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Divergent synthesis of carbosilane wedges as dendritic building blocks: a new strategy towards core functionalised carbosilane dendrimers

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Abstract: A divergent route for the synthesis of carbosilane wedges containing either a bromine or amine as a focal point has been developed for the construction of core functionalised dendrimers; carbosilane dendrimers up to the third generation containing a 1,3,5-benzene triamide core capable of binding guest molecules *via* hydrogen bonding have been prepared.

Keywords: dendrimers, molecular recognition, complexation, amino acids

Dendrimers are interesting macromolecules that have fascinated chemists, biologists and material scientists for more than two decades owing to their well-defined, highly branched structures and physical properties.[1] The propensity of dendrimers to intercalate guest molecules and their potential application in drug delivery[2] and gene therapy[3] has attracted a lot of attention since the early developments in dendrimer chemistry. Dendrimers specifically designed for the molecular recognition of substrates,[4] including chiral molecules,[5] have been synthesised by connecting wedges (dendrons) to receptors. Part of our research aims at the introduction of catalytic centres[6] and binding sites in the core of the highly apolar carbosilane dendrimers. Carbosilane dendrimers are usually prepared *via* a divergent method[7] consisting of a repetitive sequence of hydrosilylations and Grignard alkenylations.[8] This method, however, does not allow the presence of functional groups such as amides, necessary for the binding of guest molecules by hydrogen bonding, since these groups are susceptible towards hydrosilylation and/or Grignard reagents. In this communication we report the divergent synthesis of carbosilane wedges as versatile building blocks for the convergent synthesis of core functionalised carbosilane dendrimers. Carbosilane dendrimers with a 1,3,5-benzene triamide core, capable of binding guest molecules by means of hydrogen bonding, were prepared using this combined divergent/convergent strategy.

A bromide function was selected to serve as a focal point of the carbosilane wedges because it is inert under the reaction conditions mentioned above and can readily be modified by substitution reactions. 3-Bromopropyltriallyl silane (**1**), the smallest wedge, was prepared as a starting compound for the synthesis of

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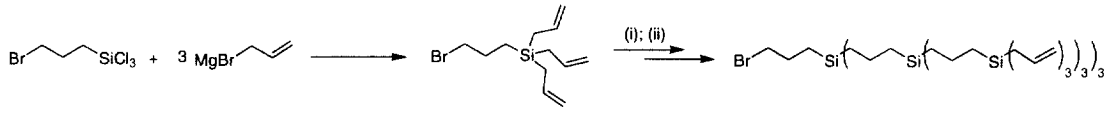
higher generations (Scheme 1). A platinum catalysed hydrosilylation of allyl bromide with trichlorosilane yielded 3-bromopropyltrichlorosilane in 70% yield after vacuum distillation, which gave **1** after a Grignard reaction with allylmagnesium bromide. Wedge **1** could be grown in the same way as described for the synthesis of carbosilane dendrimers by Van der Made et al.[8] *via* a repetitive sequence of hydrosilylation with trichlorosilane followed by a Grignard reaction with allylmagnesium bromide. No cross-coupling of the bromine functionalised wedges with the Grignard reagent nor oxidative addition on platinum was observed. Wedges up to the third generation were prepared in quantitative yields.



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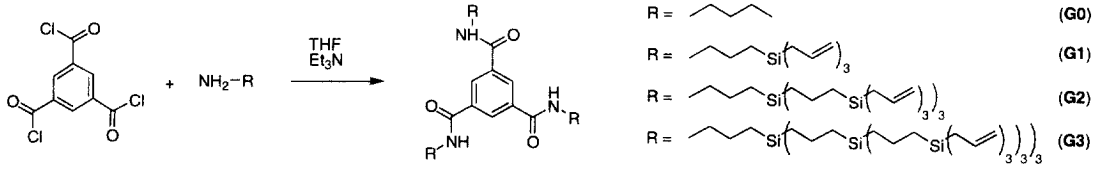
Scheme 1 Synthesis of higher generation carbosilane wedges from **1** (3rd generation wedge is shown). *Reaction conditions*: i, $HSiCl_3$, $(Bu_4N)_2Pt\ Cl_6$, r.t.; ii, (allyl)MgBr, Et_2O, reflux 4-6 hr.

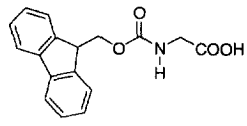


Scheme 2 Synthesis of different generation carbosilane dendrimers containing a 1,3,5-benzene triamide core.

Amine functionalised wedges were prepared by stirring the different generation bromine functionalised wedges in a large excess of liquid ammonia at 70°C under 15 bar of pressure. The amine wedges were isolated in 90 – 96% yield. Condensation of these wedges with 1,3,5-benzene tricarbonyl trichloride in dry THF in the presence of triethylamine yielded carbosilane dendrimers containing a 1,3,5-benzene triamide core (**G1** – **G3**) in 40 – 60% yield after column chromatography (Scheme 2). Benzene-1,3,5-tricarboxylic acid *tris*-butylamide (**G0**) was prepared under similar conditions. Both **G0** and **G1** are white solids, whereas **G2** and **G3** are colorless oils. All dendrimers were characterised by IR, ^1H and ^{13}C NMR, elemental analysis and MALDI-TOF mass spectrometry.[9]

Binding studies were performed in dry $CDCl_3$ with **G0** – **G3** using FMOC-glycine (**2**), *Z*-glutamic acid 1-methylester (**3**) and propionic acid (**4**) as the guest molecules. ^1H-NMR titration experiments were employed to determine the association constants K_a (M^{-1}) and complexation induced shifts δ_{CIS} (Hz). The shifts of the

aromatic and amide protons of the dendrimers were monitored during the titration experiments[10] (Table 1). Good fitting curves were obtained when the formation of 1:1 complexes was assumed.



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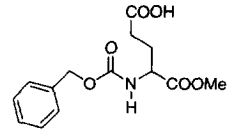

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Table 1 Association constants K_a and complexation induced shifts δ_{CIS} of the dendrimer-guest complexes in $CDCl_3$.

dendrimer	guest	K_a (M^{-1}) [a]	$\delta_{CIS, NH}$ (Hz)	$\delta_{CIS, ArH}$ (Hz)
G0	**2**	87	352 ± 2	92 ± 2
G1	**2**	69	298 ± 7	78 ± 2
G2	**2**	65	190 ± 5	56 ± 2
G3	**2**	5[b]		
G0	**3**	40	314 ± 4	100 ± 2
G1	**3**	38	283 ± 12	88 ± 3
G2	**3**	10	343 ± 53	95 ± 2
G3	**3**	5[b]		
G2	**4**	24	418 ± 6	142 ± 2

[a]Calculated from the shifts of the aromatic and amide protons of the dendrimer, estimated error 10%.

[b]Estimated K values; due to the small shifts no accurate calculations could be made.

The observed shifts of the NMR signals of the amide protons present in the dendrimers clearly indicates that binding of the guest molecules is based on hydrogen bonding. This is substantiated by IR measurements of the hosts showing a new, lowered amide N-H stretching vibration upon complexing a guest molecule. For example, complexation of **G2** (ν_{NH} = 3448 cm^{-1}) with **4** results in the appearance of a NH stretching vibration at 3385 cm^{-1}. The association constants reveal that the binding with guests **2** and **3** is slightly weaker in higher generation dendrimers. The small decrease in binding constant is likely due to the increase in steric demand, as has been observed previously by others.[4b] The low association constant found for **4** compared to **2** suggests that the amide bond in **2** contributes to the binding with the dendrimer core. Amino acid **3** is bound weaker than **2** which might be attributed to the steric bulk around the amide bond in **3** or a different hydrogen bond pattern.

A drop in δ_{CIS} value is observed for the higher generation hosts upon complexation with **2**, indicating that the geometry of the host-guest complexes of **G2** differ from that of **G0** and **G1**. This drop in δ_{CIS} is not observed upon complexation of guest **3** suggesting that these complexes adopt a similar geometry.

In conclusion, we have synthesised in a divergent manner a novel series of carbosilane dendritic wedges with either a bromine or amine as focal point. These compounds allow a straightforward synthesis of core functionalised carbosilane dendrimers. Carbosilane dendrimers containing a 1,3,5-benzene triamide core can easily be prepared using this combined divergent/convergent strategy. Molecular recognition based on hydrogen bonding in carbosilane dendrimers has been demonstrated.

Notes and references

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9. Selected data **G0**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 3H), 7.33 (broad t, 3H), 3.38 (q, J = 6.4 Hz, 6H), 1.57 (quintet, J = 7.3 Hz, 6H), 1.38 (sextet, J = 7.4 Hz, 6H) and 0.95 (t, J = 7.3 Hz, 9H) ppm; Anal. Calcd. for $C_{21}H_{33}N_3O_3$: C, 67.17, H, 8.86, N, 11.19. Found: C, 66.86, H, 8.76, N, 11.22. **G1**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 3H), 6.54 (t, J = 5.6 Hz, 3H), 5.78 (m, 9H), 4.90 (m, 18H), 3.45 (q, J = 6.7 Hz, 6H), 1.63 (m, 6H), 1.62 (d, J = 8.0 Hz, 18H) and 0.66 (m, 6H) ppm; MALDI-TOF MS *m/z* 890 $[M + Ag]^+$. **G2**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 3H), 6.44 (t, J = 5.6 Hz, 3H), 5.77 (m, 27H), 4.88 (m, 54H), 3.44 (q, J = 6.7 Hz, 6H), 1.58 (m, 6H), 1,58 (d, J = 8.0 Hz, 54H), 1.36 (M, 18H), 0.67 (m, 18H), 0.59 (m, 18H) and 0.54 (m, 6H) ppm; MALDI-TOF MS *m/z* 2261 $[M + Ag]^+$; Anal. Calcd. for $C_{126}H_{213}N_3O_3Si_{12}$: C, 70.22, H, 9.96, N, 1.95. Found: C, 69.99, H, 10.01, N, 1.91. **G3**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 3H), 6.43 (broad t, 3H), 5.77 (m, 81H), 4.89 (m, 162H), 3.42 (q, J = 5.8 Hz, 6H), 1.59 (m, 6H), 1.36 (m, 72H), 0.66 (m, 72H) and 0.61 ppm (m, 78H); MALDI-TOF MS *m/z* 6375 $[M + Ag]^+$; Anal. Calcd. for $C_{369}H_{645}N_3O_3Si_{30}$: C, 70.71, H, 10.37, N, 0.67. Found: C, 70.52, H, 10.22, N, 0.68.
10. The ^{1}H NMR titration experiments (300 MHz) were performed in $CDCl_3$ that was previously distilled from calcium hydride and stored on molecular sieves (4Å). The dendrimer concentration in the prepared solutions was *ca.* 5 mM and contained up to 5 equivalents of guest except for the titration with propionic acid in which the dendrimer concentration was 14 mM and solutions containing up to 10 equivalents of acid were measured. The association constants and complexation induced shifts were obtained by non-linear least-squares fitting using the GraFit 4.0 software package. The uncertainties are the standard deviations determined by the error analysis of the program.