Bifunctional Building Blocks for Glyco-Architectures by $TiCl_4$-Promoted Ring Opening of Cyclodextrin Derivatives

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During our studies on the preparation of blocklike substituted 1,4-glucans by cationic ring-opening polymerization,[1,2] we found that $TiCl_4$ behaves differently from common initiators like $Et_3O^+X^-$ ($X = PF_6$, $SbCl_6$), $BF_3{\cdot}Et_2O$, or methyl triflate, causing only ring opening under formation of α-maltooligosyl chlorides bearing one free hydroxyl group (4-OH) at the nonreducing end. These compounds are valuable building blocks for the preparation of new glyco-architectures since they are easily accessible starting materials for direct glycosylations or the preparation of a variety of oligomeric glycosyl donors like alkyl glycosides, thioglycosides, or azides. We successfully carried out and optimized the $TiCl_4$-promoted ring opening with per-*O*-methylated, per-*O*-ethylated, and temporarily protected per-*O*-allylated cyclodextrins of various ring size. ^1H NMR spectroscopy and high-pressure liquid chromatography−evaporative light-scattering detection (HPLC-ELSD) were used to characterize the products.

Introduction

Because of their ability to form inclusion complexes, cyclodextrins (CDs) play an important role in enantioselective chromatography, as depot formers, and for transport processes. From the chemical point of view, the most remarkable feature is the difference in the reactivities of the three different hydroxyl functions allowing regioselective transformations and thus preparation of defined uniform compounds as well as fine adjustment of the properties like solubility or complexation behavior.

Several efforts have been made to obtain oligosaccharides that can be used as macromonomers for the synthesis of polysaccharide structures. Starting from amylose and cellulose, partial degradation yields a complex mixture of oligosaccharides that requires laborious fractionation to get compounds of defined size. This strategy has recently been exploited for the synthesis of cellooligomers from cellulose triacetate by partial pivaloylysis.[3] For maltooligomers up to degree of polymerization (DP) 8, it is more advantagious to submit cyclodextrins to ring opening. Sakairi et al. successfully carried out the fission of one glycosidic linkage in fully acetylated α-, *β*-, and *γ*-CDs by restricted acetolysis using Ac_2O/H_2SO_4.[4] Later, Hoffmann et al. improved the acetolysis of per-*O*-acetylated CDs using Ac_2O/70% $HClO_4$.[5] The resulting maltooligosaccharides have been used as starting materials for the synthesis of amylose by polycondensation[6] and of new cyclodextrin derivatives by intramolecular glycoside formation.[4,7] Starting from per-*O*-acetylated maltooligosaccharides, their synthesis requires conversion into phenyl thioglycosides (glycosyl donor) and the multistep formation of an unsubstituted nonreducing end (glycosyl acceptor) via deacetylation, introduction of a terminal 4,6-*O*-benzylidene group, benzylation of all remaining hydroxy groups, and finally regioselective reductive opening of the benzylidene group to give the 2,3,6-*O*-benzylated phenyl thioglycosides. Other cyclodextrin analogues have been prepared by oxidative coupling of two alkynyl-groups or by 1,3-dipolar cycloaddition of an azido and an alkynyl group, introduced at the reducing and the nonreducing terminal glycosyl residues[8] or by other insertions of spacer molecules.[9] Lesur et al. were the first ones to apply the ring opening of cyclodextrins for the synthesis of regioselectively derivatized maltooligosaccharides by acetolysis of 2,3-di-*O*-acyl-6-bromo-6-deoxy-CDs and the corresponding 6-azido derivatives, in up to 32% yield.[10]

In a similar way, acetolysis of per-*O*-benzoylated CDs results in 2,3,6-per-*O*-benzoylated oligosaccharides, bearing acetyl groups at both newly formed ends.[11] Their conversion into the corresponding phenyl thioglycosides and selective hydrolysis of the acetyl group at the nonreducing end without affecting the more stable benzoyl groups gives bifunctional oligosaccharides in only three steps starting from the protected CDs.

The concept of restricted acetolysis of cyclodextrin derivatives has been extended to per-*O*-methylated α- and *β*-CD by the use of Ac_2O/30% $HClO_4$ resulting in the corresponding 2,3,6-*O*-methylated maltooligosaccharides in 43% and 75% yield, respectively.[12] To further simplify the preparation of bifunctional 2,3,6-per-*O*-methylated oligosaccharides, Sakairi and Kuzuhara developed the restricted thiolysis of permethylated CDs.[13] Cleavage of the ring in the presence of phenyltrimethylsilane and $ZnBr_2$ followed by in-situ benzoylation of the nonreducing end yields phenyl 2,3,6-*O*-methyl thiomaltooligosaccharides as a terminal 4-*O*-benzoate in up to 41% yield.

In this paper, we report on a new strategy for synthesizing bifunctional oligosaccharides that combines the ring opening of cyclodextrins with the formation of a glycosyl chloride (Figure 1). In 1901, Koenigs and Knorr introduced glycosyl chlorides and bromides as powerful and versatile glycosyl donors in silver-assisted glycosylation reactions.[14] Since then, this method has been extensively studied, approved, and used for the preparation of a broad variety of glycosides, di- and oligosaccharides. Besides the classical insoluble promoters Ag_2O and Ag_2CO_3, several other halophilic catalysts like soluble AgOTf[15] and the mercury salts $HgBr_2$ and $Hg(CN)_2$[16] are used. Because of the intrinsic lability of glycosyl halides, especially bromides, several other glycosyl donors like trichloroacetimidates and alkyl or the above-mentioned aryl thioglycosides have

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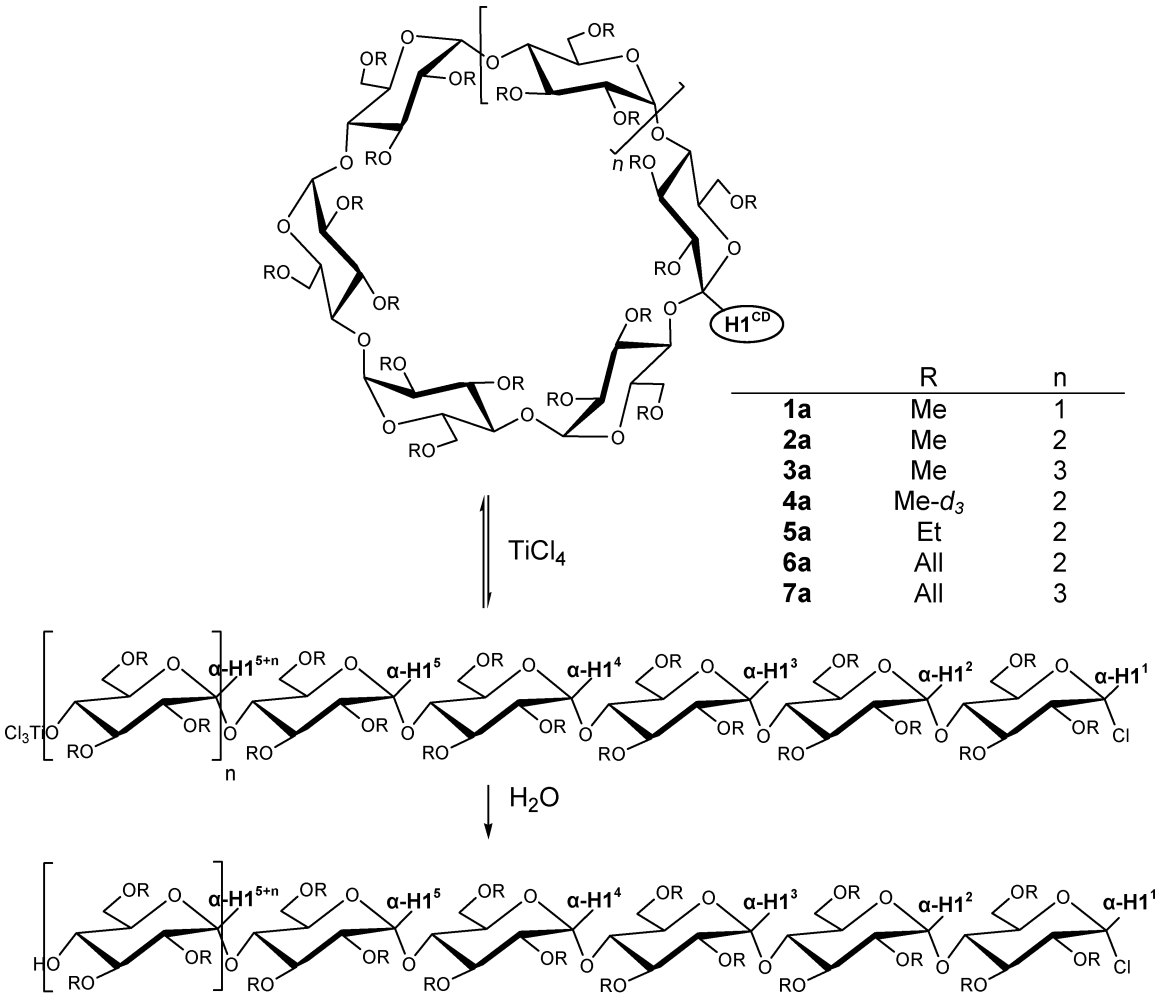

	R	n
1a	Me	1
2a	Me	2
3a	Me	3
4a	Me-d_3	2
5a	Et	2
6a	All	2
7a	All	3

	R	n
1b	Me	1
2b	Me	2
3b	Me	3
4b	Me-d_3	2
5b	Et	2
6b	All	2
7b	All	3

Figure 1. $TiCl_4$ promoted ring opening of CD derivatives **1a**−**7a** to mixtures of maltooligosyl chlorides **1b**−**7b**.

been proven to be valuable compounds for the synthesis of di- or oligosaccharides without having displaced glycosyl halides but, on the contrary, having extended the diversity of glycosyl donors. Furthermore, glycosyl chlorides can be used as precursors for the mentioned glycosyl donors which are accessible either by direct displacement of the chlorine or after hydrolysis. This fact makes the maltooligosyl chlorides, we report herein, even more interesting as building blocks in carbohydrate chemistry.

Experimental Section

General. All solvents and reagents were purchased from the following companies: Fisher Scientific, Fluka Chemie GmbH, Merck, Carl Roth GmbH & Co, J. T. Baker, and Acros Organics. They were of highest purity available; the solvents were of HPLC grade. α-, β-, and γ-cyclodextrins were a gift of W. A. König, University of Hamburg. For purification, Sephadex LH 20 and silica gel 60 (63−200 μm, Merck) were used. Thin-layer chromatography (TLC) was performed with silica gel 60 on aluminum foils, 20 cm × 20 cm, from Merck. Detection was carried out by heating after dipping in sulfuric acid in ethanol (10%).

^{1}H NMR Spectroscopy. ^{1}H NMR spectra were recorded of solutions in $CDCl_3$ on a Bruker AMX 300 instrument (300 MHz).

High-Pressure Liquid Chromatography (HPLC). Analyses were performed on a Beckman System Gold HPLC equipped with a Phenomenex Gemini 5 μm RP 18 column, 250 × 4.6 mm, and a PL-ELS 2100 evaporating light-scattering detector from Polymer Laboratories (settings: gas flow, 1.6 L/min; evaporation temperature, 55 °C; nebulizer temperature, 40 °C). Methanol was used as solvent (0.8 mL/min).

About 20−30 mg of the ring-opening product of All_{21}-β-CD (**6b**) and All_{24}-γ-CD (**7b**) was dissolved in 0.1 M methanolic hydrochloric acid and was concentrated to dryness in a stream of nitrogen at room temperature. The procedure was repeated a second time with methanolic hydrochloric acid and two times with methanol. The resulting methyl 2,3,6-*O*-allyl-maltooligosaccharides **6c** and **7c** were again dissolved and

diluted to yield a concentration of 0.5−1.0 mg/mL. Twenty microliters of this solution was applied.

Per-*O*-Alkylation of Cyclodextrins. The syntheses of per-*O*-methylated α-, *β*-, and *γ*-cyclodextrins (**1a**, **2a**, **and 3a**), per-*O*-deuteromethylated *β*-cyclodextrin (**4a**), and per-*O*-ethylated *β*-cyclodextrin (**5a**) were carried out as described[1] according to a modified procedure introduced by Ciucanu and Kerek.[17]

Hexakis[2,3,6-tri-*O*-methyl]-α-cyclodextrin (Me_{18}-α-CD, 1a), Octakis[2,3,6-tri-*O*-methyl]-*γ*-cyclodextrin (Me_{24}-*γ*-CD, 3a). The raw products were purified by column chromatography on Sephadex LH 20 with CH_2Cl_2/CH_3OH (2:1). The yield was about 80−85% for both.

Me_{18}-α-CD (**1.1**): Anal. calcd for Me_{18}-α-CD ($C_{54}H_{96}O_{30}$): C (52.92), H (7.91). Found: C (52.97), H (8.21); TLC (acetone/hexane, 2:1, v/v): R_f 0.76; ESIMS: *m*/*z* 1248 [Me_{18}-α-CD + Na]$^+$; ^{1}H NMR (CD_3Cl): *δ* 5.07 (d, 6 H, J = 3.0 Hz, α-H1^{CD}).

Me_{24}-*γ*-CD (**3.1**): Anal. calcd for Me_{24}-*γ*-CD ($C_{72}H_{128}O_{40}$): C (52.92), H (7.91). Found: C (52.56), H (7.90); TLC (acetone/hexane, 2:1, v/v): R_f 0.71; ESIMS: *m*/*z* 1656 [Me_{24}-*γ*-CD + Na]$^+$; ^{1}H NMR (CD_3Cl): *δ* 5.20 (d, 8 H, J = 3.4 Hz, H1^{CD}).

^{1}H NMR data were in agreement with the literature.[13,18]

Heptakis[2,3,6-tri-*O*-methyl]-*β*-cyclodextrin (Me_{21}-*β*-CD, 2a). The raw product was purified by recrystallization from hexane/acetone, yielding 92% Me_{21}-*β*-CD as a white, crystalline solid.

Anal. calcd for Me_{21}-*β*-CD ($C_{63}H_{112}O_{35}$): C (52.92), H (7.91). Found: C (53.17), H (8.10); TLC (acetone/hexane, 2:1, v/v): R_f 0.77; ESIMS: *m*/*z* 1451 [M + Na]$^+$, 737 [M + 2Na]$^{2+}$; ^{1}H NMR (CD_3Cl): *δ* 5.15 (d, 7 H, J = 3.1 Hz, H1^{CD}), data were in agreement with the literature.[18]

Heptakis[2,3,6-tri-*O*-ethyl]-*β*-cyclodextrin (Et_{21}-*β*-CD, 5a). Ethylation of 3.05 g (2.69 mmol) *β*-CD according to the above-mentioned procedure provided only incompletely ethylated compounds. The raw product was dissolved in DMSO (80 mL) and was per-*O*-ethylated with NaOH (6 g) and EtI (9 mL). Extractive workup followed by column chromatography on silica with hexane/acetone (2:0.7) yielded 3.22 g Et_{21}-*β*-CD (1.87 mmol, 69.5%).

Anal. calcd for Et_{21}-*β*-CD ($C_{84}H_{154}O_{35}$): C (58.50), H (9.02). Found: C (59.00), H (9.41); TLC (hexane/acetone, 2:0.7, v/v): R_f 0.62; ESIMS: 1746 [M + Na]$^+$, 885 [M + 2Na]$^{2+}$; ^{1}H NMR (CD_3Cl): *δ* 1.22 (m, 63 H, $-OCH_2CH_3$), 3.29 (dd, J = 3.5 Hz, 9.6 Hz, 7 H, H2^{CD}), 3.52 (m, 21 H, $-C6-OCH_2CH_3$, H3^{CD}), 3.76 (m, 42 H, H4^{CD}, H6a^{CD}, $-C2-OCH_2CH_3$, $C3-OCH_2CH_3$), 3.96 (d, J = 10.0 Hz, 7 H, H5^{CD}), 4.05 (dd, J = 7.1 Hz, 8.7 Hz, H6b^{CD}), 5.23 (d, J = 3.5 Hz, 7 H, H1^{CD}).

Heptakis[2,3,6-tri-*O*-allyl]-*β*-cyclodextrin (All_{21}-*β*-CD, 6a). *β*-CD (2.51 g, 2.21 mmol) was dissolved in freshly distilled DMF (44 mL, 20 mL/mmol CD). NaH (3.9 g, 163 mmol, 3.5 equiv/OH), previously washed with petroleum ether, was added and the suspension was stirred for 1 h. Allyl bromide (14 mL, 162 mmol, 3.5 equiv/OH) was added dropwise and the temperature was held between 35 and 40 °C. Further NaH (3.9 g) and allylbromide (14 mL) were added after 24 h. After a total reaction time of 2 days, the reaction was quenched with methanol (12.5 mL) and was poured into water (0.5 L). Isolation was carried out by extraction with dichloromethane (3 × 100 mL). The combined organic phases were washed with water (3 × 400 mL), were dried over Na_2SO_4, and were evaporated. Column chromatography on silica, using petroleum ether/ethyl acetate (2:1) for the first column and petroleum ether/ethyl actetae (1:1) for the second one, provided 3.16 g All_{21}-*β*-CD (1.60 mmol, 72.4%) as an oil.

TLC (petroleum ether/ethyl acetate (2:1): R_f 0.57. ESIMS: 1998 [M + Na]$^+$, 1010.5 [M + 2Na]$^{2+}$. ^{1}H NMR (CD_3Cl): *δ* 5.25 (d, 7 H, J = 3.4 Hz, H1^{CD}), data are in agreement with the literature.[19]

Octakis[2,3,6-tri-*O*-allyl]-*γ*-cyclodextrin (All_{24}-*γ*-CD, 7a). Following the procedure for the preparation of All_{21}-*β*-CD, with the exception of the column chromatographic purification, 1.0 g *γ*-CD (0.77 mmol) gave 0.73 g (0.32 mmol, 42%) All_{24}-*γ*-CD as oil. Column chromatography was performed using petroleum ether/ethyl acetate (3:1).

Anal. calcd for All_{24}-*γ*-CD ($C_{120}H_{176}O_{40}$): C (63.80), H (7.87). Found: C (64.32), H (8.18); TLC (petroleum ether/ethylacetate, 3:1): R_f 0.67; ESIMS: 1151 [M + 2Na].[19]

$TiCl_4$-Promoted Ring Opening of Cyclodextrin Derivatives to Maltooligosyl Chlorides (1b−7b). Reactions up to 5 mL scale were carried out in V-vials. For larger volumes, two-neck round-bottom flasks were used. CH_2Cl_2 was dried over CaH_2 and was distilled over molecular sieve (4 Å) prior to use. The typical procedure was as follows: The predried cyclodextrins (**1a−7b**) were weighed in the reaction vessel and were dried at 70 °C in high vacuum for at least 3 h. An appropriate volume of a freshly prepared solution of $TiCl_4$ in CH_2Cl_2 (44 *μ*L $TiCl_4$/mL = 0.4 mmol/mL) was added to a solution of the CD derivative in CH_2Cl_2 (0.1 mmol CD/mL). If required, addition of the $TiCl_4$-solution was repeated after half the reaction time. The solution immediately turned yellow after addition of $TiCl_4$. Finally, the reaction was quenched by pouring it into cold, saturated $NaHCO_3$ solution. The aqueous solution was extracted three times with CH_2Cl_2, and the organic phases were combined, were washed with water, and were dried over Na_2SO_4. The solvent was removed in a stream of nitrogen or was evaporated using a vacuum rotary evaporator. The conversion into linear products **1b−7b** and their average DP and content of *β*-glycosidic linkages were determined on the basis of the H1 signals in the ^{1}H NMR spectra and, in the case of allyl derivatives, by HPLC/evaporative light-scattering detection (ELSD). The products were stored at −30 °C.

Results and Discussion

General Aspects. During our studies of the cationic ring-openig polymerization of cyclodextrin derivatives, we found that $TiCl_4$ promotes the ring opening of per-*O*-methylated (**1a−4a**), per-*O*-ethylated (**5a**), and per-*O*-allylated CDs (**6a, 6b**) to α-maltooligosyl chlorides **1b−7b** (Figure 1). We regard these components as valuable bifunctional building blocks for the preparation of new glyco-structures and thus focused on optimizing this reaction.

To investigate whether undesired products are formed, electrospray ionization (ESI) and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were recorded from methanolic solutions of the ring-opening products of mixtures of **2a** and **4a**. Since the newly formed glycosyl chlorides **2b** and **4b** are not stable in the presence of alcohols, they are converted into the corresponding methyl maltooligosaccharides **2c** and **4c** even if freshly prepared solutions are used as can be seen from the MALDI-TOF mass spectrum in Figure 2. The glycosyl chlorides can be detected when acetonitrile is used as the solvent (spectra not shown). The ring-opening reaction yields a mixture of the main products **2b** and **4b** besides small amounts of residual educts **2a** and **4a** and shorter maltooligosyl chlorides. The presence of the latter indicates that the $TiCl_4$ mediated cleavage is not only restricted to ring opening. Furthermore, the ring opening of the mixture of **2a** and **4a** provides the opportunity to investigate the occurrence of transglycosylation reactions by the formation of compounds consisting of methylated and deuteromethylated anhydroglycosyl units. The absence of these compounds and compounds with DP higher than expected indicates that transglycosylation does not occur under these conditions.

Besides their instability toward nucleophiles like alcohols, glycosyl chlorides are also sensitive to acidic conditions as was obvious from TLC when used for monitoring the reaction. The resulting linear maltooligosyl chlorides moved more slowly than the corresponding CDs. Prolonged exposure to silica prior to development of the TLC sheet caused partial decomposition of the maltooligosyl chlorides and appearance of a third spot with

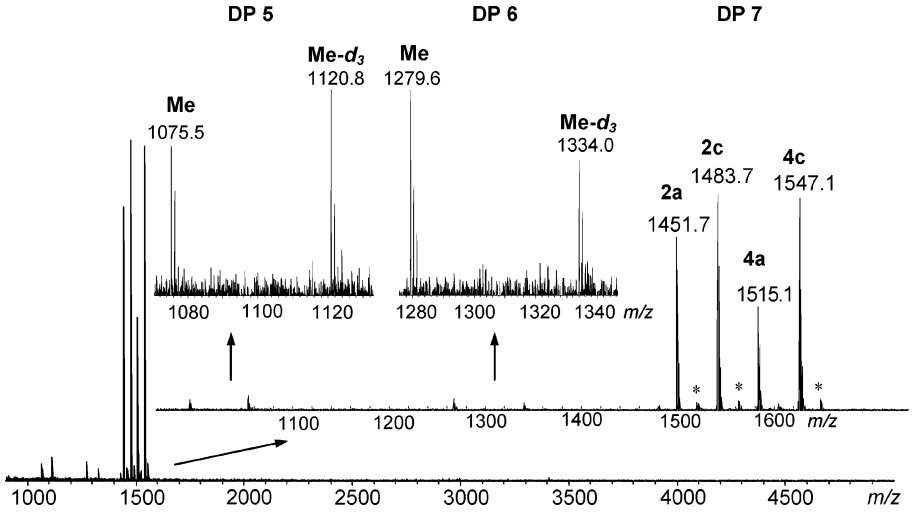

Figure 2. Ring opening of an equimolar mixture of Me_{21}-β-CD (**2a**) and (Me-d_3)$_{21}$-β-CD (**4a**) with 2 × 0.75 equiv $TiCl_4$ at 10 °C after 42 h. Enlarged regions of DP 5−7 in the MALDI-TOF mass spectra of methyl maltooligosaccharides in **2c** and **4c** obtained from **2b** and **4b** after dissolution in methanol. The abbreviations above the *m*/*z* values of $[M + Na]^+$ indicate the substituents at positions 2, 3, and 6. The signals marked with an asterisk represent potassium adducts $[M + K]^+$.

lower R_f values that is formed from the respective 1,4-unsubstituted maltooligosaccharide. Therefore, development of the TLC should be carried out immediately after sample application. For the same reason, column chromatography on silica is not suitable for the purification and separation of the raw mixture. In contrast to this, neutral or weakly basic conditions do not cause any degradation and allow simple workup by quenching with cold saturated $NaHCO_3$ solution, extracting with dichloromethane, and washing with cold water. The recoveries for all ring-opening reactions were between 80 and 100%.

If isolation of the macromonomers is required, we recommend purification after direct glycosylation of the maltooligosyl chlorides **1b**−**7b** or after transformation into more stable glycosyl donors like alkyl or thioglycosides to avoid decomposition. However, since knowledge of the degree of conversion into linear compounds and the average DP of the raw product was required to find out appropriate and defined conditions for further transformations, we focused on the analysis of the product with respect to the contribution of shorter maltooligosyl chlorides formed as side products and residual CD. ESI mass spectrometry does not permit quantification of complex mixtures so that characterization of the raw product was carried out by ^{1}H NMR spectroscopy. The conversion into linear maltooligosyl chlorides (conv [%]), their average degree of polymerization (DP), and the content of β-glycosidic linkages in the linear product (β [%]) were calculated from the ratios of the diagnostically valuable H1-signals between δ 4.0 and 6.3 (Figure 3) according to eqs 1−3. In the equations, *n* is 1 for α-CDs, 2 for β-CDs, and 3 for γ-CDs.

$$\text{conv}\,[\%] = \frac{[\Sigma I(\alpha\text{-H1}^{1-(5+n)}) + I(\beta\text{-H1})]\cdot 100}{\Sigma I(\alpha\text{-H1}^{1-(5+n)}) + I(\beta\text{-H1}) + I(\text{H1}^{\text{CD}})} \quad (1)$$

$$\text{DP} = \frac{\Sigma I(\alpha\text{-H1}^{1-(5+n)}) + I(\beta\text{-H1})}{I(\alpha\text{-H1}^{1})} \quad (2)$$

$$\beta\,[\%] = \frac{I(\beta\text{-H1})\cdot 100}{\Sigma I(\alpha\text{-H1}^{1-(5+n)}) + I(\beta\text{-H1}) + I(\text{H1}^{\text{CD}})} \quad (3)$$

In spite of competing chain degradation and the lability of the products, the preparation of maltooligosyl chlorides is possible in high yields, provided that the conditions are carefully adjusted. The optimization of the $TiCl_4$ promoted ring opening of the CD derivatives is discussed in the next sections followed by mechanistic considerations.

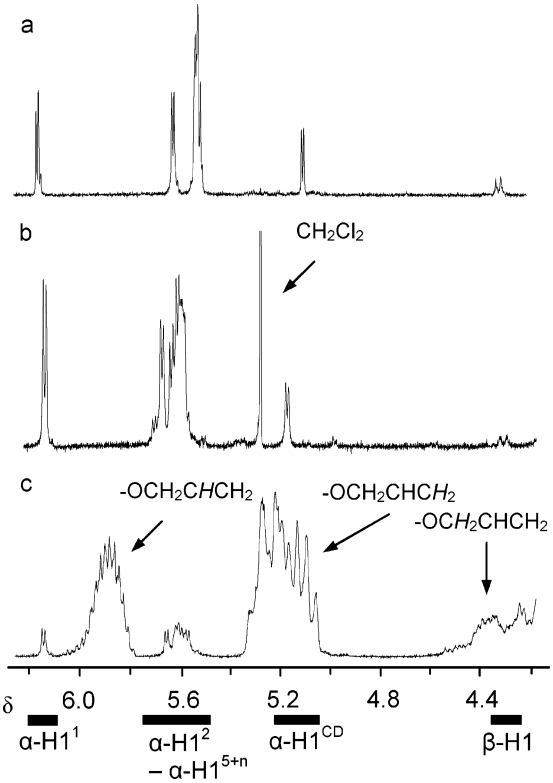

Figure 3. Diagnostically valuable H1-signals in the ^{1}H NMR spectra (300 MHz) of (a) **2b** obtained from ring opening of Me_{21}-β-CD (**2a**) with 2 × 0.75 equiv $TiCl_4$ after 45 h, (b) **5b** from Et_{21}-β-CD (**5a**) with 2 × 0.6 equiv $TiCl_4$ after 40 h, and (c) **6b** from All_{21}-β-CD (**6a**) with 2 × 0.6 equiv $TiCl_4$ after 44 h. Reactions were carried out in CH_2Cl_2 at 10 °C. Spectra were recorded in $CDCl_3$ after extractive workup. For assignment of the H1-signals, see Figure 1.

Ring Opening of Per-*O*-methylated Cyclodextrins (1a−4a) and Per-*O*-ethylated Cyclodextrins (5a). The $TiCl_4$ promoted ring opening to maltooligosyl chlorides was first observed with per-*O*-methylated CDs (Me-CDs, **1a**−**4a**) and was optimized by variation of the reaction time, the temperature,

Table 1. Influence of the Amount of $TiCl_4$ (equiv $TiCl_4$/CD) and the Reaction Temperature (T [°C]) on the $TiCl_4$ Promoted Ring Opening of Me_{18}-α-CD (**1a**), Me_{21-}-β-CD (**2a**), and Me_{24}-γ-CD (**3a**)[a]

entry	prod.	equiv $TiCl_4$/CD	T [°C]	t [h]	conv [%]	DP	β [%]
1	**1b**	2 × 0.75	10	44	62	5.5	4.3
2		2 × 0.60	10	45	52	5.9	4.2
3		2 × 0.50	10	45	41	6.0	3.5
4	**2b**	2.0	rt	24	98	4.7	5.5
5		1.5	rt	24	94	5.3	3.6
6		1.0	rt	24	66	6.8	1.4
7		2 × 0.75	rt	42	89	5.6	3.0
8		2 × 0.75	10	45	91	6.6	5.0
9		2 × 0.50	10	45	72	6.7	4.0
10	**3b**	2 × 0.75	10	44	92	7.9	1.3
11		2 × 0.60	10	45	91	7.6	2.1
12		2 × 0.50	10	45	79	8.2	1.0

[a] The product mixtures **1b**, **2b**, and **3b** are characterized by the conversion into linear products (conv [%]), the average degree of polymerization (DP), and the content of β-glycosidic linkages (β [%]) of the linear components. Data are calculated from H1 signals in ^{1}H NMR spectra according to eqs 1−3.

and the amount of $TiCl_4$ per CD (equiv $TiCl_4$). The characterization of the product mixtures was accomplished by ^{1}H NMR spectroscopy. Because of their equivalence, the anomeric protons of the CDs ($H1^{CD}$) only show one doublet at δ 5.07 (Me_{18}-α-CD, **1a**), δ 5.15 (Me_{21}-β-CD, **2a**), and δ 5.20 (Me_{24}-γ-CD, **3a**), respectively (Figure 3a). After ring opening, the former equivalent protons are represented by three signals whereupon α-H1,[1] at the reducing end next to the chlorine, gives a dublett at δ 6.15. The remaining α-H1 signals (α-$H1^2$−α-$H1^{5+n}$) are located between δ 5.50 and 5.70. One of these signals, either α-$H1^2$ or α-$H1^{5+n}$, is slightly shifted downfield. The appearance of a dublett at δ 4.30 with a coupling constant of 7.9 Hz indicates the formation of 1−5% β-glycosidic linkages (β-H1) within the linear chain. Its chemical shift is in agreement with those of β-glycosidic linkages in methylated α,β-glucans obtained from cationic ring-opening polymerization of Me-CDs.[1,2,20] Possible pathways for the formation of β-glycosidic linkages are discussed later.

Increasing amounts of $TiCl_4$ do not only cause enhanced ring opening of Me_{21}-β-CD (**2a**) but also glucosidic cleavage and subsequently lower average DPs of the resulting 2,3,6-*O*-methylated maltooligosyl chlorides **2b** (Table 1). Reaction with 2 equiv $TiCl_4$/CD yielded 98% **2b** with an average DP of 4.7 (entry 4) whereas a DP of 6.8 was achieved in a yield of 66% using 1 equiv $TiCl_4$ (entry 6). Further increase of the DP without loss of the degree of conversion was achieved by a two-step addition of $TiCl_4$ and by lowering the temperature to 10 °C. Thus, ring opening at 10 °C with 1.5 equiv $TiCl_4$ added in two portions at 0.75 equiv each, gives 91% **2b** with an average DP of 6.6 (entry 8). The content of β-glycosidic linkages increases in the presence of excess $TiCl_4$ (entry 4 vs 6).

In the next step, ring opening of Me_{18}-α-CD (**1a**) and Me_{24}-γ-CD (**3a)** was performed. Me_{18}-α-CD (**1a**) exhibits lower reactivity compared to Me_{21}-β-CD (**2a**) and Me_{24}-γ-CD (**3a**) since the access to the glycosidic oxygens which are directed into the cavity is more hindered in smaller rings. This observation is in agreement with the order of reactivity in cationic ring-opening polymerization (CROP).[20] From Me_{18}-α-CD (**1a**), 2,3,6-*O*-methylated maltooligosyl chlorides **1b** were obtained in only 62% yield with 2 × 0.75 equiv (entry 1) and in 41% yield using 2 × 0.5 equiv $TiCl_4$ (entry 3). The average DP values were 5.5 and 6.0, respectively.

Table 2. Influence of the Amount of $TiCl_4$ (equiv $TiCl_4$/CD) and the Reaction Temperature (T [°C]) on the $TiCl_4$ Promoted Ring Opening of Et_{21}-β-CD (**5a**)[a]

entry	prod.	equiv $TiCl_4$/CD	T [°C]	t [h]	conv [%]	DP	β [%]
1	**5b**	2	rt	44	100	3.4	15.7
2		1.5	rt	44	100	4.1	10.5
3		1	rt	44	95	5.5	3.2
4		2 × 0.6	rt	44	94	5.5	3.1
5		2 × 0.5	rt	44	95	5.5	3.4
6		2 × 0.6	10	44	92	5.5	2.4
7		2 × 0.6	0	44	79	6.8	<1
8		2 × 0.6	0	88	73	6.9	<1

[a] The product mixtures **5b** are characterized by the conversion into linear products (conv [%]), the average degree of polymerization (DP), and the content of β-glycosidic linkages (β [%]) of the linear components. Data are calculated from H1-signals in ^{1}H NMR spectra according to eqs 1−3.

Ring opening of Me_{24}-γ-CD (3a) with 2 × 0.75 equiv $TiCl_4$ was very successful providing 92% linear products 3b with an average DP of 7.9 (entry 10). The conversion into 3b and the DP did not significantly change when 2 × 0.6 equiv was used. Even when the amount of $TiCl_4$ was reduced to 2 × 0.5 equiv, almost 80% 3b was obtained that had not undergone any detectable chain degradation (entry 12). The amount of β-glycosidic linkages was only between 1.0 and 2.1%.

Surprisingly, ring opening of per-*O*-ethylated β-CD (Et_{21}-β-CD, **5a**) resulted in higher conversion into maltooligosyl chlorides **5b** compared to Me_{21}-β-CD (**2a**) (Table 2). Thus, 1 equiv $TiCl_4$ is sufficient to achieve almost quantitative ring opening and provided 95% **5b** with DP 5.5 (entry 3) compared to 66% conversion and DP 6.8 for **2b**. As before, the temperature was decreased and $TiCl_4$ was added in two portions at the beginning and after half of the total reaction time to get higher DPs. Ring opening with 2 × 0.6 equiv $TiCl_4$ at 10 °C yielded 92% linear products **5b** with n average DP of 5.5, and hence, neither showed significant decrease of conversion nor improvement of the DP (entry 5). Only when the reaction was carried out at 0 °C, the DP increased to 6.8, while the conversion decreased to 79% (entry 6). Prolonged reaction time did not effect either higher conversion or significant increase in the DP (entry 7). Extensive formation of β-glycosidic linkages up to 15.7% was observed when excess $TiCl_4$ was used (entries 1 and 2). On the other hand, equimolar ratios or stepwise addition of $TiCl_4$ (2 × 0.6 equiv) significantly reduced the content of β-glycosidic linkages to 3.1% for the reaction at room temperature (entry 4) and to <1% at 0 °C (entries 7 and 8).

Ring Opening of Per-*O*-allylated Cyclodextrins (6a, 7a). To get maltooligosaccharide derivatives that can be deprotected and optionally further derivatized, we submitted per-*O*-allylated β- and γ-CD (All_{21}-β-CD, **6a**, and All_{24}-γ-CD, **7a**) to ring-opening conditions. Allyl groups can be derivatized at the double bond or cleaved off to recover free hydroxyl groups.[21,22]

The characterization of the 2,3,6-*O*-allylated maltooligosyl chlorides **6b** and **7b** was accomplished by ^{1}H NMR spectroscopy and HPLC (Table 3). In ^{1}H NMR spectra, α-H1-signals of the linear oligomers are clearly separated from other signals whereas the β-H1- and $H1^{CD}$-signals are overlapped by allyl protons (Figure 3c). Therefore, the DP can only be estimated from eq 2 without considering possible β-glycosidic linkages. The extent of ring opening can only be estimated from the signal intensity of the CH-protons of all allyl substituents $I(OCH_2CHCH_2)$ at δ

Table 3. Influence of the Amount of $TiCl_4$ (equiv $TiCl_4$/CD) and the Reaction Temperature (T [°C]) on the $TiCl_4$ Promoted Ring Opening of All_{21}-β-CD (**6a**) and All_{24}-γ-CD (**7a**)[a]

entry	prod.	equiv $TiCl_4$/CD	T [°C]	t [h]	DP	$conv_{min}$ − $conv_{max}$ [%]	DP_{HPLC}	$conv_{HPLC}$ [%]	Mol%(DPx)
1	**6b**	2 × 0.6	rt	45	5.6	55−65	5.5	63	42
2		2 × 0.6	10	45	5.8	51−62	6.0	62	46
3		2 × 0.6	0	87	6.4	23−27	6.3	16	15
4		2 × 0.75	0	87	6.3	29−32	6.3	26	24
5	**7b**	2 × 0.6	rt	18	6.3	65−82	n.d.	n.d.	n.d.
6		2 × 0.6	10	18	7.3	45−50	7.3	53	43
7		2 × 0.6	0	40	7.6	37−39	n.d.	n.d.	n.d.

[a] The minimum and the maximum conversion into the linear products **6b** and **7b** ($conv_{min}$ [%], $conv_{max}$ [%]) and the average degree of polymerization (DP) were determined by ^{1}H NMR spectroscopy from the α-H1 and $-OCH_2CHCH_2$ signals according to eqs 2, 4, and 5. HPLC analysis of the product mixture after transformation into the methyl maltooligosaccharides **6c** and **7c** provides the average degree of polymerization (DP_{HPLC}), the conversion ($conv_{HPLC}$ [%]), and the molar fraction Mol%(DPx) [%] with $x = 7$ for **6b** and $x = 8$ for **7b**. n.d.: not determined.

5.9 and its percentage representing the allyl groups of the linear product $I(OCH_2CHCH_2)_{lin}$. The latter is calculated from the summarized integrals of all α-H1-signals divided by that of α-H1[1] and is multiplied by 3 because every AGU carries three allyl groups (eq 4, n is 1 for α-CDs, 2 for β-CDs, and 3 for γ-CDs). The ratio between $I(OCH_2CHCH_2)_{lin}$ and $I(OCH_2CHCH_2)$ gives the conversion that can be regarded as the real conversion provided that no β-glycosidic linkages have been formed or as the minimum value $conv_{min}$ [%] for a product with an unknown content of β-glycosidic linkages according to eq 5.

$$I(OCH_2CHCH_2)_{lin} = 3 \cdot \frac{I(\alpha\text{-H1}^{1-(5+n)})}{I(\alpha\text{-H1}^{1})} \quad (4)$$

$$conv_{min}[\%] = \frac{100 \cdot I(OCH_2CHCH_2)_{lin}}{I(OCH_2CHCH_2)} \quad (5)$$

$$conv_{max}[\%] = \frac{100 \cdot (5+n) \cdot I(\alpha\text{-H1}^{1})}{I(OCH_2CHCH_2)} \quad (6)$$

The higher the content of β-glycosidic linkages in the linear products, the larger is the real conversion. The maximum conversion $conv_{max}$ [%] is reached when no chain degradation occurs. Then, the fraction in eq 4 can be simplified to $(5 + n) \cdot I(\alpha\text{-H1}^1)$. For calculating $conv_{max}$[%], eq 6 is applied. These two parameters, $conv_{min}$ and $conv_{max}$, specify the possible range of conversion for a sample with a given ratio between the signals of $\alpha\text{-H1}^{1-(5+n)}$ and $-OCH_2CHCH_2$ and an unknown content of β-glycosidic linkages.

To prove the results, the raw products **6b** and **7b** were analyzed by RP-HPLC with evaporative light-scattering detection (ELSD). Since methanol was used as solvent, the 2,3,6-*O*-allylated maltooligosyl chlorides **6b** and **7b** were converted into methyl glycosides **6c** and **7c** with 0.1 M methanolic hydrochloric acid prior to measurement to prevent interference of reactions during the analysis. In contrast to the 2,3,6-*O*-methylated maltooligosyl chlorides, weakly acidic conditions were required to achieve complete conversion into the methyl glycosides. The signals of the methyl maltooligosaccharides **6c** and **7c** were assigned by LC-ESI-MS. As can be seen from the chromatogram of **6c**, each DP gives one major signal (Figure 4). Isomers, either the corresponding anomer or oligomers bearing β-glycosidic linkages, could only be detected for the two largest oligomers with the most intense signals. Additionally, $TiCl_4$-promoted ring opening and methanolysis of the chlorides cause deallylation to a very small degree as is obvious from signals between 12 and 14 min which have been assigned

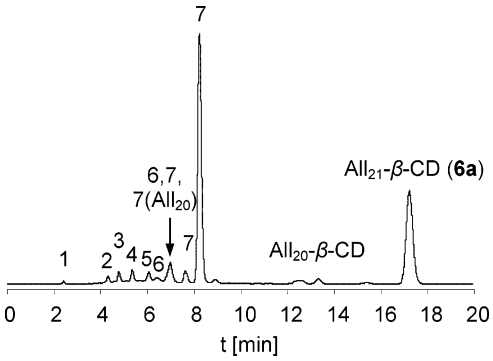

Figure 4. HPLC chromatogram of 2,3,6-*O*-allylated methyl maltooligosaccharides **6c** obtained from the ring opening of All_{21}-β-CD (**6a**) with 2 × 0.6 equiv $TiCl_4$ at room temperature (rt) for 45 h and subsequent treatment with methanolic HCl (0.1 mol/L). HPLC separation on a Phenomenex Gemini RP 18 column (0.8 mL/min methanol), detector: ELSD. Numbers above the peaks represent the DP values which have been assigned using LC-ESI-MS.

to All_{20}-β-CD and from the signal at 7 min which refers to compounds with DP 6 and 7, from which the latter has partly lost one allyl group. Since ELS detectors are mass-selective, the area of each signal is divided by the respective DP to get the corrected areas (A_{corr}^{DPx} and A_{corr}^{AllCD}). They correspond to the molar distribution of the compounds and are used to calculate the average degree of polymerization DP_{HPLC} and the conversion into linear products $conv_{HPLC}$ [%] according to eqs 7 and 8, respectively. Furthermore, the molar fraction of the main product, Mol%(DPx), with $x = 7$ for All_{21}-β-CD and 8 for All_{24}-γ-CD, is obtained from eq 9 and is listed in Table 3. Since the hexasaccharide seemed to be the major compound in the peak at 7 min as can be seen from LC-ESI-MS, DP 6 was used to calculate its corrected area.

The data obtained from the HPLC chromatograms are in good agreement with the data calculated from the corresponding ^{1}H NMR spectra indicating that both methods are suitable for characterizing the products. Deviations could arise from incorrect integration of the small H1-signals in the neighborhood to the large $-OCH_2CHCH_2$ signals in the ^{1}H NMR spectra or from a nonlinear relationship between the response of the ELS detector and the DP.

$$DP_{HPLC} = \frac{\sum_{x=1}^{5+n} (A_{corr}^{DPx} \cdot DPx)}{\sum_{x+1}^{5+n} A_{corr}^{DPx}} \quad (7)$$

$$\mathrm{conv}_{\mathrm{HPLC}} = \frac{100 \cdot \sum_{x=1}^{5+n} A_{\mathrm{corr}}^{\mathrm{DP}x}}{A_{\mathrm{corr}}^{\mathrm{AllCD}} + \sum_{x=1}^{5+n} A_{\mathrm{corr}}^{\mathrm{DP}x}} \quad (8)$$

$$\mathrm{Mol\%(DP}x) = \frac{100 \cdot A_{\mathrm{corr}}^{\mathrm{DP}x}}{A_{\mathrm{corr}}^{\mathrm{AllCD}} + \sum_{x=1}^{5+n} A_{\mathrm{corr}}^{\mathrm{DP}x}} \quad (9)$$

Ring opening of All_{21}-β-CD (**6a**) turned out to be less efficient than for the alkylated homologous. Lower conversion into **6b** was accompanied by enhanced chain degradation. To minimize chain degradation, only 2×0.6 equiv $TiCl_4$ was used. At room temperature, between 55 and 65% of All_{21}-β-CD (**6a**) was converted into linear products **6b** with an average DP of about 5.5 (Table 3, entry 1). Lowering the temperature increases the DP up to 6.3−6.4 (entry 3). However, at the same time, the conversion drops to 16−27%. The use of 2×0.75 equiv $TiCl_4$ provided 26−32% **6b** with a moderately lower DP of 6.3 (entry 4). Higher DP values up to 7.6 were obtained when the larger All_{24}-γ-CD (**7a**) was submitted to ring opening (entries 5−7). The conversion into 2,3,6-*O*-allylated maltooligosyl chlorides **7b** moderately increased compared to All_{21}-β-CD (**6a**), likely because of better accessibility of the glycosidic oxygen atoms.

Per-*O*-acetylated and per-*O*-benzoylated CDs that have been used as starting materials for ring-opening reactions by restricted acetolysis do not undergo $TiCl_4$ promoted ring opening even in the presence of a large excess $TiCl_4$ at higher temperatures. This might be partly due to the deactivating effect of the acyl substituent at position 2 on the glycosidic bond or, more probably, as a consequence of preferred complexation of $TiCl_4$ by acyl groups.

Mechanistic Aspects. The Lewis acid promoted cationic ring-opening polymerization of CDs only proceeds in the absence of nucleophilic reagents that otherwise would react with the propagating carboxonium ion.[1,2,20] However, $TiCl_4$ reacts differently and apparently prevents the polymerization by chloride ion transfer to the intermediate carboxonium ion. α-Glucosyl chlorides are formed exclusively because of a strong anomeric effect. Chloride transfer from $TiCl_4$ is well-known for the synthesis of glycosyl chlorides from the corresponding β-acetates or β-benzoates.[23,24]

In contrast to these reactions, the action of $TiCl_4$ on alkyl β-glycosides does not produce glycosyl chlorides but causes anomerization to the α-anomers.[25−30] The question whether this reaction proceeds by an intramolecular process was investigated by Lemieux and Shyluk who anomerized a racemic mixture of ^{14}C-labeled methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside and unlabeled methyl 2,3,4,6-tetra-*O*-acetyl-β-L-glucopyranoside with $TiCl_4$.[29] The method of isotopic dilution showed that the radioactivity was exclusively located in the D-enantiomer and thus gave evidence for an intramolecular process. Several mechanisms have been proposed. Lee et al. expected the reaction to occur via simultaneous complexation of $TiCl_4$ to the exocyclic and the endocyclic glycosidic oxygen atoms, formation of an acyclic carboxonium ion, and rotation of the C1−C2 bond (Figure 5a, path I).[27] Koto et al. investigated the anomerization in the presence of group IV metal chlorides and proposed a mechanism in which the formation of the acyclic carboxonium ion is facilitated by coordination of $TiCl_4$ to C6−OR and the endocyclic oxygen (Figure 5a, path II).[28] The same mechanism was proposed by Mukaiyama et al. who applied $MgBr_2 \cdot Et_2O$ and only catalytic amounts of $TiCl_4$ to minimize the formation of byproducts.[30] Subsequent stabilization involves chloride ion shift to an acylic haloacetal that undergoes rotation of the C1−C2 bond. Coordination of a second $TiCl_4$ molecule to C2−OR (R = Bn) and the exocyclic oxygen is regarded to be the reason for the high α-stereoselectivity of the resulting methyl α-glucoside which was obtained in 90−100% yield.

The cleavage of α-glycosidic linkages in cyclodextrins must proceed via cleavage of the exoglycosidic linkage between glycosyl units, probably facilitated by chelation to the exocyclic oxygen and C3−OR or C6−OR of unit Y (Figure 5b, paths III and IV). Complexation to C2−OR is also possible but is not considered to have any influence on the ring opening since chlorine shift has not been observed for simple alkyl α-glycosides, in which complexation to C2−OR can also occur. However, chelate complexes involving C2−OR could stabilize the α-conformation as proposed by Mukaiyama et al.[30]

In our experiments, we observed β-glycosidic linkages only in the linear products and not in the cyclodextrins, while formation of β-glycosidic linkages in cyclodextrins has been observed during the early stage of CROP with $BF_3 \cdot Et_2O$.[2] Independently, whether ring opening under chlorine transfer and anomerization proceed via the same or different complexes, this observation indicates that chloride formation is favored over anomerization, possibly because of the highly rigid and therefore conformationally less flexible CD-ring. Because of chlorine transfer to the carboxonium ion, the ends of the chains become neutral and are no longer attracted as an internal ion pair, so back-biting reactions become unlikely (path III and IV). As already discussed above, transglycosylation reactions can be excluded as possible pathways for the formation of β-glycosidic linkages (Figure 2).

To get more information about the $TiCl_4$−CD complex, we recorded ^{1}H NMR spectra of the freshly prepared complex of Me_{21}-β-CD (**2a**) (Figure 6b). Although CD_2Cl_2 was dried with CaH_2 and was distilled prior to use, a white precipitate was formed after addition of $TiCl_4$. Therefore, $CDCl_3$ was used which does not cause any problems. The spectra were recorded at −30 °C to avoid ring opening during the measurement. Obviously, all signals in the spectrum of the complex are broadened compared to the signals in the spectrum of Me_{21}-β-CD (**2a**) at −30 °C (Figure 6a). We attribute this phenomenon either to a supramolecular structure that might result from Ti-bridges between CDs or to a highly dynamic complexation of $TiCl_4$ to the oxygen atoms. The chemical shifts of the protons $H1^{CD}$ (δ 5.098), $H2^{CD}$ (δ 3.164), $H5^{CD}$ (δ 3.734), $H6b^{CD}$ (δ 3.794), C2−OCH_3^{CD}(δ 3.449), C3−OCH_3^{CD} (δ 3.609), and C6−OCH_3^{CD} (δ 3.449) are not significantly changed in the presence of $TiCl_4$. The chemical shifts of $H3^{CD}$ (δ 3.440), $H4^{CD}$ (δ 3.568), and $H6a^{CD}$ (δ 3.492) were determined from an HSQC spectrum (Figure 6c). The largest changes were observed for $H2^{CD}$ with only $\Delta\delta$ +0.007 ppm and $H1^{CD}$ with $\Delta\delta$ +0.004 ppm, which could point to interactions to $TiCl_4$. Furthermore, a range of small signals appeared between δ 4.0 and 5.6 in the ^{1}H NMR spectrum (not all shown) and at δ 3.535 (marked with an arrow). In contrast to the first ones, the latter gives a cross-peak which was located in the area of the signals of the methoxy groups. Provided that complexation causes a downfield shift, this signal could be assigned to C2−OCH_3 or C6−OCH_3 coordinated to $TiCl_4$.

Our interpretation of the results, namely, complexation to H1, H2, and C6OCH_3 or C2OCH_3, is consistent with the mechanism we proposed for the ring opening involving C6−OR (path III

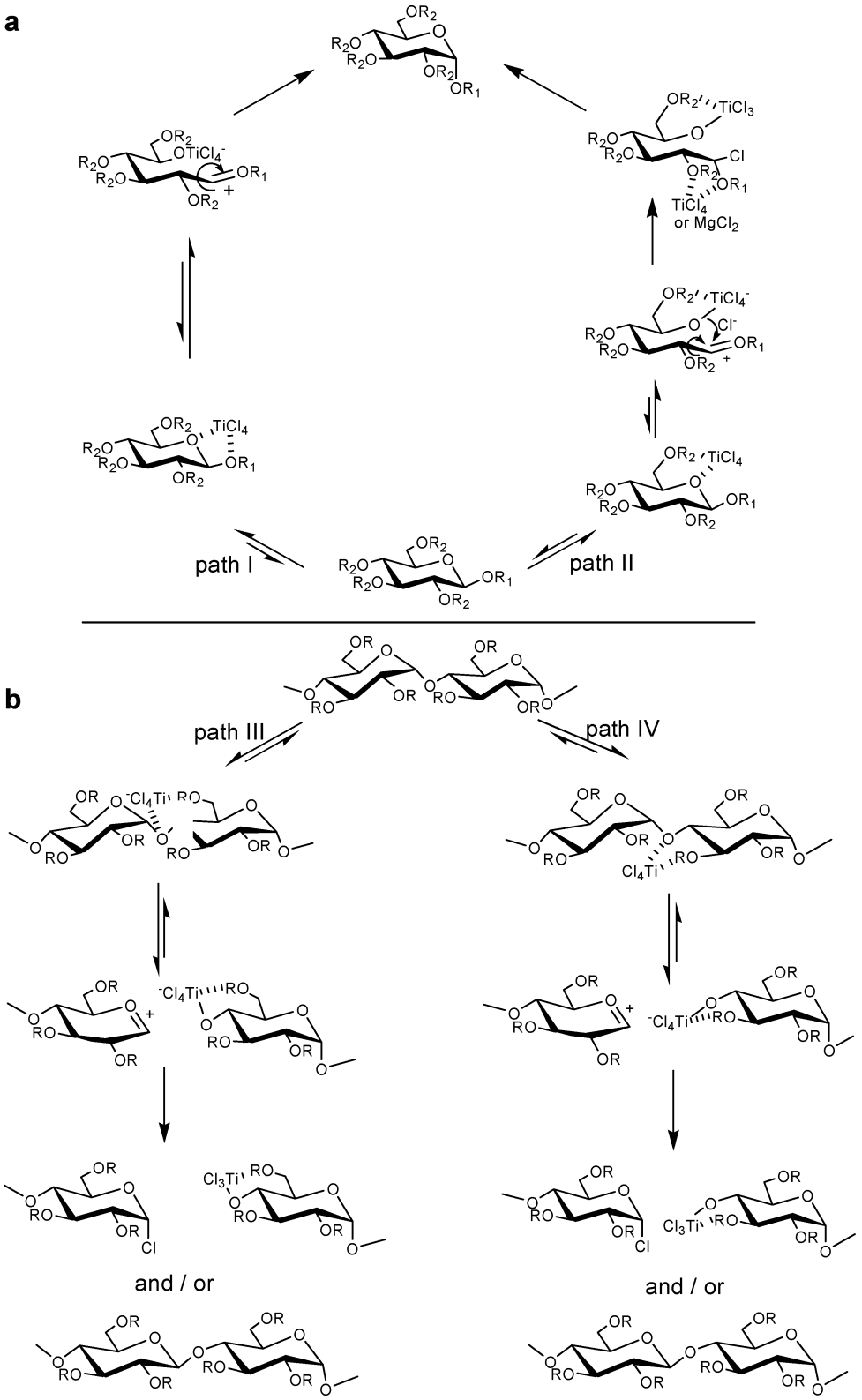

Figure 5. Proposed mechanisms of (a) the anomerization of alkyl β-glycosides (path I: $R_1 = R_2 =$ Me, path II: $R_1 =$ Me, $R_2 =$ Bn) and of (b) the cleavage and the anomerization of α-glycosidic linkages observed during ring opening of CD derivatives (path III and IV: R = Me, Et, All).

in Figure 5b) and supports our assumption that complexation to C2−OR, which has been considered to stabilize the α-configuration of glycosidic linkages during anomerization, also takes place (path II in Figure 5a). These results surely do not answer the question why $TiCl_4$ reacts differently with CDs compared to alkyl glycosides and require further investigation but provide an indication for the complexation behavior of $TiCl_4$.

Conclusion

The $TiCl_4$ promoted ring opening allows the preparation of activated bifunctional oligosaccharides from Me-CDs (**1a**−**4a**), Et-CD (**5a**), and All-CDs (**6a**, **7a**) to the corresponding oligomeric glycosyl chlorides (**1b**−**7b**) in good yields provided that the reaction conditions are carefully adjusted. Because of

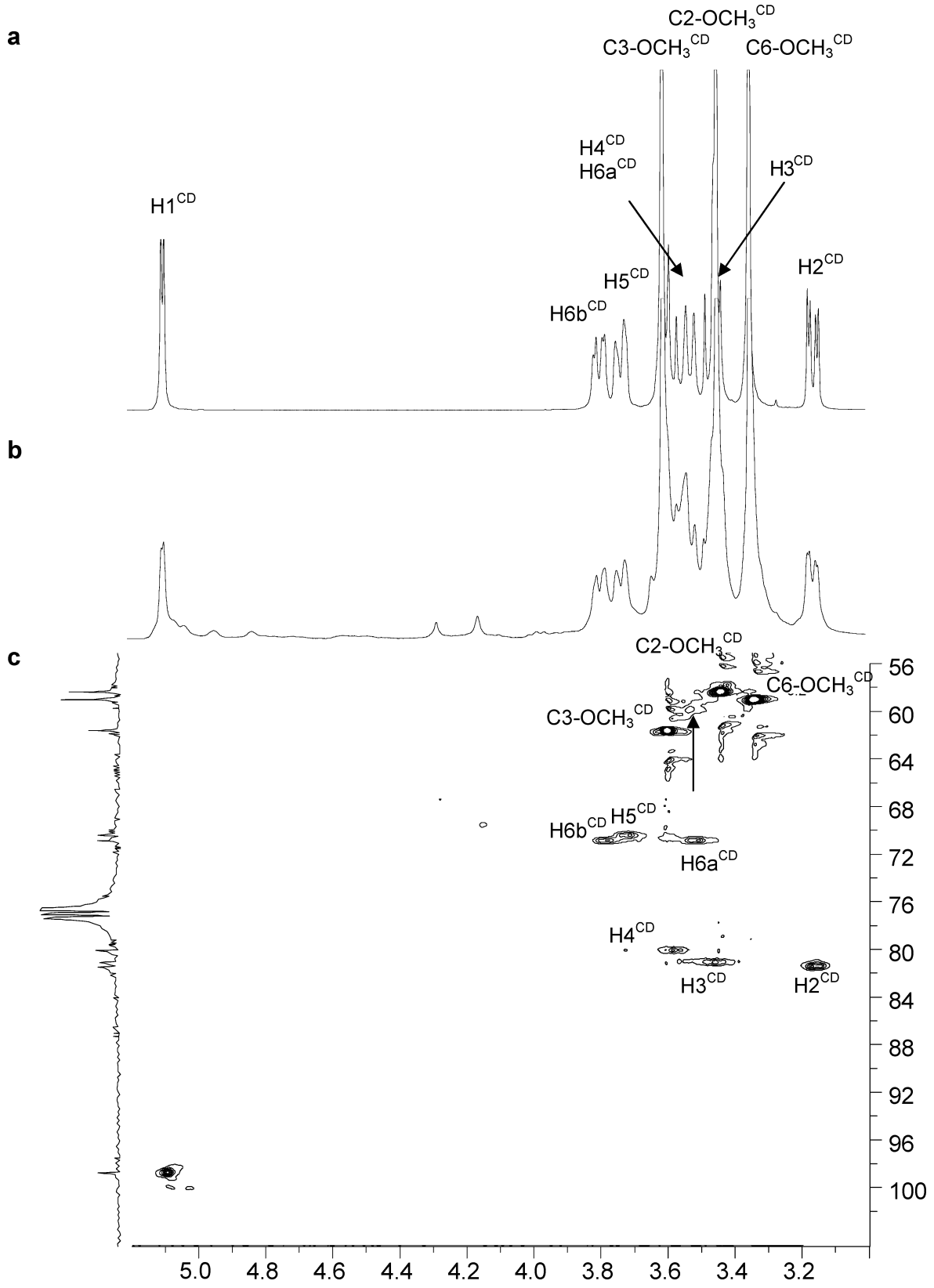

Figure 6. ^{1}H NMR spectra of (a) Me_{21}-β-CD (**2a**), (b) the mixture of Me_{21}-d_3-β-CD (**4a**) and 0.8 equiv $TiCl_4$/CD, and (c) its HSQC spectrum. All spectra were recorded in $CDCl_3$ at −30 °C.

the sensitivity of glycosyl chlorides, the product mixtures were not further purified or separated but were directly characterized by ESI- and MALDI-TOF-MS, HPLC-ELSD, and ^{1}H NMR spectroscopy. The conversion into linear products (conv [%]), their average degree of polymerization (DP), and the content of β-glycosidic linkages (β [%]) were calculated from the H1-signals. These parameters were optimized by careful adjustment of the temperature and the amount of $TiCl_4$. With Me_{18}-α-CD (**1a**) and Me_{21}-β-CD (**2a**), best results were achieved with 1.5 equiv $TiCl_4$, added in two steps, whereas a total of 1.2 equiv was sufficient for Me_{24}-γ-CD (**3a**). The reactions were carried out at 10 °C and provided 62−91% 2,3,6-*O*-methylated mal-

tooligosyl chlorides **1b**−**4b** with an average DP between 5.5 and 7.6, depending on the ring size. The reactivity rose with increasing ring size. Et_{21}-β-CD (**5a**) showed higher reactivity compared to the methylated analogue and provided 79% 2,3,6-*O*-ethylated maltooligosyl chlorides **5b** with DP 6.8 and β = 0.9%. The content of β-glycosidic linkages increased dramatically when excess $TiCl_4$ was used. All-CDs (**6a**, **7a**) proved to be less reactive toward ring opening favoring chain degradation. The best results were obtained using All_{24}-γ-CD (**7a**) at 0 °C yielding 37−39% linear products (**7b**) with a DP of 7.6.

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