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COMMUNICATION

Regioselective openings of proximally sulfato-capped cyclodextrins

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Sulfato groups capping one or two pairs of adjacent glucose units in methylated cyclodextrin (CD) derivatives have been found to undergo regioselective openings with various nucleophiles; the reported methodology opens the way to the efficient synthesis of tridifferentiated α - and β -cyclodextrins that constitute key starting materials for the preparation of heteropolydentate cavitands.

Naturally-occurring cyclodextrins (CDs) are cyclic oligosaccharides made up of six, seven and eight equivalent α -1,4-linked glucopyranose units, respectively, for the most common ones, α -, β - and γ -CD.¹ Because of their non-toxicity and their exceptional host-guest properties in water,^{2,3} they have found a wide range of applications in fields as diverse as drug formulation,⁴ biomimetic chemistry^{5,6} and catalysis.⁷⁻⁹ Their chemical modification^{10,11} has also attracted a great deal of attention as access to tailor-made CDs responding to specific requirements becomes possible if some of the hydroxyl groups that decorate the CD torus can be substituted at given locations.

However, because of the highly symmetrical nature of the native CDs, differentiating their numerous identical hydroxyl groups remains a challenge that has only been met with success recently. One of the most elegant approaches relies on the partial and regioselective removal of bulky benzyl protecting groups from the

narrower rim of perbenzylated CDs, in which steric effects are maximized, by DIBAL.¹²⁻¹⁵ Steric hindrance generated by *O*-benzyl groups has also proved pivotal to the regiospecific opening through nucleophilic attack of a sulfato group capping the A,D units of a benzylated β -CD.^{16,17} Recently, we have shown that proximal capping of methylated α - and β -CD scaffolds with sulfato units can be achieved straightforwardly.¹⁸ In this paper we show that the cyclic sulfates **1-3** can be used effectively for the synthesis of tridifferentiated CDs.

Achieving a highly regioselective nucleophilic attack on the sulfato bridges is here much more of a challenge as bulky benzyl groups, which might facilitate discrimination of the attack position, are no longer present. We were delighted to observe that regiospecific opening of sulfato groups took place both in the singly and doubly capped α -CDs (**1** and **3** respectively) provided the nucleophile is not only bulky, but also powerful enough for the reaction to occur at low temperature. Thus, treatment of **1** with lithium diphenylphosphide at -78°C and subsequent phosphorus protection with BH_3 followed by hydrolysis of the sulfate anion afforded cavitand **5a** in 97 % overall yield (Scheme 1; Table 1, entry 1).

Scheme 1 Reactivity of monosulfates **1** and **2**.

The C_2 -symmetric, diphosphine-borane **7a** (Scheme 2; Table 1, entry 8) was obtained from **3** according to the same procedure in 60 % yield, as a single regioisomer. Both **5a** and **7a** bear three different, pro-coordinating groups at precise locations on the CD scaffold.

Scheme 2 Reactivity of disulfate **3**.

Careful examination of the X-ray crystal structure of disulfate **3** gives a strong indication of which carbon atoms are more susceptible to nucleophilic substitution (Fig. 1).¹⁸ The C-6^A is clearly available for backside attack, whereas the approach of the nucleophile on C-6^B is partially blocked by neighbouring glucose unit C (the same comment holds for their symmetric counterparts, C-6^D and C-6^E, respectively).

Fig. 1 X-ray structure of the C_2 disulfate doubly capped derivative **3** (side-view of the CD scaffold). This spacefill view shows that the C-6^A atom (in green) is perfectly positioned for nucleophilic backside attack compared to its C-6^B counterpart (in blue). The solvent molecules are not shown.

Full NMR assignment of phosphine-borane **5a** using 2D COSY, TOCSY, HMQC and ROESY NMR experiments confirmed glucose unit A as being the only one having undergone nucleophilic attack. In the case of doubly capped species, full NMR assignment of oxidized diphosphine **10** as well as a single-crystal X-ray diffraction study (Fig. 2) carried out for **7a** confirmed the phosphination of the A and D glucose units.

Fig. 2 X-ray structure of the diphosphine borane adduct **7a** (side-view). This structure shows one of the P-BH₃ entities plunging into the cavity. The solvent molecules are not shown.

Interestingly, in the solid state, a BH₃ moiety is nested at the cavity entrance, its upper part being protected by the four PPH rings, so as to lead to full encapsulation of this borane unit. The second BH₃ unit is pushed away from the CD.

Table 1 Experimental conditions for the opening of **1**, **2** and **3**.

Entry	CD	Nu ^a	n ^b	Solvent	T (°C)	Product [Yld (%)]	re (%) ^c
1	1	Ph ₂ P ⁻	2.2	THF	-78	5a [97] ^e	100
2	1		4	DMF	0	5b + 6b [92] ^d	87
3	1	N ₃ ⁻	5	DMF	50	5c + 6c [98] ^d	59
4	1	N ₃ ⁻	4	DMF	0	5c + 6c [94] ^d	67
5	1		4	DMF	0	5d + 6d [91] ^d	50
6	2	Ph ₂ P ⁻	2.2	THF	-78	5e + 6e [95] ^e	22
7	2		12	DMF	0	5f + 6f [76] ^d	23
8	3	Ph ₂ P ⁻	3.5	THF	-78	7a [60] ^e	100
9	3		8	DMF	0	7b + 8b [82] ^d	33

^a Nucleophile; ^b Equivalents of nucleophile; ^c Regioisomeric excess determined by ¹H NMR and/or HPLC, $re = ([5]-[6])/([5]+[6])$ for entries 1-7, $re = ([7]-[8])/([7]+[8])$ for entries 8 and 9; ^d Yield of regioisomers mixture after acidic work-up; ^e Yield of regioisomers mixture after borane protection and acidic work-up. Compounds **5a**, **5e**, **6e**, and **7a** are BH₃-protected phosphines.

In stark contrast with the results obtained by Bols,¹⁶ moderate regioselectivities were observed with the small azide and thioacetate nucleophilic anions (Table 1, entries 3-5). Not surprisingly, the opening reaction with sodium azide is temperature sensitive. Cooling the same reaction mixture from 50°C to 0°C increased the regioisomeric excess by 8 % (Table 1, entry 4), confirming that the reaction operates under kinetic control. The regioselectivity was further improved by using the

medium-sized phthalimide anion instead of azide (Table 1, entry 2). Thus, tridifferentiated CD **5b**, which could be separated from its regioisomer **6b** by standard column chromatography, was recovered in 87% isolated yield vs. 5 % yield for **6b**. An X-ray crystal structure of **5b** proved that the nucleophilic attack had once again taken place mainly on the A glucose unit of sulfato-capped CD **1** (Fig. 3). Similarly to the X-ray crystal structure of **7a**, the bulky grafted group, in this case phthalimide, closes the primary face without penetrating the cavity.

Fig. 3 X-ray structure of the major regioisomer of phthalimide **5b** (side-view). The solvent molecules are not shown.

Performing the same reaction with the doubly capped CD **3** (Scheme 2; Table 1, entry 9) gave C_2 -symmetric **7b** as the major regioisomer (isolated yield 50%). The only possible C_1 -symmetric regioisomer (**8b**) was isolated in 28 % yield, but the presence of the second conceivable C_2 -symmetric species (**9b**) was not detected. This is hardly surprising as the formation of the latter is strongly disfavoured considering the outcome of the reaction between **1** and potassium phthalimide. Again, full assignment by NMR spectroscopy confirmed the same substitution pattern in N-containing **7b** as in P-containing **7a**. Note that tridifferentiated CD **7b** constitutes a key intermediate for accessing C_2 -symmetric nitrogen ligands as the phthalimide groups may easily be converted into primary amino groups. Similar sulfate openings were also conducted on singly capped β -CD **2**, but much lower regioselectivities were observed (Scheme 1; Table 1, entry 6-7), even in the presence of lithium diphenylphosphide at -78°C . It seems that the higher radius of curvature or/and flexibility of the methylated β -CD scaffold compared to its α -CD counterpart results in a poorer differentiation between the two CD C-6^A and C-6^B carbon atoms involved in the cyclic sulfate opening.

Conclusions

In summary, sulfato groups capping adjacent glucose units of methylated CDs have been shown to undergo regioselective openings with various nucleophiles. This methodology is currently extended to A,C and A,D-capped species in order to access new tridifferentiated CDs aimed at the constitution of a library of heteropolydentate CD ligands for asymmetric homogeneous catalysis and molecular recognition.

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Notes and references

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[‡] Crystal data for $\text{C}_{60}\text{H}_{95}\text{NO}_{31} \cdot 0.5\text{CH}_2\text{Cl}_2 \cdot \text{H}_2\text{O} \cdot 1.5\text{C}_5\text{H}_{12}$ (**5**·BH₃·0.5CH₂Cl₂·H₂O·1.5C₅H₁₂), $M_r = 1495.07$; monoclinic; $P2_1$; $a = 15.2970(10)$, $b = 15.7262(8)$, $c = 16.6710(10)$ Å, $\beta = 90.778(6)^\circ$; $V = 4010.1(4)$ Å³; $Z = 2$; $\rho_{\text{calcd}} = 1.238$ Mg·m⁻³; $\lambda(\text{MoK}_\alpha) = 0.71073$ Å; $\mu = 0.129$ mm⁻¹; $F(000) = 1608$; $T = 120$ K; 917 variables and 7789 observations with $I > 2.0\sigma(I)$; $R = 0.0680$, $R_w = 0.1911$, and $S_w = 0.830$; $\Delta\rho < 0.929$ e·Å⁻³. CCDC 826891. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

[§] Crystal data for $\text{C}_{74}\text{H}_{112}\text{B}_2\text{O}_{28}\text{P}_2 \cdot 3\text{CH}_2\text{Cl}_2 \cdot 1.5\text{C}_5\text{H}_{12}$ (**7**(BH₃)₂·3CH₂Cl₂·1.5C₅H₁₂), $M_r = 1896.19$; orthorhombic; $P2_12_12_1$; $a = 16.0969(4)$, $b = 22.4367(5)$, $c = 27.7517(7)$ Å; $V = 10022.8(4)$ Å³; $Z = 4$; $\rho_{\text{calcd}} = 1.257$ Mg·m⁻³; $\lambda(\text{MoK}_\alpha) = 0.71073$ Å; $\mu = 0.274$ mm⁻¹; $F(000) = 4036$; $T = 120$ K; 1029 variables and 8413 observations with $I > 2.0\sigma(I)$; $R = 0.0935$, $R_w = 0.2645$, and $S_w = 0.932$; $\Delta\rho < 0.658$ e·Å⁻³. CCDC 822184. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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