Synthesis of new hybrid macromolecules with cyclo-dendritic architecture

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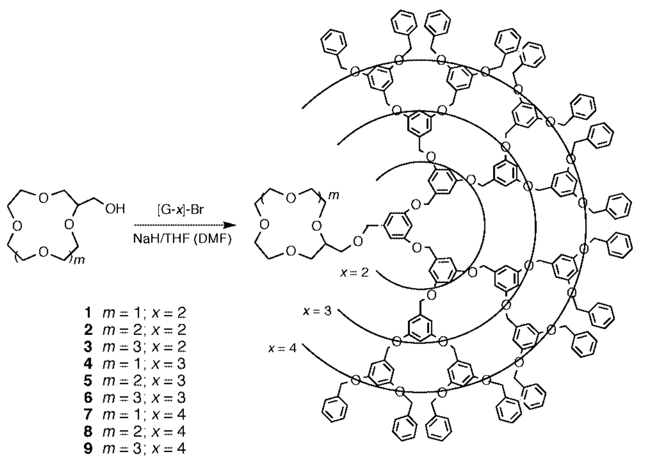
Novel cyclo-dendritic hybrid macromolecules were synthesized using preformed blocks: hydroxymethyl crown ethers and poly(benzyl ether) monodendrons.

The highly symmetrical three-dimensional shape of dendrimers and their fractal construction make them excellent and unique biological models.[1] It is already known that the dendritic shell can provide specific and selective microenvironments greatly affecting host–guest interactions.[2,3] The combination of dendrimers and other macromolecular topologies as building blocks is an attractive and promising approach in the development of suitable biological replicas for the study of molecular recognition and other cell processes.[4,5]

Compounds containing both crown ethers and dendritic wedges might have interesting ligating properties.[6] The first example of this type was published by Percec and co-workers in 1993.[7] DCC-mediated transesterification was used to produce molecules containing a crown ether moiety and taper-shaped fragments that could also be regarded as first-generation monodendrons. In subsequent papers the same authors reported the intriguing self-assembling properties of these compounds that were able to form unique cylindrical supramolecular structures upon interaction with metal salts.[8] However, the investigation was limited only to a single type of crown ether (15-crown-5) and first-generation monodendrons with flat geometry. The influence of the size and shape of the reactive fragments and the reaction conditions on the formation of the cyclo-dendritic hybrids has not been explored.

Here we report the synthesis of a new series of hybrid compounds **1**–**9** (Scheme 1) containing crown ethers of different sizes and three generations of poly(benzyl ether) dendrimers with different geometry. These compounds can bind alkali and alkaline-earth metal ions *via* their crown ether cavities and complex other guest molecules through the voids and the peripheral shell in the dendritic part of the molecule. In distinction to previous reports, the Williamson reaction was used to create an ether bond between the dendrons and 2-hydroxymethyl crown ethers.



Scheme 1

The synthetic strategy for the formation of the dendritic crowns involves a reaction between two preformed fragments. Previously we have shown that this approach is a versatile tool for the generation of different types of dendrimer-containing hybrid macromolecules.[9] Because of the proven accessibility of the functional group at the 'focal' point of the dendrimer[10] it could be applied also in the present study. Earlier we found that linear aliphatic polyethers used as one of the building blocks in the formation of dendritic hybrids have a noticeable auto-acceleration effect on the Williamson reaction employed for their formation.[10] Therefore one of the additional goals in the present investigation is to trace the eventual influence of the size of the cyclic polyether on the speed and the efficiency of the synthetic procedure. The dendritic bromides were synthesized by a known method[11] and the 2-hydroxymethyl crown ethers (from Aldrich) were used without further purification.

Initially we explored the synthetic pathway based on typical phase-transfer reaction conditions that was successfully applied in the synthesis of the poly(benzyl ether) dendrimers.[10] The reaction, performed in refluxing acetone with K_2CO_3 and 18-crown-6 as catalyst, afforded a complex mixture, which did not contain the desired product. Stronger bases like dry THF/NaH or DMF/NaH systems proved to be more efficient. In a typical reaction procedure NaH (4 mmol) was added as a powder to a solution of 0.1 mmol of 2-hydroxymethyl-crown ether and 0.105 mmol of dendritic bromide in 10 ml dry THF. The reaction mixture was stirred under nitrogen at room temperature for 140 h. The progress of the reaction was monitored by TLC (CH_2Cl_2–Et_2O = 9:1). After no further change was observed the reaction was stopped and THF was evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using gradient elution with a mixture of CH_2Cl_2–Et_2O for products containing the 12-crown-4 fragment (from 98:2 to 75:25 v/v) or CH_2Cl_2–acetone for larger cycles. When DMF was employed as the solvent at the end of the reaction the solution was precipitated into cold water and the crude filtered product was subsequently chromatographed.

The compounds composed of a second-generation dendritic bromide and all three 2-hydroxymethyl crown ethers are heavy oils; those of the higher generations are white foamy glassy solids. All reaction products were purified by flash chromatography and their purity was determined by TLC (single spot) on silica gel plates with fluorescent indicator and SEC at 40 °C in THF (single peak with double UV and RI detection). Their structure was confirmed by ^{1}H NMR spectroscopy.† All compounds yielded satisfactory elemental analyses and all exhibited very good correlation with the calculated molecular masses as evidenced by their MALDI-TOF spectra.

A summary of the reagents, reaction conditions and yields of the products is presented in Table 1. It can be seen that the Williamson synthesis performed in THF with NaH produced the desired products after long period of time in moderate yields. DMF (due to its higher polarity) facilitates the reaction and

Table 1 Influence of the reaction conditions and reagents' size on the yields of the cyclo-dendritic macromolecule[a]

Compound	Dendritic bromide	Crown ether	Yield (%) (purified)	*t*/h
1	[G-2]-Br	2-OH-12-crown-4	34.1	140
2	[G-2]-Br	2-OH-15-crown-5	29.2 (38.3)[b]	120 (24)[b]
3	[G-2]-Br	2-OH-18-crown-6	30.7 (37.1)[b]	96 (36)[b]
4	[G-3]-Br	2-OH-12-crown-4	20.2	140
5	[G-3]-Br	2-OH-15-crown-5	28.5 (45.4)[b]	120 (10)[b]
6	[G-3]-Br	2-OH-18-crown-6	24.1 (47.0)[b]	140 (24)[b]
7	[G-4]-Br	2-OH-12-crown-4	16.2 (17.0)[b]	140 (24)[b]
8	[G-4]-Br	2-OH-15-crown-5	21.5 (22.0)[b]	140 (24)[b]
9	[G-4]-Br	2-OH-18-crown-6	40.5 (39.8)[b]	140 (24)[b]

[a] Reaction conditions: dry THF, NaH, 5% excess of dendritic bromide. [b] Reactions performed in DMF at 70 °C.

improves the yields over reduced reaction times. An increase in reaction temperature to 70 °C and higher did not influence the reaction rate and the yields. To our surprise the ring size of the crown ethers did not effect substantially their nucleophilicity and all three of them have similar reactivity in the reaction with dendritic bromides. One would have expected 2-hydroxy-15-crown-5 to react faster and more effectively because of its additional complex binding towards Na^+, and this is partially true for the lower generations, but not with the fourth-generation dendritic bromide. The results from this study are not very conclusive in terms of dendritic activity. The change from a flat, two-dimensional geometry (second generation) to a globular shape (fourth generation) effects slightly the reactivity of the dendritic wedges. Despite the shielding effect of the large dendritic fragments, the focal point functionalities are still readily accessible for nucleophilic attack even in the fourth generation and this reconfirms our previous findings for the reactivity of dendrimers in Williamson reactions[10] and as macroinitiators for anionic ring-opening polymerization.[12]

The physical properties, self-assembling and binding capabilities of the new cyclo-dendritic hybrids are currently under investigation.

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Notes and references

† *Selected data* for **1**: δ_H($CDCl_3$, 200 MHz) 3.2–3.8 (7H, br), 4.45 (2H, s), 4.8–5.2 (12H, m), 6.5–6.8 (9H, d), 7.0–7.7 (20H, m); *m/z* (MALDI-TOF) 958.0 ($M^+ + Na^+$). For **2**: δ_H($CDCl_3$, 200 MHz) 3.3–3.9 (21H, br), 4.5 (2H, s), 4.8–5.2 (12H, m), 6.4–6.8 (9H, d), 7.0–7.7 (20H, m); *m/z* (MALDI-TOF) 1000.7 ($M^+ + Na^+$). For **3**: δ_H($CDCl_3$, 200 MHz) 3.4–3.8 (25H, br), 4.5 (2H, s), 4.8–5.2 (12H, m), 6.5–6.8 (9H, d), 7.0–7.7 (20H, br); *m/z* (MALDI-TOF) 1043.9 ($M^+ + Na^+$). For **4**: δ_H($CDCl_3$, 200 MHz) 3.4–3.8 (17H, br), 4.5 (2H, s), 4.8–5.2 (28H, m), 6.5–6.8 (21H, d), 7.0–7.7 (40H, m); *m/z* (MALDI-TOF) 1805.1 ($M^+ + Na^+$). For **5**: δ_H($CDCl_3$, 200 MHz) 3.4–3.8 (21H, br), 4.5 (2H, s), 4.8–5.2 (28H, m), 6.5–6.8 (21H, d), 7.0–7.7 (40H, m); *m/z* (MALDI-TOF) 1853.5 ($M^+ + Na^+$). For **6**: δ_H($CDCl_3$, 200 MHz) 3.4–3.8 (25H, br), 4.5 (2H, s), 4.8–5.2 (28H, br), 6.5–6.8 (21H, d), 7.0–7.7 (40H, m); *m/z* (MALDI-TOF) 1894.0 ($M^+ + Na^+$). For **7**: δ_H($CDCl_3$, 200 MHz) 3.4–3.9 (17H, br), 4.45 (2H, s), 4.7–5.2 (60H, m), 6.4–6.8 (45H, d), 7.0–7.6 (80H, m), *m/z* (MALDI-TOF) 3523.5 ($M^+ + 2Na^+$). For **8**: δ_H($CDCl_3$, 200 MHz) 3.4–3.8 (21H, br), 4.45 (2H, s), 4.6–5.2 (60H, m), 6.4–6.8 (45H, d), 7.0–7.7 (80H, m); *m/z* (MALDI-TOF) 3545.4 ($M^+ + Na^+$). For **9**: δ_H($CDCl_3$, 200 MHz) 3.4–3.8 (25H, br), 4.5 (2H, s), 4.6–5.2 (60H, m), 6.4–6.8 (45H, d), 7.0–7.6 (80H, m); *m/z* (MALDI-TOF) 3589.8 ($M^+ + Na^+$).

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