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The synthesis of [2], [3] and [4]rotaxanes and semirotaxanes†

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The cucurbituril-catalysed synthesis of [2], [3] and [4]semirotaxanes allows access to regioselectively pure, 1,3-disubstituted mono-, bis- and tris-triazoles in high yield after dethreading.

A number of features render the macrocycle cucurbituril **1** an attractive choice to become incorporated into rotaxinated structures. This rigid, nonadecacyclic ligand possesses a hydrophobic interior capable of encapsulating as an upper limit five-membered alicycles, and 1,4-disubstituted benzene rings.[1] The two identical carbonyl-decorated portals of 4 Å diameter, which allow access to the 5.5 Å wide interior bind very strongly to organic mono- and di-ammonium ions as well as a wide variety of mono- and divalent metal ions.[1,2] In particular, the ability of cucurbituril to encapsulate aliphatic linear diammonium ions and the pH-dependent nature of the binding interactions have been used to design molecular switches,[3,4] and both solid[5,6] and solution state (pseudo)polyrotaxanes.[7–9]

Little though has been made of the most characteristic property associated with cucurbituril which is its ability to catalyse 1,3-dipolar cycloaddition reactions (Fig. 1) which has been applied to the synthesis of catalytically self-threaded polyrotaxanes.[1,8] Detailed kinetic studies by Mock *et al*. have led to the mechanistic picture in which an azide-substituted ammonium ion and an alkyne-derived ammonium ion form a ternary complex with cucurbituril.[1,10] The strong ion–dipole binding interactions between the portals of cucurbituril and each of the ammonium ions generates a pressure inside the cavity due to steric crowding. The release of the steric strain is channelled into the formation of the corresponding triazole derivative, a process, which by its very nature is regioselective (Fig. 1).[1,10] Highly relevant to our own efforts are recent investigations by Sanders *et al*.[11] and Philp *et al*.,[12] in which both groups have shown that it is possible to drive the regioselective formation of a particular Diels–Alder product through the involvement of elegantly designed synthetic receptors.

In the following we will demonstrate how the catalytic ability of cucurbituril can be harnessed for the preparation of [2], [3] and [4]rotaxanes and semirotaxanes in high yields. More significantly we show that efficient dethreading of [*n*]semirotaxanes allows isolation of regioselectively pure 1,3-disubstituted triazole compounds. To the best of our knowledge this is the only synthetic method which gives direct access to the 4-regioisomer of 1,3-triazole derivatives without the need for the separation of regioisomers[13,14] and should therefore be an attractive proposition in natural product synthesis.

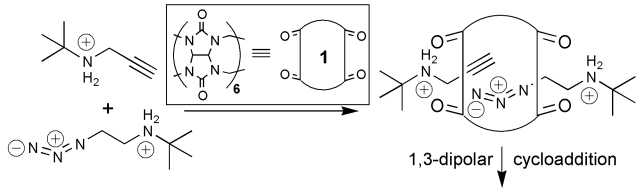

Fig. 1 An example of a 1,3-dipolar cycloaddition reaction catalysed by cucurbituril.

In Fig. 2 we have summarised the alkyne (**2**, **3**, **7** and **8**) and azido-functionalised (**4**–**6**) ammonium salts employed as starting materials and the various rotaxanes, pseudo- and semirotaxanes products (**9**–**16**) that were formed.§ In a typical experiment alkyne and azide ammonium salts were dissolved in 6N aqueous HCl before cucurbituril was added. The molar ratio of each component was chosen according to the molar ratio required to obtain the desired product. For example in the synthesis of [3]rotaxane **12**, compounds **1**, **3** and **6** were mixed in a molar ratio of 2:2:1. After stirring for 72 h at room temperature the solvent was removed under reduced pressure and the amorphous residue was suspended in hot water to remove unreacted cucurbituril by membrane filtration (0.45 μm pore diameter). The filtrate was precipitated into acetone, collected and dried. All [*n*]rotaxanes, [*n*]semi-, and [*n*]pseudorotaxanes were obtained in good to very good yield as shown in Table 1.

All compounds gave satisfactory mass spectrometry (Table 1), ^{1}H-NMR and ^{13}C-NMR data (supplementary material†). The absence of any additional ^{13}C signals related to starting material or other impurities was strong evidence for the high purity of the obtained rotaxanes (^{13}C spectra in supplementary material†). Elemental analysis on the other hand was complicated by the documented hygroscopic nature of both the parent macrocycle and the organic ammonium ions present in these

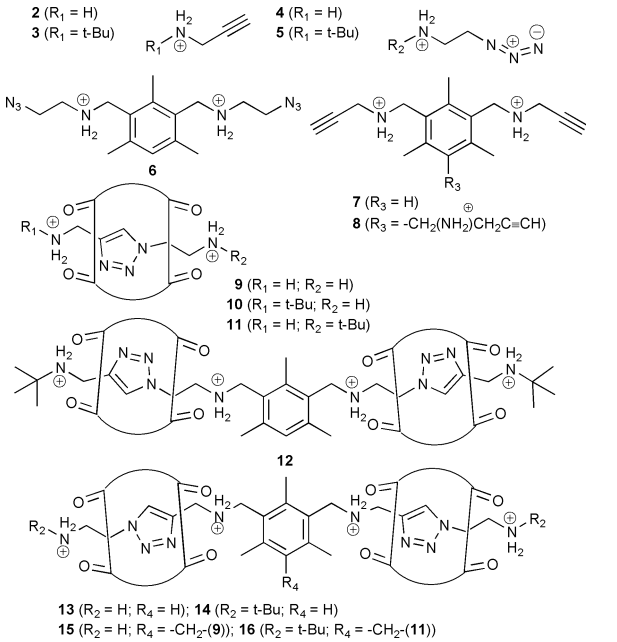

Fig. 2 Summary of alkyne and azide starting materials and all [*n*]rotaxanes, [*n*]semi- and pseudorotaxanes synthesised from them. (Cl^- counterions are omitted for clarity.)

† Electronic supplementary information (ESI) available: synthesis of compounds **13** and **16** and NMR data for compounds **9**–**16**. See http://www.rsc.org/suppdata/cc/b1/b109256c/

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Table 1 Analytical data for compounds **9**–**21**

Compound	Yield (%)	MS data	Elemental analysis	Compound[e]	Yield (%)
9	57	1138[d] [**9** − 2HCl]$^+$	$C_5H_{13}N_5Cl_2\cdot(C_{36}H_{36}N_{24}O_{12}) \times 8\ H_2O$ Calc.: C, 36.28; H, 4.98; N, 29.93 Found: C, 36.38; H, 4.69; N, 28.65%	**17**[a]	69
10	68	n.d.	n.d.	**18**[a]	71
11	68	1194[b] [**11** − 2HCl]$^+$	$C_9H_{21}N_5Cl_2\cdot(C_{36}H_{36}N_{24}O_{12}) \times 7\ H_2O$ Calc.: C, 38.82; H, 5.10; N, 29.19 Found: C, 38.58; H, 4.99; N, 29.57%	**19**[a]	65
12	71	2572.50[c] [**12** − 3Cl]$^+$	$C_{29}H_{54}N_{10}Cl_4\cdot(C_{36}H_{36}N_{24}O_{12})_2 \times 18\ H_2O$ Calc.: C, 40,42; H, 5.40; N, 26.08 Found: C, 39.33; H, 5.29; N, 26.32%	—	—
13	48	2420[d] [**13** − 4HCl]$^+$	$C_{21}H_{38}N_{10}Cl_4\cdot(C_{36}H_{36}N_{24}O_{12})_2 \times 31\ H_2O$ Calc.: C, 35.62; H, 4.73; N, 26.12 Found: C, 35.75; H, 5.55; N, 26.00%	**20**[a]	59
14	76	2573.10[c] [**14** − 3Cl]$^+$	$C_{29}H_{54}N_{10}Cl_4\cdot(C_{36}H_{36}N_{24}O_{12})_2 \times 21H_2O$ Calc.: C, 39.69; H, 5.54; N, 26.58 Found: C, 39.42; H, 5.39; N, 26.91%	—	—
15	63	3567[d] [**15** − 6HCl]$^+$	$C_{27}H_{51}N_{15}C_{16}\cdot(C_{36}H_{36}N_{24}O_{12})_3 \times 40\ H_2O$ Calc.: C, 35.96; H, 5.34; N, 27.02 Found: C, 35.53; H, 4.51; N, 27.36%	**21**[a]	55
16	75	3910[d] [**16**+Na − 2Cl]	$C_{39}H_{75}N_{15}Cl_6\cdot(C_{36}H_{36}N_{24}O_{12})_3 \times 35\ H_2O$ Calc.: C, 38.48; H, 5.56; N, 26.56 Found: C, 38.47; H, 4.86; N, 26.02%	—	—

[a] Yields obtained without isolation of the intermediate pseudo- or semirotaxane. Mass spectral data obtained by [b] (FAB + ve). [c] ES-MS; [d] MALDI-TOF; n.d. not determined. [e] Satisfactory MS data could not be obtained for compounds 17–21. The pH controlled dethreading of semi- and pseudorotaxanes **9**, **10**, **11**, **13** and **15** was achieved by slowly adding a saturated aqueous NaOH solution to the reaction mixture. The aqueous phase was extracted with chloroform to isolate triazoles **17**–**21**.

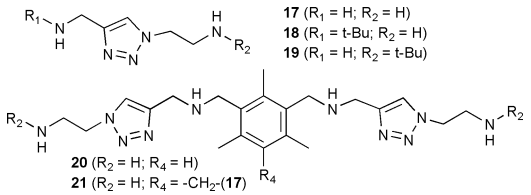

Fig. 3 Regioselectively pure 1,3-disubstituted triazoles **17**–**21** obtained after pH controlled dethreading.

rotaxanes and have prevented us so far from obtaining dehydrated samples despite prolonged drying even at elevated temperatures. Therefore the calculated microanalytical data were in good agreement with the experimental data once appropriate equivalents of water were added to the theoretical composition. The corresponding yields have been adjusted accordingly (Table 1).

A particularly helpful feature for the ^{1}H-NMR analysis was the large chemical shift differences encountered for the triazole proton. After successful catalytic self-threading the triazole moiety is located in the hydrophobic interior of cucurbituril showing a slightly broadened singlet close to 6.5 ppm. In the case of the [*n*]semi-, and [*n*]pseudorotaxanes it was possible to dethread the encapsulated triazoles **17**–**21** (Fig. 3) through extraction of the corresponding basified aqueous solution with chloroform in good yield (Table 1). The chemical shift of the triazole proton in the neutral compounds **17**–**21** was found to be around 7.5 ppm (in $CDCl_3$). This value moves further downfield to about 8.5 ppm when the same compounds (**17**–**21**) were dissolved in DCl–D_2O (20% (w/w). In the fortunate case of the [3]rotaxanes **12**–**14** we were able to make use of the integral of the lone phenyl proton which we compared to the integral for the triazole proton. The expected ratio of 2 : 1 (triazole : phenyl) was found in every case. We also determined the regioselectivity of our self-threading reactions by using the triazole proton as the sensitive probe. The triazole proton was assigned as a singlet for all compounds without exception. Reasonable doubt about the reliability of the triazole proton when encapsulated inside cucurbituril was dispelled once ^{1}H-NMR spectra of the unthreaded triazoles **17**–**21** also exhibited only one singlet in the ^{1}H-NMR and only two aromatic resonances in the ^{13}C-NMR spectra. Finally we also prepared triazole **19** from compounds **2** and **5** in the absence of cucurbituril in 6 N HCl at 90 °C for 48 h and obtained a 45 : 55 mixture of the 1,2- (5-isomer) and 1,3- (4-isomer) regioisomers as expected.

We have demonstrated that the self-threading process catalysed by cucurbituril is a very efficient synthetic tool to prepare [2], [3] and [4]rotaxanes, semi- and pseudorotaxanes. Dethreading of [*n*]semirotaxanes yields regioselectively pure triazole compounds.

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Notes and references

§ Compounds **3**–**5** have been synthesised according to procedures by Mock *et al.*[1] and compounds **1**, **6** and **7** by using the preparative information by Tuncel and Steinke.[8] All compounds gave satisfactory analytical data (see Table 1 and supplementary material†).

Preparation procedure: Synthesis of [4]rotaxane **16**.

Cucurbituril **1** (150.0 mg, 151.0 μmol) was dissolved in 6N HCl (4 ml) and stirred at rt for 30 min. Trisalkyne **8** (21.7 mg, 50.3 μmol) followed by azide **5** (27.0 mg, 151 μmol) were added under vigorous stirring to obtain a clear solution which was further stirred at rt for 72 h. The solvent was removed under reduced pressure to yield a light yellow film which was suspended in hot water (4 ml) at 80 °C and stirred for 1 h. Undissolved excess cucurbituril was removed by filtration. The remaining filtrate was precipitated into acetone (10 ml) and a white precipitate was collected by centrifugation. This was dried *in vacuo* over P_2O_5 for one week to afford title compound **16**.

Yield: 177.4 mg (89%) (with 35 H_2O).

1 W. L. Mock, *Top. Curr. Chem.*, 1995, **175**, 1.
2 J. Buschmann, K. Jansen, C. Meschke and E. Schollmeyer, *J. Sol. Chem.*, 1998, **27**, 135.
3 J. W. Lee, K. P. Kim and K. Kim, *Chem. Commun.*, 2001, 1042.
4 W. L. Mock and J. Pierpont, *J. Chem. Soc., Chem. Commun.*, 1990, 1509.
5 E. Lee, J. Kim, J. Heo, D. Whang and K. Kim, *Angew. Chem., Int. Ed.*, 2001, **40**, 399.
6 E. Lee, J. Heo and K. Kim, *Angew. Chem., Int. Ed.*, 2000, **39**, 2699.
7 C. Meschke, H.-J. Buschmann and E. Schollmeyer, *Polymer*, 1998, **40**, 945.
8 D. Tuncel and J. H. G. Steinke, *Chem. Commun.*, 1999, 1509.
9 D. Tuncel and J. H. G. Steinke, *Chem. Commun.*, 2001, 253.
10 W. L. Mock, A. Irra, J. P. Websiec and M. Adhya, *J. Org. Chem.*, 1989, **54**, 5302.
11 Z. Clyde-Watson, A. Vidal-Ferran, L. J. Twyman, C. J. Walter, D. W. J. McCallien, S. Fanni, N. Bampos, R. S. Wylie and J. K. M. Sanders, *New J. Chem.*, 1998, **22**, 493.
12 A. Robertson, D. Philp and N. Spencer, *Tetrahedron*, 1999, **55**, 11365.
13 K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, 1998, **98**, 863.
14 L. Fisera, V. Ondrus, J. Kuban, P. Micuch, I. Blanarikova and V. Jager, *J. Heterocycl. Chem.*, 2000, **37**, 551.