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Enhanced Reactivity of Dendrons in the Passerini Three-Component Reaction

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Polymer chemistry has embraced multicomponent reactions for synthesizing multifunctional materials, including structurally perfect multimodal dendrimers. An unexpected substituent effect dramatically shortens the time required for the convergent synthesis of dendrimers via the Passerini three-component reaction.

Multicomponent reactions offer strategic advantages for the synthesis of structurally complex polymers.[1,2] Multifunctional materials can be prepared from simpler polymers by introducing two or more new functionalities at each side-chain[3] or chain-end[4,5] functional group. In this way, multicomponent reactions have begun to address the synthetic challenges[6] of synthesizing multifunctional dendrimers.[7] We have demonstrated an approach in which three different component dendrons are transformed into a dendrimer via the Passerini reaction,[8] however long reaction times are a disadvantage to our approach.

　　Poor reactivity of dendrons has also been observed in polymerization reactions. Separating the polymerizable group from the apex branch point of the dendron with an unbranched linker group has been shown to greatly improve the reactivity of dendritic macromonomers.[9] We reasoned that short linkers in the dendrons would result in faster reactions by reducing the steric interactions between the reactants. Gratifyingly, we observed very short reaction times for Passerini reactions with dendron **1b** (Fig. 1). Contrary to our expectation, though, the distance between the apex branch point and the reactive functional groups added by the linkers is not the reason for the observed reactivity. Rather, an unexpected electronic effect greatly enhances the reactivity of the dendritic aldehyde **1b** in the Passerini reaction.
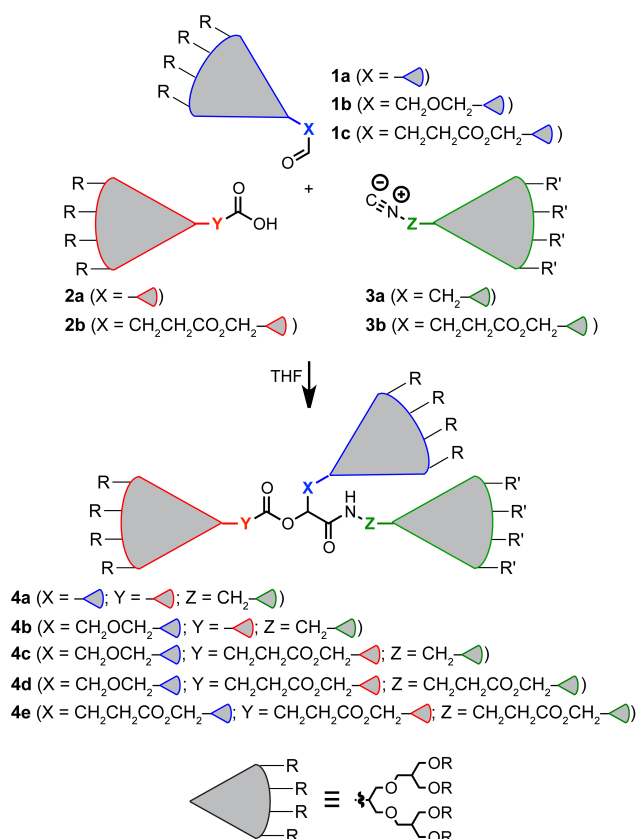

Fig. 1. Passerini reactions of second-generation dendrons revealed an unexpected substituent effect in the aldehyde component **1**. For dendrons **1** and **2** and dendrimers **4**, R = $C_{10}H_{21}$. For dendron **3a** and dendrimers **4a**, **4b**, and **4c**, R' = Bn; and for dendron **3b** and dendrimers **4d** and **4e**, R' = $C_{10}H_{21}$.

Passerini reactions of second-generation dendrons in THF were investigated to test our hypothesis (Fig. 1 and Table 1). We have used poly(alkyl ether) dendrons as our model system, because the alkyl ether linkage is chemically robust and the dendrons are conveniently prepared in a convergent manner.[10] The multicomponent reactions were monitored by ^{1}H NMR spectroscopy and were judged to be complete when the aldehyde resonance at δ 9.7 ppm disappeared. We previously reported that the Passerini reaction of dendrons **1a**, **2a**, and **3a** was complete after 65 h and dendrimer **4a** was obtained in 43% yield.[8] This reaction served as our benchmark for the slow reaction of dendrons without linkers between the apical branch point and the functional groups involved in the Passerini reaction. When a short linker was introduced to only the aldehyde component we observed a significant improvement of the reaction time. Aldehyde **1b** was reacted with carboxylic acid **2a** and isocyanide **3a**. The reaction was judged to be complete after 24 h, and the product (**4b**) was isolated in 49% yield. This result supported our hypothesis that relieving steric interactions between the reactants would yield faster Passerini reactions of dendrons.

Table 1. Reaction times and yields for the Passerini three-component reaction of second-generation dendrons.

Aldehyde	Carboxylic Acid	Isocyanide	Time[a]	Dendrimer (yield)
1a	**2a**	**3a**	65 h	**4a** (43%)[b]
1b	**2a**	**3a**	24 h	**4b** (49%)
1b	**2b**	**3a**	24 h	**4c** (52%)
1b	**2b**	**3b**	24 h	**4d** (74%)
1c	**2b**	**3b**	72 h	**4e** (52%)

[a]Time required for the aldehyde resonance at δ 9.7 ppm to disappear. [b]Data from reference 8.

Following the logic of our hypothesis we expected that introducing linkers into the carboxylic acid and isocyanide components would further reduce the overall time of reaction. Dendrons **2b** and **3b** include short linkers derived from succinic anhydride and β-alanine, respectively. When dendron **1b** was subjected to the Passerini reaction with **2b** and **3a** or with **2b** and **3b**, however, we did not observe any additional rate enhancement compared to the reaction of **1b** with **2a** and **3a**. These results could be rationalized by speculating that relieving steric bulk in any one of the components was sufficient to promote the Passerini reaction of second-generation dendrons.

What caught us by surprise was the reaction of aldehyde **1c** with **2b** and **3b**. Aldehyde **1c** includes a linker that is derived from 4-pentenoic acid and is longer than the linker in **1b**. We expected that aldehyde **1c** would perform as well as or even better than aldehyde **1b** in the Passerini reaction with **2b** and **3b**. Even though the linker in **1c** is longer than the linker in **1b**, the Passerini reaction with **1c** reached completion only after 72 h. This is similar to the reaction time for second-generation dendrons without linkers (i.e., **1a**, **2a**, and **3a**).[8] The dramatic reactivity difference between the aldehydes **1b** and **1c** was corroborated in Passerini reactions

of first-generation analogues of **1b**, **1c**, **2b**, and **3b** (see Supporting Information). Clearly, the enhanced reactivity we observed in Passerini reactions with aldehyde **1b** is due to something other than steric effects.

Such a dramatic increase of the reaction rate as we see for aldehyde **1b** compared to **1a** or **1c** is likely the result of an electronic effect, however this has not been reported for Passerini reactions. Ganem and coworkers have reported that chloride, azide, and sulfonate ester substituents on the α-carbon of ketones accelerate the Passerini reaction under solvent-free conditions.[11] However, less strongly withdrawing groups (e.g., acetate) showed no rate enhancement.[11] We, therefore, were surprised by the high reactivity of aldehyde **1b** in the Passerini reaction. The prevailing view of the Passerini reaction mechanism involves nucleophilic attack at the carbonyl by the isocyanide. Whether this is the rate-determining step is unclear,[12] but sufficiently strong electron-withdrawing substituents should increase the electrophilicity of the aldehyde by stabilizing the tetrahedral intermediate in a manner analogous to that observed for hydration of aldehydes.[13]
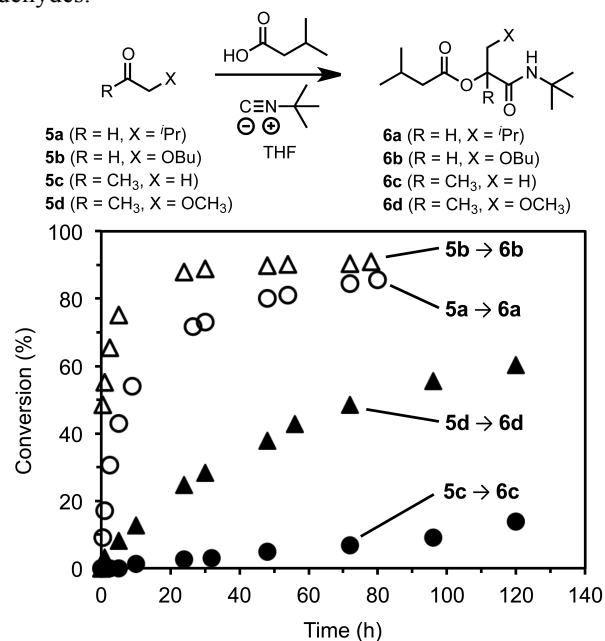

5a (R = H, X = [i]Pr)
5b (R = H, X = OBu)
5c (R = CH$_3$, X = H)
5d (R = CH$_3$, X = OCH$_3$)

6a (R = H, X = [i]Pr)
6b (R = H, X = OBu)
6c (R = CH$_3$, X = H)
6d (R = CH$_3$, X = OCH$_3$)

Fig. 2. Plot of reaction conversion for Passerini reactions of isovaleric acid and *t*-butylisocyanide in THF with isovaleraldehyde (**5a**) (○), α-butoxyacetaldehyde (**5b**) (△), acetone (**5c**) (●), and methoxyacetone (**5d**) (▲) ([**5**]$_0$:[CO$_2$H]$_0$:[N≡C]$_0$ = 1:1.1:1.1, [**5**]$_0$ = 0.7 M).

To validate our observation that ether substituents on the α-carbon of the carbonyl component enhance the rate of the Passerini reaction, we monitored the progress of reactions involving small-molecule reactants. We compared two aldehydes and two ketones in Passerini reactions with isovaleric acid and *t*-butylisocyanide (Fig. 2). Isovaleraldehyde (**5a**) and acetone (**5c**) were used as the carbonyl components in control experiments lacking any
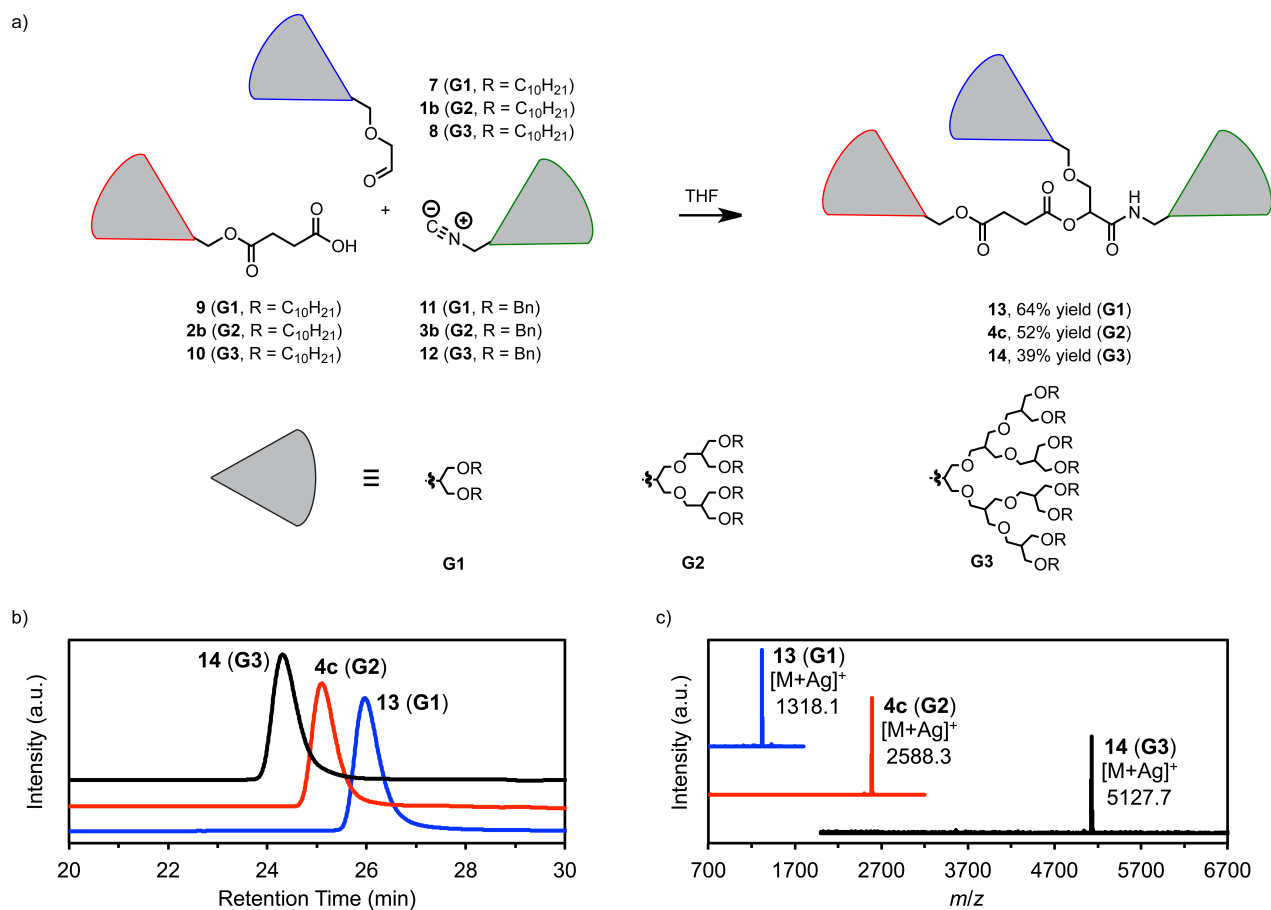
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Fig. 3. a) Three generations of three-component dendrimers synthesized via the Passerini reaction. b) Gel permeation chromatograms of the dendrimers **13** (blue), **4c** (red), and **14** (black). c) MALDI-TOF Mass spectra of the dendrimers **13** (blue), **4c** (red), and **14** (black).

activating substituents. α-Butoxyacetaldehyde (**5b**) and methoxyacetone (**5d**) served as reactants representative of the activated dendritic aldehyde component **1b**. The reactions were performed at room temperature in THF, and the reaction progress was determined from ^{1}H NMR spectra of aliquots taken at different times. It is evident from the data plotted in Fig. 2 that aldehydes react significantly faster than ketones. Furthermore, the aldehyde (**5b**) and the ketone (**5d**) with ether substituents on the α-carbon undergo the Passerini reaction in THF much faster than the corresponding control compound. The Passerini reaction is accelerated in less polar solvents (e.g., CH_2Cl_2)[12b,14] or under solvent-free conditions.[15] We observed faster reaction kinetics in CH_2Cl_2 and could not distinguish the rate enhancement due to the ether substituent in this solvent (see Supporting Information). We conclude from these observations that the accelerating effect of weakly electron withdrawing groups is magnified in slow reactions.

Three generations of three-component dendrimers were synthesized via the Passerini reaction and taking advantage of the enhanced reactivity of ether-substituted aldehydes (Fig. 3a). The time required to reach completion of the Passerini reaction increased with increasing generation of the component dendrons. It is noteworthy, though, that the reaction of third-generation dendrons **8**, **10**, and **12** was complete after 44 h, which is less time than that required for Passerini reactions of dendrons, regardless of generation, when an unactivated aldehyde component was used. The dendrimers were purified by flash column chromatography. Gel permeation chromatography (GPC) traces of the dendrimers were monomodal and symmetric (Fig. 3b), which confirms that there are no residual dendrons in the isolated products. The narrow molecular weight distribution (M_w/M_n) for each dendrimer is further evidence for the homogeneity of the products. MALDI-TOF Mass spectra of the dendrimers (Fig. 3c) confirmed the identity of the products, and showed

no evidence for residual starting materials or two-component reaction products.

Short linkers are commonly used to achieve better reactivity of dendrons by reducing crowding of the apex functional group, but we have found an electronic effect that accelerates the convergent synthesis of dendrimers via the Passerini reaction. A heteroatom substituent on the α-carbon of the carbonyl component dramatically reduced the reaction time of first- and second-generation dendrons compared to components with a longer linker or no linker at all. This unexpected reactivity provides a design principle for the convergent synthesis of higher generation dendrimers via the Passerini three-component reaction. Furthermore, this insight may help to increase the achievable molecular weight for linear polymers[2] and the degree of functionalization that can be achieved in post-polymerization modification reactions.[3-5]

Notes and references

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