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Enzyme Models

# Zinc and Copper Complexes of Methylated Di- and Tetraaminocyclodextrins

Julia Warren[a] and Mikael Bols*[a]

**Abstract:** The α- and β-cyclodextrins with two dimethylamino groups or two trimethylethylenediamino groups attached to the primary face were synthesized and their p$K_a$ values were determined by potentiometric titration. The complexation of the four cyclodextrin analogues with zinc and copper was studied by NMR and showed one or two cyclodextrins bound to the metal. Inclusion of 4-halophenols in the metal complexes were also studied.

## Introduction

Molecular recognition and selective catalysis are areas of significant interest as chemistry strives for greater refinement and sustainability. Observing the chemistry of nature, it seems obvious that artificially created enzymes and receptors will find an important role in tomorrow's production, pharmaceuticals and diagnostics. However, these artificial devices must be comparatively simple to prepare and function efficiently in water. Incorporating metals in the supramolecular devices is a simple way to achieve binding and catalysis that mimics many natural enzymes and receptors containing metal ions.[1] Therefore, the use of cyclodextrins, which are inexpensive and water soluble, as the supramolecular host in metal binding devices is very attractive.[2]

Several groups have been interested in developing artificial metalloenzymes based on cyclodextrins.[3] Recently we reported that iron complexes of cyclodextrin diacids could catalyze the oxidation of benzylic alcohols by hydrogen peroxide presumably by creating a metalloenzyme-like active site.[4] The cyclodextrin acid iron complexes have a very simple yet attractive structure **A** where the metal is held just above the cyclodextrin cavity so it can interact with bound substrate (Figure 1). In this work we became interested in investigating related compounds with more efficient complex binding properties that would generate highly specified complexes. For this amino-groups caught our attention as they are a common feature of many strong metal ligands.[5] As the ligand should be resistant to oxidation tertiary amines was selected in order to create metal complexes such as **B**. In this paper we report the preparation of bidentate dimethylaminocyclodextrins and methyl-(dimethylaminoethyl)aminocyclodextrins and investigate their complexation of zinc and copper ions.

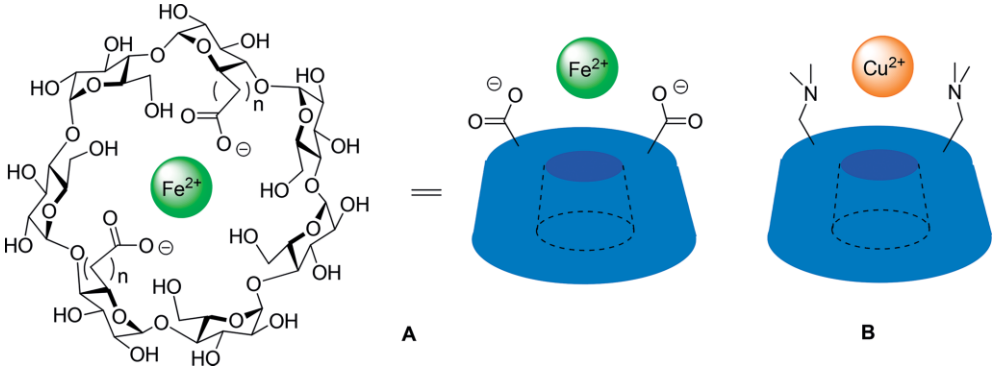



Figure 1. An iron cyclodextrin complex previously studied (**A**) and a copper complex (**B**) prepared in this work.

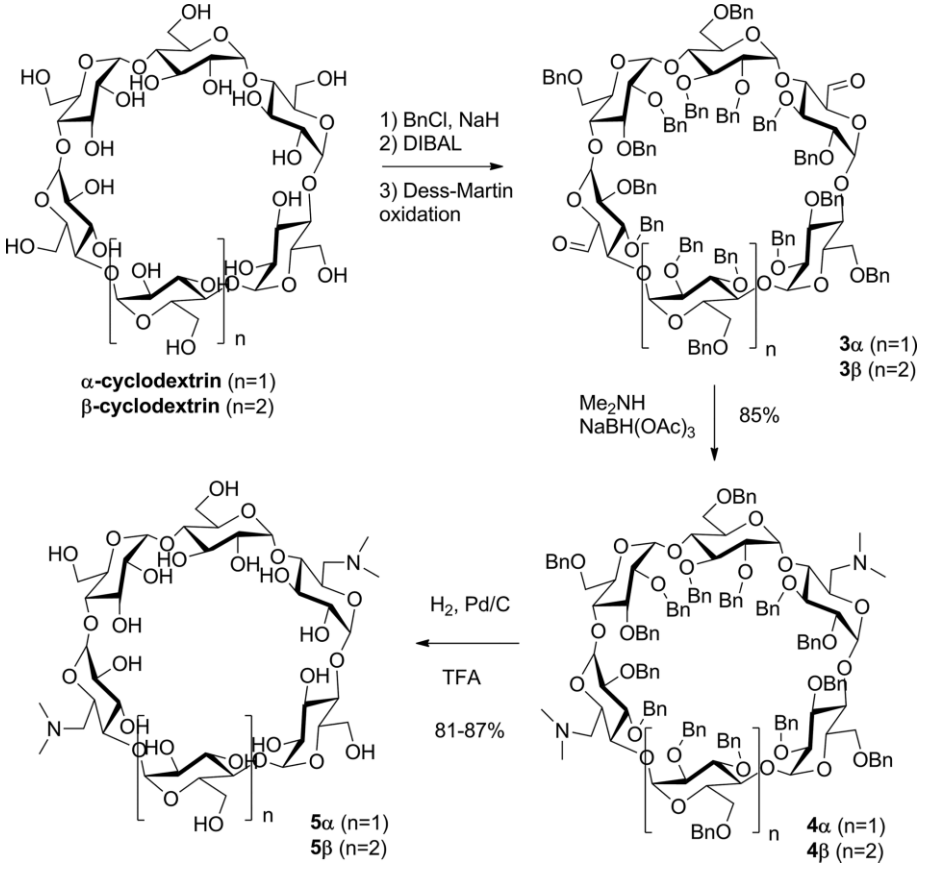
## Results and Discussion

The target aminocyclodextrins were prepared using the established perbenzylation and selective DIBAL promoted didebenzylation methodology that makes the $6^A$,$6^D$ positions in α- and β-cyclodextrins accessible.[6] Commercially available α- or β-cy-

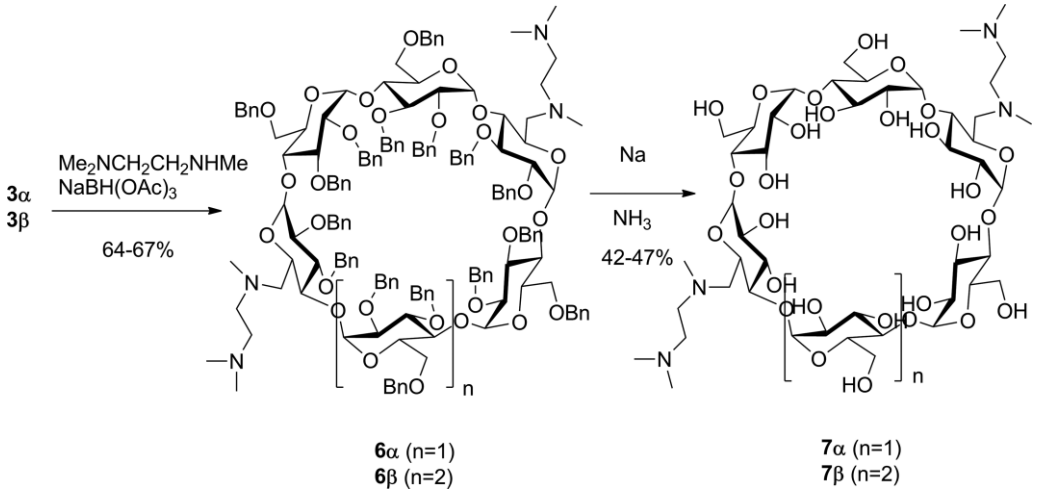
[a] *Department of chemistry, University of Copenhagen, Universitetsparken 5, 2100 København Ø, Denmark*
*E-mail: bols@chem.ku.dk*
*www.ki.ku.dk*

*Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201801554.*

clodextrin were subjected to perbenzylation with benzyl chloride and sodium hydride in DMSO, reaction with excess DIBAL in toluene to give didebenzylation at the $6^A$ and $6^D$ positions and oxidation of the liberated primary alcohols with Dess–Martin periodinane to give the dialdehydes **3α** or **3β**, respectively (Scheme 1). Reductive amination of **3α** or **3β** with dimethylamine and sodium triacetoxyborohydride gave the desired diamines **4α** or **4β**, respectively. In both cases 85 % yield were obtained. Finally, the benzyl groups were removed by hydrogenolysis with palladium on carbon and hydrogen. It is well known that the presence of amines inhibits the hydrogenolysis of benzyl groups. It was therefore necessary to add a 10 % excess of trifluoroacetic acid (TFA) with respect to the amines to make the reaction proceed, and the addition of TFA to the reaction obviously means that the products were obtained as salts. In order to isolate the free amines, the com-




Scheme 1. Synthesis of diamines **5α** and **5β**.




Scheme 2. Synthesis of tetraamines **7α** and **7β**.

pounds were treated with a basic ion-exchange resin and after this procedure 81 % of the diamine **5α** was obtained from **4α**, and 87 % of the diamine **5β** was obtained from **4β** (Scheme 1).

The tetraaminocyclodextrins were obtained by reductive amination of **3α** or **3β** with 1,1,2-trimethylethylenediamine and sodium triacetoxyborohydride (Scheme 2). This gave the expected tetraamines **6α** or **6β** in 67 % and 64 % yield, respectively. Finally, the compounds were debenzylated. Hydrogenolysis after addition of excess TFA as described above was not successful, perhaps because complete protonation of the less basic amines is difficult with TFA. Instead a dissolving metal reduction was used: **6α** or **6β** were treated with sodium in liquid ammonia, which gave the fully deprotected tetraamines **7α** or **7β** in 42 % or 47 % yield, respectively (Scheme 2).

With the target compounds in hand we determined the base strength of the amines by potentiometric titration. Since the p$K_a$ values of the conjugate acids of these amines are less than three units apart it is not possible to extract the values directly from the raw titration curve (see supporting information S2). Yet since the titration curves of different polyamines differ significantly, the p$K_a$ values can be extracted by comparing the actual titration curve with a simulated curve.[7] This method has not previously been reported for polyamine systems. Therefore, the method was tested with several amines and multiprotic systems (Table 1). It was found with the test compounds tetramethyl ethylenediamine, L-DOPA & gluthathione that the method gave results in good agreement with literature values.

Table 1. p$K_a$ values of the cyclodextrin amines and a series of test compounds used to validate the method. For the test compounds the literature value is given in parenthesis.

| Compound | p$K_a$ (1) | p$K_a$ (2) | p$K_a$ (3) | p$K_a$ (4) |
|---|---|---|---|---|
| $Me_2NCH_2CH_2NMe_2$ | 5.78 (5.85) | 8.99 (8.97) | – | – |
| L-Dopa | 2.65 (2.12) | 8.94 (8.72) | 9.78 (9.96) | 11.64 (11.79) |
| Glutathione | 2.12 (2.12) | 3.2 (3.53) | 8.37 (8.66) | 9.59 (9.12) |
| **5α** | 6.0 | 7.79 | – | – |
| **5β** | 7.57 | 9.3 | – | – |
| **7α** | 2.23 | 2.96 | 9.51 | 10.16 |
| **7β** | 3.83 | 3.94 | 7.7 | 8.46 |

Then the p$K_a$ values of the cyclodextrin amines were determined and are shown in Table 1. The p$K_a$ values are assigned as shown in Figure 2: The fully protonated polyamines are obviously more acidic than partially protonated amines because of statistical and electrostatic effects. In the fully protonated tetraamines the more acidic protons are on the amines closest to the cyclodextrin torus, because these amines have an electron withdrawing oxygen atom β to the amine while the terminal amines do not.

It is well known that in both simple diacids and diamines, the p$K_a$ is dependent on the distance between the groups. For example, 1,2-diaminoethane has p$K_a$ values of 9.9, 6.9 while 1,3-diaminopropane has p$K_a$ 10.6, 8.9. Based on standard carbon–carbon and carbo–nitrogen bond lengths, the 1.5 Å difference in length results in p$K_a$ values that are one to two orders of magnitude in difference. α-cyclodextrin has an internal diameter of 5.7 Å whereas β-cyclodextrin has an internal diameter of

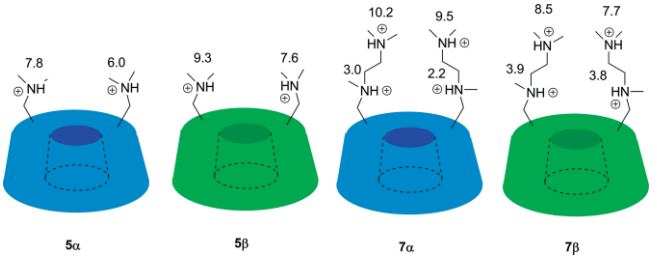



Figure 2. p$K_a$ assignments for compounds **5** & **7**. Blue torus is α-cyclodextrin, while green torus is β-cyclodextrin.

7.8 Å, a difference of 2.1 Å. The difference in the p$K_a$ values of **5α** and **5β** are due to the closer spatial orientation of the dimethylamine along the primary face. **7α** and **7β** follow the same pattern for p$K_a$ (1) and p$K_a$ (2). The opposite pattern in p$K_a$ (3) and p$K_a$ (4) indicating a different chemical environment in the terminal dimethylamino groups. Due to the restricted ring size of the **7α**, it is sterically preferable that the amines may be oriented such that the distance between them is significantly increased. Alternatively, the larger diameter of **7β** alleviates any steric hindrance, permitting greater interaction between the protonated/deprotonated terminal amines.

The binding of zinc and copper ions to the cyclodextrin amines was evaluated. When zinc triflate was added to **5α** in $D_2O$ in the NMR tube a downfield shift of the *N*-methyl groups was observed clearly indicating binding (supporting information S6). Plotting the chemical shift change vs. added metal ion concentration gave a hyperbolic binding curve. Similar behavior was observed when copper triflate was added to **5α** (supporting information S7), and when zinc or copper triflate was added to **5β**, **7α** or **7β** (supporting information S8–12). For the tetraamines **7α** or **7β** the greatest chemical shift changes were seen in the terminal *N*-methyl groups suggesting that the two terminal amines that were predominately involved in metal complexation.

Several different binding stoichiometries can be imagined for these complexation events besides 1 to 1 binding; two or more metal ions might bind to the aminocyclodextrin or several cyclodextrins may complex to a single one metal ion (Figure 3). The binding of two or more metal ions to a single aminocyclodextrin can be excluded by the observation that essentially complete chemical shift change was reached before 2 equivalents of metal was added to the cyclodextrin. In some cases, essentially complete chemical shift change had been reached before one equivalent of metal salt was added indicating that more than one cyclodextrin was binding the metal ion. Based on this observation the only realistic binding modes are 1:1 and 2:1 binding (Figure 3 & 4). To distinguish between these binding modes the amount of added zinc or copper was plotted against the relative chemical shift change observed (Δ) as defined as $\Delta = (\delta\text{-}\delta_{start})/(\delta_{end}\text{-}\delta_{start})$. The theoretical curves for binding are given in Figure 4 and in supporting information (see details).

These theoretical curves were fitted to the data points by varying K to find the best possible fit. In some cases, the best fit was for 1:1 binding, but predominately 2:1 binding gave the best fit. After the mode of binding had been determined the constant K was determined by linear regression of either

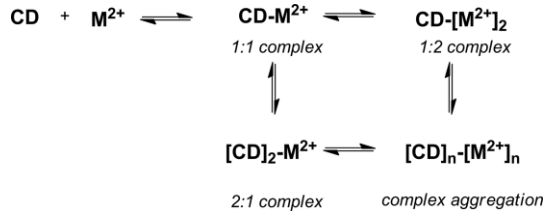



Figure 3. Different binding stoichiometries of the metal CD complexes.

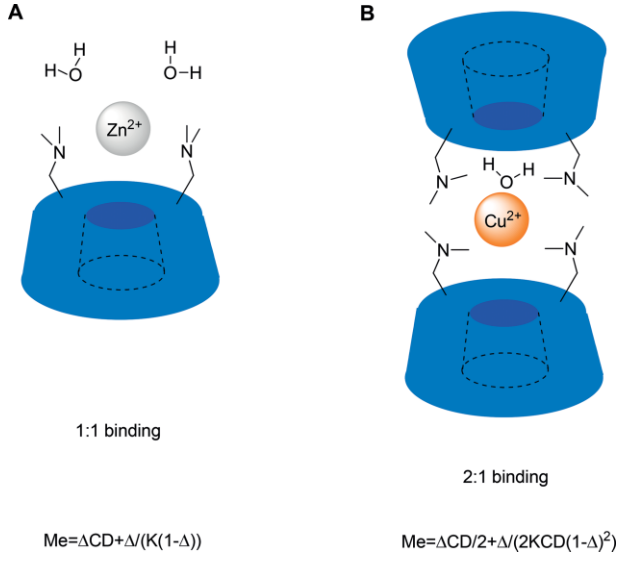



Figure 4. The two modes of metal binding (**A** or **B**) displayed by the cyclodextrin amines **5** and **7** and the corresponding relationships between concentration of added metal ($M^{2+}$), starting concentration of cyclodextrin (CD), Δ being fraction of chemical shift change that has occurred and K being the binding constant of the complex. Putative water molecule ligands have been added.

equation (1) $\Delta/(1 - \Delta) = K([M^{2+}] - \Delta[CD])$ for 1:1 binding or (2) $\Delta/(1 - \Delta)^2 = K(2[CD][M^{2+}] - \Delta[CD]^2)$ for 2:1 binding (see supporting information S3–4). This procedure gave the values of the binding constants given in Table 2.

These results (Table 2) mean that the diamines **5α** and **5β** binds $Zn^{2+}$ as a 1:1 complex. The magnitude of the binding constant is intermediate: In equimolar solutions of 0.1 to 1 mM of aminocyclodextrin and zinc **5α/β** binds about half the $Zn^{2+}$.

Diamines **5α** and **5β** binds $Cu^{2+}$ as a 2:1 complex (Table 2) with tetravalent coordination state as seen in Figure 4B. This is seen clearly from the binding curves that are inconsistent with 1:1 binding. This difference in behavior towards $Zn^{2+}$ and $Cu^{2+}$ is probably caused by a higher affinity of the amino-groups for the copper ion.

The tetraamine **7α** binds both $Zn^{2+}$ and $Cu^{2+}$ as a 2:1 complex (Table 2) with tetravalent coordination state as seen in Figure 4B. Again, the binding curves are inconsistent with 1:1 binding and 3 different methyl groups are observed in the complexes consistent with structure **B** where the terminal amines are coordinated to the metal ion. The binding-strength is as high as for the 2:1 complexes of **5α/β**.

The tetraamine **7β** binds Zn as 2:1 complex with an affinity very close to that found for **7α** (Table 2). However $Cu^{2+}$ was not bound by **7β** in a manner that fitted 1:1 or 2:1 binding. We suspect that in this case oligomeric structures are being formed.

The predominance of 2:1 binding of $Cu^{2+}$ is apparent in the titration as saturation of *N*-methyl signal in the $^1$H NMR at less than one equivalent. Of further significance is that as more equivalents of the metal are added, no change in the *N*-methyl chemical shift is noted. Although it cannot be entirely excluded that a 1:1 complex exists in insignificant amounts, the data indicates exclusive presence of the 2:1 binding mode. Further stoichiometric determination, such as the contiunous variation method (Job plot) are inapproiate in supramolecular systems.[8]

The effect of the metal-cyclodextrin complex on the ability to form an inclusion complex with small organic ligands was studied. 4-halophenols were selected as the ideal probe for this as they contain only aromatic signals and are readily water soluble. Initially the inclusion complex of **5α** and 4-chlorophenol was examined without Zn present. The ligand was added to **5α** (Figure 5) in increasing concentration resulting in a change in the chemical shift the H-3/H-5 protons, particularly in the H-5 of the amino modified sugar units; a small change in chemical shift was observed in the *N*-methyl groups. This suggests an interaction between the phenol and the amino-groups and inclusion of the phenol.

On the other hand, when 4-chlorophenol was added to the $Zn^{2+}$ complex of **5α** no chemical shift change was observed in *N*-methyl groups (Figure 6). This suggests that the presence of the substrate chlorophenol does not influence the Zn complexation to the cyclodextrin. A slight up-field shift of the chlorophenol upon addition and a chemical shift changes in the H3/H5 signals suggest that the chlorophenol is bound in the cavity nevertheless.

Diffusion-order spectroscopy (DOSY) was used to confirm the inclusion complex. The DOSY spectrum for the α-diaminocyclodextrin-4-chlorophenol system indicated sufficient occupation of the cavity. However, when the 4-chlorophenol was added to the Zn-α diaminocyclodextrin system we could not confirm the inclusion complex in this manner as no cross peak of the 4-chlorophenol occurred at the same diffusion coefficient as the cyclodextrin. This suggests the presence of Zn changes the accessibility of the cavity, perhaps due to electronic or

Table 2. $K_b$ values for binding of cyclodextrin amines to metals.

| Compound | [CDZn]/[Zn][CD] | [CDZn]/[Zn][CD]$^2$ | [CDCu]/[Cu][CD] | [CDCu]/[Cu][CD]$^2$ |
|---|---|---|---|---|
| **5α** | 5759 ± 248 | – | – | 3.56 (±0.33) × $10^9$ |
| **5β** | 9265 ± 764 | – | – | 6.05 (±0.38) × $10^{10}$ |
| **7α** | – | 3.09 (±0.43) × $10^9$ | – | 1.30 (±0.06) × $10^{10}$ |
| **7β** | – | 1.72 (±0.12) × $10^9$ | – | – |

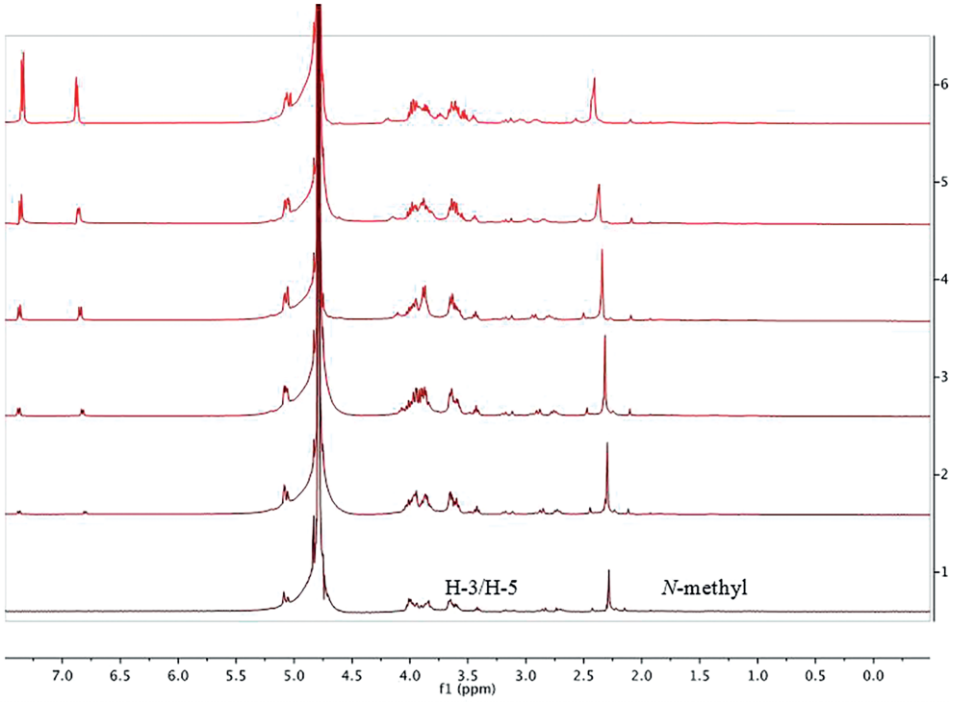



Figure 5. $^1$H NMR spectrum of **5α** in $D_2O$ with ca. 0, 0.125, 0.25, 0.5, 1 and 2 equiv. of 4-chlorophenol added.

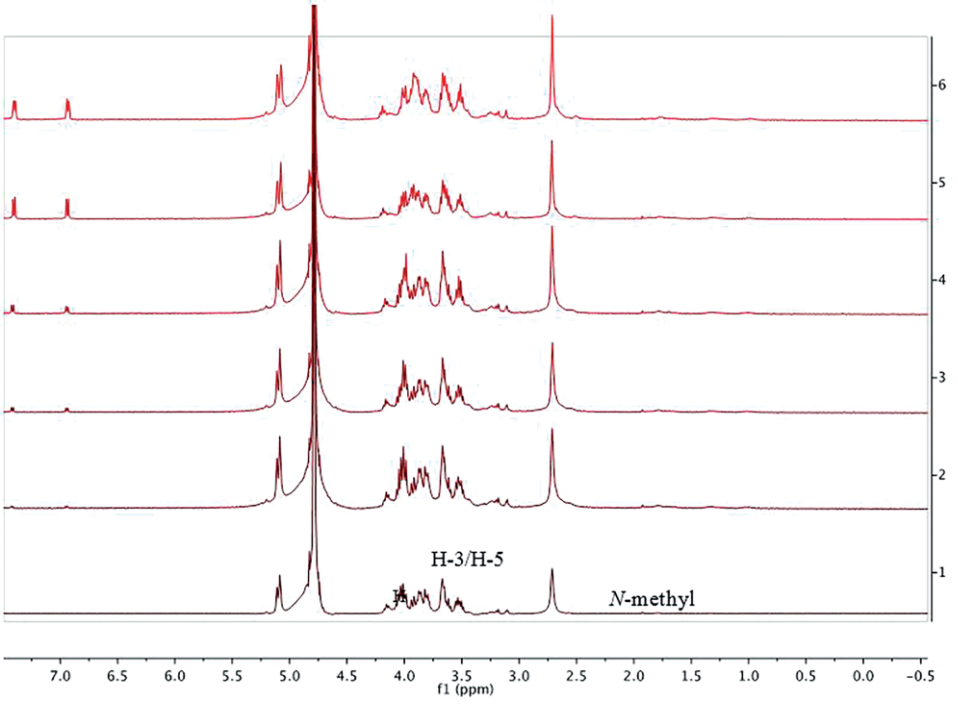



Figure 6. $^1$H NMR spectrum of **5α** and $Zn(OTf)_2$ (1 equiv.) in $D_2O$ with ca. 0, 0.125, 0.25, 0.5, 1 and 2 equiv. of 4-chlorophenol added.

global conformational changes in the cyclodextrin itself. 2-D ROESY indicated the same effect. An interaction was observed between the cyclodextrin H-3/H-5 and the phenol protons in the absence of $Zn^{2+}$. Upon the addition of $Zn^{2+}$ this interaction was not observable.

## Conclusions

In this paper we have shown that cyclodextrin di- and tetra-amines form 1:1 or 2:1 complexes with $Zn^{2+}$ and $Cu^{2+}$ ions. Furthermore, we have observed the effect of metal complexa-

tion on substrate uptake. Abridged titration and 2D NMR analysis of the diamine **5α** with 4-chlorophenol indicate that substrate uptake is more favorable in the absence of metal complexation. Although the Zn complex of **5α** displays a weakened capacity for inclusion complex formation, both the metal and organic substrate simultaneously complex the cyclodextrin; this reinforces the potential these complexes to function as metalloenzymes. The metalloenzymatic potential of these complexes will be explored in a further study.

## Experimental Section

**General Information:** Air and water sensitive reactions were carried out under nitrogen (balloon technique). All commercially available chemicals and solvents were used as received. $^1$H NMR spectra was measured on a Bruker instrument with cryo-probe at 500 MHz. $^{13}$C NMR was measured on the same instrument but at 126 MHz. NMR solvents used were $CDCl_3$ (referenced to $\delta_H$ = 7.26 ppm and $\delta_C$ = 77.16) and $D_2O$ (referenced to $\delta_H$ = 4.79 ppm). Coupling constants (*J*) was given in Hertz (Hz). Anhydrous solvents were collected from an IT (Innovative Technology) installation of the model PS-MD-05. Thin-layer chromatography (TLC) was performed on precoated (silica 60) aluminum plates with fluorescence indicator. Flash column chromatography was carried out on silica ($SiO_2$) with particle size of 40–63 μm from ROTH. Optical rotation was measured on an Anton Paar MCP 300 polarimeter with a 50 × 5 mm cuvette. High resolution mass spectrometry (HR-MS) was carried out on a FT-ICR spectrometer using either matrix assisted laser desorption ionization (MALDI) with dithranol as matrix or electrospray ionization (ESI+) with methanol + 1 % TFA.

**6$^A$,6$^D$-Dialdehydo-2,3,6-per-*O*-benzyl-α- or β-cyclodextrin (3α or 3β):** α- or β-cyclodextrin (8 g, 8.2 mmol or 7.0 mmol) was dried overnight at 60 °C. It was dissolved in dry DMSO (150 mL) and placed under an inert atmosphere. NaH (12 g for α or 10.2 g for β, 60 % oil, 0.30 or 0.26 mol) was added slowly and the reaction was stirred for 1 h. Benzyl chloride (37.4 g for α or 30.9 g for β, 295 mmol or 244 mmol) was added dropwise, and the reaction was stirred overnight at room temperature. The progress was monitored by TLC (petroleum ether/EtOAC, 3:1). Upon complete conversion water was added to the reaction slowly (300 mL). Diethyl ether (150 mL) was added, and the reaction was stirred at room temp. for a further 30 min. The reaction mixture was extracted with diethyl ether (4 × 100 mL). The ether was dried by anhydrous $MgSO_4$ and concentrated. The crude reaction mixture was purified by flash chromatography (petroleum ether/EtOAc, 9:1 → 3:1). Per-*O*-benzyl-α- or β-cyclodextrin was obtained as a brittle, white foam (18.7 g, 88 % yield for α or 17.2 g, 83 % for β).

The per-*O*-benzyl-α or β-cyclodextrin (18.7 g, 7.2 mmol for α or 14.9 g, 5.07 mmol for β) was dissolved in a minimal volume of dry toluene (70 mL) under an inert atmosphere. DIBAL-H (1.5 M in toluene, 96 mL, 144 mmol for α or 70 mL, 105 mmol for β) was added slowly. The reaction was stirred at 60 °C under a nitrogen stream, permitting concentration of the reagents. The reaction progress was monitored by TLC (petroleum ether/EtOAc, 3:1) until the major product was the desired dideprotected species, 2 h. The mixture was poured over a 1 M HCl/ice slurry (400 mL). Ethyl acetate (400 mL) was added and the new mixture stirred for 1 h until two phases were visible. The aqueous phase was extracted with ethyl acetate (3 × 200 mL). The organic phases were concentrated and purified by flash chromatography (petroleum ether/EtOAc, 3:1 → 2.5:1). The product 2$^{A–F}$,3 $^{A–F}$,6$^{B,C,E,F}$-hexadeca-*O*-benzyl-α-cyclodextrin (13.2 g, 76 %) or 2$^{A–G}$,3$^{A–G}$,6$^{B,C,E,F,G}$-nonadeca-*O*-benzyl-β-cyclodextrin (10.9 g, 78 %) was obtained as a brittle white foam.

To a stirred solution of 2$^{A–F}$,3$^{A–F}$,6$^{B,C,E,F}$-hexadeca-*O*-benzyl-α-cyclodextrin (3.3 g, 1.37 mmol) or 2$^{A–G}$,3$^{A–G}$,6$^{B,C,E,F,G}$-nonadeca-*O*-benzyl-β-cyclodextrin (5.3 g, 1.92 mmol) in $CH_2Cl_2$ (100 mL), Dess–Martin periodinane (4.1 g, 9.59 mmol) was added. The reaction was stirred under $N_2$ until complete conversion to the aldehyde was observed by crude $^1$H NMR (2 h). The reaction was then quenched by addition of $Et_2O$ (50 mL) and a solution of sat. aq. $NaHCO_3$ (50 mL) containing $Na_2S_2O_3$ (8.5 g) and stirred for a further 30 min. The aqueous phase was extracted with more ether (3 × 50 mL) and the organic extracts were washed with sat. $NaHCO_3$ (4 × 50 mL), brine (1 × 50 mL) and dried with $MgSO_4$. The organic solution was concentrated, affording the crude dialdehyde **3**α (3.1 g, 95 % yield) or **3**β (5.3 g, 100 % yield)[9] as a brittle white foam that was used without further purification.

**6$^A$,6$^D$-Dideoxy-6$^A$,6$^D$-di(dimethyl)amino-2$^{A–F}$,3$^{A–F}$,6$^{B,C,E,F}$-hexadeca-*O*-benzyl-α-cyclodextrin (4α):**[10] The 6$^A$,6$^D$-dialdehydo-2$^{A–F}$,3$^{A–F}$,6$^{B,C,E,F}$-hexadeca-*O*-benzyl-α-cyclodextrin (**3α**, 2.32 g, 0.96 mmol) was dissolved in $CH_2Cl_2$ (50 mL) and placed under $N_2$. Dimethylamine (2.2 eq, 1.06 mL of 2 M in THF) was added. $NaBH(OAc)_3$ (2.02 g, 9.6 mmol) was added, and the reaction was stirred for 2 h at room temperature. The reaction progress was monitored by TLC (PE/EtOAc, 3:2). Upon observed completion, the reaction was quenched with addition of saturated aq. $NaHCO_3$ (50 mL) and water (50 mL) and stirred for an additional 20 min. The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate extracts were combined and washed with aqueous saturated $NaHCO_3$ (5 × 50 mL), $H_2O$ (3 × 50 mL), brine (1 × 50 mL) and dried with anhydrous $MgSO_4$. They were concentrated and purified by flash chromatography (petroleum ether/EtOAc, 3:2, 1 % $Et_3N$), affording **4α** (2.00 g, 85 %) as a brittle white foam. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.28–7.07 (m, 40 H, H-Ar), 5.30 [d,$^3J$(1,2) = 3.5 Hz, 1 H,H-1], 5.26 (d,$^2J$ = 10.8 Hz, 1 H, CHPh), 5.15 (d,$^2J$ = 11.01 Hz, 1 H, CHPh), 5.09 [d,$^3J$(1,2) = 3.4 Hz, 1 H,H-1], 5.03 (d,$^2J$ = 11.3 Hz, 1 H, CHPh), 4.88–4.80 (m, H-1, 3 H, 2 × CHPh), 4.53–4.40 (m,8 H, 8 × CHPh), 4.34 (d $^2J$ = 12.1 Hz, 1 H, CHPh), 4.17 (m, 2 H, H-4), 4.08–3.80 (m, 10 H, 1 × H-4, 3 × H-3, 3 × H-5, 2 × H-6), 3.55 (m, 1 H, H-6), 3.52–3.47 (m, 3 H, H-6; 2 × H-2), 3.33 [dd, $^3J$(1,2) = 3.3 Hz,$^3J$(2,3) = 9.8 Hz, 1 H, H-2], 2.97 [dd, $^3J$(5,6) = 5.5, $^2J$(6,6) = 13.8 Hz, 1 H; $CH_2N(CH_3)_2$], 2.21 ppm [d, $^2J$(6,6) = 13.7 Hz, 1 H; $CH_2N(CH_3)_2$]. $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 139.73, 139.64, 139.61, 138.67, 138.60, 138.54, 138.43, 138.41 (8 × C-Ar$^{quat}$), 128.40–127.0 (40 X C-Ar$^{tert}$), 99.03, 98.83, 98.38 (3 × C-1), 81.94, 81.36, 81.15 (3 × C-4), 80.84 80.37, 79.62, (3 × C-3), 79.59, 78.74, 78.201 (3 × C-2) 75.86, 75.72, 75.13, 73.50, 73.38, 72.99, 72.74, 72.65 (8 × $CH_2$Ph), 71.75, 71.54, 71.36 (3 × C-5), 69.17, 69.00 (2 × C6), 59.26 $CH_2N(CH_3)_2$, 47.00 ppm [4 × N($CH_3$)$_2$]. HRMS (MALDI): *m/z* calcd. for $C_{152}H_{166}N_2O_{28}$: 2468.1699[M + H]$^+$, found 2468.16408.

**6$^A$,6$^D$-Dideoxy-6$^A$,6$^D$-di(dimethyl)amino-α-cyclodextrin (5α):** To a stirred solution of 6$^A$,6$^D$-di(dimethyl)amino-hexadeca-*O*-benzyl-α-cyclodextrin (1 g, 0.41 mmol) in EtOAc/MeOH (1:1, 50 mL) was added 10 % Pd on activated charcoal (1.3 g) in portions. The reaction vessel was filled first with $N_2$ and then flushed with $H_2$ three times. Finally, TFA (70 μL, 104 mg, 2.2eq) was added, and the reaction was stirred under the $H_2$ atmosphere (ca. 1.2 bar) for 24 h. The Pd/C was removed by filtration through Celite, and the solvent was evaporated giving a residue of the 6$^A$,6$^D$-dideoxy-6$^A$,6$^D$-di(dimethyl)amino-α-cyclodextrin trifluoroacetate salt. The trifluoroacetate anion was removed by dissolution of the salt in water and sub-

jecting it to ion exchange chromatography on a Amberlite IRA-410 $OH^-$ column. The water was removed from the aqueous eluates, which afforded $6^A,6^D$-dideoxy-$6^A,6^D$-di(dimethyl)amino-α-cyclodextrin as a white amorpheous solid (0.340 g; 81 % yield). $[\alpha]_D^{25}$ = +111.40. $^1$H NMR (500 MHz, $D_2O$): $\delta$ = 5.09 [dd $^3J$(1,2) = 5.9, $J$ = 3.41, 1 H; H-1] 5.05 [d $^3J$(1,2) = 3.12, 1 H; H-1], 4.02–3.82(m, 24 H, 4 × H-6, 6 × H-3, 6 × H-5), 3.67–3.58 (m, 10 H 4 × H-4, 6 × H-2), 3.42 (t, $J$ = 8.9, 2 H,H-4), 2.83, [d, $^2J$(6,6) = 13.1 Hz, 2 H; $CH_2N(CH_3)_2$], 2.69, [dd, $^2J$(6,6) = 13.7, $J$ = 9.34 2 H; $CH_2N(CH_3)_2$], 2.27 [s, 12 H, $CH_2N(CH_3)_2$]. $^{13}$C NMR (126 MHz, $D_2O$): $\delta$ = 101.54, 101.42, 100.98, (3 × C-1) 84.22, 81.31, 81.03 (3 × C-4), 73.25, 73.21, 73.10 (3 × C-3), 72.67, 72.09, 71.60, 71.56, 69.25(C5), 60.70, 60.41 (2 × C6), 59.27, $CH_2N(CH_3)_2$, 44.77 {[4 × $N(CH_3)_2$]}. HRMS (ESP): $m/z$ calcd. for $C_{40}H_{70}N_2O_{28}$: 1027.41879 $[M + H]^+$, found 1027.41923.

**$6^A,6^D$-Dideoxy-$6^A,6^D$-di(dimethyl)amino-nonadeca-*O*-benzyl-β-cyclodextrin (4β):** The $6^A,6^D$-dialdehydo-nonadeca-*O*-benzyl-β-cyclodextrin[9,12] (1.71 g, 0.60 mmol) was dissolved in $CH_2Cl_2$ (50 mL) and placed under $N_2$. Dimethylamine (1.32 mmol, 2.2 equiv., 0.670 mL of 2 M in THF) was added. $NaBH(OAc)_3$ (1.27 g, 6 mmol) was added and the reaction was stirred for 2 h at room temp. The reaction progress was monitored by TLC (petroleum ether/EtOAc, 3:2). Upon observed completion, the reaction was quenched with addition of saturated aq. $NaHCO_3$ (50 mL) and water (50 mL) and stirred for an additional 20 min. The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate extracts were combined and washed with $NaHCO_3$ aq. (5 × 50 mL), $H_2O$ (3 × 50 mL), brine (1 × 50 mL) and dried with anhydrous $MgSO_4$. It was then concentrated and the crude was purified by flash chromatography (petroleum ether/EtOAc, 3:2, 2 % $Et_3N$), affording **4**[11] as a brittle white foam (1.49 g, 85 % yield). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.24 –7.01 (m, 95 H, H-Ar) 5.41[d,$^3J$(1,2) = 3.6 Hz, 1 H; H-1], 5.33 [d,$^3J$(1,2) = 3.4 Hz, 1 H; H-1], 5.27 [d,$^3J$(1,2) = 3.4 Hz, 1 H; H-1] 5.19 [d,$^3J$(1,2) = 3.7 Hz, 1 H; H-1], 5.16 (m, 1 H, CHPh), 5.12 (m, 1 H, CHPh), 5.11 [d,$^3J$(1,2) = 3.9 Hz, 1 H; H-1], 5.08 (m, 1 H, CHPh), 5.02–4.96 (m, 3 H, CHPh), 4.94 [d,$^3J$(1,2) = 3.2 Hz, 1 H, H-1], 4.91 [d,$^3J$(1,2) = 3.1 Hz, 1 H; H-1], 4.86 (d,$^2J$ = 11.2 Hz, 2 H; CHPh), 4.79 (d,$^2J$ = 11.0 Hz, 2 H, CHPh), 4.75–4.7 (m, 5 H, CHPh), 4.60 (d,$^2J$ = 12.3 Hz, 2 H; CHPh), 4.52 (d,$^2J$ = 8.30 Hz, 1 H; CHPh), 4.50 (d,$^2J$ = 8.2 Hz, 1 H; CHPh), 4.47–4.36 (m, 18 H, CHPh) 4.13 (m, 2 H, 2 × H-6), 4.07–3.85 (m, 26 H, 7 × H-3, 7 × H-5, 7 × H-2, 5 × H-6), 3.47–3.34 (m, 12 H, 4 × H-4, 7 × H-6), 3.35 (dt, $J$ = 9.5, 2.7 Hz, 2 H, 2 × H-4), 2.91–2.81 [m, 2 H, $CH_2N(CH_3)_2$], 2.77 [dd, $J$ = 13.6, 6.3 Hz, 2 H, $CH_2N(CH_3)_2$], 2.09 (s, 6 H, 2 × $CH_3$), 2.07 ppm (s, 6 H, 2 × $CH_3$). $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 98.70 (2C), 98.57, 98.47, 98.39, 98.23, 98.17 (7 × C-1), 81.36, 81.22, 81.02 (4C), 80.93 (2C), 80.45, 80.40, 80.15, 79.49, 79.45 (2C), 79.30, 79.21, 78.98, 78.92, 78.81, 78.73, 78.61, (7 × C-2, 7 × C-3, 7 × C-4), 76.10, 76.02, 75.64, 75.42, 75.19, 74.81, 73.53, 73.43 (2C), 73.37 (3C), 73.04, 72.97, 72.93, 72.86, 72.80, 72.57, 72.46 (19 × CHPh), 71.75, 71.65, 71.60, 71.53, 71.43, 71.38, 71.03 (7 × C-5), 69.44, 69.28, 69.23, 69.18, 69.09, (5 × C-6), 60.28, 59.58, [2 × $CH_2N(CH_3)_2$], 46.96, 46.92 ppm (2 × $CH_3$). HRMS (MALDI): $m/z$ calcd. for $C_{179}H_{194}N_2O_{33}$: 2900.3637 $[M + H]^+$, found 2900.31804.

**$6^A,6^D$-Dideoxy-$6^A,6^D$-di(dimethyl)amino-β-cyclodextrin (5β):** To a stirred solution of $6^A,6^D$-di(dimethyl)amino-nonadeca-*O*-benzyl-β-cyclodextrin (**4β**, 0.70 g, 0.24 mmol) in EtOAc/MeOH (1:1, 40 mL) was added 10 % Pd on activated charcoal (0.85 g) in portions. The reaction vessel was filled first with $N_2$ and then flushed with $H_2$. TFA (40 µL, 60 mg, 2.2 equiv.) was added and the reaction was stirred under the $H_2$ atmosphere (ca. 1.2 bar) for 36 h. The Pd/C was removed by filtration through Celite and the solvent was evaporated giving a residue of the $6^A,6^D$-dideoxy-$6^A,6^D$-di(dimethyl)amino-β-cyclodextrin trifluoroacetate salt. The counterion was removed by redissolving the salt in water and ion exchange chromatography on an Amberlite IRA-410 $OH^-$ column. The water was removed from the aqueous eluents, affording $6^A,6^D$-dideoxy-$6^A,6^D$-di(dimethyl)amino-β-cyclodextrin[11] (**5β**, 0.250 g, 87 % yield). $[\alpha]_D^{25}$ = +129.3. $^1$H NMR (500 MHz, $D_2O$): $\delta$ = 4.99–4.95 (m, 7 H, 7 × H-1), 3.88–3.68 (m, 25 H, 7 × H-3, 7 × H-5, 7 × H-2, 4 × H-6), 3.54–3.46 (m, 10 H, 6 × H-6, 4 × H-4), 3.40 (q, $J$ = 8.8 Hz, 2 H; 2 × H-6), 3.33 (t, $J$ = 9 Hz, 2 H; 2 × H-4), 3.27- 2.19 [m, 2 H, $CH_2N(CH_3)_2$], 3.07 [t, $J$ = 11.1 Hz, 2 H, $CH_2N(CH_3)_2$], 2.61 [s, 6 H, $CH_2N(CH_3)_2$], 2.59 ppm [s, 6 H, $CH_2N(CH_3)_2$]. $^{13}$C NMR (125 MHz, $D_2O$): $\delta$ = 101.94, 101.92 (2C), 101.87, 101.78, 100.90, 100.80 (7 × C-1), 83.68 (2C), 81.70, 81.60, 81.24, 79.97, 79.90 (7 × C-4), 73.01, 72.97, 72.93, 72.59, 72.47 (5 × C-5), 72.11 (2C), 72.08 (4C), 72.02, 71.96 (2C), 71.83 (2C), 71.71 (2C), 71.56, (7 × C-3, 7 × C-2) 67.18, 66.97 (2 × C-5), 60.83, 60.73, 60.39, 60.28 (2C) (5 × C-6), 58.35, 58.27 [2 × $CH_2N(CH_3)_2$], 43.64 (4 × $CH_3$). HRMS (ESP): $m/z$ calcd. for $C_{46}H_{80}N_2O_{33}$: 1189.47161 $[M + H]^+$, found 1189.47199.

**$6^A,6^D$-Dideoxy-$6^A,6^D$-di($N^1,N^1,N^2$-trimethylethane-1,2-diamino)-$2^{A-F},3^{A-F},6^{B,C,E,F}$-hexadeca-*O*-benzyl-α-cyclodextrin (6α):** The $6^A,6^D$-dialdehydo-hexadeca-*O*-benzyl-α-cyclodextrin (**3α**, 3 g, 1.24 mmol) dissolved in DCM 60 mL and placed under $N_2$. $N^1,N^1,N^2$-trimethylethane-1,2-diamine (280 mg, 2.73 mmol, 360 uL) and $NaBH(OAc)_3$ (2.6 g, 12.4 mmol) were added, and the reaction was stirred for 2.5 h at room temp. The reaction progress was monitored by TLC (petroleum ether/EtOAc, 1:2). Upon observed completion, the reaction was quenched with saturated aq. $NaHCO_3$ (50 mL) and water (50 mL) and was stirred for an additional 20 min. The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate extracts were combined and washed with $NaHCO_3$ aq. (5 × 50 mL), $H_2O$ (3 × 50 mL), brine (1 × 50 mL) and dried with anhydrous $MgSO_4$. It was then concentrated and the residue was purified by flash chromatography (EtOAc, 3 % $Et_3N$), affording **6α** as a brittle white foam (2.14 g, 67 % yield). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.25–7.06 (40 H; H-Ar), 5.39 (br. s, 1 H, H-1), 5.28 (d, $^2J$ = 10.8 Hz, 1 H, CHPh), 5.20 (d, $^2J$ = 11.0 Hz, 1 H, CHPh), 5.17 (m, 1 H, H-1), 4.97 (d, $^2J$ = 11.0 Hz, 1 H, CHPh), 4.87 (d, $^2J$ = 11.0 Hz, 2 H, CHPh), 4.83 (m, 1 H, H-1), 4.80 (d, $^2J$ = 10.9 Hz, 1 H, CHPh),4.56 (d, $^2J$ = 12.3 Hz, 1 H, CHPh), 4.48–4.35 (m, 9 H, 9 × CHPh), 4.29 (d, $^2J$ = 12.11 Hz, 1 H, CHPh), 4.17–4.01 (m, 6 H, 3 × H-4, 3 × H-3), 3.97 (d, $J$ = 11.0 Hz, 1 H; H-5), 3.85 (d, $J$ = 9.8 Hz, 1 H; H-5), 3.81 (m, 1 H, H-5), 3.56 $J$(6,6) = 10.8 Hz, 1 H; H-63.50–3.42 (m, 3 H, 3 × H-2) 3.32 [dd $^3J$ (5,6) = 3.3, $^3J$ (6,6) = 9.2 Hz, 1 H; H-6], 3.18 [d, $^2J$ = 11.5 Hz, 2 H, $CH_2N(CH_3)$], 2.5 [br. s, 1 H; $CH_2N(CH_3)$], 2.39–2.23 [m, 4 H, $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 2.10 ppm (s, 9 H, 3 × $CH_3$). $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 139.64, 139.62, 139.56, 138.67, 138.56, 138.53, 138.39, 138.34 (8 × C-Ar$^{quat}$), 128.43–126.96 (40 X C-Ar$^{tert}$), 98.87, 98.24 (2C) (3 × C-1), 81.52, 81.42, 81.24 (3 × C-4), 80.86 (2C), 79.94 (3 × C-3), 79.82, 79.28, 78.72 (3 × C2), 76.07, 75.79, 74.98, 73.64, 73.42, 73.05, 72.82, 72.44 (8 × $CH_2$Ph), 72.30 (C-5), 71.47, 71.42 (2 × C-5), 69.33, 69.06 (2 × C-6), 58.03, 57.63 [2 × $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 45.94 [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 43.48 ppm [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$]. HRMS (MALDI): $m/z$ calcd. for $C_{158}H_{180}N_4O_{28}$: 2582.28569 $[M + H]^+$, found 2582.28061.

**$6^A,6^D$-Dideoxy-$6^A,6^D$-di($N^1,N^1,N^2$-trimethylethane-1,2-diamino)-α-cyclodextrin (7α):** To liquid ammonia (200 mL) at –78 °C under a $N_2$ atmosphere, sodium (2.0 g, 180 equiv.) was added piecewise. The resulting mixture was stirred at –78 °C until full dissolution was achieved. The cyclodextrin derivative **6α** (1.2 g, 0.465 mmol) dissolved in THF (3 mL) was added dropwise. The reaction was stirred for 4 h before quenching with 96 % EtOH. The mixture was allowed to reach room temperature was stirred overnight to evapo-

rate any residual ammonia. The EtOH was removed by rotary evaporation, and the resulting solid was dissolved in water. The sodium salts were removed by sending the solution through an ion exchange column of IR-120 resin ($H^+$ form), discarding the acidic eluate and subsequent isolation of the desired cyclodextrin **7α** by elution from the column with 6 % aqueous ammonia. Coevaporation with toluene afforded **7α** (0.212 g, 0.186 mmol) in a 42 % yield as an off-white amorphous solid. $[\alpha]_D^{25}$ = +110.91. $^1$H NMR (500 MHz, $D_2O$): $\delta$ = 4.99 (m, 6 H, H-1), 3.94–3.74 (m, 18 H, 6 × H-3, 2 × H-5, 4 × H-6, 6 H-2), 3.58–3.49 (m, 8 H, 4 × H-5, 4 × H-4), 3.36 (t, $J$ = 3 h, 2 H; H-4), 2.81 [d, $^2J$(6,6) = 13.5 Hz, 2 H; $CH_2$NR], 2.69–2.62 [m, 10 H, $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 2.37[s, 12 H, 2 × $N(CH_3)_2$], 2.22 ppm [s, 6 H, 2 × $CH_2N(CH_3)CH_2$]. $^{13}$C NMR (126 MHz, $D_2O$): $\delta$ = 101.43, 101.31, 101.17 (3 × C-1), 83.92 (2C), 81.07 (3 × C-4), 73.24, 73.21, 73.19 (3 × C-3), 72.35, 72.17 (2 × C-5), 71.70, 71.66, 71.57 (3 × C-2), 69.70 (C-5), 60.53, 60.40 (2 × C-6), 57.54 [$CH_2N(CH_3)$-$(CH_2)_2N(CH_3)_2$], 54.74 [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 53.98 [$CH_2N(CH_3)$-$CH_2CH_2N(CH_3)_2$], 43.79 [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 41.94 ppm [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$]. HRMS (ESP): *m/z* calcd. for $C_{46}H_{84}N_4O_{28}$: 1141.53448 $[M + H]^+$, found 1141.5325.

**6$^A$,6$^D$-Dideoxy-6$^A$,6$^D$-di(*N*$^1$,*N*$^1$,*N*$^2$-trimethylethane-1,2-diamino)-nonadeca-*O*-benzyl-β-cyclodextrin (6β):** The 6$^A$,6$^D$-dialdehydohexanona-*O*-benzyl-β-cyclodextrin (1.89 g, 0.67 mmol) was dissolved in dichloromethane (40 mL) and placed under $N_2$. *N*$^1$,*N*$^1$,*N*$^2$-trimethylethane-1,2-diamine (151 mg, 1.47 mmol, 200 µL) was added. $NaBH(OAc)_3$ (1.41 g, 6.7 mmol) was added, and the reaction was stirred for 2 h at room temp. The reaction progress was monitored by TLC (petroleum ether/EtOAc, 1:2). Upon observed completion, the reaction was quenched with saturated aq. $NaHCO_3$ (50 mL) and water (50 mL) and stirred for an additional 20 min. The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate extracts were combined and washed with $NaHCO_3$ aq. (5 × 50 mL), $H_2O$ (3 × 50 mL), brine (1 × 50 mL) and dried with anhydrous $MgSO_4$. It was then concentrated and the crude was purified by flash chromatography (EtOAc, 3 % $Et_3N$), affording a brittle white foam of **6β** (1.29 g, 64 % yield). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.30–7.02 (m, 95 H, H-Ar), 5.44–5.38 (m, 2 H, H-1), 5.30 [d,$^3J$(1,2) = 3.1 Hz, 1 H; H-1], 5.25 [d,$^3J$(1,2) = 3.5 Hz, 1 H; H-1] 5.19 (dd, $J$ = 10.4, $J$ = 6.0, 2 H; CHPh) 5.09 (t, $J$ = 11.4 Hz, 2 H; CHPh), 5.03 (t, $J$ = 2.99, 2 H, H-1), 4.95 (t, $J$ = 11.3 Hz, 2 H, CHPh), 4.85–4.73 (m, 7 H, CHPh), 4.56–4.37 (m, 24 H, CHPh), 4.16 (d, $J$ = 10.4 Hz, 2 H, H-6), 4.11–3.90 (m, 28 H, 6 × H-6, 7 × H-5, 7 × H-3, 4 × H-4, 4 × H-2), 3.61 (d, $J$ = 10.8 Hz, 3 H, 3 × H-6), 3.57–3.48 (m, 8 H, 5 × H-6, 3 × H-2, H-4) 3.39 (dd, $J$ = 9.4, 3.3 Hz, 2 H, 2 × H-4), 3.15 [dd, $J$ = 13.7, 4.9 Hz, 1 H, $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 3.08 [dd, $J$ = 13.4, 4.0 Hz, 1 H, $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 2.60 [m, 2 H, $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 2.51–2.39 (m, 4 H), 2.31 (m, 4 H), $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$, 2.16 ppm (s, 18 H, 6 × $CH_3$). $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 139.57, 139.54, 139.49, 139.42, 139.39, 139.38, 138.61, 138.58, 138.53, 138.49, 138.40, 138.39, 138.37, 138.35, 138.32, (19 X C-Ar$^{quart}$), 128.40–127.00 (95 X C-Ar$^{tert}$), 98.49 (2C), 98.35 (2C), 98.20, 98.15, 98.09 (7 × C-1), 81.40, 81.37, 81.05, 81.03, 80.99, 80.90, 80.86 (7 × C-3), 80.74, 80.19, 79.99, 79.61, 79.59 (2C), 79.46 (2C), 79.13, 79.03, 78.93, 78.66, 78.57, 78.35 (7 × C-4, 7 × C-2), 75.97, 75.88, 75.79, 75.54, 75.31, 75.17, 75.04, 73.47, 73.45, 73.43, 73.38, 73.36, 72.96, 72.93, 72.77, 72.66, 72.63, 72.54, 72.50 (19 × $CH_2$Ph), 72.29, 71.91 (2C), 71.71 (2C) (5 × C-5), 71.47, 71.37 (2 × C-5), 69.46, 69.32 [5 × C-6, 2 × $CH_2N(CH_3)$R], 58.41, 58.08, 57.72, 56.86, 56.78 [4 × $CH_2N(CH_3)$-$CH_2CH_2N(CH_3)_2$], 46.03, 45.99 [2 × $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 43.49, 43.40 ppm [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], HRMS (ESP): *m/z* calcd. for $C_{185}H_{208}N_4O_{33}H^{2+}$: 1508.24500 $[M + H]^{2+}$, found 1508.27075.

**6$^A$,6$^D$-Dideoxy-6$^A$,6$^D$-di(*N*$^1$,*N*$^1$,*N*$^2$-trimethylethane-1,2-diamino)-β-cyclodextrin (7β):** To a stirred solution of the liquid ammonia (300 mL) at −78 °C under a $N_2$ atmosphere, sodium (3.0 g, 180 equiv.) was added piecewise. The resulting mixture was stirred at −78 until full dissolution was achieved. The cyclodextrin (2.2 g, 0.73 mmol) was dissolved in THF (4.5 mL) and added dropwise. The reaction was stirred for 4 h before quenching with 96 % EtOH. The quenched mixture was allowed to reach room temperature overnight in order to allow the ammonia to evaporate gently. The EtOH was removed by rotary evaporation and the resulting solid was dissolved in water. The sodium salts were removed by sending the solution through an ion exchange column of IR-120 ($H^+$-form), discarding the acidic eluate and subsequent isolation of the desired tetraamine by elution with 6 % aqueous ammonia. Coevaporation with toluene afforded the desired cyclodextrin **7β** (0.435 g, 47 % yield) as an off-white amorphous solid. $[\alpha]_D^{25}$ = +107.97. $^1$H NMR (500 MHz, $D_2O$): $\delta$ = 4.99 (br. s, 7 H, 7 × H-1), 3.85–3.71 (m, 26 H, 7 × H-3, 7 × H-5, 7 × H-2, 5 × H-6) 3.58- 3.49 (m, 14, 5 × H-4, 7 × H-6), 3.34 (t, $J$ = 9.19, 2 H, H-4), 2.94–2.73 (m, 12 H), 2.63 (s, 6 H, 2 × $CH_3$), 2.62 (s, 6 H, 2 × $CH_3$), 2.26 (s, 6 H, $CH_3$), 2.24 ppm (s, 6 H, $CH_3$). $^{13}$C NMR (125 MHz, $D_2O$): $\delta$ = 101.94 (2 × C-1), 101.60 (4 × C-1), 83.80, 83.72 (2 × C-4$^{A,D}$), 81.16 (2C), 81.08, 80.90, 80.79 (5 × C-4), 73.12, 73.11, 73.07 (2C), 72.99 (5 × C-5), 72.12 (3C), 72.10 (3C), 72.02 (6C), 71.93, 68.97 (7 × C-3, 7 × C-2), 68.89 (2 × C-5$^{A,D}$), 60.30, 60.25, 60.22, 60.19, 60.16 (5 × C-6), 56.74, 54.78, 52.29, 52.10 [2 × $CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 43.45 [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 43.42 [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 42.21 [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$], 42.06 ppm [$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$]. HRMS (ESP): *m/z* calcd. for $C_{52}H_{94}N_4O_{33}H^{2+}$: 652.29729 $[M + H]^{2+}$, found 652.29893.

**Supporting Information** (see footnote on the first page of this article): Supporting information containing NMR spectra of compounds **4**–**7**, methodology, theory and data for NMR titrations and p$K_a$ titration curves.

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**Keywords:** Amines · Complexes · Zinc · NMR titration · Copper

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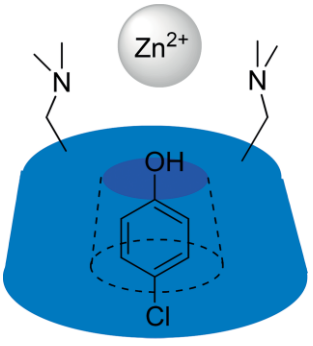
**Enzyme Models**






The α- and β-cyclodextrins with two dimethylamino groups or two trimethylethylenediamino groups attached to the primary face were synthesized and their p$K_a$ values were determined by potentiometric titration. The complexation of the four cyclodextrin analogues with zinc and copper was studied by NMR and showed one or two cyclodextrins bound to the metal.

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