To family, my home.

"The meeting of two personalities is like the contact of two chemical substances: if there is any reaction, both are transformed."

Carl Jung

Swiss psychologist (1875 - 1961)

Acknowledgements

One page is not enough to express all the gratitude to all the people involved who, directly or indirectly, allowed me to grow as a person and to produce this thesis.

First of all I would like to thank Professor Maria Teresa Barros for the patience and knowledge she gave me through my academic life and for the important role she had on my development as a young scientist, letting me take part on one of the most friendly and intellectually stimulating work group I have ever had the pleasure to work with.

To my tutor, Dr. Krasimira Petrova, for her guidance and availability whenever I needed. All the talks and discussions contributed greatly for my development as person and as a good researcher.

To my co-tutor, Dr. Vitor Alves, for his continuous sympathy and patience explaining all the new techniques I needed and that enriched my thesis with new and exciting information.

To my office partner, PhD student Carina Crucho, who became an unexpected and very good friend of mine. Her intelligence and outstanding practical skills gave me a sense of purpose on what to achieve as a scientist and enabled me to greatly improve my laboratory skills.

I thank my close friends,

Personally to Marisa Alves whose intelligence, friendship and infinite patience allowed me to surpass all my personal and scientific frustrations and for all the support she continues to give me. I'm forever grateful.

To Ricardo Cortes, for all the support he gave me during all the work and writing of these thesis and for the friendship we still maintain.

To Diana and Cátia for all the coffees and fun moments we had together throughout our friendship.

To Carlos Farinha and Rui Guerreiro, two of my best friends to whom I apologize my absence sometimes, I thank you for all the insights.

To Francis Solajes, a special thank you.

Last but not least I thank my family,

My grandparents and sister, Adelina, Jaime and Filipa for the outstanding support they gave me through all my life, my parents, José e Ana, although geographically distant, they are really close in my mind and heart. My uncle, António Dias, who's expertise in chemistry and kind support helped me write this thesis and continue to help me grow as a person.

Also to all the people I didn't mention, everyone that crossed my life's path and contributed to my achievements. Thank you all.

Abstract

There has been a worldwide acknowledgement that nature derived saccharides can provide the raw materials needed for the production of numerous industrial consumer goods. As such, sucrose is a low molecular weight renewable carbohydrate feedstock from which it is possible to elaborate new materials, like water-soluble and/or amphiphilic and biocompatible polymers.

In this thesis we will describe some synthetic procedures (both conventional synthesis protocols (CSP) and microwave assisted protocols (MAPs)) by introducing and altering sugar hydroxyl groups, with the intent to produce functionalized polymers for use as biodegradable/biocompatible polymers with sugar linked side chains. The most widely used method for the synthesis of poly(vinyl saccharide)s has been based on free radical polymerizations of vinyl sugars.

In this work, eleven compounds based on sucrose derivatization were synthesized using anhydrides, bromide halides, silyl chlorides, non-selective esterification and Mitsunobu reaction. Optimization and scale-up studies were made on monomer synthesis. Four of these compounds were used as monomers for radical copolymerization with styrene using as catalysts 2,2'-Azobis(2-methylpropionitrile) and sodium persulfate whether organic solvents or water was used as reaction media.

From this copolymerization's, four polymers were obtained and polystyrene was also synthesized to be used as a standard for comparison. The polymers, poly(1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryloyl sucrose)-co-polystyrene, poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene, poly(6-O-methacryloyl sucrose)-co-polystyrene and poly(O-methacryloyl sucrose)-co-polystyrene, were characterized by Proton nuclear magnetic resonance (to assess sucrose vinyl ester/styrene ratio), Fourier transform infrared spectroscopy, Differential scanning calorimetry, Powder X-ray diffraction, Atomic force microscopy (topology studies as thin films and aggregates), Viscometry and polarimetry.

Keywords: derivatized sucrose, biocompatibility, biodegradability, conventional synthesis protocols, microwave assisted protocols, vinyl esters, monomers, copolymers, styrene, viscosity, differential scanning calorimetry, atomic force microscopy

Resumo

Glúcidos provenientes de fontes naturais tem vindo a ser reconhecidos mundialmente como óptimos materiais de partida para a produção industrial de inúmeros bens de consumo. Além disso, a sacarose é um hidrato de carbono de baixo peso molecular e uma matéria-prima renovável a partir da qual é possível produzir novos materiais, como polímeros solúveis em água e/ou anfifílicos e polímeros biocompatíveis.

Nesta tese estão descritos procedimentos sintéticos (procedimentos convencionais (CSP) e síntese assistida por microondas (MAP)) para introduzir grupos funcionais e/ou alterar os grupos hidroxilo existentes, com a intenção de produzir polímeros funcionalizados com com glúcidos nas cadeias laterais, para uso como polímeros biodegradáveis/biocompatíveis. Os métodos mais utilizados para a síntese de poli(vinilsacárido)s são baseados em polímerizações radicalares de açucares vinílicos.

Neste trabalho foram sintetizados onze compostos baseados na sacarose, usando anidridos, haletos de alquilo, cloretos de sililo, esterificação não selectiva e reacção de Mitsunobu. Foram efectuados estudos de optimização e aumento de escala nas sínteses dos monómeros. Quatro destes compostos foram usados como monómeros para copolimerização radicalar com o estireno, usando como catalisadores o 2,2'-Azobis(2-metilpropionitrilo) e persulfato de sódio dependendo se se usou solventes orgânicos ou água como meio reaccional.

Foram obtidos quarto polímeros a partir da copolimerização dos monómeros com o estireno e também se sintetizou o polistireno para ser usado como padrão de comparação nas caracterizações. Os polímeros obtidos, poli(1',2,3,3',4,4',6-hepta-*O*-benzil-6'-*O*-metacriloíl sacarose)-co-polistireno, poli(1',2,3,3',4,4',6'-hepta-*O*-acetil-6-*O*-metacriloil sacarose)-co-polistireno, poli(6-*O*-metacriloil sacarose)-co-polistireno e poli(*O*-metacriloil sacarose)-co-polistirene, foram caracterizados por Ressonância magnética nuclear (para determinar a razão éster vinílico de sacarose/estireno), Espectroscopia de infra-vermelho, Calorimetria diferencial de varrimento, Difracção de raios-x de pós, Microscopia de força atómica (estudos topológicos de filmes e agregados), Viscosimetria e Polarimetria.

Palavras-Chave: sacarose derivatizada, biocompatibilidade, biodegradabilidade, métodos de síntese convencionais, métodos de síntese por microondas, ésteres vinílicos, monómeros, copolímeros, estireno, viscosidade, calorimetria diferencial de varrimento, microscopia de força atómica.

Table of Contents

Abstract v
Resumo vii
Image Index xv
Table Index xx
Abbreviations List xii
Compounds List xxii
Chapter I Introduction 1
I.1 Green Chemistry and Sustainable Development 2
I.1.1 Greenness Analysis 5
I.1.1.1 Biodegradability and Biocompatibility 5
I.1.1.2 Global Material Economy (GME) and Factor *E* 6
I.1.1.3 Ecological Chemical Synthesis 8
I.2 Carbohydrates 10
I.2.1 Monosaccharides and Disaccharides 10
I.2.1.1 Aldoses e Ketoses 11
I.2.1.2 Monosaccharides Have Asymmetric Centers 12
I.2.1.3 Monosaccharides Cyclic Structures 13
I.2.1.4 Glycosidic Bond 18
I.2.2 Sucrose Chemistry 20
I.2.2.1 Functionalization of sucrose hydroxyl groups 20
I.2.2.2 Mitsunobu Reaction for sucrose esterification 21
I.2.2.3 Microwave assisted Protocols (MAPs) 24
I.2 Macromolecules 25
I.3.1 Monomers 25
I.3.2 Polymers 26
I.3.2.1 Methods of Polymer Synthesis 27
I.3.2.1.1 Sucrose containing polymers 31
I.3.2.2 Polymers in solution 32
I.3.2.3 Solvents and Solubility 33
I.3.2.4 Polymers solution viscosity 34
I.3.2.5 Polymers in Drug delivery systems 38
Chapter II Discussion and Results 39
II.1 Preamble 40

II.2 Modified sucrose monomers and polymers – general schemes 41
II.3 Synthesis of modified sucrose monomers 44
II.3.1 Sucrose selective esterification by protection strategies - synthesis of 1',2,3,3',4,4',6 – hepta-*O*-benzyl-6'-*O*-methacryloyl-sucrose (5) 44
II.3.2 Selective esterification by Mitsunobu Reaction - Synthesis of 6-*O*-methacryloyl Sucrose (8) and 6,6'-*O*-methacryloyl sucrose (9) 54
II.3.3 Synthesis of 1',2,3,3',4,4',6' – hepta-*O*-acetyl-6-*O*-metacryloyl sucrose (10) 56
II.3.4 Non-selective esterification - synthesis of *O*-methacryloyl Sucrose (11) 59
II.3.5 Acetylation of non-selective esters - synthesis of acetylated mono-methacryloyl-sucrose (12) 60
II.4 Polymerization reaction of modified sucrose based vinyl esters with styrene – synthesis of polyvinyl saccharides 63
II.4.1 Synthesis of copolymer poly(1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl)-copolystyrene-sucrose (29) 65
II.4.2 Synthesis of copolymer poly(6-*O*-methacryolyl-sucrose)-copolystyrene-sucrose (30) 67
II.4.3 Synthesis of copolymer poly(*O*-methacryloyl-sucrose)-copolystyrene-sucrose (31) 68
II.4.4 Synthesis of copolymer poly(1,2',3,3',4,4',6'-hepta-*O*-acetyl-6-*O* methacryloyl-sucrose)-copolystyrene-sucrose (32) 68
II.4.5 Synthesis of polystyrene (33) 69
II.5 Polymer characterization studies 72
II.5.1Viscosimetry 72
II.5.2 Differential scanning calorimetry (DSC) 73
II.5.3 X-ray diffraction (XRD) 75
II.5.4 Atomic force microscopy (AFM) 77
II.6 Conclusions 79
Chapter III Methods and Materials 80
III.1 Preamble 81
III.1.1 Solvents 82
III.1.1.1 Dimethylformamide (DMF) 82
III.1.1.2 Dichloromethane 82
III.1.1.3 Pyridine (Pyr) 82
III.2 Monomer Synthesis 83
III.2.1 Sucrose 83
III.2.2 Synthesis of 6'-*O*-*tert*-butyldiphenylsylil-sucrose (2) 83
III.2.2.1 Conventional synthesis protocol (CSP) 83

III.2.2.2 Microwave Assisted Protocol (MAP) 84
III.2.3 Synthesis of 6,6'-*O*-di-tertbutyldiphenylsylil-sucrose (6) 84
III.2.3.1 Conventional synthesis protocol (CSP) 85
III.2.3.2 Microwave Assisted Protocol (MAP) 85
III.2.4 Synthesis of 1',2,3,3',4,4',6-hepta-*O*-benzil-6'-*O*-*tert*-butyldiphenylsylil-sucrose (3) 86
III.2.4.1 Conventional synthesis protocol (CSP) 86
III.2.4.2 Microwave assisted protocol (MAP) 86
III.2.5 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6,6'-di-*O*-*tert*-butyldiphenylsylil-sucrose (7) 87
III.2.5.1 Conventional synthesis protocol (CSP) 87
III.2.5.2 Microwave assisted protocol (MAP) 87
III.2.6 Synthesis of 1',2,3,3',4,4',6-hepta-*O*-benzyl-sucrose (4) 88
III.2.6.1 Conventional synthesis protocol (CSP) 88
III.2.6.2 Microwave assisted protocol (MAP) 89
III.2.7 Synthesis of 1',2,3,3',4,4',6–hepta-*O*-benzyl-6'-*O*- methacryloyl -sucrose (5): 89
III.2.7.1 Conventional synthesis protocol (CSP) 89
III.2.8 Synthesis of 6-*O*-metacryloyl sucrose (8) 90
III.2.8.1 Conventional synthesis protocol (CSP) 90
III.2.9 Synthesis of 6,6'-*O*-metacryloyl sucrose (9) 91
III.2.9.1 Conventional synthesis protocol (CSP) 91
III.2.10 Synthesis of monomethacrylated sucrose (*O*-methacryloyl sucrose) (11) 92
III.2.10.1 Conventional synthesis protocol (CSP) in DMF 92
III.2.10.2 Conventional synthesis protocol (CSP) in pyridine 92
III.2.11 Synthesis of 1',2,3,3',4,4',6'–hepta-*O*-acetyl-6-*O*-metacryloyl sucrose (10) 93
III.2.11.1 Conventional synthesis protocol (CSP) 93
III.2.12 Synthesis of Acetylated methacryl sucrose (12) 94
III.2.12.1 Conventional Synthesis Protocol (CSP) 94
III.3 Polymer Synthesis 95
III.3.1 Conventional synthesis protocol (CSP) for poly(1',2,3,3',4,4',6–hepta-*O*-benzyl-6'-*O*-metacryloyl sucrose)-co-polystyrene (29) 95
III.3.2 Conventional synthesis protocol (CSP) for poly(6-*O*-metacryloyl sucrose)-co-polystyrene (30) 96
III.3.2.1 Conventional synthesis protocol (CSP) in DMF 96
III.3.2.2 Conventional synthesis protocol (CSP) in H_2O 96

III.3.3 Conventional synthesis protocol (CSP) for poly(*O*-methacryloyl sucrose)-co-polystyrene (31) 97

III.3.3.1 Conventional synthesis protocol (CSP) in DMF 97

III.3.3.2 Conventional synthesis protocol (CSP) in H_2O 97

III.3.4 Conventional synthesis protocol (CSP) for poly(1',2,3,3',4,4',6'-hepta-*O*-acetyl-6-*O*-methacryloyl sucrose)-co-polystyrene (32) 98

III.3.5 Conventional synthesis protocol (CSP) for polystyrene (33)..... 99

III.3.5.1 Conventional synthesis protocol (CSP) in toluene 99

III.3.5.2 Conventional synthesis protocol (CSP) in H_2O 99

Chapter IV Bibliography 101

List of abbreviations

^{13}C - NMR	Carbon Nuclear Magnetic Ressonance
^{1}H - NMR	Proton Nuclear Magnetic Ressonance
u	Wave number (cm-1)
δ	Chemical shift
t	Relaxation time
AA	Acetic anhydride
Ac	Acetyl
AcOEt	Ethyl acetate
Ar	Aromatic
Bn	Benzyl
c.	Concentration (g/100mL)
CSP	Conventional synthesis protocol
d	duplet
dd	duplet of duplets
DEAD	diethylazodicarboxylate
DIAD	diisopropylazodicarboxylate
DMAP	4-dimethylpyridine
DMF	N,N-dimethylformamide
eq.	equivalents
Et	Ethyl
FC	Flash Chromatography
FTIR	Fourier transform infrared spectroscopy
GC	Green Chemistry
Glc	Glucose
h.	hour(s)
Hex.	Hexane
J	Coupling Constant
m	multiplet (NMR) or medium (FTIR)
Me	Methyl
MA	Methacrylic anhydride
MAP	Microwave Assisted Protocol
min.	minute(s)
MW	Microwave
NMR	Nuclear Magnetic Ressonance
Ph	Phenyl
ppm	parts per million
Pyr	Pyridine

Rf	Retention factor
r.t.	room temperature
s	singlet
t	triplet
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	tert-butyldiphenylsilyl chloride
td	triplet of duplets
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane

Image Index

Figure I 1-Model of green chemistry policy and knowledge areas 4
Figure I 2 Single reaction involving the reactants A (molecular mass, M_A and stoichiometric coefficient v_A) and B (molecular mass, M_B and stoichiometric coefficient v_B) 7
Figure I 3 Biomass chemical composition 9
Figure I 4 Representative monosaccharides (a) Two trioses, an aldose and a ketose. The carbonyl group in each is shaded. (b) Two common hexoses. (c) The pentose components of nucleic acids. D-Ribose is a component of ribonucleic acid (RNA), and 2-deoxy-Dribose is a component of deoxyribonucleic acid (DNA) 12
Figure I 5 Three ways to represent the two stereoisomers of glyceraldehyde. 12
Figure I 6 D-Glucose and two of its epimers are shown as projection formulas. Each epimer differs from D-glucose in the configuration at one chiral center (shaded red). 13
Figure I 7 Formation of hemiacetals and hemiketals. 14
Figure I 8 Example of a furanose conversion in pyranose through hemiacetal formation. 14
Figure I 9 Formation of the two cyclic forms of D-glucose. Reaction between the aldehyde group at C-1 and the hydroxyl group at C-5 forms a hemiacetal linkage, producing either of two stereoisomers, the *α* and *β* anomers, which differ only in the stereochemistry around the hemiacetal carbon. 15
Figure I 10 Pyranoses and furanoses. The pyranose forms of D-glucose and the furanose forms of D-fructose are shown here as Haworth perspective formulas. The edges of the ring nearest the reader are represented by bold lines 16
Figure I 11 Conformational formulas of pyranoses. (a) Two chair forms of the pyranose ring. Substituents on the ring carbons may be either axial (ax), projecting parallel to the vertical axis through the ring, or equatorial (eq), projecting roughly perpendicular to this axis. (b) A chair conformation of *α*-D-glucopyranose 17
Figure I 12 Formation of maltose. A disaccharide is formed from two monosaccharides (here, two molecules of D-glucose) when an -OH (alcohol) of one glucose molecule (right) condenses with the intramolecular hemiacetal of the other glucose molecule (left), with elimination of H_2O and formation of an *O*-glycosidic bond. The reversal of this reaction is hydrolysis—attack by H_2O on the glycosidic bond. 18
Figure I 13 Sucrose and Lactose, two of the most common disaccharides 19
Figure I 14 Sucrose structure showing primary hydroxyl groups (blue) in the positions 1',6 and 6' and secondary hydroxyl groups (purple) in the positions 1, 2, 3, 3', 4 and 4' 20
Figure I 15 TBDPS-OR, TBDPS ether protection group 21
Figure I 16 BnOR, Benzyl ether protection group 21
Figure I 17 Ac-OR, Acetic acid esters, Acetate esters, Acetates 21
Figure I 18 General reaction scheme for esterification and amination using the Mitsunobu reaction 22
Figure I 19 Mechanism for the Mitsunobu reaction 22

Figure I 20 Side reaction that can happen under Mitsunobu conditions 23
Figure I 21 General reaction scheme for the Appel reaction 23
Figure I 22 Mechanism for the Appel reaction 23
Figure I 23 Image of the microwave apparatus used by Barros and team. 24
Figure I 24 Sucrose functionalization with MAPs 25
Figure I 25 Structure and mechanism of an azo radical polymerization initiator - AIBN 28
Figure I 26 Structure and mechanism of an organic peroxo radical polymerization initiator – Sodium peroxodisulfate 29
Figure I 27 Structures of some selectively obtained sucrose monomers 32
Figure I 28 Classification of the solvent on the ability to dissolve a polymer: good, theta or poor. 33
Figure I 29 Hydrostatic head ('U' tube) viscometers: (a) Ostwald; (b) Ubbelohde; and (c) reverse flow 37
Figure I 30 Types of conjugate polymer based drug delivery structures 38
Figure II 1 Sucrose selective derivatization using anhydrides, bromide halides and silyl chlorides and radical copolymerization with styrene 41
Figure II 2 Sucrose selective derivatization by Mitsunobu reaction and radical copolymerization with styrene 42
Figure II 3 Sucrose non-selective derivatization using anhydrides and radical copolymerization with styrene 43
Figure II 4 Synthetic scheme for selective esterification of sucrose based on protection strategies: i) TBDPSCl, pyridine, 4-DMAP, (CSP – r. t.; MAP – 100 ºC); ii) BnBr, DMF, NaH, (CSP – r. t.; MAP – 150 ºC); iii) TBAF, THF, CSP – r. t.; MAP – 65 ºC).; iv) AM, CH_2Cl_2, Et_3N, 4-DMAP, r.t. 44
Figure II 5 Mechanism for 4-DMAP action on silylation catalysis 45
Figure II 6 Mechanism for the protection of sucrose hydroxyl OH-6' with TBDPS 45
Figure II 7 Scheme of the byproduct that are formed when using protection/deprotection strategies in sucrose selective esterification: i) TBDPSCl, pyridine, 4-DMAP, (CSP – r. t.; MAP – 100 ºC); ii) BnBr, DMF, NaH, (CSP – r. t.; MAP – 150 ºC) 47
Figure II 8 Mechanism for the protection of 6'-*O*-*tert*-butyldiphenylsylil-sucrose (2) free hydroxyls with benzyl groups,, synthesizing 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-TBDPS-sucrose (3)..... 49
Figure II 9 Example of a TLC obtained for reaction in section II.3.1: a) octabenzylated sucrose b) 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-TBDPS-sucrose (3) with R_f=0.54 and c) 1',2,3,3',4,4',-hexa-*O*-benzyl-6,6'-*O*-diTBDPS-sucrose (7) - elution with hexane-diethyl ether, 3:1 50
Figure II 10 Mechanism for the removal of TBDPS from 1',2,3,3',4,4',6-hepta-*O*-benzyl-sucrose (4) with a fluoride source, TBAF 51
Figure II 11 Mechanism for the formation of a selective vinyl ester on the 6-OH position..... 52
Figure II 12 Synthetic scheme for selective esterification of sucrose by mitsunobu reaction to produce 6-*O*-methacryloyl-sucrose (8): v) Ph_3P, DMF, DIAD, methacrylic acid, r.t., 72 h (CSP)54

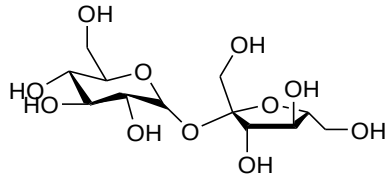
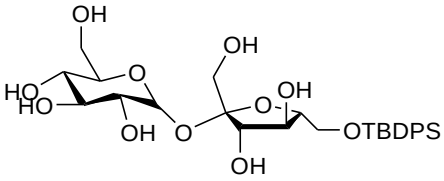
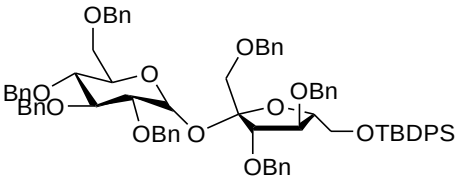
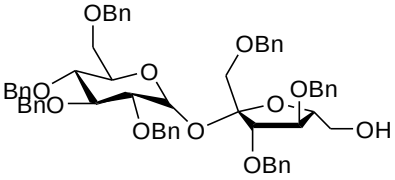
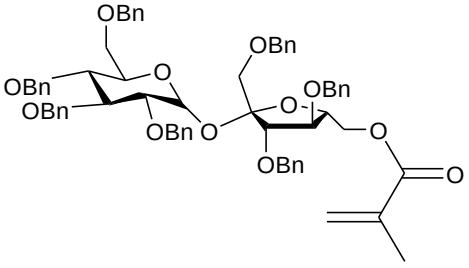
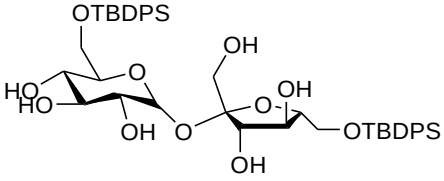
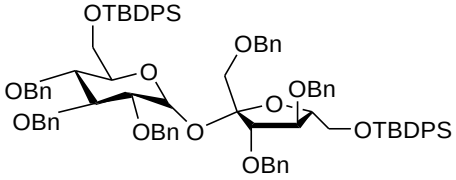
Figure II 13 Synthetic scheme for selective esterification of sucrose by mitsunobu reaction to produce 6,6'-*O*-methacryloyl sucrose (8): v) Ph_3P, DMF, DIAD, methacrylic acid, r.t., 72 h (CSP) 54
Figure II 14 Selective esterification mechanism in Mitsunobu conditions to synthesize 6-*O*-methacryloyl-sucrose (8) 55
Figure II 15 Synthetic scheme for selective esterification of sucrose to produce 1',2,3,3',4,4',6' – hepta-*O*-acetyl-6-*O*-metacryloyl sucrose (10): v) Ph_3P, DMF, DIAD, methacrylic acid, r.t., 72 h; vi) Pyridine, Acetic Anhydride, 4-DMAP, 24h 56
Figure II 16 Mechanism for the acetylation of the alcohol groups in sucrose using 4-DMAP as an acyl transfer catalyst synthesis of 1',2,3,3',4,4',6' – hepta-*O*-acetyl-6-*O*-metacryloyl sucrose (10) 57
Figure II 17 Synthetic scheme for non-selective esterification of sucrose to produce *O*-methacryloyl Sucrose (10): vii) Pyridine, Et_3N, 4-DMAP, methacrylic anhydride, r.t., 24h 59
Figure II 18 Synthetic scheme for the acetylation of the non-selective ester of sucrose (11) to produce acetylated mono-methacryloyl sucrose (12): viii) Pyridine, 4-DMAP, acetic anhydride, r.t., 24h 60
Figure II 19 Oxidation structures of hydroquinone: a) benzoquinone; b)semiquinone; c) hydroquinone 62
Figure II 20 Mechanism for thermal decomposition of polymerization radical initiators AIBN (26) and sodium persulfate (28) 63
Figure II 21 Mechanism for the formation of a prepolymer, a radical template that starts a polymerization process 63
Figure II 22 Mechanism for the propagation of the radical copolymerization with modified sucrose based vinyl esters with styrene (27) 64
Figure II 23 Reaction of peroxy radicals with a general hydrocarbon 64
Figure II 24 Influence of radical peroxides in a polymer chain growth 65
Figure II 25 Synthetic scheme for the radical copolymerization of 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl sucrose (5) with styrene (27) to produce poly(1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl sucrose)-co-polystyrene (29): ix) Toluene, AIBN (1%w/w), styrene, 85 ºC, 48h 65
Figure II 26 ^{1}H-NMR spectra for poly(1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl sucrose)-co-polystyrene (29) as an example for the determination of sucrose vinyl ester/styrene ratio. .. 66
Figure II 27 Synthetic scheme for the radical copolymerization of 6-*O*-methacryolyl-sucrose (8) with styrene (27) to produce poly(6-*O*-methacryolyl sucrose)-co-polystyrene (30): x) a - DMF, AIBN (1%w/w), styrene, 85 ºC, 24h.; b – H_2O, $Na_2S_2O_8$ (1%w/w), 85 ºC, 24h 67
Figure II 28 Synthetic scheme for the radical copolymerization of *O*-methacryloyl-sucrose (11) with styrene (27) to produce poly(*O*-methacryloyl sucrose)-co-polystyrene (31): xi) a - DMF, AIBN (1%w/w), styrene, 85 ºC, 24h.; b – H_2O, $Na_2S_2O_8$ (1%w/w), 85 ºC, 24h. 68
Figure II 29 Synthetic scheme for the radical copolymerization of 1',2,3,3',4,4',6'-hepta-*O*-acetyl--6-*O*-methacryloyl-sucrose (10) with styrene (27) to produce poly(1',2,3,3',4,4',6'-hepta-*O*-

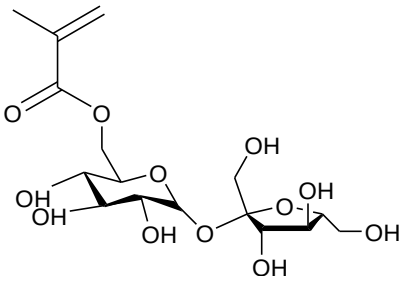
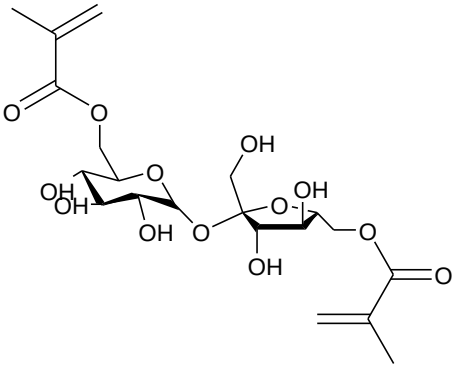
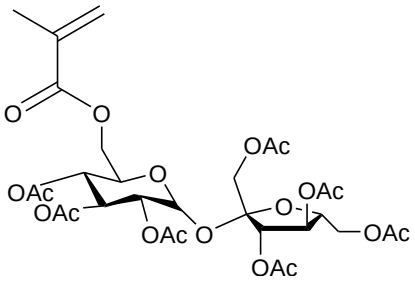
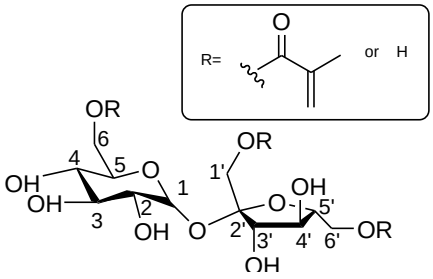
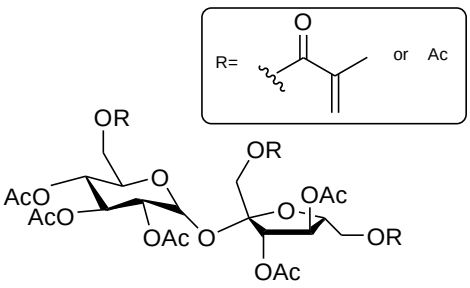
acetyl--6-*O*-methacryloyl sucrose)-co-polystyrene (32): xii) Toluene, AIBN (1%w/w), styrene, 85 ºC, 48h 68
Figure II 30 Synthetic scheme for the radical polymerization of styrene (27) to produce polystyrene (33): xiii) a - Toluene, AIBN (1%w/w), styrene, 70 ºC, 48h.; b – H_2O-Acetone (3:1), $Na_2S_2O_8$ (1%w/w), styrene, 70 ºC, 48h 69
Figure II 31 DSC thermogram of polystyrene (33). Method: 25 ºC – 300 ºC, 10 ºC/min 73
Figure II 32 DSC thermogram of poly(O-methacryloyl sucrose)-co-polystyrene (31). Method: 25 ºC – 300 ºC, 10 ºC/min 74
Figure II 33 DSC thermogram of poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32) 74
Figure II 34 XRD diffractogram of polystyrene (33). Scan mode: continuous; scan speed: 1.000 deg/min; sampling width: 0.020 deg; scan range: 5.000 to 70.000 deg 75
Figure II 35 XRD diffractogram of poly(*O*-methacryloyl sucrose)-co-polystyrene (31). Scan mode: continuous; scan speed: 1.000 deg/min; sampling width: 0.020 deg; scan range: 5.000 to 70.000 deg 76
Figure II 36 XRD diffractogram of poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32). Scan mode: continuous; scan speed: 1.000 deg/min; sampling width: 0.020 deg; scan range: 5.000 to 70.000 deg 76
Figure II 37 AFM topological images of poly(*O*-methacryloyl sucrose)-co-polystyrene (31). Solution 1 mg/mL (MeOH-$CHCl_3$, 1:3) coating. (a) top image; (b) 3D image 77
Figure II 38 AFM topological images of poly(*O*-methacryloyl sucrose)-co-polystyrene (31). Solution 0.25 mg/mL (MeOH-$CHCl_3$, 2:1) coating. (a) top image; (b) 3D image 78
Figure II 39 AFM topological images of poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32), 1 mg/ml ($CHCl_3$) coating. (a) top image; (b) 3D image 78

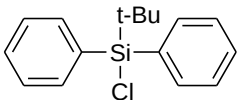
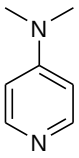
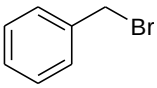
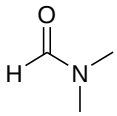
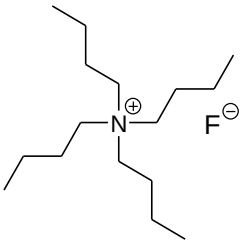
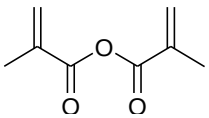
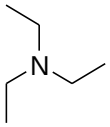
Table Index

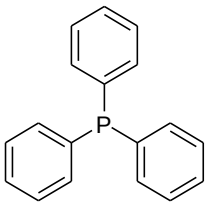
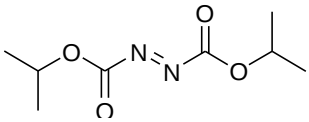
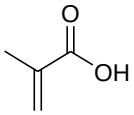
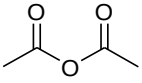
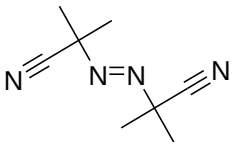
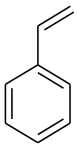
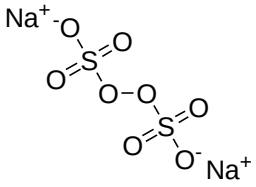
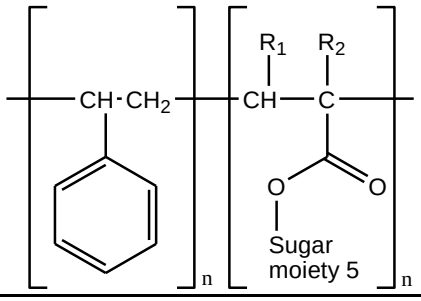
Table I 1 Values of Reaction Parameters in Typical Polymerizations..... 30
Table II 1 Reaction and Spectra characteristics for the byproducts 6 and 7 46
Table II 2 Reaction and Spectra characteristics for the products 6'-O-TBDPS-sucrose (2) and 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-TBDPS-sucrose (3) 48
Table II 3 Reaction and Spectra characteristics of and 1',2,3,3',4,4',6 – hepta-*O*-benzyl-6'-*O*-methacryloyl-sucrose 53
Table II 4 Reaction and Spectra characteristics for the mitsunobu ester obtained using sucrose as substrate, 6-O-methacryloyl sucrose (8) and 6,6'-O-methacryloyl sucrose (9)..... 58
Table II 5 Reaction and Spectra characteristics for the non-selective esters obtained using sucrose as substrate, *O*-methacryloyl sucrose (11) and acetylated monomethacrylated sucrose (12) 61
Table II 6 Monomers and polymers synthesized and their physical characteristics – Viscosity, specific rotation and (modified sucrose vinyl ester)/styrene ratio 70

List of compounds

1		Sucrose
2		6'-*O*-*tert*-butyldiphenylsylil-sucrose
3		1',2,3,3',4,4',6-hepta-*O*-benzil-6'-*O*-*tert*-butyldiphenylsylil-sucrose
4		1',2,3,3',4,4',6-hepta-*O*-benzyl-sucrose
5		1',2,3,3',4,4',6–hepta-*O*-benzyl-6'-*O*-methacryloyl -sucrose
6		6,6'-*O*-di-tertbutyldiphenylsylil-sucrose
7		1',2,3,3',4,4'-hexa-*O*-benzyl-6,6'-di-*O*-*tert*-butyldiphenylsylil-sucrose

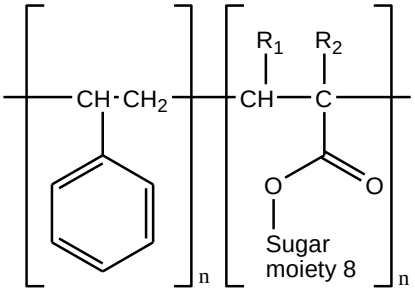
8		6-*O*-methacryloyl sucrose
9		6,6'-*O*-methacryloyl sucrose
10		1',2,3,3',4,4',6'–hepta-*O*-acetyl-6-*O*-methacryloyl sucrose
11		monomethacrylated sucrose (*O*-methacryloyl sucrose)
12		Acetylated monomethacrylated sucrose

13		*tert*-butyldiphenylsilyl chloride
14		Pyridine
15		4-(Dimethylamino)pyridine
16		Benzyl bromide
17		*N,N*-Dimethylformamide
18		Tetrabutylammonium fluoride
19		Tetrahydrofuran
20		Methacrylic anhydride
21		Triethylamine

22		Triphenylphosphine
23		Diisopropyl azodicarboxylate
24		Methacrylic acid
25		Acetic anhydride
26		2,2'-Azobis(2-methylpropionitrile)
27		Styrene
28		Sodium persulfate
29	R_1=CH_3, R_2=H 	poly(1',2,3,3',4,4',6–hepta-*O*-benzyl-6'-*O*-metacryloyl sucrose)-co-polystyrene

R_1=CH_3, R_2=H

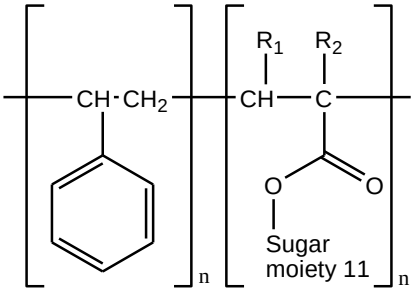
30



poly(6-*O*-metacryloyl sucrose)-co-polystyrene

R_1=CH_3, R_2=H

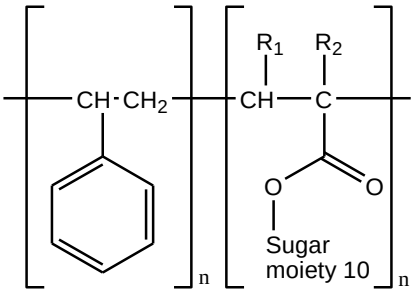
31



poly(*O*-methacryloyl sucrose)-co-polystyrene

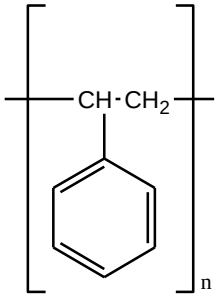
R_1=CH_3, R_2=H

32



poly(1',2,3,3',4,4',6'-hepta-*O*-acetyl-6-*O*-methacryloyl sucrose)-co-polystyrene

33



polystyrene

Chapter I Introduction

I.1 Green Chemistry and Sustainable development

"As crude a weapon as the cave man's club, the chemical barrage has been hurled against the fabric of life - a fabric on the one hand delicate and destructible, on the other miraculously tough and resilient, and capable of striking back in unexpected ways. These extraordinary capacities of life have been ignored by the practitioners of chemical control who have brought to their task no "high-minded orientation," no humility before the vast forces with which they tamper."

Rachel Carson in

Silent Spring, 1962

The publication of Rachel Carson's- *Silent Spring* was one of the roots of the current preoccupation with Green Chemistry and Sustainability and this public concern can be traced back to the environmental movement of the 1960s and 1970s. The environmental movement did not have a broad industrial or social impact however, probably because emphasis was placed largely on the environmental problems than devising technological solutions. The prevailing opinion was that chemistry was the problem rather than the solution.

Attention on the negative side effects of a multitude of chemical products on our natural environment became of the utmost importance and the solution is clearly not any chemistry but new and better chemistry, which is cleaner, greener chemistry.

Henceforth, nowadays we can define green chemistry and sustainable development as follows: *'Green chemistry efficiently utilizes (preferably renewable) raw material, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products, promoting development that meets the needs of the present generations without compromising the ability of future generations to meet their own needs'.*[1]

Later on in the 1990s, Paul Anastas and John C. Warner of the United States Environmental Protection Agency (EPA) developed twelve principles of green chemistry, which determine officially the definition of green chemistry in practice as the:

i) design of processes to maximize the amount of raw material that ends up in the product;

ii) use of safe, environment-benign substances, including solvents, whenever possible;

iii) design of energy efficient processes;

iv) best form of waste disposal: not to create it in the first place.

And the twelve principles are:

1st) It is better to prevent waste than to treat or clean up waste after it is formed.

2nd) Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3rd) Synthetic methodologies (wherever practical) should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4th) Chemical products should be designed to preserve efficacy of function while reducing toxicity.

5th) The use of auxiliary substances (e.g. solvents, separation agents) should be made unnecessary wherever possible and innocuous when used.

6th) Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

7th) A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.

8th) Reduce derivatives - Unnecessary derivatization (blocking group, protection/deprotection, and temporary modification) should be avoided whenever possible.

9th) Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10th) Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

11th) Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12th) Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.[2]

To get a mental image of the connection between different policy/knowledge areas related to green chemistry, Jesper Sjöström from *Research Policy Institute, Lund University* have developed a model[3], Figure I-1. It consists of the three partly overlapping parts: (1) "*the green sector*" (agriculture and forestry), (2) *industrial biotechnology* (biotechnology) and (3) *green chemistry principles* (chemistry).

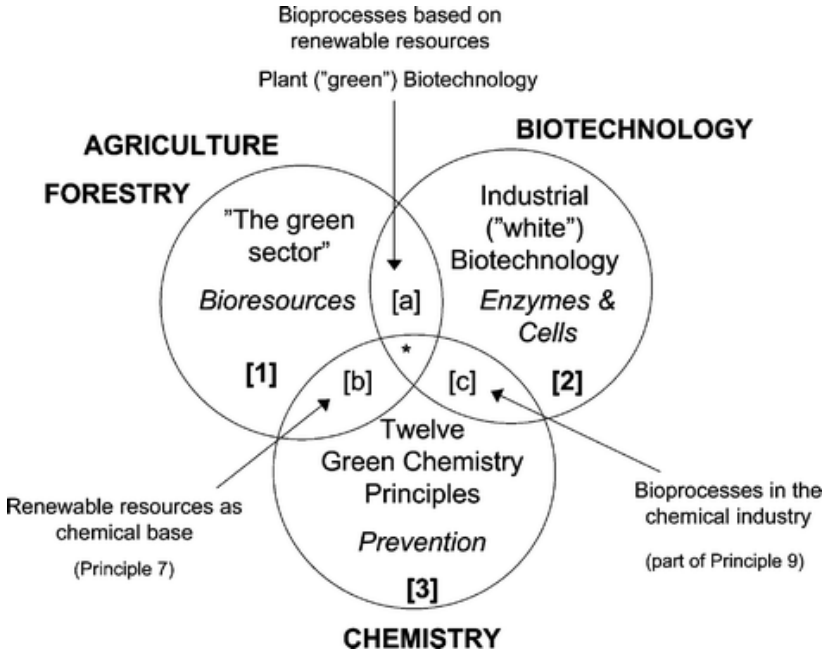


FIGURE I 31 Model of green chemistry policy and knowledge areas

This way, the twelve principles of green chemistry can be seen as the knowledge "marriage" between chemical practice and industrial ecology. Much of the activities in the early green chemistry movement were founded on principles for eco-improvements of chemical reactions. However, industrial ecology deals with eco-principles on an industrial level and with management and assessments. Examples of industrial ecology activities are cleaner production, interlinking of material flows and recycling, services instead of products, eco technology (*e.g.* green engineering[1]), life-cycle assessments, risk assessments[2], environmental management and cleaner products.

[1] Green engineering is defined by the Green Chemistry Institute as "The design, commercialization, and use of processes and products that are feasible and economical while minimizing the generation of pollution at the source and the risk to human health and the environment"

[2] Life-cycle assessment (LCA) is defined by the Green Chemistry Institute as "An objective process to evaluate the environmental burdens associated with a product, process, or activity by identifying energy and materials used and wastes released to the environment; used to evaluate and implement opportunities for environmental improvements".

I.1.1 Greenness Analysis

I.1.1.1 Biodegradability and Biocompatibility

Throughout this thesis we will follow a line of thought using chemical synthesis wherein two important characteristics are always present, biodegradability and biocompatibility. The main idea is that using raw material from renewable sources we can base our action on the characteristic structural features of the natural source. It is important to dispel from start the erroneous one-to-one association of biodegradability and biocompatibility of a polymer synthesized with raw materials from renewable sources, which is incorrect, although this is often the case, polymers with fossil origin can be biodegradable. It is equally wrong to assume that a material based on natural sources should be defined as *green*, since its origin does not necessarily imply a synthetic procedure involving green chemistry procedures[4].

On the other hand, the most important factor that distinguishes a biomaterial from any other material is its ability to exist in contact with tissues of the human body without causing unacceptable degree of harm to that body. It has become clear that there are very many different ways in which materials and tissues interact such that this co-existence may be compromised, and the search for biomaterials that are able to provide for the best performance in devices has been based on the acquisition of knowledge and understanding about these interactions[5].

In the literature there is evidence that compounds from *green* sources and/or not involving green chemistry procedures can be biodegradable/biocompatible, as polymers produced from raw materials from renewable sources can be non-biodegradable/biocompatible.

Bearing in mind these considerations, biodegradability and biocompatibility can be defined as:

Biodegradability: breakdown of a substance catalyzed by enzymes in vitro or in vivo. This may be characterized for purpose of hazard assessment as:

1. Primary: Alteration of the chemical structure of a substance resulting in loss of a specific property of that substance.
2. Environmentally acceptable: Biodegradation to such an extent as to remove undesirable properties of the compound. This often corresponds to primary biodegradation but it depends on the circumstances under which the products are discharged into the environment.
3. Ultimate: Complete breakdown of a compound to either fully oxidized or reduced simple molecules (such as carbon dioxide/methane, nitrate/ammonium, and water). It should be noted that the products of biodegradation can be more harmful than the substance degraded[6].

Biocompatibility (and biomaterials): it is an expression of the benignity of the relation between a material and its biological environment. Some would extend that definition to include adequate functionality in a given biological context[7]. To be more precise, *'Biocompatibility refers to the ability of a material to perform with an appropriate host response in a specific situation'*[8].

I.1.1.2 Global Material Economy (GME) and Factor *E*

After the official definition of green chemistry and the establishment of its twelve rules, the world was in need of a scientific tool to evaluate the greenness of a product – Green Chemistry parameters (GC). This evaluation is considered to be a social, economic and scientific challenge in chemistry. Augé and Scherrmann published a paper proposing a new paradigm to determine the global material economy of a whole sequence of reactions. They have demonstrated mathematically that this key metric is directly proportional to the global atom economy of the corresponding total synthesis and that it can be applied to any process.

Since the publication of their paper[9], a mathematical algorithm to calculate the GME, whatever the number of points of convergence in the synthesis allowing the determination in mass of the greenness of a product with respect to all the starting materials involved in the total synthesis. For this thesis we used the algorithm for a linear reaction sequence which is an easy and accurate method for GME determination.

Although the atom economy is useful to choose a synthetic pathway, it is not sufficient to have a correct evaluation of the material economy of the reaction - the formation of the product requires not only the use of reactants, but also other materials such as solvents, catalysts, acids and bases used in the work-up - so we choose to use the reaction mass efficiency (RME) defined by the percentage of the mass of the reactants that remains in the product:

$$RME = \frac{mass\ of\ product}{mass\ of\ reactants} \quad (1)$$

To fulfill our need to include all other reagents as referred earlier, mass intensity (or mass index), MI, and the Sheldon *E*-factor, allow a better evaluation of material economy:

$$MI = \frac{total\ mass\ used\ in\ the\ process}{mass\ of\ product} \quad (2)$$

$$E = \frac{total\ mass\ of\ waste}{mass\ of\ product} \quad (3)$$

By waste we define all the by-products, non-reacting start material, auxiliaries, catalysts and any additives (acid, bases, salts and solvents in the reaction and work-up – extraction, washing, separation, recrystallization, chromatography support if not recycled, etc…).

$$MI = E + 1 \quad (4)$$

As we said, we apply these formulas to a linear reaction sequence (Figure I 2):

$$\nu_A A + \nu_B B \xrightarrow{\text{auxiliaries}} \nu_P P$$

FIGURE I 32 Single reaction involving the reactants **A** (molecular mass, M_A and stoichiometric coefficient ν_A) and **B** (molecular mass, M_B and stoichiometric coefficient ν_B)

This linear reaction synthesis can be characterized by atom economy (AE), yield (ε), excess of B with respect to A (b), the mass of auxiliaries (S) and the stoichiometric ratio (φ) where the ratio of molar amounts of the two reagents is defined as follows(x, y are the number of moles of reactants A and B, respectively):

$$\varphi = \frac{\frac{x}{\nu_B}}{\frac{y}{\nu_A}} \quad (5)$$

And where,

$$b = \frac{(\varphi - 1)\nu_B M_B}{\nu_A M_A + \nu_B M_A} = \frac{mass\ of\ the\ excess\ of\ B}{mass\ of\ reactants\ in\ stoichimetric\ amount} \quad (6)$$

And,

$$s = \frac{S}{\frac{x}{\nu_A}(\nu_A M_A + \nu_B M_A)} = \frac{mass\ of\ the\ auxiliaries}{mass\ of\ reactants\ in\ stoichimetric\ amount} \quad (7)$$

We will include (6) and (7) in the Mass Index:

$$MI = \frac{1 + b + s}{\varepsilon AE} \quad (8)$$

When dealing with a total synthesis of a product P we define the Global Atomic Economy (GAE), that is, the maximum mass of product which can be obtained from the mass of reactants used.

$$GAE = \frac{\nu_P M_P}{\sum \nu_i M_i} \quad (9)$$

And the Global Mass Economy (GME):

$$GME = \frac{mass\ of\ product\ P}{total\ mass\ used\ in\ total\ synthesis} = \frac{1}{MI} \quad (10)$$

Using these two parameters, we can predict that GME<GAE, and this conception is an indicator of greenness and is defined as the inverse of the mass index.

I.1.1.3 Ecological Chemical Synthesis

Since the publication of Rachel Carson's, *Silent Spring* in 1962, about half a century ago, many changes have occurred in the world's mentality. Particularly, people are more aware of their influence in the environment and developed a consciousness about the negative impact human activities can have to other beings living on Earth.

All the procedures created to develop a *greener* society are well spread around the world and can be easily represented by many activities we do nowadays. Probably the most notorious changes that occurred were in science research and we can find many advantages on the use of starting materials from renewable stocks when compared to the use of petrochemicals:

a) A huge array of diverse materials, frequently stereochemically and enantiomerically defined, is available from biomass giving the user many new structural features to exploit.
b) Many products of the chemical industry are oxygenated. There are few general ways to add oxygen to crude oil derived hydrocarbons, and many of them require the use of toxic reagents in stoichiometric amounts resulting in severe waste disposal problems. Biomass is already highly oxygenated, and could be used to avoid problems with oxidation[10].
c) Increased use of biomass would extend the lifetime of diminishing crude oil supplies. The use of biomass could be a way to mitigate the buildup of CO_2 in the atmosphere because the use of biomass as a feedstock results in no net increase in atmospheric CO_2 content[1112].
d) A chemicals industry incorporating a significant percentage of renewable materials is secure because the feedstock supplies are domestic. Biomass is a more flexible feedstock than is crude oil[13]. Crude oil is formed and its composition set by geological forces. With the advent of genetic engineering, the tailoring of certain plants to produce high levels of specific chemicals is possible.

The chemical composition of biomass varies among species, but plants consist of about 25% lignin and 75% carbohydrates or sugars. The carbohydrate fraction consists of many sugar molecules linked together in long chains or polymers. Two larger carbohydrate categories that have significant value are cellulose and hemicellulose. The lignin fraction consists of non-sugar type molecules (Figure I 3).

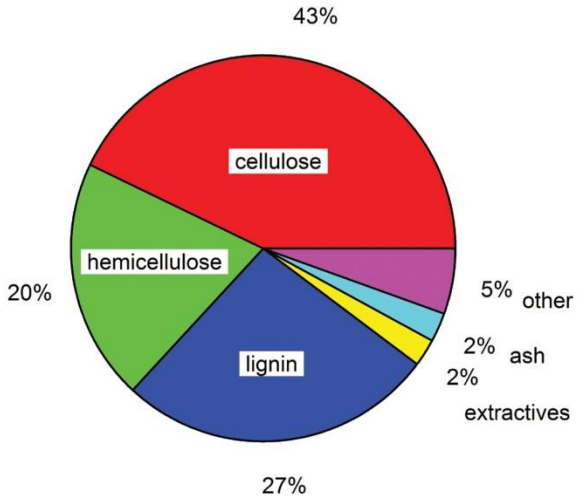


FIGURE I 33 Biomass chemical composition

However, several disadvantages have also been described[14]:

a) Existing economic circumstances are an important issue because renewable feedstocks based industry must be compared to the existing petrochemical industry as the products from both serve the same marketplace.
b) The petrochemical industry is huge and highly efficient in all stages of operation. The mechanisms and operation of its processes are well understood and give single products of high purity. The biomass industry is still developing processes that possess these features.
c) Many of the biomass sources being considered as chemical feedstocks have traditionally been used as sources of food. The justification for diverting part of this resource to chemical production has been questioned. Biomass also requires space to grow, and the environmental impact of large scale biomass plantations has been examined.
d) Biomass is necessarily seasonal, leading to peaks and valleys in the supply of feedstock. The chemical producer using biomass needs a regular day to day supply, and must be assured that the material used at the beginning of the year will be the same quality as that used at the end of the year.
e) The wide range of materials that comprise biomass could be a detriment if new processes need to be developed for each feedstock. The building blocks extracted from biomass are foreign to traditional chemical producers and must be demonstrated to function similarly to existing building blocks.

These transformations of lignin, cellulose, and hemicellulose demonstrate how renewables can be used as starting templates for chemical synthesis. In considering ways to increase the use of renewables for production of chemicals, new techniques in organic synthesis, environmentally friendly processing, and catalysis, will be of great importance.

Combining the use of renewable materials as sources of chemical feedstocks with new technology will lead to processes as efficient as those currently used for the conversion of petrochemicals.

I.2 Carbohydrates

One of the most important classes of molecules we can encounter in a living system is the so-called carbohydrates commonly named sugars. From primordial times, when the first organic substances were being naturally synthesized, sugars were one of the first molecules to appear by polymerization of formaldehyde (CH_2O) in reactions catalyzed by divalent cations, alumina, or clays. These compounds are the basic components of biological molecules because of their abundance as organic substances in prebiotic times[15].

Certain carbohydrates (sugar and starch) are a dietary staple in most parts of the world, and the oxidation of carbohydrates is the central energy-yielding pathway in most non photosynthetic cells.

Insoluble carbohydrate polymers can be naturally or synthetically used: they serve as structural and protective elements in the cell walls of bacteria and plants and in the connective tissues of animals. Other carbohydrate polymers lubricate skeletal joints and participate in recognition and adhesion between cells. More complex carbohydrate polymers covalently attached to proteins or lipids act as signals that determine the intracellular location or metabolic fate of these hybrid molecules, called **glycoconjugates.**

This is arguably the most important family of renewable resources in terms of its vast potential to provide directly a remarkable variety of macromolecular materials[16].

I.2.1 Monosaccharides and Disaccharides

Carbohydrates are polyhydroxy aldehydes or ketones, or substances that yield such compounds on hydrolysis. Many, but not all, carbohydrates have the empirical formula $(CH_2O)_n$; some also contain nitrogen, phosphorus, or sulfur. There are three major size classes of carbohydrates: monosaccharides, oligosaccharides, and polysaccharides (the word “saccharide” is derived from the Greek *sakcharon,* meaning “sugar”).

Monosaccharides, the simplest of the carbohydrates, consist of a single polyhydroxy aldehyde or ketone unit, with two or more hydroxyl groups; the six-carbon monosaccharides glucose and fructose have five hydroxyl groups. Many of the carbon atoms to which hydroxyl groups are attached are chiral centers, which give rise to the many sugar stereoisomers found in nature. The most abundant monosaccharide in nature is the six-carbon sugar D-glucose, sometimes referred to as dextrose. Monosaccharides of more than four carbons often switch from the acyclic (open-chain) form to a cyclic form (Anomers), through a nucleophilic addition reaction between the carbonyl group and one of the hydroxyls of the same molecule. The

reaction creates a ring of carbon atoms closed by one bridging oxygen atom. The resulting molecule has a hemiacetal or hemiketal group, depending on whether the linear form was an aldose or a ketose. The reaction is easily reversed, yielding the original open-chain form[17].

Oligosaccharides consist of short chains of monosaccharide units, or residues, joined by characteristic linkages called glycosidic bonds. The most abundant are the **disaccharides,** with two monosaccharide units.

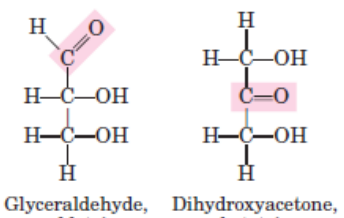
Typical is sucrose (cane sugar), which consists of the six-carbon sugars D-glucose and D-fructose. All common monosaccharides and disaccharides have names ending with the suffix "-ose." In cells, most oligosaccharides consisting of three or more units do not occur as free entities but are joined to nonsugar molecules (lipids or proteins) in glycoconjugates.

The **polysaccharides** are sugar polymers containing more than 20 or so monosaccharide units, and some have hundreds or thousands of units. Some polysaccharides, such as cellulose, are linear chains; others, such as glycogen, are branched. Both glycogen and cellulose consist of recurring units of D-glucose, but they differ in the type of glycosidic linkage and consequently have strikingly different properties and biological roles[18].

I.2.1.1 Aldoses and Ketoses

Monosaccharides are colorless, crystalline solids that are freely soluble in water but insoluble in non-polar solvents. Most have a sweet taste. The backbones of common monosaccharide molecules are unbranched carbon chains in which all the carbon atoms are linked by single bonds. In the open-chain form, one of the carbon atoms is double-bonded to an oxygen atom to form a carbonyl group; each of the other carbon atoms has a hydroxyl group. If the carbonyl group is at an end of the carbon chain (that is, in an aldehyde group) the monosaccharide is an **aldose;** if the carbonyl group is at any other position (in a ketone group) the monosaccharide is a **ketose.** The simplest monosaccharides are the two three-carbon trioses: glyceraldehyde, an aldotriose, and dihydroxyacetone, a ketotriose (Figure I 4a).

Monosaccharides with four, five, six, and seven carbon atoms in their backbones are called, respectively, tetroses, pentoses, hexoses, and heptoses. There are aldoses and ketoses of each of these chain lengths: aldotetroses and ketotetroses, aldopentoses and ketopentoses, and so on. The hexoses, which include the aldohexose D-glucose and the ketohexose D-fructose (Figure I 4b),are the most common monosaccharides in nature. The aldopentoses D-ribose and 2-deoxy-D-ribose (Figure I 4c) are components of nucleotides and nucleic acids.



(a)

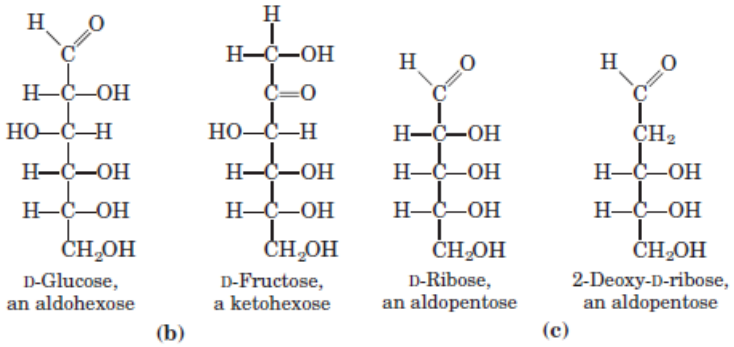


FIGURE I 34 Representative monosaccharides (a) Two trioses, an aldose and a ketose. The carbonyl group in each is shaded. **(b)** Two common hexoses. **(c)** The pentose components of nucleic acids. D-Ribose is a component of ribonucleic acid (RNA), and 2-deoxy-Dribose is a component of deoxyribonucleic acid (DNA).

I.2.1.2 Monosaccharides Have Asymmetric Centers

All the monosaccharides except dihydroxyacetone contain one or more asymmetric (chiral) carbon atoms and thus occur in optically active isomeric forms. The simplest aldose, glyceraldehyde, contains one chiral center (the middle carbon atom) and therefore has two different optical isomers, or enantiomers (Figure I 5).

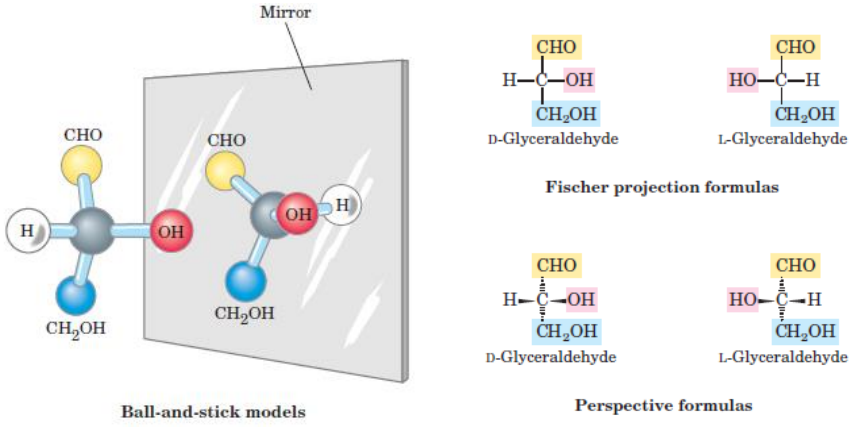


FIGURE I 35 Three ways to represent the two stereoisomers of glyceraldehyde.

By convention, one of these two forms is designated the D isomer, the other the L isomer. In general, a molecule with *n* chiral centers can have 2^n stereoisomers. Glyceraldehyde has $2^1=2$; the aldohexoses, with four chiral centers, have $2^4=16$ stereoisomers. The stereoisomers of monosaccharides of each carbon-chain length can be divided into two groups that differ in the configuration about the chiral center *most distant* from the carbonyl carbon. Those in which the configuration at this reference carbon is the same as that of D-glyceraldehyde are designated D isomers, and those with the same configuration as L-glyceraldehyde are L isomers. When the hydroxyl group on the reference carbon is on the right in the projection formula, the sugar is the D isomer; when on the left, it is the L isomer. Of the 16

possible aldohexoses, eight are D forms and eight are L. Most of the hexoses of living organisms are D isomers.

Figure I 6 shows the structures of the D stereoisomers of all the aldoses and ketoses having three to six carbon atoms. The carbons of a sugar are numbered beginning at the end of the chain nearest the carbonyl group. Each of the eight D-aldohexoses, which differ in the stereochemistry at C-2, C-3, or C-4, has its own name: D-glucose, D-galactose, D-mannose, and so forth. Two sugars that differ only in the configuration around one carbon atom are called **epimers;** D-glucose and D-mannose, which differ only in the stereochemistry at C-2, are epimers, as are D-glucose and D-galactose (which differ at C-4) (Figure. I–6). Some sugars occur naturally in their L form; examples are L-arabinose and the L isomers of some sugar derivatives that are common components of glycoconjugates.

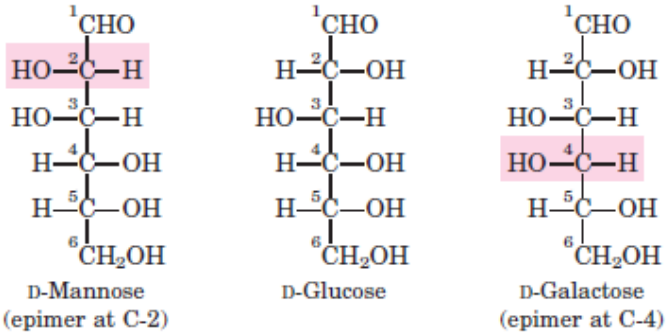


FIGURE I 36 D-Glucose and two of its epimers are shown. Each epimer differs from D-glucose in the configuration at one chiral center (shaded red).

I.2.1.3 Monosaccharides Cyclic Structures

In fact, in aqueous solution, aldotetroses and all monosaccharides with five or more carbon atoms in the backbone occur predominantly as cyclic (ring) structures in which the carbonyl group has formed a covalent bond with the oxygen of a hydroxyl group along the chain. The formation of these ring structures is the result of a general reaction between alcohols and aldehydes or ketones to form derivatives called **hemiacetals** or **hemiketals** (Figure I 7), which contain an additional asymmetric carbon atom and thus can exist in two stereoisomeric forms.

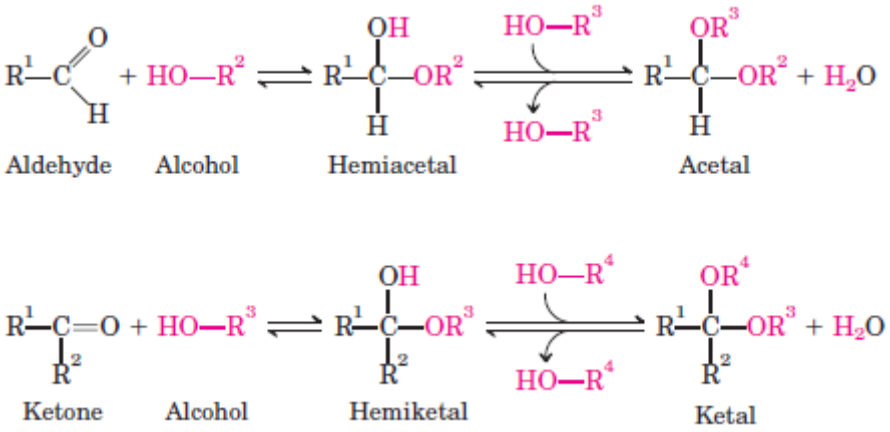


FIGURE I 37 Formation of hemiacetals and hemiketals.

An aldehyde or ketone can react with an alcohol in a 1:1 ratio to yield a hemiacetal or hemiketal, respectively, creating a new chiral center at the carbonyl carbon. Substitution of a second alcohol molecule produces an acetal or ketal. When the second alcohol is part of another sugar molecule, the bond produced is a glycosidic bond (Figure I 8).

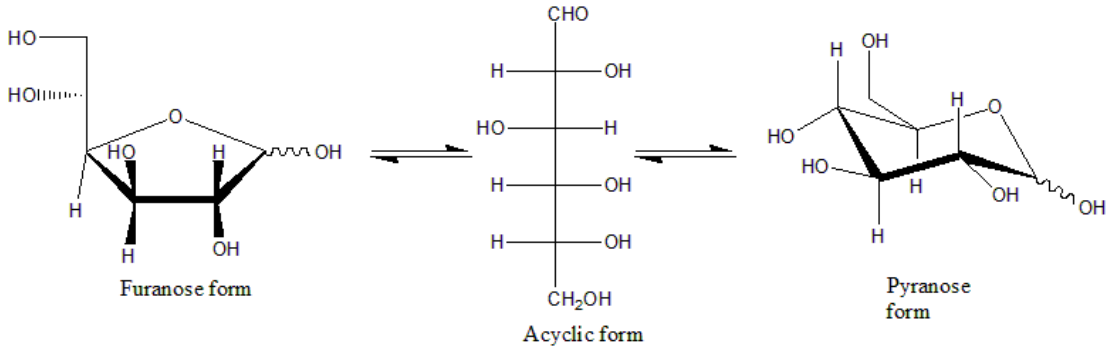


FIGURE I 38 Example of a furanose conversion in pyranose through hemiacetal formation.

For example, D-glucose exists in solution as an intramolecular hemiacetal in which the free hydroxyl group at C-5 has reacted with the aldehydic C-1, rendering the latter carbon asymmetric and producing two stereoisomers, designated *α* and *β* (Figure I 9).

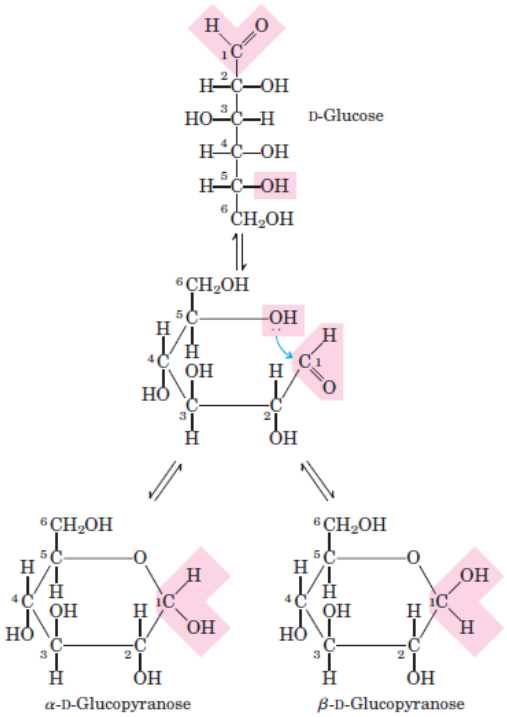


FIGURE I 39 Formation of the two cyclic forms of D-glucose. Reaction between the aldehyde group at C-1 and the hydroxyl group at C-5 forms a hemiacetal linkage, producing either of two stereoisomers, the *α* and *β* anomers, which differ only in the stereochemistry around the hemiacetal carbon.

These six-membered ring compounds are called **pyranoses** because they resemble the six-membered ring compound pyran (Figure I 10). The systematic names for the two ring forms of D-glucose are α-D-glucopyranose and *β*-D-glucopyranose. Aldohexoses also exist in cyclic forms having five-membered rings, which, because they resemble the five-membered ring compound furan, are called **furanoses**. However, the six-membered aldopyranose ring is much more stable than the aldofuranose ring and predominates in aldohexose solutions. Only aldoses having five or more carbon atoms can form pyranose rings. Isomeric forms of monosaccharides that differ only in their configuration about the hemiacetal or hemiketal carbon atom are called **anomers**. The hemiacetal (or carbonyl) carbon atom is called the **anomeric carbon**.

The *α* and *β* anomers of D-glucose interconvert in aqueous solution by a process called **mutarotation**. Thus, a solution of *α*-D-glucose and a solution of *β*-D-glucose eventually form identical equilibrium mixtures having identical optical properties. This mixture consists of about one-third *α*-D glucose, two-thirds *β*-D-glucose, and very small amounts of the linear and five-membered ring (glucofuranose) forms. Ketohexoses also occur in *α* and *β* anomeric forms. In these compounds the hydroxyl group at C-5 (or C-6) reacts with the keto group at C-2, forming a furanose (or pyranose) ring containing a hemiketal linkage (Figure I 7). D-Fructose readily forms the furanose ring (Figure I 10); the more common anomer of this sugar in combined forms or in derivatives is *β*-D-fructofuranose.

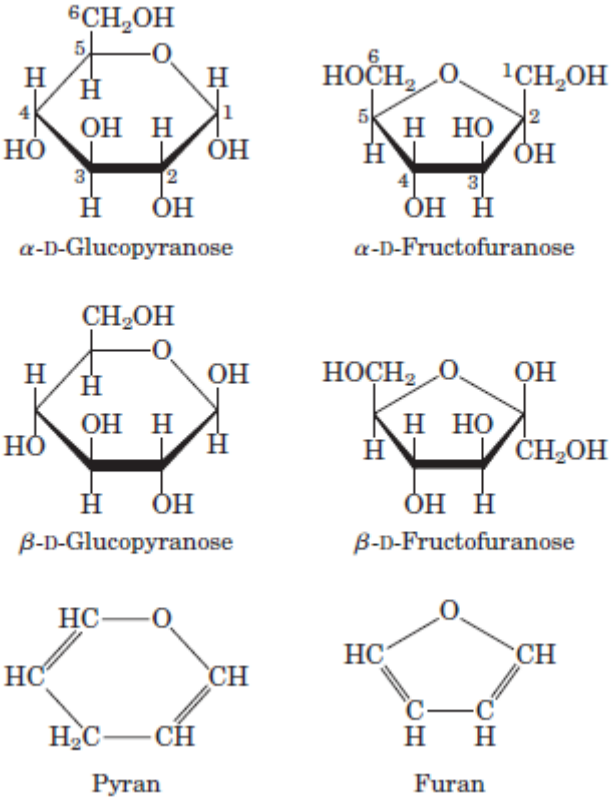


FIGURE I 40 Pyranoses and furanoses. The pyranose forms of D-glucose and the furanose forms of D-fructose are shown here as Haworth perspective formulas. The edges of the ring nearest to the reader are represented by bold lines.

In all these D isomers, the chiral carbon *most distant from the carbonyl carbon* has the same configuration as the chiral carbon in D-glyceraldehyde.

Haworth perspective formulas like those in Figure I 10 are commonly used to show the stereochemistry of ring forms of monosaccharides. However, the six-membered pyranose ring is not planar, as Haworth perspectives suggest, but tends to assume either of two “chair” conformations (Figure I 11).

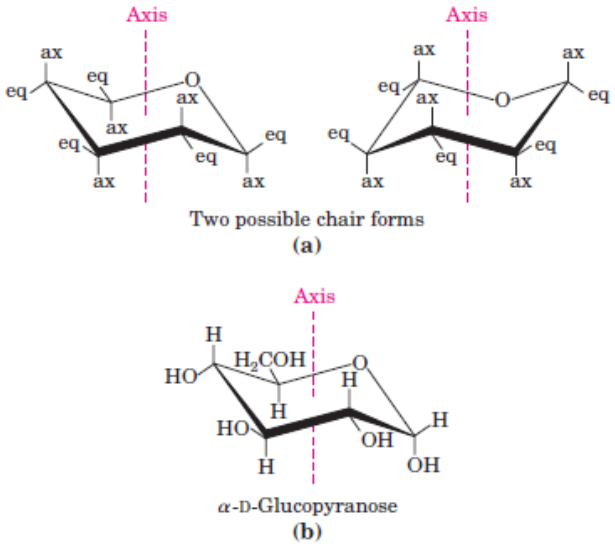


FIGURE I 41 Conformational formulas of pyranoses. (a) Two chair forms of the pyranose ring. Substituents on the ring carbons may be either axial (ax), projecting parallel to the vertical axis through the ring, or equatorial (eq), projecting roughly perpendicular to this axis. **(b)** A chair conformation of *α*-D-glucopyranose

I.2.1.4 Glycosidic Bond

Disaccharides (such as maltose, lactose, and sucrose) consist of two monosaccharides joined covalently by an ***O*-glycosidic bond,** which is formed when a hydroxyl group of one sugar reacts with the anomeric carbon of the other (Figure I 12).

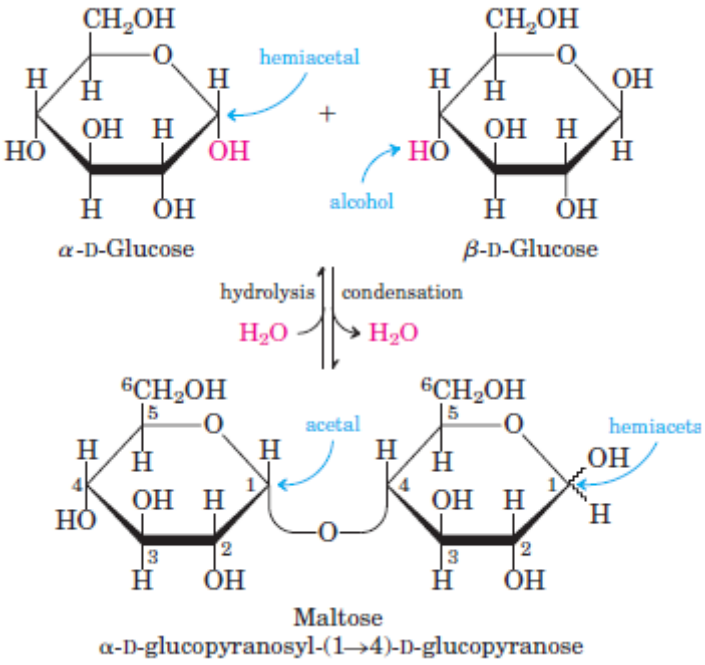


FIGURE I 42 Formation of maltose. A disaccharide is formed from two monosaccharides (here, two molecules of D-glucose) when an -OH (alcohol) of one glucose molecule (right) condenses with the intramolecular hemiacetal of the other glucose molecule (left), with elimination of H_2O and formation of an *O*-glycosidic bond. The reversal of this reaction is hydrolysis—attack by H_2O on the glycosidic bond.

Glycosidic bonds are readily hydrolyzed by acid but resist cleavage by base. Thus disaccharides can be hydrolyzed to yield their free monosaccharide components by boiling with dilute acid. *N*-glycosyl bonds join the anomeric carbon of a sugar to a nitrogen atom in glycoproteins. The oxidation of a sugar's anomeric carbon by cupric or ferric ion (the reaction that defines a reducing sugar) occurs only with the linear form, which exists in equilibrium with the cyclic form(s). When the anomeric carbon is involved in a glycosidic bond, that sugar residue cannot assume a linear form and therefore becomes a nonreducing sugar. In describing disaccharides or polysaccharides, the end of a chain with a free anomeric carbon (one not involved in a glycosidic bond) is commonly called the **reducing end.**

The disaccharide maltose (Figure I 12) contains two D-glucose residues joined by a glycosidic linkage between C-1 (the anomeric carbon) of one glucose residue and C-4 of the

other. Because the disaccharide retains a free anomeric carbon (C-1 of the glucose residue on the right in Figure I 12), maltose is a reducing sugar.

The configuration of the anomeric carbon atom in the glycosidic linkage is *α*. The glucose residue with the free anomeric carbon is capable of existing in *α*- and *β*-pyranose forms. By convention, the name describes the compound with its nonreducing end to the left, and we can "build up" the name in the following order: (1) Give the configuration (*α* or *β*) at the anomeric carbon joining the first monosaccharide unit (on the left) to the second. (2) Name the nonreducing residue; to distinguish five- and six-membered ring structures, insert "furano" or "pyrano" into the name. (3) Indicate in parentheses the two carbon atoms joined by the glycosidic bond, with an arrow connecting the two numbers; for example, (1→4) shows that C-1 of the first-named sugar residue is joined to C-4 of the second. (4) Name the second residue. Following this convention for naming oligosaccharides, maltose is *α*-D-glucopyranosyl-(1→4)- D-glucopyranose. In this abbreviated nomenclature, maltose is Glc(*α*1→4)Glc. The disaccharide lactose (Figure I 13), which yields D-galactose and D-glucose on hydrolysis, occurs naturally only in milk. The anomeric carbon of the glucose residue is available for oxidation, and thus lactose is a reducing disaccharide. Its abbreviated name is Gal(*β*1→4)Glc. Sucrose (table sugar) is a disaccharide of glucose and fructose. It is formed by plants but not by animals. In contrast to maltose and lactose, sucrose contains no free anomeric carbon atom; the anomeric carbons of both monosaccharide units are involved in the glycosidic bond (Figure I 13).

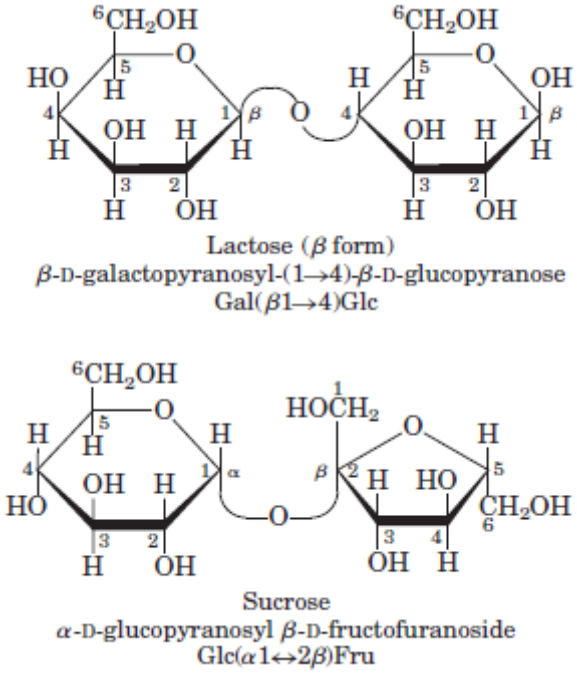


FIGURE I 43 Sucrose and Lactose, two of the most common disaccharides

Sucrose is therefore a nonreducing sugar. Nonreducing disaccharides are named glycosides; in this case, the positions joined are the anomeric carbons. In the abbreviated

nomenclature, a double-headed arrow connects the symbols specifying the anomeric carbons and their configurations.

I.2.2 Sucrose Chemistry

The abbreviated name of sucrose is either Glc(*α*1↔2*β*)Fru or Fru(*β*2↔1*α*)Glc. Sucrose is a major intermediate product of photosynthesis; in many plants it is the principal form in which sugar is transported from the leaves to other parts of the plant body.

Sucrose is an extremely versatile molecule, representing an enormous challenge to organic chemists because of its polyfunctional structure. Given to the extremely important applications of derivatives of this sugar and its low market price, sucrose based reactions are very economically viable.

To be able to use sucrose as a viable chemical starting material, it is important to study the protection of free hydroxyl groups. The development of protection and deprotection methods, both selective and efficient, can be essential when making selective transformations of polyfunctional molecules like sucrose.

The synthesis method for sucrose polyfunctionalization is based on the modification of sucrose primary hydroxyl groups as shown in Figure I 14. In the reactions studied, sucrose primary groups tend to react first, thus faster, than the secondary hydroxyl groups. Using this specific property of sucrose it is possible to design an appropriate synthesis route to functionalize a specific hydroxyl group in a particular position.

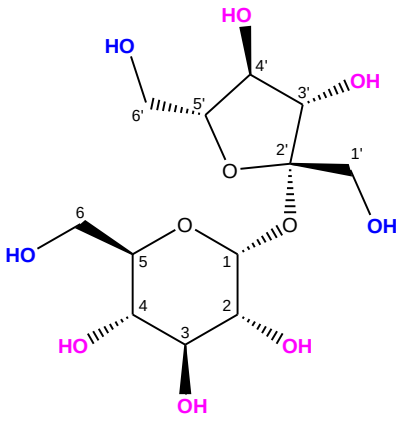


FIGURE I 44 Sucrose structure showing primary hydroxyl groups (blue) in the positions 1',6 and 6' and secondary hydroxyl groups (purple) in the positions 1, 2, 3, 3', 4 and 4'

I.2.2.1 Functionalization of sucrose hydroxyl groups

In this thesis, the synthesis of sucrose vinyl esters was aimed, thus it is important to explain synthetic routes and protection/deprotection approach in ether or ester synthesis. In a protection/deprotection approach ester derivatives are used as protecting groups[19] (*tert*-butyldiphenylsilane – TBDPS) that, due to its high steric hindrance allow a good selectivity

during the protection process[20]. As sucrose has eight different hydroxyl groups, the protection of the remaining hydroxyl groups can be carried out with benzyl groups (BnOR) and acetate groups (AcOR), to differentiate from other hydroxyl groups. With this kind of strategy, the study of selective and efficient deprotection techniques of silicon ethers is of the utmost importance.

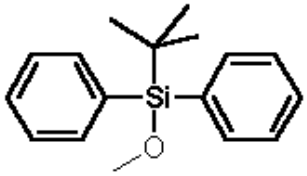


FIGURE I 45 TBDPS-OR, TBDPS ether protection group

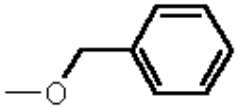


FIGURE I 46 BnOR, Benzyl ether protection group

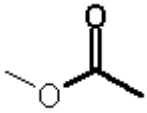


FIGURE I 47 Ac-OR, Acetic acid esters, Acetate esters, Acetates

For this three kinds of protection groups, the deprotection method is different and they can be used to build a synthesis strategy for selective functionalization of polyalcohol's.

I.2.2.2 Mitsunobu Reaction for sucrose esterification

Selective synthesis of sucrose vinyl esters in organic solvents can be achieved by the Mitsunobu reaction or by coupling agents, for example, the compound N,N'-dicyclohexylcarbodiimide (DCC)[21].

The Mitsunobu reaction[22] avoids a protection/deprotection routes, as it is selective and allows the esterification of sucrose positions 6 and 6', where the 6-OH position is preferred to the 6'-OH position and it is one of the many methods that were used in this work for sucrose derivatization[23].This reaction, as shown on Figure I 18, allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers and various other compounds. The nucleophile employed should be acidic, since one of the reagents (DEAD, diethylazodicarboxylate or DIAD, diisopropylazodicarboxylate) must be protonated during the course of the reaction to prevent side reactions (Figure I 20).

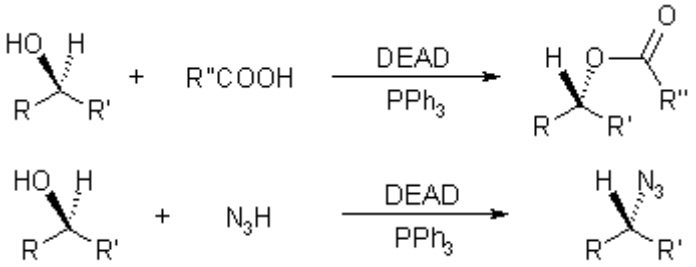


FIGURE I 48 General reaction scheme for esterfication and amination using the Mitsunobu reaction

The triphenylphosphine combines with the azodicarboxylate (DEAD or DIAD) to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving group. Substitution by the carboxylate, mercaptyl, or other nucleophile completes the process (Figure I 19).

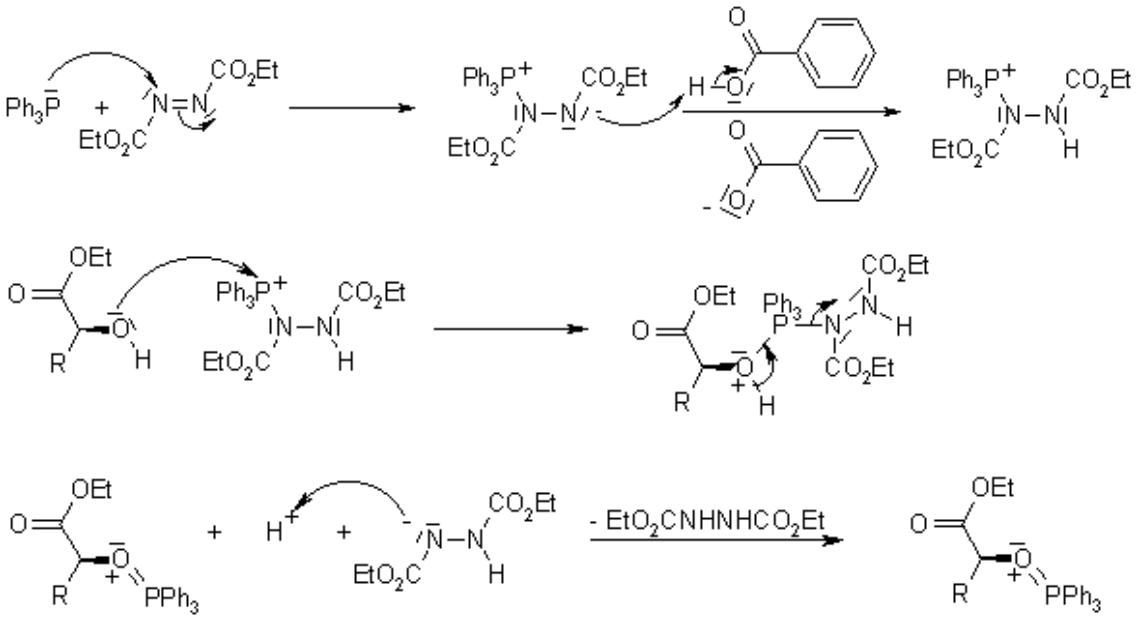
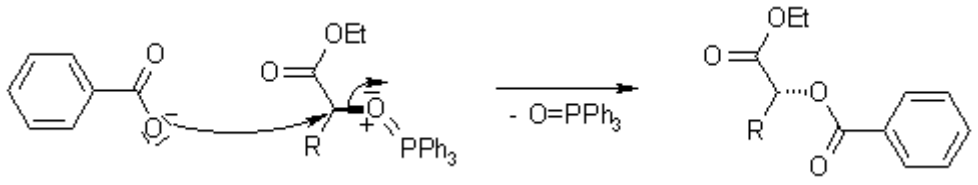


FIGURE I 49 Mechanism for the Mitsunobu reaction

The reaction proceeds with clean inversion, which makes the Mitsunobu Reaction with secondary alcohols a powerful method for the inversion of stereogenic centers in natural product synthesis.



Side reaction (Figure I 20):

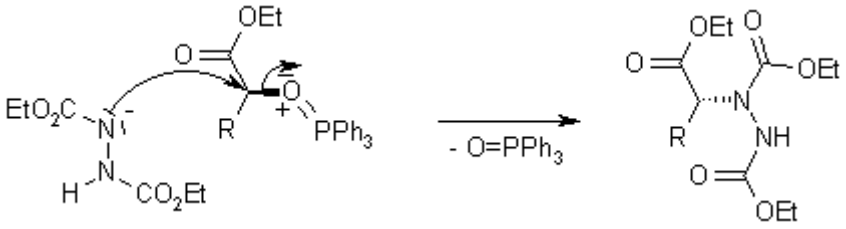


FIGURE I 50 Inversion of configuration and side reaction that can occur under Mitsunobu conditions

New protocols, which allow better removal of side products and/or the conversion of more basic nucleophiles, have been developed[24]. In a similar way, it is possible to formulate a synthesis route based on similar reactions as the Appel reaction (Figure I 21).

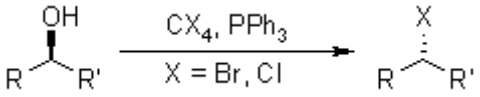


FIGURE I 51 General reaction scheme for the Appel reaction

The reaction of triphenylphosphine and tetrahalomethanes (CCl_4, CBr_4) with alcohols is a ready method to convert an alcohol to the corresponding alkyl halide under mild conditions. The yields are normally high. This reaction is somewhat similar to the Mitsunobu Reaction, where the combination of a phosphine, a diazo compound as a coupling reagent, and a nucleophile are used to invert the stereochemistry of an alcohol or displace it.

The reaction proceeds by activation of the triphenylphosphine by reaction with the tetrahalomethane, followed by attack of the alcohol oxygen at phosphorus to generate an oxyphosphonium intermediate. The oxygen is then transformed into a leaving group, and an S_N2 displacement by halide takes place, proceeding with inversion of configuration if the carbon is asymmetric[25] (Figure I 22).

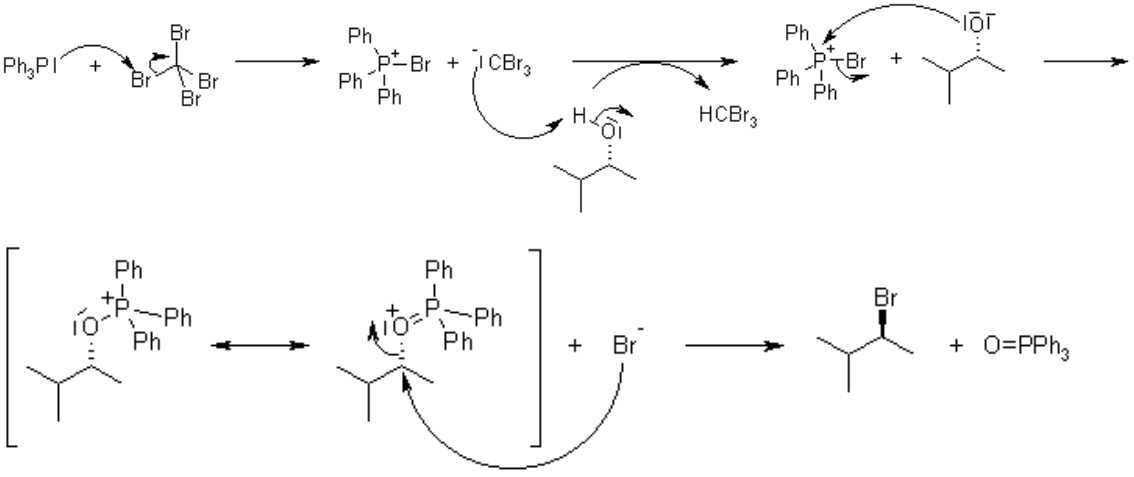


FIGURE I 52 Mechanism for the Appel reaction

I.2.2.3 Microwave assisted Protocols (MAPs)

Microwave-enhanced synthesis has been extended to almost all areas of chemistry[26] with the exception of carbohydrate chemistry which has suffered a certain delay, as is testified by the limited number of applications[27,28]; In particular, there were some concerns of using this technique previously to sucrose chemistry, and the general opinion was that the method is hampered by competitive degradation of sucrose because of its thermal instability[29]. A method to overcome these limitations and to apply highly efficient and fast synthetic protocols for the synthesis of a series of sugar monomers under microwave irradiation is presented. These alternative protocols allowed a significant decrease of the reaction time to achieve useful sucrose derivatives, compared to other known routes[30]. In all cases, a comparison was made between results obtained with conventional and microwave-assisted methods.

The key point to successful synthesis under microwave irradiation is to use proper equipment, especially designed for chemical laboratories. Monomodal microwave equipment has overcome the uncertainties associated with domestic microwave ovens, as it offers much more precise control over conditions of temperature and pressure than any previous technology and the software provides simplified process monitoring and control, which results in accurate, reproducible reaction conditions[31]. The energy transfer in a microwave-assisted reaction is incredibly quick, and only by programming temperature control the decomposition of the substrates has been avoided and comparatively high yields have been obtained in short reaction times. In this method, as the temperature reaches the input value, the power is reduced so that the reaction mixture does not exceed the set point. It then stays at a lower level in order to maintain the set temperature throughout the entire reaction. The microwave apparatus used in microwave-assisted synthesis is shown in Figure I 23.

FIGURE I 53 Image of the microwave apparatus used by Barros and team.

The methods used to produce and purify carbohydrate derivatives are often tedious and complex, which makes the selective synthesis of sucrose derivatives laborious and new, simpler

procedures are needed. In the development of new carbohydrates or in their transformations there is a need for faster and cleaner methods which can be provided by microwave heating. The library of microwave assisted protocols, presented in this chapter, allows significant reduction of time and energy and potential automatization of tedious multi-step synthesis. As an example, shown on Figure I 24, it is represented a synthesis path solely made with microwave-assisted protocols (MAPs)[32].

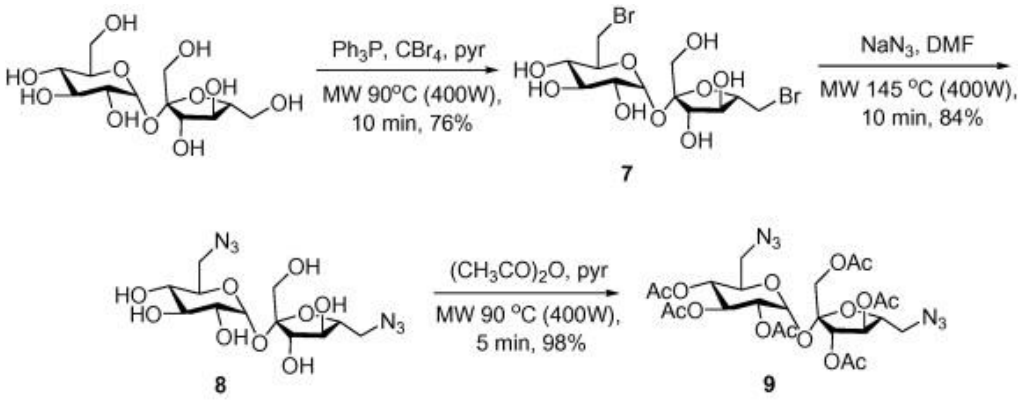


FIGURE I 54 Sucrose functionalization with MAPs

I.3 Macromolecules

Nature have used long chain molecules for a variety of central applications long before man discovered the use of plastic materials for similar purposes: for the longest time in our history, we were unable to produce tailor-made macromolecules for protection, clothes and housing. Instead, we applied the polymeric material as it was provided by nature as wool, leather, cotton, wood or straw. Only with the onset of industrialization in the 19th century did these renewable raw materials become the limiting factor for further growth, and chemists began developing artificial macromolecules based on fossil carbon sources like coal, oil and gas.

Step-by-step, synthetic macromolecules supplemented or substituted classic materials due to their easy processability, global availability, low price and weight. Even today this process is still progressing. It is expected that polymers will replace metals in many electrical and optical applications. In fact, we are standing at the verge of a ‘plastics in electronics’ era.

I.3.1 Monomers[33]

In a chemical reaction between two molecules, the constitution of the reaction product can be unequivocally deduced if the starting materials possess functional groups that react selectively under the chosen conditions. If an organic compound contains one reactive group

that can give rise to one linkage in the intended reaction, it is called monofunctional; for two, three, or more groups it is called bi-, tri-, or oligo-functional, respectively. However, this statement concerning the functionality of a compound is only significant in relation to a specific reaction. For example, monounsaturated compounds, epoxides and cyclic esters are monofunctional in their addition reactions with monofunctional compounds, but bifunctional in chain growth polymerizations.

Molecules suitable for the formation of macromolecules must be at least bifunctional with respect to the desired polymerizations; they are termed monomers. Linear macromolecules result from the coupling of bifunctional molecules with each other or with other bifunctional molecules; in contrast, branched or crosslinked polymers are formed when tri- or poly-functional compounds are involved.

I.3.2 Polymers

Conventional macromolecules (or polymers) consist of a minimum of several hundred covalently linked atoms and have molar masses clearly above 10^3 g/mol. The degree of polymerization, *P*, and the molecular weight, *M*, are the most important characteristics of macromolecular substances because nearly all properties in solution and in bulk depend on them. The *degree of polymerization* indicates how many monomer units are linked to form the polymer chain. The *molecular weight* of a homopolymer is given by equation 11:

$$M = P.M_{ru} \quad (11)$$

where M_{ru} stands for the molar mass of the monomer repeating unit. While pure low-molecular-weight substances consist of molecules of identical structure and size, this is generally not the case for macromolecular substances. They instead consist on a mixture of macromolecules of similar structure but different degrees of polymerization and molecular weights. Therefore, they are called polydisperse. As a result of this polydispersity, the values of *P* and *M* are only mean values, called $\bar{P}$ and $\bar{M}$.

Macromolecules may be classified according to different criteria. One criterion is whether the material is *natura*l or *synthetic* in origin. Cellulose, lignin, starch, silk, wool, chitin, natural rubber, polypeptides (proteins), polyesters (polyhydroxybutyrate), and nucleic acids (DNA, RNA) are examples of naturally occurring polymers while polyethylene, polystyrene, polyurethanes or polyamides are representative of their synthetic counterparts. When natural polymers are modified by chemical conversions (cellulose → cellulose acetate, for example), the products are called *modified natural polymers*.

At the same time, the macromolecules might be classified according to whether their chains have only one kind of atoms – like carbon – in the backbone (*isochains*) or different

elements (*heterochains*) Concerning their chain architecture, polymers are subdivided into *linear, branched, comb-like, crosslinked, dendritic,* or *star-like* systems.
Moreover, polymers are quite often classified according to the number of different types of monomers they are prepared from. When produced from one single type of monomer, they are called *homopolymers* (a). If a second or third type of monomer is involved in the polymer synthesis , the resulting materials are called *binary*, *tertiary*,…*copolymers.* In addition, a distinction is also made on how different monomers are arranged in the resulting copolymers chains, distinguishing among others: (b) alternating-, (c) statistic-, (d) block-, and (e) graft-copolymers.

Finally, for practical reasons it is useful to classify polymeric materials according to where and how they are employed. A common subdivision is that into *structural polymers* and *functional polymers*. Structural polymers are characterized by – and are used because of – their good mechanical, thermal and chemical properties. Functional polymers, in contrast, have completely different properties. They can assume specific chemical or physical functions in devices for microelectronics, biomedical applications, analytics, synthesis, cosmetics or hygiene.

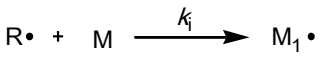
I.3.2.1 Methods of Polymer Synthesis

The formation of synthetic polymers is a process which occurs via chemical connection of many hundreds up to many thousands of monomer molecules. As a result, macromolecular chains are formed. They are, in general, linear, but can be branched, hyperbranched, or crosslinked as well. However, depending on the number of different monomers and how they are connected, homo- or one of the various kinds of copolymers can result. The chemical process of chain formation may be subdivided roughly into two classes, depending on whether it proceeds as a chain-growth or as a step-growth reaction.

In this work we will concentrate our efforts on producing polymers using copolymerization methods by radical reaction for a chain growth polymerization. This type of polymerization is characterized by the occurrence of activated species (initiators)/active centers. They add one monomer molecule after the other in a way that at the terminus of each new species formed by a monomer addition step, an activated center is created which again is able to add the next monomer molecule. For our purposes, such species are formed from compounds which create radicals via homolytic bond scission, consisting of a sequence of three steps – *initiation*, *propagation* and *termination*. The initiation step is considered to involve two reactions. The first is the production of free radicals by any one of a number of reactions. The usual case is the homolytic dissociation of an initiator species **I** to yield a pair of radicals **R•**,

$$I \xrightarrow{k_d} R\bullet$$

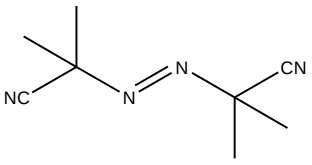
Where k_d is the rate constant for the catalyst dissociation. The second part of the initiation involves the addition of this radical to the fist monomer molecule, **M•** to produce the chain initiating radical **M_1•**,



where **M** represents a monomer molecule and k_i is the rate constant for the initiation step, and the radical **R•** is often referred to as an initiator radical or primary radical to distinguish it from the chain-initiating species (**M_1•**).

In the polymerizations that occur in this work we used azo and peroxo compounds as radical initiators.

Azo compounds that are specially suitable as initiators for radical polymerizations are those in which the azo group in bonded on both sides to tertiary carbon atoms that carry nitrile or ester groups in addition to alkyl groups. They are stable at room temperature, but decompose thermally above 40 ºC, or photochemically below 40 ºC, giving substituted alkyl radicals and liberating nitrogen. The most important azo compound is 2,2'-azobis(2-methylpropionitrile) – **AIBN** (Figure I 25)



2,2'-Azobis(2-methylpropionitrile)

AIBN

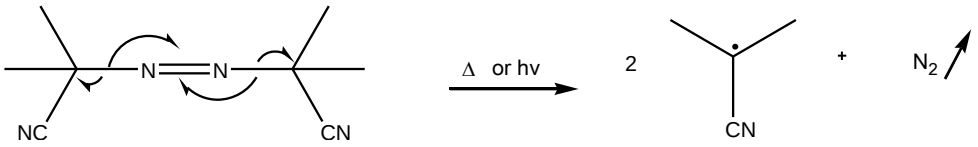
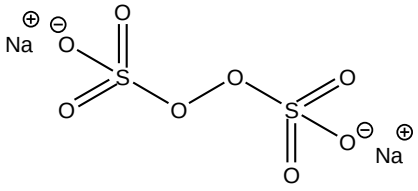


FIGURE I 55 Structure and mechanism of an azo radical polymerization initiator - AIBN

Organic and inorganic peroxo compounds are especially important as initiators of radical polymerizations. Hydroperoxides, dialkyl peroxides, diacyl peroxides, and peresters are typical peroxo compounds. Since they dissolve not only in organic solvents but also in most monomers, they are suitable for solution polymerization as well as bulk or bead polymerization. Their decomposition can be brought about either thermally, or by irradiation with light, or by redox reactions. For initiation by thermal decomposition of peroxo compounds an acceptable rate of polymerization is generally attained only above 50 ºC. Hydrogen peroxide is mainly used as a component of a redox initiator; in contrast, potassium, ammonium or sodium peroxodisulfate (concentration 0.1-1 wt% with respect to monomer), Figure I 26, are very

frequently used without a reducing agent, since even at 30 ºC they decompose thermally into radicals that can initiate polymerization.



Sodium peroxodisulfate

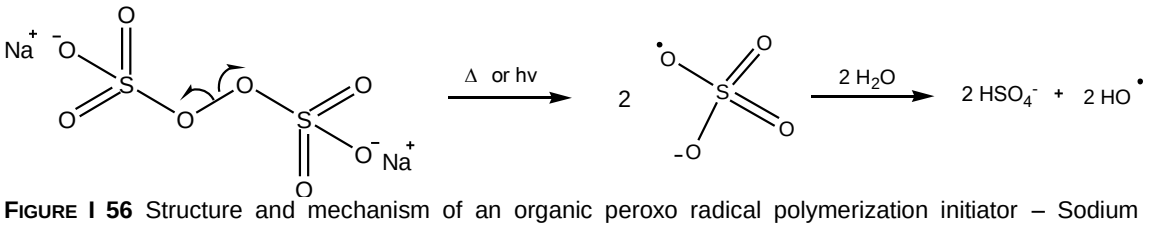
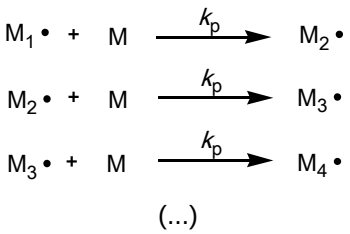
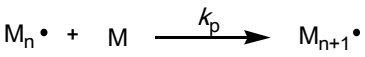


FIGURE I 56 Structure and mechanism of an organic peroxo radical polymerization initiator – Sodium peroxodisulfate

Propagation consists of the growth of $\mathbf{M_1}\bullet$ by the successive additions of large numbers (hundreds and perhaps thousands) of monomer molecules. Each addition creates a new radical that has the same identity as the one previously, except that it is larger by one monomer unit. The successive additions may be represented by,



or in general terms



Where k_p is the rate constant for the propagation. Propagation with growth of the chain to high-polymer proportions takes place very rapidly. The value of k_p for most monomers is in the range 10^2-10^4 $Lmol^{-1}s^{-1}$. This is a high rate constant – much higher than those usually encountered in step polymerizations (see Table I-1).

Table I 1 Values of Reaction Parameters in Typical Polymerizations

Reactants[a]	**T** (ºC)	***k* x 10^3** ($Lmol^{-1}s^{-1}$)	E_a ($KJmol^{-1}$)	ΔH ($KJmol^{-1}$)
Polyester				
$HO(CH_2)_{10}OH + HOOC(CH_2)_4COOH$	161	7.5 $x10^{-2}$	59.4	
$HO(CH_2)_{10}OH + HOOC(CH_2)_4COOHc$	161	1.6		
HOCH2CH2OH + *p*-HOOC-Φ-COOH	150	-		-10.9
$HO(CH_2)_6OH + ClOC(CH_2)_8COCl$	58.8	2.9	41	
p-$HOCH_2CH_2OOC$-Φ-$COOCH_2CH_2OH$	27.5	0.5	188	
p-$HOCH_2CH_2OOC$-Φ-$COOCH_2CH_2Ohd$	27.5	10	58.6	
Polyamide				
$H_2N(CH_2)_6NH_2 + HOOC(CH_2)_8COOH$	185	1.0	100.4	
Piperazine + *p*-Cl-CO-Φ-CO-Cl		10^7-10^8		
$H_2N(CH_2)_5COOH$	235			-24
Polyurethane				
m-OCN-Φ-NCO + $HOCH_2CH_2OCO(CH_2)_4COOCH_2CH_2OH$	60	0.40[e]	31.4	
m-OCN-Φ-NCO þ HOCH2CH2OCO(CH2)4COOCH2CH2OH	60	0.23[f]	35.0	
Phenol-formaldehyde polymer				
Φ-OH + H_2CO[c]	75	1.1[g]	77.4	
Φ-OH + H_2CO[h]	75	0.048[g]	76.6	

[a] Uncatalyzed unless otherwise noted.

[b] 1 cal = 4.184 J.

[c] Acid-catalyzed.

[d] Catalyzed by Sb_2O_3.

[e] k_1 value.

[f] k_2 value.

[g] Average k for all functional groups.

[h] Base-catalyzed.

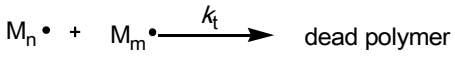
At some point, the propagation polymer chain stops growing and terminates. Termination with the annihilation of the radical centers occurs by bimolecular reaction between radicals. Two radicals react with each other by *combination* (*coupling*) or, more rarely, by *disproportionation*, in which a hydrogen radical that is *beta* to one radical center is transferred to another radical center. This results in the formation of two polymer molecules – one saturated and one unsaturated.

Termination can also occur by a combination of coupling and disproportionation. The two different modes can be represented in general terms by

$$M_n\bullet + M_m\bullet \xrightarrow{k_{tc}} M_{n+m}\bullet$$

$$M_n\bullet + M_m\bullet \xrightarrow{k_{td}} M_n + M_m$$

where k_{tc} and k_{td} are the rate constants for termination by coupling and disproportionation respectively. One can also express the termination step by



The term *dead polymer* signifies the cessation of growth for the propagating radical. The propagation reaction would proceed indefinitely until all the monomer in a reaction system were exhausted if it were not for the strong tendency towards termination. Typical termination constants are in the range of 10^6-10^8 $Lmol^{-1}s^{-1}$ or orders of magnitude greater than the propagation rate constants. The much greater value of k_t compared to k_p, does not prevent propagation because the radical species are present in very low concentrations and because the polymerization rate is dependent on only the one-half power of k_t.

1.3.2.1.1 Sucrose containing polymers

Petrochemical derived polymers (such as polystyrene), functionalized with sugar, to form biodegradable polymers is a recently discovered application of a sugar linked synthetic polymer[34]. The class of sugar based polymers, generally known as poly(vinylsaccharide)s, has also been investigated for a variety of applications, particularly in the biomedical field[35].The most widely used method for the synthesis of poly(vinylsaccharide)s was based on the free radical polymerizations of vinyl sugars[36]. An extensive review of the preparation and applications of this type of polymers is available[3738], that has described various applications of glyconjugate polymers in the biological and biomedical fields. Synthetic carbohydrate-based polymers having pendant sugar residues are of great interest, not only as simplified models for biopolymers bearing oligosacharides, but also as artificial glycoconjugates in biochemistry and medicine.

The introduction of sugars into polymeric molecules can bestow new properties, such as increased polarity, chirality, biodegradability, and biocompatibility. Sucrose-containing polymers, having a polyvinyl backbone and pendant sucrose moieties, have been obtained by polymerization or copolymerization of sucrose derivatives – esters, ethers, and acetals, bearing a carbon-carbon double bond (Figure I 27)[39].The monomers have been prepared either by multistep synthesis, leading to defined compounds and subsequently a well-defined polymerization processes[40,41,42,43,44], or by direct functionalization of unprotected sucrose, leading to mixtures of isomers and therefore to more complex polymers[45].

A number of monomers has been synthesized from sucrose during the last decades, as presented in Figure I 27. Nonselective derivatization of free sucrose to provide “statistical” mixtures that might find industrial applications were not of interest to us since undefined polymeric structures result. Also, the di- and tri- substituted derivatives were not of interest, as they result in cross-linked networks.

The first selectively obtained monomer described was the substituted derivative at the three primary positions, then there appeared substituted or hydrolyzed isopropylidene derivatives with free or acetylated hydroxyl groups, which were also a mixture of 2 isomers[46]. To the best of our knowledge, mono-unsaturated sucrose esters at the 1'-position were selectively obtained only with the aid of enzymes (Figure I 27)[47,48]

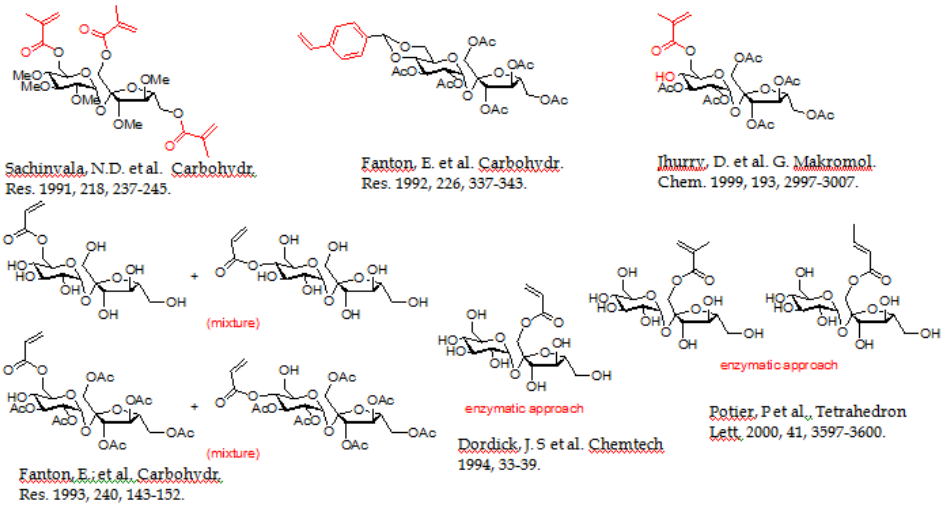


FIGURE I 57 Structures of some selectively obtained sucrose monomers

The direct transformation of unprotected sucrose in the context of the preparation of derivatives of industrial interest is a challenging task[49]. In general, it is accepted that bulky substituents like *tert*-butyldiphenylsilyl (TBDPS), are introduced at the primary positions in the order 6-OH ≈ 6'-OH > 1'-OH[50]. Since sucrose has eight chemically active hydroxyl groups, regiosselective derivatization is important in the selective synthesis of sucrose-containing linear polymers[51,52,53] and other new compounds. The route to selective derivatization of the 6'-position of the sucrose, developed in our laboratory[5455] allowed us to obtain the fully benzylated sucrose with only the 6'-hydroxyl unprotected in three steps from sucrose. These monomers could be converted into pure linear polymers, avoiding the formation of mixtures of di- and higher substituted unsaturated esters, which results in cross-linked polymers[56]. Saccharide containing synthetic polymers has attracted great attention because of their potential as biotechnological, pharmacological, and medical materials[57].

I.3.2.2 Polymers in solution

Polymer solutions are important because many polymer synthesis as well as most procedures for their characterization are carried out in solution. Polymer solutions are furthermore essential in the processing of some polymers to fibers, preparation of polymer blends, coatings and adhesives. Moreover, polymer solutions are applied because of their high

viscosity (thickeners). Also mixtures of polymers might be considered as solutions: polymer blends represent (homogeneous or heterogeneous) “solutions” of high-molecular-weight solute in a high-molecular-weight “solvent”, Figure I 28.

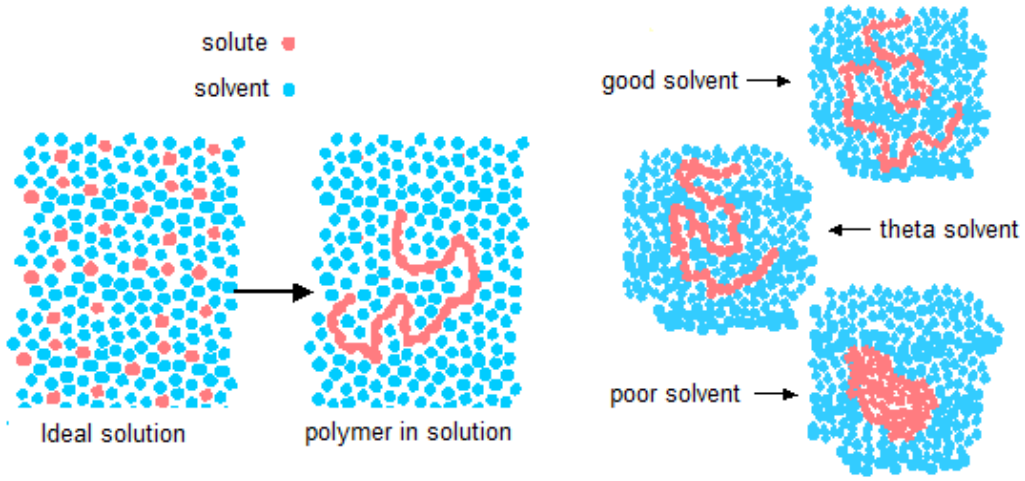


FIGURE I 58 Classification of the solvent according to the hability to dissolve a polymer: good, theta or poor.

In a dilute solution, the behavior of macromolecules is quite different to that of common low-molecular-weight molecules. For example, the shape of a macromolecular coil is subject to permanent dynamic changes, and the coils are in a more or less swollen state when compared to their “unperturbed” (solid state) dimensions. As a result, it is expected that polymer solutions tend to be viscous even at low concentrations[58].

However, the most fundamental difference between low- and high-molecular-weight materials is that polymeric substances are not composed of structurally and molecularly uniform molecules. Thus, even if they have an identical analytical composition, the individual chain molecules differ in their structure, configuration, conformation, as well as in their molecular size. Hence, there is a mixture of molecules of different size, i.e., a molecular-weight distribution, where the compounds are called *polydisperse.*

I.3.2.3 Solvents and Solubility

In some specific cases, dissolved macromolecules take up a predicted shape, of isolated chain molecules. In general, however, the interaction between solvent molecules and macromolecules has significant effects on the chain dimensions.

We can distinguish these interactions according to the type of solvent where the macromolecule is dissolved, “poor” solvents or “good” solvents.

In “poor” solvents, the interactions between polymer segments and solvent molecules are not that much different from those between chain segments. Hence, the coil dimensions tend towards those of an unperturbed chain: if the dimension of the unperturbed coil is identical to that in solution, the conditions ate called ϑ conditions (ϑ solvent, ϑ temperature).

In “good” solvents, on the other hand, the interaction of chain segments and solvent molecules is preferred over the interaction between chain segments, and a good solvation of the macromolecules takes place. Here, the coils contain a considerable amount of trapped solvent and thus are drastically expanded in their dimensions with respect to the unperturbed coil. The trapped solvent is in a state of continuous exchange (by diffusion) with the surrounding solvent, but is nevertheless fixed to an extent that, in many situations, it may be regarded as moving with the coil as a whole. The macromolecular coils are thus comparable with small swollen gel particles that, like a fully soaked sponge, consist of a framework (the coiled macromolecules) and the embedded solvent.

With increasing concentration of the polymer solution, the coils take up a greater proportion of the total volume until finally, at a “critical” concentration c*, there is mutual contact between the coils. At still higher concentrations, the coils interpenetrate or, if this is not possible on account of incompatibility effects, the interaction may be confined to the boundary regions.

Depending on the molecular weight of the macromolecules and the quality of the solvent, the coil volume macromolecules in solution may be 200 to 1000 times larger than the chain volume itself. Thus, such a swollen gel particle may consist of more than 99% solvent. Since the diameter of such gel coils may be between ten and several hundred nanometers – again depending on the molecular weight and solvent – these solutions may be classified as colloids. However, in contrast to the colloidal particles of classic dispersions, the colloidal particles in macromolecular solutions are identical with the solvated macromolecular coils: they may therefore be termed “molecular colloids”. There are some every-day commercially available colloids, for example, pigmented ink, mayonnaise, gelatin, whipped cream or hair spray.

I.3.2.4 Polymers solution viscosity

The properties of solutions of macromolecular substances depend on the solvent, the temperature, and the molecular weight of the chain molecules. Hence, the (average) molecular weight of polymers can be determined by measuring the solution properties such as the viscosity of dilute solutions. However, prior to this, some details have to be known about the solubility of the polymer to be analyzed. When the solubility of a polymer has to be determined, it is important to realize that macromolecules often show behavioral extremes; they may be either infinitely soluble in a solvent, completely insoluble, or only swellable to a well-defined extent. Saturated solutions in contact with a nonswollen solid phase, as is normally observed with low-molecular-weight compounds, do not occur in the case of polymeric materials. The suitability of a solvent for a specific polymer, therefore, cannot be quantified in terms of classic

saturated solution. It is much better expressed in terms of the amount of a precipitant that must be added to the polymer solution to initiate precipitation (cloud point). A more exact measure for the quality of a solvent is the second virial coefficient of the osmotic pressure determined for the corresponding solution, or the viscosity numbers in different solvents.

Swelling in solvents is a typical feature of macromolecules that exceed a certain molecular weight. One aspect of this is that macromolecular compounds can take up large amounts of solvent, forming a gel, with a marked increase of volume. If this process does not lead to a homogeneous solution at the end, it is called “limited swelling”; unlimited swelling, on the other hand, is synonymous with complete dissolution. The extent of swelling depends on the chemical nature of the polymer, the molecular weight, the swelling medium, and the temperature. For crosslinked polymers, which are of course insoluble, it is a measure of the degree of crosslinking.

When a polymer is dissolved in a solvent, it makes the solution viscous. The caused thickening effect can be used to estimate a macromolecule’s molecular weight because the higher the molecular weight, the more viscous the polymer solution will be. This is reasonable because the higher the molecular weight, the bigger the hydrodynamic volume is, and being bigger, the polymer molecule can block more motion of the solvent molecules. Also, the bigger a polymer is, the stronger its secondary forces are. So the higher the molecular weight, the more strongly solvent molecules will be bound to the polymer. This reduces even more the mobility of the solvent molecules.

For most polymers there is a definite relationship between molecular weight and solution viscosity. The viscosity method of molecular-weight determination was introduced by Staudinger. However, it is applicable only to linear and slightly branched molecules; it fails mostly for sphere-like or strongly branched molecules (globular proteins, glycogens). For the determination of the molecular weight of a polymer via solution viscosity measurements it is not necessary to determine absolute values of the solution viscosity. In principle, it is enough to measure the time *t* which a given volume of the polymer solution needs to flow through the capillary and to compare this with the time t_0 which is needed by the pure solvent. Then, to have a first measure of the viscosity-increasing effect of the polymer to be analyzed, the elution or flow time, *t* of the polymer solution at a given concentration, *c*, is divided by t_0. This quotient is called the relative viscosity η_{rel}:

$$\frac{t}{t_0} = \eta_{rel} \quad (11)$$

However, the required information is the difference in the elution times of the solution and the pure solvent relative to the elution time of the pure solvent. Therefore, the elution time of the pure solvent, t_0, is subtracted from the elution time of the solution, *t*. The thus obtained result is divided by t_0. The resulting quantity is called specific viscosity, η_{sp}, which is a dimensionless quantity:

$$\frac{t - t_0}{t_0} = \eta_{sp} \quad (12)$$

If the measurement is made in a capillary viscometer of specified dimensions and at low polymer concentration (so that the density of the solution is approximately the same as that of the solvent), the viscosities η and η_0 are represented to a good approximation by the elution times *t* and t_0:

$$\frac{t - t_0}{t_0} = \eta_{sp} \approx \frac{\eta - \eta_0}{\eta_0} \quad (13)$$

If this value is divided by the concentration *c* of the polymer in solution, one obtains the reduced specific viscosity:

$$\frac{\eta_{sp}}{c} = \eta_{red} \quad (14)$$

Polymer solutions are never ideal since dissolved macromolecules influence each other even at very low concentration. On the other hand, a reliable correlation of solution viscosity and molecular weight is only possible if the dissolved macromolecules are not affected by mutual interactions: they must be actually independent of each other. Therefore, the viscosity of polymer solutions should be determined at infinite dilution. However, such measurements are impossible in practice. So one works at an as low as possible polymers concentration and extrapolates the obtained values to zero concentration. To do so, the elution time measurements are not only carried out for one single polymer concentration but for varying polymer concentrations. For each solution, the value of the reduced specific viscosity is figured out (the data will make evident that this quantity is clearly concentration-dependent even at the lowest possible polymer concentrations). Then, the limiting value (intrinsic viscosity, Staudinger index or limiting viscosity number) [η] is determined as a reliable measure of the viscosity behavior of the isolated thread-like molecule at infinite dilution:

$$[\eta] = \lim_{c \to 0} \frac{\eta_{sp}}{c} \quad (15)$$

Practically, the η_{sp}/c values are plotted against the concentration, *c*, and linear extrapolation is done. [η] is obtained as the y-axis intersect. Since η_{sp} is dimensionless, [η] has units of reciprocal concentration (e.g., l/g or dl/g). Hence in viscosity measurements the concentration units must always be stated. It is possible to use the following apparatus to carry out viscosity measurements:

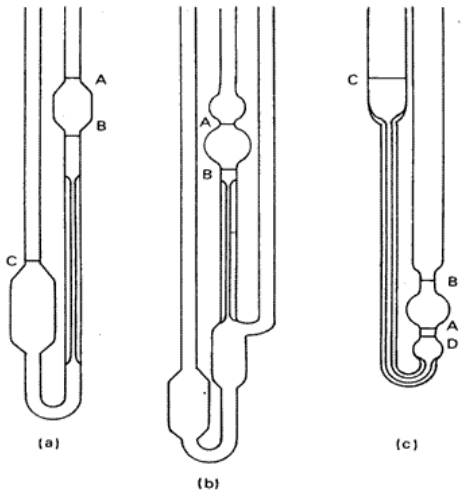


FIGURE I 59 Hydrostatic head ('U' tube) viscometers: (a) Ostwald; (b) Ubbelohde; and (c) reverse flow

The Ostwald, Ubbelohde and reverse flow hydrostatic head viscometers (Figure I 29) are the most popular for general and high precision measurement of the viscosity of thin Newtonian fluids. The time for the fluid to fall or rise between marks A and B (which is proportional to the kinematic viscosity) determines the flow rate *Q*. The pressure drop DP is calculated from the head of fluid. The viscosity can be determined from these values and the geometry of the viscometer. The use of tube viscometers such as these is covered in various standards. These relatively cheap, easy to use viscometers are capable of high reproducibility and repeatability. Since the intrinsic viscosity depends not only on the size of the macromolecules but also on its shape, on the solvent, and on the temperature, there is no simple relationship for the direct calculation of molecular weights from viscosity measurements. However, the Mark-Houwink-Kuhn equation gives a general description of how the molecular weight can be calculated from the intrinsic viscosity:

$$[\eta] = K.M^a \quad (16)$$

M is the viscosity average molecular weight, and K and a are the Mark-Houwink constants. There is a specific set of Mark-Houwink constants for every polymer-solvent combination. So one has to know their values for the applied polymer-solvent combination in order to obtain an accurate measure of molecular weight. Therefore, for a new polymer, for which no Mark-Houwink constants are available, no good measure can be achieved. Under these conditions, one obtains only a qualitative idea of whether molecular weight is high or low. One is, therefore, always obliged to establish for each polymer a calibration curve or calibration function by comparison with an absolute method. This, however, is only valid for a given solvent and temperature.

I.3.2.5 Polymers in Drug delivery systems

Recent years have witnessed significant advances in controlled drug delivery using polymeric materials. Polymeric hydrogels are gaining more attention as drug delivery systems, especially for the controlled release of pharmaceutically active peptides and proteins[5960].
Hydrogels have been widely used in many biomedical applications including contact lenses, wound dressings, artificial organs, and delivery carriers for bioactive agents because of their high degree of biocompatibility[6162].High water content and low interfacial tension with the surrounding biological environment impart biocompatibility to the hydrogels[63].
Stimuli responsive polymers have the possibility to achieve a specific drug release in response to internal or external stimuli[64].Stimuli such as changes in pH, temperature, and glucose concentrations help stimuli-responsive polymers achieve a desired function[65].Biologically, adhesive delivery systems offer important advantages[66]. These types of structures can be achieved by different techniques originating different architectures (Figure I 30).

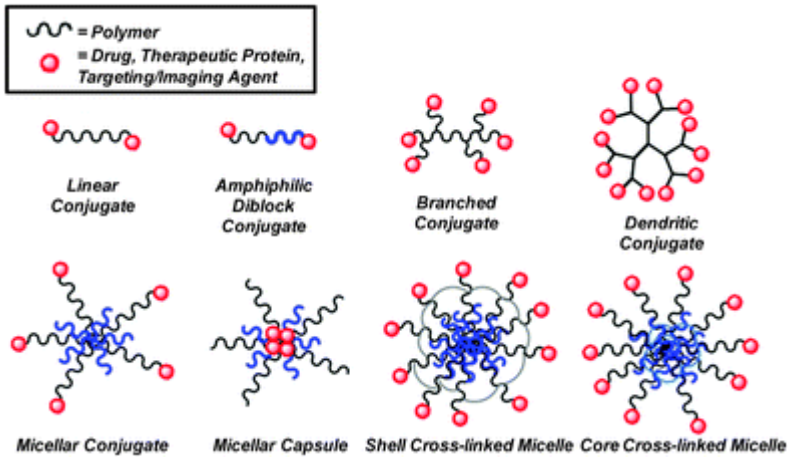


FIGURE I 60 Types of conjugate polymer based drug delivery structures

Hydrophilic polymers and hydrogels containing carboxyl groups have displayed bioadhesive properties[67]. These polymers maintain contact with the intestinal epithelium for extended periods of time and actually penetrate it through and between the cells. Synthetic polymers containing side-chain carbohydrates are considered high value polymeric materials because of their potential as biocompatible materials with medical applications. These applications are generally based on the fact that cell–cell interactions between oligosaccharides and lipids play an important role in various life processes[68]. Polystyrene was studied, given both its pendent lactose residues and its application as substratum for liver cell cultures[69]. An excellent review about stereoselective organic reactions in water has been recently published[70].

Chapter II Results and Discussion

II.1 Preamble

The sugar used in this thesis was sucrose and its chemistry turned out to be challenging due to high functionalization of this compounds, hence we need to use a selective protection approach to synthesize sucrose derivatives, while trying to use to the fullest extent all green chemistry principles. Using sucrose as a starting material presents some difficulties because of its solubility in organic solvents. As it has eight hydroxyl groups, to our knowledge, is soluble in very few solvents besides water: Dimethylformamide (DMF), Dimethylsulfoxide (DMSO) and pyridine. On the other hand, this solvents are aprotic and polar, with high boiling points (153 ºC, 189 ºC and 115 ºC, respectively) making them quite useful for microwave reactions as they allow a uniform and fast heating of the reaction media.

Throughout this thesis we intended to synthesize and characterize hydrophilic and hydrophobic polymers by co-polymerization of styrene with modified sucrose monomers.

Because of the potential advantages offered by sugar-based polymeric systems, we initiated the design and synthesis of sucrose-containing possible biocompatible and biodegradable polymers for drug delivery/tissue engineering applications.

Bearing this in mind, this work starts with synthesis of sucrose monomers and polymers by various techniques, and we describe the methods adopted in the synthesis. Later on in this chapter we will discuss the synthesis and characterization of the co-polymers obtained and their surface shape and physical properties.

II.2 Modified sucrose monomers and polymers – general schemes

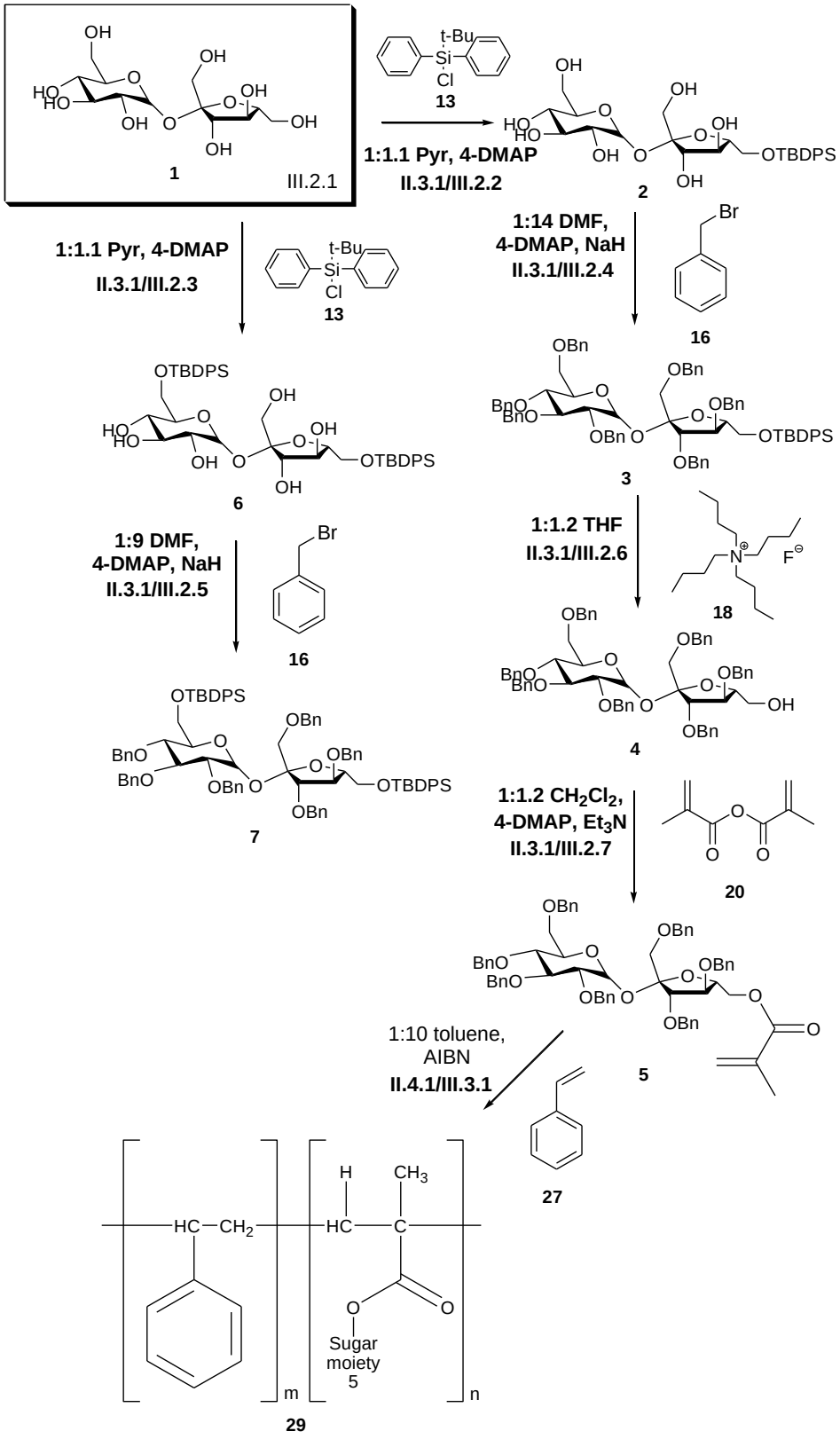


FIGURE II 1 – Sucrose selective derivatization using anhydrides, bromide halides and silyl chlorides and radical copolymerization with styrene

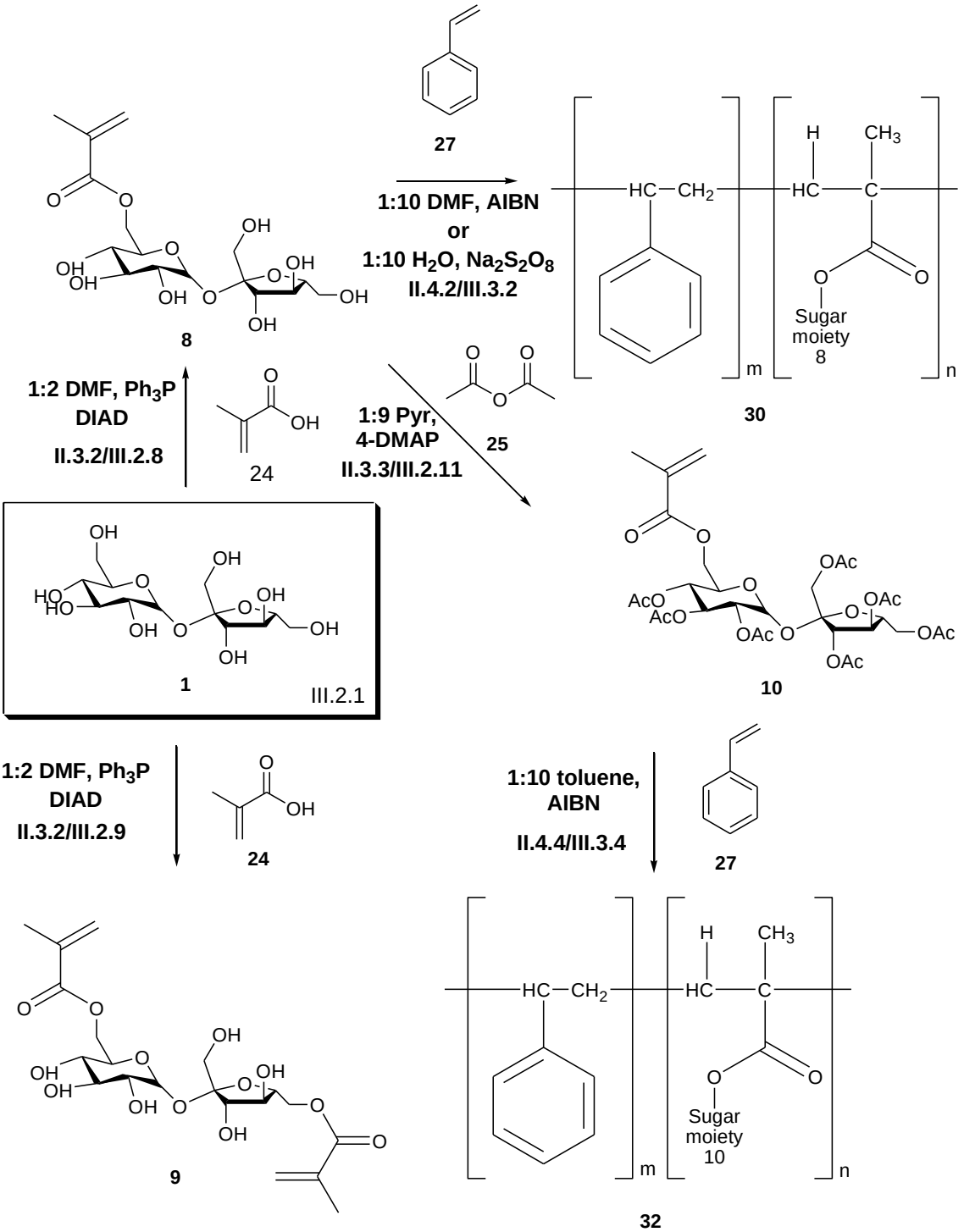


FIGURE II 2 Sucrose selective derivatization by Mitsunobu reaction and radical copolymerization with styrene

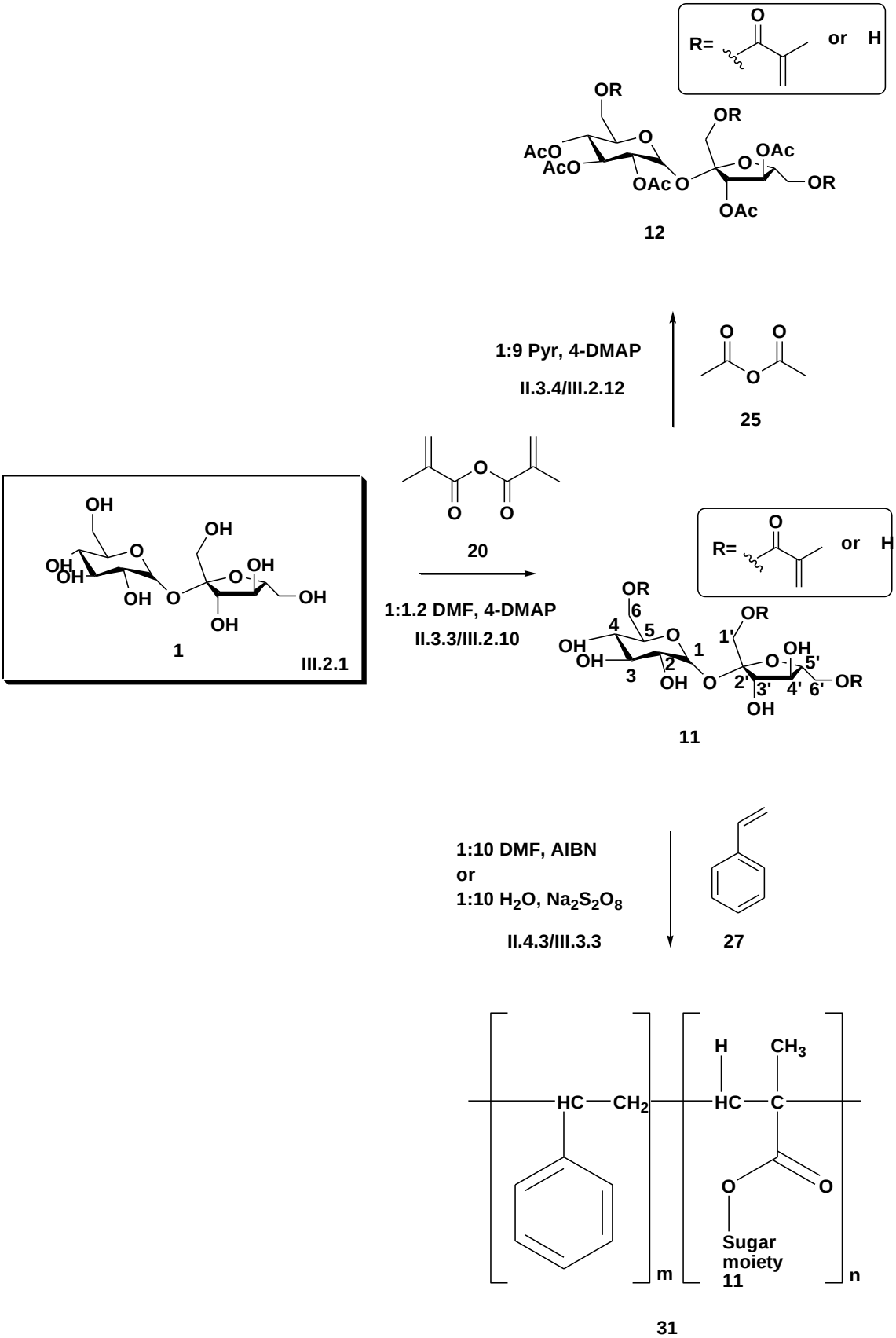


FIGURE II 3 Sucrose non-selective derivatization using anhydrides and radical copolymerization with styrene

II.3 Synthesis of modified sucrose monomers

The molecule used to synthesize all monomers that are going to be studied was sucrose **(1)**. The aim of this work is, through different approaches, to produce modified sucrose monomers with a methacrylate group in a primary position. This was the chosen approach to produce functionalized monomers because in order to synthesize co-polymers using free radical polymerization its very useful and common to have vinyl monomers as polymerization precursors.

Knowing that the hydroxyl groups in positions 6 and 6' are the most accessible in esterification conditions, a basic media was used in most cases (Et_3N) for sucrose to react and using a proper solvent for nucleophilic substitution.

II.3.1 Sucrose selective esterification by protection strategies - synthesis of 1',2,3,3',4,4',6 – hepta-*O*-benzyl-6'-*O*-methacryloyl-sucrose (5)

The procedure used to produce a functionalized monomer for polymer synthesis using sucrose as a starting material can be summarized as shown in Figure II 4:

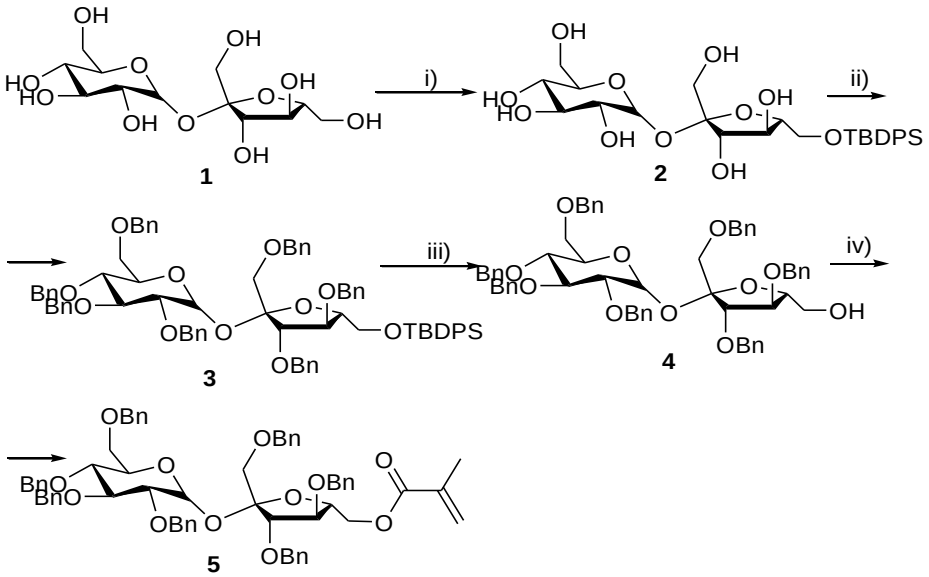


FIGURE II 4 Synthetic scheme for selective esterification of sucrose based on protection strategies: i) TBDPSCl, pyridine, 4-DMAP, (CSP – r. t.; MAP – 100 ºC); ii) BnBr, DMF, NaH, (CSP – r. t.; MAP – 150 ºC); iii) TBAF, THF, CSP – r. t.; MAP – 65 ºC).; iv) AM, CH_2Cl_2, Et_3N, 4-DMAP, r.t.

First, sucrose was finely powdered to ease dissolution at room temperature in all solvents used. The protection reaction took place using TBDPSCl as the silylation protection group. To catalyze this reaction we added a catalytic amount of 4-DMAP and this catalyst's role was to activate TBDPSCl by enhancing its reactivity towards the sucrose hydroxyl groups. The activation reaction happens as shown in Figure II 5:

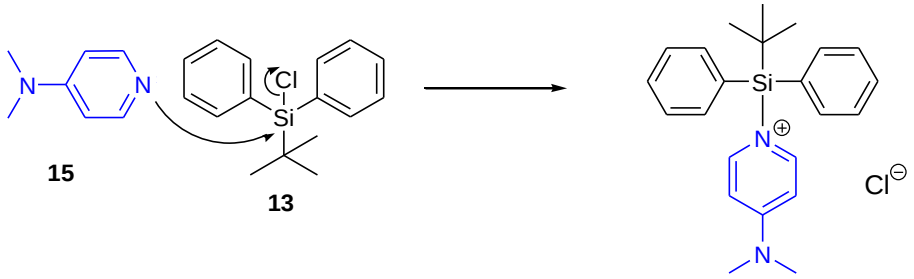


FIGURE II 5 Mechanism for 4-DMAP action on silylation substrate

Through this protection method sucrose was selectively protected in position 6' with the protecting group *tert*-butyldiphenylsilyl (TBDPS) yielding 57% through CSP and 33% through MAP after gradient purification by flash chromatography. The selectivity was due to the steric hindrance of the protecting group and the reactivity sequence of this protection is as follows: OH-6'>OH-6. The reaction stops as soon as the double protected compound is formed in order to maximize the yield. The mechanism for the selective protection of hydroxyl OH-6' is represented in Figure II 6.

This type of approach is directed to selective protection-deprotection of silyl ethers of sucrose, based on the fact that the primary alcohol groups are more reactive than the secondary and that between the primary hydroxyls there is a relatively well defined difference in reactivity[71]. Therefore, Compounds **(2)**, **(3)**, **(4)** and **(5)** are thoroughly studied on the first publications of Barros research group[72,73].

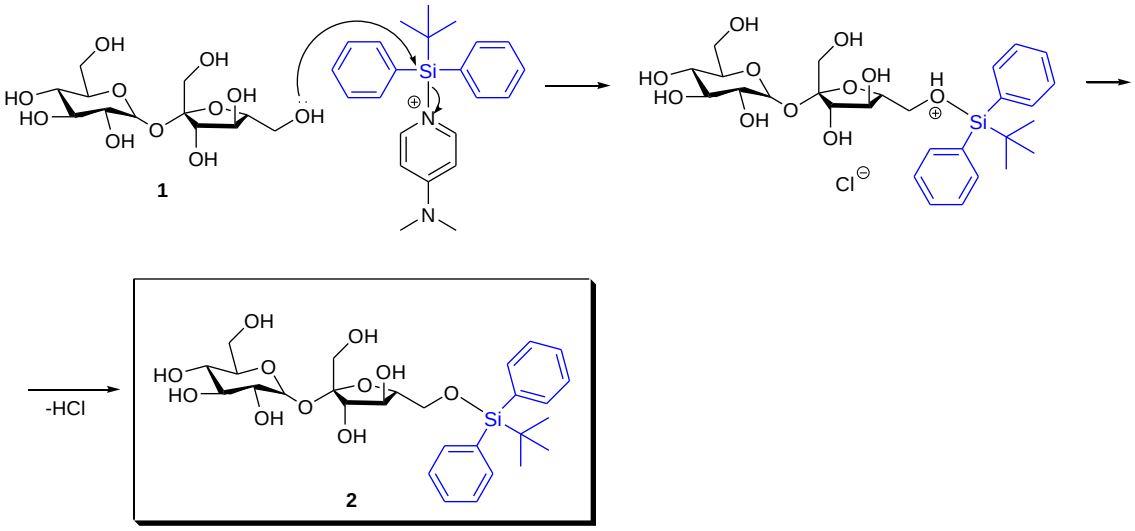
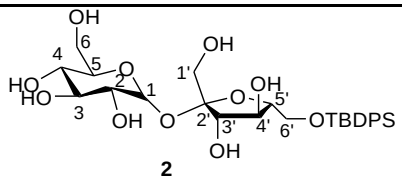
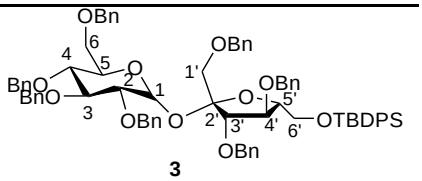


FIGURE II 6 Mechanism for the protection of sucrose hydroxyl OH-6' with TBDPS

TABLE II 1 Reaction and Spectra characteristics for the products 6'-O-TBDPS-sucrose **(2)** and 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-TBDPS-sucrose **(3)**

Structure		 **2**	 **3**
Yield (%)	**CSP**	57	76
	MAP	33	71
R. time (min)	**CSP**	120-180	150
	MAP	18	5
1H-NMR δ (ppm)		(400 MHz, DMSO-d6) 7.66 (m, 4H, Ar-*H*) 7.41 (m, 6H, Ar-*H*) 5.24 (d, *J*=3.1Hz, ^{1}H, H-1) 3.90 (t, *J*=9.7Hz, 1H) 3.79 (d, *J*=8.2Hz, 2H) 3.73 (m, 1H) 3.63 (m, 1H) 3.44 (m, 7H) 3.35 (s, O*H*, H_2O) 3.14 (dd, *J*=10.3, 3.7Hz, 1H) 3.07 (t, *J*=9.3Hz, 1H) 0.99 (s, 9H, CH_3)	(400 MHz, $CDCl_3$) 7.65 (t, 5 H, *J* 6.3 Hz, Ar-H) 7.40-7.09 (m, 40 H, Ar-H) 5.76 (d, 1H, *J* 3.4 Hz, H-1) 4.80 (dd, 2H, *J* = 16.6, 10.9 Hz) 4.65-4.70 (m, 4H) 4.50-4.58 (m, 14H, Ar- CH_2) 4.29 (t, 1 H, *J* 6.9 Hz) 4.24 (d, 1H, *J* = 12.1 Hz) 4.05 (q, 1H, *J* 5.4 Hz) 3.99- 3.90 (m, 3 H) 3.86 (t, 1 H, *J* 9.2 Hz) 3.75 (d, 1H, J=11.0Hz) 3.63 (t, 1H, J=9.6Hz) 3.53 (d, 1 H, *J* 11.0 Hz), 3.48-3.38 (m, 2 H) 3.27 (d, 1 H, *J* 10.3 Hz) 1.02 (s, 9 H, CH_3)
13C-NMR δ (ppm)		(100 MHz, DMSO-d6) 127.8 (C_{Ar}) 104.4 (C-2') 91.5 (C-1) 82.2 76.8 74.6 73.1 72.6 71.7 70.0 (C-2,3,3',4,4',5,5') 65.7 (C-1')	(100 MHz, $CDCl_3$) 127.4-138.9 (CAr) 104.6 (C-2') 89.8 (C-1) 84.2 82.7 82.0 81.3 79.9 75.5 74.7 73.4

60.8 (C-6,6')	73.3
26.7 (CH_3)	73.1
18.9 ($CSi(CH_3)_3$)	72.4
	72.1
	71.2
	70.6 (C-2,3,3',4,4',5,5', 6 x OCH_2Ph ar
	C-1')
	65.0 (C-6,6')
	26.9 (CH_3)
	19.3, ($CSi(CH_3)_3$)

In this protection reaction with TBDPSCl, the mono-protected product in the 6'-OH **(2)** is obtained at a Rf=0.35, and the di-substituted product **(6)** at a higher Rf, due to its lower polarity.

Nevertheless, even though the reaction is stopped as soon as this byproduct is formed, its yield is 10% by CSP and 27% by MAP. The TLC elutions were made with a solution of Ethyl acetate-Acetone-water, 10:10:1 with revelation with a solution of 10% H_2SO_4 in MeOH and heat drying. The purification in both CSP and MAP occurred using gradient elution starting with Ethyl acetate, Ethyl acetate-Acetone-water, 100:100:1 and Ethyl acetate-acetone-water, 10:10:1.

In this case, the difference in yields between CSP and MAP methods depend on the reaction time. In CSP it is easier to detect the formation of **(6)** and thus improve the yield of **(2),** with 57% in 2-3 hours reaction. In the case of MAP method, 33% yield was in 5 min reaction time. The advantage of the MAP protocols is the extremely reduced reaction time. The byproduct reactions are shown in Figure II 7.

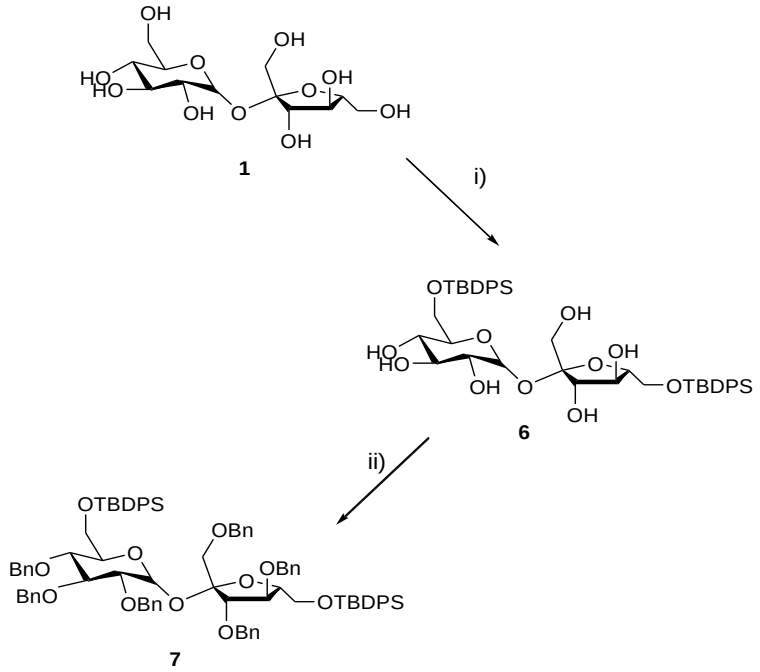
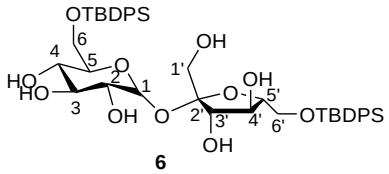
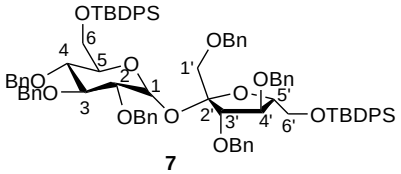


FIGURE II 7 Scheme of the byproduct that are formed when using protection/deprotection strategies in sucrose selective esterification: i) TBDPSCl, pyridine, 4-DMAP, (CSP – r. t.; MAP – 100 ºC); ii) BnBr, DMF, NaH, (CSP – r. t.; MAP – 150 ºC).

These byproducts are considered as such because they are di-substituted with TBDPS and the deprotection method would free both 6-OH and 6'-OH positions and both would be esterified, producing monomers with two unsaturated ester ends. This would produce cross-linked polymers by radical polymerization, because the polymerization reaction could occur, theoretically, on either of the unsaturated ester positions and create long distance covalent bonds in the polymer chains. The purpose of this thesis is to produce comb-like polymers so the monomers needed are the ones with only one unsaturated end in the form of an ester, for example, 1',2,3,3',4,4',6-hepta-O-benzyl-6'-O-methacryloyl sucrose **(5)**. The information about the byproducts (Table II 2) is still described if it is needed for future research on cross-linked polymers.

TABLE II 2 Reaction and Spectra characteristics for the byproducts 6 and 7

Structure		 **6**	 **7**
Yield	**CSP**	10	12
(%)	**MAP**	27	10
R. time	**CSP**	120-180	90
(min)	**MAP**	18	5
1H-NMR δ (ppm)		(400 MHz, $CDCl_3$) 7.57 (m, 8H, Ar-*H*) 7.25 (m, 12H, Ar-*H*) 5.15 (d, *J*=3.1Hz, 1H, H-1) 3.96 (m, 3H) 3.79 (m, 1H) 3.73 (m, 1H) 3.68 (m, 4) 3.44 (m, 4H) 0.93 (s, 9H, CH_3) 0.90 (s, 9H, CH_3)	(400 MHz, $CDCl_3$) 7.64 (m, 10H, Ar-*H*) 7.42 (m, 40H, Ar-*H*) 5.23 (d, 1H, *J1,2* =3.1Hz, H-1) 4.86 (d, 2H, *J6A,6B*=10.6Hz, H-6) 4.66 (m, 7H, H-3,3',4,4', Ar- CH_2) 4.46 (3d, 3H, Ar-CH_2) 4.32 (m, 2H, Ar-CH_2) 4.14 (m, 1H, H-5) 3.98 (m, 2H, H- 6') 3.82 (m, 2H, H-1') 3.60 (m, 3H, H-5', Ar-CH_2) 3.50 (dd, 1H, *J1,2*=3.2Hz, *J2,3*=9.6Hz, H-2) 3.43 (dd, 2H, *J*=10.2Hz, Ar-CH_2) 1.07 (s, 9H, CH_3) 1.05 (s, 9H, CH_3).
13C-NMR		(400 MHz, DMSO-d6)	(100 MHz, $CDCl_3$)

δ (ppm)	127.9 (CAr)	138.0 (Cq benzyl groups)
	105.0 (C-2')	127.6 (CAr)
	92.2 (C-1)	104.4 (C-2')
	82.4	89.5 (C-1)
	76.8	84.3
	75.0	82.2
	73.2	82.0
	72.7	80.7
	71.9	77.3
	69.6 (C-2,3,3',4,4',5,5')	76.7
	65.8 (C-1')	75.8
	63.3	74.7
	62.1 (C-6,6')	73.5
	26.8 (CH_3)	72.6
	19.0 ($CSi(CH_3)_3$)	72.4
		71.9
		71.6
		69.5 (C-2,3,3',4,4',5,5', 6 x OCH2Ph e C-1')
		62.3 (C-6,6')
		26.9 (CH_3)
		19.3 ($CSi(CH_3)_3$)

The evidence that sucrose has one of its –OH groups substituted with TBDPS in compound **(2)** is given by ^{1}H-NMR and ^{13}C-NMR spectra. In the ^{1}H-NMR, the signals for the unshielded aromatic protons on 7.66 ppm and 7.41 ppm and three $–CH_3$ groups at 0.99 ppm evidence the presence of two benzyl groups and the *tert*-butyl group, together with the backbone protons of sucrose in the range of 3.07-5.24 ppm, as shown in Table II 1.

After this protection step, 6'-O-*tert*-butyldiphenylsylil-sucrose **(2)** is protected with benzyl groups in the remaining positions, using a non-selective reaction of benzyl bromide (BnBr) in DMF (Figure II 7). 14 equivalents of BnBr were used, 2 equivalents for each free hydroxyl group, to guarantee complete protection. In this reaction, sodium hydride is used a base to ease benzylation by proton removal of the remaining free hydroxyl groups in compound **(2)**. The catalytic reaction occurs as demonstrated in Figure II 8, between NaH and the protons from –OH groups, releasing H_2 gas. This reaction required especial security procedures due to highly flammable H_2 release and BnBr fumes that have tear-gas properties. By CSP, the reaction takes 2.5 hours (76% yield, r.t.) to occur and by MAP 5 min (71% yields, 300 W, 150 ºC) and was stopped as soon as compound **(2)** is absent, confirmed by TLC monitoring (elution hexane-ethyl acetate, 5:1). In both protocols, the purification occurred by gradient flash chromatography followed by liquid-liquid extraction of the benzylated compounds to organic phase (diethyl ether). The inclusion of seven benzyl groups after benzylation to synthesize 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-TBDPS-sucrose **(3)** is confirmed by an additional 35 protons in the aromatic region between 7.40-7.65 ppm. In this compound the anomeric proton suffered a dislocation in its chemical shift to 5.76 ppm due to the presence of the electronically dense benzyl groups that shield the anomeric proton, shown in Table II 1.

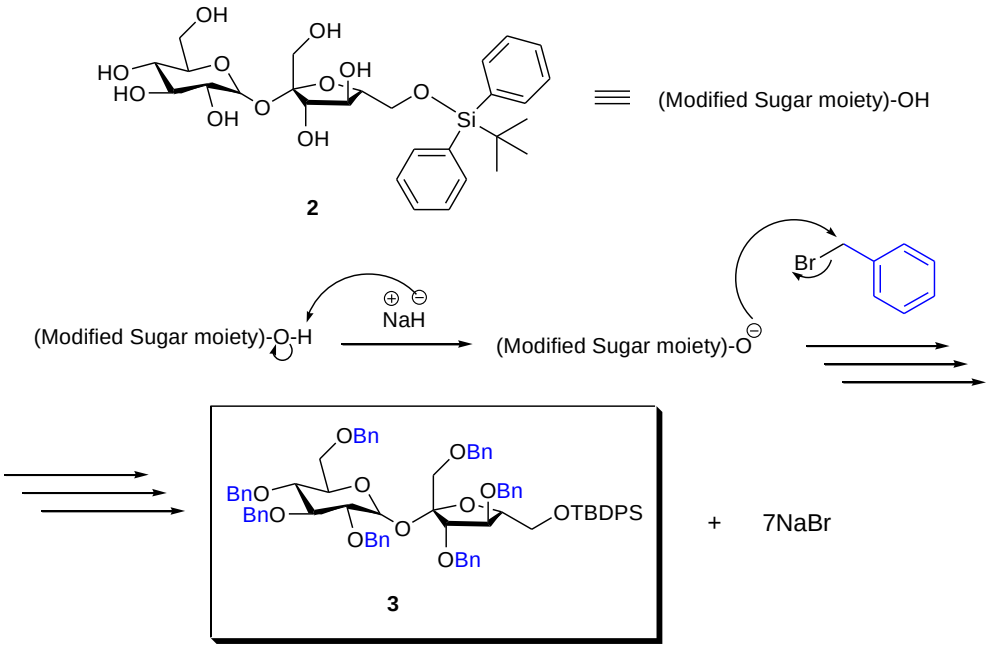


FIGURE II 8 Mechanism for the protection of 6'-O-*tert*-butyldiphenylsylil-sucrose **(2)** free hydroxyls with benzyl groups,, synthesizing 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-TBDPS-sucrose **(3)**

As a byproduct of this reaction, if the reaction time is longer than needed, the octabenzylated product is formed by extrusion of the protection group TBDPS (Figure II 9), and it can be detected by TLC as a spot that appears at the lowest R_f after the spot of **(3)**.

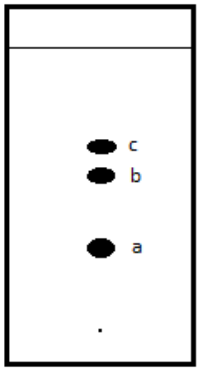


FIGURE II 9 Example of a TLC obtained for reaction in section II.3.1: a) octabenzylated sucrose b) 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-TBDPS-sucrose **(3)** with R_f=0.54 and c) 1',2,3,3',4,4',-hexa-*O*-benzyl-6,6'-*O*-diTBDPS-sucrose **(7)** - elution with hexane-diethyl ether, 3:1

Until now, the strategy was to protect selectively the hydroxyl position with one type of protecting group (TBDPS) and protect all the other positions with a different protecting group, benzyl groups, to produce 1',2,3,3',4,4',6–hepta–*O*–benzyl–6'–O-*tert*-butyldiphenylsilyl-sucrose **(3)**, a very hydrophobic molecule. This protection with Bn groups was used because the methods of deprotection are different and we can selectively remove TBDPS, maintaining all other groups still protected with Bn group. In this case, tetrabutylammonium fluoride (TBAF) was specifically used for the removal of TBDPS, as a fluoride ion source. This reagent is specific for this removal because of the F-Si bond strength; they are among the strongest sigma bonds, much stronger than a Si-O bond. For this reason, the fluoride ion bonds to Si, releasing the modified sugar moiety of **(3)**. This mechanism is described in Figure II 10.

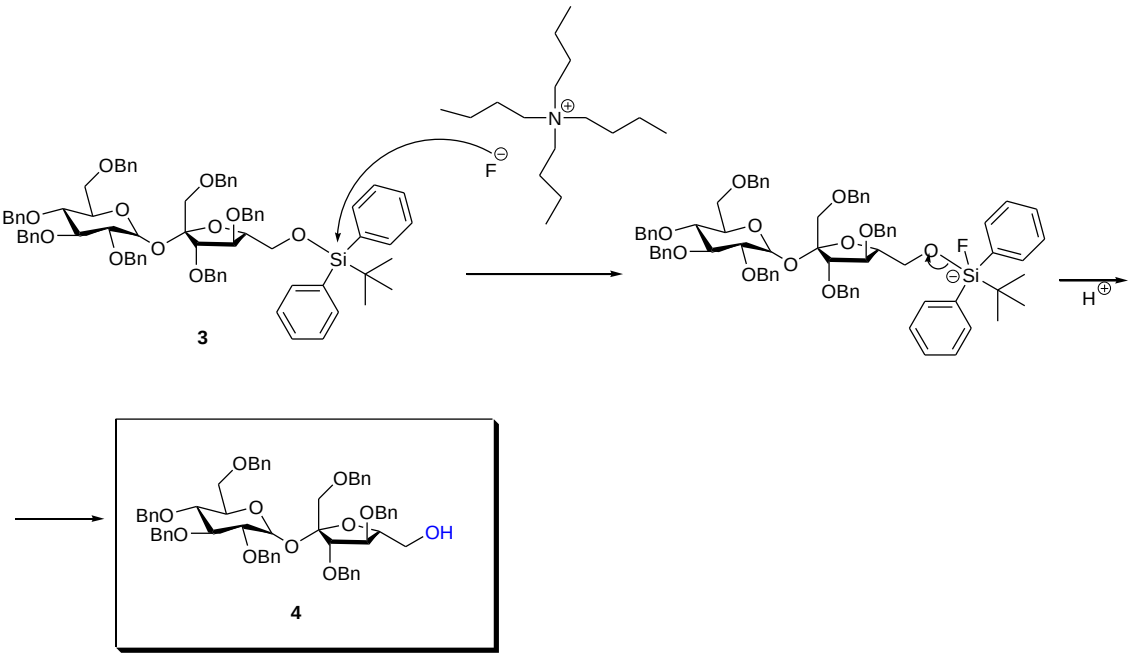


FIGURE II 10 Mechanism for the removal of TBDPS to form 1',2,3,3',4,4',6-hepta-*O*-benzyl-sucrose **(4)** with a fluoride source, TBAF

Both CSP and MAP methods produced 1',2,3,3',4,4',6-hepta-*O*-benzyl-sucrose **(4)** after isocratic flash chromatography purification with 750 mL of hexane-ethyl acetate, 5:1, with 70% yield (CSP- r.t.; MAP- 300 W, 65 ºC). The purity of **(4)** was accessed by specific rotation, +29.6 (c, 1.1, $CHCl_3$), and by ^{1}H-NMR. It is possible to see the presence of sucrose backbone in the chemical shift range of 3.24-5.54 ppm and absence of the tert-butyl groups and benzyl group protons of TBDPS, Table II 3.

After this step, it is possible to selectively insert a vinyl ester group in the 6'-OH position, by simple nucleophilic substitution. To perform esterification on the 6'-OH position of **(4),** methacrylic anhydride was used, catalyzed by 4-DMAP and triethylamine (Et_3N). Esterification procedures for alcohol groups are frequently done using anhydrides or acid chlorides. These compounds react with the alcohol, in the presence of a base, originating the corresponding ester. The alcohol is nucleophilic and attacks the carbonyl group, the electrophilic center. The base removes the proton from the alcohol. If anhydrides are used, the leaving group is a carboxylate. For the acid chlorides, the formation of the ester is achieved along with chloride elimination[74]. The general mechanism for an esterification process using an anhydride in basic media is shown on Figure II 11.

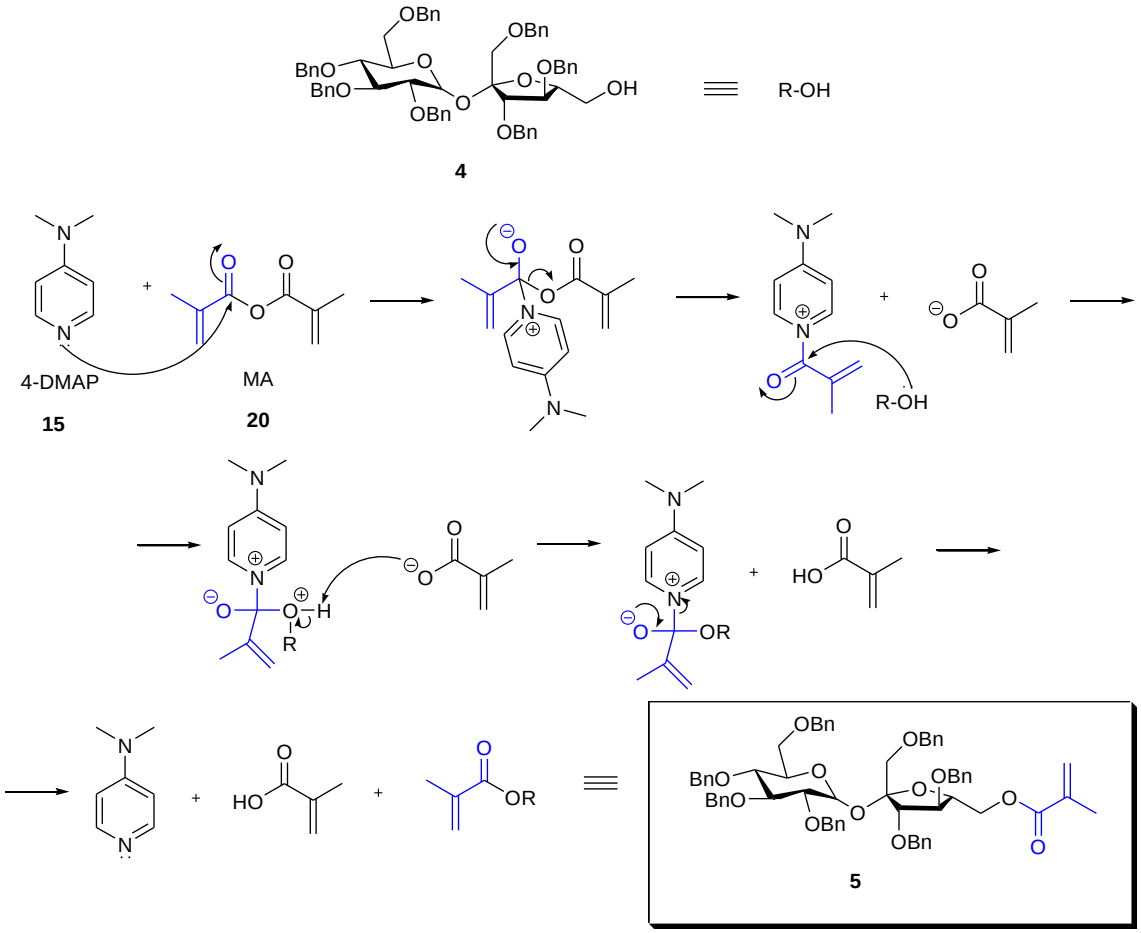
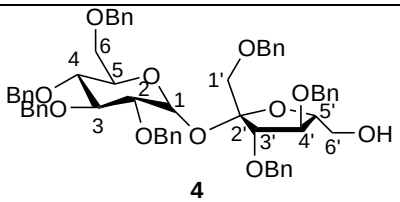
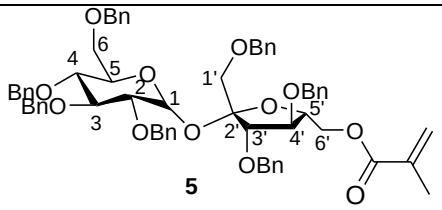


FIGURE II 11 Mechanism for the formation of a selective vinyl ester on the 6-OH position[75]

In this case, 4-DMAP acts as an acyl transfer catalyst that works in a basic media, the added Et_3N, by combining itself with methacrylic anhydride and forming an active compound that eases esterification processes. This is the final reaction that originates the first functionalized sucrose monomer that can be used for radical copolymerization with styrene. The compound 1',2,3,3',4,4',6-hepta-O-benzyl-6'-O-methacryloyl sucrose **(5)** was obtained from **(4)** with a yield of 69% (CSP, r.t) and was purified by flash chromatography using gradient elution starting with Hexane, Hexane-Ethyl acetate, 5:1 and Hexane-Ethyl acetate, 3:1. The compound 1',2,3,3',4,4',6-hepta-O-benzyl-6'-O-methacryloyl sucrose **(5)** obtained is a yellowish oil and its structure is confirmed by ^{1}H-NMR spectroscopy in Table II 3. Sucrose backbone protons are detected in the chemical shift region of 3.93-4.18 ppm and 4.79-6.15 ppm. The aromatic protons from the benzyl groups are found at 7.13-7.37 ppm and its methylene groups $–CH_2$- protons in the region of 4.33-4.72 ppm. The protons from the ester groups in the 6'-OH position are found at 2.00 ppm for the $–CH_3$ of the methacryloyl and 3.47-3.55 ppm for the $=CH_2$ group.

The purity was also accessed by specific rotation of +46.9 (*c*, 1.0, $CHCl_3$).

TABLE II 3 Reaction and Spectra characteristics of 1',2,3,3',4,4',6 – hepta-*O*-benzyl-6'-*O*-methacryloyl sucrose (5)

Structure		 **4**	 **5**
Yield (%)	**CSP**	70	69
	MAP	70	
R. time (min)	**CSP**	1440*	1440*
	MAP	5	
1H-NMR δ (ppm)		(400 MHz, $CDCl_3$)	
		7.33 – 7.1 (m, 35H, Ar-*H*)	(400 MHz, $CDCl_3$)
		7.11 – 7.10 (m, 1H, Ar- *H*)	7.37-7.13 (m, 35H)
		5.54 (d, 1 H, *J*=3.0 Hz, H-1)	6.15 (d, J=3.6Hz, 1H)
		4.83 (d, 1 H, *J*=10.85 Hz, CH_2-Ph)	5.55 (d, J=3.6Hz, 1H)
		4.78 (d, 1 H, *J* =10.9 Hz, CH_2-Ph)	5.72 (d, J=3.7Hz, 1H)
		4.67 – 4.59	4.83 (d, J=11.0Hz, 1H)
		(m, 12H, CH_2-Ph and H-5'),	4.79 (d, J=11.0 Hz, 1H)
		4.41 (m, 1H, H-3')	4.72- 4.33 (m, 14H)
		4.28 (d, 1 H, *J* 12.1 Hz, H-3)	4.18 (d, J=12.0Hz, 1H)
		4.47-4.44 (dd, 1 H, *J* = 10.9, 8.0 Hz, H-1	4.11 (dd, J=11.2, 5.5 Hz, 1H)
		4.42- 4.28 (m, 1H, H-6)	4.09-4.05 (m, 1H)
		4.00 – 3.97 (m, 1 H, H-6)	3.93 (t, J=9.2 Hz, 1H)
		3.74-3.71 (m, 1H, H-4')	3.75-3.62 (m, 3H)
		3.60 (t, 1 H, *J* 9.63 Hz, H-2)	3.55-3.47 (m, 2H)
		3.57 – 3.46 (m, 3 H, H-1', H-5, H-4)	2.00 (s, 3H)
		3.24 (d, 2 H, *J* 9.45 Hz, H-6', H-5')	

***reaction let overnight

II.3.2 Selective esterification by Mitsunobu Reaction - Synthesis of 6-*O*-methacryloyl Sucrose (8) and 6,6'-*O*-methacryloyl sucrose (9)

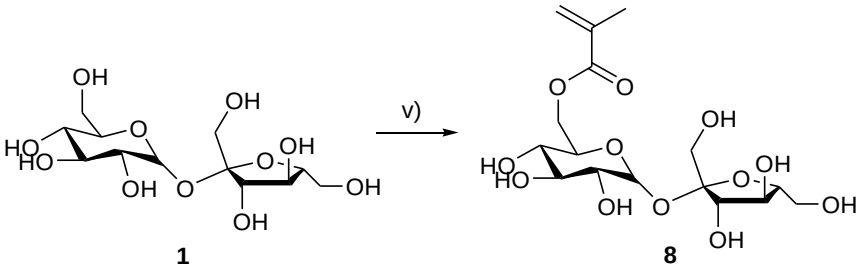


FIGURE II 12 Synthetic scheme for selective esterification of sucrose by mitsunobu reaction to produce 6-*O*-methacryloyl-sucrose (8): v) Ph_3P, DMF, DIAD, methacrylic acid, r.t., 72 h (CSP)

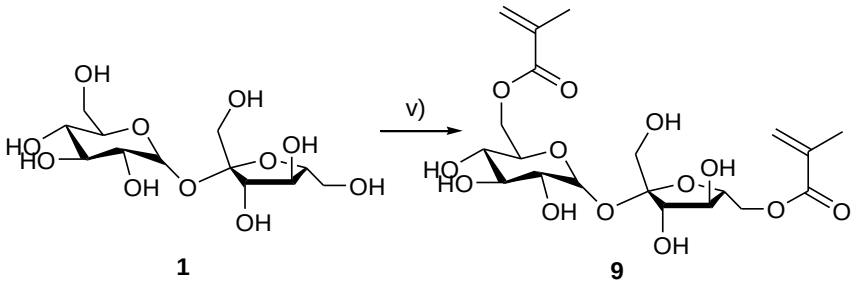


FIGURE II 13 Synthetic scheme for selective esterification of sucrose by Mitsunobu reaction to produce 6,6'-*O*-methacryloyl-sucrose (8): v) Ph_3P, DMF, DIAD, methacrylic acid, r.t., 72 h (CSP)

As shown in Figure II 12 and Figure II 13, sucrose **(1)** was esterified using Mitsunobu conditions with the objective of producing a selectively esterified sucrose based monomer. This reaction occurs under specific conditions with the use of appropriate reagents and it was used to synthesize 6-*O*-methacryloyl-sucrose **(8)** and 6.6'-O-dimethacryloyl-sucrose **(9)**. Once again, compound **(9)** is considered a byproduct as it is not needed as a monomer for being esterified with vinyl ester in two positions. The reaction is stopped as soon as the di-ester **(9)** is formed (TLC monitoring with acetate-methanol-water, 5:2:1) and 6-O-methacryloyl-sucrose was obtained by CSP after reacting for 72h (62% yield, r.t.). A liquid-liquid extraction was performed before purification, extracting compounds **(8)** and **(9)** to the aqueous phase. Purification occurred using flash chromatography eluting with Ethyl acetate-acetone-water, 10:10:1 and the purity of **(8)** was accessed by specific rotation, ^{1}H-NMR, ^{13}C-NMR and FTIR. The specific rotation obtained +30.3 º (c, 0.9, MeOH). On ^{1}H-NMR we can identify all the protons from sucrose backbone in the chemical shift range of 3.37-5.27 ppm. The anomeric proton is found as a duplet at 5.27 ppm with a coupling constant ($J_{1\text{-}2}$) with proton H-2 of 3.4 Hz. Methacryloyl protons are found at 1.80 ppm for the -CH_3 group, and the protons from the methylene group are found not to be equivalent (heterotopic) as they appear as two different signals, one at 6.02

ppm and other at 5.61 ppm as singlets. In the FTIR spectra it is observed at 3429 cm^{-1} the stretching of O-H groups, at 1707 cm^{-1} the carbonyl stretching and the saturated C-H bond at 2930 cm^{-1}.

The Mitsunobu reaction is defined as a bimolecular nucleophilic substitution (S_N2). The mechanism is demonstrated in Figure II 14.

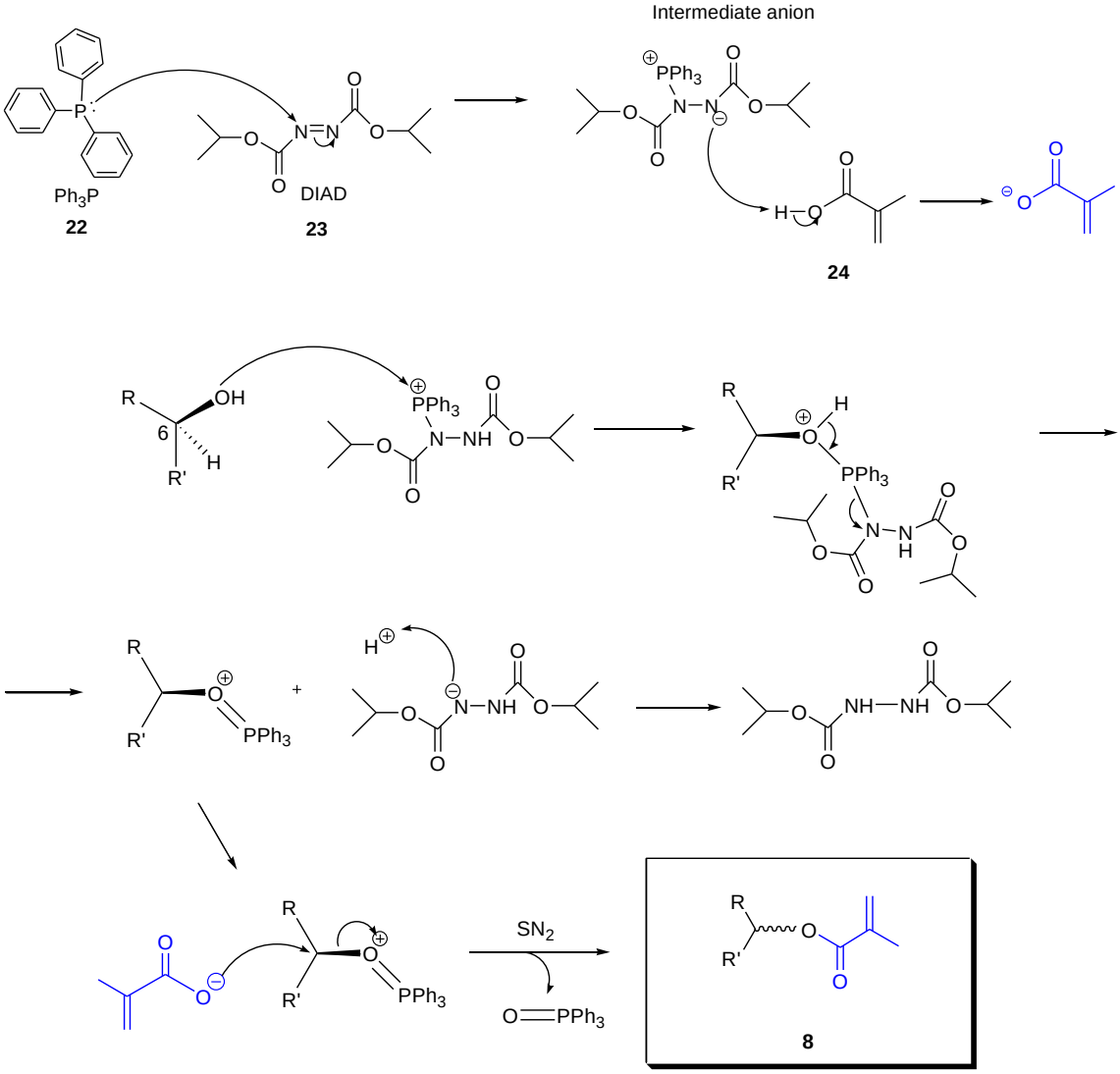


FIGURE II 14 Selective esterification mechanism in Mitsunobu conditions to synthesize 6-*O*-methacryloyl-sucrose **(8)**

This reaction starts with triphenylphosphine **(22)** phosphorus addition to the weak N=N π-bond of diisopropyl azodicarboxylate – DIAD **(23)**, originating an anion stabilized by the DIAD's ester groups. This anion is basic enough to remove the methacrylic acid's **(24)** proton. In the next step, as oxygen and phosphorus have an enormous affinity, the alkoxide ion attacks the positive charge placed on the phosphorus atom originating a second anion stabilized by ester groups, as before. This anion combines itself with the 6'-OH alcohol group in sucrose, regenerating the DIAD molecule by proton abstraction, origination a phosphine oxide by S_N2.

This reaction driving force is the breaking of a weak N=N π-bond and subsequent formation of two N-H bonds and one P=O bond.

The Mitsunobu reaction method as used by Barros et al. (M.T. Barros et al. 2011) is often used to substitute -OH groups by other groups with inversion of configuration. In this case, as the substitutions occur at the achiral carbons C-6 and C-6', inversion of configuration is not relevant. Such a process performed on free sucrose affords 6,1',6'-triesters or 6,6'-diesters[76], establishing the reactivity of hydroxyl groups as 6-OH > 6'-OH >1'-OH > secondary OH groups. This procedure has to be done very carefully, ensuring that moisture is completely absent in all the reaction stages and it is done by dissolving the acid and triphenylphosphine in a dry DMF solution with sucrose. The reaction mixture is cooled in an ice bath and DIAD is carefully added under argon atmosphere.

This procedure has the advantage of an excellent selectivity for primary hydroxyl groups versus secondary, as shown for sucrose only substituted on positions 6 and 6'. This procedure avoids the use of protecting groups and therefore, many reaction steps when compared to protection/deprotection methodologies of the primary groups. Even though the yield is low, it compensates by the reduced number of steps and the corresponding purification procedures.

II.3.3 Synthesis of 1',2,3,3',4,4',6' – hepta-*O*-acetyl-6-*O*-metacryloyl sucrose (10)

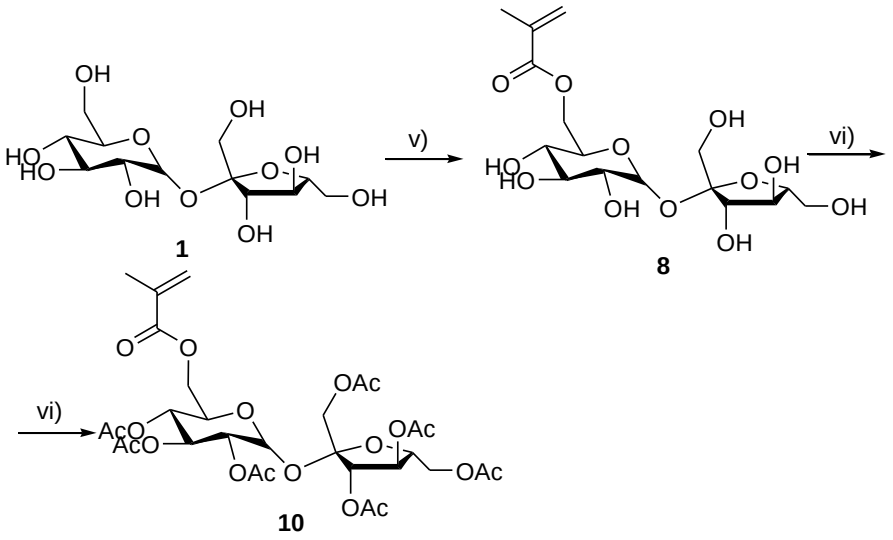


FIGURE II 15 Synthetic scheme for selective esterification of sucrose to produce 1',2,3,3',4,4',6' – hepta-*O*-acetyl-6-*O*-metacryloyl sucrose (10): v) Ph_3P, DMF, DIAD, methacrylic acid, r.t., 72 h; vi) Pyridine, Acetic Anhydride, 4-DMAP, 24h

After the synthesis of **(8)** by using Mitsunobu esterification conditions, we can easily acetylate the remaining positions by simple S_N2 reaction with acetic anhydride. It is common opinion in the literature, that acetylation of the sugar derivatives facilitates and simplifies the NMR analysis[77,78] so, this acetylation was made to better characterize and confirm the structure

of the compound with free hydroxyl groups **(8)** and also to produce a hydrophobic monomer for polymer synthesis, Figure II 15.

This reaction takes place in pyridine at room temperature with the catalyst 4-DMAP acting as an acyl transfer catalyst in basic media, as described before. The acetylation mechanism is exactly as the one with methacrylic anhydride (shown in Figure II 11, page 52), the only difference is the intermediate that facilitates the acetylation process as shown in Figure II 16.

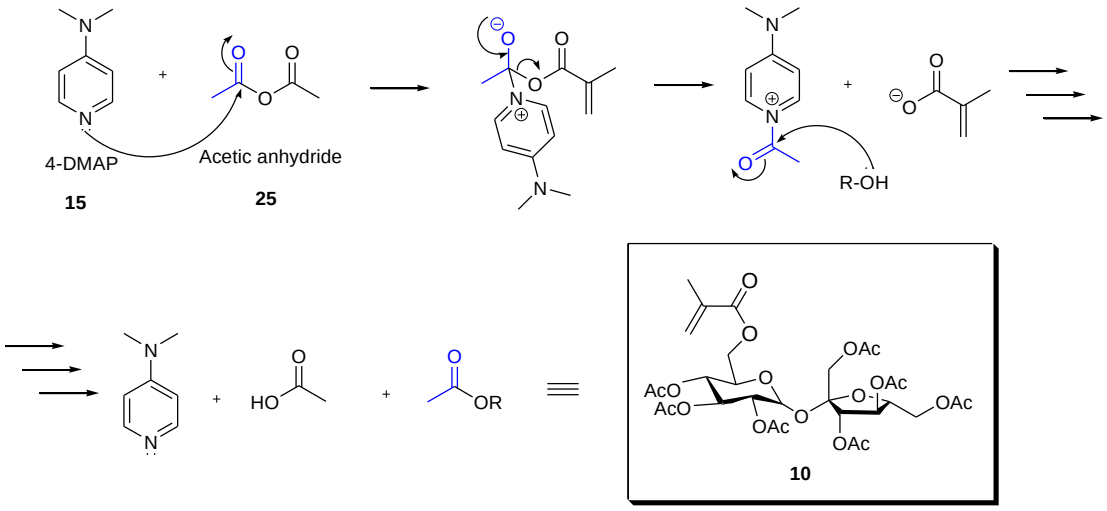
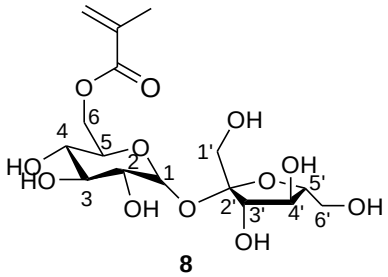
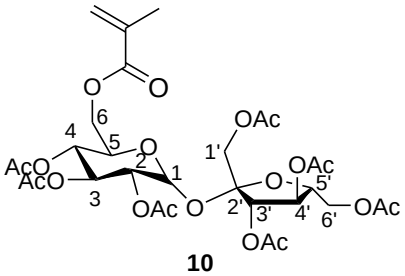


FIGURE II 16 Mechanism for the acetylation of the alcohol groups of sucrose using 4-DMAP as an acyl transfer catalyst synthesis of 1',2,3,3',4,4',6' – hepta-*O*-acetyl-6-*O*-metacryloyl sucrose **(10)**

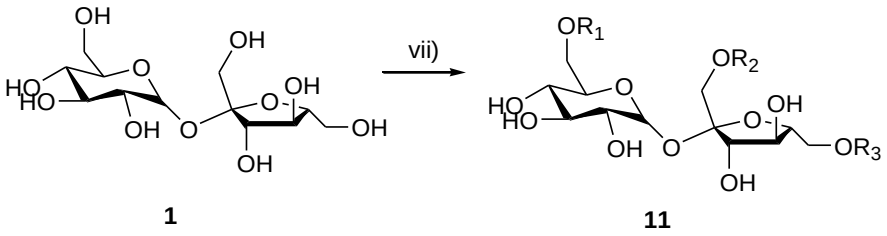
The reaction was stopped when verified by TLC (elution with Ethyl acetate-acetone-water, 10:10:1) that 6-*O*-methacryloyl-sucrose **(8)** was absent and the work-up was a liquid-liquid extraction where the aqueous phase is an 1M HCL solution to neutralize pyridine. Compound 1',2,3,3',4,4',6' – hepta-*O*-acetyl-6-*O*-metacryloyl sucrose **(10)** was extracted to an organic phase (diethyl ether) and purified by isocratic flash chromatography using a solution of Hexane-Ethyl acetate, 1:1). Using CSP this reaction had a yield of 58% after reacting for 24h at room temperature. The purity of the compound obtained was accessed by ^{1}H-NMR, ^{13}C-NMR, FTIR and specific rotation. By the ^{1}H-NMR experience, we observe the anomeric proton chemical shift changes to 5.70 ppm as it occurred for compound **(5)**, due to shielding effects of the acetyl protecting groups. The methyl group from methacryloyl appears at 1.97 ppm as a singlet and the methylene group protons as they are heterotopic one appears at 6.21 ppm and the other at 5.63 ppm. The acetyl groups appear as singlets in the chemical shift range of 2.02-2.18 ppm and sucrose backbone protons appear at the 4.18-5.46 ppm range except the anomeric that is dislocated to a higher field (Table II 4).

TABLE II 4 Reaction and Spectra characteristics for the mitsunobu ester obtained using sucrose as substrate, 6-O-methacryloyl sucrose (8) and 6,6'-O-methacryloyl sucrose (9)

Structure		 **8**	 **10**
Yield (%)	**CSP**	62	58
R. time (h)	**CSP**	72	24
1H-NMR δ (ppm)		(400 MHz, D_2O) 6.02 (1H, s, =CH_2*a*) 5.61 (1H, s, =CH_2*b*) 5.27 (1H, d, $J_{1\text{-}2}$=3.4 Hz, H_1) 4.34 (2H, dq, $J_{6a\text{-}5}$=4.3 Hz, $J_{6a\text{-}6b}$=12.2 Hz $J_{H6\text{-}COO}$=30.7 Hz, $H_{6a,b}$) 4.08 (1H, d, $J_{3'\text{-}4'}$=8.7 Hz, $H_{3'}$) 4.03-3.95 (1H, m, H_5) 3.87 (1H, t, $J_{3'\text{-}4'\text{-}5'}$=8.6 Hz, $H_{4'}$) 3.82- 3.73 (1H, m, $H_{5'}$) 3.73-3.60 (3H, m, $H_{6'a,b}$ + H_3) 3.54 (2H, s, $H_{1'}$) 3.44 (1H, dd, $J_{1\text{-}2}$=3.5 Hz, $J_{2\text{-}3}$=9.8 Hz, H_2 3.37 (1H, t, $J_{3\text{-}4\text{-}5}$=9.5 Hz, H_4) 1.80 (3H, s, -CH_3)	(400 MHz, $CDCl_3$) 6.21 (1H, d, $J_{CH2a\text{-}CH2b}$ = 13.6Hz, C CH_{2a} 5.70 (1H, d, $J_{1\text{-}2}$ = 3.6Hz,H_1) 5.63 (1H, d, $J_{CH2b\text{-}CH2a}$ = 10.8 Hz, C C*H*2b) 5.46 (1H, d, $J_{3\text{-}4}$ = 4.8 Hz, H_3) 5.44 (1H, t, $J_{2\text{-}3}$ = $J_{3\text{-}4}$ = 9.9 Hz, H_3) 5.38 (1H, t, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 4.8 Hz, H_4) 5.13 (1H, t, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 9.8 Hz, H_4) 4.82 (1H, dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{2\text{-}3}$ = 10.4 H H_2) 4.28 (8H, m, H_5, H_6, H_6, H_5, H_1) 2.18 (3H, s, CH_3O) 2.12 (3H, s, CH_3O) 2.11 (3H, s, CH_3O) 2.10 (3H, s, CH_3O) 2.03 (3H, s, CH_3O) 2.02 (3H, s, CH_3O) 1.97 (3H, s, –CH_3).
13C-NMR δ (ppm)		(100 MHz, D_2O) 169.7 (-COO-) 135.9 (COO(CH_3)*C*=) 127.6 (*C*H_2=) 104.1 ($C_{2'}$) 92.4 (C_1) 81.7 ($C_{5'}$) 76.8 ($C_{3'}$)	(100 MHz, $CDCl_3$) 170.5–169.4 (8-COO–) 135.9 (COO(CH_3)*C*) 127.6 (*C*H_2) 104.1 ($C_{2'}$) 90.0 (C_1) 79.2 (C_5) 75.8 (C_3)

	74.5 ($C_{4'}$)	75.1 (C_4)
	72.7 (C_3)	70.3 (C_2)
	71.4 (C_2)	69.8 (C_3)
	70.8 (C_5)	68.6 (C_5)
	70.0 (C_4)	68.4 (C_4)
	64.0 (C_6)	63.6 (C_6)
	63.0 ($C_{6'}$)	62.9 (C_1)
	61.8 ($C_{1'}$)	60.7 ($C_{6'}$)
	17.8 (CH_3)	20.6 ($7CH_3CO$)
		17.8 (CH_3).
FTIR v_{max} (KBr) cm^{-1}	3429 (O-H)	2857 (C–H, sat.)
	2930 (C-H, sat.)	1756 (C O)
	1707 (C=O)	1370 (C–C–C)
	1325 (C-C-C)	1221 (C–O–C ester)
	1138 (C-C-O)	1178 (C–C–O;C C)
	1054 (C-O-C)	1038 (C–O–C)

II.3.4 Non-selective esterification - synthesis of *O*-methacryloyl sucrose (11)



1 **11**

R_1= $COC(CH_3)=CH_2$; R_2=H; R_3=H or
R_1=H; R_2= $COC(CH_3)=CH_2$; R_3=H or
R_1=H; R_2=H; R_3= $COC(CH_3)=CH_2$

FIGURE II 17 Synthetic scheme for non-selective esterification of sucrose to produce *O*-methacryloyl Sucrose (10): vii) Pyridine, Et_3N, 4-DMAP, methacrylic anhydride, r.t., 24h

The mechanism of a non-selective esterification is the same as described in Figure II 11, page 52 and the acetylation process occurs as described in figure II 16, page 57. In this kind of esterification to synthesize *O*-methacryloyl sucrose, we can only predict that the primary alcohol are being esterified first but cannot be sure on the esterification position. It is random process without selectivity and can occur first in the 6-OH, 1'-OH or 6'-OH positions. The purpose of synthesizing monomers using a no-selective process is to evaluate if the esterification process of the monomer will influence the polymer produced, both in chemical and physical properties.

In this reaction, sucrose **(1)** reacted with methacrylic anhydride with the acyl transfer catalyst, 4-DMAP and the reaction was tested in two solvents, DMF and Pyr. In DMF it yields 47% (CSP, r.t., 24h) and in Pyr yields 51% (CSP, r.t., 24h). This indicates that the best solvent for this non-selective esterification is Pyr. Even though the difference in yield is not that significant, it is possible to synthesize a larger quantity of *O*-methacryloyl-sucrose **(11)** in this esterification conditions using pyridine as solvent. Both reactions were stopped as soon as the di-ester product (TLC monitoring elution with Ethyl acetate-acetone-water, 10:10:1) was formed so the reason for the improved yield in Pyr is that the basicity of a Pyr media is more suitable than DMF for an acetylation process in this reaction conditions. The product (11) obtained in both reactions was purified by isocratic flash chromatography elution with Ethyl acetate-acetone-water, 10:10:1 and the purity of the compound accessed by ^{1}H-NMR and ^{13}C-NMR as described in Table II 5.

II.3.5 Acetylation of non-selective esters - synthesis of acetylated mono-methacryloyl-sucrose (12)

The acetylation of the non-selective ester, *O*-methacryloyl-sucrose **(11)** was done in the same conditions as the acetylation of the Mitsunobu ester, 6-*O*-methacryloyl-sucrose **(10)**, section II.3.3, as shown in Figure II 18.

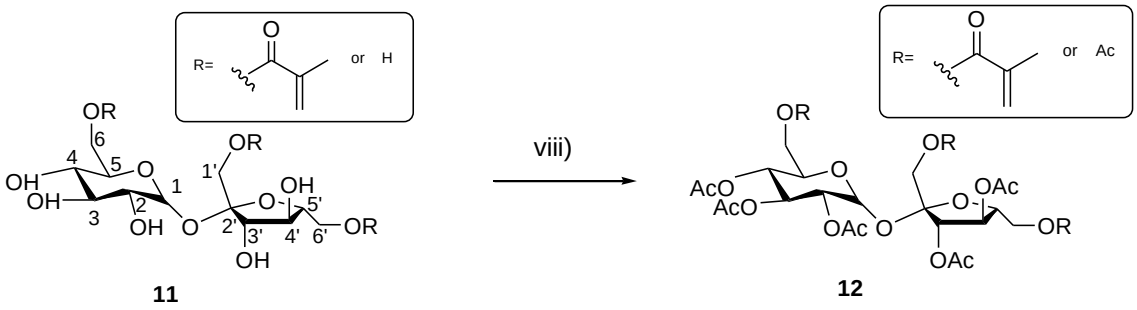
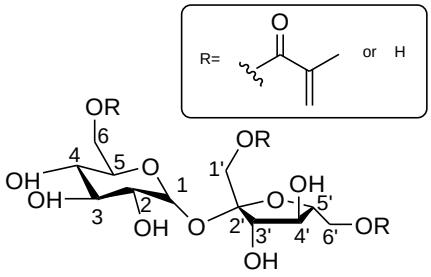
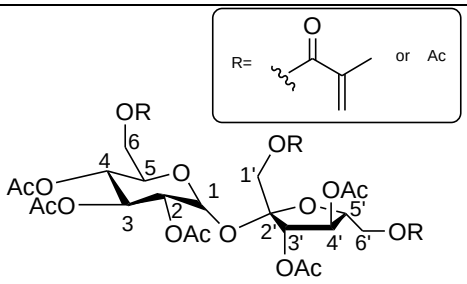


FIGURE II 18 Synthetic scheme for the acetylation of the non-selective ester of sucrose (11) to produce acetylated mono-methacryloyl sucrose (12): viii) Pyridine, 4-DMAP, acetic anhydride, r.t., 24h, (12): R=methacryl or Ac.

As it is, the acetylation of **(11)** produces a sucrose mono-ester in one of its primary positions acetylated in the remaining seven non-functionalized hydroxyl positions, Figure II 18. The reaction yielded 45% (CSP, r.t., 24h). As determined before, Pyr was used to carry out the acetylation reaction as it was considered the best solvent to do this type of reaction. The purity of the acetylated non-selective mono-ester **(12)** was accessed by ^{1}H-NMR and ^{13}C-NMR.

TABLE II 5 Reaction and Spectra characteristics for the non-selective esters obtained using sucrose as substrate, *O*-methacryloyl sucrose (11) and acetylated monomethacrylated sucrose (12)

Structure		 **11**	 **12** R=methacryl or Ac
Yield (%)	**CSP DMF**	47	45*
	CSP Pyr	51	
R. time (h)	**CSP DMF**	24	24*
	CSP Pyr	24	
1H-NMR δ (ppm)		(400 MHz, D_2O) 6.15-6.05(1H, =CH_α) 5.75-5.63(1H, =CH_β) 5.47 (d, $J_{1\text{-}2}$ = 3.4Hz, H-1) 5.36 (d, $J_{1\text{-}2}$ = 3.7Hz) 5.29 (d, $J_{1\text{-}2}$ = 3.3Hz, H-1) 4.33 (m, 1H, H-3') 4.11 (m, 1H, H-5) 4.01 (m, 1H, H-4') 3.92 (m, 1H, H-5'), 3.71 (m, 5H, H-6, H-6', H-3) 3.58 (m, 2H, H-1') 3.42 (m, 2H, H-2, H-4) 1.84(s, 3H, CH_3);	(400 MHz, $CDCl_3$) 6.17 (d, J = 13.6 Hz, 1H, =CH_α) 5.70 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1H, H-1) 5.62 (d, J = 10.8 Hz, 1H, =CH_β) 5.44 (t+d, $J_{2\text{-}3\text{-}4}$ = 9.9 Hz, $J_{3'\text{-}4'}$ = 4.8 Hz, 2H, H_3, $H_{3'}$) 5.38 (t, $J_{3'\text{-}4'\text{-}5'}$ = 4.8 Hz, 1H, $H_{4'}$) 5.13 (t, $J_{3\text{-}4\text{-}5}$ = 9.8 Hz, 1H, H_4) 4.82 (dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{2\text{-}3}$ = 10.4 Hz, 1H H_2) 4.43-4.17 (m, 8H, H_5, $H_{6'}$, H_6, $H_{5'}$, $H_{1'}$) 2.18 (s, 3H, CH_3) 2.11 (s, 3H, CH_3) 2.11 (s, 3H, CH_3) 2.09 (s, 3H, CH_3) 2.03 (s, 3H, CH_3) 2.02 (s, 3H, CH_3) 1.97 (s, 3H, CH_3) 1.96 (s, 3H, CH_3);
13C-NMR δ (ppm)		(100 MHz, D_2O) 169.0 (*C*OO) 135.7 (quat. *C*=)	(100 MHz, $CDCl_3$) 170.5-169.4 (8-COO-) 135.9 (COO(CH_3)*C*=)

127.6 (=*C*H_2)	127.6 (*C*H_2=)
102.8 (*C*-2')	104.1 ($C_{2'}$)
89.9 (*C*-1)	90.0 (C_1)
69.5 (7*C*H-sucrose skeleton)	79.2 ($C_{5'}$)
60.3 (3*C*H_2-sucrose skeleton)	75.8 ($C_{3'}$)
17.7 (*C*H_3)	75.1 ($C_{4'}$)
	70.3 (C_2)
	69.8 (C_3)
	68.6 (C_5)
	68.4 (C_4)
	63.6 ($C_{6'}$)
	62.9 ($C_{1'}$)
	60.7 (C_6)
	20.6 (7*C*H_3CO)
	17.8 (CH_3)

***solvent: Pyr

It is also advised to use the modified sucrose vinyl ester instantly for the polymerization reaction due to its high probability of autopolymerization. If it needs to be stored, it can be kept cool with a radical inhibitor. In the synthesis described above, hydroquinone (also benzene-1,4-diol or quinol) was used to inhibit polymerization between the modified sucrose vinyl esters as it can accept single electrons from free radical formation. The mechanism of action of hydroquinone is shown in Figure II 19.

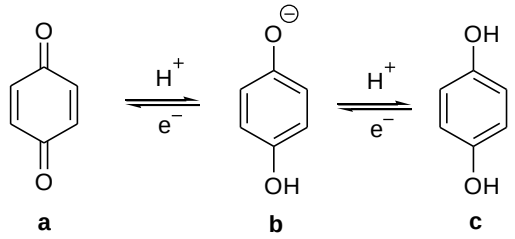


FIGURE II 19 Oxidation structures of hydroquinone: a) benzoquinone; b)semiquinone; c) hydroquinone

II.4 Polymerization reaction of modified sucrose based vinyl esters with styrene – synthesis of polyvinyl saccharides

After performing the monomer synthesis, the aim of this thesis was to produce hydrophilic and hydrophobic comb-like copolymers, reacting each monomer with styrene in the presence of a radical initiator. The polymerization reactions were made using two different types of radical initiators 2,2'-Azobis(2-methylpropionitrile) **(26)** and sodium persulfate **(28)**. They decompose thermally above 40 ºC so all polymerization procedures were made at a T > 40 ºC, Figure II 20.

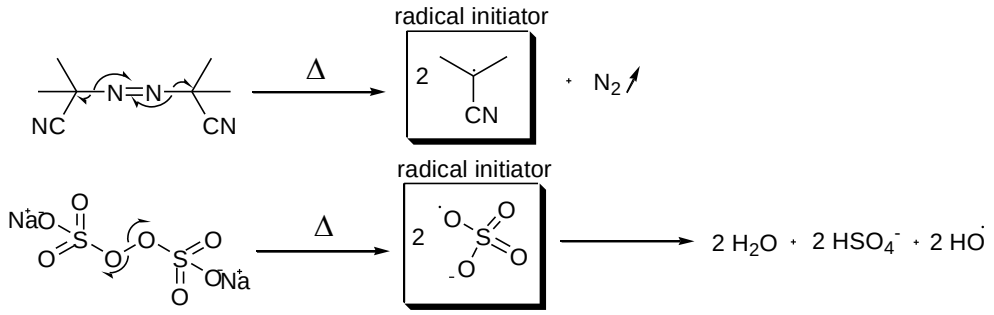
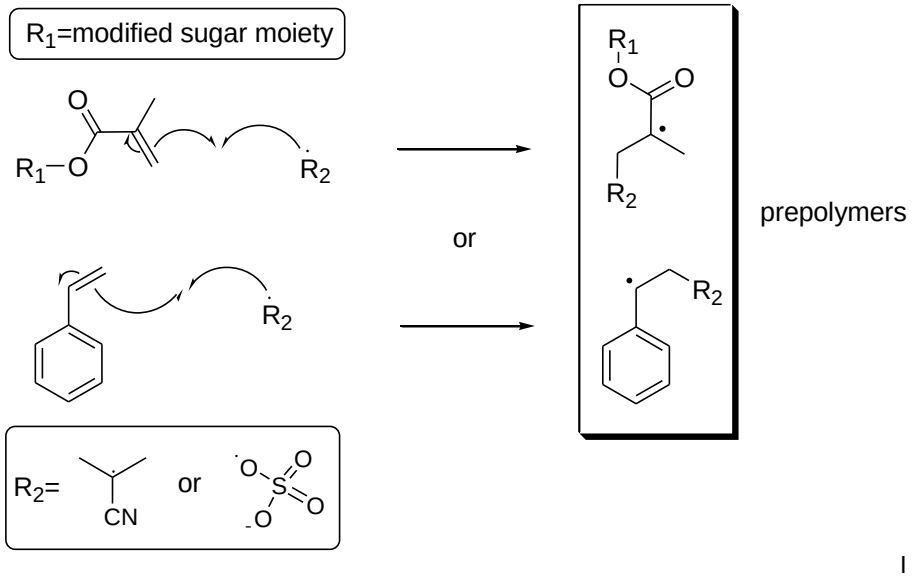


FIGURE II 20 Mechanism for thermal decomposition of polymerization radical initiators AIBN (26) and sodium persulfate (28)

All the radical polymerization that are going to be described have a common mechanism as shown in Figure II 21.



I

FIGURE II 21 Mechanism for the formation of a prepolymer, a radical initiation that starts a polymerization process

The radicals formed are theoretically the most stable, hence the structure presented on the figure above. The choice of these prepolymer radical structures is based on two aspects: the first being that stability increases in the order methyl < primary < secondary < tertiary carbons because of the bond dissociation energies. The easiest bond to break by homolytic bond cleavage results in a more stable radical; and the second is that free radicals are stabilized by adjacent atoms with lone pairs, as the ones from the carbonyl -C=O bond[79]. In the case of AIBN, a certain amount of tetramethylsuccinic acid dinitrile is formed by the combination of the primary radicals, while some methacrylonitrile and iso-butyronitrile are formed by disproportionation of the primary radicals.

After the prepolymer is formed, it reacts again by radical polymerization with and unsaturated compound in the solvent media such as another molecule of sucrose vinyl ester or styrene. This is a random process that incorporates the sugar vinyl ester and styrene in a comb-like chain copolymer (Figure II 22).

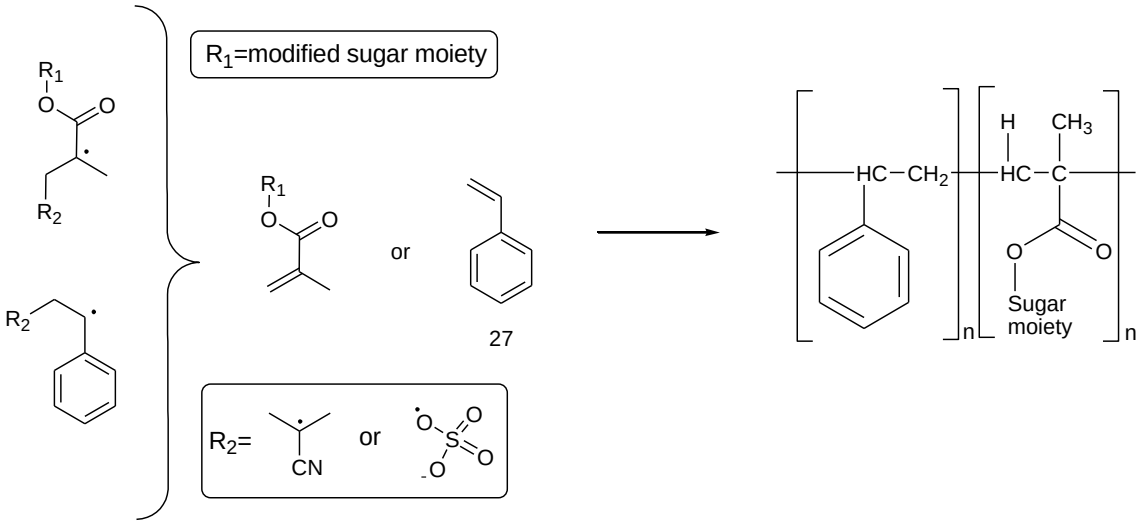


FIGURE II 22 Mechanism for the propagation of the radical copolymerization of sucrose vinyl esters with styrene **(27)**

In polymer synthesis, it is of the utmost importance to make reactions under argon atmosphere for moisture and oxygen exclusion. Molecular oxygen is known to react very rapidly with hydrocarbon radicals with the formation of peroxy radicals (Figure II 23):

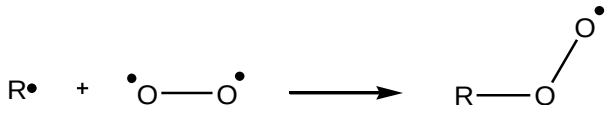


FIGURE II 23 Reaction to form peroxy radicals

Peroxy radicals are much less reactive than most alkyl (or aryl) radical, but they can add a further monomer molecule, regenerating an alkyl radical, which can react again with oxygen.

The rate of consumption of monomer, relative to that in the absence of oxygen, is substantially reduced. An alternating addition of unsaturated monomer and oxygen is observed, resulting in the formation of polymeric peroxide (copolymerization with molecular oxygen):

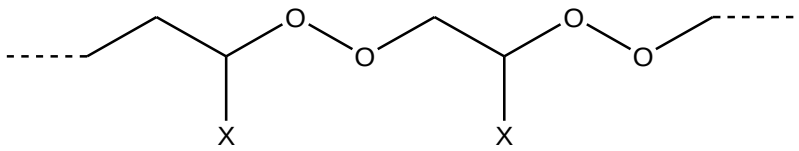


FIGURE II 24 Influence of radical peroxides in a polymer chain growth

Normal polymerization commences only after complete consumption of the oxygen; this is then accelerated by the formation of additional initiating radicals through the thermal decomposition of the polymeric peroxide. Thus, molecular oxygen at first inhibits the polymerization, but after consumption there is an accelerating action.

It is thus clear why atmospheric oxygen must be carefully excluded during radical polymerizations. This was done by bubbling an inert gas (i.e. argon) in the reaction media for some time.

The polymerization reaction terminates when a radical molecule reacts and turns neutral, not converting itself in another radical. This can happen when all the reactants finish or if oxygen is introduced in the reaction media by opening the reaction vessel, for example.

II.4.1 Synthesis of copolymer poly(1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl sucrose)-co-polystyrene (29)

Reactions for copolymer synthesis and polystyrene synthesis are shown below in Figures II 25, II 27, II 28, II 29, II 30:

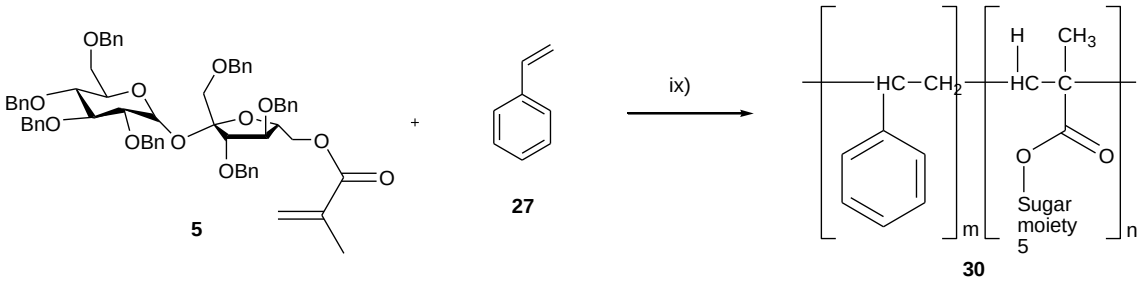


FIGURE II 25 Synthetic scheme for the radical copolymerization of 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl-sucrose **(5)** with styrene **(27)** to produce poly(1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl sucrose)-co-polystyrene **(29)**: ix) Toluene, AIBN (1%w/w), styrene, 85 ºC, 48h

In the reaction to synthesize poly(1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl sucrose)-co-polystyrene **(29)** it was used 10 equivalents of styrene for 1 equivalent of 1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl-sucrose **(5)** to facilitate the polymerization

procedure, i. e., using a proportion of modified sugar/styrene of 1:10, styrene acts as a spacer on the polymeric chain, making the reaction with the methacryl sugar ester easier. As modified sugar vinyl esters are much larger molecules than styrene, it is harder to do a polymerization reaction due to its bulkiness, what can cause steric hindrance on the radical copolymerization. By maintaining a proportion of 1:10 it was though that was guaranteed to obtain a polymer with an average incorporation of sugar vinyl ester in the styrene chain of 1:10. The ratio of sucrose vinyl ester/styrene was accessed by the ^{1}H-NMR spectra, where it could be verified that copolymer **(29)** had ratio of approximately 1:9, as shown on Figure II 26.

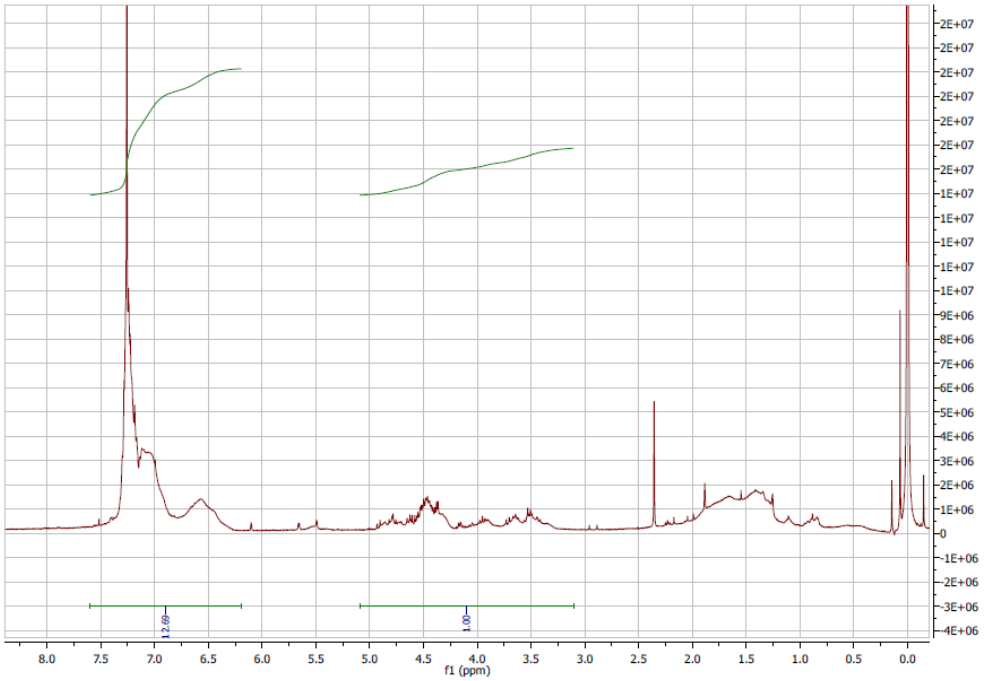


FIGURE II 26 ^{1}H-NMR spectra for poly(1',2,3,3',4,4',6-hepta-*O*-benzyl-6'-*O*-methacryolyl sucrose)-co-polystyrene **(29)** as an example for the determination of sucrose vinyl ester/styrene ratio.

The chemical shift region from 3 ppm to 5 ppm is used as a standard region for the sugar backbone protons. This means that, we have 14 protons (sugar backbone) + 14 protons (7xCH_2 from benzyl groups) = 28 protons. So, on average, 1 sugar vinyl ester proton integrates for 0.0357.

On the other hand, the aromatic region from 6.25 ppm to 7.75 ppm, we have 35 protons (7x5 benzyl groups) and 5 protons from styrene = 40 protons. This means that a proton from styrene integrates for 0.320.

Considering the following equation:

$$\frac{1\ mol\ sucrose\ vinyl\ ester}{0.0357} = \frac{x\ mol\ styrene}{0.320}$$

For each mol of sucrose we have:

$$\frac{1x0.320}{0.0357} = 8.96 \approx 9$$

In this reaction (Figure II 26), it was also possible to assess that this polymer has optical properties with a specific rotation of +15.81 º.

The remaining reactions were performed in similar fashion, starting with the same proportions of styrene and modified sucrose vinyl ester and after obtaining the polymer the proportion was also accessed also by the ^{1}H-NMR spectra.

II.4.2 Synthesis of copolymer poly(6-*O*-methacryolyl sucrose)-co-polystyrene (30)

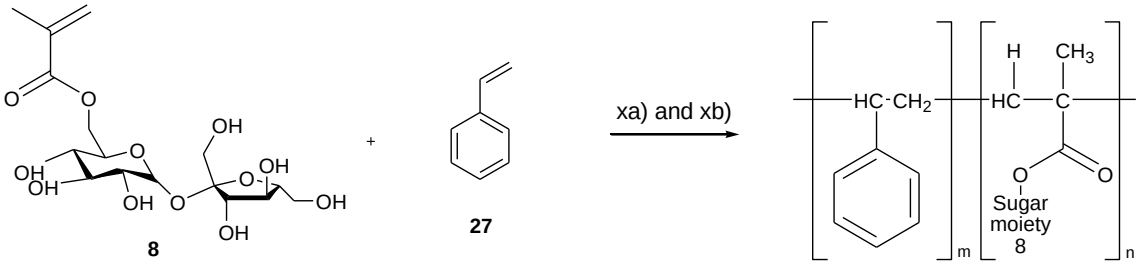


FIGURE II 27 Synthetic scheme for the radical copolymerization of 6-*O*-methacryolyl-sucrose **(8)** with styrene **(27)** to produce poly(6-*O*-methacryolyl sucrose)-co-polystyrene-**(30)**: x) a - DMF, AIBN (1%w/w), 85 ºC, 24h.; x) b – H_2O, $Na_2S_2O_8$ (1%w/w), 85 ºC, 24h

Some of the polymer syntheses were carried out in water as water plays an essential role in life processes; however its use as a solvent has been limited in organic synthesis. Despite the fact that it is the cheapest, safest and most nontoxic solvent in the world, its presence is generally avoided. The use of water as a medium for organic reactions is therefore one of the latest challenges for modern organic chemists.

In copolymerization shown of Figure II 27, reactions occurred identically, both in reaction time and sugar vinyl ester/styrene ratio in the copolymer chain. The ratio of sucrose vinyl ester/styrene was accessed by the ^{1}H-NMR spectra, where it could be verified that copolymer **(30)** had ratio of approximately 1:19.

II.4.3 Synthesis of copolymer poly(*O*-methacryloyl sucrose)-co-polystyrene (31)

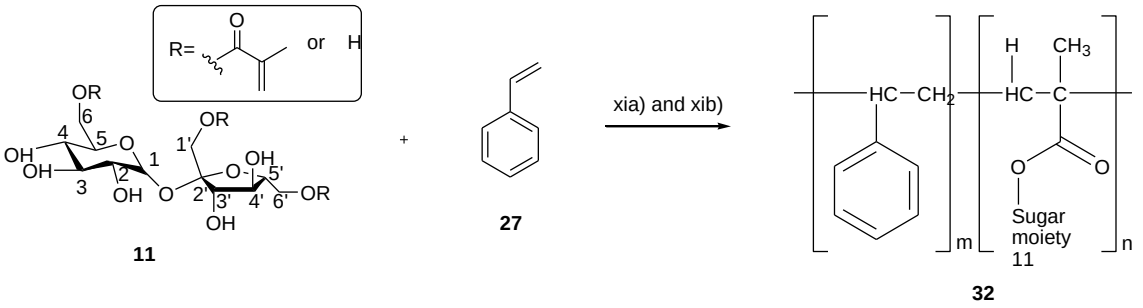


FIGURE II 28 Synthetic scheme for the radical copolymerization of *O*-methacryloyl-sucrose **(11)** with styrene **(27)** to produce poly(*O*-methacryloyl sucrose)-co-polystyrene-**(31)**: xi) a - DMF, AIBN (1%w/w), 85 ºC, 24h.; xi) b – H_2O, $Na_2S_2O_8$ (1%w/w), 85 ºC, 24h.

The ratio of sucrose vinyl ester/styrene was accessed by the ^{1}H-NMR spectra, where it could be verified that copolymer **(31)** had ratio of approximately 1:20.

II.4.4 Synthesis of copolymer poly(1,2',3,3',4,4',6'-hepta-*O*-acetyl-6-*O* methacryloyl sucrose)-co-polystyrene (32)

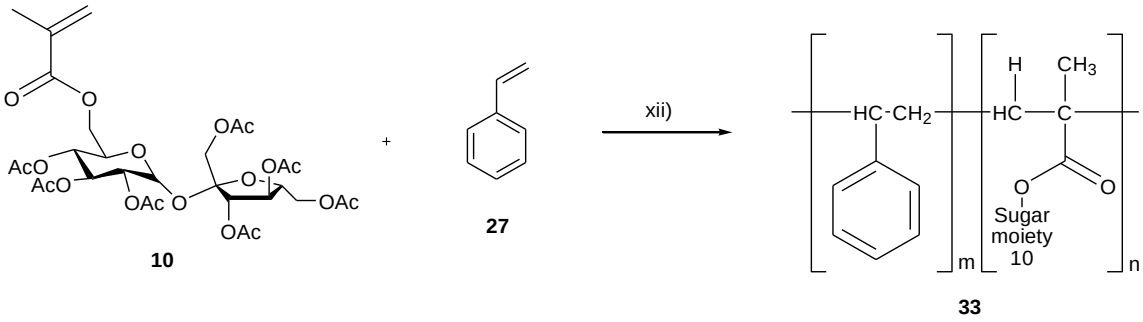
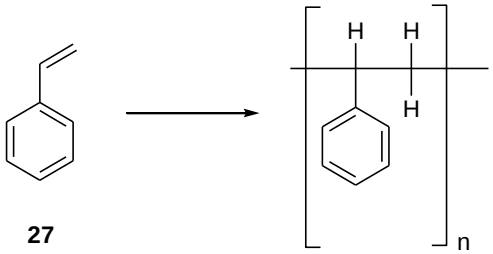


FIGURE II 29 Synthetic scheme for the radical copolymerization of 1',2,3,3',4,4',6'-hepta-*O*-acetyl--6-*O*-methacryloyl sucrose **(10)** with styrene **(27)** to produce poly(1',2,3,3',4,4',6'-hepta-*O*-acetyl--6-*O*-methacryloyl sucrose)-co-polystyrene **(32)**: xii) Toluene, AIBN (1%w/w), styrene, 85 ºC, 48h

In the reaction shown above, it was also possible to assess that this polymer has optical properties with a specific rotation of +4.24 º.

The ratio of sucrose vinyl ester/styrene was accessed by the ^{1}H-NMR spectra, where it could be verified that copolymer **(32)** had ratio of approximately 1:36, as shown on Figure II 29.

II.4.5 Synthesis of polystyrene (33)

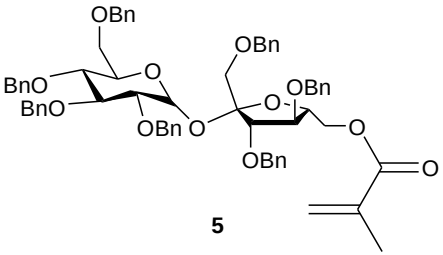
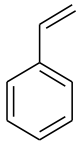
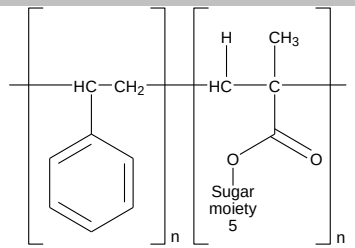
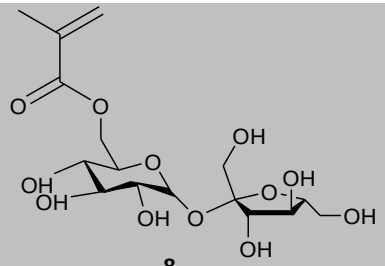
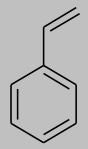
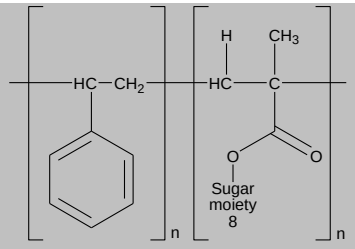
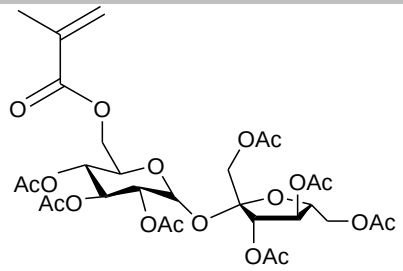
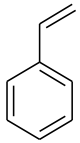
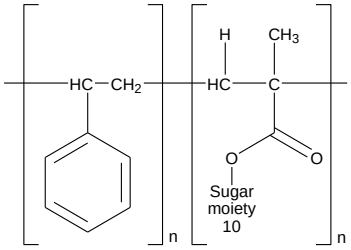


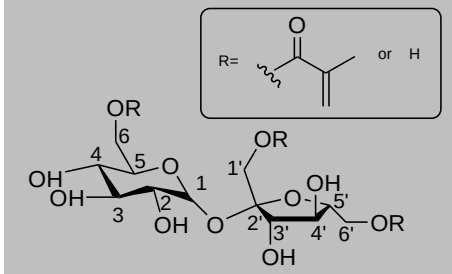
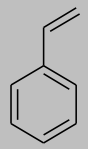
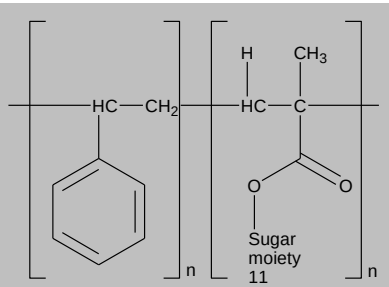
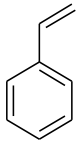
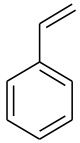
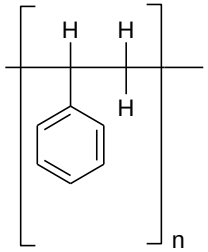
27 **33**

FIGURE II 30 Synthetic scheme for the radical polymerization of styrene **(27)** to produce polystyrene **(33)**: xiii) a - Toluene, AIBN (1%w/w), styrene, 70 ºC, 48h.; b – H_2O-Acetone (3:1), $Na_2S_2O_8$ (1%w/w), styrene, 70 ºC, 48h

Polystyrene was synthesized using the same synthesis pathways as the sucrose vinyl esters copolymers so we can have a standard polymer to compare both the chemical and physical characterizations.

TABLE II 6 Monomers and polymers synthesized and their physical characteristics – Viscosity, specific rotation and (modified sucrose vinyl ester)/styrene ratio

Monomer 1	Monomer 2	Polymer	Initiator	η_{rel} (g/dL)*	concentration polymer (%)	Solvent	$[\alpha]_D^{20}$	$\frac{[sugar]}{[styrene]}$
 **5**	 **27**	 **29**	AIBN	1.08	10	toluene	+15.81 (c,1.0, $CHCl_3$)	1:9
 **8**	 **27**	 **30**	AIBN	1.05	10	DMSO	-[a]	1:19
			$Na_2S_2O_8$	2.98	10	$CHCl_3$	-[a]	1:19
 **10**	 **27**	 **32**	AIBN	1.01	1	$CHCl_3$	+4.24 (c,1.0, $CHCl_3$)	1:36

 **11**	 **27**	 **31**	$Na_2S_2O_8$	1.01	7.2	$CHCl_3$	-[a]	1:20
 **27**	 **27**	 **34**	AIBN	1.04	3.1	toluene	-[b]	-
			$Na_2S_2O_8$	1.17	10	H_2O	-[b]	-

[a]it was not possible to dissolve the polymer in any of the available solvents
[b]polystyrene does not have optical properties

II.5 Polymer characterization studies

II.5.1 Viscometry

As it can be verified by Table II 6, on average all polymers produced have low viscosity at relatively high concentration (10% polymer in solution). This range of viscosities obtained, do not allow the calculation of an intrinsic viscosity because intrinsic viscosity is defined as the viscosity of a polymer when its concentration tends to zero. However, it is possible to determine polymers relative viscosity, η_{rel}, which represents the contribution of the polymer in solution to the solution's viscosity.

The low viscosities observed 1.01-2.98 g/dL in most polymers at a concentration of 10% may be due to intrinsic properties of the polymers or due to the solvents used to its determination. The viscosities may have been determined on "poor" solvents and could be repeated using other solvents. However there is a problem, usually this type of polymers, after a certain time in powder form, take a long time to dissolve in an appropriate solvent or do not dissolve at all. More dissolution studies have to be performed in order to find a good solvent for each polymer synthesized.

On the other hand, these low viscosities may be explained by the polymers themselves. They can have low molecular weight and thus the folding in solution creates low size packed polymer particles that cannot allow a great volume of solvent inside and therefore, not contributing significantly to the solution viscosity.

II.5.2 Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) analyzes thermal transitions occurring in polymer samples when they are cooled down or heated up under inert atmosphere. Melting and glass transition temperatures might be determined as well as the various transitions in liquid crystalline mesophases. To explore the thermal transitions of some of the polymers synthesized in this thesis, DSC was performed first to polystyrene (33), to be used as a standard thermogram. The result is shown on Figure II 31:

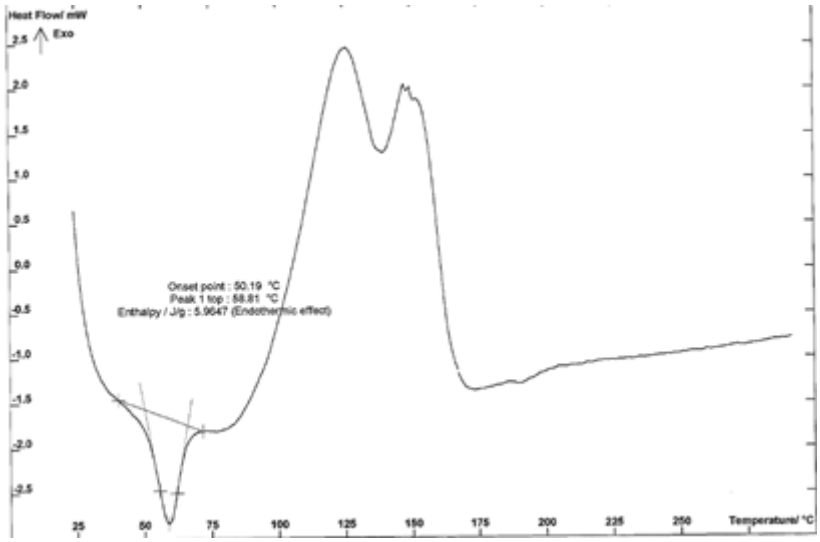


FIGURE II 31 DSC thermogram of polystyrene (33). Method: 25 ºC – 300 ºC, 10 ºC/min

In polystyrene (33) thermogram, Figure II 31, it can be identified in this range of temperatures, an endothermic effect at 58.81 ºC with an enthalpy of 5.9647 J/g. This effect can represent the melting temperature as the sample absorbs heat during melting with an endothermic peak appearing in the DSC plot. The heat of melting is obtained by measuring the peak area. At temperatures between 100 ºC and 155 ºC exothermic and other unidentified endothermic process appear, probably due to a molecular reorganization within the polymer.

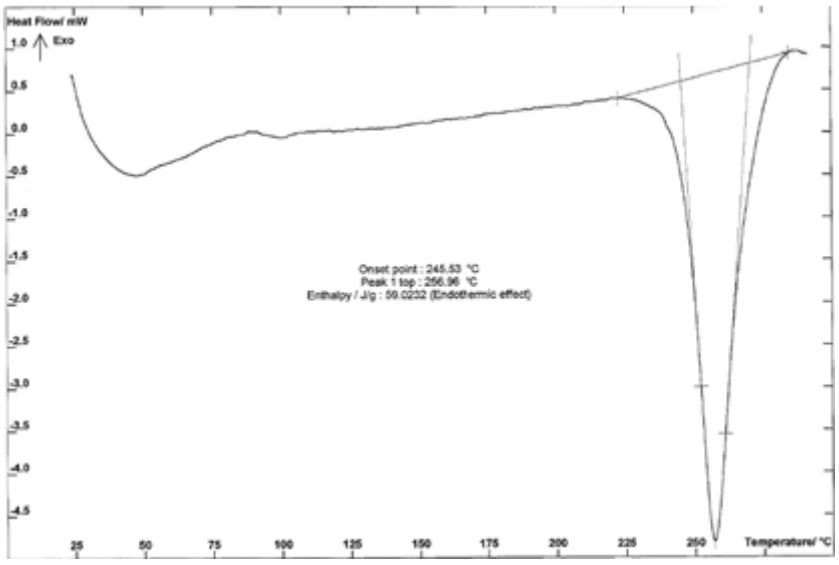


FIGURE II 32 DSC thermogram of poly(O-methacryloyl sucrose)-co-polystyrene (31). Method: 25 ºC – 300 ºC, 10 ºC/min

For poly(O-methacryloyl sucrose)-co-polystyrene (31), the DSC thermogram (Figure II 32) shows a glass transition temperature at T_g=50 ºC together with a strong sharp endothermic effect, its melting temperature, at T_m=256.96 ºC with enthalpy of 59.0232 J/g. Above T_g, the polymer chains are much more mobile and thus might move into a more ordered arrangement, they may assume a crystalline or liquid-crystalline order. In this case, it is possible to observe in Figure II 32, that at about 90 ºC there is a small exothermic effect that can be taken as the crystallization temperature and it can be assumed that this polymer assumes a crystalline order after glass transition temperature.

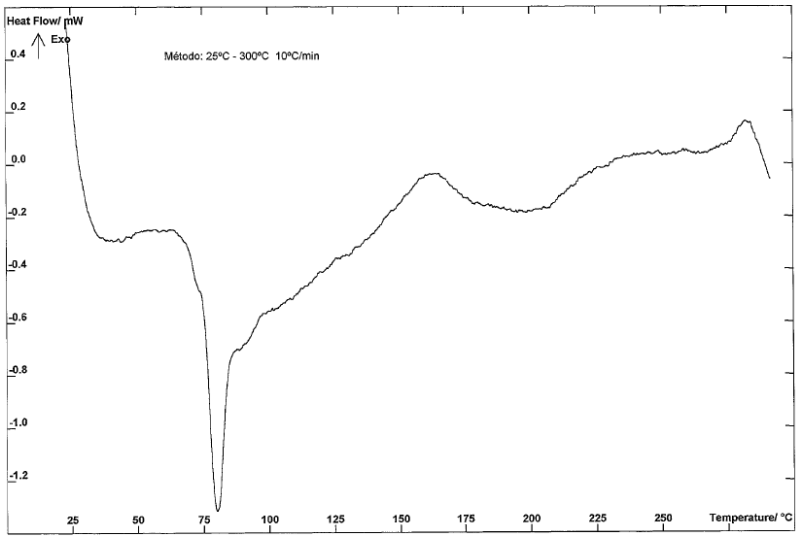


FIGURE II 33 DSC thermogram of poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32)

For polymer poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32), the DSC thermogram (Figure II 33), shows a possible glass transition temperature at T_g=40 ºC and a strong undefined endothermic effect at approximately 80 ºC. The observation and the exact position of glass transition temperature (T_g), and especially of crystallization temperature (T_c) and melting temperature (T_m) are strongly dependent on the thermal history of the sample. Therefore, in this case, more DSC temperature cycles would be needed to improve the quality of the thermogram and for us to be able to determine the temperature characteristics of this polymer. Nevertheless, amorphous polymers will not show crystallization or melting peaks but a glass transition. DSC measurements can be used, moreover, to determine how much of a polymer sample is crystalline.

II.5.3 X ray diffraction (XRD)

Relative to other methods of analysis, powder diffraction allows for rapid, non-destructive analysis of multi-component mixtures without the need for extensive sample preparation. The method has been historically used for the identification and classification of minerals, but it can be used for any materials, even amorphous ones, so long as a suitable reference pattern is known or can be constructed.

For the polymers produced, the use of X-ray diffraction studies provides information about the crystallinity and allows phase identification of the polymers produced in powder form. The most widespread use of powder diffraction is in the identification (if known) and/or characterization of crystalline solids, each of which produces a distinctive diffraction pattern. Both the positions (corresponding to lattice spacing's) and the relative intensity of the lines are indicative of a particular phase and material, providing a "fingerprint" for comparison.

First, for comparison with new synthesized polymers, polystyrene **(33)** was analyzed by X-ray diffraction, producing the following diffractogram (Figure II 34):

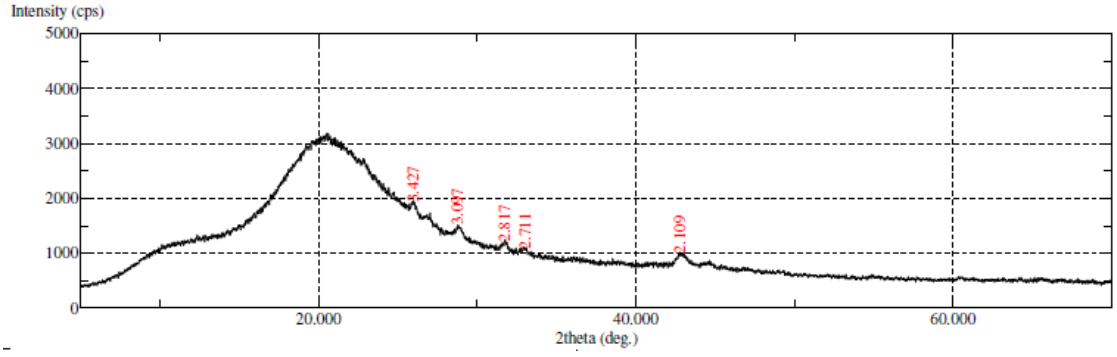


FIGURE II 34 XRD diffractogram of polystyrene (33). Scan mode: continuous; scan speed: 1.000 deg/min; sampling width: 0.020 deg; scan range: 5.000 to 70.000 deg.

As it is observed, it is possible to define a series of peaks but there is a broad background signal. Polystyrene **(33)** shows a semicrystalline behaviour, *i.e.* part of the material forms an ordered crystallite by folding of the molecule. A single polymer molecule may well be folded into two different, adjacent crystallites and thus form a tie between the two. The tie part is prevented from crystallizing. The result is that the crystallinity will never reach 100%.

Copolymer poly(*O*-methacryloyl sucrose)-co-polystyrene (31) and poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl)-copolystyrene sucrose (32) were also characterized by XRD, as shown in Figures II 35 and II 36:

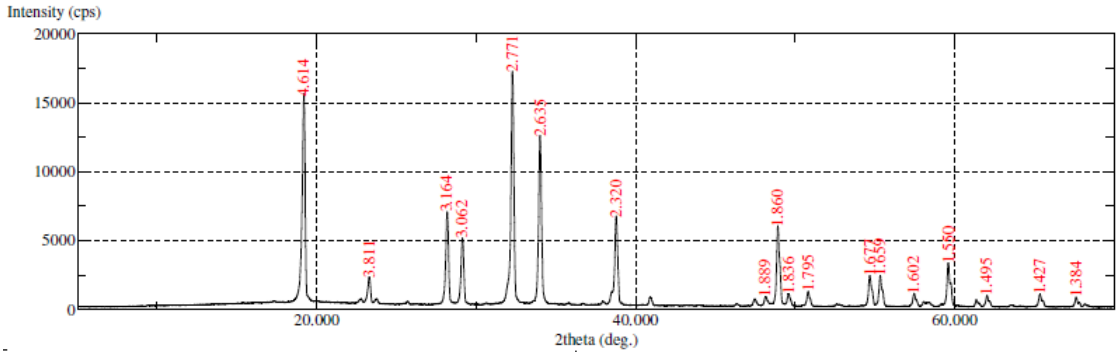


FIGURE II 35 XRD diffractogram of poly(*O*-methacryloyl sucrose)-co-polystyrene (31). Scan mode: continuous; scan speed: 1.000 deg/min; sampling width: 0.020 deg; scan range: 5.000 to 70.000 deg.

The XRD diffractogram above shows that poly(*O*-methacryloyl sucrose)-co-polystyrene (31), the hydrophilic copolymer, as a crystalline structure. By this diffractogram there can be identified many sharp peaks that are the "fingerprint" diffraction pattern for this new synthesized crystalline polymer. That also indicates that the insertion of *O*-methacryloyl sucrose (11), a hydrophilic monomer, in a polystyrene polymeric chain improves the crystallinity of the polystyrene.

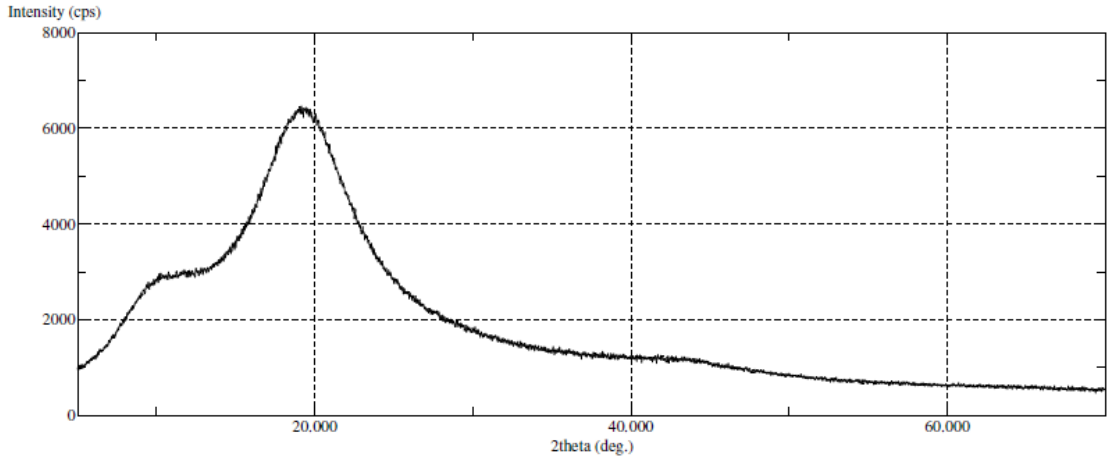


FIGURE II 36 XRD diffractogram of poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32). Scan mode: continuous; scan speed: 1.000 deg/min; sampling width: 0.020 deg; scan range: 5.000 to 70.000 deg.

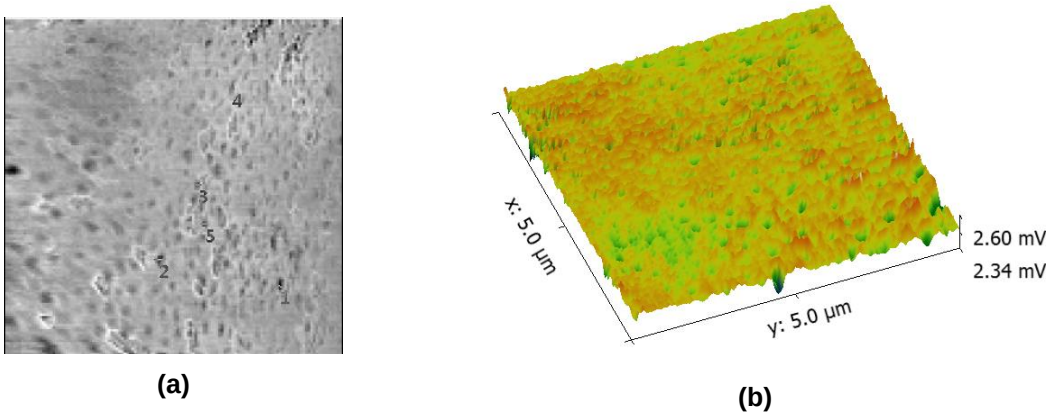
As it is observed on the diffractogram above, the hydrophobic polymer (32) is completely amorphous because no sharp peaks are observed and what characterizes this polymer is a broad background signal. This diffraction pattern of poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32) determines that the polymer is an amorphous powder indicating that the insertion of the hydrophobic sucrose vinyl ester,

1',2,3,3',4,4',6'-hepta-*O*-acetyl-6-*O*-methacryloyl sucrose (10) on the polymeric chain eliminates the semicrystallinity of polystyrene.

II.5.4 Atomic force microscopy (AFM)

Atomic force microscopy (AFM) was used in this thesis as a method of microscopy to provide information about the polymers surface in a thin film. It was used the *tapping mode*, as it is a potent technique that allows high resolution topographic imaging of sample surfaces that are easily damaged, loosely hold to their substrate, or difficult to image by other techniques.

For polymer poly(*O*-methacryloyl)-copolystyrene sucrose (31) it is possible to observe (Figure II 37) that as a thin film coat it is highly porous, and the pores are evenly distributed through the surface area, with an average pore size of 90 nm.



(a) **(b)**

FIGURE II 37 AFM topological images of poly(*O*-methacryloyl sucrose)-co-polystyrene (31). Solution 1 mg/mL (MeOH-$CHCl_3$, 1:3) coating. (a) top image; (b) 3D image

If the sample preparation method is different (Figure II 38), using a different concentration of polymer in a different combination of solvents, it is possible to produce polymer particles with approximately 980 nm in size.

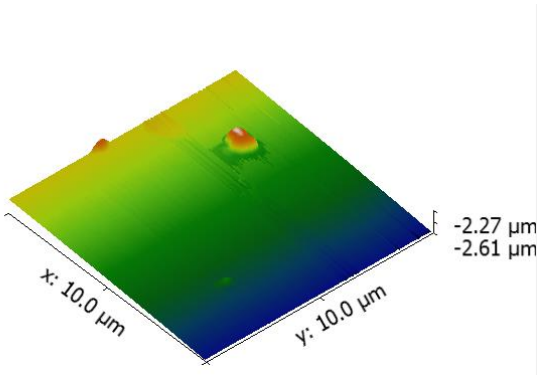


FIGURE II 38 AFM topological images of poly(*O*-methacryloyl sucrose)-co-polystyrene (31). Solution 0.25 mg/mL (MeOH-$CHCl_3$, 2:1) coating. (a) top image; (b) 3D image

Polymer poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32) prepared as a thin film coat, has a random distribution of pores and sizes (Figure II 39). This may be a property of this amorphous polymer or it can behave differently with other type of sample preparation method.

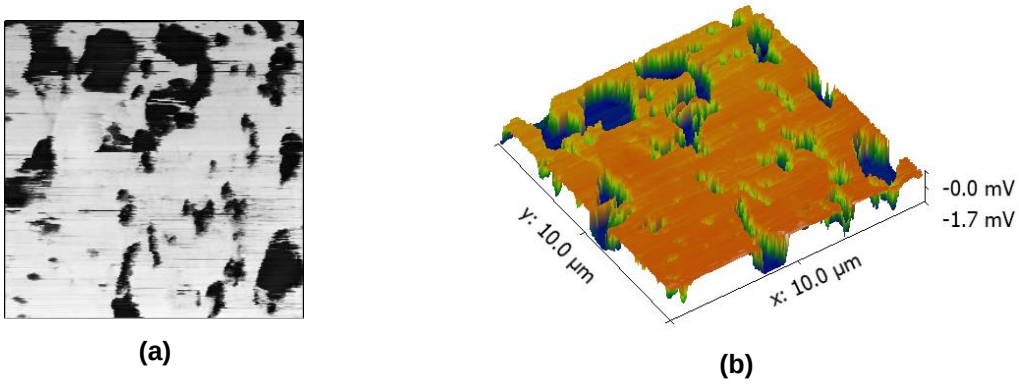


FIGURE II 39 AFM topological images of poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32), 1 mg/ml ($CHCl_3$) coating. (a) top image; (b) 3D image

This technique is highly dependent on the sample preparation methods so we need to optimize the conditions to produce a good picture.

II.6 Conclusions

The objective of this work was the synthesis of sugar vinyl ester monomers its copolymerization with styrene to produce sugar containing hydrophilic and hydrophobic polymers with potential application in medicine.

The protocols used to synthesize the monomers were based on synthesis protocols already known and published. Nevertheless, some of them were optimized and all were scaled-up using 1 to 5 grams of sucrose. All monomers produced were modified sucrose vinyl esters and were used to copolymerize with styrene using radical copolymerization, both in organic solvents and also in water, a novelty in this kind of polymerizations.

Four polymers were synthesized, two of them hydrophilic (30 and 31) and two hydrophobic (29 and 32) and where chemically and physically characterized.

In general, all sugar based vinyl ester polymers synthesized have low relative viscosity, η_{rel}, and that can happen because of intrinsic properties of the polymers (low "hydro"dynamic volume, compact folding in solution) or due to the solvents used for its dissolutions (the use of "poor" solvents). More research is needed to find out how to improve viscosity of a solution with this type of polymers so it is possible to determine an intrinsic viscosity, giving us more information about this type of polymers in solution.

The hydrophilic polymer, poly(*O*-methacryloyl sucrose)-co-polystyrene (31) was found to be able to form porous film coats at high concentrations, evenly distributed on a mica matrix. At lower concentrations it can assume the shape of spherical beads, both topologies assessed by AFM. It was also determined by DSC and XRD that it is crystalline when in powder form exhibiting a high melting point.

The hydrophobic polymer, poly(1',2,3,3',4,4',6'-hepta-O-acetyl-6-O-methacryloyl sucrose)-co-polystyrene (32), is amorphous in powder form (confirmed by DSC and XRD) and when applied as a thin film coat on a surface it also exhibits an amorphous behaviour (confirmed by AFM).

It was also determined that polystyrene is semicrystalline and its crystallinity can be improved or diminished depending on the co-monomer that is inserted in its polymeric chain.

Apparently, there can be a relationship between the hydrophilic/hydrophobic behaviour of a sugar based polymer and its crystallinity in powder form, the ability to form nanoparticles and the porosity when used as thin film coats. The latter observations can be taken in consideration for the continuity of this work.

Chapter III Methods and Materials

III.1 Preamble

i) Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz for ^{1}H and at 100 MHz for ^{13}C, in $CDCl_3$, d^6-DMSO, D_2O or $CDCl_3$ with chemical shift values (δ) in ppm downfield from TMS (0 ppm) or the solvent residual peak of D_2O (4.79 ppm), d^6-DMSO (2.50 ppm) or $CDCl_3$ (7.24 ppm) as internal standard.
The chemical shifts (δ) for a proton spectra were expressed in parts per million (ppm) and the data for proton spectra was presented in the following order: deuterated solvent, signal chemical shift (δ), relative intensity, spin multiplicity (s – singlet, d – duplet, t – triplet, m – multiplet, dd – duplet of duplets, td – triplet of duplets), coupling constant (*J*, in Hz) and molecule peak attribution if possible.
The data for carbon spectra was presented in the following order: solvent, chemical shift (δ), molecule attribution if possible.

ii) Optical rotations were measured at 20 ºC on an AA-1000 polarimeter Optical Activity, LTD (0.5 dm cell) at 589 nm (D-sodium stripe) using the solvent indicated in each case.

iii) Infrared (IR) spectra were recorded on a Brucker Tensor 27 spectrophotometer FTIR spectra were recorded on Perkin-Elmer Spectrum 1000 model apparatus in KBr dispersions for solid samples or NaCl dispersions for oil samples.
In each spectra description we only identify the more intense and characteristic bands. The data obtained is presented in the following order: sample support (NaCl or KBr); frequency of the maximum absorption band (v_{max} in cm^{-1}); band type: s (strong), m (medium), w (weak), b (broad); attribution to a functional group in a molecule if possible.

iv) The reactions performed using a monomodal microwave reactor MicroSynth Lab station (Milestone, USA) (www.milestonesrl.com) in open flasks equipped with temperature control sensor and magnetic stirring.

v) The reactions were followed by thin layer chromatography (TLC) with stripes of silica 60 G/UV_{254} Macherey-Nagel with 0.20 mm thickness in aluminium support. After each elution with solutions indicated in each case, the TLC stripes were observed under UV light using a 254 nm lamp (Vilber-Lourmat) and followed revealed in a solution of ethanol-sulfuric acid 8:2 or methanol/sulfuric acid 10:1. For each compound purification we used 'flash' column chromatography with silica gel Merck (0.035-0.070 nm) prepared with the appropriate solvent indicated in each method. The yields are all isolated yields after silica gel 'flash' chromatography.

vi) For weight measures a Sartorius BL210S was used, with ±0.05 mg precision.

vii) Melting points were measured using an Electrothermal Melting Point Apparatus.

viii) Viscosity studies were made using a Ubbelohde viscometer with stable tank temperature at 25 ºC.

ix) Differential scanning calorimetry studies were carried out in a Setaram, France, DSC 131. This equipment works in temperatures ranges from -150 ºC and +550 ºC at heating and cooling velocities between 0.001 and 50 ºC / min. The heating flux signal varies between -100 and + 100 mW with a resolution of ± 0.2 µW.

x) Atomic force microscopy studies were carried out in a TT-AFM apparatus from AFM workshop™.

xi) X ray crystallography diffraction polymer studies were carried out using the polymer as powder and the experimental diffraction data was collected using a CCD Bruker APEX II difractometer

III.1.1 Solvents

Reagents and solvents were purified/dried by standard procedures (Perrin et al., 1980) and were bought from Sigma-Aldrich, Fluka or Merck.
Solvents were evaporated at reduced pressure using a rotatory evaporator Büchi R-210 coupled with water bath B-491 and vacuum pump V-700 with vacuum model V-801. Solvent remains from each reaction were evaporated using an Edwards's model vacuum pump.

III.1.1.1 Dimethylformamide (DMF)

Dry DMF was obtained by adding BaO to a DMF filled round bottom flask under argon atmosphere and with magnetic stirring for 24h. The dry DMF was then filtered and vacuum distilled, collected to a dark glass bottle under argon atmosphere and containing 3 A molecular sieves previously activated in a hoven at 300 ºC.

III.1.1.2 Dichloromethane

Dry dichloromethane was obtained adding calcium hydride with heating and reflux for one hour previously to its use. The solvent was collected to from the reserve round flask with a syringe and used immediately for each reaction.

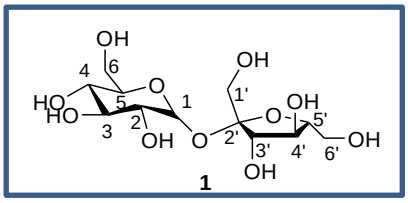
III.1.1.3 Pyridine (Pyr)

Dry pyridine was obtained by adding BaO to a pyridine filled round bottom flask under argon atmosphere and with magnetic stirring for 24h. The dry pyridine was then filtered and vacuum distilled, collected to a dark glass bottle under argon atmosphere, containing 3 Å molecular sieves previously activated in a hoven for two days at 300 ºC.

III.2 Monomer Synthesis

III.2.1 Sucrose

The NMR data was obtained online from Spectral Data Base for Organic Compounds (SDBS, 2013).



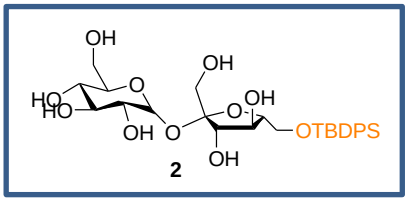
1

Rf = 0.31 eluted with AcOEt:MeOH:H_2O, 5:2:1.

^{1}H-NMR (D_2O) δ=5.42 (1 H, d, *J* = 3.6 Hz, H-1), 4.22 (1H, d, *J* = 8.8 Hz, H-3'), 4.06 (1H, t, *J* = 8.4 Hz, H-4'), 3.92 – 3,74 (7H, m, H-5', H-5, 2xH-6', 2xH-6, H-3), 3.68 (2H, s, H-1'), 3.58 – 3.55 (1H, dd, *J* = 4 e 10 Hz, H-2), 3.48 (1H, t, *J* = 9.6 Hz,H-4) ppm.

^{13}C-NMR ($CDCl_3$) δ = 104.7 ($C_{2'}$), 93.2 (C_1), 82.4 ($C_{5'}$), 77.5 ($C_{3'}$), 75.1 ($C_{4'}$), 73.7 (C_3), 73.4 (C_5), 72.1 (C_2), 70.3 (C_4), 63.4 ($C_{6'}$), 62.5 ($C_{1'}$), 61.2 (C_6) ppm.

III.2.2 Synthesis of 6'-*O*-*tert*-butyldiphenylsilyl sucrose (2)



2

III.2.2.1 Conventional synthesis protocol (CSP):

Sucrose (5g, 14.6 mmol, 1 eq.) previously pulverized to powder and a catalytic amount of 4-DMAP (0.1 eq.) were added to a 250 mL round bottom flask with 70 mL in dry pyridine. The mixture was dissolved at 70ºC in a paraffin bath and stirred with exclusion of moisture for 30 min. After total dissolution, the flask was cooled to room temperature and then TBDPSCl (16.1 mmol, 1.1 eq.) was added dropwise for 15 min and the reaction monitored by TLC (Ethyl acetate-Acetone-water, 10:10:1). After 2 to 3 hours the reaction was stopped by solvent evaporation in a rotatory evaporator and the mixture purified by column chromatography (Gradient elution: Ethyl Acetate (500 mL); Ethyl acetate-Acetone-water, 100:100:1 (750 mL); (Ethyl acetate-Acetone-water, 10:10:1) (500 mL), obtaining 4.832 g (η=57%) of **2** as a white powder.

III.2.2.2 Microwave Assisted Protocol (MAP):

Sucrose (5g, 14,6 mmol, 1 eq.) previously pulverized to powder and a catalytic amount of 4-DMAP were added to a 250 mL round bottom flask with 70 mL pyridine. The mixture was dissolved at 70 ºC in a paraffin bath and stirred with exclusion of moisture for 30 min. After total dissolution, the flask was cooled to room temperature and then TBDPSCl (16,100 mmol, 1.1 eq.) was added dropwise and the reaction monitored by TLC (Ethyl acetate-Acetone-water, 10:10:1).

The mixture was subjected to microwave irradiation and monitored by TLC (maximum power 300W, set program cycle: 20 ºC to 100 ºC in 1 min, 100 ºC for 5 min, 7 min gas exhaustion at room temperature) for three cycles (18 minutes of irradiation). When the di-substituted product was formed (confirmed by TLC, eluted with ethyl acetate-acetone-water) the reaction was stopped by solvent evaporation at the rotatory evaporator. Temperature was monitored in real-time by a probe inside the flask during the whole process. The mixture was purified by column chromatography (Gradient elution: Ethyl Acetate (500 mL); Ethyl acetate-Acetone-water, 100:100:1 (750 mL); (Ethyl acetate-Acetone-water, 10:10:1) (500 mL), obtaining 2.797 g (η=33%) of **(2)** as a yellowish solid.

Rf =0.35 eluted with Ethyl acetate-Acetone-water, 10:10:1.

$[\alpha]_D^{20}$ =+40.2º (c 1.1, CH_3OH);

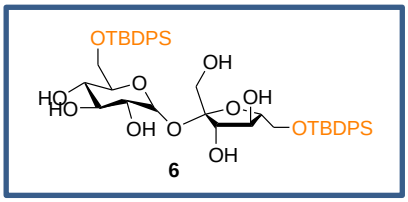
m.p. = 179-184 ºC;

^{1}H NMR (400 MHz, DMSO-d6): δ= 7.66 (m, 4H, Ar-*H*), 7.41 (m, 6H, Ar-*H*), 5.24 (d, *J*=3.1Hz, ^{1}H, H-1), 3.90 (t, *J*=9.7Hz, 1H), 3.79 (d, *J*=8.2Hz, 2H), 3.73 (m, 1H), 3.63 (m, 1H), 3.44 (m, 7H), 3.35 (s, O*H*, H_2O), 3.14 (dd, *J*=10.3, 3.7Hz, 1H), 3.07 (t, *J*=9.3Hz, 1H), 0.99 (s, 9H, CH_3) ppm.

^{13}C NMR (100 MHz, DMSO-d6) δ= 135.1, 133.2, 129.7, 127.8 (C_{Ar}), 104.4 (C-2'), 91.5 (C-1), 82.2, 76.8, 74.6, 73.1, 72.6, 71.7, 70.0 (C-2,3,3',4,4',5,5'), 65.7 (C-1'), 62.1, 60.8 (C-6,6'), 26.7 (CH_3), 18.9 ($CSi(CH_3)_3$) ppm.

IV: ν_{max} (KBr): 3306 (O-H), 2930, 2856 (C-H, sat.), 1471 (Si-Ar), 1428, 1378 (C-C-C), 1278 (Si-C), 1142 (C-C-O), 1112 (Si-Ar), 1054 (C-O-C), 824 (Ar) cm^{-1}.

III.2.3 Synthesis of 6,6'-*O*-di-tertbutyldiphenylsylil-sucrose (6):



6

III.2.3.1 Conventional synthesis protocol (CSP):

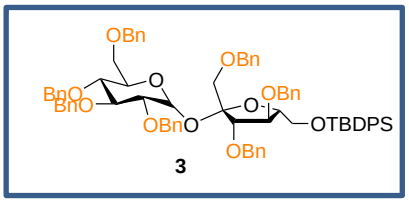
Sucrose (5g, 14.6 mmol, 1 eq.) previously pulverized to powder and a catalytic amount of 4-DMAP (0.1 eq.) were added to a 250 mL round bottom flask with 70 mL in dry pyridine. The mixture was dissolved at 70ºC in a paraffin bath and stirred with exclusion of moisture for 30 min. After total dissolution, the flask was cooled to room temperature and then TBDPSCl (16.1 mmol, 1.1 eq.) was added dropwise (15 min) and the reaction monitored by TLC (Ethyl acetate-Acetone-water, 10:10:1). After 2-3 hours, the reaction was stopped by solvent evaporation at the rotatory evaporator and the mixture purified by column chromatography (Gradient elution: Ethyl Acetate (500 mL); Ethyl acetate-Acetone-water, 100:100:1 (750 mL); (Ethyl acetate-Acetone-water, 10:10:1) (500 mL), obtaining 1.196 g (η=10%) of **6** as a white powder.

III.2.3.2 Microwave Assisted Protocol (MAP):

Sucrose (5 g, 14,6 mmol, 1 eq.) previously pulverized to powder and a catalytic amount of 4-DMAP were added to a 250 mL round bottom flask with 70 mL in pyridine. The mixture was dissolved at 70 ºC in a paraffin bath and stirred with exclusion of moisture for 30 min. After total dissolution, the flask was cooled to room temperature and then TBDPSCl (16,1 mmol, 1,1 eq.) was added dropwise and the reaction monitored by TLC (Ethyl acetate-Acetone-water, 10:10:1). The mixture was subjected to microwave irradiation and monitored by TLC (maximum power 300W, set program cycle: 20 ºC to 100 ºC in 1 min, 100 ºC for 5 min, 7 min gas exhaustion at room temperature) for three cycles (18 minutes of irradiation). When the di-substituted product was formed (confirmed by TLC, eluted with ethyl acetate-acetone-water, 10:10:1) the reaction was stopped by solvent evaporation at the rotatory evaporator. Temperature was monitored in real-time by a probe inside the flask during the reaction. The mixture was purified by column chromatography (Gradient elution: Ethyl Acetate (500 mL); Ethyl acetate-Acetone-water, 100:100:1 (750 mL); (Ethyl acetate-Acetone-water, 10:10:1) (500 mL), obtaining 3.229 g (η=27%) as a white powder.

$[\alpha]_D^{20}$ =+28.9º (c 1.0, CH_3OH);
m.p. = 178-181 °C
^{1}H NMR ($CDCl_3$): δ=7.57 (m, 8H, Ar-*H*), 7.25 (m, 12H, Ar-*H*), 5.15 (d, *J*=3.1Hz, 1H, H-1), 3.96 (m, 3H), 3.79 (m, 1H), 3.73 (m, 1H), 3.68 (m, 4), 3.44 (m, 4H), 0.93 (s, 9H, CH_3), 0.90 (s, 9H, CH_3) ppm.
^{13}C NMR (DMSO-d6) δ=135.2, 133.3, 129.7, 127.9 (CAr), 105.0 (C-2'), 92.2 (C-1), 82.4, 76.8, 75.0, 73.2, 72.7, 71.9, 69.6 (C-2,3,3',4,4',5,5'), 65.8 (C-1'), 63.3, 62.1 (C-6,6'), 26.8 (CH_3), 19.0 (CSi(CH_3)$_3$) ppm.
IV: ν_{max} (KBr): 3385 (O-H), 2928, 2855 (C-H, sat.), 1472 (Si-Ar), 1427, 1390, 1362 (C-C-C), 1266 (Si-C), 1113 (Si-Ar), 1011 (C-O-C), 824 (Ar) cm^{-1}.

III.2.4 Synthesis of 1',2,3,3',4,4',6-hepta-*O*-benzil-6'-*O*-*tert*-butyldiphenylsilyl sucrose (3):



3

III.2.4.1 Conventional synthesis protocol (CSP):

To a 250 mL round bottom flask, 2.006 g of 6'-*O*-*tert*-butyldiphenylsilylsucrose **(2)** (3.45 mmol, 1 eq.) were added and 42,2 mg of 4-DMAP (0.35 mmol, 0.1 eq.) with exclusion of moisture. The dissolution of this mixture occurred in 35 mL of distilled dry DMF, at room temperature for 5 min. After dissolution, the flask was cooled to 0ºC and 1.371 g of NaH (38.6 mmol, 11.2 eq., 60% suspension in oil) were quickly and carefully added, letting the mixture stir during 30 min. At last, 5 mL of BnBr (48.3 mmol, 14 eq. (2 eq. for each free hydroxyl group)) were added dropwise, for 15 min at 0ºC. Reaction occurred for 2.5h at room temperature. The reaction was stopped by adding water to the reaction mixture as soon as reagent **(2)** was absent (confirmed by TLC eluted with hexane-ethyl acetate 5:1). Then a diethyl ether-water extraction was performed with 3x5 mL diethyl ether for extraction and washed with 3x2,5 mL of distilled water. The combined organic phase was washed with H_2O (2x40mL), dried with Na_2SO_4 and concentrated by solvent evaporation. The extracted products were purified by column chromatography (Hexane-Ethyl acetate 5:1) (750 mL), obtaining 3.177 g (η=76%) as a colorless oil.

III.2.4.2 Microwave assisted protocol (MAP):

To a solution of 6'-O-*terc*-butyldiphenilsylil sucrose **(2)** (1.720 mmol, 1 eq.), in 10 mL of dry DMF at 0 ºC, we added slowly 0.722 g of NaH (19.2 mmol, 60% oil suspension, 11.2 eq.). After 20 min, 4.123 g (24.110 mmol, 14 eq.) of benzyl bromide were added dropwise, for 15 min. The reaction mixture was put under microwave and irradiated for 5 min with temperature control at 150 ºC and a power of 300 W. The reaction was followed by TCL and stopped when the initial reagent was absent. The reaction mixture was then washed with 100 mL of cold water and the reaction product extracted with diethyl ether (4x60mL). The combined organic phase was washed again with H_2O (2x40mL), dried with Na_2SO_4 and concentrated by solvent evaporation. The product was purified by column chromatography (eluent Hexane-Ethyl Acetate-5:1), obtaining 1.480 g of **3** as a colorless oil (η=71%).

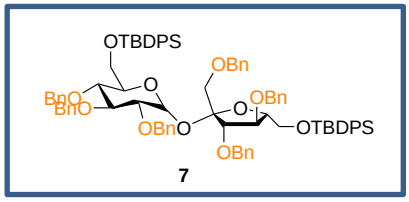
Rf = 0.54 eluted with Hexane-Ethyl acetate, 3:1.

$[\alpha]_D^{20}$ =+46.20 (*c* 1.30, $CHCl_3$)

^{1}H NMR ($CDCl_3$): δ= 7.65 (t, 5 H, *J* 6.3 Hz, Ar-H), 7.40-7.09 (m, 40 H, Ar-H), 5.76 (d, 1H, *J* 3.4 Hz, H-1), 4.80 (dd, 2H, *J* = 16.6, 10.9 Hz), 4.65 (m, 4H), 4.50 (m, 14H, Ar- C*H*$_2$), 4.29 (t, 1 H, *J* 6.9 Hz), 4.24 (d, 1H, *J* = 12.1 Hz), 4.05 (q, 1H, *J* 5.4 Hz), 3.99- 3.90 (m, 3 H), 3.86 (t, 1 H, *J* 9.2 Hz), 3.75 (d, 1H, J=11.0Hz), 3.63 (t, 1H, J=9.6Hz), 3.53 (d, 1 H, *J* 11.0 Hz), 3.48-3.38 (m, 2 H), 3.27 (d, 1 H, *J* 10.3 Hz), 1.02 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$): δ= 127.4-138.9 (*C*Ar), 104.6 (C-2'), 89.8 (C-1), 84.2, 82.7, 82.0, 81.3, 79.9, 75.5, 74.7, 73.4, 73.3, 73.1, 72.4, 72.1, 71.2, 70.6 (C-2,3,3',4,4',5,5', 6 x OCH_2Ph and C-1'), 68.4, 65.0 (C-6,6'), 26.9 (*C*H_3), 19.3, (*C*Si$(CH_3)_3$).

III.2.5 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6,6'-di-*O*-*tert*-butyldiphenylsilyl sucrose (7):



7

III.2.5.1 Conventional synthesis protocol (CSP):

To a 100 mL round bottom flask 1.002 g of 6,6'-di-*O*-*tert*-butyldiphenylsilyl-sucrose **(6)** (1.220 mmol, 1 eq.) were added to 25 mL of dry DMF under argon atmosphere and magnetic stirring for 5 min. After complete dissolution the mixture was cooled to 0ºC and 0.4586 g NaH (11.0 mmol, 9 eq., 60% oil suspension) were added carefully and at once to minimize contact with air. After 15 min of stirring, 1.8 mL of BnBr (15.0 mmol, 9 eq.) was added. After 1.5 h reacting, it is verified by TLC (elution with Ethyl acetate-acetone-water 10:10:1 and Hexane-Ethyl acetate 5:1) the absence of compound **(6)** and the reaction was stopped by extraction of the benzylated compounds with 3x15 mL of diethyl ether and washed with 3x15 mL of distilled water. The combined organic fase was dried with Na_2SO_4 for 10 min. The products were purified by column chromatography using gradient elution (Hexane (250 mL), solution of Hexane-Ethyl Acetate 9:1 (500 mL) and Hexane-Ethyl Acetate 5:1 (500 mL)), obtaining 0.199 g (η=12%) as a colorless oil.

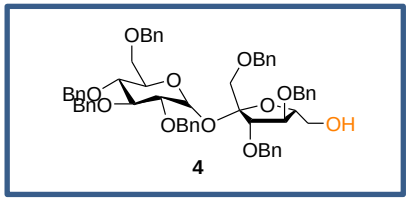
III.2.5.2 Microwave assisted protocol (MAP):

To a solution of 6'-O-*terc*-butyldiphenilsilyl sucrose **(6)** (1.72 mmol, 1 eq.), in 10 mL of dry DMF at 0 ºC, we added slowly 0.722 g of NaH (19.20 mmol, 60% oil suspension, 11.2 eq.). After 20 min, 4.123 g of benzyl bromide (24.11 mmol, 14 eq.) were added dropwise, for 15 min. The reaction mixture was put under microwave and irradiated for 5 min with temperature control at 150 ºC and a maximum power of 300 W. The reaction was followed by TCL and stopped when the initial reagent was absent and a second spot was detected in the TLC (higher R_f). The

reaction mixture was then washed with 100 mL of cold water and the reaction product extracted with diethyl ether (4x60mL). The combined organic phase was washed with H_2O (2x40mL), dried with Na_2SO_4 and concentrated by solvent evaporation. The product was purified by column chromatography (eluent Hexane-Ethyl Acetate-5:1), obtaining 0.234 g (η=10%) of **(7)** as a colorless oil.

$[\alpha]_D^{20}$ = +29,8º (c 1.0, CH_3OH)
^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.64 (m, 10H, Ar-*H*), 7.42 (m, 40H, Ar-*H*), 5.23 (d, 1H, *J1,2* =3.1Hz, H-1), 4.86 (d, 2H, *J6A,6B*=10.6Hz, H-6), 4.66 (m, 7H, H-3,3',4,4', Ar- CH_2), 4.46 (3d, 3H, Ar-CH_2), 4.32 (m, 2H, Ar-CH_2), 4.14 (m, 1H, H-5), 3.98 (m, 2H, H- 6'), 3.82 (m, 2H, H-1'), 3.60 (m, 3H, H-5', Ar-CH_2), 3.50 (dd, 1H, *J1,2*=3.2Hz, *J2,3*=9.6Hz, H-2), 3.43 (dd, 2H, *J*=10.2Hz, Ar-CH_2), 1.07 (s, 9H, CH_3), 1.05 (s, 9H, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$): δ= 139.0, 138.3, 138.1, 138.0 (Cq grupos benzilo), 129.6, 128.2, 127.8, 127.7, 127.6 (CAr), 104.4 (C-2'), 89.5 (C-1), 84.3, 82.2, 82.0, 80.7, 77.3, 76.7, 75.8, 74.7, 73.5, 72.6, 72.4, 71.9, 71.6, 69.5 (C-2,3,3',4,4',5,5', 6 x OCH2Ph e C-1'), 64.6, 62.3 (C-6,6'), 26.9 (*C*H_3), 19.3 (*C*Si(CH_3)$_3$) ppm.

III.2.6 Synthesis of 1',2,3,3',4,4',6-hepta-*O*-benzyl sucrose (4):



4

III.2.6.1 Conventional synthesis protocol (CSP):

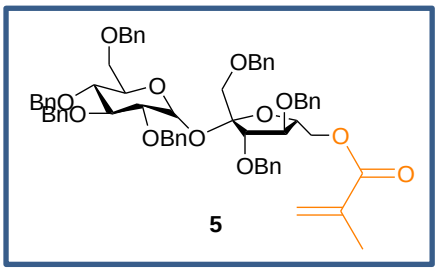
To a 100 mL round bottom flask, 2.0058 g of **(3)** (1.66 mmol, 1 eq.) were added with 40 mL of distilled and dry THF. The mixture was let under magnetic stirring during 5 min under argon atmosphere to ensure absence of moisture. After total dissolution 2 mL of TBAF (2 mmol, 1,2 eq.) were carefully and dropwise added. After 24h it is verified by TLC (Hexane-Ethyl Acetate 5:1) that the starting material was absent and the reaction was stopped by solvent evaporation. Then the product was extracted to the organic fase with 3x10 mL of diethyl ether and washed with 3x5 mL of distilled water. The combined organic fase was dried for 10 min with Na_2SO_4 and then vacuum filtered. The compound was purified by column chromatography and eluted with 750 mL of a solution of hexane-Ethyl acetate 5:1, obtaining 1.131 g (η=70%) as a colorless oil.

III.2.6.2 Microwave assisted protocol (MAP):

To a solution of **(3)** (0.500 g, 0.41 mmol), in dry THF (10 ml), at 0 ºC and under argon atmosphere for moisture exclusion, we added 0.500 mL of tetrabutylammonium fluoride (TBAF, 1M solution in THF, 0.500 mmol). The reaction mixture was then microwave irradiated for 5 min, with temperature control at 65 ºC and maximum power at 300W. The reaction was monitored by TLC (elution with Hexane-Ethyl acetate 5:1) revealing that **3** was almost totally absent. The solvent was then evaporated and the pellet was dissolved in 30 mL of dichloromethane, washed with water (2x10 mL) and the organic phase dried with Na_2SO_4. The compound was purified by column chromatography eluted with 750 mL of a solution of hexane-Ethyl acetate 5:1, obtaining 0.281 g (η=70%) as a colorless oil.

Rf = 0.26 eluted with Hexane-Ethyl acetate, 3:1.
$[\alpha]_D^{20}$ = +29,6º (c 1.1, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.33 – 7.19 (m, 35H, Ar-*H*), 7.11 – 7.10 (m, 1H, Ar- *H*) 5.54 (d, 1 H, *J* 3.0 Hz, H-1), 4.83 (d, 1 H, *J* 10.85 Hz, C*H*$_2$-Ph), 4.78 (d, 1 H, *J* =10.9 Hz, C*H*$_2$-Ph), 4.67 – 4.59 (m, 12H, C*H*$_2$-Ph and H-5'), 4.41 (m, 1H, H-3'), 4.28 (d, 1 H, *J* 12.1 Hz, H-3), 4.47-4.44 (dd, 1 H, *J* = 10.9, 8.0 Hz, H-1'), 4.42- 4.28 (m, 1H, H-6) 4.00 – 3.97 (m, 1 H, H-6), 3.74-3.71 (m, 1H, H-4') 3.60 (t, 1 H, *J* 9.63 Hz, H-2), 3.57 – 3.46 (m, 3 H, H-1', H-5, H-4), 3.24 (d, 2 H, *J* 9.45 Hz, H-6', H-5') ppm.
^{13}C NMR (100MHz, $CDCl_3$) δ=127.6-138.7 (*C*Ar), 103.8 (C-2'), 91.1 (C-1), 83.6, 81.7, 81.2, 79.5, 79.4, 77.3, 77.0, 76.7, 75.6, 74.9, 73.5, 73.4, 72.9, 72.5, 71.3, 71.2 (C- 2,3,3',4,4',5,5', 6 x OCH_2Ph and C-1'), 67.9, 61.2 (C-6,6') ppm.

III.2.7 Synthesis of 1',2,3,3',4,4',6–hepta-*O*-benzyl-6'-*O*-methacryloyl sucrose (5):



5

III.2.7.1 Conventional synthesis protocol (CSP):

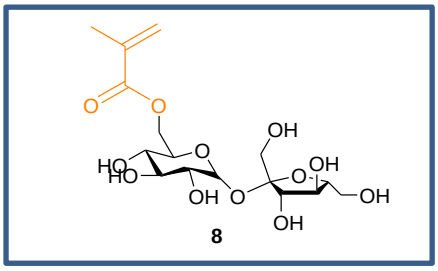
To a 25 mL round bottom flask, 1,0093 g of **(4)** (1.030 mmol, 1eq.) was added in 10 mL of distilled CH_2Cl_2. The dissolution occurred for 5 min under magnetic stirring and argon atmosphere. After complete dissolution 0.2 mL of Et_3N (1.300 mmol, 1.3 eq.) and 12.7 mg of 4-DMAP (0.1 mmol, 0.1 eq. (catalytic amount)), were added. The mixture was let to stir for 5 min.

After dissolution of all mixture compounds 0.200 mL of methacrylic anhydride (1.3 mmol, 1.3 eq.) were carefully and dropwise added, letting the reaction occur for 24h. The reaction was stopped by solvent evaporation when verified by TLC (Hexane-Ethyl acetate, 3:1) that the entire initial reagent was consumed. The product was purified by column chromatography using gradient elution (Hexane (250 mL), Hexane-Ethyl acetate, 5:1, and Hexane-Ethyl acetate, 3:1), obtaining 0.740 g (η=69%) as a yellowish oil.

$[\alpha]_D^{20}$ = +46.9º (c 1.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.13 (m, 35H), 6.15 (d, J 3.6Hz, 1H), 5.55 (d, J 3.6Hz, 1H), 5.72 (d, J 3.7Hz, 1H), 4.83 (d, J 11.0Hz, 1H), 4.79 (d, J 11.0 Hz, 1H), 4.72- 4.33 (m, 14H), 4.18 (d, J 12.0Hz, 1H), 4.11 (dd, J 11.2, 5.5 Hz, 1H),4.09-4.05 (m, 1H), 3.93 (t, J 9.2 Hz, 1H), 3.75-3.62 (m, 3H), 3.55-3.47 (m, 2H), 2.00 (s, 3H).

III.2.8 Synthesis of 6-*O*-metacryloyl sucrose (8):



8

III.2.8.1 Conventional synthesis protocol (CSP):

To a 50 mL round bottom flask, previously dried for 30 min in an incubator at 115 ºC and cooled to room temperature in a dessicator, 1.511 g of sucrose (4.41 mmol, 1 eq.) previously pulverized to powder, and 3.06 g of PPh_3 (11.7 mmol, 2.6 eq.) were added (both of the reagents were dried at 70 ºC for 30 min) to 22.5 mL of dry DMF. This initial mixture was dissolved completely under magnetic stirring for 20 min at 70 ºC in oil bath and with exclusion of moisture. After complete dissolution, the flask as cooled to 0 ºC and 2.3 mL of DIAD (11.7 mmol, 2.6 eq.) were added dropwise for 5 min. After this mixture was homogenized for 20 min 0.74 mL of methacrylic acid (8.76 mmol, 2 eq.) was added. The mixture was let to stir for 30 min at room temperature. The reaction occurred for 72h and we stopped it by solvent evaporation after verifying by TLC (Ethyl acetate-methanol-water, 5:2:1) the formation of the di-ester. The esters were extracted with 3x15 mL of distilled water and washed with 3x10 mL of CH_2Cl_2. After concentrating the water fractions (sucrose and esters) we washed the organic fase once more with 15 mL of distilled water. After water evaporation, the esters produced were purified by column chromatography using isocratic elution (Ethyl acetate-acetone-water, 10:10:1) obtaining 0.928 g (η=62%) for the mono-ester, as a yellowish oil.

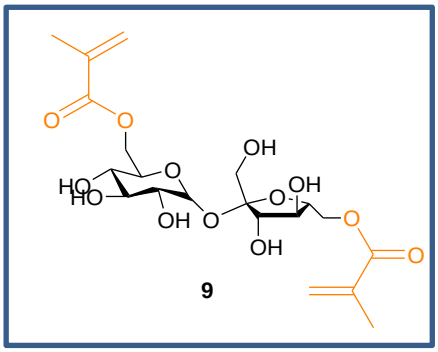
$[\alpha]_D^{20}$ = +30.3º (c 0.9, CH_3OH);

^{1}H NMR (400 MHz, D_2O): δ= 6.02 (1H, s, =CH_2*a*), 5.61 (1H, s, =CH_2*b*), 5.27 (1H, d, $J_{1\text{-}2}$=3.4 Hz, H_1), 4.34 (2H, dq, $J_{6a\text{-}5}$=4.3 Hz, $J_{6a\text{-}6b}$=12.2 Hz, $J_{H6\text{-}COO}$=30.7 Hz, $H_{6a,b}$), 4.08 (1H, d, $J_{3'\text{-}4'}$=8.7 Hz, $H_{3'}$), 4.03-3.95 (1H, m, H_5), 3.87 (1H, t, $J_{3'\text{-}4'\text{-}5'}$=8.6 Hz, $H_{4'}$), 3.82- 3.73 (1H, m, $H_{5'}$), 3.73-3.60 (3H, m, $H_{6'a,b}$ + H_3), 3.54 (2H, s, $H_{1'}$), 3.44 (1H, dd, $J_{1\text{-}2}$=3.5 Hz, $J_{2\text{-}3}$=9.8 Hz, H_2), 3.37 (1H, t, $J_{3\text{-}4\text{-}5}$=9.5 Hz, H_4), 1.80 (3H, s, -CH_3) ppm.

^{13}C NMR (100 MHz, D_2O): δ= 169.7 (-COO-), 135.9 (COO(CH_3)*C*=), 127.6 (*C*H_2=), 104.1 ($C_{2'}$), 92.4 (C_1), 81.7 ($C_{5'}$), 76.8 ($C_{3'}$), 74.5 ($C_{4'}$), 72.7 (C_3), 71.4 (C_2), 70.8 (C_5), 70.0 (C_4), 64.0 (C_6), 63.0 ($C_{6'}$), 61.8 ($C_{1'}$), 17.8 (CH_3) ppm.

IV: ν_{max} (KBr): 3429 (O-H), 2930 (C-H, sat.), 1707 (C=O), 1439, 1325 (C-C-C), 1245, 1138 (C-C-O), 1054 (C-O-C) cm^{-1}.

III.2.9 Synthesis of 6,6'-*O*-metacryloyl sucrose (9):



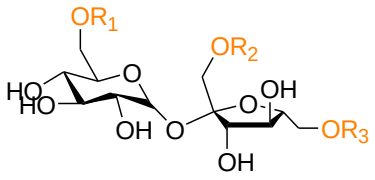
9

III.2.9.1 Conventional synthesis protocol (CSP):

On a 50 mL two entry round bottom flask, previously dried for 30 min in an incubator at 115 ºC and cooled to room temperature in a dessicator, 1.511 g of sucrose (4.410 mmol, 1 eq.) was added, previously pulverized to powder, and 3.060 g of PPh_3 (11.7 mmol, 2.6 eq.), (both of the reagents were vacuum dried at 70 ºC for 30 min) to 22.5 mL of dry DMF. This initial mixture was completely dissolved under magnetic stirring for 20 min at 70 ºC in oil bath and with exclusion of moisture. After complete dissolution, the flask as cooled to 0 ºC and 2.3 mL of DIAD (11.7 mmol, 2.6 eq.) were added dropwise for 5 min. After this mixture was homogenized for 20 min we added 0.74 mL of methacrylic acid (8.760 mmol, 2 eq.) and the mixture was let to stir for 30 min at room temperature. The reaction occurred for 72h and stopped by solvent evaporation after verifying by TLC (Ethyl acetate-methanol-water, 5:2:1) the formation of the di-ester. The esters were extracted with 3x15 mL of distilled water and washed with 3x10 mL of CH_2Cl_2. After concentrating the water fractions (sucrose and esters) the organic fase was washed once more with 15 mL of distilled water. After water evaporation, the esters produced were purified by column chromatography using isocratic elution (Ethyl acetate-acetone-water, 10:10:1) obtaining 0.502 g (η=34%) for the di-ester, as a yellowish oil.

^{1}H NMR (400 MHz, D_2O): δ= 6.13 (1H, s, =CH_2a_1), 5.61 (1H, s, =CH_2b_1), 5.72 (1H, s, =CH_2a_2, 5.71 (1H, s, =CH_2b_2) 5.47 (1H, d, $J_{1\text{-}2}$=3.4 Hz, H_1), 3.40-4.60 (13H, m, sucrose backbone) 1.90 (6H, s, -CH_3) ppm.

III.2.10 Synthesis of monomethacrylated sucrose (*O*-methacryloyl sucrose) (11):



11

R1= COC(CH_3)=CH_2; R2=H; R3=H or
R1=H; R2= COC(CH_3)=CH_2; R3=H or
R1=H; R2=H; R3= COC(CH_3)=CH_2

III.2.10.1 Conventional synthesis protocol (CSP) in DMF:

2 g of sucrose (5,840 mmol, 1 eq.), previously pulverized to a powder, to a 100 mL round bottom flask with 11.7 mg of 4-DMAP (0.584 mmol, 0.1 eq. cat.) and 30 mL of dry DMF, under magnetic stirring and argon atmosphere for moisture exclusion. The mixture was put on an oil bath at 60 ºC for complete dissolution of its components. Then the mixture was cooled to 0 ºC and added 2 mL (7.010 mmol, 1.2 eq.) and 1 mL of methacrylic anhydride (7.010 mmol, 1.2 eq.) carefully and let stir for 20 min after which the reaction occurred for 24h at room temperature. The reaction was stopped by solvent evaporation as soon as the formation of the di-ester is observed by TLC (Ethyl acetate-acetone-water, 10:10:1) and the resulting esters purified by column chromatography eluting with a solution of Ethyl acetate-acetone-water, 10:10:1, obtaining 1.135 g (η=47%) of mono-ester as a yellowish oil.

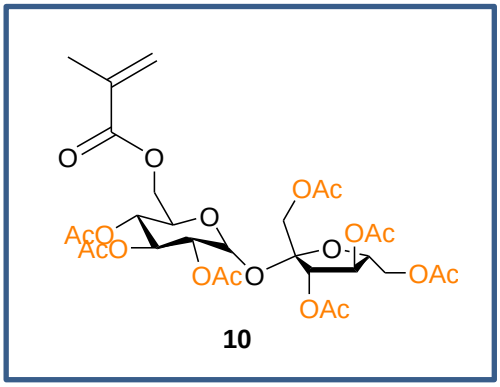
III.2.10.2 Conventional synthesis protocol (CSP) in pyridine:

Sucrose was added to a 100 mL round bottom flask, 2g (5,840 mmol, 1 eq.), previously pulverized to a powder, with 11.7 mg of 4-DMAP (0.584 mmol, 0.1 eq. (catalytic amount)) and 30 mL of dry pyridine, under magnetic stirring and argon atmosphere for moisture exclusion. The mixture was put on an oil bath at 60 ºC for complete dissolution of its components. Then the mixture was cooled to 0 ºC and added 2 mL (7.010 mmol, 1.2 eq.) and 1 mL of methacrylic anhydride (7.010 mmol, 1.2 eq.) was carefully added and let stir for 20 min after which the reaction occurred for 24h at room temperature. The reaction was stopped by solvent evaporation as soon as the formation of the di-ester is observed by TLC (Ethyl acetate-acetone-

water, 10:10:1). The esters were purified by column chromatography eluting with a solution of Ethyl acetate-acetone-water, obtaining 1.181 g of mono-ester (η=51%), as a faint yellow oil.

^{1}H NMR (D_2O): δ= 6.15-6.05(1H, =CH_{α}), 5.75-5.63(1H, =CH_{β}), 5.47 (d, $J_{1\text{-}2}$ = 3.4Hz, H-1), 5.36 (d, $J_{1\text{-}2}$ = 3.7Hz), 5.29 (d, $J_{1\text{-}2}$ = 3.3Hz, H-1), 4.33 (m, 1H, H-3'), 4.11 (m, 1H, H-5), 4.01 (m, 1H, H-4'), 3.92 (m, 1H, H-5'), 3.71 (m, 5H, H-6, H-6', H-3), 3.58 (m, 2H, H-1'), 3.42 (m, 2H, H-2, H-4), 1.84(s, 3H, CH_3);
^{13}C NMR (D_2O): δ = 169.7, 169.1, 169.0 (*C*OO), 135.9, 135.7 (quat. *C*=), 128.3, 127.9, 127.6 (=*C*H_2), 104.4, 104.1, 102.8 (*C*-2'), 93.1, 92.6, 92.4, 89.9 (*C*-1), 82.7, 81.9, 81.8, 78.8, 78.3, 77.2, 76.8, 76.7, 75.8, 75.1, 74.5, 74.4, 74.2, 73.8, 73.3, 73.2, 72.9, 72.7, 71.5, 71.3, 70.8, 70.7, 70.0, 69.7, 69.6, 69.5 (7*C*H-sucrose skeleton), 66.4, 64.0, 63.3, 63.0, 62.8, 62.3, 61.8, 61.6, 61.3, 60.7, 60.5, 60.3 (3*C*H_2-sucrose skeleton), 17.7 (*C*H_3).

III.2.11 Synthesis of 1',2,3,3',4,4',6'–hepta-*O*-acetyl-6-*O*-metacryloyl sucrose (10):



10

III.2.11.1 Conventional synthesis protocol (CSP):

To a two neck 50 mL round bottom flask, 0.500 g (1.220 mmol, 1 eq.) of 6-O-methacryloyl-sucrose **(8)** was added and 1.04 mL of acetic anhydride (11 mmol, 9 eq.), 15 mg of 4-DMAP (0.122 mmol, 0.1 eq. (catalytic amount)) and 10 mL pyridine. The dissolution occurred at 0º C under magnetic stirring and argon atmosphere to exclude moisture. After complete dissolution, the reaction occurred for 24h at room temperature. The reaction stopped when verified by TLC (Ethyl acetate-acetone-water, 10:10:1) that all the starting material was consumed. The reaction work-up was done by extracting with diethyl ether-aqueous solution (1M HCl), concentrating the wanted product in the organic fase, extracting with 3x5 mL of diethyl ether and washing with 3x3 mL of HCl 1M aqueous solution. The organic fase was dried with Na_2SO_4 for 10 min, filtered and then the diethyl ether was evaporated. The compounds obtained were purified by column chromatography with isocratic elution (Hexane-Ethyl acetate, 1:1), obtaining 0.286 g (η=58%) of product, as a faint yellow oil.

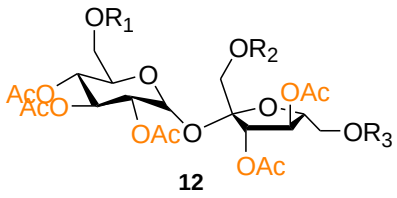
$[\alpha]_D^{20}$ = +31.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): 6.21 (1H, d, $J_{CH2a-CH2b}$ = 13.6Hz, C CH_{2a}), 5.70 (1H, d, J_{1-2} = 3.6Hz,H_1), 5.63 (1H, d, $J_{CH2b-CH2a}$ = 10.8 Hz, C CH2b), 5.46 (1H, d, J_{3-4} = 4.8 Hz, H_3), 5.44 (1H, t, J_{2-3} = J_{3-4} = 9.9 Hz, H_3), 5.38 (1H, t, J_{3-4} = J_{4-5} = 4.8 Hz, H_4), 5.13 (1H, t, J_{3-4} = J_{4-5} = 9.8 Hz, H_4), 4.82 (1H, dd, J_{1-2} = 3.7 Hz, J_{2-3} = 10.4 Hz, H_2), 4.28 (8H, m, H_5, H_6, H_6, H_5, H_1), 2.18 (3H, s, CH_3O), 2.12 (3H, s, CH_3O), 2.11 (3H, s, CH_3O), 2.10 (3H, s, CH_3O), 2.03 (3H, s, CH_3O), 2.02 (3H, s, CH_3O), 1.97 (3H, s, –CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 170.5–169.4 (8-COO–), 135.9 (COO(CH_3)C), 127.6 (CH_2), 104.1 (C_2), 90.0 (C_1), 79.2 (C_5), 75.8 (C_3), 75.1 (C_4), 70.3 (C_2), 69.8 (C_3), 68.6 (C_5), 68.4 (C_4), 63.6 (C_6), 62.9 (C_1), 60.7 (C_6), 20.6 (7CH$_3$CO), 17.8 (CH_3).

IR: ν_{max} (KBr): 2957, 2932, 2857 (C–H, sat.), 1756 (C O), 1428, 1370 (C–C–C), 1221 (C–O–C ester), 1178 (C–C–O;C C), 1038 (C–O–C) cm^{-1}.

III.2.12 Synthesis of Acetylated methacryl sucrose (12):



12

R_1= COC(CH_3)=CH_2; R_2=H; R_3=H or
R_1=H; R_2= COC(CH_3)=CH_2; R_3=H or
R_1=H; R_2=H; R_3= COC(CH_3)=CH_2

III.2.12.1 Conventional Synthesis Protocol (CSP):

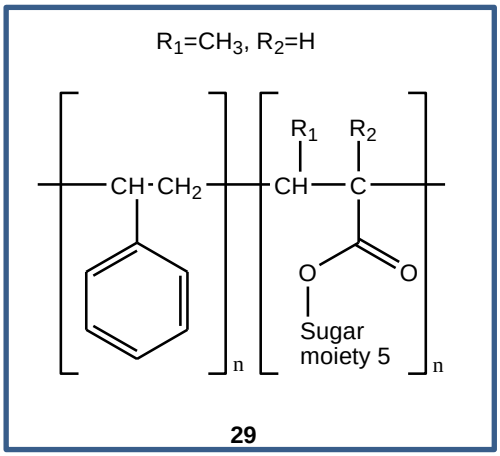
On a two neck 50 mL round bottom flask, 0.500 g (1.220 mmol, 1 eq.) of monomethacrylated sucrose **(11)** was added and 1.040 mL of acetic anhydride (11 mmol, 9 eq.), 15 mg of 4-DMAP (0.122 mmol, 0.1 eq. (cat.)) and 10 mL pyridine. The dissolution occurred at 0º C under magnetic stirring and argon atmosphere to exclude moisture. After complete dissolution, the reaction occurred for 24h at room temperature. The reaction stopped when verified by TLC (Ethyl acetate-acetone-water, 10:10:1) that all the starting material was consumed. The reaction work-up was done by extracting with diethyl ether-aqueous solution (1M HCl), concentrating the wanted product in the organic fase, extracting with 3x5 mL of diethyl ether and washing with 3x3 mL of HCl 1M aqueous solution. The organic fase was dried with Na_2SO_4 for 10 min, filtered and then the diethyl ether was evaporated. The compounds obtained were purified by column chromatography with isocratic elution (Hexane-Ethyl acetate, 1:1), obtaining 0.387 g of product (η=45%), as a faint yellow oil.

^{1}H NMR ($CDCl_3$): δ= 6.17 (d, J = 13.6 Hz, 1H, =CH_{α}), 5.70 (d, J_{1-2} = 3.6 Hz, 1H, H-1), 5.62 (d, J = 10.8 Hz, 1H, =CH_{β}), 5.44 (t+d, J_{2-3-4} = 9.9 Hz, $J_{3'-4'}$ = 4.8 Hz, 2H, H_3, $H_{3'}$), 5.38 (t, $J_{3'-4'-5'}$ = 4.8 Hz, 1H, $H_{4'}$), 5.13 (t, J_{3-4-5} = 9.8 Hz, 1H, H_4), 4.82 (dd, J_{1-2} = 3.7 Hz, J_{2-3} = 10.4 Hz, 1H, H_2), 4.43-

4.17 (m, 8H, H_5, $H_{6'}$, H_6, $H_{5'}$, $H_{1'}$), 2.18 (s, 3H, C*H*$_3$), 2.11 (s, 3H, C*H*$_3$), 2.11 (s, 3H, C*H*$_3$), 2.09 (s, 3H, C*H*$_3$), 2.03 (s, 3H, C*H*$_3$), 2.02 (s, 3H, C*H*$_3$), 1.97 (s, 3H, C*H*$_3$), 1.96 (s, 3H, C*H*$_3$);
^{13}C NMR ($CDCl_3$): 170.5-169.4 (8-COO-), 135.9 (COO(CH_3)*C*=), 127.6 (*C*H_2=), 104.1 ($C_{2'}$), 90.0 (C_1), 79.2 ($C_{5'}$), 75.8 ($C_{3'}$), 75.1 ($C_{4'}$), 70.3 (C_2), 69.8 (C_3), 68.6 (C_5), 68.4 (C_4), 63.6 ($C_{6'}$), 62.9 ($C_{1'}$), 60.7 (C_6), 20.6 (7*C*H_3CO), 17.8 (CH_3).

III.3 Polymer Synthesis

III.3.1 Conventional synthesis protocol (CSP) for poly(1',2,3,3',4,4',6–hepta-*O*-benzyl-6'-*O*-metacryloyl sucrose)-co-polystyrene (29):

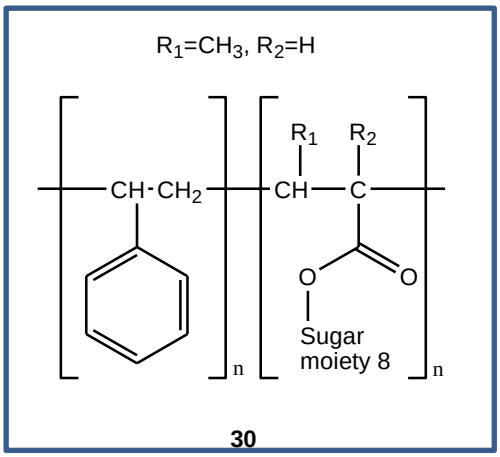


29

To a 50 mL round bottom flask, 0.749 g of **(5)** (0.720 mmol, 1 eq.) was added and 8 mL of toluene, under magnetic stirring and argon atmosphere for moisture exclusion. After complete dissolution for 5 min we added 15 mg of AIBN (1% weight of each monomer) and 0.9 mL of styrene (7.200 mmol, 10 eq.). After complete dissolution for 5 min, the mixture was deaerated with direct injection of argon in the reaction media for 2h after which we let the reaction occur in an oil bath at 85 ºC for 48h. The reaction was stopped when a drop of the reaction media precipitates in cold methanol.
The flask was cooled to room temperature and the work-up was made by precipitating the polymer synthesized introducing the reaction mixture dropwise in 15 mL of cold methanol (0 ºC). The precipitate was vacuum filtered and washed with cold methanol and dried in a dessicator for 2h. The polymer created was analyzed by ^{1}H-NMR and calculated that the incorporation of sugar monomer have the molar ratio of 1:11 (sugar monomer:styrene).

$[\alpha]_D^{20}$ = +15.81 (*c* 1.0, $CHCl_3$).
Relative viscosity (η_{rel}) = 1.08 (c, 10% polymer in toluene)

III.3.2 Conventional synthesis protocol (CSP) for poly(6-*O*-metacryloyl sucrose)-co-polystyrene (30):



30

III.3.2.1 Conventional synthesis protocol (CSP) in DMF:

On a 25 mL round bottom flask, 0.500 g (1.220 mmol, 1 eq.) of 6-*O*-metacryloyl-sucrose **(8)** was added with 22 mg of AIBN (1% weight of each monomer) in 8 mL of anhydrous DMF. After complete dissolution of the reagents, 1.400 mL of styrene (12.20 mmol, 10 eq.) was added dropwise under argon atmosphere and magnetic stirring. The dissolution occurred at room temperature for 20 min after which the mixture was deaerated for 2h by direct argon injection. The reaction occurred for 24h in oil bath at 85 ºC and was stopped when a drop of the reaction media precipitates in cold methanol. The flask was cooled to room temperature and the work-up was made by precipitating the polymer synthesized introducing the reaction mixture dropwise in 15 mL of cold methanol (0 ºC). The precipitate was vacuum filtered, washed with cold methanol and dried by vacuum and kept in a dessicator for storage.

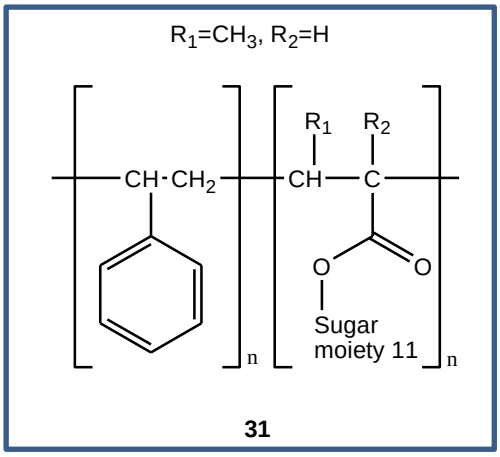
III.3.2.2 Conventional synthesis protocol (CSP) in H_2O:

To a 25 mL round bottom flask 0.500 g (1.220 mmol, 1 eq.) of 6-*O*-metacryloyl-sucrose **(8)** was added with 22 mg of $Na_2S_2O_8$ (1% weight of each monomer) in 8 mL of distilled H_2O and 1.40 mL of styrene (12.20 mmol, 10 eq.) under argon atmosphere to exclude moisture and magnetic stirring. The dissolution occurred at room temperature for 20 min. The reaction mixture was deaerated for 2h and the reaction occurred for 24h in oil bath at 85 ºC. The reaction was stopped when we verify that a drop of the reaction media precipitated in cold methanol.

The flask was cooled to room temperature and the work-up was made by precipitating the polymer synthesized introducing the reaction mixture dropwise in 15 mL of cold methanol (0 ºC). The precipitate was vacuum filtered, washed with cold methanol and vacuum dried and kept in a dessicator for storage.

Relative viscosity (η_{rel}) = 1.05 (*c*, 10% polymer in DMSO)

III.3.3 Conventional synthesis protocol (CSP) for poly(*O*-methacryloyl sucrose)-co-polystyrene (31):



31

III.3.3.1 Conventional synthesis protocol (CSP) in DMF:

On a 50 mL round bottom flask 0.500 g (1.220 mmol, 1 eq.) of *O*-methacryloyl-sucrose **(11)** was introduced with 22 mg of AIBN (1% weight of each monomer), 25 mL of anhydrous DMF and 1.400 mL of styrene (12.200 mmol, 10 eq.) under magnetic stirring and argon atmosphere to exclude moisture. The dissolution of all reaction components occurred at room temperature for 20 min after which the mixture was deaerated for 2h by direct argon injection in the reaction media. The reaction occurred for 24h in oil bath at 85 ºC and was stopped when we verify that a drop of the reaction media precipitated in cold methanol. The flask was cooled to room temperature and the work-up was made by precipitating the polymer synthesized introducing the reaction mixture dropwise in 15 mL of cold methanol (0 ºC). The precipitate was vacuum filtered, washed with cold methanol and vacuum dried and kept in a dessicator for storage.

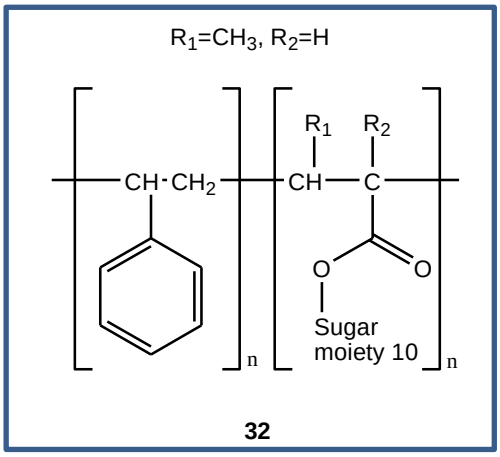
III.3.3.2 Conventional synthesis protocol (CSP) in H_2O:

O-methacryloyl-sucrose **(11)** 0.500 g (1.220 mmol, 1 eq.), was introduced with 33 mg of $Na_2S_2O_8$ (1% weight of each monomer) in a flask with 25 mL of distilled water and 1.400 mL of styrene (12,2 mmol, 10 eq.) under magnetic stirring and argon atmosphere to exclude moisture. The dissolution of all reaction components happened at room temperature for 20 min after which the mixture was deaerated for 2h by direct argon injection in the reaction media. The reaction occurred for 24h in oil bath at 85 ºC and was stopped when a drop of the reaction media precipitated in cold methanol. The flask was cooled to room temperature and the work-up was made by precipitating the polymer synthesized introducing the reaction mixture dropwise in

15 mL of cold methanol (0 ºC). The precipitate was vacuum filtered, washed with cold methanol, vacuum dried and kept in a dessicator for storage.

$[\alpha]_D^{20}$ = (*c* 1.0, $CHCl_3$).
Relative viscosity (η_{rel}) = 1.01 (7% polymer in $CHCl_3$)

III.3.4 Conventional synthesis protocol (CSP) for poly(1',2,3,3',4,4',6'-hepta-*O*-acetyl-6-*O*-methacryloyl sucrose)-co-polystyrene (32):

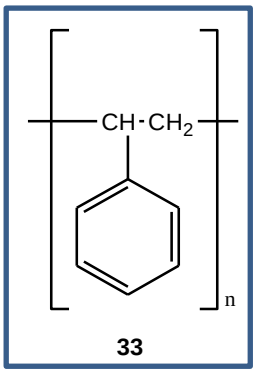


32

To a 50 mL round bottom flask, 0.268 g of **(10)** (0.381 mol, 1 eq.) was added and 6 mL of toluene, under magnetic stirring and argon atmosphere for moisture exclusion. After complete dissolution for 5 min we added 6,882 mg of AIBN (1% weight of each monomer) and 0.437 mL of styrene (3.810 mmol, 10 eq.). After complete dissolution for 5 min, the mixture was deaerated with direct injection of argon in the reaction media for 4h after which we let the reaction occur in an oil bath at 85 ºC for 48h. The reaction was stopped when a drop of the reaction media precipitates in cold methanol. The flask was cooled to room temperature and the work-up was made by precipitating the polymer synthesized introducing the reaction mixture dropwise in 15 mL of cold methanol (0 ºC). The precipitate was vacuum filtered on a Hirsh, washed with cold methanol and dried in a dessicator for 2h.

$[\alpha]_D^{20}$ = +4.24 (*c* 1.0, $CHCl_3$).
Relative viscosity (η_{rel}) = 2.98 (10% polymer in $CHCl_3$)

III.3.5 Conventional synthesis protocol (CSP) for polystyrene (33):



33

III.3.5.1 Conventional synthesis protocol (CSP) in toluene:

To a 100 mL round bottom flask, 2.210 mL g of styrene (19.200 mmol, 1 eq.) was added and 30 mL of toluene, under magnetic stirring and argon atmosphere for moisture exclusion. After complete dissolution for 5 min we added 31.500 mg of AIBN (1% weight of styrene). After complete dissolution for 5 min, the mixture was deaerated with direct injection of argon in the reaction media for 2h after which we let the reaction occur in an oil bath at 70 ºC for 48h. The reaction was stopped when a drop of the reaction media precipitates in cold methanol.

The flask was cooled to room temperature and the work-up was made by precipitating the polymer synthesized introducing the reaction mixture dropwise in 15 mL of cold methanol (0 ºC). The precipitate was vacuum filtered on a Hirsh, washed with cold methanol and dried in a dessicator for 2h, resulting in 0.305 g of a fine white powder.

Relative viscosity (η_{rel}) = 1.04 (3% polymer in toluene)

III.3.5.2 Conventional synthesis protocol (CSP) in H_2O:

To a 100 mL round bottom flask, 2.210 mL g of styrene (19.200 mmol, 1 eq.) was added and 30 mL of H_2O and 10 mL of acetone (mixture 3:1 H_2O:Acetone), under magnetic stirring and argon atmosphere for moisture exclusion. After complete dissolution for 5 min we added 45.700 mg of sodium persulfate (1% weight of styrene). After complete dissolution for 5 min, the mixture was deaerated with direct injection of argon in the reaction media for 2h after which we let the reaction occur in an oil bath at 70 ºC for 48h. The reaction was stopped when a drop of the reaction media precipitates in cold methanol.

The flask was cooled to room temperature and the work-up was made by precipitating the polymer synthesized introducing the reaction mixture dropwise in 15 mL of cold methanol (0 ºC). The precipitate was vacuum filtered on a Hirsh, washed with cold methanol and dried in a dessicator for 2h, resulting in 1.132 g of a fine white powder.

Relative viscosity (η_{rel}) = 1.17 (10% polymer in toluene)

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