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Orientational isomers of α-cyclodextrin [2]semi-rotaxanes with asymmetric dicationic threads†

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Two series of novel dicationic threading molecules $[Quin(CH_2)_{10}R]^{2+}$ and $[3,5\text{-}Lut(CH_2)_{10}R]^{2+}$, where $Quin^+$ = quinuclidinium, $3,5\text{-}Lut^+$ = 3,5-lutidinium, and $R^+ = N(CH_3)_3^+$ and $N(CH_3)_2CH_2CH_3^+$, form [2]semi-rotaxanes with α-cyclodextrin (α-CD) in aqueous solution. The quinuclidinium and 3,5-lutidinium are sufficiently bulky to prevent threading while the R^+ groups allow for slow threading by α-CD at 25 °C. The resulting [2]semi-rotaxanes exist in two orientational isomers owing to the asymmetry of both the α-CD cavity and the threading molecules. Two-dimensional ^{1}H NMR spectroscopy and kinetics experiments reveal that the isomer in which the narrower rim (primary OHs) is positioned near the R^+ group is the kinetically preferred isomer, while the other isomer is the thermodynamically preferred product. The kinetics and mechanism of the formation, dissociation, and interconversion of the two isomers have been determined at 25 °C.

Introduction

Rotaxanes[1,2] are supramolecular complexes comprised of a cyclic molecular bead threaded by a linear chain which is stoppered by bulky end units, which prevent the complex from dissociating into its cyclic and linear molecular components. A large number of [2]rotaxanes ([*n*] designates the number of cyclic and linear components) have been assembled employing a variety of cyclic components, including the cyclodextrins (CDs),[3] a series of cyclic oligosaccharides normally consisting of six (α-CD), seven (β-CD), or eight (γ-CD) α-(1→4)-linked D-(+)-glucopyranose units. Possessing hydrophobic interior cavities and hydrophilic rims, bearing primary and secondary hydroxyl groups, these host molecules are capable of forming stable inclusion complexes with hydrophobic organic compounds in aqueous solution.[4] Pseudorotaxanes, in which the end units are not sufficiently bulky to prevent the dissociation of the cyclic and linear components, and rotaxanes of cyclodextrins have been prepared using a variety of organic and transition metal complex end groups.[5,6] The majority of cyclodextrin rotaxanes have symmetrical threads,[7–10] such that there is only one orientation of the CD with respect to the thread. Rotaxanes that are threaded by a linear chain bearing two different stopper units may exist as two orientational isomers owing to the asymmetry of the cyclodextrin.[10c,11–16] In some cases, only one of the orientational isomers is observed, while in other rotaxane systems, there is a slight preference observed for one isomer over the other. Isnin and Kaifer reported the preparation of orientational isomers of a zwitterionic α-CD [2]rotaxane with ferrocenyl methyl and naphthalenesulfonate stoppers.[11] In a recent report, an α-CD [2]rotaxane with a thread composed of a central azobenzene and two different bulky naphthalimide end groups was prepared by a Suzuki coupling in the presence of α-CD.[16] A ROESY NMR spectrum confirmed the presence of only one orientational isomer. Anderson and co-workers have reported the assembly of [2]- and [3]-rotaxanes of α-cyclodextrin with asymmetric cyanine dye threads.[14a,b] While the [2]rotaxanes show a slight preference for one orientation, the [3]rotaxane is found in only one isomer, with the narrow rims of the two cyclodextrins facing each other. They also have prepared a [2]rotaxane of an asymmetric chlorotriazine-functionalized azo dye with hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin, which exhibits a single isomer,[14c] which is attributed to the extremely strong binding between the cyclodextrin and the azo dye amine precursor.

In this study a series of [2]semi-rotaxanes of α-cyclodextrin have been assembled in aqueous solution using the following dicationic threads (Fig. 1): $[3,5\text{-}Lut(CH_2)_{10}N(CH_3)_3]^{2+}$ (**1**), $[3,5\text{-}Lut(CH_2)_{10}N(CH_3)_2CH_2CH_3]^{2+}$ (**2**) (where $3,5\text{-}Lut^+$ = 3,5-lutidinium), $[Quin(CH_2)_{10}N(CH_3)_3]^{2+}$ (**3**), and $[Quin(CH_2)_{10}N(CH_3)_2CH_2CH_3]^{2+}$ (**4**) (where $Quin^+$ = quinuclidinium). Both of the spherical $Quin^+$ and planar $3,5\text{-}Lut^+$ end groups are sufficiently large as to prevent the threading of α-cyclodextrin over them. In a previous study, using the symmetrical dication threads $[(CH_3)_3N(CH_2)_{10}N(CH_3)_3]^{2+}$ (**5**) and $[CH_3CH_2(CH_3)_3N(CH_2)_{10}N(CH_3)_2CH_2CH_3]^{2+}$ (**6**), we have shown that with the $N(CH_3)_3^+$ and $N(CH_3)_2CH_2CH_3^+$ end groups, which are comparable in size to the α-CD cavity, relatively slow threading processes occur at room temperature.[8] In the present study, the resulting threaded species may therefore be referred to as [2]semi-rotaxanes. The kinetics of the slow formation, dissociation and isomer conversion reactions of the [2]semi-rotaxanes were measured at 25 °C by using ^{1}H NMR spectroscopy. The orientations of the two isomers of the semi-rotaxanes were determined by 2D NMR experiments.

Results and discussion

The asymmetric dicationic threads used in this study (Fig. 1) may be synthesized by two approaches, differing by the order in which the bulky Quin or 3,5-Lut groups or the trialkylammonium groups are reacted with the $X(CH_2)_{10}X$ (X = Br or I) starting material. Higher yields of purified products were obtained for the $[R(CH_2)_{10}N(CH_3)_3]^{2+}$ threads (**1**) and (**3**) when the 3,5-lutidine or quinuclidine, respectively, are reacted with the corresponding $[R(CH_2)_{10}N(CH_3)_3]^+$ intermediate. For the $[R(CH_2)_{10}N(CH_3)_2CH_2CH_3]^{2+}$ species (**2**) and (**4**), dimethylethylamine was reacted with the appropriate $[R(CH_2)_{10}X]^+$ intermediate to form the compounds. The compounds with the $3,5\text{-}Lut^+$ end group were isolated as iodide salts, while the quinuclidinium compounds were prepared as bromide salts. The ^{1}H NMR chemical shifts for the compounds are presented in Fig. 1.

The quinuclidinium ($Quin^+$) and 3,5-lutidinium ($3,5\text{-}Lut^+$) end groups are bulky enough to prevent the α-CD from threading

† Electronic supplementary information (ESI) available: observed semi-rotaxane formation rate constants and NOESY NMR spectrum. See http://www.rsc.org/suppdata/ob/b4/b418055k/

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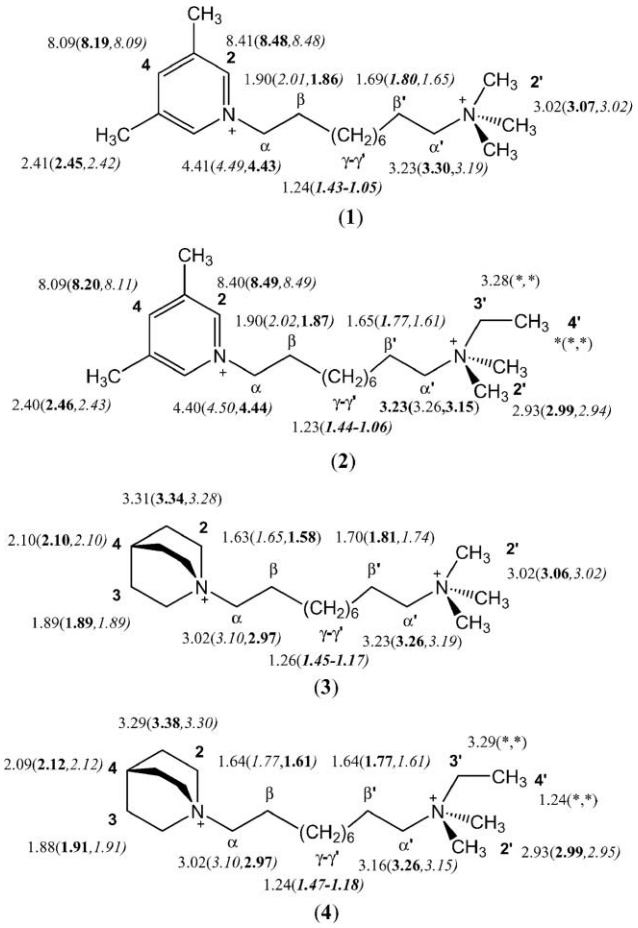


Fig. 1 ^{1}H NMR chemical shifts for the guest protons before and after inclusion in α-CD. The chemical shifts listed before the brackets are for the protons prior to inclusion, while those within the brackets are the guests in the semi-rotaxanes. The chemical shifts for the kinetically preferred isomer are given in italics, while the chemical shifts for the thermodynamically preferred isomer are in bold numbers. The proton resonances which are obscured by other guest, host, or solvent peaks are indicated by *.

over them. No rotaxane formation occurs between α-CD and either $[Quin(CH_2)_{10}Quin]^{2+}$ and $[3,5\text{-}Lut(CH_2)_{10}3,5\text{-}Lut]^{2+}$, even after prolonged time at elevated temperatures. In the threads synthesized in this study, the trialkylammonium groups are comparable in size to the α-CD cavity and permit slow threading processes to occur at room temperature. The rate constants for the formation of symmetrical [2]pseudorotaxanes with threads (**5**) and (**6**) were determined to be $(1.64 \pm 0.22) \times 10^{-1}$ and $(5.83 \pm 0.38) \times 10^{-3}$ dm^3 mol^{-1} s^{-1} at 25 °C.[8]

With the asymmetry of the α-cyclodextrin, the threads in the present study may pass over the quaternary ammonium end group in two directions, leading with either the wider rims (lined with the secondary 2-OH and 3-OH groups) or narrower rim (primary 6-OH groups) resulting in two orientational isomers. The orientational isomers may be distinguished from each other in the ^{1}H NMR spectra of the semi-rotaxanes, which display unique resonances for the two species (Fig. 1). This phenomenon is most readily observed in the methyl protons on the ammonium end group and in the β-CH_2 protons on the polymethylene chain. In the case of the β-CH_2 protons, for example, the upfield resonance corresponds to the isomer with the wider rim of α-CD near the ammonium R^+ group, whereas the upfield methyl resonances on R^+ correspond to the α-CD chain in the kinetically preferred product are in proximity to the internal H5 protons on the narrow end of the α-CD.

The [2]semi-rotaxanes were also observed in aqueous solution by electrospray mass spectrometry (ES^+-MS), with peaks at m/z = 639.4, 646.4, 641.5, and 648.5 found as expected for $[\mathbf{1}\cdot\alpha\text{-CD}]^{2+}$, $[\mathbf{2}\cdot\alpha\text{-CD}]^{2+}$, $[\mathbf{3}\cdot\alpha\text{-CD}]^{2+}$, and $[\mathbf{4}\cdot\alpha\text{-CD}]^{2+}$, respectively.

The kinetics of the slow formation of the α-CD semi-rotaxanes in aqueous solution were measured at 25 °C using ^{1}H NMR spectroscopy (Fig. 2). The rate constants for the formation of the two orientational isomers (k_1^{obs} and k_2^{obs}) were determined independently using the two resonances for the β-CH_2 protons. The downfield signal was observed to increase relatively quickly to a maximum (k_1^{obs}) and then decay slowly (k_{12}^{obs}). The upfield resonance also increased quickly at first (k_2^{obs}) and then more slowly at longer times (k_{12}^{obs}). The intensity of the resonance for the free thread decreased in a monotonic exponential fashion.

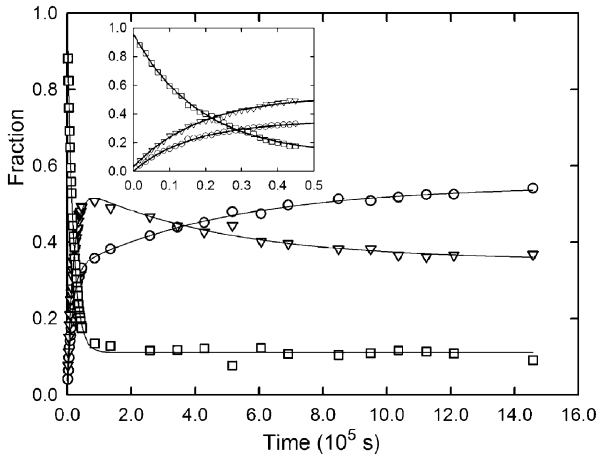


Fig. 2 Kinetics of the formation of $[3,5\text{-}Lut(CH_2)_{10}NEtMe_2\cdot\alpha\text{-CD}]^{2+}$ with 2.22×10^{-2} M α-CD, following the ^{1}H NMR proton resonances of (□) the uncomplexed guest, (▽) the 'kinetically' preferred product, and (○) the 'thermodynamically' preferred product. Inset: plot of the first 5×10^4 s of the experiment.

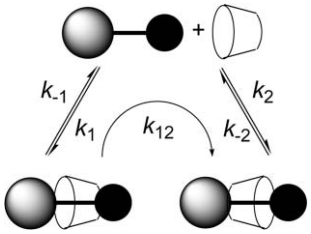
The kinetic data for the formation of the semi-rotaxane were fit to double exponential curves with the first, faster portion corresponding to k_1 or k_2, the rate constants for the formations of the two orientational isomers. Plots of both k_1^{obs} and k_2^{obs} against [α-CD] were linear, with the slopes corresponding to the second-order rate constants k_1 and k_2, respectively (Table 1). The second, slower portion corresponds to the rate constant k_{12} for the conversion of the kinetically preferred isomer to the thermodynamically preferred isomer. The rate constants for the slower processes are independent of the α-CD concentrations,

Table 1 Rate and stability constants for the self-assembly of α-cyclodextrin [2]semi-rotaxanes at 25 °C in D_2O [I = 0.10 mol dm^{-3} (NaCl)]

Thread	10^3k_1/dm^3 mol^{-1} s^{-1}	10^3k_2/dm^3 mol^{-1} s^{-1}	10^6k_{-1}/s^{-1}	10^6k_{-2}/s^{-1}	K_1/dm^3 mol^{-1}	K_2/dm^3 mol^{-1}
1	36.7 ± 3.6	17.5 ± 2.0	86.5 ± 0.8	16.4 ± 0.4	424 ± 42	1070 ± 125
2	1.69 ± 0.21	1.09 ± 0.11	2.55 ± 0.22	1.20 ± 0.02	660 ± 100	908 ± 93
3	39.4 ± 1.5	17.6 ± 1.0	68.4 ± 1.6	24.2 ± 0.3	576 ± 26	727 ± 42
4	2.51 ± 0.10	1.84 ± 0.40	4.03 ± 0.42	1.80 ± 0.13	620 ± 140	1020 ± 230
5	164 ± 22[a]		104 ± 1[a]		1580 ± 220[a]	
6	5.83 ± 0.38[a]		5.4 ± 0.2[a]		1080 ± 110[a]	

[a] Ref. 8.

consistent with a process whose rate is determined by the dissociation of the kinetically preferred isomer (Scheme 1).



Scheme 1 Schematic representation of the formation, dissociation, and isomer conversion processes for the α-CD [2]semi-rotaxanes with threads **1**–**4**.

The observed kinetic behavior is suggestive of a more rapid formation of a kinetically preferred orientational isomer, followed by its slower conversion to the more thermodynamically preferred isomer.

The formation rate constants k_1 and k_2 are presented in Table 1, along with the rate constants for the formation of the corresponding symmetrical dicationic $[R(CH_2)_{10}R]^{2+}$ threads.[8] While the symmetric guests studied previously may be threaded from both ends, the asymmetric guests in the present study may only be threaded from one end. The overall formation rate constants, $k_1 + k_2$, are slightly less than half of the values reported for the corresponding symmetrical $R(CH_2)_{10}R^{2+}$ threads, suggesting that the nature of the bulky $Quin^+$ and Lut^+ end groups have little effect on the rate of initial formation of the [2]semi-rotaxanes.

Using a purified sample (excess α-CD was removed by recrystallization from aqueous acetone) of [2]semi-rotaxane $[Quin(CH_2)_{10}N(CH_3)_2CH_2CH_3\cdot\alpha\text{-CD}]^{2+}$, a ROESY NMR spectrum was obtained, which indicated that the kinetically preferred isomer is produced when the α-CD moiety slips over the $N(CH_3)_2CH_2CH_3^+$ end with its wider rim leading. From the ROESY spectrum, NOE signals can be seen between the H3 protons of α-CD (wider end) and the guest's Hβ proton resonance at 1.77 ppm and between the H5 protons of α-CD (narrower end) and the Hβ resonance at 1.61 ppm. It had been determined from a COSY spectrum of this semi-rotaxane that both signals are a product of two overlapping proton resonances. The signal at 1.77 ppm consists of $H\beta_1$ (kinetic isomer) and $H\beta'_2$ (thermodynamic isomer), while the 1.66 ppm resonance is from $H\beta'_1$ and $H\beta_2$. Therefore, without knowing which protons of the pair the NOE signals refer to, the orientations of the α-CD are determined to be the narrower and wider ends nearer the $Quin^+$ end group in the thermodynamic and kinetic isomers, respectively.

The ROESY spectrum also gives evidence as to the structure of the [2]semi-rotaxane. The methyl proton resonance of the $N(CH_3)_2CH_2CH_3^+$ end group for both isomers exhibits NOE signals to the Hβ resonances at 1.77 and 1.61 ppm. This implies that the portion of the polymethylene chain closest to the $N(CH_3)_2CH_2CH_3^+$ end group may be folded over such that the methyl and Hβ protons are close in space. This would occur if the α-CD moiety rests closer to the quinuclidinium group. From the behaviour of the chemical shifts (Fig. 1) for the Hα and Hβ protons (more upfield for the thermodynamic isomer) compared with the Hα′ and Hβ′ protons (more upfield for the kinetic isomer) for each of the semi-rotaxanes, it is reasonable to conclude that the α-CD is oriented in the same fashion with the other semi-rotaxanes as with $[Quin(CH_2)_{10}N(CH_3)_2CH_2CH_3\cdot\alpha\text{-CD}]^{2+}$.

The rate constants for the dissociation of the semi-rotaxanes could be obtained through the addition of a large excess of a competing guest, $bpy(CH_2)_{12}bpy^{2+}$ (bpy = 4,4′-bipyridinium, $K_{\alpha\text{-CD}} = 3700\ dm^3\ mol^{-1}$), to the solution of the semi-rotaxanes at 25 °C. The reactions were monitored by ^1H NMR following the proton resonances of the two orientational isomers over several days. The values of k_{-1} and k_{-2}, for the kinetically and thermodynamically preferred isomers, respectively, are presented in Table 1. The relative magnitudes of the dissociation rate constants depend upon the bulkiness of the threaded trialkylammonium end group, and to a lesser degree the nature of the stopper end group, the quinuclidinium or 3,5-lutidinium. The stability constants for the semi-rotaxanes K_1 and K_2 were determined from ratios k_1/k_{-1} and k_2/k_{-2}, respectively, and are presented in Table 1. These values are similar in magnitude for a variety of other dicationic threads with a decamethylene chain connecting the end groups.[7–10]

Using a steady-state approximation for the free thread concentration, the rate constant k_{12} for the orientation isomer conversion may be expressed in terms of the rate of dissociation of the kinetically preferred isomer, k_{-1}, and the formation rate constants k_1 and k_2; $k_{12} = (k_{-2}k_1 + k_{-1}k_2)/(k_1 + k_2)$. The observed values of k_{12} and the values calculated from this equation (Table 2) are in good agreement with one another.

The relative amounts of the two orientational isomers at equilibrium, determined by integrations of the isomer resonances in the ^1H NMR spectra are given in Table 2. The relative magnitudes of both the formation and dissociation rate constants for the two isomers contribute to their relative stability, with the dissociation rate constants of slightly more importance than their relative rates of formation. While the nature of the ammonium groups would affect the rate constants for both the formation and dissociation rate constants, the dissociation rate constants could also be affected by the nature of the bulky $Quin^+$ and 3,5-Lut^+ groups.

The dicationic threads with the $N(CH_3)_3^+$ end groups exhibit greater selectivity between the kinetic and thermodynamic isomers in the formation rate constants than the threads with the $N(CH_3)_2CH_2CH_3^+$ end groups. A possible explanation for this is that one end of the α-CD can slip partially over the $N(CH_3)_3^+$ end group without undergoing significant structural distortion, whereas the bulkier $N(CH_3)_2CH_2CH_3^+$ end group requires more extensive structural rearrangement of the α-CD cavity no matter which end of the α-CD is threaded first. Preliminary studies on the effect of the polymethylene chain length on the kinetics of the formations of the kinetic and thermodynamic isomers have been carried out using the $[3,5\text{-}Lut(CH_2)_8N(CH_3)_3]^{2+}$ thread. The rate constant for the formation of the thermodynamic isomer is the same $[(1.78 \pm 0.59) \times 10^{-2}\ dm^3\ mol^{-1}\ s^{-1}]$ as that determined for thread **1** (with a decamethylene chain), whereas the rate constant for the formation of the kinetic isomer is about three times faster,

Table 2 Rate constants for the conversion of the kinetically preferred to the thermodynamically preferred orientational isomers and the percentages of the two isomers of the $[R'(CH_2)_{10}R\cdot\alpha\text{-CD}]^{2+}$ [2]semi-rotaxanes at equilibrium at 25 °C

Thread	$10^6 k_{12}^{obs}/s^{-1}$	$10^6 k_{12}^{calc}/s^{-1}$ [a]	Kinetic product (%)	Thermo product (%)
1	35 ± 15	39 ± 7	36 ± 2	64 ± 2
2	2.0 ± 0.1	1.7 ± 0.1	38 ± 1	62 ± 1
3	30 ± 3	38 ± 8	[b]	[b]
4	1.8 ± 0.7	2.7 ± 0.3	42 ± 4	58 ± 4

[a] $k_{12}^{calc} = (k_{-1}k_2 + k_{-2}k_1)/(k_1 + k_2)$. [b] Values could not be calculated for this ligand because the proton resonances were obscured by other peaks.

$(1.03 \pm 0.23) \times 10^{-1}$ dm^3 mol^{-1} s^{-1}, that found for **1** (Table 1). This suggests that the polymethylene chain and/or the bulky Quin$^+$ or 3,5-Lut$^+$ group at the other end of the thread may have some influence on the rate of semi-rotaxane formation.

The dissociation rate constants are more sensitive to the orientations of the semi-rotaxanes than are the formation rate constants, suggesting that the source of the relative stabilities of the kinetic and thermodynamic isomers comes from the preferences of the narrow and wide rims of the α-CD for the two types of end groups. The more stable isomers have the bulkier Quin$^+$ or 3,5-Lut$^+$ end groups adjacent to the primary hydroxyl groups of the narrow end of the α-CD. It may be that these groups are more easily accommodated in the more flexible –CH_2OH substituents on the narrow α-CD rim, as the structural differences in the these two end groups (aliphatic *vs.* aromatic) would tend to rule against any specific common bonding interactions with the α-CD.

Experimental

The α-cyclodextrin (Aldrich) was dried for at least 12 h at 80 °C under vacuum before use. The quinuclidine hydrochloride, 3,5-lutidine, trimethylamine hydrochloride, dimethylethylamine, and 4-*tert*-butylpyridine were used as received from Aldrich. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300, 400, and 500 spectrometers in D_2O and the assignments were confirmed using COSY (proton) and HMBC and HMQC (carbon) 2D experiments. The kinetics of the formation of the α-CD semi-rotaxanes of the $[R'(CH_2)_{10}R]^{2+}$ [R′$^+$ = Quin$^+$ or 3,5-Lut$^+$ and R$^+$ = $N(CH_3)_3^+$ or $N(CH_3)_2CH_2CH_3^+$] were followed by ^{1}H NMR. For the threads with the 3,5-Lut$^+$ end group, the lutidinium methyl proton resonances were monitored, while for threads containing the Quin$^+$ end group, the resonances for the methyl groups on the trialkylammonium end groups were followed. For the latter systems, however, inclusion of the dicationic threads into the α-CD cavity results in the overlap of one of these methyl resonances with that of the uncomplexed guest (L). This problem was resolved by using the relative integration of the H1 resonances for the complexed and uncomplexed α-CD to determine [L·CD] [eqn. (1)],

$$[L \cdot CD] = [CD]_{total} \frac{\text{Area}\,(H1_{comp})}{\text{Area}\,(H1_{comp}) + \text{Area}\,(H1_{uncompl})} \qquad (1)$$

and then the area of the obscured upfield methyl proton (A_{up}) could be calculated from $A_{up} = (A_{tot}[L{\cdot}CD]/[L]_{tot}) - A_{down}$, where A_{tot} is the total area of the uncomplexed and both complex proton resonances, and A_{down} is the area of the unobscured downfield resonance of the semi-rotaxane.

In a typical experiment, 0.600 mL of a solution containing $[R'(CH_2)_{10}R]^{2+}$ (2 mM) and 0.10 mol dm^{-3} NaCl were added to a weighed quantity of α-CD (5–100 mg). The resulting solution was thoroughly mixed and then transferred to an NMR tube. The solution was equilibrated to 298 ± 0.5 K and spectra were taken at timed intervals for at least four half-lives. The solution was then left at 298 K in a water bath for a further 10–15 half-lives and addition spectra were taken to establish the extent of semi-rotaxane formation at equilibrium.

The orientations of the cyclodextrins in the semi-rotaxanes in this study were determined using 2D ROESY experiments on the Bruker Avance 500 spectrometer, with equilibrated samples containing 1×10^{-3} mol dm^{-3} α-CD and 2×10^{-3} mol dm^{-3} $[R'(CH_2)_{10}R]^{2+}$. The electrospray mass spectrometry measurements were obtained on a VG Quattro mass spectrometer, a quadrupole instrument with an atmospheric pressure electrospray ionization source and a mass range for single charged ions of 4000. Samples were prepared as solutions in distilled water containing the guest (2.5×10^{-3} mol dm^{-3}) and α-CD (2.5×10^{-2} mol dm^{-3}). The elemental analyses were performed by Canadian Microanalytical Services Ltd., Delta, B.C.

Preparation of [3,5-Lut$(CH_2)_{10}$Br]Br

3,5-Lutidine (17 mmol) was dissolved in 60 mL of toluene and added dropwise to a solution of 1,10-dibromodecane (26 mmol) dissolved in 25 mL of a 4 : 1 toluene–DMF mixture. After standing for one week, the solution was reduced in volume to 20 mL *in vacuo*, followed by the addition of 80 mL of diethyl ether. Upon cooling on ice, a white precipitate formed, which was filtered and washed with diethyl ether. The solid was extracted with acetone over several hours to separate the [3,5-Lut$(CH_2)_{10}$Br]Br (soluble in acetone) from the [3,5-Lut$(CH_2)_{10}$3,5-Lut]Br_2 compound (insoluble in acetone). The filtered solution was reduced in volume to precipitate the product (10%). Mp 68–70 °C; Found: C, 50.45; H, 7.13; N, 3.67. $C_{17}H_{39}N_2Br_2$ requires C, 50.14; H, 7.1; N, 3.44%; δ_H (300 MHz; D_2O) 8.40 (s, 2H, s, H2), 8.09 (s, 1H, s, H4), 4.40 (2H, t, $J_{\alpha,\beta}$ = 7.2 Hz, Hα), 3.42 (2H, t, $J_{\alpha',\beta'}$ 6.8, Hα′), 2.40 (6H, s, H5), 1.89 (2H, m, Hβ), 1.75 (2H, m, Hβ′), 1.32 (2H, m, Hγ′), 1.20 (10H, m, Hγ–Hδ′).

Preparation of [Quin$(CH_2)_{10}$Br]Br

Quinuclidine hydrochloride (34 mmol) was dissolved in 400 mL of ethanol and mixed in a 1 : 1 molar ratio with K_2CO_3. The solution was stirred for 12 h after which the resulting potassium chloride was removed by filtration. The ethanol solution was reduced *in vacuo* and the resulting precipitate extracted with 60 mL of toluene over several hours. This solution was added dropwise to a stirred solution of 1,10-dibromodecane (34 mmol) in 20 mL of toluene. The precipitate that formed over the next 12 h was collected, washed with diethyl ether and dried *in vacuo* to yield a white solid (30%). Mp 66–67 °C; Found: C, 48.24; H, 8.04; N, 3.28. $C_{17}H_{34}N_2Br_2{\cdot}0.5H_2O$ requires C, 48.58; H, 8.15; N, 3.33%; δ_H (300 MHz; D_2O) 3.44 (2H, t, $J_{\alpha',\beta'}$ = 6.8 Hz, Hα′), 3.29 (6H, m, H2), 3.00 (2H, m, Hα), 2.09 (1H, m, H4), 1.89 (6H, m, H3), 1.77 (2H, quartet, $J_{\alpha',\beta'}$ and $J_{\beta',\gamma'}$ 6.8 Hβ′), 1.62 (2H, m Hβ), 1.34 (2H, m Hγ′), 1.24 (10H, m, Hγ–Hδ′).

Preparations of [$(H_3C)_3N(CH_2)_{10}$X]X (X = Br and I)

The compounds [$(H_3C)_3N(CH_2)_{10}$Br]Br and [$(H_3C)_3N(CH_2)_{10}$I]I were prepared by modifications of the method of Gray *et al*.[17]

Preparation of [$(H_3C)_3N(CH_2)_{10}$Br]Br. A solution of KOH (11 mmol) in 60 mL of ethanol was added dropwise over the course of 6 h to a mixture of 1,10-dibromodecane (14 mmol) and trimethylamine hydrochloride (9 mmol), dissolved in a minimum of ethanol. The solution was left in an airtight reaction vessel, without stirring, for three days. The precipitated KCl was removed and the filtrate was reduced in volume to approximately 10 mL and added to 100 mL of diethyl ether cooled on ice. The crude white precipitate was collected, washed with diethyl ether and extracted for several hours with 200 mL of acetone. The undissolved precipitate, containing $[(H_3C)_3N(CH_2)_{10}N(CH_3)_3]Br_2$, was removed and the acetone filtrate reduced in volume to approximately 10 mL. Addition of this solution to 100 mL of diethyl ether cooled on ice resulted in a precipitate that was washed with diethyl ether and dried *in vacuo* to yield a white solid (30%). Mp 112–114 °C; Found: C, 44.08; H, 8.02; N, 3.90. $C_{13}H_{29}NBr_2$ requires C, 43.69; H, 8.19; N, 3.92%; δ_H (400 MHz; D_2O) 3.43 (2H, t, $J_{\alpha',\beta'}$ = 6.8 Hz, Hα′), 3.21 (2H, m, Hα), 3.00 (9H, s, H2 and H4), 1.76 (2H, m, Hβ′), 1.68 (2H, m, Hβ), 1.34 (2H, m, Hγ′), 1.27 (6H, m, Hγ–Hδ′).

Preparation of [$(H_3C)_3N(CH_2)_{10}$I]I. The compound [$(H_3C)_3N(CH_2)_{10}$I]I was prepared in a similar manner as the bromide salt above, using 1,10-diiododecane and allowing the reaction to proceed for 10 d in a sealed vessel (60%). Mp 141–143 °C; Found: C, 34.13; H, 6.39; N, 3.02. $C_{13}H_{29}NI_2$ requires C, 34.45; H, 6.45; N, 3.09%; δ_H (400 MHz; D_2O) 3.17 (4H, m, Hα and Hα′), 2.97 (9H, s, H2 and H4), 1.66 (4H, m, Hβ and Hβ′), 1.21 (12H, m, Hγ–Hγ′).

Preparation of [3,5-Lut$(CH_2)_{10}N(CH_3)_3$]I_2 ([1]I_2)

3,5-Lutidine (5.7 mmol) and [$(H_3C)_3N(CH_2)_{10}$I]I (1.1 mmol) were mixed together in 15 mL of DMF and left stirring for 48 h at 50 °C. The cooled solution was added to excess diethyl ether (100 mL) causing a yellow oil to form. The oil was dissolved in a 1 : 1 MeOH–acetone solution, after which diethyl ether was added slowly to the solution until it became cloudy. Upon cooling on ice, a brown precipitate formed. Repeating the recrystallization, washing with diethyl ether and drying under vacuum yielded a white solid (22%). Mp 181–182 °C; Found: C, 42.84; H, 6.87; N, 4.93. $C_{20}H_{38}N_2I_2$ requires C, 42.87; H, 6.84; N, 5.00%; δ_H (400 MHz; D_2O) 8.41 (2H, s, H2), 8.09 (1H, s, H4), 4.41 (2H, t, $J_{\alpha,\beta} = 7.2$ Hz, Hα), 3.23 (2H, m, Hα′), 3.02 (9H, s, H2′), 2.41 (6H, s, 3- and 5-CH_3), 1.90 (2H, m, Hβ), 1.69 (2H, m, Hβ′), 1.24 (12H, m, Hγ–Hγ′); δ_C (100 MHz; D_2O) 146.8 (C4), 141.2 (C2), 139.2 (C3), 67.10 (Cα′), 61.8 (Cα), 53.15 (C2′), 30.73 (Cβ), 28.56 (Cε and Cε′), 28.38 (Cδ′), 28.30 (Cδ), 25.69 (Cγ′), 25.46 (Cγ), 22.56 (Cβ′), 17.81 (3- and 5-CH_3).

Preparation of [3,5-Lut$(CH_2)_{10}N(CH_3)_2(CH_2CH_3)$]$I_2$ ([2]I_2)

Dimethylethylamine (180 mmol) and [3,5-Lut$(CH_2)_{10}$Br]Br (18 mmol) were mixed together in 10 mL of DMF and stirred for one week at 50 °C. The solution was then cooled and added to 100 mL of diethyl ether resulting in the formation of yellow oil, which was extracted with acetone to removed unreacted starting materials and dissolved in 50 mL of ethanol. A large excess of NaI was added and the solution was stirred for 12 h. The solution was filtered to remove undissolved NaI and then reduced to dryness *in vacuo*. The resulting solid was extracted for 12 h with chloroform, which was then filtered to remove the remaining NaI. The chloroform solution was reduced to dryness *in vacuo* leaving yellow oil, which was repeatedly dissolved in acetone and precipitated by adding diethyl ether with vigorous scraping. The precipitate was washed with diethyl ether and dried under vacuum to yield a white solid (12%). Mp 137–139 °C; Found: C, 44.40; H, 7.06; N, 4.78. $C_{21}H_{40}N_2I_2$ requires C, 43.91; H, 7.02; N, 4.88%; δ_H (400 MHz; D_2O) 8.40 (2H, s, H2), 8.09 (1H, s, H4), 4.40 (2H, t, $J_{\alpha',\beta} = 7.2$ Hz, Hα), 3.28 (2H, quartet, $J_{3',4'}$ 7.2, H3′), 3.16 (2H, m, Hα′), 2.93 (6H, s, H2′), 2.40 (6H, s, 3- and 5-CH_3), 1.90 (2H, m, Hβ), 1.65 (2H, m, Hβ′), 1.23 (15H, m, Hγ–Hγ′ and H4′); δ_C (100 MHz; D_2O) 146.8 (C4), 141.2 (C2), 139.2 (C3), 63.84 (Cα′), 61.79 (Cα), 59.80 (C3′), 50.25 (C2′), 30.72 (Cβ), 28.57 (Cε and Cε′), 28.40 (Cδ′), 28.30 (Cδ), 25.76 (Cγ′), 25.45 (Cγ), 22.07 (Cβ′), 17.77 (3- and 5-CH_3), 7.78 (C4′).

Preparation of [Quin$(CH_2)_{10}N(CH_3)_3$]Br_2 ([3]Br_2)

Quinuclidine hydrochloride (14 mmol) and K_2CO_3 (17 mmol) were mixed in 80 mL of ethanol and stirred for 12 h. The KCl precipitate was removed by filtration and the solution was reduced to dryness under vacuum. The resulting solid was extracted with 100 mL of chloroform, which in turn was evaporated to dryness under vacuum. The resulting oil was dissolved in 10 mL of DMF and added to a solution of [$(H_3C)_3N(CH_2)_{10}$Br]Br (3 mmol) in 20 mL of DMF. After stirring at 50 °C for three days, the solution was cooled and added to 100 mL of diethyl ether. The precipitate was collected, washed with acetone and dried under vacuum to yield a light brown solid (73%). Mp > 200 °C; Found: C, 49.58; H, 8.81; N, 5.69. $C_{20}H_{42}N_2Br_2{\cdot}H_2O$ requires C, 49.39; H, 8.70; N, 5.76%; δ_H (400 MHz; D_2O) 3.31 (6H, m, H2), 3.23 (2H, m, Hα′), 3.02 (2H, m, Hα), 3.02 (9H, m, H2′ and H4′), 2.10 (1H, m, H4), 1.89 (6H, m, H3), 1.70 (2H, m, Hβ′), 1.63 (2H, m, Hβ), 1.26 (12H, m, Hγ–Hγ′); δ_C (100 MHz; D_2O) 67.10 (Cα′), 64.68 (Cα), 54.87 (C2), 53.12 (C2′, C3′, and C4′), 28.58 (Cε and Cε′), 28.39 (Cδ and Cδ′), 25.98 (Cγ), 25.71 (Cγ′), 23.71 (C3), 22.55 (Cβ′), 21.72 (Cβ), 19.41 (C4).

Preparation of [Quin$(CH_2)_{10}N(CH_3)_2(CH_2CH_3)$]$Br_2$ ([4]Br_2)

Dimethylethylamine (12 mmol) and [Quin$(CH_2)_{10}$Br]Br (2.5 mmol) were mixed in 15 mL of DMF and stirred for 4 d at 50 °C. The solution was cooled and added to 100 mL of diethyl ether. The white precipitate that formed was collected and extracted with 200 mL of acetone to remove any remaining starting materials. The remaining precipitate was dissolved in a minimum of ethanol and added to 100 mL of diethyl ether. The precipitate was collected, washed with acetone and dried under vacuum to yield a white solid (45%). Mp > 200 °C; Found: C, 51.09; G, 9.11; N, 5.58. $C_{21}H_{44}N_2Br_2{\cdot}0.5H_2O$ requires C, 51.12; H, 9.19; N, 5.68%; δ_H (400 MHz; D_2O) 3.29 (8H, m, H3′ and H2), 3.16 (2H, m, Hα′), 3.00 (2H, m, Hα), 2.93 (6H, s, H2′), 2.09 (1H, m, H4), 1.88 (6H, m, H3), 1.64 (4H, m, Hα′ and Hβ′), 1.24 (15H, m, Hγ–Hγ′ and H4′); δ_C (100 MHz; D_2O) 66.66 (Cα), 63.82 (Cα′), 59.78 (C3′), 54.84 (C2), 50.20 (C2′), 28.58 (Cε and Cε′), 28.41 (Cδ′), 28.38 (Cδ), 25.96 (Cγ), 25.77 (Cγ′), 23.68 (C3), 22.05 (Cβ′), 21.69 (Cβ), 19.38 (C4), 7.73 (C4′).

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