Metal-driven ligand assembly in the synthesis of cyclodextrin [2] and [3]rotaxanes†

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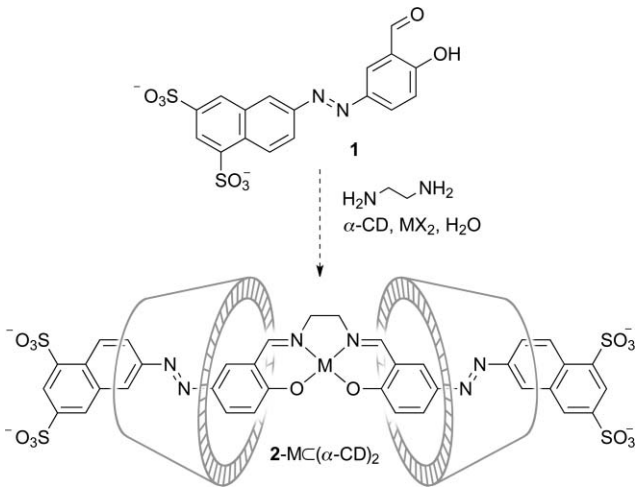
Cyclodextrin [2] and [3]rotaxanes have been synthesised by use of a metal-driven ligand formation methodology. The kinetically stable cobalt(III) complexes formed act as either linking or capping groups, the function being selected by manipulation of the reaction conditions to promote the formation of either 2 : 1 or 1 : 1 complexes, respectively. In all cases, mixtures of isomers containing different α-cyclodextrin orientations were observed. All three orientational isomers of the [3]rotaxane were isolated and structurally characterized by 2D NMR.

Introduction

The use of transition metals to direct the formation of supramolecular structures, such as rotaxanes and catenanes,[1] has been widely investigated due to the potential applications of these structures as nano-mechanical devices.[2] Often metal ions have been used to preorganise molecular components so that they react to form interlocked structures. This template-directed strategy can be very efficient, producing mechanically interlocked molecular architectures in good yield. Cyclodextrin-based rotaxanes[3] have generally been synthesized through hydrophobic binding rather than metal-directed assembly. Metal complexes have therefore been limited to capping groups,[4] with the exception of some polydisperse polyrotaxane structures in which metal complexes act as bridges.[5] Herein, we report the synthesis of kinetically stable cyclodextrin [2]rotaxanes and [3]rotaxanes, where metal complexation serves to drive the *in-situ* formation of the ligand and traps the cyclodextrins to form rotaxanes.



Scheme 1 Proposed synthesis of a metallosalen-based [3]rotaxane.

Results and discussion

The original aim of this project was to synthesise salen-bridged rotaxanes (Scheme 1). In order to utilize hydrophobic interactions to form the inclusion complexes, the synthesis was performed in aqueous solution and we hoped to use metal complexation to drive the assembly of the salen bridge. The aqueous synthesis of salen complexes has been reported, and this reaction has been used to link double stranded DNA.[6] Metallo-salen complexes and their derivatives have found use as catalysts in various asymmetric reactions, most notably cobalt(III) in the ring-opening of epoxides,[7] and the presence of the cyclodextrins (CDs) would be expected to control the approach of substrates to the catalytic site in a [3]rotaxane such as **2**-M⊂(α-CD)$_2$.

The reaction shown in Scheme 1 was initially tested in the absence of α-CD using cobalt(II). When an aqueous solution of cobalt(II) acetate is added to a red solution of azo dye aldehyde **1** (prepared by azo coupling of salicylaldehyde to the naphthyl diazonium salt) and ethylene diamine (EDA) the solution immediately becomes dark brown. One major product is observed by reversed-phase HPLC under a number of reaction conditions. ESMS analysis of the reaction mixture indicates that a bissalicylideneimine **3**$_2$-Co complex is formed (Scheme 2), rather than a salen complex. Several other metal salts ($FeCl_2$, $FeCl_3$, $Cr(OAc)_3$, $ZnCl_2$ and $NiCl_2$) were also screened to assess their ability to drive the assembly, but only Zn(II) was found to be moderately successful, requiring the use of excess EDA and $ZnCl_2$ to drive the formation. ESMS analysis again showed the formation of the **3**$_2$-Zn complex (Fig. 1).

The labilities of the two dumbbell compounds were tested by monitoring changes in the UV-vis spectra upon addition of α-CD to **3**$_2$-Co and **3**$_2$-Zn in aqueous solution. It was found that **3**$_2$-Co is kinetically inert, showing no significant binding to α-CD over several hours, whereas **3**$_2$-Zn is labile, allowing immediate formation of the pseudo-[3]rotaxane **3**$_2$-Zn⊂(α-CD)$_2$. The observed changes were instantaneous upon addition of α-CD, allowing the determination of the equilibrium constant for this process: $K = (7.1 \pm 0.9) \times 10^3\ M^{-1}$. The kinetic stability of the

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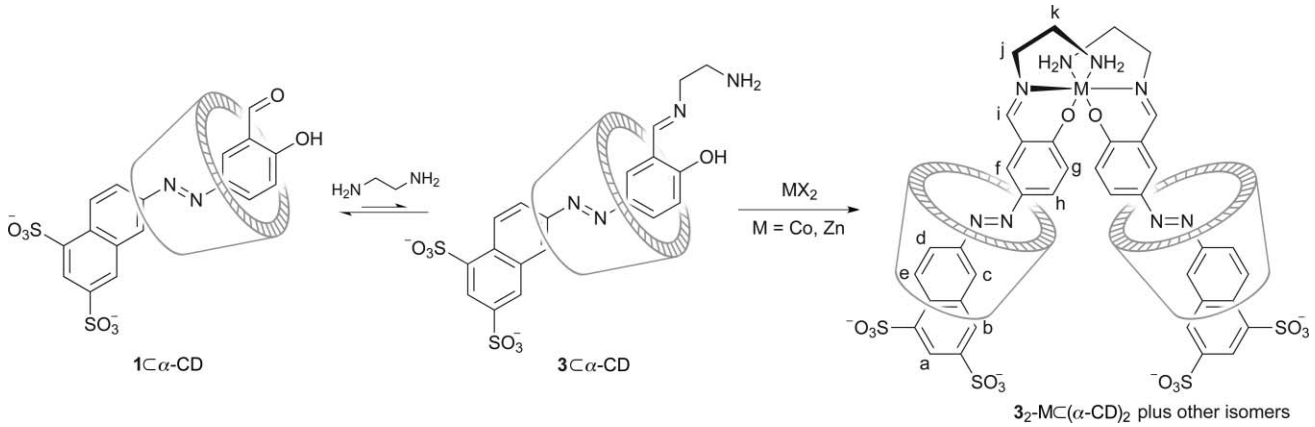
† Electronic supplementary information (ESI) available: complexation studies of **1**, **3** and **3**$_2$-Zn and NOESY characterisation of the rotaxanes. See DOI: 10.1039/b616621k



Scheme 2 Formation of a metal-coordination linked [3]rotaxane in aqueous solution.

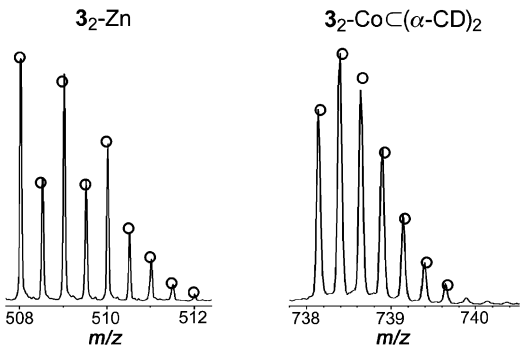


Fig. 1 ESMS analysis of $\mathbf{3}_2$-Zn ([M + 2H]$^{2-}$) and $\mathbf{3}_2$-Co⊂(α-CD)$_2$ (M^{4-}), showing observed spectra and calculated isotopic distributions (circles).

cobalt complex is due to the *in-situ* oxidation of the labile Co(II) to the inert Co(III) under the basic reaction conditions. The sharp ^{1}H NMR spectrum in d_6-DMSO (Fig. 2) also confirms that it is a diamagnetic Co(III) complex rather than a paramagnetic Co(II) complex. The use of this metal should therefore enable the kinetic trapping of the inclusion complex **3**⊂α-CD to form a [3]rotaxane.

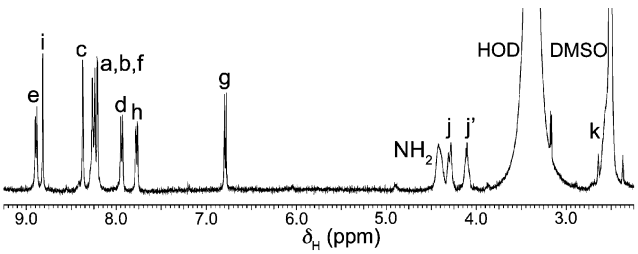


Fig. 2 ^{1}H NMR (500 MHz, d_6-DMSO) of the $\mathbf{3}_2$-Co dumbbell (assignment based on the labelling system in Scheme 2. Signal k' is obscured by the DMSO solvent signal).

Many bissalicylideneimine cobalt(III) complexes have been characterized crystallographically[8] and shown to adopt a meridional structure, so it seemed likely that $\mathbf{3}_2$-Co would have the same geometry about the Co atom and this was confirmed by ^{1}H NMR analysis (Fig. 2). The two CH_2 groups of the $\mathbf{3}_2$-Co dumbbell (H_j and H_k) each gave two sets of diastereotopic protons, consistent with the fixed conformation about the metal ion. The ^{1}H NMR spectrum of $\mathbf{3}_2$-Zn is simpler, with no evidence of diastereotopic protons, suggesting that the complex is labile in d_6-DMSO.

^{1}H NMR analysis (D_2O, 298 K, [**1**] = 46 mM) showed that the position of the equilibrium between aldehyde **1** and imine **3** is sensitive to the presence of α-CD. For example, in the absence of α-CD two equivalents of EDA is sufficient to give 90% conversion to imine **3**. In the presence of two equivalents of α-CD, however, very little change was observed upon addition of two equivalents of EDA. Evidently imine **3** has a lower affinity for α-CD than aldehyde **1**, however the addition of half an equivalent of $Co(OAc)_2$ gave 75% conversion to a mixture of the [2] and [3]rotaxanes, showing that metal complexation can drive the formation of $\mathbf{3}_2$-Co. Further optimization of the reaction showed that efficient conversion to $\mathbf{3}_2$-Co [3]rotaxanes can be achieved by using two equivalents of EDA, three equivalents of α-CD, and half an equivalent of $Co(OAc)_2$, giving $\mathbf{3}_2$-Co⊂(α-CD)$_2$ in 70% conversion (determined by HPLC analysis and ESMS; Fig. 1). Thus, by harnessing both hydrophobic and coordination interactions, efficient formation of a [3]rotaxane can be achieved from a seven component mixture.

^{1}H NMR analysis in D_2O of the [3]rotaxane $\mathbf{3}_2$-Co⊂(α-CD)$_2$ produced from this reaction shows that it is a mixture of stereoisomers. The cone-shaped α-CD leads to the formation of three isomers, based on the orientation of the two α-CD rings relative to each other. We were unable to resolve these isomers by reverse-phase HPLC, but preparative anion exchange chromatography enabled the three isomerically pure [3]rotaxanes to be isolated with head–head $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*hh* (11%), head–tail $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*ht* (38%), and tail–tail $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*tt* (2%) orientations (Fig. 3). Integration of the signals in the NMR of the initial mixture indicated these isomers formed in a ratio of 1 : 1.5 : 0.7 (*hh* : *ht* : *tt*). This is close to the expected statistical ratio, 1 : 2 : 1 (*hh* : *ht* : *tt*), though there is evidently bias towards the head–head structure, with the 5,6-rim near the naphthalene stopper. This same bias is present to a greater extent in the inclusion complex **1**⊂α-CD. ^{1}H NMR analysis shows that there is slow exchange between the two threading orientations of **1**⊂α-CD, with a 2 : 1 preference in favour of the isomer with the 5,6-rim towards the sulfonate groups, which would imply a 4 : 4 : 1 mixture of the [3]rotaxane isomers (*hh* : *ht* : *tt*). Molecular modeling indicates that the meridional geometry about the Co brings the α-CDs into contact (Fig. 4),

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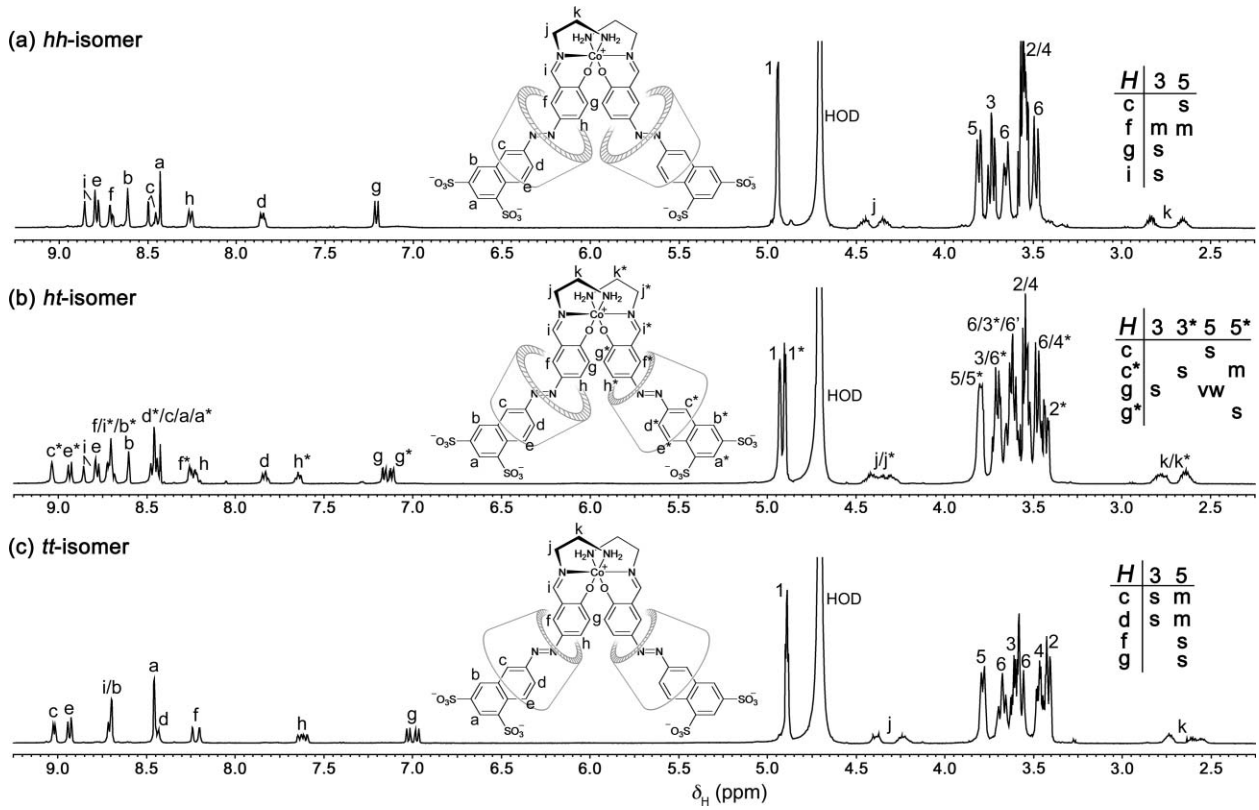

Fig. 3 ^{1}H NMR (500 MHz, D_2O) and selected cyclodextrin–aromatic NOE interactions of (a) $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*hh*, (b) $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*ht* and (c) $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*tt* [cyclodextrin numbering begins at the anomeric position and ends at the primary hydroxyl; s = strong, m = medium, vw = very weak].

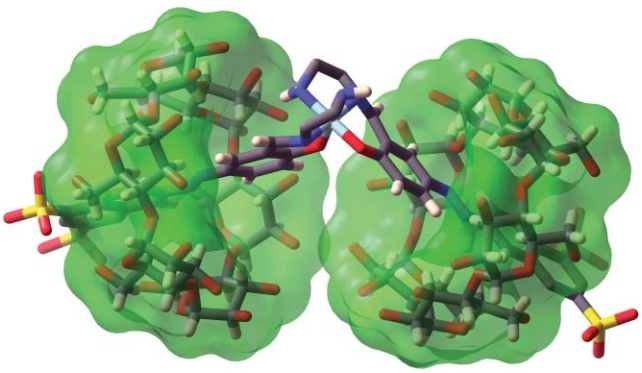

Fig. 4 Molecular model of $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*hh* (calculated geometry).

suggesting that the steric interaction may destabilize $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*hh* and $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*ht* relative to $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*tt*.

The orientations of the α-CD macrocycles in the three isomers were determined by 2D NOESY analysis. In $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*hh*, for example, the naphthalene proton H_d shows strong NOEs to H_5 and H_6 on the narrow rim of the α-CD, whereas H_g shows an NOE to H_3, confirming that the 2,3-rim of the α-CD is oriented towards the metal complex. Conversely, H_d of $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*tt* shows a strong NOE to H_3 (and H_g to H_5 and H_6) so that the 5,6-rim is oriented towards the metal complex. $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*ht* shows both sets of NOE correlations as the α-CD rings have opposite orientations to one another.

The ^{1}H NMR spectra of the isomers also reveal some splitting of the signals, the magnitude of which varies between the isomers. This splitting arises because of the chiral natures of the cyclodextrin and the octahedral Co(III) complex; each rotaxane isomer (*hh*, *ht* or *tt*) consists of a mixture of two diastereomers with different chirality at the cobalt center. The effect is most clearly seen in the ^{1}H NMR spectrum of $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*tt* (Fig. 3(c)), in which H_f, H_g and H_h are each split into two peaks separated by at least 0.04 ppm. These diastereomers are not formed in equal amounts for $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*hh* and $\mathbf{3}_2$-Co⊂(α-CD)$_2$-*ht*, which were found to have diastereomeric excesses of 25 and 20% respectively (determined by integration of the ^{1}H NMR signals), showing that there is some enantioselectivity in the formation of the metal complex. Close inspection of the 2D NOESY spectra shows that the α-CD ring threads further over the imine proton from the wider 3-end, indicating that this selectivity arises from the closer proximity of the α-CD to the metal complex when the 3-rim is oriented towards the ligating end of the molecule.

During the synthesis of the [3]rotaxane $\mathbf{3}_2$-Co⊂(α-CD)$_2$, another peak was also seen in the HPLC analysis that corresponds to a more hydrophilic molecule. Its UV-vis spectrum resembles those of the [3]rotaxanes, suggesting that it may be another metal complex rotaxane. This species was isolated as one isomer during the purification of $\mathbf{3}_2$-Co⊂(α-CD)$_2$ and shown to be the 1 : 1 complex **3**-Co(EDA)(H_2O)⊂α-CD-*h* by ^{1}H NMR and ESMS (Fig. 5). The presence of the coordinated EDA ligand was confirmed by the appearance of four diastereotopic protons in the ^{1}H NMR spectrum, consistent with two conformationally restricted CH_2

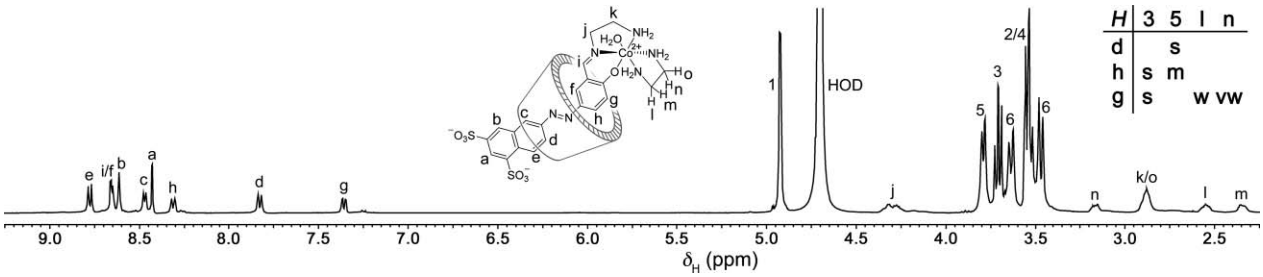

Fig. 5 ^{1}H NMR (500 MHz, D_2O) and selected NOE interactions of **3**-Co(EDA)(H_2O)⊂α-CD-*h* (s = strong, m = medium, w = weak, v = very weak).

groups in an asymmetric environment. Further evidence was provided by the observation of weak NOEs from H_g to the axial protons (H_l and H_n) of the two CH_2 groups. Optimization of the reaction conditions showed that this [2]rotaxane could be synthesized in 84% conversion (by HPLC) using an excess of both EDA (14 equiv.) and $Co(OAc)_2$ (8 equiv.) at a lower concentration of **1** (23 mM) with three equivalents of α-CD. Purification by anion exchange chromatography enabled **3**-Co(EDA)(H_2O)⊂α-CD to be isolated as a 2 : 1 mixture of the head and tail isomers in 59% yield. This observed 2 : 1 ratio of isomers is in agreement with the argument that steric interactions between the two α-CDs in $\mathbf{3}_2$-Co⊂(α-CD)$_2$ lead to destabilisation of the *hh* and *ht* isomers relative to the *tt*.

Conclusions

We have discovered a facile and efficient method of forming cyclodextrin rotaxanes *via* the *in-situ* formation of a salicylideneimine ligand and complexation to a cobalt ion. By manipulating the reaction conditions, the metal complex formed can either act as a stopper to give [2]rotaxanes, or as a linking group to give [3]rotaxanes. For the first time it has been possible to isolate and structurally characterise all three orientational isomers of a cyclodextrin [3]rotaxane. This chemistry forms a valuable addition to the methodology for creating threaded architectures such as rotaxanes and catenanes.

Experimental

All materials and reagents were purchased from commercial sources. ^{1}H and ^{13}C NMR spectra were recorded at 298 K on a Brüker AV500 spectrometer with a $^{13}C\{^1H\}$ cryoprobe. NOE experiments were carried out on Brüker DRX500 and AV500 spectrometers (NOESY mixing time: 400 ms, 298 K). ^{1}H NMR studies of the pre-complexation equilibria were performed on a Brüker DPX250 spectrometer. High resolution ESI-MS was carried out on a Brüker MicroTof platform (resolution: 10000 FHM). UV-vis analyses were performed on a Perkin-Elmer Lambda-6 spectrometer. HPLC analyses were carried out on an Agilent HP1100 workstation equipped with a diode-array detector, using a Zorbax Eclipse XDB C8 column (4.6 × 25 mm, 5 μm particle size) and a two solvent gradient system (solvent A = aqueous dicyclohexylammonium phosphate (2.5 g l^{-1}) and solvent B = methanol). Dialysis was carried out in an Amicon 8200 Ultrafiltration cell using Amicon Millipore 1000 MWCO ultrafiltration membranes at 4 bar N_2 pressure.

Azo salicylaldehyde 1 sodium salt

-Aminonaphthalene-1,3-disulfonic acid disodium salt (75.0 g, 0.22 mol) was dissolved in H_2O (200 ml), cooled to 0 °C and conc. HCl (40 ml, 12 M) was added. $NaNO_2$ (14.5 g, 0.22 mol) was dissolved in H_2O (10 ml) and added slowly until a positive starch iodide paper test was obtained, keeping the temperature below 5 °C. Salicylaldehyde (22.7 ml, 0.21 mol) was dissolved in basic water (pH 9, 50 ml) and cooled to 0 °C. The diazonium solution was added slowly, keeping the pH around 4.5 with 2 M NaOH. Once addition was complete, the mixture was stirred overnight. The product was salted out by the addition of NaCl solid (100 g l^{-1}). The resultant slurry was filtered and the solid was dialyzed for 6 h using cellulose tubing (MWCO 12000, Sigma). The solvent was then removed to give aldehyde **1** as an orange solid (38.0 g, 36%); λ_{max}(H_2O)/nm (ε/dm^3 mol^{-1} cm^{-1} 22900); δ_H(500 MHz, D_2O) 6.34 (d, ^3J 8.8), 7.05 (1 H, d, ^4J 2.1), 7.12 (1 H, dd, ^3J 8.8, ^4J 2.1), 7.51 (1 H, dd, ^3J 9.1, ^4J 1.3), 7.60 (1 H, s), 7.94 (1 H, s), 8.08 (1 H, s), 8.26 (1 H, d, ^3J 9.1), 9.26 (1 H, s); δ_C(125 MHz, D_2O) 117.7, 118.9, 119.5, 123.3, 126.5, 127.7, 128.4, 129.4, 129.6, 129.8, 133.1, 139.4, 139.6, 143.5, 148.7, 162.2, 196.0 ppm; *m*/*z* (ESI) 434.9971 (calculated for $C_{17}H_{11}N_2O_8S_2^-$ (M^-) 434.9951).

Dumbbell $\mathbf{3}_2$-Co ammonium salt

Aldehyde **1** (500 mg, 1.04 mmol) and ethylene diamine (71 μl, 1.04 mmol) were dissolved in H_2O (23 ml). $Co(OAc)_2{\cdot}4H_2O$ (259 mg, 1.04 mmol) was dissolved in H_2O (1.0 ml) and added dropwise to the mixture giving a dark brown solution. After 20 minutes, the solution was dialyzed through a 1000 MWCO cellulose membrane under 4 bar N_2 pressure with H_2O for 1 day (2 l). After concentration to 100 ml, aqueous ammonia (10 ml) was added and dialysis continued for a further two days (4 l). Removal of the solvent under reduced pressure and drying under vacuum at 60 °C gave the ammonium salt of $\mathbf{3}_2$-Co as a black solid (308 mg, 56%); λ_{max}(H_2O)/nm 400 (ε/dm^3 mol^{-1} cm^{-1} 54800); δ_H(500 MHz, d_6-DMSO) 2.56 (4 H, br s), 4.06–4.15 (2 H, m), 4.26–4.34 (2 H, m), 4.42 (4 H, br s), 6.79 (2 H, d, ^3J 9.2), 7.77 (2 H, dd, ^3J 9.2, ^4J 1.8), 7.94 (d, 9.3 Hz, 2H), 8.21 (2 H, d, ^4J 1.8), 8.24 (2 H, s), 8.26 (2 H, s), 8.37 (2 H, s), 8.82 (2 H, s), 8.89 (2 H, d, ^3J 9.3); δ_C(125 MHz, d_6-DMSO) 43.9, 61.2, 116.6, 119.1, 123.3, 124.0, 125.4 (2 × C), 126.3, 128.7, 129.7 (2 × C), 133.5 (2 × C), 133.9, 141.9, 149.5, 166.3, 168.4; *m*/*z* (ESI) 505 ([M + H]$^{2-}$).

Dumbbell $\mathbf{3}_2$-Zn ethylene diamine salt

Aldehyde **1** (5.0 g, 10.4 mmol) and ethylene diamine (7.0 ml, 104 mmol) were dissolved in H_2O (100 ml). $ZnCl_2$ (7.2 g,

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52.0 mmol) was added to give a bright orange viscous solution. The product was precipitated by the addition of EtOH, filtered and washed with EtOH and Et_2O. Drying at 40 °C gave **3**$_2$-Zn as a bright orange solid (3.0 g, 57%); $\lambda_{max}(H_2O)$/nm 401 (ε/dm^3 mol^{-1} cm^{-1} 42700); δ_H(500 MHz, d_6-DMSO) 2.67 (4 H, br s), 2.84 (4 H, br s), 3.25 (4 H, br s), 3.56 (4 H, t, ^3J 5.3), 6.72 (2 H, d, ^3J 8.9), 7.89 (2 H, dd, ^3J 8.9, ^4J 2.4), 7.94 (2 H, dd, ^3J 9.3, ^4J 1.8), 7.97 (2 H d, ^4J 2.2), 8.25 (2 H, s), 8.28 (2 H, d, ^4J 1.6), 8.33 (2 H, d, ^4J 1.8), 8.61 (2 H, s), 8.89 (2 H, d, ^3J 9.3); δ_C(125 MHz, d_6-DMSO) 40.1, 55.7, 116.8, 118.8, 123.7, 123.9, 124.8, 125.5, 126.2, 128.6, 129.3, 133.5, 135.2, 140.6, 143.9, 144.9, 149.8, 167.8, 174.7 ppm; *m/z* (ESI) 508.02 ([M + 2H]$^{2-}$.

[3]Rotaxanes 3$_2$-Co⊂(α-CD)$_2$ ammonium salt

Aldehyde **1** (50 mg, 104 μmol), α-cyclodextrin (306 mg, 314 μmol), and ethylene diamine (14 μl, 208 μmol) were dissolved in H_2O (2.3 ml), before $Co(OAc)_2{\cdot}4H_2O$ (13 mg, 52 μmol) was added to give a dark brown solution. After 20 minutes, the mixture was loaded onto an anion exchange resin (DEAE cellulose, Whatman) and washed with H_2O (500 ml) till it ran clear. The [2]rotaxane **3**-Co(EDA)(H_2O)⊂(α-CD)-*h* was eluted with aqueous $(NH_4)_2CO_3$ (5 g l^{-1}) till clear. **3**$_2$-Co⊂(α-CD)$_2$-*tt* was eluted with aqueous $(NH_4)_2CO_3$ (7.5 g l^{-1}) till clear, followed by **3**$_2$-Co⊂(α-CD)$_2$-*ht* with aqueous $(NH_4)_2CO_3$ (10 to 15 g l^{-1}, 1 l). The salt concentration was increased in further 5 g l^{-1} increments (500 ml) until **3**$_2$-Co⊂(α-CD)$_2$-*hh* eluted with 30 to 35 g l^{-1} aqueous $(NH_4)_2CO_3$ (1.5 l). The three isomers were then further purified by removal of the solvents and flushing through a small pad of reverse phase silica (C18, Aldrich) with H_2O. Solvent removal under reduced pressure and drying under vacuum at 60 °C gave the pure [3]rotaxanes as the ammonium salts.

3$_2$-Co⊂(α-CD)$_2$-*hh*: brown solid (17.4 mg, 11%); $\lambda_{max}(H_2O)$/nm 410 (ε/dm^3 mol^{-1} cm^{-1} 63700); δ_H(500 MHz, D_2O) 2.61–2.70 (4 H, m), 2.79–2.88 (4 H, m), 3.46–3.51 (24 H, m), 3.52–4.58 (48 H, m), 3.62–3.69 (24 H, m), 3.70–3.77 (24 H, m), 3.81 (24 H, d, ^3J 9.6), 4.30–4.39 (4 H, m), 4.41–4.49 (4 H, m), 4.94 (24 H, d, ^3J 3.2), 7.21 (4 H, d, ^3J 9.1), 7.85 (4 H, m), 8.26 (4 H, m), 8.43 (4 H, m), 8.46 (2 H, s), 8.50 (2 H, s), 8.61 (4 H, s), 8.70 (2 H, d, ^4J 1.9), 8.72 (2 H, d, ^4J 2.0), 8.77–8.82 (6 H, m), 8.86 (2 H, s); δ_C(125 MHz, D_2O) 16.8, 43.1, 57.4, 59.8, 60.9, 71.61, 71.63, 71.9, 73.6, 81.1, 101.8, 117.4, 117.6, 118.37, 118.43, 123.5, 124.5, 124.8, 127.5, 128.6, 129.0, 129.9, 130.1, 134.0, 138.4, 138.7, 140.18, 140.21, 140.25, 140.28, 143.1, 143.2, 150.0, 150.1, 166.0, 167.3, 167.5; *m/z* (ESI) 738.39 (M^{4-}).

3$_2$-Co⊂(α-CD)$_2$-*ht*: brown solid (48.1 mg, 38%); $\lambda_{max}(H_2O)$/nm 412 (ε/dm^3 mol^{-1} cm^{-1} 69200); δ_H(500 MHz, D_2O) 2.58–2.69 (4 H, m), 2.71–2.85 (4 H, m), 3.43 (12 H, dd, ^3J 9.8, ^3J 3.2), 3.45–3.50 (24 H, m), 3.51–.57 (24 H, m), 3.58–3.67 (36 H, m), 3.67–3.75 (24 H, m), 3.76–3.85 (24 H, m), 4.24–4.47 (8 H, m), 4.90 (12 H, d, ^3J 3.2), 4.93 (12 H, br s), 7.09–7.13 (12 H, m), 7.14–7.18 (2 H, m), 7.62–7.67 (2 H, m), 7.81–86 (2 H, m), 8.21–8.28 (4 H, m), 8.42 (1 H, d, ^4J 1.3), 8.43–8.48 (4 H, m), 8.48 (1 H, s), 8.60 (2 H, s), 8.68–8.73 (6 H, m), 8.76–8.80 (3 H, m), 8.86 (1 H, s), 8.93 (2 H, d, ^3J 9.3), 9.03 (2 H, s); δ_C(125 MHz, D_2O) 16.8, 30.2, 42.55,42.60, 42.9, 43.0, 57.4, 59.8, 60.3, 60.9, 71.57, 71.60, 71.7, 71.8, 71.9, 73.4, 73.6, 81.1, 81.2, 81.3, 101.8, 101.9, 117.4, 117.6, 118.3, 118.4, 118,9, 118.96, 119.02, 122.7, 123.2, 123.3, 123.5, 123.6, 123.9, 124.5, 124.9, 127.2, 127.5, 127.8, 128.5, 128.8, 129.3, 129.9, 130.07, 130.10, 130.3, 133.5, 133.98, 134.00, 137.8, 138.0, 138.3, 138.9, 140.2, 140.3, 140.37, 140.42, 142.80, 142.83, 143.1, 143.2, 150.0, 150.1, 166.0, 167.0, 167.06, 167.14, 167.30, 167.34, 167.36; *m/z* (ESI) 738.91 (M^{4-}).

3$_2$-Co⊂(α-CD)$_2$-*tt*: brown solid (2.9 mg, 2%); $\lambda_{max}(H_2O)$/nm 414 (ε/dm^3 mol^{-1} cm^{-1} 55900); δ_H(500 MHz, D_2O) 2.51–2.64 (4 H, m), 2.69–2.78 (4 H, m), 3.38–3.44 (24 H, m), 3.44–3.50 (24 H, m), 3.53–3.64 (48 H, m), 3.64–3.72 (24 H, m), 3.75–3.82 (24 H, m), 4.18–4.28 (4 H, m), 4.34–4.43 (4 H, m), 4.89 (24 H, m), 6.97 (2 H, d, ^3J 9.3), 7.02 (2 H, d, ^3J 9.2), 7.60 (2 H, dd, ^3J 9.2, ^4J 1.9), 7.64 (2 H, dd, ^3J 9.3, ^4J 1.6), 8.20 (2 H, d, ^4J 1.6), 8.24 (2 H, d, ^4J 1.9), 8.43 (4 H, s), 8.46 (4 H, d, ^4J 1.5), 8.67–8.74 (8 H, m), 8.93 (4 H, d, ^3J 9.3) 9.01 (2 H, s), 9.03 (2 H, s); δ_C(125 MHz, D_2O) 42.0, 42.2, 60.2, 60.3, 61.1, 61.4, 71.8, 71.9, 73.4, 81.2, 81.3, 101.9, 118.9, 119.0, 122.8, 123.16, 123.24, 123.3, 123.6, 127.2, 129.2, 130.1, 130.17, 130.24, 133.4, 137.5, 137.8, 140.37, 140.42, 142.5, 142.7, 150.1, 167.1, 167.5, 167.7; *m/z* (ESI) 738.41 (M^{4-}).

3-Co(EDA)(H_2O)⊂α-CD-*h*: brown solid (10.3 mg, 16%); $\lambda_{max}(H_2O)$/nm 405 (ε/dm^3 mol^{-1} cm^{-1} 26400); δ_H(500 MHz, D_2O) 2.30–2.39 (2 H, m), 2.50–2.59 (2 H, m), 2.82–2.95 (6 H, m), 3.13–3.20 (2 H, m), 3.43–3.50 (12 H, m), 3.50–3.57 (24 H, m), 3.60–3.66 (12 H, m), 3.68–3.74 (12 H, m), 3.79 (12 H, d, ^3J 9.5), 4.22–4.38 (4 H, m), 4.92 (12 H, d, ^3J 3.2), 7.33–7.38 (2 H, m), 7.83 (2 H, dd, ^3J 9.3, ^4J 1.2), 8.31 (2 H, d, ^3J 9.1), 8.43 (2 H, d, ^4J 1.5), 8.47 (1 H, d, ^4J 1.2), 8.48 (1 H, d, ^4J 1.2), 8.61 (2 H, s), 8.78 (2 H, d, ^3J 9.3); δ_C(500 MHz, D_2O) 42.6, 43.5, 43.6, 45.4, 45.5, 59.7, 61.6, 61.7, 71.5, 71.6, 73.6, 81.2, 101.8, 117.25, 117.33, 123.5, 123.7, 124.5, 127.5, 128.9, 129.9, 130.1, 134.0, 138.9, 140.2, 140.3, 143.00, 143.02, 149.9, 167.2, 167.28, 168.33; *m/z* (ESI) 782.16 ([M − H_2O − H]$^{2-}$).

[2]Rotaxanes 3-Co(EDA)(H_2O)⊂α-CD

1 (100 mg, 208 μmol), α-cyclodextrin (612 mg, 629 μmol) and ethylene diamine (200 ml, 2.96 mmol) were dissolved in H_2O (9.0 ml), before $Co(OAc)_2{\cdot}4H_2O$ (416 mg, 1.67 mmol) was added. After 20 minutes, the mixture was loaded onto an anion exchange resin (DEAE cellulose, Whatman) and eluted with H_2O, collecting once the excess α-cyclodextrin and $Co(OAc)_2$ had run off. The fractions containing the product were combined, concentrated and passed through a small pad of reverse phase silica (C18, Aldrich). The solvent was removed and drying under vacuum at 60 °C gave a 2 : 1 mixture of **3**-Co(EDA)(H_2O)⊂α-CD-*h* and **3**-Co(EDA)(H_2O)⊂α-CD-*t* as a black solid (195 mg, 59%); δ_H(500 MHz, D_2O) 2.27–2.38 (3 H, m), 2.46–2.60 (3 H, m), 2.80–2.95 (9 H, m), 3.13–3.22 (3 H, m), 3.40–3.44 (6 H, m), 3.44–3.50 (18 H, m), 3.50–3.58 (24 H, m), 3.58–3.66 (24 H, m), 3.66–3.74 (18 H, m), 3.75–3.83 (18 H, m), 4.21–4.39 (6 H, m), 4.31 (6 H, d, ^3J 3.2), 4.92 (12 H, d, ^3J 3.3), 7.27–7.32 (1 H, m), 7.33–7.40 (2 H, m), 7.69 (1 H, dd, ^3J 9.1, ^4J 1.6), 7.82 (2 H, dd, ^3J 9.3, ^4J 1.0), 8.18–8.25 (1 H, m), 8.31 (2 H, d, ^3J 9.1), 8.39–8.49 (6 H, m), 8.53–8.57 (1 H, m), 8.61 (2 H, s), 8.66 (4 H, br s), 8.70 (1 H, s), 8.77 (2 H, d, ^3J 9.3), 8.92 (1 H, d, ^3J 9.2), 9.04 (1 H, s); δ_C(125 MHz, D_2O) 42.6, 43.5, 45.1, 45.3, 59.7, 60.3, 61.6, 71.4, 71.5, 71.58, 71.60, 71.80, 71.83, 73.4, 73.6, 81.2, 81.3, 101.8, 101.9, 117.2, 117.30, 117.31, 118.11, 118.14, 118.8, 122.6, 122.7, 123.5, 123.6, 123.7, 123.8, 124.2, 124.5, 127.2, 127.5, 128.87, 128.91, 129.3, 129.9, 130.1, 130.3, 133.4, 134.0, 138.0, 138.1, 138.9, 140.2, 140.3, 140.40,

140.43, 142.8, 143.00, 143.02, 149.9, 150.1, 167.2, 167.3, 168.30, 168.32; m/z (ESI) 782.14 ($[M - H_2O - H]^{2-}$).

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