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## A new solid-supported iterative divergent/convergent strategy for the synthesis of dendrimers

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Abstract—A rapid and convenient solid-supported iterative divergent/convergent approach was developed to prepare rigid phenylacetylene dendrimers. The generation number grows very rapidly and the purification at each step is very simple. © 2001 Elsevier Science Ltd. All rights reserved.

Dendrimers are highly-branched, perfectly symmetrical, tree-like macromolecules emanating from a central core. The advent of dendrimers represents a major breakthrough in synthetic chemistry. Recently they have evolved from a laboratory curiosity into an important trend in current chemistry, attracting increasing attention from a broad community of scientists.

Dendrimers can usually be synthesized by either a convergent<sup>1</sup> or a divergent approach.<sup>2</sup> In the divergent approach, the growth of dendrimers starts from a multi-functional core, and one branching unit after another is attached to the core molecule step by step. Through a series of reaction and purification, the dendrimers grow outwards until steric effects prevent further reactions of the end groups. Scheme 1 (left) shows a scheme for the divergent approach. The convergent

method takes the reverse course. The skeleton is constructed stepwise starting from the end groups towards the inside and is finally treated with a multifunctional core molecule to yield the dendrimers. Scheme 1 (right) shows the scheme for the convergent approach.

Problems usually occur in the divergent approach from the incomplete reaction of the end groups, since these structural defects accumulate with the build-up of the next generation. Because the by-products have very similar physical properties, chromatographic separation is not always successful. Hence, higher generations of divergently built-up dendrimers always contain certain structural defects. In the convergent method, a segment growing with each reaction step is coupled with only one branching unit. It is usually difficult to construct





Scheme 1. The divergent (left) and convergent (right) strategy for synthesis of dendrimers.

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higher generations due to the steric problems arising from the reaction of segments and the core molecule.

The reactions of the end group in the solid-phase synthesis of dendrimers were completed by using large excesses of reagents and the product was purified easily by extensive washing.<sup>3,4</sup> Therefore, the difficulty derived from incomplete reactions or steric problems for divergent or convergent routes may be overcome. In this communication, a rapid and convenient solid-supported iterative divergent/convergent approach was developed to prepare dendrimers. The advantages of this approach are that the generation number grows very rapidly and the purification at each step is very simple.

Scheme 2 outlines the synthetic approach. A solid-supported monomer with two inactive end groups X was divided into two portions. In one portion, the end group X was activated by converting to X'. The other portion was activated by breaking the covalent link between the monomer and solid resin to give an active monomer bearing a Y' group at the core. Cross-coupling reaction of the two activated portions eliminated X'Y', forming the solid-supported second generation monodendron, a type of asymmetric dendrimer, possessing the same end groups as the monomer. This procedure can be repeated with a doubling of generation number after each iteration, while the generation number grows step by step in either the divergent or convergent strategy. Moreover, large excess of reagents used in this procedure causes the purification process to be as simple as a matter of extensive washing, whereas purification is a repeated and time-consuming in either the divergent or the convergent strategy. Therefore, in this approach, the generation number grows exponentially and the purification at each step is very simple. At the same time, both the core  $(P-Gn-(X')_{2n})$  and the branching unit  $(Y'-Gn-(X)_{2^n})$  grow during the formation of the molecular skeleton, indicating that both divergent and convergent concepts were involved. Therefore, such a synthetic strategy overcomes the shortcomings existent in both divergent and convergent routes. This approach was employed to prepare phenylacetylene dendrimers, which are promising electroluminescent and NLO materials.

The Merrifield's peptide resin-supported monomer was prepared according to Scheme 3. 2,6-Diiodo-4-nitro-

phenol was converted into its potassium salts with  $K_2CO_3$  in acetone, and 3,5-diiodo-4-ethoxy-nitrobenzen 1 was obtained in 95% yield by addition of ethyl iodide. The nitro group in compound 1 was reduced into an amino group by reacting with SnCl<sub>2</sub>·2H<sub>2</sub>O in alcohol at elevated temperature, 3,5-diiodo-4-ethoxy-aniline 2 was obtained in 98% yield. Reaction of compound 2 with  $BF_3$ ·Et<sub>2</sub>O and *tert*-butyl nitrite at -20°C gave (3,5diiodo-4-ethoxy) diazonium tetrafluoroborate 3 in 90% yield. The resulting diazonium tetrafluoroborate salt reacted with *n*-propylaminomethyl polystyrene<sup>5</sup> under basic conditions like  $(K_2CO_3)$  in DMF to give polymersupported aryliodides 4. Finally, the Heck-Cassar-Sonogashira–Hagihara reaction<sup>6</sup> of compound 4 and excess trimethylsilylacetylene in the presence of  $Pd(dba)_2$ -CuI-PPh<sub>3</sub> gave the polymer-supported monomer 5.

The starting monomer 5 was then divided into two portions. The trimethylsilyl groups in one portion were removed and replaced with hydrogen atoms by reaction with tetrabutylammonium fluoride (TBAF) in THF to give polymer-supported diacetylene P-G1-(H)<sub>2</sub>. The other portion was heated to 115°C in methyl iodide in a sealed tube to give aryl iodide I-G1-(TMS)2.4 Similar Heck-Cassar-Sonogashira-Hagihara reaction of P-G1-(H)<sub>2</sub> and I-G1-(TMS)<sub>2</sub> gave the second generation polymer-supported monodendron P-G2-(TMS)<sub>4</sub>. This procedure was repeated with a doubling of generation number after an iteration to give the fourth generation polymer-supported monodendron P-G4-(TMS)16, which was followed by deprotection of the triazene linkage from the solid support with MeI to give the highly soluble fourth generation monodendron I-G4-(TMS)<sub>16</sub>.

Transmittance FT-IR spectroscopy followed the whole solid-phase approach. The peaks at 2157 ( $\pm$ 1) cm<sup>-1</sup> in **P-G1-(TMS)**<sub>2</sub>, **P-G2-(TMS)**<sub>4</sub> and **P-G4-(TMS)**<sub>16</sub> were characteristic of the stretching vibration for a carbon–carbon triple bond in trimethylsilyl-protected acetylenes. However, after desilylation, the peak at 3311 cm<sup>-1</sup> was observed in **P-G1-(H)**<sub>2</sub> and **P-G2-(H)**<sub>4</sub>, which was characteristic of the stretching vibration for carbon–hydrogen in the terminal acetylene. **I-G1-(TMS)**<sub>2</sub> and **I-G2-(TMS)**<sub>4</sub> were confirmed by NMR and EI-MS. As for **I-G4-(TMS)**<sub>16</sub>, its molecular weight was



Scheme 2. Solid-supported iterative divergent/convergent strategy for synthesis of dendrimers.



Scheme 3. Synthesis of phenylacetylene dendrimers by a solid-supported iterative divergent/convergent approach. (a) TBAF, THF; (b) MeI, 115°C; (c) Pd(dba)<sub>2</sub>-CuI-PPh<sub>3</sub>, 2:1 (v/v) NEt<sub>3</sub>/THF, 70°C.

confirmed by matrix-assisted laser desorption/ionization mass spectroscopy (MALI-MS 3804.4), and four distinguished peaks from 7.808 to 7.558 ppm with integration of 1:2:4:8 were observed in its <sup>1</sup>H NMR spectrum.<sup>7</sup>

In conclusion, an efficient solid-supported iterative divergent/convergent synthetic strategy was developed to prepare soluble phenylacetylene dendrimers. The advantages of this approach are that the generation number grows very rapidly and the purification at each step is very simple.

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- Selected characterization data of the first, second and fourth generation monodendrons.
  *I-GI-(TMS)*<sub>2</sub>: IR 2959, 2899, 2156, 1559, 1477, 1442, 1385, 1249, 1002, 843, 759, 700, 651 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.67 (s, 2H), 4.24 (q, *J*=14 Hz, 2H), 1.41 (t, *J*=7.2 Hz, 3H), 0.24 (s, 18H); EI-MS. Calcd for [M]<sup>+</sup>: m/e 440. Found: m/e 440.
  *I-G2-(TMS)*<sub>4</sub>: IR 2959, 2899, 2217, 2156, 1561, 1478, 1447, 1384, 1249, 1033, 1006, 843, 759, 698, 649 cm<sup>-1</sup>; <sup>1</sup>H

1447, 1384, 1249, 1033, 1006, 843, 759, 698, 649 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (s, 2H), 7.52 (s, 4H), 4.33 (overlapping q, *J*=14 Hz, 6H), 1.46 (overlapping t, *J*=7.2

Hz, 9H), 0.26 (s, 36H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  162.08, 160.78, 141.59, 136.62, 119.81, 118.22, 117.99, 99.87, 99.79, 92.93, 85.31, 84.08, 70.31, 69.95, 15.94, 15.76, -0.221; EI-MS. Calcd for [M]<sup>+</sup>: m/e 920. Found: m/e 919.

*I-G4-(TMS)*<sub>16</sub>: IR 2960, 2898, 2216, 2156, 1588, 1558, 1478, 1446, 1384, 1249, 1104, 1034, 1008, 842, 758, 698,

649, 615 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.81 (s, 2H), 7.64 (s, 4H), 7.60 (s, 8H), 7.56 (s, 16H), 4.37 (overlapping q, *J*=14 Hz, 30H), 1.50 (overlapping t, *J*=7.2 Hz, 45H), 0.265 (s, 144H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  162.06, 161.06, 146.60, 136.67, 136.30, 118.23, 99.86, 92.41, 84.78, 70.38, 69.97, 29.66, 16.00, 15.77, -0.213; MALDI-TOF MS: calcd for [M]<sup>+</sup>: m/e 3805.7. Found: m/e 3804.4.