"Click" Chemistry and Radical Polymerization: Potential Loss of Orthogonality

Vincent Ladmiral,[†] Thomas M. Legge,[†] Youliang Zhao,[†,§] and Sébastien Perrier*[,‡]

The University of Leeds, Leeds LS2 9JT, U.K., and Key Centre for Polymer Colloids, School of Chemistry, the University of Sydney, Sydney NSW 2006, Australia

Received May 7, 2008; Revised Manuscript Received July 3, 2008

ABSTRACT: The noncatalyzed cycloaddition of azides with electron-poor olefins was investigated in conditions mimicking those of living radical polymerization. The pathway of this reaction was investigated, and model reactions were designed to study this reaction with various types of monomers (*N*-isopropylacrylamide, dimethylacrylamide, methyl acrylate, methyl methacrylate, and styrene). We found that the azide undergoes 1,3-cycloaddition with the double bond of these monomers, in the absence of catalyst, at high temperatures (60 °C) and for long reaction times. This side reaction can be of dramatic significance as it impairs the orthogonality of copper-catalyzed azide−alkyne cycloaddition ("click chemistry"); short polymerization time and low temperatures should be targeted to limit these side reactions.

Introduction

Click chemistry, the category of perfect reaction first described in 2001 by Sharpless and co-workers,[1] and its best example, the copper-catalyzed azide−alkyne cycloaddition (CuAAC),[2] have been the object of intensive research over the past 7 years. CuAAC in particular is viewed as a very useful and versatile addition to the synthesis toolbox and has been applied to nearly all the areas of chemistry.[3] This reaction is especially relevant to modern polymer synthesis, where high-yielding precise organic reactions are coupled with controlled polymer syntheses methods to create highly sophisticated materials.[4] Living radical polymerization (LRP) techniques are such polymer synthesis methods, which have rapidly developed as ways to manufacture polymers of controlled architectures and topologies and to engineer new functional materials. These techniques share a number of key features with CuAAC such as robustness, versatility, and excellent tolerance toward functional groups. Recently, a number of research groups have combined LRP and CuAAC to synthesize functional polymers. Typically, LRP is used to synthesize well-defined polymeric architectures, which are subsequently functionalized using CuAAC. This strategy has been applied to produce polymers of various architectures (block copolymers,[5] graft,[6] star,[7] hyperbranched,[8] telechelic,[9] multifunctional,[10] surface-tethered,[11] and cyclic[12] polymers), macromonomers,[13] self-assembly structures such as micelles,[14] shell cross-linked nanoparticles,[15] nanocapsules,[16] and polymersomes,[17] and bioconjugates.[18] Azide or terminal alkyne groups are introduced in the polymer before or during the polymerization using functional initiators, chain transfer agents, or monomers or after the polymerization by modification of the end or pendent groups. The postpolymerization procedure is efficient but might be hindered by incomplete functionalization of the polymers, leading to poorly defined macromolecules or decreased atom efficiency of the synthesis. The use of functional reactants helps to overcome this problem, as long as azides and alkynes are compatible with the experimental conditions of polymerizations. It is well-known that acetylene groups can undergo radical addition reactions, and they are usually protected using trialkylsilyl groups to avoid side reactions during polymerization. Azides, on the other hand, do not require protective chemistry and are more widely used to introduce a functional group prepolymerization. However, careful observation of the recent literature regarding the combination of CuAAC and LRP suggests that azides may also be involved in side reactions during polymerization, although the effect seems to have often been overlooked. Indeed, only Benicewitz and co-workers have reported the loss of azide functionalities during polymerization, and they suggested the formation of triazolines from the 1,3-cycloaddition of a vinyl bond onto an azide moiety between two azide-functional methacrylate monomers.[19] During our own work on the synthesis of chain-end functional poly(*N*-isopropylacrylamide) via CuAAC, we made similar observations and decided to investigate further the occurrence of side reactions between azides and vinyl groups.

* Corresponding author: Fax +61 2 9351 3329; Tel +61 2 9351 3366; e-mail s.perrier@chem.usyd.edu.au.
[†] University of Leeds.
[‡] University of Sydney.
[§] Present address: School of Chemistry and Chemical Engineering, Suzhou University, 199 Ren Ai Road, Suzhou Dushu Lake Higher Education Town, Suzhou 215123, China.

Experimental Section

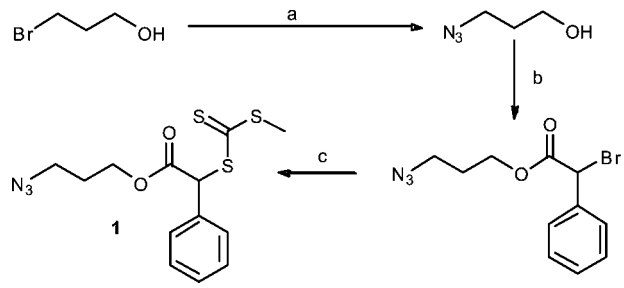
All solvents, monomers, and other chemicals were purchased from Aldrich unless otherwise stated. Methyl acrylate (MA), *N,N*-dimethylacrylamide (DMA), methyl methacrylate (MMA), and styrene (St) were passed through a basic alumina (Brockmann I) column to remove the inhibitor before use. *N*-Isopropylacrylamide (NIPAAM) was recrystallized twice from mixtures of hexane and toluene prior to use. Other chemicals were of analytical grade and used as received. 1,4-Dioxane-d_8 (99% D, contains 0.03% (v/v) TMS) was used as received. 2,2-Azobis(isobutyronitrile) (AIBN, 99%, Fisher) was recrystallized twice from ethanol. Methyl α-bromophenylacetate (97%) was supplied from Aldrich. Air- and moisture-sensitive compounds were manipulated using standard Schlenk techniques under a nitrogen atmosphere.

Gel Permeation Chromatography (GPC). Molecular weight distributions were recorded using gel permeation chromatography (GPC) at ambient temperature using a system equipped with a Polymer Laboratories 5.0 μm-bead-size guard column (50 × 7.5 mm) and two Polymer Laboratories PLgel 5 μm MIXED-C columns (molecular weight range of 2 000 000−500 g mol^{-1}) with a differential refractive index detector (Shodex, RI-101). Tetrahydrofuran was used as an eluent at a flow rate of 1 mL min^{-1}, and toluene was used as a flow rate marker. Polystyrene in the range of 7 500 000−580 g/mol were used for calibrations.

NMR Spectroscopy. Both ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker 400 UltraShield spec-

10.1021/ma8010262 CCC: $40.75
Published on Web 08/15/2008

Scheme 1[a]



[a] Reagents and conditions: (a) NaN_3, acetone:water (6:1), reflux, 24 h; (b) α-bromophenylacetic acid, DMAP, DCC, CH_2Cl_2, ambient temperature, 24 h; (c) sodium methyl trithiocarbonate, Et_2O:H_2O (1:1), ambient temperature, 24 h.

trometer at 25 °C, and chloroform-*d* with 0.3% TMS was used as a solvent, unless otherwise stated.

Fourier Transform Infrared Spectroscopy (FT-IR). FTIR spectra were recorded using a Perkin-Elmer Spectrum One Infrared Fourier transform spectrometer in the region between 4000 and 400 cm^{-1}. The contact sampler was a horizontal internal reflectance accessory (ATR) with a resolution of 4 cm^{-1}. Scan speed was set at 0.5 cm/s with 100 scans performed per sample.

***S*-Azidopropanoxycarbonylphenylmethyl Trithiocarbonate (1).** Sodium azide (9.35 g, 143 mmol) and 3-bromo-1-propanol (10 g, 71 mmol) were refluxed (80 °C) overnight in an acetone/water mix (6:1). The product was extracted into diethyl ether, washed with water, and dried over sodium sulfate to yield 3-azido-1-propanol (5.7 g, 56.4 mmol; yield: 79%).

N,N-Dicyclohexylcarbodiimide (11.6 g, 56 mmol) was added dropwise to a cooled solution (ice−water bath) of 2-bromo-2-phenylacetic acid (12.12 g, 56 mmol), 3-azido-1-propanol (5.7 g 56 mmol), 4-DMAP (0.68 g, 5.6 mmol), and dry DCM (as solvent). The solution was stirred for 4 h, and the resulting precipitate (*N,N*-dicyclohexylurea) was removed by filtration. The desired compound, 3-azidopropyl 2-bromo-2-phenylacetate was isolated by flash chromatography on silica (*n*-hexane:ethyl acetate, 6:1) (9.1 g, 31 mmol; yield: 55%).

Carbon disulfide (2.6 g, 34 mmol) in diethyl ether (as solvent) was added to a 21% solution of sodium thiomethoxide ($NaSCH_3$) in water (8.65 mL, 28 mmol) at room temperature. The biphasic solution was vigorously stirred for 4 h, after which time 3-azidopropyl 2-bromo-2-phenylacetate (8.5 g, 28 mmol) was added dropwise over 15 min. The reaction was stirred overnight, after which time NaCl was added and the product extracted into ethyl acetate. HCl was added (37%, 10 mL), and the organic phase was washed with water (3 × 100 mL). The organic phase was concentrated and dried over sodium sulfate. Compound was isolated as a yellow oil by column chromatography on silica (*n*-hexane: ethyl acetate, 5:1) (7.7 g, 23 mmol; yield: 81%). ^1H NMR ($CDCl_3$, 298 K, 400 MHz) δ (ppm from TMS): 1.87 (2H, m, $CH_2-CH_2-CH_2$), 2.73 (3H, m, SCH_3) 3.29 (2H, m, CH_2-N_3), 4.25 (2H, m, $O-CH_2$), 5.79 (1H, s, −S(Ph)CH), 7.35−7.40 (5H, m, Ar−H). ^{13}C NMR ($CDCl_3$, 298 K, 100 MHz) δ (ppm from TMS): 20.32 (CH_3), 28.08 ($CH_2CH_2N_3$), 62.90 (CH_2N_3), 47.96 (CH), 58.92 ($O-CH_2$) 128.79, 128.96, 129.15, 129.25, 129.54, 132.50 (CH of Ar), 175.16 (C═O), 221.95 (CS_2). FTIR (cm^{-1}): 2090 ($C-N_3$); 1731 (C═O); 1605−1444 (aromatic skeleton area). EA: Found; C: 45.9%, H: 4.25%, N: 11.9% S: 28.34% (Anal. Calcd; C: 45.73%, H: 4.43%, N: 12.31%, S: 28.17%).

Benzyl Azide. To a round-bottom flask was added benzyl chloride (2.53 g, 20 mmol), sodium azide (6.50 g, 100 mmol), and DMSO (20 mL), and the mixture was stirred at 90 °C overnight. After cooling to ambient temperature, the mixture was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane thrice, and the organic phase was combined and dried over $MgSO_4$ overnight. After concentration, benzyl azide (2.10 g, 78.9% of yield) was obtained as a colorless oil. ^1H NMR ($CDCl_3$): δ 7.31−7.41 (m, 5H, PhH), 4.34 (s, 2H, CH_2).

Table 1. RAFT Polymerization of NIPAAM in 1,4-Dioxane at 60 °C for 20 h

entry	$[\mathbf{1}]_0$:$[I]_0$:$[M]_0$[a]	conv (%)	$M_{n,theo}$[b]	$M_{n,GPC}$[c]	$M_{n,NMR}$[d]	PDI
1	1:0.2:17	96	1844	2600	1800	1.12
2	1:0.2:26	97	2850	5100	3300	1.07
3	1:0.2:35	96	3797	5300	3900	1.05
4	1:0.2:100	94	10622	10600	8300	1.07

[a] I = AIBN, M = NIPAAM. In 1,4-dioxane (w/v wrt monomer = 1:2). [b] Calculated with $M_{n,theo} = ([M]_0/[\mathbf{1}]_0) \times conv \times MW_{NIPAAM} + MW_{\mathbf{1}}$. [c] Determined by GPC using PMMA standards. [d] Determined by ^1H NMR comparing the signals of SCH_3 (2.4 ppm) and $CH(CH_3)_2$ (1.5 ppm).

Reaction of Benzyl Azide with Vinyl Monomers. In a typical run, to a round flask was added benzyl azide (0.266 g, 2.0 mmol) and NIPAAM (0.905 g, 8.0 mmol) under nitrogen, and then dioxane was added dropwise until the total volume was 8.0 mL. The flask was placed into an oil bath preheated to 60 °C for 20 h, and the mixture was concentrated under reduced pressure. ^1H NMR spectra of the crude product revealed that 79.3% of benzyl azide was consumed. Other reactions were conducted according to similar conditions, and the conversion was determined by comparison of the integrated signals of phenyl protons (7.2−7.4 ppm) and unreacted CH_2N_3 (4.34 ppm).

Typical Polymerization of NIPAAM. NIPAAM (5.01 g, 0.0442 mol) was dissolved in 1,4-dioxane (w/v wrt monomer = 1:2) with **1** (0.1479 g, 4.42×10^{-4} mol) and AIBN (0.014 50 g, 0.88×10^{-4} mol). The [monomer]:[CTA]:[AIBN] ratio was 100:1:0.2. The polymerization was deoxygenated by freeze−pump−thaw, and the reaction was left for 20 h at 60 °C in an oil bath.

Results and Discussion

Reversible addition−fragmentation chain transfer (RAFT) is a well-established radical polymerization technique that allows the synthesis of polymeric architectures of very-well controlled molecular weight distribution and functionality;[20−23] RAFT has already been successfully employed with CuAAC, by introducing azides and alkyne groups either as end groups or as monomers.[5b,c,7c,8,9b,d,13a,15,19] In previous work, we reported the facile synthesis of functional chain transfer agents with a phenyl acetate as R group, which can control the polymerization of a variety of monomers.[24−27] We adapted this synthetic procedure to produce the chain transfer agent **1**, which has a similar structure and shows an azide moiety. **1** was synthesized via the reaction of a trithiocarbonate salt, with 3-azidopropyl 2-bromo-2-phenylacetate as shown in Scheme 1. Flash chromatography afforded **1** in 40% yield. The presence of the azide group was confirmed by ^1H NMR with the CH_2N_3 signal at 3.3 ppm and by FT-IR spectroscopy showing the characteristic azide band at 2092 cm^{-1}.

Table 1 summarizes the polymers that were synthesized using **1**. Polymerizations were undertaken for 20 h to ensure that high conversions were reached. Molecular weights of the final polymers were close to the targeted molecular weights and the polydispersities were low (<1.12), indicative of a very well controlled polymerization system, with low levels of termination.

Careful observation of the NMR spectra of the polymers failed to identify the signal of the methylene group adjacent to the azide. Additional characterizations by FT-IR showed no band at 2092 cm^{-1}, thus confirming the absence of azide groups in the polymers (Figure 1).

Interestingly, this disappearance of azide groups during polymerization has also been observed in previous studies but remained unexplained.[9c] The pioneering work of Huisgen[28] and L'Abbé[29] has shown that azides can undergo 1,3-dipolar cycloaddition on electron-deficient olefins, and this reaction is generally stereo- and regioselective. However, the cycloaddition

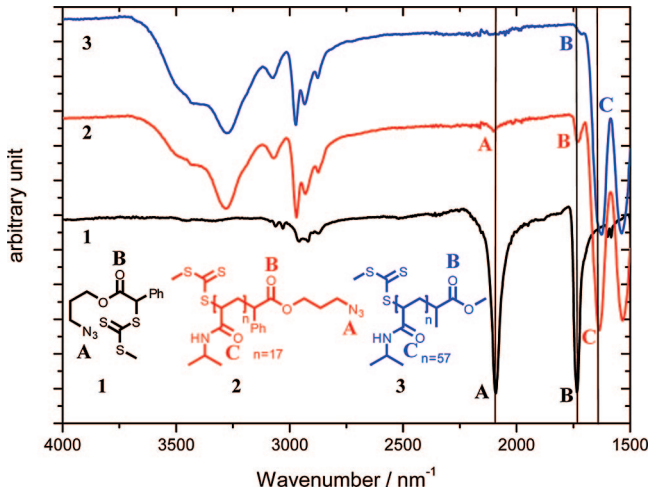


Figure 1. FT-IR showing the loss of azide after polymerization of NIPAAM using **1**.

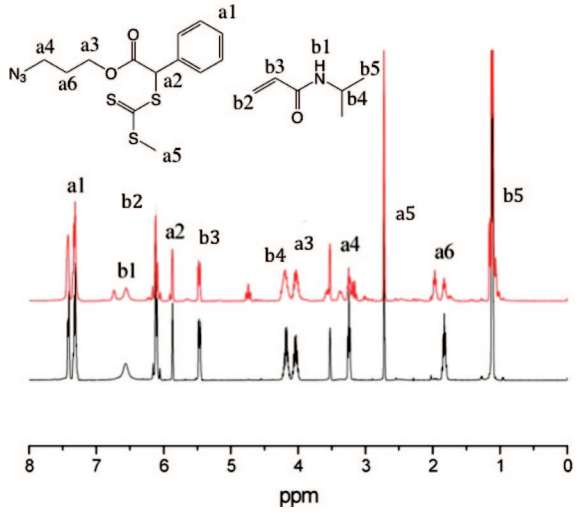


Figure 2. ^{1}H NMR spectra showing reaction of **1** with NIPAAM, at 60 °C in 1,4-dioxane-d_8: (black line) time = 0; (red line) time = 800 min.

is very slow, with reaction times lasting for weeks or even months at room temperature, to reach low yields. The low stability of the triazolines was thought to prohibit the use of high temperatures, and employing high pressure was proposed as a mean to accelerate such reactions.[30] From this work, and despite the higher temperatures of our reactions, we postulated that the disappearance of the azide moiety could be due to side reactions with the vinyl group of the monomer, and we carried out a model online ^{1}H NMR experiment to follow the reaction. A Young's tap NMR tube containing a degassed solution of **1** and NIPAAM (molar ratio = 1:1.85) in 1,4-dioxane-d_8 was heated to 60 °C (to mimic polymerization conditions) and placed in a spectrometer, and NMR spectra were recorded every 10 min for 13 h to assess the kinetics of azide consumption. A ratio 1:1.85 was chosen to allow for accurate integration of the peaks representing the various species formed or consumed during reaction. The NMR peaks of the different functional groups were monitored with respect to the aromatic protons of **1** (see Figure 2). The reliability of the analysis is demonstrated by the constant integration values throughout reaction time of the signals of C*H*$(CH_3)_2$ and CH$(CH_3)_2$ of NIPAAM and S−C*H*$_3$ and C(O)O−C*H*$_2$ of **1**, as expected. (Note that the slight variations in the integrations of the peaks of C*H*$(CH_3)_2$ and

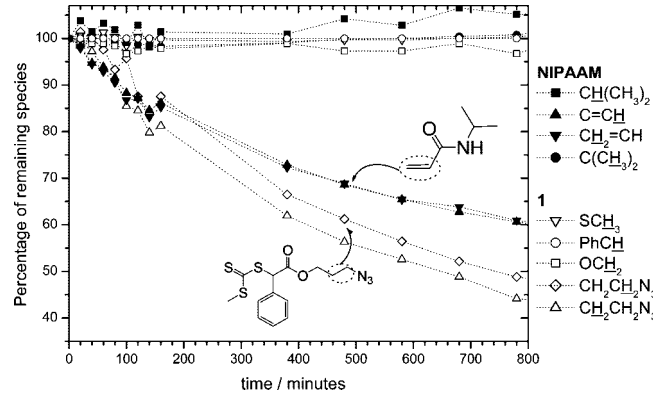


Figure 3. Percentage of remaining species, from selected integrations of ^{1}H NMR signals for **1** and NIPAAM in 1,4-dioxane-d_8 in the ratio of 1:1.85 at 60 °C. The signals are calibrated to the intensity of the aromatic protons of **1** (NH of NIPAAM is excluded due to interference from emerging signals).

C(O)O−C*H*$_2$ may be explained by their overlapping.) On the other hand, the signals of C*H*$_2$N$_3$ in **1** and of the vinyl protons of NIPAAM decrease rapidly early in the reaction, with a loss of 13% of both the azide and the vinyl group within 2 h and 45% and 30%, respectively, after 8 h (see Figure 3), which represents a typical polymerization time to reach high monomer conversions. After 13 h, only 47% of the azide groups and 60% of the monomer remain. This suggests that the stoichiometry of the reaction varies from a ratio **1**:NIPAAM of 1:1 early in the reaction to 1:1.4 later in the reaction (see text below for further discussion on this point). It is key to note that this azide loss is expected to be even more significant in typical polymerization conditions, for which the azide group is in the presence of a very large excess of monomers.

Huisgen et al. have reported the cycloaddition of phenyl azide with acrylonitrile at room temperature to give a mixture of a triazoline and aziridine.[28] Broeckx et al. demonstrated that other electron-poor olefins could yield similar products, although the reaction was very slow and performed at room temperature.[29] We propose therefore the reaction pathway highlighted in Figure 4. In the presence of NIPAAM, **1** undergoes 1,3-dipolar cycloaddition with the azide to form preferentially the 1,4-regioisomer over the 1,5-regioisomer triazoline (**2**), due to the substituent effect of the amide group of NIPAAM.[31] The synthesis of the triazoline in the reaction was confirmed by high-resolution mass spectroscopy. The triazoline **2** can either degrade to the aziridine **3**[28,29] or isomerize to the open-chain azo compound **4**, as expected from triazoline with electron-withdrawing substituents in the 4-position.[28] LC-MS confirmed the formation of **3**. **4** may undergo a second cycloaddition with another molecule of NIPAAM to give the pyrazoline **5**,[29] which was identified by high-resolution mass spectroscopy. Note that **4** may also undergo a Michael addition on the double bond of NIPAAM, although no evidence of the product was observed by ^{1}H NMR spectroscopy, and we expect the diazo moiety to be more reactive than the amine.[29] Additional evidence of the formation of **3** and **5** during polymerization was also given by MALDI analyses of the poly(NIPAAM) synthesized using **1** as CTA. Indeed, four different polymers were observed: (1) a small fraction of azide-functionalized polymer, (2) polymers containing the aziridine group, (3) polymer terminated with a pyrazoline analogue to **5**, and (4) a polymer which terminal groups could not be identified (see Supporting Information). Note that MALDI analysis of RAFT synthesized polymers is not always reliable,[32] but we believe these analyses support well the reaction pathway we propose. The online ^{1}H NMR experiment suggests that early in the reaction (up to 2 h) one azide

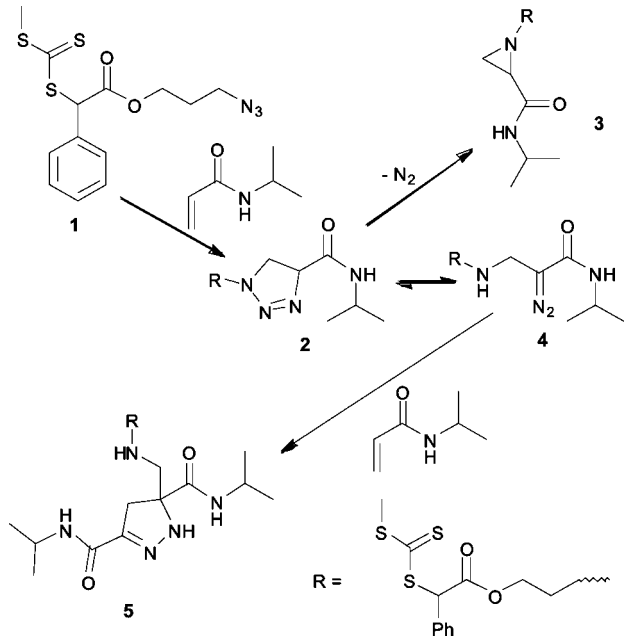


Figure 4. Proposed decomposition pathway of **1** in the presence of NIPAAM.

Table 2. Results for the Cycloaddition of Various Monomers with Benzyl Azide in Dioxane at 60 °C for 20 h

entry	monomer	$[M]_0/[BzN_3]_0$[a]	conv (%)[b]
1	NIPAAM	2	70.6
2	NIPAAM	4	79.3
3	MA	4	95.2
4	MMA	4	27.2
5	DMA	4	89.4
6	St	4	<5.0

[a] $[M]_0 = 1.0$ mol/L. [b] Determined by ^{1}H NMR.

group reacts with one molecule of monomer. The stoichiometry then increases to two azide groups reacting with nearly three vinyl groups (**1**:NIPAAM = 1:1.4, see above), leading to the formation after 13 h of **3** and **5** in a 1:1 ratio (Figure 3). This ratio is also confirmed by the LC-MS analysis (see Supporting Information). It is remarkable that the reaction occurs in such a short frame of time, without the use of catalyst[2] or high pressure.[30]

These results prompted us to investigate the behavior of other monomers in the presence of azides. We examined the reaction of benzyl azide with electron-poor olefins in typical polymerization conditions (1,4-dioxane, 60 °C, 20 h). A long reaction time (20 h) was used to assess the kinetics of azide consumption. Benzyl azide was selected as model azide compound, as the conversion of azide can be measured by ^{1}H NMR by comparing the integrations of the aromatic protons (7.3−7.4 ppm) and the methylene group adjacent to the azide (4.34 ppm). Table 2 presents the results of this study and reveals the dramatic effects that such side reactions may have on the final product. We demonstrated that in presence of an acrylate (methyl acrylate, MA) up to 95% of the azide group is lost within 20 h. Also, the addition of MA on the azide leads to a mixture of the 1,4- and 1,5-regioisomers, while sole the 1,4-regioisomer is obtained for the other monomers. In the same time frame, acrylamides also react readily with azide groups, leading to a loss of 70.6−79.3% in the case of *N*-isopropylacrylamide (NIPAAM) and 89.4% in the case of dimethylacrylamide (DMA). Reactions with a methacrylate (methyl methacrylate, MMA) have lower yield, although almost a third of the original azide is lost. Styrene is far less reactive than other monomers, with less than 5% of the original azide being lost during reaction. The reactivity difference between the various monomers is mainly due to the electron-withdrawing effect of the double bonds substituent. Acrylamides have a lower electron-withdrawing effect than acrylate, thus leading to a relative increase in the electron density of the double bond. In the case of MMA, the steric hindrance of the methyl group on the double bond may explain the lower reactivity of monomer. Styrene poor reactivity is due to the delocalization of the double bond to the benzene ring. A further remark concerns the stoichiometry of the reaction. The reaction path we propose involves the addition of two olefins for one azide—however, a large excess of olefin is present during polymerization (typically ratios monomer/azide >100), and we expect this may enhance the rate of azide loss. This point is exemplified by comparing the effect of two stoichiometries in the reaction between NIPAAM and benzyl azide. A ratio NIPAAM/azide = 2/1 leads to 70.6% azide loss, while a ratio NIPAAM/azide = 4/1 increases the azide conversion to 79.3%.

Careful observation of the recent literature regarding the combination of CuAAC and LRP demonstrates the significance of the side reaction investigated in this paper and underlines the fact that it has often been overlooked. Indeed, to date, Benicewicz and co-workers[19] and Lee et al.[33] are the only researchers who have reported the loss of azide when in the presence of methacrylate and acrylate derivatives, respectively, and suggested that a cycloaddition with the double bond of the monomer may be involved. However, the cycloaddition of azide with monomers is likely to be responsible for the azide-free polystyrene chains detected by Neoh and co-workers[7c] and for the broad PDI or shoulders visible in chromatograms of block copolymers obtained by clicking azide and alkyne homopolymers[5b,c,34] The way to circumvent this side reaction and preserve high end-group fidelity is to keep the polymerization time short and/or work at low temperatures.[9b,d,19]

In summary, we examined the cycloaddition of azides with various commonly used monomers in LRP for long reaction times. FT-IR and NMR showed the loss of azide moiety in poly(NIPAAM) obtained using an azido-functionalized trithiocarbonate RAFT agent. Model reactions were designed to investigate this disappearance. NMR and mass spectroscopy were used to identify the side products, and a reaction pathway was proposed. This side reaction occurs with most monomers and can be of dramatic significance as it impairs the orthogonality of CuAAC. In order to limit this side reaction during polymerization, the reaction time should be kept short and/or temperatures should be kept low.

Acknowledgment. The authors acknowledge financial support from ICI (T.M.L.) and EPSRC (Y.Z., V.L.).

Supporting Information Available: ^{1}H NMR spectra of azide RAFT agent **1**, MALDI-ToF MS for PNIPAAM, and LC-MS showing the various side products of azide reaction with NIPAAM. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
(2) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
(3) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262.
(4) (a) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 2–10. (b) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1369–1380. (c) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200–1205. (d) Evans, R. A. *Aust. J. Chem.* **2007**, *60* (6), 384–395.
(5) (a) Opsteen, J. A.; van Hest, J. C. M. *Chem. Commun.* **2005**, *1*, 57–59. (b) Simon Ting, S. R.; Granville, A. M.; Quémener, D.; Davis,

T. P.; Stenzel, M. H.; Barner-Kowollik, C. *Aust. J. Chem.* **2007**, *60*, 405–409. (c) Quémener, D.; Davis, T. P.; Barner-Kowollik, C.; Stenzel, M. H. *Chem. Commun.* **2006**, *48*, 5051–5053.
(6) (a) Tsarevsky, N. V.; Bencherif, S. A.; Matyjaszewski, K. *Macromolecules* **2007**, *40*, 4439–4445. (b) Jiang, X.; Lok, M. C.; Hennink, W. E. *Bioconjugate Chem.* **2007**, *18*, 2077–2084.
(7) (a) Gao, H.; Matyjaszewski, K. *Macromolecules* **2006**, *39*, 4960–4965. (b) Whittaker, M. R.; Urbani, C. N.; Monteiro, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 11360–11361. (c) Zhu, J.; Zhu, X.; Kang, E. T.; Neoh, K. G. *Polymer* **2007**, *48*, 6992–6999. (d) Altintas, O.; Hizal, G.; Tunca, U. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5699–5707.
(8) Vogt, A. P.; Gondi, S. R.; Sumerlin, B. S. *Aust. J. Chem.* **2007**, *60*, 396–399.
(9) (a) Tsarevsky, N. V.; Sumerlin, B. S.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 3558–3561. (b) Gondi, S. R.; Vogt, A. P.; Sumerlin, B. S. *Macromolecules* **2007**, *40*, 474–481. (c) Mantovani, G.; Ladmiral, V.; Tao, L.; Haddleton, D. M. *Chem. Commun.* **2005**, *16*, 2089–2091. (d) De, P.; Gondi, S. R.; Sumerlin, B. S. *Biomacromolecules* **2008**, *9*, 1064–1070.
(10) (a) Sumerlin, B. S.; Tsarevsky, N. V.; Louche, G.; Lee, R. Y.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 7540–7545. (b) Malkoch, M.; Thibault, R. J.; Drockenmuller, E.; Messerschmidt, M.; Voit, B.; Russell, T. P.; Hawker, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 14942–14949. (c) Ladmiral, V.; Mantovani, G.; Clarkson, G. J.; Cauet, S.; Irwin, J. L.; Haddleton, D. M. *J. Am. Chem. Soc.* **2006**, *128*, 4823–4830.
(11) (a) Chen, G.; Tao, L.; Mantovani, G.; Geng, J.; Nystro1m, D.; Haddleton, D. M. *Macromolecules* **2007**, *40*, 7513–7520. (b) Ranjan, R.; Brittain, W. J. *Macromolecules* **2007**, *40*, 6217–6223.
(12) (a) Xu, J.; Ye, J.; Liu, S. *Macromolecules* **2007**, *40*, 9103–9110. (b) Laurent, B. A.; Grayson, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 4238–4239.
(13) (a) Vogt, A. P.; Sumerlin, B. S. *Macromolecules* **2006**, *39*, 5286–5292. (b) Johnson, J. A.; Finn, M. G.; Koberstein, J. T.; Turro, N. J. *Macromolecules* **2007**, *40*, 3589–3598. (c) Liu, Q.; Chen, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 6103–6113. (d) Lutz, J. F.; Börner, H. G.; Weichenhan, K. *Macromol. Rapid Commun.* **2005**, *26*, 514–518.
(14) Zhang, J.; Zhou, Y.; Zhu, Z.; Ge, Z.; Liu, S. *Macromolecules* **2008**, *41*, 1444–1454.
(15) (a) Joralemon, M. J.; O'Reilly, R. K.; Hawker, C. J.; Wooley, K. L. *J. Am. Chem. Soc.* **2005**, *127*, 16892–16899. (b) O'Reilly, R. K.; Joralemon, M. J.; Hawker, C. J.; Wooley, K. L. *New J. Chem.* **2007**, *31*, 718–724.
(16) Such, G. K.; Tjipto, E.; Postma, A.; Johnston, A. P. R.; Caruso, F. *Nano Lett.* **2007**, *7*, 1706–1710.
(17) Opsteen, J. A.; Brinkhuis, R. P.; Teeuwen, R. L. M.; Löwik, D. W. P. M.; van Hest, J. C. M. *Chem. Commun.* **2007**, *30*, 3136–3138.
(18) (a) Lutz, J.-F.; Börner., H. G.; Weichenhan, K. *Macromolecules* **2006**, *39*, 6376–6383. (b) Reynhout, I. C.; Cornelissen, J. J. L. M.; Nolte, R. J. M. *J. Am. Chem. Soc.* **2007**, *129*, 2327–2332. (c) Le Droumaguet, B.; Mantovani, G.; Haddleton, D. M.; Velonia, K. *J. Mater. Chem.* **2007**, *17*, 1916–1922. (d) Gupta, S. S.; Raja, K. S.; Kaltgrad, E.; Strable, E.; Finn, M. G. *Chem. Commun.* **2005**, *34*, 4315–4317.
(19) Li, Y.; Yang, J.; Benicewicz, B. C. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 4300–4308.
(20) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559–5562.
(21) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2005**, *58*, 379–410.
(22) Perrier, S.; Takolpuckdee, P. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5347–5393.
(23) Favier, A.; Charreyre, M. T. *Macromol. Rapid Commun.* **2006**, *27*, 653–692.
(24) Perrier, S.; Takolpuckdee, P.; Westwood, J.; Lewis, D. M. *Macromolecules* **2004**, *37*, 2709–2717.
(25) Takolpuckdee, P.; Mars, C. A.; Perrier, S.; Archibald, S. J. *Macromolecules* **2005**, *38*, 1057–1060.
(26) Takolpuckdee, P.; Westwood, J.; Lewis, D. M.; Perrier, S. *Macromol. Symp.* **2004**, *216*, 23–35.
(27) Takolpuckdee, P.; Mars, C. A.; Perrier, S. *Org. Lett.* **2005**, *7*, 3449–3452.
(28) Huisgen, R.; Szeimies, G.; Mobius, L. *Chem. Ber.* **1966**, *99*, 475.
(29) Broeckx, W.; Overbergh, N.; Samyn, C.; Smets, G.; L'abbe, G. *Tetrahedron* **1971**, *27*, 3527–3534.
(30) Anderson, G. T.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 6946–6948.
(31) (a) Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1966**, *99*, 475. (b) Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014. (c) Huisgen, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 1138.
(32) (a) Firestone, R. A. *J. Org. Chem.* **1972**, *37*, 2181–2191. (b) Vana, P.; Albertin, L.; Barner, L.; Davis, T. P.; Barner-Kowollik, C. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 4032–4037.
(33) Lee, J. W.; Kim, J. H.; Kim, B.-K.; Kim, J. H.; Shin, W. S.; Jin, S.-H. *Tetrahedron* **2006**, *62*, 9193–9200.
(34) Jiang, X.; Lok, M. C.; Hennink, W. E. *Bioconjugate Chem.* **2007**, *18*, 2077–2084.

MA8010262