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Copper-Catalyzed vs Thermal Step Growth Polymerization of Starch-Derived α-Azide−ω-Alkyne Dianhydrohexitol Stereoisomers: To Click or Not To Click?

Céline Besset,[†,‡] Sandra Binauld,[†] Mathias Ibert,[‡] Patrick Fuertes,[‡] Jean-Pierre Pascault,[†] Etienne Fleury,[†] Julien Bernard,*[,†] and Eric Drockenmuller*[,†]

[†]*INSA de Lyon, Ingénierie des Matériaux Polymères (IMP, UMR CNRS 5223), Université Claude Bernard Lyon 1, 69622 Villeurbanne Cedex, France and* [‡]*Division Recherche, Roquette Frères, 62080 Lestrem Cedex, France*

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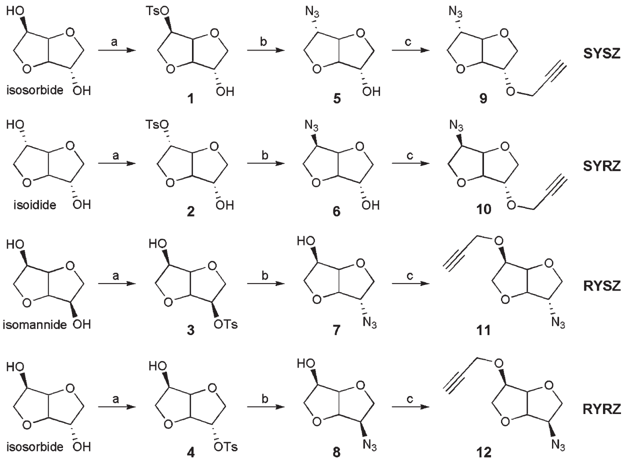
Within a few decades materials science has considerably widened its scope of applications with a panel of efficient and versatile synthetic methods affording an astonishing diversity of complex multifunctional macromolecular architectures. Recently, the highly efficient, orthogonal and regiospecific copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC),[1] one of the most reliable example of the "click chemistry" concept,[2] has opened new perspectives for the design of polymer materials with targeted properties and the modification of 2D and 3D substrates.[3] A tremendous palette of functionalized (co)polymers, macrocycles, block copolymers, star and hyperbranched polymers, dendrimers, polymer bioconjugates, and networks has thus been described. The benefits of CuAAC have also been widely applied to the field of step growth polymerization, allowing the design of a new class of macromolecules with 1,4-disubstituted 1,2,3-triazole within the repeating unit. Outpassing the limitations of thermal 1,3-dipolar Huisgen polyaddition in solution (low reactivity, high temperatures, limited yields),[4] CuAAC polyaddition of diazide and dialkyne monomers has been extensively investigated.[5] Emerging strategies have focused on the CuAAC polyaddition of α-azide−ω-alkyne monomers yielding polytriazole (co)polymers with tunable structure and properties.[6] However, these approaches are generally limited by the poor solubility and the low polymerization degree (DP_n) of the resulting materials. Also, while copper(I) catalysis ensures a regioselective polyaddition, the binding properties of the multiple triazole rings along the polymer backbone complicate catalyst extraction. Such residuals may alter the properties of the resulting materials and jeopardize their potential applications.[7]

Herein, we present the synthesis of α-azide−ω-alkyne 1,4:3,6-dianhydrohexitols with controlled stereochemistry from starch-derived isosorbide, isomannide, and isoidide as well as a detailed study of their polyaddition by CuAAC in solution or by catalyst- and solvent-free 1,3-dipolar Huisgen cycloaddition. The resulting library of isomeric dianhydrohexitol/triazole-based polymers allows a fine investigation of the structure/properties relationship. Particularly, a fundamental insight into the influence of monomer stereochemistry (RR, RS, SR, SS) as well as polyaddition regiospecificity (1,4- or 1,4/1,5-triazoles) on the physicochemical properties of the resulting polymers is thus accessible. Finally, the questionable benefits of copper catalysis over thermal Huisgen cycloaddition in the field of step growth polymerization are discussed.



a) TsCl, pyridine,R.T.; b) NaN$_3$, DMF, 140 °C; c) Propargyl bromide, NaH, 18-crown-6, DMF, R.T.

Figure 1. Synthesis of α-azide−ω-alkyne 1,4:3,6-dianhydrohexitol stereoisomers from isosorbide, isoidide, and isomannide.

1,4:3,6-Dianhydrohexitols, especially isosorbide and isomannide, can be readily obtained through sequential hydrogenation and dehydration of D-glucose and D-mannose, respectively.[8] In the context of fossil fuels rising costs and rarification, these diols issued from abundant and renewable agro-resources have attracted considerable attention in the field of materials science. Indeed, 1,4:3,6-dianhydrohexitols have been thoroughly investigated as bio-sourced monomers for the step growth polymerization industry.[9] However, the relatively low reactivity of the secondary alcohols has encouraged the development of derivatives with enhanced reactivity.[10] In this context, we have developed the synthesis of α-azide−ω-alkyne 1,4:3,6-dianhydrohexitol stereoisomers in order to generate polytriazoles with controlled stereochemistry by azide−alkyne cycloaddition. Such AB + AB step growth polymerization strategy has many advantages such as circumventing stoichiometry issues inherent to AA + BB systems, designing polymers with a high weight fraction of bio-sourced monomer, and handling monomers with a reasonable content of nitrogen atoms.[11] α-Azide−ω-alkyne dianhydrohexitol stereoisomers **9**−**12** (RR, RS, SR, SS) were thus obtained from isosorbide, isoidide, and isomannide using a three-step synthetic pathway (Figure 1). Nucleophilic substitution of tailor-made monotosylates **1**−**4** by sodium azide yielded azide derivatives **5**−**8** with configuration inversion of the adjacent carbon atom. Alkylation of the remaining hydroxyl group by propargyl bromide was then performed at room temperature to avoid any undesirable step growth polymerization. Monomers **9**−**12** were stored at −20 °C, a temperature below which no traces of coupling products could be observed by ^{1}H NMR after several months of storage.

Monomers **9**−**12** were then polymerized by CuAAC step growth polymerization in solution to investigate the influence of monomer stereochemistry on the physicochemical properties of the resulting polytriazoles (Figure 2). Relatively high monomer concentrations (1 M in DMSO) were employed in order to limit the formation of cyclic species.[6c] Under these conditions, polymerization of each monomer resulted in the formation of a physical gel that could be rapidly dissolved by

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*Corresponding authors. E-mail: julien.bernard@insa-lyon.fr (J.B.); eric.drockenmuller@univ-lyon1.fr (E.D.).

postpolymerization addition of solvent. Despite the physical gelation of the polymerization media, the polyadditions proceeded up to high conversions furnishing, after purification, polytriazoles **13**−**16** with excellent yields (Table 1).

The regioselectivity of the CuAAC step growth polymerization was clearly demonstrated by ^{1}H NMR (example for **13** in Figure 3) with the appearance of a single signal at 8.16 ppm characteristic of 1,4-disubstituted 1,2,3-triazoles. Also, the formation of polytriazole chains was confirmed by the significant downfield shift of most protons from the 1,4:3,6-dianhydrohexitol moiety as well as the disappearance of the signals of alkyne and azide groups.

Polytriazoles **13**−**16** were then characterized by SEC in DMSO at 120 °C using universal calibration (dual detection RI/viscosimetry) to corroborate ^{1}H NMR analysis. Unfortunately, while **13** and **15** readily dissolve in DMSO at 120 °C, **14** and **16** are hardly soluble at this temperature, most probably reflecting an effect of monomer stereochemistry. In the case of **13** and **15**, SEC analysis confirmed the preparation of polymers with molar masses (M_n) of ca. 7000 g/mol (Table 1). These relatively low values of M_n and high values of PDI most likely stem from the physical gelation of the polymerization medium that hampers the significant chain growth generally occurring at the end of the polyaddition process. DSC analysis of polytriazoles **13**−**16** highlights their amorphous behavior and the high T_g values resulting from the rigidity of the 1,4:3,6-dianhydrohexitol and triazole segments. Interestingly, the values of T_g are significantly impacted by monomer stereochemistry, with a minimum of 140 °C for **13** (SYSZ) and a maximum of 173 °C for **16** (RYRZ). However, the relatively high thermal resistance of polytriazoles **13**−**16** was only slightly influenced by monomer stereochemistry (T_{d10} = 314−340 °C).

Whereas rising efforts are dedicated to the development of metal-free click reactions,[12] the influence of azide−alkyne cycloaddition regioselectivity on polytriazole properties has been addressed lately.[13] In order to overcome problems inherent to the use of copper catalyst and investigate the influence of polyaddition regioselectivity on physicochemical properties of the resulting polytriazoles, catalyst-free polyaddition of **9**−**12** was performed in bulk (Figure 4). Interestingly, the monomer conversion and thus the DP_n of the resulting polytriazoles could be precisely adjusted with the polyaddition temperature. Indeed, once the T_g of the growing polytriazoles reaches the reaction temperature, the system vitrifies impeding further chain growth. As shown by ^{1}H NMR, reactive solid materials with DP_n of 3 and 5 are obtained from **9** after several weeks at respectively 4 and 25 °C, while temperatures above $T_{g\infty}$ ensure quantitative conversion of the monomer and obtaining high DP_n polytriazoles.

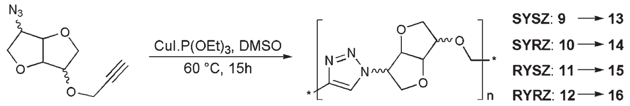

Figure 2. Synthesis of polytriazoles **13**−**16** by CuAAC polyaddition in DMSO.

To determine appropriate storage conditions and thermal processing of these materials, the concomitant evolutions of monomer conversion and T_g with temperature during polyaddition of **9** and **12** were precisely monitored by DSC (Figure 5, Figures S1 and S2 in the Supporting Information).

No significant influence of monomer stereochemistry on the rate of polymerization could be observed for monomers **9** and **12**. It must be pointed out that polymerizations can be completed within minutes by applying appropriate curing conditions. The particularly high reactivity of monomers **9**−**12** at low temperatures and the possibilities to perform precure steps and to process solid reactive oligomers are key features of this versatile approach. Polyaddition of monomers **9** and **12** at different heating rates were monitored by DSC in order to determine the polyaddition activation energy using the Kissinger method (Figures S3 and S4 in the Supporting Information).[14] Similar values (74 and 79 kJ/mol for **9** and **12**, respectively) were obtained confirming that thermal azide−alkyne cycloaddition is not affected by monomer stereochemistry.

The nonregioselective character of this copper-free polyaddition process was highlighted by ^{1}H NMR. Indeed, ca. 2:1 signal

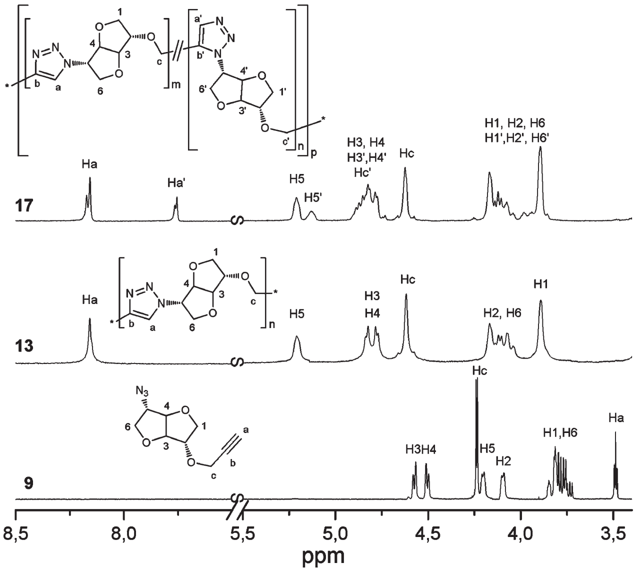

Figure 3. ^{1}H NMR spectra (DMSO-d_6) of monomer **9** and polytriazoles **13** and **17** obtained respectively by CuAAC polyaddition in DMSO and, catalyst- and solvent-free polyaddition.

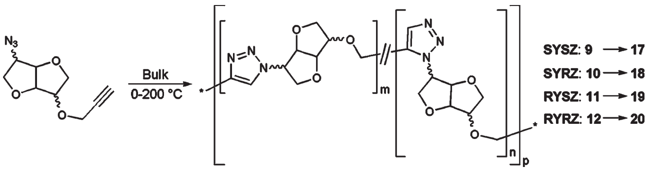

Figure 4. Synthesis of polytriazoles **17**−**20** by catalyst- and solvent-free azide−alkyne cycloaddition.

Table 1. Properties of Polytriazoles 13−**20 Synthesized by CuAAC in DMSO or by Catalyst and Solvent Free Azide**−**Alkyne Cycloaddition**

no.	condition	monomer	stereo.	yield (%)	1,4/1,5[a]	M_n (g/mol)[b]	DP_n[b]	PDI[b]	$T_{g\infty}$ (°C)	T_{d10} (°C)[c]
13	DMSO	**9**	SYSZ	95	100/0	6900	33	28.7	140	323
14	DMSO	**10**	SYRZ	95	100/0	*d*	*d*	*d*	146	325
15	DMSO	**11**	RYSZ	94	100/0	7500	36	21.4	141	314
16	DMSO	**12**	RYRZ	88	100/0	*d*	*d*	*d*	173	340
17	bulk	**9**	SYSZ	100	2.0/1.0	11500	55	5.5	132	359
18	bulk	**10**	SYRZ	100	1.9/1.0	8900	42	1.3	136	354
19	bulk	**11**	RYSZ	100	1.8/1.0	31900	152	1.9	124	360
20	bulk	**12**	RYRZ	100	1.8/1.0	9900	47	3.3	159	356

[a] From ^{1}H NMR. [b] From SEC (dual detection RI/viscosimetry) in DMSO at 120 °C. [c] Temperature at 10 wt % loss. [d] Partially soluble in DMSO at 120 °C.

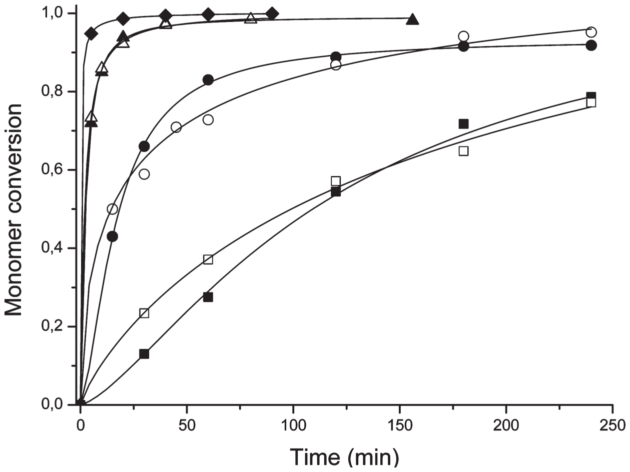

Figure 5. Monomer conversion vs reaction time for the catalyst-free polyaddition in bulk of monomers **9** (□, ○, Δ) and **12** (■, ●, ▲, ◆) at 70 °C (□, ■), 90 °C (○, ●), 120 °C (Δ, ▲), and 140 °C (◆).

ratios of 1,4- and 1,5-disubstituted 1,2,3-triazoles (at respectively 8.16 and 7.76 ppm for **17** in Figure 3) were observed in the purified polymers (Table 1). In addition, no traces of alkyne and azide chain ends could be discerned by ^{1}H NMR and FTIR. Finally, SEC, DSC, and ATG experiments provided further input on the influence of polyaddition regioselectivity on the physicochemical properties of polytriazoles. First, a significant solubility enhancement was observed as, conversely to their analogues **13**−**16**, polytriazoles **17**−**20** are readily soluble in DMSO at room temperature. SEC experiments underlined the generation of polytriazoles with higher M_n and sharper molar mass distributions than those obtained for **13**−**16**, consistent with a homogeneous polymerization medium. Whereas the absence of catalytic system clearly facilitates the process, the consequent loss of regioselectivity only slightly affects the thermal properties of the resulting polytriazoles as a ca. 10−15 °C decrease in the T_g values was measured. As for **13**−**16**, the influence of monomer stereochemistry on T_g is maintained with a maximum value of 159 °C for **20** (RYRZ). Compared to **13**−**16**, polytriazoles **17**−**20** exhibit a higher resistance to thermal degradation (T_{d10} = 354−360 °C) independently of monomer stereochemistry. This most probably stems from the higher M_n of **17**−**20** which reduce the contribution of chain ends in the degradation mechanism.

As a conclusion, CuAAC polyaddition in DMSO and thermal polyaddition of tailor-made α-azide−ω-alkyne dianhydrohexitol stereoisomers afford bio-sourced polytriazoles having T_g values highly dependent on monomer stereochemistry. Compared to previous studies on thermal Huisgen polyaddition, the particularly high reactivity of these monomers afforded the completion of the reaction after short reaction times at moderate temperatures. Also, the possibility to adjust DP_n with reaction temperature and to process reactive solid oligomers obtained by precure steps reflects the robustness of this polyaddition process. Finally, whereas the benefits of CuAAC in polymer science are numerous, its application to step growth polymerization of α-azide−ω-alkyne 1,4:3,6-dianhydrohexitols is detrimental. Indeed, while CuAAC polyaddition in solution generates poorly soluble low M_n polytriazoles and requires several purification steps, thermal polyaddition in bulk provides polytriazoles with enhanced solubility, high M_n, and comparable thermal properties using tunable and versatile processing conditions.

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Supporting Information Available: Syntheses and characterization methods, kinetic monitoring, and determination of the polyaddition activation energy by DSC. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
(2) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
(3) (a) Iha, R. K.; Wooley, K. L.; Nyström, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J. *Chem. Rev.* **2009**, *109*, 5620–5686. (b) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 2–10. (c) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197–2208. (d) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2008**, *29*, 952–981. (e) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015. (f) Carlmark, A.; Hawker, C. J.; Hult, A.; Malkoch, M. *Chem. Soc. Rev.* **2009**, *38*, 352–362. (g) Nebhani, L.; Barner-Kowollik, C. *Adv. Mater.* **2009**, *21*, 3442–3468. (h) Vogt, A. P.; Sumerlin, B. S. *Macromolecules* **2009**, DOI: 10.1021/ma901447e.
(4) (a) Baldwin, M. G.; Johnson, K. E.; Lovinger, J. A.; Parker, C. O. *J. Polym. Sci., Part B: Polym. Lett.* **1967**, *5*, 803–806. (b) Wan, L.; Tian, J.; Huang, J.; Hu, Y.; Huang, F.; Du, L. *J. Macromol. Sci., Part A: Pure Appl. Chem.* **2007**, *44*, 175–181. (c) Katritzky, A. R.; Meher, N. K.; Hanci, S.; Gyanda, R.; Tala, S. R.; Mathai, S.; Duran, R. S.; Bernard, S.; Sabri, F.; Singh, S. K.; Doskocz, J.; Ciaramitaro, D. A. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 238–256.
(5) (a) Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4392–4403. (b) van Steenis, D. J.; David, O. R.; van Strijdonck, G. P.; van Maarseveen, J. H.; Reek, J. N. *Chem. Commun.* **2005**, 4333–4335. (c) Srinivasachari, S.; Liu, Y.; Zhang, G.; Prevette, L.; Reineke, T. M. *J. Am. Chem. Soc.* **2006**, *128*, 8176–8184. (d) Zhu, Y.; Huang, Y.; Meng, W.-D.; Li, H.; Qing, F.-L. *Polymer* **2006**, *47*, 6272–6279. (e) Liu, X.-M.; Thakur, A.; Wang, D. *Biomacromolecules* **2007**, *8*, 2653–2658. (f) Meudtner, R. M.; Hecht, S. *Macromol. Rapid Commun.* **2008**, *29*, 347–351. (g) Binauld, S.; Boisson, F.; Hamaide, T.; Pascault, J.-P.; Drockenmuller, E.; Fleury, E. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5506–5517. (h) Nagao, Y.; Takasu, A. *Macromol. Rapid Commun.* **2009**, *30*, 199–203. (i) Ooya, T.; Inoue, D.; Choi, H. S.; Kobayashi, Y.; Loethen, S.; Thompson, D. H.; Ko, Y. H.; Kim, K.; Yui, N. *Org. Lett.* **2006**, *8*, 3159–3162.
(6) (a) Tsarevsky, N. V.; Sumerlin, B. S.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 3558–3561. (b) van Dijk, M.; Nollet, M. L.; Weijers, P.; Dechesne, A. C.; Nostrum, C. F.; Hennink, W. E.; Rijkers, D. T. S.; Liskamp, R. M. J. *Biomacromolecules* **2008**, *9*, 2834–2843. (c) Binauld, S.; Damiron, D.; Hamaide, T.; Pascault, J.-P.; Fleury, E.; Drockenmuller, E. *Chem. Commun.* **2008**, 4138–4141. (d) Xue, X.; Zhu, J.; Zhang, W.; Zhang, Z.; Zhu, X. *Polymer* **2009**, *50*, 4512–4519.
(7) (a) Qin, A.; Tang, L.; Lam, J. W. Y.; Jim, C. K. W.; Yu, Y.; Zhao, H.; Sun, J.; Tang, B. Z. *Adv. Funct. Mater.* **2009**, *19*, 1891–1900. (b) Codelli, J. A.; Baskin, J. M.; Agard, N. J.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 11486–11493.
(8) (a) Fleche, G.; Huchette, M. *Starch/Staerke* **1986**, *38*, 26–30. (b) Fleche, G.; Fuertes, P.; Tamion, R.; Wyart, H. Patent WO 2001094352.
(9) (a) Kricheldorf, H. R. *Rev. Macromol. Chem. Phys.* **1997**, *4*, 599–631. (b) Fenouillot, F.; Rousseau, A.; Colomines, G.; Saint-Loup, R.; Pascault, J.-P. *Prog. Polym. Sci.* **2009**, DOI: 10.1016/j.progpolymsci.2009.10.001. (d) http://www.biohub.fr/.
(10) (a) Thiem, J.; Lüders, H. *Starch/Staerke* **1984**, *36*, 170–176. (b) Thiem, J.; Lüders, H. *Makromol. Chem.* **1986**, *187*, 2775–2785. (c) Caouthar, A.; Loupy, A.; Bortolussi, M.; Blais, J. C.; Dubreucq, L.; Meddour, A. J. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 6480–6491. (d) Caouthar, A.; Roger, P.; Tessier, M.; Chatti, S.; Blais, J. C.; Bortolussi, M. *Eur. Polym. J.* **2007**, *43*, 220–230.
(11) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240.
(12) (a) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2–5. (b) Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4900–4908. (c) Singh, I.; Zarafshani, Z.; Lutz, J.-F.; Heaney, F. *Macromolecules* **2009**, *42*, 5411–5413.
(13) Nulwala, H.; Takizawa, K.; Odukale, A.; Khan, A.; Thibault, R. J.; Taft, B. R.; Lipshutz, B. H.; Hawker, C. J. *Macromolecules* **2009**, *42*, 6068–6074.
(14) Kissinger, H. E. *Anal. Chem.* **1957**, *29*, 1702–1706.