Godinho, Rosana Nogueira, Nuno Gama, and Artur Ferreira\*

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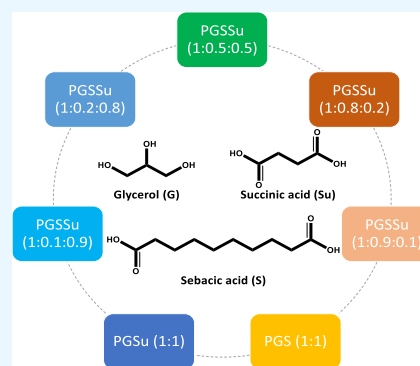
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**ABSTRACT:** In this study, poly(glycerol-co-diacids) prepolymers were produced using different ratios of glycerol (G), sebacic acid (S), and succinic acid (Su) (molar ratios: GS 1:1, GSSu 1:0.9:0.1, GSSu 1:0.8:0.2, GSSu 1:0.5:0.5, GSSu 1:0.2:0.8, GSSu 1:0.1:0.9, GSu 1:1). All polycondensation reactions were performed at 150 °C until reaching a degree of polymerization of  $\approx 55\%$ , inferred by the water volume collected from a reactor. We concluded that the reaction time is correlated with the ratio of diacids used, that is, the increase in succinic acid is proportional to a decrease in the duration of the reaction. In fact, the reaction of poly(glycerol sebacate) (PGS 1:1) is twice as slow as the reaction of poly(glycerol succinate) (PGSu 1:1). The obtained prepolymers were analyzed by electrospray ionization mass spectrometry (ESI-MS) and  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance (NMR). Besides its catalytic influence in poly(glycerol)/ether bond formation, the presence of succinic acid also contributes to a mass growth of ester oligomers, the formation of cyclic structures, a greater number of oligomers detected, and a difference in mass distribution. When compared with PGS (1:1), and even at lower ratios, the prepolymers produced with succinic acid presented mass peak characteristics of oligomer species with a glycerol unit as its end group in higher abundance. Generally, the most abundant oligomers have molecular weights between 400 and 800 g/mol.



## INTRODUCTION

Glycerol-based polyesters have been largely investigated in the last two decades, and they have become an emerging family of bio-based polymers that can be of future help in shifting to a more sustainable way of plastic consumption. Their structural characteristics can be adapted to different requirements, and the possibility of functionalization after polymerization using unreacted hydroxyl groups is a relevant asset.<sup>1,2</sup>

Poly(glycerol sebacate) (PGS) is a well-known glycerol-based polyester, which was first reported as a biocompatible material in 2002.<sup>3</sup> However, PGS was previously reported as a biodegradable material by Nagata et al.<sup>4,5</sup> in 1990s under the term “Yg10”. PGS has received notable attention from the scientific community, and many studies as well as some reviews have been published on the matter.<sup>6–15</sup>

There are other poly(glycerol-co-diacids) described in the literature,<sup>1,2,4,5,16,17</sup> but they received much less interest than PGS. It is the case of poly(glycerol succinate) (PGSu), which has the potential to gain importance in the near future but, so far, only a few scientific publications have focused on reporting its synthesis. Some authors described the synthesis of PGSu using glycerol and succinic acid.<sup>4,5,16,18–23</sup> For example, Nagata et al.<sup>4,5</sup> produced PGSu, named “Yg4”, as well as other poly(glycerol-co-diacids) by polycondensation at very high temperatures ( $\geq 200$  °C) to evaluate the properties of those materials.<sup>4,5</sup> PGSu was obtained by polycondensation at 150 °C to produce internal fixation bone screws.<sup>18</sup> Using Lewis acid (dibutyltin(IV)oxide) as a catalyst, the degree of

branching of polyesters was investigated.<sup>16</sup> Bio-based nonionic surfactants were produced based on PGSu oligomers obtained by polycondensation at 120 °C,<sup>19</sup> and branched PGSu oligoesters were produced at 190 °C.<sup>20,21</sup> Valerio et al.<sup>22</sup> produced PGSu at 180 °C with different sources of glycerol. Based on the same methodology to produce PGSu, Valerio et al.<sup>23</sup> blended it with poly(butylene succinate).

Besides polycondensation, the PGSu molecular structure was also produced with other reagents.<sup>24–28</sup> Succinctly, PGSu produced by succinic anhydride and glycerol was applied as an eco-friendly plasticizer for poly(L-lactic acid) (PLLA) and poly(L-lactide-co-caprolactone) (PLCL).<sup>24</sup> Recently, Wrzeczniak et al.<sup>28</sup> described mathematically the process of PGSu production using succinic anhydride and glycerol. Moreover, PGSu nanogels for dermal delivery were produced from glycidol and succinic anhydride.<sup>27</sup> Dendritic macromolecules with PGSu structures were produced with benzylidene glycerol and succinic anhydride.<sup>25,26</sup>

Finally, there are some other relevant studies, in which PGSu was modified and used in combination with other materials.

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For example, PGSu was combined with maleic anhydride to produce poly(glycerol succinate-*co*-maleate) (PGSMA), a copolymer that has been used in blends with other polymers.<sup>29–32</sup>

In general, the most common way of producing poly(glycerol-*co*-diacids) is based on the esterification of glycerol with diacids without the intervention of a catalyst and using a temperature between 120 and 140 °C.<sup>9</sup> Some research groups adopted higher temperatures (150–230 °C)<sup>4,5,20–23,33–39</sup> and thus were able to produce these polymers faster. However, in our opinion, there is still a need for an attentive evaluation of the influence of temperature in the types of oligomers formed, as well as possible occurrences of side reactions, such as etherification of glycerol resulting in poly(glycerol)ether segments.

When it comes to the characterization of polymers, mass spectrometry analysis is a powerful tool commonly used, and some groups have successfully implemented it to identify ester oligomers. Still, this technique has the potential to offer much more information. For instance, it can be used to obtain data on the nature of the bonds present in the molecule studied like ether bonds between glycerol units.

In one of our previous works, Godinho et al.<sup>40</sup> produced a PGS prepolymer (pPGS) by enzymatic synthesis, using *Candida antarctica* lipase B free (CALB) and lipase B immobilized Novozym 435 (N435) with crude glycerol and “pure” glycerol and later analyzed it by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). This technique did not give us, at the time, evidence of multibranched or hyperbranched mass structures. Therefore, we can say that mass peaks indicative of ether oligomers, or oligomers with ether segments, were not detected, confirming that enzymatic synthesis contributes to a better control of the polymer's linear growth while also preventing undesirable side reactions.

The study by Kafouris et al.<sup>41</sup> is another work worth of enumeration, which explored the synthesis of PGS by changing the glycerol and diacid ratio. To characterize the resulting oligomers, they performed electrospray ionization mass spectrometry (ESI-MS) and processed the obtained data in detail. This work demonstrated that different glycerol and diacid ratios promote changes in the oligomeric composition of prepolymers. Theoretically, the focus should have been put on identifying oligomers produced by esterification between glycerol and sebacic acid. However, they paid attention to other oligomers explained by the 1,5-hydrogen rearrangement of sebacic acid but did not indicate the presence of ether oligomers.

Likewise, Moorhoff et al.<sup>42</sup> chose ESI-MS to analyze the mass of their pPGS. They detected and identified many polyester oligomers, but some of the remaining peaks were ignored. Looking at their data, it is not possible to verify if these peaks can be oligoethers or oligomers with ether bonds.

Also, Ning et al.<sup>43</sup> synthesized pPGS and analyzed it by ESI-MS at different reaction times. They treated the data carefully but did not consider peaks that cannot be explained by esterification of glycerol with sebacic acid ( $\approx m/z$  551 and  $\approx m/z$  625) nor the branched structures like hyperbranched SG(S)S ( $\approx m/z$  644) and branched SG(S)SGS ( $\approx m/z$  901).

Maliger et al.<sup>44</sup> determined the pPGS oligomers produced by MALDI-TOF. They did a more general analysis of the data they collected based on the spacing between peaks, and how that determined the different end groups and growth but never

objectively proceeded to identify the oligomers. Looking at their MALDI data, it is possible to find some mass peaks that correspond, theoretically, to the mass of oligomers with ether bonds between glycerol units. For instance, cyclic GSGSGGGGGG ( $m/z$  961) or cyclic GSGGGGGGGGGG ( $m/z$  998), and cyclic GSGGGGGGGGGG ( $m/z$  1072) at equal distance ( $m/z$  74), could be justified by the peaks in brackets, which were pointed by the authors in their discussion of results.

As a last example, Khongphow et al.<sup>19</sup> produced PGSu and characterized the resulting oligomers by liquid chromatography-mass spectrometry (LC-MS). Their focus was put on looking for peaks that could explain repetitions of glycerol-succinic units (GSu), so it is possible that oligomers produced by side reactions such as etherification were not considered carefully. A quick analysis of their LC-MS data allowed us to find a peak that may indicate the presence of an oligomer with an ether bond GSuGSuGSuGSuGG ( $m/z$  884, positive acquisition with counterion sodium mass).

Therefore, and based on the literature mentioned above, we decided to develop a detailed study using ESI-MS to assess the size, abundance, and types of oligomers formed, with special attention to possible oligomers with ether bonds. Regarding the decision of which reagents to use, it is well known that the poly(glycerol)ether reaction is catalyzed by a strong acid such as sulfuric acid.<sup>45,46</sup> However, the use of a combination of a stronger diacid (succinic acid— $pK_a$  values: 3.83 and 5.13<sup>47</sup>) and a weaker diacid (sebacic acid— $pK_a$  values: 4.72 and 5.45<sup>48</sup>) allowed the additional opportunity to evaluate and compare whether the acidity power of the reagents can increase the presence of oligomers with ether bonds. For that reason, we used seven combinations of glycerol, sebacic acid, and/or succinic acid to produce prepolymers at 150 °C without the use of catalysts. We hope to elucidate on the outcomes of synthesizing poly(glycerol-*co*-diacids) using two diacids simultaneously.

## EXPERIMENTAL SECTION

**Materials.** Glycerol, sebacic acid, succinic acid, and solvents used were purchased from Sigma-Aldrich with 99% purity. Deuterated NMR acetone- $d_6$  (99.9 atom % D) was also from Sigma-Aldrich.

**Synthesis of Prepolymers.** All syntheses were performed at a 1:1 molar ratio of glycerol (G) to diacids [sebacic (S) and/or succinic (Su) acid]. The seven reagents' ratios performed were PGS (1:1), PGSSu (1:0.9:0.1), PGSSu (1:0.8:0.2), PGSSu (1:0.5:0.5), PGSSu (1:0.2:0.8), PGSSu (1:0.1:0.9), and PGSu (1:1). The reactions were executed in batch mode. As an example, in PGSSu (1:0.5:0.5), 35 g of glycerol (0.38 mol), 38.38 g of sebacic acid (0.19 mol), and 22.42 g of succinic acid (0.19 mol) were placed together in a PARR reactor. All of the other ratios followed the same logic, always using 35 g of glycerol.

Prepolymers were synthesized in the PARR reactor with a stainless-steel vessel of 300 mL, and a controller PARR 4843 was used for heating and temperature management. The agitation system was adapted to work with a CAT R100 overhead stirrer with RPM control and torque monitoring.

The reactor system was programmed to execute a temperature ramp of 42 min until it reached 150 °C ( $t_0$ ). Stirring started at 70 RPM until 100 °C and then increased to 100 RPM until the end of the reaction. All reactions took place under  $N_2$  flow to avoid oxidation phenomena and drag the

water resulting from polycondensation out of the reactor. Reactions ended when the degree of polymerization was  $\approx 55\%$  ( $t_{\text{end}}$ ), as measured by the water collected in a 20 mL graduated cylinder in real time, outside the reactor. All reactions used 0.38 mol of diacid molecules so, to achieve a degree of polymerization of  $\approx 55\%$ , we considered half the conversion of carboxylic acid groups into ester bonds, which corresponds to  $\approx 7.5$  mL in water.

### Electrospray Ionization Mass Spectrometry (ESI-MS).

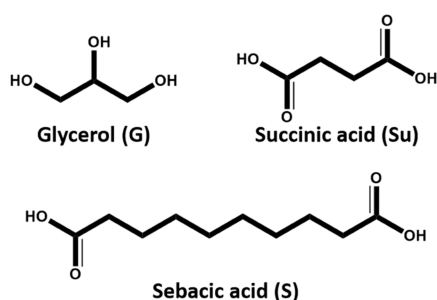
An electrospray mass spectrometer is a linear ion trap mass spectrometer LXQ (ThermoFinnigan, San Jose, CA). Data acquisition and analysis were performed using the Xcalibur Data System (version 2.0, ThermoFinnigan, San Jose, CA).

ESI conditions in the electrospray linear ion trap mass spectrometer (ThermoFinnigan) were as follows: the electrospray voltage was 4.7 kV in negative mode and 5 kV in positive mode; the capillary temperature was 275 °C; and the sheath gas flow was 25 U. Full-scan MS spectra were acquired with a 50 ms maximum ionization time. Mass signals were considered between  $m/z$  200 and 2000 and defined in relative abundance (RA), which means the area of the mass peaks. Prepolymers were dissolved in methanol to obtain a concentration of 1 mg/mL.

**Nuclear Magnetic Resonance (NMR).**  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra were recorded on a Bruker Avance III 300 Hz using acetone- $d_6$  as the solvent. 40 mg of prepolymer samples was dissolved in 0.6 mL of deuterated solvent and transferred to NMR tubes.

## RESULTS AND DISCUSSION

**Prepolymer Synthesis.** Synthesis of PGS, PGSSu, and PGSSu prepolymers was obtained by polycondensation of sebacic acid (S), succinic (Su) acid, or both acids, respectively, with glycerol (G). Chemical representation of each of these three monomers is shown in Figure 1.



**Figure 1.** Monomers used for the prepolymer synthesis: glycerol (G), succinic acid (Su), and sebacic acid (S).

At first, the medium in which these reactions of polycondensation will occur is heterogeneous, so the heating distribution is uneven. Only when low-molecular-weight oligomers are formed, the medium becomes a homogeneous liquid, and thus, the increase in temperature turns uniform. The mentioned reactions of polycondensation were carried out in a reactor equipped with a stainless-steel vessel. Because there is no visibility to its interior, some caution was considered to carry out the experience successfully. Therefore, a 42 min temperature ramp was established until 150 °C was reached since the flash point of succinic acid occurred close to 160 °C.<sup>49</sup> This proved to be a reliable way of not only preventing overheating but also allowing the reaction medium

to achieve a homogeneous liquid state before reaching the final temperature. Also, the existence of a  $\text{N}_2$  flow attested its importance in avoiding the occurrence of secondary reactions such as unwanted oxidations, as well as in expelling any resulting water from the reactor, which in turn becomes the way of estimating the degree of polymerization of the obtained prepolymer. Based on our experience<sup>40</sup> and prior bibliographic knowledge of different physical states of PGS polymers,<sup>50</sup> we decided to perform these reactions only up to a degree of polymerization of  $\approx 55\%$  to avoid gel point and high viscosity prepolymers. At this degree of polymerization, the prepolymers are still easy to dissolve and obtain a homogeneous solution, which allows proper analysis by ESI-MS. The resulting materials are white and very soft waxes at room temperature, like Vaseline, apart from PGSSu prepolymer, which is uncolored and transparent. At 70 °C, all prepolymers are liquids.

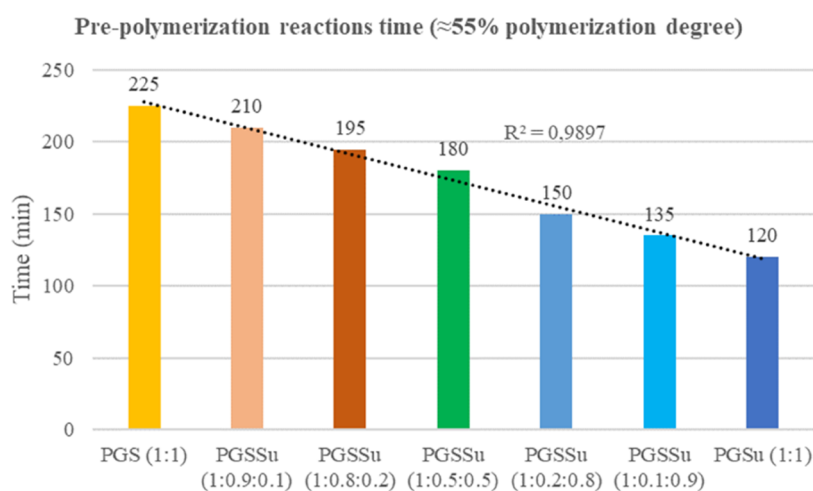
Figure 2 shows the time required to reach a degree of polymerization of  $\approx 55\%$ , which is based on the water collected from the reactor for the seven reagent ratios tested: PGS (1:1), yellow; PGSSu (1:0.9:0.1), light pink; PGSSu (1:0.8:0.2), dark orange; PGSSu (1:0.5:0.5), green; PGSSu (1:0.2:0.8), blue; PGSSu (1:0.1:0.9), light blue; and PGSu (1:1) dark blue. The colors assigned to each prepolymer are arbitrary, and this color scheme is maintained throughout this document and its Supporting Information.

Synthesis of PGS (1:1) required 225 min, being the slowest reaction. On the contrary, the fastest reaction was accomplished when the prepolymer was obtained by total replacement of sebacic acid with succinic acid (PGSu), in 120 min, which almost corresponded to a time reduction by half. In fact, the progressive replacement of sebacic acid with succinic acid promoted a gradual reduction of the reaction time, which we believe that it can be explained by the difference in physicochemical properties of sebacic and succinic diacids.<sup>49,51</sup> For example, succinic acid (C4) is a smaller molecule than sebacic acid (C10), causing a distinct reactivity behavior under the same reaction conditions. In addition, the  $\text{pK}_a$  values are distinct between these acids, as noted above, indicating that succinic acid is stronger. A solid correlation was observed between the sebacic/succinic ratio and the reaction time ( $R^2 = 0.9897$ ) (Figure 2).

**Prepolymer ESI-MS Characterization.** Obtained prepolymers were characterized by positive acquisition ESI-MS (sodium counterion), a very sensitive technique that can acquire a wide range of masses from  $m/z$  200 to  $m/z$  2000. By using this method, we can infer the composition of the oligomers and their structure based on the comparison between their theoretical predictable masses and the acquired mass peaks. Supporting Information Table S8 consists of a list of predicted oligomer masses (organized from dimers to icosamers), and these masses were based on the esterification and etherification reactions between the reactants in Figure 1. Additionally, we gathered all experiment data obtained (from Figures S1–S7) and compiled a list of total oligomers detected for each prepolymer, also available in the submitted Supporting Information, from Tables S1–S7.

Table 1 shows a summary of the number of oligomers identified, organized by bond type (ester, ether, or both), along with some specific structures that can be indirectly assumed through examination of the masses acquired. For instance, ester oligomers were inferred from detected masses that are characteristic of a reaction of esterification between glycerol and diacids. Likewise, ether oligomers were deduced from





**Figure 2.** Reaction time required to achieve a degree of polymerization up to 55%, with the indication of the proportion of each reagent used: PGS (1:1), yellow; PGSSu (1:0.9:0.1), light pink; PGSSu (1:0.8:0.2), dark orange; PGSSu (1:0.5:0.5), green; PGSSu (1:0.2:0.8), blue; PGSSu (1:0.1:0.9), light blue; PGSu (1:1), dark blue.

**Table 1. Summary of the Number of Identified Mass Peaks Obtained by Positive Acquisition ESI-MS (Sodium Counterion) That Can Be Supported by the Presence of Oligomers Based on Ester Bonds, Ether Bonds, or Both, and the Number of Detected Mass Peaks Explained Only by Oligomers with Specific Structures for All Synthesized Prepolymers**

	PGS (1:1)	PGSSu (1:0.9:0.1)	PGSSu (1:0.8:0.2)	PGSSu (1:0.5:0.5)	PGSSu (1:0.2:0.8)	PGSSu (1:0.1:0.9)	PGSu (1:1)
Ester oligomers	28	72	72	81	91	60	36
Ether oligomers - Poly(glycerol)	5	5	2	3	2	5	8
Ether/ester oligomers	8	22	19	40	14	14	19
<b>Oligomers identified (total)</b>	<b>41</b>	<b>99</b>	<b>93</b>	<b>123</b>	<b>108</b>	<b>79</b>	<b>63</b>
<b>Number of masses detected and explained only by oligomers with nonlinear specific structures</b>							
Cyclic oligomers	6	10	9	35	11	19	23
Branched oligomers	4	12	11	15	15	8	7
Hyperbranched oligomers	2	4	3	4	3	4	2

detected masses that represent a glycerol–glycerol reaction (GG...) and ether/ester oligomers from detected masses that are justified in presence of at least two more G units than diacid units. The sum of these three groups makes the total number of identified oligomers, from which it is possible to correlate some oligomer masses with specific structures. For example, cyclic oligomers have a characteristic loop in its structure that can be easily assumed based on  $m/z$  18 reduction, corresponding to the loss of a  $H_2O$  molecule from the extra bond. Branched oligomers can be justified by  $G_n + Acids_{n+(2\leq)}$ , where “ $n$ ” is the number of existing G units. Finally, hyperbranched oligomers are a particular form of branched molecules from which all hydroxyl groups of glycerol have reacted ( $G_n + Acids_{n+n+1}$ ). It is important to note that some oligomers can belong to two different groups and be counted as cyclic and branched or simply counted as hyperbranched.

By looking at Table 1, we can already pinpoint three distinct conclusions. First, for all prepolymers, most part of the detected mass peaks (>50% of the total) corresponded to ester oligomers, as expected. Second, simultaneously using two diacids promoted an increase in the total number of identified oligomers, when compared to reactions that only used one diacid. This was already expected since three reactants offer much more oligomer possibilities than two reactants. In fact, when diacids were used in a 50/50 ratio, like PGSSu (1:0.5:0.5), the number of oligomers identified was the

highest, counting a total of 123. Finally, when comparing the results of using sebacic acid alone versus succinic acid, we realize that succinic acid demonstrates higher reactivity and acidity power (Table 1). Particularly, the increase in the ratio of succinic acid pointed to a growth of cyclic oligomers. PGSu (1:1) contained more oligomers than PGS (1:1) in every type of bond mentioned above. This difference (63 and 41, respectively) is highly influenced by the increase in oligomers with ether bonds.

Nevertheless, and taking a deeper look, Table 2 shows some oligomers of interest using a heatmap-like approach, with RA {values} displayed in MS spectral data (please refer to the supporting information, from S1–S7).

GSGS tetramer ( $m/z$  557.6 – RA{100}), GSGSGS hexamer ( $m/z$  815.9 – RA{44}), and GSGSG pentamer ( $m/z$  631.7 – RA{41}) are the three most abundant oligomers in PGS (1:1), exactly as observed by Kafouris et al.<sup>41</sup> for this same ratio of reactants, but the latter used a lower temperature and a much longer reaction time. However, Kafouris et al.<sup>41</sup> indicated that the intensity of the GS dimer ( $m/z$  299.3) was significantly higher, and the larger oligomers detected were nonamers. In our work, we detected mass peaks corresponding to ester tridecamers (S1) but with lower RA{<1}. GGGGGGGG heptamer ( $m/z$  559.5 – RA {7}) and the GSGGGGGGGG nonamer ( $m/z$  559.5 – RA {6}) were the most abundant oligomers detected with ether bonds.

Table 2. Compilation of Some Relevant Oligomers Identified from ESI-MS Data Processing Presented in a Heatmap-like Approach<sup>a</sup>

Oligomers	Mass ( <i>m/z</i> with Na <sup>+</sup> counterion)	Relative Abundance (RA) of oligomers in each prepolymer						
		PGS (1:1)	PGSSu (1:0.9:0.1)	PGSSu (1:0.8:0.2)	PGSSu (1:0.5:0.5)	PGSSu (1:0.2:0.8)	PGSSu (1:0.1:0.9)	PGSu (1:1)
(2) GSu	215.158	.	.	.	16	16	16	15
(1) S	225.30	1	12	17	16	4	.	.
(3) GSuG	289.237	.	4	10	32	39	44	38
(2) GS	299.318	15	36	46	36	17	.	.
(3) SuGSu	315.233	.	3	4	8	9	8	8
(3) GSG	373.397	25	61	69	58	27	11	.
(4) GSuGSu	389.312	.	3	4	20	38	24	30
(3) SuGS	399.393	.	9	15	68	19	31	.
(4) SuG(Su)Su hyperbranched	415.308	.	.	.	19	4	11	9
(5) GSuGSuG	463.391	.	.	10	52	100	100	100
(4) GSGSu	473.472	.	13	29	46	53	15	.
(3) SGS	483.553	34	28	33	23	8	.	.
(5) SuGSuGSu	489.387	.	3	.	20	24	16	19
(4) SuG(Su)S hyperbranched	499.468	.	5	5	13	.	.	.
(6) GSuGSuGG cyclic	519.455	.	.	.	85	.	.	33
(4) GSGS cyclic	539.617	6	9	9	.	.	.	.
(7) GGGGGG cyclic	541.542	.	.	.	89	.	.	34
(5) GSuGSG	547.551	.	25	51	100	71	30	.
(4) GSGS	557.632	100	78	87	39	16	.	.
(7) GGGGGG	559.557	7	.	.	.	.	7	.
(6) GSuGSuGSu	563.466	.	3	4	93	58	32	63
(7) GSuGGGG	585.553	.	3	4	84	.	.	32
(7) GSuGSuGSuG cyclic	619.53	.	16	20	96	24	50	38
(6) GSuGSuGS cyclic	629.611	.	.	.	63	7	5	.
(5) GSGSG	631.711	41	100	100	55	14	.	.
(7) GSuGSuGSuG	637.545	.	8	.	26	66	71	86
(6) GSuGSuGS	647.626	.	.	12	38	57	17	.
(7) SuGSuGSuGSu	663.541	.	13	18	84	31	43	39
(4) SG(S)S hyperbranched	667.788	3	.	.	.	.	.	.
(9) GGGGGGGG	707.715	.	11	14	83	17	34	33
(7) GSuGSuGSG	721.705	.	.	11	55	59	28	.
(6) GSuGSGS	731.786	.	17	35	31	25	.	.
(8) GSuGSuGSuGSu	737.62	.	.	.	.	37	23	34
(5) SGSGS	741.867	29	27	25	.	.	.	.
(8) GSuGSGGGG cyclic	751.773	.	9	11	79	13	27	.
(8) GSuGSuGSGG	795.784	.	7	9	71	11	21	.
(7) GSuGSGSG	805.865	.	20	38	55	20	.	.
(9) GSuGSuGSuGSuG	811.699	.	.	.	15	31	40	51
(6) GSGSGS	815.946	44	56	56	18	.	.	.
(9) GSGGGGGG	817.871	6	8	8	.	.	.	.
(8) GSuGSuGSuGS	821.78	.	4	5	19	44	14	.
(7) GSGSGSG	890.025	15	55	51	20	.	.	.
(9) GSuGSuGSuGSGG	895.859	.	.	.	20	36	20	.
(10) GSuGSuGSuGSuGSu	911.774	.	.	.	.	17	13	18
(11) GSuGSuGSuGSuGSuG	985.853	.	.	.	.	11	16	22
(7) SGSGSGS	1000.181	18	16	14	8	.	.	.
(8) GSGSGSGS	1074.26	17	24	19	5	.	.	.
(12) GSuGSuGSuGSuGSuGSu	1085.928	.	.	.	5	6	5	7
(9) GSGSGSGSG	1148.339	5	17	14	16	.	.	.
(9) SGSGSGSGS	1258.495	6	6	5	.	.	.	.
(10) GSGSGSGSGS	1332.574	5	7	5	.	.	.	.

Oligomers colors Key

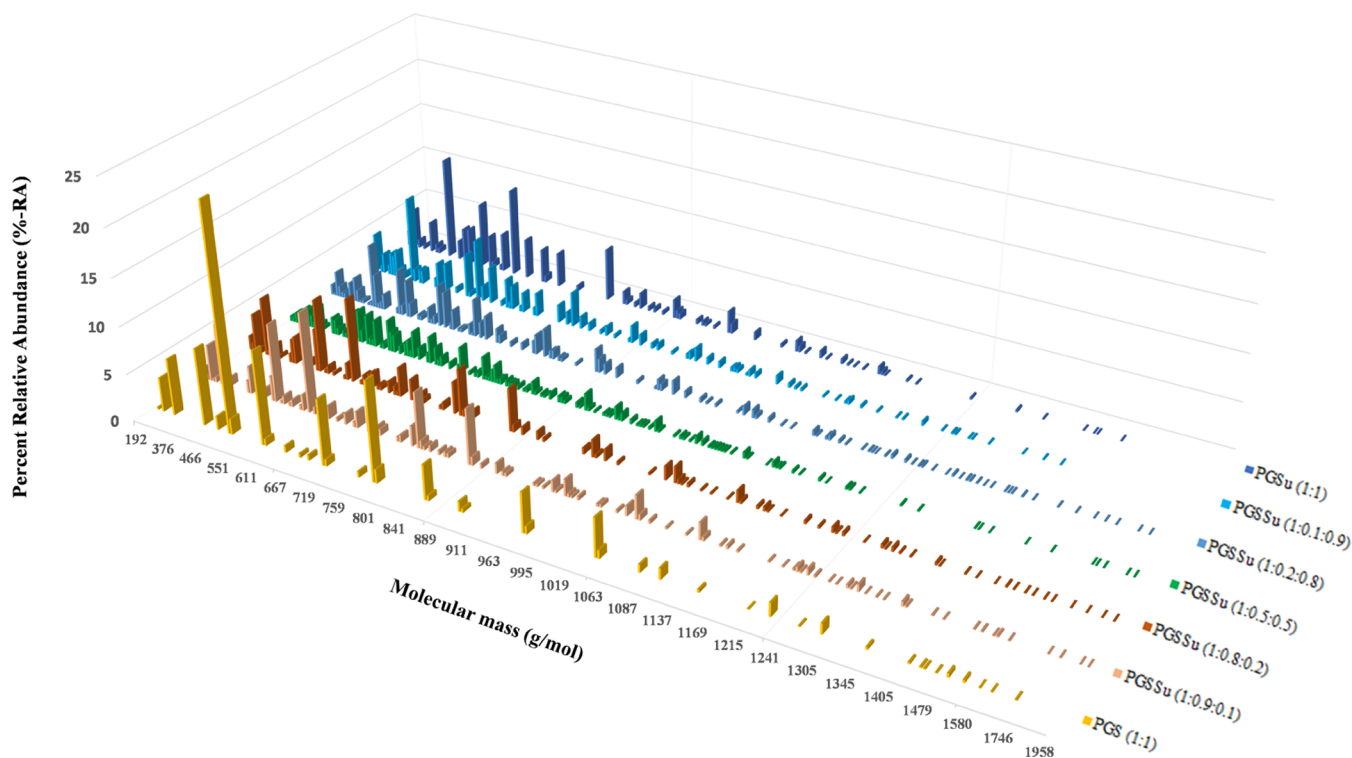
Mass justifies oligoesters from Su and G

Mass justifies oligoesters from S and G

Mass justifies oligoesters from Su, S and G

Mass justifies oligomers with ether bonds

<sup>a</sup>For every prepolymer synthesized was established a chromatic key, ranging from white relative abundance (RA) {0} to red – RA {100}.



**Figure 3.** Mass distribution profile in percent relative abundance (%-RA) for each prepolymer, obtained from ESI-MS data processing.

Doing a comparison between the prepolymers that were produced using only one diacid, it is noticeable that PGSu (1:1) has poly(glycerol) oligomers in a much higher RA than PGS (1:1). Indeed, there are situations where specific poly(glycerol) oligomers were only detected when succinic acid was used like the GGGGGGGG nonamer ( $m/z$  707.7). Furthermore, PGSu (1:1) had the highest number of poly(glycerol) oligomers detected ( $n = 8$ ) when compared to PGS (1:1). Thus, in this case, the usage of succinic acid had a greater catalytic influence on the occurring etherification between glycerol molecules (than the one from sebacic acid) in the synthesis of prepolymers.

Regarding the situations in which both diacids were used, for instance, PGSSu (1:0.9:0.1) and PGSSu (1:0.8:0.2) were synthesized by replacing sebacic acid with 10 and 20% of succinic acid, respectively. Consequently, consistent changes were observed in the composition of both prepolymers. For example, the S monomer ( $m/z$  225.3) that in PGS (1:1) reacted almost completely (RA {1}) presented a higher abundance in those two prepolymers (RA {12} and RA {17}, respectively). Also, the GSu dimer ( $m/z$  215.1) was not detected, indicating that all groups of succinic acid were fully reacted. Therefore, we can additionally conclude that when succinic acid is present, some sebacic acid molecules do not react. Moreover, the most abundant oligomers change when compared to PGS (1:1). In PGSSu (1:0.9:0.1) and PGSSu (1:0.8:0.2), the most abundant oligomers were those with higher molecular weight, such as the GSGSG pentamer ( $m/z$  631.7 – RA {100}). Indeed, it seems that the presence of succinic acid induces the formation of oligomers with G-ends, such as the GSG trimer ( $m/z$  373.3), GSGSGSG heptamer ( $m/z$  890.3), or GSGSGSGSG nonamer ( $m/z$  1148.3), whose RA in PGS (1:1) was significantly lower. Plus, oligomers containing two diacids were identified, and the most abundant one was also a pentamer with G-ends GSuGSG ( $m/z$  547.5).

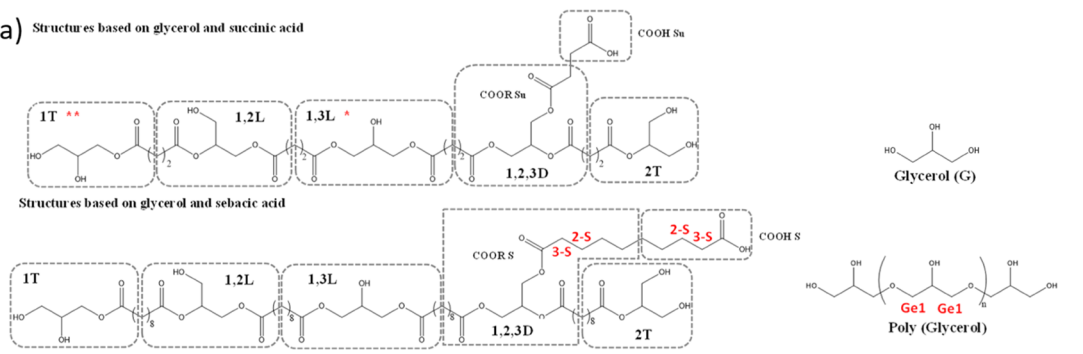
The PGSSu prepolymer (1:0.5:0.5) showed the highest number of oligomers with high RA, from which the GSuGSG pentamer ( $m/z$  547.5 – RA {100}) was the most abundant. This observation goes in accordance with the diacid ratio of 50/50. Interestingly, the %-RA of this GSuGSG pentamer ( $m/z$  547.5) followed the proportion of diacids throughout the different prepolymers obtained. The GSu dimer ( $m/z$  215.1) and the S monomer ( $m/z$  225.3) were also detected, and so was the poly(glycerol) GGGGGGGG nonamer ( $m/z$  707.7 – RA {83}) in high abundance. In general, there was a large mixture of oligomer species in this prepolymer, many cyclic oligomers with ether bonds with high RA {values}, and the trend toward G-end oligomers remained.

Some relevant changes in the composition of the following prepolymers were observed: PGSSu (1:0.2:0.8) and PGSSu (1:0.1:0.9), with succinic acid as the main component, and PGSu (1:1), with succinic acid as its only diacid. On the one hand, the GSuGSuG pentamer ( $m/z$  463.3 – RA {100}) was the most abundant oligomer. On the other hand, these prepolymers registered higher RA {values} for oligomers with ether bonds and for cyclic oligomers when compared to the prepolymers produced with sebacic acid as its main reagent.

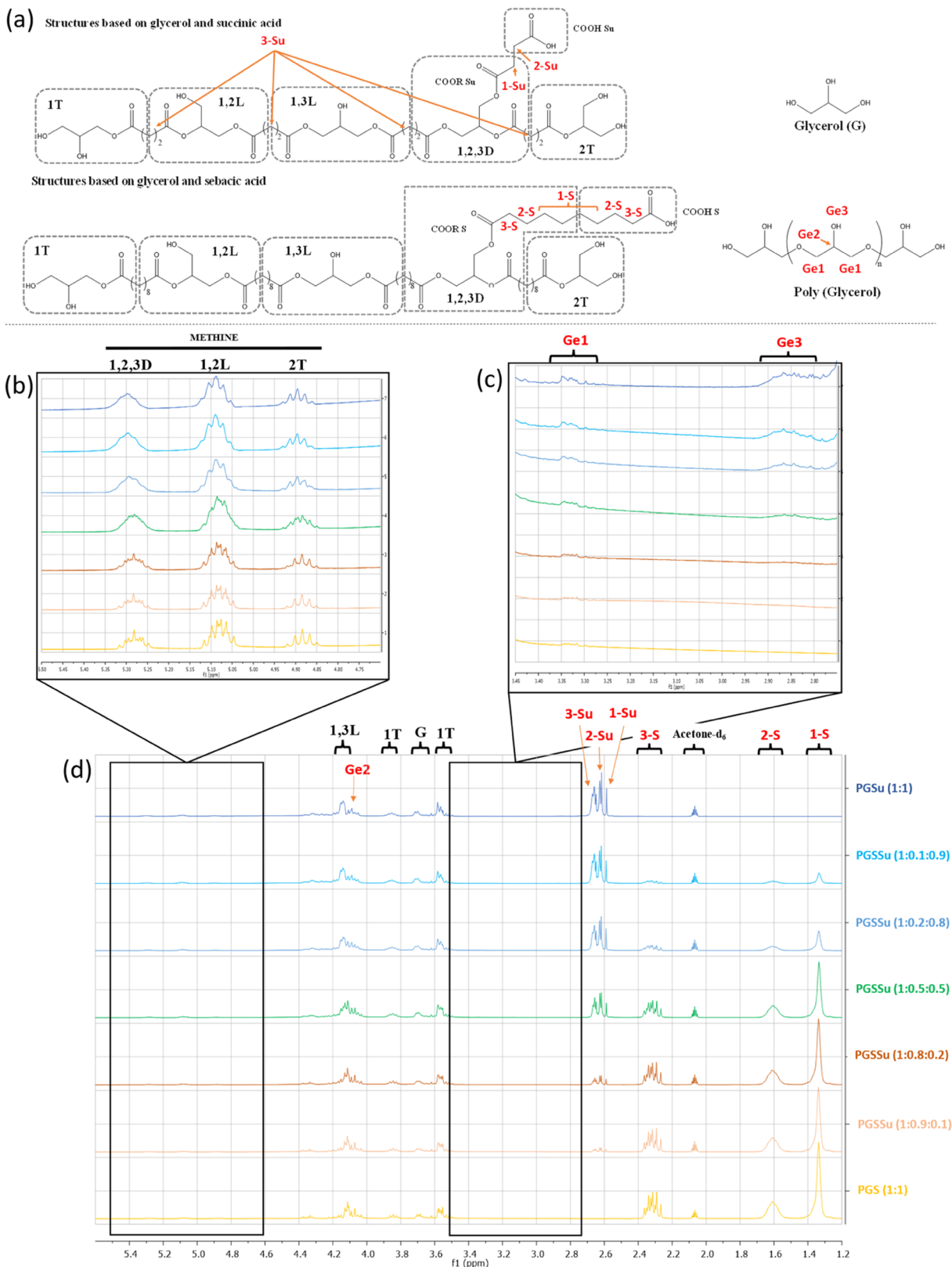
By analyzing in detail, the previously mentioned prepolymers, PGSSu (1:0.2:0.8), had a clear tendency to contain G-ended oligomers. The four most abundant oligomers were GSuGSuG pentamer ( $m/z$  463.3 – RA {100}), GSuGSG pentamer ( $m/z$  547.5 – RA {71}), GSuGSuGSuG heptamer ( $m/z$  637.5 – RA {66}), and GSuGSuGSG heptamer ( $m/z$  637.5 – RA {59}). As for PGSSu (1:0.1:0.9), most of the S-only oligomers disappeared except the GSG trimer ( $m/z$  373.3 – RA {11}), and the S monomer ( $m/z$  225 – RA {3}) was fully consumed. Three of the most abundant oligomers also revealed a tendency for G-ends, such as GSuG trimer ( $m/z$  289.2 – RA {44}), GSuGSuGSuG heptamer ( $m/z$  637.5 – RA {71}), or GSuGSuGSuGSuG nonamer ( $m/z$  811.6 – RA

$^{13}\text{C}$  NMR data

(a) Structures based on glycerol and succinic acid



**Figure 4.** (a) Substitution pattern of PGSu/PGS composed of the terminal (1T and 2T), linear (1,3L and 1,2L), dendritic (1,2,3D) glyceridic units, glycerol and poly(glycerol); (b)  $^{13}\text{C}$  NMR spectra (72.3–72.6 ppm); (c)  $^{13}\text{C}$  NMR spectra (60–76 ppm); and (d) full  $^{13}\text{C}$  NMR spectra of PGS (1:1), PGSSu (1:0.9:0.1), PGSSu (1:0.8:0.2), PGSSu (1:0.5:0.5), PGSSu (1:0.2:0.8), PGSSu (1:0.1:0.9), and PGSu (1:1).

$^1\text{H}$  NMR data

**Figure 5.** (a) Substitution pattern of PGSu/PGS composed of the terminal (1T and 2T), linear (1,3L and 1,2L), dendritic (1,2,3D) glyceridic units, glycerol and poly(glycerol); (b)  $^1\text{H}$  NMR spectra (4.6–5.5 ppm); (c)  $^1\text{H}$  NMR spectra (2.7–3.45 ppm); and (d) full  $^1\text{H}$  NMR spectra of PGS (1:1), PGSSu (1:0.9:0.1), PGSSu (1:0.8:0.2), PGSSu (1:0.5:0.5), PGSSu (1:0.2:0.8), PGSSu (1:0.1:0.9), and PGSu (1:1).



{40}). Lastly, the PGSu prepolymer (1:1) showed many mass peaks in high RA characteristic of oligomers with G-ends, as seen in previous prepolymers. However, oligomers such as the GSuGSuGSu hexamer ( $m/z$  563.4) and the SuGSuGSuGSu heptamer ( $m/z$  637.5) were present in high RA values as well.

**Mass Distribution Comparison.** For a better understanding and comparison of the mass distribution profile among the different prepolymers synthesized (Support information, from S1–S7), RA values were used to normalize percent relative abundance (%-RA) obtainment. To accomplish that, %-RA was calculated like Ning et al.<sup>43</sup> did, by taking the RA value of the mass peak corresponding to each oligomer in question and dividing it by the total sum of RA of all mass peaks identified for monomers, dimers, and oligomers.

Figure 3 shows the mass distribution profile for each prepolymer based on all mass peaks identified, expressed in %-RA. Clearly, the most abundant oligomers among the resulting prepolymers were the ones which had a molecular mass under 900 g/mol.

PGSSu (1:0.5:0.5) had more identified peaks ( $n = 123$ , see Table 1) and a much wider mass distribution, with the most abundant peaks representing only 3.5%-RA. In contrast, PGS (1:1) had less identified peaks ( $n = 41$ , see Table 1) and a narrower mass distribution, with higher %-RA values registered for a reduced number of oligomers. Particularly, the most abundant oligomer represented 24%-RA, and the set constituted by the four most abundant oligomers accounted for more than 50%-RA. In conclusion, the introduction of succinic acid contributed to a wider mass distribution profile and a great number of oligomers with higher masses (>900 g/mol).

**NMR Analysis.** Figures 4 and 5 compile the information obtained by NMR carbon ( $^{13}\text{C}$ ) and proton ( $^1\text{H}$ ), respectively. In both figures, panel “(a)” shows the chemical structures that are identified in each analysis, supporting the interpretation and presentation of the data.

The progressive substitution of sebacic acid with succinic acid is perfectly perceived as we look at the obtained NMR spectra, principally on signal regions from 1.2–1.8 and 2.2–2.8 ppm ( $^1\text{H}$  NMR-Figure 5d) and at 20–40 ppm ( $^{13}\text{C}$  NMR-Figure 4d).

Residual glycerol (Gly), 1-monosubstituted glycerol terminal units (1T), 2-monosubstituted glycerol terminal units (2T), 1,2-disubstituted linear glycerol units (1,2L), 1,3-disubstituted linear glycerol units (1,3L), dendritic units (1,2,3D), and sebacic acid and succinic acid signals were detected in both  $^{13}\text{C}$  and  $^1\text{H}$  NMR (Figures 4 and 5). This observation is in agreement with previously reported work on poly(glycerol-*co*-diacid) synthesis.<sup>43,52–55</sup>

In Figure 4, the signals used to identify the 1T, 2T, 1,2L, and 1,3L units accompany the progressive transition in ratio of the diacids used. These signals slightly shifted to an inferior value of ppm due to the presence of ester bonds between succinic acid and glycerol. For example, at about 70 ppm, the transition from the signal of the 1T unit due to binding with sebacic acid (70.1 ppm) to that of binding with succinic acid (69.9 ppm) is fully perceptible. Further, in PGSSuc (1:0.5:0.5), where both diacids were used in the same ratio, two peaks are present side by side in different regions. The 1T and 1.3L methylene carbons of prepolymers with a higher proportion of succinic acid are especially identified with red “\*\*\*” and “\*\*”, respectively. This particular identification is due to the

significant distance between the signs of these carbons, as one diacid is replaced by the other (Figure 4c).

In addition, 1,2,3D unit signals are very weak or almost undetected, principally in  $^{13}\text{C}$  NMR. This goes in accordance with ESI-MS results, which also revealed mass peaks indicative of hyperbranched oligomers in low or zero abundance. 1T and 1,3L signals are undoubtedly the strongest ones (Figure 4c).

Still regarding  $^{13}\text{C}$  NMR spectra, the region from 170 to 180 ppm shows the carbon shift from acid to ester (Figure 4d). The signals from the carboxylic acid moieties and ester moieties have similar intensities. This observation confirms the degree of polymerization around 50% of the resulting prepolymers, and reference used to stop the reactions of synthesis. Particularly, in PGSSuc (1:0.5:0.5), it is possible to observe 3 peaks instead of 2 due to the relevant and simultaneous presence of both diacids. It is also important to note that the succinic acid signal is superimposed on the ester sebacate signal, which results in the presence of only 3 signals instead of 4.

Finally, the presence of poly(glycerol) was undeniable since it is possible to observe distinctive signals that can only be obtained in the presence of ether bonds. Those signals are very weak, but they become more intense as the proportion of succinic acid surpasses that of sebacic acid, being in line with what was obtained from the ESI-MS data processing. Indeed, PGSu (1:1) has the strongest signals corresponding to the presence of ether bonds. In Figure 5c, it is possible to observe a signal around 3.3–3.35 ppm that corresponds to protons near ether bonds in units 1,3L ether and a signal around 2.9 ppm from the proton in the central hydroxyl group.

The signal that represents the central carbon proton is closely located to other signals that can be explained by ester bonds from glycerol at 4.1 ppm (Figure 5d). As for  $^{13}\text{C}$  NMR spectra, particularly those of PGSu (1:1) and PGSSu (1:0.1:0.9), the only distinctive signal indicative of ether bonds is at 72.4 ppm, which corresponds to the carbons that establish 1,3L ether bonds (Figure 4b). In fact, it was only possible to detect the linear ether structure formed by the reaction of primary hydroxyl groups.

## CONCLUSIONS

Our work demonstrates that the time for the synthesis of poly(glycerol-*co*-diacids) is correlated with the type of diacid used. The introduction of succinic acid makes it possible to significantly reduce the reaction time. The same molar amount of succinic acid reacts twice as faster as the same amount of sebacic acid. Also, the progressive increment in succinic acid ratio proportionally reduces the reaction time needed to reach a degree of polymerization of  $\approx 55\%$ .

ESI-MS analysis allowed us to evaluate differences in the composition of the prepolymers synthesized with different proportions of sebacic acid and succinic acid. The results obtained indicate that succinic acid contributes to a wider mass distribution profile and a greater presence of ether oligomers and cyclic structures. Additionally, the presence of succinic acid not only has a catalytic influence on the formation of poly(glycerol) but also contributes to a mass growth of ester oligomers, even in a small amount as 10%. The presence of succinic acid also enhances the formation of oligomers with a glycerol unit termination.

Overall, the most abundant oligomers have a mass between 400 and 800 g/mol. The difference in the amount of ether oligomers between PGS (1:1) and PGSu (1:1) is clear with the

data obtained from ESI-MS. An additional analysis, based on NMR, corroborates it.

Our results indicate that, under these same conditions, the presence of succinic acid potentiates the occurrence of side reactions, in comparison with sebacic acid. This work considers the possible formation of polyether segments during the synthesis of poly(glycerol-co-diacid) type polyesters, something that has not been studied in previous literature. The presence of poly(glycerol) is small, but even when used in small amounts, the presence of ether bonds in polymeric chains has the potential to significantly alter the chemical and physical properties of the materials. Future work will involve investigating the influence that temperature has on this type of side reaction (poly(glycerol) synthesis) during poly(glycerol-co-diacid) synthesis and how this may influence the material properties.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c00648>.

Original ESI-MS spectrum; list of identified masses and graphic data in RA and %-RA for each prepolymer; and sheet with calculations of the theoretical masses of predicted oligomers organized from dimers until icosamers (XLSX)

## ■ AUTHOR INFORMATION

### Corresponding Author

Artur Ferreira – CICECO—Aveiro Institute of Materials, University of Aveiro, Aveiro 3810-193, Portugal; ESTGA—Águeda School of Technology and Management, Águeda 3750-127, Portugal; [orcid.org/0000-0003-1785-4048](https://orcid.org/0000-0003-1785-4048); Email: [artur.ferreira@ua.pt](mailto:artur.ferreira@ua.pt)

### Authors

Bruno Godinho – CICECO—Aveiro Institute of Materials, University of Aveiro, Aveiro 3810-193, Portugal  
Rosana Nogueira – CICECO—Aveiro Institute of Materials, University of Aveiro, Aveiro 3810-193, Portugal  
Nuno Gama – CICECO—Aveiro Institute of Materials, University of Aveiro, Aveiro 3810-193, Portugal; [orcid.org/0000-0002-1865-098X](https://orcid.org/0000-0002-1865-098X)

Complete contact information is available at:

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### Author Contributions

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### Notes

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