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Direct Synthesis of an Oligomeric Series of Interlocked, Cyclodextrin-Based [*c*2]Daisy Chains

Lisa Randone,[a] Hideki Onagi,[a] Stephen F. Lincoln,[b] and Christopher J. Easton*[a]

Abstract: Despite their anticipated utility and aesthetic appeal, attempts to prepare extended molecular daisy chains have been thwarted by preferential formation of cyclic dimers ([*c*2]-rotaxanes). Previously, circumventing this limitation, an alternative type of molecular chain has been synthesized by linking pre-prepared [*c*2]rotaxanes already interlocked with bulky capping groups. Instead of this step-wise approach, here we describe the direct self-assembly of dimeric complexes and their in situ oligomerization, which simultaneously interlocks the dimers so that no prior capping of the complexes is required. Eight individual supramolecular species, including a tetramer, hexamer, octamer and decamer series, have been isolated and characterized. The decamer is derived from sixteen molecular components, through ten highly selective reactions of six equivalents of bifunctional linking reagent with five self-assembled dimeric cyclodextrin inclusion complexes, all in one pot.

Introduction

Mechanically-interlocked, molecular daisy chains have attracted considerable attention as challenging targets for synthesis, due to their aesthetic appeal and potential utility as components of functional materials.[1-5] Conceptually, they are comprised of hermaphroditic monomer units having both host and guest recognition sites, assembled into linear and cyclic chains, and physically blocked to prevent dissociation of the components (Figure 1). Although these arrangements are simple to imagine, in practice and with very few exceptions,[5-7] related syntheses generally produce only [*c*2]-species.[8-11] This occurs because the corresponding cyclic-dimeric complexes are formed in preference to those that would lead to [*c*n]- (n > 2) and acyclic (*a*n) chains. This bias results from the greater thermodynamic stability of complexes having the least number of monomer units that still allow every guest component to be included in a host and every host moiety to have an included guest.

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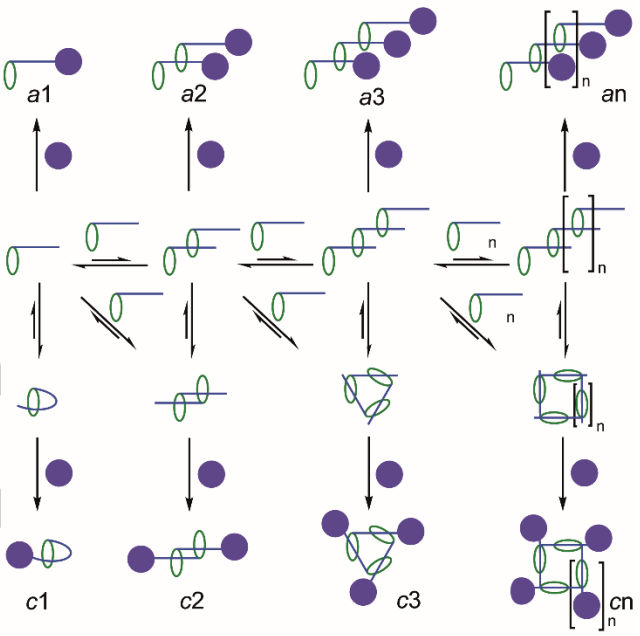


Figure 1. Conceptual formation of linear and cyclic, molecular daisy chains, and related species.

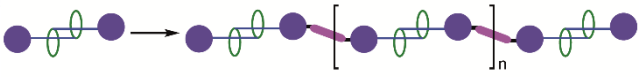
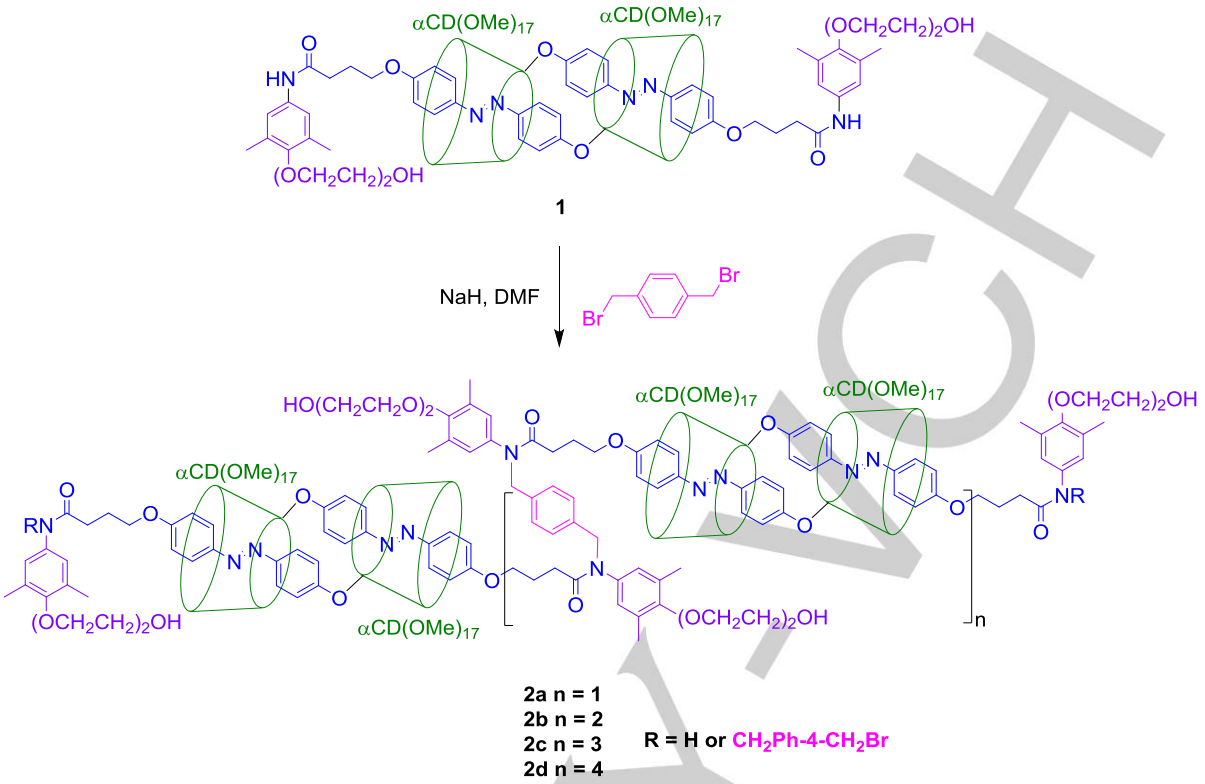


Figure 2. Representation of the production of molecular chains from pre-prepared, capped [*c*2]rotaxanes.

An alternative type of molecular chain may be prepared without this limitation, by linking [*c*2]rotaxanes that are already mechanically interlocked with covalently-attached, bulky capping groups (Figure 2).[4,12-21] In various cases that have been reported, oligomerization of dimers of this type has been accomplished through covalent modification of the blocking groups,[4,12-14] while dynamic metal chelation[15,16] and hydrogen-bonding[17,18,19,20] have been used for their polymerization. As an example of the former of these methods, Kaneda et al.,[12] produced the tetrameric, hexameric, octameric and decameric cyclodextrin derivatives **2a-d** (n = 1-4) in the ratio 33:14:4:2 from the dimer **1** (Scheme 1). In a similar way, Grubbs and Stoddart et al.,[4,13,14] employed acyclic-diene metathesis and double-Cu-catalyzed-Huisgen 1,3-dipolar cycloaddition (Click chemistry), to give mixtures of oligomerized [*c*2]rotaxanes. Molecular chains of this configuration retain the inherently-flexible rotaxane units, in some cases with switchable behavior.[12-19]



Scheme 1. Preparation of oligomeric chains of [*c*2]rotaxanes reported by Kaneda et al.[12]

In a recent, seminal paper, Harada et al.,[22] reported the incorporation of a dimeric cyclodextrin complex into a polymer gel network, and demonstrated photochemically-induced expansion and contraction of the gel in accord with the corresponding realignment of the incorporated complex. More recently, Guiseppone and Buhler et al.,[23] used Click chemistry to prepare chemical gels incorporating cyclodextrin dimers. Their gels expanded and contracted in response to pH changes. Here, we describe a related strategy for the direct synthesis of a homologous series of interlocked, cyclodextrin-based [*c*2]daisy-chains. It involves self-assembly of dimeric complexes and their in situ oligomerization, which simultaneously interlocks the dimers to produce the [*c*2]rotaxane moieties (Figure 3). Unlike previous reports,[4,12-20] it does not require prior synthesis of a capped [*c*2]rotaxane. It produces discrete molecular entities, including a cyclodextrin tetramer, hexamer, octamer and decamer, which have been separated and individually characterized. In the case of the decamer, its formation constitutes the condensation of sixteen molecular components, through self-assembly of ten cyclodextrin derivatives into five dimeric complexes, and their interlocking through ten covalent bond forming reactions with six bifunctional linking reagents.

Results and Discussion

In developing this direct synthesis of daisy-chain oligomers, we first tried a variety of alternatives that were unsuccessful, but

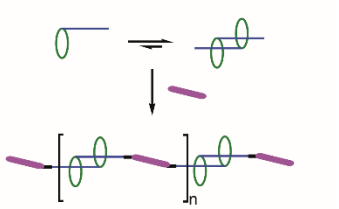
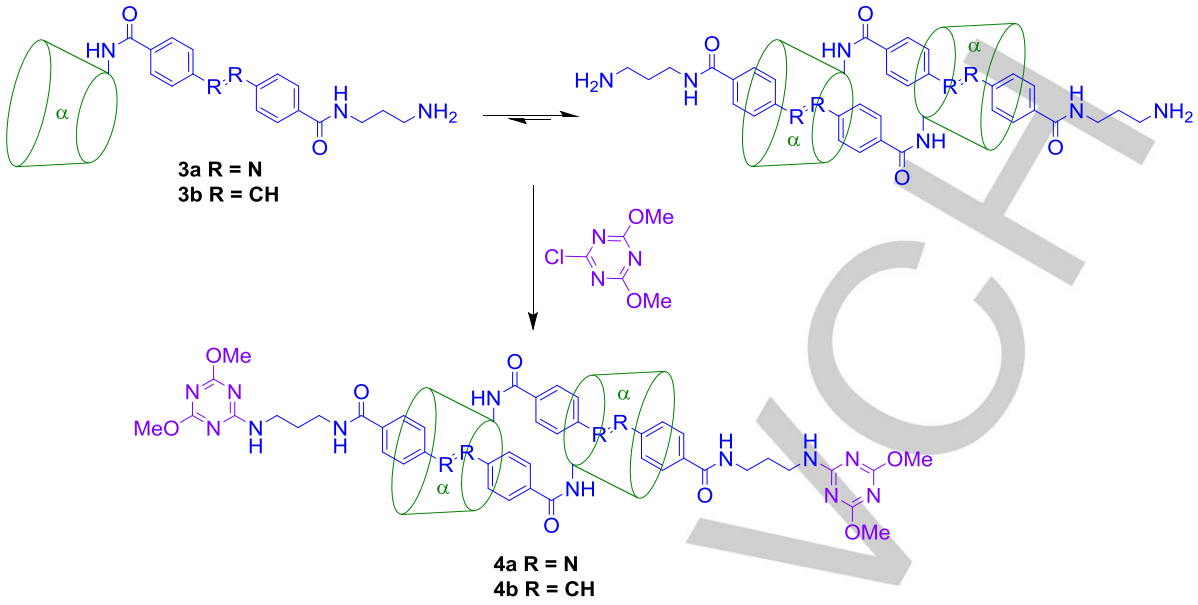


Figure 3. Representation of the direct synthesis of molecular chains of [*c*2]rotaxanes, by linking and simultaneously interlocking self-assembled dimeric complexes.

they highlight the challenges faced. An aqueous medium is normally required to accomplish cyclodextrin host-guest complexation, and therefore the linking reagents had to be compatible with this solvent. This had not been necessary in the indirect synthesis reported previously by Kaneda et al.,[12] where the complexation and linking were performed separately, so the synthesis of their [*c*2]rotaxane was performed in aqueous methanol and their subsequent oligomerization employed NaH in DMF. Earlier, we had prepared the cyclodextrin [*c*2]rotaxanes **4a,b** through reaction of the hermaphroditic monomers **3a,b** with 2-chloro-4,6-dimethoxy-1,3,5-triazine in water (Scheme 2),[10,24] so our initial attempts involved the monomer **3a** and bifunctional triazine variants such as 2,4-dichloro-6-methoxy-1,3,5-triazine as potential linkers. However, these reactions were all ineffective due to competing hydrolysis of the triazines and their side reactions with cyclodextrin hydroxyl groups.



Scheme 2. Synthesis of the [c2]rotaxanes **4a,b**.[10,24]

Takata et al.,[25,26] used 2-bromo- and 3,5-dimethylphenylisocyanate as capping reagents to produce the [3]rotaxanes **5a** and **5b**, respectively (Figure 4). While we reproduced the synthesis of **5b** without difficulty, attempts to adapt that method using 4-bromo-2,6-dimethylphenylisocyanate gave only very small amounts of the analogue **5c**, as determined by HPLC and MALDI-TOF mass spectrometry, even after extended reaction times and with large excesses of the isocyanate. Likewise, treatment of the monomer **3a** with 4-bromo-2,6-dimethylphenylisocyanate afforded only a trace of the [c2]rotaxane **6**. In principal, this material could have been elaborated to chains of [c2]rotaxanes, but its synthesis on any useful scale proved to be impractical. Instead, we next focused on reaction of the cyclodextrin derivative **3a** with 1,4-phenyldiisocyanate. This afforded small amounts of species that were isolated by HPLC and tentatively identified, on the basis of their MALDI-TOF mass spectra, as a linear tetramer, cyclic dimer and cyclic tetramer having structures analogous to those representing **9a**, **11** and **12** in Figure 5. Other water-soluble products were monomeric and trimeric. In addition, a relatively large amount of precipitate formed in the reaction mixture, which appeared to be derived from the production of carbamates through reaction of cyclodextrin hydroxyl groups with the diisocyanate. In an attempt to avoid this, we prepared the permethylated cyclodextrin analogue of the monomer **3a**, but the MALDI-TOF mass spectrum of the product of its reaction with the diisocyanate again showed only traces of dimer, trimer and tetramer, but no evidence of higher oligomers. Experimental details are provided in the Supporting Information.

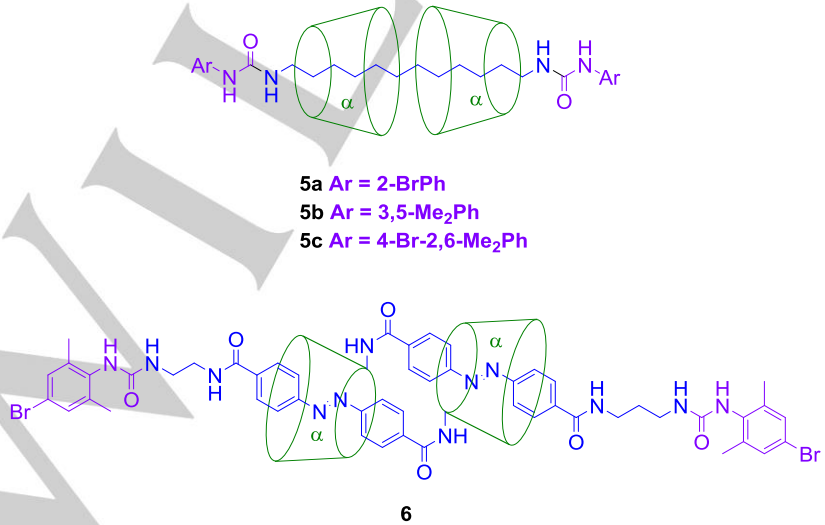
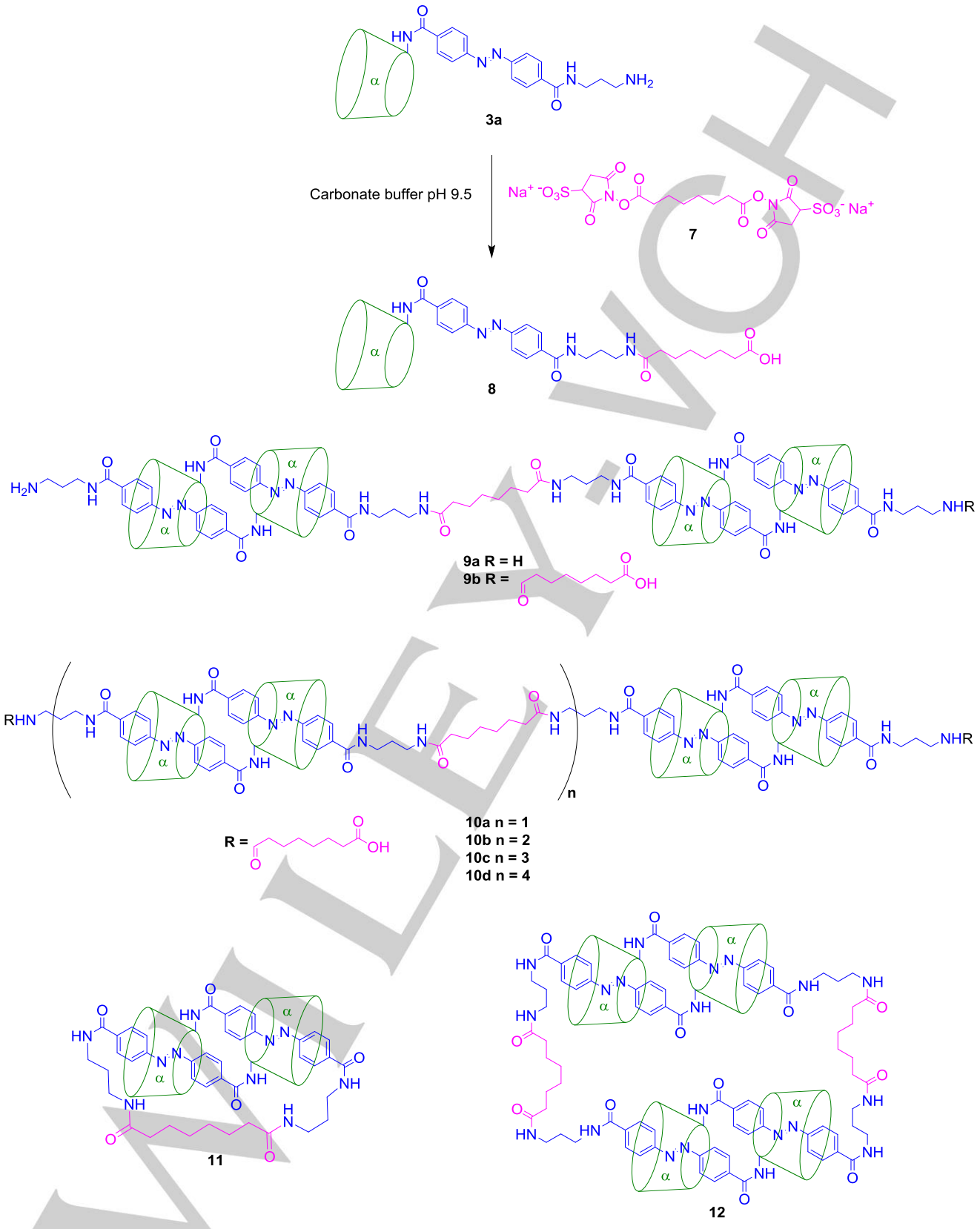


Figure 4. Structures of the [c2]rotaxanes **5a**,[25,26] **5b**,[25,26] **5c** and **6**.



Scheme 3. Synthesis of interlocked [c2]daisy chains through reaction of the cyclodextrin **3a** with the suberic acid derivative **7**.

We also investigated several bis-activated dicarboxylic acids as possible linking reagents. Generally, these also afforded complex product mixtures, complicated by reagent hydrolysis and side reactions with the cyclodextrin **3a**, until we tried the suberic acid derivative **7** (Sigma-Aldrich Chem. Co.). It is water-soluble and known to react selectively with primary amines, under mild conditions, in aqueous media.[27,28] Consequently, it has been used extensively in biological chemistry, as a cross-linking agent to prepare protein-protein, receptor-ligand and hapten-carrier molecule conjugates. With the cyclodextrin **3a**, it finally afforded a series of oligomers of interlocked [*c*2]daisy-chains (Scheme 3, Figure 5).

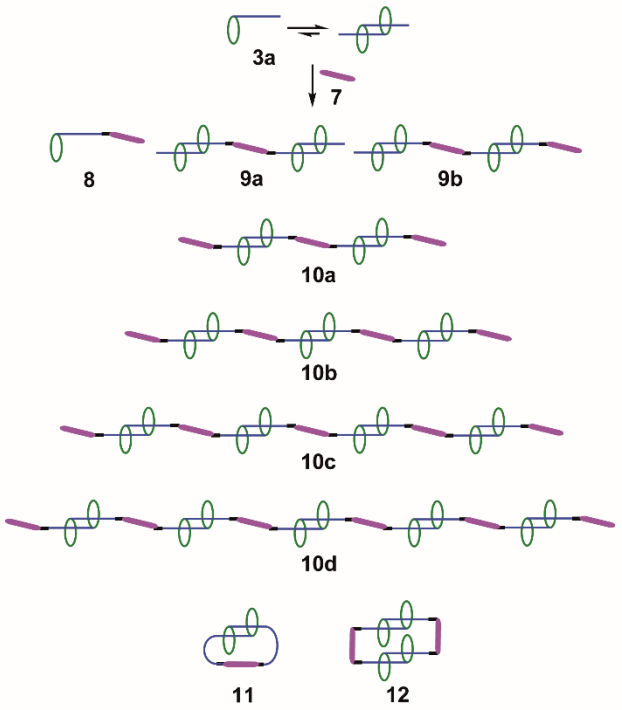


Figure 5. Representation of the production of interlocked [*c*2]daisy chains shown in Scheme 3.

A representative reaction was carried out with the cyclodextrin **3a** (120 mM) and the linking reagent **7** (0.6 equiv.), at room temperature in pH 9.5 carbonate buffer. This pH was chosen so as to maintain the amino group of the cyclodextrin **3a** as the nucleophilic free-base, while minimizing deprotonation and therefore reactivity of the cyclodextrin hydroxyl groups. At 1 mM concentration and higher, aqueous solutions of the cyclodextrin **3a** show concentration-independent ^{1}H NMR spectra with cross-correlations in the ROESY NMR spectra between cyclodextrin and azobenzene proton resonances, indicating effectively complete formation of a symmetric host-guest complex. A 20 mM concentration of the cyclodextrin **3a** was used in the synthesis of **4a**.[10,24] Therefore, the concentration of **3a** used here greatly exceeds that required to expect full self-assembly into a dimeric complex and [*c*2]rotaxane formation.

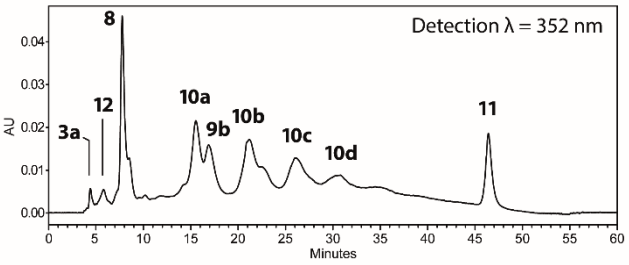


Figure 6. HPLC analysis of the mixture of products obtained from reaction of the cyclodextrin **3a** with the suberic acid derivative **7** after 3 days.

After 24 h, fractionation of the reaction mixture using HPLC afforded pure samples of each of the major components; the tetrameric species **9a** and **9b**, as well as the starting monomer **3a** and its suberic acid derivative **8** (See Supporting Information for details). Further reaction occurred with extended reaction times until, after 3 days, only a trace of the unreacted monomer **3a** remained and the tetramer **9a** was no longer detected using the same reverse-phase analytical method. Instead, normal-phase HPLC analysis (Figure 6), suitable for larger and more polar species, showed that the major components of the product mixture after this time were the derivatized monomer **8**, some of the tetramer **9b**, and an oligomeric series of linearly-linked [c2]daisy chains, of which the tetramer **10a**, hexamer **10b**, octamer **10c** and decamer **10d** were each separated by HPLC. Samples of the cyclic dimer **11** and of a species that was tentatively identified as the cyclic tetramer **12** were also isolated.

Each of the separated compounds **8**, **9a,b**, **10a-d** and **11** was characterized using HPLC, mass spectrometry and NMR spectroscopy (See Supporting Information for details). HPLC analysis with a photodiode array detector showed a single component in every case, with a λ_{max} at 332 nm for compound **8**, but near 340-345 nm for the others. These wavelengths are typical of *trans*-azobenzene moieties, with the shift to higher wavelength for **9a,b**, **10a-d** and **11** being characteristic of inclusion in a cyclodextrin.[29,30] The mass spectra all displayed diagnostic $[M+Na]^+$ ions. More detailed information was provided by the NMR spectra. In particular, the relative integrals for the azobenzene (δ7.6-8.6 ppm), propyl $CONHCH_2C\mathbf{H}_2CH_2NHCO$- (~δ1.85-2.00 ppm) and -$CONHCH_2C\mathbf{H}_2CH_2NH_2$ (~δ2.10 ppm), and octyl -$C\mathbf{H}_2CH_2CH_2CO$- (~δ1.30-1.45 ppm), -$CH_2C\mathbf{H}_2CH_2CO$- (~δ1.55-1.75 ppm), -$CH_2CH_2C\mathbf{H}_2CONH$- (~δ2.25-2.35 ppm) and -$CH_2CH_2C\mathbf{H}_2CO_2H$ (~δ2.40-2.45 ppm) proton resonances uniquely define each structure, including the extent of substitution of the terminal groups with suberic acid. Each of the compounds **8**, **9a,b**, **10a-d** and **11** showed a very similar, single set of aromatic proton resonances, indicating that all the azobenzenes are in the same type of environment. Cross-peaks in ROESY NMR spectra established that this is when the azobenzene moieties are included in cyclodextrin cavities. In the case of the monomer **8**, the inclusion is consistent with formation of a dimeric complex under the conditions used to record the NMR spectra in D_2O. This inclusion is not reflected in the HPLC data because very little complexation occurs in the much more dilute aqueous acetonitrile solution eluting from the HPLC column. For **9a**,**b**, **10a-d** and **11**, the simplicity of their NMR

spectra only matches oligomers of [*c*2]rotaxanes and there was no evidence of the formation of other [*c*n]- or [*a*n]-species. It was only practical to isolate a small sample of compound **12** but its λ_{max} at 345 nm and MALDI-TOF mass spectrum (*m*/*z* 5420, $[M+Na]^+$) are diagnostic of the assigned structure. The HPLC retention times of the cyclic dimer **11** and tetramer **12** are strikingly dissimilar (Figure 6). Under the normal-phase conditions of this analysis, the dimer **11** has a much longer retention time and therefore appears to be significantly more polar. A possible reason for this is that geometric constraints in this small ring system force the cyclodextrin units out of alignment and expose more of their hydroxyl groups to solvent.

The production of compounds **9a,b**, **10a-d**, **11** and **12** involves an intricate balance of competing processes. Formation of **9a** occurs through a dimeric inclusion complex of the cyclodextrin **3a** reacting with a second complex formed between **3a** and the product of reaction of **3a** with the bifunctional linking reagent **7**. A competing cyclization of this asymmetric complex leads to **11**. The symmetric and asymmetric complexes are in dynamic equilibrium and **3a** may be either free or included when it reacts with **7**. One possible route to **9b** and **10a** is through sequential reactions of **9a** with **7**, followed by hydrolysis of the end-groups, but there are various other pathways. Indeed, some hydrolysis of **7** is likely to occur even before its attachment to a cyclodextrin. Consequently, **9b** and **10a** are likely to be formed in multiple ways, from **3a**, **8** and the hydroxysuccinimide ester of **8**, and the range of their inclusion complexes. The situation with **10b-d** is even more complex. With **10d**, for example, it could be produced either through coupling of various dimeric and octameric cyclodextrin species, or from tetramers reacting with hexamers. Formation of **12** results from cyclization of the hydroxysuccinimide ester of **9b**, which would be in competition with oligomerization of this ester and its hydrolysis to give **9b**. An obvious consequence of this competition is that the relative proportion of **12** in the product mixture increases by a factor of around 10 when the concentration of the cyclodextrin **3a** used in the reaction is reduced from 120 mM to 30 mM.

The interlocked species **9a,b**, **10a-d** and **11** exhibit switchable behavior characteristic of *cis*-*trans* isomerization of azobenzenes.[22,24,31] In preliminary photochemical experiments (see Supporting Information for details), irradiation at 350 nm of methanol solutions of all-*trans* **10a**, **10d** and **11** resulted in 50, 55 and 60% *trans* to *cis* conversion at the photostationary state, which was reached after around 15, 2 and 60 minutes, respectively. Species **10a** and **10d** fully reverted to their *trans*-forms on irradiation at 420 nm for 10 min. At the same wavelength, the cyclic dimer **11** only reverted from 60% *cis* to 50% even after longer periods of irradiation, but when the methanol was removed and replaced with water, the *trans*-form was quantitatively restored. Aqueous solutions of **10a**, **10d** and **11** irradiated at 350 nm showed lower degrees of isomerization at the photostationary state, with respective *trans* to *cis* conversions of 40, 30 and 20%. In this solvent, all three species showed full reversion to the *trans*-isomers after irradiation for 10 min at 420 nm. It was impractical to study the conformational changes associated with interconversions such as these, due to *cis*- to *trans*-azobenzene conversion occurring spontaneously in the dark at room temperature.

Conclusions

In summary, therefore, compounds **9a**,**b**, **10a-d**, **11** and **12** are produced through self-assembly of dimeric cyclodextrin complexes and their in situ oligomerization, in competition with cyclization and hydrolysis. The oligomerization (or cyclization in the case of **11**) also serves to mechanically interlock the dimers, so that no prior capping of the complexes is required. Instead, the direct syntheses of these chains of [*c*2]rotaxanes rely on the high thermodynamic stability of the complexes in water, used as the reaction solvent, and the marked selectivity of reaction of hydroxysuccinimide esters with amines in preference to both the cyclodextrin hydroxyl groups and the water. Considering the decamer **10d**, as an example, it is formed by self-assembly of ten modules of cyclodextrin derivative into five dimeric complexes, and their interlocking with six modules of bifunctional linking reagent. This one-pot condensation of sixteen molecular components involves ten reactions between hydroxysuccinimide ester and amino moieties, during which there are only two competing ester hydrolysis reactions that produce the carboxylic acid end groups. Initial photochemical experiments illustrate the potential utility of this class of compounds in functional supramolecular assemblies and materials.

Experimental Section

(*E*)-4-((4-((6^A-Deoxy-α-cyclodextrin-6^A-yl)carbamoyl)phenyl)diazenyl) benzoic acid

A solution of 6^A-amino-6^A-deoxy-α-cyclodextrin[32] (1.60 g, 1.65 mmol) and Et_3N (0.2 mL, 1.4 mmol) in anhydrous DMF (20 mL) was added drop-wise over 0.5 h to a solution of azobenzene-4,4'-dicarboxylic acid (1.78 g, 6.6 mmol), BOP (1.06 g, 2.4 mmol) and Et_3N (3.2 mL, 23 mmol) in anhydrous DMF (24 mL), under nitrogen. The resultant mixture was stirred overnight at room temperature, before it was added drop-wise into ice-cooled acetone (0.5 L), with stirring. The orange precipitate that formed was separated by centrifugation, washed with acetone (6 × 50 mL) then Et_2O (2 × 50 mL), and dried under vacuum, before it was dissolved in water (0.5 L). The solution was acidified to pH ~2 with HCl before it was applied to a Diaion HP-20 column (185 x 45 mm). The column was then eluted with water that had been acidified with HCl to pH ~2 (3 L), until the eluate was free of the starting aminocyclodextrin, as determined by TLC. A gradient of methanol-acidified water was then applied, and the title compound eluted with 30-40% methanol (~ 10 L). Fractions containing this material were combined and lyophilized to give an orange powder (1.11 g, 55%). R_f = 0.55 (*n*-butanol/ethanol/water 5:4:3); m.p. 228-231 °C (dec.); ^{1}H NMR (400 MHz, D_2O): δ = 8.51 (d, *J* = 8.2 Hz, 2H), 8.40 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 5.16–4.96 (m, 6H), 4.32–3.25 (m, 36H); HRMS (ESI): *m*/*z* calcd for $C_{50}H_{69}N_3O_{32}Na$ $[M+Na]^+$ 1246.3762, found 1246.3738; HPLC: t_R 9.7 min (column: YMC ODS-AQ, 250 × 20 mm, eluent MeCN/H_2O (0.1% TFA) 1:4, flow rate 15 mL min^{-1}).

(*E*)-*tert*-Butyl (3-(4-((4-((6^A-deoxy-α-cyclodextrin-6^A-yl)carbamoyl) phenyl)diazenyl)benzamido)propyl)carbamate

A solution of (*E*)-4-((4-((6^A-deoxy-α-cyclodextrin-6^A-yl)carbamoyl)phenyl) diazenyl)benzoic acid (1.11 g, 0.91 mmol), *tert*-butyl (3-aminopropyl) carbamate (0.25 g, 1.4 mmol), BOP (0.49 g, 1.1 mmol) and Et_3N (0.1 mL, 0.72 mmol) in anhydrous DMF (15 mL) was stirred overnight at room temperature, before it was added drop-wise into ice-cooled acetone (0.5 L), with stirring. The orange precipitate that formed was separated by centrifugation, washed with acetone (5 × 200 mL), and dried under vacuum, before it was dissolved in water (0.5 L). The solution was applied to a Diaion HP-20 column (185 x 45 mm). The column was then eluted with water (1 L), followed by a gradient of methanol-water. The starting material eluted with 5-40% methanol, while the title compound eluted with 45-80% methanol. Fractions containing this material were combined and lyophilized to give an orange powder (1.02 g, 81%). R_f = 0.74 (*n*-butanol/ethanol/water 5:4:3); ^{1}H NMR (400 MHz, D_2O): δ = 8.52 (d, *J* = 8.0 Hz, 2H), 8.19 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 5.16–4.87 (m, 6H), 4.31–3.14 (m, 40H), 1.88 (m, 2H), 1.47 (s, 9H); HRMS (ESI): *m*/*z* calcd for $C_{58}H_{86}N_5O_{33}$ $[M+H]^+$ 1380.5205, found 1380.5212.

(*E*)-*N*-(3-Aminopropyl)-4-((4-((6^A-deoxy-α-cyclodextrin-6^A-yl)carbamoyl)phenyl)diazenyl)benzamide (3a)

A solution of (*E*)-*tert*-butyl (3-(4-((4-((6^A-deoxy-α-cyclodextrin-6^A-yl)carbamoyl)phenyl)diazenyl)benzamido)-propyl)carbamate (0.20 g, 0.15 mmol) in TFA (10 mL) cooled to 5 °C was stirred for 1.5 h, before it was concentrated under vacuum to dryness, to give a red film. The film was washed with diethyl ether (3 x 5 mL) to obtain a fine precipitate, which was dried under vacuum overnight, to give the trifluoroacetate salt of the title compound as an orange powder (170 mg, 81%). R_f = 0.14 (*i*-propanol/ethanol/water/acetic acid 5:4:3:2); m.p. 219-223 °C (dec.); ^{1}H NMR (400 MHz, D_2O): δ = 8.53 (d, *J* = 8.0 Hz, 2H), 8.20 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 5.16–4.86 (m, 6H), 4.32–2.81 (m, 40H), 2.12–2.00 (m, 2H); HRMS (ESI): *m*/*z* calcd for $C_{53}H_{78}N_5O_{31}$ $[M+H]^+$ 1280.4681, found 1280.4688; HPLC: t_R 18.1 min (column: Agilent Zorbax SB C18 3.5 µm, 150 x 4.6 mm, eluent gradient MeCN/H_2O (0.1% TFA) – MeCN 5% 0-3 min, 5-47% 3-20 min, 47% 20-30 min, flow rate 1 mL min^{-1}); HPLC: t_R 4.2 min (column: Grace Prevail Carbohydrate ES 9 µm, 300 x 20 mm, eluent gradient MeCN/H_2O (0.1% TFA) – MeCN 70-60% 0-40 min, 60-30% 40-45 min, 30% 45-60 min, flow rate 10 mL min^{-1}).

Reaction of (*E*)-*N*-(3-aminopropyl)-4-((4-((6^A-deoxy-α-cyclodextrin-6^A-yl)carbamoyl)phenyl)diazenyl)-benzamide (3a) with suberic acid bis(3-sulfonato-*N*-hydroxysuccinimide ester) disodium salt (7)

In a representative reaction, the trifluoroacetate salt of the cyclodextrin **3a** (80 mg, 62 µmol, 120 mM) was added to pH 9.5 carbonate buffer (0.5 mL, 100 mM), and the mixture was stirred at room temperature for 15 min. The suberic acid derivative **7** (22 mg, 38 µmol, 0.6 equiv.) was then added, and stirring was continued at room temperature for 3 days. HPLC analysis of the product mixture (Figure 6) after that time showed the presence of the unreacted starting material **3a**, its suberic acid derivative **8**, the cyclodextrin tetramers **9b** and **10a**, the oligomers **10b**, **10c** and **10d**, the cyclic dimer **11** and a tetrameric species **12**. Samples of **8**, **9b**, **10a**-**10d**, **11** and **12** were isolated using preparative HPLC. When the reaction product was analyzed after 1 day instead of 3, HPLC analysis showed the presence of **3a**, **8**, and the cyclodextrin tetramers **9a** and **9b**. A sample of **9a** was also isolated using preparative HPLC. HPLC was carried out using a Grace Prevail Carbohydrate ES 9 µm (300 x 20 mm) column, with a gradient eluent of MeCN/H_2O (0.1% TFA) – MeCN 70-60% 0-40 min, 60-30% 40-45 min, 30% 45-60 min, at a flow rate of 10 mL min^{-1}, monitoring at 352 nm.

Cyclodextrin monomer 8. HPLC: t_R 8.0 min, λ_{max} 332 nm; ^{1}H NMR (400 MHz, D_2O): δ = 8.52 (d, *J* = 8.1 Hz, 2H), 8.19 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 5.20–4.90 (m, 6H), 4.40–2.90 (m, 40H), 2.41 (t, *J* = 7.3 Hz, 2H, -$CH_2CH_2CH_2CO_2H$), 2.30 (t, *J* = 7.3 Hz, 2H, -$CH_2CH_2CH_2CONH$-), 1.95–1.85 (m, 2H, -$CONHCH_2CH_2CH_2NHCO$-), 1.71–1.58 (m, 4H, -$CH_2CH_2CH_2CO$-), 1.40–1.33 (m, 4H, -$CH_2CH_2CH_2CO$-); MALDI-TOF MS: *m*/*z* calcd for $C_{61}H_{89}N_5O_{34}Na$ $[M+Na]^+$ 1459, found 1460; HRMS (ESI): m/z calcd for $C_{61}H_{88}N_5O_{34}$ $[M-H]^-$ 1434.5316, found 1434.5312.

Linear tetrameric daisy chain 9a. HPLC: t_R 16.2 min, λ_{max} 342 nm; ^{1}H NMR (600 MHz, D_2O): δ = 8.55 (d, *J* = 8.2 Hz, 8H), 8.23 (d, *J* = 8.2 Hz, 8H), 7.77 (d, *J* = 8.2 Hz, 8H), 7.72 (d, *J* = 8.2 Hz, 8H), 5.21–4.87 (m, 24H), 4.34–2.99 (m, 160H), 2.34 (t, *J* = 7.4 Hz, 4H, -$CH_2CH_2CH_2CONH$-), 2.13–2.08 (m, 4H, -$CONHCH_2CH_2CH_2NH2$), 1.97–1.91 (m, 4H, -$CONHCH_2CH_2CH_2NHCO$-), 1.72–1.65 (m, 4H, -$CH_2CH_2CH_2CO$-), 1.42–1.38 (m, 4H, -$CH_2CH_2CH_2CO$-); MALDI-TOF MS: *m*/*z* calcd for $C_{220}H_{318}N_{20}O_{126}Na$ $[M+Na]^+$ 5282, found 5286; HRMS (ESI): *m*/*z* calcd for $C_{220}H_{319}N_{20}O_{126}$ $[M+H]^+$ 5259.9264, found 5259.9455.

Linear tetrameric daisy chain 9b. HPLC: t_R 16.9 min, λ_{max} 340 nm; ^{1}H NMR (600 MHz, D_2O): δ = 8.55 (d, *J* = 8.0 Hz, 8H), 8.23 (d, *J* = 8.0 Hz, 8H), 7.77 (d, *J* = 8.0 Hz, 8H), 7.72 (d, *J* = 8.0 Hz, 8H), 5.20–4.88 (m, 24H), 4.40–3.00 (m, 160H), 2.44 (t, *J* = 7.4 Hz, 2H, -$CH_2CH_2CH_2CO_2H$), 2.34 (t, *J* = 7.4 Hz, 6H, -$CH_2CH_2CH_2CONH$-), 2.13–2.08 (m, 2H, -$CONHCH_2CH_2CH_2NH_2$), 1.97–1.91 (m, 6H, -$CONHCH_2CH_2CH_2NHCO$-), 1.72–1.65 (m, 8H, -$CH_2CH_2CH_2CO$-), 1.42–1.38 (m, 8H, -$CH_2CH_2CH_2CO$-); MALDI-TOF MS: *m*/*z* calcd for $C_{228}H_{330}N_{20}O_{129}Na$ $[M+Na]^+$ 5438, found 5437; HRMS (ESI): *m*/*z* calcd for $C_{228}H_{331}N_{20}O_{129}$ $[M+H]^+$ 5416.0051, found 5416.0273.

Linear tetrameric daisy chain 10a. HPLC: t_R 15.7 min, λ_{max} 343 nm; ^{1}H NMR (400 MHz, D_2O): δ = 8.52 (d, *J* = 8.0 Hz, 8H), 8.20 (d, *J* = 8.0 Hz, 8H), 7.74 (d, *J* = 8.0 Hz, 8H), 7.68 (d, *J* = 8.0 Hz, 8H), 5.20–4.88 (m, 24H), 4.36–2.97 (m, 160H), 2.40 (t, *J* = 7.4 Hz, 4H, -$CH_2CH_2CH_2CO_2H$), 2.30 (t, *J* = 7.4 Hz, 8H, -$CH_2CH_2CH_2CONH$-), 1.95–1.86 (m, 8H, -$CONHCH_2CH_2CH_2NHCO$-), 1.70–1.58 (m, 12H, -$CH_2CH_2CH_2CO$-), 1.42–1.31 (m, 12H, -$CH_2CH_2CH_2CO$-); MALDI-TOF MS: *m*/*z* calcd for $C_{236}H_{342}N_{20}O_{132}Na$ $[M+Na]^+$ 5594, found 5591; HRMS (ESI): *m*/*z* calcd for $C_{236}H_{343}N_{20}O_{132}$ $[M+H]^+$ 5572.0830, found 5572.0961.

Linear hexameric daisy chain 10b. HPLC: t_R 21.7 min, λ_{max} 342 nm; ^{1}H NMR (400 MHz, D_2O): δ = 8.52 (d, *J* = 8.0 Hz, 12H), 8.19 (d, *J* = 8.0 Hz, 12H), 7.73 (d, *J* = 8.0 Hz, 12H), 7.68 (d, *J* = 8.0 Hz, 12H), 5.20–4.88 (m, 36H), 4.33–2.95 (m, 240H), 2.40 (t, *J* = 7.4 Hz, 4H, -$CH_2CH_2CH_2CO_2H$), 2.31 (t, *J* = 7.4 Hz, 12H, -$CH_2CH_2CH_2CONH$-), 1.95–1.87 (m, 12H, -$CONHCH_2CH_2CH_2NHCO$-), 1.70–1.58 (m, 16H, -$CH_2CH_2CH_2CO$-), 1.41–1.32 (m, 16H, -$CH_2CH_2CH_2CO$-); MALDI-TOF MS: *m*/*z* calcd for $C_{350}H_{506}N_{30}O_{196}Na$ $[M+Na]^+$ 8293, found 8290; HRMS (ESI): *m*/*z* calcd for $C_{350}H_{507}N_{30}O_{196}$ $[M+H]^+$ 8270.0746, found 8270.0883.

Linear octameric daisy chain 10c. HPLC: t_R 26.7 min, λ_{max} 342 nm; ^{1}H NMR (400 MHz, D_2O): δ = 8.52 (d, *J* = 8.0 Hz, 16H), 8.19 (d, *J* = 8.0 Hz, 16H), 7.73 (d, *J* = 8.0 Hz, 16H), 7.68 (d, *J* = 8.0 Hz, 16H), 5.16–4.93 (m, 48H), 4.33–2.95 (m, 320H), 2.40 (t, *J* = 7.4 Hz, 4H, -$CH_2CH_2CH_2CO_2H$), 2.30 (t, *J* = 7.4 Hz, 16H, -$CH_2CH_2CH_2CONH$-), 1.95–1.86 (m, 16H, -$CONHCH_2CH_2CH_2NHCO$-), 1.70–1.59 (m, 20H, -$CH_2CH_2CH_2CO$-), 1.42–1.33 (m, 20H, -$CH_2CH_2CH_2CO$-); MALDI-TOF MS: *m*/*z* calcd for $C_{464}H_{670}N_{40}O_{260}Na$ $[M+Na]^+$ 10991, found 10986; HRMS (ESI): *m*/*z* calcd for $C_{464}H_{671}N_{40}O_{260}$ $[M+H]^+$ 10968.0676, found 10968.1170.

Linear decameric daisy chain 10d. HPLC: t_R 32.0 min, λ_{max} 341 nm; ^{1}H NMR (400 MHz, D_2O): δ = 8.51 (d, *J* = 8.0 Hz, 20H), 8.19 (d, *J* = 8.0 Hz,

20H), 7.73 (d, *J* = 8.0 Hz, 20H), 7.68 (d, *J* = 8.0 Hz, 20H), 5.16–4.93 (m, 60H), 4.33–2.94 (m, 400H), 2.40 (t, *J* = 7.4 Hz, 4H, -$CH_2CH_2C\mathbf{H}_2CO_2H$), 2.30 (t, *J* = 7.4 Hz, 20H, -$CH_2CH_2C\mathbf{H}_2CONH$-), 1.95–1.85 (m, 20H, -$CONHCH_2C\mathbf{H}_2CH_2NHCO$-), 1.70–1.58 (m, 24H, -$CH_2C\mathbf{H}_2CH_2CO$-), 1.42–1.33 (m, 24H, -$C\mathbf{H}_2CH_2CH_2CO$-); MALDI-TOF MS: *m*/*z* calcd for $C_{578}H_{834}N_{50}O_{324}Na$ $[M+Na]^+$ 13690, found 13689.

Cyclic dimeric daisy chain 11. HPLC: t_R 46.7 min, λ_{max} 342 nm; ^1H NMR (600 MHz, D_2O): δ = 8.55 (d, *J* = 8.0 Hz, 4H), 8.23 (d, *J* = 8.0 Hz, 4H), 7.77 (d, *J* = 8.0 Hz, 4H), 7.72 (d, *J* = 8.0 Hz, 4H), 5.16–4.93 (m, 12H), 4.36–2.98 (m, 80H), 2.34 (t, *J* = 7.0 Hz, 4H, -$CH_2CH_2C\mathbf{H}_2CONH$-), 1.97–1.91 (m, 4H, -$CONHCH_2C\mathbf{H}_2CH_2NHCO$-), 1.72–1.64 (m, 4H, -$CH_2C\mathbf{H}_2CH_2CO$-), 1.43–1.37 (m, 4H, -$C\mathbf{H}_2CH_2CH_2CO$-); MALDI-TOF MS: *m*/*z* calcd for $C_{114}H_{164}N_{10}O_{64}Na$ $[M+Na]^+$ 2721, found 2722.

Cyclic tetrameric daisy chain 12. HPLC: t_R 5.8 min, λ_{max} 345 nm; MALDI-TOF MS: *m*/*z* calcd for $C_{228}H_{328}N_{20}O_{128}Na$ $[M+Na]^+$ 5420, found 5420.

Photochemical Experiments

Solutions of **10a**, **10d** and **11** in methanol or water in a 1 cm quartz cuvette, prepared to an absorbance of around 0.5 at 340 nm, were irradiated at 25 °C in a Luzchem photoreactor fitted with Hitachi FL8BL-B 8 Watt lamps (350 nm) or Luzchem LZC-420 8 Watt lamps (420 nm). Reactions monitored using UV-visible spectroscopy showed decreases or increases in the absorbance near 340-345 nm, characteristic of *trans*-azobenzenes, and corresponding increases or decreases in the absorbance near 270 nm, characteristic of *cis*-azobenzenes, related in each case through an isosbestic point near 290 nm.[22,24,29] The ratios of *cis*- and *trans*-azobenzenes in mixtures were calculated from the percentage change in the absorbance at the λ_{max} of the *trans*-isomers, assuming negligible absorbance of the *cis*-isomers at that wavelength.

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Keywords: Cyclodextrins • Rotaxanes • Daisy chains • Oligomers • Inclusion complexes

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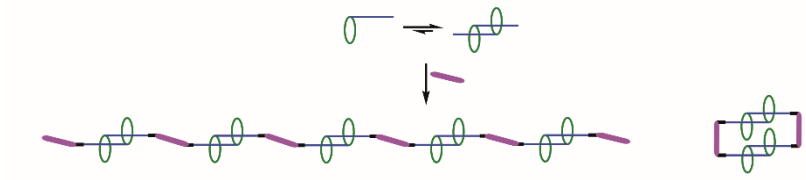

A direct approach is reported for the preparation of a linearly linked series of [*c*2]rotaxanes and cyclic analogues, including those illustrated, through oligomerization and simultaneous interlocking of self-assembled, dimeric cyclodextrin inclusion complexes.

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Direct Synthesis of an Oligomeric Series of Interlocked, Cyclodextrin-Based [*c*2]Daisy Chains