Control of Surface Functionality in the Synthesis of Dendritic Macromolecules Using the Convergent-Growth Approach

Dendritic macromolecules such as the "starburst" dendrimers[1,2] are characterized by entanglement-free hyperbranched structures that contain a very large number of chain ends at the periphery of the macromolecules. The traditional approach[1-6] to such dendritic structures involves the addition of a polyfunctional monomer to a central core containing two or more coupling sites. This is followed by sequential addition–modification steps with outward growth from the central core and with the formation of an increasingly large amount of identical chain ends at the outer boundaries of the polymer. While this approach is very successful, it offers little opportunity for the placement of just *one* or any limited number of reactive functionalities at the periphery of the macromolecule.

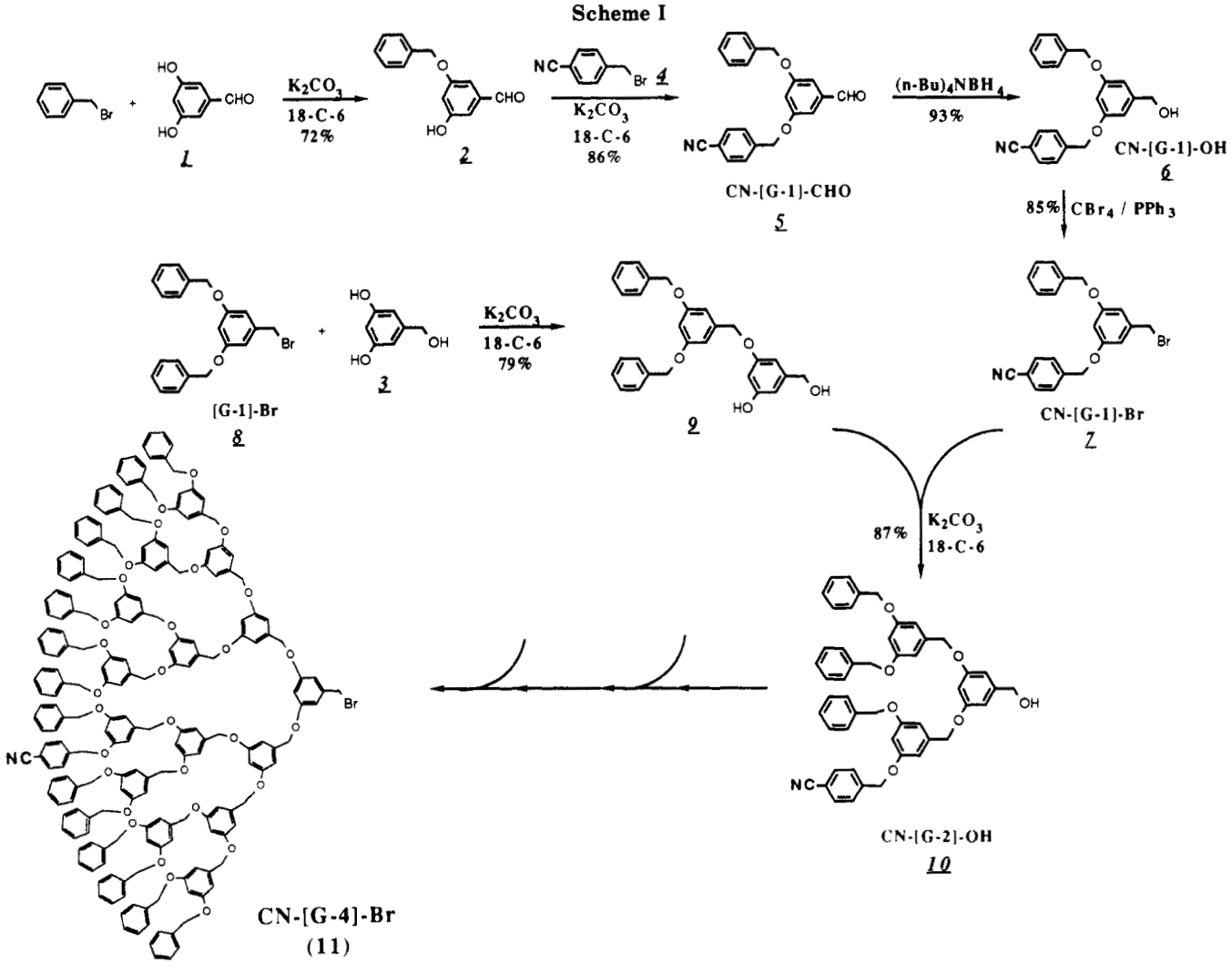
In contrast, the "convergent-growth" approach we have demonstrated recently[7] appears ideally suited for the preparation of hyperbranched macromolecules in which control over both the *number* and the *placement* of end functionalities is achieved. This convergent-growth approach has two significant differences when compared to the starburst approach. First, growth begins at the periphery of the macromolecule, the final reaction being attachment of several dendritic fragments to a polyfunctional core. Second, each generation growth step requires only a limited number of reactions (in this case, two) instead of an increasingly larger number of reaction for starburst growth. We report the first preparation of highly unsymmetrical dendritic macromolecules containing a predetermined and well-defined number of functionalities at their periphery.

Dendritic macromolecules containing one, two, or three cyano functionalities at their periphery were selected as targets. The cyano group was chosen for its compatibility with the reaction conditions employed for growth and its ready transformation into other useful functional groups (e.g., CO_2H, CH_2NH_2). Employing the same type of chemistry, as reported earlier[7] for the synthesis of unsubstituted dendritic polyethers, we monoalkylate the slightly modified monomer unit, 3,5-dihydroxybenzaldehyde (1), with benzyl bromide to give the phenol **2** (Scheme I).

In a departure from previous methodology, it was found necessary to employ **1** as the monomer unit for the first-generation compounds, [G-1], since nonactivated benzyl bromides undergo significant C-alkylation with 3,5-dihydroxybenzyl alcohol (**3**), whereas no C-alkylation was detected for **1**. In latter generations activated 3,5-dioxybenzyl bromides are used and no C-alkylations are detected for their reactions with **3**.

Reaction of the phenol **2** with *p*-cyanobenzyl bromide (**4**) allowed introduction of the cyano substituent; the resultant unsymmetrical first-generation aldehyde CN–[G-1]–CHO (**5**) was isolated in 86% yield after purification. Reduction of the aldehyde **5** with tetra-*n*-butylammonium borohydride[8] gave the alcohol **6** in 93% yield;

Scheme I



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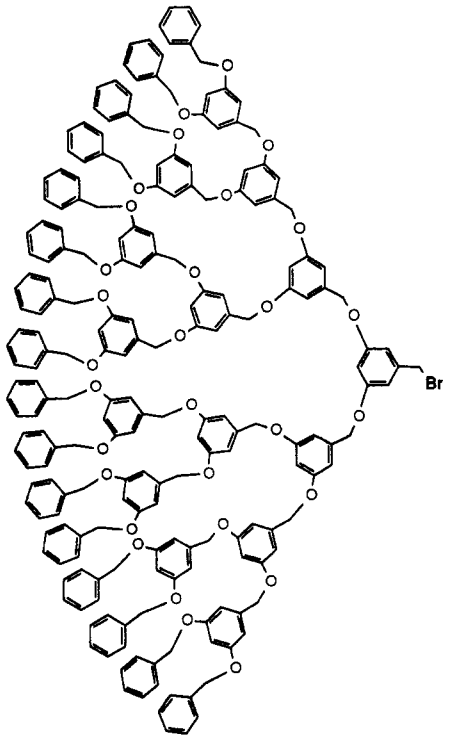
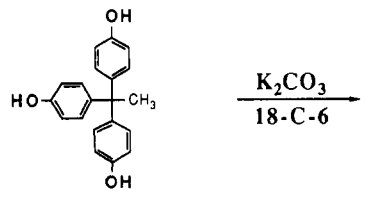
Scheme II



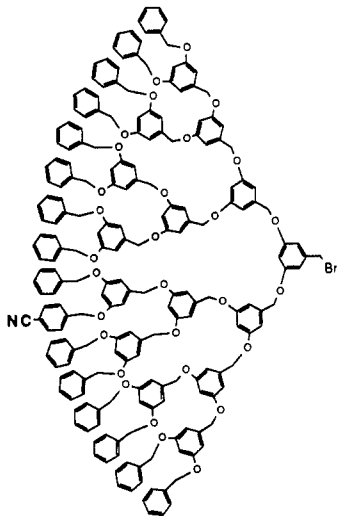
(13) [G-4]-Br



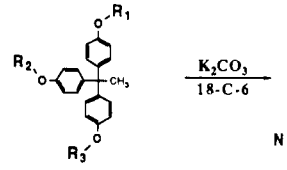
R_1= R_2= [G-4], R_3= H (14)

R_1= [G-4], R_2= R_3= H (15)

Scheme III



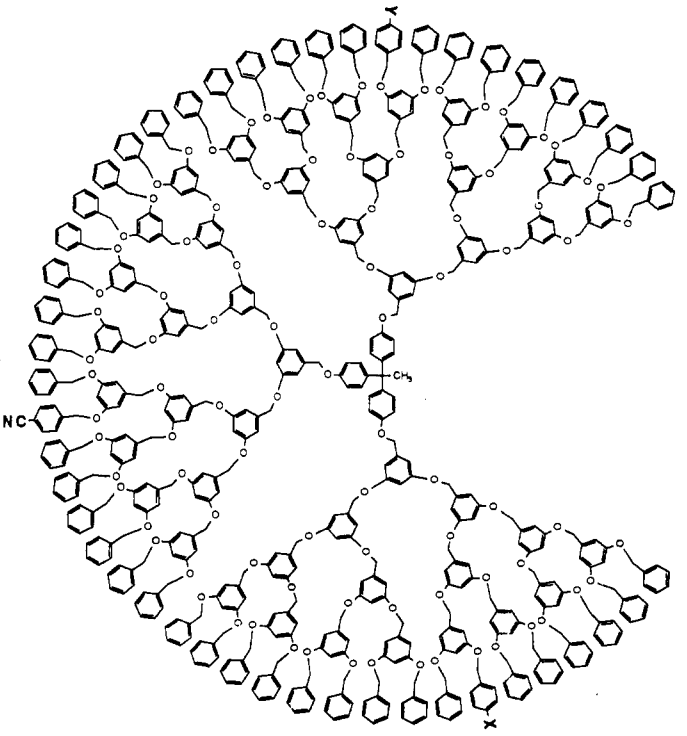
(11) CN-[G-4]-Br



R_1= R_2= [G-4], R_3= H (14)

R_1= [G-4], R_2= R_3= H (15)

R_1= R_2= R_3= H (12)



X = Y = H (CN-[G-4])-[C]-[G-4]$_2$ (16)

X = H, Y = CN (CN-[G-4])$_2$-[C]-[G-4] (17)

X = Y = CN (CN-[G-4])$_3$-[C] (18)

conversion to the corresponding bromide **7** was by reaction with carbon tetrabromide/triphenylphosphine. Since the bromides are now 3,5-dioxy substituted, 3,5-dihydroxybenzyl alcohol (**3**) was used as the monomer unit, thus eliminating the reduction step. Therefore coupling of the unsubstituted first-generation bromide [G-1]–Br (**8**) with

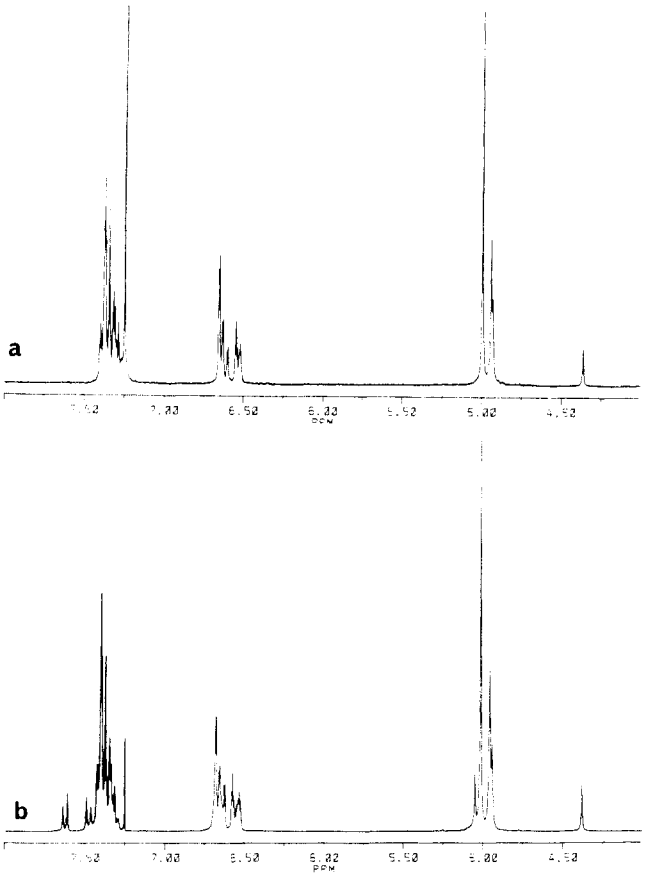


Figure 1. 300-MHz ^1H NMR spectra of **20** (a) and **19** (b).

Table I
Nominal and Polystyrene-Equivalent (GPC) Molecular Weight Data

structure	compd	nominal mol wt[a]	polystyrene-equiv mol wt[b] M_n	M_w	M_w/M_n
11	CN-[G-4]-Br	3 380	3150	3180	1.01
	[G-4]-Br	3 355	3125	3160	1.01
16	CN-[G-4]-[C]-$[G\text{-}4]_2$	10 152	6800	6930	1.02
17	$[CN\text{-}[G\text{-}4]]_2$-[C]-[G-4]	10 177	6910	7020	1.02
18	$[CN\text{-}[G\text{-}4]]_3$-[C]	10 202	6860	6990	1.02

[a] Calculated according to ref 9. [b] GPC calibrated with narrow-dispersity polystyrene standards.

5 equiv of **3** gave the monoalkylated product **9** in 79% yield. Reaction of **9** with the corresponding substituted first-generation bromide, **8**, in a 1:1 ratio gave the monocyano-substituted second-generation alcohol CN-[G-2]-OH (**10**) in 87% yield after purification. Repetition of the three-step process, monoalkylation with an unsubstituted bromide, alkylation with the corresponding monocyano-substituted bromide, and finally conversion of the alcohol function at the "focal" point to the reactive bromide function lead to successive generations up to CN-[G-4]-Br (**11**). High yields were obtained for each step, and the products could be easily purified by either recrystallization or flash chromatography.

The final reaction, attachment to a polyfunctional core, in this case 1,1,1-tris(4′-hydroxyphenyl)ethane [C]-$(OH)_3$ (**12**) can also be used to control the number and placement of functionalities on the periphery of the dendritic macromolecule. By employment of the same stepwise alkylation procedure, the core **12** (10 equiv) was alkylated with the unsubstituted dendritic bromide **13** (1 equiv) to give a mixture of dialkylated, $[G\text{-}4]_2$-[C]-OH (**14**; 41%), and monoalkylated core molecules, [G-4]-[C]-$(OH)_2$ (**15**; 33%), that can be easily separated and purified by flash chromatography due to the presence of one and two free phenolic hydroxyls, respectively (Scheme II). Alkylation of **14** with 1 equiv of CN-[G-4]-Br (**11**) gave the dendritic polyether [CN]-[G-4]-[C]-$[G\text{-}4]_2$ (**16**) in 80% yield after purification; **16** carries a single cyano substituent at its periphery. Similarly, reaction of **15** with 2 equiv of **11** gives, after purification, a dendritic macromolecule $[CN\text{-}[G\text{-}4]]_2$-[C]-[G-4] (**17**) with two cyano functionalities at its periphery. Finally, reaction of the unalkylated core **12** with 3 equiv of **11** gave the dendritic macromolecule $[CN\text{-}[G\text{-}4]]_3$-[C] (**18**) in 77% yield. In the case of **18** an element of symmetry is introduced as each dendritic "wedge" unit carries a single cyano functional group and the final macromolecule carries three cyano groups on its periphery (Scheme III).

All compounds were characterized and their purity determined by standard methods.[7] Figure 1 shows the 300-MHz ^1H NMR spectra of both the monocyano-substituted (**19**) and unsubstituted (**20**) third-generation bromides. The molecules differ by a single cyano functional group on the periphery and a number of distinguishing features are apparent. First, the methylene region of **19** is more complex, as the symmetry of the molecule is disrupted by the single cyano substituent. Second, and more importantly, an ABq is observed at lower field (7.46 and 7.61 ppm) to the resonances for the exterior phenyl rings (7.30–7.40 ppm), consistent with an exterior phenyl ring substituted by a cyano functionality. Integration confirms the presence of a single cyano substituent at the periphery of **19**. In addition, EI or FAB mass spectra of the dendritic "wedges" (smaller than [G-4]) only show the molecular ion corresponding to single cyano substitution. For example, CN-[G-3]-OH, which has a nominal molecular weight[9] of 1617, showed M^+ at 1617 and 1618 (ca. 1:1) ($C_{106}H_{91}NO_{15}$). IR and elemental analysis supported the structural assignment. The polydispersity and molecular size data obtained by GPC were consistent with earlier findings for the corresponding unsubstituted derivatives[7] (Table I).

In conclusion, we have demonstrated that the "convergent" approach offers unparalleled control over the placement and number of functional groups at the periphery of dendritic macromolecules. This is not possible through the established divergent or "starburst" approach, and it is the first reported case of accurate control of surface functionality in the field of dendritic macromolecules. We are currently extending this approach to the preparation of novel molecular dipoles.

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(9) Calculated on the basis of C = 12.00, H = 1.00, O = 16.00.

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