– 5 –

Sugars as Monomers

J.A. Galbis and M.G. García-Martín

ABSTRACT

Sustained efforts have been extensively devoted to prepare new polymers based on renewable resources and with higher degradability. Of the different natural sources, carbohydrates stand out as highly convenient raw materials because they are inexpensive, readily available, and provide great stereochemical diversity. This chapter describes the potential of sugar-based monomers as precursors to a wide variety of macromolecular materials, with particular emphasis on both the mechanisms of polymerization and the properties of the ensuing products.

Keywords

Sugar-based monomers, Carbohydrate monomers, Bifunctional sugar derivatives, Alditols, Aminosugars, Aldonic acids, Aldaric acids

5.1 INTRODUCTION

Biodegradable polymers obtained from renewable natural sources are currently receiving increasing attention because they are an alternative to the traditional petroleum-based plastics. Solid-waste management of plastics of agricultural or alimentary origin is demanding a rapid development of new biodegradable plastics. Another important application is in biomedicine, and in this field, biocompatibility is a required feature for resorbable biomedical devices.

Carbohydrates are an important natural source of building blocks for the synthesis of biodegradable polymers, especially for biomedical applications, because of their inherent properties of biocompatibility and biodegradability, and for the design of optically active polymers containing stereocentres in the repeating unit. There are various reasons for the interest in carbohydrates as polymer building blocks namely, (a) they are easily available, some even coming from agricultural wastes; (b) they are found in a very rich variety of chemical structures with great stereochemical diversity; and, above all, (c) they constitute a renewable source thanks to solar energy. Unfortunately, polycondensation of monomers derived from sugars is not straightforward. In the first place, their multifunctionality must usually be reduced, making use of appropriate protecting groups to prevent side reactions leading to undesirable products. Secondly, in order to obtain regio and stereoregular polymers, strict control of the stereochemical course of the polymerization is required. Otherwise, random orientation of the chiral unit will lead to atactic polymers.

Some reviews have recently been published on the synthetic carbohydrate-based polymers and glycopolymers [1–6]. However, they refer mainly to poly(vinylsaccharide)s and other conventional functionalized polymers having sugars as groups pendant from the main chain of the polymer. In this chapter, we shall describe those sugar-based monomers which lead to polymers having the sugar units incorporated into the main chain. The topic has also been excellently reviewed [7–10], but as the interest in this kind of carbohydrate-based polymer has been steadily increasing, a considerable number of papers have been published on the subject during the last few years.

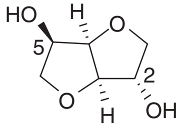
The following sections report on the synthesis and polymerization of this type of sugar-derived monomers that have been published mainly during the past decade.

5.2 ALDITOLS

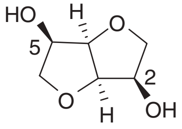
Acyclic alditols are sometimes referred to as glycitols or polyols. Polyols occur extensively in nature, but aldoses and ketoses can be reduced to alditols with the generation of new hydroxyl groups from the carbonyl functions; thus, D-glucose gives D-glucitol, trivially referred to as 'sorbitol'. The reduction of ketoses generates a new stereogenic centre, and gives two epimeric alditols; for example, D-fructose produces D-mannitol and D-glucitol.

5.2.1 Anhydroalditols

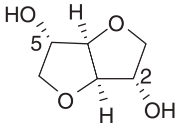
The thermally stable 1,4:3,6-dianhydrohexitols are the carbohydrate-based monomers most widely employed in the synthesis of chiral polymers because they are easily available. The three stereoisomeric dianhydroalditol monomers, having 1,4:3,6-dianhydro-D-*gluco*, -D-*manno*, and -L-*ido* configurations, have attracted increasing interest as building blocks for the synthesis of polycondensates, as reported by Kricheldorf [8]. These dianhydroalditols are referred to as isosorbide (DAS or DAG), isomannide (DAM), and isoidide (DAI). DAS is commercially produced in large quantities from starch by hydrolysis, subsequent reduction, and acid-catalyzed intramolecular dehydration. DAM is also readily available from D-mannose, by reduction and dehydration. Since L-idose is a rare sugar, and its synthesis from D-glucose requires several steps, DAI is obtained from DAS by a three-step procedure. DAS and DAM are currently commercially available. The DAS-based polymers are non-stereoregular, in contrast to those based on DAM and DAI, which are stereoregular.



D-*gluco* (DAS or DAG)
Isosorbide



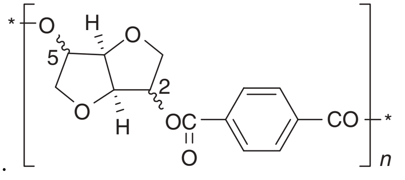
D-*manno* (DAM)
Isomannide



L-*ido* (DAI)
Isoidide

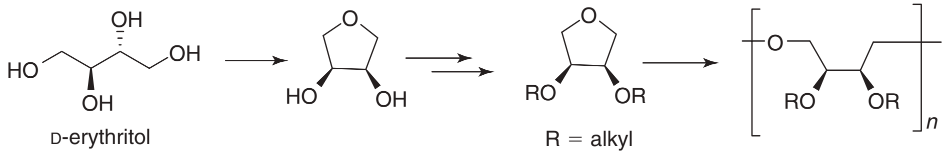
The thermostability of these dianhydroalditol monomers may be higher than that of other aliphatic diols, which raises the T_g of the corresponding polymers. The most representative dianhydroalditol-based polymers that have been synthesized are polyesters, polycarbonates, polyethers, poly(ester carbonate)s, poly(ester anhydride)s, polyurethanes, polyureas, and poly(ester amide)s.

Thiem *et al.* prepared low-molecular weight polyterephthalates [11, 12] by melting condensation of terephthalic acid dichloride and 1,4:3,6-dianhydrohexitols. DAM turned out to be too labile under these conditions, giving cross-linked products. Storbeck *et al.* reinvestigated [13] the synthesis and characterization of these polyterephthalates; the reaction conditions were optimized, and pyridine was found to be the most useful acceptor of hydrogen chloride.

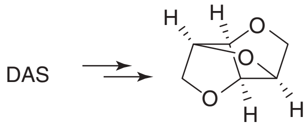


5-endo/2-exo, D-*gluco*
5-endo/2-endo, D-*manno*
5-exo/2-exo, L-*ido*

Poly(oxytetramethylene) is extensively used as a softening segment for polyurethane production. Thiem *et al.* studied, as an alternative, the ring-opening polymerization of 1,4-anhydro-2,3-di-*O*-alkyl-D-erythritols [14–16] using super-acids $HFSO_3$ and HCF_3SO_3, which led to novel functionalized poly(2,3-dialkoxytetramethylene)s. As previously demonstrated for ring-opening polymerization of carbohydrate acetals, as well as ethers, enhanced amounts of catalyst were required, in contrast to the case of non-carbohydrate starting materials.

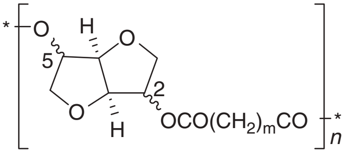


Base-catalyzed intramolecular-nucleophilic substitution of various DAS derivatives led to the formation of 1,4:2,5:3,6-trianhydro-D-mannitol, a tricyclic system of three interlinked oxolane rings, which afforded oligomeric soluble materials by ring-opening polymerization after treatment with CF_3SO_3H [17]. Ring-opening copolymerization of 1,4-anhydro-2,3-di-*O*-ethyl-D-erythritol or 1,4:2,5:3,6-trianhydro-D-mannitol with tetrahydrofuran (THF), using CF_3SO_3H as catalyst, afforded a series of copolyether polyols [18]. The polymers had medium molecular weights, with approximately 10 per cent of carbohydrate constituent.



Braun and Bergmann [19, 20] used DAS and DAM for the syntheses of polyesters, polyethers, polyurethanes, and polycarbonates. They reported that the thermal and mechanical properties of the obtained polymers were similar to those of the respective counterparts obtained from usual petrochemical raw materials.

Okada *et al.* have worked extensively on biodegradable polymers based on dianhydroalditols as carbohydrate renewable resources. A series of polyesters were synthesized by the bulk polycondensation of the respective three stereoisomeric dianhydroalditols (DAS, DAM, and DAI) with aliphatic dicarboxylic acid dichlorides of 2–10 methylene groups [21, 22]. It was found that the biodegradability of the polyesters varied significantly depending on their molecular structures.

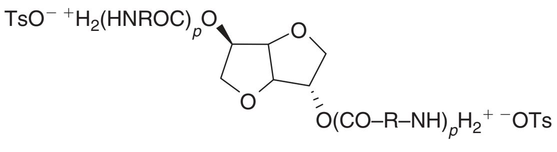


5-endo/2-exo, D-*gluco*
5-endo/2-endo, D-*manno*
5-exo/2-exo, L-*ido*

m = 2–10

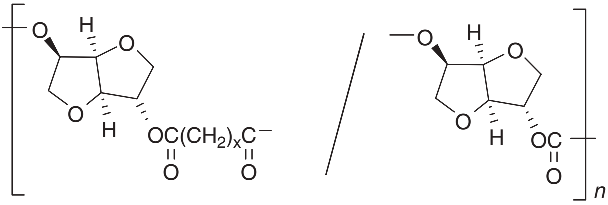
DAS or DAM was also used as comonomer with dimethyl dialkanoates and monomers containing furan rings, for the synthesis of copolyesters by bulk polycondensations, in the presence of titanium isopropoxide or tetrabutyl-1,3-dichloro-distannoxane [23, 24]. In general, the biodegradability of the copolyesters of DAS decreased with increasing difuran dicarboxylate content, and copolymers containing sebacic acid units showed higher biodegradability. The enzymatic degradability of the polyesters based on isomeric 1,4:3,6-dianhydrohexitols and sebacic acid was found to decrease in the order DAS > DAM > DAI [25].

The synthesis and biodegradation behaviour of poly(ester amide)s composed of DAS, α-amino acid, and aliphatic dicarboxylic acid units were also described by Okada [26]. These products were synthesized by solution polycondensation of various combinations of *p*-toluenesulphonic acid salts of *O,O′*-bis-(α-aminoacyl)-1,4:3,6-dianhydro-D-glucitol and bis(*p*-nitrophenyl) esters of aliphatic dicarboxylic acids with methylene chain lengths of 4–10. The *p*-toluenesulphonic acid salts were obtained by the reactions of DAS with alanine, glycine, and glycylglycine, respectively, in the presence of *p*-toluenesulphonic acid. The poly(ester amide)s were, in general, degraded more slowly than the corresponding polyesters having the same aliphatic dicarboxylic acid units, both in composted soil and in an activated sludge.



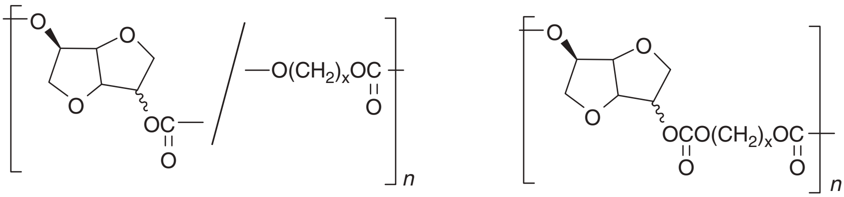
R = CHMe or CH_2

Poly(ester carbonate)s with different compositions were synthesized by bulk polycondensation of DAS with diphenyl sebacate and diphenyl carbonate in the presence of zinc acetate as a catalyst [27]. Biodegradability was found to be highest for the poly(ester carbonate)s with carbonate contents of 10–20 mol per cent, and to decrease markedly for those with the carbonate content above 50 mol per cent.



Okada published in 2002 a couple of reviews on biodegradable polymers from DAS and DAM and their related compounds [28] and chemical synthesis [29].

Novel random and alternating copolycarbonates from 1,4:3,6-dianhydrohexitols and aliphatic diols were synthesized in bulk or solution polycondensations [30]. Bulk polycondensations of 1,4:3,6-dianhydro-2,5-bis-*O*-(phenoxycarbonyl)-D-glucitol and -D-mannitol with α,ω-alkanediols of different number of methylene groups, afforded random copolycarbonates. However, solution polycondensations of the corresponding *p*-(nitrophenoxycarbonyl) monomers in solution gave well-defined copolycarbonates having regular structures consisting of alternating sugar carbonate and aliphatic carbonate moieties.

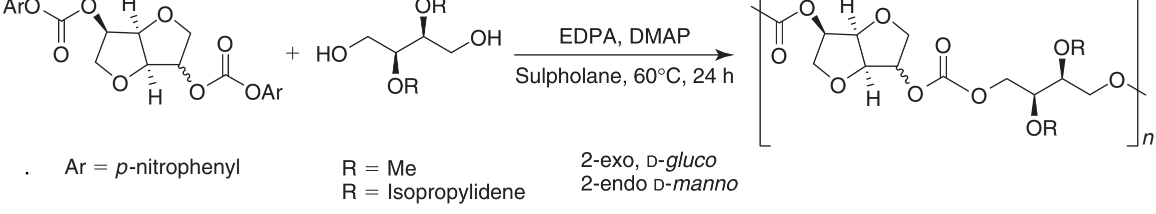


$x = 4, 6, 8, 10$

Random copolycarbonates Alternating copolycarbonates

The environmental and enzymatic degradability of copolycarbonates consisting of DAS and DAM and alkylene diols or oligo(ethylene glycols) was investigated [31].

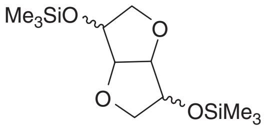
Tartaric acid has also attracted a great deal of interest as a substrate for the synthesis of functional polymers based on carbohydrates; for example, L-tartaric acid is a natural product mainly obtained from a large variety of fruits. Okada has recently accomplished the study of novel polycarbonates with pendant functional groups, based on 1,4:3,6-dianhydrohexitols and L-tartaric acid derivatives [32]. Solution polycondensations of 1,4:3,6-dianhydro-bis-*O*-(*p*-nitrophenoxycarbonyl)hexitols and 2,3-di-*O*-methyl-L-erythritol or 2,3-*O*-isopropylidene-L-erythritol afforded polycarbonates having pendant methoxy or isopropylidene groups, respectively. Subsequent acid-catalyzed deprotection of the isopropylidene groups gave well-defined polycarbonates having pendant hydroxyl groups regularly distributed along the polymer chain. The degradation of these polymers was remarkably fast.



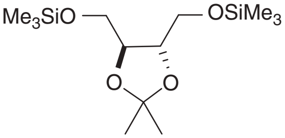
The 1,4:3,6-dianhydroalditols (mainly) and other saccharide derivatives were found to be useful chiral components of cholesteric materials with interesting optical properties, capable of forming Grandjean textures [8]. Chirality plays an important role in combination with the liquid crystalline (LC) character of both low- or high-molecular weight materials. A systematic study reported by Vill *et al.* [33] on the twisting power of DAS, DAM, and DAI derivatives contributed to increasing the interest in these monomers as building blocks of cholesteric polymers.

Appropriate combinations of monomers should be sought that allow the incorporation of the sugar component without loss of the LC character, because the stereochemistry of the sugar diols is highly unfavourable for an LC character of their polymers – in fact, all homopolymers derived from sugar diols are isotropic. Kricheldorf studied LC cholesteric copoly(ester-imide)s based on DAS or DAM [8]. The comonomers to obtain these chiral thermotropic polymers were *N*-(4-carboxyphenyl)trimellitimide, 4-aminobenzoic trimellitimide, 4-aminocinnamic acid trimellitimide, adipic acid, 1,6-hexanediol, and 1,6-bis(4-carboxyphenoxyl)hexane. Apparently, the poly(ester-imide) chains are so stiff that the twisting power of the sugar diol has little effect.

Cholesteric polyesters were prepared from silylated derivatives of 2,3-di-*O*-isopropylidene-D-threitol, DAS, or DAM with dicarboxylic acid dichlorides by polycondensation in solution [34]. Trifluoroacetic acid–water allowed an easy cleavage of the isopropylidene group without hydrolysis of the polyester. All these polyesters formed a broad cholesteric phase, and the polymers containing 5 or 10 mol per cent sugar diol displayed a blue Grandjean texture.

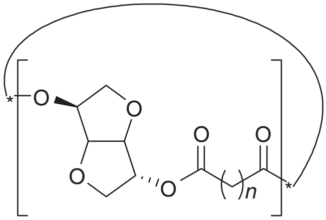


5-endo/2-exo, D-*gluco*
5-endo/2-endo, D-*manno*



Photosetting cholesteric polyesters derived from DAS and 4-hydroxycinnamic acid [35], and from 2,5-bis(dode cyloxy)terephthalic acid and 4,4′-dihydroxybiphenyl, were also described [36].

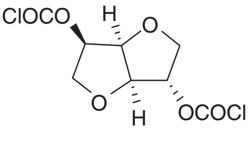
Cyclic aliphatic polyesters of DAS were prepared by polycondensation with aliphatic dicarboxylic acid dichlorides with pyridine as catalyst and HCl acceptor [37]. Cyclic polyesters were isolated by a selective extraction of the linear polymers.



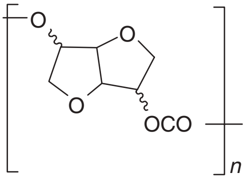
n = 4, 6, 8, 10

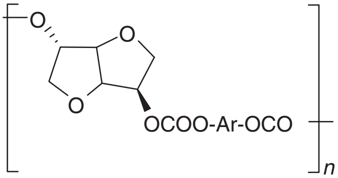
Recently, Kricheldorf has published the synthesis of copolyesters by ring-opening copolymerization of DAS, ϵ-caprolactone, and suberic acid in the presence of catalysts [38].

DAS- and DAM-homopolycarbonates have been prepared by different authors [20, 39]. The interfacial polycondensation, typical for the synthesis of aromatic polycarbonates, is not useful with alditols, including DAS, because they are water-soluble and less acidic than diphenols. The DAS-homopolycarbonate was prepared by phosgenation of the sugar diol, with phosgene or diphosgene in pyridine-containing solvent mixtures at low temperatures. The polycondensation of the DAS-bischloroformate in pyridine is an alternative approach.



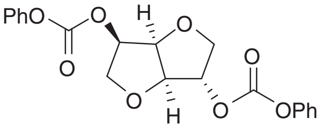
DAS-bischloroformate





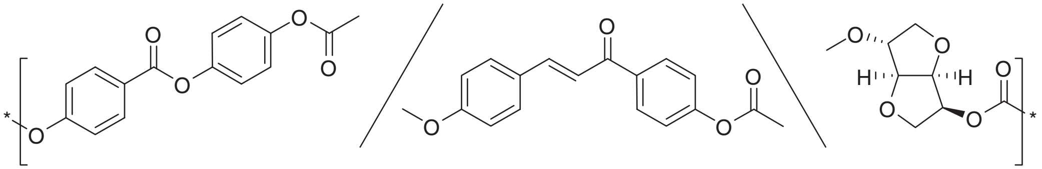
Ar = Phenols or bisphenols

Cholesteric polycarbonates derived from DAS bis(phenyl carbonate), methyl hydroquinone, and 4,4′-dihydrobiphenyl were better obtained by polycondensation in pyridine-containing organic solvents, as reported by Kricheldorf *et al.* [39]. Trichloromethylchloroformate (TCF) was successfully used for all these polycondensations. The use of solid TCF is advantageous over phosgene because it is easy to apply in stoichiometric amounts, easy to store, and commercially available.

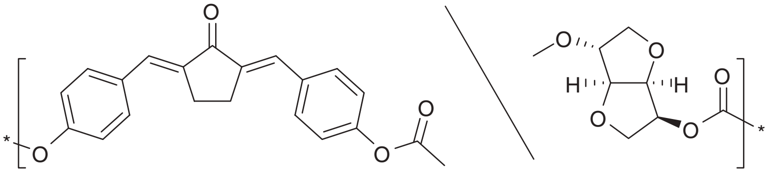


DAS bis(phenylcarbonate)

The same group also synthesized a series of ternary polycarbonates derived from DAS-chloroformate, hydroquinone 4-hydroxybenzoate (HQHB) as mesogenic diphenol, and 4,4′-dihydroxychalcone in pyridine [40]. Particularly noteworthy is the finding that the alternating copolycarbonate of HQHB formed a broad cholesteric phase, despite the unfavourable stereochemistry of DAS. The ternary copolycarbonates formed a cholesteric melt and a Grandjean texture upon shearing. It seems that the combination of DAS and carbonate groups is more favourable for the stabilization of a cholesteric molecular order than is the combination of DAS and ester groups.

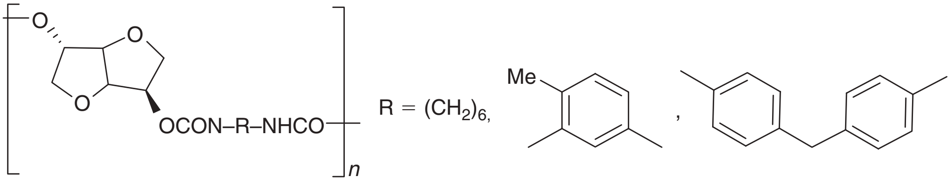


Cholesteric polycarbonates derived from DAS and 2,5-bis(4′-hydroxybenzylidene)cyclopentanone have also been described [41].

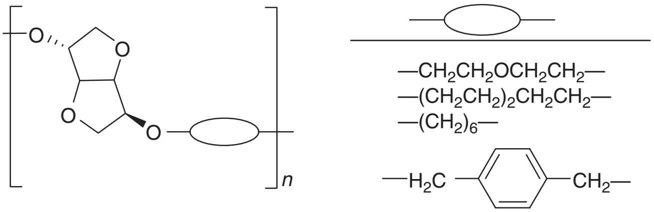


Recently, DAS and equimolar amounts of various diols were polycondensed with diphosgene in pyridine. Different bisphenols, 1,3-bis(4-hydroxybenzyloxy) propane, and 1,4-cyclohexanediol were used as comonomers [42]. In some cases, large amounts of cyclic oligo- and polycarbonates were formed.

Polyurethanes containing DAS have been prepared by several research groups, and complex polyurethanes with an elastomeric character and good mechanical properties were described in a few patents [8]. These polymers were obtained from DAS and diisocyanates in the presence of suitable catalysts (*e.g.* Braun and Bergmann used triethylamine in dimethylsulphoxide [20]).



Polyethers derived from DAS were mentioned in a patent describing the synthesis and properties of epoxy resins, and linear polyethers were prepared from free DAS, which was reacted with α,ω-bischloroalkanes or 1,6-dibromohexane [8].



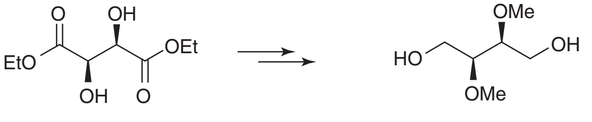
A series of polyphosphites, polyphosphates, polythiophosphates, and other polymers containing sulphone functions, based on DAS, have also been described [8, 43].

Recently, an efficient synthesis of polyethers from DAS and 1,8-dibromo or dimesyl octane by microwave-assisted phase transfer catalysis has been reported [44].

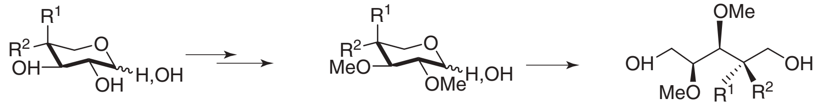
5.2.2 *O*-protected alditols

The most common *O*-protecting groups of the secondary hydroxyl groups of the alditol monomers are acetal, ester, and ether groups. The ether group is of course the most resistant *O*-protecting group of alditol monomers under the polycondensation reaction conditions, but also the most difficult to remove from the resulting polymers.

Within the framework of systematic research to explore the potential of sugar-based polymers, Muñoz-Guerra along with Galbis *et al.* have employed various *O*-methyl alditol derivatives to prepare novel polymers, as well as chemical modification of other well-known materials. Poly(ethylene terephthalate) (PET), poly(ethylene isophthalate) (PEI), and poly(butylene terephthalate) (PBT) have been chemically modified by insertion of a series of *O*-methyl alditols. Among them, 2,3-di-*O*-methyl-L-threitol was inserted into PET [45] and the preparation of PET and PEI analogues by total replacement of the ethylene glycol (EG) units with 2,3,4,5-tetra-*O*-methyl-hexitols having D-*manno* and *galacto* configurations [46]. They also obtained analogues to PET, PEI, and PBT by using 2,3,4-tri-*O*-methyl-L-arabinitol or 2,3,4-tri-*O*-methyl-xylitol [47, 48]. The *O*-methyl-alditol monomers used are easily obtained from the respective commercially available diethyl L-tartrate, pentoses, and hexitols [46, 49, 50].

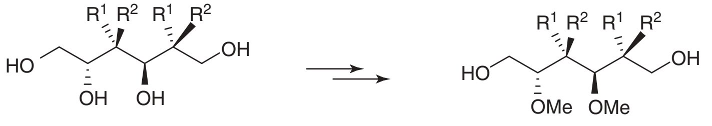


L-threitol



Sugar	R1	R2
L-arabinose	OH	H
D-xylose	H	OH

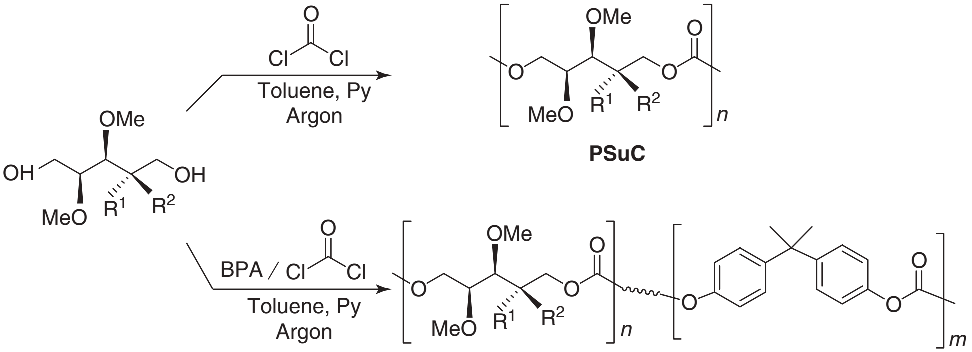
Sugar	R1	R2
L-arabinitol (**Ar**)	OMe	H
Xylitol (**Xy**)	H	OMe



D-mannitol, R^1 = OH, R^2 = H
D-galactitol, R^1= H, R^2 = OH

D-mannitol, R^1 = OMe, R^2 = H
D-galactitol, R^1 = H, R^2 = OMe

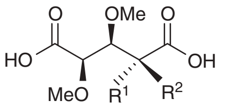
Galbis *et al*. have also described the use of 2,3,4-tri-*O*-methyl-L-arabinitol and 2,3,4-tri-*O*-methyl-xylitol in the synthesis of polycarbonates and polyesters. These pentitols were polycondensed using a commercial solution of phosgene in toluene; whereby, homopolycarbonates (PsuC) and copolycarbonates with BPA, P(Su-*co*-BPAC), were obtained in high yields [51]. Both showed high resistance to chemical hydrolysis; however, they were enzymatically degraded in different degrees. The fastest degradation promoted by lipase B from *Candida antarctica* was observed for the fully xylitol-based polycarbonate, followed by copolycarbonates also based on xylitol, which revealed a marked stereospecificity of the enzyme towards this sugar.



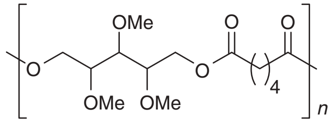
P(Su-*co*-BPAC)

Su	R^1	R^2
Ar	OMe	H
Xy	H	OMe

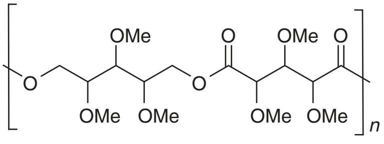
A variety of carbohydrate-based linear polyesters [52] of the poly(alkylene dicarboxylate) type were obtained by polycondensation reactions of the alditols 2,3,4-tri-*O*-methyl-L-arabinitol and 2,3,4-tri-*O*-methyl-xylitol, and aldaric acids 2,3,4-tri-*O*-methyl-L-arabinaric acid and 2,3,4-tri-*O*-methyl-xylaric acid. Butanediol and adipic acid were also used as comonomers. Copolyesters of the poly(alkylene-*co*-arylene dicarboxylate) type were obtained using bisphenols as comonomers. Chemical polycondensation reactions were conducted in bulk or in solution. Enzymatic polycondensation reactions of adipic acid with the above-mentioned alditols were carried out successfully using Lipozyme® and Novozyme® 435. The hydrolytic degradations of some of these polyesters were also described.



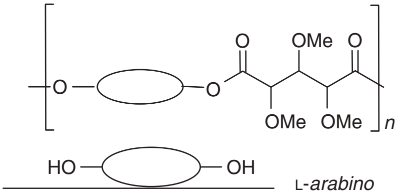
Aldaric acid	R^1	R^2
2Ar, L-arabinaric	OMe	H
2Xy, Xylaric	H	OMe



L-arabino
Xylo

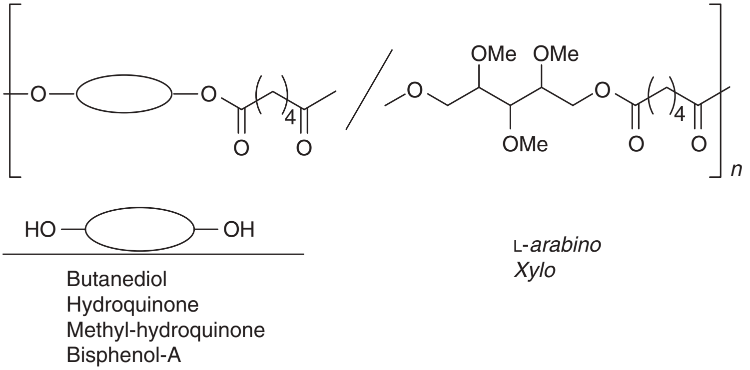


L-arabino-L-arabino
Xylo-Xylo

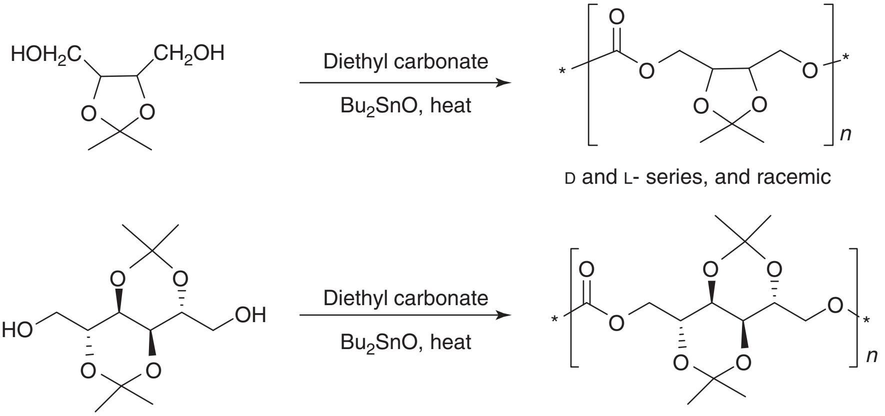


Butanediol
Bisphenol-A

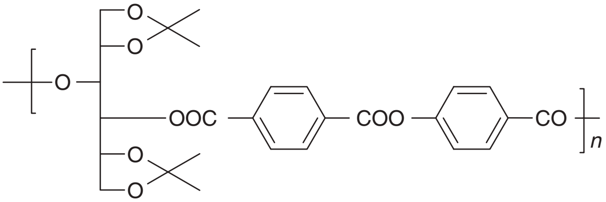
L-arabino
Xylo



Bioerodible polymers having pendant functional groups are of particular interest, since they are capable of covalent pro-drug formation. Acemoglu *et al.* [53] prepared biodegradable poly(hydroxyalkylene carbonate)s from the optically active and racemic 2,3-*O*-isopropylidene-threitol and 2,4:3,5-di-*O*-isopropylidene-L-mannitol with diethyl carbonate in the presence of dibutyl tin oxide. The isopropylidene groups of the polycarbonates were hydrolyzed, and derivations were made on the hydroxy groups to obtain esters, orthoesters, and carbamates. The deprotected polycarbonates were water-soluble, and degraded in a few weeks by a mechanism in which hydroxy groups were shown to participate.



The first apparently cholesteric polyester derived from an alditol such as 1,2:5,6-di-*O*-isopropylidene-D-mannitol was reported by Chiellini *et al.* [54]. Surprisingly, an acidolytic deprotection yielded a seemingly thermotropic polyester.



5.2.3 Unprotected alditols

For the last few years, Kobayashi's and Gross's groups have been independently working on the synthesis of alditol-based polyesters by lipases as catalysts for selective polyol polymerizations. Lipases and proteases are well known as providing regioselectivity during esterification reactions at mild temperatures. In addition to this, the use of enzymes in polyester synthesis is noteworthy from the standpoint of 'green chemistry'. The first example of a sugar alcohol used as monomer in an enzyme-catalyzed polymerization was reported by Kobayashi *et al.* [55]. In this case, the activation of carboxylic acids with electron-withdrawing groups was thought to be necessary. They proved the regioselective polymerization at positions 1 and 6 of D-glucitol (sorbitol) and divinyl sebacate, using lipase derived from *Candida antarctica* in acetonitrile.

Alditols are insoluble in non-polar organic media; instead, they are soluble in polar solvents such as pyridine, dimethyl sulphoxide, 2-pyrrolidone, and acetone. However, these solvents cause large reductions in enzyme activity. A simple and versatile strategy for performing selective lipase-catalyzed condensation polymerizations between dicarboxylic acids and polyols was explored by Gross's group. Instead of using organic solvents, the monomers adipic acid, glycerol, and sorbitol were solubilized within binary or ternary mixtures [56]. Thus, the polymerization reactions were performed without activation of adipic acid. Immobilized Lipase B from *Candida antarctica* (Novozyme 435) catalyzed bulk polycondensations of three monomers, forming a monophasic ternary mixture that resulted in hyperbranched polyesters with octanediol–adipate and glycerol–adipate repeating units [57]. The key to the success of the method is the use of a highly active and selective lipase as the catalyst, as well as adjusting the reaction mixture so that it is monophasic. Thus, polyesters containing many hydroxyl functionalities, such as poly(sorbityl adipate), were prepared without the need to use protection–deprotection chemistry.

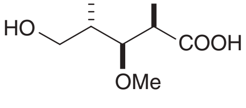
Kobayashi *et al.* have worked extensively on enzymic polymerization for the synthesis of both novel and natural oligo- and polysaccharides [58–61]. They induced the regioselective polymerization of divinyl ester with triols by lipase catalysis, to give soluble polymers of relatively high-molecular weight. The 1,3-disubstituted glyceride unit was mainly formed from glycerol and immobilized lipase derived from *Candida antarctica*, and the microstructure depended on the lipase origin [62]. They also accomplished the enzymatic syntheses of a new class of crosslinkable polyesters by the polymerization of divinyl sebacate and glycerol, using *Candida antarctica* lipase in the presence of unsaturated higher fatty acids; thus, the polyesters had an unsaturated group in the side chain [63, 64]. Biodegradable epoxide-containing polyesters derived from glycerol and unsaturated fatty acids were also enzymatically synthesized [65]. Kobayashi has recently published a review on the enzymatic synthesis of polyesters via polycondensation [66].

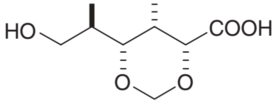
Very recently, Gross *et al.* reported the use of various unprotected alditols, such as erythritol, xylitol, ribitol, D-mannitol, D-glucitol, and D-galactitol, in the preparation of 'sweet polyesters' obtained by lipase-catalyzed polycondensation with 1,8-octanediol and adipic acid [67]. Polymerizations were performed under conditions that allowed vacuum regulation and pressure for water removal, and the selected lipase was N435 (*Candida antarctica* Lipase B, physically immobilized on Lewatit beads). It was found that the polyol reactivity is determined by the stereochemical configuration of carbons closest to terminal hydroxyl groups. The (*R*,*R*) configuration at C2/C5 of D-mannitol is a key factor that led to rapid formation of the corresponding polyesters with high-molecular weights.

5.3 ALDONIC ACIDS AND LACTONES

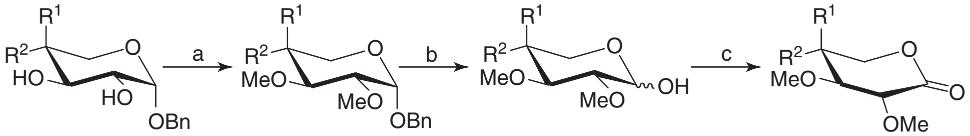
Aliphatic polyesters may be classified into two groups, depending on the bond constitution of the monomers: poly(hydroxy acid)s (*i.e.* polyhydroxyalkanoates (PHAs)) and poly(alkylene dicarboxylate)s [68]. The former are polymers of hydroxy acids (α, β,…ω-hydroxy acids), obtained by ring-opening polymerization or polycondensation reactions. The latter are synthesized by the polycondensation reaction of diols with dicarboxylic acids. Aldonic and aldaric acids can be used to prepare both groups of polyesters.

The polycondensation reaction of aldonic acids to render polyesters has not been much explored. However, pioneering papers describing this kind of polycondensation are known. Drew and Haworth [69] described the polycondensation of 2,3,4-tri-*O*-methyl-L-arabinonic acid through its 1,5-lactone, to give an oligomeric material not completely characterized. Later, Mehltretter and Mellies [70] studied the polyesterification of the difunctional *O*-protected sugar 2,4;3,5-di-*O*-methylene-D-gluconic acid, obtaining low-molecular weight polyesters.





We have described an easy preparation of 2,3,4-tri-*O*-methyl-D-xylose and 2,3,4-tri-*O*-methyl-L-arabinose [50], which can be oxidized to give the corresponding lactones [71], susceptible to ring-opening polymerization. However, in our hands, all the attempts to polymerize these lactones were unsuccessful.

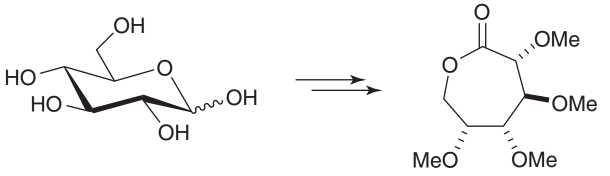


L-*arabino* R^1 = OH, R^2 = H
D-xylo R^1 = H, R^2 = OH

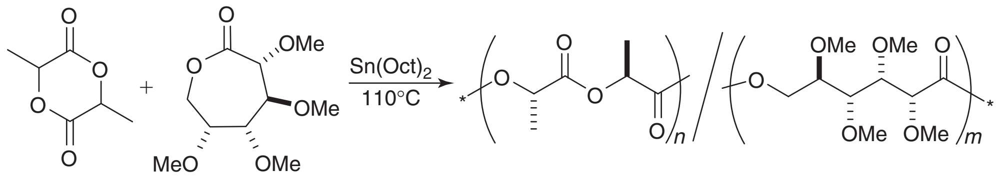
L-*arabino* R^1 = OMe, R^2 = H
D-xylo R^1 = H, R^2 = OMe

(a) MeI, KOH, Me_2SO; (b) H_2, Pd-C, MeOH; (c) PCC.

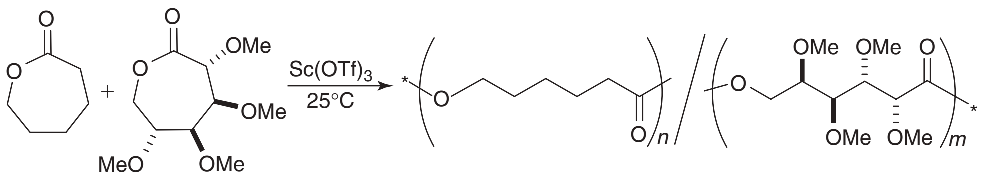
2,3,4,5-Tetra-*O*-methyl-D-glucono-1,6-lactone has been prepared from D-glucose as a crystalline compound in acceptable yields by two different routes [72].



Although the assays of homopolymerization of this lactone were also unsuccessful, we carried out a copolymerization experiment by the bulk ring-opening polymerization of a mixture of L-lactide and 2,3,4,5-tetra-*O*-methyl-D-glucono-1,6-lactone, in a ratio of 5:1, using tin (II) 2-ethylhexanoate ($SnOct_2$) as initiator. From the copolymerization reaction mixture, we obtained two copolymers, containing 1.3 and 2.2 per cent of the carbohydrate monomer, respectively, as determined by NMR studies.



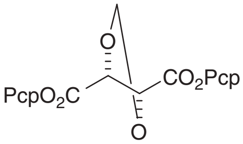
Recently, Varela *et al.* [73] obtained similar results from 2,3,4,5-tetra-*O*-methyl-D-galactono-1,6-lactone. The homopolymerization of this lactone, promoted by aluminium isopropoxide [$Al(O^iPr)_3$] or scandium triflate [$Sc(OTf)_3$], was attempted, but failed in both cases. The copolymerization with ε-caprolactone, using scandium triflate as initiator, gave a low-molecular weight copolymer (~3 000) with an incorporation of the sugar to the polymeric chain of about 10 per cent, as estimated by NMR.

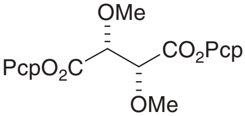


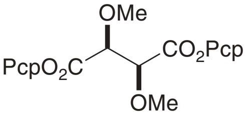
5.4 ALDARIC ACIDS

Unprotected and *O*-protected aldaric acids have been extensively used in polycondensation reactions, mainly in the preparation of polyamides and polyesters. A review has been published on potentially important aldaric acids as monomers for the preparation of polyamides [74].

Muñoz-Guerra *et al.* carried out a detailed study on polytartaramides (*i.e.* polyamides derived from tartaric acid). Various types of polytartaramide, differing either in the diamine used as comonomer, or in the nature of the *O*-protecting groups used to block the two secondary hydroxyl groups of the tartaric acid, have been synthesized, and their properties evaluated in connection with their structure.

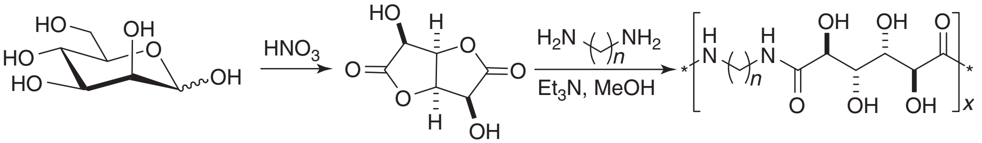


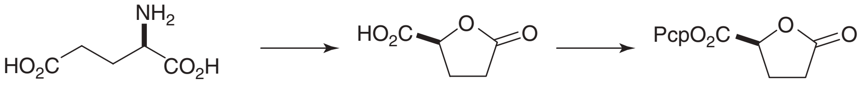




Thus, stereoregular polyamides were prepared from bis(pentachlorophenyl) 2,3-*O*-methylene-L-tartrate [75] and bis(pentachlorophenyl) 2,3-di-*O*-methyl-L-tartrate [76], and their crystal structure [77] and hydrolytic degradation [78] carefully investigated. Stereocopolyamides derived from 2,3-di-*O*-methyl-D- and -L-tartaric acids and hexamethylenediamine, with enantiomeric D/L ratios ranging from 1:9 to 1:1, were also obtained by the active ester polycondensation method [79]. The crystal structure of the ensuing racemic copolyamides obtained from the racemic mixture of 2,3-di-*O*-methyl-D- and -L-tartaric acids and hexamethylenediamine, or by equimolecular mixture of the two enantiomerically pure D- and L-polyamides, was investigated [80]. The same group also described the preparation of poly(ester amide)s derived from 2,3-di-*O*-methyl-L-tartaric acid, more sensitive to hydrolysis than the polyamides, and their mechanism of hydrolytic degradation has been investigated in relation with their microstructure [81]. Aregic [82] and regioregular [83] polytartaramides made from di-*O*-methyl-L-tartaric acid and ethyl L-lysine have been reported. Recently [84], the same authors prepared a series of polyamides from hexamethylenediamine and the pentachlorophenyl esters of 2,3-di-*O*-acyl-L-tartaric acid by polycondensation in solution. Both *O*-alkanoyl and *O*-benzoyl esters were used as hydroxyl-protecting groups. The controlled hydrolysis of the protecting groups yielded poly(hexamethylene-L-tartaramide)s with different content of free hydroxyl groups.

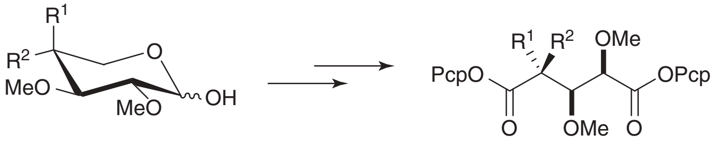
Kiely *et al.* initiated the preparation of a novel type of stereoregular and non-stereoregular hydroxylated nylons (polyhydroxypolyamides) by the direct polycondensation of alkyl esters of unprotected aldaric acids (D-glucaric, galactaric, xylaric, D-mannaric) and their lactones, with linear aliphatic and arylalkylenediamines [85–88], and with aza- and oxa-alkylenediamines [89, 90]. They obtained high yields of solid polymers with low-molecular weight, some of them being soluble in water. The mechanism of formation [91], conformational analysis [92], and adhesive properties [93] of these polyhydroxypolyamides were also studied.





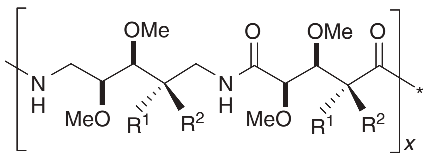
Varela *et al.* described some stereoregular hydroxylated polymannaramides [94] by the reaction of D-mannaro-1,4:6,3-dilactone with even-numbered alkylenediamines ($n = 2, 6, 8, 10, 12$). Hydroxylated stereoregular and non-stereoregular polyamides were also prepared by the same authors [95] from hexamethylene diamine and pentachlorophenyl (2*S*)-5-oxo-2-tetrahydrofurancarboxylate, synthesized [96] from the chiral (2*S*)-2-hydroxypentanedioic acid 5,2-lactone. The latter was obtained [97] by deamination of the easily available L-glutamic acid.

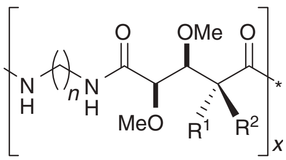
Galbis *et al.* [50] described the preparation of the pentachlorophenyl esters of 2,3,4-tri-*O*-methyl-L-arabinaric (and xylaric) acids as suitable bifunctional monomers for linear polycondensations.



L-*arabino* R^1= OMe, R^2 = H
D-*xylo* R^1 = H, R^2 = OMe

García-Martín *et al*. reported [98] on the AABB polyamides based on these pentaric acids. Two different types of polycondensate were prepared: fully sugar-based polyamides (**PA–ArAr** and **PA–XyXy**), and polyamides derived from aldaric acids and aliphatic diamines (**PA–*n*Ar** and **PA–*n*Xy**, ***n*** = 6, 8, 12). In all these cases, *aregic* polymers were formed, since both sugar configurations lack the C_2 axis.



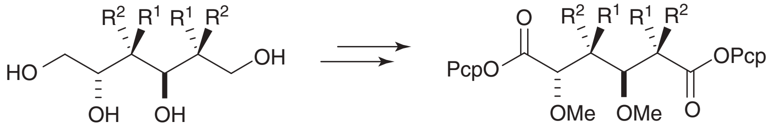


PA–ArAr R^1 = OMe, R^2 = H
PA–XyXy R^1 = H, R^2 = OMe

PA–*n*Ar R^1 = OMe, R^2 = H
PA–*n*Xy R^1 = H, R^2 = OMe

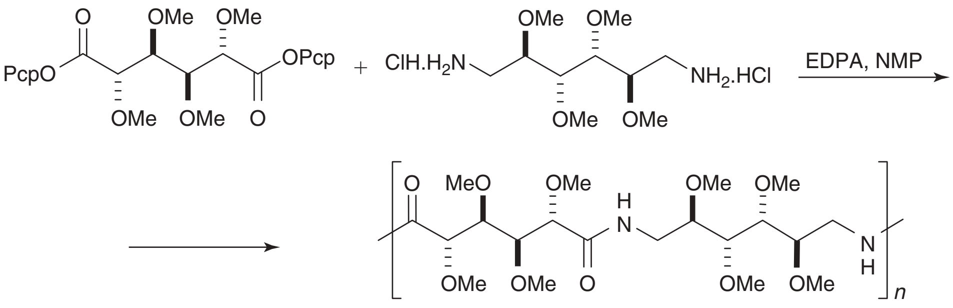
Recently [52], a variety of carbohydrate-based linear homo- and co-polyesters were obtained from these pentaric acids by polycondensation reactions (see Section 5.2.2).

2,3,4,5-Tetra-*O*-methyl-D-mannaric and galactaric acids and their bis(pentachlorophenyl) esters have been prepared [99] as crystalline compounds, in good yields, from D-mannitol and galactitol, respectively. A new stereoregular fully sugar-based polyamide, analogous to Nylon 66, has also been prepared [99] by polycondensation of bis(pentachlorophenyl) 2,3,4,5-tetra-*O*-methyl-D-mannarate with 1,6-diamino-1,6-dideoxy-2,3,4,5-tetra-*O*-methyl-D-mannitol dihydrochloride [100].



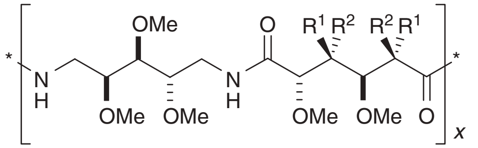
D-mannitol R^1 = OH, R^2 = H
Galactitol R^1 = H, R^2 = OH

D-*manno* R^1 = OMe, R^2 = H
Galacto R^1 = H, R^2 = OMe

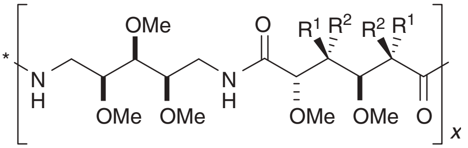


Pcp: pentaclhoropenyl; DCC: dicyclohexylcarbodiimide; NMP: *N*-methylpyrrolidinone

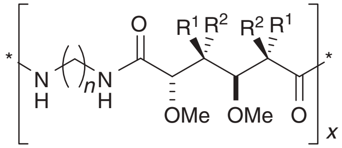
Some other fully sugar-based polyamides have been obtained from these activated hexaric acids and the 1,5-diamino-2,3,4-tri-*O*-methyl-pentitols having the L-*arabino* and *xylo* configuration [101].



PA–ArMn R^1 = OMe, R^2 = H
PA–ArGa R^1 = H, R^2 = OMe



PA–XyMn R^1 = OMe, R^2 = H
PA–XyGa R^1 = H, R^2 = OMe



PA–*n*Mn R^1 = OMe, R^2 = H
PA–*n*Ga R^1 = H, R^2 = OMe

We also prepared [101] a series of polyamides (**PA–*n*Su**) derived from these hexaric acids and non-carbohydrate alkylenediamines with even number of methylenes (*n* = 4, 6, 8, 10, 12).

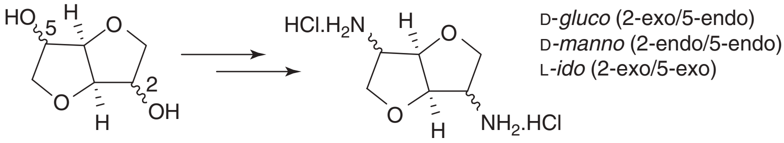
5.5 AMINOSUGARS

Polyamides and polyurethanes are the most widely studied carbohydrate-based polymers. The preparation of hydrophilic nylon-type polyamides containing sugars was a great challenge, as reported in two reviews by Thiem [7] and Varela [10]. In general, carbohydrate-based monomers present low-thermal stability; thus, initial approaches to the synthesis of polyamides by melt polycondensation led only to brittle fibers of low-molecular weights. The interfacial polycondensation technique made possible the synthesis of the first chiral nylon-type polyamide based on carbohydrates. The polymerizable sugar monomers required for the synthesis of polyamides should be diamino-sugars, aldaric acids, or aminoaldonic acids. As mentioned above, the multifunctionality of the sugars requires several protection and deprotection steps. The introduction of amino groups is generally accomplished by the preparation of a sulphonyl ester, nucleophilic displacement by azide, and subsequent hydrogenation. Alternative methods have also been described [7].

5.5.1 Diaminoanhydroalditols

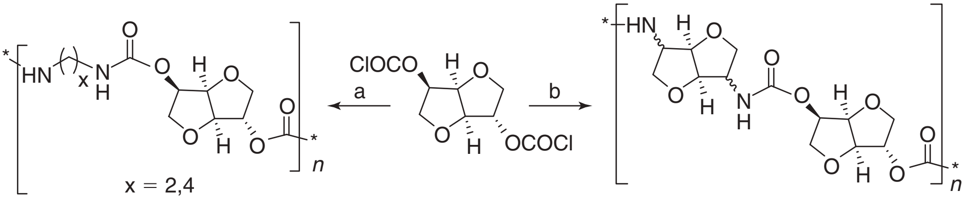
Carbohydrates such as saccharose, D-glucitol, and diaminosaccharides such as trehalose, have been widely used for the syntheses of highly functionalized polyol-based polyurethanes. The preparation of polyurethanes by the reaction of dianhydrohexitols with aliphatic diisocyanates was explored in 1983, and technical applications of dianhydrohexitols were found as chain extenders in polyurethane syntheses, as patented.

The stable 2,5-diamino-2,5-dideoxy-1,4:3,6-dianhydrohexitol dihydrochlorides with D-*gluco*, L-*ido*, and D-*manno* configurations were prepared by Thiem *et al.* according to known procedures.



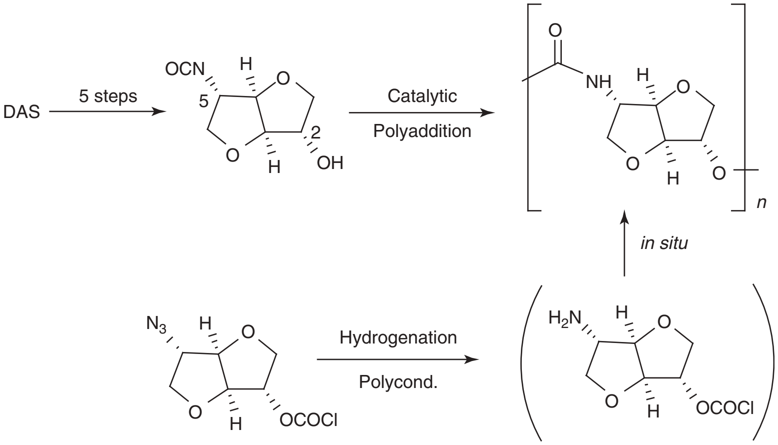
D-*gluco* (2-exo/5-endo)
D-*manno* (2-endo/5-endo)
L-*ido* (2-exo/5-exo)

They developed an initial approach to novel polyurethanes with these diamino monomers, aliphatic diamines, and the bischloroformate of DAS, by phase transfer polycondensation [102].

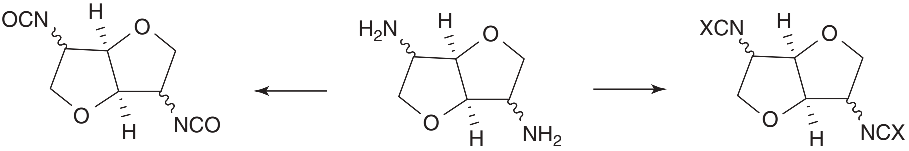


a: $(CH_2)_n(\overset{+}{N}H_3)_2\ (C_2O_4^{2-})$ b: Diamino-DAS, diamino-DAM or diamino-DAI

The catalyzed polyaddition of the monomer 2-deoxy-1,4:3,6-dianhydro-2-isocyanato-L-iditol gave the corresponding polyurethane [103]. However, the intermediate aminochloroformyl derivative underwent spontaneous polycondensation by catalytic hydrogenation.



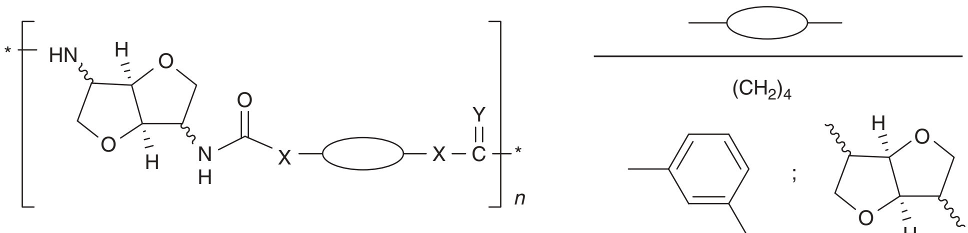
The stable diamino dihydrochlorides of the dianhydrohexitols were transformed into the corresponding diisocyanates by reaction with phosgene [104].



D-*gluco*
D-*manno*

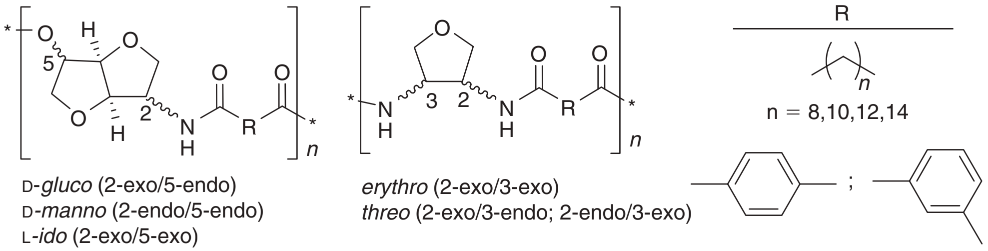
L-*ido* X = O, S

The addition of phosgene proceeded better when the amino groups were orientated out of the molecular plane (*exo* configuration); thus, the yields of the three isomer derivatives decreased in the order L-*ido*, D-*gluco*, and D-*manno*. The use of diphosgene gave unsuccessful results. The dithiodiisocyanato derivatives were prepared from the corresponding diamino-dianhydrohexitol and thiophosgene, and the same stereochemical reasons gave best yields for the L-*ido* compound. Polyurethanes and polyureas were synthesized from the D-*gluco*, D-*manno*, and L-*ido* monomers, and poly(thio)urethanes and poly(thio)ureas from the corresponding L-*ido* monomer.

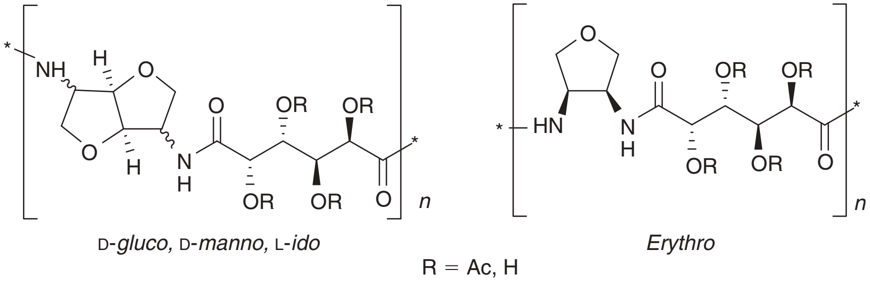


X, Y = O, S, N

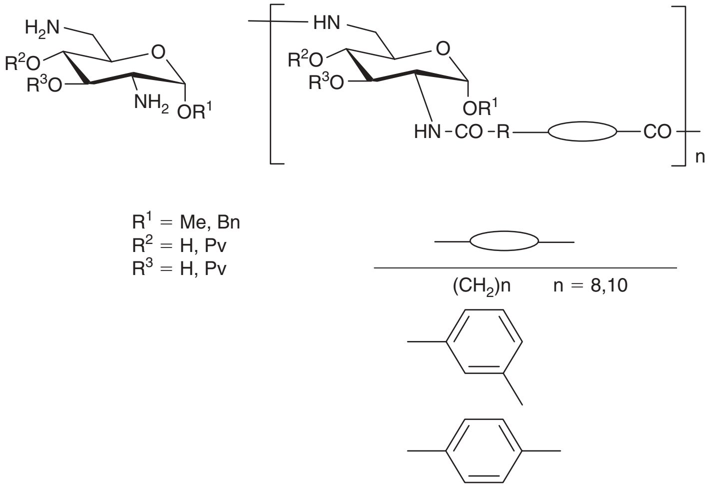
The interfacial polycondensation of 2,3-diamino-1,4-anhydro-anhydroalditols with D,L-*threo* and *erythro* configurations, and the three 2,5-diamino-1,4:3,6-dianhydrohexitol derivatives with purchasable aromatic and aliphatic dicarboxylic acid chlorides, gave polyamides that were fully characterized [105].

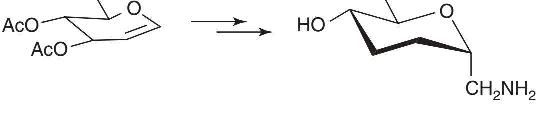


Hydrophilic polyamides were prepared by the polycondensation reaction of 2,3,4,5-tetra-*O*-acetyl-galactaroyl dichloride with diaminoanhydroalditols [106].



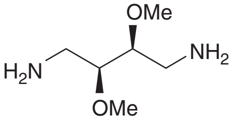
Polyamides derived from D-glucose and D-glucosamine by interfacial and solution polycondensations of the sugar diamino derivatives with aromatic and aliphatic acyl chlorides have also been described [107]. The presence of an anomeric benzyl group did not decrease the reactivity of the 2-amino function. Similar chiral polyamides were synthesized from the 1,7-diamino derivative, which was prepared from D-glucal.



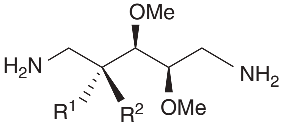


5.5.2 Amino- and diaminoalditols

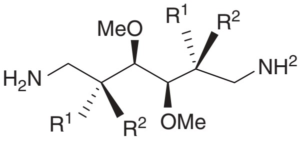
Muñoz-Guerra *et al.* and Galbis *et al.* initiated in the past decade a systematic study of a series of sugar-based AABB linear polyamides. These polyamides are derived from appropriately *O*-protected aldaric acids and 1,ω-diamino-dideoxyalditols. The diaminoalditol monomers of L-*threo*, L-*arabino*, *xylo*, D-*manno*, and L-*ido* configurations were obtained from the corresponding alditols, having the secondary hydroxyl groups protected as methyl ether.



L-*threo*

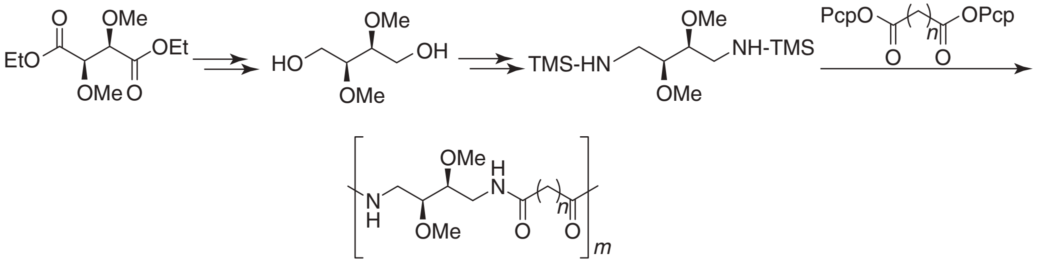


L-*arabino*, R^1 = OMe, R^2 = H
xylo R^1 = H, R^2 = OMe



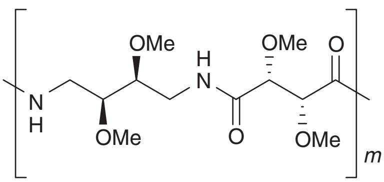
D-*manno*, R^1 = OMe, R^2 = H
L-*ido*, R^1 = H, R^2 = OMe

The transformation of the primary hydroxyl groups into the amino function was carried out by the usual procedure (sulphonation-nucleophilic displacement by azide-reduction). Thus, Muñoz-Guerra *et al.* synthesized (2*S*,3*S*)-2,3-di-methoxy-1,4-butanediamine [49] from natural L-tartaric acid as a raw material, to prepare stereoregular polytartaramides (Nylon 4,*n* analogues). Since L-tartaric acid contains a C_2 symmetry axis, the resulting polyamides are regiochemically ordered. The polycondensation in a chloroform solution of this diamine, activated as the *N,N′*-bis(trimethylsilyl) derivative, with activated pentachlorophenyl esters of aliphatic dicarboxylic acids, afforded stereoregular polyamides. This method allows polycondensations under mild conditions, and the corresponding polyamides are obtained in good yields and with acceptable molecular weights. Because of their stereoregularity, these substituted polyamides present an interesting combination of properties since they are highly crystalline, have mechanical properties comparable to those of Nylons, and may undergo hydrolytic degradation under physiological conditions.

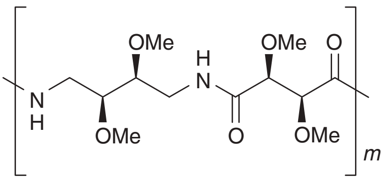


n = 4, 6, 8, 10, 12

Muñoz-Guerra *et al.* also studied stereoregular polyamides fully based on D- and L-tartaric acid [108]. The bispentachlorophenyl esters of both 2,3-di-*O*-methyl-tartaric acids were condensed with (2*S*,3*S*)-2,3-dimethoxy-1,4-butanediamine to obtain optically active (PTA–LL) and racemic (PTA–LD) polytartaramides. Fibre-oriented and powder X-ray studies of these polyamides demonstrated that PTA–LL crystallized in an orthorhombic lattice, whereas PTA–LD seemed to adopt a triclinic structure. In both cases, the polymeric chain appears to be in a folded conformation, more contracted than in the common γ-form of conventional Nylons.

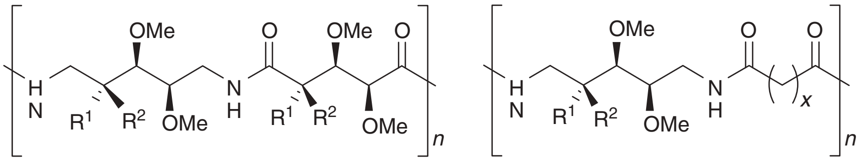


PTA-LL



PTA-LD

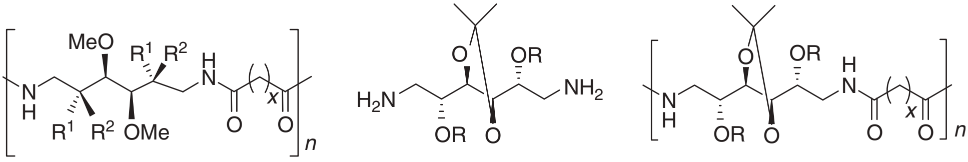
The 1,5-diamino-1,5-dideoxy-2,3,4-tri-*O*-methylpentitols of L-*arabino* and *xylo* configurations [50] gave aregic polyamides when polycondensated with activated aliphatic dicarboxylic acids or aldaric acids [98]. Those polyamides, entirely based on xylose were, as expected, not optically active.



L-*arabino*, R^1 = OMe, R^2 = H
xylo, R^1 = H, R_2 = OMe

x = 8, 10

The synthesis of 1,6-diamino-1,6-dideoxy-2,3,4,5-tetra-*O*-methyl-D-mannitol and its L-iditol analogue from D-mannitol has been described [100]. These diamines, containing a two-fold axis, gave stereoregular AABB polyamides on polycondensation with terephthaloyl dichloride and dipentachlorophenyl esters, or dichlorides of aliphatic dicarboxylic acids, in solution or under interfacial polycondensation conditions [99, 109]. In spite of the regioregularity present in the polymeric chains, these optically active polyamides could not be crystallized.



x = 0, 2, 4, 6, 8

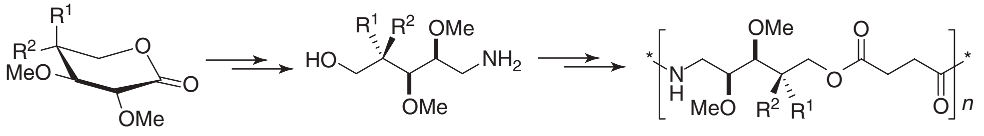
PA-Mn*n*, R^1 = OMe, R^2 = H
PA-Id*n* R^1 = H, R^2 = OMe

R = H, Me

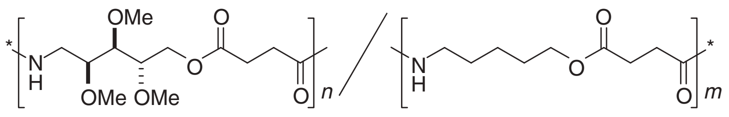
x = 2, 4, 6, 8,10

1,6-Diamino-1,6-dideoxy-2,5-di-*O*-methyl-3,4-*O*-isopropylidene-D-mannitol was also prepared and polymerized with active esters of dicarboxylic acids to give the corresponding polyamides. Aregic polyamides of the AABB type were also obtained by the polycondensation of 1,5-diamino-1,5-dideoxypentitols of L-*arabino* and *xylo* configurations with activated and *O*-methyl D-mannaric and galactaric acids [101].

We have also prepared 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol and -D-xylitol, which were transformed into a series of poly(ester amide)s [110, 111] and copoly(ester amide)s [112], whose structure and properties were carefully studied. Their hydrolytic degradation was also investigated, and a mechanism proposed for this process [113–115].

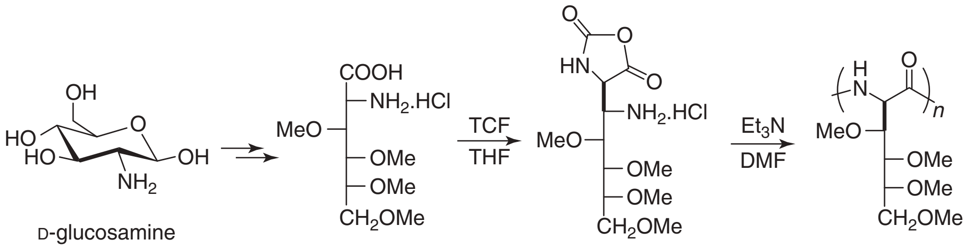


L-*arabino* R^1 = OMe, R^2 = H
Xylo R^1 = H, R^2 = OMe

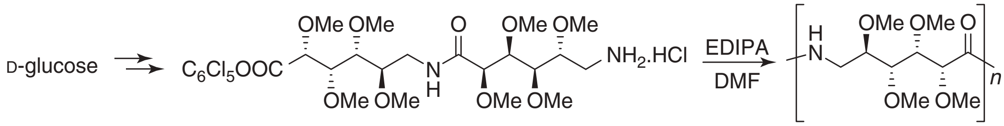


5.5.3 Aminoaldonic acids

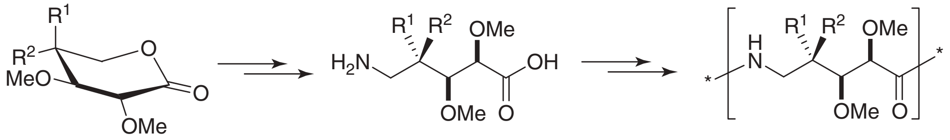
Galbis *et al.* synthesized two stereoregular polygluconamides starting from D-glucosamine and D-glucose [116]. The synthesis of the polyamide of the polypeptide type [116, 117] was accomplished by the ring-opening polymerization of the *N*-carboxyanhydride obtained by treatment of 2-amino-2-deoxy-3,4,5,6-tetra-*O*-methyl-D-gluconic acid hydrochloride, in turn obtained from D-glucosamine, with TCF in THF.



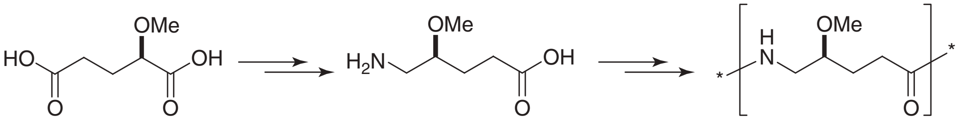
A methoxylated polyamide analogous to Nylon 6 was obtained in several steps from D-glucose [116, 118] through the preparation of a dimeric active ester of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-gluconic acid. This polyamide was highly crystalline, and gave resistant films with a spherulitic texture.



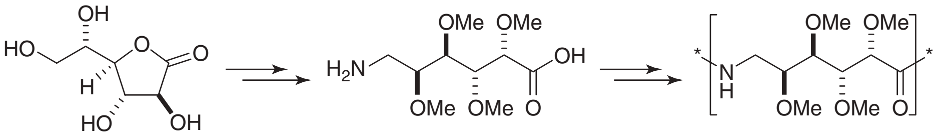
The same group described the syntheses of some derivatives of 5-amino-5-deoxy-L-arabinonic acid, 5-amino-5-deoxy-D-xylonic acid, and (*S*)-5-amino-4-hydroxypentanoic acid, which were performed in several steps from L-arabinose, D-xylose, and (*S*)-(+)-glutamic acid, respectively [119]. These monomers were polymerized to give methoxylated homo and copolyamides analogous to Nylon 5 [120, 121].



L-*arabino* R^1 = OMe, R^2 = H
Xylo R^1 = H, R^2 = OMe

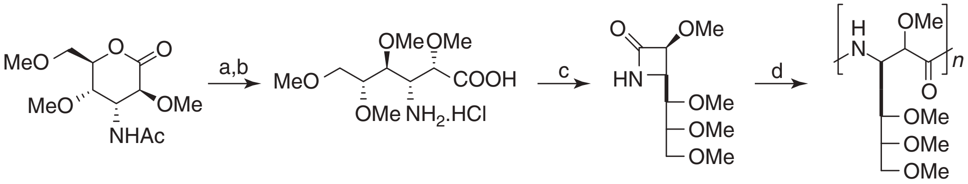


Romero Zaliz and Varela [122] recently prepared, from the D- and L-galactono-1,4-lactones, the corresponding 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-(and L-)galactonic acids, which were polymerized by the procedure described by Galbis *et al.* [116] to give stereoregular sugar-based polyamides analogous to Nylon 6 [123].



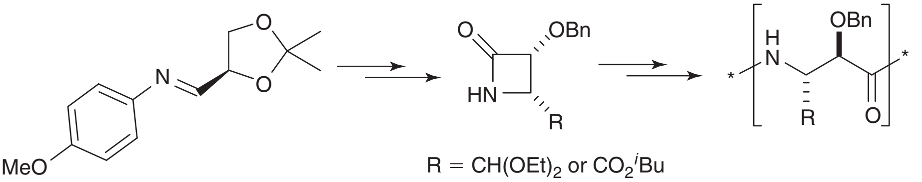
Fleet *et al.* described some oligomers of *O*-protected-6-amino-6-deoxy-D-allonate [124] and D-galactonate [125], as intermediates for the preparation of polyhydroxylated Nylon 6 analogues.

A chiral β-polyamide of the Nylon 3 type was also synthesized [126, 127] by Galbis *et al.* by the ring-opening polymerization of the β-lactam derived from 3-amino-3-deoxy-2,4,5,6-tetra-*O*-methyl-D-altronic acid.



(a) MeI, HOH, THF; (b) 4M HCl; (c) 1. DIPEA, MeCN; 2. MsCl, $NaHCO_3$, MeCN; (d) K^tOBu, CH_2Cl_2.

Some other chiral Nylon 3 analogues have also been prepared by the same authors by the ring-opening polymerization of chiral β-lactams derived from D-glyceraldehyde [128, 129]. Both the enantiomerically pure (2*R*,3*R*) and the racemic (2*R*,3*R* and 2*S*,3*S*) β-polyamides were obtained, and their properties compared.

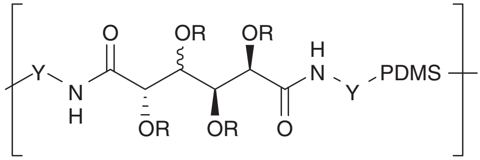


R = $CH(OEt)_2$ or $CO_2{}^iBu$

5.6 MISCELLANEOUS

Several modified D-glycosylamine and D-glucosamine monomers were synthesized by Thiem *et al.* to carry out catalytic polymerizations leading to polymers with urea, urethane, and amide linkages [130]. The reactivity of these monomers was studied, and it was found that the anomeric hydroxyl groups were more reactive than the amino groups. With selectively blocked D-glucosamine monomers, the reaction yielded preferentially polyurethanes incorporating the anomeric hydroxy function.

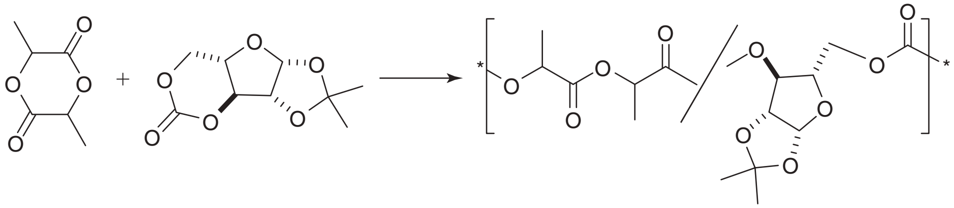
Very recently, Thiem *et al.* explored the synthesis and degradability of novel carbohydrate-segmented silicones polyamides, obtained from activated glucaric and galactaric acid derivatives and different α,ω-diaminoalkyl polydimethylsiloxanes [131]. Galactaric acid-segmented silicones display a higher T_g than their glucaric acid analogues. These materials can be partially degraded by enzymes, with the amide bond functioning as a predetermined breaking point.



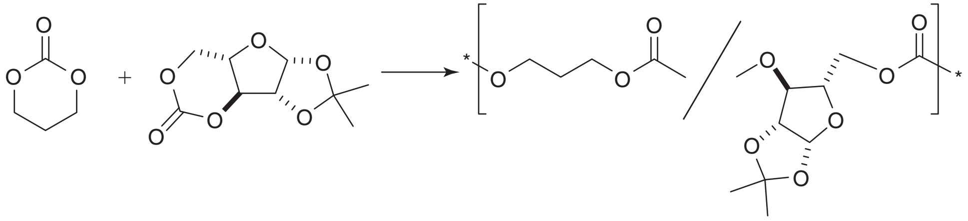
R = Ac or H
Y = $(CH_2)_2NH(CH_2)_3$ or $(CH_2)_3$
PDMS = $SiMe_2(SiMe_2O)_{70}$ or $SiMe_2(SiMe_2O)_{15}$

The same authors prepared a series of allyl-group-containing bifunctional carbohydrate derivatives that were reacted with hydrodimethylsilyl-terminated polysiloxane using Speier's catalyst [132].

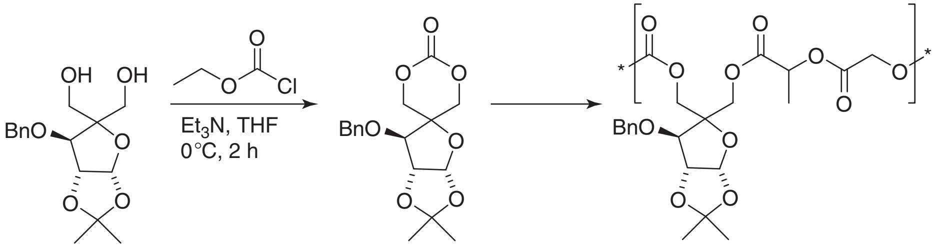
Chen and Gross [133] synthesized high-molecular weight copolycarbonates derived from L-lactide and the 3,5-cyclic carbonate of 1,2-*O*-isopropylidene-D-xylofuranose. The best results were obtained using $Sn(Oct)_2$ as catalyst, with 83:17 mol/mol ratio of the comonomers. Even though the monomer reactivity ratio of L-lactide is much greater than that of the xylose monomer, very short sugar segment lengths were formed. This fact was explained by intramolecular exchange reactions or a xylose monomer insertion reaction during propagation, or by other, more-complex phenomena. Subsequent deprotection of the ketal structure of the copolymer was successfully carried out using CF_3COOH.



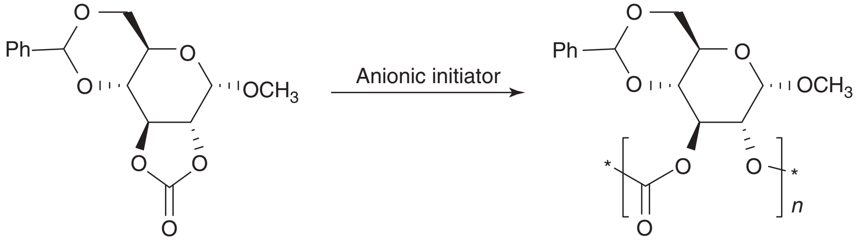
The same xylose monomer was homopolymerized by ring-opening polymerization [134] with different organometallic catalysts such as methylaluminoxane (MAO), $AlEt_3 \cdot 0.5\ H_2O$, $^t BuO^- K^+$, $ZnEt_2 \cdot 0.5\ H_2O$, and $Y(O^i Pr)_3$. In another study, the same authors also polymerized the xylose monomer with trimethylene carbonate in the presence of catalysts; the best results were obtained using MAO and $ZnEt_2 \cdot 0.5\ H_2O$ [135]. Copolymers containing 8–83 per cent of xylose presented an alternating structure and were amorphous. The ketal deprotection was also carried out; and the resulting polymers were soluble in dimethylformamide (DMF), which suggested low chain crosslinking. The original polymers presented increased T_g as the xylose content increased, whereas the T_g of the unprotected copolymers decreased.



The new 4,4′-cyclic carbonate monomer of 1,2-isopropylidene-3-benzyloxy-D-pentofuranose was copolymerized with L-lactide in the presence of $Sn(Oct)_2$ at 130°C [136]. The benzyl ether and ketal groups were selectively removed, so that the units within the copolymers could have one, two, or three hydroxyl groups.



The ring-opening polymerization of the cyclic carbonate methyl 4,6-*O*-benzylidene-2,3-*O*-carbonyl-α-D-glucopyranoside has recently been described. This polymerizes at relatively low temperatures (60°C), without any elimination of carbon dioxide, to give polycarbonates in good yields and medium molecular weights [137].



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Furan Derivatives and Furan Chemistry at the Service of Macromolecular Materials

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ABSTRACT

This chapter reports the most relevant aspects related to the preparation and the characterization of macromolecular structures incorporating furan heterocycles or moieties arising from them. It begins with a short discussion on the major chemical features of furans and on the synthesis of furfural and hydroxymethylfurfural, which constitute the basic precursors to monomers suitable for both chain- and step-growth polymerizations. It then deals with the free radical, cationic, anionic and stereospecific polymerization and copolymerizations and with step-growth systems of suitable furan monomers. Particular emphasis is placed on furan polyesters, polyamides, polyurethanes and conjugated oligomers as the most promising macromolecular architectures. The next section is devoted to the application of the Diels–Alder reaction to the synthesis and properties of linear, crosslinked and dendritic macromolecules, with a strong accent on the reversible nature of these constructions. Finally, the aging of furan polymers is briefly discussed.

Keywords

Furan, Furfural, Hydroxymethylfurfural, Furan polymers, Chain polymerizations, Step-growth polymerizations, Furan polyesters, Furan polyamides, Furan polyurethanes, Furan-containing conjugated oligomers, Diels–Alder reaction, Dendrimers, Reversible crosslinking

6.1 INTRODUCTION

Furan derivatives are ubiquitous in nature in a wide variety of structures, but all of them appear in very modest amounts within specific vegetable and animal (including human) species. The interest of these compounds is mostly relevant to phytochemists and other natural product practitioners [1]. The chemistry associated with the furan heterocycle has been the subject of extensive studies over the last century and is sill a very active field of research because of its important repercussions in areas such as synthons, pharmaceuticals and other fine chemicals [2], liquid crystals [3], as well as polymer science and technology [4]. The classic treatise by Dunlop and Peters [5], which placed furan chemistry in a highly visible perspective, was followed by a number of comprehensive reviews and monographs which progressively updated the state of the art [1–4].

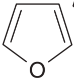
The purpose of this chapter is to deal exclusively with the use of furan compounds and the exploitation of specific features related to furan chemistry with the aim of synthesizing polymeric materials. Implicit in this treatment is the fact that vegetable renewable resources, in the form of mono, oligo and polysaccharides, are excellent sources of two first generation furans which, in turn, represent sources of a variety of monomers and other derivatives relevant to polymer synthesis. Although this topic has been reviewed on previous occasions [4], important advances have enriched it in recent years. An attempt will therefore be made to provide here a balanced treatment covering both the most salient achievements reported in the past several decades and novel promising contributions and perspectives.

Two striking differences distinguish the essence of this chapter from most other chapters, namely: (i) the fact that the furan compounds relevant to polymer synthesis are not found as such in nature but are instead obtained from parent renewable resources and (ii) it is possible in principle to envisage a whole new realm of polymer materials based on furan monomers and furan chemistry, covering a very wide spectrum of macromolecular structures. Concerning the first point, the massive availability of saccharidic precursors and their relatively simple conversion into furan derivatives, eliminate in fact any apparent problem of absence of such natural structures. As for the second point, its unique relevance has to do with the potential perspective of a viable alternative to the present reality based on polymer chemistry derived from fossil resources. In other words, the biomass refinery concept would be applied here to the synthesis of different furan monomers, simulating the equivalent petroleum counterpart.

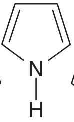
The impressive achievements of the petroleum-based synthesis of monomers, and the huge success of the ensuing polymeric materials, are ineluctable realities which combine pervasive technical performances with remarkable economy (at least for the time being). It follows that the challenges faced by the possibility of a novel branch of polymer chemistry based on furan monomers are daunting. We hope to show in this chapter that daunting does not mean impossible within a realistic framework of research efforts and time span.

6.2 THE FURAN HETEROCYCLE AND SOME OF ITS CHEMICAL FEATURES

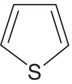
Furan (**1**), a volatile colourless liquid with an aromatic scent, is one of the major representatives of the five-member unsaturated heterocycle family, which also includes pyrrole (**2**) and thiophene (**3**), as well as several other less widespread homologues.



(1)

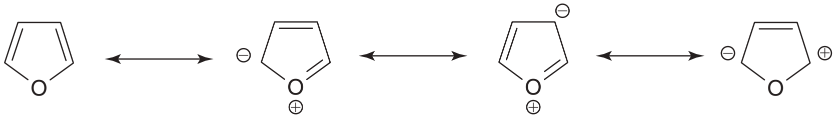


(2)



(3)

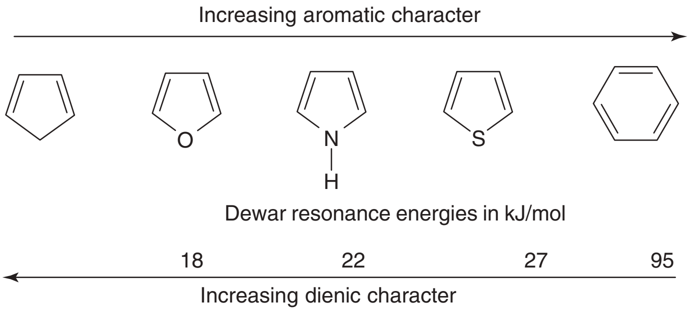
Molecular orbital calculations provide the following set of resonance-contributing structures for the furan heterocycle:



(1) **(1a)** **(1b)** **(1c)**

In furan chemistry, substitution reactions, such as alkylation, halogenation, sulphonation and nitration, occur regioselectively at C2 and/or C5 when these positions are not substituted, suggesting that **1a** is the dominant resonance structure. Compared with its classical homologues **2** and **3**, furan displays the lowest aromatic and the highest dienic character, as illustrated in Scheme 6.1 which also gives the two limiting structures of benzene and cyclopentadiene, respectively.

This predominant dienic character represents a peculiar chemical feature that bears important mechanistic consequences in both organic chemistry and more especially here, in original approaches to macromolecular synthe-



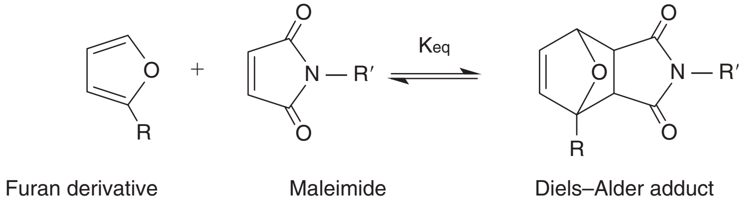
Scheme 6.1

sis. Probably the most exemplary of these consequences is the ease with which furan and some of its derivatives undergo the Diels–Alder (DA) reaction as dienes. Of all cycloadditions, this is perhaps the most emblematic because of its widespread use in organic syntheses involving a large combination of dienes and dienophiles [6]. It is not excessive to assert that the DA reaction between furan and maleic anhydride represents the very symbol of this reversible interaction, as found in many organic chemistry textbooks.

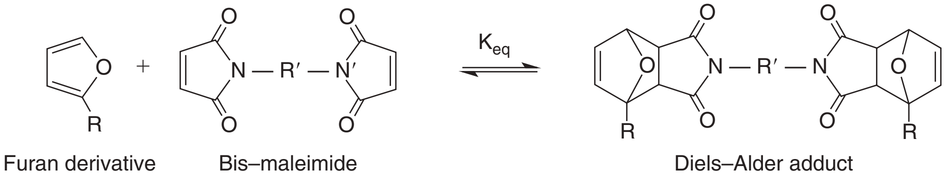
The following examples of DA cyclizations (Schemes 6.2–6.4) illustrate schematically the formation of the corresponding adducts using either a mono- or a bis-dienophile and emphasize the reversibility of these reactions which is promoted by an increase in temperature.

The extension of these mechanisms to DA reagents bearing multiple functionalities opens the way to various original approaches to polymer syntheses as discussed below.

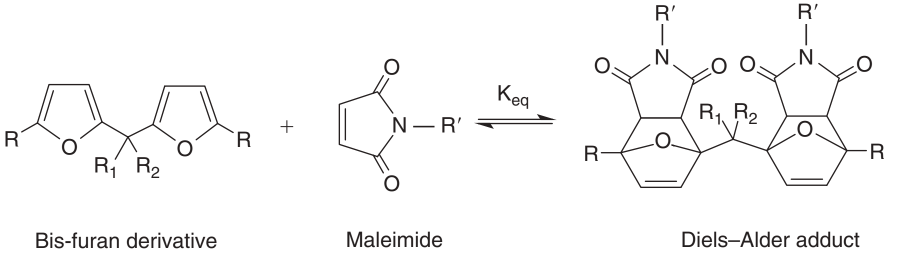
The pronounced regioselectivity of the electrophilic substitution at the unsubstituted C2 and C5 positions (see Scheme 6.5), can also be exploited for building interesting macromolecular architectures by cationic polymerization as illustrated in Section 6.5.2.



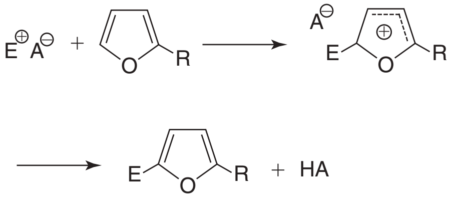
Scheme 6.2



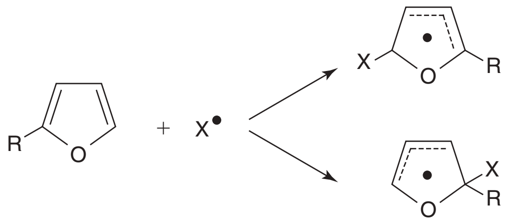
Scheme 6.3



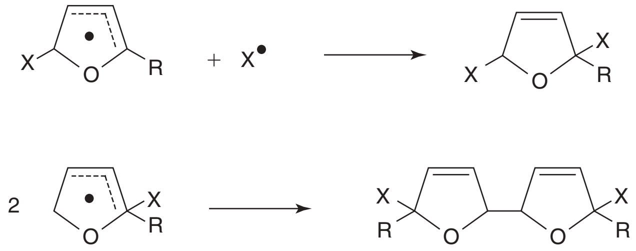
Scheme 6.4



Scheme 6.5



Scheme 6.6



Scheme 6.7

Scheme 6.8

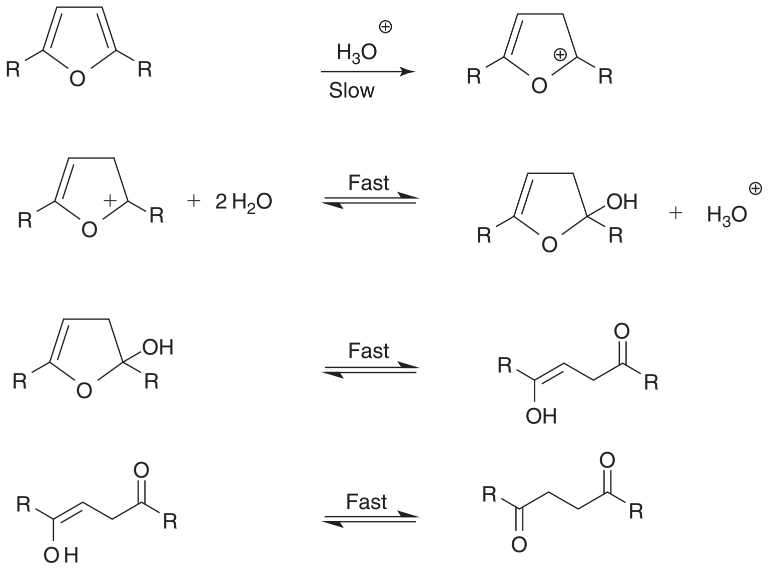
Another peculiar feature of the furan heterocycle has to do with its behaviour in the presence of free radicals. The addition of primary radicals occurs predominantly at C2 or C5, with a kinetic preference for the unsubstituted position. The resulting furan radicals differ in structure (Scheme 6.6), but display a common sluggishness towards propagation with further furanic substrate molecules because of their relatively good stabilization. The two major reaction pathways open to these intermediates are therefore either coupling with other primary radicals (or among themselves) to give various mono- and di-dihydrofurans (Scheme 6.7) or homolytic aromatic substitution resulting in the corresponding novel furan structure (Scheme 6.8) [4d, 7].

The fact that the typical furyl radicals in Scheme 6.6 are unable to propagate in the classical mode of free radical polymerization because of their resonance stabilization, has profound consequences in terms of the reactivity of furan monomers in this type of polymerization and the role of furan derivatives as possible perturbing agents in free radical chain reactions in general. These specific aspects will be illustrated below.

The sensitivity of the furan ring to acid-catalyzed hydrolysis must finally be mentioned as one of its typical chemical features. Its intervention in the context of this monograph must be seen as an undesired event to be avoided, or at least minimized, since its mechanism leads to the destruction of the heterocycle with the formation of aliphatic carbonyl compounds, as illustrated in the simplified Scheme 6.9. It is therefore clear that any polymerization system requiring the preservation of the furan or cognate structures in the final product would be marred by side reactions caused by the presence of moisture in an acidic medium. Curiously, the acid-catalyzed hydrolysis of 2,5-dimethyfuran in a water–ethanol medium shows self-oscillating features [8].

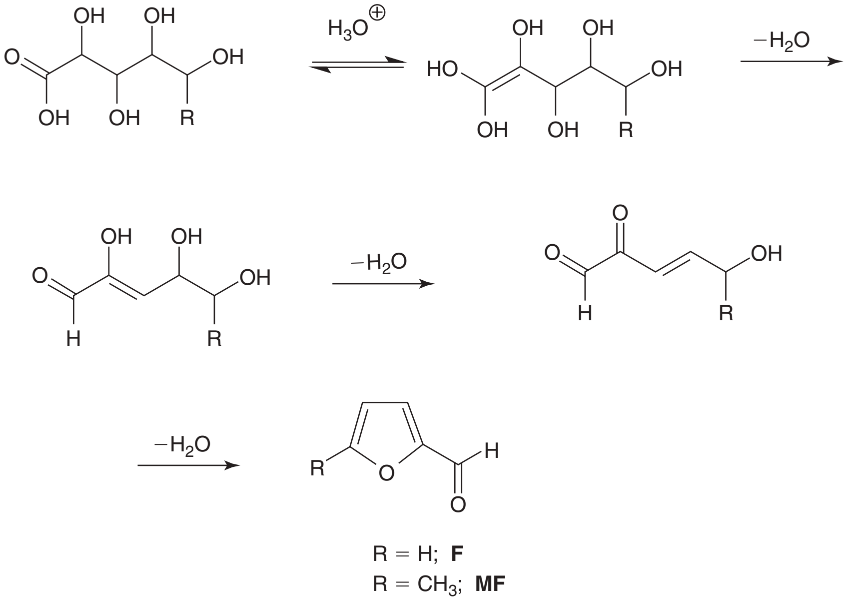
6.3 FURFURAL AND HYDROXYMETHYLFURFURAL

Furfural or 2-furancarboxyaldehyde (**F**) was first obtained in the early nineteenth century and became an industrial commodity about a century later, to reach an industrial production today of some 280 000 tons per year [9]. It can be readily and economically prepared from a vast array of agricultural and forestry wastes containing pentoses (see Chapter 13) in sufficient amounts to justify a commercial exploitation. Examples of these renewable resources are corn cobs, oat and rice hulls, sugarcane bagasse, cotton seeds, olive husks and stones, as well



Scheme 6.9

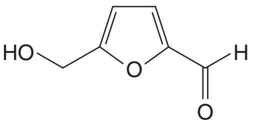
as wood chips. This lack of specificity explains why **F** is produced industrially all over the globe, irrespective of the geo-economic context, simply because virtually every country cultivates a species containing pentoses. Yields up to about 15 per cent of **F** with respect to dry matter are obtained from processes which always involve an aqueous acidic medium and fairly high temperature [10]. The reaction sequence leading to **F** first goes through the hydrolysis of the polymeric pentoses down to the corresponding monosaccharide (aldopentose), which is then dehydrated progressively and finally cyclized to give **F** (from xylose), and in much smaller proportions, 5-methylfurfural (**MF**) (from rhamnose) as shown in Scheme 6.10. **F** and **MF** are then separated by distillation.



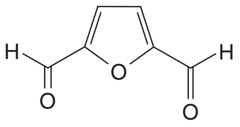
Scheme 6.10

At the current market price of about \$1 per kg [9], **F** is a viable chemical commodity, both as such and as a precursor to other furan and non-furan derivatives.

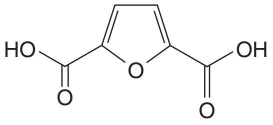
Hydroxymethylfurfural or 2-hydoxymethyl-5-furancarboxyaldehyde (**HMF**) represents the other major first generation furan derivative whose synthesis is carried out from hexoses in the form of the corresponding mono, oligo and polysaccharides through a sequential mechanism entirely equivalent to that shown in Scheme 6.10, but ending with **HMF**. This process has been the object of much laboratory and technological research without reaching yet beyond the stage of pilot plants [4e, 11]. Recent promising novel approaches [12] suggest that the industrial production of **HMF** could soon become a reality. Given the high sensitivity of this compound to resinification induced by acidic impurities and other agents, it seems likely that its commercialization might involve its preliminary transformation into the corresponding dialdehyde (2,5-furancarboxydialdehyde, **FCDA**) or diacid (2,5-furandicarboxylic acid, **FDCA**).



HMF



FCDA



FDCA

These two basic furan derivatives obtained directly from cheap vegetable resources find important uses as chemical precursors in a variety of industrial and fine chemical processes which are well documented [4e, 11, 13]. Only those leading to furan monomers and to other compounds which can be exploited in polymer synthesis will be examined further hereafter.

6.4 FURAN MONOMERS

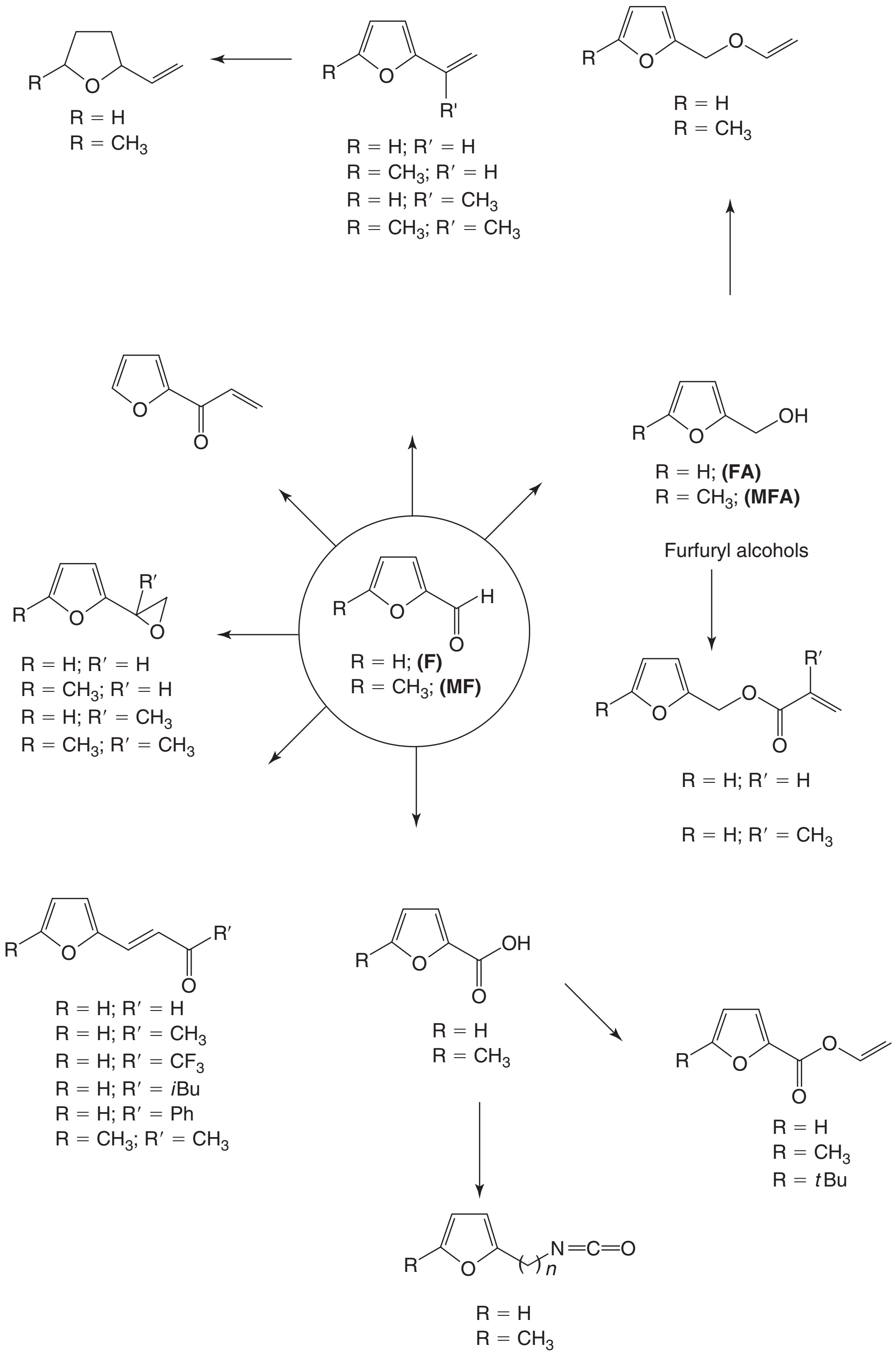
F and **MF** are typical precursors to furan monomers bearing a moiety which can be polymerized by chain-reaction mechanisms. Scheme 6.11 provides a non-exhaustive array of entries into such structures, which have all been synthesized, characterized and polymerized [4]. A major exception to this general postulate is constituted by furfuryl alcohol (2-hydroxymethylfuran, **FA**), which is in fact still today the most important commercially available furan compound, obtained by the catalytic reduction of **F** involving more than 80 per cent of its world production. **FA** is widely used as a polycondensation monomer and does not therefore belong to the class of compounds shown in Scheme 6.11.

HMF on the other hand, is ideally suited as a precursor to bifunctional furan monomers to be used in step growth reactions as shown in Scheme 6.12 which includes **FDCA** and **FCDA**. Again, all these compounds were synthesized and used to prepare the corresponding polycondensates, like polyesters, polyamides, polyurethanes, etc [4].

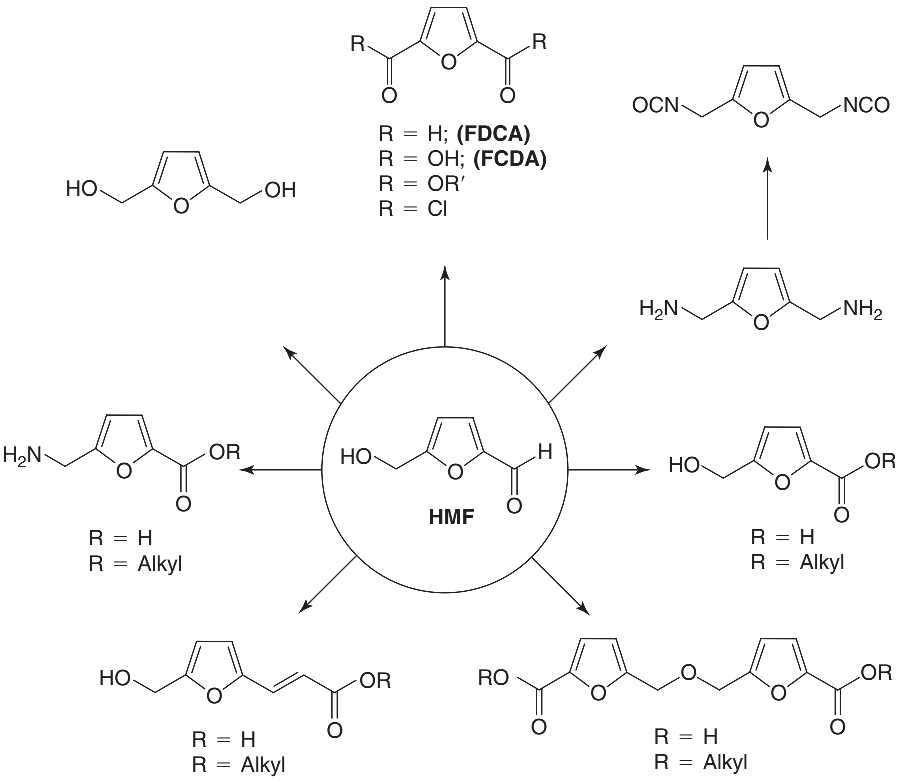
Another approach to the synthesis of bifunctional monomers which has also been widely explored, calls upon the acid-catalyzed condensation of the corresponding monofunctional furan derivatives with an aldehyde or a ketone, as shown in Scheme 6.13 [4].

These difuranic monomers were also the object of detailed polycondensation studies, as discussed below.

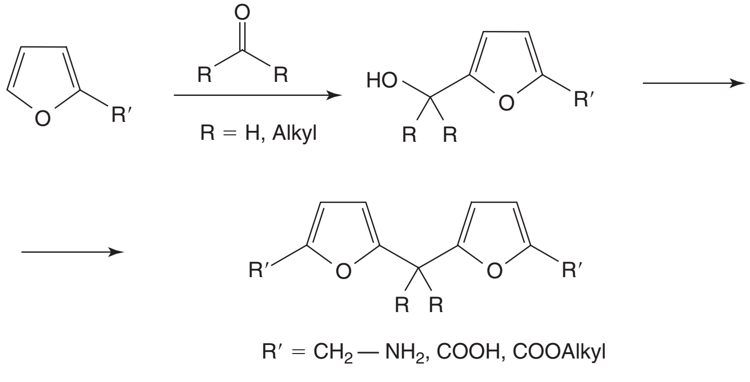
All the monomer structures shown in Schemes 6.11–6.13 are in fact the furan counterparts of the typical aliphatic and aromatic monomers that have been synthesized from petrochemical precursors and widely studied since the beginning of last century. In other words, the only original characters of these novel families is, on the one hand the fact that they all bear one or several furan heterocycles and, on the other hand, the fact that they all derive from precursors which are based on vegetable renewable resources.


R = H
R = CH3
R = H; R′ = H
R = CH3; R′ = H
R = H; R′ = CH3
R = CH3; R′ = CH3
R = H
R = CH3
R = H; (FA)
R = CH3; (MFA)
Furfuryl alcohols
R = H; (F)
R = CH3; (MF)
R = H; R′ = H
R = CH3; R′ = H
R = H; R′ = CH3
R = CH3; R′ = CH3
R = H; R′ = H
R = H; R′ = CH3
R = H; R′ = H
R = H; R′ = CH3
R = H; R′ = CF3
R = H; R′ = iBu
R = H; R′ = Ph
R = CH3; R′ = CH3
R = H
R = CH3
R = H
R = CH3
R = tBu
R = H
R = CH3

Scheme 6.11



Scheme 6.12



Scheme 6.13

Whereas the monomers shown in Scheme 6.11 are specifically suited for chain polymerization reactions through the moieties external to the ring and thus give rise to polymers or copolymers with the heterocycle pendant to their backbone, the monomers shown in Schemes 6.12 and 6.13 give rise to polycondensate architectures in which the heterocycle is an integral part of the backbone.

6.5 POLYMERS FROM CHAIN REACTIONS

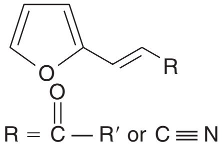
The monomers appearing in Scheme 6.11 are all susceptible to polymerize via chain reactions but, according to their specific structure, their actual response to different types of initiation varies considerably. The organization of this section follows therefore the nature of the polymerization mechanism, viz. via free radical, cationic, anionic and stereospecific initiation.

6.5.1 Free radical polymerization

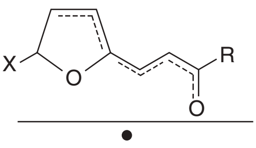
Given the mechanistic considerations related to the reaction of furans with free radicals (see Schemes 6.6–6.8), it follows that among the monomer structures shown in Scheme 6.11, two limiting behaviours were to be expected, as indeed confirmed experimentally. On the one hand, furan monomers bearing an alkenyl moiety deprived of any stabilizing environment after its transformation into a free radical are not expected to polymerize to any sensible extent because the preferred free radical structure would be that involving the much more stable furyl moiety. This was indeed the behaviour observed with 2-vinyl furoate [4d, 7]. On the other hand, a pronounced stabilization of the alkenyl moiety by an adequate structure, in fact higher than that of the alternative furyl radical, would favour the normal chain growth, which was exactly what happened with furfuryl acrylates and methacrylates [4d], although, even with these monomers, chain branching and crosslinking were found to occur in modest amounts at high conversions [14], indicating that some furyl radicals were indeed formed by the attack of primary or macromolecular radicals onto the rings pendant to the formed polymer chains. Intermediate situations were also studied, notably with 2-vinyl furan [4d].

Copolymerization systems involving the combination of a furan monomer and a conventional counterpart, confirmed this general state of affairs in that only the use of polymerizable furan monomers yielded the expected copolymers. Conversely, comonomers like 2-vinyl furoate either retarded the homopolymerization of well-stabilized standard monomers like methacrylates, or actually inhibited the polymerization of poorly stabilized conventional monomers like vinyl acetate [4d, 7].

In conclusion, although only a modest number of furan monomers responded adequately to free radical initiation, interesting fallout related to the peculiar behaviour of the furan heterocycle in this chemical environment was its exploitation in the synthesis of novel inhibitors based on the generic formula **4**. The trapping of a free radical $X^{\bullet}$ by such molecules produces the corresponding highly stabilized Structure **5**, in which the unpaired electron is delocalized over the entire conjugated moiety. This family of compounds displayed a very high efficiency in stopping free radical based reactions like polymerizations, photochemical processes and oxidations, indeed higher than that of most conventional inhibitors [4d, 7].



(4)



(5)

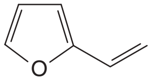
A recent extension of this inhibiting strategy [15] was applied in the context of the free radical functionalization of polypropylene during its processing in the melt. Furanacrylic derivatives bearing the basic Fu—CH═CH—C═O moiety, as in Structure **4**, were found to reduce considerably the extent of polymer degradation produced by the free radical chain reactions arising when the typical maleic anhydride/peroxide pair is used without an inhibitor.

Although furan and its methylated homologues do not polymerize by free radical initiation for the reasons discussed above, their DA adducts as well as their 1:1 charge transfer complexes with maleic anhydride are sensitive to this type of activation and give polymers with different structural units and molecular weights in the region of a few thousand [4d]. The properties of these materials have not been the subject of any published study, and hence their possible applications cannot be assessed. Recently, difurylmethane was also copolymerized with maleic anhydride to give a branched alternating copolymer [16].

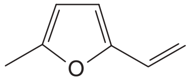
6.5.2 Cationic polymerization

Furan and its methylated homologues undergo cationic polymerization initiated by both Lewis and Brønsted acids, but the fact that the ensuing branched products (DP = 50–300) bear complex and irreproducible structures, made up of both dihydro- and tetrahydro-furan rings [4a, 4d], casts serious doubts about their interest as materials. Claims related to the synthesis of regular macromolecular structures with these monomers were not substantiated by convincing spectroscopic evidence.

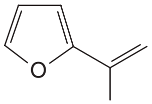
2-Alkenylfurans are readily activated by even the mildest cationic initiators because of their pronounced nucleophilic character. A comprehensive study of these systems involved the four homologues 2-vinylfuran (**VF**), 2-vinyl-5-methylfuran (**MVF**), 2-isopropenylfuran (**IPF**) and 2-isopropenyl-5-methylfuran (**MIPF**) and various Lewis and Brønsted acids (mostly trifluoroacetic acid) [4d].



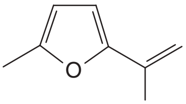
VF



MVF

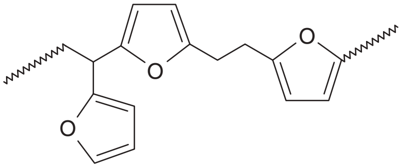


IPF



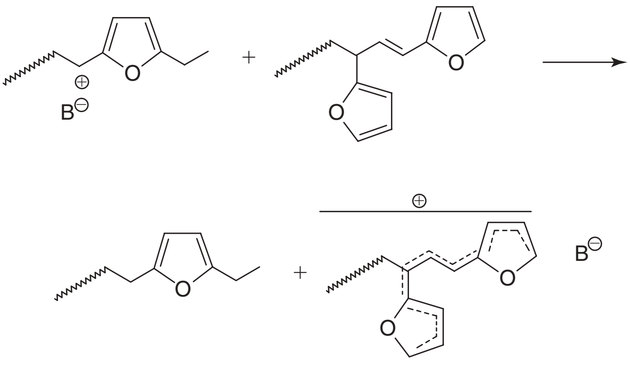
MIPF

The choice of these monomers was dictated by preliminary results which showed that **VF** gave polymers bearing different units, which suggested the occurrence of two types of side reactions accompanying the expected propagation through the vinyl unsaturation. On the one hand, an active species could add onto a monomer molecule through an alkylation reaction at C5 (occurring through both normal and anti-Markovnikoff substitutions), instead of incorporating it through the normal vinyl growth. This was to generate Structure **6**. To verify this possibility, **MVF** was tested and indeed the monomer sequence of the ensuing polymer followed the expected regular enchainment through the vinyl moiety.



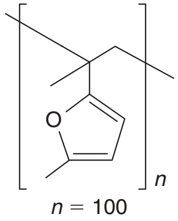
(6)

On the other hand, both poly(**VF**) and poly(**MVF**) were found to contain conjugated unsaturated sequences, formed during the polymerization, but also after complete conversion (giving rise to electronic spectra with bathochromically shifting maxima, all the way into the visible), thus suggesting that the monomer was not involved in the mechanism of their generation. The possibility of hydride/proton losses through reactions between terminally unsaturated polymer molecule and an active species (Scheme 6.14) was confirmed by the fact that **IPF** produced macromolecules deprived of polyunsaturations, although of course these polymers bore the units testifying to the occurrence of C5 alkylation.



Scheme 6.14

Both side reactions could therefore be eliminated by calling upon **MIPF**, which gave the regular Structure **7**, with DPs close to 100, when polymerized at low temperature to reduce the impact of chain-transfer reactions.



(7)

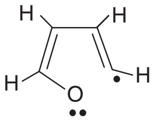
An interesting exploitation of the complicated behaviour of **VF** in cationic polymerization consisted in pushing the anomalous reactions to the extreme by using very strong initiators like triflic acid in relatively high concentrations within the bulk monomer and leaving the mixture to stand at room temperature well beyond the complete monomer consumption. These conditions led to black insoluble products because the extent of conjugated sequences had been maximized and the branching associated with alkylation reactions had been allowed to form a polymer network. These materials displayed a very high proton affinity (up to 60 meq g^{-1}) in organic media, promoted by the strong nucleophilic character of the long conjugated sequences and could be used as proton exchange resins, since they could be easily regenerated by an alkali treatment [4d, 17]. This process has also been applied to prepare silica particles covered with the **VF** resin [18].

Other furan monomers which polymerize cationically include 2-furfuryl vinyl ether, 2-vinyl furoate (albeit through a polyalkylation mechanism giving a polyester incorporating the ring into the polymer backbone), **F** and **MF** as co-monomers in conjunction with substituted styrenes and vinyl ethers, as well as 2-furfurylidene methyl ketone (obtained by the base-catalyzed condensation of **F** with acetone) and its homologues [4d].

In a different vein, the high reactivity of the furan heterocycle towards electrophilic substitution at its C2 and C5 positions has been exploited in cationic polymerization to prepare functional oligomers and block copolymers. Thus, in the polymerization of isobutene, 2-methylfuran plays the role of dominant transfer agent with respect to the monomer transfer reaction and gives oligomers bearing a furan end group, which can be appropriately modified, for example by the DA reaction [4a]. An extension of this concept uses bifuran derivatives to play the role of joining moiety by allowing two successive alkylation reactions arising from the sequential cationic polymerization of two different monomers, thus producing the corresponding block copolymers [4a]. This original strategy, developed and patented some 20 years ago [4a, 19], was recently revived in a couple of laboratories, without any appreciable qualitative novelty [20, 21]. Of course, this strategy can also be applied to insert grafts onto a trunk polymer bearing pendant furan moieties with free C5 positions. In this case, the cationic polymerization of the future graft is conducted in the presence of the trunk so that grafting-onto takes place.

6.5.3 Anionic polymerization

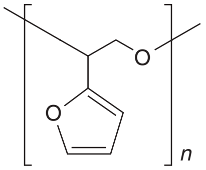
The preparation of 2-furyl lithium as an intermediate in organic synthesis is a routine operation. However, sodium naphthalene does not give 2-furyl sodium with furan, but only a resinous product, and sodium was reported to react with furan at 4 K to give the radical anion **8**, which again generates a mixture of unidentified oligomeric products [4d].



(8)

2-Alkenylfurans do not polymerize under the effect of conventional anionic initiators and the only system which produced a modest yield of polymer (regular structure, DP ∼ 100) involved **VF** with sodium biphenyl in HMTP at room temperature [4d]. Monomer conversions higher than about 10 per cent could not be attained, despite a thorough study of the relevant reaction conditions.

2-Furyloxirane (**FO**) is very prone to anionic initiation through the opening of the epoxide ring, even with such mild nucleophiles as alcohols, and gives the corresponding polyether [4d, 4e]. Whereas conventional initiators like tBuOK induced both the α and the β opening of the ring and gave therefore irregular polymer structures in terms of both monomer enchainment and stereospecificity, $Al(iPrO)_3$ acted regiospecifically at the α position and produced regular macromolecules with appreciable tacticity (**9**), as revealed by ^{13}C NMR spectroscopy [4d].

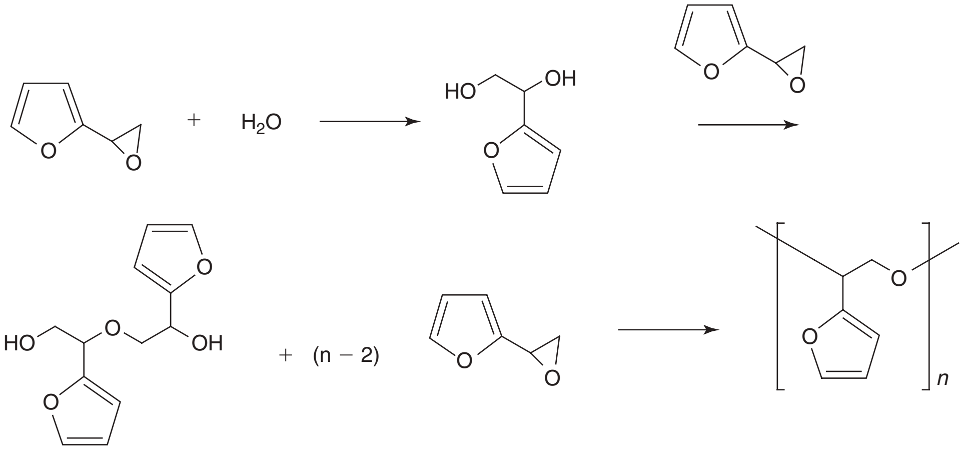


(9)

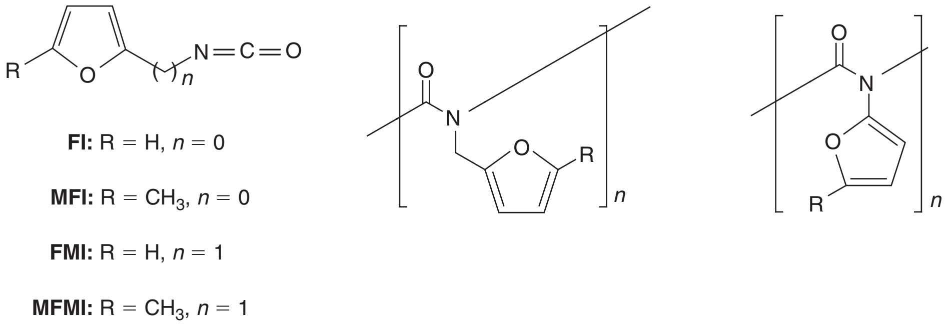
The fact that alcohols are sufficiently nucleophilic to initiate the anionic polymerization of **FO** (a unique feature, not shared by other epoxides, including styrene oxide), provides a useful way of preparing block, star and graft copolymers from, respectively, diols, polyols and OH-bearing polymers such as cellulose and poly(vinyl alcohol). The **FO** blocks and grafts however, are oligomeric in size, because transfer reactions limit their growth [4d].

Another interesting and unique peculiarity related to the behaviour of this monomer is its reactivity towards traces of moisture, without any catalyst. This spontaneous ring opening generates the corresponding diol, which in turn initiates the polymerization of the excess **FO**, as shown in Scheme 6.15. In other words, **FO** polymerizes in the presence of traces of water! [4d].

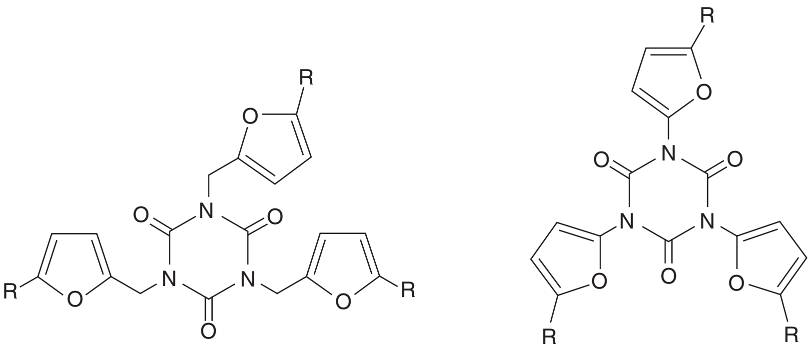
Furan isocyanates **FI**, **MFI**, **FMI** and **MFMI** were found to give mixtures of polymers (Scheme 6.16) and cyclic trimers (Scheme 6.17) when activated with classical anionic initiators like *n*BuLi and sodium naphthalene,



Scheme 6.15



Scheme 6.16



Scheme 6.17

whereas NaCN, the classical promoter of aliphatic isocyanate polymerization, failed to polymerize them, probably because the cyanide anion interacted preferentially with the furan heterocycle. Solvent of low polarity favoured the formation of polymers, as opposed to polar media, which induced predominantly the formation of the corresponding cyclic trimers [4a].

Other monomers which were found to respond positively to anionic polymerization were the 2-furfurylidene ketones, which gave phantom polymers following a propagation mechanism involving the isomerization of the active species before each addition step [4d, 4e].

6.5.4 Stereospecific polymerization

Apart from the partial tacticity of the poly**FO** prepared with $Al(iPrO)_3$ mentioned in the preceding section, no other report of the synthesis of a stereoregular furan polymer has appeared to the best of our knowledge. Numerous attempts to prepare such structures from 2-alkenylfurans using a variety of catalytic combinations failed [4d]. This aspect deserves more attention, because there are no obvious reasons that would exclude *a priori* the possibility of synthesizing stereoregular (and crystallizable) poly(alkenylfuran)s.

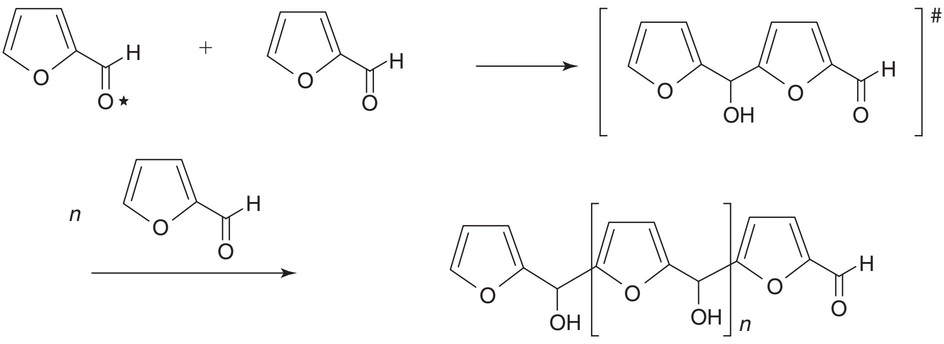
6.6 POLYMERS FROM STEP-GROWTH REACTIONS

Before examining the behaviour of the monomers in Schemes 6.12 and 6.13, it is important to summarize the major aspects related to the polycondensation of **F** and **FA**, since these processes provide interesting materials, despite their complexity and the irregular nature of the ensuing resins.

6.6.1 The resinification of furfural

F is seldom employed on its own as a monomer, mostly because the resinous products it produces under the effect of heat and/or acid catalysis are blackish crosslinked materials of little practical interest [4a, 4d]. Some of the mechanistic features of these systems have however been elucidated [4d, 22]. Interestingly, the liquid-phase photoirradiation of **F** [4d] produced linear oligomers whose basic structure suggested condensation reactions, but no intervention of free radicals, viz. Scheme 6.18.

The condensation products of **F** with acetone constitute interesting precursors to resins which have found applications as adhesives, corrosion-resistant coatings and floors for the chemical industry [4a, 4c, 4d]. Numerous other monomer combinations involving **F** have been exploited to prepare materials for different uses [4a, 4c, 4d] and recent additions to these studies include chelate polymers for the adsorption of metal ions [23], nanocomposites incorporating Fe_2O_3 [24], an investigation of the reductive electrochemical polymerization of **F** in acetonitrile [25] and the anticorrosion protection offered by the ensuing polymer [26].



Scheme 6.18

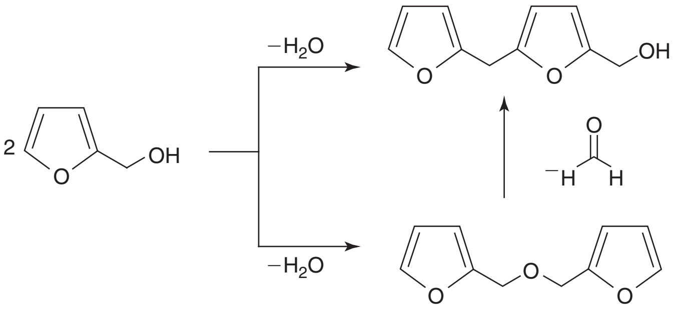
Finally, a considerable amount of work has been devoted to the development of wood adhesives consisting of resins in which furfural is used in conjunction with phenol and formaldehyde or in which furfural-based diamines and diisocyanates were the basic components [27, 28].

Notwithstanding these and other contributions, the role of **F** as a monomer or comonomer is unlikely to acquire a major impact in polymer technology, as compared to **FA**, which has a decisive part to play, as discussed in the next section.

6.6.2 The self-condensation of furfuryl alcohol

FA is the dominant furan commodity on the market precisely because it has provided for decades, and is still providing today, a number of processes and resins, which fulfil precise and outstanding performances in various technological areas. These systems and materials represent as yet by far the most important industrial issues related to furan-based polymers.

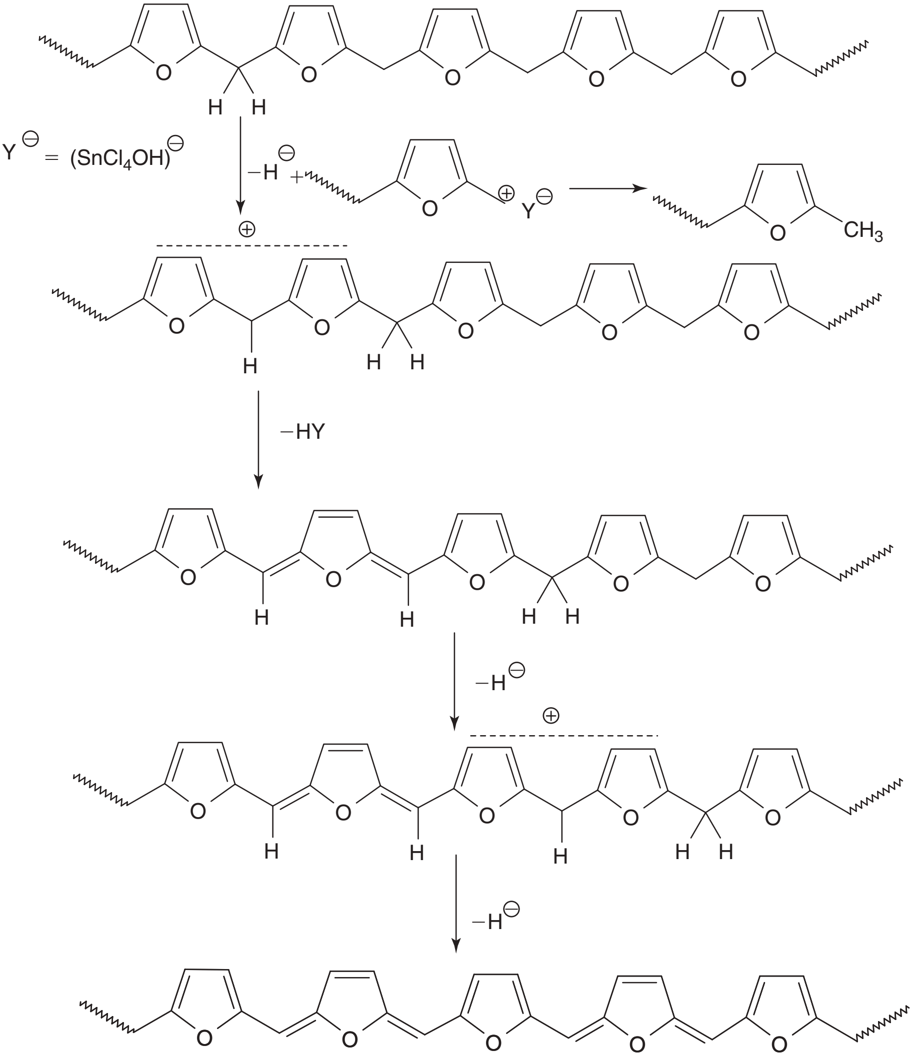
First the chemistry will be discussed. The intricate set of reactions that compose the acid-catalyzed and the polycondensation of **FA** constitute the most attentively searched puzzle in the realm of furan polymers because of striking contradictions between an expectedly straightforward macromolecular growth and a surprisingly complex behaviour. Given the by-now well-argumented reactivity of the furan ring in terms of its regiospecific electrophilic substitution at C5, the predominant reaction characterizing the self-condensation of **FA** should lead to a linear poly(2,5-furylmethylene), that is a linear colourless thermoplastic material, following the overall Scheme 6.19, even allowing for some head-to-head condensations giving occasional —CH_2—O—CH_2— bridges.



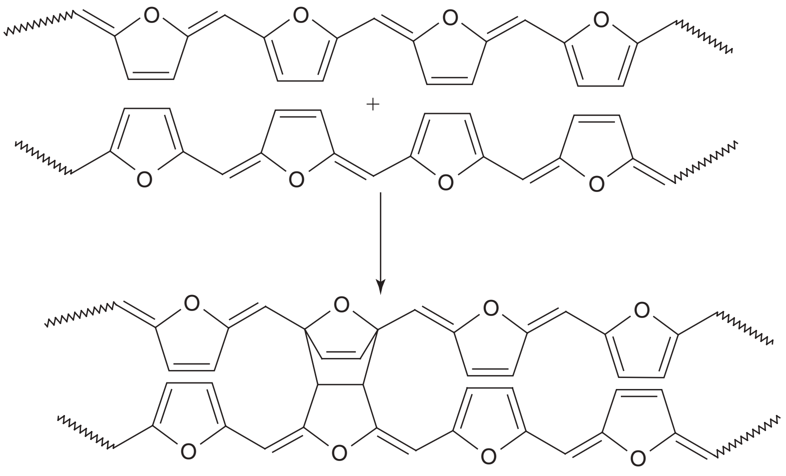
Scheme 6.19

The reality with all such systems, independent of the specific experimental conditions (strength and concentration of the acid, temperature, type of solvent used, if any), is qualitatively different to such a degree that it has puzzled chemists for decades. In fact, although the expected self-condensation reaction shown in Scheme 6.19 does indeed represent the basic growth mechanism, other important events intervene to modify drastically the polymer structure, to the point that the actual product is crosslinked and deeply coloured [4c, 4d].

It was only 20 years ago that the details of the two reactions responsible for these structural anomalies, which alter in a fundamental way the properties of polyFA, were unravelled, thanks to a systematic investigation involving the use of several model compounds. Whereas the details of this study can be found in the original publication, suffice it to give here a brief account of the essential issues. The colour build-up is mechanistically similar to that observed in the cationic polymerization of 2-vinylfuran and stems from the ease of hydride loss associated with a C—H bond in which the carbon atom is directly linked to the furan heterocycle (here to two of them, which makes much more likely). The driving force is of course the stabilization of the ensuing carbenium ion, which can subsequently readily induce a proton loss giving a neutral unsaturated moiety. The repetition of this cycle generates conjugated sequences, as shown in Scheme 6.20.



Scheme 6.20



Scheme 6.21

It is only after the formation of some of these unsaturated moieties and of the accompanying ═CH— sites linking a furan ring to an exounsaturated 2,5-dihydrofuran counterpart, that the polymer chains begin to couple through a DA mechanism (Scheme 6.21) and this leads to their eventual crosslinking.

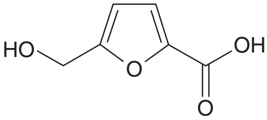
Given the ineluctable fact that both 'side' reactions are intrinsic to the very nature of the -2,5-Fu—CH_2— unit formed in the initial **FA** self-condensation oligomers, no obvious way to avoid, or indeed minimize them, has yet been found.

Despite these inevitable drawbacks, **FA**-based resins have found numerous useful applications, which have not ceased to multiply. The classical uses of these resins [4c, 4d, 27], for some of which they are practically irreplaceable, include metal casting cores and moulds, corrosion-resistant coatings, polymer concretes, wood adhesives and binders, sand consolidation and well plugging, low flammability and low smoke release materials and carbonaceous products including graphitic electrodes and carbon micro-particles. Recent additions to this wide catalogue of applications relate to novel polymer concretes [29], wood preservation [30] and stabilization [31], lignocellulosic fibre surface treatment [32] and also high-tech materials like micro- and meso-porous carbon, carbon-silica [33] and PFA-silica materials [34], nanostructured and nanocomposite carbons [35] and Nafion-PFA [36] and sol–gel-based nanocomposites [37].

The future of **FA** as a cheap precursor to a variety of useful materials appears therefore to reflect a growing exploitation in traditional as well as state-of-the-art technologies. Additionally, as pointed out in various subsequent sections, **FA** is finding other novel utilizations as precursor to multifunctional furan monomers.

6.6.3 Polyesters

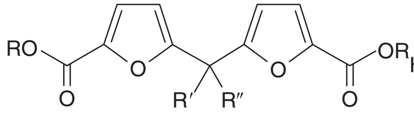
The pioneering work carried out in Moore's laboratory in the 1970s and 1980s represents the first systematic approach to furan polyesters (after numerous isolated and rather qualitative publications on the topic), which were prepared from 2,5-furandicarboxylic derivatives in conjunction with aliphatic, furanic and tetrahydrofuranic diols as well as with bisphenol A [4d, 4e]. In the same period, the furan hydroxyacid **10** was polymerized to give both linear and cyclic oligomers at relatively low temperatures, but its condensation with ethylene glycol produced black intractable resins [4d, 38].



(10)

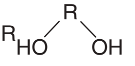
The synthesis of polyesters based on various furan diacids derivatives and dianhydrosugar diols [4d, 39] were reported in the context of biomass-derived polymers with biodegradable properties, but regrettably these studies were not pursued.

A series of studies based on the combination of the difuran–dicarboxylic derivatives **11** and a wide choice of diols **12** were undertaken recently using all the classical procedures for the synthesis of polyesters **13**, namely transesterification, condensation between the acid chloride moiety and the OH function and direct condensation. This comprehensive investigation included the structural characterization of all the polymers obtained, the determination of their molecular weight and molecular weight distribution, as well as of the thermal transitions and stability. From this broad set of results, interesting structure properties relationships could be drawn [4e].



R′ and R″ = H, CH_3, Ph, ...

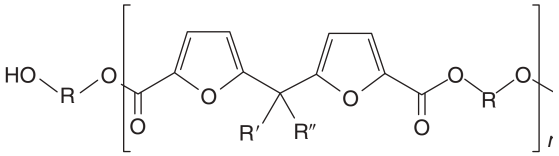
(11)



R = $(CH_2)_m$

R = Ph

(12)

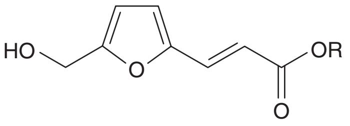


R = —$(CH_2)_m$, *p*-Ph, ...

(13)

Thus, for example, the glass transition temperature varied considerably as a function of both the nature of the groups appended on the carbon atom joining the two furan rings in **11** and the structure of the diol **12,** in particular when going from aliphatic to aromatic homologues.

In another vein, the polytransesterification of monomer **14**, readily obtained from **HMF**, yielded the interesting material **15** because of the photosensitivity of the -2,5-Fu—CO—CH=CH— moiety (see Section 6.7.2) which reacted by coupling with another such moiety (statistically belonging to another polyester chain), thus ultimately providing a rigid crosslinked product. Copolymers based on **14** and aliphatic hydroxyesters were also prepared and the ensuing crosslinked materials displayed glass transition temperatures well below room temperature and were therefore elastomers [40].



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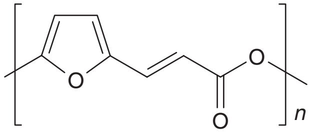


(15)

It is well known that fully aromatic polyesters are intractable materials in terms of processing because they are sparingly soluble even in very polar solvents and they start degrading before reaching their melting temperature. The replacement of up to 50 per cent of the aromatic dicarboxylic moieties by 2,5-furan counterparts was shown to reduce Tm correspondingly and make these copolyesters more apt to be processed, while keeping the required mechanical properties [4d].

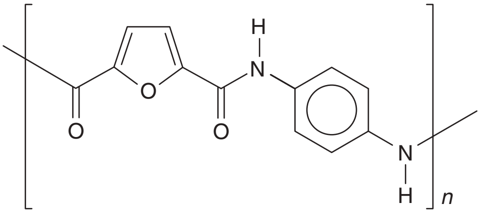
Two recent additions to the topic of furan-based polyesters include macromolecular structures synthesized from 2,5-bis(hydroxymethyl)furan and various natural dicarboxylic acids such as succinic, fumaric and maleic acid [41] and the ring-closing depolymerization of polyesters **13** [42].

Curiously, to the best of our knowledge, no detailed study is available on the synthesis of the polyester arising from 2,5-furan dicarboxylic acid in combination with ethylene glycol, viz. the exact counterpart of PET which is by far the most widespread commercial polyester. The obvious interest of comparing the performances of the two polymers stems from the possibility of proposing a novel material, alternative to PET, based on a diacid readily available from the oxidation of **HMF** (a classical example of a compound derived from renewable resources as discussed above in Section 6.3). This void is presently being fulfilled in ongoing research carried out at Aveiro University.

6.6.4 Polyamides

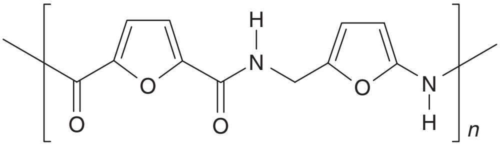
As with furan polyesters, following a number of isolated and rather qualitative studies, a real scientific interest in furan-based polyamides began in the 1980s with a thorough study carried out in Moore's laboratory [43] which called upon the use of 2,5-furan dicarboxylic monomers in conjunction with aliphatic diamines. These new 'nylons' were however not inspected in terms of molecular weight, crystallinity or physical properties.

A series of furan-aromatic polyamides were prepared at a later date using the then novel technique called 'direct condensation', which was applied to the polycondensation of both 2,5- and 3,4-dicarboxylic acids with a number of aromatic diamines [4d, 4e]. All these polymers were thoroughly characterized and showed regular structures, high molecular weights and interesting crystallization and thermal properties, thus indicating that a novel class of material similar to aramides could be prepared using the furan diacid instead of the corresponding aromatic monomer. In particular, the polyamide **16**, arising from the simple combination of the 2,5-furan diacid (readily prepared by the oxidation of **HMF**) with 1,4-phenylene diamine, displayed properties entirely comparable to those of the homologous Kevlar. These included a remarkable thermal stability, up to 400°C, very pronounced mechanical properties and lyotropic liquid crystal behaviour.

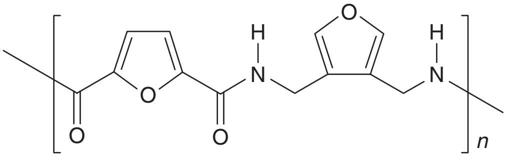


(16)

The corresponding all-furan polyamides **17–19**, obtained with 2,5- and 3,4-bis(furfuryl) amines, were also prepared and characterized but gave disappointing properties particularly in terms of thermal stability because of the lability of the hydrogen atoms in the methylene groups attached to the amine-derived furan rings.



(17)



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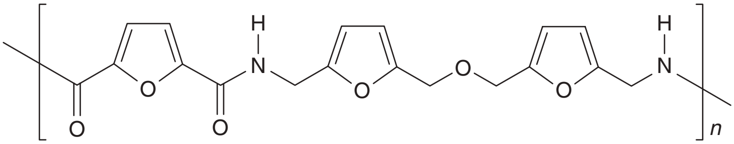
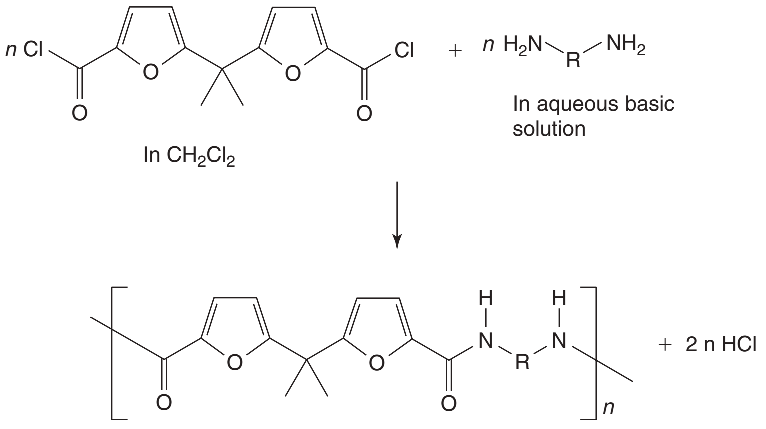


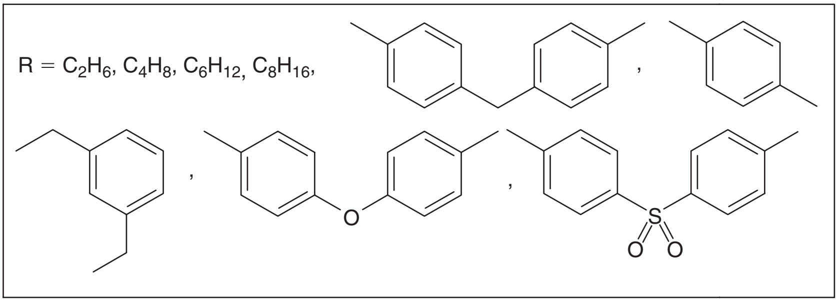
(19)

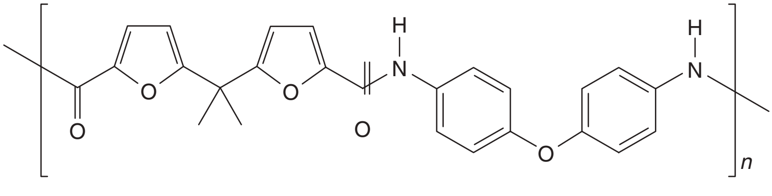
Recently, a systematic study has been undertaken dealing with the synthesis and characterization of a wide spectrum of furan polyamides **20** which simulate the structures of polyesters **13** since they were prepared using monomers **11** and a large choice of both aliphatic and aromatic diamines including furan homologues [4e, 44].

Again, different synthetic procedures were applied in order to optimize both polymer yields and molecular weights and very instructive relationships could be drawn from the multiplicity of the ensuing macromolecular structures. Figure 6.1 shows the ^{1}H-NMR spectrum of polyamide **20a** and Fig. 6.2 the DSC tracing of polyamide **20b**.

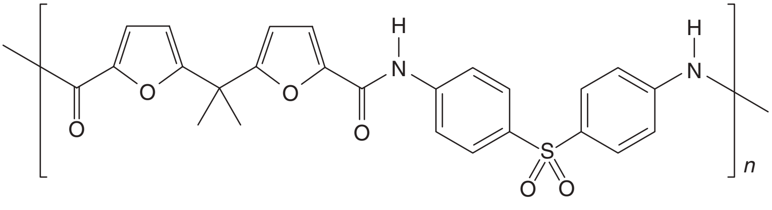

In CH2Cl2
In aqueous basic solution
+ 2 n HCl

(20)


R = C2H6, C4H8, C6H12, C8H16,



(**20a**)



(**20b**)

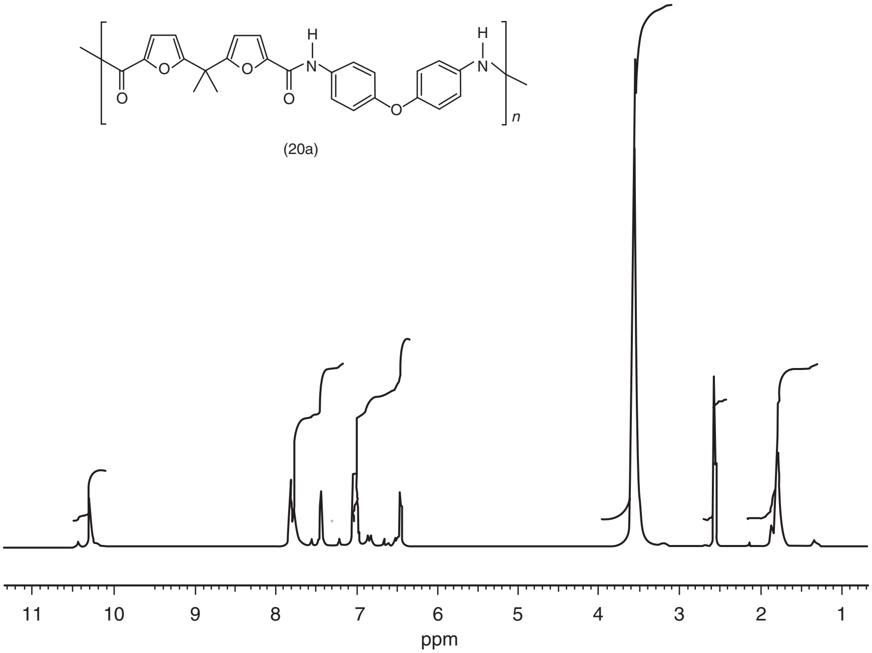


Figure 6.1 ^{1}H-NMR spectrum of polyamide **20a**, reported in Reference [44a]. (Reproduced by permission of the Elsevier. Copyright 2004. Reprinted from Reference [44a]).

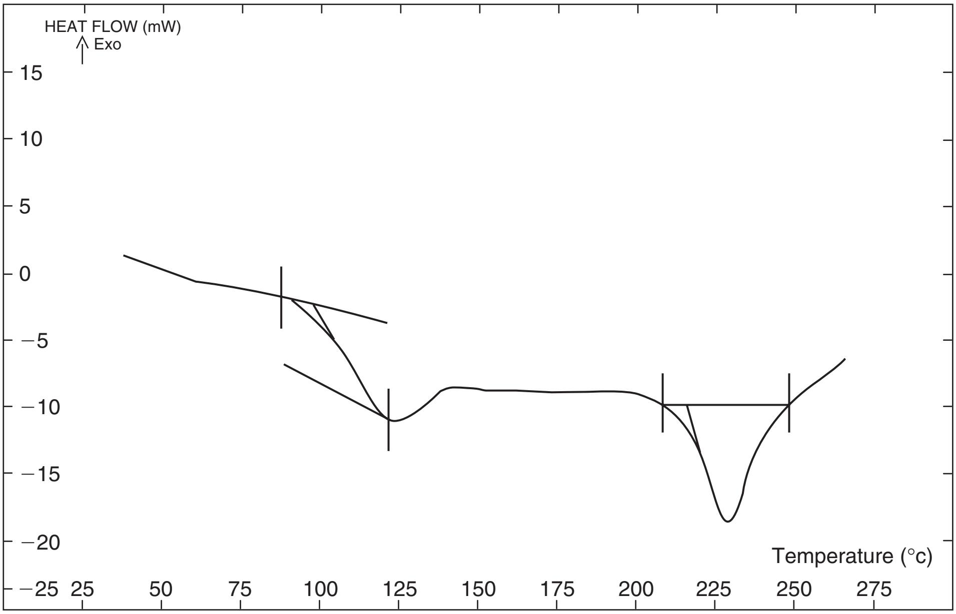
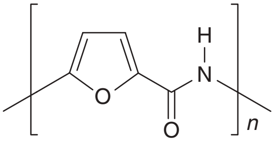


Figure 6.2 DSC tracing of polyamide **20b**, reported in Reference [44a]. (Reproduced by permission of Elsevier. Copyright 2004. Reprinted from Reference [44a]).

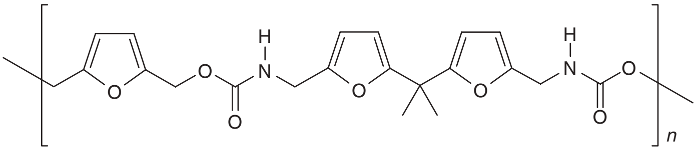
A peculiar route to a unique furan polyamide was applied to *N*-hydroxymethylfuramide prepared *in situ* from 2-furamide and an excess of formaldehyde, which gave rise to polymer **21** by an acid-catalyzed polycondensation mechanism involving the C5 electrophilic substitution of the heterocycle [4e].



(21)

6.6.5 Polyurethanes

Once more, the interest in furan-based polyurethanes was scanty before a very thorough approach to the issue was carried out by us in the 1990s [4d, 4e]. This investigation involved the synthesis of both model compounds and new monomers bearing isocyanate functions, the study of the kinetics of their condensation reactions with alcohols and diols, the preparation and characterization of model mono- and di-urethanes and finally the actual systematic synthesis of a whole spectrum of polyurethanes. These polymers bore the furan ring in the main chain (*e.g.* **22**) and/or as pendant moieties (*e.g.* **23**). The heterocycles arose from either the diisocyanate monomer, or the diol, or from both. Other moieties incorporated in these linear polyurethanes included aliphatic (*e.g.* **24**, **25**) and aromatic (*e.g.* **23**) structures.



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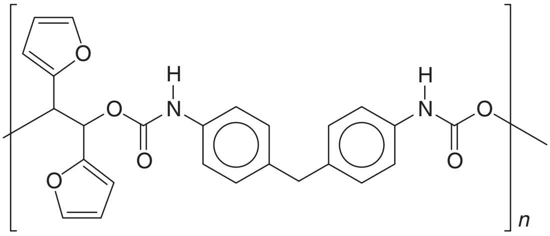
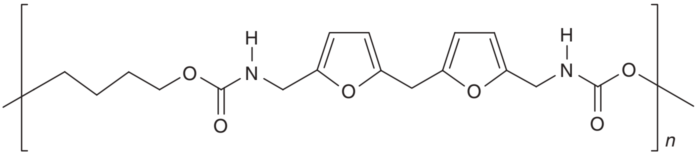
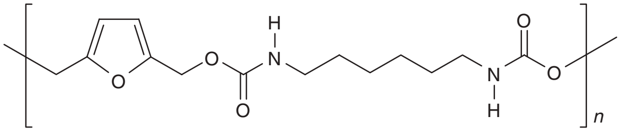


(23)



(24)

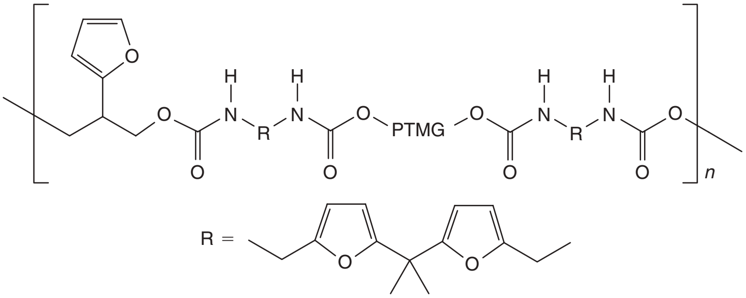


(25)

This comprehensive study showed first of all that the use of both types of furan monomers did not entail the occurrence of any unwanted side reaction, since all the polymers displayed a perfectly regular structure, as assessed by FTIR and NMR spectroscopy.

The second observation has to do with the very pronounced reactivity of furan isocyanates towards alcohols, higher than that of aromatic counterparts, even when the NCO group is separated from the heterocycle by a methylene spacer. This was so dramatic that in fact 2,5-furandiisocyanate could not be of any practical use because of its excessive nervousness.

The most relevant outcome here has to do of course with the structure–property relationships gathered from this investigation which gave clear-cut information about Tg, Tm and the corresponding extent of crystallization, thermal stability, mechanical properties and phase separation phenomena associated with a series of thermoplastic elastomers, like **26**, prepared together with all the other linear materials.



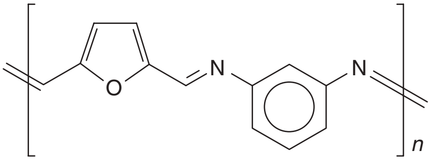
PTMG = PolyTetraMethylene Glycol

(26)

6.6.6 Other polymers

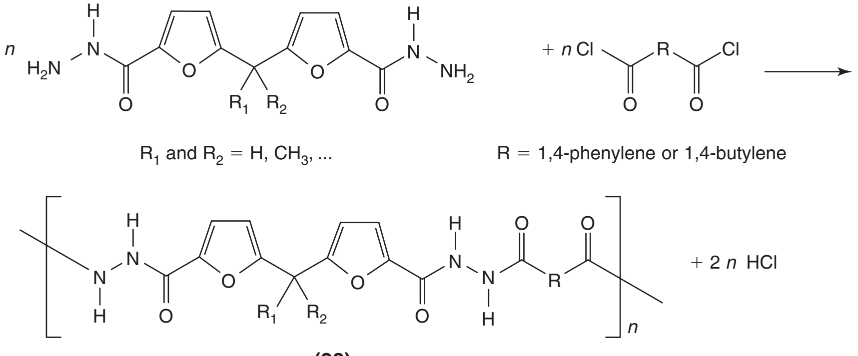
Among the numerous furan polymers derived from polycondensation involving systems other than polyesters, polyamides or polyurethanes, the most relevant materials include:

- polyschiff bases prepared from 2,5-furandicarboxaldehyde (readily obtained from the controlled oxidation of **HMF**) and aromatic diamines (*e.g.* **27**) and similar systems, including co-polyschiff bases incorporating flexible oligoether segments [4d, 4e];

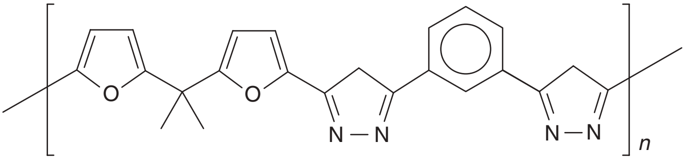


(27)

- polyethers following a single study of the phase-transfer condensation of 2,5-bis(hydroxymethyl) furan with various dibenzylic halides [4d];
- polyhydrazides formed from furan 2,5-dihrazides and diacid chlorides (*e.g.* **28**) and the corresponding poly-1,3,4-polyoxadiazoles arising from their dehydration (*e.g.* **29**) [4e, 45];

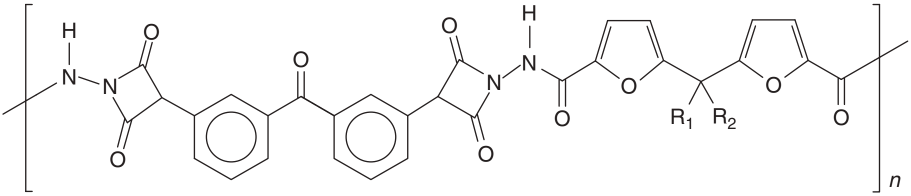


(28)



(29)

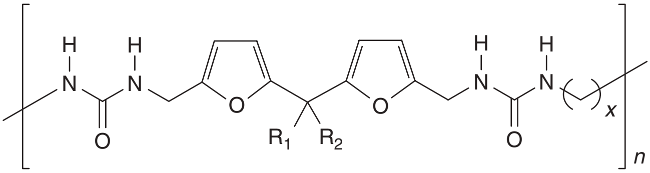
- polyamide-imides synthesized in solution from aromatic dianhydrides and 2-furoic acid dihydrazides (*e.g.* **30**) [46];



$R_1/R_2 = CH_3/CH_3;\ CH_3/C_6H_5;\ CH_3/C_2H_5;\ CH_3/C_5H_{11};\ CH_3/CF_3$

(30)

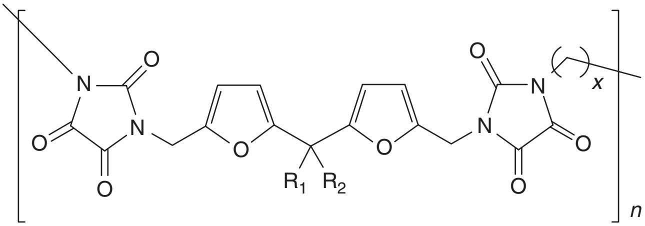
- polyureas (*e.g.* **31**) and poly(parabanic acid)s (*e.g.* **32**) obtained, respectively, from difuran diamines and aliphatic diisocyanates and the subsequent heterocyclization with oxalyl chloride [47];



$R_1/R_2 = CH_3/CH_3;\ C_2H_5/C_2H_5;\ CH_3/H;\ CH_{13}/H$

$x = 4, 6$ and 8

(31)

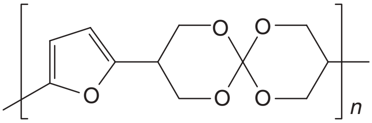


$R_1/R_2 = CH_3/CH_3;\ C_2H_5/C_2H_5;\ CH_3/H;\ CH_{13}/H$

$x = 4, 6$ and 8

(32)

- quasi-spiro polyacetals (*e.g.* **33**) arising from the polycondensation of 2,5-furandicarboxaldehyde with pentaerithritol [4d, 4e];



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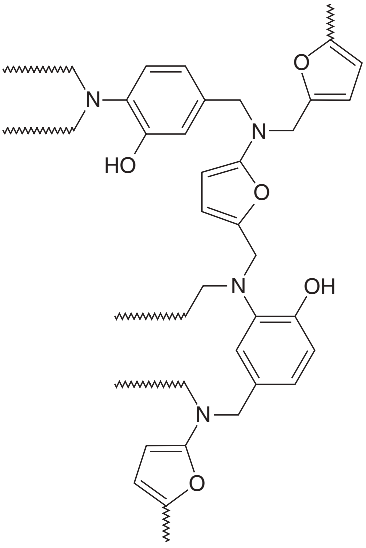


Scheme 6.22

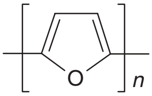
- polybenzoxazines prepared from furan-containing benzoxazines by temperature-driven ring opening leading to crosslinked structures, as shown in Scheme 6.22 [48].

6.7 CONJUGATED OLIGOMERS AND POLYMERS

The growing interest in conjugated macromolecular structures, associated with their possible high-tech applications, as in opto-electronic devices, has spurred a large variety of materials based on aliphatic, aromatic and heterocyclic [49] moieties linked in various modes. The possibility of introducing the furan heterocycle in these polymers has obviously retained the attention of specialists, particularly in view of the success of related structures based on thiophene and pyrrole. These studies can be divided into two types of approaches, namely polymers and copolymers synthesized using furan itself (or 2-alkylfurans) and polymers bearing 2,5-furylvinylene moieties.

6.7.1 Polyfuran

Despite numerous attempts at synthesizing the ideal polymer **34** [4d, 49, 50] the preparation of polyfuran has not been a clear-cut issue in terms of structural assessment and material performance.



(34)

Whether by chemical or electro-chemical means, the expected structure has eluded chemists for some 25 years because what is in fact obtained is a material which suggests the existence of extensive conjugation by its blackish colour, but whose macromolecular architecture is much more irregular and complicated than the linear chain **34**, notwithstanding some claims related to a thorough structural elucidation. It follows that what all these authors happily call ‘polyfuran’ is true to its name only because it is obtained by polymerizing furan, albeit through insofar

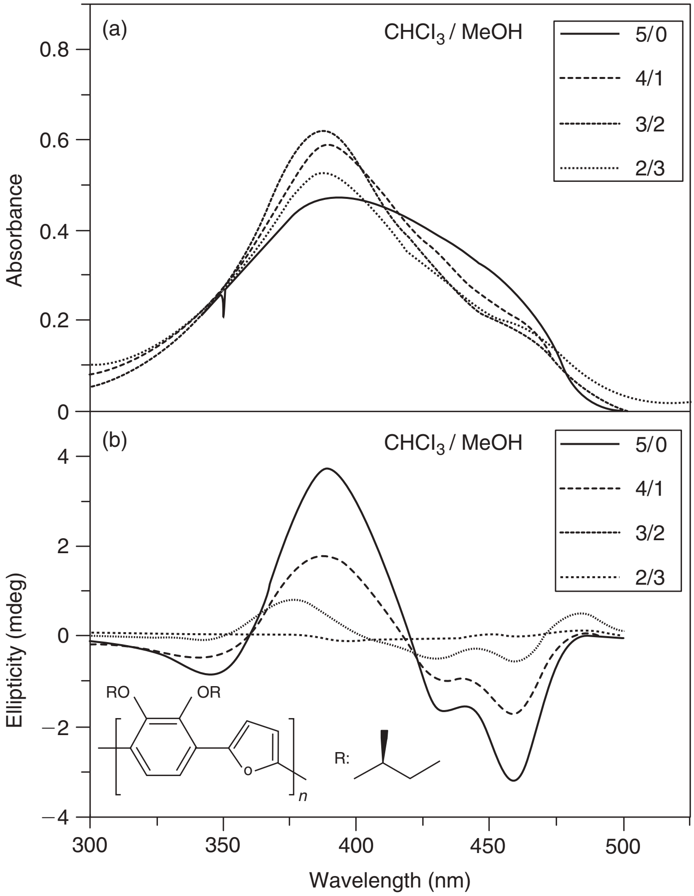


Figure 6.3 Solvatochromic studies of poly(1,4-(2,3-di-(*S*)-2-methylbutoxyphenylene)-*alt*-2,5-furan) in different solvents: (a) UV–vis measurements; (b) CD measurements, reported in Reference [53b]. (Reproduced by permission of the American Chemical Society. Copyright 2002. Reprinted from Reference [53b]).

obscure mechanisms. This state of affairs is reflected by the fact that these materials have not achieved any of the success that the homologous polypyrrole and polythiophene have enjoyed.

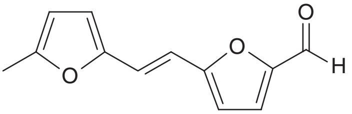
The insertion of furan moieties within the macromolecular structure composed mostly of other conjugated units, like homologous heterocycles [51], substituted anilines [52] or aromatic rings [53], has been much more successful in terms of structure regularity. Among these, mixed furan–thiophene oligomers have been prepared and thoroughly characterized [54]. Figure 6.3 shows the UV-vis and the circular dichroism features of one of these conjugated structures in solvent mixtures.

A recent addition to this rather modest field, consists in preparing polyfuran composites with both inorganic and carbon nanoparticles [55].

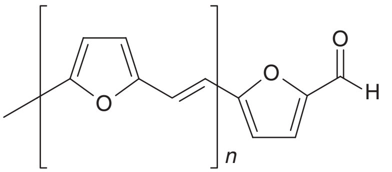
6.7.2 Poly(2,5-furylene vinylene)

The success of poly(1,4-phenylene vinylene) (**PPV**) and its derivatives was accompanied by studies aimed at preparing similar structures in which the aromatic ring was substituted by a heteroaromatic counterpart [56]. The furan homologue was first prepared using a synthetic process which simulated that of **PPV**, but in those studies more emphasis was placed on the characterization of the reactive intermediates rather than on the final polymer [4d, 56].

A radically different approach was developed in later years which gave the possibility of building stepwise the units of poly(2,5-furylene vinylene) (**PFV**) from the dimer **35** to polymers **36** with DPs reaching about 100 and to isolate well-defined pure oligomers [4e, 57]. This synthesis is based on the base-catalyzed self-condensation of **MF** through a mechanism which only allows the reaction between the terminal aldehyde group of the growing macromolecule with the methyl group of the *monomer*, as shown in Scheme 6.23.



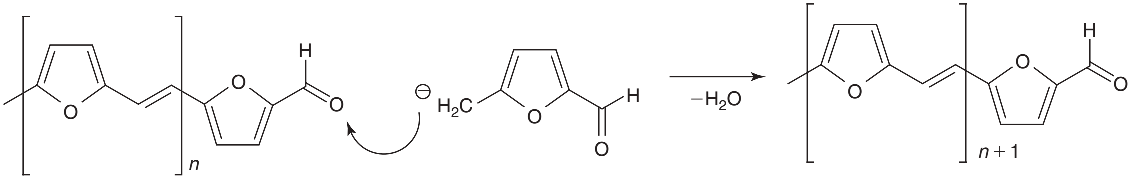
(35)



(36)

The electrical conductivity of **36** was close to $1\,\mathrm{S\,cm^{-1}}$ at room temperature. Its brittle consistency made it difficult to process films from it but, thanks to the terminal aldehyde group, block copolymers could readily be prepared by reacting these monofunctional conjugated polymers with mono- or di-functional polyethers bearing terminal primary amino groups and possessing very low glass transition temperatures. The ensuing internally plastified materials were readily soluble in common solvents, and thus easily processable [4d].

In a more specific study, pure individual oligomers with DPs ranging from 2 to 5 and oligomeric mixtures with DPs of 6 to 10 were synthesized and thoroughly characterized in terms of their structure and electronic spectra before and after protonation [4d, 57]. This investigation also involved the preparation of the thiophene analogues as well as furan–thiophene mixed oligomers. All these compounds were found to display a pronounced photoluminescent behaviour [57] and the wavelength of the emitted radiation increased with their DP, enabling to cover the entire visible spectrum. This feature is illustrated in Fig. 6.4 for the specific case of the oligo(furylene vinylene) series.



Scheme 6.23

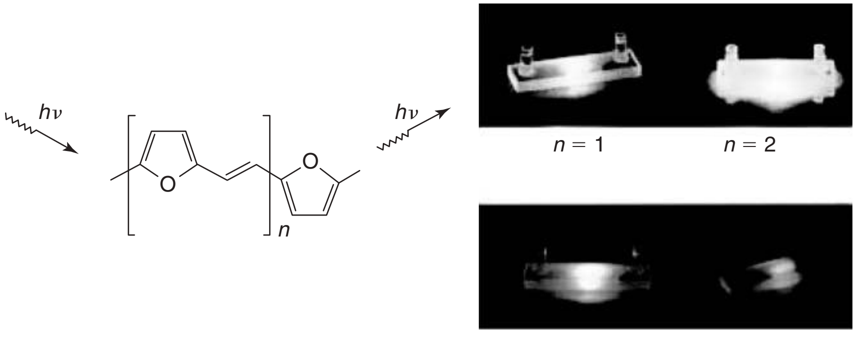
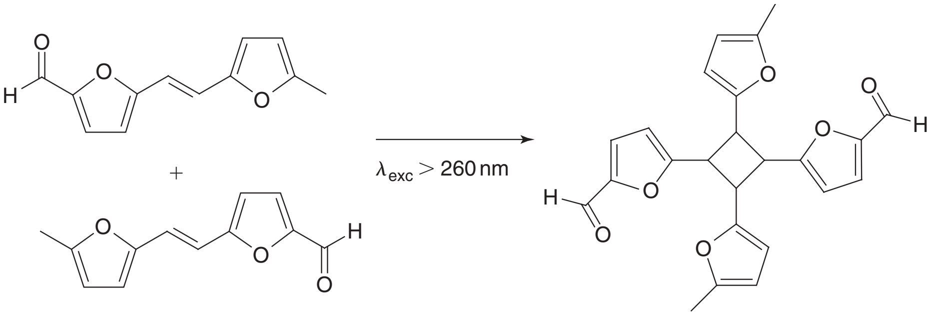


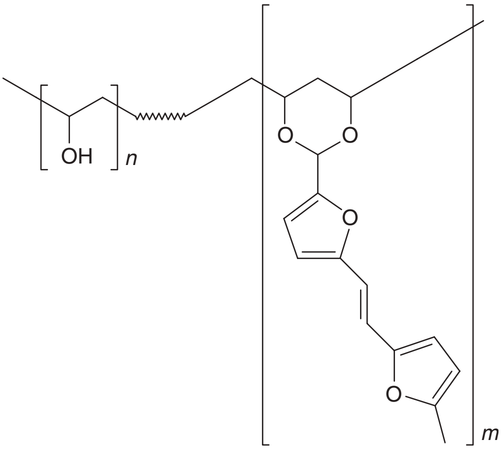
Figure 6.4 Photoluminescence of oligo(furylene vinylene)s of different lengths [57b] (see colour plate section).



Scheme 6.24

Dimer **35** was found to possess a straightforward single photo-chemical pathway which led to its dimerization when it was irradiated with near UV light, as shown in Scheme 6.24 [4d, 58]. Later studies showed that this behaviour was indeed common to molecules bearing the general Fu—CH═CH—C═O chromophore [58].

This photo-chemical feature was exploited in a number of investigations dealing with the possibility of preparing photocrosslinkable polymers. Thus poly(vinyl alcohol) was modified by condensing dimer **35** with two of its OH groups, which appended the furan chromophores by forming acetal moieties. The ensuing polymer **37**, with as little as 5 per cent photosensitive units, readily crosslinked in a few minutes under the irradiation of a standard medium-pressure mercury lamp [59]. In another application, Schiff bases were prepared between dimer **35** and mono-, di- and tri-functional Jeffamines. Following irradiation of these photosensitive oligomers, macrodimers, linear polymers and crosslinked structures were obtained, respectively, through the coupling of the terminal chromophores. These materials displayed interesting properties as polymer electrolytes [60]. A recent addition to this strategy called upon the introduction of the same furan chromophores as infrequent side groups to the chitosan backbone, together with grafted oligo(ethylene oxide) branches. The ensuing material had excellent film-forming aptitudes and was of course also a very good iron conductor because of the abundant polyether grafts and when irradiated, it crosslinked to give dimensionally stable thin films [61].



(37)

Whereas all the above materials bore the photosensitive moiety as side or end groups, the unsaturated polyester **15** and its copolymers were characterized by the presence of a similar chromophore as part of the main polymer chain. This internal placement did not hinder its photo reactivity [62], since these materials readily crosslinked upon irradiation [40].

It is worth noting that all these latter examples of materials whose key feature calls upon a specific behaviour of furan moieties, require modest contributions from these heterocycles in terms of its quantitative presence in the macromolecules. This situation is similar to that described in Section 6.5.2, in which furan derivatives were used to modify the end groups of some polymers or to synthesize block copolymers by cationic polymerization. In both instances, therefore, it is not the dominant presence of the heterocycle that determines the specific properties of the final materials (as in the case of polymers and copolymers bearing furan monomer units), but instead the fact that a small or even minute percentage of these structures introduces an original mechanistic feature, associated with the peculiar chemistry of the heterocycle, which transforms the behaviour and properties of the final material. This crucial point will be met again in the context of the application of the DA reaction in Section 6.8.

Cyclic oligomers bearing some resemblance to the open-ended **PVF**s, were recently reported, albeit in very small yields, from the reaction of furan with perfluorobenzaldehyde [63]. Their absorption spectra, centred between 500 and 600 nm, reflected a substantial degree of conjugation.

6.8 THE APPLICATION OF THE DA REACTION TO FURAN POLYMERS

The strategies which make use of the DA reaction to prepare original polymers are discussed here with specific reference to the diene–dienophile combination consisting of a furan and a maleimide ring, respectively. We first reviewed this topic a decade ago [4d] and returned to it very recently [64]. However, the growing interest in developing novel functional materials using this approach justifies a brief treatment here with up-to-date contributions. The other interesting application of DA adducts in macromolecular synthesis calls upon their ring opening metathesis polymerization (ROMP), which has been reviewed previously by us [4d] and, because it has not received further attention since that critical coverage, will not be dealt with here.

Before tackling the aspects related to reversible macromolecular structures, a recent study on surfactants deserves a brief mention here because of its originality, albeit outside the realm of polymer materials. The idea consists in preparing amphiphilic structures in which the hydrophilic moiety is separated from the hydrophobic one by a DC adduct [65]. The surfactant displays its expected activity in aqueous media until the temperature is raised close to their boiling point, where it decomposes by the retro-DA reaction, thus generating two surface-inactive fragments. Because of the very low concentration of these fragments, associated with the classical values of surfactant utilization, the kinetics of recombination of the two fragments to regenerate the original structure is far too low to envisage such an event. The application of this principle falls into the broader area, very topical today, of degradable surfactants. Thus, surfactant **38** was synthesized and its thermo-reversible character tested, as shown in Fig. 6.5, which represents the ^{1}H-NMR spectra of **38** after solid state heating at different temperatures.

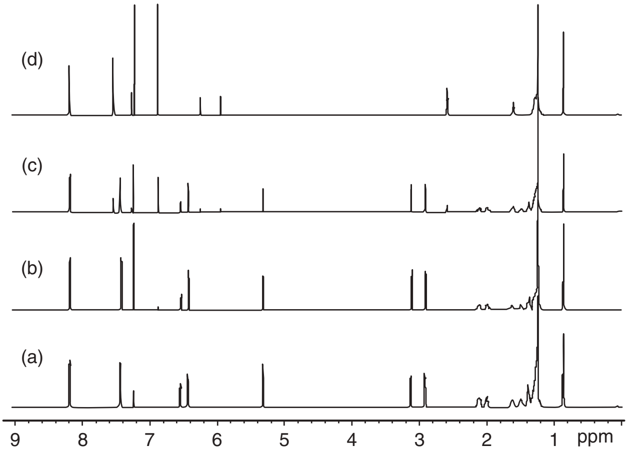


Figure 6.5 ^{1}H-NMR spectra of **38** after solid state heating for 30 min for (a) 25°C, (b) 105°C, (c) 120°C and (d) 125°C, reported in Reference [65] (Reproduced by permission of American Chemical Society. Copyright 2005. Reprinted from Reference [65]).

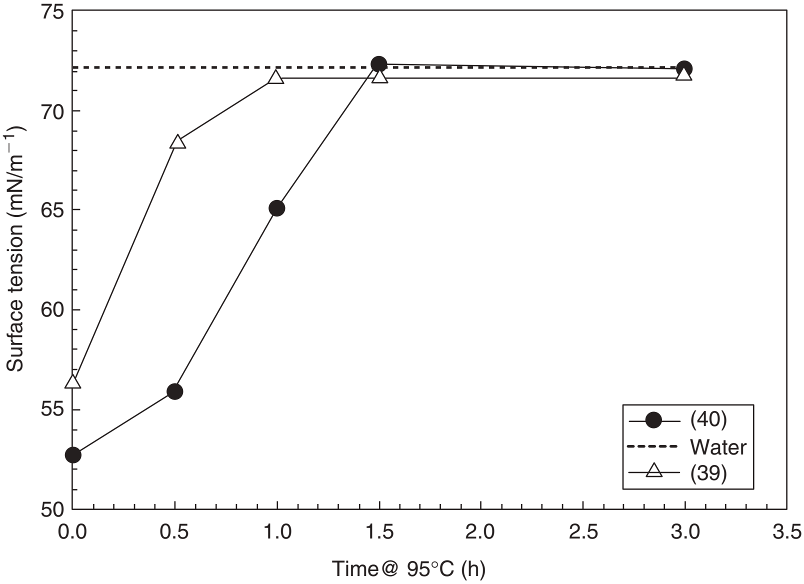
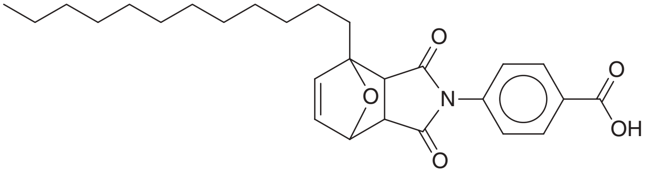


Figure 6.6 Changes in the dynamic surface tension of aqueous solutions of **39** and **40**, as a function of time at 95°C, reported in Reference [65] (Reproduced by permission of the American Chemical Society. Copyright 2005. Reprinted from Reference [65]).

Figure 6.6 represents the changes in dynamic surface tension (operated in an equilibrium mode) for 20 mM aqueous solutions of anionic surfactants **39** and **40**, as a function of time at 95°C and measured at 26°C. The dashed line represents the surface tension value of water at 25°C (72.1 mN m^{-1}).



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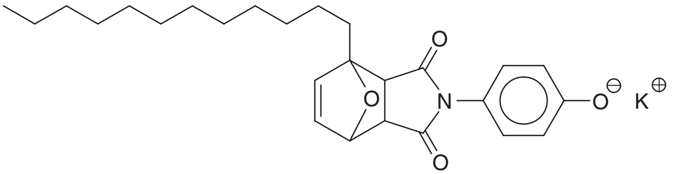

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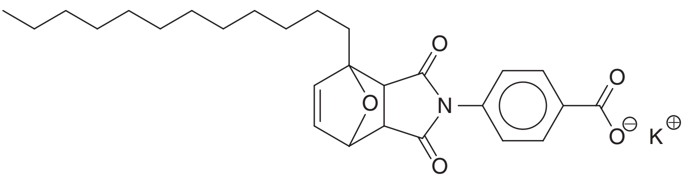

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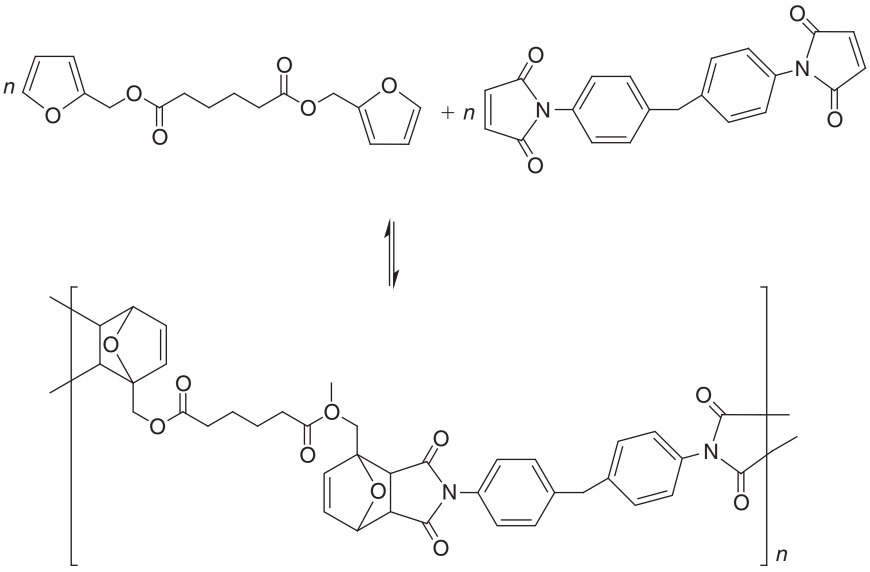


Scheme 6.25

6.8.1 Linear step-growth polymerization

The vast majority of systems falling within this category are based on the use of a bismaleimide and a difuran derivative, viz. a classical linear polycondensation of the A-A + B-B type. Since this synthetic challenge was first tackled some 20 years ago [4d, 64], numerous investigations have been published with different monomer combinations and with different approaches both in terms of the experimental conditions used for the polymer synthesis and the characterization and purpose of the ensuing materials [4d, 64].

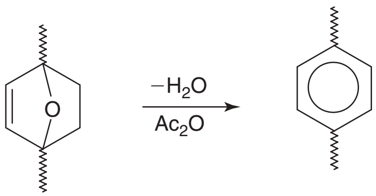
Among the most thorough studies of these systems, Kuramoto *et al.* [66] were the first to carry out both the polymerization and the thermal depolymerization of the ensuing DA polyadduct as shown in Scheme 6.25.

A few years later, Brand and Klapper [67] paid closer attention to the reversibility of this linear polycondensation using NMR spectroscopy and viscosity measurements, also applied to model compounds. This fine piece of research represents, in our view, the best example of how to approach these complex systems, an example which has not been followed systematically in subsequent studies.

As a rule, the molecular weights obtained in these syntheses are not particularly high because, on the one hand, the use of relatively elevated temperatures shifts the equilibrium in favour of a growing contribution of the retro-DA reaction (viz. depolymerization) and on the other, polymers tend to lose their solubility as their DP increases, thus precipitating out of the reaction medium.

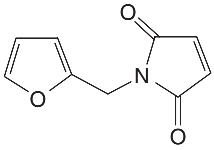
The interest in synthesizing thermoplastic polymers made up of DA adduct units, bridged by moieties bearing different flexible or rigid structures, can vary from one investigation to another. The reversible character associated with the DA reaction is of course one of the primary motives for these studies because it opens the way to preparing materials which can be thermally depolymerized (in the case of furan–maleimide adducts just above 100°C) in view of their ablation and/or recycling. Conversely, in other applications, the polymer structure obtained in these syntheses should be preserved even at high temperatures and, in that case, the chemical modification of the adduct to render it thermally stable, becomes indispensable. The aromatization of the DA adduct through a catalyzed dehydration reaction (Scheme 6.26) is a typical solution to this requirement.

The use of a single A-B monomer bearing both the furan and the maleimide ring represents an interesting alternative to this type of polymer synthesis because, as in all polycondensation reactions, this approach ensures the ideal initial stoichiometry. One such monomer (**41**) was prepared, characterized and polymerized, [68] but the single methylene bridge joining the two complementary DA rings made the structure susceptible to degradation, that



Scheme 6.26

is **41** turned out to be difficult to handle. Work is in progress in the Aveiro laboratory to prepare more manageable structures of this type.



(41)

The only other study of this nature known to us describes the synthesis of two other A-B monomers [64] as well as their solution and bulk polymerization, but the proposed mechanism for their chain growth is unclear. The aim of this investigation was to prepare thermally stable materials and therefore the DA adducts in the polymers were aromatized by dehydration with acetic anhydride.

6.8.2 Networks and dendrimers

The extension of these DA-based polymerizations to multi-functional furan and/or maleimide monomers naturally leads to crosslinked materials, whose original feature is related to the fact that they can be readily decrosslinked by a simple thermal treatment. Since the first report of a mendable material based on this principle, but applied in cycles [69], several similar studies have appeared in the literature [64] including interesting applications in the realm of thermally removable foams [64] and adhesives [64]. It seems likely that such a simple and useful strategy will continue to draw attention for the preparation of novel intelligent materials.

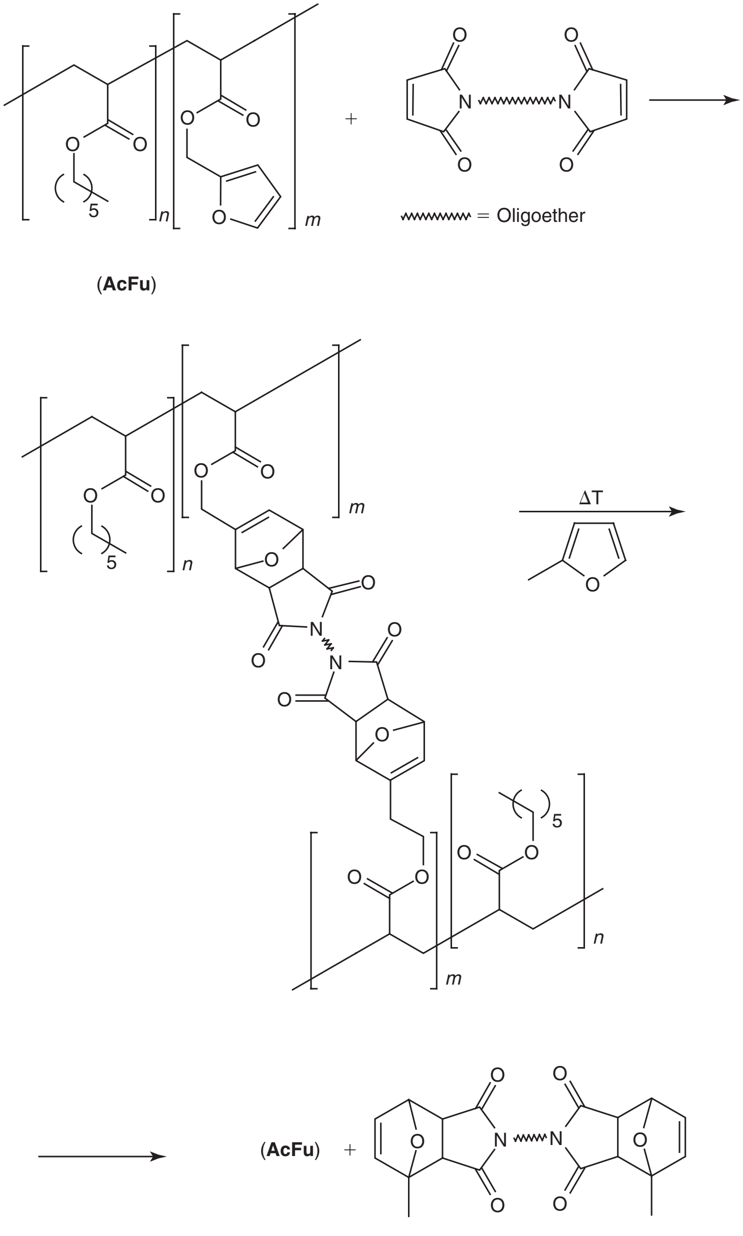
Another approach leading to non-linear macromolecular structures incorporating DA adducts has been put forward recently in the form of thermally reversible dendrimers [64, 70]. This interesting piece of research describes aromatic ether architectures joined by DA adducts and reaching up to the third generation. The backward mechanism, based on the retro-DA reaction progressively reduced this structure to lower generations.

6.8.3 Reversible crosslinking of linear polymers

Perhaps the most active area within the broader scope discussed here, refers to the preparation of linear polymers bearing pendant furan or maleimide moieties and their DA-based crosslinking with the complementary bi-functional reagent, viz. a bismaleimide or difuran compound, respectively [64]. The obvious reason for the growing interest in these materials relates to the possibility of recycling them after a simple thermal treatment capable of reverting their structure to the original linear thermoplastic architecture. The first example of this strategy which immediately comes to mind, is the possibility of recycling tyres, a major industrial and ecological issue yet to be solved.

After the pioneering study that Stevens and Jenkins published in 1979 [71], a real interest in this topic started only more than 10 years later with a series of studies aimed at testing the feasibility of the reversible pathway [64].

The best approach to this type of system included an original concept based on the necessity of trapping the difunctional molecule liberated during the retro-DA undoing of the crosslinked polymer in order to avoid a subsequent reconstruction of the network upon cooling [64]. This was successfully achieved by introducing in the decrosslinking medium an excess of mono-functional DA reagent (*e.g.* 2-methylfuran in the case of the liberation



Scheme 6.27

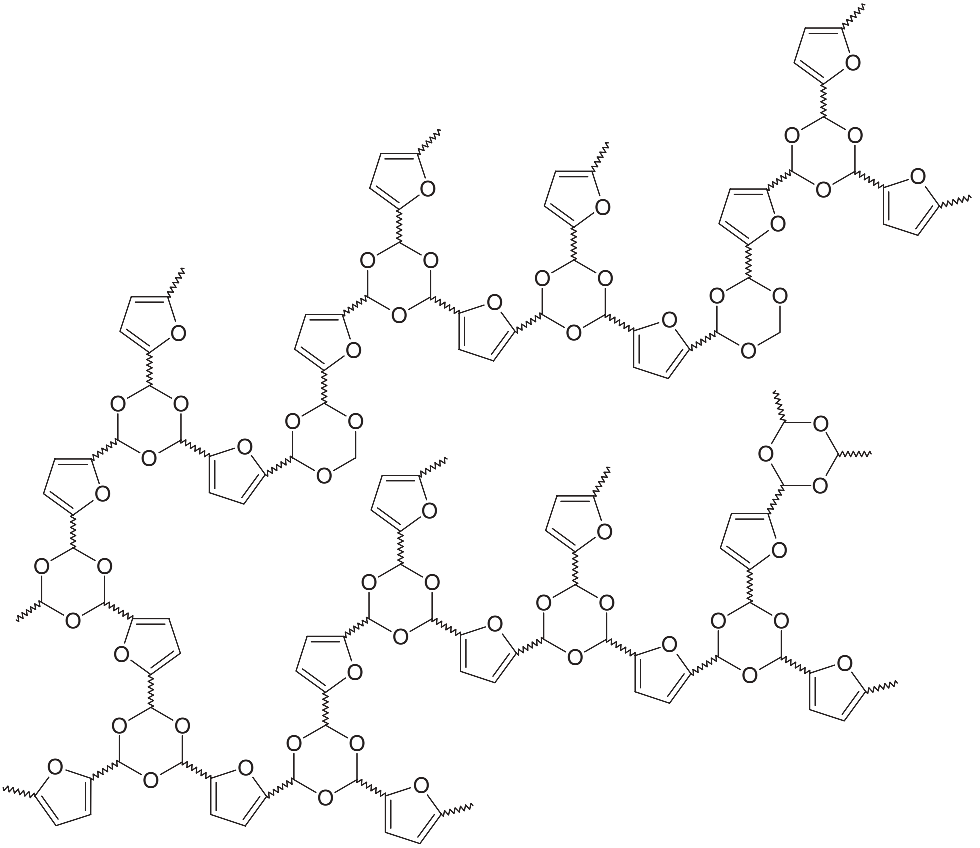
of a bismaleimide and *N*-methylmaleimide when a difuran compound is liberated). In this way, styrene-type [72] and acrylic [73] copolymers with pendant furan moieties, as well as silicone structures bearing pendant maleimide groups [73], were first crosslinked with a bismaleimide and a difuran derivative, respectively. Subsequently, these networks were suspended in appropriate media containing the monofunctional trapping molecule and heated at reflux just above 100°C, whereby the original linear copolymers were progressively regenerated as shown by the corresponding solubilization of the material. Thus, the DA/retro-DA mechanism reached a full cycle with the complete recovery of the starting thermoplastic copolymers even after their solution was cooled down to room temperature. An example of this cycle is shown in Scheme 6.27 [73].

Several experimental observations [64] have shown that the retro-DA reaction becomes kinetically relevant in this context at about 100°C and virtually negligible below about 70°C.

In the past few years, the application of these principles has acquired an enhanced relevance, as reflected by the numerous publications, which have appeared since our latest review [64], both with linear [74] and crosslinked [75] structures.

6.9 MISCELLANEOUS DENDRIMERS

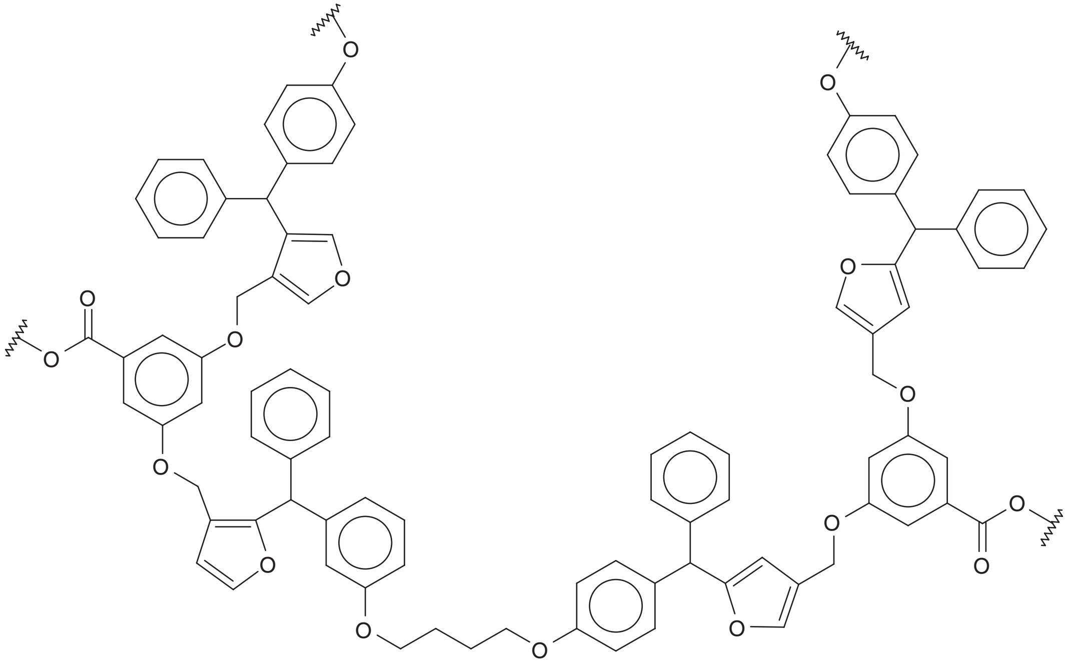
Two recent papers on furan-containing dendrimers have been added to the original work based on the DA reaction discussed in Section 6.8.2. The first describes the formation of star polymers induced by the cyclotrimerization of furan derivatives bearing aliphatic aldehyde functions attached at the 2 and 5 ring positions [76]. This hyperbranched structure was therefore generated by the formation of trifunctional acetal moieties, as shown in **42**, and should therefore be readily hydrolyzed making the whole process reversible, although this latter aspect was not pointed out by the authors.



(42)

The other approach was based on the acid-catalyzed coupling between a phenolic group and the C5 position of the furan ring [77] which gave rise to the second generation dendrimer, **43**. This approach gave rise to the preparation of novel molecular resists based on first generation dendrimers incorporating furan moieties. Figure 6.7 shows the SEM micrograph of the resist film formulated with **44**.

A novel hybrid dendritic copolymer bearing conjugated photosensitive furan rings was also prepared with the aim of developing crosslinkable polymer electrolytes [78].



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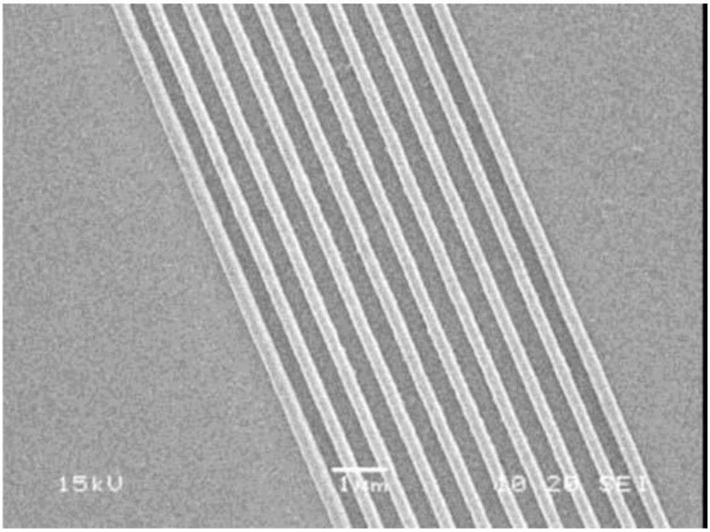
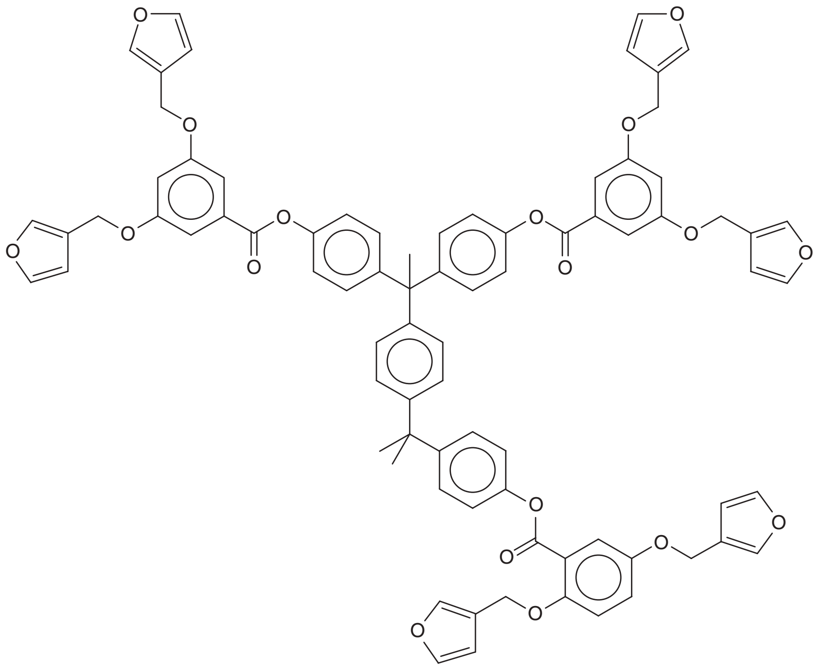


Figure 6.7 SEM image of negative-tone line and space patterns for the resist film formulated with **44**, reported in Reference [77] (Reproduced by permission of Wiley-VCH Verlag GmbH & Co. KGaA. Copyright 2006. Reprinted from Reference [77]).

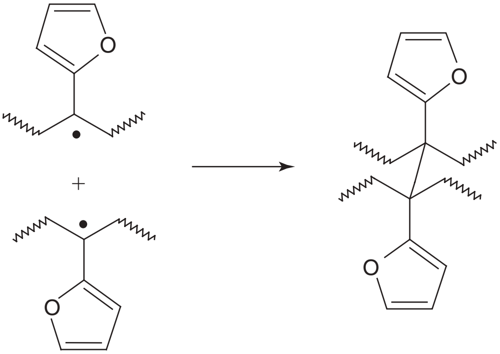


(44)

6.10 THE AGING OF FURAN POLYMERS

By far the most fragile structures in furan polymers are a tertiary C—H bond attached to one or more heterocycles and a secondary C—H bond attached to two rings. This high lability arises from the fact that, independent of the specific nature of the living H species, namely a proton, a hydride ion or a hydrogen atom, the intermediate structure that will be left is strongly stabilized by the adjacent heterocycle thanks to its dienic character. In other words, whether this intermediate is a carbanion, a carbenium ion or a free radical, the charge or the unpaired electron will be delocalized over the neighbouring furan ring(s).

The ease with which this mechanism occurs has already been emphasized when discussing the side reactions associated with the cationic polymerization of 2-vinylfurans (Section 6.5.2) and with the self-condensation of furfuryl alcohol (Section 6.6.2). However, its negative impact is also found, albeit with slower rates, in isolated furan polymers which possess the culprit C—H moiety as in the case of poly(2-vinylfuran) which slowly develops an insoluble fraction caused by the free radical mechanism shown in Scheme 6.28. These reactions are also responsible for the colour that is often associated with furan polymers.



Scheme 6.28

Secondary C—H bonds attached to a single furan ring do not display such a pronounced lability, as shown by polymers like furfuryl acrylates which do not suffer substantial aging.

It must be emphasized that the presence of carbonyl groups attached to furan rings represents on the contrary an element of stabilization in furan polymers. Thus, for example, furan polyesters and polyamides are white and do not suffer any structural modification over very long periods of time.

6.11 CONCLUSIONS

This condensed survey of how furan monomers and furan chemistry can benefit polymer science hopefully provides two major reflections. The first has to do with the fact that it is possible in principle to build a comprehensive new family of macromolecular materials in which some, if not all, of the precursors are derived from renewable resources. In other words, there is no intrinsic limit to the variety of furan monomers that can be synthesized from **F**, **HMF** and their homologues and hence no limit to the polymers and copolymers that they can generate. This constitutes an encouraging potential in terms of the possibility of gradually replacing fossil-derived monomers and polymers by this alternative family.

The second reflection concerns a more qualitative aspect, namely the fact that some peculiarities associated with the chemistry of the furan heterocycle can be put to the advantage of preparing materials with specific functional properties, otherwise difficult to realize. Ample evidence of these unique features is provided in this chapter.

As with other domains dealt with in this book, the road ahead is much longer than what has been achieved up to now in the general endeavour to make polymers from renewable resources. Whether the competition with the existing materials derived from dwindling resources will be successful or not depends almost entirely on the very concrete issue of the extent of financial sponsoring these novel research initiatives will receive.

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Surfactants from Renewable Sources: Synthesis and Applications

Thierry Benvegnu, Daniel Plusquellec and Loïc Lemiègre

ABSTRACT

The development of surfactants based on natural renewable resources is a concept that is gaining recognition from the detergent and cosmetic industries. This new class of biocompatible and biodegradable surfactants should be a response to the increasing consumer demand for products that are both greener and more powerful. The present chapter reviews the major contributions to the synthesis and characterization of amphiphilic molecules derived from natural oils and fats (lipophilic moiety) and incorporating sugar-, polyol- or ionic-type residues as the polar headgroups. It covers various aspects of their synthesis, industrial production, applications and regulations.

Keywords

Surfactants, Renewable resources, Carbohydrates, Polyols, Oils, Fats, Cationic emulsifiers, Gemini, Bolaamphiphiles synthesis, Surface properties, Applications

7.1 INTRODUCTION

Surfactants are one of the most representative chemical commodities, not only in terms of quantity, but also in view of the great variety of applications in household, industry and agriculture areas [1]. These 'surface-active agents' have in common the same basic molecular structure – a hydrophilic moiety (polar head group) attached to a hydrophobic backbone (alkyl chain) (Fig. 7.1) – and these two parts provide a compound with interfacial activity and give rise to a wide range of surface chemistry functions: wetting, emulsifying, softening, solubilizing, foaming/defoaming, rheology-modifying, detergency and surface conditioning.

The current world wide production of surfactants amounts to around 12.5 million tons with a growth rate of 500 000 t per year. About 60 per cent of the surfactant production is used in household detergents, 30 per cent in industrial and technical applications (as antistatic agents, lubricants and levelling agents, example for textile production, as flotation agents, for example in mining, oil production and wastewater treatment and as emulsifiers in the food industry, in road constructions and for the production of dies, coatings and plastics), 7 per cent in industrial and institutional cleaning and 6 per cent in personal care. The surfactant consumption is expected to grow at an average annual rate of 2 per cent in North America, to 3.7 million tons in 2010, and by 1.5 per cent in Western Europe, to about 2.5 million tons over the same period. Growth rates are expected to be higher in developing markets, with 3.3 per cent per year predicted for Latin America and 4.2 per cent per year for Asia over the 2000–2010 period [2].

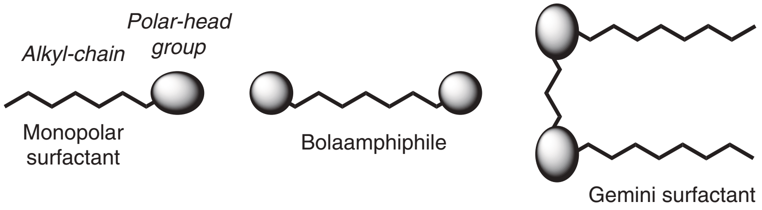

Figure 7.1 Schematic representation of mono and bipolar surfactants.

Surfactant molecules can be broadly divided into four groups, according to their electrical charge in water solution. These groups are anionic (negative charge), cationic (positive charge), non-ionic (no charge), or amphoteric (the molecules contain both positive and negative charges). The anionic surfactants are the 'traditional' ones to which belong, among others, common soaps and they are still the commercially most important. Non-ionic counterparts constitute a smaller group, but are the fastest growing, whereas the other two groups are comparatively small on the market. Properties of surfactants are additionally governed by the alkyl chain length of their hydrophobic part: wetting agents (C_8–C_{10}), detergents (C_{12}–C_{16}), emulsifiers and softeners (C_{18}–C_{22}).

Surfactants can be derived from both petrochemical feedstock and renewable resources (plant and animal oils, microorganisms). They were originally made from renewable resources like fats and oils, whereas today, the majority is of petrochemical origin. But things may slowly be beginning to turn back. The current pressure to move away from non-renewable petroleum feedstocks and towards plants as raw materials has led to considerable effort to develop surfactants from oleochemical feedstocks or other vegetable sources. Many recently developed surfactants are an attempt to satisfy the modern consumers' desire for products to be 'more natural'. Like most plant-based products, surfactants derived from renewable raw materials (RRMs) are characterized by their positive impact on the environment, biodegradability, low or non-toxicity and innocuousness for human health. In addition, the use of renewables in surfactant production can contribute to save fossil resources, such as crude oil and natural gas, and to the reduction of fossil carbon dioxide emissions (CO_2) and hence could be part of a strategy to mitigate the greenhouse effect. There is a good chance that the use of biomass could contribute to these goals, because the quantity of carbon dioxide originated from biomass is equivalent to the amount which was previously withdrawn from the atmosphere during its growth. Finally, the natural origin of these surfactant molecules is a significant communication and marketing asset.

These features, in conjunction with the rising consumer interest for agricultural products, have driven a strong progression in plant-based surfactants. The European market in surfactants represented in 2002 a volume of approximately 2.5 million tons, of which around 25 per cent came from plants. The stakes are thus high for a truly renewable alternative in this sector, and could represent several thousand hectares of crops, knowing that it takes around 60 000 hectares of cropland to produce 100 000 tons of vegetable-based surfactants.

Among surfactants based on renewable chemicals, some are made entirely with RRM (*e.g.* they are 100 per cent natural), whereas others possess only a hydrophobic portion based on RRM (hemipetrochemicals). Vegetable oils furnish fatty chains (acids, alcohols, amines, esters) with a carbon chain length comprised between either 8 and 18 (saturated caprylic, capric, lauric, myristic, palmitic and stearic chains from tropical coconut, palm or palm kernel oils) or 18 and 22 (unsaturated oleic, linoleic, and linolenic chains from European rapeseed and sunflower oils). In this chapter, we will focus on the synthesis and applications of surfactants from entirely natural and renewable resources. We will first study carbohydrate-based surfactants that are gaining more and more recognition from a number of industries ranging from agrochemicals to personal care products and food. We will also discuss (poly)glycerol ester-type surfactants derived entirely from oleochemicals that contribute to increase the value of the major secondary product of oleochemistry (*i.e.* glycerol). Following that, we will present recent research on biodegradable cationic emulsifiers for road industry or cosmetics. In all of these surfactants, the basic structure is that of a single (or multiple) lipophilic tail carrying a single hydrophilic head group as most surfactant development has been confined to this arrangement. However, a more radical approach is to use one or two lipophiles and two hydrophiles in the same molecule. These structures, known as bolaamphiphile (or bolas) and Gemini (or dimeric) surfactants (Fig. 7.1), will be described in the last part of the chapter. As a conclusion, we will finally analyse the perspectives for RRM surfactants in the context of new regulatory policies (notably REACH).

7.2 CARBOHYDRATE-BASED SURFACTANTS

Carbohydrate-based surfactants are the final result of a product concept that is based on the greatest possible use of renewable resources. Whereas the derivatization of fats and oils to produce a variety of different surfactants for a broad range of applications has a long tradition and is well established, the production of surfactants based on fats, oils, and carbohydrates on a larger industrial scale is relatively new. Considering the amphiphilic structure of a typical surfactant with a hydrophilic head group and a hydrophobic tail, it has always been a challenge to attach a carbohydrate molecule as a perfect polar head, due to its numerous hydroxyl groups, to a fat and oil derivative such as a fatty acid or a fatty alcohol. Sugar surfactants have several rather flexible properties. Furthermore, sugar esters and alkyl glycosides are generally non-toxic and non-cumulative. Their properties are temperature insensitive, in contrast to the likewise non-ionic alkyl-PEG surfactants [3]. Although scientists have reported numerous ways of making ester or glycosidic linkages and also described a large number of different carbohydrates used in such reactions, it is clear from an industrial perspective that only a few carbohydrates fulfil the criteria of price, quality, and availability to be interesting raw materials. These include sucrose from sugar beet or sugar-cane (0.3 €/kg; worldwide production 120 000 000 t per year), glucose derived from starches (0.6 €/kg; worldwide production 5 000 000 t per year), sorbitol as the hydrogenated glucose derivatives (0.7 € per kg; worldwide production 900 000 t per year), lactose from mammalian milk (0.6 € per kg; worldwide production 295 000 t per year), and possibly pentoses (wheat straw, wheat bran) and uronic acids (beet pulps, citrus peels or algae). The prices given are intended as a benchmark, rather than a basis of negotiations between producers and customers. Quotations for less pure products are, in part, sizably lower, and thus may readily be used for large-scale preparative purposes.

7.2.1 Sucrose esters

Of all the natural sugars used as renewable sources of raw materials, sucrose **1** is produced by almost every green plant and is therefore widespread in nature. With an annual production of 120 000 000 tons, it represents the world's most abundantly produced organic compound; moreover, sucrose is available at very low cost that is, 0.3 € per kg and at a very high level of purity. Large volume markets of surfactants represent therefore an obvious target for sucrose.

A prerequisite for transforming sucrose into non-ionic surfactants is the introduction of a long alkyl or acyl chain at one of its eight hydroxyls. Sucrose acid esters, more commonly known as sucrose esters or sucroesters, fit the requirements for green chemistry development because they are both biodegradable and can be produced from cheap, renewable and widely available resources: cane or beets sucrose and fat or oil triglycerides. Most of sucroesters are odourless and tasteless, or slightly bitter, allowing them to find applications both in food and personal care products.

Sucrose is a non-reducing disaccharide composed of a α-D-glucopyranosyl unit bonded to the anomeric carbon of a β-D-fructofuranoside (Fig. 7.2). The acid lability of the glycosidic linkage, coupled with the insolubility of sucrose in most common organic solvents, limits its chemical reactions.

The original preparation of sucrose esters of fatty acids involves the transesterification of a triglyceride molecule with sucrose in the presence of a basic catalyst at 90°C in *N*,*N*-dimethylformamide (DMF) as solvent (Fig. 7.3) [4].

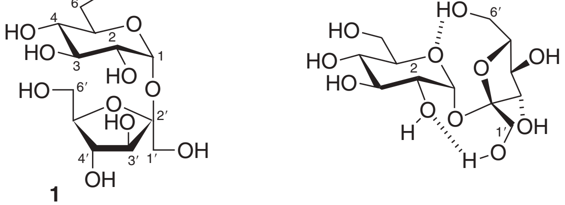

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Figure 7.2 Common representation of the chemical formula of sucrose and its intramolecular hydrogen bonds in its crystallized form.

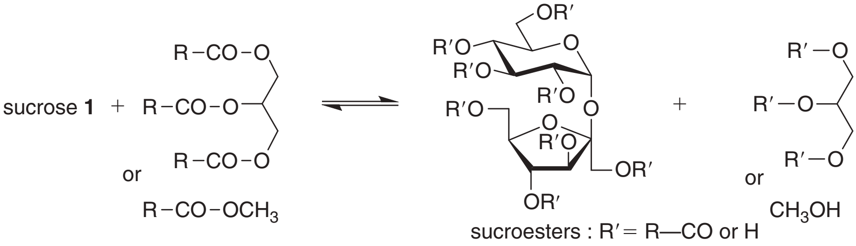


Figure 7.3 Commercial routes to sucroesters.

DMF was later replaced by dimethylsulphoxide (DMSO), a less expensive and less toxic solvent. The reaction product contains more than 50 per cent of monoesters, di- and higher esters, unreacted sucrose and di- and triglycerides.

Fatty acid methyl esters are currently used in transesterification reactions with sucrose. The formation of methanol, which can be distilled off, drives the esterification process in favour of the sucrose ester and improves yields. A solvent-less process using a slurry of sucrose and potassium carbonate in fatty acid methyl ester or triglyceride oil at 130°C has been developed more recently [5].

These procedures are commonly used to produce sucrose esters such as stearates, tallowates, oleates, palmitates, myristates and laurates that are actually complex product mixtures containing 70 per cent of monoester and 30 per cent of di-, tri- and poly-esters. Global production of sucroesters is estimated at 5 000 t per year.

The demand for such compounds and therefore their market value, could still increase substantially if the reaction processes, especially for the synthesis of well-defined products, can be further optimized.

The selective monoacylation of free sucrose encounters regioisomer problems owing to (i) rather similar reactivities of the eight hydroxyl groups and (ii) easy intramolecular migrations of acyl groups in the unprotected derivatives. The eight hydroxyl groups, numbered as shown in Fig. 7.2, include (i) three primary hydroxyls at carbons 6, 6′ and at neopentylic carbon 1′; (ii) five secondary hydroxyls at carbons 2,3,4, 3′ and 4′. Theoretically, the reaction of sucrose with one molar equivalent of acylating reagent may therefore provide eight possible regioisomeric monoesters. Nevertheless, regioselective chemical modifications of the free substrate have already been proposed [6].

In modifying sucrose for the preparation of sucrose esters, great attention must be focused on the structure, the conformation of sucrose in solution, the reaction conditions (solvent, electrophilic reagent, catalysis, temperature, etc.) and the purification procedures of the reaction product.

Indeed, the solution conformation of sucrose is surmized to depend on the nature of the solvent and therefore the disruption of one or both of the intramolecular hydrogen bonds that are present in the crystal structure. For aprotic polar solvents such as DMSO and DMF, the occurrence of two conformations with competitive intramolecular hydrogen bonds was suggested, namely 2-O•••HO-1′ and 2-O•••HO-3′, the equilibrium being in favour of the former (Fig. 7.4) [7].

The conformation of sucrose in water is more controversial, but it is now generally accepted that there are no direct intramolecular hydrogen bonds between the glucose and the fructose moieties. However, some data reveal the existence of indirect ones, an interresidue waterbridge linking the glucose-2-*O* with the fructosyl-1-*O*. The linkage geometry in aqueous solution closely resembles that found in the crystal and in polar aprotic solvents [7a]. Chemists have to keep in mind the possible connections between the structure of sucrose and the relative reactivities of its different hydroxyls.

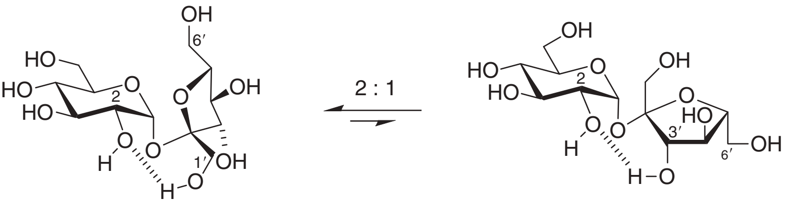


Figure 7.4 The conformation of sucrose in polar aprotic solvents such as DMSO and DMF.

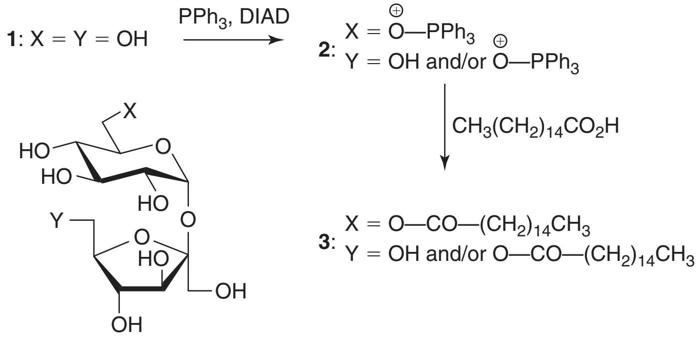


Figure 7.5 Synthesis of 6-*O* (6′-*O*)-(di)palmitoyl sucrose by a Mitsunobu approach.

Acylation of the least hindered 6 and 6′ hydroxyl groups can be achieved in low to moderate yields using exceptionally mild reaction conditions or the 6-position can be acylated with bulky acid chlorides that is, pivaloyl chloride [8]. In a different approach, the application of the Mitsunobu reaction allowed Bottle and Jenkins [9] to prepare bulky oxophosphonium intermediates at the primary 6 and/or 6′-positions. A substitution reaction by palmitate led to the 6-*O*-palmitoyl sucrose (Fig. 7.5). Interestingly, the 6-position appeared to be more reactive than the 6′; but, nevertheless, the 6-6′-dipalmitate could be synthesized by using a 2.6 molar equivalent of palmitic acid. However, the neopentylic-like 1′-position is considerably more hindered in such a substitution process.

An interesting approach to the regioselective synthesis of 6-*O*-acyl sucrose involves the use of sucrose dibutylstannyl-acetal intermediate **4** (Fig. 7.6). This acetal reacted with fatty anhydrides in DMF at room temperature giving, in all cases, the single product 6-*O*-acyl sucrose **5** [10]. In order to avoid the production of toxic tin by-products, our own contribution was based on a quite different one-pot strategy and made possible the acylation of free sucrose with *N*-acyl-thiazolidine-2-thiones **6** in DMF and in the presence of 1,8-diazabicyclo(5.4.0)-undec-7-ene (DBU). Long chain 6-*O*-acyl sucroses were isolated in 60 per cent yields [11]. Compounds **5** could also be easily obtained by the quantitative intramolecular isomerizations of 2-*O*-acyl sucroses (vide supra) in the presence of DBU in DMF at room temperature.

The preferential reaction of the 6-hydroxyl group of sucrose with *N*-acyl-thiazolidine-2-thiones **6** in the presence of DBU is noteworthy. Indeed, we have also shown that regioselectivity was enhanced towards 6′-*O*-acylsucroses **8** (*i.e.* acylation of the fructosyl moiety) when a weaker base, such as 1,4-diazabicyclo(2.2.2)octane (DABCO), was used. Best results are obtained with 3-acyl-5-methyl-1,3,4-thiadiazol-2(3 H)-thiones **7** in DMF at low temperature [12]. Such conditions give predominantly 6′-*O*-acylsucroses **8** along with 6-*O*- and 1′-*O*-acylates,

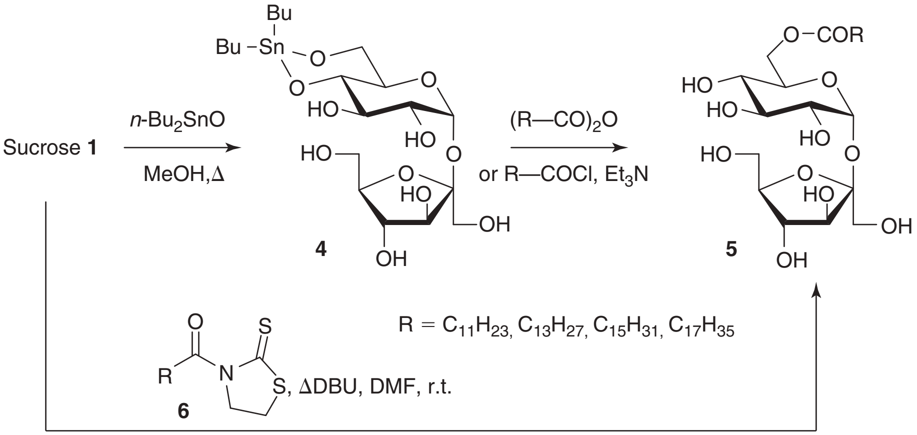
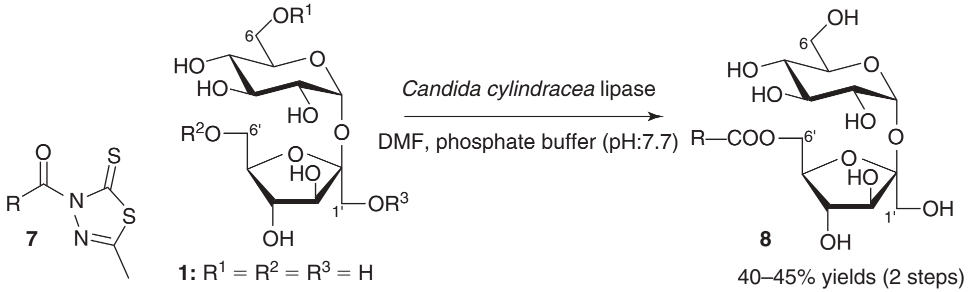


Figure 7.6 Synthesis of 6-*O*-acyl sucroses via a dibutylstannylene acetal approach(10) or a one-pot approach using *N*-acyl-thiazolidine-2-thiones (11).



1: $R^1 = R^2 = R^3 = H$
5: $R^1 = R$—CO; $R^2 = R^3 = H$ (25–30%)
8: $R^1 = R^3 = H$; $R^2 = R$—CO (65%)
9: $R^1 = R^2 = H$; $R^3 = R$—CO (5–10%)

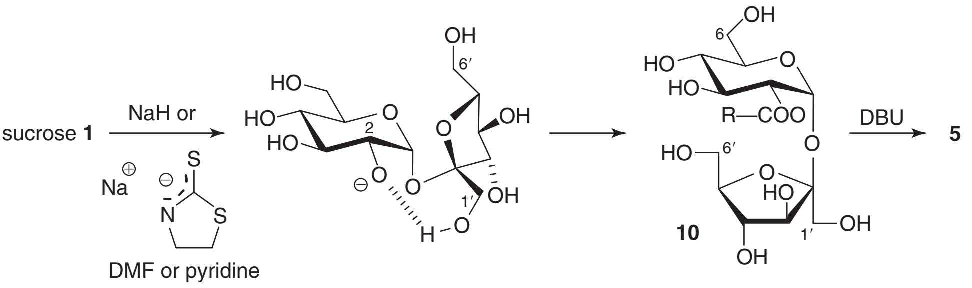
Figure 7.7 Regioselective synthesis of 6′-*O*-acylsucroses.

5 and **9** respectively (Fig. 7.7). To make the purification of esters **8** easier, we predicted that *Candida cylindracea* lipase (CCL) could deacylate the by-products as indeed verified for the elimination of esters **5** from the crude mixtures.

In order to rationalize these data, one can assume that DABCO acts as a weak base (when compared with DBU) as well as a nucleophilic catalyst. DABCO deprotonates therefore the more acidic hydroxyls of sucrose, the more nucleophilic alkoxides (*i.e.* C-2 and C-6′ hydroxyls) that are intramolecularly hydrogen bonded (Fig. 7.4) [6b]. On the other hand, reagents **7** could easily lead with DABCO to bulky loose ion pairs which preferably acylate the less hindered alkoxide, that is to say the C6′.

Regioselective base activation of the more acidic hydroxyl group to the more nucleophilic alkoxide may therefore be considered as a powerful entry into well-defined derivatives of sucrose. As indicated earlier, 2-oxygen of sucrose is involved in an intramolecular or an indirect hydrogen bond. The direct consequence on the acidity of the OH group, and therefore on the nucleophilicity of the resulting 2-oxyanion, may be expected. We anticipated that the gradual addition of a base into a solution containing unprotected sucrose and a suitable acylating reagent that did not react on the base, would activate the 2-OH group to a more nucleophilic alkoxide. Indeed, when NaH (catalytic amount) was added to a solution of sucrose and 3-lauroylthiazolidine-2-thione **6** ($R = C_{11}H_{23}$) in pyridine or DMF, the reaction mixture gave a 70 per cent yield of 2-*O*-lauroylsucrose [8]. This procedure was extended to a variety of fatty acid derivatives and was further successfully used to prepare 6-*O*-acylsucroses through the controlled intramolecular isomerization with DBU (Fig. 7.8) [11].

The use of hydrolytic enzymes in organic solvents represents an alternative approach for the regioselective synthesis of sucroesters. Of particular interest are vinyl esters of fatty acids which are used to drive the esterification process to completion through tautomerization of the enol by-product to the corresponding aldehyde (Fig. 7.9).



$R = CH_3(CH_2)_7, CH_3(CH_2)_{10}, CH_3(CH_2)_6$

Figure 7.8 Regioselective synthesis of 2-*O*-acylsucroses.

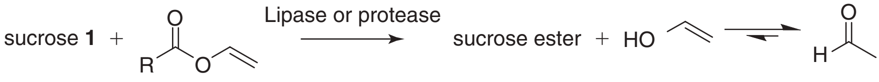


Figure 7.9 Enolesters in transesterification procedures.

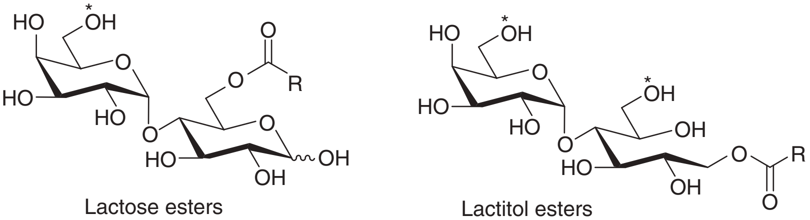


Figure 7.10 The structures of lactose and lactitol mono-ester surfactants. The asterisks denote alternative locations for the fatty acid substitution.

Thus, 6-*O*-lauroyl(pamitoyl)sucroses were obtained in 70–80 per cent yields by performing the transesterification in a mixture of *tert*-amyl alcohol and DMSO in the presence of lipase from *Humicola lanuginose* [13].

Proteases can also catalyse the esterification of carbohydrates. Thus 1′-*O*-butyl sucrose was prepared from sucrose and trichloroethyl butyrate with subtilisin in anhydrous DMF [14]. This strategy has been extended to commercially available insoluble crosslinked forms of subtilisin to prepare regiospecifically 1′-*O*-acylsucroses from fatty acids and vinyl esters in high yields [15].

A judicious choice of electrophilic reagent, catalyst and/or reaction medium is a requirement for a regioselective synthesis of well defined sucrose esters. Three main processes are observed: secondary 2-OH selective reactions based on electronic factors; primary OH groups, that is, 6-OH and/or 6′-OH selective reactions based on steric hindrance and 1′-OH selective reaction based on protease catalysis. These reactions open new routes to sucrose esters as products of commercial significance or as intermediates in sugar chemistry. As an example, the placement of a protective ester group at the 6-position of the glycopyranoyl moiety and the subsequent chlorination and cleavage of the ester group provide high intensity, non-metabolizable sweeteners [16].

Sucrose esters of fatty acids having 12 or more carbon atoms display surface active properties. Most of them are odourless and tasteless (or slightly bitter) allowing them to find applications both in food and personal care products [17]. Sucroesters were approved and freely permitted in Japan for use as food additives in 1959 for both their emulsifying ability and their heat stability. In addition, they are well known to protect food proteins from thermal denaturation and inhibit the growth of *Escherichia coli* and other bacteria.

Covering a wide hydrophilic – lipophilic – balance (HLB) range, monoesters can be used to stabilize ‘oil-in-water’emulsions, whereas higher esters give more lipophilic surfactants which can stabilize ‘water-in-oil’ emulsions.

The surface activity of some well defined monoesters of sucrose [10] and their self-organizing properties [18] have been described recently revealing exceptionally low critical micellar concentration (CMC) values and original self-organizing arrangements, respectively. The physical, chemical and biological properties of most pure derivatives still need to be evaluated and their scale up to be developed for other important applications in the cosmetic and pharmaceutical industries that require pure compounds.

Additional disaccharidic esters such as lactose and lactitol esters with varying alkyl chain lengths were reported in the literature (Fig. 7.10) [19]. These derivatives behave similarly to sucrose esters with the same hydrocarbon chain length, although they have a tendency towards closer packing at the air–water interface for the open chain type.

7.2.2 Alkyl polyglycosides and analogues

The sugar surfactants of choice for industries such as agrochemicals and detergents are not the sucrose esters, which are often considered to be rather too expensive, but another set of sugar surfactants, the so-called alkyl glucosides

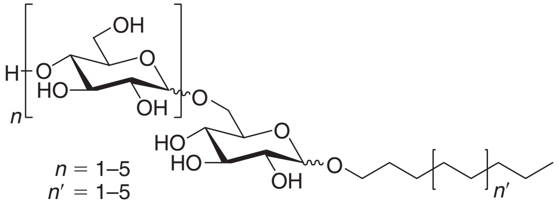


Figure 7.11 Alkyl polyglycosides (APG).

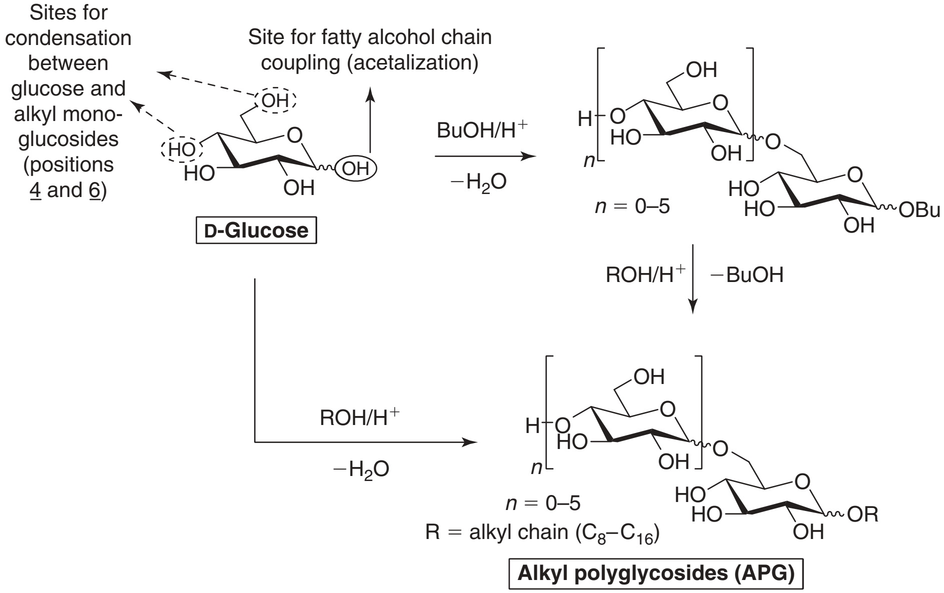


Figure 7.12 Reaction pathways for the industrial production of APG.

(AGs) or alkyl polyglycosides (APG – a registered trademark of Henkel). APG consumption represents a world market of 100 000 t per year, including 50 000 tons for Europe, and is growing fast. Marketed originally in the late 1970s, they are produced today mainly by Cognis (capacity of 50 000 t per year), SEPPIC, Kao, Zeneca, Union carbide and BASF. APGs consist of fatty alcohols mainly obtained from coconut or palm kernel oil (C_{12-14} fatty alcohols) and palm or rapeseed oil (C_{16-18} fatty alcohols) as the hydrophobic part (also from petrochemicals), and glucose obtained from corn starch, wheat or potatoes, as the hydrophilic part, their hydrophilicity varying through the degree of oligomerization (Fig. 7.11). APG are complex mixtures of isomers characterized by a polysaccharide unit varying between 1 and 6 (commercially available APG have an average degree of polymerization between 1.3 and 1.6).

The industrial production of APG requires at least three manufacturing operations. The first stage is the acid-catalyzed condensation (acetalization) between glucose and an aliphatic alcohol (Fig. 7.12).

There are currently two acetalization methods that are used industrially: (1) the direct acetalization consists of condensing glucose and an alcohol directly in a solvent-free reaction (Fischer glycosidation); (2) the transacetalization requires the preliminary synthesis of a butylpolyglucoside (carried out without solvent and catalyzed by an acid) which then reacts with an aliphatic alcohol. The transacetalization has the advantage of using cheap sources of glucose such as glucose syrup or starch, whereas direct acetalization, although simpler, requires more expensive anhydrous glucose. Whatever the method of acetalization used, the resulting APG is always obtained in the form of a complex mixture. The diversity of products formed can be explained partly because of the various possibilities of isomerization (furanoside, *e.g.* five-membered cycle or pyranoside, *e.g.* six-membered cycle, forms) and anomerization (α and β) known to occur with sugars under acidic conditions, the

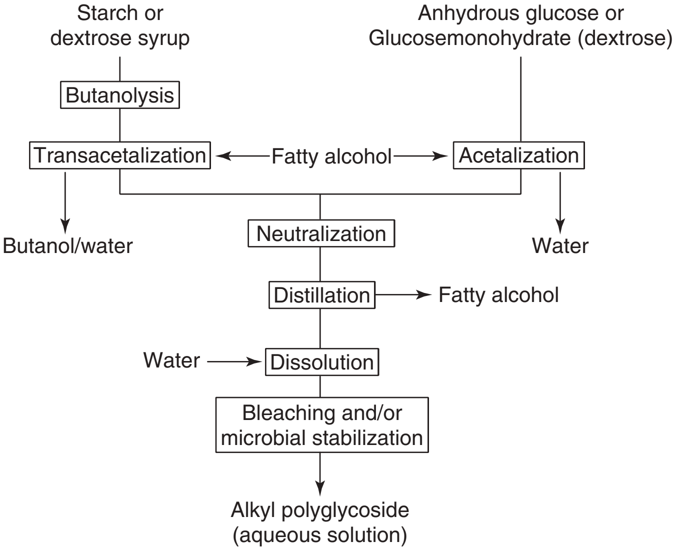


Figure 7.13 Flow diagram for the production of alkyl polyglycosides based on different carbohydrate sources.

pyranoside forms (>90 per cent) and alpha anomers (>65 per cent) being dominant. Next, the condensation between glucose and monoglucosides leads to polymerization giving alkyl polyglucosides. Monoglucosides have four hydroxyl groups that are liable to be acetalized, but for stereoisomeric reasons, the 1→4 and 1→6 bonds are favoured. A reduction of reaction products can be achieved by varying some parameters during the acetalization step, such as temperature, pressure, type of catalyst and alcohol quantity. The second manufacturing stage consists in stopping the acetalization reaction by neutralising the acid catalyst. As the acetalization reaction requires an excess of alcohol, the third stage consists in the elimination of this excess by distillation. In some cases, additional refining steps are envisaged comprising APG bleaching and microbial stabilization (Fig. 7.13).

Polyglycosides with a short alkyl chain (C_8–C_{10}) are readily water-soluble and applicable for a wide range of surfactants from mild furniture-care products to industrial cleaning agents; those with a medium chain length (C_{12}–C_{14}) show a strong synergistic effect in combination with other surfactants, and are suitable for detergents, all-purpose cleaners, shampoos and cleansing cosmetics. The long-chain homologues (C_{16}–C_{18}), insoluble in water, find applications in cosmetic creams because of their good oil/water emulsifying properties. The advantages of APG in comparison with other surfactants are numerous: (1) unlike most surfactants (such as non-ionic ethoxylates), they do not precipitate from solution at high temperatures (*i.e.* they do not exhibit a cloud point phenomenon) so they can be used without fear of phase separation. And because of their far greater tolerance to high-electrolyte concentration than any other non-ionic surfactants, APG can be added to highly ionic products (pesticides); (2) in regard to their ecological (complete and rapid biodegradation in the environment both aerobically and anaerobically, mainly resulting from the presence of an acetal linkage), toxicological, and dermatological properties, APG have extraordinary product safety characteristics. They have a good compatibility with eyes, skin and mucous membranes and even reduce irritant effects of surfactant combinations. The synergistic interactions between APG and most traditional primary surfactants commonly used in detergents, such as linear alkylbenzene sulphonate (LAS), mean that they make ideal cosurfactants; (3) in personal care products, they represent a new concept in compatibility, properties and care. One of Cognis's APG products, called Lamesoft P065, a lamellar dispersion of the monoglyceride GMO in an APG, is used in body washes and soap bars, and has also shown to be effective in two-in-one shampoos, making clear formulations possible [20].

APGs are not the only examples of sugar-based surfactants resulting from a glycosidation reaction (acetalization) of carbohydrates. Alkyl monoglucosides were prepared using standard glycosylation reactions (Koenigs–knorr syntheses) to prepare specific glycosides; for instance, β-1-*n*-octyl-D-glucopyranoside is widely used in biomembrane research for the extraction of water-insoluble membrane proteins without denaturation (Fig. 7.14). It is

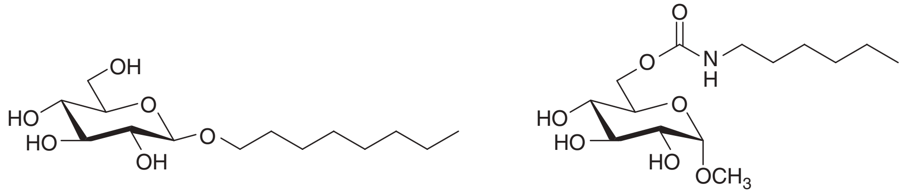

β-*n*-octyl-D-glycopyranoside
HECAMEG

Figure 7.14 Structure of glucoside surfactants for membrane studies.

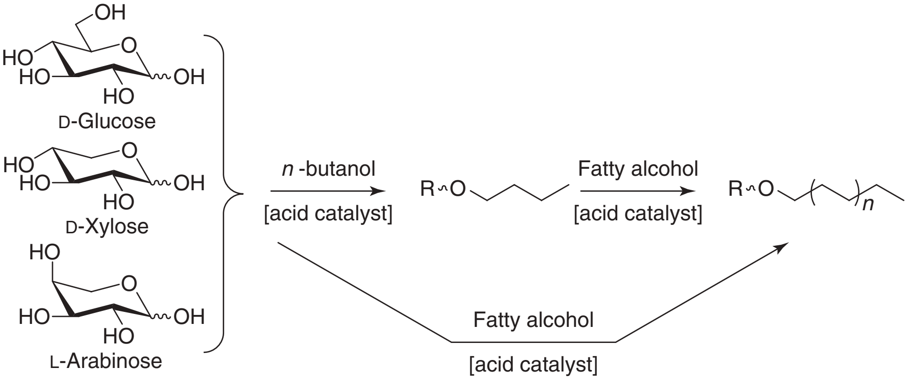
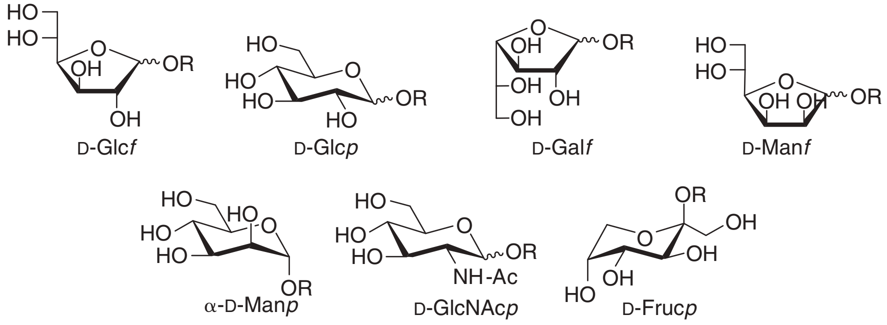


Figure 7.15 Reaction pathways for the industrial production of bran-based surfactants.

preferred over other non-ionic surfactants, such as polyethylene glycol alkyl ethers, because it has a very high CMC, and hence, it can easily be separated from the proteins by dialysis. The syntheses of *n*-alkyl-β-D-glucosides require expensive reagents (silver catalysts) and are rather time-consuming (several steps). Additional glucose-derivatives such as 6-*O*-(*N*-heptylcarbamoyl)-methyl-α-D-glucopyranoside (HECAMEG), a very mild surfactant useful for membrane protein studies, were synthesized by a simple and low cost procedure from methyl-α-D-glucopyranoside [21].

More recently, monosaccharide mixtures of pentoses, easily available from wheat straw and wheat bran, were used by Soliance, a subsidiary of ARD (Agro Industry R & D – owned by a consortium of French agricultural cooperatives specialized in wheat and sugar beet production) for the preparation of bran-based surfactants. Wheat straw provides mainly pentoses: L-arabinose and D-xylose; wheat bran gives a mixture of pentoses and glucose. All these monosaccharides, or mixtures thereof, can be used as starting materials in the acetalization step (Fig. 7.15), following the same strategies as for APG production (direct glycosidation or synthesis of butylglycosides followed by a transglycosylation reaction using fatty alcohols). The pentoses derived from hemicellulose have the advantage of being more reactive than glucose during the glycosidation reaction, allowing gentler reaction temperatures, and hence improving the energy efficiency of the process. During the reaction, an oligomerization of the saccharides occurs. Using various starting mixtures, a wide range of amphiphiles can be obtained with good foaming and detergency (C_8–C_{14} alkyl chain length) or emulsifying (C_{14}–C_{22} alkyl chain length) properties (Soliance already markets an emulsifier under the name of Emuliance®) [22].

Innovative research was also developed for the production of monosaccharidic surfactants through a direct synthesis of tautomerically and anomerically pure alkyl glycosides from unprotected sugars. The Fischer glycosylation of fatty alcohols is the most commonly used method for preparing alkyl glycosides (see APG and pentose derivatives), but the reaction invariably produces mixtures of α,β-glycopyranosides and corresponding furanosides owing to: (i) tautomeric equilibria and (ii) *in situ* anomerizations. Thus, it was found that, depending on the promoter and on the reaction conditions, either alkyl glycofuranosides from D-glucose (D-Glc*f*), D-galactose (D-Gal*f*) or D-mannose (D-Man*f*) or pyranosidic derivatives (D-Glc*p*), (D-Man*p*), (D-GlcNAc) and (D-Fruc*p*) from D-glucose, D-mannose, *N*-acetyl-D-glucosamine and a ketose of commercial significance, D-fructose, were obtained in

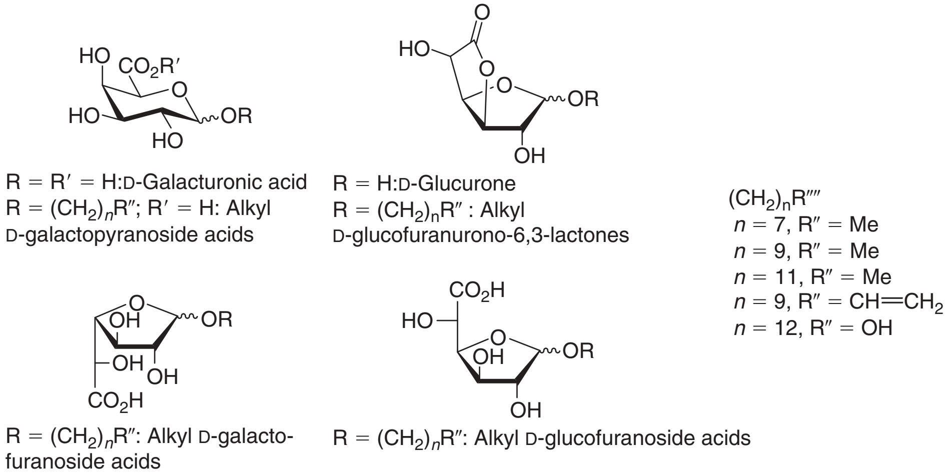


R = saturated or unsaturated C_8–C_{11} alkyl chain

Figure 7.16 Alkyl D-glycosides from *O*-unprotected sugars using $FeCl_3$ or $BF_3.OEt_2$ as catalysts.

moderate-to-good yields (Fig. 7.16). The synthesis of tautomerically and anomerically well-defined alkyl *O*-glycosides from unprotected carbohydrates requires: (i) a faster reaction of the alcohol with the sugar than the self-condensation of the monosaccharide and (ii) control of the equilibria involving substrates, intermediates and products, including the control of the final α,β stereoselectivity of the products. In order to avoid the self-condensation of monosaccharides, the reactions are performed in heterogeneous media, the unprotected carbohydrates being slightly soluble in solvents such as tetrahydrofuran (THF), 1,4-dioxane, acetonitrile and dichloromethane. After experimentation, it was found that the glycosylation reaction indeed occurred at room temperature and was best achieved in THF by the use of iron(III) chloride or boron trifluoride ethyl etherate Lewis acids as promoters. Interestingly, a dichotomy between $FeCl_3$ and $BF_3.OEt_2$ was noteworthy in terms of furanosides/pyranosides ratio since alkyl D-glycofuranosides could be obtained as the single products with the former promoter, whereas the thermodynamically more stable pyranosides were exclusively isolated in the presence of the latter [23]. The surface tension and critical micellar concentration of the alkyl glycosides were determined by tensiometric measurements. Furanosides generally possess very interesting surfactant properties. They are able to reduce the surface tension of pure water by more than $40\,mN\,m^{-1}$. Thus, the surface tension values above the cmc varied between 25 and $30\,mN\,m^{-1}$, whereas those obtained for the tautomeric pyranosic compounds are generally greater than $30\,mN\,m^{-1}$. Furanosides are therefore more efficient surfactants than the corresponding pyranosides. This result probably reflects a greater destructuring effect of the furanosides on the 3D structure of water. Consequently, the shape of the glucidic moiety has a great influence on the micellization for amphiphiles of similar chain lengths and polarities, and this effect could constitute a new factor to modulate surfactant properties [24]. In the case of D-fructopyranosides, atypical liquid crystalline self-organisation properties were found, probably resulting from the amphiphilicity of the fructopyranosides [25].

Uronic acids (*e.g.* alkyl glycosiduronic acids) were also employed as starting materials for the preparation of carboxylic acid-containing carbohydrate surfactants. Beet and citrus pulp supply D-galacturonic acid from pectins. D-Glucofuranurono-6,3-lactone (‘D-glucurone’) can be isolated from wheat bran. Finally, brown algae furnish D-mannuronic acid and L-guluronic acid that compose the heteropolysaccharide alginates. The direct synthesis of tautomerically and anomerically pure glycosiduronic acids from *O*-unprotected uronic acids remains particularly difficult owing to (i) the requirement of a higher activation at the anomeric position for uronic acids, in comparison with their neutral analogues; (ii) tautomeric equilibria of some sugars in solution; (iii) *in situ* anomerizations; and (iv) competitive *O*-glycosidation and esterification processes. Alkyl D-galactofuranosiduronic acids were synthesized by the direct glycosidation of totally *O*-unprotected D-galacturonic acid with fatty alcohols in heterogeneous media using THF as a solvent, ferric chloride as a promoter and calcium chloride as an additive [26]. The furanosiduronic acids were obtained in 50–80 per cent overall yields with a high β-stereoselectivity (typically $\alpha \approx \beta$ 1:9). The β-anomers crystallized out of diethyl ether-light petroleum mixtures, thus affording anomerically pure compounds. Alkyl D-galactopyranosiduronic acids were prepared through a procedure involving (Fig. 7.17): (i) glycosidation of D-galacturonic acid with fatty alcohols in THF in the presence of $BF_3.OEt_2$ at 30°C; (ii) concentration of the reaction mixture (total evaporation of THF) at 30°C under reduced pressure for *in situ* isomerization (furanosides -> pyranosides) and anomerization ($\beta > \alpha$); (iii) saponification ($2.5\,mol\,dm^{-3}$ NaOH in water: acetone; 15 min at room temperature) and removal of fatty alcohol by extraction; (iv) acidification



R = R′ = H:D-Galacturonic acid
R = $(CH_2)_nR''$; R′ = H: Alkyl D-galactopyranoside acids

R = H:D-Glucurone
R = $(CH_2)_nR''$: Alkyl D-glucofuranurono-6,3-lactones

$(CH_2)_nR'''$
$n = 7$, R″ = Me
$n = 9$, R″ = Me
$n = 11$, R″ = Me
$n = 9$, R″ = CH=CH$_2$
$n = 12$, R″ = OH

R = $(CH_2)_nR''$: Alkyl D-galactofuranoside acids

R = $(CH_2)_nR''$: Alkyl D-glucofuranoside acids

Figure 7.17 Alkyl D-glycosiduronates from O-unprotected D-uronic acids using $FeCl_3$ or $BF_3.OEt_2$ as catalysts.

of the aqueous phase and isolation of the α-galactopyranosiduronic acids by extraction. In the D-glucuronic series, treatment of D-glucurone with fatty alcohols and $BF_3.OEt_2$ in refluxing THF provided crystalline furanoside lactones in good-to-excellent yields and high stereoselectivity (β:α = 10:1) which could be saponified in high yields into crystalline β-D-glucofuranosidic acids. These results are of much interest since they represent one of the very few examples where *O*-glycosiduronic acids have been synthesized without protecting groups. These compounds should find applications as new surfactants [27] and liquid crystals [28].

More recently, novel biocompatible surfactants derived from alginate were developed for applications in detergents and cosmetics [29]. These surfactants are characterized by the presence of a monosaccharidic α-D-mannuronate residue attached to one or two fatty alcohols through ester and/or glycosidic linkages. Alginate, a heteropolysaccharide from brown algae, is composed of (1,4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) units in the form of homopolymeric (MM- or GG-blocks) and heteropolymeric sequences (MG- or GM-blocks). Controlled acid hydrolysis of commercially available alginate from *Laminaria digitata* gives saturated oligomannuronates on a multigram scale (Fig. 7.18). Subsequent one-pot acid glycosidic bond hydrolysis, esterification and stereocontrolled Fischer glycosidation in butanol with the related oligouronates, using methanesulphonic acid, efficiently provides *n*-butyl-(*n*-butyl α-D-mannopyranosiduronate). Double-tailed amphiphiles were next obtained from this key intermediate by transesterification/transglycosylation processes in fatty alcohols. Aqueous

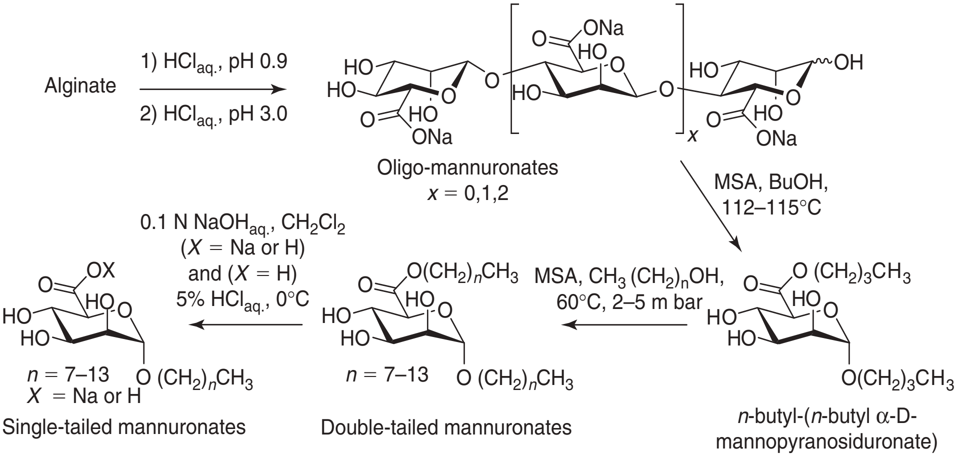


Figure 7.18 Stereoselective synthesis of α-D-mannuronate surfactants.

basic and acid treatments furnished anionic or neutral single-tailed surfactants. These original alginate-derived amphiphiles exhibit attractive surface-tension and foaming properties. Anionic and neutral single tailed surfactants with C_{12}–C_{14} fatty chains reduce the surface tension to values (29–30 mN m^{-1}) comparable to those obtained with commercial non-ionic surfactants (Polyethylene glycol, APG). In all cases, carboxylate derivatives exhibited higher cmc values than their neutral counterparts (0.28–1.62 mmol L^{-1} for anionic compounds and 0.13–0.16 mmol L^{-1} for neutral counterparts). Mannuronic acid derivatives are high-foaming surfactants which can be compared with the ether sulphate derivative. In particular, similar values are observed for surfactant with a C_{12} aliphatic chain and SDS, both in regard to foam performance and foam stability. Finally, the variability of the double-tailed amphiphiles, in terms of hydrophilic-hydrophobic balance, also permits to envisage additional applications such as oil-in-water and water-in-oil emulsions. Preliminary results show that very stable emulsions can be obtained with vegetable (sunflower) and mineral (paraffin) oil and fatty esters (capric/caprylic) formulations, including these new amphiphiles. Furthermore, with the aim of reducing the cost of these surfactants (price of alginates: 11–12 € per kg), additional procedures were recently carried out directly on brown seaweeds (<0.2 € per kg), to provide oligomannuronates in quite satisfactory yields (12.5 per cent) [30]. These promising results may allow the production of these novel alkyl D-mannopyranosiduronate surfactants with an overall cost compatible with their potential application markets.

7.2.3 Fatty acid glucamides

An advantageous property of glycosides and amides over esters is that they are less sensitive to hydrolysis under alkaline conditions. Thus, fatty acid glucamides with a linear headgroup derived from D-glucitol coupled *via* an amide linkage to an alkyl chain were developed as additional glucose-derived surfactants. The synthesis to produce *N*-methyl-*N*-acyl glucamides involves the reductive amination of D-glucose with methylamine, which smoothly generates the corresponding aminoalditol (Fig. 7.19). In a subsequent reaction step, this intermediate is converted with fatty acid methyl esters to the corresponding fatty acid amide carrying a methyl group and a pentahydroxylated six-carbon chain at the amido nitrogen. To avoid significant amounts of unreacted *N*-methylglucamine, which could be considered as precursors for potentially carcinogenic nitrosamines, Procter & Gamble developed an optional reaction with acetic anhydride in the finished product. Free secondary amines are acetylated in this step, and the resulting acetates can remain in the final product [31]. Among these surfactants, oleoyl-*N*-methyl-glucamide was additionally synthesized enzymatically [32].

Like APG, glucamides show synergetic effects with other types of surfactants and due to their polyol structure, they have a low-irritation potential. Disadvantages of glucamides are their affinity towards calcium ions and their low solubility and therefore they always have to be formulated with sequestering agents in order to avoid precipitation. *N*-Methyllauroylglucamine enters in dish-washing compositions [33]. Today, the main producers are Pfizer, Hatco and Clariant with an estimated total production capacity of approximately 40 000 t per year. They are only used in detergency. Lactose-derived glycamides, namely *N*-acetyl-*N*-alkyllactosylamines (*N*-alkyl-aminolactitols)

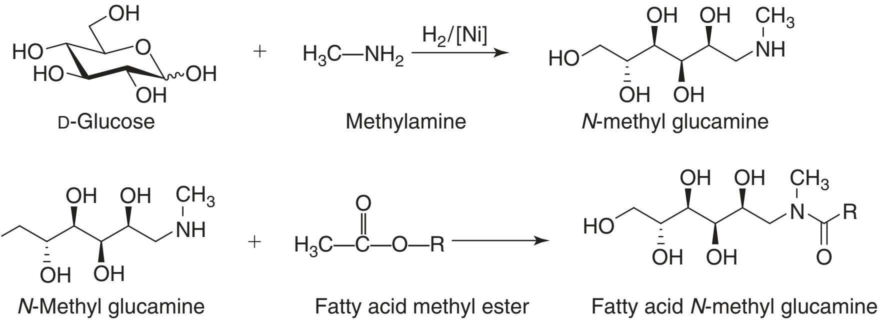


Figure 7.19 Two-step synthesis of fatty acid glucamides by reductive alkylation of methylamine with glucose using Raney nickel as the hydrogenation catalyst to obtain *N*-methyl glucamine, which is acylated by a base-catalyzed reaction with fatty acid methyl ester in a second step.

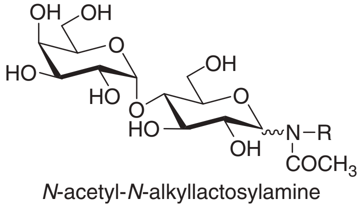


Figure 7.20 Structure of *N*-acetyl-*N*-alkyllactosylamine

were recently synthesized and exhibited attractive interfacial properties, particularly suitable for the extraction of proteins from membranes (Fig. 7.20) [34].

7.2.4 Sorbitan esters

Another class of carbohydrate-derived surfactants, called sorbitan esters (anhydro sorbitol) is derived from sorbitol, a hexitol produced by the catalytic reduction of glucose. In acidic conditions, sorbitol is dehydrated to sorbitan and even further to bicyclic isosorbide. Sorbitan fatty acid esters, commercially available as 'Span' surfactants, can be produced by a direct or indirect industrial process (Fig. 7.21). The first industrial route is based on a two-step procedure, with acid-catalyzed sorbitol cyclization to sorbitan, followed by a high-temperature alkali-catalyzed transesterification [35]. Acid catalysts include H_3PO_2, H_3PO_3, *p*TosOH; [36] and bases are simply NaOH or KOH. In these procedures, pressure, temperature and catalysts are adjusted to minimize colour development in the product. Phosphoric acid of medium strength catalyses the conversion of sorbitol to sorbitan in high yields at 230°C, the subsequent dehydration to isosorbide proceeding at a significantly lower rate, so that phosphoric acid represents a selective catalyst. However, the dehydration products are mainly of a dark colour. The best colour can be allegedly achieved by a NaH_2PO_4 catalysis [37]. Partial esters of sorbitol can also be prepared by enzymatic esterification [38]. In the second process, sorbitan esters are produced by direct base- or acid-catalyzed reactions of sorbitol with fatty acids at elevated temperature, or by base-catalysed transesterifications of sorbitol with triglycerides or fatty acid methyl esters [36d, 39]. Homogeneous catalysts, either acids (H_2SO_4, H_3PO_2, *p*TosOH) or alkalis (NaOH, KOH, alkaline carbonates) are generally used in the absence of a solvent. Depending on the type and amount of fatty materials used, various sorbitan esters (e.g., laureates, oleats or stearates) are produced with

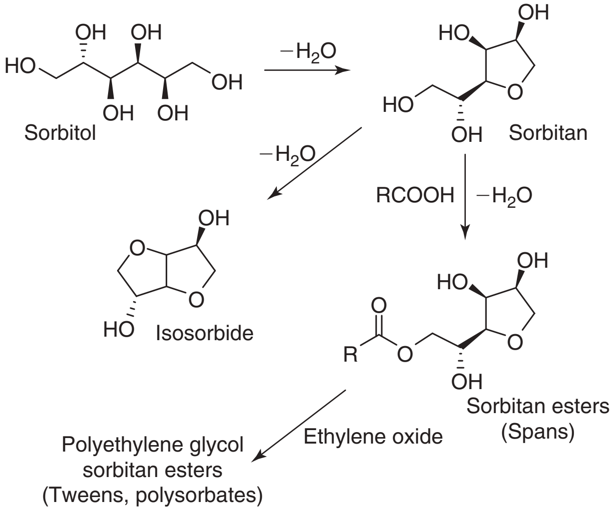


Figure 7.21 Synthesis of sorbitan esters by intramolecular dehydration of sorbitol in the presence of an acid at 150–200°C and subsequent base-catalyzed esterification with fatty acids at 200–250°C.

hydrophilic–lipophilic balance (HLB) values in a range of 1–8. The annual world production of sorbitan esters exceeds 25 000 tons (main manufacturers: Akcros, Dai-ichi Kogyo, Cognis, Kao and SEPPIC). These products are used as emulsifiers and solubilizers in food, cosmetic and pharmaceutical products. The Spans become more water-soluble when polyoxyethylene chains are grafted onto their cyclic moiety. These products are known as Tweens or polysorbates [40] and have found applications in the same fields.

7.3 SURFACTANTS BASED ON RRMs ENTIRELY FROM OLEOCHEMISTRY: POLYGLYCEROL ESTERS

The valorization of a raw material reaches an optimum when secondary products are also exploited. The main secondary product of oleochemistry is glycerol (coproduct of triglyceride hydrolysis and methanolysis processes), with a growing contribution from industrial vegetable oils. Within this context, the use of glycerol, as well as vegetable oils, as starting materials for the manufacture of surfactants represents a convenient strategy for the development of surface-active products entirely derived from oleochemistry. Glycerol itself is not suitable as a primary constituent of the hydrophilic part of the surfactant and polyglycerols are needed to increase the hydrophilicity and to adjust the hydrophilic–hydrophobic balance (HLB) of the products. Fatty acid esters of these polyols, called polyglycerol esters (PGE), have been developed leading to applications in cosmetic or food emulsifiers. Perhaps they will not substitute ethoxylates but rather play a role in several niche markets. New compounds could find applications in offshore oil drilling, in the decontamination of polluted soils, or in the protection of wood [41]. In general, the preparation of PGE involves two subsequent steps, viz. (1) the polymerization of glycerol in the presence of a small amount of alkali (base catalysis) and (2) esterification of the resulting polyglycerol. Conventional methods to polymerize glycerol require drastic process conditions, namely temperatures above 200°C in the presence of homogeneous alkaline catalysts (hydroxides, carbonates and oxides of several metals). The condensation reaction usually involves the more reactive terminal hydroxyl groups of the glycerol molecules, but some branched and even cyclic by-products, resulting from the reaction of the secondary hydroxyl groups, are always formed (Fig. 7.22). Carbon dioxide or nitrogen is bubbled through the reaction mixture to prevent dehydration of glycerol to the undesired acrolein. New catalyst systems have been recently proposed for the selective oligomerization of glycerol. Stable active and basic mesoporous catalysts were used for the chemo- and regioselective conversion of glycerol to linear oligoglycerols. For example, mesoporous solids modified by ceasium impregnation led, with the best selectivity and yield, to di- and tri-glycerol [42]. Additionally, the alkaline (KOH) polymerization of glycidol at a reaction temperature of ca. 120°C was found to afford selectively the linear polyglycerols [43].

The production of fatty acid esters of polyglycerols has been usually achieved through (1) direct esterification of the polyol using either alkali [44] or acid catalysts [45], (2) transesterification of the polyol with a triglyceride or a fatty acid methyl ester in the presence of a suitable alkaline catalyst [46] or (3) addition polymerization of glycidol to a fatty acid or to a fatty acid monoglyceride catalyzed by acids [47]. These processes generally lead to the formation of mixtures in which the fatty acid chains are distributed among all available hydroxyl groups, whose proportions mainly depend on temperature and reagent molar ratio. Moreover, the molecular composition

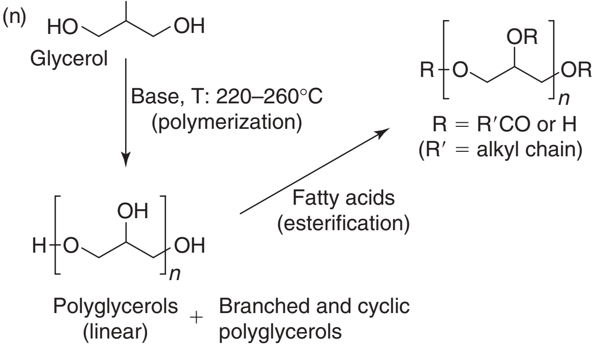


Figure 7.22 Synthesis of polyglycerol esters.

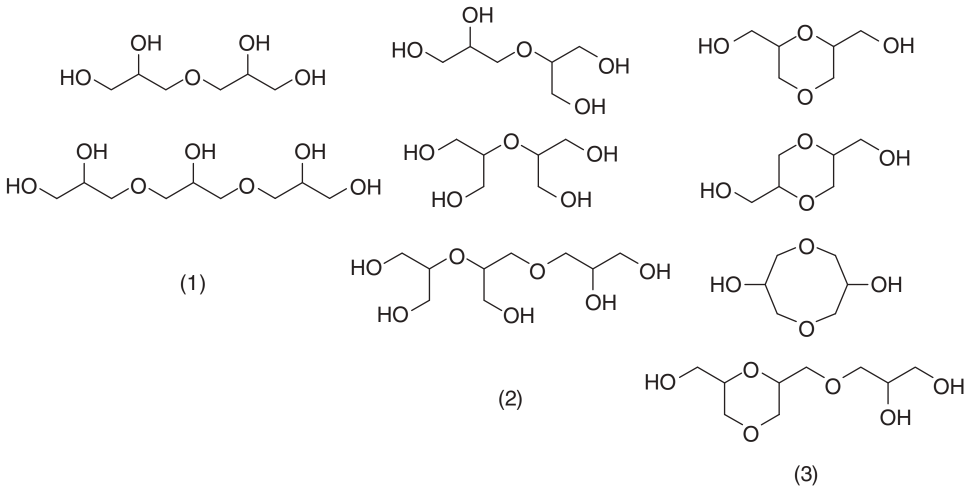


Figure 7.23 Some examples of di- and triglycerol isomers (1), (2) and (3) being respectively linear, branched and cyclic isomers.

of the product is very difficult to determine and correlations between structure and performances cannot be established precisely. Within this context, the project 'Polyglycerols chemistry ecology and applications of polyglycerol esters' (FAIR-CT96-1829) provided a complete description of polyglycerol-based surfactants to clarify the relationship between structure and environmental impact, on the one hand, and the physico-chemical properties, on the other hand, of PGEs [48]. The synthesis of selected linear, branched and cyclic polyglycerols (Fig. 7.23) with a defined degree of oligomerization (2–6) and their regiocontrolled monoesterification or monoetherification with C_{12} or $C_{18:1}$ fatty chains furnished important information relative to (1) their detergent properties (low cmc values and good surface activity; all polyglycerols have low-interfacial tension against *n*-decane and therefore good emulsification capability and a very pronounced foaming behaviour); (2) skin irritation (the position of the acyl/alkyl chain determines the toxicity of linear surfactants; the nature, number and location of neighbouring hydroxyl functions, primary or secondary, on the polyglycerol backbone influence the irritation score); (3) biodegradability (linear polyglycerols are more biodegradable than branched and cyclic structures); (4) ecotoxicity and bioaccumulation (increasing lipophilicity and decreasing polymerization lead to higher toxicity).

Polyglycerols have been known since the beginning of the twentieth century. However, due to the difficulties encountered for the industrial development of high-purity products, it is only in the last decade that their uses increased. Solvay is the world-leader in the production of high purity polyglycerols and manufactures diglycerol, a distilled product of 90 per cent minimum purity, and polyglycerol-3, a grade with a narrow oligomer distribution typically containing a minimum 80 per cent of di-, tri-, and tetraglycerol. As a result of their multifunctional properties and harmless nature, PGE are used in many applications in food [49] and cosmetic industries [50]. They notably function as emulsifiers, dispersants, thickeners, solubilizers minimum, spreading agents and emollients. More recently, new industrial applications based on PGEs have been developed. This includes their utilization as antifogging and antistatic additives, lubricants and plasticizers [51].

7.4 NOVEL BIODEGRADABLE PLANT-DERIVED CATIONIC EMULSIFIERS FOR ROAD CONSTRUCTION AND COSMETICS

Cationic surfactants fall into several categories depending on the nature of their cationic polar heads. Some of them have functional groups susceptible to protonation (*e.g.* amines) and thus display cationic properties particularly in acidic media, while others, such as quaternary ammonium salts, exhibit a permanent positive charge. In household products, cationic surfactants are primarily applied in fabric softeners and hair preparations. Other applications of cationic surfactants include disinfectants and biocides, emulsifiers, wetting agents and processing additives. By volume, the most important cationic surfactants in household products are the alkyl ester ammonium salts that

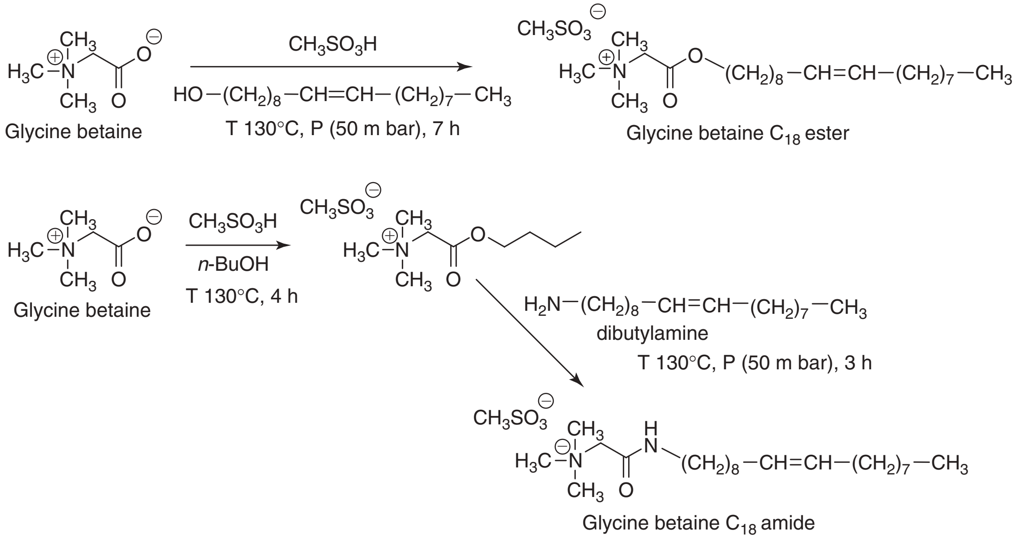


Figure 7.24 Synthesis of glycine betaine C_{18} ester and amide.

are used in fabric softeners (esterquats). These surfactants generally have an acute aquatic toxicity and a low-ultimate biodegradability and their use was recently reduced or even abandoned in certain European countries like Germany and Netherlands. These undesirable effects on the environment, coupled with the consumer demand for 'greener' products, are leading manufacturers to focus on the production of cationic surfactants from alternative, less harmful raw materials. Glycine betaine, a not very expensive natural substance possessing a quaternary trimethylalkylammonium moiety and a carboxylate function, constitutes a prime raw material for the preparation of biodegradable and biocompatible cationic surfactants (Fig. 7.24). Accounting for 27 per cent in weight of molasses of sugar beet and obtained after extraction of saccharose, it remains currently a little developed by-product of the sugar-industry. Within this context, novel glycine betaine esters and amides were recently produced from tropical oils (copra, palm kernel) or European oils (sunflower, rapeseed), conveniently, economically and with an environmentally acceptable process (no solvent, no waste) [52]. In particular, fatty chains with 18 carbon atoms derived from European vegetable oils have been used for their emulsifying properties compatible with numerous industrial and technical applications (road bitumen emulsifying applications, emulsions for uses in cosmetics).

The environment-friendly synthesis of glycine betaine esters was carried out through the direct esterification reaction between glycine betaine and fatty alcohols, preferably stearic and oleic alcohols, catalyzed by methanesulphonic acid without any solvent (Fig. 7.24). Glycine betaine amides were prepared in two steps: first, glycine betaine reacts with *n*-butanol in the presence of methanesulphonic acid as catalyst. In a second step, the short butyl chain is replaced by a longer chain in an aminolysis reaction with fatty amines, particularly C_{18} stearic and oleic amines. Purification procedures (precipitation in organic solvents like *n*-butanol or ethanol, or use of crude mixtures obtained without any additional treatment) furnished a large variety of emulsifying formulations characterized by various compositions (several controlled ratios of residual free glycine betaine, fatty alcohols, methanesulphonic acid). The scale-up of one oleic ester-based mixture obtained without any purification was performed on a 60 kg scale for road making application. In road construction, bitumen products are typically applied in conjunction with a mineral aggregate.

The good adhesion properties of bitumen to aggregates allows it to act as a binder, while the aggregate provides mechanical strength. At ambient temperature, bitumen is a highly viscous to almost solid substance that is extremely difficult to work with, but can, however, be changed into a workable form by applying heat, by blending it with petroleum solvents or by emulsification in water. Working with bitumen at high temperatures (150–180°C) is very dangerous, with a risk of serious burns and requires moreover costly equipment for heating, storage and application, which must be performed on-site. Bitumen that has been mixed with petroleum solvents is more workable, but the solvents, usually kerosene, are fire hazards and produce hydrocarbon emissions contributing to air pollution. In contrast, bitumen emulsions can be applied without heating (although they are still prepared at moderately high temperatures) and do not have the handling and environmental hazards associated with hot mixes. Bitumen emulsions also improve adhesion to aggregates, and can be applied in a good range of weather conditions [53]. The bitumen is dispersed throughout the continuous water phase as minute particles, typically 0.1–5 μm in diameter, as an oil-in-water emulsion. Bitumen–water emulsions must break in a controlled manner upon being laid with the mineral aggregate and, as a function of the speed of this breaking process, various technologies for road making are used: surface dressing with rapid breaking emulsions (the emulsion is sprayed onto the road surface and chippings are spread on top and normally rolled to ensure proper embedment and alignment) and cold mixes (this category covers several different technologies, among which open-graded storable cold asphalt for patch working, combined cement/bitumen emulsion mixes and dense-graded cold asphalt for wearing course) that require slower breaking emulsions. The emulsifier in a bitumen emulsion system has thus three functions: it reduces the interfacial tension between bitumen and water, stabilizes the emulsion and assists the adhesion of the bitumen. Cationic emulsifiers for bitumen emulsions are usually employed in Europe (2 000 000 tons of bitumen emulsion produced per year), particularly in France, which produces 50 per cent of the total European bitumen emulsion (0.2–2 per cent of surfactants). Commercially available cationic emulsifiers are mainly surfactants that are ionized in an acidic environment and include polyamines, amidoamines and imidazolines, which are the most widely used emulsifiers. These cationic surfactants, that come entirely or partially from petrochemicals, were found to exhibit a low biodegradability and a high aquatic toxicity. Within this context, glycine betaine C_{18} esters represent a new family of plant-derived emulsifiers that limit environmental pollution. These formulations were found to have very promising physico-chemical properties in terms of their use in surface dressing technologies, namely, chemical stability, viscosity of formulation, bitumen emulsifying properties (adhesivity, emulsion breaking) and a high biodegradability (ultimate biodegradability above 70 per cent, according to OECD 301) [54]. After an experimental phase (1 000 m road coating using a bitumen emulsion based on the glycine betaine oleic ester surfactant), the project arrives today at the stage of industrial development for the production, on a large scale, of this new vegetable-derived surfactant, which should make it possible to exploit important quantities of raw materials of agricultural origin (in particular European oils) in non-food fields. Additional applications of these novel biodegradable cationic surfactants in cosmetic formulations (shampoos, body washes, creams) are currently being developed [52].

7.5 GEMINI SURFACTANTS AND BOLAAMPHIPHILES

Changes in the molecular structure of surfactants characterized by a single hydrophobic tail connected to an ionic or non-ionic polar headgroup have attracted the attention of chemists. In particular, the covalent linking of two hydrophilic groups was envisaged to yield surfactant dimers such as Gemini surfactants and bolaamphiphiles. Even if several dimeric surfactants have been synthesized and patented for more than 50 years (especially cationic ones), only few examples related to renewable sources can be found. However, as these bipolar surfactants show interesting surface tension lowering, rheological and self-organizing properties, the number of publications and patents is expected to increase rapidly in the next few years.

7.5.1 Gemini surfactants

Gemini surfactants are defined as surfactants made up of two identical amphiphilic moieties connected at the level of the headgroups, or of the alkyl chains, but still very close to the head groups, by a spacer group which can be hydrophobic, flexible, or rigid (Fig. 7.25).

In the field of Gemini amphiphiles from renewable sources, sugar derivatives are of special interest. Two types of sugar gemini surfactants can be distinguished, viz. those involving pyranoses and those containing reduced carbohydrates. Engberts *et al.* described sugar-based Gemini surfactants **11** possessing both reduced glucoside and mannoside derivatives combined with oleyl, oleoyl or saturated chains through an oligoethylene glycol or

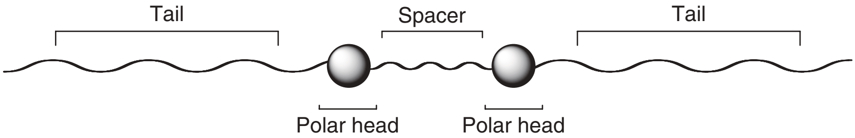
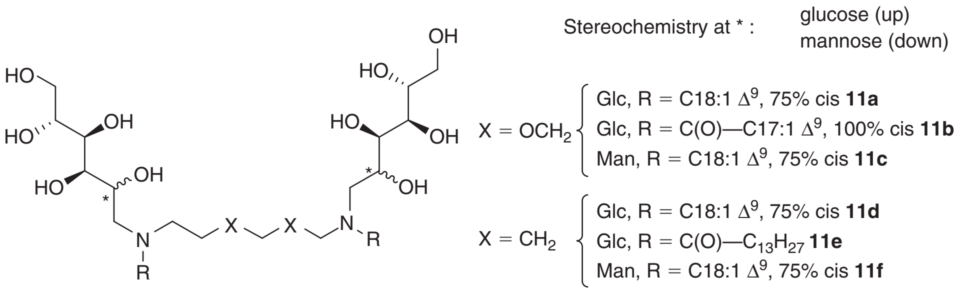


Figure 7.25 Schematic representation of gemini surfactants.

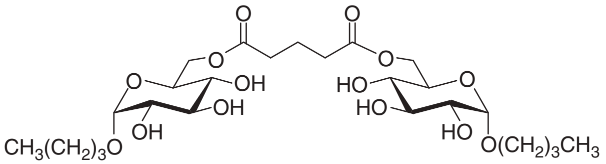


Stereochemistry at * : glucose (up)
mannose (down)

$X = OCH_2$
Glc, R = C18:1 Δ^9, 75% cis **11a**
Glc, R = C(O)—C17:1 Δ^9, 100% cis **11b**
Man, R = C18:1 Δ^9, 75% cis **11c**

$X = CH_2$
Glc, R = C18:1 Δ^9, 75% cis **11d**
Glc, R = C(O)—$C_{13}H_{27}$ **11e**
Man, R = C18:1 Δ^9, 75% cis **11f**

Figure 7.26 Representative examples of sugar-based Gemini surfactants (reduced sugars).



12

Figure 7.27 Sugar-based Gemini surfactant **12**.

oligomethylene spacer (Fig. 7.26) [55]. Their synthesis involves the preparation of a dimeric structure followed by a double reductive amination of D-glucose or D-mannose in the presence of an oligomethylene or an oligoethylene glycol diamine (spacer). Then, the acylation or alkylation reaction is conducted under standard conditions (respectively acylation with a long chain anhydride and reductive amination of long-chain aldehydes).

The incorporation of cyclic carbohydrates into Gemini surfactants was developed by Castro *et al.* (Fig. 7.27) [56]. These sugar geminis have been synthesized from AGs which can be easily prepared *via* a Fisher-type glycosylation reaction of free glucose by *n*-butanol. Convenient protection of the sugar moiety, followed by selective deprotection of the primary alcohol, permits the formation of gemini **12** by a double esterification with propanedicarboxylic acid.

Formally, Gemini surfactants possess a structure resembling a pair of conventional single-chain surfactants covalently connected by a spacer. It is therefore appropriate to compare Gemini and conventional surfactant properties and, in doing so, intriguing results appear. Indeed, Gemini show generally a low cms, good oil solubilization and the formation of threadlike micelles [57]. These properties, and especially their high-surface activity, are the reason for the multiple applications of Gemini in detergency, cosmetics, pharmaceuticals, food, metallurgy, paints, oilfields and polymers. In particular, carbohydrate-derived Gemini have been described in a number of patents by Procter & Gamble in which they are claimed as components in laundry, cleaning, fabric, and personal care compositions [58].

7.5.2 Bolaamphiphiles

The term 'bolaamphiphile' or 'bola' is related to structures composed of a hydrophobic core bearing two polar headgroups at opposite ends (Fig. 7.28) [59]. They are naturally found in archaebacteria microorganisms where they

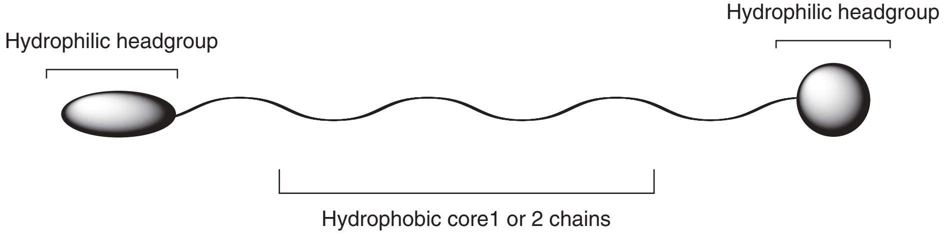


Figure 7.28 Schematic representation of a bolaamphiphile.

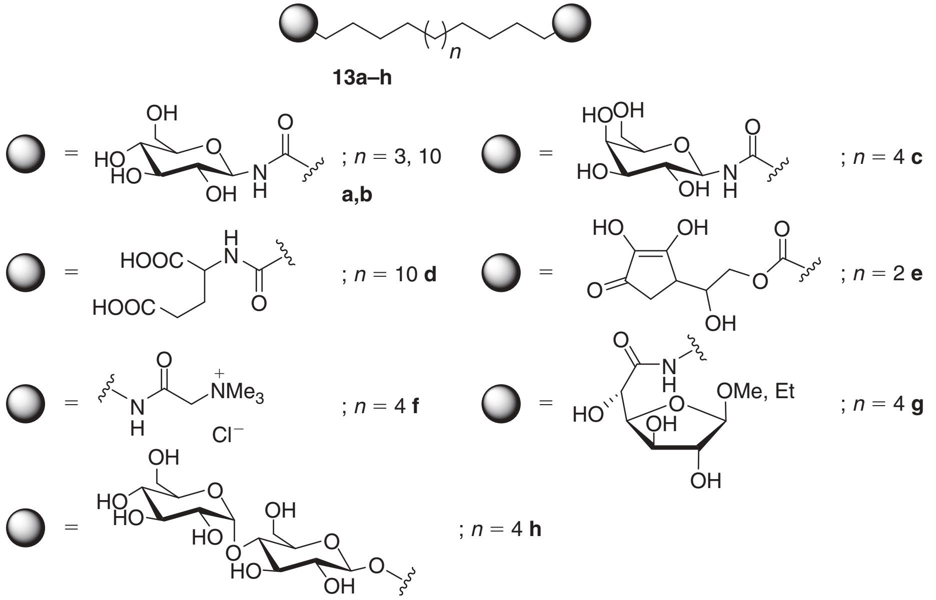


Figure 7.29 Symmetrical bolaamphiphiles possessing a single polymethylene bridging chain.

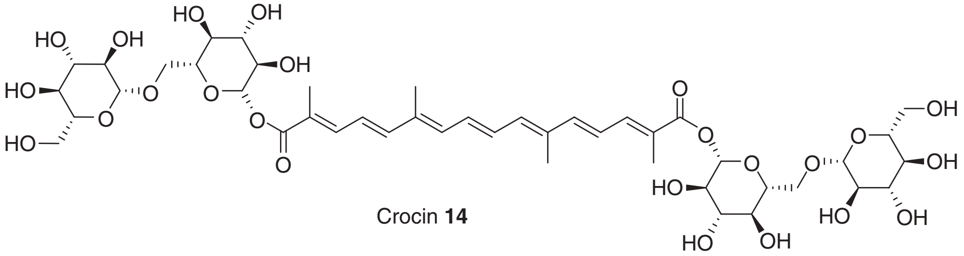


Figure 7.30 Natural carotenoid glycoside crocin **14**.

improve significantly the integrity of lipid membranes under extreme conditions (high or low temperatures, low pH, high salinity) [60]. Due to their particular structures and properties, synthetic bolas have been prepared, thus enlarging the family of surfactants and the possibilities of new applications. Here we will focus on bolas issued from renewable sources and characterized by the presence of a single bridging chain.

Among the synthetic bolaamphiphiles reported in the literature, only few are issued from renewable sources, mainly fatty acids and sugar derivatives (Fig. 7.29). Pyranose bolaamphiphiles **13a–c** were prepared by the condensation of β-1-aminoglucosides with the corresponding α,ω-dicarboxylic acid chlorides [61]. Both glucose **13a,b** and galactose **13c** derivatives were synthesized with three lengths of oligomethylene chains ($n = 3, 4, 10$). Furanose-type headgroups were introduced through an amide linkage between D-glucuronolactone and a saturated C_{12} α, ω-diamine, thus providing diamides **13g** [62]. Standard glycosylation methods were used to introduce two disaccharide polar headgroups into the terminal sites of 1,12-dodecanediol (**13h**) [63]. Additionally, glutamic acid [64], glycine betaine [65] or vitamin C [66] were also used as natural starting materials for the production of neutral or ionic bipolar surfactants.

Substituted and/or unsaturated lipophilic chains, such as carotenoids, are also available and can be combined with two sugars polar ends affording neutral surfactants like crocin **14,** a natural carotenoid disaccharide (*ca.* 25 per cent of saffron) (Fig. 7.30) [67].

Access to unsymmetrical derivatives was envisaged, especially to study symmetrical or dissymmetrical organization of bolas in lipid membranes. They are usually prepared by selective reactions of one functional group of the unprotected symmetrical hydrophobic core. Shimizu and Masuda [68] developed the synthesis of bolaamphiphiles **15a–g** containing an oligomethylene chain connected with a sugar at one end and a free carboxylic acid

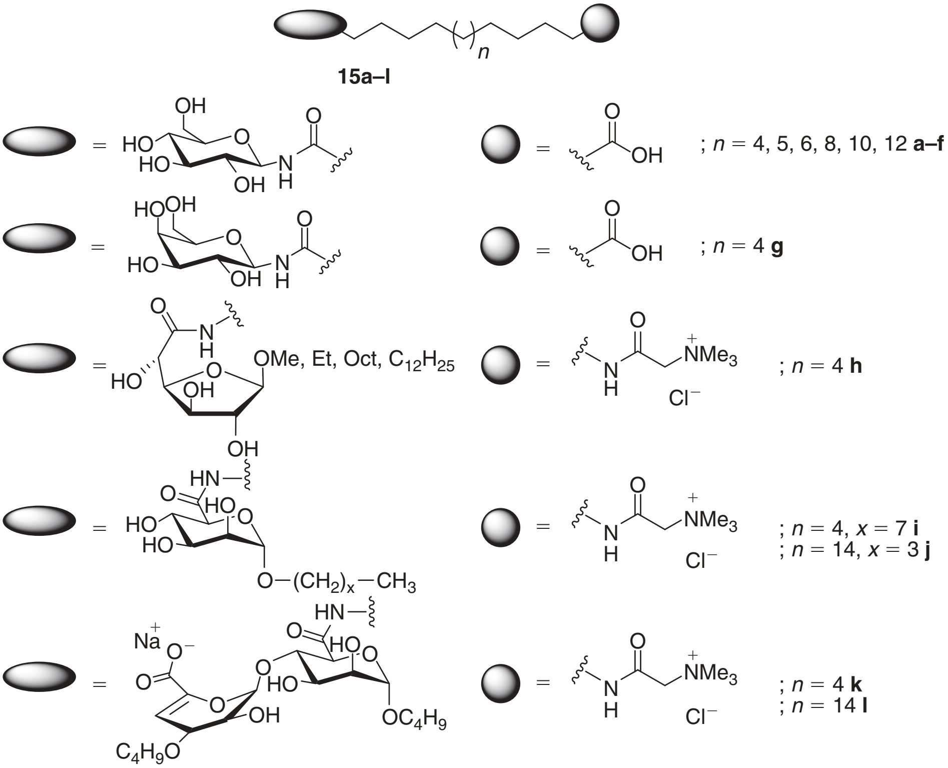


Figure 7.31 Unsymmetrical bolaamphiphiles possessing a single polymethylene bridging chain.

at the other. The preparation of these unsymmetrical surfactants involves the reaction of oligomethylene (14–22 methylenes) dicarboxylic acid chlorides with one equivalent of β-1-amino-glucoside or -galactoside (Fig. 7.31). Recently, Benvegnu *et al.* [69] described the synthesis of surfactants **15h–l** derived from D-glucurone or alginate oligosaccharides as sugar moieties and containing positively-charged glycine betaine. They are easily accessible through the reaction of monoester or lactone carbohydrates with an alkyl diamine chain, followed by a condensation of the second free primary amine with an activated glycine betaine derivative.

Bolaform surfactants are generally less effective than conventional surfactants, but they often display unusual self-assembling properties. Compared with monopolar surfactants, the additional polar headgroup of bolaamphiphiles generally induces both a higher water solubility increasing the cmc and the surface tension, and a decrease in the aggregation number. Bolaamphiphiles can span a membrane, having one headgroup on the outside of the membrane and one on the inside. Extremophile membranes are stabilized in this way [59a]. The results obtained for the synthetic bipolar surfactants possessing a polymethylene linker and natural polar headgroups clearly demonstrated the existence of complex relationships between chain composition, spacers and headgroups that influence the structure of their supramolecular aggregates (monolayered or bilayered vesicles, disks, fibers, ribbons, nanotubes and helices), the stretched or U-bent conformation of the lipids, as well as the kinetics of their interconversion (Fig. 7.32) [55, 59, 62, 63, 69]. Additionally, dissymmetrical arrangements in tubular assemblies [68] and in monocrystals [70] have been found in the case of some unsymmetrical structures.

When particular functions such as thiol, alcohol, carboxylic acid, nitrile or silyl derivatives, are present at one end of the bolas, they can easily stack on solid surfaces like gold, silver, copper or silica and form planar molecular monolayer (coated particles) (Fig. 7.33). The hydrophobic core may serve as a barrier or a solvent and the available headgroup allows molecular recognition in solution.

The potential applications of bolaamphiphiles include the formation of monolayer vesicles for drug/gene delivery, ultra thin monolayer membranes, inclusion of functionalities into membranes, and disruption of biological membranes [59a].

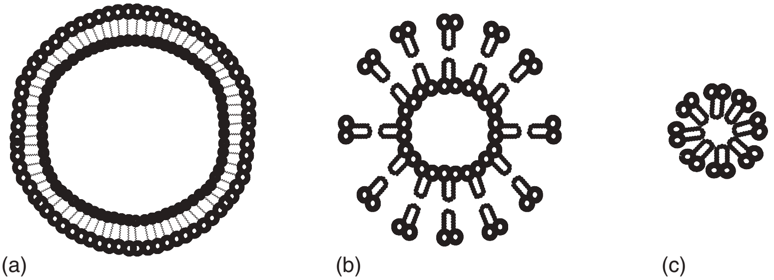


Figure 7.32 Organization of bolaamphiphiles in (a) a monolayer membrane, (b) a U-bent bilayer membrane and (c) a U-bent micelle.

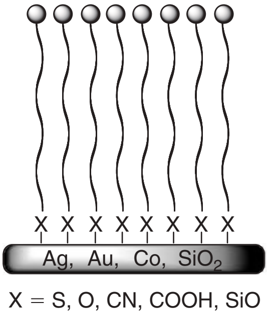


Figure 7.33 Schematic representation of monolayer coated particles.

7.6 CONCLUSIONS AND PERSPECTIVES

It seems clear that with the examples of recent product innovations from RRMs, the successful development of environmentally compatible and powerful surfactants in the sense of a sustained development has been demonstrated. RRMs are biocompatible, usually easily biodegradable and generally non-toxic, unless they have been chemically modified by undesired functional groups. These properties are particularly important in the context of the growing number of European laws, regulations and directives. The new European Detergent Regulation that entered into force in October 2005 is the most recent one. The main elements of this regulation are additional requirements with respect to ultimate biodegradability (60 per cent degradation within 28 days) of surfactants, special new requirements for the additional declarations of detergent ingredients on the packaging, including possible sensitizing ingredients, and additional compulsory information concerning detergent formulations to be provided for medical professionals and consumers (Commission Regulation (EC) No 907/2006 of 20 June 2006 amending Regulation (EC) No 648/2004 of the European Parliament and of the Council on detergents, Official Journal of the European Union). The proposed new biodegradation tests ensure a higher level of environmental protection, especially of the aquatic environment. While previous legislation was only applicable to anionic and nonionic surfactants, this Regulation includes all four surfactant families: anionic, non-ionic, cationic and amphoteric. Consequently, innovative research and development in new biodegradable products, particularly for the introduction of new cationic surfactants, should be favoured in order to propose alternatives to non-compliant surfactants found in formulations impacted by the European Detergent Regulation.

Other EU initiatives include REACH (Registration, Evaluation and Authorization of Chemicals) to help regulate new and existing chemical substances. The surfactant industry will be largely sensitive to the profile and the requirements of the future REACH legislation. In general, surfactants are manufactured in quantities greater than 1 t per year (industry would be obliged to register all marketed chemicals above 1 ton annually within 11 years). Consequently, the major surface-active components will need registration under REACH. The positive impact of this new regulation on the development of RRM-based surfactants is not so obvious if we consider the high entrance barrier expected for the introduction of new substances [71].

To make more surfactants based on RRMs commercially viable, more innovation is needed, since technical constraints often limit the applicability of renewables. If the barriers to vegetable-derived chemicals inherent in the EINECS (European Inventory of Existing Commercial Chemical Substances)/ELINCS (European List of Notified Chemical Substances) system were removed, such innovation would be facilitated. Much applied research has to be encouraged and supported by national trade organizations (ACTIN in the UK, FNR in Germany, AGRICE in France, AIACE in Italy) and by the European Commission. Finally, the policy measures introduced to reduce greenhouse gas emissions might shift the balance of competition between RRM and fossil raw materials in favour of the former and thus act as drivers for an increased industrial use of renewable raw material [1c].

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– 8 –

Tannins: Major Sources, Properties and Applications

Antonio Pizzi

ABSTRACT

After a brief historical introduction and the distinction between hydrolysable and condensed tannins, a description of their chemistry and a short historical review on their use in leather tanning, the more recent developments in tannins for adhesives with and without the use of any aldehyde-yielding compounds, even without the use of any hardeners, are described. Examples of the use of tannins for other industrial, nonleather, applications are reported. In particular, this chapter focuses briefly on their new intended use in the medical and pharmaceutical fields. New data on their antiviral effectiveness against a great number of different viruses compared to their higher, lower or absent cytotoxicity are also presented.

Keywords

Tannins, History, Sources, Adhesives, Wood, Resins, Antiviral activity, Cytotoxicity, Leather, Nonleather uses, Pharmaceutical, Medical

8.1 HISTORY OF TANNINS EXTRACTION

Tannins are a renewable resource that is ‘coming of age’ in several fields different from their usual, classical application, namely hide tanning to produce heavy duty leather. Leather tanning has been used for centuries, millennia in fact, by immersing hides in pits in which tree bark or wood rich in tannin, such as oak, had been left in. This method took up to one full year to produce good leather. However, the actual tannin extraction industry is relatively more recent. It started in Lyon, France and in northern Italy in the 1850s to satisfy the need for black dyes for silk clothes. As the fashion of women silk blouses waned towards the 1870s, the multitude of small chestnut tannin extraction factories that had sprung up underwent a dramatic change of fortune, many going into bankruptcy and closing down, others combining to build enough critical mass to find an alternative use for tannin extract [1].

The few surviving producers, managed to convince the leather manufacturers that, by dissolving tannin extract in the treatment pits, leather could be manufactured in just 1 month, instead of the 1 year it took on an average with the traditional bark bath technology. As a consequence, the tannin extraction industry started its second life for an application quite different from the original one. The advantages of tannin extract in leather making, and the timesaving involved by its use, were such that the industry underwent rapid expansion and prospered. The short availability of materials in Europe to satisfy the rapidly growing demand for tannin extracts for leather prompted the opening of factories in far-away countries and the use of new types of tannins. Thus, in the early 1900s, tannin factories using quebracho tannin from South America and Mimosa tannin from Southern and Central Africa started their extraction in industrial quantities and exported them to the main northern hemisphere markets.

The two World Wars gave a considerable impulse to the expansion of tannin extraction, considering that all the armies marched on shoes with leather soles. To give a typical quantitative example, in 1946, just after the end of World War II, a major producer such as South Africa manufactured about 110 000 metric tons of dry tannin extract solids. That year however, was the zenith of the use of vegetable tannins for leather making, because from then on rubber and neoprene soles in everyday shoes, cheaper and readily available, progressively replaced leather counterparts. By the beginning of the 1970s, the total tanning production was down to 72 000 tons per year. This was followed by a further decrease in a period in which hides supply dwindled, due to the decrease and difficulties of cattle farming in the 1960s and 1970s. Finally, the considerable shift in customers' tastes in shoes, which came about with the comfortable sport and leisure shoes 'boom', gave a final blow to the use of tannins in leather making. It is interesting that today the same country that produced 110 000 tons of tannin extract in 1946, now only produces 42 000, only half of which are still used for leather manufacture.

As a consequence of the steady dwindling in tannin sales for leather, in the 1960s and 1970s the industry started to desperately look for new applications for these natural products. After all, they had survived the collapse of the silk dyes market more than a century earlier, and a new lease of life could perhaps be found in other fields. Many applications were tried, from varnish primers for metals, which effectively were in use in Britain for some time during the 1960s and 1970s, to antipollution flocculating agents that were successful for about 15 years in the 1970s and 1980s, before being superseded by better synthetic materials [18]. About 600 tons tannin per year, are still in use as ore flotation agents, especially in a couple of feldspar mines in southern Africa [18]. Furthermore, fluidifying agents for drilling mud and superplasticizing additives for cement were developed [101]. To the best knowledge of the author, about 70–80 tons per year of tannin-based cement additives are still used. The main use found, however, was for tannin adhesives for wood panels and other wood products. Production started in 1973 and reached 4 500 dry tons/year of tannin by 1978, and this figure has now risen to around 25 000.

The application of tannins as wood adhesives contributed to save a few tannin extraction factories and to stabilize the situation in some major producing countries, but did not translate into an immediate and definitive rescue of that industry. Worldwide, leather still consumes more tannin than adhesive formulations. This is because oil-derived synthetic adhesives are cheaper than the tannin-based counterparts. The first oil crisis of 1974 at least convinced a few southern hemisphere industrialists (in Australia, South Africa and New Zealand) to use tannin adhesives to avoid the difficulties of supplying synthetic adhesives. The phenomenon persisted with a couple of still existing exceptions, but it did not take off in Europe or North America. Synthetic adhesives became cheap again and in abundant supply after 1974, being strongly 'pushed' by all the big chemical companies. Considerable renewed interest in tannins started again after the year 2000 as a result of two factors: (i) the recent marked increase in oil prices that raised disproportionately the market price of all synthetic adhesives, thus favouring natural raw materials. As a consequence, tannin has now become much cheaper than phenol and competes with the cheapest adhesive of them all, urea–formaldehyde resins; (ii) the recent severe tightening of formaldehyde emission regulations, mainly the introduction of the extremely severe Japanese standard, a regulation that is now starting to spill over into other countries [2, 3].

Although tannin adhesives are now fast becoming an interesting industrial proposition as an alternative to synthetic homologues, the use of tannins is expanding rapidly to an even more interesting field, namely to the pharmaceutical/medicine areas. Thus, a fourth market transformation has started and it appears set to overtake tannin transformation into wood adhesives, at least in terms of monetary added value. The therapeutic virtues of the addition of tannins in wine (consequence of the so-called French Paradox), the use of tannins to cure some gastrointestinal diseases, the increasing use of tannins as food supplements in North America, and the research on the beneficial effects of tannins in a multitude of diseases, even serious ones such as cancer and virus-induced sicknesses, are in full swing. This is because the value added to the base cost of tannins is considerable. Indeed, since tannins to be used for human consumption must obviously be thoroughly purified, their price is 40–50 times higher than that of tannins for industrial applications.

8.2 MAJOR SOURCES

The sources of tannins are very varied. There is a multitude of trees and shrubs which contain tannins. For both hydrolysable and condensed structures, the species rich in tannins are many. Notable for either their present or past economic and/or industrial importance are black wattle or black mimosa bark (*Acacia mearnsii*), quebracho wood (*Schinopsis balansae or lorentzii*), oak bark (*Quercus* spp.), chestnut wood (*Castanea sativa*), mangrove wood, *Acacia catechù*, *Uncaria gambir*, sumach, myrabolans (*Terminalia* and *Phyllantus* tree species), divi-divi (*Caesalpina coraria*), algarobilla chilena, tara, and the bark of several species of pines and firs, among them *Pinus radiata* and *Pinus nigra*, not counting even more plants with extractable tannins.

As regards the tannin origin by location, the areas of strong industrial production today are Brazil, South Africa, India, Zimbabwe, Tanzania for mimosa tannin; Argentina for quebracho tannin; Indonesia for mangrove and for cube Gambier tannins; and Italy and Slovenia for chestnut tannin. There are many other small to very small producers a bit everywhere, for example, small pine tannin factories in Turkey and Chile, an oak tannin factory in Poland and a grape pip tannin factory in France.

8.3 USES

The variety of uses of tannins has been illustrated in the introduction. Some, which were important in the past but are no longer now, will not be described, as the literature on the subject is extant [1, 14, 15, 18]. The major existing uses or past uses of tannins are listed below, and the more important will be developed later in more detail.

(1) Leather manufacture.
(2) Adhesives, in particular wood adhesives.
(3) Wine, beer and fruit juices additives.
(4) Ore flotation agents.
(5) Cement superplasticizers.
(6) Medical and pharmaceutical applications.

Of these, leather manufacture will only be briefly discussed as it is beyond the scope of this review and because extensive technical and scientific literature is available on the subject [1, 5, 7, 14, 15–19, 27]. Suffice it to say that it is the interaction between the phenolic hydroxy groups of the tannins and the polar groups of proteins that give rise to a very strongly associated whole.

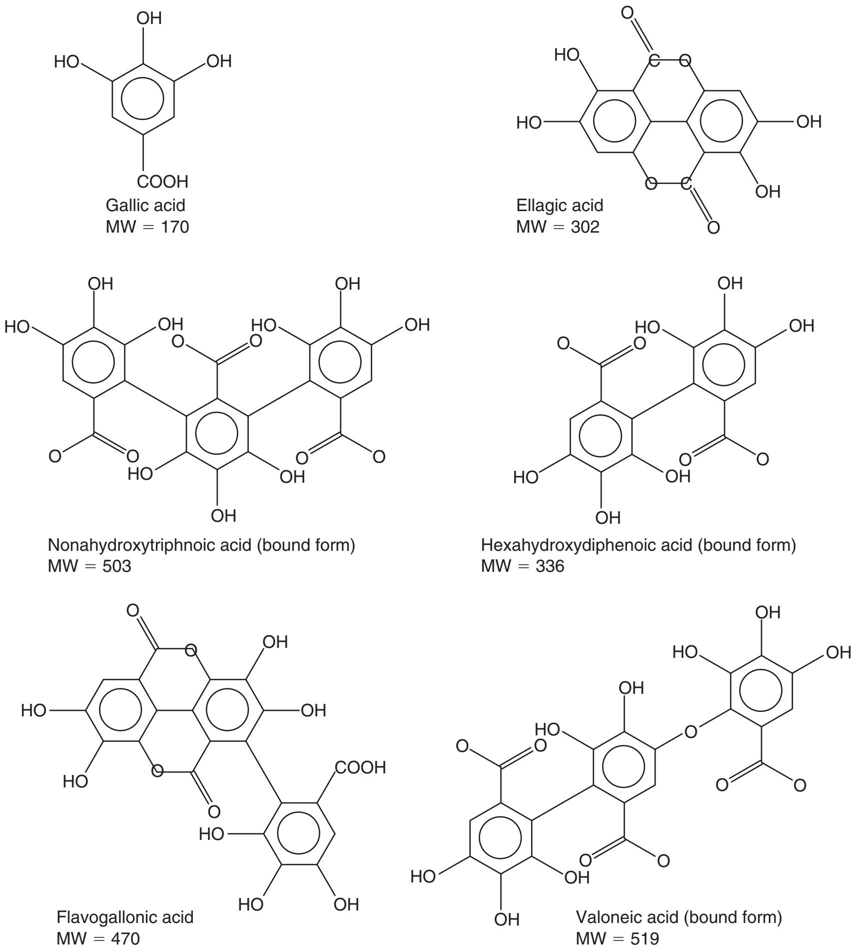
8.4 TANNIN STRUCTURE

The term natural vegetable tannins is used loosely to define two broad classes of chemical compounds of mainly phenolic nature, namely condensed or polyflavonoid tannins and hydrolysable tannins. The recognized oligomeric nature of condensed tannins [4–7] contrasts with the allegedly nonpolymeric nature of hydrolysable tannins [5–7].

8.4.1 Hydrolysable tannins

Hydrolysable tannins, including chestnut (*Castanea sativa*), myrabolans (*Terminalia* and *Phyllantus* tree species), divi-divi (*Caesalpina coraria*), tara, algarobilla, valonea, oak and several other commercial tannin extracts are reputed to be mixtures of simple phenols such as gallic and ellagic acids and of esters of a sugar, mainly glucose, with gallic and digallic acids, and with more complex structures containing ellagic acid (Fig. 8.1).

Notwithstanding their alleged lack of a polymeric nature, they can form complex structures. It must be noted first that carbohydrates are intimately and covalently linked to the phenolic moieties in the structure of



Gallic acid
MW = 170

Ellagic acid
MW = 302

Nonahydroxytriphnoic acid (bound form)
MW = 503

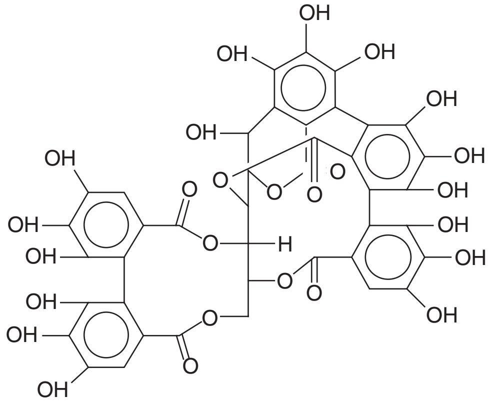
Hexahydroxydiphenoic acid (bound form)
MW = 336

Flavogallonic acid
MW = 470

Valoneic acid (bound form)
MW = 519

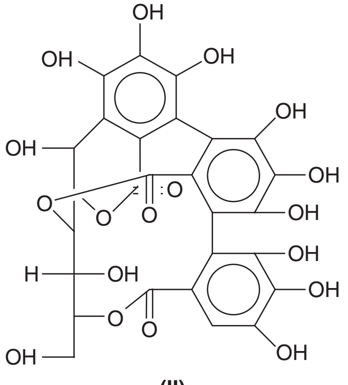
Figure 8.1 Chemical species characteristic of the low molecular weight fraction of hydrolysable tannins.

these tannins, and are therefore to be considered as part of the tannin itself. Indeed, several studies [4, 5] identified the major constituents of the main commercial hydrolysable tannin, chestnut tannin extract (an ellagitannin), as the positional isomers castalagin and vescalagin (**I**), present respectively in 14.2 and 16.2 per cent by mass.



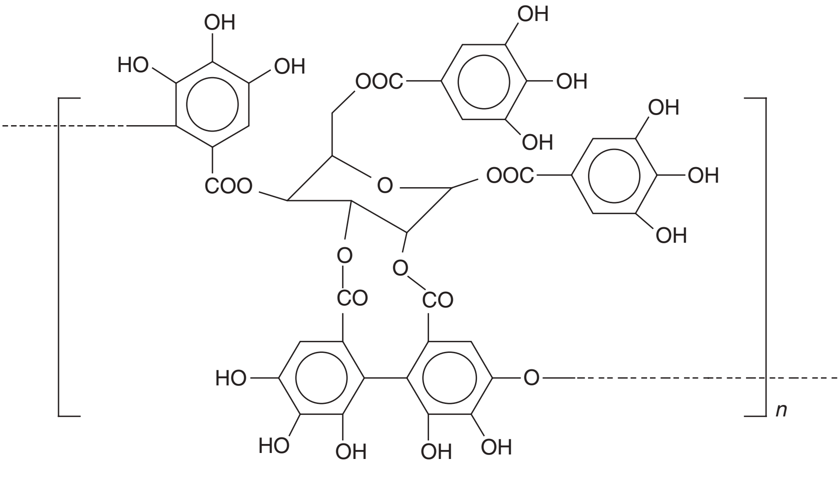
(I)

The rest of the tannin was found to contain 6.6 per cent of the positional isomers castalin and vescalin (**II**) [4, 5], 6 per cent of gallic acid, and 3 per cent of pentagalloyl glucose monomer.



(II)

It must be pointed out however that the authors of the study advancing relative composition percentages [5] clearly state that the disadvantage of the chromatographic technique they used is its strong adsorption of several types of tannins, particularly tannins composed of large molecules. This limitation might well slant the percentages of lower to higher molecular weight components in the analysis of the chestnut extract [4]. Notwithstanding such a limitation, two classes of compounds have however mass predominance in chestnut tannins, namely 28.8 per cent of small molecules, the formula of which is shown in Fig. 1, and 25.4 per cent (or higher, see reasons above) of an unknown and difficult to isolate fraction of apparently a very much higher molecular weight [5] and a very low TLC Rf. This fraction appears to be composed of a number of closely related components giving a continuous TLC smudge of Rf values between 0 and 0.33, which has recently been identified as a mixture of oligomers of pentagalloyl glucose [8], leading to the hypothesis that castalagin, vescalagin, vescalin and castelin are nothing but the hydrolysis of the real structure of the tannin as present in nature [8]. Circumstantial evidence strongly suggests that their repeat unit is:

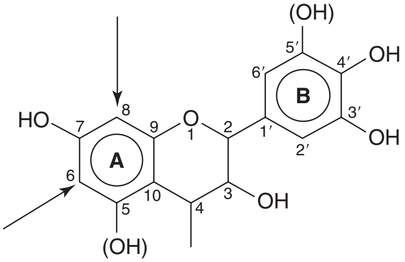


Although these tannins can be reacted with formaldehyde and other aldehydes, the rates of these interactions are low, and they are therefore not favoured for the preparation of resins. They have, however, been used successfully as partial substitutes (up to 50 per cent) of phenol in the manufacture of phenol–formaldehyde resins [9, 10]. Their chemical behaviour towards formaldehyde is analogous to that of simple phenols of low reactivity and their moderate use as phenol substitutes in the above-mentioned resins does not present difficulties. Their lack of macromolecular structure, the low level of phenol substitution they allow, their low nucleophilicity, limited worldwide production and relatively high price, somewhat decrease their chemical and economical interest for resin production. Consequently, their main use is for leather tanning where their performance, especially in terms of clarity of colour and light resistance, is truly excellent.

8.4.2 Condensed (polyflavonoid) tannins

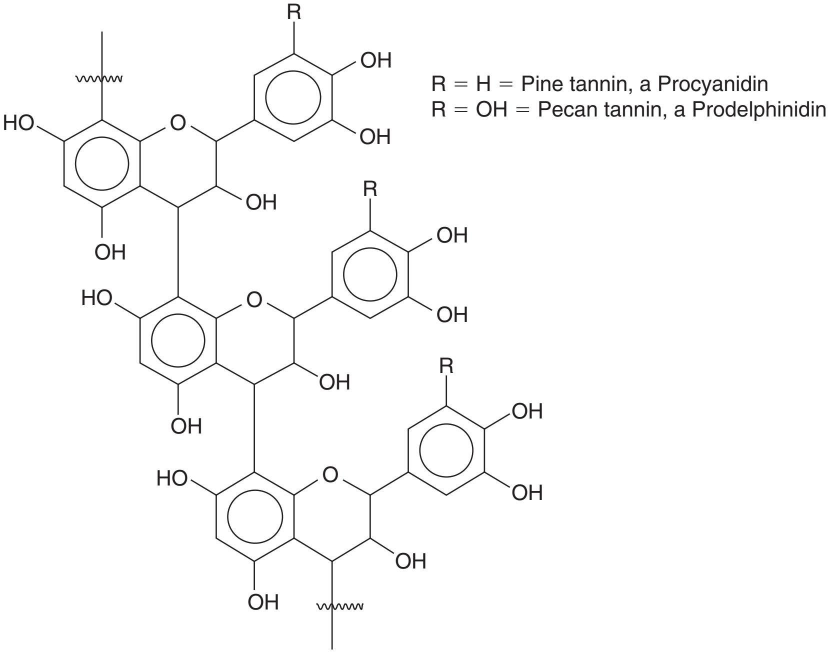
Condensed tannins constitute more than 90 per cent of the total world production of commercial tannins (200 000 tons per year) [11]. Their high reactivity towards aldehydes and other reagents renders them both chemically and economically more interesting for the preparation of adhesives, resins and other applications apart from leather tanning. The main commercial species, such as mimosa and quebracho, also yield excellent heavy duty leather. Condensed tannins and their flavonoid precursors are known for their wide distribution in nature and particularly for their substantial concentration in the wood and bark of various trees. These include various *Acacia* (wattle or mimosa bark extract), *Schinopsis* (quebracho wood extract), *Tsuga* (hemlock bark extract), *Rhus* (sumach extract) species, and various *Pinus* bark extract species, from which commercial tannin extracts are manufactured.

The structure of the flavonoid constituting the main monomer of condensed tannins may be represented as follows:



This flavonoid unit is repeated 2–11 times in mimosa and quebracho tannins [11, 12], with an average degree of polymerization of 4–5, and up to 30 times for pine tannins, with an average degree of polymerization of 6–7 for their soluble extract fraction [13]. The nucleophilic centres on the A-ring of a flavonoid unit tend to be more reactive in aromatic substitution, than those found on the B-ring. This is due to the vicinal hydroxyl substituents, which cause general activation in the B-ring, without any localized effects such as those found in the A-ring [11].

The following three-unit fragment illustrates two typical tannin structures:



Formaldehyde and other aldehydes react with tannins to induce polymerization through methylene bridge linkages at reactive positions on the flavonoid molecules, mainly the A-rings. The reactive positions of the A-rings are the 6 *or* 8 locations (according to the type of tannin) of all the flavonoid units, and both of them for the upper terminal flavonoid units. The A-rings of mimosa and quebracho tannins show reactivity towards formaldehyde comparable to that of resorcinol [11, 14–17]. Assuming the reactivity of phenol to be 1 and that of resorcinol to be 10, the A-rings have a reactivity of 8–9. However, because of their size and shape, the tannin molecules lose their mobility and flexibility at a relatively low level of condensation with formaldehyde, so that the available reactive sites are too far apart for further methylene bridge formation. The result may be incomplete polymerization and therefore poor material properties. Bridging agents with longer molecules should be capable of joining the distances that are too long for methylene bridges. Alternatively, other techniques can be used to solve this problem [11, 100].

In condensed tannins from mimosa bark, the main polyphenolic pattern is represented by flavonoid analogues based on resorcinol A-rings and pyrogallol B-rings. These constitute about 70 per cent of the tannins. The secondary but parallel pattern is based on resorcinol A-rings and catechol B-rings [11, 14]. These tannins represent about 25 per cent of the total of mimosa bark tannin fraction. The remaining parts of the condensed tannin extract are the 'nontannins' [14]. They may be subdivided into carbohydrates, hydrocolloid gums and small amino and imino acid fractions [11, 14]. The hydrocolloid gums vary in concentration from 3 to 6 per cent and contribute significantly to the viscosity of the extract despite their low concentration [11, 14]. Similar flavonoid A- and B-ring patterns also exist in quebracho wood extract (*Schinopsis balansae*, and *Lorentzii*) [15–17], but no phloroglucinol A-ring pattern, or probably a much lower quantity of it, exists in the quebracho extract [17–19]. Similar patterns to wattle (mimosa) and quebracho are encountered in hemlock and Douglas fir bark extracts. Completely different patterns and relationships are found instead in pine tannins [20–22] which present only two main patterns: one represented by flavonoid analogues based on phloroglucinol A-rings and catechol B-rings [20, 22] and the other, present in a much lower proportion, represented by phloroglucinol A-rings and phenol B-rings [20, 22]. The A-rings of pine tannins then possess only the phloroglucinol type of structure, much more reactive towards formaldehyde than a resorcinol-type counterpart, with important consequences in the use of these tannins for adhesives.

8.5 ANALYSIS

Various methods of analysis are available for the determination of tannin content. These methods can generally be grouped into two broad classes:

(1) *Methods aimed at the determination of tannin material content in the extract*: The classical method of this type still used is the hide-powder method. These methods were devised to determine which percentage of the extract would participate in leather tanning. Their main drawback for their use in adhesives is their incapacity of detecting and determining the approximate 3–6 per cent of monoflavonoids and biflavonoids, or phenolic 'nontannins', present in the extract, which do not contribute to tanning capacity, but which do definitely react with formaldehyde and contribute to adhesive preparation.

(2) *Methods aimed at the determination of phenolic materials present in the extract that can be reacted with formaldehyde*: These methods were devised particularly for tanning extract used in adhesives and are all based on the determination of some of the products of the reaction of the flavonoids with formaldehyde.

The accepted methods of the first type comprise the hide-powder method [23], the refractometric method and various visible ultraviolet, and infrared spectroscopic methods. The accepted methods of the second type include comparative methods such as the Stiasny–Orth method [24, 25] and its modifications, all these being gravimetric methods today largely obsolete due to the lack of reliability consequent to the coprecipitation of some carbohydrates together with the phenolic material of the tannin extract and to the results being expressed in an absolute value, which is never convertible to a percentage of useful material in the extract. The Lemme sodium bisulphite backtitration method [26], the ultraviolet spectrophotometric molibdate ion method [27], and the infrared spectrophotometric methods [28] give instead correct percentage results.

8.6 A FEW CONSIDERATIONS ON LEATHER MANUFACTURE

The leather tanning industry is one of the most ancient processes still in operation. Extensive reviews and articles on the use of vegetable tannins in leather making exist [1, 5, 7, 14, 15–19, 27]. A brief general and comparative outline of vegetable versus other types of tanning is given here for the information of the reader who might not know this industry. Although the technology of leather manufacture has evolved over centuries, and even in recent years, the basic principles for the production of leather have remained essentially the same. Hide proteins, mainly collagen, are rendered insoluble and dimensionally more stable by treatment with chemical products able to join them and thus render them both more resistant to mechanical wear and less susceptible to biological degradation and other types of attack. The main products used today for leather tanning are (i) acid salts of trivalent chromium, mainly used for the manufacture of soft leathers for shoe uppers and for leather bags; (ii) forestry-derived, natural vegetable tannins, such as chestnut and flavonoid extracts, mainly used for the manufacture of heavy, rigid and hard leathers for shoe soles, saddles, belts and other implements subject to intensive wear; (iii) aldehydes, in particular formaldehyde and glutaraldehyde; (iv) sulphonated synthetic polymers, such as acid phenol–formaldehyde novolak-type resins and (v) a number of other synthetic resins and compounds (acrylics, oxazolidines, aminoplastic resin, etc.).

Each of the products mentioned above is more apt than the others to the manufacture of certain specific types of leather. The fact remains however, that the first two in the above list account for more than 90 per cent of all the leather manufactured today, and that the process based on trivalent chromium salts accounts by itself for about 70 per cent of the total. Chrome tanning is particularly suited for soft leather, as it does not affect hide flexibility and renders the leather very lightfast and very stable both chemically and physically. It produces leather of excellent antishrinkage ability, as indicated by its high shrinkage temperature in testing. The forestry-derived vegetable tannins have, instead, a strong astringent effect (they fix very effectively on the collagen structure) and give considerable ‘body’, hardness and toughness to the leather produced with them. However, they have the considerable disadvantage of exhibiting marked darkening problems when exposed to light and, even worse, to shrink at a much lower temperature. It is these two main disadvantages that have somewhat limited their application in relation to the ubiquitousness of chromium salts. Conversely, their combination with some synthetic resins such as MUF [29, 30], give light-coloured leathers presenting high resistance to light-induced degradation, as well as other advantages similar to those of chrome tanning.

Chromium salts are becoming less acceptable in many types of industry due to potential effluent pollution. Furthermore, well-defined quality standards as regards leather product skin-contact allergic reactions, have also been introduced for finished products, for instance in leather clothing and interior car linings. In this respect, two of the requirement limits to comply with are the amount of both leachable trivalent chromium, which generally does not constitute a problem, and of one of its tanning derivatives, namely the more dangerous, highly toxic hexavalent chromium salts. Recent norms [31, 32] limit severely the proportion of these compounds in leathers to be used in direct contact with human skin, such as watch straps, shoe uppers, etc.). Furthermore, the treatment of tanning waste waters represents one of the major problems in the leather industry, especially today that the relevant European Commission norms impose ever more stringent effluent limits. The waste waters are generally treated to abate (never eliminate) chromium salt residues. However it has proved difficult to find suitable alternatives to chromium salts up to now.

In the case of natural tannins, their sensitivity to photo-oxydation limits their use to applications where such a characteristic is of no consequence. It is the tannin phenolic structure itself which renders photo-oxydation possible [33], with transformation of tannin phenolic groups to coloured quinones, but it has been shown that this effect can be drastically limited if the tannins are condensed with sulphonated synthetic aminoplast resins such as MUF [29, 30]. Conversely, while the use of synthetic aminoplast resins is developing in the tanning industry, as they give leathers of a certain degree of softness and flexibility, and particularly suitable for colouring, their weak point is the excessive and inevitable presence of free formaldehyde [34] and their poor tanning capability due to their low astringency. Polyphenolic vegetable tannins are well known to act as powerful free formaldehyde scavengers, as they react rapidly and irreversibly with this compound [11, 35]. Their combination with aminoplast MUF resins thus reduces markedly the photo-oxydation of vegetable tannins through synergy with the synthetic resin, reduces formaldehyde emission to just about zero, yields relatively soft but also tough leather and eliminates the need for chromium salts. Furthermore, such a mix can achieve leather shrinkage temperatures that at least match the chromium salt performance on this parameter.

8.7 TANNIN-BASED ADHESIVES

8.7.1 Wood adhesives

In condensed polyflavonoid tannin molecules, the A-rings of the constituent flavonoid units retain only one highly reactive nucleophilic centre, the remainder accommodating the interflavonoid bonds. Resorcinolic A-rings (wattle) show reactivity towards formaldehyde comparable to, though slightly lower than, that of resorcinol [36]. Phloroglucinolic A-rings (pine) behave instead as phloroglucinol [37]. Pyrogallol or catechol B-rings are by comparison unreactive and may be activated by anion formation only at relatively high pH [38]. Hence the B-rings do not participate in the reaction except at high pH values (pH 10), where the reactivity towards formaldehyde of the A-rings is so high that the ensuing tannin–formaldehyde adhesives have unacceptably short pot lives [36]. In the usual tannin adhesive practice, only the A-rings are used to generate the network. With regard to the pH dependence of the reaction with formaldehyde, it is generally accepted that the reaction rate of wattle tannins with formaldehyde is the slowest in the pH range 4.0–4.5 [39]; for pine tannins, the range is between 3.3 and 3.9.

Formaldehyde is generally the aldehyde used in the preparation, setting and curing of tannin-based adhesives. It is normally added to the tannin extract solution at the required pH, preferably in its polymeric form of paraformaldehyde, which is capable of fairly rapid depolymerization under alkaline conditions, and as urea–formalin concentrates. Hexamethylenetetramine (hexamine) may also be added to these resins because of its potential formaldehyde releasing action under heat. Hexamine is, however, unstable in acid media [40], but becomes more stable with increasing pH values. Hence, under alkaline conditions, the liberation of formaldehyde might not be as rapid and as efficient as wanted. Also, it has been fairly widely reported, with a few notable exceptions [41], that bonds formed with hexamine as hardener are not as boil resistant [42] as those formed by paraformaldehyde. The reaction of formaldehyde with tannins may be controlled by the addition of alcohols to the system. Under these circumstances, some of the formaldehyde is stabilized by the formation of hemiacetals (*e.g.* $CH_2(OH)(OCH_3)$) if methanol is used [11, 37]. When the adhesive is cured at an elevated temperature, the alcohol is driven off at a fairly constant rate and formaldehyde is progressively released from the hermiacetal. This ensures that less formaldehyde is volatilized when the reactants reach curing the curing temperature and that the pot life of the adhesive is extended. Other aldehydes have also been substituted for formaldehyde [11, 36, 39, 41].

In the reaction of polyflavonoid tannins with formaldehyde two competitive mechanisms take place:

(1) The reaction of the aldehyde with tannin and with low molecular weight tannin–a1dehyde condensates, which is responsible for the aldehyde consumption.
(2) The liberation of formaldehyde, which become available again for reaction. This release is probably due to the decomposition of the unstable $—CH_2—O—CH_2—$ ether bridges initially formed into $—CH_2—$ counterparts.
(3) In the case of some tannins (*e.g.* quebracho tannin) a third important reaction occurs, namely the simultaneous hydrolysis of some interflavonoid bonds, hence a depolymerization reaction, partly counteracting and thus slowing down the hardening process [12, 42, 43].

Considering the fact that the two major existing industrial polyflavonoid tannins, namely mimosa and quebracho tannins, are very similar and both composed of mixed prorobinetinidins and profisetinidins, it was difficult to rationalize this anomalous behaviour of quebracho tannin. It has now been possible to determine by both NMR [42] and particularly by laser desorption mass spectrometry (MALDI–TOF), applied to mimosa and quebracho tannins and some of their modified derivatives [12] that: (i) mimosa tannin is predominantly composed of prorobinetinidins, while quebracho is predominantly composed of profisetinidins; (ii) mimosa tannin is heavily branched due to the presence of considerable proportions of ‘angular’ units in its structure, while quebracho tannin is almost completely linear [12]. This latter structural difference is the one which contributes to the considerable differences in viscosity of water solutions of the two tannins and which induces the interflavonoid link of quebracho to be more easily hydrolysable, because of the linear structure of this tannin. This feature confirms the NMR findings [12, 42] showing that this tannin is subject to polymerization/depolymerization equilibria. The specificity of the quebracho structure also explains the decrease in viscosity arising from acid/base treatments to yield tannin adhesive intermediates after a certain level of hydrolysis of the tannin itself and not only of the carbohydrates present in the extract (see also Section 8.4). Such a tannin hydrolysis does not appear to occur with mimosa tannin in which the interflavonoid link is completely stable against this attach.

It is interesting to note that whereas $—CH_2—O—CH_2—$ ether bridged compounds have been isolated for the phenol–formaldehyde [40] reaction, their existence for fast-reacting phenols such as resorcinol and phloroglucinol has been postulated, but they have never been isolated, since these two phenols have always been considered too reactive towards formaldehyde. They are detected indirectly by the surge in the concentration of formaldehyde observed in kinetic studies, as a consequence of the methylene ether bridge decomposition [44].

When heated in the presence of strong mineral acids, condensed tannins are subject to two competitive reactions. One is degradative leading to lower molecular weight products, and the second is condensative, as a result of the hydrolysis of heterocyclic rings (*p*-hydroxybenzyl ether links) [38]. The generated *p*-hydroxybenzylcarbenium ions condense randomly with nucleophilic centres on other tannin units to form 'phlobaphenes' or 'tanner's red' [38, 45–47]. Other modes of condensation (*e.g.* free radical coupling of B-ring catechol units) cannot be excluded in the presence of atmospheric oxygen. In predominantly aqueous conditions, the formation of phlobaphene or insoluble condensates predominates. These reactions, characteristic of tannins and not of synthetic phenolic resins, must be taken into account when formulating tannin adhesives.

The sulphitation of tannins is one of the oldest and most useful reactions in flavonoid chemistry. Slightly sulphited water is sometimes used to increase tannin extraction from the bark containing it. In certain types of adhesives, the total effect of sulphitation has both negative and positive connotations. The latter aspects are related to both a higher concentration of tannin phenolics in adhesive applications, due to enhanced solubility and decreased viscosity, and to a higher moisture retention by the tannin resins, giving a slower adhesive film dry-out and hence a longer assembly time [48]. As for the negative aspects, the presence of sulphonate groups promotes a higher sensitivity to moisture with a consequent adhesive deterioration and bad water resistance of the cured glue line even with adequate crosslinking [48–51].

In recent years, the importance of the marked colloidal nature of tannin extract solutions has come to the fore [42, 43, 52–60]. It is the presence of both polymeric carbohydrates in the extract, as well as of the higher molecular fraction of the polyphenolic tannins, which determines the colloidal state of tannin extract solutions in water [42, 52]. This feature affects many of the reactions which lead to the formation and curing of tannin adhesives, to the point where reactions not thought possible in solution become instead, not only possible, but, the favoured ones [42, 52]. Conversely, reactions mooted to be of determinant importance when found on models not in a colloidal state, have in reality been shown to be inconsequential to tannin adhesives and their applications [35, 59].

8.8 TECHNOLOGY OF INDUSTRIAL TANNIN ADHESIVES

8.8.1 Wood adhesives

The purity of vegetable tannin extracts varies considerably. Commercial wattle bark extracts normally contain 70–80 per cent active phenolic ingredients. The nontannin fraction, consisting mainly of simple sugars and high molecular weight hydrocolloid gums, does not participate in the resin formation with formaldehyde. Sugars reduce the strength and water resistance in direct proportion to the amount added. Their effect is a mere dilution effect of the adhesive resin solids, with the consequent proportional worsening of adhesive properties. The hydrocolloid gums, instead, have a much more marked effect on both original strength and water resistance of the adhesive [11, 37, 58]. If it is assumed that the nontannins in tannin extracts have a similar influence on adhesive properties, it can be expected that unfortified tannin–formaldehyde networks can achieve only 70–80 per cent of the performance shown by synthetic adhesives.

In many glued wood products, the demands on the glue line are so high that unmodified tannin adhesives are unsuitable. The possibility of refining extracts has proved fruitless largely because the intimate association between the various constituents makes industrial fractionation difficult. Fortification is in many cases the most practical approach to reducing the effect of impurities and generally consists of copolymerization of the tannin with phenolic or aminoplastic resins [36, 37, 58, 61]. It can be carried out during the manufacture of the adhesive resin, during gluemix assembly, just before use, or during adhesive use. If added in sufficient quantity, various synthetic resins have been found effective in reducing the nontannin fraction to below 20 per cent and in overcoming other structural problems [36, 37]. The main resins used are phenol–formaldehyde and urea–formaldehyde resols with a medium-to-high methylol group content. These resins can fulfil the functions of hardeners, fortifiers, or both. Generally, they are used as fortifiers in between 10 and 20 per cent of total adhesive solids, with paraformaldehyde used as a hardener. Such an approach is the favourite one for marine-grade plywood adhesives. These fortifiers are particularly suitable for the resorcinol types of condensed tannins, such as mimosa. They can be copolymerized with the tannins during resin manufacture, during use, or both [11, 35–37, 58]. Copolymerization and curing are based on the condensation of the tannin with the methylol groups carried by the synthetic resin. Since tannin molecules are generally large, the rate of molecular growth in relation to the rate of linkage is high, so that tannin adhesives generally tend to have fast gelling and curing times and shorter pot lives than those of synthetic phenolic adhesives. From the point of view of reactivity, phloroglucinol tannins, such as pine tannins, are much faster than mainly resorcinol tannins such as mimosa. The usual ways of slowing them down and, for instance, lengthening the adhesive pot life are:

(1) To add alcohols to the adhesive mix to form hemiacetals with formaldehyde which therefore act as retardants of the tannin–formaldehyde reaction.
(2) To adjust the adhesive pH to obtain the required pot life and rate of curing.
(3) To use hexamine as a hardener which, under the current conditions, gives a very long pot life at ambient temperature but still a fast curing time at higher temperatures.

The viscosity of bark extracts is strongly dependent on concentration and increased very rapidly above 50 per cent. Compared to synthetic resins, tannin extracts are more viscous at the concentrations normally required in adhesives. The high viscosity of aqueous solutions of condensed tannins is due to the following causes, in order of importance:

(1) *Presence of high molecular weight hydrocolloid gums in the tannin extract* [58, 60]: The viscosity is directly proportional to the amount of gums present in the extract [58, 60].
(2) *Tannin–tannin, tannin–gum and gum–gum hydrogen bonds*: Aqueous tannin extract solutions are not true solutions but, rather, colloidal suspensions in which water access to all parts of the molecules present is very slow. As a consequence, it is difficult to eliminate intermolecular hydrogen bonds by dilution only [58, 60].
(3) *Presence of high molecular weight tannins in the extract* [12, 58, 60].

The high viscosity of tannin extract solutions has also been correlated to the proportion of very high molecular weight tannins present in the extract. This effect is not well defined. In most adhesive applications, such as in plywood adhesives, the viscosity is not critical and can be manipulated by dilution.

In the case of particleboard adhesives, the decrease in viscosity is, instead, an important prerequisite. When reacted with formaldehyde, unmodified condensed tannins give adhesives having characteristics that do not suit particleboard manufacture, namely, high viscosity, low strength and poor water resistance. The most commonly used process to eliminate these disadvantages in the preparation of tannin-based particleboard adhesives consists of a series of subsequent acid and alkaline treatments of the tannin extract, causing hydrolysis of the gums to simple sugars and some tannin structural changes, thus improving the viscosity, strength and water resistance of the unfortified tannin–formaldehyde adhesive [11, 35]. Furthermore, such treatments may cause the partial rearrangement of the flavonoid molecules that causes liberation of some resorcinol *in situ* in the tannin, rendering it more reactive, allowing better crosslinking with formaldehyde and, ultimately, yielding an adhesive which, without addition of any fortifier resins, gives a truly excellent performance for exterior-grade particleboard [11, 35]. This modification cannot be carried out too extensively, in order to avoid the precipitation of the tannin from the solution by the formation of 'phlobaphenes'.

Typical results are shown in Table 8.1.

Table 8.1

Unfortified tannin–formaldehyde adhesives obtained by acid–alkali treatment, for exterior-grade particleboard: Example of industrial board results [11, 77, 78]

	Swelling after a 2 h boil				
Panel density (g/cm^3)	Measured wet (%)	Measured dry (irreversible swelling) (%)	Original internal bond (IB) tensile perpendicular (kg/cm^2)	IB after a 2 h boil (kg/cm^2)	Cyclic test after five cycles measured (%)
0.700	11.0	0.0	13.0	9.0	3.0

Particular gluing and pressing techniques have been developed for tannin particleboard adhesives [62, 63] to achieve pressing times much shorter than those traditionally obtained with synthetic phenol–formaldehyde adhesives, although recent advances in the latter materials have markedly limited such an advantage [64, 65]. Pressing times of 7 s mm^{-1} of panel thickness have been achieved and of 9 s mm^{-1} at 190–200°C pressing temperatures are in daily operation: these are pressing times that are becoming comparable to those obtainable with urea–formaldehyde or melamine–formaldehyde resins at the same pressing temperatures. The success of these simple types of particleboard adhesives relies heavily on industrial application technologies rather than just on the preparation technology of the adhesive itself [58, 62, 66]. A considerable advantage is the much higher moisture content of the resinated chips tolerable with these adhesives than with any of the synthetic phenolic and aminoresin counterparts. In the case of wood particleboard and of oriented strandboard (OSB) panels, the technology so developed allows hot-pressing at moisture contents of around 24 per cent, against values of 12 per cent for traditional synthetic adhesives, and presents other advantages as well [58, 66, 67].

The best adhesive formulation for phloroglucinolic tannins, such as pine tannin extracts is, instead, a comparatively new and is also capable of giving excellent results when using resorcinol tannins such as a wattle tannin extract [68–71]. The adhesive gluemix consists only of a mix of an unmodified tannin extract 50 per cent solution to which paraformaldehyde and polymeric nonemulsifiable 4,4′-diphenylmethane diisocyanate (commercial pMDI) are added [68–71]. The proportion of tannin extract solids to pMDI can be as high as 70/30 w/w, but can be much lower in pMDI content. This adhesive is based on the peculiar mechanism by which the pMDI in water, is hardly deactivated to polyureas because it reacts faster with the hydroxymethyl groups of a formaldehyde-based resin, be it a tannin or another resin [69, 71].

The properties of the particleboards manufactured with this system using pine tannin adhesives are listed in Table 8.2. The results obtained with this system are quite good and not too different from those produced by some of the other tannin adhesives already described. In the case of phloroglucinolic tannin extracts, no pH adjustment of the solution is needed. One point that was given close consideration is the deactivating effect of water on the isocyanate group of pMDI. It has been found that the amount of deactivation by water in a concentrated solution (50 per cent or over) of a phenol is much lower than previously thought [68–71]. This is the reason why aqueous tannin extract solutions and pMDI can be mixed without any substantial pMDI deactivation by the water present.

The quest to decrease or completely eliminate formaldehyde emission from wood panels bonded with adhesives, although not really necessary in tannin adhesives due to their very low emission (as with most phenolic adhesives), has nonetheless promoted here too some research to further reduce formaldehyde emission. This has centred into two lines of investigation: (i) tannin autocondensation (see paragraph D later on), and (ii) the use of a hardener not emitting at all, simply because no aldehyde has been added to the tannin [72–74]. Methylolated nitroparaffins and, in particular, the simpler and least expensive exponent of their class, namely trishydroxymethyl nitromethane [72, 73], function well as hardeners for a variety of tannin-based adhesives, while affording considerable side advantages to the adhesive and to the bonded wood joint. In panel products such as particleboard, medium density fibreboard and plywood, the joint performance which is obtained is of the exterior/marine-grade type, combined with a very advantageous and very considerable lengthening in gluemix pot life is obtained. Furthermore, the use of this hardener is coupled with such a marked reduction in formaldehyde emission from the bonded wood panel that it is limited exclusively to the formaldehyde released only by the heated wood, or even less, thus functioning as a mild depressant of emission from the wood itself. Moreover, trishydroxymethyl nitromethane can be mixed in any proportion with traditional formaldehyde-based hardeners for tannin adhesives, its proportional substitution of such hardeners inducing a correspondingly marked decrease in the formaldehyde emission of the wood panel, without affecting its exterior/marine-grade

Table 8.2

Properties of a particleboard manufactured using pine tannin adhesives

	Swelling after a 2 h boil				
Panel density	Measured wet (%)	Measured dry (irreversible swelling) (%)	Original internal bond (IB), tensile perpendicular (kg/cm^2)	IB after a 2 h boil (kg/cm^2)	IB retention after a 2 h boil (%)
0.690	15.0	4.3	8.4	4.3	51

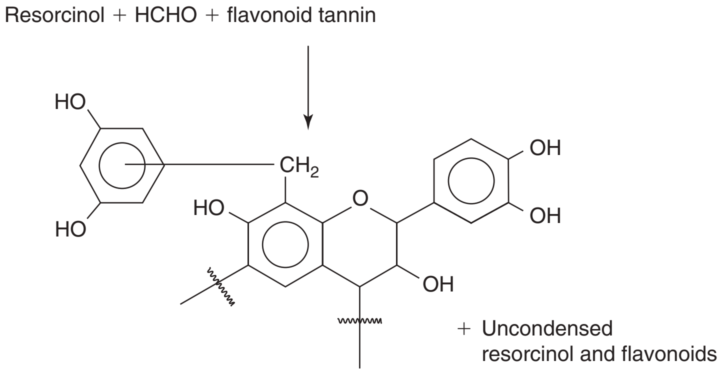
performance. Medium density fibreboard (MDF) industrial plant trials confirmed all the properties reported above [72, 73]. A cheaper but equally effective alternative to hydroxymethylated nitroparaffins is the use of hexamine as tannin hardener. This sometimes causes problems of an early agglomeration in some tannins [74] and a better solution which overcames this drawback was to use a mixture of formaldehyde and an ammonium salt as the hardener.

8.8.2 Corrugated cardboard adhesives

The adhesives developed for the manufacture of damp-ply-resistant corrugated cardboard are based on the addition of spray-dried wattle extract, urea–formaldehyde resin, and formaldehyde to a typical Stein–Hall starch formula with 18–22 per cent starch content [75, 76]. The wattle tannin–urea–formaldehyde copolymer formed *in situ* and any free formaldehyde left in the glue line are absorbed by the wattle tannin extract. The wattle extract powder should be added at level of 4–5 per cent of the total starch content of the mix (*i.e.* carrier plus slurry). Successful results can be achieved in the range of 2–12 per cent of the total starch content, but 4 per cent is the recommended starting level. The final level is determined by the degree of water hardness and desired bond quality. This wattle extract UF-fortifier system is highly flexible and can be adapted to damp-proof a multitude of basic starch formulations.

8.8.3 Cold-setting laminating and fingerjointing adhesives for wood

A series of different novolak-like materials are prepared by copolymerization of resorcinol with resorcinol A-rings of polyflavonoids, such as condensed tannins [77–79]. The copolymers formed have been used as cold-setting exterior-grade wood adhesives, complying with the relevant international specifications. Several formulations are used. The system most commonly employed commercially relies on the simultaneous copolymerization of resorcinol and of the tannin resorcinol A-ring, thanks to their comparable reactivity towards formaldehyde. The following scheme summarizes the principle of this system:



The final mixture is an adhesive that can be set and cured at ambient temperature by the addition of paraformaldehyde. Other cold-set systems exist and are described in the more specialized literature [11, 77–79]. Some typical results obtained with these adhesives are given in Table 8.3.

Table 8.3

Typical results of tannin–resorcinol–formaldehyde cold-setting adhesives used on beech strips according to British Standard BS 1204 [80]

	Dry	After 24 h cold-water soak	After 6 h boil
Tensile strength (N)	3 200–3 800	2 300–2 900	2 200–2 800
Wood failure (%)	90–100	75–100	80–100

A particularly interesting system now used extensively in several southern hemisphere countries is the so-called honeymoon' fast-setting, separate-application system [81, 82]. In this process, one of the surfaces to be mated in the joint is spread with a standard synthetic phenol–resorcinol–formaldehyde adhesive plus a paraformaldehyde hardner. The second surface is spread with a 50 per cent tannin solution at pH 12. When the two surfaces are jointed, fingerjoints develop enough strength to be installed within 30 min and laminated beams (glulam) need to be clamped for only 2.5–3 h instead of the traditional 16–24 h, with a consequent considerable increase in factory productivity. This adhesive system also provides full weather- and boil-proof capabilities.

8.8.4 TYRE CORD ADHESIVES

Another application of condensed tannin extracts that has proved technically successful is as a tyre cord adhesive. Both thermosetting tannin formulation [83] and tannin–resorcinol–formaldehyde formulations have been tested successfully.

8.9 NEW CONCEPTS AND PRINCIPLES

8.9.1 Surface catalysis

As in the case of other formaldehyde-based resins, the interaction energies of tannins with cellulose obtained by molecular mechanics calculations [59] tend to confirm the effect of surface catalysis induced by cellulose also on the curing and hardening reaction of tannin adhesives. The considerable energies of interactions obtained can effectively explain a weakening of the heterocycle ether bond leading to the accelerated and easier opening of the pyran ring in a flavonoid unit, as well as the ease with which hardening by self-condensation can occur. As in synthetic formaldehyde-based resins, the same effect explains the decrease in the activation energy of the condensation of polyflavonoids with formaldehyde leading to exterior wood adhesives curing and hardening [84].

8.9.2 Hardening by tannins self-condensation

The self-condensation reactions characteristic of polyflavonoid tannins have only recently been used to prepare adhesive polycondensates hardening in the absence of aldehydes [85]. This self-condensation reaction is based on the opening under alkaline and acid conditions of the O1—C2 bond of the flavonoid repeating unit and the subsequent condensation of the reactive centre formed at C2 with the free C6 or C8 sites of a flavonoid unit on another tannin chain [85–89]. Although this reaction may lead to considerable increases in viscosity, gelling does not generally occur. However, gelling does occur when the reaction takes place (i) in the presence of small amounts of dissolved silica (silicic acid or silicates) catalyst and some other catalysts [85–90], and (ii) on a lignocellulosic surface [89]. In the case of the more reactive procyanidin- and prodelphinidin-type tannins, such as pine tannin, cellulose catalysis is more than enough to cause hardening and to produce boards of strength satisfying the relevant standards for interior-grade panels [89]. In the case of the less reactive tannins, such as mimosa and quebracho, the presence of a dissolved silica or silicate catalyst is essential to achieve the panel strength required by the relevant standards. Self-condensation reactions have been shown to contribute considerably to the dry strength of wood panels bonded with tannins, but to be relatively inconsequential in contributing to the bonded-panel exterior-grade properties, which are instead attained by polycondensation reactions with aldehydes [89–91]. Combinations of tannin self-condensation and reactions with aldehydes, and combinations of radical and ionic reaction, have been used to decrease the proportion of aldehyde hardener needed, as well as to decrease considerably further the already low formaldehyde emission caused by the use of tannin adhesives [89–91].

8.10 CEMENT SUPERPLASTICIZERS

Plasticizers or dispersion agents are additives which are incorporated into concrete to improve its workability, reduce its water content needs, and enhance its strength development. Unfortunately, these properties are mutually exclusive. Thus, all plasticizers also cause retardation in the setting and in the early strength development of concrete. Superplasticizers are, instead, substances that in small amounts are able to strongly fluidify a cement mix *without* retarding its setting. Heavily sulphonated melamine–formaldehyde resins are the only other superplasticizers known in cement technology, other than tannins. This enhanced workability without any addition of extra water entails neither a loss of final strength, nor any gross retardation of concrete strength. Furthermore, no decrease in initial strength is observed. Their remarkable plasticizing action is demonstrated by slumps of 200 mm without increases in water content or by water reduction of up to 30 per cent [92].

The effect of a superplasticizer is due to its sulphonic groups being oriented towards water, but also adsorbing on the cement grain surface in sufficient numbers to form a monolayer around the grain. The combination of electrostatic repulsion and large ionic size brings about a rapid dispersion of the individual cement grains. In doing so, water trapped within the original flocks is released and can contribute to the mobility of the cement paste and, hence, to the workability of the concrete. Superplasticizers do not cause much reduction in the surface tension of water. The adsorption of the anions on the surface of the cement grain is also less tenacious than in the case of retarders and the course of the hydration reaction is not hindered at normal dosage levels. It follows that, for normal superplasticizers, there is no significant retardation of setting and hardening.

Polyflavonoid tannins have structures capable of complexing metallic ions such as Fe^{2+}/Fe^{3+} and aluminium ions through the ortho hydroxyl groups of the B-ring of the flavonoid units [11]. They can also be sulphonated, and often are, to improve their solubility in water, with the consequent opening of their etherocyclic pyran ring and the introduction of sulphonic groups at the C2 sites of some of the flavonoid units [11]. They also contain up to 20 per cent monomeric and polymeric carbohydrates. Notwithstanding the well-known retarding effect of carbohydrates on cement, this is not the case in the presence of the tannins in the tannin extract. These characteristics render polyflavonoid tannins an interesting material for use as dispersing/plasticizing agents for cements, which are materials mostly composed of calcium and iron silicates and aluminates.

Sulphonated mimosa, quebracho and pine tannin extracts all behave well as cement superplasticizers, with mimosa and pine being the better ones [93]. A dosage of 0.25–0.5 per cent in cement has a noticeable effect of fluidification. The tannin extract cement superplasticizing behaviour was ascribed to the balance of different effects, namely (1) their increase in molecular weight by self-condensation induced by the presence of silicate and aluminium components of cement [72, 73, 93]; (2) the decrease first and then the stabilization of the molecular weight and the improved solubility induced by the introduction of sulphonic groups in the tannin structure and (3) the stabilization of the molecular weight induced by the addition of urea, through its hindrance to tannin self-condensation and its decrease of the tannin extracts colloidal association in water.

8.11 MEDICAL/PHARMACEUTICAL APPLICATIONS

Tannins are well known to have an antimicrobial activity. This is logical as their capability to tan proteins means that they will complex irreversibly also with the proteins in bacterial membranes, thus inhibiting any activity they might have. It follows that, pharmaceuticals containing tannins and aimed at curing bacterial intestinal infections have been around already for some time. Some studies on their anticavity effectiveness have also been conducted [94]. Additionally, the use of tannins in other pharmaceutical medical applications, have been reported, particularly concerning their antitumour and anticancer activity [95–98]. More recently, work on their antiviral effectiveness has been conducted [99]. The data in Tables 4 to 11 present preliminary results obtained on the antiviral activity of 12 different flavonoid and hydrolysable tannins, obtained at the medical department of Leuven University [99]. These results evaluated both the effectiveness of 12 different tannins, as measured by the Minimum Inhibitory Concentration (MIC) required to reduce virus-induced cytopathogenicity by 50 per cent. The lower the MIC value, the better the compound as an antiviral substance. Equally important, the results in the tables report the Minimum Cytotoxic Concentration (MCC) required to cause a microscopically detectable alteration in the normal cell morphology. The higher the MCC, the less toxic is the compound to the patient's cells and the better it is as an antiviral substance. Thus, what is sought is the lowest possible MIC and the highest possible MCC. These results were obtained as *in vitro* screening tests, which implies that *in vivo* conformations are required. Nonetheless, their novelty and thoroughness justify their full report here. Different tannins have been shown to be very effective against different viruses, the nature of the different polyphenolic groups being the cause of this behaviour. Most likely, they tan the proteins and associate with the carbohydrates of the virus membrane, through an interaction similar to that associating them with hide proteins and carbohydrates to give leather.

Table 8.4

Tannin concentration required to protect CEM cells against the cytopathogenicity of HIV by 50% (MIC)

Anti-HIV-1 and -HIV-2 activity of the compounds in human T-lymphocyte (CEM) cells

Compound	EC$_{50}$ (μg/ml)	EC$_{50}$ (μg/ml)
	HIV-1	HIV-2
1. Mimosa tannin	6.0 ± 0.0	>20
2. Mimosa tanin intermediate [100]	5.0 ± 1.4	>20
3. Chestnut tannin	1.4 ± 0.5	>20
4. Tara + Chestnut mix	5.0 ± 1.4	>20
5. Quebracho standard	6.5 ± 0.7	>20
6. Quebracho highly purified	7.5 ± 0.7	>20
7. Quebracho highly sulphited	7.0 ± 1.4	>20
8. Pecan nut tannin	5.0 ± 1.4	>20
9. Cube Gambier	9.0 ± 1.4	>20
10. Radiata pine tannin	7.0 ± 1.4	>20
11. Maritime pine tannin	7.5 ± 0.7	>20
12. Sumach tannin	11.0 ± 1.4	>20
13. Spruce tannin	>100	>100

EC$_{50}$ = effective concentration or concentration required to protect CEM cells against the cytopathogenicity of HIV by 50%

Table 8.5

Cytotoxicity and antiviral activity of compounds in HEL cell cultures, Herpes and vesicular stomatitis viruses. Tannins added prior to virus administration

Cytotoxicity and antiviral activity of compounds in E$_6$SM cell cultures

Compound	Minimum cytotoxic concentration^a (μg/ml)	Minimum inhibitory concentration^b (μg/ml)				
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Vaccinia virus	Vesicular stomatitis virus	Herpes simplex virus^{-1} TK$^-$ KOS ACV^r
1	200	40	16	16	>80	40
2	⩾40	40	16	16	>80	40
3	⩾40	40	16	16	>80	47
4	⩾40	40	48	16	>80	47
5	40	47	36	16	>80	47
6	40	80	36	16	>80	47
7	⩾40	40	40	16	>80	36
8	40	16	16	16	>80	36
9	8	>80	>80	>80	>80	>80
10	40	40	>80	16	>80	40
11	40	>80	>80	80	>80	47
12	40	36	36	16	>80	36
13	40	>16	>16	>16	>16	>16
Brivudin	>400	0.128	400	16	>400	>400
Ribavirin	>400	>400	>400	400	>400	>400
Acyclovir	>400	0.384	0.128	>400	>400	48
Ganciclovir	>100	0.0064	0.0064	100	>100	2.4

[a] Required to cause a microscopically detectable alteration of normal cell morphology.

[b] Required to reduce virus-induced cytopathogenicity by 50%.

Table 8.6

Cytotoxicity and antiviral activity of compounds in HEL cell cultures, vesicular stomatitis, Coxsackie and respiratory syncytial viruses

Cytotoxicity and antiviral activity of compounds in HeLa cell cultures

Compound	Minimum cytotoxic concentration^a (μg/ml)	Minimum inhibitory concentration^b (μ/ml)		
		Vesicular stomatitis virus	Coxsackie virus B4	Respiratory syncytial virus
1	400	>80	>80	12 ± 5
2	400	>80	>80	12 ± 5
3	400	>80	>80	43 ± 4
4	400	43.4 ± 4	>80	35 ± 7
5	400	>80	>80	40 ± 0.2
6	400	>80	>80	40 ± 0.2
7	400	>80	>80	43 ± 5
8	400	>80	>80	9 ± 1
9	400	>80	>80	>80
10	400	>80	>80	40 ± 0.2
11	400	>80	>80	40 ± 0.2
12	80	>16	>16	>16
13	⩾80	>80	>80	>80
Brivudin	>400	>400	>400	>400
(S)-DHPA	>400	400	>400	>400
Ribavirin	>400	48	240	9.4

[a] Required to cause a microscopically detectable alteration of normal cell morphology.

[b] Required to reduce virus-induced cytopathogenicity by 50%.

Table 8.7

Inhibitory effects of tannins on the proliferation of murine leukemia cells (L1210/0), murine mammary carcinoma cells (FM3A) and human T-lymphocyte cells (Molt4/C8, CEM/0)

Compound	IC$_{50}$ (μg/ml)^a			
	L1210/0	FM3A/0	Molt4/C8	CEM/0
1	18 ± 0	153 ± 66	74 ± 18	58 ± 0
2	16 ± 1	148 ± 74	66 ± 27	61 ± 1
3	17 ± 0	141 ± 7	98 ± 22	65 ± 2
4	17 ± 0	114 ± 1	75 ± 57	56 ± 0
5	12 ± 4	76 ± 16	20 ± 1	51 ± 30
6	15 ± 2	79 ± 27	33 ± 21	45 ± 27
7	14 ± 2	82 ± 26	40 ± 27	55 ± 25
8	21 ± 6	⩾200	81 ± 7	66 ± 11
9	13 ± 4	80 ± 22	17 ± 2	18 ± 1
10	65 ± 4	⩾200	65 ± 28	71 ± 9
11	53 ± 23	⩾200	94 ± 1	111 ± 40
12	17 ± 0	18 ± 1	17 ± 0	18 ± 2
13	49 ± 16	>200	145 ± 78	83 ± 20

[a] 50% inhibitory concentration.

Table 8.8

Cytotoxicity and antiviral activity of compounds in HEL cell cultures, influenza viruses. Compounds added prior to virus administration

Cytotoxicity and antiviral activity of compounds in MDCK cell cultures				
Compound	Minimum cytotoxic concentration[a] (μg/ml)	EC$_{50}$		
		Influenza A H1N1	Influenza A H3N2	Influenza B
		MTS	MTS	MTS
1	100	3.3 ± 1.2	1.7 ± 1.3	2.3 ± 1.9
2	100	2.2 ± 0.1	1.7 ± 0.6	2.3 ± 1.5
3	100	4.0 ± 2.8	2.0 ± 0	1.4 ± 0.8
4	33.3	4.1 ± 2.8	2.2 ± 0.8	1.4 ± 0.9
5	100	1.7 ± 0.1	2.1 ± 0.4	3.5 ± 3.2
6	100	5.4 ± 3.8	3.7 ± 1.6	3.6 ± 3.0
7	100	4.4 ± 2.8	1.9 ± 0.4	3.4 ± 3.0
8	33.3	2.1 ± 0.1	3.0 ± 1.5	1.8 ± 1.1
9	100	5.5 ± 4.6	4.4 ± 3.6	2.7 ± 2.6
10	100	4.2 ± 3.1	2.7 ± 1.0	2.7 ± 2.7
11	100	2.9 ± 1.2	2.2 ± 0.3	1.5 ± 1.1
12	20	2.0 ± 1.6	0.9 ± 0.2	2.6 ± 1.9
13	100	9.9 ± 5.7	9.5 ± 4.8	1.9 ± 1.9
Oseltamivir carboxylate (μM)	>100	0.05	0.65	10.65
Ribavirin (μM)	60	4.55	6.32	9.07
Amantadin (μM)	>100	21.39	0.78	>100
Rimantadin (μM)	>100	18.45	0.05	>100

[a] Required to cause a microscopically detectable alteration of normal cell morphology.

Table 8.9

Cytotoxicity and antiviral activity of compounds in HEL cell cultures, Corona viruses

	Feline Corona virus (FIPV)		Human Corona (SARS) virus	
	EC50 (μg/ml)	CC50 (μg/ml)	EC50 (μg/ml)	CC50 (μg/ml)
1	52 ± 19	>100	>100	>100
2	67 ± 47	>100	>100	>100
3	49 ± 17	>100	>100	>100
4	43 ± 2	>100	>100	>100
5	49 ± 10	⩾100	44 ± 10	>100
6	55 ± 19	>100	49 ± 21	>100
7	32 ± 1	>100	40 ± 1	>100
8	72 ± 40	>100	>100	>100
9	⩾100	>100	>100	>100
10	20 ± 21	>100	>100	>100
11	44 ± 5	>100	56 ± 13	>100
12	7.8 ± 8.0	81 ± 13	>100	>100
13	63 ± 32	>100	>100	>100

Table 8.10

Cytotoxicity and antiviral activity of compounds in HEL cell cultures, Herpes and Vaccinia viruses. Tannins added after virus administration

Cytotoxicity and antiviral activity of compounds in HEL cell cultures

Compound	Minimum cytotoxic concentration[a] (μg/ml)	Minimum inhibitory concentration[b] (μg/ml)				
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Vaccinia virus	Vesicular stomatitis virus	Herpes simplex virus^{-1} TK^{-} KOS ACV^{r}
1	200	6 ± 2	1.8 ± 0.2	>40	>40	6 ± 2
2	200	4 ± 0	2 ± 1	8 ± 0	>40	4 ± 0
3	200	15 ± 1	3 ± 1	24 ± 1	>40	17 ± 3
4	200	15 ± 1	8 ± 0	24 ± 1	>40	20 ± 2
5	⩾40	>40	>40	20 ± 2	>40	>40
6	⩾40	>40	8 ± 0	>40	>40	>40
7	⩾40	8 ± 0	>40	20 ± 2	>40	>40
8	40	4 ± 0	4 ± 0	8 ± 0	>8	4 ± 0
9	⩾40	>40	>40	>40	>40	>40
10	40	8 ± 0	4 ± 0	8 ± 0	>8	>8
11	40	>8	8 ± 0	>8	>8	>8
12	40	>8	8 ± 0	>8	>8	>8
13	200	>40	>40	>40	>40	>40
Brivudin (μM)[c]	>250	0.016	10	6	>250	50
Ribavirin (μ)[c]	>250	250	50	30	50	250
Acyclovir (μM)[c]	>250	0.08	0.08	>250	>250	50
Ganciclovir (μM)[c]	>100	0.0064	0.032	>100	>100	12
Compounds added prior to virus administration						

[a] Required to cause a microscopically detectable alteration of normal cell morphology.

[b] Required to reduce virus-induced cytopathogenicity by 50%.

[c] Controls.

Table 8.11

Cytotoxicity and antiviral activity of compounds in Vero cell cultures, influenza viruses

Cytotoxicity and antiviral activity of compounds in Vero cell cultures

Compound	Minimum cytotoxic concentration[a] (μg/ml)	Minimum inhibitory concentration[b] (μg/ml)				
		Para-influenza-3 virus	Reovirus-1	Sindbis virus	Coxsackie virus B4	Punta Toro virus
1	400	>80	>80	>80	>80	>80
2	>400	>400	>400	149.5 ± 24	149.5 ± 24	169.5 ± 13
3	400	>80	>80	>80	>80	>80
4	400	>80	>80	>80	>80	>80
5	400	>80	>80	>80	>80	>80
6	400	>80	>80	>80	>80	>80
7	80	>40	>40	>40	>40	>40
8	80	>40	>40	>40	>40	>40
9	400	>80	>80	>80	>80	>80
10	400	>80	>80	>80	>80	>80
11	400	>80	>80	>80	>80	>80
12	400	>80	>80	80	>80	>80
13	80	>16	>16	>16	>16	>16
Brivudin[c]	>400	>400	>400	>400	>400	>400
(S)-DHPA[c]	>400	>400	>400	>400	>400	>400
Ribavirin[c]	>400	240	80	240	>400	240

[a] Required to cause a microscopically detectable alteration of normal cell morphology.

[b] Required to reduce virus-induced cytopathogenicity by 50%.

[c] Controls.

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