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Solid-phase template-directed synthesis of a [2]rotaxane using a solid-phase stopper

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Received (in Cambridge, UK) 29th August 2001, Accepted 10th December 2001
First published as an Advance Article on the web 17th January 2002

The first synthesis of a rotaxane by solid phase chemistry has been achieved, using the resin bead as a 'Mega' stopper during the synthesis. One of the advantages of this methodology over traditional solution routes include the ability to use mass action to drive the chemistry, without complicating the purification process.

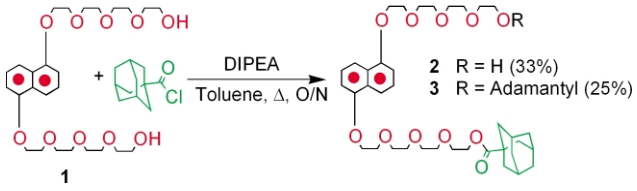
Since the first example of peptide synthesis by Merrifield in 1963,[1] solid phase chemistry has undergone a dramatic evolution. Today, a wide range of organic reactions can be carried out on the solid support to generate an impressive range of molecules.[2] Nevertheless, despite an intense interest, synthetic supramolecular chemistry[3] has not been exploited by solid phase chemists. The only example of which we are aware,[4] was the synthesis of a complex obtained by threading an alkyl chain inside a macrocycle immobolised on Merrifield resin using trityl stoppers. However, this was non-templated and required 70 cycles of reaction to give the final threaded complex in a 6% yield. Here, we wish to report the first solid-phase template-directed synthesis of [2]rotaxane.

[2]Rotaxanes[5] are molecules composed of one macrocycle encircling a dumbbell-shaped component. These compounds could only be prepared in low yielding reactions, until the advent of supramolecular chemistry which allowed the synthetic chemist to use non-covalent interactions in a template-directed synthesis.[6] One of the main difficulties encountered in the synthesis of donor–acceptor rotaxanes is their purification. We thus investigated the effect of the nature of the solid support on the synthesis of these compounds, using the inherent advantages of solid-phase chemistry with the use of high concentrations of reagents to drive the reaction to completion and the ease of filtration to remove excess reagents and salts, to obtain pure materials. In this study, a [2]rotaxane composed of a polyether chain, of the appropriate length,[7] incorporating a 1,5-dioxynaphthalene unit and terminating in an adamantyl derivative was employed to template the formation of cyclobis-(paraquat-*p*-phenylene) around the π-electron rich recognition site.

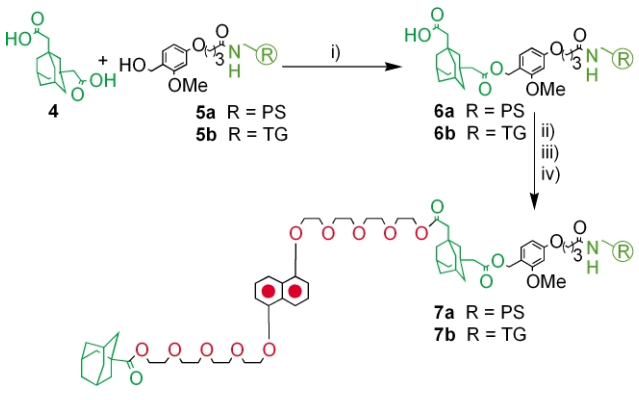
1,5-dioxynaphthalene polyether **1** was prepared in solution according to a literature procedure.[8] Reaction of **1** with adamantyl chloride, in the presence of DIPEA in toluene, gave a mixture of monoprotected and diprotected material **2** (33%) and **3** (25%), with **2** having one end free to be anchored to a solid support (Scheme 1). Solid-phase studies were carried out on either a polystyrene 1% DVB cross-linked resin (0.66 mmol g^{-1}) **5a** or TentaGel (0.27 mmol g^{-1}) **5b** with the acid cleavable linker; hydroxymethylmethoxyphenoxybutyric acid (HMPB linker).[9] 1,3-Adamantanediacetic acid **4** was loaded onto the resins **5a** and **5b**. From the cleavage from resins **6a** and **6b**, 90% and a nearly quantitative amount of 1,3-adamantanediacetic acid were recovered respectively. The best conditions for the attachment of the 1,5-dioxynaphthalene-based acyclic polyether **2** to the resin, were by pre-activation of the immobilised acid functionality with HOBt and DIC to give the activated HOBt esters, followed by treatment of the pre-swollen resins (using toluene) with DMAP in toluene for 3 days at reflux (Scheme 2).

The dumbbell compound was obtained following cleavage from the polystyrene resin **7a** and was then used to template the formation of cyclobis(paraquat-*p*-phenylene) in solution affording an authentic sample of [2]rotaxane **10·4PF$_6$** in a yield of 43% after column purification, ion-exchange and precipitation. Template synthesis was then studied on the solid phase. Resins **7a** and **7b** were reacted with a mixture of **8·2PF$_6$**[10] and **9** in NMP, DMF or DMSO and in the presence or absence of salts ($AgPF_6$ or NaI) (Scheme 3). After washing, the resins were submitted to TFA cleavage and the crude solutions were analysed by reverse phase HPLC. Table 1 gives the percentage of **10·4X** detected by HPLC (λ = 254 nm).

The best conditions found for the synthesis of the [2]rotaxane using solid-phase methods employed polystyrene resins with NMP as solvent and NaI or no counter ion to give [2]rotaxane in HPLC purities of 93% and 95% respectively, although DMF with polystyrene resin with no salt was also highly efficient. In these three cases, no trace of the starting material **8** was detected showing the completion of the conversion of the naphthalene template into [2]rotaxane. Clearly, two of the main advantages of solid-phase synthesis were being fully exploited here, firstly the ability to drive reactions to completion through mass action

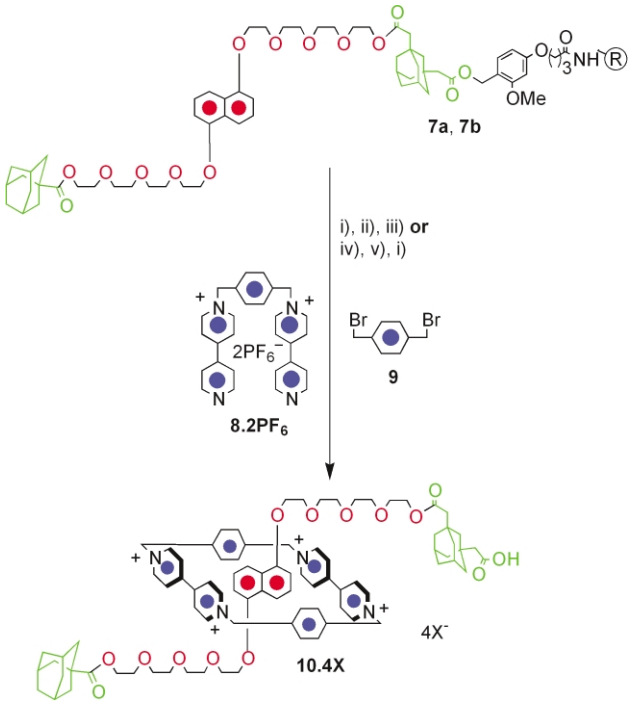


Scheme 1 Synthesis of the monoprotected dioxynaphthalene acyclic ether unit.



Scheme 2 Synthesis of the 'dumbbell' on solid phase. (i) **4** (2 eq.), HOBt (2 eq.), DIC (2 eq.), DMAP (1 eq.), DMF, rt, 2 days; (ii) DIC (10 eq.), HOBt (10 eq.), DMF, rt, 3 h; (iii) resin washed with DMF and pre-swollen in toluene; (iv) **2** (1.7 eq.), DMAP (1.7 eq.), toluene, Δ, 3 days.

DOI: 10.1039/b107813p



Scheme 3 Solution and solid-phase synthesis of [2]Rotaxane **10·4X**. (i) 60% TFA, 5% H_2O in DCM, rt, 4 h; (ii) **8·2PF$_6$**, **9**, CH_3CN, rt, 11 days; (iii) NH_4PF_6, (iv) **8·2PF$_6$**, **9**, rt, 3 weeks, others conditions (see Table); (v) resin washed with DMF, MeOH, NH_4Claq, MeOH–H_2O (1 : 1).

Table 1 Purity of **10·4X** determined by HPLC

		Salt		
Resin	Solvent	None	$AgPF_6$	NaI
7a	NMP	95%	0%	93%
7a	DMF	92%	8%	51%
7a	DMSO	7%	4%	0%
7b	NMP	3%	67%	0%
7b	DMF	15%	38%	64%
7b	DMSO	3%	0%	0%

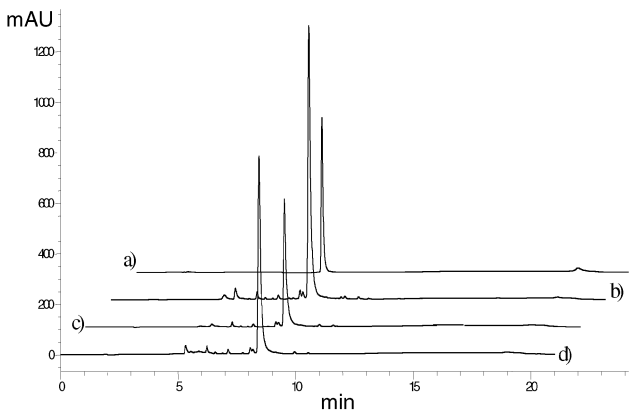


Fig. 1 HPLC traces recorded at 254 nm (a) authentic sample of rotaxane **10·4PF$_6$**, (b) from reaction of **7a** in NMP with NaI, (c) from reaction of **7a** in NMP without counter ion, (d) from reaction of **7a** in DMF without counter ion. (b, c, d = crude reaction mixture).

using high concentration of reagents and secondly the ease of purification following completion of reaction. This is clearly demonstrated by the excellent purities shown by HPLC (Fig. 1).[11]

In general, the polystyrene resin was found to be superior to TentaGel, despite the better swelling properties of the latter in polar solvents. Reactions employing DMSO as solvent gave poor results due to the poor swelling properties of resins in DMSO. With TentaGel, a PS-PEG based resin, the failure can be attributed to the ether's ability to compete with the acyclic polyether oxygens for interactions with the acidic hydrogens of the cyclophane component.

In conclusion, we have demonstrated that complete conversion of a naphthalene template into a [2]rotaxane in excellent purity could be achieved using a template-directed synthesis on solid-phase.

The authors thank the BBSRC (51/BO9512) for funding DO.

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11 Selected data for **10·4PF$_6$**, δ_H (400 MHz, CD_3COCD_3, 25 °C) 9.23 (bs, 4H, H_α), 9.08 (bs, 4H, $H_{\alpha'}$), 8.20 (bs, 4H, H_β), 7.71 (bs, 4H, $H_{\beta'}$), 6.34 (d, 2H, J = 7.5 Hz, H_{napht}); 6.13 (t, 2H, J = 8.0 Hz, H_{napht}), 5.99 (bs, 8H, N–CH_2); 4.38 (m, 4H, CH_2–O); 4.22 (m, 4H, CH_2–O); 3.98 (m, 4H, CH_2–O); 3.87 (m, 4H, CH_2–O); 3.76 (m, 4H, CH_2–O); 3.65 (m, 4H, CH_2–O); 3.50 (m, 4H, CH_2–O); 3.32 (m, 4H, CH_2–O); 2.7 (d, 2H, J = 7.5 Hz, H_{napht}); 2.0–1.20 (m, 33H, $H_{adamantyl}$). *m/z* (ES+ve): 357.6 [M − $4PF_6$]$^{4+}$ (100%), 525.0 [M − $3PF_6$]$^{3+}$ (60%), 859.9 [M − $2PF_6$]$^{2+}$ (10%).