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**COMMUNICATION**

# ATRP, subsequent azide substitution and 'click' chemistry: three reactions using one catalyst in one pot†

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**This communication describes a novel and fast reaction to substitute the living chain end after Atom Transfer Radical Polymerization (ATRP) by an azide functionality. The reaction is catalyzed by the ATRP catalyst at room temperature in aqueous solution and can be followed by a 'click' reaction using again the same catalyst.**

Atom Transfer Radical Polymerization (ATRP) and Copper-catalyzed Azide–Alkyne Cycloaddition (CuAAC) 'click' chemistry have both become established techniques.[1,2] In addition, the combination of these two techniques is becoming increasingly popular.[3] This popularity is in part due to the fact that ATRP and CuAAC can be catalyzed by the same copper complexes.[3b,c,4] Using azide- or alkyne functionalized monomers and/or initiators, CuAAC and ATRP have been performed sequentially and even simultaneously.[3d,e,5] On the other hand, the highly popular approach of 'clicking' to the living ATRP chain end has not been reported in a one-pot procedure, since this approach requires conversion of the living R–Br (or, less commonly, R–Cl) chain end into R–$N_3$ before a CuAAC reaction can be performed.[6] This azidation is usually carried out by an $S_N2$ reaction using a large excess of $NaN_3$ in *N*,*N*-dimethylformamide (DMF) overnight and, in the case of chloride-terminated polymers, requires elevated temperatures.[6b,7]

In this communication, we present a novel, non-$S_N2$ reaction for azidation of the living chain end, catalyzed by an ATRP copper catalyst. This method has several advantages over the traditional $S_N2$ substitution, namely a very short reaction time with only a small excess of $NaN_3$, compatibility with aqueous solvents and the possibility to perform ATRP, azidation of the living chain end and 'clicking' to it in a one-pot procedure with all three reactions catalyzed by the same catalyst.

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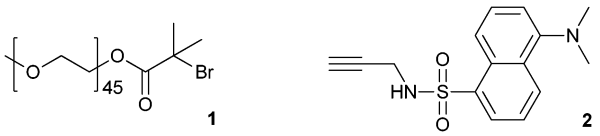



**Fig. 1** Structures of the ATRP macro-initiator and dansyl-propargylamide.

Macro-initiator **1** (Fig. 1) was synthesized from poly(ethylene glycol) monomethyl ether (mPEG) (2 kDa) and 2-bromoisobutyrylbromide. This macro-initiator was used to demonstrate the substitution of bromide by azide, catalyzed by an ATRP catalyst.

In a typical experiment, **1**, the ATRP catalyst CuBr/$CuBr_2$/bipyridyl(Bpy) (0.6 : 0.4 : 2) and $NaN_3$ (1.2 eq.) were dissolved in $CD_3CN/D_2O$ (3 : 7). At regular time intervals a sample was taken and diluted with air-saturated $D_2O$ to quench the reaction. Conversion was determined using $^1H$ NMR by comparing the integrals of the peaks at 1.97 ppm ($-C(CH_3)_2-Br$) and 1.55 ppm ($-C(CH_3)_2-N_3$).[7b,8]

Within 20 min, the reaction reached 95% conversion ($k$ = 0.42 L $mol^{-1}$ $s^{-1}$) (Fig. 2 and Fig. S1, ESI†). When a two-fold excess of $NaN_3$ was used, quantitative conversion to the azide was achieved within 5 min. It was shown that the

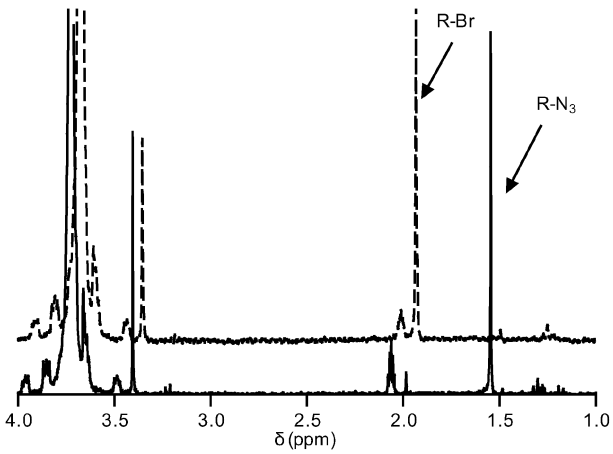
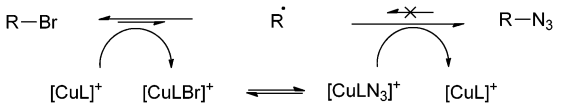



**Fig. 2** $^1H$ NMR spectra of the azidation reaction with a CuBr/$CuBr_2$/Bpy catalyst after 20 min (bottom) and the control reaction without the catalyst after 18 h (top, shifted by 0.05 ppm for clarity). Arrows indicate the $-C(CH_3)_2-X$ peaks.




**Scheme 1** Proposed reaction sequence of copper-catalyzed substitution of a bromide by an azide. L = ligand.

conversion was <5% in 18 h in the absence of any copper species as catalyst (Fig. 2), an indication that the substitution reaction is not based on an $S_N2$-type mechanism. The fast kinetics and mild, aqueous conditions of the copper-catalyzed substitution reaction are a significant improvement compared to the traditional substitution method which uses a large excess (~10×) of $NaN_3$ in DMF overnight. Especially for tertiary halides (like compound **1**, or methacrylate polymers), the traditional $S_N2$ reaction in DMF requires extended reaction time (and/or high temperature) to reach completion.[7]

We expect the mechanism of the copper-catalyzed azidation to be similar to the process of 'halogen exchange' in ATRP (Scheme 1).[9] During the ATRP process, a copper catalyst homolytically removes a halogen from the living chain end, leaving a radical and allowing chain propagation, and reforms the polymer–halide bond in a dynamic equilibrium. In doing so, the catalyst can exchange different halogen species.[9] The azide ion (commonly called a pseudohalogen)[10] is readily oxidized by copper(II)[11] and thus can also participate in this exchange reaction.

Since ATRP using chloride initiators generally proceeds slower than ATRP using bromide initiators[12] it was expected that the copper-catalyzed substitution of chloride by azide would proceed slower as well. To investigate this, **1** was first incubated with a $CuCl/CuCl_2$/Bpy catalyst to obtain the chloride chain end, as evidenced by a shift of the $–C(CH_3)_2–X$ peak in the NMR spectrum from 1.97 to 1.83 ppm. Subsequent substitution of this chloride by a two-fold excess of $NaN_3$ proceeds to only 30% in 2 h (Fig. 3). To improve the azidation reaction for chloride chain ends, the effects of increasing the azide concentration, Cu(I)/Cu(II) ratio (by addition of ascorbic acid) and temperature were examined. Fig. 3 shows that increasing the temperature from room

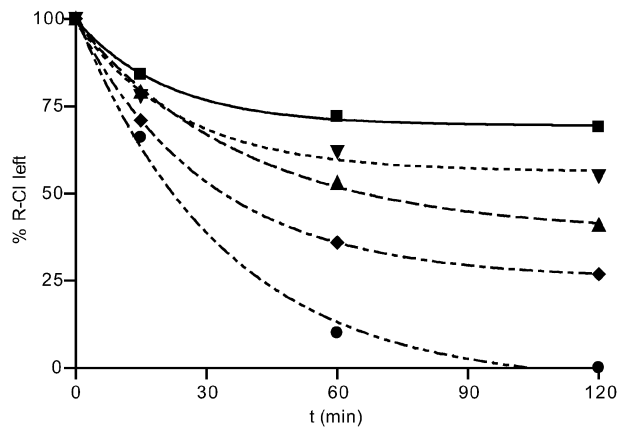



**Fig. 3** Optimization of chloride chain end substitution by azide: (■) 2 eq. $NaN_3$, (▼) 10 eq. $NaN_3$, (▲) 2 eq. $NaN_3$ + 10 eq. ascorbic acid, (◆) 2 eq. $NaN_3$ at 40 °C, (●) 10 eq. $NaN_3$ + 10 eq. ascorbic acid at 40 °C.

temperature to 40 °C more than doubles the conversion after 2 h. Furthermore, both increasing the concentration of azide and raising the Cu(I)/Cu(II) ratio (and thereby increasing the concentration of radicals) individually increase the reaction rate. These findings indicate that the reaction occurs between a polymer chain radical and an azide-containing species, consistent with Scheme 1.

Increasing the Cu(I)/Cu(II) ratio has two effects, namely an increase in radical concentration but also a decrease in the concentration of the Cu(II)–azide complex. Since the net effect is an increase in the reaction rate, it can be concluded that the radical formation is the rate-limiting step. This is corroborated by the fact that the rate increase by raising just the azide concentration is relatively small (Fig. 3).

The combined effect of raising the temperature and adding excess $NaN_3$ and reducing agent was found effective to drive the reaction to completion within 2 h. This is still a significant improvement compared to the traditional $S_N2$-substitution of chlorides, which is generally slow and incomplete.[7b]

In the next experiment, the full three reactions in a one pot sequence of ATRP, azide substitution and CuAAC were carried out. Oligo(ethylene glycol) monomethyl ether methacrylate (OEGMA, $M_n$ = 300 g mol$^{-1}$) was polymerized using **1** under the same conditions as the substitution experiment. At 80% monomer conversion (determined by $^1$H NMR), 2 mol. equiv. (to chain ends) of $NaN_3$ was added to the reaction mixture. After 5 min, a peak at 1.57 ppm could clearly be observed by $^1$H NMR, which corresponds to $–C(CH_3)N_3–COOR$ (Fig. S2, ESI†). Re-activation of the azide-substituted chain end does not occur, since the monomer conversion (determined by $^1$H NMR) had not increased one hour after addition of azide. After substituting the living chain end with azide, without intermediate work-up, 1 mol. equiv. of the fluorophore dansyl-propargylamide **2** (Fig. 1) was added to the reaction mixture and allowed to react overnight at room temperature. Then, the polymer was analyzed by Gel Permeation Chromatography (GPC) with both Refractive Index (RI) and fluorescence detection. The similar shapes of the two GPC traces as presented in Fig. 4a clearly show that the pOEGMA polymer has been fluorescently labeled with **2**. From the peak integrals in Fig. 4a, the yield of the 'click' reaction was calculated to be 70% (tertiary azides and bipyridyl are known to be the poorest substrates[8] and ligand,[4] respectively, for CuAAC). On the other hand, a control reaction without azide did not result in labeling. These findings prove that ATRP, azide substitution and CuAAC can all be catalyzed by the same copper complex, in a three reaction one pot procedure. Furthermore, addition of TEMPO inhibited the substitution by azide (Fig. S3, ESI†), which supports the proposed radical mechanism.

To demonstrate the broad applicability of the procedure, it was also applied to a different monomer/catalyst ligand pair, namely *N*-isopropylacrylamide (NIPAm) and tris[2-(dimethylamino)ethyl]amine ($Me_6$tren). This combination of the monomer and catalyst resulted in quantitative labeling of the polymer (Fig. 4b). We expect that the reaction is generally applicable to any monomer/catalyst pair suitable for ATRP, including hydrophobic monomers in aprotic media (see also Fig. S4, ESI†).

In conclusion, this study shows that ATRP catalysts can very efficiently and irreversibly substitute a bromide or chloride on a

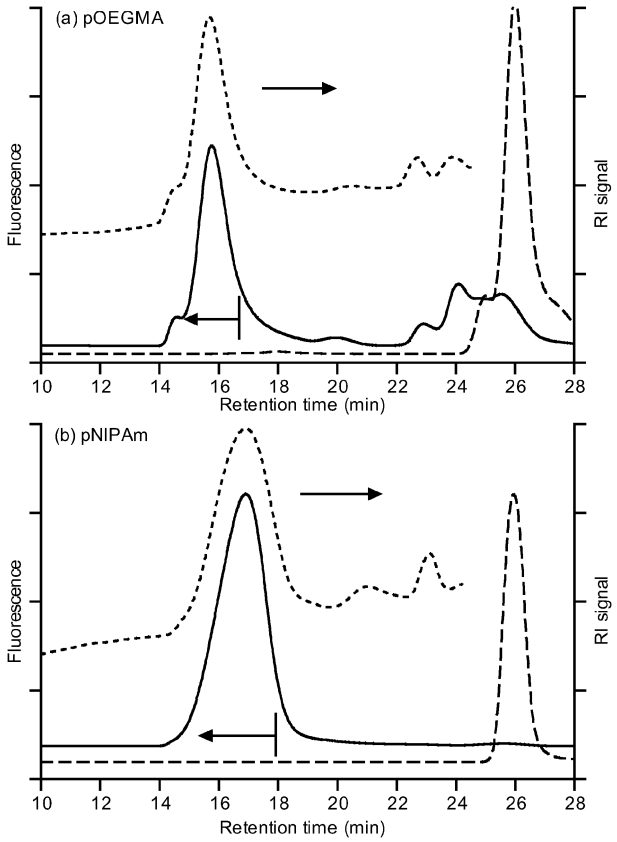



**Fig. 4** (a) GPC traces of fluorescently labelled pOEGMA (top and middle) and the control reaction to which no azide was added (bottom). (b) GPC traces of fluorescently labelled pNIPAm (top and middle) and the control reaction to which no azide was added (bottom).

living ATRP chain end by an azide. Furthermore, we have demonstrated for two different monomer/catalyst pairs that this reaction allows ATRP, azide substitution and CuAAC subsequently in a one-pot procedure, with all three reactions catalyzed by the same copper complex. This one-pot procedure greatly simplifies the increasingly popular procedure of 'clicking' a functional unit to a living ATRP chain end. Moreover, the compatibility with aqueous conditions makes this method ideally suitable for end-functionalization of bioconjugated polymers.

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