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Bio-Based Polyurethanes from Carbohydrate Monomers

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María Violante de Paz and Elsa Galbis

Additional information is available at the end of the chapter

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Abstract

The production of sustainable and environmentally friendly materials constitutes a growing field of attention. The incorporation of sugar-derived units into traditional step-growth polymers such as polyamides, polyesters, and polyurethanes is a healthy method to prepare novel biodegradable and biocompatible materials for application in the biomedical field and other sectors such as foodstuff packaging.

Keywords: monosaccharides, sugar-based monomers, synthesis, chemical structure, degradability, thermal properties

1. Introduction

The exhaustible nature of the oil reserves and the pollution that oil-based technological polymers cause on the environment because of their low degradability have intensified the interest in natural renewing resources for the chemical synthesis of polymers. Thus, sustained efforts have been extensively devoted to render new polymers based on natural renewing resources with higher degradability [1, 2].

Among the diverse natural sources, carbohydrates constitute highly convenient raw materials because they are inexpensive, readily available, and provide great stereochemical diversity. They are produced in large amounts by plants and microorganisms every year, and in some cases they even come from agricultural wastes. So, in the last few decades many research groups have been investigating on the preparation of new polymers, analogous to the more significant technical polymers, but based on monomers synthesized from natural and available sugars [3]. However, although several polymers have been synthesized using sugar-derived

monomers with free hydroxyl groups [4–6], most syntheses of high-molecular-weight linear polymers involve derivatives having the hydroxyl groups appropriately blocked [3, 7].

Synthetic polymers obtained from sugar-based monomers are innocuous for human health. Their hydrophilic nature ensures a greater hydrolytic degradability [3], and reduces their environmental impact compared to classic polymers. Thus, the incorporation of sugar-derived units into traditional step-growth polymers constitutes an excellent approach to prepare novel biodegradable and biocompatible materials for application in the biomedical field and other sectors such as foodstuff packaging.

This chapter describes polyurethanes (PU) having the sugar units incorporated into the main chain. This topic has been partially reviewed before, but during the recent years numerous papers on the subject have been published. Thus, the following sections report on the syntheses, main properties, and applications of this type of sugar-based polymers that have been published mainly during the past decade. Patents have not been included so as to make the reference list more concise.

2. Synthesis of linear sugar-based polyurethanes (PU)

2.1. From diol-diisocyanate

Among the different procedures followed for the synthesis of [AABB]-type polyurethanes (PU), the most widely used is the classical isocyanate-based route, a polyaddition reaction of diols (or polyols) and diisocyanates (or polyisocyanates) (**Figure 1, Table 1**). This is a simple synthetic method conducted under inert atmosphere and in the absence of moisture at room temperature or above (from 25 to 80°C), either in solution or in bulk, with excellent conversions within 3–24 h for an extensive group of starting monomers. When the preparation of sugar-based PU is attended, the isocyanate-based method has been the route of choice so far, the sugar moiety being generally incorporated into the diol monomer.

Focusing on the preparation of sugar-based PU by the classical method, the solvents most commonly used are *N,N*-dimethylformamide (DMF) [11], *N,N*-dimethylacetamide (DMAc) [13], tetrahydrofuran (THF) [19] and, to a lesser extent, butanone [26], dimethylsulfoxide (DMSO), and hexamethylphosphoramide (HMPA) [31]. The polymerization can be catalyzed by a metal catalyst, the organotin catalyst dibutyltin dilaurate (DBTDL, **Figure 2**) [32] being the most widely used. Other metal catalysts are the commercial tin mercaptide esters registered as Metatin™ [18] and tetrabutyl titanate (TBT) [6]. Tertiary amines can also accelerate the polymerization process, and among them, the most extensively selected catalysts are 1,4-diazabicyclo[2.2.2]octane (DABCO) [10] and *N,N*-dimethylcyclohexylamine (DMCHA) [33]. Triethylamine (TEA) was chosen as (co-)catalyst in the preparation of segmented [27] and cross-linked [34] PU.

High temperatures and the incorporation of a liquid diol or polyol in the formulation, namely polyethylene glycol (PEG) [35–37], polyglycerol (PGL) [38], polypropylene glycol (PPG) [38, 39], and polycaprolactone (PCL) [40] are required when the polymerization is performed in bulk.

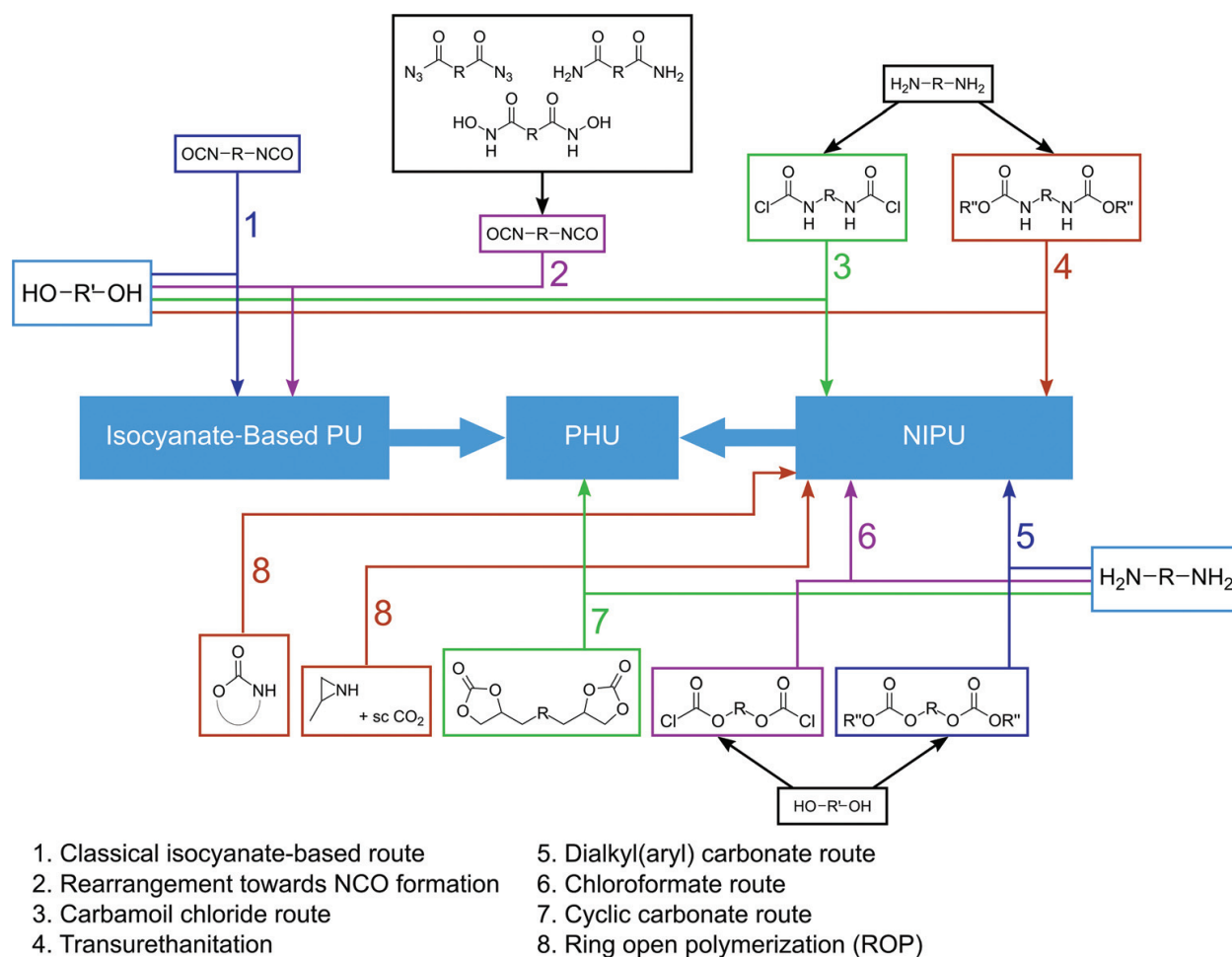
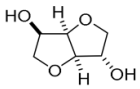
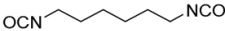
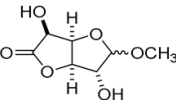
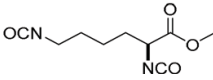
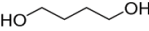
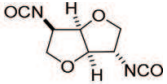
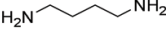
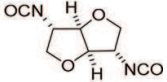
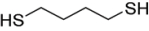
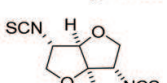
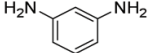
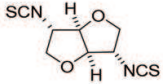
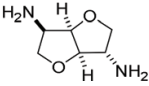
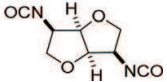
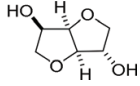
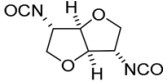

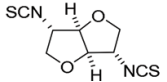
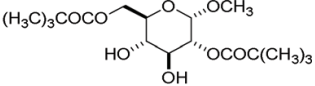
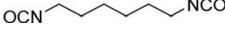
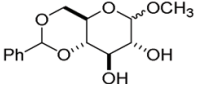
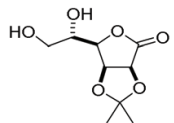
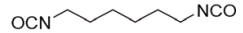
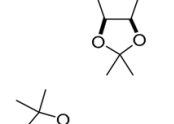
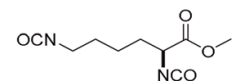
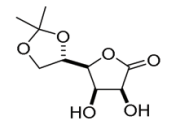
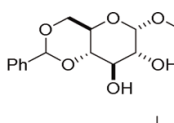
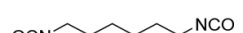
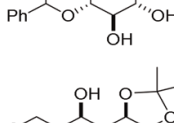
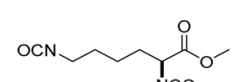
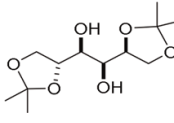
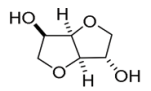
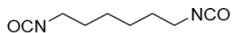
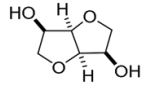
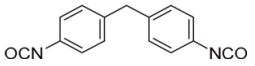
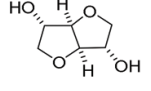
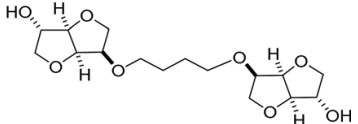


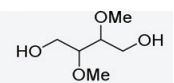
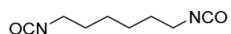
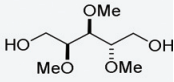
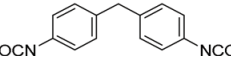
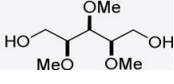
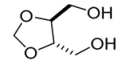
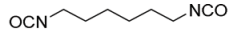
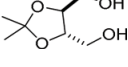
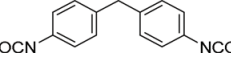
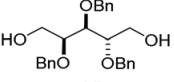
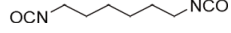
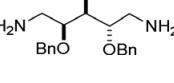
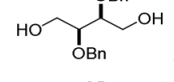
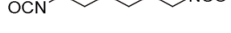
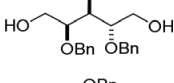
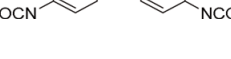
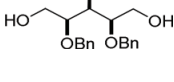
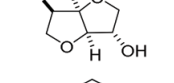
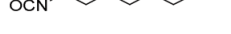
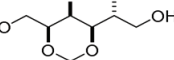
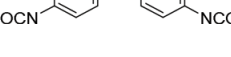
Figure 1. Most common synthetic routes to polyurethanes.

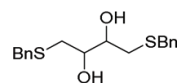
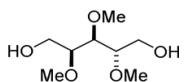
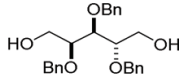
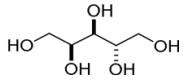
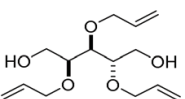
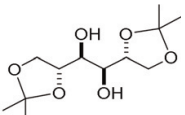
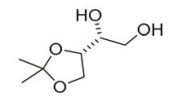
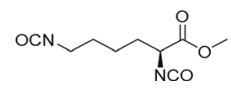
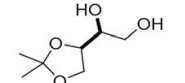
In sugar-based PU, the polyisocyanates and polyisothiocyanates most widely used are displayed in **Figure 3**, most of them being commercially available.

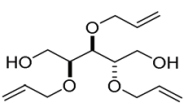
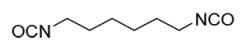
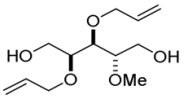
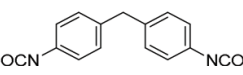
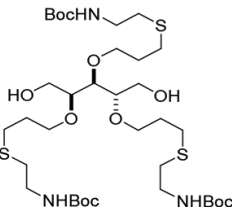
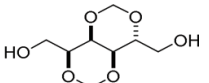
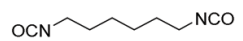
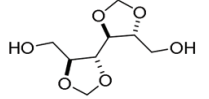
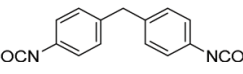
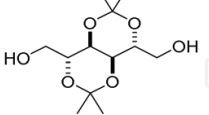
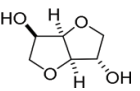
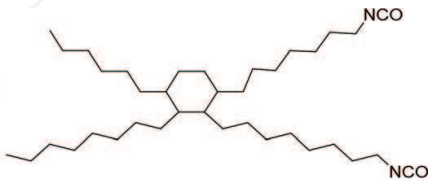
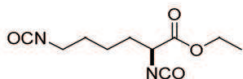
Other isocyanate-based routes are those in which a rearrangement of several acyl derivatives such as acyl azides (Curtius rearrangement), carboxamides (Hofmann rearrangement), and hydroxamic acid (Lossen rearrangement) conducts to the isocyanate monomer *in situ* (**Figure 1**). Thus, an article on the preparation of bio-renewable polyurethanes through Curtius rearrangement has been published. Initially, the synthesis of two new non-hindered diisocyanates based on isosorbide (**1**) and isomannide (**20**) without using petroleum-based reagents was attempted. The diisocyanates formation was carried out as follows: first, diols **1** or **20** were esterified with succinic anhydride in bulk at 120°C; second, the acidic derivatives were transformed into the corresponding diacid chlorides at low temperature, and lastly the diacid chlorides led to the diisocyanate derivatives **47** and **48** *via* a two-step Curtius rearrangement with overall conversions ranging from 52 to 60% [28]. Both diisocyanates were proved to be useful as starting materials in the preparation of two PU: a stereoregular PU (with *D-manno* configuration in all the monomers) and a non-stereoregular PU (with *D-gluco* configuration).

Diol/diamine	Diiso(thio)cyanates	Reaction conditions	T_g	Others	References
1	 3		DMF, 25°C, 72 h, DBTDL	-	[8]
2	 4				
5	 10		DMAc, 80°C, 24 h, DBTDL	From 48 to 112°C	[9]
6	 11				
7	 11				
8	 12				
9	 13				
1	 11		DMAc, 80°C, 24 h, DBTDL		[9]
	 12				
14	 3		THF, reflux, 60 h, DABCO	-	[10]
15					

Diol/diamine	Diiso(thio)cyanates	Reaction conditions	T_g	Others	References	
16	 3		DMF, 25°C, 48 h, DBTDL	–	Desprotection → PHU	[11]
	 4					
17						
18	 3		DMF, 25/50°C, 24/48/72 h, DBTDL		Desprotection → PHU	[12]
	 4					
19						
1	 3		DMAc, 80°C, 24 h, DBTDL	From 77 to 183°C	[13]	
20	 23					
21						
22						

Diol/diamine	Diiso(thio)cyanates	Reaction conditions	T_g	Others	References		
24		3		THF/DMF, 25/40°C, 3/24 h, DBTDL	From 22 to 110°C	[14]	
25		23					
26							
27		3		DMF, 40°C, 24 h, DBTDL Codiol: BD	From 35 to 126°C	Desprotection → PHU	[15]
28		23					
29		3		THF/DMAc, 25°C, 1/3 h, DBTDL	36°C, 108°C		[16]
30							
31		3		THF/DMF, 25°C, 3/24 h, DBTDL Codiol: BD, PD	From 21 to 79°C	Desprotection → PHU	[17]
29		23					
32							
1		3		DMF/bulk, 25/130°C, 24 h, DBTDL/METATIN Codiol: PCL-3000/BD	From -60 to -3°C	Segmented co-PU	[18]
33		23					

Diol/diamine	Diiso(thio)cyanates	Reaction conditions	T_g	Others	References
34	 3	OCN(CH ₂) ₆ NCO	DMF/THF, 25/70°C, 3/5/7 h, DBTDL Codiol: TEG	From -15 to 23°C	[19, 20]
25	 3	OCN(CH ₂) ₆ NCO	THF/DMAc, 25/-17°C, 1.5/3 h, DBTDL Codiol: DiT	From 1 to 36°C	[21]
29					
35					
36	 3	OCN(CH ₂) ₆ NCO	DMF, 60°C, 5 h, DBTDL	9°C, 16°C	Functionalization by thiol-ene click reaction → PHU [22]
37	 3	OCN(CH ₂) ₆ NCO	DMF, 50/70/80°C, 12/24 h, DBTDL Codiol: PTMG-650	-	Desprotection → PHU [23]
38		 4			
39					

Diol/diamine	Diiso(thio)cyanates	Reaction conditions	T_g	Others	References
36 	3 	DMF, 25°C, 5 h, DBTDL Codiol: DiT	From -21 to 91°C	Functionalization by thiol-ene click reaction → PHU; → free COOH; → free NH ₂	[24, 25]
40 	23 				
41 					
42 	3 	DMF, 40/60°C, 48 h, DBTDL	From 50 to 161°C	Desprotection → PHU	[7]
43 	23 				
44 					
1 	45 	Butanone, 30/70°C, 5/7 h, DBTDL/TEA	From 18 to 58°C	Dispersion	[26, 27]
	46 				

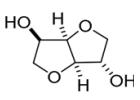
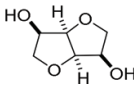
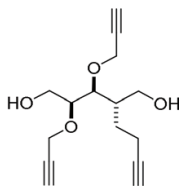
Diol/diamine	Diiso(thio)cyanates	Reaction conditions	T_g	Others	References
1	 47	DMF, 120°C, 48 h, DBTDL	78°C, 81°C		[28, 29]
20	 48				
49	 3	THF, 25°C, 24 h, DBTDL Codiol: DiT, BD, Octanediol	From -5 to 76°C	Alkyne-azide click reaction Dodecyl azide, Triethyleneglycol azide, PEG-750 azide	[30]

Table 1. Summarized literature about linear sugar-based PU prepared from diisocyanates.

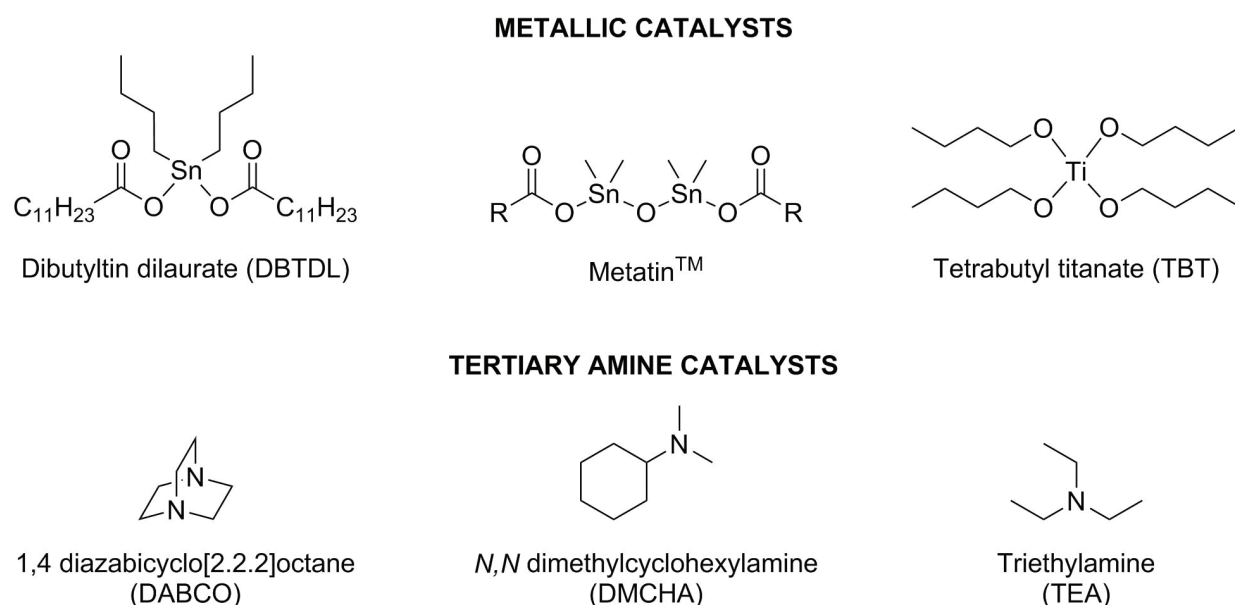


Figure 2. Catalysts for the synthesis of PU via diisocyanate-based polymerization.

To conduct the synthesis of linear [AB]-type homopolyurethanes, both the nucleophilic and the electrophilic groups (e.g., hydroxyl and isocyanate groups [32, 41, 42]) need to be present in one sole monomer (**Table 2**).

Thiem and coworkers were the first to attempt this approach with success in order to synthesize sugar-based PU. They published the preparation of 2-deoxy-1,4:3,6-dianhydro-2-isocyanato-L-*iditol* (**50**) from isosorbide (**Figure 4**), and the difunctional monomer proved to be suitable to polymerize in the presence of a catalyst [32].

The synthesis of a galactitol-based PU from the α, ω -hydroxyl isocyanate monomer **52** was carried out similarly to the abovementioned *iditol*-based PU. The preparation of the monomer 1-deoxy-1-isocyanato-2,3:4,5-di-*O*-isopropylidene-*D*-galactitol (**52**) was conducted from *D*-galactono-1,4-lactone by a four-step route. The monomer was then polymerized in THF in the presence of zirconium(IV) acetylacetonate [Zr(acac)₄] as catalyst. The removal of the acetal-protecting groups led to a galactitol-based polyhydroxyurethane (PHU) [41]. In addition, Kolender et al. synthesized a glucitol-based PU by polymerization of another α, ω -hydroxyl isocyanate monomer, the 1-deoxy-1-isocyanato-2,3,4,5-tri-*O*-methyl-*D*-glucitol (**53**) [42].

2.2. Eco-friendly methods (isocyanate or/and stannous free) to prepare PU

Although polymerization reactions of diisocyanates with diols are the main method to synthesize linear PUs, in the last few years and due to the toxicity of stannous catalysts and common aromatic diisocyanates such as 4,4'-methylenediphenyl diisocyanate (MDI) and toluene diisocyanate (TDI), a large number of works have been reported in literature on the synthesis of isocyanate-free PU, also called non-isocyanate PU (NIPU) (**Figure 1, Table 3**). Two interesting reviews have been recently published in which alternative pathways for PU syntheses are studied in detail [43, 44].

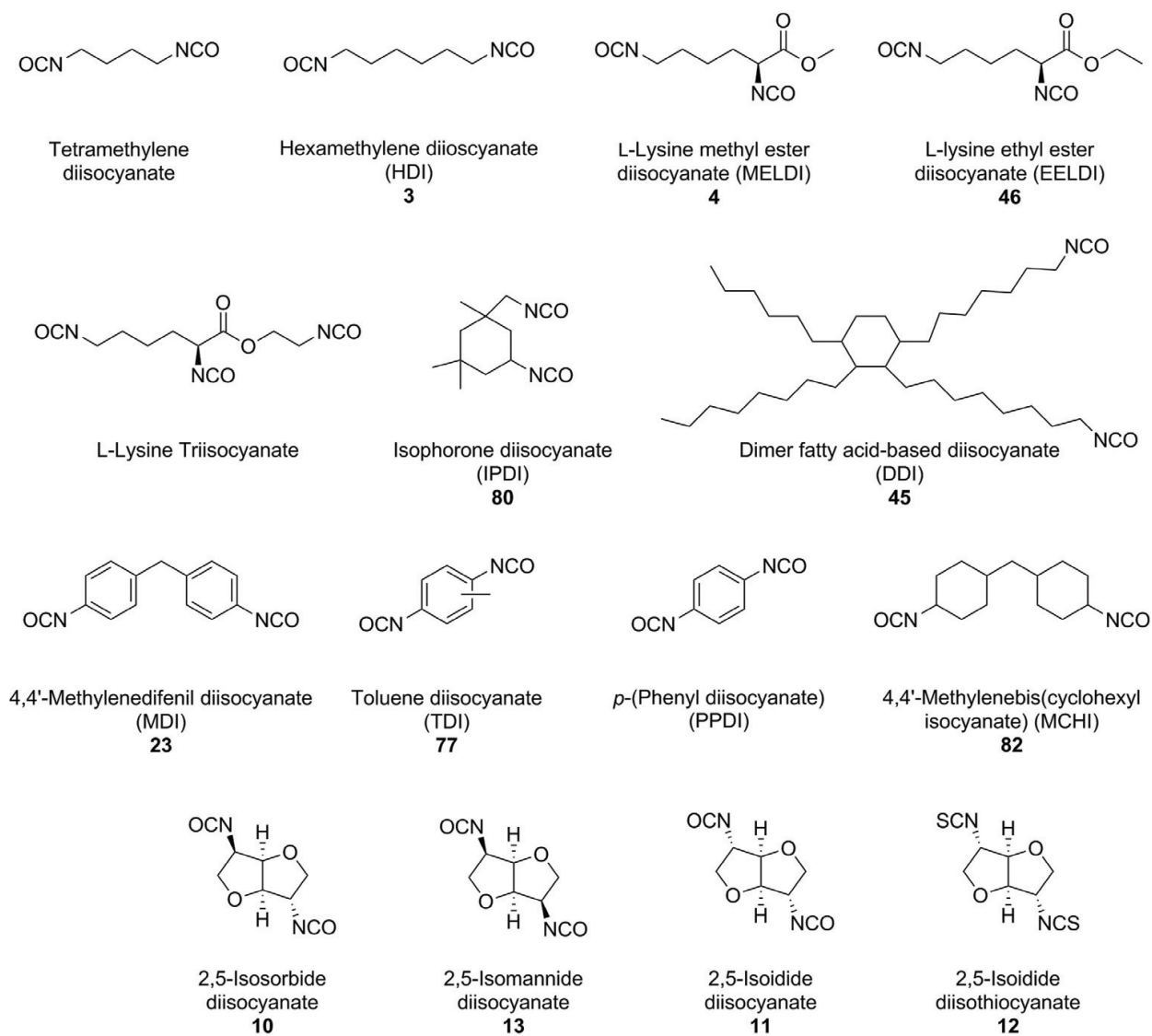


Figure 3. Chemical structure of the most common polyisocyanates and polyisothiocyanates used in the synthesis of sugar-based PU.

2.2.1. Dicarbamate and diols

One of the methods to use is the transesterification polymerization between a dicarbamate and a diol in which the side product is an alcohol, usually of low-molecular weight. For example, linear polyurethanes with free hydroxyl groups have been successfully prepared by Galbis et al. [6] from xylitol (**55**) and the aliphatic carbamates dimethyl hexamethylenedicarbamate (HDC, **56**) or di-*tert*-butyl-4,4'-diphenyl methyl dicarbamate (MDC, **59**), to render NIPU with enhanced hydrophilic character.

2.2.2. Bis(chloroformate) and diamines

To avoid the use of diisocyanates, a variety of new materials can also be obtained by polycondensation of diamines with freshly prepared bis(chloroformate)s. For example, two reactive bis

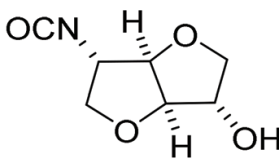
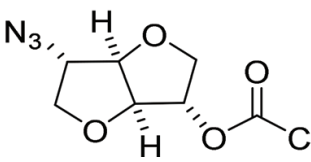
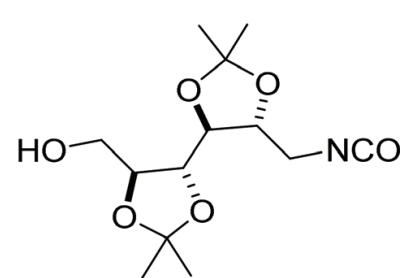
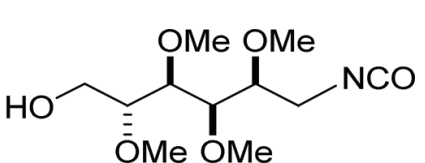
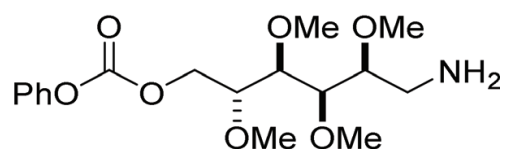
Monomer	Solvent	T_g	Others	References
50 	DMAC/MeOH, 80°C, DBTDL	-		[32]
51 	THF, 60°C, 48 h, Zr(acac) ₄	-	Desprotection → PHU	[41]
52 	THF/DMF, 40°C, 16/72 h, Zr(acac) ₄	-		[42]
53 				
54 				

Table 2. Selected examples of the use of a sole carbohydrate-based monomer for the preparation of PU.

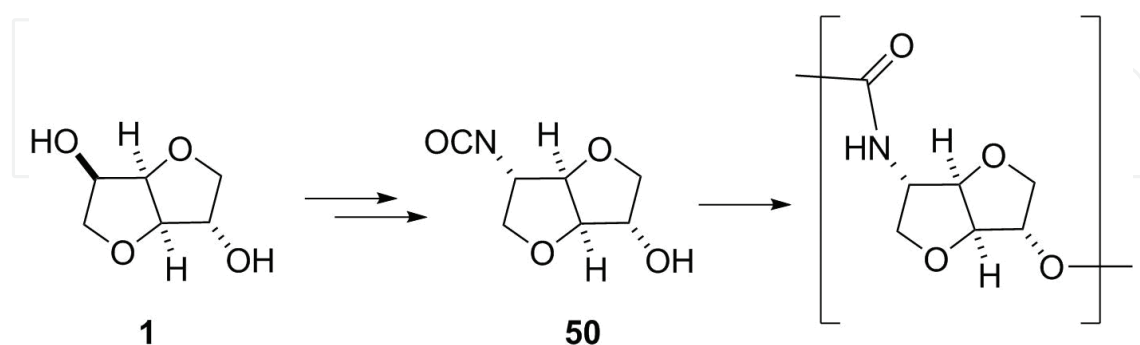
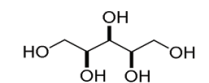
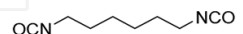
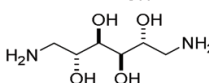

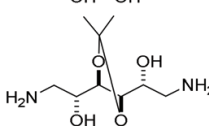
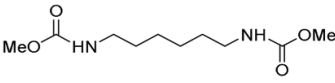
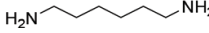
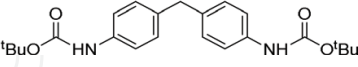
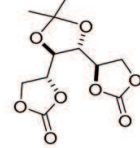
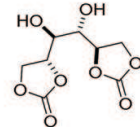
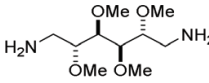
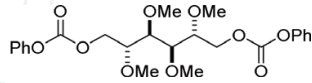


Figure 4. PU based on 2 deoxy-1,4:3,6-dianhydro-2-isocyanato-L-idoitol (50).

(chloroformates) were formed from methyl ether diols of L-arabinitol and xylitol (**73**, **74**, **Figure 5**). They were polymerized with commercial diamines (cystamine and cystine dimethyl ester) by interfacial polycondensation using sodium lauryl sulfate as surfactant [48]. The new

Diol/diamine	Dielectrophile	Reaction conditions	T_g	Others	References
55			Bulk/DMF/DMSO/DMAc, -60/-20/25/100/170°C, 0.5/1/5/6 h, no cat/DBTDL/TBT	PHU	[6]
56					
57					
60			THF/Diglyme/DMAc, 25/45/65/80°C, 12/24 h, no cat.	PHU	[45]
					
					
63			THF/DME, 85°C, 2/4/7 h, no cat.	From 38 to 61°C	[46]
64	$\text{H}_2\text{N}-(\text{CH}_2)_x-\text{NH}_2$ $x = 4, 6, 10$				

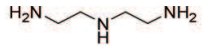
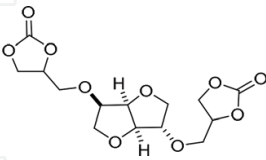
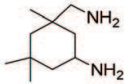

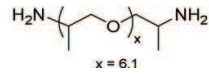
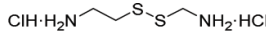
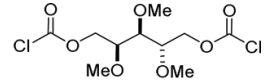
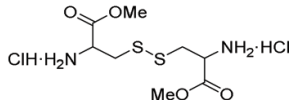
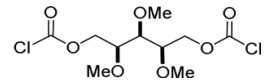
Diol/diamine	Dielectrophile	Reaction conditions	T_g	Others	References
66 	70 	DMF, 25°C, 12 h, cat. (not disclosed)	From -8 to 59°C		[47]
67 					
68 					
69 					
71 	73 	Toluene-water, 25°C, 0.5 h, sodium lauryl sulfate	From 35 to 63°C	Interfacial polycondensation	[48]
72 	74 				

Table 3. Summarized literature about linear sugar-based PU prepared by eco-friendly alternative pathways.

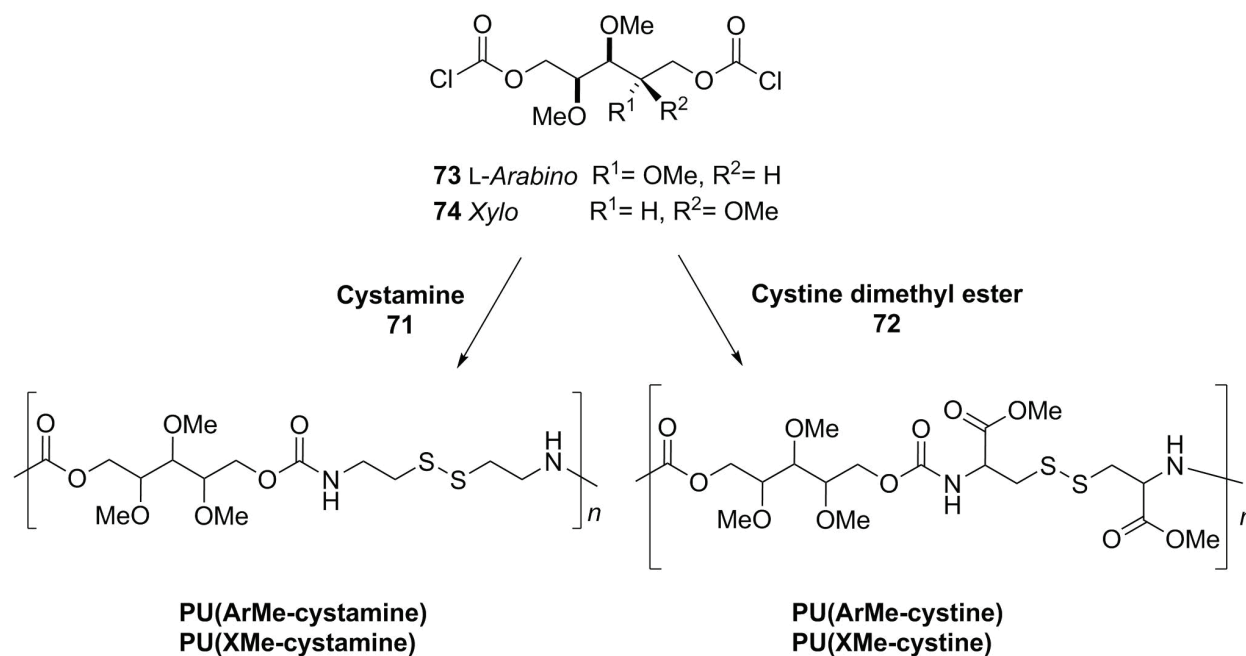


Figure 5. Reduction-sensitive homopolyurethanes from diamines and bis(chloroformate)s.

NIPU, bearing the labile disulfide bond in their structure, were degradable under reductive environments.

It was demonstrated that the presence of methoxycarbonyl side groups in the PU makes those materials more degradable, not only under hydrolytic conditions but also under reductive environments, probably due to their lower crystallinity and a better water/glutathione penetration in their structure. Moreover, differential scanning calorimetry (DSC) studies showed that the incorporation of the abovementioned pendant methoxycarbonyl groups into the homopolymers resulted in a more rigid material.

This synthetic method provides a useful tool toward the synthesis of chemical diverse NIPU because of the large set of commercial diamines available and the excellent on-hand chemical procedures for the synthesis of amines.

2.2.3. Dialkyl(or aryl)carbonate and diamines

The polycondensation reaction between dialkyl- and diarylcarbonates with diamines is another alternative method for the preparation of NIPU (**Figure 1**). Varela et al. reported the preparation of the diarylcarbonate 1,6-di-*O*-phenyloxycarbonyl-2,3,4,5-tetra-*O*-methyl-D-mannitol (**65**) and its use as comonomer in the preparation of some NIPU at 85°C [46].

The reaction of an α,ω -amino-arylcarbonate monomer, 1-amino-1-deoxy-2,3,4,5-tetra-*O*-methyl-6-*O*-phenyloxycarbonyl-D-glucitol hydrochloride (**54**), was tested for the preparation of sugar-based [AB]-polyurethane (**Figure 6**). Thus, the free hydroxyl group from the starting material was activated by means of the preparation of the phenylcarbonate derivative and further self-polymerized in THF in the presence of diisopropylethylamine (DIPEA), rendering a D-glucitol-based PU with low-molecular weight [42].

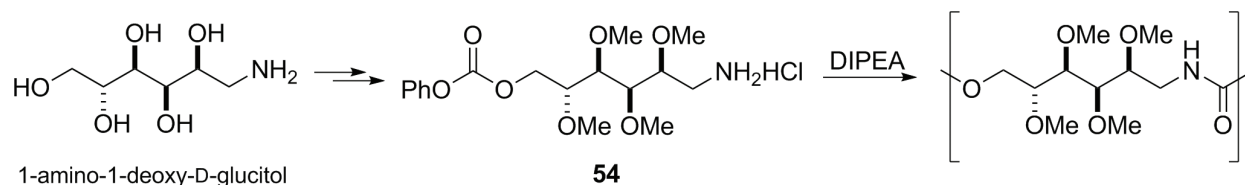


Figure 6. Synthesis of [AB]-polyurethane from 1-amino-1-deoxy-D-glucitol.

2.2.4. Dicyclocarbonates and diamines

Among the numerous pathways leading to NIPU, the polyaddition of cyclic carbonates with amines seems to be the most interesting route, and it is being widely investigated by numerous research groups (**Figure 1**). This method has been tested in sugar derivatives by Prömpers et al. They reported the preparation of PHU from D-mannitol-1,2:5,6-dicyclocarbonate **62** and its 3,4-*O*-isopropylidene derivative **61** with hexamethylenediamine (**60**) [45].

Similarly, Besse et al. reported the preparation of linear and branched isosorbide-based polyhydroxyurethanes, with low T_g values (from -8 to 59°C) [47]. The isosorbide-based dicyclocarbonate monomer **70** (**Figure 7**) was prepared from a diepoxide according to the method previously described by Brocas et al. [49].

However, this route displays two major drawbacks: the low reactivity between cyclic carbonates and amines, and a limited degree of advancement of reaction during the room-temperature polymerization that leads to low-molecular-weight PHU. Consequently, highly polydisperse, low-molecular-weight materials were isolated.

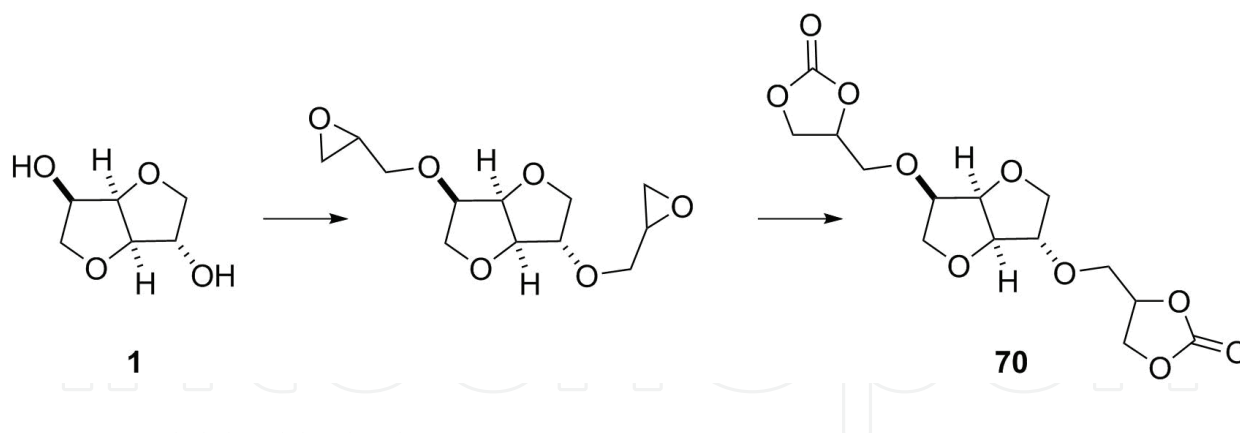
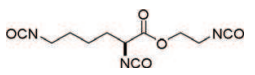
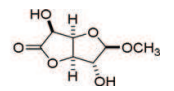
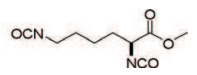
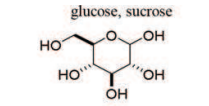
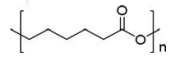
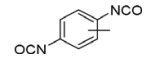
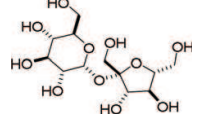
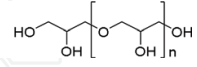
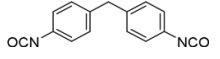
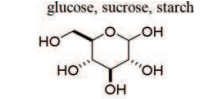
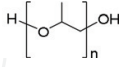
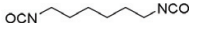
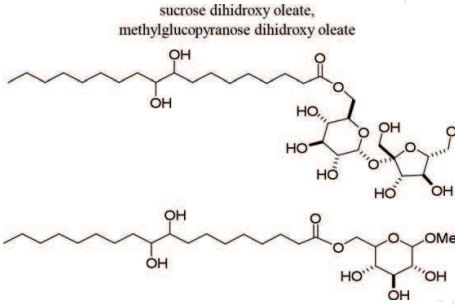
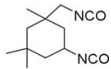
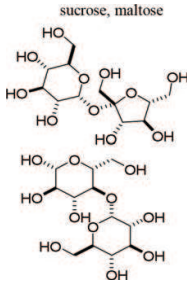
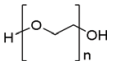
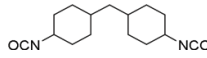
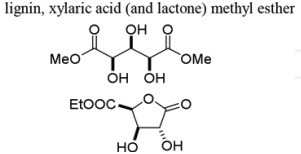
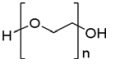
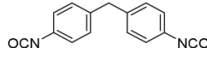


Figure 7. Isosorbide-based dicyclocarbonate monomer.

3. Synthesis of cross-linked sugar-based PU and segmented PU

For the preparation of cross-linked sugar-based PU, a monomer with functionality above two is required. Just one work was found in which the cross-linker was a triisocyanate derived from L-lysine derivative [35]. In general, the cross-linking is accomplished by the use of a mono- or a disaccharide with all its hydroxyl groups unprotected. Thus, glucose and sucrose are widely used in the formulations of carbohydrates-based networks [38–40, 50, 51] although

Cross-linker	Dinucleophile	Dielectrophile	Reaction conditions	T_g	Others	References
	75 	4 	DMF, 27°C, 72 h, DBTDL Codiol: PEG-1000	–	Gel	[35]
 glucose, sucrose	76 	77 	Bulk, 60/100°C, 1.5/48 h, no cat. Codiol: BD	–		[40, 50]
 sucrose	78 	23 	Bulk, –, –, DMCHA	–	Foam	[33]
 glucose, sucrose, starch	79 	3 	Bulk, 20/80°C, 3 h, DBTDL	–	Foam	[38]

Cross-linker	Dinucleophile	Dielectrophile	Reaction conditions	T_g	Others	References
<p>sucrose dihydroxy oleate, methylglucopyranose dihydroxy oleate</p> 		<p>80</p> 	THF/DMF, 60°C, 2/20 h, DBTDL	39°C, 111° C	Linear or cross-linked depending on the solvent	[51]
<p>sucrose, maltose</p> 	<p>81</p> 	<p>82</p> 	THF, 90°C, 5 h, no cat.	From -38 to -8°C	Adhesives	[36]
<p>lignin, xylic acid (and lactone) methyl ester</p> 	<p>81</p> 	<p>23</p> 	DMF, 20/40/60°C, 25 h, DBTDL Codiol: PEG-1500	From 95 to 132°C	Film	[37]

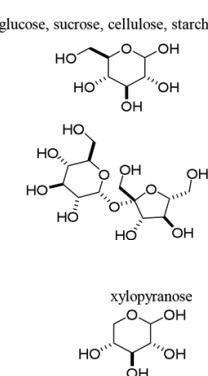
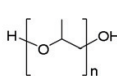
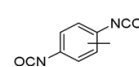
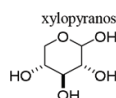
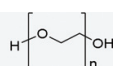
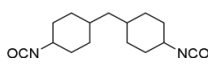
Cross-linker	Dinucleophile	Dielectrophile	Reaction conditions	T_g	Others	References
glucose, sucrose, cellulose, starch, castor oil 	79 	77 	THF, 25/80°C, 6 h, DBTDL	From -58 to -31°C	Film	[39]
xylopyranose 	81 	82 	THF-DMF 9:1, 90°C, 8 h, TEA	From -58 to -18°C	Tissue adhesive	[34]

Table 4. Selected examples of the use of monosaccharides and disaccharides for the preparation of cross-linked PU.

other monosaccharide and disaccharide derivatives such as xylaric acid [37], maltose [36], and glucosides [51] have also been chosen (**Table 4**). For example, Ates et al. [34, 36] prepared some non-aromatic cross-linked polyurethanes with potential use as surgical tissue adhesives. PEG diol **81** and 4,4'-methylenebis(cyclohexyl isocyanate) (MCHI, **82**) were polymerized with a certain amount of a sugar (maltose, sucrose, or xylose) as cross-linker. The reaction was carried out in THF or DMF-THF mixtures, at high temperatures in the absence of catalyst or adding triethylamine (TEA). The material cross-linked with xylose **55** [34] displayed high adhesiveness and biocompatibility properties, making it suitable for being used in the medical field. Depending on the final use of the cross-linked material, the reaction can be conducted in bulk [33, 38, 40, 50].

The use of flexible aliphatic polyether/polyester chains such as PCL **76** [18], PGL **78** [33], PEG **81** [35–37], PPG **79** [38, 39], or oleic ester derivatives [51] (in combination with other diols) can lead to segmented PU as well as carbohydrates-based cross-linked materials with differentiated regions. The synthesis can be carried out “one pot,” in which the polyols are incorporated into the polymer feed together with the sugar-based monomers and the other components. For example, the synthesis of highly functionalized low-molecular-weight polyether-polyols initiated by PGL and mixtures of PGL and sucrose has been described [33]. In the “one pot” preparation of rigid polyurethane foams in bulk and using MDI as diisocyanate, the polyether and/or polyols constituted the soft segment.

Even though materials obtained “one pot” displayed good physical and mechanical properties, excellent dimensional stability as well as low friability, an improvement of microphase separation can be accomplished when the polymerization is performed in two stages and the flexible polyol is incorporated in the first step [23, 26, 27]. The last step promotes the formation of urethane or urea linkages, in the so-called hard region with a high density of hydrogen bonds that provides stiffness to that section and elastomeric properties to the final product.

4. Synthesis of PU using bicyclic monomers derived from 1,4:3,6-dianhydrohexitols

The 1,4:3,6-dianhydrohexitols (**1**, **20**, **21**) have been used as rigid monomers in the synthesis of PU. Polyurethanes containing isosorbide (**1**) have been prepared by several research groups, and complex polyurethanes with elastomeric character and good mechanical properties gave rise to many patents. They were obtained from isosorbide and diisocyanates in the presence of suitable catalysts (**Table 1**). Thus, catalytic polymerization of 2-deoxy-1,4:3,6-dianhydro-2-isocyanate-L-*iditol* (**50**) afforded the corresponding AB-type polyurethane (**Figure 4**). Bachmann et al. [32] described an alternative synthesis through the 2-azido-5-*O*-chloroformyl-1,2-dideoxy-1,4:3,6-dianhydro-L-*iditol* (**51**) which underwent spontaneous polycondensation, after catalytic hydrogenation, *via* the 2-amino-5-*O*-chloroformyl isoidide. The same authors also described the transformation of the 2,5-diamino-dianhydrohexitols **9**, **83**, and **84** into the corresponding diisocyanates **10**, **11**, and **13** (**Figure 8**) which was achieved by reaction with phosgene [9]. A dithiodiisocyanate derivative (**12**) was prepared from the 2,5-diamino-2,5-dideoxy-dianhydro-

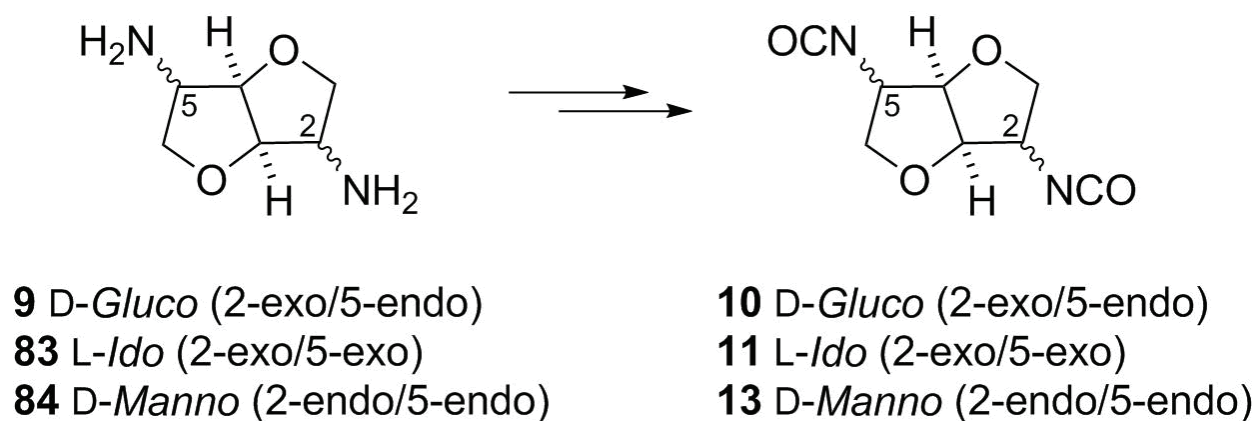


Figure 8. Diisocyanates obtained from 2,5-diamino-dianhydrohexitols.

L-iodide (**83**) and thiophosgene, which yielded poly(thio)urethanes and poly(thio)ureas by reaction with the diamino-monomers (**9**, **83**, **84**).

Beldi et al. [13] studied the polymerization of 1,6-hexamethylene diisocyanate (**3**, HDI) and 4,4'-methylenediphenyl diisocyanate (**23**, MDI) with the 1:4,3:6-dianhydrohexitols (**1**, **20**, **21**) as well as another novel isosorbide-based ether-diol in DMAc. They established the nature of the end groups and the fraction of cyclic and noncyclic polyurethanes by nuclear magnetic resonance (NMR) and Matrix-Assisted Laser Desorption/Ionization-Time-Of-Flight Mass Spectrometry (MALDI-TOF MS), and demonstrated that the two combined techniques provide a robust method for the identification of structures, chain terminations, and by-products derived from side reactions.

Muñoz-Guerra et al. [18] prepared segmented PU from hydroxyl-end-capped polycaprolactone (3000 g/mol) as soft segment, diisocyanates HDI (**3**) or MDI (**23**) and 1,4-butanediol, isosorbide (**1**), and/or 2,4:3,5-di-O-methylene-D-glucitol (**33**) as extenders. The comparative effect of the preparation method (in solution or in bulk) and the influence of the selected extender (**1** or **33**), on the properties of the resulting segmented PU, were evaluated. Hydrolytic degradability was significantly increased by the presence of sugar units, although polymer degradation took place fundamentally by hydrolysis of the polyester soft segment. The same authors also carried out a comparative study of non-segmented polyurethanes with the purpose of evaluating the effect of the replacement of 1,4-butanediol by **1**. The polymerizations were accomplished by standard methods using HDI and MDI as isocyanates [52]. It was observed that T_g values of PU increased with the content in isosorbide.

Koning et al. have investigated water-borne polyurethanes based on isosorbide (**1**) and other renewable building blocks, such as amino acids and fatty acids [26, 27, 53]. The synthesis of water-dispersible polyurethanes prepolymers was carried out from **1**, ethyl ester L-lysine diisocyanate (**46**), dimethylpropionic acid, and a dimer fatty acid-based diisocyanate [53]. The regioselectivities of the endo- and exo-OH functional groups of **1** and the primary ϵ -NCO and secondary α -NCO of **46** were found to have only minor consequences for the formation of NCO-terminated PU prepolymers. PU dispersions prepared from these four-component prepolymers showed good storage stability. Fully renewable poly(ester urethane urea)s (PEU) were also synthesized from bio-based starting materials: the renewable polyester diol poly(1,2-dimethylethylene adipate), isosorbide diisocyanate (**11**), and

diaminoisoidide (**83**) as chain extender. The authors found that the PEU based on the isoidide diisocyanate (**11**) exhibited satisfactory thermal and mechanical properties [54].

Thermoplastic and cross-linked bio-based PU with tailored properties and high renewable carbon content were synthesized from isosorbide (**1**), 1,3-propanediol, and 1,1,1-tris-(hydroxymethyl) propane as the cross-linker reagent, in bulk by varying the molar ratio of the components and without using any chemical catalysts [55].

5. Other conformationally restricted linear PU

The bicyclic structures of the dianhydrohexitols (**1**, **20**, **21**) provide conformational restriction and stiffness to the polymer chain, with a significant increase in the T_g . Galbis et al. [7] reported new conformationally restricted linear polyurethanes based on bicyclic carbohydrate-based monomers having *D-gluco*, *galacto*, and *D-manno* configurations (**33**, **43**, **44**) and their secondary hydroxyl groups protected as cyclic acetals (**Figure 9**). The T_g values of these conformationally restricted polymers were similar to those observed for the polyurethanes [PU(Is-HDI) and PU(Is-MDI)] based on the isosorbide (**1**) [52] and higher than their acyclic analogs. They also proved that the diacetalization of the sugar unit of the polyurethane chain improved the thermal stability, which was comparable to those based on isosorbide.

The two orthoesters **86** and **87** having a rigid adamantane-like structure (**Figure 10**), obtained from naturally occurring *myo*-inositol (**85**), were used as new triol- and diol-type monomers to give the corresponding networked and linear polyurethanes by polyaddition reaction with diisocyanates [56].

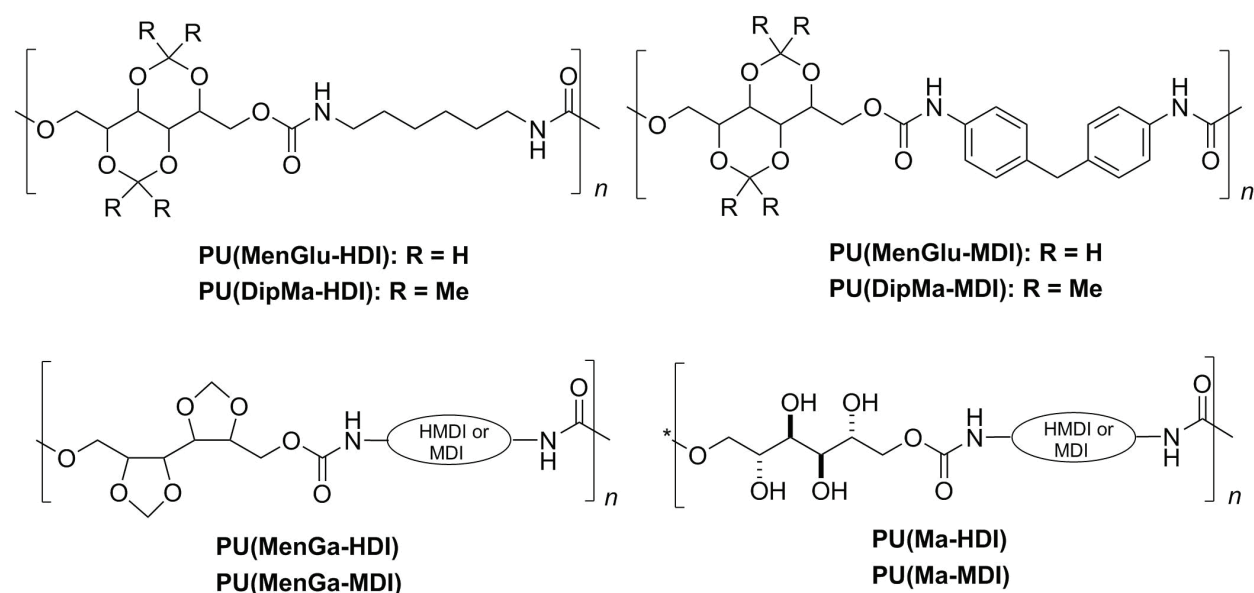


Figure 9. Conformationally restricted hydroxy-polyurethanes based on hexitols.

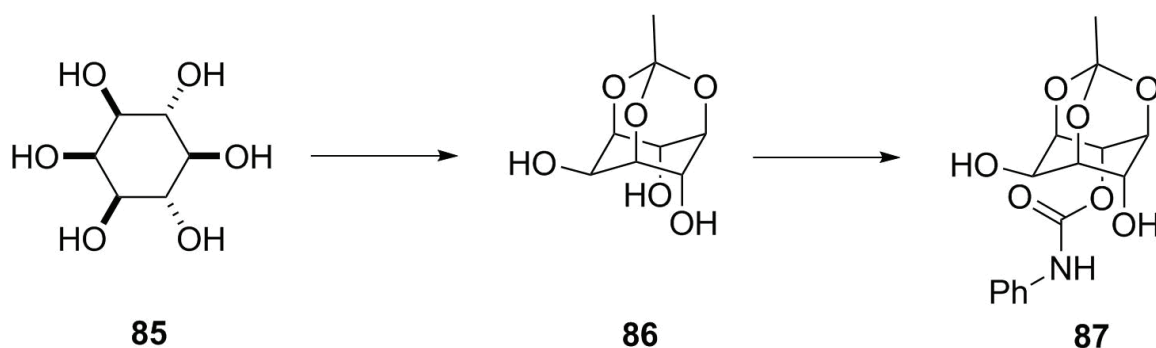


Figure 10. *myo*-Inositol-based rigid adamantane-like monomers.

The linear polyurethanes obtained from **87** showed high values of T_g , ranging from 105 to 177°C, due to the rigidity of the adamantane-like structure units introduced into the main chains. T_g 's of the networked polyurethanes obtained from **86** were higher than those of the linear polyurethanes, and ranged from 155 to 248°C.

6. PU with enhanced hydrophilicity

PU with free hydroxyl groups (PHU) have been synthesized from acetalized sugar-based monomers, mainly isopropylidene and benzylidene groups, which are very easily cleaved under acidic conditions. Thus, deacetalization of those polyurethanes containing di-*O*-isopropylidene-*D*-mannitol units (**44**) yielded multihydroxy polymers in good yields without apparent degradation of the polymer chain (Figure 9) [7]. The latter polymers showed enhanced hydrophilicity and hydrolytic degradability as well as lower T_g values and thermal stability than their acetalized counterparts.

Methyl 2,6-di-*O*-pivaloyl- α -*D*-glucopyranoside (**14**) or methyl 4,6-*O*-benzylidene- α -*D*-glucopyranoside (**15**) catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) were polymerized with HDI [10]. Likewise, diol **15** was also copolymerized with the methyl ester of L-lysine diisocyanate (**4**) [35] and HDI as well as the diol 1,2:5,6-di-*O*-isopropylidene-*D*-glucitol (**19**). The corresponding polyhydroxy PUs were obtained by deprotection in aqueous trifluoroacetic acid solution.

A stereoregular polyhydroxy [AB]-polyurethane was prepared from 1-deoxy-1-isocyanate-2,3:4,5-di-*O*-isopropylidene-*D*-galactitol (**52**) (prepared from 1-amino-1-deoxy-2,3:4,5-di-*O*-isopropylidene-*D*-galactitol) and the subsequent hydrolysis of the isopropylidene groups (Figure 11) [41]. No data on the degradation studies were provided.

Polyaddition reaction of L-gulonic acid-based diols (**16**, **17**) to diisocyanates, followed by the hydrolysis of the isopropylidene groups, yielded PU containing lactone rings and free hydroxyl groups in the main polymer chains (Figure 12) [11]. The free hydroxyl groups also enhanced the hydrolysis of lactone rings and, hence, of carbamate groups in the polyurethanes. The multihydroxy polyurethane prepared from L-gulonolactone **16** and HDI was degradable at pH 8.0 under mild temperatures.

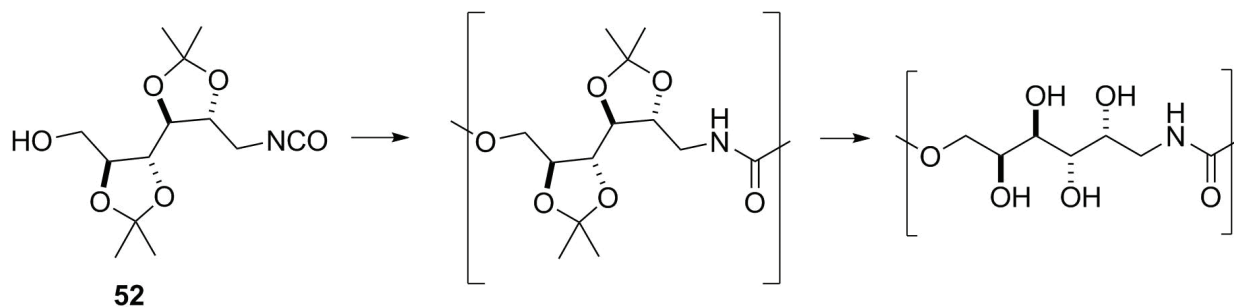


Figure 11. [AB]-Polyurethanes from 1-deoxy-1-isocyanate-2,3:4,5-di-O-isopropylidene-D-galactitol.

1,2:5,6-di-O-Isopropylidene-D-mannitol (**37**) and 1,2-O-isopropylidene-D/L-erythritol (**38/39**) were the starting materials for the preparation of new linear multihydroxy polyurethanes by polyaddition with HDI and MELDI (**4**), and subsequent deprotection in acidic media [23]. Likewise, copolyurethanes from **37** and poly(oxytetramethylene) glycol were also prepared to estimate the effects of the D-mannitol unit on their degradability.

The O-benzyl derivatives **29**, **31**, and **32** with L-arabino, L-threo, and xylo configurations, respectively, were used to prepare PU, and the effect of pendant bulky benzyl groups in the polymer chain was investigated [16, 17]. The removal of benzyl groups was attempted by hydrogenolysis, and the best results were obtained for the PU derived from L-threitol and HDI, which became debenzylated up to 70%. It was found that O-benzylated PU were highly resistant to hydrolytic degradation, whereas PU with free hydroxyl groups degraded to a great extent under physiological conditions.

To achieve a facile preparation of sugar-based multihydroxy PU, the use of unprotected saccharides was also investigated. Thiem et al. reported the synthesis of novel PU and polyureas based

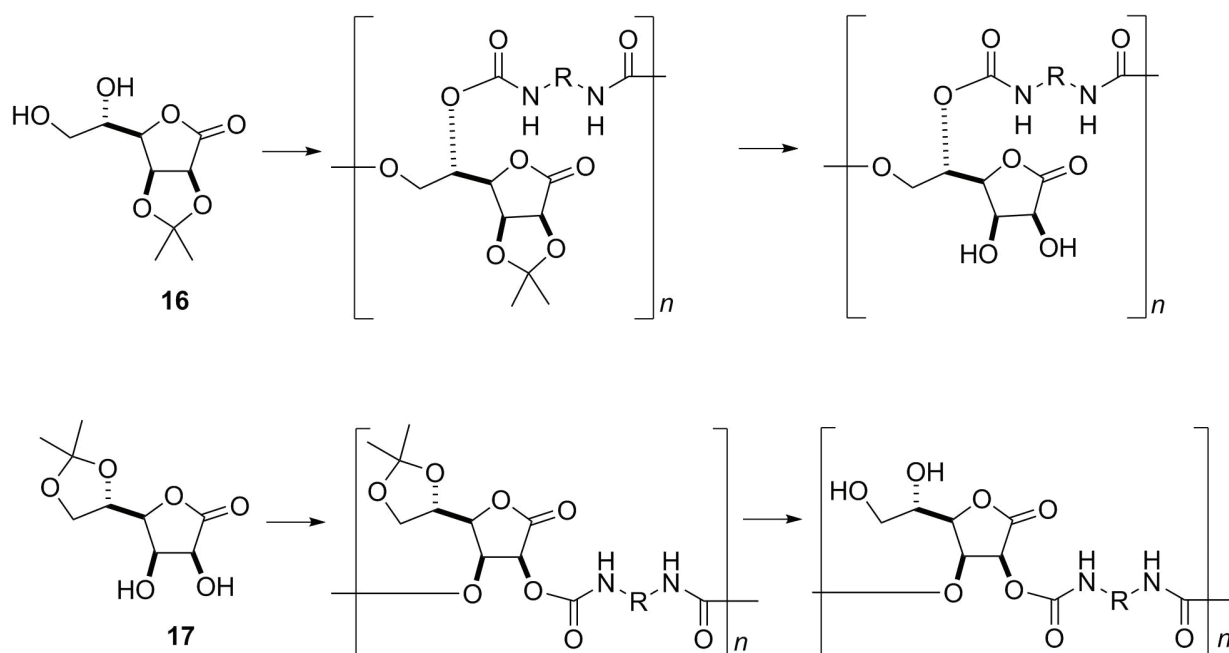


Figure 12. Polyaddition of L-gulonic acid-based diols to diisocyanates.

on modified glycosylamines and glucosamines by catalytic polymerizations [31]. It was found that the anomeric hydroxyl groups were more reactive than the amino groups.

The selective reaction of primary hydroxyl groups of xylitol (**55**) with dimethyl hexamethylene dicarbamate (HDC, **56**) or di-*tert*-butyl-4,4'-diphenyl methyl dicarbamate (MDC, **59**) led to two new linear polyurethanes [PU(X-HDC) and PU(X-MDC)] (**Figure 13**) [6]. Likewise, by the reaction of xylitol with the analogous diisocyanates HDI or MDI, similar polyurethanes [PU(X-HDI) and PU(X-MDI)] were obtained. However, the reaction conditions needed to be adjusted, and so low temperatures were required. Even so, a certain degree of cross-linking was encountered because of the higher reactivity of the diisocyanate comonomers. PU(X-MDC) and PU(X-MDC) were semicrystalline materials showing well-defined melting transitions with high melting enthalpies.

Two novel sugar-based polyol monomers from methyl α -D-glucopyranoside and sucrose and epoxidized methyl oleate were synthesized (**Figure 14**) [51]. Linear and cross-linked PU were obtained by polyaddition with isophorone diisocyanate (**80**) as comonomer, at 60°C using DBTDL as catalyst. The amphiphilic nature of the sugar-based monomers had a marked impact on the final product isolated. Thus, linear or cross-linked PU were obtained depending on the solvent used, that is, DMF or THF. It was found that the polyol monomers were fully soluble in DMF, and therefore cross-linked PU were obtained. By contrast, the formation of linear PU with one pendant sugar moiety per monomer unit was attained in THF. The hydroxyl functions from the sugar moiety were quasi nonreactive under those conditions due to the self-assembly of the sugar-based polyols into nanoparticle structures.

Although polyurethanes are widely investigated, their sulfur analogs, polythiourethanes (PTU), are a relatively poorly investigated group of polymeric materials [57]. The synthesis and characterization of a new linear functional polythiourethane based on D,L-1,4-dithiothreitol [PTU(DTT-HDI)] has been accomplished (**Figure 15**), and its properties as excipient in drug release formulations investigated [58]. This PU with free hydroxyl groups in its structure showed a major ability

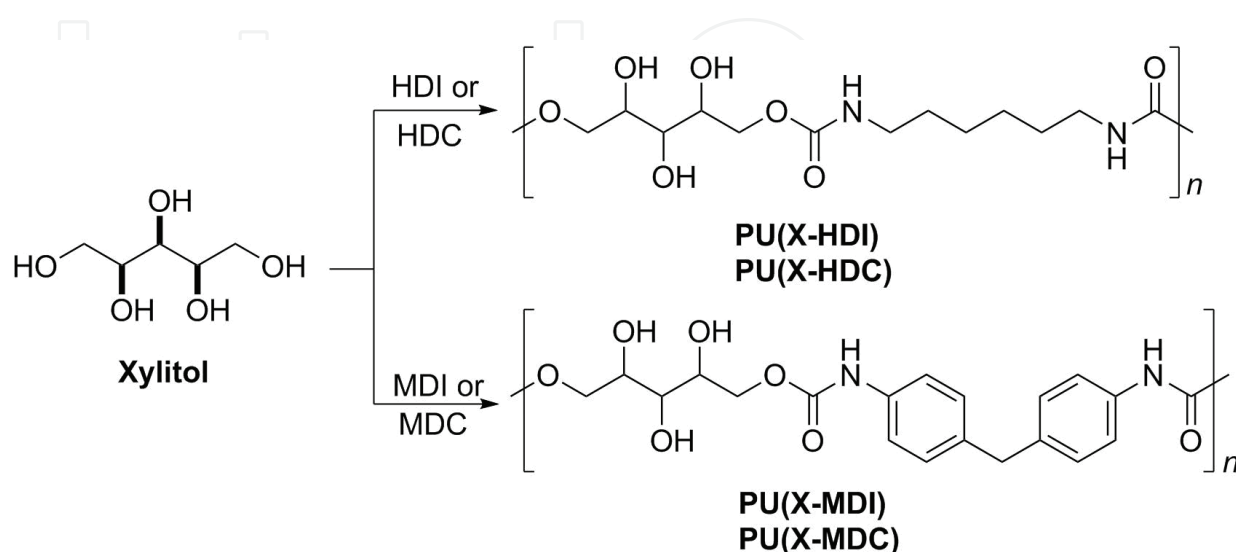
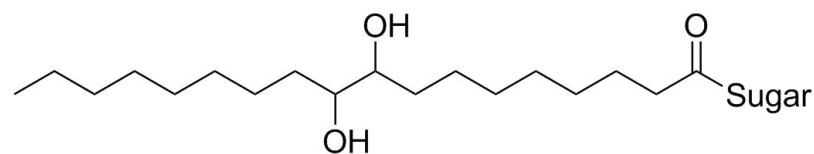
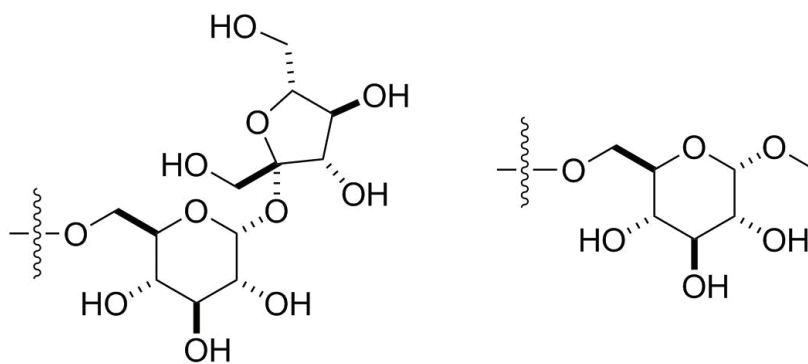


Figure 13. Linear polyurethanes with enhanced hydrophilicity.



Sugar:



Sucrose

Glucose

Figure 14. Diol monomers synthesized from methyl α -D-glucopyranoside or sucrose and epoxidized methyl oleate.

to form matrix systems and promoted a significant decrease in the release rate of the model drug theophylline; as a result, it proved to be an excellent controlled release matrix forming excipient.

An homopolyurethane with free secondary hydroxyl groups based on 3,4-*O*-isopropylidene-D-mannitol and 2,2'-dithiodiethyl diisocyanate has been used as sustained matrix forming excipient for site-specific drug release in the gastrointestinal tract [59].

The reaction of diglycerol dicarbonate, synthesized from diglycerol and dimethyl carbonate, and various diamines led to amorphous poly(hydroxy urethane)s, in bulk at mild temperatures, without any catalyst. The abundance of hydroxyl groups along the polymer backbones allows curing purposes and/or further functionalization [60]. Very rigid polyurethane foams with high cross-linking density were obtained from sorbitol-based polyols. The cross-linking density of the formed PU network was directly modified by the polyol mixture ratio, and microstructure and properties also changed in consonance. The incorporation of different amounts of a diol with longer chain length between hydroxyl groups allowed fixing the rigidity of the foams [61].

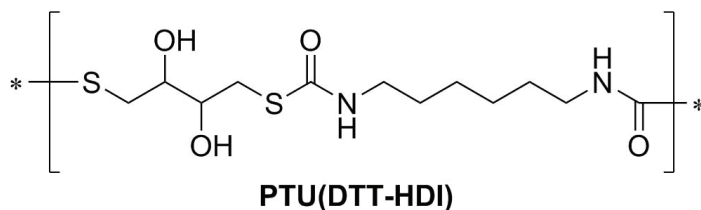


Figure 15. Structure of D,L-1,4-dithiothreitol-based polyurethane.

7. Degradable PU

7.1. Hydrolytic: non-enzyme and enzyme-mediated degradation

The *O*-protected L-threitol, L-arabinitol, and xylitol diols (**24–26**, **29**, **31**, **32**) were used [14] to prepare a series of linear [AABB]-type PU (**Figure 16**) by polyaddition reaction to HDI (**3**) and MDI (**23**). The *O*-methyl-protected polyurethanes derived from **38** and **39** were amorphous and their T_g was highly dependent on the aliphatic or aromatic nature of the diisocyanate used. The hydrodegradability of these PU was conditioned by the number of methoxy side groups present in the repeating unit.

The hydrophilic polyurethanes PU(X-MDC) and PU(X-MDC) (**Figure 13**) obtained by the reaction of xylitol with dimethyl hexamethylene dicarbamate (HDC) or di-*tert*-butyl-4,4'-diphenyl methyl dicarbamate (MDC) [6] were hydrolytically degradable under physiological conditions, in contrast with less-hydrophilic linear polyurethanes previously described [14].

In order to enhance degradability, a series of homo- and copolyurethanes containing the hydrophilic monomer [triethylene glycol (TEG)] and 1,4-di-*S*-benzyl-D,L-dithiothreitol (DTTSBn) (**34**) with HDI (**3**) [19] was synthesized (**Figure 17**). Enzymatic degradation studies were carried out with a variety of proteolytic and esterase enzymes. They were thermally stable up to 250°C, and PU(TEG-HDI) homopolymer was degraded under physiological conditions. In addition, a study of the properties of this PU as matrix-forming excipient for controlled drug delivery was carried out [20].

7.2. Reductive degradation

Galbis et al. reported the introduction of disulfide linkage into the polymer backbone of novel reduction-sensitive biodegradable sugar-based polyurethanes. Although hydrolytical degradation of PU has been extensively reported, a faster degradation method under milder degradation conditions was achieved mediated by glutathione (GSH) [21]. Thus, polyaddition reactions of mixtures of 2,2'-dithiodiethanol (DiT) and 2,3,4-tri-*O*-methyl-L-arabinitol (**25**), 2,3,4-tri-*O*-benzyl-L-arabinitol (**29**) or L-arabinitol (**35**) to HDI (**3**) were carried out (**Figure 18**). PU(DiT-HDI) homopolymer exhibited high crystallinity but the introduction of the L-arabinitol-based diols led to a reduction in the crystallinity of the copolymers. All the copolyurethanes were biodegraded under physiological conditions being crystallinity an important factor in the degradation rate. Thus, the amorphous copolymers with low DiT repeating unit contents were more easily cleaved, despite the lower disulfide ratio. Their DiT repeating units do not pack into semicrystalline segments and

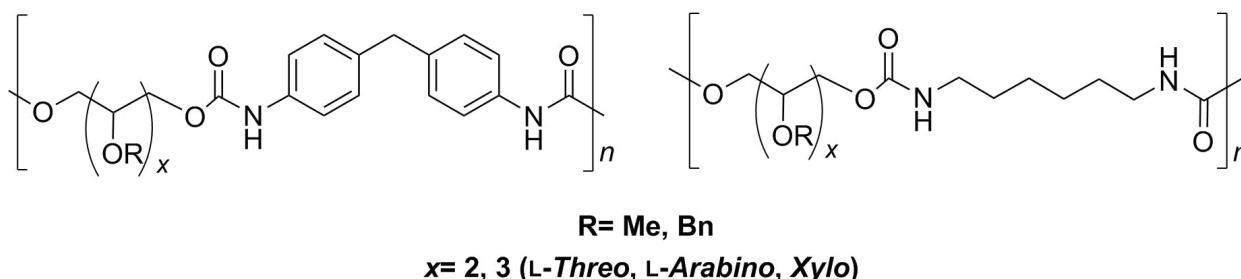


Figure 16. Linear polyurethanes derived from *O*-protected alditols.

were, as a result, more accessible to the reducing agent. Therefore, the amorphous copolymers PU [(ArBn₈₀-DiT₂₀)-HMDI] and PU[(ArMe₈₀-DiT₂₀)-HMDI] were those with enhanced degradation trends.

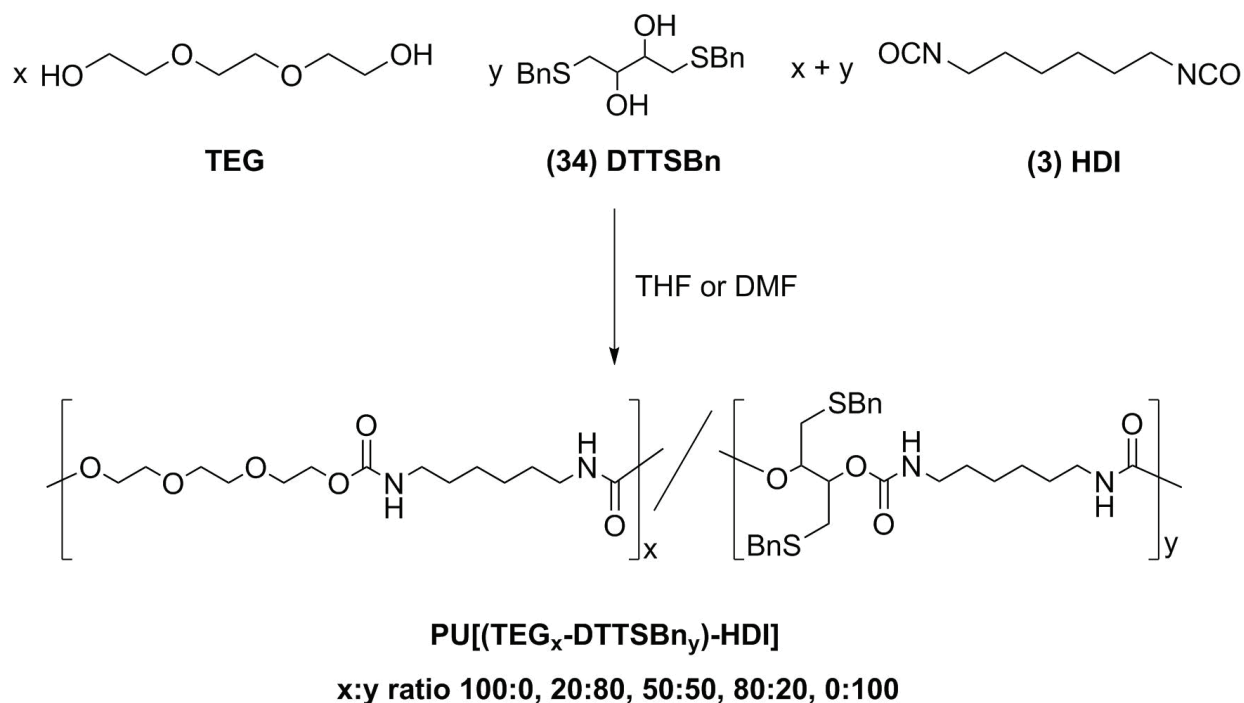


Figure 17. Copolyurethanes derived from 1,4-di-S-benzyl-D,L-dithiothreitol.

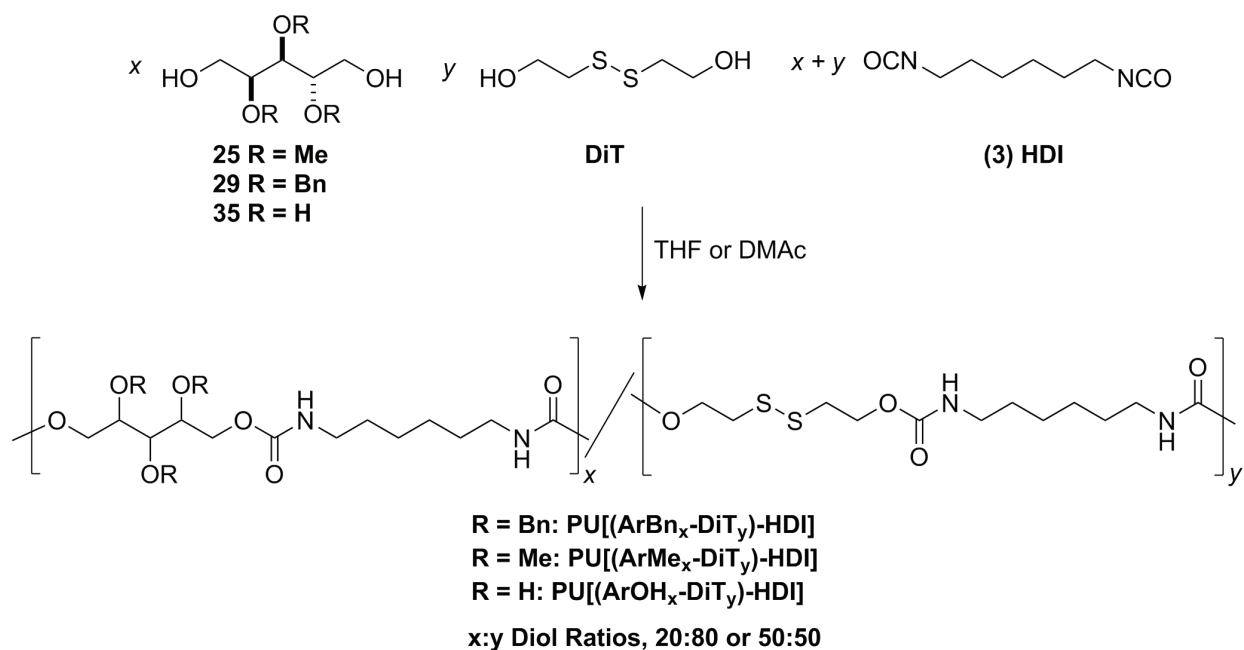


Figure 18. Copolyurethanes degradable by glutathione under physiological conditions.

8. Functional PU

The chemical modification of polymers is an important task for further applications. In this sense, click chemistry (CC) is the most popular approach to achieve chemical transformations; for instance, the thiol-ene coupling reaction of a thiol and an alkene/alkyne and the alkyne-azide cycloaddition reaction.

Galbis et al. described the preparation of new polymerizable diols based on di- and tri-*O*-allyl- and tri-*O*-propargyl-*L*-arabinitol derivatives prepared from *L*-arabinitol (**36**, **40**, **49**) as versatile materials for the preparation of tailor-made polyurethanes with varied degrees of functionalization, such as NHBoc, carboxylic or 1,2-dihydroxyethyl side groups (**Figures 19–21**) [22, 24]. This strategy provides a simple and versatile platform for the design of new materials whose functionality can be easily modified to anchor diverse biologically active molecules. From

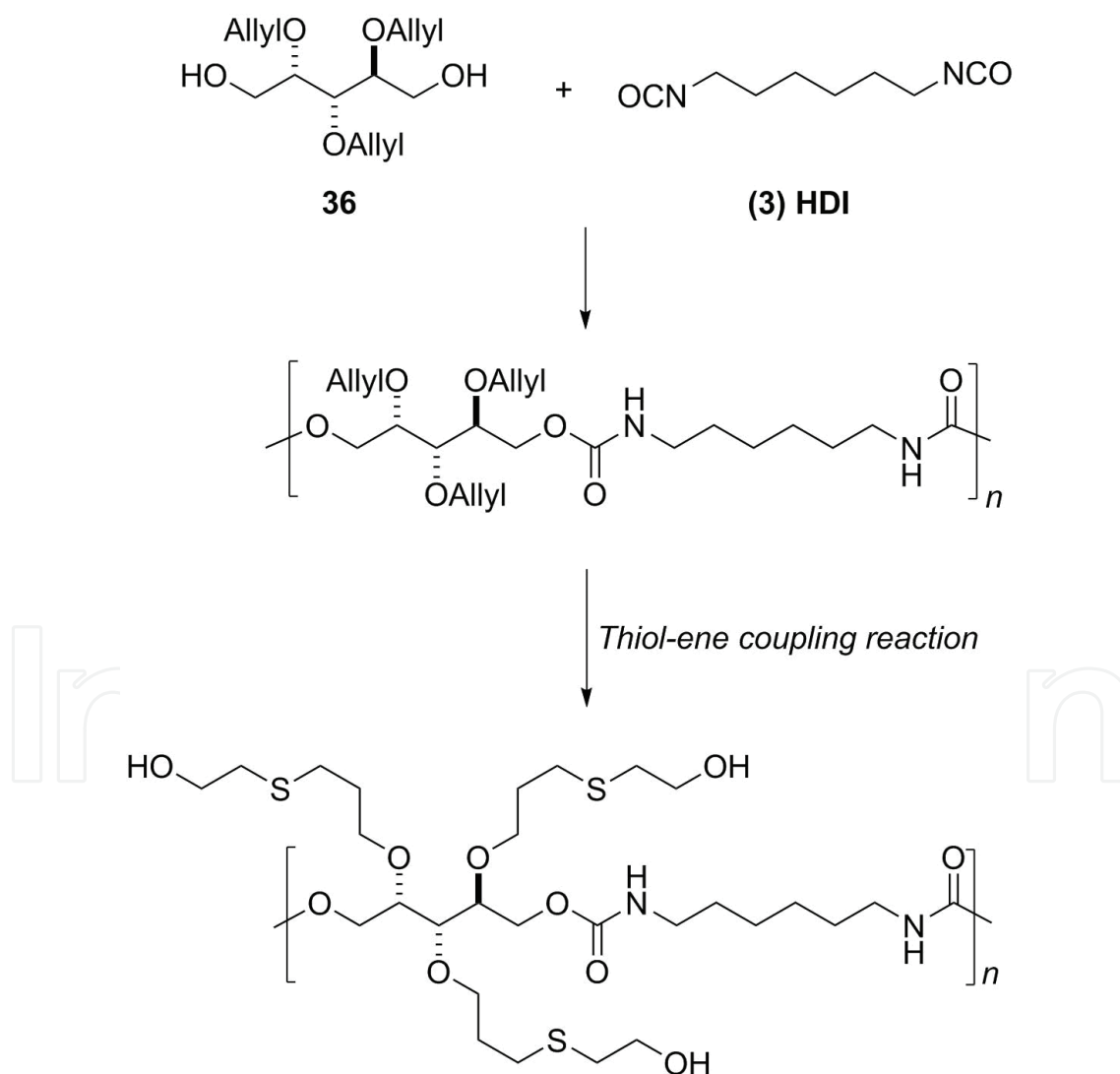


Figure 19. Functionalization of *O*-allyl polyurethanes by the click thiol-ene reaction.

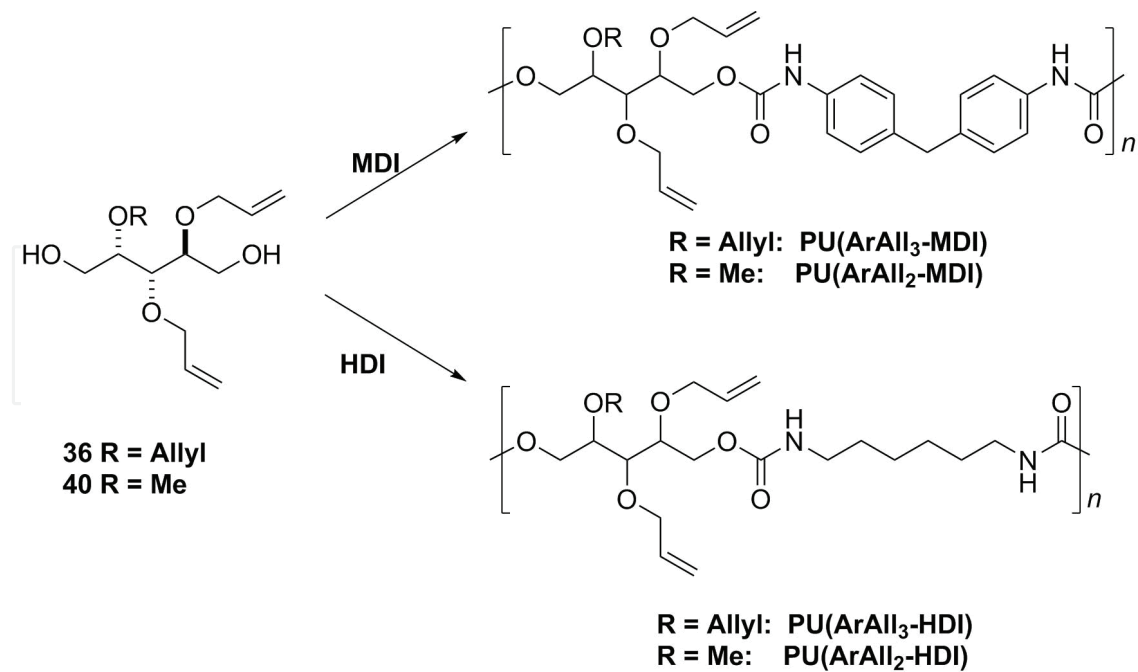


Figure 20. Synthesis of allyl homopolyurethanes.

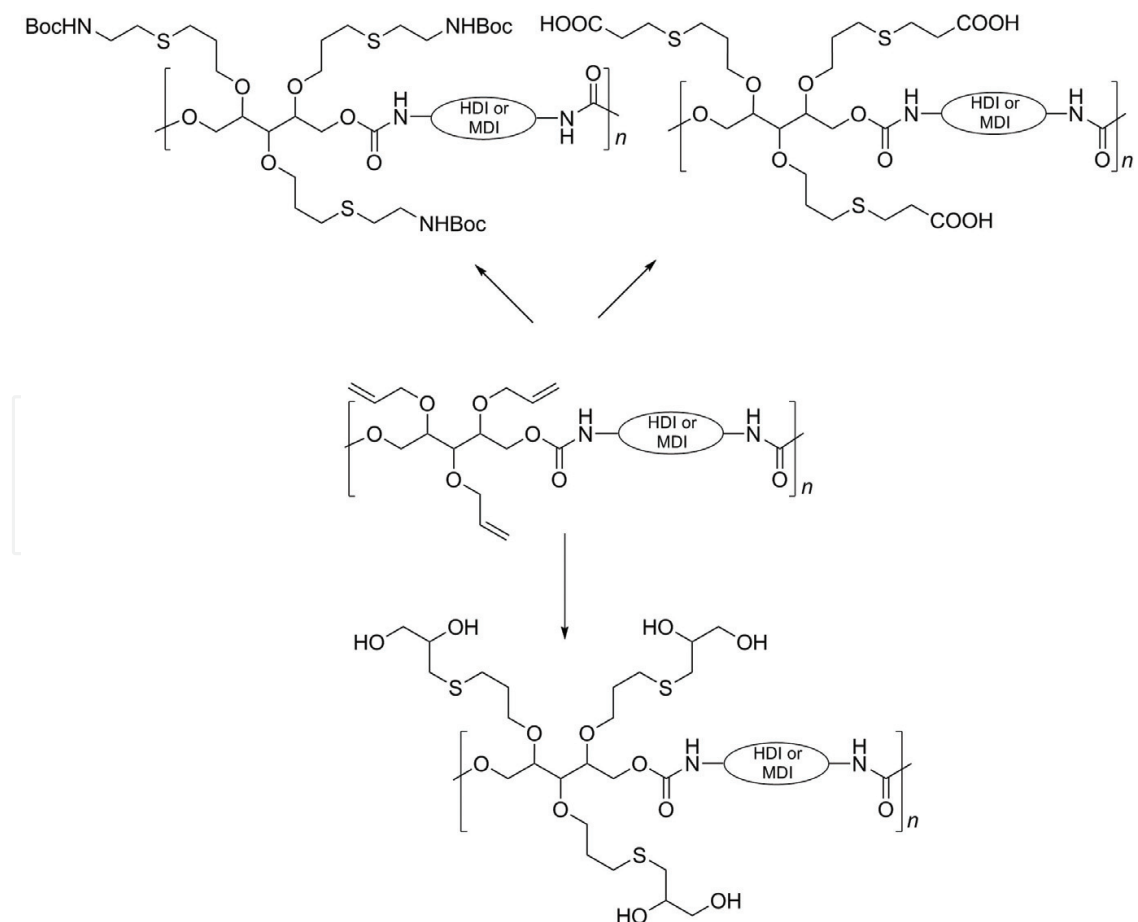


Figure 21. Functional polyurethanes prepared by click reactions on *O*-allyl polyurethanes.

Similarly, the preparation of PU with well-defined “tunable” macromolecular comb-like architectures was successfully accomplished [30] by means of a two-step procedure: preparation of multipropargyl copolyurethanes based on the tri-*O*-propargyl-L-arabinitol derivative **49** and DiT and their subsequent derivatization via alkyne-azide click reaction with chemically diverse azides—dodecyl azide, triethylene glycol azide, and polyethylene glycol azide. This methodology allowed the generation of PU with an extensive chemical diversity that has been unapproachable until now. It is remarkable that a wide variation in degradability under reductive environment could be attained simply by adjusting the chemical structure of the polymer to synthesize.

9. Conclusions

Monosaccharide-based polyurethanes (PU) have been usually prepared by step-growth polymerization from diisocyanates and sugar-based diols but, in the last years, and due to the toxicity of stannous catalysts and common aromatic diisocyanates, other eco-friendly methods have been developed and many works have been reported on the synthesis of isocyanate-free PU, also called non-isocyanate PU (NIPU). Although most syntheses of high-molecular-weight linear polyurethanes involve monosaccharide derivatives having the hydroxyl groups appropriately blocked, several PU with enhanced hydrophilicity and hydrolytic degradability have been synthesized using sugar-derived monomers with free hydroxyl groups or by deprotection of PU prepared from *O*-protected sugar-based monomers.

In order to enhance degradability, a series of homo- and copolyurethanes containing the hydrophilic monomer [triethylene glycol (TEG)] was synthesized. The introduction of disulfide linkage into the polymer backbone of novel reduction-sensitive biodegradable sugar-based polyurethanes has also been reported. Thus, a faster glutathione-mediated degradation method was accomplished under milder degradation conditions.

The chemical modification of PU is important in order to search further applications. Click chemistry (CC) is the most widely used approach to achieve these chemical transformations; for instance, the thiol-ene/yne coupling reaction and the alkyne-azide cycloaddition reaction. In this sense, di- and tri-*O*-allyl- and tri-*O*-propargyl-L-arabinitol derivatives have been used as versatile materials for the preparation of tailor-made polyurethanes with varied degrees of functionalization.

We can conclude that it is viable to prepare monosaccharide-based polyurethanes analogous to the more qualified conventional polymers, but having a larger functionality and an enhanced hydrophilicity and degradability. However, in most cases, the high costs that represent the preparation of the monomers restrict the application of these polymers to the biomedical and other specialized fields.

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