Living Polymerization

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Simultaneous Copper(I)-Catalyzed Azide–Alkyne Cycloaddition (CuAAC) and Living Radical Polymerization[**]

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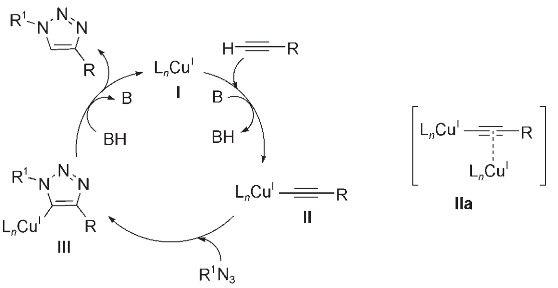
Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) is a member of the family of click reactions[1] that is receiving a steeply growing interest.[2] This has led to its use in the synthesis of a range of materials, including dendrimers, hydrogels, drugs, and functional polymers.[3] The mechanism of CuAAC appears to be relatively complex and is not yet fully understood, at least in terms of the exact nature of the copper-containing species involved in the catalytic cycle. Recent studies have also shown that in some cases more than one catalytically active copper species may contribute to the formation of the triazole "clicked" products.[4] In addition, the ability of $\mathrm{Cu^I}$ to coordinate a number of species in solution, including ligands, solvents, organic buffers, reactants and final products, in a very dynamic equilibrium and to disproportionate to $\mathrm{Cu^0}$ and $\mathrm{Cu^{II}}$ in polar environments further complicates the catalytic process.

The first step in the catalysis of CuAAC is the formation of $\mathrm{Cu^I}$ acetylides **I** from $\mathrm{Cu^I}$ species, 1-alkynes, and a base (Scheme 1). $\mathrm{Cu^I}$ acetylides have a tendency to form μ-coordinate bridged aggregates analogous to **IIa**.[5] Studies have indicated that such species might play an important role in CuAAC reactions.[4,5b,6] This also might be responsible for the second-order dependence on the concentration of copper species, as observed by Finn, Fokin and co-workers in many cases, both in the presence[4,6b] and absence[7] of stabilizing ligands. Interestingly, Straub and co-workers also suggested that, with some very bulky substrates and coordinating ligands, CuAAC may even occur without the formation of such μ-coordinate bridged $\mathrm{Cu^I}$ aggregates.[8] The second step is the reaction of $\mathrm{Cu^I}$ acetylides with organic azides to give $\mathrm{Cu^I}$ triazolides **III**, presumably via a six-membered metallacycle.[2a,6c,9] Recently, the first example of a stable complex **III**, a 14-valence electrons $\mathrm{Cu^I}$ triazolide bearing a N-heterocyclic carbene (NHC) ligand, has been isolated, fully characterized and employed as a CuAAC catalyst, providing direct evidence of the existence of such triazolide "click" intermediates.[8] The final step is the proteolysis of **III** to give a 1,4-substituted 1,2,3-triazole and recover the copper catalyst **I**.



Scheme 1. Simplified proposed catalytic cycle for the CuAAC reaction.[6b] All of the copper species are likely to exist in equilibrium with higher-order aggregates. Complexes such as **IIa**, in particular, seem to play an important role in the process.

Living radical polymerization is a powerful method to obtain macromolecules with controllable properties and architectures. The most widely studied of these techniques, transition-metal-mediated living radical polymerization (TMM LRP, often termed ATRP),[10] shares a number of attractive features with CuAAC, including high tolerance towards unprotected functional groups and protic solvents. In a simplified mechanism, for Cu-catalyzed LRP, a $\mathrm{Cu^I}$ complex reacts reversibly with a suitable organic halide to give a radical-based propagating species and a $\mathrm{Cu^{II}}$ complex. Percec et al. have further suggested that in polar media the $\mathrm{Cu^I}$ catalyst undergoes significant disproportionation to $\mathrm{Cu^{II}}$ and $\mathrm{Cu^0}$ and the $\mathrm{Cu^0}$ species activates the organic halide via a single-electron transfer mechanism (SET-LRP) to give a radical propagating species and a $\mathrm{Cu^I}$ complex, which subsequently disproportionates to a $\mathrm{Cu^{II}}$ end-capping complex, necessary to control the polymerization process.[11] Thus at present the mechanism of both processes seems to be not yet fully understood and both require further investigation; it appears that the mechanisms of CuAAC and LRP may have little in common.

Modular processes that sequentially combine CuAAC and LRP have proven to be a powerful route to functional polymers with complex macromolecular architectures.[12] We have previously shown that CuAAC and LRP can share the same $\mathrm{Cu^IBr}$-iminopyridine catalytic system in a sequential one-pot reaction.[13] Sequential CuAAC/LRP one-pot processes using other catalytic systems have also been reported.[14] The aim of the present study was to investigate catalytic systems in which CuAAC and LRP could occur simultaneously and if so, to combine them to develop a novel synthetic tool for the synthesis of functional molecular materials.

For this study, an alkyne-containing monomer, propargyl methacrylate (**1**), an organic azide (1-octyl azide (**2**), methoxytriethylene glycol azide (**3**) or 2′-azidoethyl-α-mannopyranoside (**4**)), a LRP initiator and CuBr/*N*-ethyl pyridine-

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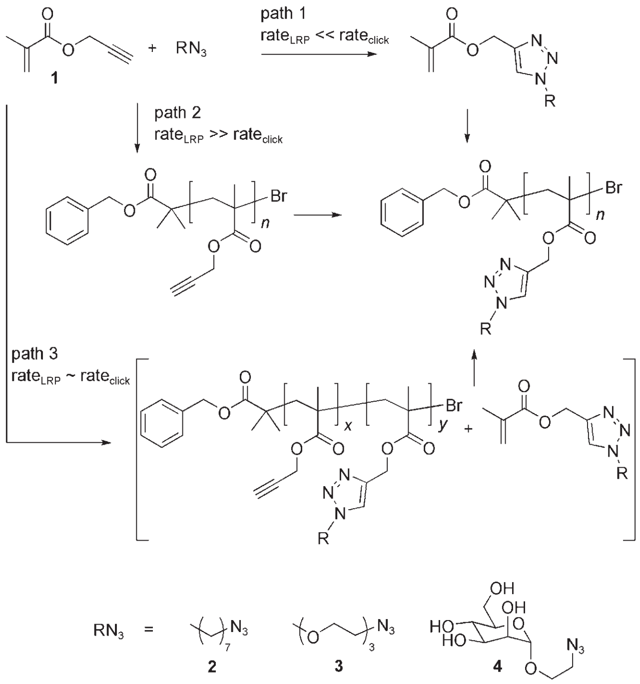

Scheme 2. One-pot CuAAC/LRP process: possible pathways (benzyl 2-bromoisobutyrate was employed as the polymerization initiator).

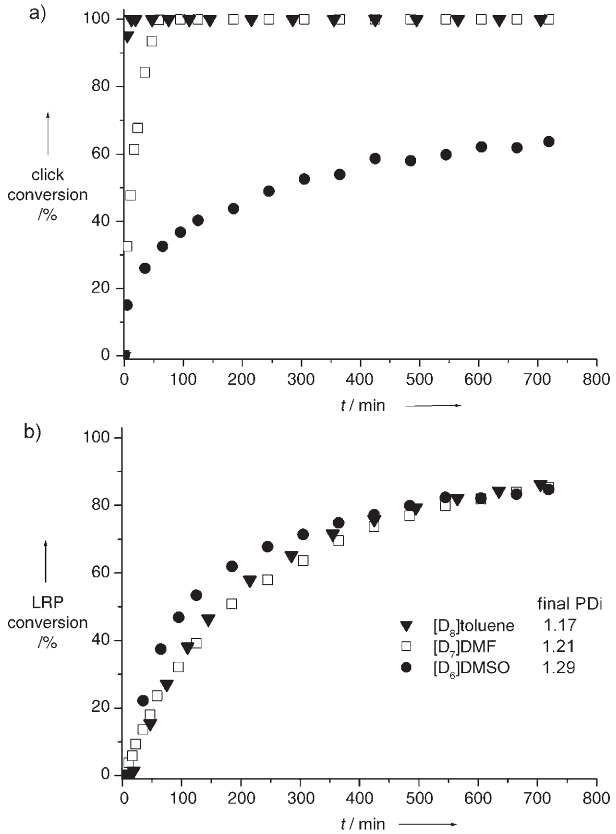

Figure 1. CuAAC/LRP in different solvents: alkyne monomer (**1**) and triethyleneglycol azide (**3**) in [D$_8$]toluene (▼), [D$_7$]DMF (□), and [D$_6$]DMSO (●). Reaction conditions: [initiator]/[**1**]/[**3**]/[Cu^{I}Br]/[ligand]/[Et$_3$N] = 1:50:100:1:2:5. "Click conversion" (a) refers to the conversion of alkyne units, both in the monomer **1** and in the polymer backbone, into 1,2,3-triazole moieties. "LRP conversion" (b) refers to the polymerization of both **1** and its corresponding clicked monomer analogue. PDi: polydispersity index.

imine/triethylamine as catalyst were employed (Scheme 2). A number of experimental parameters, including solvent, catalyst concentration, temperature and nature of the azide, were systematically varied. To enable efficient monitoring of the kinetics of the two processes in real time, all of the reactions were conducted in NMR tubes at the required temperature with ^{1}H NMR spectra recorded at 7 min intervals.

In [D$_8$]toluene as solvent at 60 °C, the processes were found to be sequential, following path 1 in Scheme 2. The CuAAC reactions using both azides **2** and **3** were found to proceed virtually to completion prior to the polymerization starting. Subsequent polymerization of the resulting "clicked" monomer yielded a final polymer where all side-groups were derived from the azide.

[D$_6$]DMSO as solvent, generally regarded as a less-than-optimal solvent for the CuAAC reaction, was also assessed. As octyl azide (**2**) was not completely soluble in [D$_6$]DMSO (and known to form aggregates responsible for "non conventional" CuAAC kinetics in polar environments[4]), triethyleneglycol azide (**3**) was employed. Under these conditions the two reactions were found to proceed concurrently, with the click reaction significantly slower and the rate of the polymerization slightly higher than with toluene as solvent. In [D$_7$]DMF the two reactions were again observed to proceed simultaneously. However, the rate of the click reaction was significantly higher than in [D$_6$]DMSO, whereas the rate of the polymerization was similar to when toluene was used as the solvent (Figure 1).

All polymerization reactions, in all solvents, showed a significant deviation away from linear first-order kinetics (see Supporting Information), which is likely to be the result of the complex set of equilibria existing in solution. In toluene, the polymerization rate increased after some time; the opposite was observed in DMSO. Whilst the reasons for the increased rate of the polymerization with time in toluene still remain unclear, in DMSO the decreasing polymerization rate may be an effect of the increasing number of 1-alkyne and triazole moieties able to coordinate copper species in the polymer backbone, which may result in a reduced amount of available copper catalyst in the system.

Simultaneous CuAAC and LRP require a complex set of reactions and equilibria to occur efficiently at the same time (Scheme 2, path 3). Polymerization of both the un-clicked **1** and clicked monomers leads to polymers bearing both 1-alkyne and functional 1,2,3-triazole as the pendant units, as was also observed from ^{1}H NMR analysis (Figure 2). Conversely, CuAAC can occur both on the unreacted alkyne-functional monomer **1** and on the 1-alkyne groups present in the growing polymer chain. If the click reaction does not proceed to completion, the final macromolecular product will be a copolymer containing a certain amount of "un-clicked" 1-alkyne functionalities.

In DMSO, the catalyst concentration was found to have a significant effect on the rate of CuAAC (Figure 3). Virtually complete conversion of alkyne moieties in the reaction mixture could be achieved by simple judicious tuning of the

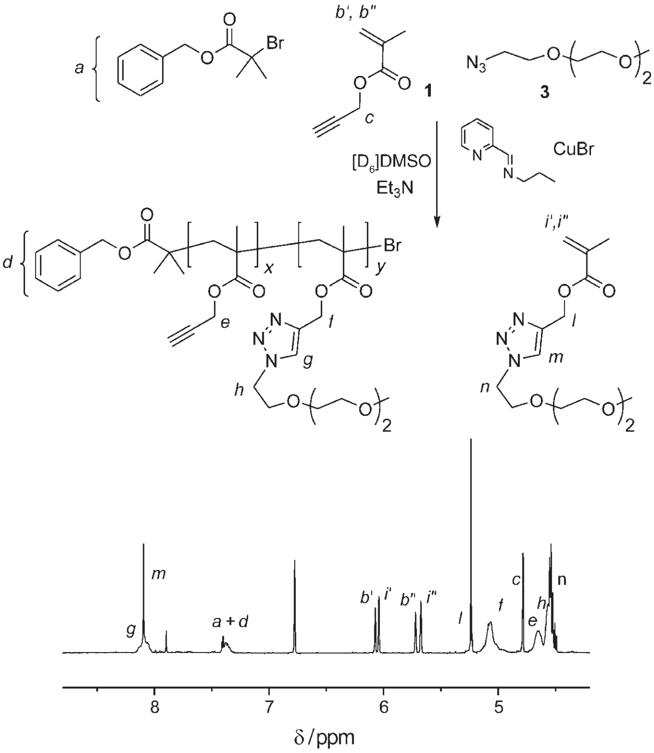

Figure 2. Partial ^{1}H NMR spectrum of reaction mixture after 157 min in [D$_6$]DMSO. Reaction conditions: [initiator]/[**1**]/[**3**]/[Cu^{I}Br]/[ligand]/[Et$_3$N] = 1:50:100:1:2:5.

concentration of [Cu^{I}Br]/[ligand]. Interestingly, in these experiments the polymerization showed only a small rate increase with increased catalyst concentration (Figure 3).

Conversely, in toluene, under otherwise identical experimental conditions, the rate of the LRP reaction was found to be greatly dependent on the concentration of the catalyst (see Supporting Information). The rate of CuAAC under the range of catalyst concentrations employed was too high to allow any conclusions regarding the effect of the copper concentration on the click process under these reaction conditions. Even though the polymerization could be significantly accelerated by increasing the concentration of copper species in solution, the CuAAC was still found to be faster than LRP for all cases. Decreasing the temperature from 60 to 30 °C caused a decrease in the rate of the polymerization, whereas the rate of the CuAAC remained extremely high.

A comparison of rates of LRP vs. click conversion shows that in the presence of a relatively small catalyst loading the rate of CuAAC in DMSO tends to be slower than (or at least comparable to) that of polymerization, whilst in toluene, or DMF, the click process is faster than polymerization (Figure 4). In the absence of the iminopyridine ligand, in [D$_6$]DMSO at 60 °C, the CuAAC reaction was slightly faster than when the chelating ligand was employed. This may be explained by the formation of inactive species when an excess of ligand is used, as suggested by Finn and co-workers.[6b] Interestingly, LRP also showed to proceed under these conditions, only at a slower rate, indicating that either the formed triazoles, triethylamine or the solvent, or a combination of these, may act as a ligand to complex the copper species and catalyze the polymerization. Size exclusion chromatography (SEC) analysis of the resulting polymer, however, showed a higher PDi (1.55) compared to when an iminopyridine ligand was used, indicating that the polymer-

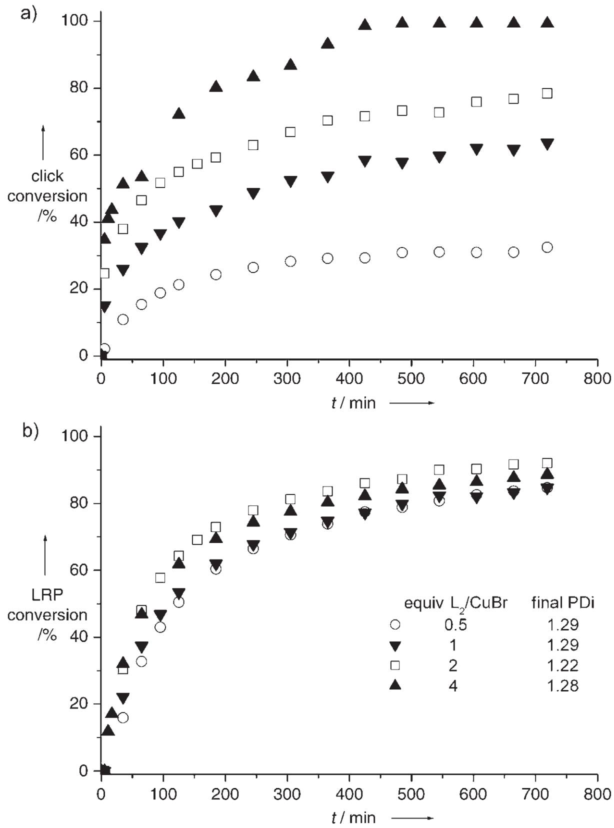

Figure 3. CuAAC/LRP at different copper concentration: alkyne monomer (**1**) with triethyleneglycol azide (**3**) in [D$_6$]DMSO at different catalyst concentrations. Reaction conditions: [initiator]/[**1**]/[**3**]/[Et$_3$N] = 1:50:100:5. Equivalents of L$_2$/Cu^{I}Br (L: *N*-ethyl pyridineimine): 0.5 (○), 1 (▼), 2 (□), and 4 (▲).

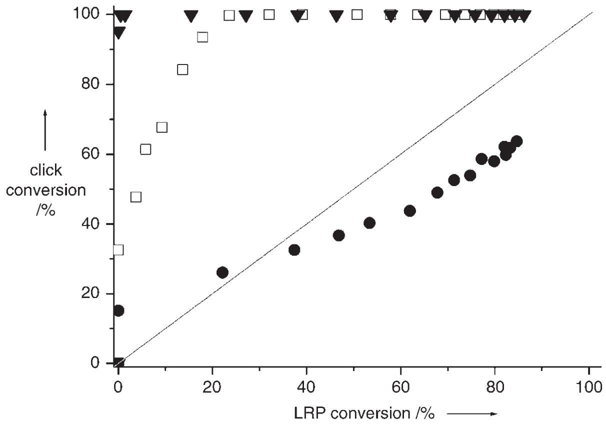

Figure 4. LRP vs. click conversion for CuAAC/LRP in different solvent media: alkyne monomer (**1**) and triethyleneglycol azide (**3**) in [D$_8$]toluene (▼),[D$_7$]DMF (□), and [D$_6$]DMSO (●). Reaction conditions: [initiator]/[**1**]/[**3**]/[Cu^{I}Br]/[ligand]/[Et$_3$N] = 1:50:100:1:2:5. The solid line represents the theoretical case of LRP conversion = click conversion.

ization without added ligand was largely uncontrolled. To evaluate whether a certain extent of click reaction occurred thermally, via a non-copper catalyzed pathway, a one-pot experiment was also conducted, at 60 °C, without the addition of any copper species. ^{1}H NMR analysis revealed that after 10 h no clicked products were present. Homopolymerizations of **1** in the absence of any azide, conducted in toluene and DMSO, led to polymers with broad molecular weight distribution (PDi = 1.53–1.88), in agreement with previous reports.[14b] This behavior may be ascribed to chain transfer to the 1-alkyne moieties, amongst other things, and highlights the importance of minimizing the amount of un-clicked alkyne groups in the growing polymer.

Synthesis of multivalent ligands presenting multiple copies of carbohydrate-binding epitopes for protein receptor recognition is an area that could benefit from novel and efficient synthetic strategies. The decreased number of reaction steps compared to post-functionalization of an alkyne-functional polymer with sugar azides[12h] would offer an alternative and complementary route to such functional glycopolymers. A one-pot CuAAC-LRP process would also avoid the use of sugar functional methacrylate monomers, which are known to be prone to self-polymerize.

Mannose-functional polymers were prepared by CuAAC-LRP from propargyl methacrylate (**1**) and 2′-azidoethyl-α-mannopyranoside (**4**). DMSO was used as solvent as it solubilizes the mannose azide starting material, **1**, and the polymer product. Online ^{1}H NMR showed that the two reactions occurred simultaneously, with the polymerization slower than when triethyleneglycol azide (**3**) was used. Increasing the catalyst concentration increased the rate of both LRP and CuAAC. The latter aspect allowed to largely limit the amount of un-clicked alkyne groups that was present in the final polymer when relatively low concentration of copper catalyst was employed. SEC analysis of the resulting glycopolymers showed PDi = 1.12–1.14, indicating controlled polymerization.

In conclusion, we report to our best knowledge the first copper-catalyzed one-pot simultaneous CuAAC-LRP process. A Cu$^{\mathrm{I}}$Br/iminopyridine catalytic system was found to efficiently catalyze both processes under a range of different experimental conditions. The relative rates of CuAAC and LRP can be tuned by appropriate changes of a number of parameters that include the concentration of the copper species, the nature of the solvent employed and the temperature at which reactions are conducted. The rate of the CuAAC process appeared to be relatively sensitive to the nature of the solvent employed, which may be at least in part explained in terms of the different ability of the various solvents to coordinate the copper center, affecting the complicated series of equilibria occurring during the catalytic process.

In addition, the implementation of this concept for the synthesis of glycopolymers yielded well-defined materials in a simplified manner, and we believe that this concept can be used as a versatile synthetic tool in many different applications.

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