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Multisite Functionalized Dendritic Macromolecules Prepared via Metalation by Superbases and Reaction with Electrophiles

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Dendritic macromolecules are highly branched polymers with controlled architecture and unique properties.[1,2] Their chemical and physical properties have been shown to be greatly affected by their chain-end functionalities and internal composition.[3] We now report a method for the introduction of functional groups into internal sites of preformed dendritic poly(benzyl ethers). This approach, coupled to our earlier work[3] on the peripheral (chain-end) functionalization of dendritic macromolecules, provides access to a broad spectrum of highly novel globular molecules with functionalization within the globule itself or at its periphery.

In these experiments, the dendrimer assigned as [G-4]-OH in Scheme I was used as starting material. Control over functionalization sites is due to H-atom reactivity differences. The benzyl ether dendrimer[1] [G-4]-OH contains a total of 46 activated H-sites: 31 sites consisting of H-atoms in the benzylic positions, and 15 H-atoms located on aromatic rings between the two oxygen substituents. It was assumed that these H-atoms could undergo an easy hydrogen–metal exchange (metalation) in reactions with strong bases like superbases (SBs). In reactions with substrates, SBs give rise to a heavier alkali metal derivative of the substrate,[4–7] as shown in the following equation:

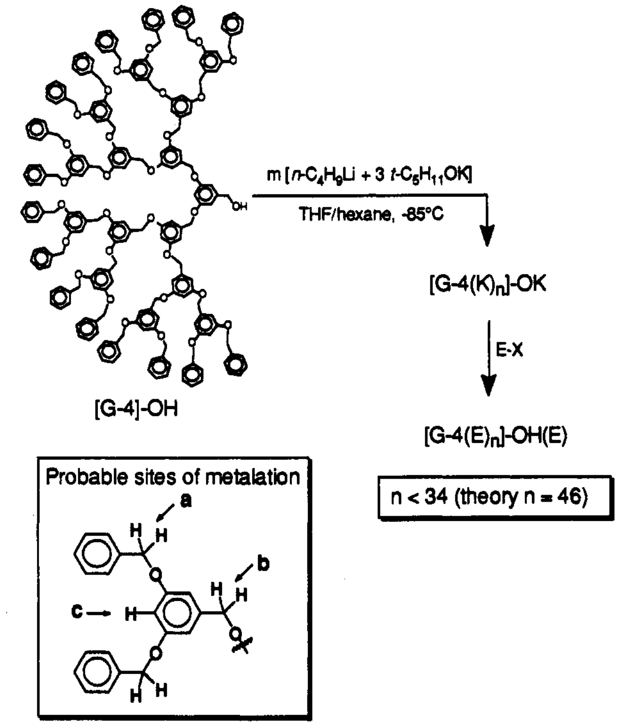
$$R_1H + [R_2Li + R_3OK] \rightarrow R_1K + R_2H + R_3OLi \qquad (pK(R_2H) > pK(R_1H))$$

The potassium derivative of the substrate then reacts easily with electrophiles to yield a substituted substrate.

The metalation of [G-4]-OH by a superbase (SB) prepared from butyllithium and 3 equiv of potassium *tert*-pentoxide[5] proceeds smoothly in THF/hexane mixture at −85 °C to afford polymetalated [G-4]-OH[8] (Scheme I). In the quenching step, an electrophile is added[8] (see Table I for reagents), and a polysubstituted dendrimer is isolated in good yield.

The number and location of metal atoms introduced into [G-4]-OH were estimated by ^{1}H NMR after reaction with electrophiles. Signals of the peripheral aromatic ring protons (7.6–6.9 ppm) were used as internal standard in these analyses. It was assumed that reactions of metalated [G-4]-OH with electrophiles were quantitative and that the peripheral aromatic ring protons remained untouched during metalation due to their much lower acidity. Table I shows clearly that benzylic protons (5.1–4.9 ppm) are substituted much more easily by an alkali metal than the protons of internal aromatic rings (6.7–6.5 ppm), despite the fact that these are located between two oxygen substituents.

Scheme I



The ^{1}H NMR spectra[1] of [G-4]-OH and of dendrimers [G-4(Si(CH$_3$)$_3$)$_{\sim 30}$]-OH and [G-4(CO$_2$CH$_3$)$_{\sim 30}$]-OH provide confirmation of the substitution with upfield or downfield shifts observed for the dendrimer protons according to the properties of the substituents. For example, the signals of the peripheral aromatic ring protons appear between 7.34 and 7.26 ppm in the unsubstituted [G-4]-OH, while they are found between 7.13 and 7.02 ppm in the substituted dendrimer [G-4(Si(CH$_3$)$_3$)$_{\sim 30}$]-OH. There is essentially no signal downfield of 7.25 ppm in this dendrimer, which would correspond to peripheral aromatic ring protons of the unsubstituted [G-4]-OH. This indicates that in the metalation of [G-4]-OH the peripheral benzylic groups are metalated more readily than other activated H-atoms. This is confirmed by the product from quenching with D$_2$O, in which the resonance for the peripheral benzylic groups decreases in intensity relative to the resonance for the internal benzylic sites. These findings may result from easier accessibility to the reagent, as well as some electronic effects. For [G-4(CO$_2$CH$_3$)$_{\sim 30}$]-OH, the peripheral ring protons are observed between 7.60 and 7.25 ppm, as expected for the protons of a molecule substituted with electron-withdrawing groups. The resonances of the protons of the carboxylated benzylic sites also shift to 5.7–5.4 ppm.

Experiments with D$_2$O quenching at various time intervals show that the metalation of the dendrimer is fast, with the majority of metal atoms (about 27) being introduced within the first 5 min. Further substitution is very slow, and only ca. 10% of additional sites become metalated within the next 24 h. Thus, the introduction of more than 30 metal atoms per [G-4]-OH is possible only under forcing conditions. The product, isolated after metalation for 24 h at −85 °C, is identical in terms of NMR and polydispersity to those isolated after shorter reaction times, confirming the relatively high stability of the polyanion under these conditions. In contrast, an almost complete rearrangement of the polyanion is observed at room temperature within 10 min.

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(8) SB was prepared by mixing a 1 M solution of potassium *tert*-pentoxide in THF (3 equiv) with a 1.2 M solution of butyllithium in hexane (1 equiv) at −85 °C. A THF solution of [G-4]-OH (typically 0.100 mmol in 5 mL of THF; ratio SB/[G-4]-OH given in Table I) was then added, and the red solution was stirred further at −85 °C for the time given in Table I. After addition of an electrophile and stirring for 15 min, the substituted [G-4]-OH was isolated by precipitation in hexane (deuterated or carboxylated [G-4]-OH) or in 90% methanol (other derivatives). For NMR data, averages of several measurements are presented in Table I.

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Table I. Multisite Substituted Dendrimers, [G-4(E)$_n$]-OH, via Metalation by Superbase (SB) and Reaction with an Electrophile

[SB]/[[G-4]-OH]	metalation time (min)	introduced group or atom E[a]	yield (mol %)[b]	number and location of E[c]			effectiveness of SB, F[d] (%)	mol wt of dendrimers[e]		
				aromatic	benzylic	total		M_n(calcd)[f]	M_n(found)	M_w/M_n
23	60	D	96	3	18	21	92	3312	3600	1.02
23	60	$Si(CH_3)_3$	89			22	96	4879	4900	1.02
46	5	D	90	4	23	27	59	3318	3700	1.02
46	60	D	90	5	21	26	57			
46	300	D	91	5	22	27	59			
46	1380	D	85	7	23	30	65	3321	3600	1.01
46	60	$Si(CH_3)_3$	91			29	63	5385	6250	1.02
46	60	$C_{18}H_{37}$	92			~33[g]	~72[g]	11 623	13 400	1.03
46	360	COOH	100			28,[h] 24[i]	61	4916[h]	4700[h]	1.07
92	60	D	93	8	26	34	37	3325	3500	1.04
92	60	$Si(CH_3)_3$	62			31	34	5529	5900	1.06

[a] For introduction of group or atom E, the following electrophiles were used: D_2O, $(CH_3)_3SiCl$, $C_{18}H_{37}Br$, and CO_2. [b] Mol wt of the product calculated according to *f*. [c] From ^1H NMR data. [d] Effectiveness $F = n(E)100/[\text{molar ratio (SB/[G-4]-OH)}]$. [e] SEC absolute data. [f] $M_n(\text{calcd}) = 3\,291 - n(E) + nMW(E)$. [g] The mass ratio dendrimer/C18 groups is very low, and therefore the NMR estimation is less accurate. [h] After esterification with CH_2N_2. [i] Titration with methanolic NaOH.

This side reaction is probably a Wittig rearrangement[9] that occurs without fragmentation of the dendrimer.

The number of metalated sites increases with increasing SB/[G-4]-OH ratio. However, it is not possible to substitute all of the 46 potential reaction sites under the conditions used. With a ratio SB/[G-4]-OH = 46, only ca. 30 H-atoms can be exchanged for metal atoms. Even with a two-fold excess of SB relative to all active H-atoms (SB/[G-4]-OH = 92), only about 34 H-atoms can be substituted (Table I). Therefore, the efficiency of SB, defined as $F = n(E)100/[\text{molar ratio (SB/[G-4]-OH)}]$, is low in this case. At lower SB/[G-4]-OH ratios, the effectiveness of SB increases and reaches ca. 95% for SB/[G-4]-OH = 23. It appears that this extent of metalation is much easier to achieve.

The metalation of dendrimers followed by reaction with electrophiles provides access to multifunctionalized dendrimers. These products may exhibit new properties, for example, enhanced or segmented hydrophilic or hydrophobic behavior. Due to the high reactivity of the organopotassium intermediate, the choice of suitable electrophiles is broad, and a variety of new products is accessible. We have demonstrated the attachment of long alkyl chains, silicon groups, deuterium, and carboxylic acid groups to sites throughout the dendritic structure. Reaction of a metalated [G-4]-OH with CO_2 gives rise to a poly(carboxylic acid) bearing ca. 30 carboxylic groups that can be solubilized in water after neutralization. Reaction with octadecyl bromide gives a hydrophobic material which is soluble in hexane, unlike [G-4]-OH. The preparation of unusual globular amphiphilic molecules is under study.

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