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# Aza-capped cyclodextrins for intra-cavity metal complexation†

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**Aza-capped, methylated cyclodextrins (CDs) were obtained in high yields by reacting the soft nitrogen nucleophile 2-nitrobenzenesulfonamide with either A,B-dimesylated CDs in basic media or their diol analogues under Mitsunobu reaction conditions followed by deprotection with thiophenol. A methyl pyridine substituent was grafted on the N atom of these secondary amines. When built on an α-CD scaffold, the resulting tertiary amine no longer undergoes nitrogen inversion at room temperature and behaves as a confining ligand, opening the way to intra-cavity metal complexation and promoting the formation of supramolecular helices.**

Molecular receptors equipped with inwardly directed donor atoms are valuable ligands for forcing a metal centred reaction, whether catalytic or not, to take place within a molecular cavity.[1] This feature may promote high selectivity, notably enantioselectivity, if the host molecule is an optically active one such as a rigidly capped cyclodextrin (CD) derivative.[2] Previous work has shown that connecting two C-6 carbon atoms of adjacent CD glucose units through a single donor atom (Fig. 1) may provide rigidity and adequate orientation of the heteroatom lone pair.[3] So far, soft donor atoms, such as sulphur[4] or phosphorus,[3] have been successfully incorporated into the CD framework, because reagents containing them constitute excellent nucleophiles that can give rise to efficient ring-closure with CD-based dimesylates without the occurrence of undesired elimination reactions.[5] On the other hand, nitrogen-containing analogues of the heteroatom-capped CDs

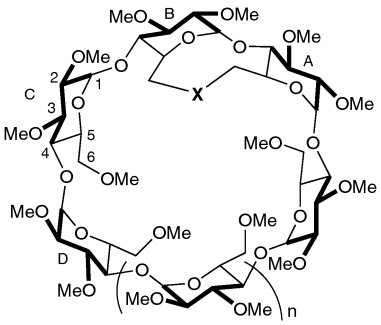


Fig. 1 Heteroatom-capped α-CDs ($n$ = 1) and β-CDs ($n$ = 2); X = PPh or S (previous work), X = NR (this work). Carbon atom numbering is shown for only one glucose unit.

are much more difficult to access because of the hardness of the smaller nitrogen atom, in particular when using amides as capping reagents. Our interest for nitrogen as a capping atom stems from the fact that it is not sensitive to oxidation like phosphorus(III) and offers many more possibilities for derivatisation than the divalent sulphur atom. Herein, we describe the preparation of a range of aza-capped CDs relying on the use of the nitrogen nucleophile 2-nitrobenzenesulfonamide (2-NsNH$_2$) as a capping agent[6] and their use as confining nitrogen ligands for intra-cavity metal complexation.

We were delighted to observe that two adjacent glucose units can be effectively bridged *via* a ring-closing double *N*-alkylation of 2-NsNH$_2$ with diol **1** or dimesylate **2** without the need of high dilution conditions. Thus, upon reacting 2-NsNH$_2$ with diol **1**, diisopropylazodicarboxylate (DIAD) and PPh$_3$ in toluene, the desired 11-membered Ns-amide **3** was obtained in 61% yield. The cyclisation could also be achieved in higher yield (94%) by reacting dimesylate **2** with 2-NsNH$_2$ in basic media ($K_2CO_3$).[7] Effective ring-closure was also effective with the larger β-CD-based diol **4** or dimesylate **5** and gave Ns-amide **6** in respectively 60% and 65% yields. The removal of the Ns group from both **3** and **6** using mild deprotection conditions[6] (PhSH, $Cs_2CO_3$, and MeCN) was achieved without affecting the CD core

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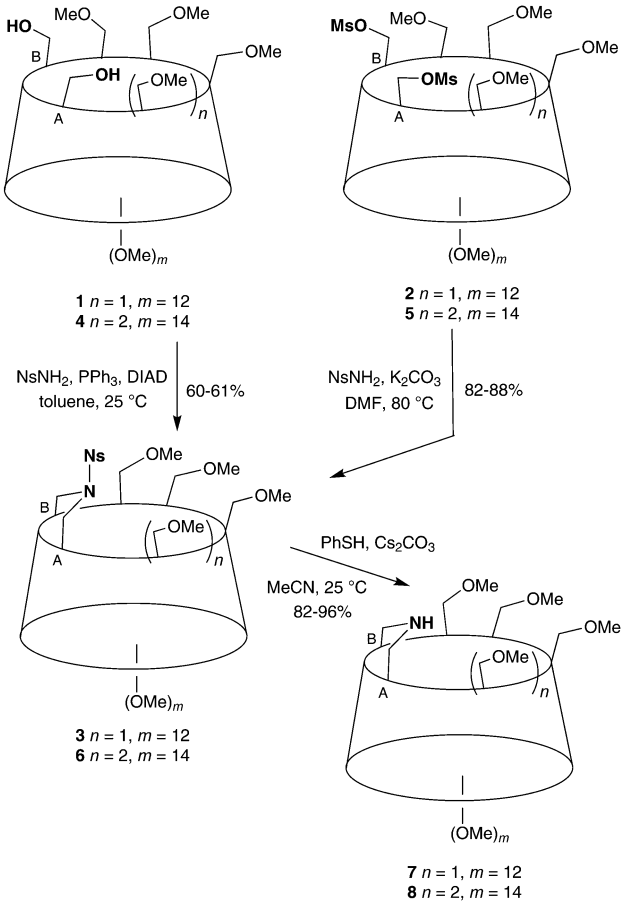
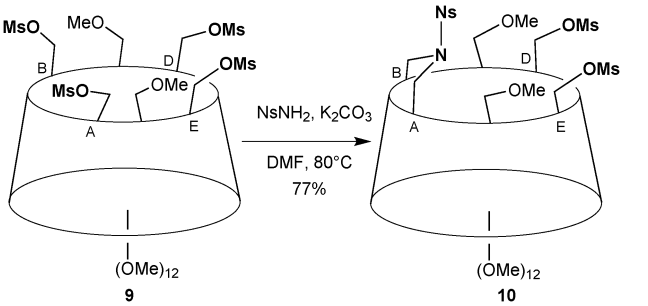
† Electronic supplementary information (ESI) available: Synthesis and characterization data. CCDC 1400713 and 1546409. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc06434a



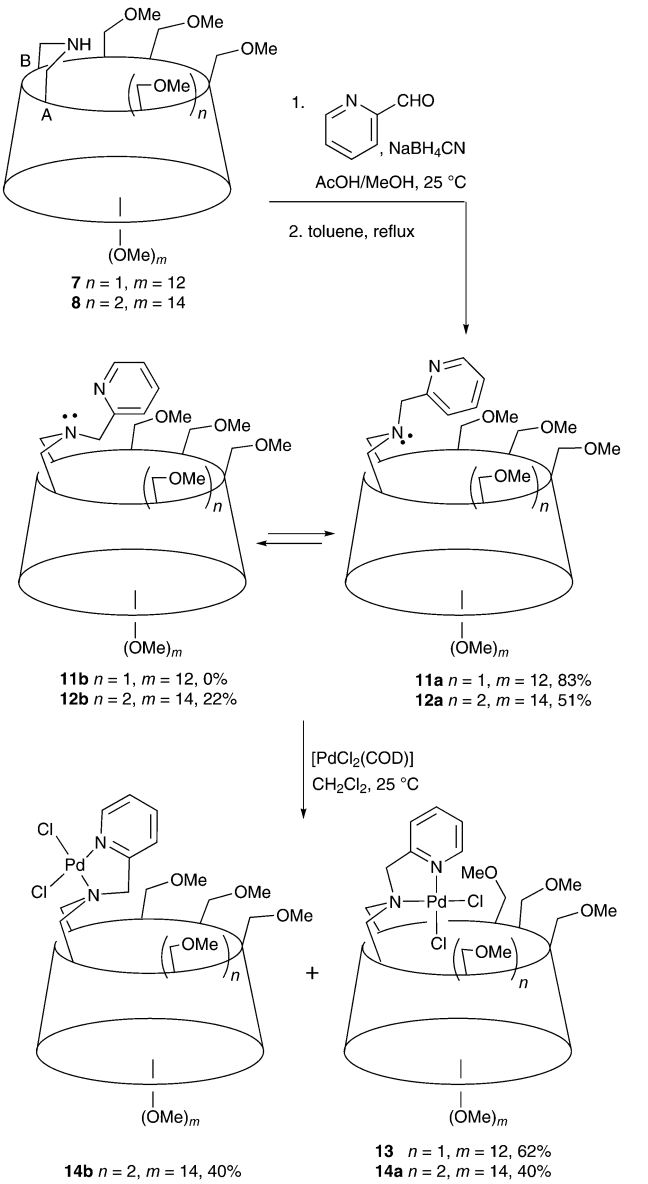

Scheme 1 Two different ways of accessing aza-capped CDs having a short NH handle.

to give respectively the aza-capped CD derivatives **7** and **8** in 96% and 82% yields (Scheme 1). Surprisingly, when submitting tetramesylate **9**[8] to two equivalents of 2-$NsNH_2$, the expected doubly capped species was not formed. Instead, only one nitrogen bridging unit could be installed on the macrocyclic structure to give monocapped **10** in 77% yield, leaving the two adjacent mesylate units unaffected, presumably because of the steric hindrance caused by the introduced nosyl unit. Such a reaction constitutes a new way of accessing tridifferentiated α-CD derivatives in a regiospecific manner since no AC bridge is being formed (Scheme 2).[9]

Because P(III) bridges linking two glucose units in methylated cyclodextrins have their lone pair oriented towards the centre of the cavity,[3a] we wondered whether a trivalent nitrogen atom would behave in the same way. This is a lot more challenging because the inversion barrier is much lower for nitrogen than for phosphorus. We decided to embark on the synthesis of 2-pyridylmethylamines **11** and **12**, which were expected to behave as chelating ligands towards $d^8$ cations and force the metal unit to stay in the cavity provided the nitrogen inversion barrier is blocked and the bridging nitrogen atom behaves as a metal confining donor atom (Scheme 3). Thus, secondary amine **7** was reacted with 2-pyridinecarboxaldehyde under reductive amination conditions ($NaBH_3CN$, AcOH and MeOH) to give the desired bidentate




Scheme 2 Synthesis of a tridifferentiated monocapped α-CD derivative.




Scheme 3 Synthesis of *N,N* bidentate ligands **11a** and **12a/b** and metal complexation.

ligand in 83% yield. The reaction mixture consisted of a 9 : 1 mixture of the two diastereomers **11a/b**, which could not be separated. However, the minor compound fully converted into

the major one upon refluxing the mixture in toluene for 14 h. Unlike **11a/b**, their β-CD analogues **12a/b** slowly exchange on the NMR time scale as revealed by a variable NMR study. The two interconverting invertomers **12a/b** could be detected in a 75/25 ratio below the coalescence temperature (−20 °C). Clearly, nitrogen inversion cannot be frozen in the more flexible β-CD macrocyclic structure and exclusive formation of one invertomer is not observed despite the fact that one of them is thermodynamically favoured over the other. A proof that the nitrogen lone pair of the trialkylamine unit is oriented towards the centre of the cavity in **11a** came from a ROESY NMR experiment, which revealed spatial proximity between the four H-6 protons of the A,B-bridged glucose units and the methylenic $CH_2$-Py protons (see ESI†). Similar observations were made for complex **13**, which was obtained as a single product by reacting **11a** with [$PdCl_2$(COD)]. The presence of downfield-shifted inner-cavity H-5 protons in **13** also revealed the location of at least one chlorido ligand inside the CD cavity ($\delta$ (H-5) up to 5.59 ppm and $\Delta\delta \geq 1.43$ ppm compared to **11a**)[2b,10] and therefore is a further confirmation of the *endo* orientation of the nitrogen lone pair. A single crystal diffraction study of **13** allowed us to establish its molecular structure (Fig. 2).‡ Surprisingly, the square planar $PdCl_2N_2$ unit is not perpendicular to the CD upper rim plane (defined by the O-4 atoms) but markedly tilted towards the glucose unit F, the two planes forming an angle of about 70°. The metal–organic cap has no major influence on the CD torus as its overall shape stays circular and all glucose units retain their usual $^4C_1$ conformations. Inspection of the crystal lattice revealed the presence of discrete left-handed,[11] four-folded helices[12] in which the successive CD complexes are plugged one into the other.§ Weak hydrogen bonds between the pyridine H-3/H-4 protons and the CD buried chlorine atom[10,13] (H···Cl separations ranging from 2.76 Å to 3.26 Å) are responsible for the observed supramolecular arrays.¶ The helical nature of the endless assemblies likely results from the marked tilt imposed on the rigid pyridine ring by metal chelation.[12c]

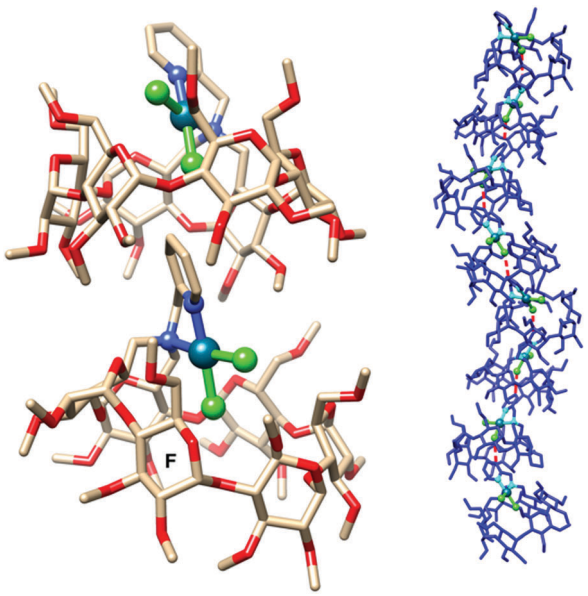



Fig. 2 Molecular structure of two successive CD complexes **13** arranged in a head-to-tail fashion (left) and the supramolecular helix (right) they are part of in the solid state. The red dotted lines represent short contacts between H-3/H-4 pyridine protons and a CD buried chlorine atom of its neighbouring complex. $CH_2Cl_2$ solvent molecules lying between the helical arrangements are omitted for clarity.

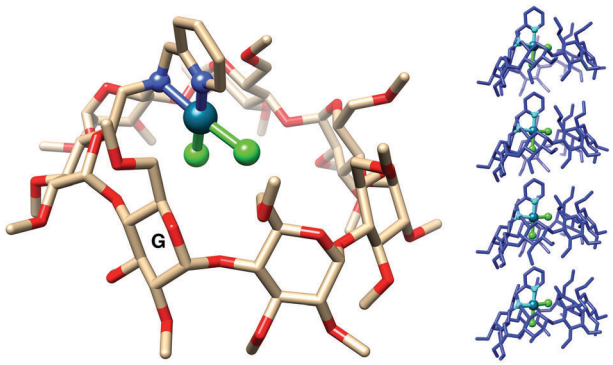



Fig. 3 Molecular structure of CD complex **14a** showing inclusion of the $PdCl_2$ unit (left) and columnar arrangement of the CDs in the crystal (right). The two $CH_2Cl_2$ solvent molecules that lie between the CD units in the columnar arrays have been omitted for clarity.

The reaction of **12a/b** with [$PdCl_2$(COD)] in $CH_2Cl_2$ gave a 1 : 1 mixture of the two diastereomeric complexes **14a/b**, confirming that in the case of the larger β-CD-based amine, the control of the stereochemistry of the bridging nitrogen atom is not possible. Owing to their different steric properties, the equilibrating ligands **12a** and **12b** resulted in a mixture of **14a/b** displaying a ratio different from that of **12a/b**. Single crystals of the *endo* complex **14a**‖ could be obtained by the diffusion of pentane into a $CH_2Cl_2$ solution of the **14a/b** mixture. The molecular structure (Fig. 3) bears strong resemblance to that of **13**, the square planar $PdCl_2N_2$ unit being tilted towards the unit G and making an angle of 75.3° with the CD upper rim plane. The major difference between the two structures is that **14a** does no longer form helical assemblies in the solid, but columnar arrays instead, as direct connection between the CD units *via* hydrogen bonding does not occur in this case.

In conclusion, we have shown, for the first time, that two adjacent glucose units in both methylated α- and β-cyclodextrin derivatives can be connected through the very short NH spacer. In methylated CDs equipped with a tertiary amine cap, nitrogen inversion can be blocked at room temperature provided the aglycone *N*-substituent is bulky enough and the cyclo-oligosaccharide core is sufficiently rigid as in the small α-CD derivatives. Because the heteroatom lone pair is inwardly directed in these ligands, it can be used to confine a metal centre to a well-defined cavity, opening the way for nitrogen-based metal catalysts operating in a restricted chiral space.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

‡ Crystal data for $C_{118.5}H_{194.5}Cl_{11.5}N_4O_{56}Pd_2$, $M_\Gamma$ = 3191.74; orthorhombic; $P2_12_12_1$; $a$ = 15.7481(2), $b$ = 31.2188(5), $c$ = 33.7366(4) Å; $V$ = 16586.2(4) Å$^3$; $Z$ = 4; $\rho_{calcd}$ = 1.278 Mg m$^{-3}$; $\lambda$(Cu-K$_\alpha$) = 1.54184 Å; $\mu$ = 4.116 mm$^{-1}$;

$F(000)$ = 6676; $T$ = 150 K; 1748 variables and 29211 observations with $I > 2.0\sigma(I)$; calcd $w = 1/[\sigma^2(F_o^2) + (0.2000P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$ with the resulting $R$ = 0.1236, $R_W$ = 0.3546, and $S_w$ = 1.531; $\Delta\rho < 2.960$ e Å$^{-3}$. CCDC 1400713.†

§ In the helical superstructures of **13**, the CD complexes are only connected to each other *via* the encapsulated ''PdCl($NC_6H_4$)'' subunits without extra hydrogen bonds involving the macrocyclic moieties as usually observed in existing CD-based supramolecular helices.

¶ Similar intra-cavity weak hydrogen bonds involving a metal-bound anion and an aromatic proton of a neighbouring CD complex have already been observed. They result in the formation of columnar, yet non-helical arrangements (see ref. 13).

‖ Crystal data for $C_{69}H_{116}Cl_6N_2O_{33}Pd$, $M_\Gamma$ = 1820.73; orthorhombic; $P2_12_12$; $a$ = 28.2881(8), $b$ = 29.3527(8), $c$ = 10.8184(3) Å; $V$ = 8982.9(4) Å$^3$; $Z$ = 4; $\rho_{calcd}$ = 1.346 Mg m$^{-3}$; $\lambda$(Cu-K$_\alpha$) = 1.54178 Å; $\mu$ = 3.976 mm$^{-1}$; $F(000)$ = 3824; $T$ = 173 K; 1045 variables and 11401 observations with $I > 2.0\sigma(I)$; calcd $w = 1/[\sigma^2(F_o^2) + (0.0475P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$ with the resulting $R$ = 0.0575, $R_W$ = 0.1365, and $S_w$ = 1.048; $\Delta\rho < 0.555$ e Å$^{-3}$. CCDC 1546409.†

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