Review

Ring-Opening of Cyclodextrins: An Efficient Route to Pure Maltohexa-, Hepta-, and Octaoses

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Abstract: Many preparations of maltooligosaccharides have been described in literature, essentially using enzymatic or biotechnological processes. These compounds, derived from starch, are well-known as prebiotic agents. The use of maltohexa-, hepta-, and octaoses as synthons in organic synthesis was also well documented in literature. They can indeed be obtained as single compounds by the cyclodextrins' ring-opening. This reaction has been studied for many years, varying the protecting and functional groups and the reaction conditions, leading to functionalized oligomaltoses. These compounds are of wide interest in various fields. They have a strong potential as scaffolds for multivalence in chemobiology, as building blocks for the production of biomimetic pseudo-glycopeptides, as well as monomers for the preparation of materials. In view of the importance of these oligomaltoses, this review focuses on the different methodologies allowing access to them via chemical and enzymatic ring-opening of cyclodextrins.

Keywords: cyclodextrins; maltooligosaccharides; building blocks; platform molecules; monomers

1. Introduction

Oligomaltoses (OMs) are linear oligosaccharides composed of glucose units linked by α-1,4 linkages. As defined, OM, like other oligomers, are made of 2 to 10 monomer units this number of units is also named degree of polymerization (DP). Since 1955 [1], the preparation of OM was investigated using enzymes from different sources to perform transglycosylation from maltose or by the degradation of starch by various α-amylases.

Nigam and Giri [1] studied the synthesis of linear OM from maltose by rat liver enzyme. They obtained a mixture mainly containing maltotriose and maltotetraose. In 1960, they demonstrated that a non-isolated transglucosidase from green gram [2] was able to catalyse the transglucosylation reaction from 10 g of maltose, producing 190 mg of maltotriose and 85 mg of maltotetraose. It was shown that other sources of enzymes as from moulds [2] led preferentially to branched oligosaccharides (isomaltosides, isomaltotriose). Moreover, α-transglucosidase from *Aspergillus niger* was able to catalyse from maltose, the synthesis of panose, which is also a branched trisaccharide (Glc-α-1,6-Glc-α-1,4-Glc). However, *Saccharomyces cerevisiae* α-glucosidase did not catalyse transglycosylation in tested conditions [3]. This approach was improved by using more complex substrates such as maltotriose with maltogenic amylase (MAG1) from *Bacillus lehensis* G1, which was treated by a structure-guided protein engineering approach to improve its catalytic properties [4]. Conversion of the reactions was generally higher, but the products consisted of a mixture of DP 2 to DP 7 in varying proportions depending on the nature of the mutant. The use of α-ᴅ-maltosyl fluoride as a substrate was also demonstrated to be effective using α-amylase from *Aspergillus oryzae*. The reaction led to a total substrate conversion leading

to a mixture of DP 2 to DP 7, the major component being maltotetraose [5]. Starting from the 6'-*O*-methyl α-maltosyl fluoride, Driguez et al. prepared a mixture of DP 2, 4, 6, and 8 using cyclodextrin glycosyltransferase as a catalyst with 49% yield [6]. The aim of their work was the cyclisation of the latter for the synthesis of modified CDs. Therefore, they did not try to optimize the production of OM.

Another way for the synthesis of OM was the degradation of starch by various α-amylases in the presence of benzyl alcohol [7]. The only compound synthesized was 1-*O*-benzyl-α-maltoside, no higher DP was observed. In more classical conditions, Niu et al. [8] detected the formation of OM by degradation of starch catalysed with the thermostable α-amylase from *Bacillus licheniformis*. The pentamaltoside was the main product of the mixture, which contained OM from DP 1 to DP 6.

While enzymatic catalysis leads to mixtures produced in relatively small amounts, the chemical synthesis of pure linear OM with high DP is complex. The total synthesis of hexamaltooligosaccharides with various protecting groups was achieved by Takahashi et al. in 14 steps from maltose in 4% overall yield [9]. Starting from these products, they pursued their work by synthesizing octamaltooligosaccharides in 21% yield using a protected β-maltosyl fluoride donor [10].

The chemical synthesis of linear high DP OM is much more efficient by the opening of cyclodextrins (CDs). The α, β, and γ-CDs are cyclic oligosaccharides composed of 6, 7, or 8 glucose units respectively linked by a α-1,4 glycosidic bond (Scheme 1). They are industrially prepared using CD glucanotransferase on starch [11]. Very recently, β-CD was also prepared with 70% yield from maltose using the same enzyme and 1-adamantane carboxylic acid as supramolecular template to control the reaction [12].

n = 1 α-CD
n = 2 β-CD
n = 3 γ-CD
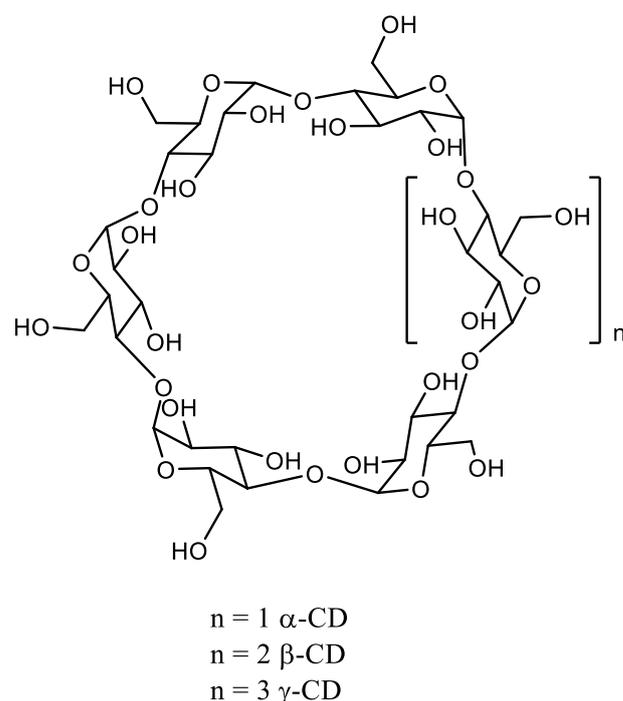
Scheme 1. The most common cyclodextrins.

CDs are available in rather large quantity with well-characterized structures. Among CDs, the β-CD is a fairly cheap raw material.

Firstly, we will review herein the enzymatic opening of CDs. Then the different reactions described in literature for OM preparations by CDs chemical opening will be described. Finally, we will discuss the different applications of these molecules of interest through further functionalization.

2. Enzymatic Ring Opening of Cyclodextrins

A review of CD degrading enzymes (Cyclomaltodextrinases, EC 3.2.1.54, cyclomaltodextrin hydrolases) and α-amylases from microbial sources (*Bacillus coagulans*, *B. macerans*, alkalophilic *Bacillus* sp., *Pseudomonas*, among others) was published in 1992 [13]. The authors analyzed the action pattern of these enzymes and found that they could open CDs to lead to the corresponding OM. For example, the action of *Pseudomonas* α-amylase on α-CD results in a very rapid accumulation of maltohexaose, but then the latter is degraded to smaller molecules, mainly maltotriose, maltose and glucose. A similar behavior was reported by H. Bender for a CD-degrading enzyme isolated from *Flavobacterium* sp. The enzyme hydrolyzed OM and CDs to glucose, maltose, and maltotriose [14].

Uchida et al. [15] reported the use of cyclomaltodextrinase from *Bacillus sphaericus* E-244 for the preparation of maltoheptaose (from β-CD) and maltooctaose (from γ-CD). The enzyme has not only a CD-hydrolyzing activity (decycling of CDs) but also a coupling activity (transfer of a D-glucose unit). They described the enzymatic synthesis of maltoocta- and nonaose from CDs and D-glucose by the coupling reaction catalyzed by cyclomaltodextrinase (Scheme 2). However, the preparation of maltohexa-, hepta- and/or octaose by this approach required further purification, because small molecules such as glucose, maltose, and maltotriose were also formed.

n = 5   β-CD
n = 6   γ-CD

n = 5   maltooctaose
n = 6   maltononaose
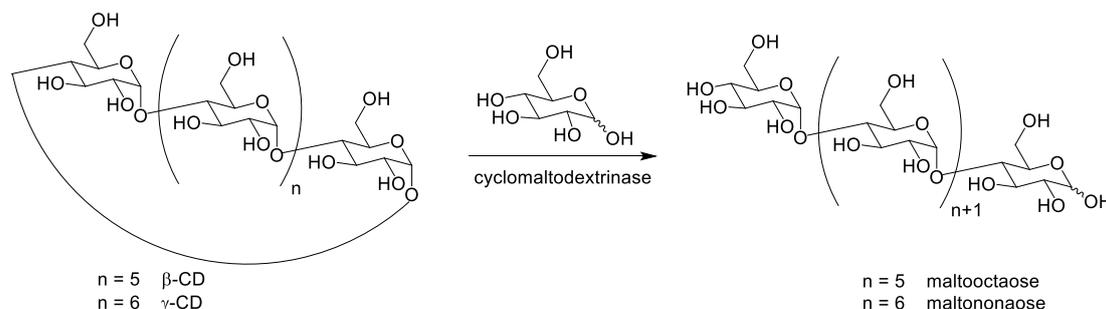
Scheme 2. CDs opening and transglycosylation using cyclomaltodextrinase.

These limitations were circumvented by Fraschini et al. [16] by using modified CDs in one primary position (oxidized to carboxylic acid) and two different enzymes: CD glucanotransferase (CGTase) and amyloglucosidase. They obtained mainly tri- and tetrasaccharide derivatives, thus avoiding further degradation.

PFTA, a thermostable amylase from *Pyrococcus furiosus*, was cloned and expressed in *Escherichia coli*. Unlike CD-hydrolyzing enzymes, which were known to produce mainly maltose starting from CDs, PFTA liberated various small OM (from mono- to heptasaccharide) [17]. The difference in the rate of CDs opening (fast) and the hydrolytic activity on the resulting open-chain OM (slow) was exploited to obtain mixtures rich in maltohexaose, maltoheptaose, and maltooctaose from α-, β-, and γ-CD, respectively (Scheme 3) [18].

n = 4   α-CD
n = 5   β-CD
n = 6   γ-CD

n = 4   maltohexaose
n = 5   maltoheptaose
n = 6   maltooctaose
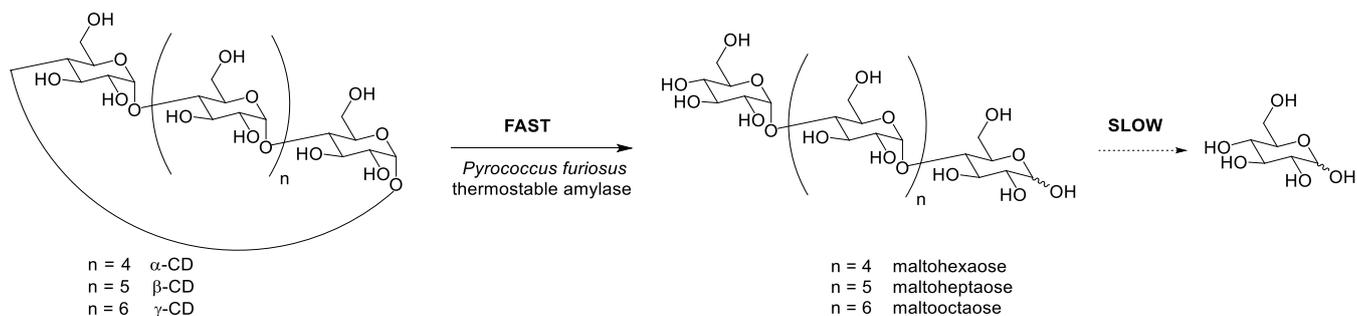
Scheme 3. Fast-opening activity of the amylase from *Pyrococcus furiosus*.

In a different approach, several mutations of a maltogenic amylase (MAG1) from *Bacillus lehensis* G1 were performed, in order to decrease its hydrolytic activity and to modulate its transglycosylation properties [4]. Interestingly, hydrolysis suppression was caused by the Y377F mutation, allowing the formation of OM with higher DPs (up to maltoheptaose).

CD glucanotransferases (CGTase) mainly produce CDs starting from linear OM. Koo et al. [19] performed site-directed saturation mutagenesis on the +1 substrate-binding residue H233 of CD glucanotransferase CGTase from alkalophilic *Bacillus* sp. I-5 to prepare specific-length oligosaccharides. The obtained mutant CGTase, H233Y, hydrolyzed β-CD to afford mainly maltoheptaose. A kinetic study of H233Y showed that the kcat/Km value of β-CD was seven-fold greater than that of maltoheptaose, which accounts for the accumulation of the latter. In the mutant, the position of the +1 subsite is changed, and as a consequence, the hydrolysis of the maltoheptaose resulting from the ring-opening of CD is very slow. CGTase H233Y had ring-opening activity using β-CD but did not exhibit transglycosylation activity, which resulted in an accumulation of maltoheptaose with a high purity.

Unfortunately, enzymatical approaches usually lead to complex mixtures of free linear OM of various DPs. The isolation of a specific DP is difficult and requires several chromatographic steps, lowering the final yields. Moreover, the functionalization of such compounds is challenging. The chemical approach is thus more interesting to yield such functionalized OM.

3. Acetolytic Cleavage of Cyclodextrins

The viability of the acetolytic cleavage process in the production of OM from CD derivatives has evolved since the middle of the last century [20–23]. The early efforts to selectively prepare these oligomers were unsuccessful and led to a mixture of mono and oligomers, in which the amount of the desired hexa-, hepta-, or octa-malto-oligosaccharides did not exceed 2–4% [20–23]. In 1990, Lipták and co-inventors [24] patented their research results on the acetolysis of *per*acetylated CDs using a mixture of acetic anhydride and sulfuric acid. To increase the efficiency of previous procedures, they optimized the reaction conditions by varying the amount of sulfuric acid between 1–10% in acetic anhydride, the temperature (0–100 °C), and the reaction time [24]. The Table 1 summarizes the results for the acetolysis of *per*acetylated α-CD.

Table 1. Optimization of the acetolysis of *per*acetyl-α-cyclodextrin.

Entry	Temperature (°C)	Time (h)	Sulfuric Acid Conc. (vol%)	Yield %
1	0	72	6	35
2	30	30	6	35
3	40	11	6	38
4	50	10	2	35
5	50	4	6	49
6	50	1.5	10	35
7	60	2	6	43
8	78	0.5	6	40
9	100	0.1	6	40

The best yield was obtained using a mixture of sulfuric acid (6 %) in acetic anhydride at 50 °C for 4 h leading to the formation of icosa-*O*-acetylmaltohexaose (entry 5). Similar results were obtained for the preparation of tricosa-*O*-acetylmaltoheptaose and hexacosa-*O*-acetylmaltooctaose from *per*acetylated β- and γ-CD, respectively. The reaction conditions used for entry 4 of the Table 1 were repeated by Sakairi et al [25]. They found that the formation of icosa-*O*-acetylmaltohexaose can reach 47% after 20 h of stirring (Scheme 4).
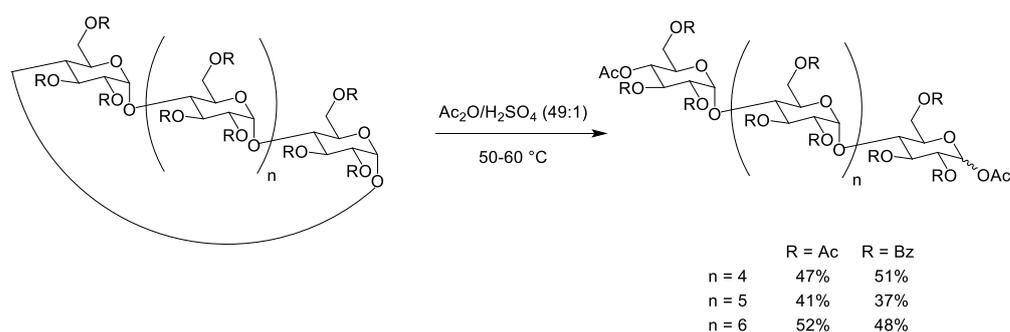
Scheme 4. Ring-opening of CDs by acetolysis reaction optimized by Sakair et al.

During this process, the fission of a single glycosidic bond was observed and two acetyl groups were introduced, one at the reducing end and another at the non-reducing end of the linear OM. The maltoheptamer and maltooctamer were also prepared from *per*acetyl-β- and γ-CDs in 41% and 52 %, respectively.

In another study, Sakairi et al. [26] extended this method to *per* benzoylated CDs to prepare partially benzoylated OM derivatives having acetyl groups at reducing and non-reducing ends, though these derivatives are useful for the preparation of various derivatives substituted at both ends. Starting from *per*benzoylated CDs and using a similar procedure [26] gave $1^I,4^{VI}$-di-*O*-acetyl derivative of octadeca-*O*-benzoyl-α-maltohexaose, $1^I,4^{VI}$-di-*O*-acetylated heneicosa-*O*-benzoyl-α-maltoheptaose, and tetracosa-*O*-benzoyl-α-maltooctaose in 51%, 37%, and 48% yield, respectively (Scheme 4). Other attempts were performed with chloroacetic anhydride or trifluoroacetic anhydride in presence of a catalytic amount of sulfuric acid. However, these attempts failed, leading to complex mixtures. The authors assumed that this was due to the random cleavage of the glycosidic bond and the intra- or inter-molecular migration of acetyl groups.

In 1995, Sakairi et al. explored the direct acetolysis of free α-CD by applying a similar procedure as described above. Under these conditions, they described the formation of icosa-*O*-acetylmaltohexaose in 20% yield only [27]. The low yield is the consequence of a low selectivity of the reaction, because of its exothermic nature. The resulting compounds were obtained after crystallization in toluene followed by silica gel column chromatography.

In 1999 Yoshida et al. [28] described the synthesis of *per*acetylated maltoheptaose in 35% yield from acetylated β-CD using the procedure previously reported by Sakairi et al. in 1991 [25]. Similar reaction conditions were used by Haddleton et al. leading to the same compound (40–50% yields) [29].

More recently, Djedaïni-Pilard et al. [30] significantly improved this procedure. In their conditions, they described the formation of di-*O*-acetylated maltohexaose, -heptaose, and -octaose derivatives from *per-O*-benzoylated α-, β-, and γ-CD in 70–82% yields. Thus, the authors extended this method to the ring-opening of CDs halogenated in primary positions to lead to novel C-6 modified OM.

To prepare these halogenated maltoheptaose derivatives (Scheme 5), more laborious acetolysis conditions were required. The concentration of sulfuric acid and reaction times were increased to allow the formation of $1^I,2^{I–VII},3^{I–VII},4^{VII}$-hexadeca-*O*-acetyl-$6^{I–VII}$-heptabromo-$6^{I–VII}$-heptadeoxy-α-maltoheptaose and $1^I,4^{VII}$-di-*O*-acetyl-$2^{I–VII},3^{I–VII}$-tetradeca-*O*-benzoyl-$6^{I–VII}$-heptabromo-$6^{I–VII}$-heptadeoxy-α-maltoheptaose in 16% and 32% yields, respectively.
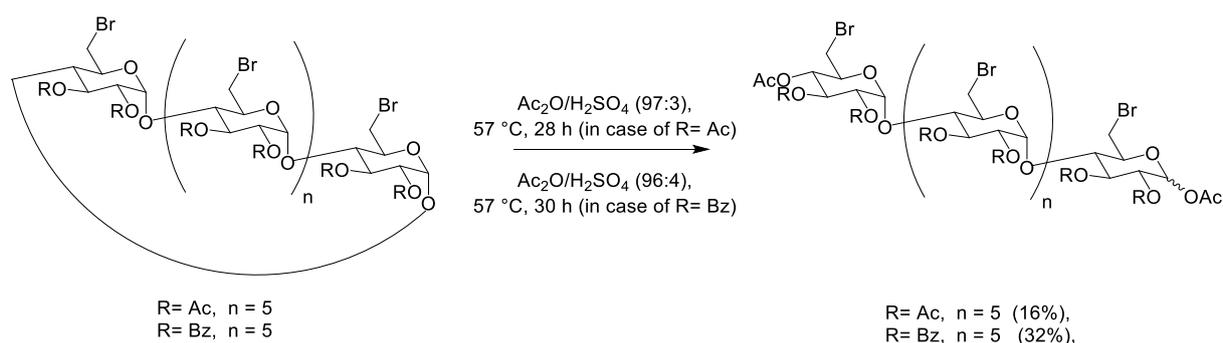
Scheme 5. Synthesis of *C*-6 halogenated maltohexaose.

Another assay was performed by the authors [30]. Starting from heptakis(6-azido-2,3-di-*O*-benzoyl-6-deoxy)-β-CD (Scheme 6), and applying similar conditions, they obtained $1^I,4^{VII}$-di-*O*-acetyl-6^{I-VII}-heptaazido-$2^{I-VII},3^{I-VII}$-tetradeca-*O*-benzoyl-6^{I-VII}-heptadeoxy-α-maltoheptaose in 30% yield. It was observed that the esterified *per*-(6-substituted-6-deoxy)-β-CD is more resistant to acetolysis than the *per-O*-esterified analogue. The formation of these linear azidated or halogenated OM via the ring-opening of modified cyclodextrins remains very advantageous compared to their synthesis by direct azidation or halogenation of linear OM.
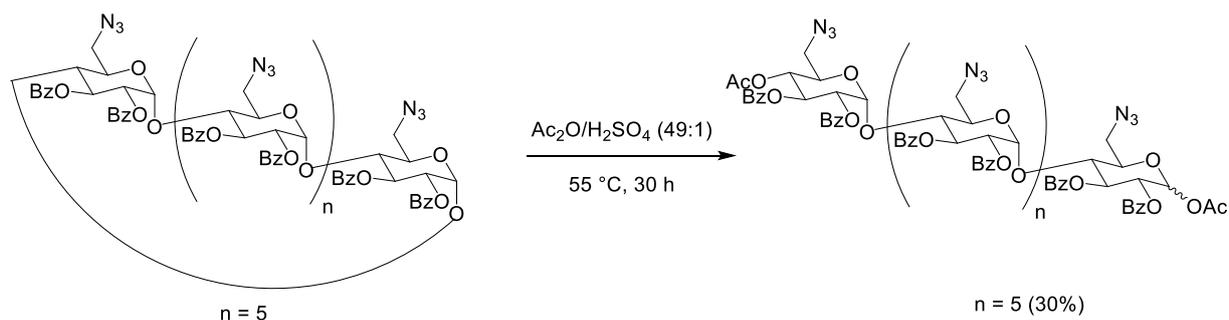
Scheme 6. Synthesis of heptakis (6-azido-2,3-di-*O*-benzoyl-6-deoxy)-β-CD.

Using the same procedure, in 24h, the *per*benzoylated monoiodo-β-CD was opened by acetolysis leading to a mixture of regioisomers of monoiodomaltoheptaose. More interestingly, the *per*benzoylated monoazido-β-CD led to only one regioisomer of azido maltoheptaose with 73% yield (Scheme 7) [31].
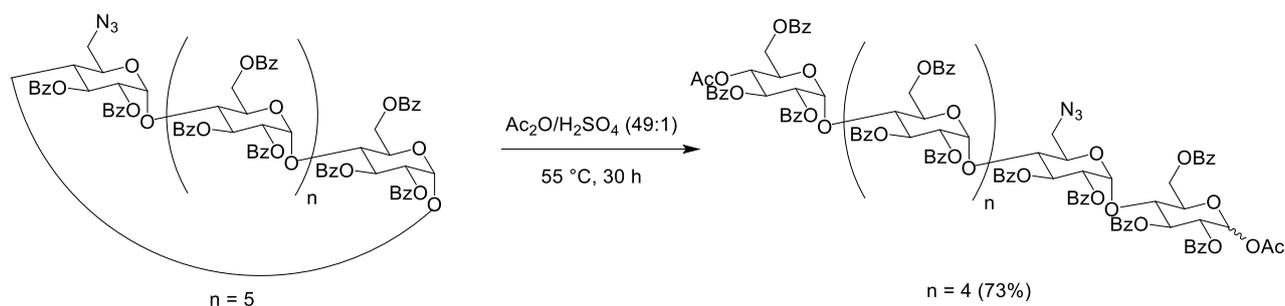

Scheme 7. Mono *per*benzoylated β-CD opening leading to one regioisomer with high yield.

4. Ring-Opening Cyclodextrins Using Other Acidic Conditions

*4.1. Ring-Opening Cyclodextrins Using Brønsted Acids (HClO₄)*

With a pKa of -8, *per*chloric acid HClO₄ is a stronger acid than sulfuric acid. In 2001, with the aim of preparing specific neoCDs, Vasella et al. [32] performed the ring-opening of *per*acetylated α-CD, carrying out acetolysis by a method derived from that developed by Lipták et al [24]. This procedure consisted in reacting *per*acetylated α-CD with Ac₂O, in the presence of HClO₄ (70% by weight aqueous solution) at 0 °C for 20 h. After crystallization in ethanol, they obtained the desired *per*acetylated maltohexaose in 95% yield (α/β > 9/1) (Scheme 8). This reaction wasconfirmed in 2010 by Lehn et al. [33], which described
similar yields.
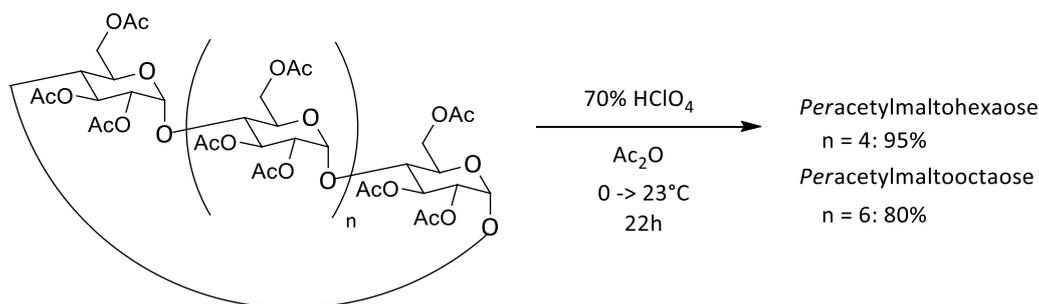
**Scheme 8.** Acetolysis in the presence of *per*chloric acid.

Since the use of *per*chloric acid led to a better yield than in the case of sulfuric acid, the following year the authors described the application of this new procedure to *per*acetylated γ-CD. [34] Under these conditions, acetylated maltooctaose was obtained in 80% yield, again after crystallization in ethanol.

In 2002, Ikeda et al. [35] attempted to apply this procedure to the opening of a *per*methylated α-CD unsuccessfully. They obtained a complex mixture including low molecular weight sugars. Since the acetolysis procedure by the H₂SO₄-Ac₂O couple was not more efficient, they optimized the opening of the cyclodextrin by decreasing the amount of *per*chloric acid. By treating the *per*methylated α-CD with a 30% (instead of 70%) aqueous solution of HClO₄, without acetic anhydride at room temperature for 42h, they obtained the methylated maltohexaose in 31% yield. Without Ac₂O, this maltohexaose had two free hydroxyl groups, allowing their functionalization without deprotection steps (Scheme 9). No information on the purification method used was provided. However, an identical reaction was described in the work of Akashi et al. in 2005 [36]. Under the same conditions but with a longer stirring time (4 days instead of 42 h), the acyclic product was obtained with a yield of 43% after purification on silica gel (Scheme 9).
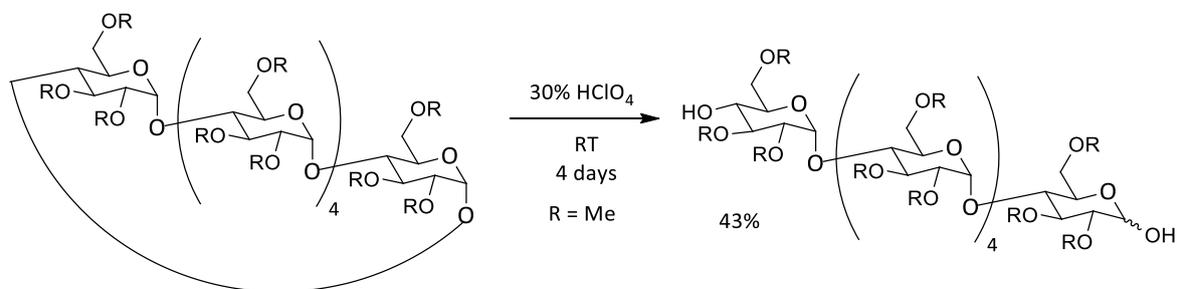

Scheme 9. Hydrolysis of methylated cyclomaltohexaose.

Djedaïni-Pilard et al. [30] employed this methodology for the preparation of a heptabrominated maltoheptaose by performing the opening of a β-CD benzoylated on the secondary positions and brominated on the primary positions. Under these conditions, the maltoheptaose can be obtained in 30% yield (Scheme 10).
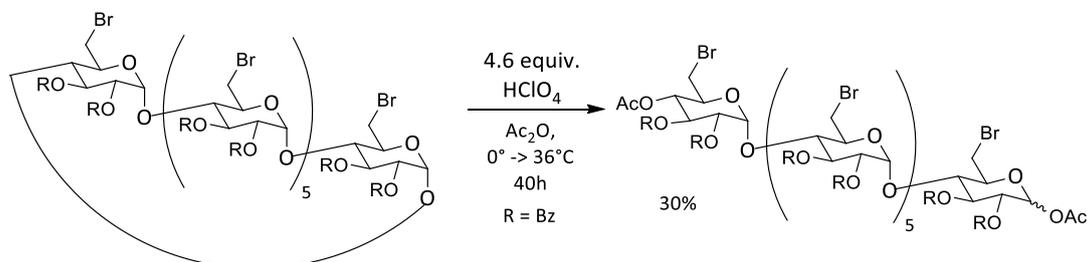
Scheme 10. Hydrolysis of a heptabromo-β-CD.

This product was then functionalized by nucleophilic substitution with LiN_3 to lead to the azido derivative in 91% yield. In 2011, Gouin et al. [37] improved the preparation of the latter by performing the ring-opening reaction directly on the heptaazido-β-CD below, at −20 °C (Scheme 11).
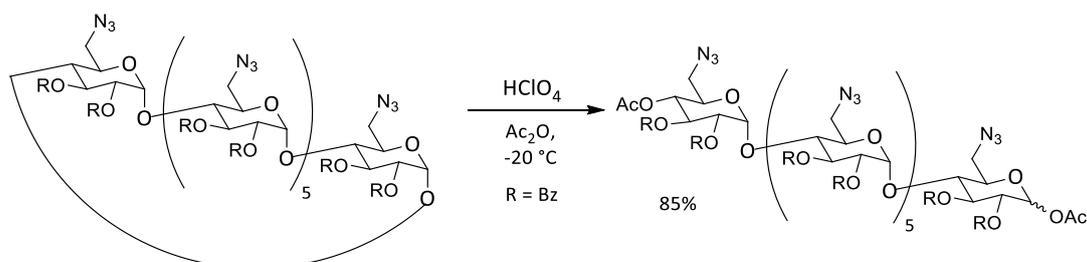
Scheme 11. Ring-opening reaction of the heptaazido-β-CD in *per*chloric acid.

More recently, Ishida et al. [38] studied the ring-opening of *per*methylated α-, β- and γ-CD using an aqueous solution of 30% *per*chloric acid. They monitored the reaction by MALDI TOF MS, demonstrating that the reaction time is a critical parameter in this reaction. It needs to be optimized to improve the yields of pure OMs without depolymerization, which occurs from 5h only. They thus isolate the hexa-, hepta-, and octamer in 52%, 46%, and 70% yields for α-, β-, and γ- respectively.

4.2. Ring-Opening of Cyclodextrins Using Sulfuric Acid and Triflic Anhydride

Very recently, our group [39] demonstrated the interest of triflic anhydride in DCM instead of acetic anhydride with sulfuric acid to perform the ring-opening of α-, β-, and γ-CD. These conditions allow the selective preparation of 1-azido derivatives, propargyl, and allyl glycosides by the opening of the corresponding *per*benzoylated CD followed by their in situ glycosylation with rather good yields and selectivity (Scheme 12).

4.3. Lewis Acid $FeCl_3$

After patenting the acetolysis method using the H_2SO_4-Ac_2O mixture in 1990, Lipták et al. [24] worked extensively on the synthesis of substrates suitable for measuring human pancreatic α-amylase activity. In 1997, instead of using the classical CD acetylation method, they tested the use of acetic anhydride in the presence of different Lewis acids ($ZnCl_2$, $AlCl_3$, $FeCl_3$) as well as several Brønsted acids (H_2SO_4, HCl, $HClO_4$) [40]. The best results were obtained using ferric chloride (Scheme 13). The amount of *per*acetylated β-CD remained low (<15%) compared to the hydrolysis products. Separation by HPLC followed by 3 successive recrystallizations in ethanol allowed to obtain the *per*acetylated maltoheptaose in 22% yield (99% purity). Regarding *per*acetylated α-CD and γ-CD, the acetolysis

procedure via FeCl$_3$.6H$_2$O led to the *per*acetylated maltohexaose and maltooctaose in 20% and 23.5% yields, respectively.
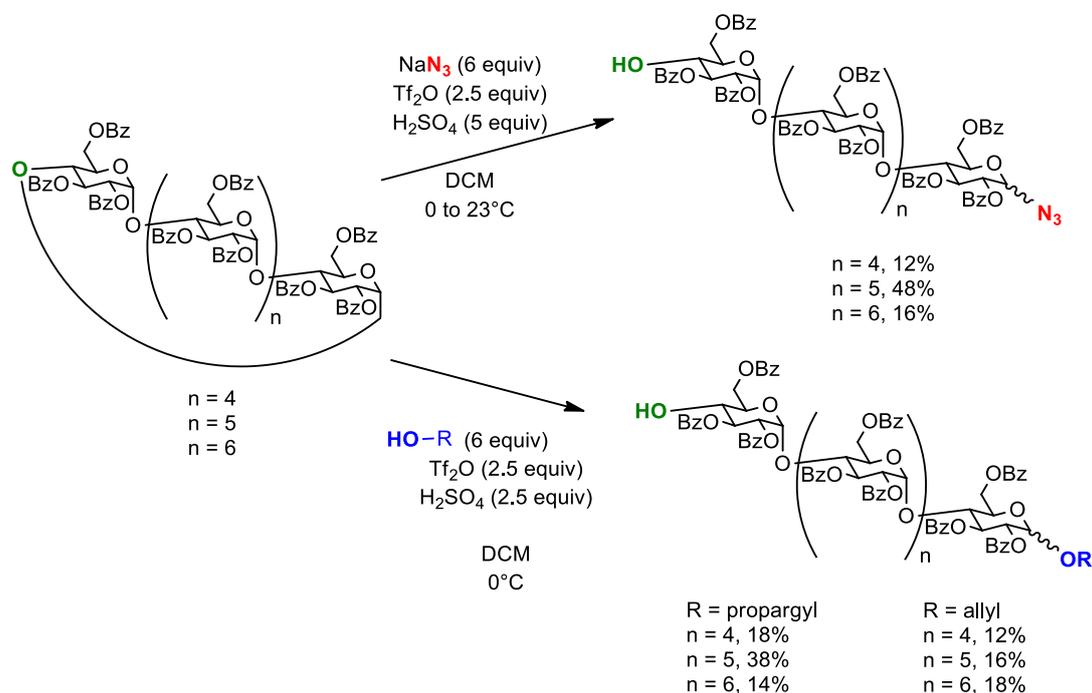
Scheme 12. Regioselective opening of the corresponding *per*benzoylated CD followed by their in situ glycosylation with various nucleophiles.
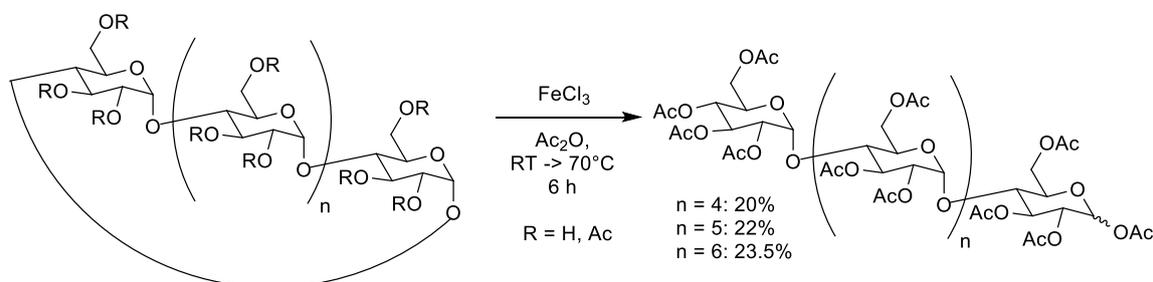
Scheme 13. Acetolysis procedure catalysed with ferric chloride.

To our knowledge, only Halila et al. [41] applied these ring-opening conditions.

4.4. Lewis Acid TiCl$_4$

Bosch et al. [42] performed the CD ring-opening in a freshly prepared solution of TiCl$_4$ in dry DCM (Scheme 14). The CD derivatives used were fully etherified by methyl, ethyl, or allyl alcohols and well dried before reaction. The reaction was monitored by TLC, and for the first time, the oligomaltosides (Scheme 14) were analyzed by ESI or MALDI Mass Spectrometry.
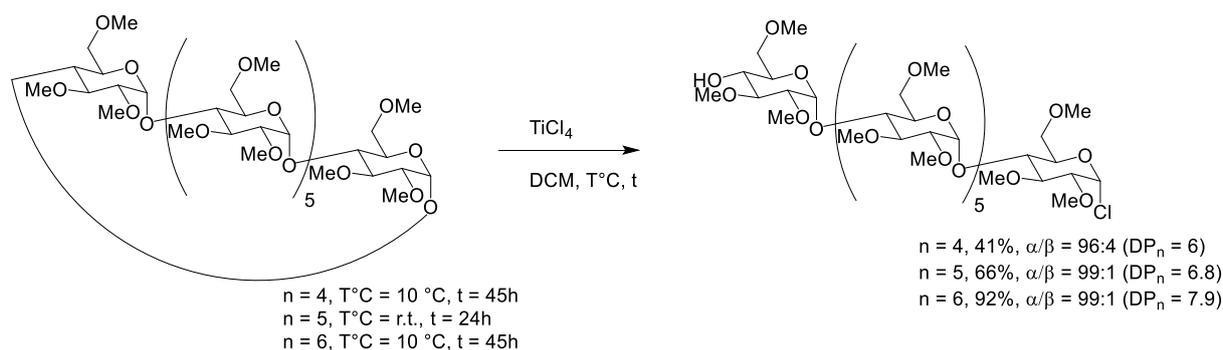
Scheme 14. α-, β-, γ- *per*methylated cyclodextrin ring-opening by TiCl$_4$ in anhydrous conditions.

Contrary to other Lewis acids, TiCl$_4$ promotes a chloride ion transfer to the intermediate oxocarbenium ion. Due to the strong anomeric effect, α-glucosyl chlorides are exclusively formed. Unfortunately, authors were unable to isolate pure DPs. They obtained mixtures with average DPs of 6, 6.8, and 7.9 from α-, β-, and γ-CD, respectively. Nevertheless, this bifunctionalization was very useful to prepare a variety of oligomeric glycosyl donors and monomers for polymerization [42].

4.5. Lewis Acid ZnI/ZnBr and Thiolysis

Sakairi and Kuzuhara investigated the ring-opening of CD by thiolysis [43,44]. The reaction of *per*methylated β-CD with trimethyl(phenylthio)silane (PhSTMS) and zinc iodide afforded 1-(phenylthiol)maltoheptaoside *O*-silylated at the 4-position of the non-reducing end as a major product. Then the latter was converted to the more stable 4-*O*-benzoyl derivative for purification, which led to the desired product in 38% yield (Scheme 15). With some changes, the reaction was applied to *per*methylated α-CD and γ-CD (28% and 41% yield, respectively). In all cases, a substantial amount of starting material (50–68%) was recovered.
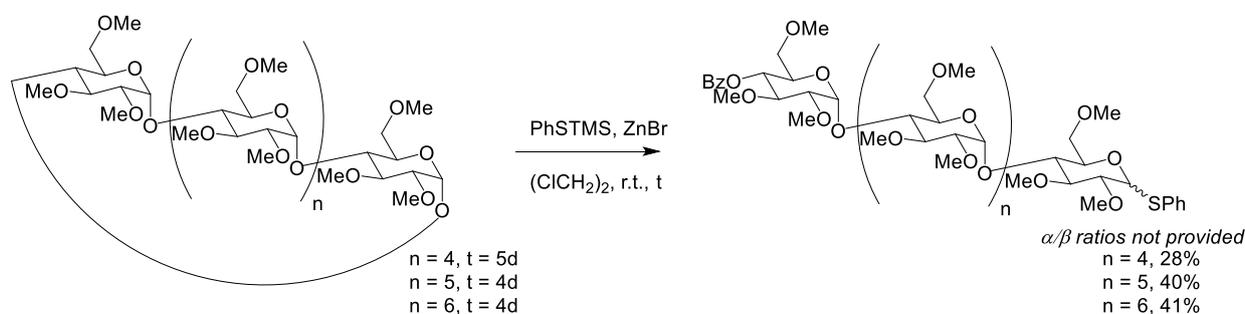
Scheme 15. Ring-opening of CD by thiolysis.

The Table 2 resumes the various conditions of acetolysis or hydrolysis for ring-opening of CD in literature. To highlight the most important parameter of the reaction, we sorted the conditions by type of acid, then by functional groups present on CDs, then by type of CD, and finally by acid concentration. We can thus see that, together with the acid concentration, the temperature and the stirring time are also important factors. We can conclude that *per*chloric acid at 0 °C led to the highest yields (95% of maltohexaose) from *per*acetylated α-CD. To avoid esterification or etherification of the cyclodextrin prior to the ring-opening, FeCl$_3$ conditions are very efficient because they led to 20–23% yield of 99% pure *per*acetylated maltooligosaccharides after three steps of recrystallization, whatever the CD.

Table 2. Conditions for ring-opening of CD (* mixture of regioisomers).

| Acid.	[Acid]	Cd	[cd]	Functional Groups		T °C	Time	α/β	Yield	Starting Material Recovered	Ref
				C-2 et C-3	C-6						
FeCl$_3$	0.074 M	α	0.3 M	none		RT then 70 °C	2.5 + 3.5h	/	20%	/	[40]
	0.074 M	β	0.3 M	none		RT then 70 °C	2.5 + 3.5h	9:1	22%	/	[40]
	0.074 M	γ	0.3 M	none		RT then 70 °C	2.5 + 3.5h	/	23.5%	/	[40]
H$_2$SO$_4$	0.373 M	α	/	Ac		50–60 °C	20 h	5.3:1	47%	46%	[25]
	1.2 M	α	/	Ac		50 °C	4 h	/	48%	/	[24]
	0.373 M	β	/	Ac		50–60 °C	20 h	/	41%	49%	[25]
	0.373 M	γ	/	Ac		50–60 °C	20 h	/	52%	37%	[25]
	0.560 M	β	0.021 M	Ac	Br	57 °C	28 h	/	16%	78%	[30]
	0.373 M	β	0.043 M	Bz	1 I and 6 Bz	55 °C	24 h	/	70% *	9%	[31]
	0.373 M	β	0.044 M	Bz	1 N$_3$ and 6 Bz	55 °C	24 h	/	73%	10%	[31]
	0.666 M	β	0.099 M	Bz		57 °C	30 h	/	32%	58%	[30]
	0.373 M	α	0.035 M	Bz		60 °C	30 h	/	82%	15%	[30]
	1.373 M	α	0.036 M	Bz		50 °C	32 h	/	51%	36%	[26]
	0.373 M	β	0.080 M	Bz		55 °C	42 h	/	76%	12%	[30]
	1.373 M	β	0.086 M	Bz		50 °C	29 h	/	37%	54%	[26]
	0.373 M	γ	0.015 M	Bz		50 °C	35 h	/	70%	17%	[30]
	1.373 M	γ	0.015 M	Bz		50 °C	27 h	/	48%	39%	[26]
	0.373 M	β	0.102 M	Bz	N$_3$	55 °C	30 h	/	30%	66%	[30]
HClO$_4$	0.086 M	α	0.019 M	Ac		0 °C	22 h	/	60%	30%	[30]
	0.087 M	α	0.019 M	Ac		0 °C	45 h	>9:1	95%	/	[32]
	0.087 M	α	0.019 M	Ac		0 °C	45 h	>9:1	95%	/	[32]
	0.084 M	β	0.018 M	Ac		0 °C	20 h	/	35%	55%	[30]
	0.086 M	β	/	Bz	Br	0 °C then 36 °C	2 × 20 h	/	30%	/	[30]
	0.036 M	β	0.0072 M	Bz	N$_3$	−20 °C	16 h	/	85%	/	[37]
ZnBr(+PhSTMS)	0.266 M	α	0.066 M	Me		RT	5 days	1:1	28%	68%	[44]
	0.2 M	β	0.2 M	Me		RT	4 days	1:1	40%	/	[44]
	0.2 M	γ	0.05 M	Me		RT	4 days	2:8	41%	/	[44]
TiCl$_4$	0.4 M	α	0.1 M	Me, Et or All		10 °C	45h	96:4	41% *	/	[42]
	0.4 M	β	0.1 M	Me, Et or All		RT	24h	99:1	66% *	/	[42]
	0.4 M	γ	0.1 M	Me, Et or All		10 °C	45h	99:1	92%*	/	[42]

5. Application Areas of Pure OM

Ring-opening of CD generally leads to pure OM, which have been used in many fields. To highlight the importance of these compounds, we split the various works described in the literature into four areas of application. In this section, we present, for each application, the different structural modifications made and the utility of the resulting compounds.

5.1. Biological Target

5.1.1. Chromogenic Substrates

OM derived from ring-opening of CDs have been widely used as chromogenic substrates. Since the late 1970s, α-amylase activity has been measured in human serums by using oligosaccharides (4-nitrophenyl glycosides) of known chain length as substrates for α-glucosidase. But the interference of endogenous glucose or pyruvate in some of these methods has been reported [45,46]. Nevertheless, the authors pointed out that the rate of degradation by amylase of substrates with a DP ≥ 7, was low. With this in mind, G. Dupuy et al. suggested, in 1987, one chromogenic substrate that was blocked at the nonreducing end [47]. The $4^7,6^7$-*O*-benzylidene-α-D-4-nitrophenylmaltoheptaoside (Scheme 16) was used to determine the α-amylase activity in serum, in a coupled assay with α-glucosidase and glucoamylase as auxiliary enzymes.
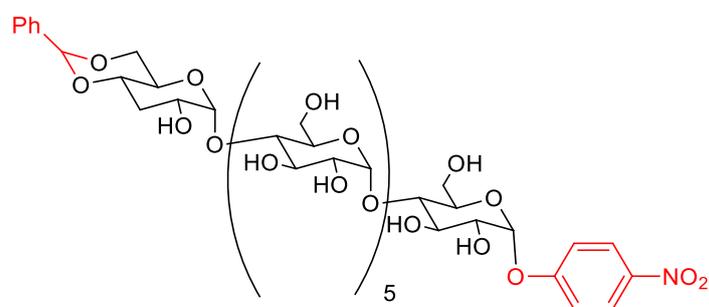
**Scheme 16.** $4^7,6^7$-*O*-benzylidene-α-D-4-nitrophenylmaltoheptaoside.

The presence of a benzylidene functional group at the non-reducing end of the substrate prevents hydrolysis by α-glucosidase. This observation was made by K. Lorentz in 1983 with the use of unprotected 4-nitrophenyloligosaccharides [48]. Using this substrate in combination with auxiliary enzymes, more than 95% of hydrolyzed substrates in the form of 4-nitrophenol glycosides were obtained. Some years later, the studies carried out by L. Kandra et al. in 1997, confirmed the efficiency of the presence of a benzylidene functional group at the non-reducing end of the substrates. They have established the action pattern of porcine pancreatic amylase (PPA) by comparing OM with or without benzylidene functional group at the non-reducing end as substrates [49]. Today, the 4-nitro and 2-chlorophenyl OM derivatives carrying a benzylidene group are still valid to measure α-amylase activity for the diagnosis of salivary gland pathologies or pancreatic disorders. In addition, the stability of the reagents guaranteed precise results. In 2010, K. Matsuoka et al. [50] reported a ten-step synthesis of a bifluorescence-label hexasaccharide for amylase assay on fluorescence resonance energy transfer (FRET). The substrate was functionalized with a naphtymethyl residue, a fluorescence donor at the *O*-6 of non-reducing end and a dansyl residue, as fluorescence acceptor at the end of a dithioheptyl chain linked to the anomeric position (Scheme 17).
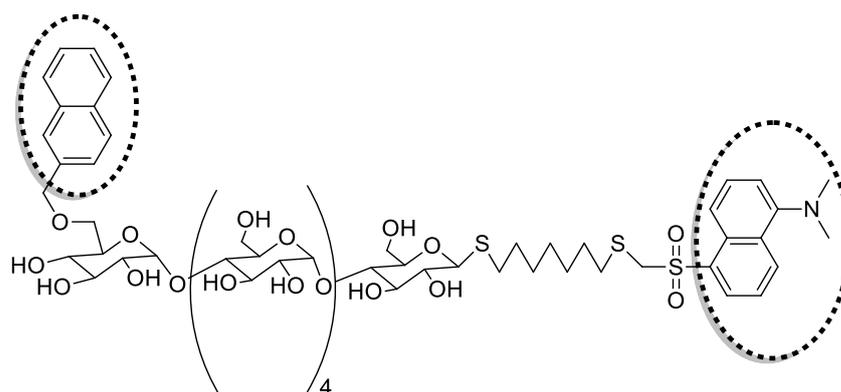
Scheme 17. Maltohexaoligosaccharide bi-fluorescence-labeled substrate [50].

5.1.2. Antioxidant Property

Linear OM obtained by ring-opening of CDs have also been used to improve the antioxidant property of puerarin. Indeed, from β-CD, D. Li et al. prepared in 2011, a class of seven transglycosylated puerarins (Scheme 18) [51].

n = 0-7
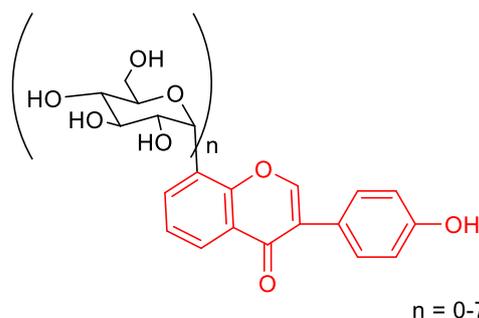
**Scheme 18.** Daidzein 8-C-glucosyl-(α-glucosyl)$_{n-1}$.

These compounds have a better water solubility while preserving the antioxidant activity.

5.2. Cyclodextrins Ring-Opening and Biopolymers

5.2.1. Anti HIV and Anticoagulant Activities

Modified OM were also used for the synthesis of biopolymers, by improving the water solubility of materials and offering interesting biological properties.

In 1998, T. Yoshida et al. reported the first synthesis of polymethacrylate polymers having sulfated maltoheptaose units with different degree of sulfation (Scheme 19). The starting material was an acetylated 1-*O*-methacryloylmaltoheptaoside (MA-AcM$_7$) [28].


R = H or SO$_3$Na
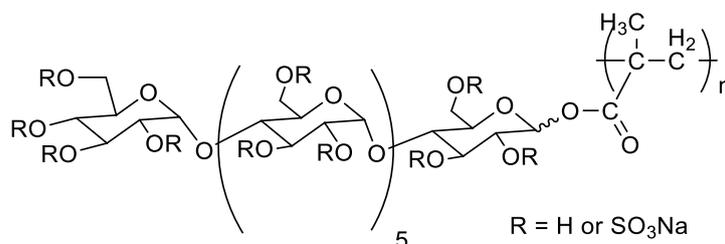
Scheme 19. Polymethacrylate derivatives having sulfated maltoheptaose units.

This polymer was used to evaluate anti-HIV and anticoagulant activities. These studies showed that the distance between branched maltoheptaose units in the polymethacrylate main chain is important for high anti-HIV activity, moderate blood anticoagulant activity, as well as low cytotoxicity.

5.2.2. Lectin Binding Properties

OM can be used in the field of constitutional dynamic chemistry. Dynamic polymers are able to adapt their structures to imposed conditions. This ability to adapt generally involves the modification of physical, optical, and biological properties. In 2010, J-M. Lehn et al. [33] proposed glycodynamers with a nonglycosydic dynamic main chain bearing lateral carbohydrate residues (Scheme 20). This study showed that this class of glycodynamic fluorescent polymers allowed the modulation of the affinity to peanut agglutinin.
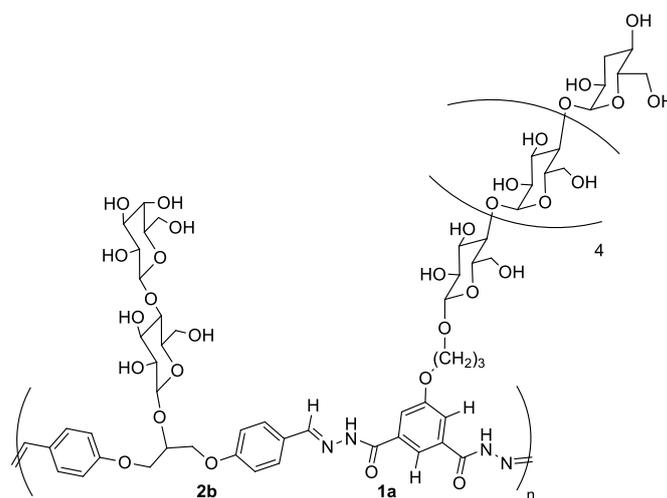
**Scheme 20.** Example of a dynamic glycopolymer [33].

5.2.3. Block Copolymers

Lithography is a field that has developed rapidly. The 193 nm optical immersion lithography technique has reached its resolution limit of about 36 nm [52]. As a result, the development of the next generation of integrated circuits, random access memories and hard disks has been a challenge for some years. In this context, several works have proposed the use of block copolymers for their periodic and well-ordered assembly capabilities with characteristics well below 36 nm.

In 2012, C. J. Ellison et al. performed the synthesis and self-assembly of block copolymers composed by naturally derived oligosaccharides coupled to a silicon-containing polystyrene [53]. The copolymers resulting from this process have a cylindrical morphology with an approximate diameter of 5 nm. We can also mention R. Borsali et al. who proposed a class of copolymers based on maltoheptaosides [41,54]. They also describe a lamellar structure smaller than 10 nm [55].

5.3. Modified Cyclodextrins

CDs are the subject of particular attention because of their very attractive physicochemical and biological properties. The inclusion of molecules in their cavities and the enzyme mimetic properties are the most common examples [56–58]. These properties have applications in cosmetics, food, pharmaceutical industries, etc. However, problems with solubility, the extreme hindrance of hydroxyl groups, and the rigidity of the CD structure have been obstacles to their use. In 1991, N. Sakairi et al. developed a strategy to introduce new functional groups, modified glycosidic units, or heterocycles in the internal structure of their cycle [25]. The resulting compounds called neoCDs, have improved properties. The strategy is carried out in three steps: (i) selective ring-opening of CD, (ii) insertion of the new entity, (iii) cyclisation through an intramolecular reaction.

Three CD analogues having a 2-deoxy-2-iodo-α-D-mannopyranosyl unit were synthesized by N. Sakairi et al (Scheme 21a) [43]. The same team has also shown that it is possible to modify α-CD by adding a 2-aminoglucose unit (Scheme 21b) [27].
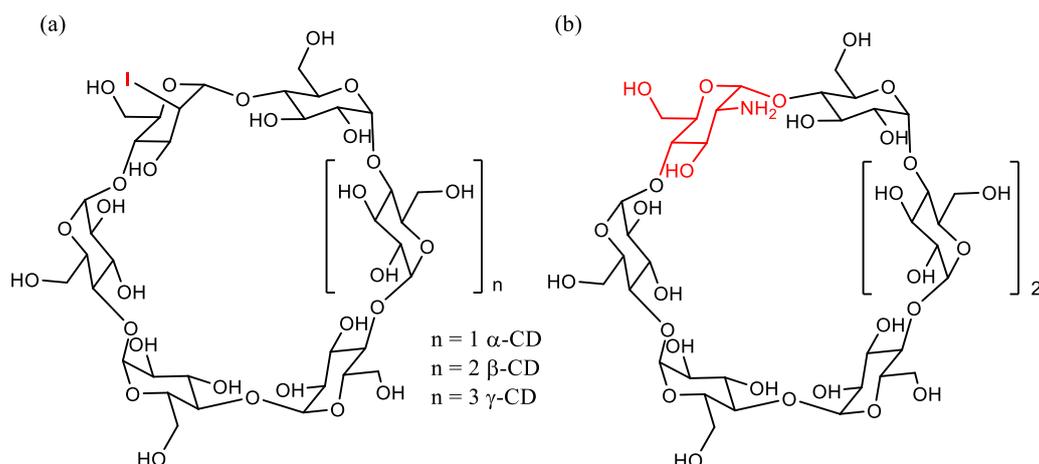
Scheme 21. Products of (**a**) mono-*C*-2 iodination of full *per*methylated CDs and (**b**) insertion of a 2-glucosamine in α-CD.

In order to improve the inclusion properties of *per*methylated α-CD, T. Kida et al. [35,36] published the ring expansion by the insertion of aromatic derivatives (Scheme 22).
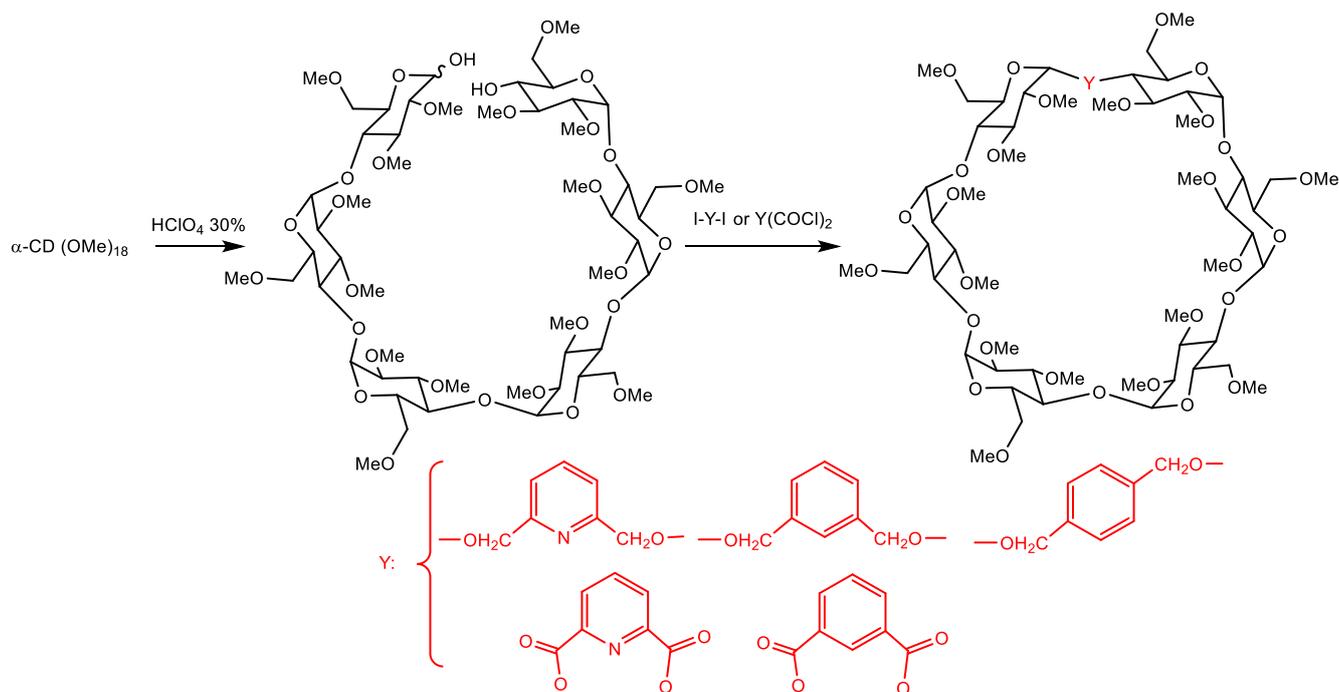

Scheme 22. Ring expansion of *per*methylated α-CD.

The new neoCDs showed improved inclusion properties of various substrates [25,43]. On the other hand buta-1,3-diyne or 1,2,3-triazole units can also be inserted into α- or γ-CDs [36].

5.4. Multivalency Support

In 2011, S. G. Gouin et al. [37] synthesized a series of heptyl α-D-mannoside (HM) glycoclusters using heptaazido OM [30] as scaffolds (Scheme 23).
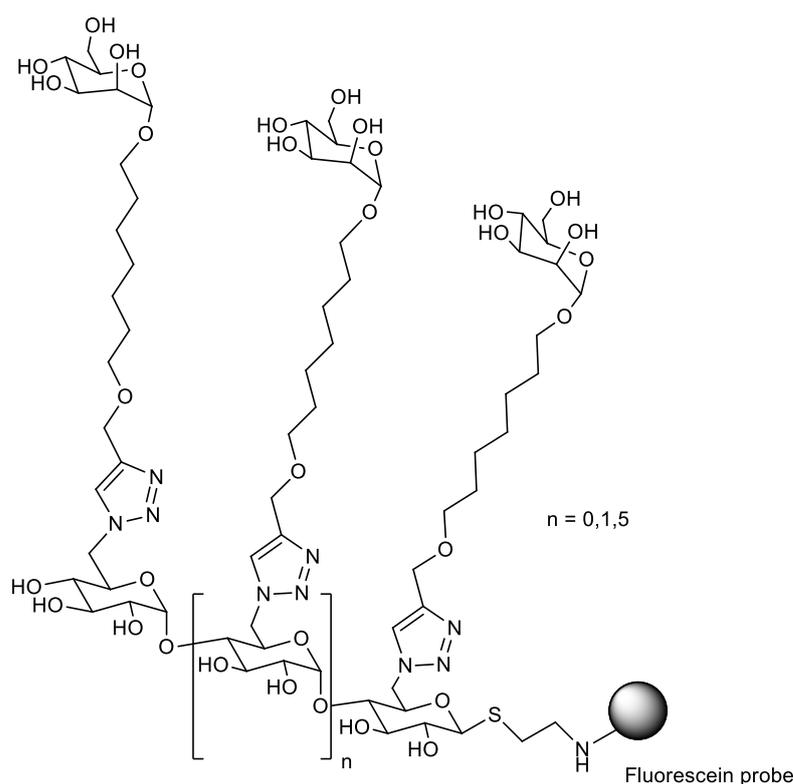
Scheme 23. Chemical structure of the HM glycoconjugate.

The multivalent ligands showed nanomolar affinities to a monomer of the FimH lectin. For the heptavalent glycocluster, a multivalent effect is observed for the haemagglutination of type-1 UTI89 *E. coli*, at concentrations as low as 60 nM. Furthermore, Field et al. [59] reported glycoclusters containing maltoheptaose units. These compounds have the potential to shape the formation of double helices observed in the crystal regions of natural starch. This could lead to improved properties of starch-based materials.

6. Conclusions

OM are useful compounds for different applications: food additives, substrates for various clinical enzymatic tests, platform molecules for multivalency and oligosaccharidic synthons for fine chemistry and biomaterial preparation. Their synthesis from starch or maltose by enzymatic routes leads to mixtures of DP that are rather difficult to separate. Moreover, the major components of the mixture are maltotriose and maltotetraose in most cases, while higher DPs are minor compounds. By total synthesis, compounds with DP superior to 6 can be obtained in about 20 steps and very low yields. The method of choice for the synthesis of hexa, hepta, or octaoses is the ring-opening of esterified, etherified, or even functionalized protected CDs. Esterified OM are easily deprotected to give access to free oligosaccharides.

Various acidic conditions have been tested to catalyze this opening like Brønsted acids (sulfuric or *per*chloric acids) and Lewis acids (TiCl$_4$, FeCl$_3$, ZnI, ZnBr). The acetic anhydride added to the reaction mixture allows to acetylate the two new hydroxyl groups. By substituting acetic anhydride with triflic anhydride, we recently demonstrated that it is possible to open the CD ring and glycosylate the anomeric position with an allyl, propargyl, or azido group, leaving a free hydroxyl group on the C4 of the non-reducing end. Only a few other direct functionalizations were reported in literature, the chloration and thiolysis.

These strategies of chemical ring-opening of CDs will certainly be the object of further developments, enabling the access to new selectively functionalized oligosaccharides of defined structure.

Conflicts of Interest: The authors declare no conflict of interest.

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