Chem 466

Lecture # 12

02/25/2014

- Kris Matyjaszewski's Frontiers lectures

  today @ 5pm } Rm. 2104
  tomorrow @ 4pm }

- Exam II, March 6, next Thursday

  March 5 office hours...
  old exam II examples to be posted on website today

- Quiz #5 $\bar{x} = 4.4$ (range 0–14)
  S.D. = 3.6

  4 bonus pts for 4-step drug conjugation strategy

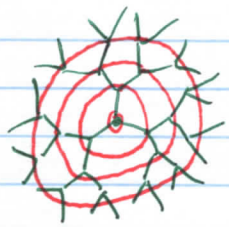
• unique viscosities for dendrimers

– generations of growth involve additions of layers of monomers

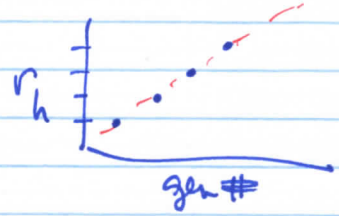
G = gen #

r_0 = repeat unit length

m_0 = repeat unit mol. wt.



⇒ volume increases cubically, because hydrodynamic radius, r_h, increases linearly (ideally)



$r_h \sim G \cdot r_0$

$\Rightarrow V_h \sim \frac{4}{3}\pi r_h^3$

(neglects conformational degrees of freedom + chain ends not all for surface)

⇒ mass increases exponentially

e.g. for A_2B monomer system grown (or attached to) from a core

mol. mass $\propto \left(2^{G-1}\right) m_0$

+ inversely, density goes through a minimum

⇒ $[\eta]$ goes through a maximum $\left(\frac{\text{vol.}}{\text{mass}}\right)$

my copy

Exact Linear Analogs of Dendritic Polyether Macromolecules: Design, Synthesis, and Unique Properties

Craig J. Hawker,*,† Eva E. Malmström,†
Curtis W. Frank,‡ and J. Patrick Kampf‡

Center for Polymeric Interfaces and Macromolecular Assemblies
IBM Almaden Research Center,
650 Harry Road, San Jose, California 95120-6099
Department of Chemical Engineering
Stanford University, Stanford, California 94305

Received June 19, 1997

The study of dendritic macromolecules has progressed at such a rapid pace in recent years that these novel materials are becoming major areas of interest from both an industrial and academic standpoint.[1] Much of this research is based on the assumption that dendrimers are inherently different from linear macromolecules and it is this inherent difference that leads to many of the observed changes in physical properties.[2] Unfortunately, this comparison is not valid since the dendritic macromolecules are compared with polydisperse linear polymers of significantly different structure. For example, the unique melt viscosity behavior of dendritic polyethers was compared with linear polystyrene and not with monodisperse linear analogs containing the same number of polyether repeat units based on 3,5-dihydroxybenzyl alcohol.[3] In this report, we describe a novel synthetic approach to monodisperse linear analogs of dendritic macromolecules and the use of this strategy for the preparation of the exact linear derivatives of the well-studied polyether dendrimers **1**.[4]

In designing the synthesis of the linear analogs it became immediately apparent that a traditional exponential growth strategy[5] involving the synthesis of dimers, tetramers, octamers, etc. would not be applicable since the number of internal repeat units of the dendrimers increased in a different numerical sequence. For example, both the exact linear analog of the fourth-generation polyether dendrimer **2** and the actual dendrimer **1** must have 15 ($2^4 - 1$) internal repeat units which is not consistent with an exponential (2^n) approach (Figure 1). A strategy for the accelerated synthesis of linear polymers with 1, 3, 7, 15, 31, ($2^n - 1$) repeat units was therefore developed. The basic strategy, outlined in Schemes 1 and 2 involves a converging dual exponential growth strategy in which two series of linear macromolecules, one with 2^n repeat units and the other with $2^n - 1$ repeat units, are prepared and then coupled to give the desired linear analogs. To obtain the exact linear analogs, the deprotected monophenolic derivatives (i.e., **9** or **14**) are coupled at each generation step with the linear oligomer containing $2^n - 1$ repeat units and a single benzyl ether chain end (i.e., **11** or **13**). For example, reaction of the first-generation bromide **11** with the monophenol **9** leads to the exact linear analog **12** of the second-generation dendritic alcohol. Bromination of **12** gives the linear [G-2]-Br derivative **13** which can then be coupled with the next generation linear monophenolic derivative **14** to give the exact linear analog of the third generation alcohol **15** which contains seven repeat units, eight benzyl ether groups, and a single hydroxymethyl chain end.

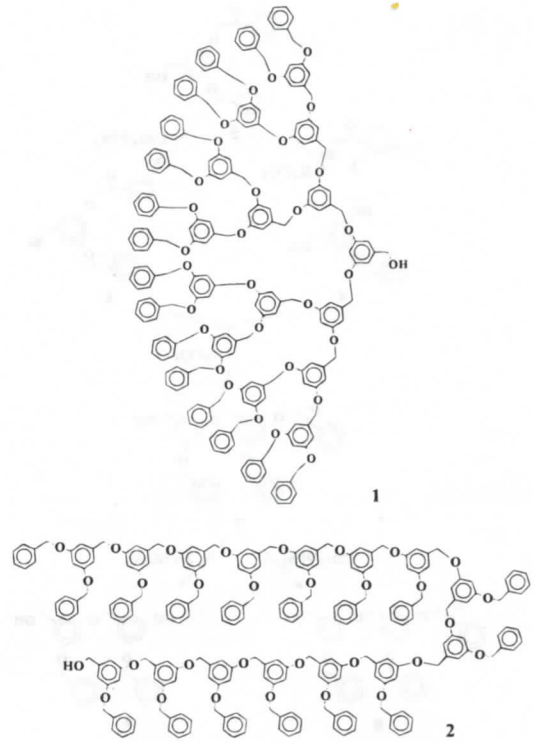


Figure 1. Comparitive structures of the fourth-generation dendritic alcohol **1** and its exact linear analog **2**.

Repetition of this strategy leads to higher generation linear analogs of the dendritic polyether macromolecules which have ***exactly*** the same number of repeat units and pseudo-chain ends as their dendritic equivalents. In essence they are macromolecular isomers of dendrimers and the synthesis has been continued up to the sixth-generation derivative. Using standard techniques developed for dendritic macromolecules,[6] the structure of the exact linear analogs and associated precursor molecules could be confirmed using a combination of ^{1}H and ^{13}C NMR spectroscopy, GPC, and MALDI mass spectrometry. As expected GPC analysis of the linear analogs showed a single peak (polydispersity less than 1.01), while MALDI mass spectrometry showed a single molecular ion corresponding to the expected molecular weight on the basis of the synthetic strategy.

SEC
MALDI
*

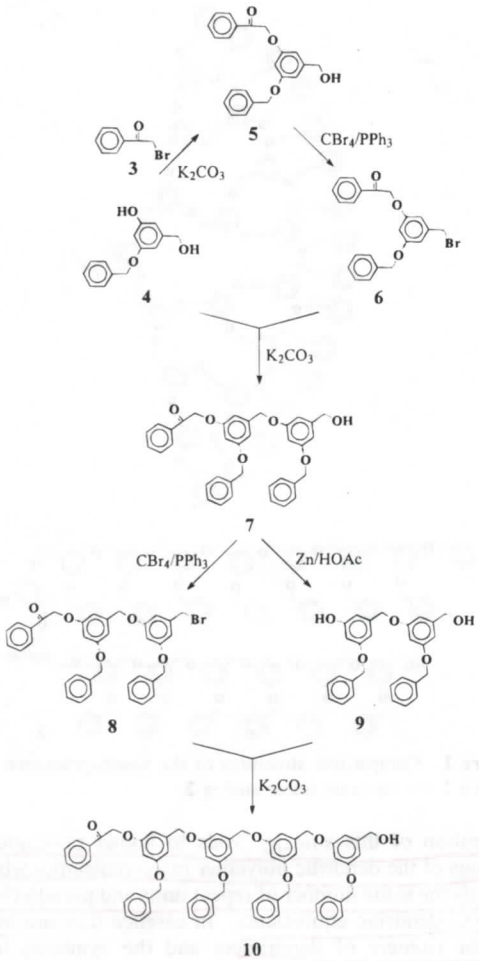
The ability to prepare the exact linear analogs of the polyether dendrimers permits an unprecedented opportunity to study the actual difference between linear and dendritic macromolecules. Initially the three-dimensional molecular size of the linear and dendritic polymers were compared by gel permeation chromatography. Interestingly, a discontinuous relationship between the hydrodynamic volumes of the exact linear analogs and the corresponding dendrimers was observed. For generations four and below, the hydrodynamic volume of the linear and dendritic macromolecules were essentially the same. However, a marked increase in the hydrodynamic volume for the linear derivatives, compared to the dendritic equivalents, was observed on going to generation five and six. For example, both the fifth generation dendrimer [G-5]-OH, **16**, and the exact linear analog **17** with 31 repeat units have molecular formulas of $C_{441}H_{380}O_{63}$ and nominal molecular weights of 6680. While these materials show the same molecular ion by MALDI, the GPC traces show

SEC +
D_h
Fig 2

(1) (a) Fréchet, J. M. J. *Science* **1994**, *263*, 1710. (b) Kim, Y. H. *Adv. Mater.* **1992**, *4*, 764. (c) Tomalia, D. A. *Adv. Mater.* **1994**, *6*, 529.
(2) (a) Bharathi, P.; Moore, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 3391. (b) Jansen, J. F.; de Brabander van den Berg, E. M.; Meijer, E. W. *Science* **1994**, *266*, 1226. (c) Mourey, T. H.; Turner, S. R.; Rubenstein, M.; Fréchet, J. M. J.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **1992**, *25*, 2401.
(3) Hawker, C. J.; Farrington, P.; Mackay, M.; Fréchet, J. M. J.; Wooley, K. L. *J. Am. Chem. Soc.* **1995**, *117*, 6123.
(4) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
(5) Zhang, J.; Moore, J. S.; Xu, Z.; Aguirre, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 2273.
(6) (a) Hawker, C. J.; Fréchet, J. M. J. In *New Methods of Polymer Synthesis*, Ebdon, J. R., Eastmond, G. C., Eds.; Chapman and Hall Publishers: New York, 1995; Vol. 2, p 290. (b) Fréchet, J. M. J.; Hawker, C. J. In *Comprehensive Polymer Science*; Aggarwal, S. L., Russo, S., Eds.; Pergammon Press: New York, 1996, p 140.

S0002-7863(97)02027-1 CCC: $14.00

Scheme 1



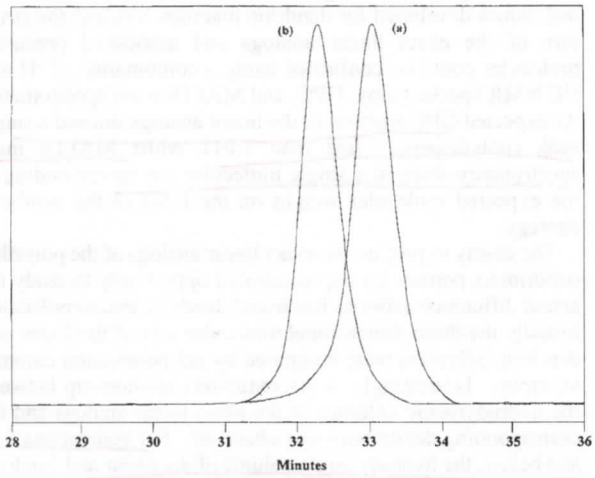
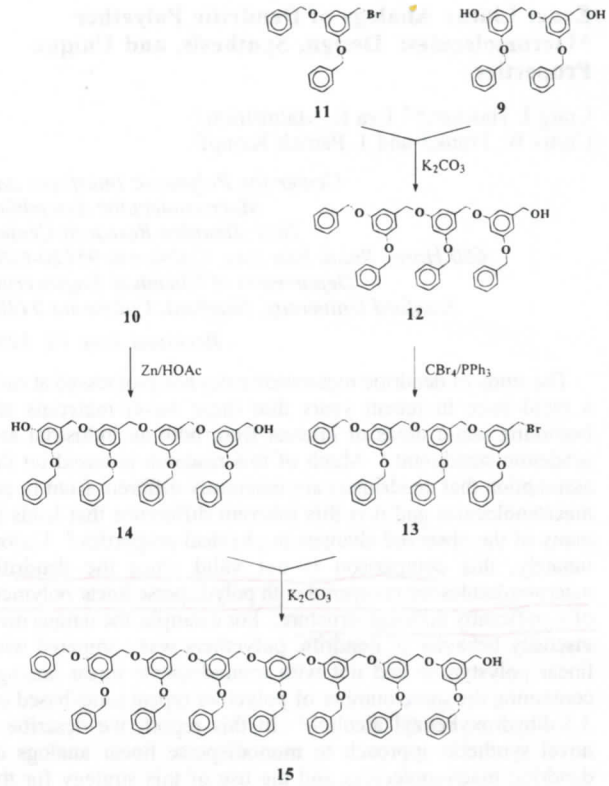


Figure 2. GPC traces for the (a) fifth generation dendritic alcohol **16**, [G-5]-OH, and (b) the corresponding exact linear analog **17**.

a significant difference in retention volume with the linear analog **17**, having an approximately 40% larger hydrodynamic volume (Figure 2). This result is fully consistent with the more compact globular structure of the dendrimer in comparison to the random coil structure of its linear analog. It is of particular interest that similar property changes, or discontinuities, between generation four and fifth has been observed for a number of other dendrimer systems and suggests a fundamental difference between linear and dendritic macromolecules may only manifest itself in higher generation materials.[7]

see m vs. V comparisons
+ relation of η vs. gen#

Scheme 2



Significant differences were also found when the solubility and crystallinity of the linear and dendritic polyethers were compared. The fifth generation dendrimer **16** is completely amorphous and shows a glass transition temperature of 42 °C. In direct contrast, the exact linear analog **17** is highly crystalline and displays a strong melting transition at 150 °C. This high level of crystallinity was also observed for all other linear analogs and results in significantly different solubility behavior when compared to the amorphous dendrimers. In fact, the linear analogs can be crystallized from THF, acetone, or chloroform; solvents in which the dendrimers are extremely soluble.

the. f

solubility

In conclusion, a double-exponential growth strategy has been developed and successfully applied to the preparation of the linear analogs of the well-studied polyether dendrimers and the physical properties of the two series of macromolecular isomers compared. Significantly, it is observed that there is essentially no difference in hydrodynamic volume between the linear and dendritic polyethers up to generation four; however, a marked difference occurs for generation five and six with the linear macromolecule having a significantly larger hydrodynamic volume in tetrahydrofuran. It is also observed that the linear analogs are highly crystalline and have low solubilities which is in direct contrast to the amorphous and highly soluble dendrimers.

Acknowledgment. The authors express their gratitude to the NSF Center for Polymeric Interfaces and Macromolecular Assemblies.

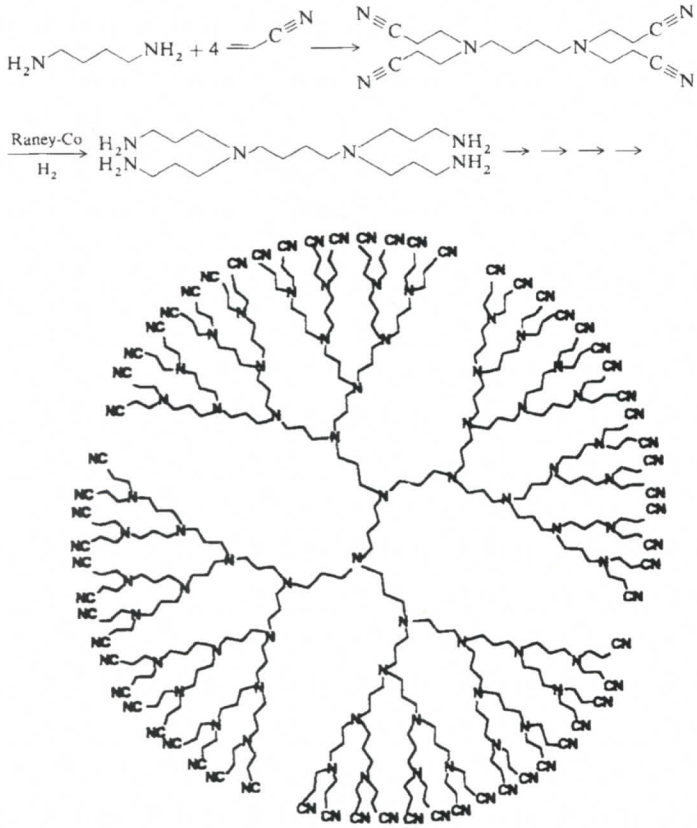
Supporting Information Available: Experimental data for compounds discussed in this work (10 pages). See any current masthead page for ordering and Internet access instructions.

JA972027X

(7) (a) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 4375. (b) Moreno-Bondi, M. C.; Orellana, G.; Turro, N. J.; Tomalia, D. A. *Macromolecules* **1990**, *23*, 912. (c) Naylor, A. M.; Goddard, W. A., III; Kiefer, G. E.; Tomalia, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 2339.

organic compounds are synthesized, or divergent, that is the construction of dendrimers can be regarded as a step polymerization with polydispersities of almost 1.[2-4] Detailed studies show that only a limited number of reaction schemes can be used for the synthesis of these dendrimers;[1,5-7] all known methods to date do not deliver pure dendrimers in large quantities, which is due to the use of sophisticated building blocks and/or (large excesses of) expensive reagents and/or complicated purifications.[6] In this paper we present a very convenient reaction sequence for the large-scale production of pure poly(propylene imine) dendrimers.

The reaction sequence presented here (Scheme 1) is based on the first approaches to dendrimeric structures by Vögtle et al. in which the low yields in the reduction hampered the synthesis of higher generations.[8] Our sequence is a repetition of a double Michael addition of acrylonitrile to primary amines, followed by the heterogeneously catalyzed hydrogenation of the nitriles, resulting in a doubling of the number of primary amines. In this sequence 1,4-diaminobutane has been used as the dendrimer core; but a variety of molecules with primary or secondary amine groups can also be used. We have optimized conditions for both reaction steps in the sequence so that this occurs almost quantitatively and with optimal selectivity.[9]



Scheme 1. Synthetic scheme for poly(propylene imine) dendrimers with diaminobutane as core.

All Michael reactions were performed similarly; 2.5–4 equivalents of acrylonitrile per primary amine are used at a concentration of 0.1 M in water; the first equivalent of acrylonitrile is added at room temperature and the second equivalent at 80 °C. The reaction time for complete conversion increases with every generation: 1 h for generation 0.5 (DAB-*dendr*-$(CN)_4$), 3 h for generation 4.5 (DAB-*dendr*-$(CN)_{64}$).[10] The excess of acrylonitrile is distilled off as a water azeotrope, leaving a clear two-phase system, from which the pure dendrimers with nitrile end groups can be isolated by pouring off the water layer. If necessary the water-soluble side products for example $HOCH_2CH_2CN$ (the Michael addition adduct of H_2O to acrylonitrile) or incompletely cyanoethylated products can be separated by washing the residue with water.

The hydrogenations of the cyanoethylated structures with H_2 (30–70 bar) and Raney/Cobalt as catalyst are also performed preferably in water. The reaction time required for complete hydrogenation increases at higher generations, but even at the higher generations this heterogeneous hydrogenation is quantitative and selective. Dendrimers with NH_2 end groups are isolated by evaporating the water from the filtered reaction mixture. The process window for a quantitative hydrogenation is small and side reactions easily occur. Three major side reactions which lead to dendrimers with structural defects have been observed, and the corresponding side products have been characterized: a) the occurrence of the retro-Michael addition during the hydrogenation, yielding secondary amines,[11] b) incomplete cyanoethylation in the Michael addition, resulting in dendrimers missing one ethyl cyanide side chain, and c) the formation of cyclic diamines and NH_3 by intramolecular addition of amines to the intermediate imines during the hydrogenation reactions. Under the optimized conditions these side products are not detectable and poly(propylene imine) dendrimers can be synthesized up to generation 4.5 with 64 terminal nitrile groups, a molecular weight of 6912 $g\,mol^{-1}$ and in quantities of several grams up to several kilograms. Apart from the first generation (0.5) which is a white crystalline solid, all other generations are colourless oils, which are readily soluble: the DAB-*dendr*-$(NH_2)_x$ in H_2O and methanol, the DAB-*dendr*-$(CN)_x$ in common organic solvents.

All products were characterized by ^1H, ^{13}C NMR and IR spectroscopy, mass spectrometry, HPLC, gel permeation chromatography (GPC), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and intrinsic viscosity. All data are consistent with the proposed dendrimer structures. NMR spectroscopy appears to be a very suitable technique to detect and assign structural failures in the outermost dendrimer generation. In the ^1H NMR spectra of the dendrimers with CN end groups the shape and intensity of the most downfield triplet of the NCH_2CH_2CN group at $\delta = 2.85$ is characteristic for defects in the outer generation, whilst the growth of the dendrimers is clearly indicated by the ratio of the integrals of the signal at $\delta = 1.40$ ($NCH_2CH_2CH_2CH_2N$ protons of the dendrimer core) to the integral of the signal at $\delta = 1.58$ ($NCH_2CH_2CH_2N$ branch protons). Incompletely cyanoethylated dendrimers are most readily concluded from additional signals in the ^{13}C NMR spectra at $\delta = 45.1$ ($NHCH_2CH_2CN$) and 18.7 ($NHCH_2CH_2CN$) as well as the products of retro-Michael additions of dendrimers with NH_2 end groups with signals at $\delta = 47.7$, 46.7, 39.1, 32.0, and 25.6.

Dendrimers with CN end groups can be separated and analyzed with HPLC. In Figure 1 a typical chromatogram of DAB-*dendr*-$(CN)_8$ from a kg-scale run is shown. From mass spectrometric experiments it has been concluded that the small peak corresponds with the fully cyanoethylated product of DAB-*dendr*-$(NH_2)_3$. If equal absorption coefficients are assumed for both compounds, the average selectivity per conversion in the first three steps is 99.8 %.

Figure 2 shows a typical gel permeation chromatogram of various dendrimers with NH_2 end groups taken from a large-scale synthesis. The absence of detectable impurities is evi-

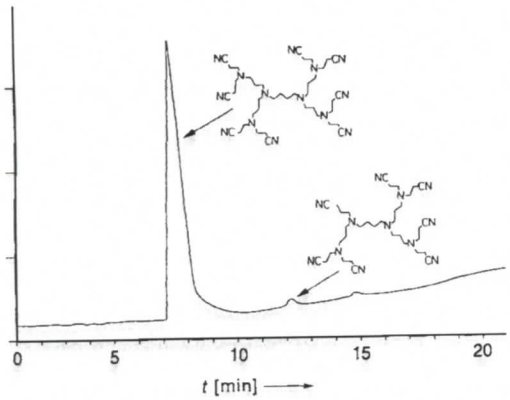


Fig. 1. Typical HPLC chromatograph of DAB-*dendr*-$(CN)_8$.

GPC:
↓ ret'n time w/ ↑ gen# (DP_n)

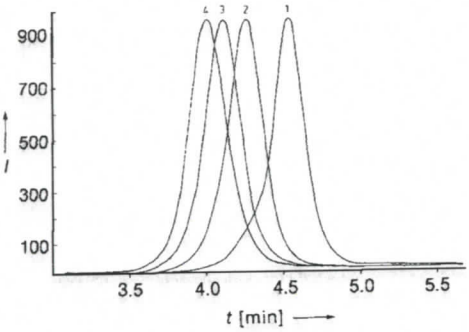


Fig. 2. Typical GPC trace of DAB-*dendr*-$(NH_2)_4$ (1), DAB-*dendr*-$(NH_2)_8$ (2), DAB-*dendr*-$(NH_2)_{16}$ (3), and DAB-*dendr*-$(NH_2)_{32}$ (4).

dent from the chromatograms. Furthermore, the characteristic relation between the molecular weight M_n and the intrinsic viscosity η is presented in Figure 3. As reported for two other classes of dendrimers, the intrinsic viscosity of the poly(propylene imine) dendrimers with CN end groups decreases with increasing molecular weight at a certain generation;[1, 12] in this case after the fourth generation.

viscosity:
↑ η w/ ↑ gen# but plateau reached + ↑ gen # should give ↓ η

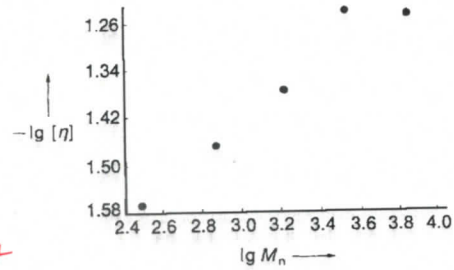


Fig. 3. Plot of $-\lg\eta$ vs. $\lg M_n$ of the various poly(propylene imine) dendrimers with CN end groups.

Thermal analysis of the dendrimers synthesized shows a number of interesting features. The glass transition temperature *T*g has been recorded with DSC (Fig. 4); in both series of dendrimers with NH_2 and CN end groups the *T*g's observed are low and an increase in *T*g is observed by increasing molecular weight. In all cases the CN dendrimers possess the highest *T*g, which is expected on basis of the dipole–dipole interaction of the CN groups. The thermal stability of the dendrimers with NH_2 end groups is unexpectably high and again increases with increasing molecular weight as determined by TGA (For DAB-*dendr*-$(NH_2)_4$, DAB-*dendr*-$(NH_2)_8$, DAB-*dendr*-$(NH_2)_{16}$, DAB-*dendr*-$(NH_2)_{32}$, TGA_{max} are 330, 378, 424, and 470 °C, respectively. For the DAB-*dendr*-$(NH_2)_8$ less than 1.0% weight loss is observed at $T = 310$ °C and scan speed 20 °C min^{-1}.) Dendrimers with CN end groups are less stable, although also in this case the stability increases at higher generations. With TGA-MS, a thermally induced retro-Michael addition is observed for DAB-*dendr*-$(CN)_{64}$, followed by a degradation similar to DAB-*dendr*-$(NH_2)_{32}$. A molecular interpretation of the latter is not possible with the data available.

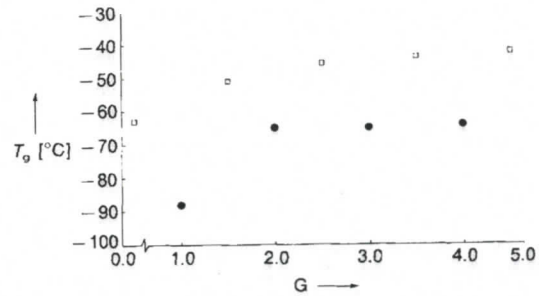


Fig. 4. Plot of the glass transition temperatures (T_g) of the poly(propylene imine) dendrimers with nitrile (□) and amino groups (●). G = generation.

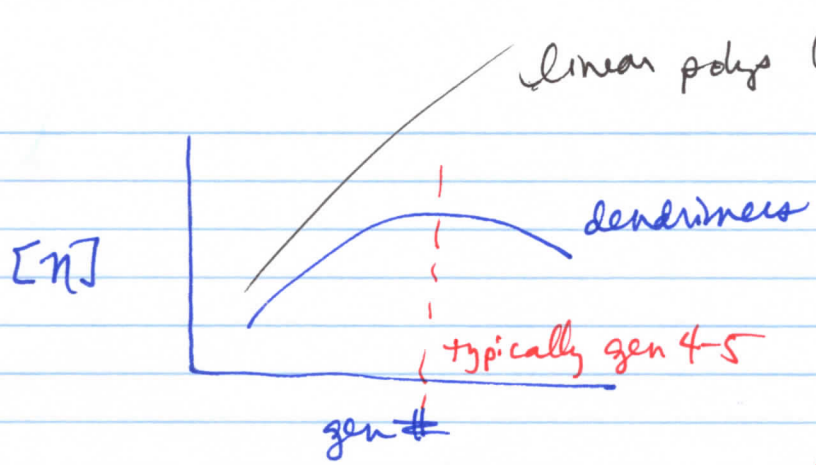
As a consequence of the extensive purifications and low yields in the first approaches,[8] it was assumed until recently that this acrylonitrile–hydrogenation sequence is not suitable for dendrimer synthesis. However, by the correct choice of reagents and reaction conditions we have shown that this reaction sequence is very efficient. The main advantages of our synthetic procedures are 1) the simple reaction and isolation procedures which can readily be scaled up; 2) the use of one solvent for all reaction steps, so that the intermediates must not be isolated; 3) the use of readily available reagents which do not have to be protected; 4) the high yields and selectivities obtained; 5) a simple purification method which can easily be applied to large-scale quantities; 6) the versitility of the reaction sequence which allows for the introduction of a variety of end and core groups.

The dendrimers with NH_2 end groups offer remarkable thermal and good hydrolytic stability, and have a low T_g. The drop in intrinsic viscosity after the fourth generation indicates that a spherical shape with a sterically hindered shell is formed at the fifth generation. The low T_g indicates that the dendrimers possess a large degree of conformational freedom, despite their hyperbranching and well-defined chemical and geometrical structure. Research into the synthesis of higher generations and the functionalization of the dendrimers is in progress.

Experimental Procedure

DAB-*dendr*-$(CN)_4$: Acrylonitrile (8.35 mol, 443 g) was added to a solution of diaminobutane (1.67 mol, 147 g) in 1.176 kg water. The exothermic reaction caused the temperature to rise to 38 °C. After this exothermic effect the reaction mixture was heated at 80 °C for 1 h to complete the addition. Then the excess of acrylonitrile was removed as a water azeotrope by vacuum distillation (16 mbar, bottom temperature 40 °C). Phase separation of the reaction mixture afforded 499 g (99%) HPLC-pure DAB-*dendr*-$(CN)_4$, which was recrystallized from methanol.

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 119$ (CN), 53.1 ($NCH_2CH_2CH_2CH_2N$), 49.4 (NCH_2CH_2-CN), 24.9 ($NCH_2CH_2CH_2CH_2N$), 16.9 (CH_2CN); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.85$ (t, 8H, NCH_2CH_2CN), 2.55 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 2.48 (t, 8H, CH_2CN), 1.55 (m, 4H, $NCH_2CH_2CH_2CH_2N$); IR (KBr): $\tilde{\nu} = 2245$ cm^{-1} (CN).



(see text Fig 9.6 + Example 9.2)

also, see E.M.M. de Brabander-van den Berg + E.W. Meijer Angew. Chem. Int. Ed. Engl. 1993, 32, 1308-1311.

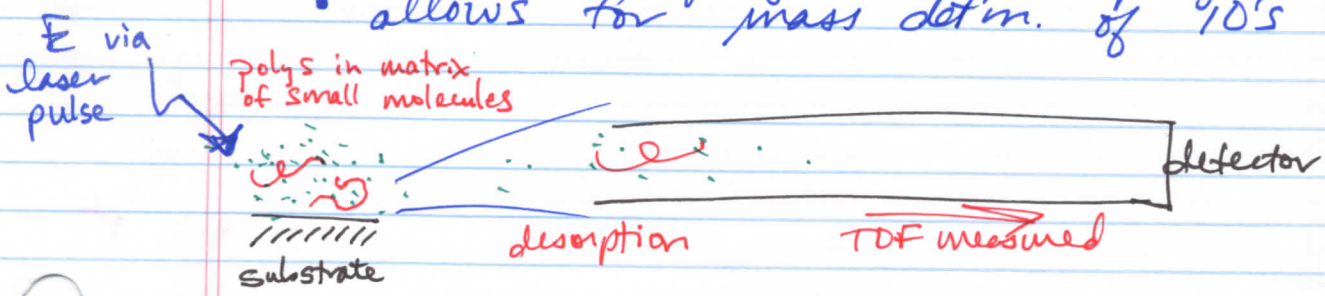
④ MALDI-tof mass spectrometry
(matrix assisted laser desorption ionization - time-of-flight) (text 1.8.3)

- gives mol. wt. distribution w/ higher resolution than SEC, but ~~diffi~~ difficult to quantify #'s of each molecular mass species, due to complicated features of desorption, ionization + flight

observes each particular molecular species w/ accuracy of MW value (m/z)

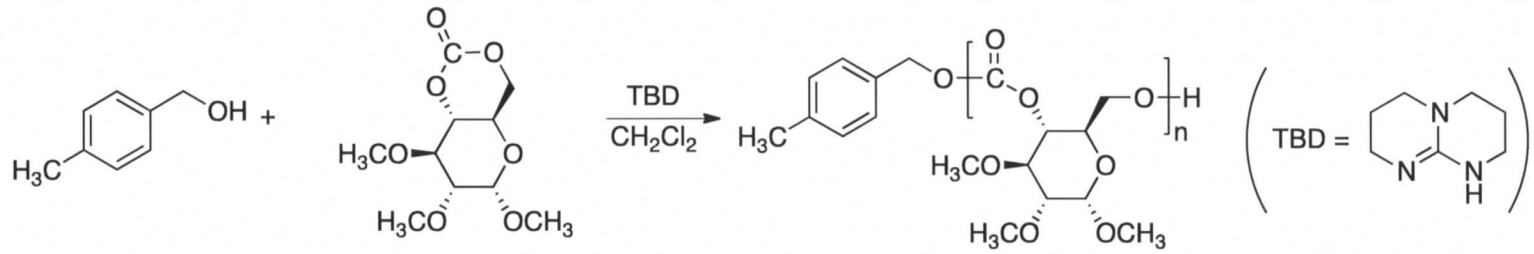
⟹ Δ MW species don't desorb + "fly" to detector w/ same efficiencies

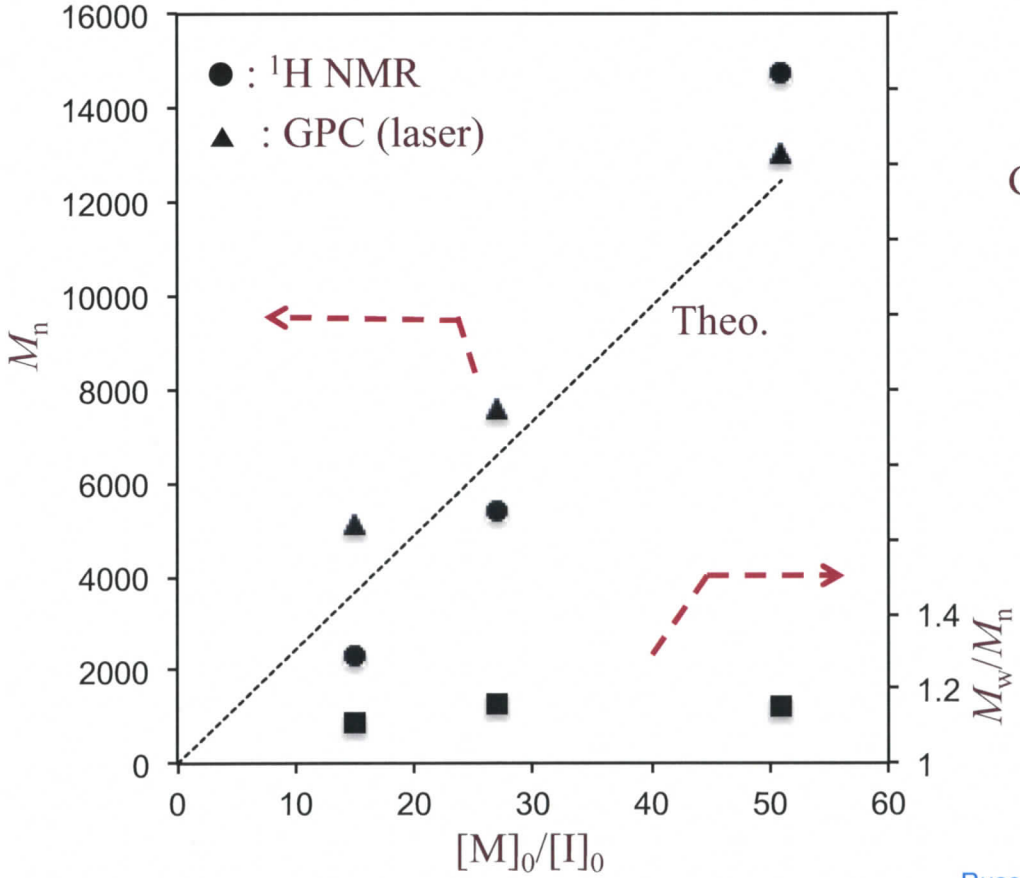
- does not fragment the polys
- allows for mass det'm. of 10's kDa

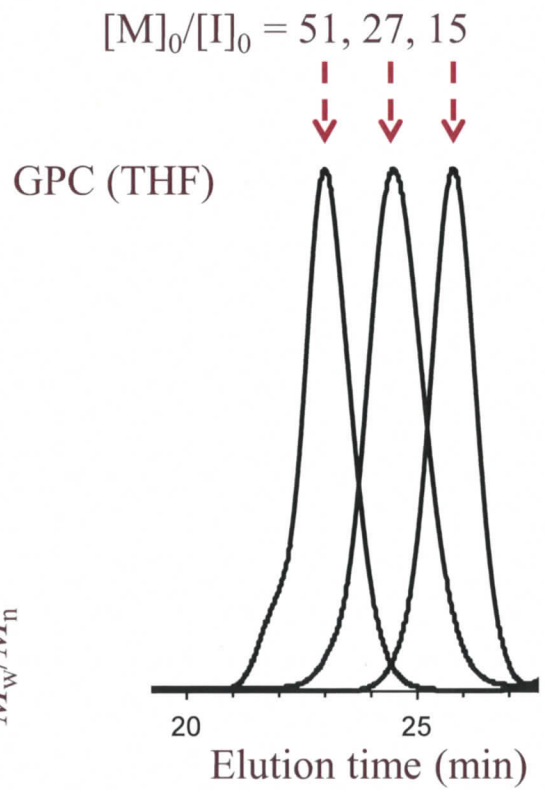


- e.g. Glucose-based Polycarbonates
  GPC (M_n) vs MALDI-tof (M_n + end groups)
  (NMR can also give M_n + end groups but w/ < accuracy)

Glucose-based Polycarbonates: GPC analysis of stoichiometry-promoted molecular weight control



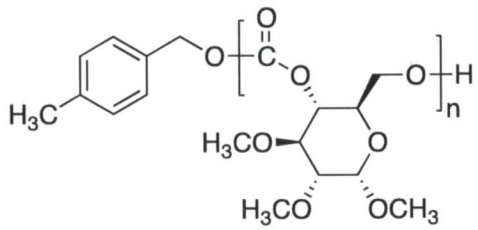




Mikami, K.; Lonnecker, A. T.; Gustafson, T. P.; Zinnel, N. F.; Pai, P.-J.; Russell, D. H.; Wooley, K. L. *J. Am. Chem. Soc.*, **2013**, *135*(18), 6826-6829.

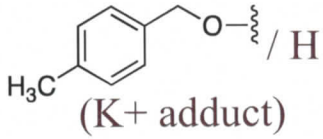
Glucose-based Polycarbonates: MALDI-tof analysis of molecular weight and chain ends

MALDI-TOF MS

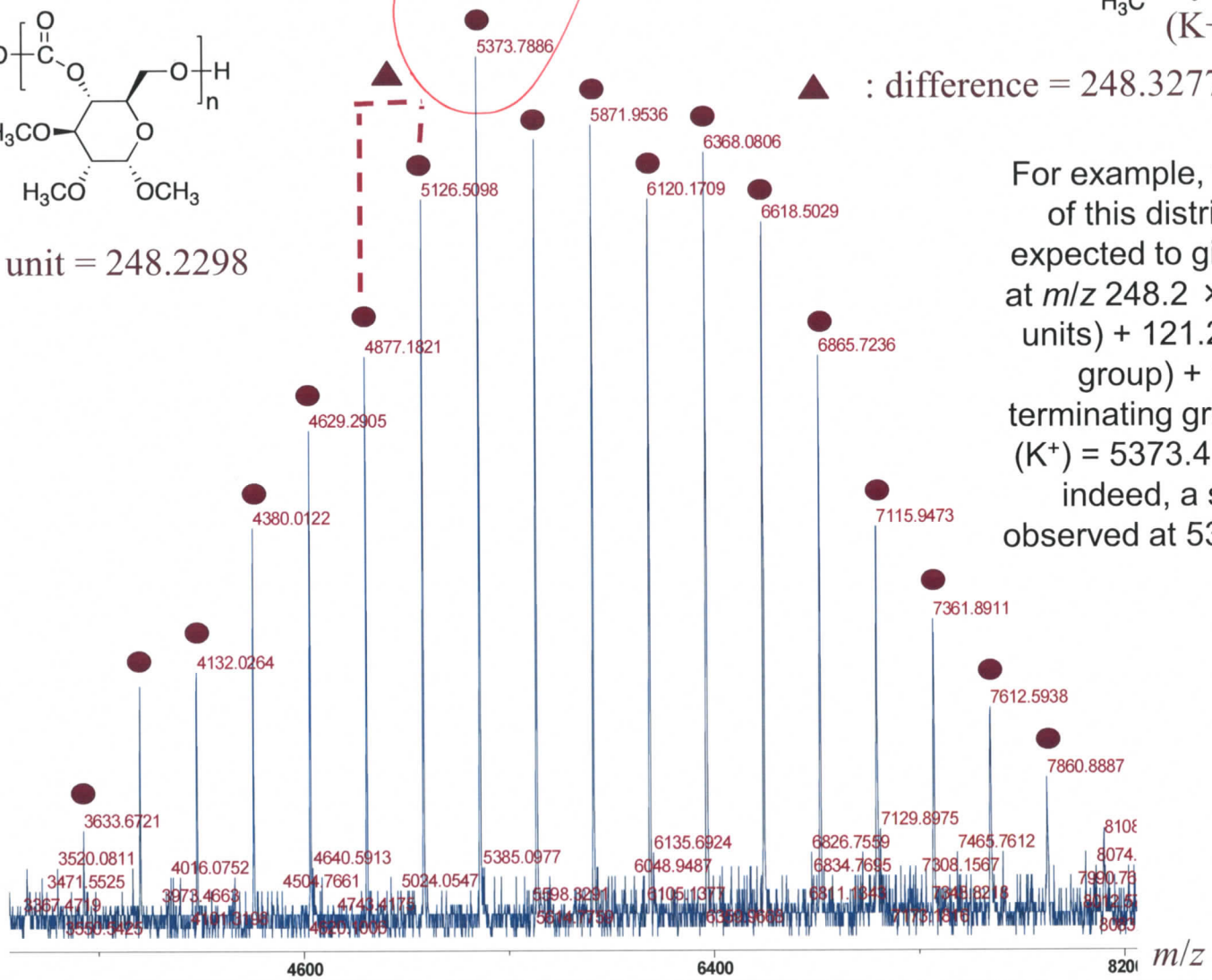


repeating unit = 248.2298

$DP_n = 21$

● : end group = 

▲ : difference = 248.3277



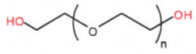
For example, the 21-mer of this distribution is expected to give a signal at *m/z* 248.2 × 21(repeat units) + 121.2 (initiating group) + 1.0 (H, terminating group) + 39.0 (K^+) = 5373.4 g/mol, and indeed, a signal is observed at 5373.8 g/mol.

POLYMER FACTORY

Your Partner in Advanced Material Science

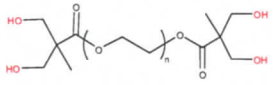
Multifunctional PEG

Polymer Factory introduces a new product line comprising of linear-dendritic hybrid materials with Polyethylene glycol cores and polyester based dendritic end-groups. The unique selling proposition of these PEG-cored dendrimers highlights the large number of terminal hydroxyl groups available for further functionalization.

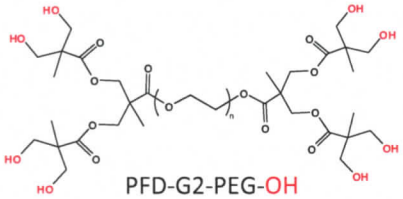


Traditional PEG-OH
Number of -OH: 2

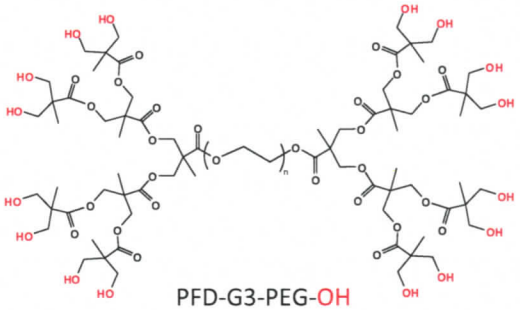
Core: PEG 6k or PEG 20k



PFD-G1-PEG-OH
Number of -OH: 4

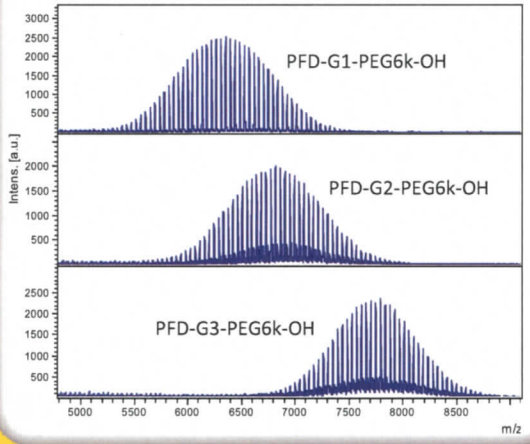


PFD-G2-PEG-OH
Number of -OH: 8

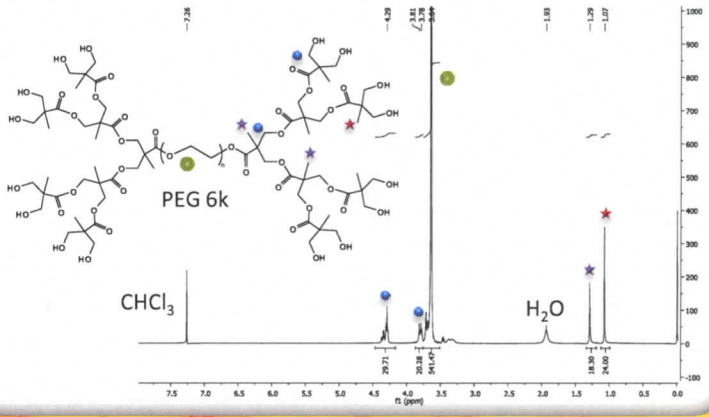


PFD-G3-PEG-OH
Number of -OH: 16

Maldi-TOF Characterization



^{1}H-NMR Characterization



Potential Applications

- Hydrogels for controlled drug release
- Multifunctional scaffolds
- Tissue engineering
- Drug delivery

Featured Material Properties

- Biocompatible, non-toxic, and water soluble
- Well-defined linear-dendritic hybrid materials
- Low polydispersity (PDI < 1.15)
- Increasing number of functional hydroxyl groups
- Readily functionalized for further modifications

Availability & Price

- Available from 250 mg up to 5 g
- Sold individually or in combinations

PRICE: 1 g PFD-G1-PEG6k-OH ➡ 275 €
3 x 250 mg kit (G1-G3) ➡ 275 €

Inquiry for pricing

Polymer Factory Sweden AB
E-mail: info@polymerfactory.com
Phone: + 46 8 718 42 00
Fax: + 46 8 790 82 83
www.polymerfactory.com

IV. Chain-growth polycondensations

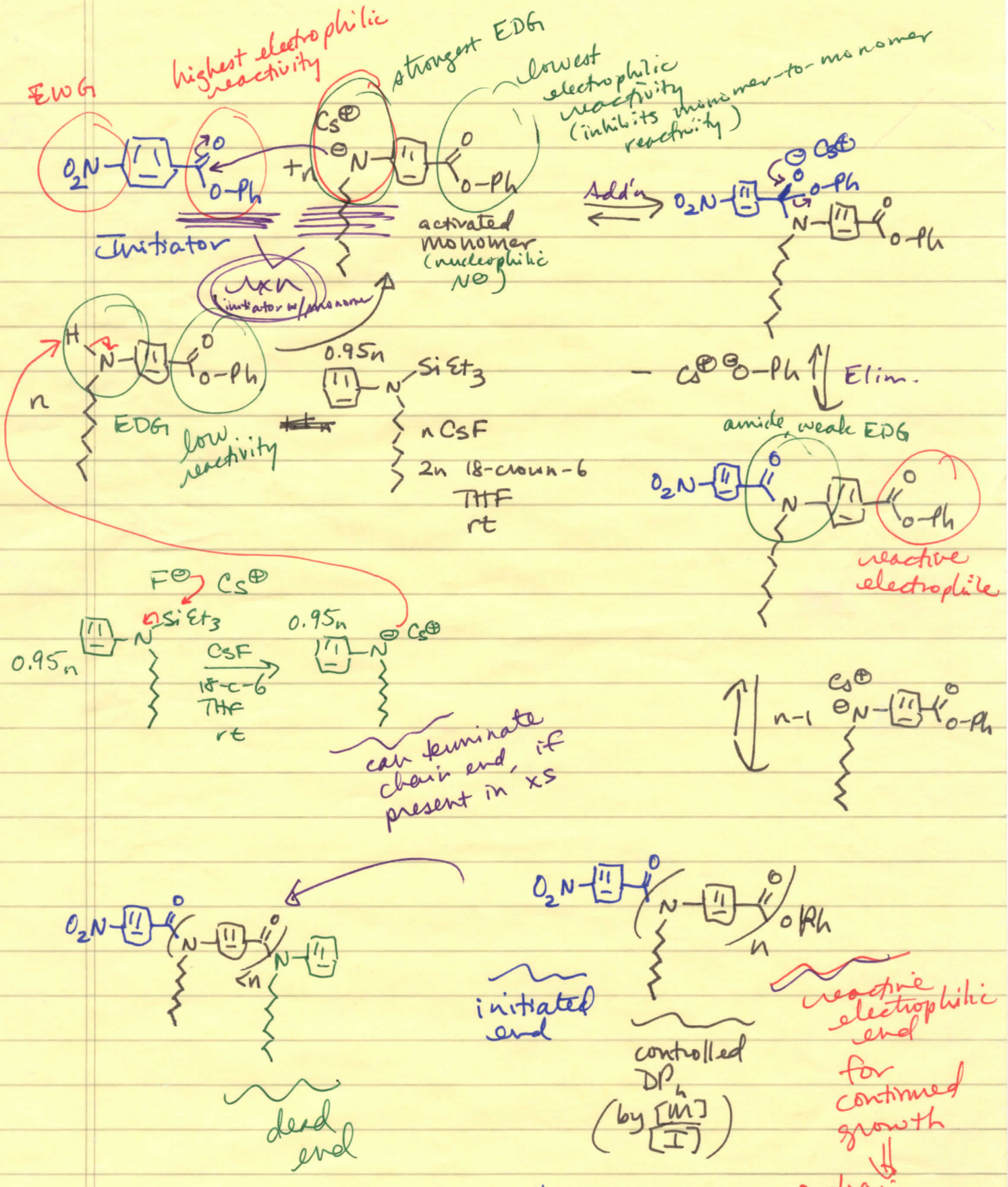
- preparation of condensation-type polymers by chain-growth polym mechanism + kinetics

  - initiator required
  - monomer undergoes rxn w/ initiator + propagating chain end, but not w/ other monomers
  - gives control over DP_n, M_n + can lead to narrow M_w/M_n

- requires clever chemistry

(1) Initial development of 1st really well-defined system reported in

T. Yokozawa, T. Asai, R. Sugi, S. Ishigooka, + S. Hiraoka J. Am. Chem. Soc. 2000, 122, 8313-1



- activated monomer undergoes rxn "only" (ideally) w/ initiator + chain end
- reactivity (electrophilicity) of initiator > chain end
  ⇒ approx all chains initiate at same time + propagate @ same rate

- α chain end carries initiator unit
- ω chain end remains reactive

⟹ hypothesis that the polym. should have living character

- To probe livingness, measure:
  1. mol. wt. distribution
  2. whether $n = \frac{[m]}{[I]}$
  3. chain length vs. time +/or % conversion
  4. ability to perform chain extension

by SEC analysis —

Fig 1

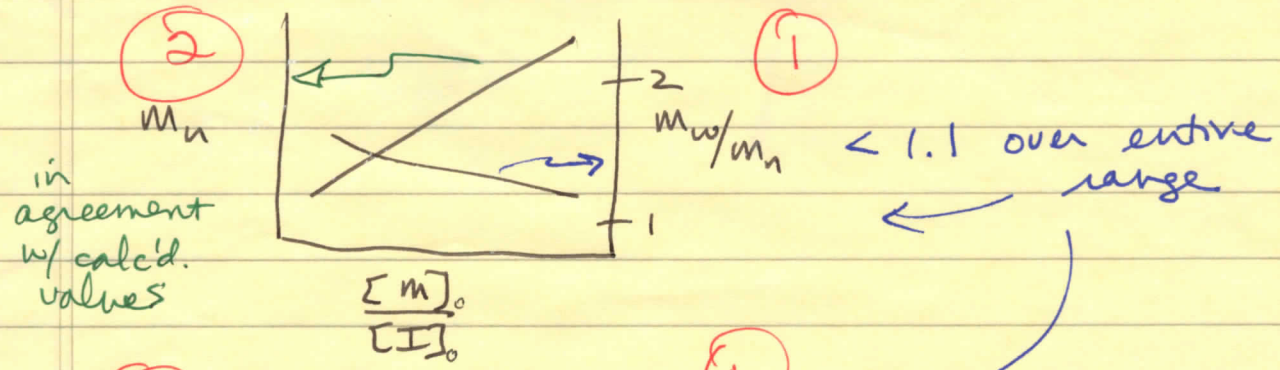


Fig 2A

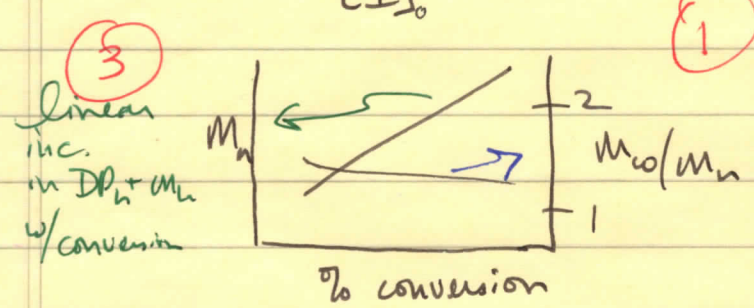
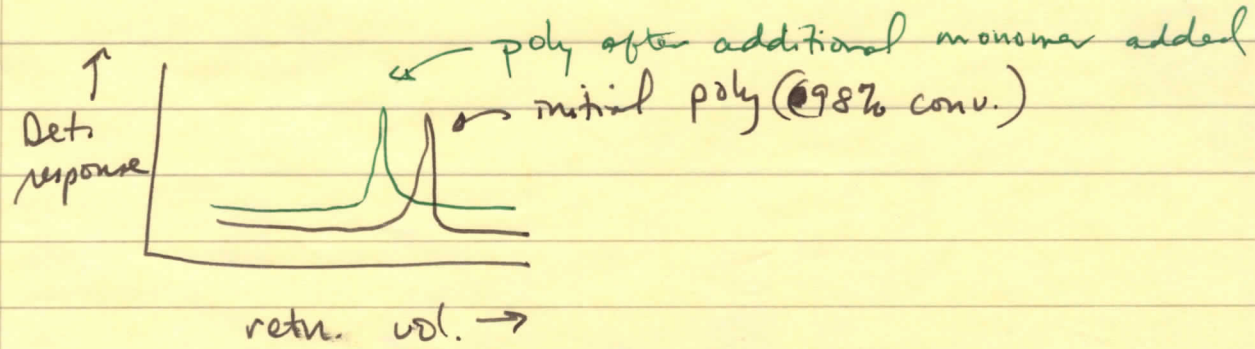


Fig 2B



"livingness" of polym. confirmed by: ① narrow mol. wt. distributions; ② correlation of $n = \frac{[m]_0}{[I]_0}$; ③ linear inc. of M_n vs. monomer conversion; ④ ability to perform chain extension (maintenance of ω-chain end reactivity)

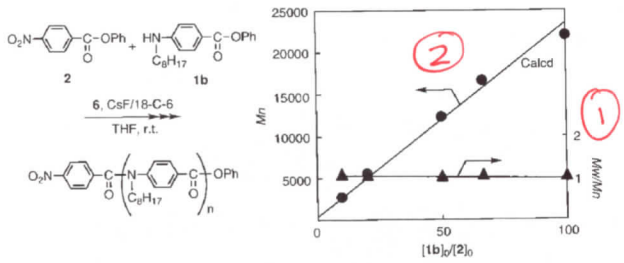


Figure 1. M_n and M_w/M_n values of poly**1b**, obtained with **6** and CsF/18-crown-6 in the presence **2** in THF at 25 °C, as a function of the feed ratio of **1b** to **2**.

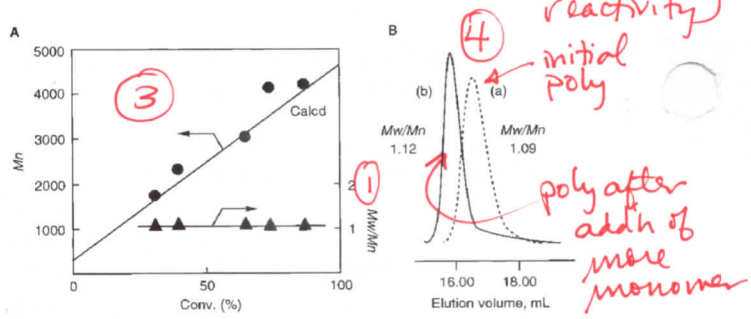


Figure 2. Demonstration of chain-growth polycondensation. (A) M_n and M_w/M_n values of poly**1b**, obtained with **6** and CsF/18-crown-6 in the presence **2** in THF at 25 °C, as a function of monomer conversion. (B) GPC profile of the monomer addition experiment in THF at room temperature: (a) prepolymer ($[\mathbf{1b}]_0/[\mathbf{2}]_0 = 20$), conversion = 98%, M_n = 4500; (b) postpolymer ([added $\mathbf{1b}]_0/[\mathbf{2}]_0 = 24$), conversion = 187%, M_n = 10000.

The polymerization of **1a** was carried out in the presence of 1.0 equiv of CsF, 2.0 equiv of 18-crown-6, and phenyl 4-nitrobenzoate **2** as an initiator in THF at room temperature to yield a polyamide quantitatively, which was soluble in THF, chloroform, dichloromethane, *N,N*-dimethylformamide (DMF), and even toluene. In the polymerization with varying the feed ratio ($[\mathbf{1a}]_0/[\mathbf{2}]_0$), the MWD of polymers was narrow ($M_w/M_n = 1.16-1.20$) when the $[\mathbf{1a}]_0/[\mathbf{2}]_0$ ratios were 10 or less but gradually increased up to 1.47 after that. Broad MWD in high $[\mathbf{1a}]_0/[\mathbf{2}]_0$ ratios may be interpreted in terms of the hydrolysis of the silyl group of monomer **1a** with a very small amount of water coming from CsF and/or 18-crown-6. Hydrolyzed **1b** would not react as a monomer but eventually worked as an initiator, and the amount of **1b** could not be neglected in high $[\mathbf{1a}]_0/[\mathbf{2}]_0$ ratios. Accordingly, we carried out the polymerization of **1b** by using *N*-triethylsilyl-*N*-octylaniline **6** as a base generated by CsF. Thus, the aminyl anion generated from **6** would abstract the proton of the amino group of **1b**, followed by polymerization in a similar manner of **1a**. If the reaction mixture was contaminated with a small amount of water, only **6** would be hydrolyzed and not affect monomer **1b**. In addition, the purification of **1b** and **6** was much easier than that of **1a**.

The polymerization of **1b** was carried out by using 1.1 equiv of **6** (Figure 1). The MWD of polymers was quite narrow and close to a monodisperse distribution, maintaining the M_w/M_n ratio below 1.1 over the whole $[\mathbf{1b}]_0/[\mathbf{2}]_0$ range. The M_n values of polymers[13] were in agreement with the calculated values assuming that one polymer chain forms per unit **2** until $M_n = 22\,000$. This result implies that the polycondensation of **1b** proceeded from initiator **2** in a chain-growth polymerization manner like living polymerizations of vinyl monomers and cyclic monomers.[14] To elucidate whether chain-growth polymerization takes place in this polycondensation, the polymerization of **1b** was carried out in the presence of 5 mol % of **2**, and the M_n values and the M_w/M_n ratios were plotted against monomer conversion (Figure 2A). The M_n values increased in proportion to conversion, and the M_w/M_n ratios were less than 1.12 over the whole conversion range. This polymerization behavior agrees with the features of living polymerizations.[14] In general polycondensations that proceed in a step polymerization manner, the molecular weight does not increase much in low conversion of monomer and is accelerated in high conversion, and the M_w/M_n ratios increase up to 2.0. Consequently, Figure 2A shows that the polycondensation of **1b** proceeds in a chain-growth polymerization manner. The character of chain-growth polymerization of this polycondensation was further demonstrated by so-called "monomer-addition" experiments where a fresh feed of **1b** and **6** was added to the prepolymer ($M_n = 4500$ (M_n(calcd) = 4780), $M_w/M_n = 1.09$) in the reaction mixture. The added **1b** feed was smoothly polymerized. The GPC chromatogram of the product (Figure 2B (b)) clearly shifted toward the higher molecular weight region, while retaining the narrow distribution ($M_n = 10\,000$ (M_n(calcd) = 9970), $M_w/M_n = 1.12$).[15] This experiment implies that this polycondensation will enable us to synthesize block copolyamides having different aminoalkyl side chains and well-defined sequences. Furthermore, we anticipate that this polycondensation will provide new approaches for the design of nanoarchitectures, which have been achieved by living polymerizations of vinyl and cyclic monomers[14] and by stepwise synthesis of dendritic macromolecules[16] and linear oligomers.[17] Experiments along these lines are in progress.

Acknowledgment. This work was supported in part by a Grant-in-Aid (10650873) for Scientific Research from the Ministry of Education, Science, and Culture, Japan.

Supporting Information Available: Synthesis of monomer **1b** and polymerization procedure (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001871B

(13) The M_ns of polyamides were estimated by gel permeation chromatography (GPC) based on polystyrene standards. However, the M_ns determined by GPC were in good agreement with those determined by ^{1}H NMR spectra.

(14) For a recent review of living polymerizations, see: Kobayashi, S. *Catalysis in Precision Polymerization*; John Wiley & Sons: New York, 1997.

(15) In the monomer-addition experiment, it was crucial to use 0.95 equiv of **6** in the first-stage polymerization. An excess amount of **6** did not react with the polymer end group during polymerization but did after the consumption of monomer to give the amide end group, which could not initiate the polymerization in the second-stage.

(16) For reviews, see: (a) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 885. (b) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665.

(17) For examples, see references in ref 12.

NOTE

Well-Defined Star-Shaped Poly(*p*-benzamide) via Chain-Growth Condensation Polymerization: Use of Tetra-Functional Porphyrin Initiator to Optimize Star Polymer Formation

KAZUO YOSHINO, AKIHIRO YOKOYAMA, TSUTOMU YOKOZAWA

Department of Material and Life Chemistry, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan

Received 20 May 2009; accepted 9 August 2009
DOI: 10.1002/pola.23686
Published online in Wiley InterScience (www.interscience.wiley.com).

Keywords: chain-growth condensation polymerization; living polymerization; polyamides; star polymers; porphyrin

INTRODUCTION

Most star polymers with controlled molecular weight and low polydispersity are synthesized by living polymerization, in which only initiation and propagation reactions, but not chain transfer reaction, take place.[1] Accordingly, the obtained star polymers are generally not contaminated with linear polymers. Recently, we have developed chain-growth condensation polymerization,[2] a kind of living polymerization yielding condensation polymers with controlled molecular weight and narrow molecular weight distribution. However, synthesis of star-shaped poly(*p*-benzamide)s through this method, using multifunctional initiators, afforded not only the desired star-shaped poly(*p*-benzamide) via chain-growth polymerization, but also a linear poly(*p*-benzamide) via self-polycondensation of the monomer when the amount of the initiator was decreased. This contamination with linear polymer was more liable to occur as compared to the case of chain-growth condensation polymerization with a monofunctional initiator under the same conditions.[3] In addition, separation of the products by means of high-performance liquid chromatography (HPLC) was necessary to confirm which product was the star polymer and which the linear polymer. However, by using an initiator containing porphyrin, the absorption maximum of which is around 430 nm and quite different from that of poly(*p*-benzamide), we could easily differentiate the star polymer bearing the porphyrin initiator unit from the linear polymer without this initiator unit by means of GPC with a variable-wavelength UV detector, and thus we could optimize the polymerization conditions for selective synthesis of star aromatic polyamides. Furthermore, there are rather few reports on the synthesis of porphyrin-cored star polymers with rigid arms, as compared with star polymers with flexible-coil polymer arms.[4] For example, porphyrin-cored star polyfluorene was synthesized by Suzuki coupling polycondensation of bromofluorene boronic ester in the presence of a porphyrin having four iodofluorene moieties. In this polymerization, the length of the arms was not controlled and the molecular weight distribution was broad.[5] Therefore, not only the synthesis, but also the properties of porphyrin-cored star polymers with well-defined rigid or semirigid arms remain to be fully established.

In this article, we investigated the chain-growth condensation polymerization of 4-(octylamino)benzoic acid esters **1** with porphyrin-cored tetra-functional initiator **3** under various conditions and optimized the conditions for selective synthesis of star-shaped poly(*p*-benzamide)s with suppression of the formation of linear self-condensed polyamides (Scheme 1).

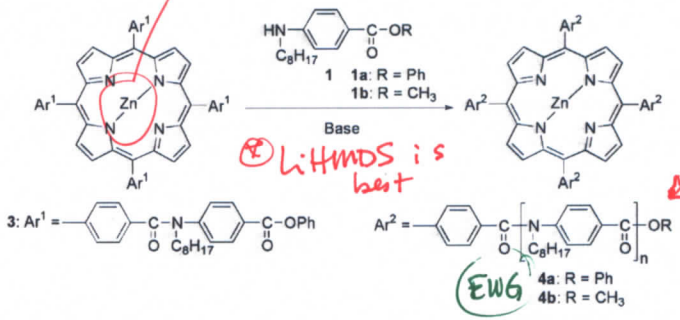
EXPERIMENTAL

Materials

Commercially available dehydrated tetrahydrofuran (stabilizer-free, Kanto) was used as a dry solvent.

Correspondence to: T. Yokozawa (E-mail: yokozt01@kanagawa-u.ac.jp)

Journal of Polymer Science: Part A: Polymer Chemistry, Vol. 47, 6328–6332 (2009)



Scheme 1. Polymerization of **1** with **3**.

Characterization

Conversion of monomers was determined by HPLC with a Japan Analytical Industry LC-909 HPLC unit (eluent: THF) using a JAIGEL column (1H-A). The M_n and M_w/M_n values of polymers were measured with a TOSOH HLC-8120 gel-permeation chromatography (GPC) unit (eluent: THF; calibration: polystyrene standards) using two TSK-gel columns (2 × Multipore H_{XL}-M). Isolation of polymer was carried out with a Japan Analytical Industry LC-908 Recycling Preparative HPLC unit (eluent: $CHCl_3$) using two TSK-gel columns (2 × $G2000H_{HR}$-M). ^{1}H and ^{13}C-NMR spectra were obtained on JEOL ECA-600 and ECA-500 spectrometers with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a JASCO FT/IE-410. Elemental analyses were performed using a Perkin-Elmer 2004 II CHN.

Synthesis of Initiator 3

Thionyl chloride (10 mL) was added to TCPP (0.494 g, 0.624 mmol), and the mixture was stirred at room temperature in darkness for 12 h. Excess thionyl chloride was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (30 mL) in the flask. To this solution was added a solution of triethylamine (0.70 mL, 5.4 mmol) and phenyl 4-(octylamino)benzoate (1.06 g, 3.25 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature in darkness for 1 h, and then the reaction was quenched with water. The organic layer was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/hexane = 3/1) to give 0.982 g of porphyrin **3** without metallic cation as a purple solid (78%, m.p. 90–92 °C).

^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 8.63 (s, 8 H), 8.24 (d, J = 8.3 Hz, 8 H), 7.98 (d, J = 7.8 Hz, 8 H), 7.65 (d, J = 8.2 Hz, 8 H), 7.43 (t, J = 7.8 Hz, 8 H), 7.33–7.27 (m, 12 H), 7.18 (d, J = 7.6 Hz, 8 H), 4.15 (t, J = 7.8 Hz, 8 H), 1.79 (quint, J = 7.7 Hz, 8 H), 1.47 (quint, J = 7.2 Hz, 8 H), 1.42–1.25 (m, 32 H), 0.91 (t, J = 7.1 Hz, 12 H), −2.98 (s, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 170.2, 164.4, 150.9, 148.6, 143.5, 135.4, 133.8, 131.3, 129.6, 127.7, 127.5, 127.19, 127.17, 126.1, 121.6, 119.2, 50.5, 31.8, 29.4, 29.3, 28.0, 27.0, 22.7, 14.1. IR (KBr, cm^{-1}): 3316, 3071, 2925, 1737, 1655, 1602, 1508, 1317, 1264, 754.

A solution of the above porphyrin (0.360 g, 0.180 mmol) and zinc(II) acetate dihydrate (0.322 g, 1.47 mmol) in $CHCl_3$ (36 mL) and MeOH (4 mL) was refluxed for 1 h. After cooling to room temperature, the reaction mixture was concentrated to dryness under reduced pressure, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2, then CH_2Cl_2/methanol = 10/1) to give 0.389 g of **3** as a purple solid (95%, m.p. 115–116 °C).

^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 8.72 (s, 8 H), 8.22 (d, J = 8.6 Hz, 8 H), 7.98 (d, J = 7.9 Hz, 8 H), 7.60 (d, J = 7.9 Hz, 8 H), 7.41 (t, J = 7.9 Hz, 8 H), 7.32–7.26 (m, 12 H), 7.17 (d, J = 7.6 Hz, 8 H), 4.11 (t, J = 7.6 Hz, 8 H), 1.76 (quint, J = 7.7 Hz, 8 H), 1.45 (quint, J = 7.2 Hz, 8 H), 1.41–1.25 (m, 32 H), 0.91 (t, J = 6.9 Hz, 12 H). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 170.2, 164.4, 150.8, 149.8, 148.6, 144.2, 135.1, 133.7, 131.9, 131.2, 129.6, 127.7, 127.5, 127.0, 126.1, 121.6, 120.1, 50.5,

extension of chain-growth polycondensations to star polys by use of multi-functional initiators (cores)

necessary to avoid acidic protons

LiHMDS is best

EWG

EDG

(lithium hexamethyldisilazide (LiHMDS) a strong, bulky base)

LiHMDS gives fast deprotonation of 1a or 1b to inhibit self polycondensation

strong EDG

less susceptible to anion attack than is ... and, then it chain end of propagating polyamide

31.8, 29.4, 29.3, 28.0, 27.0, 22.7, 14.1. IR (KBr, cm^{-1}): 3066, 2925, 1737, 1654, 1602, 1508, 1317, 1264, 754.

Anal. calcd for $C_{132}H_{128}N_8O_{12}Zn$: C, 76.08; H, 6.19; N, 5.38. Found: C, 75.72; H, 6.11; N, 5.28.

Polymerization of 1a with 2/CsF/18-crown-6

CsF (304 mg, 2.00 mmol) was placed in a round-bottomed flask equipped with a three-way stopcock, and dried at 250 °C under reduced pressure for 30 min. The flask was cooled to room temperature under an argon atmosphere. Into the flask were added a solution of phenyl 4-(octylamino)benzoate (**1a**) (651 mg, 2.00 mmol), **3** (52.4 mg, 25.1 μmol), **2** (639 mg, 1.99 mmol), and naphthalene (26.1 mg, 0.203 mmol, used as an internal standard for HPLC analysis) in dry THF (2.0 mL), and a solution of 18-crown-6 (1.06 g, 4.00 mmol) in dry THF (0.5 mL), successively. The mixture was stirred at ambient temperature for 6 h (monomer conversion = 96%), and the reaction was then quenched with saturated aqueous NH_4Cl. The whole was extracted with $CHCl_3$, and the organic layer was washed with water, and dried over anhydrous $MgSO_4$. After concentration *in vacuo*, the products were purified by preparative HPLC to give 407 mg of **4a** as a purple oil.

Polymerization of 1a by Slow Addition of 1a

CsF (61.9 mg, 0.407 mmol) was placed in a round-bottomed flask equipped with a three-way stopcock, and dried at 250 °C under reduced pressure for 30 min. The flask was cooled to room temperature under an argon atmosphere. Into the flask was added a solution of **3** (10.4 mg, 4.99 μmol), 18-crown-6 (219. mg, 0.829 mmol), and naphthalene (11.1 mg, 0.0866 mmol, used as an internal standard for HPLC analysis) in dry THF (1.0 mL). A solution of **1a** (130 mg, 0.398 mmol) and **2** (123 mg, 0.386 mmol) in dry THF (1.0 mL) was slowly added dropwise over 15 min with stirring. The mixture was stirred at ambient temperature for an additional 31 h (monomer conversion = 84%), and the reaction was then quenched with saturated aqueous NH_4Cl. The whole was extracted with $CHCl_3$, and the organic layer was washed with water, followed by drying over anhydrous $MgSO_4$. Concentration *in vacuo* gave a crude product, whose M_n and M_w/M_n were determined by GPC (M_n = 8800, M_w/M_n = 1.70). The residue was purified by preparative HPLC to give 31.4 mg of **4a** as a purple oil.

Polymerization of 1b with LiHMDS

A round-bottomed flask equipped with a three-way stopcock was purged with argon and then charged with dry THF (0.4 mL) and 1.0 M LiHMDS in THF (0.41 mL, 0.41 mmol). The flask was cooled to 10 °C under an argon atmosphere. A solution of methyl 4-(octylamino)-benzoate (**1b**) (106 mg, 0.402 mmol) and **3** (10.3 mg, 4.94 μmol) in dry THF (1.0 mL) at 10 °C was added at once into the flask containing LiHMDS with a syringe through the three-way stopcock in a stream of dry nitrogen, with stirring. Stirring was continued at 10 °C for 1.5 h, then the reaction was quenched with saturated aqueous NH_4Cl, and the whole was extracted with CH_2Cl_2. The organic layer was washed with 1 M NaOH and dried over anhydrous $MgSO_4$. Concentration *in vacuo* gave a crude product, whose M_n and M_w/M_n were determined by GPC (M_n = 15,200, M_w/M_n = 1.07). The residue was purified by preparative HPLC to give 89.4 mg of star **4b** as a purple oil (88%).

4b. M_n = 22,800 (determined by ^1H NMR), M_n (calcd.) = 20,800, M_w/M_n = 1.07.

^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.72 (s, 8 H), 7.96 (d, J = 6.9 Hz, 8 H), 7.86 (d, J = 8.6 Hz, 8 H), 7.60 (d, J = 7.5 Hz, 8 H), 7.20–6.90 (d, J = 8.2 Hz, 2n H), 6.90–6.40 (d, J = 8.2 Hz, 2n H), 4.17–3.03 (m, 2n H), 1.85–1.00 (m, 12n H), 1.00–0.70 (m, 3n H). IR (KBr, cm^{-1}): 3043, 2926, 2855, 1724, 1603, 1509, 848, 762, 706.

RESULTS AND DISCUSSION

The phenyl ester monomer **1a** was first polymerized from the Zn-porphyrin initiator **3** ($[\mathbf{1a}]_0/[\mathbf{3}]_0$ = 80) in the presence of 1.0 equivalent of *N*-octyl-*N*-triethylsilylaniline (**2**), CsF, and 2.0 equivalent of 18-crown-6 in THF at room temperature according to our reported procedure for the synthesis of star polyamides.[3] Porphyrin initiator **3** without the metallic cation was not suitable, probably because the acidic protons of the initiator disturbed the polymerization. The products were analyzed by GPC with a UV detector at 254 and 430 nm. In the case of detection at 254 nm, the GPC elution curve was bimodal [Fig. 1(A)], whereas the GPC trace detected at 430 nm showed a monomodal peak, the M_n value of which was identical with that of the main peak detected at 254 nm [Fig. 1(B)]. This means that the product corresponding to the main peak contains a porphyrin moiety, i.e., it is the desired porphyrin-cored star polymer **4a** with narrow molecular weight distribution. Accordingly, the minor peak detected at 254 nm was due to a linear polyamide formed by self-polycondensation of **1a**. When the feed ratio of monomer to initiator ($[\mathbf{1a}]_0/[\mathbf{3}]_0$) was decreased to 40 or to 20, the minor peak of the GPC elution curve decreased, but did not disappear.

initial 2000 conditions — insufficient to prevent self-polycondensation w/out connection to core

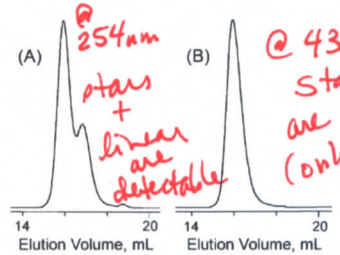


Figure 1. GPC profiles of tetra-armed star polymers **4a**, obtained by the polymerization of **1a** with **3** ($[\mathbf{1a}]_0/[\mathbf{3}]_0$ = 79.7), detected by absorption measurement at (A) 254 nm (M_n = 9700, M_w/M_n = 1.22) and (B) 430 nm (M_n = 11,400, M_w/M_n = 1.10).

GPC using PS standards ⇒ inaccurately low M_n values

narrow M_w/M_n indicates polym. control!

Table 1. Polymerization of **1b** with **3**[a]

Entry	$[\mathbf{1b}]_0/[\mathbf{3}]_0$	Temp. (°C)	Conv. (%)[b]	$M_{n,\ calcd}$	$M_{n,\ GPC}$[c]	$M_{n,\ NMR}$[d]	M_w/M_n[c]
1	80.4	−10	95	19,500	9,500	18,800	1.33
2	80.6	−30	100	20,500	10,100	20,000	1.25
3	81.4	10	100	20,600	15,200	22,800	1.07
4	80.6	25	100	20,500	15,600	24,700	1.09
5	39.5	10	100	11,000	10,700	11,900	1.05
6	120.4	10	100	29,600	22,200	32,700	1.11
7	158.5	10	100	38,400	20,500	47,900	1.25

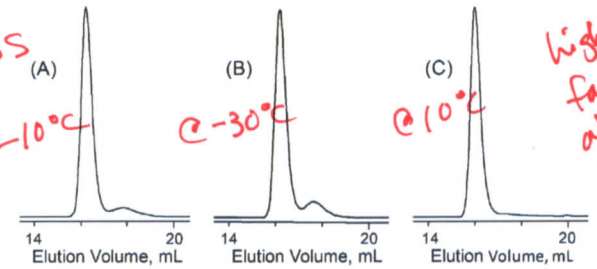
[a] Polymerization of **1b** with **3** was carried out in the presence of 1.0 equivalent of LiHMDS in THF ($[\mathbf{1b}]_0$ = 0.67 M).
[b] Determined by HPLC.
[c] Determined by GPC based on polystyrene standards (eluent: THF).
[d] Determined by ^1H NMR.

inc. $[\mathbf{1b}]_0/[\mathbf{3}]_0$ (monomer: core) gives inc. theor + observed M_n's (DP_n's)

Considering that a low concentration of the monomer would suppress the self-polycondensation of **1a**, we slowly added a solution of **1a** and **2** in THF to a solution of **3**, CsF, and 18-crown-6 in THF. Contrary to our expectation, the GPC elution curves detected both 254 nm and 430 nm showed broad molecular weight distributions (M_w/M_n = 1.70 and 1.51), respectively. Therefore, slow addition method caused not only self-polycondensation of **1a** but also production of star polymer with broad molecular weight distribution. This result implies that the base system using **2** was not strong enough to immediately abstract the proton of the amino group of **1a** added slowly to the reaction mixture.

In our previous report,[7] LiHMDS, which is a stronger base, was effective for the synthesis of linear poly(*N*-octyl-*p*-benzamide)s with defined molecular weight and narrow molecular weight distribution by polymerization of the methyl ester monomer **1b**. Therefore, the polymerization of **1b** was carried out by using LiHMDS in the presence of **3** ($[\mathbf{1b}]_0/[\mathbf{3}]_0$ = 80) at −10 °C according to the procedure used for the synthesis of linear polyamide (Table 1, entry 1). The polymerization proceeded rapidly, and the minor peak in the GPC elution curve of the product became much smaller than that of the polymer obtained by polymerization with **2**/CsF/18-crown-6 [Fig. 2(A) versus Fig. 1(A)]. The M_w/M_n ratios in Table 1 were calculated including the minor peak as an index of contamination of linear poly**1b**; the molecular weight distribution of star polymers was

w/LiHMDS



higher T gives faster H⊕ abstraction + better star formation (but, RT was too high T)

Figure 2. GPC profiles detected by absorption measurement at 254 nm of tetra-armed star polymers **4b** obtained by the polymerization of **1b** with **3** in the presence of LiHMDS in THF ($[\mathbf{1b}]_0$ = [LiHMDS]$_0$ = 0.67*M*; $[\mathbf{1b}]_0/[\mathbf{3}]_0$ = 80) at (A) −10 °C (M_n = 9500, M_w/M_n = 1.33, entry 1), (B) −30 °C (M_n = 10,100, M_w/M_n = 1.25, entry 2) and (C) 10 °C (M_n = 15,200, M_w/M_n = 1.07, entry 3).

⊕ conditions optimized by using a strong base + intermediate temperature to promote fast deprotonation + fast rxn of deprotonated monomer w/initiator + propagating chain end