Synthesis of fluorescent stilbene and tolan rotaxanes by Suzuki coupling

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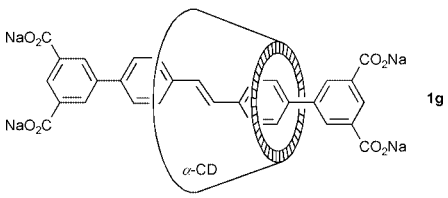
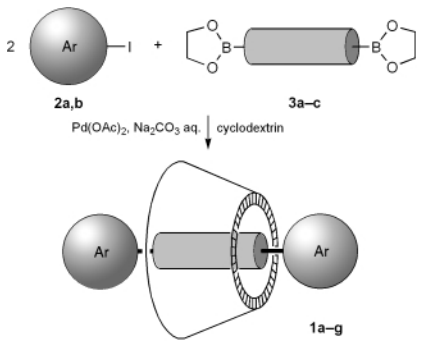
Received (in Cambridge, UK) 15th December 2000, Accepted 24th January 2001
First published as an Advance Article on the web 15th February 2001

Highly fluorescent stilbene and tolan cyclodextrin [2]rotaxanes have been synthesised in good yield using aqueous Suzuki coupling, and the crystal structure of one of these rotaxanes has been determined.

A rotaxane is a supramolecular assembly of a dumbbell locked through the cavity of a macrocycle.[1] The formation of rotaxanes provides a means of stabilising dumbbell-shaped chromophores, by shielding them from the external environment. This type of encapsulation can also enhance the fluorescence efficiency.[2] Hydrophobic binding is a convenient way of directing rotaxane formation, provided the dumbbell can be synthesised in water. Recently we reported the synthesis of poly-*p*-phenylene rotaxanes and polyrotaxanes using aqueous Suzuki coupling, although in this case the [2]rotaxane (**1a** in Table 1) was only obtained in low yield (4%).[3] While exploring the scope of this route to rotaxanes, we discovered that the right combinations of aryl iodide stopper, diboronic acid core and macrocycle components give highly fluorescent cyclodextrin encapsulated stilbenes and tolans, such as **1g**, in high yield. Previous stilbene rotaxanes have been prepared by aromatic nucleophilic substitution[4] and by slipping macrocycles over pre-formed dumbbells.[5]

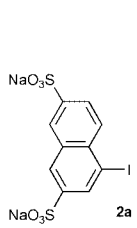
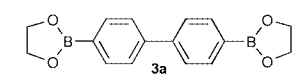
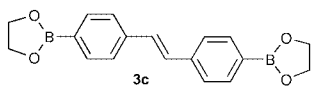
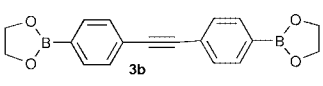
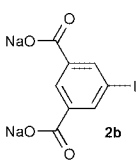
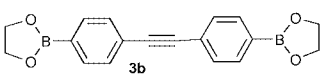
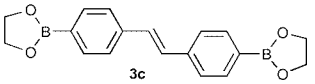
Six new rotaxanes **1b**–**g** have been prepared by reacting bulky water-soluble aryl iodides **2a** and **2b** with diboronic acids **3a**–**c**[6] in the presence of cyclodextrins (α-CD and β-CD; *ca*. 5 eq.), in aq. sodium carbonate containing palladium(II) acetate, as summarised in Scheme 1 and Table 1.† As expected, the 5-iodoisophthalic acid stopper **2b** is too narrow to form rotaxanes with β-CD, and the biphenyl diboronic acid core **3a** is too bulky to form rotaxanes with α-CD. Apart from these exceptions, all combinations of aryl iodides, diboronic acids and macrocycles yield rotaxanes. The lower yields obtained with the 1-iodonaphthalene-3,6-disulfonate stopper **2a** can be attributed to an unfavourable interaction between the bound CD and the inwardly pointing H8 of the naphthalene. The tetracarboxylate





Scheme 1

Table 1 Yields for rotaxane synthesis, and fluorescence behaviour of rotaxanes and dumbbells[a]

Stopper	Diboronic acid core	Macrocycle	Rotaxane	Yield (%) Rotaxane	Φ_F Rotaxane	Φ_F Dumbbell	λ_{max}(em)/nm Rotaxane	λ_{max}(em)/nm Dumbbell
		β-CD	**1a**	4	1.04	0.67	394	418
		α-CD	**1b**	31	1.08	0.81	387	409
		β-CD	**1c**	16	0.98		390	
		α-CD	**1d**	25	1.03	0.30	416	445
		β-CD	**1e**	14	0.72		425	
		α-CD	**1f**	50	0.99	0.89	360, 378	359, 378
		α-CD	**1g**	73	0.94	0.67	387, 406	385, 405

[a]Yields are for isolated rotaxanes; reaction conditions were similar to those detailed for **1g**. Fluorescence spectra were measured in water; quantum yields (Φ_F) are relative to quinine bisulfate in 0.5 M H_2SO_4 (Φ_F = 0.546) and are reproducible to within ± 10%.

DOI: 10.1039/b010015n

rotaxanes **1f** and **1g** are easier to isolate than the sulfonates **1a**–**e**, because they precipitate from aqueous solution at low pH. The smaller isophthalic acid stopper is still large enough to prevent unthreading of α-CD. For example **1g** shows no sign of unthreading after 10 d in D_2O at 80 °C; even after 10 d at 120 °C in d_6-DMSO no unthreading was detected.

One objective of this investigation was to explore how encapsulation affects the fluorescence efficiencies of tolan and stilbene chromophores. Comparison of the fluorescence quantum yields of all seven rotaxanes **1a**–**g** with those of their free dumbbells (Table 1) demonstrates that encapsulation always enhances the fluorescence yield. In both cases where α- and β-CD rotaxanes can be compared (**1b**/**c** and **1d**/**e**) the α-CD is found to give greater fluorescence enhancement. The cyclodextrin probably reduces the rate of non-radiative decay by restricting the flexibility of the excited state, and by hindering the approach of quenchers. A similar effect has recently been reported for stilbenes bound to antibodies.[7] Epoxidation of rotaxane **1g** and its dumbbell analogue with dimethyldioxirane was explored, in order to test the shielding of the chromophore. Dimethyldioxirane (Me_2CO_2) was selected for this experiment because it is small and highly reactive. The dumbbell reacted with dimethyldioxirane in aqueous acetone over a few hours to form the epoxide, whereas no reaction was detected with the rotaxane under the same conditions, even after 24 h, demonstrating that the C=C double bond of the rotaxane is hidden from this reagent.

In order to understand in more detail how the cyclodextrin interacts with the chromophore in these rotaxanes, we have determined the crystal structure of **1g** (as the tetracarboxylic acid).‡ To the best of our knowledge, this is the first crystal structure determination of any cyclodextrin-based rotaxane, although many such rotaxanes have been synthesised[1b] and crystal structures have been reported for cyclodextrin-based pseudorotaxanes and pseudopolyrotaxanes.[9] The α-CD sits round the centre of the chromophore (as shown in Fig. 1a). The stilbene unit is essentially planar (deviation from mean plane < 0.2 Å), with slight twists about both biphenyl links (torsional angles: 29° near the 6-rim; 24° near the 2,3-rim). The CD is distorted into an elliptical conformation, to accommodate the flat π-system, and this distortion is most pronounced around the narrower 6-rim of the macrocycle (Fig. 1b). For example the cavity width defined by the van der Waals surfaces of the H5 hydrogens is 5.3 Å for the transannular H5–H5 distance in the plane of the stilbene, but 4.0 and 4.3 Å for the other two transannular H5–H5 distances. NMR spectra show that the rotaxane is dynamic in solution at 298 K. Only one set of ^{1}H and ^{13}C glucose resonances is observed, showing that the CD rotates rapidly relative to the dumbbell. The H5 protons of the α-CD show NOEs to all six stilbene resonances, indicating that there is significant lateral motion of the macrocycle.

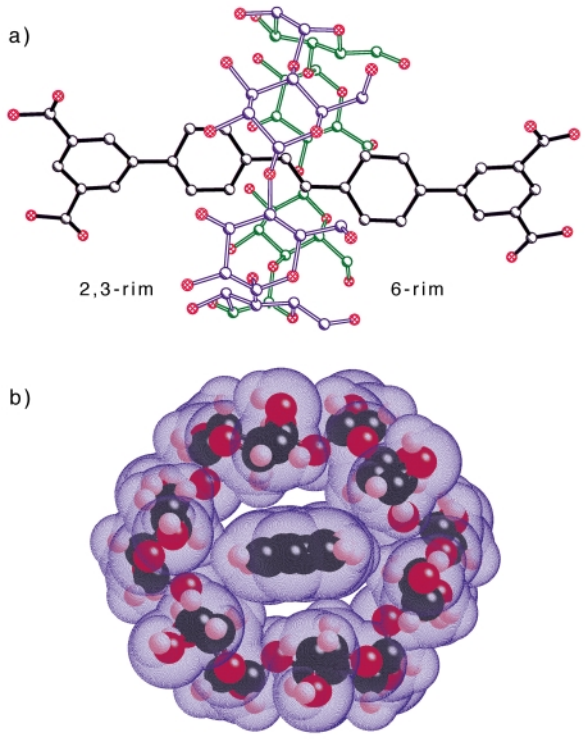


Fig. 1 Structure of rotaxane **1g** in the solid state: (a) view of whole molecule and (b) view of van der Waals surface, from the 6-rim end, with isophthalic acid units deleted for clarity.

In summary, we have shown that Suzuki coupling can be used to prepare cyclodextrin-based rotaxanes in good yield, and that this chemistry can be used to prepare stilbene and tolan rotaxanes with very high fluorescence quantum yields. The crystal structure of one of these compounds shows that the α-cyclodextrin clasps tightly round the centre of the stilbene chromophore.

This work was generously supported by the EPSRC and Avecia Ltd. We are grateful to Dr P. N. Taylor for valuable discussion, and to Dr M. G. Hutchings of DyStar UK Ltd. (Cheadle Hulme) for providing sodium 1-aminonaphthalene-3,6-disulfonate, for preparation of **2a**.

Notes and references

† Procedure for synthesis of **1g**: Water (8 cm^3), **2b** (151 mg, 0.63 mmol), **3c** (100 mg, 0.31 mmol), α-CD (1.6 g, 1.64 mmol), Na_2CO_3 (0.41 g, 3.9 mmol) and $Pd(OAc)_2$ (1.6 mg, 4 mol %) was stirred at 45 °C overnight. The mixture was diluted with Na_2CO_3 aq. (100 cm^3, 0.2 M), filtered, then acidified to pH 1 with HCl, to give a white suspension. The precipitate was separated by centrifugation, redissolved in Na_2CO_3 aq. (100 cm^3, 0.2 M), reprecipitated with acid, washed with water, dissolved in NH_3 aq. and evaporated to yield the ammonium salt of rotaxane **1g** (312 mg, 73%).

‡ Crystals of **1g** were grown over 2 weeks from aqueous solution in a 5 mm NMR tube by warming the lower region to 40 °C while the upper region was cooled to 20 °C. The structure was solved using synchrotron X-rays at Daresbury Station 9.8. *Crystal data* for **1g**: $C_{66}H_{80}O_{38}$, M = 1481.3, monoclinic, space group $I2$ (alternative setting of $C2$), a = 20.767(5), b = 13.960(3), c = 28.085(7) Å, β = 107.479(3)°; U = 7766(3) Å^3, Z = 4, λ = 0.6942 Å, μ = 0.11 mm^{-1}, T = 160 K, $R1$ = 0.164 for 9681 'observed reflections' [$F^2 > 2\sigma(F^2)$] and $wR2$ = 0.394 for all 10443 unique reflections ($\theta < 45°$). Methods and programs were as described elsewhere (ref. 8). Refinement included application of the SQUEEZE procedure (A. L. Spek, PLATON program, University of Utrecht, The Netherlands, 2000) to model diffuse electron density in two substantial voids per unit cell, presumably occupied by highly disordered solvent molecules. No H atoms were included, as they did not appear clearly in difference syntheses and those attached to oxygen atoms cannot be unambiguously placed from purely geometrical considerations. These limitations of the structural model and the weak diffraction due to disorder and crystal size and quality are reflected in the relatively high crystallographic residual factors, as is often found for cyclodextrin-containing materials. CCDC 156256. See http://www.rsc.org/suppdata/cc/b0/b010015n/ for crystallographic files in .cif format.

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