Rotaxane Synthesis

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Solid-Phase Synthesis of Oligo(phenylene ethynylene) Rotaxanes**

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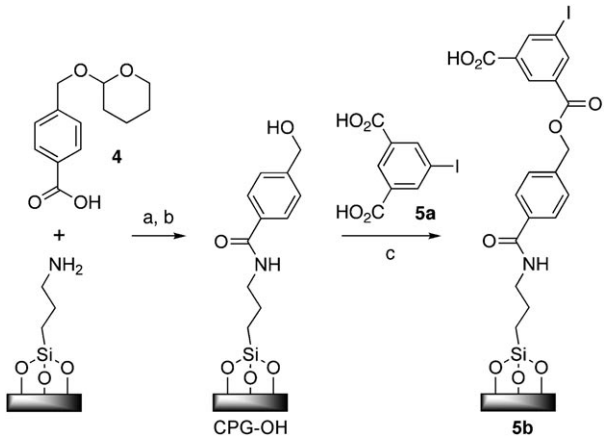
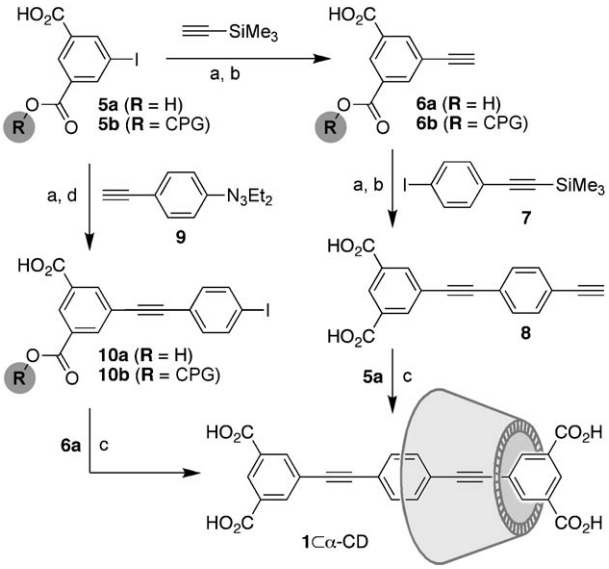
Solid-phase synthesis is an attractive method for the construction of complex linear oligomers, such as peptides and oligonucleotides, because it provides complete control of the oligomer length and sequence while avoiding the need for purification after every growth step.[1] This strategy has been exploited to synthesize π-conjugated oligomers for optoelectronic applications, such as oligo(phenylene ethynylene)s (OPEs),[2–4] oligothiophenes,[5,6] and oligo(phenylene triacetylene)s.[7] Solid-phase synthesis is also a promising strategy for the synthesis of monodisperse oligomeric "insulated molecular wires".[8] Recently we have developed the synthesis of polyrotaxane-type insulated molecular wires by threading cyclodextrin (CD) macrocycles onto a conjugated polymer chain to achieve supramolecular control of the chemical stability, photoluminescence, and electroluminescence efficiency.[8,9] Herein we report the first solid-phase synthesis of rotaxanes of this type. We have investigated the solid-phase synthesis of two [2]rotaxanes, **1**⊂α-CD and **2**⊂α-CD, and a [3]rotaxane, **3**⊂$(\alpha\text{-CD})_2$. Although rotaxanes were synthesized on the solid phase by Harrison and Harrison in 1967,[10] there have been few subsequent reports of solid-phase rotaxane synthesis,[11,12] and cyclodextrin rotaxanes[13] have not been previously prepared on a solid phase.

Our approach to the synthesis of conjugated polyrotaxanes uses the hydrophobic effect to drive the threading of cyclodextrin macrocycles onto a growing polymer chain, and thus requires aqueous conditions.[8] The challenge in translating this chemistry onto a solid support is to find a support that is compatible with the aqueous cyclodextrin-threading process. We chose controlled-pore glass because it has large rigid pores which should provide a suitable environment for aqueous host–guest chemistry, in contrast to solvent-swollen gels, which tend to exclude high-molecular-weight solutes, such as cyclodextrins.[14] Aminopropylsilylated controlled-pore glass was functionalized with a 5-iodoisophthalic acid stopper and an ester linker as shown in Scheme 1.

We first synthesized rotaxane **1**⊂α-CD using a "protected-alkyne route" via alkyne **8** (Scheme 2). This chemistry proceeds smoothly in solution, but fails on the solid phase because the terminal alkyne intermediate **6** is unstable when bound to CPG. Another problem with this route is that Glaser homo-coupling of alkyne **8** occurs as a minor side reaction



Scheme 1. Functionalization of aminopropylsilylated controlled-pore glass with the 5-iodoisophthalic acid stopper and a cleavable ester linker. Reagents: a) HBTU, DMAP, *i*Pr_2NEt, DMF; b) TsOH, MeOH, CH_2Cl_2; c) pyBOP, *i*Pr_2NEt, DMF.[15]



Scheme 2. Synthesis of rotaxane **1**⊂α-CD. Both routes gave the rotaxane when carried out in solution (R = H), but failed on the solid phase (R = CPG). Reagents: a) $[Pd_2(dba)_3]$, PPh_3, CuI, DMF, Et_3N; b) solution phase: NaOH, H_2O; solid phase: Na_2CO_3, MeOH; c) α-CD, $Pd(OAc)_2$, TPPTS, CuI, H_2O, Et_3N (followed by LiOH in the case of **10b**); d) I_2, MeCN.[15]

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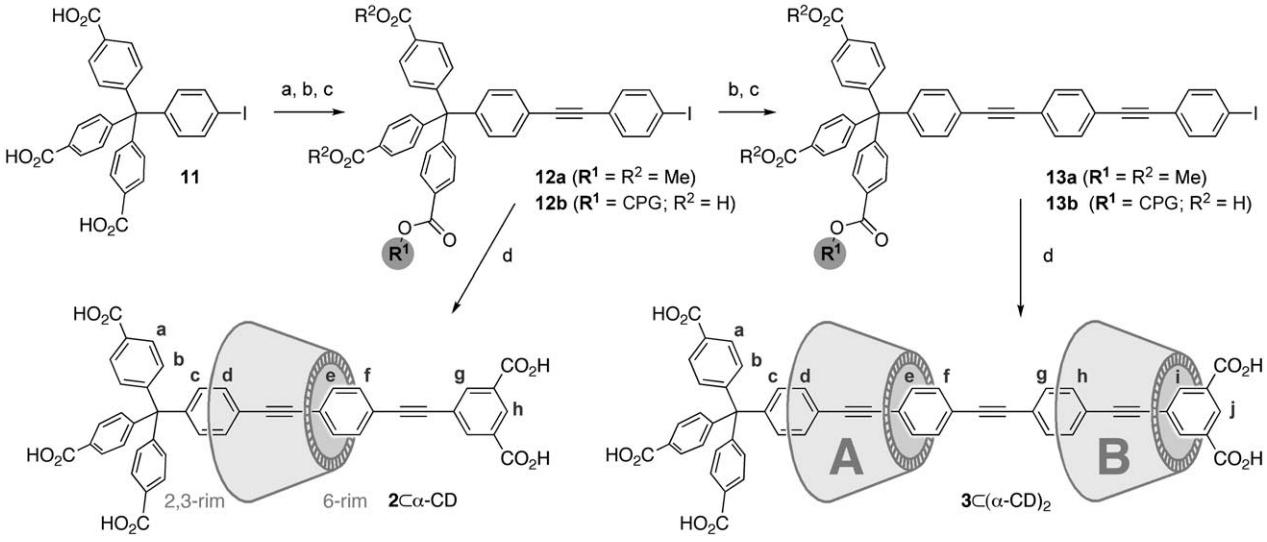
during Sonogashira cross-coupling. Thus we turned to the alternative "masked-iodide route" using triazene **9** and aryl iodide **10** (Scheme 2). In the solution phase, this route gives clean samples of the rotaxane **1**⊂α-CD (>90% yield by HPLC; 11% yield of isolated product).[16] The instability problem of terminal alkyne **6b** is avoided, but we were still unable to synthesize the rotaxane on the solid phase. In the absence of α-CD, support-bound aryl iodide **10b** reacts cleanly with alkyne **6a** under aqueous Sonogashira coupling conditions identical to those used to prepare **1**⊂α-CD in solution to give the dumbbell **1** after cleavage from the support with lithium hydroxide. However when this reaction is carried out on the solid phase in the presence of α-CD, no rotaxane is formed, and dumbbell **1** is still the main product.

After testing a variety of reaction conditions for solid-phase synthesis of **1**⊂α-CD without success, we conjectured that the environment on the surface of the support might be too crowded to allow threading of the cyclodextrin. To alleviate this congestion, we tried attaching a larger stopper to the support in place of iodoisophthalic acid **5a** to keep the OPE chains further apart. Use of the bulky tricarboxylic acid support-bound stopper **11** enabled the [2]rotaxane **2**⊂α-CD to be synthesized on the solid support and allowed us to extend this chemistry by another iteration to achieve the solid-phase synthesis of the [3]rotaxane **3**⊂$(\alpha\text{-CD})_2$ (Scheme 3). Rotaxanes **2**⊂α-CD and **3**⊂$(\alpha\text{-CD})_2$ were also synthesized by the same routes using solution-phase chemistry, giving identical products (**2**⊂α-CD: 97% conversion by HPLC, 12% yield of isolated product; **3**⊂$(\alpha\text{-CD})_2$: 63% conversion by HPLC, 2.4% yield of isolated product). The efficiency of rotaxane formation on the solid phase is similar to that in solution (HPLC analysis of solid-phase cleavage products shows that **2**⊂α-CD and **3**⊂$(\alpha\text{-CD})_2$ are formed with 83% and 85% conversion, respectively). The successful construction of [3]rotaxane **3**⊂$(\alpha\text{-CD})_2$ by solid-phase synthesis gives us confidence that this strategy could be extended to provide access to longer monodisperse insulated molecular wires.

The presence of two different stoppers in rotaxanes **2**⊂α-CD and **3**⊂$(\alpha\text{-CD})_2$ means that these compounds could exist as several stereoisomers with different threading orientations. Both rotaxanes are formed predominantly as one isomer, in solution and on the solid phase, with the wide 2,3-rims of the cyclodextrins pointing towards the large tetraarylmethane stopper. In NMR spectroscopic investigations of [2]rotaxane **2**⊂α-CD, NOEs were observed from the CD resonance H3 at the wide rim to aromatic protons b, c, d, e, and f, while proton H5 correlates with protons d, e, f, and g (see Figure 1 and Scheme 3 for atom-labeling scheme). Interestingly, protons H6 and H6′ at the narrow rim correlate strongly with protons e and g, but only weakly with proton f, implying that the α-CD is in fast exchange between two locations over the two alkyne units, spending little time on the central phenylene unit.

The two anomeric resonances ($H1_A$ and $H1_B$ of CD_A and CD_B, respectively, Figure 1) of **3**⊂$(\alpha\text{-CD})_2$ are well resolved, making it possible to assign most of the resonances of each cyclodextrin via spin diffusion. The NOESY spectrum of **3**⊂$(\alpha\text{-CD})_2$ (Figure 1a) shows a remarkably selective set of correlations: b–$H3_A$; c–$H3_A$; d–$H3_A$, $H5_A$; e–$H5_A$, $H6_A$, $H6'_A$; g–$H3_B$; h–$H3_B$, $H5_B$; and i–$H5_B$, $H6_B$, $H6'_B$. This simple pattern of interactions and the absence of any significant NOE from either cyclodextrin to proton f implies that the two cyclodextrins have well defined locations over the outer two alkyne units, as seen in the energy-minimized structure (Figure 1b).[17] At first sight it seems surprising that the two cyclodextrin units in the [3]rotaxane **3**⊂$(\alpha\text{-CD})_2$ are localized on the end alkyne units without visiting the central alkyne, whereas in the [2]rotaxane **2**⊂α-CD the cyclodextrin hops between both alkynes. The explanation is simply that the length of an OPE repeat unit (6.9 Å) is less than the length of a cyclodextrin (8.2 Å),[8] so that if the two α-CDs were to sit over adjacent alkynes, one of them would be pushed over a



Scheme 3. Solution-phase and solid-phase synthesis of rotaxanes **2**⊂α-CD and **3**⊂$(\alpha\text{-CD})_2$. Reagents and conditions: a) Solution phase: MeOH, H_2SO_4; solid phase: CPG-OH, pyBOP, iPr_2NEt; b) **5**, $[Pd_2(dba)_3]$, PPh_3, CuI, Et_3N; c) I_2; d) Solution phase: ester hydrolysis with LiOH, then **6a**, α-CD, $Pd(OAc)_2$, TPPTS, CuI, Na_2CO_3, H_2O; solid phase: **6a**, α-CD, $Pd(OAc)_2$, TPPTS, CuI, Na_2CO_3, H_2O, then LiOH.[15]

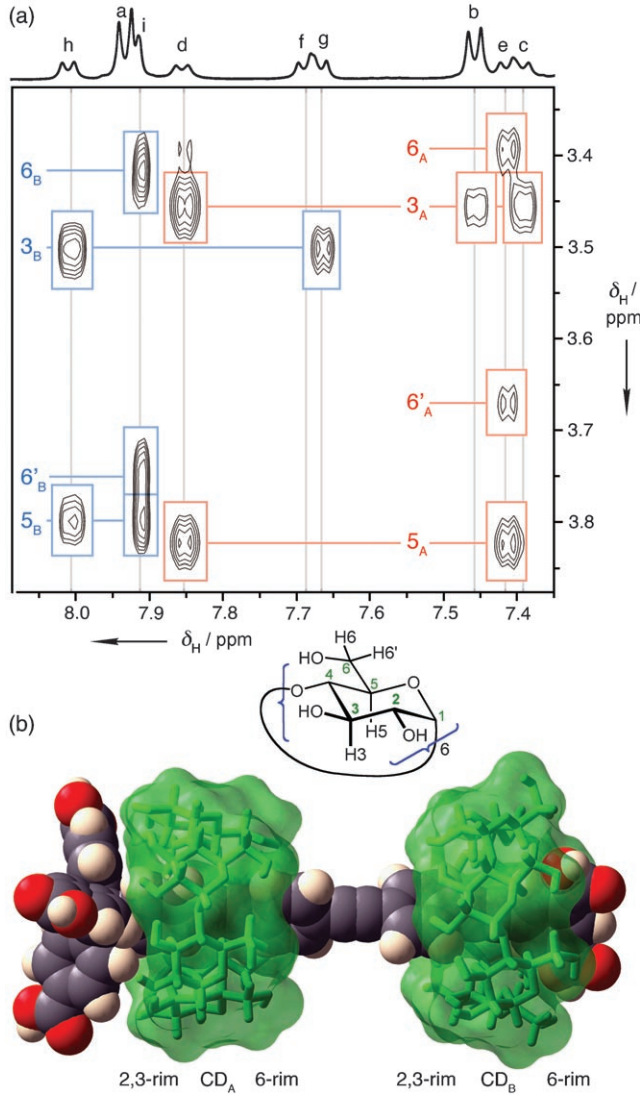


Figure 1. a) Partial NOESY spectrum of **3**⊂(α-CD)$_2$ ([D$_6$]DMSO, 298 K, 500 MHz). Cross-peaks to protons on the two cyclodextrin units (A and B) are shown in red and blue, respectively; resonances a–i are assigned to the aromatic protons as shown in Scheme 3. b) Calculated structure of **3**⊂(α-CD)$_2$ showing the van der Waals surface of **3** and the solvent-accessible surface of the α-CDs (1.4-Å probe radius).[17]

bulky phenylene residue.[18] This is the first cyclodextrin [3]rotaxane to be formed selectively as the head-to-tail isomer;[19] previous examples have been synthesized as tail-to-tail isomers (with both 6-rims at the center),[20,21] or as mixtures of stereoisomers.[22,23] This work represents the first solid-phase synthesis of a cyclodextrin rotaxane, the first solid-phase synthesis of any [3]rotaxane, and the first stereoselective synthesis of a cyclodextrin [3]rotaxane with a head-to-tail stereochemistry (with the 2,3-rims of both CDs pointing in the same direction). Use of the large tripodal anchor **11** as a grafting point during solid-phase synthesis is critical for avoiding crowding on the solid support, and will enable the final insulated molecular wires to be anchored to TiO_2 semiconductor nanoparticles.[24] The general synthetic strategy used to construct [3]rotaxane **3**⊂(α-CD)$_2$ by repeated coupling with masked aryl iodide monomers is not limited to Sonogashira coupling but could be combined with Suzuki coupling or Heck coupling to generate most varieties of π-conjugated oligomer. This methodology should be applicable to the construction of diverse insulated molecular wires, with precisely defined sequences, lengths, and end groups.

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[1] P. Seneci, *Solid-Phase Synthesis and Combinatorial Technologies*, Wiley, New York, **2000**.
[2] J. K. Young, J. C. Nelson, J. S. Moore, *J. Am. Chem. Soc.* **1994**, *116*, 10841–10842; E. L. Elliot, C. R. Ray, S. Kraft, J. R. Atkins, J. S. Moore, *J. Org. Chem.* **2006**, *71*, 5282–5290.
[3] L. Jones, J. S. Schumm, J. M. Tour, *J. Org. Chem.* **1997**, *62*, 1388–1410.
[4] S. Anderson, *Chem. Eur. J.* **2001**, *7*, 4706–4714.
[5] P. R. L. Malenfant, J. M. J. Fréchet, *Chem. Commun.* **1998**, 2657–2658.
[6] C. A. Briehn, P. Bäuerle, *Chem. Commun.* **2002**, 1015–1023.
[7] N. F. Utesch, F. Diederich, C. Boudon, J.-P. Gisselbrecht, M. Gross, *Helv. Chim. Acta* **2004**, *87*, 698–718.
[8] M. J. Frampton, H. L. Anderson, *Angew. Chem.* **2007**, *119*, 1046–1083; *Angew. Chem. Int. Ed.* **2007**, *46*, 1028–1064.
[9] F. Cacialli, J. S. Wilson, J. J. Michels, C. Daniel, C. Silva, R. H. Friend, N. Severin, P. Samori, J. P. Rabe, M. J. O'Connell, P. N. Taylor, H. L. Anderson, *Nat. Mater.* **2002**, *1*, 160–164.
[10] I. T. Harrison, S. Harrison, *J. Am. Chem. Soc.* **1967**, *89*, 5723–5724.
[11] J. A. Bravo, D. Orain, M. Bradley, *Chem. Commun.* **2002**, 194–195.
[12] K. D. Johnstone, N. Bampos, J. K. M. Sanders, M. J. Gunter, *Chem. Commun.* **2003**, 1396–1397; Y.-F. Ng, J.-C. Meillon, T. Ryan, A. P. Dominey, A. P. Davis, J. K. M. Sanders, *Angew. Chem.* **2001**, *113*, 1807–1810; *Angew. Chem. Int. Ed.* **2001**, *40*, 1757–1760.
[13] G. Wenz, B.-H. Han, A. Müller, *Chem. Rev.* **2006**, *106*, 782–817.
[14] The synthesis of **1**⊂α-CD and **2**⊂α-CD was also attempted on hydrophilic swollen gels, but rotaxane formation on these supports is less efficient than on controlled-pore glass. For example, we synthesized **2**⊂α-CD using the route shown in Scheme 3 with oligo(oxyethylene glycol) ether functionalized polystyrene in place of CPG (phenol ether linked PEG$_{400}$ on polystyrene cross-linked with 2 mol% divinylbenzene; poly(oxyethylene glycol) polymer (POP) resin, as described in M. C. McCairn, S. R. Tonge, A. J. Sutherland, *J. Org. Chem.* **2002**, *67*, 4847–4855). The product was a 50:1 mixture of **2** and **2**⊂α-CD (HPLC analysis after cleavage of the ester link with LiOH). Thus it appears that α-CD is excluded from the gel-phase support; however, it is known that large molecules, such as enzymes, enter some hydrophilic gels; see: A. Basso, B. A. Maltman, S. L. Flitsch, G. Margetts, I. Brazendale, C. Ebert, P. Linda, S. Verdelli, L. Gardossi, *Tetrahedron* **2005**, *61*, 971–976.
[15] Abbreviations: DMAP: *N*,*N*-dimethyl-4-pyridinamine; HBTU: O-(1H-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophospate; pyBOP: benzotriazol-1-yloxytris(pyrrolidino)-phosphonium hexafluorophospate; TPPTS: tris(3-sulfonatophenyl)phosphane trisodium salt; dba: *trans*,*trans*-dibenzylideneacetone; Ts: *para*-toluenesulfonyl.
[16] A similar rotaxane to **1**⊂α-CD was reported parallel to this investigation: J. S. Park, J. N. Wilson, K. I. Hardcastle, U. H. F. Bunz, M. Srinivasarao, *J. Am. Chem. Soc.* **2006**, *128*, 7714–7715.

[17] a) The geometry of **3**⊂(α-CD)$_2$ in water was calculated using MacroModel with the Merck Molecular Force Field; see: T. A. Halgren, *J. Comput. Chem.* **1999**, *20*, 720–729; T. A. Halgren, *J. Comput. Chem.* **1999**, *20*, 730–748. b) Cyclodextrins are normally represented with the 6-rim narrower than the 2,3-rim, as in Scheme 3, but the relative diameters of the rims can change with conformation. In the energy-minimized structure of **3**⊂(α-CD)$_2$ (Figure 1b), CD$_B$ adopts a conformation in which the 6-rim is wider than the 2,3-rim.
[18] A. Müller, G. Wenz, *Chem. Eur. J.* **2007**, *13*, 2218–2223.
[19] H. Yamaguchi, T. Oshikiri, A. Harada, *J. Phys. Condens. Matter* **2006**, *18*, S1809–S1816.
[20] M. R. Craig, T. D. W. Claridge, M. G. Hutchings, H. L. Anderson, *Chem. Commun.* **1999**, 1537–1538.
[21] D.-H. Qu, Q.-C. Wang, X. Ma, H. Tian, *Chem. Eur. J.* **2005**, *11*, 5929–5937.
[22] A. G. Cheetham, T. D. W. Claridge, H. L. Anderson, *Org. Biomol. Chem.* **2007**, *5*, 457–462.
[23] K. Sakamoto, Y. Takashima, H. Yamaguchi, A. Harada, *J. Org. Chem.* **2007**, *72*, 459–465.
[24] E. Galoppini, W. Guo, *J. Am. Chem. Soc.* **2001**, *123*, 4342–4343; Q. Wei, E. Galoppini, *Tetrahedron* **2004**, *60*, 8497–8508.

