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A novel 1→3 *C*-branched isocyanate monomer for resin amplification—a pseudo PS-PEG high-loading resin

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Abstract—High loading resins (up to 120 nmoles/bead) were preprared by solid-phase dendrimerisation using a novel 1→3 *C*-branched isocyanate monomer. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Dendritic molecules are highly-branched arborescent structures which have found applications in many areas of chemistry.[1] Over the past twenty years, an increasing number of diverse dendrimers have been reported based on an alteration of structural parameters such as monomer multiplicity, the distance between successive branching centres or the flexibility of the structure.[2] In 1985, Newkome et al. reported the first example of divergently constructed dendrimers utilising sp^3-carbon atoms as 1→3 branching centres.[3] These dendritic assemblies were of great interest due to the high multiplicity of branching, but their growth was often found to be difficult due to steric congestion. As a result, new 1→3 *C*-branching monomers were designed as building blocks for use in the rapid growth of dendritic macromolecules.[4] Isocyanate-based monomers possessing a triad of protected functional groups have emerged as promising candidates for such a task. The isocyanate moiety allows simple connectivity while the protected moieties prevent side-reactions.[5]

2. Results and discussion

In a project aimed at the synthesis of high-loading resin beads,[6] the utilisation of such monomers for rapid solid-phase dendrimer synthesis appeared attractive. In the preceding paper[7] we reported on the use of a 1→3 *C*-branched isocyanate monomer possessing three *tris*-(Boc) protected amines with a 3-atom spacer between the branching centre and the protected amine.[7] Although these proved to work efficiently as a means of bead-loading enhancement, limitations included the beads mechanical instability towards Boc removal with TFA and slow kinetics at high dendrimer generations. A new isocyanate monomer was designed to increase the flexibility of the structure. It was anticipated that this would render reactive sites on the resin more accessible, therefore allowing higher loadings to be reached as well as speeding up reaction rates. The design of the new monomer was supported by observations made by Newkome et al. who reported a significant drop in reactivity when constructing 1→3 *C*-branched polyols by triester amidation with 1,1,1-*tris*(hydroxymethyl)aminomethane.[3] It was observed that the use of an appropriate spacer (>3 atoms) between the branching point and the reactive centres was necessary for dendrimer growth due to steric hindrance associated with the carbon centre. The monomer **5** was therefore synthesised where the chain length was increased to five atoms (Scheme 1).

The synthesis started with three Michael additions of 1,1,1-*tris*(hydroxymethyl)aminomethane onto acrylonitrile in the presence of aqueous potassium hydroxide to yield the *tris*(nitrile)amine **1** in 64% yield. The amine was protected as the benzylcarbamate. Reduction of the nitrile groups with borane–THF complex afforded the triamine, which was reacted crude with Boc_2O to afford the *tert*-butoxycarbonyl-protected triamine **3** in 37% yield. Removal of the benzyloxycarbonyl group by hydrogenation gave the *tri*-(*t*-butylcarbamate)amine **4** in 92% yield. DMAP-induced isocyanation of the amine, using a stoichiometric amount of DMAP and Boc_2O, gave the isocyanate **5** in 91% yield.[8]

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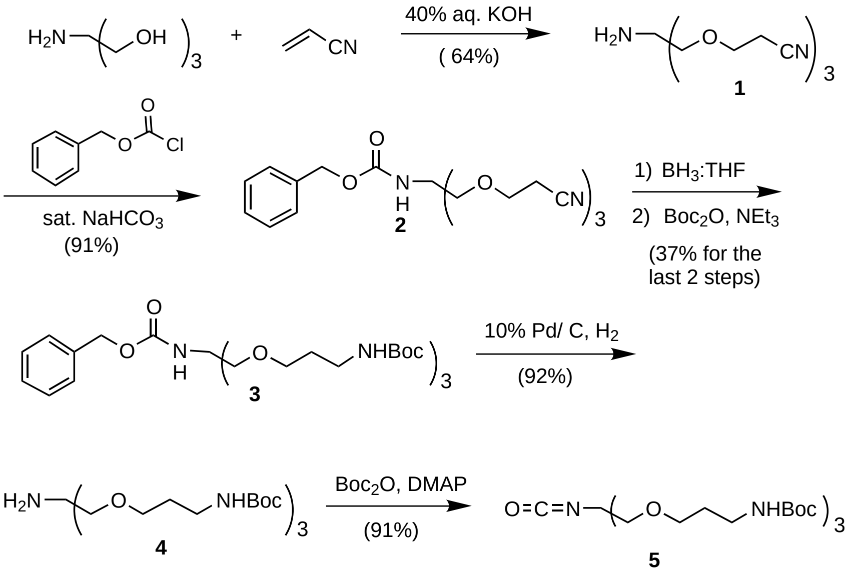
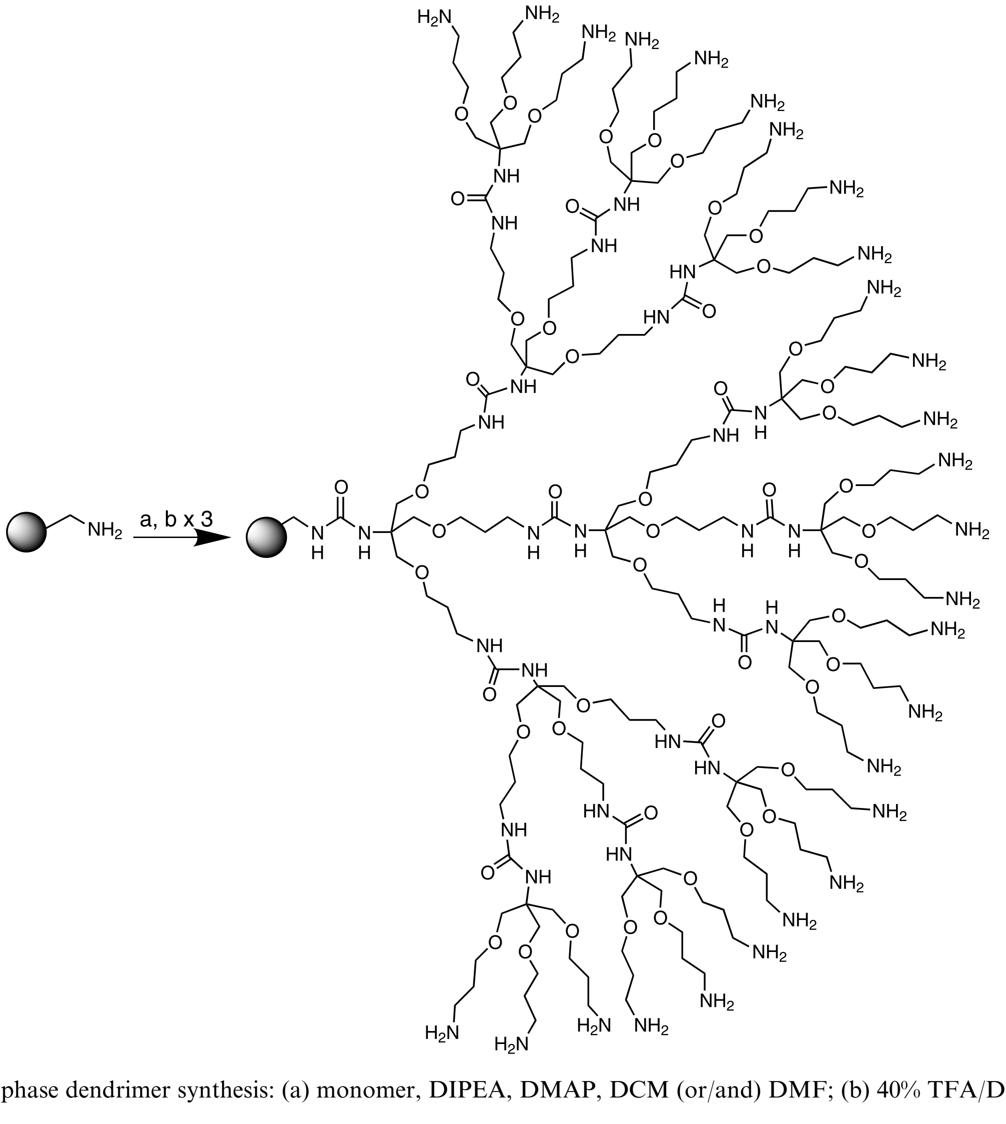


Scheme 1. Synthesis of 1→3 C-branched isocyanate monomer **5.**



Scheme 2. Solid-phase dendrimer synthesis: (a) monomer, DIPEA, DMAP, DCM (or/and) DMF; (b) 40% TFA/DCM, neutralise.

Table 1. Loading measurements on resin-bound dendrimers

Resin	Initial loading (nmol/bead)	Gen.1.0 (nmol/bead)	Gen. 2.0 (nmol/bead)	Gen. 3.0 (nmol/bead)	Overall loading increase
PS (250–300 μm)	17.9	45.9 (85%)[a]	119.4 (87%)	Broken	× 6.7 (× 5.3)[b]
PS (75–150 μm)	0.66	1.72 (87%)	4.45 (86%)	12.5 (94%)	× 18.9 (× 10.0)
TG (160 μm)	0.68	1.38 (68%)	3.49 (84%)	8.96 (72%)	× 13.2 (× 10.2)

[a] Yields based on theoretical maximum loading.

[b] Overall loading increase with short monomer.

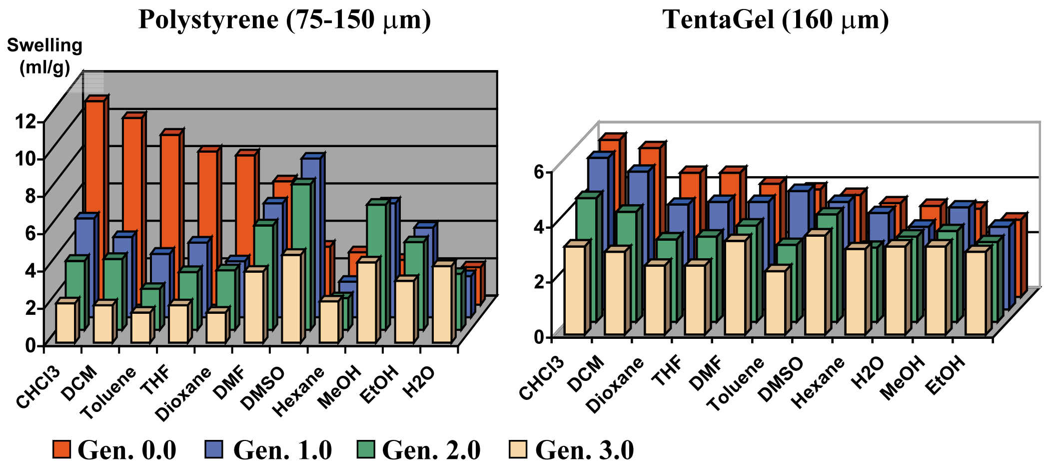


Figure 1. Swelling studies using monomer **2**.

The solid-phase dendrimer synthesis was carried out by successive addition of the monomer followed by *tert*-butoxycarbonyl deprotection with 10–40% TFA in DCM (Scheme 2).

Measurements of loading enhancement on aminomethyl polystyrene resin (250–300 μm, 1.38 mmol/g and 75–150 μm, 0.92 mmol/g) and TentaGel™ resin (160 μm, 0.46 mmol/g) are shown in Table 1.

As anticipated increasing the spacing length of the monomer greatly facilitated the generation of resin beads with higher loading due to the greater degree of flexibility minimising peripheral steric congestion. The length of the spacer that connects the branching centres thus dictates the successful addition of subsequent monomer units onto the dendritic assembly. A 19-fold increase in loading was possible on standard polystyrene resin. These PS-resin-bound dendrimers were found to swell well in polar solvents, even showing water compatibility (Fig. 1). Nevertheless, the swelling behaviour of these resins did not show a significant change in comparison to when the shorter monomer was used.[7] This indicates that the swelling of the resin is mostly dictated by the peripheral moieties rather than the length of the spacer.

Kinetic studies on the 'big' polystyrene beads based on Fmoc deprotection (Fig. 2) showed that the longer spacer significantly increased the reaction rate, although it was still found that the higher generations required longer times (12 minutes for generation 2.0, 5 minutes for generation 0.0).

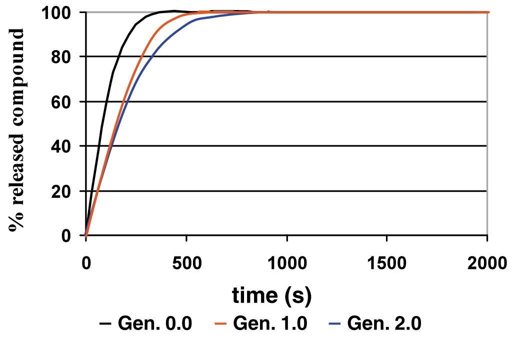


Figure 2. Kinetic studies of Fmoc release from functionalised dendrimer-resins.

3. Conclusion

Generation 2.0 therefore appeared to exhibit the optimum accessibility and flexibility, yet with a high-loading capacity (0.12 μmoles/bead!) to be ideal for combinatorial applications. These novel high-loading supports are now being used in the area of single bead screening.

References

1. Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules*: *Concepts*, *Syntheses*, *Perspectives*; Weinheim, Germany: Wiley-VCH, 1996.
2. (a) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665; (b) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 884.

3. Newkome, G. R.; Yao, Z.-q.; Baker, G. R.; Gupta, V. K. *J. Org. Chem*. **1985**, *50*, 2003.
4. (a) Newkome, G. R.; Behera, R. K.; Moorefield, C. N.; Baker, G. R. *J. Org. Chem*. **1991**, *56*, 7162; (b) Newkome, G. R.; Nayak, A.; Behera, R. K.; Moorefield, C. N.; Baker, G. R. *J. Org. Chem*. **1992**, *57*, 358.
5. (a) Newkome, G. R.; Weis, C. D.; Moorefield, C. N. *Tetrahedron Lett*. **1997**, *38*, 7053; (b) Newkome, G. R.; Weis, C. D.; Childs, B. J. *Designed Monomers Poly*. **1998**, *1*, 3.
6. Lebreton, S.; Monoghan, S.; Bradley, M. *Aldrichimca Acta* **2001**, *34*, 75.
7. Lebreton, S; Newcombe, N.; Bradley, M. *Tetrahedron Lett*. **2002**, *43*, 2475.
8. Knoelker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl*. **1995**, *37*, 2497.