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First example of "click" copper(I) catalyzed azide-alkyne cycloaddition in supercritical carbon dioxide: application to the functionalization of aliphatic polyesters

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The modification of aliphatic polyesters by the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) was successfully implemented in supercritical carbon dioxide ($scCO_2$). Due to the remarkable properties of $scCO_2$, the CuAAC reaction turned out to be quantitative even though the aliphatic polyesters used in this work were insoluble in $scCO_2$ Interestingly enough, the conditions were mild enough to prevent polymer degradation from occurring and finally, efficient removal of the catalyst (>96%) was achieved by $scCO_2$ extraction.

Introduction

Since the pioneering work of Meldal *et al.*[1] and Sharpless *et al.*,[2] the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC), which is probably the most popular "click reaction",[3] has been the subject of extensive research in very recent years for the development of macromolecular engineering.[4-13] This interest relies on the major benefits related to the CuAAC reaction, *i.e.* its versatility, high yields, stereospecificity, and the absence of undesirable by-products after reaction. Up to now, most of the works focused on the CuAAC reaction in aqueous or in organic media. Very recently, Emrick *et al.*[14] and Jérôme *et al.*,[13,15-18] showed that aliphatic polyesters can be efficiently functionalized by the CuAAC reaction. Nevertheless, many aliphatic polyesters are too sensitive to hydrolytic degradation to be functionalized by the CuAAC reaction without degradation even though some success was met by Emrick *et al.* for the functionalization of some less sensitive copolymers of poly(oxepan-2-one).[14] Interestingly enough, the implementation of the CuAAC reaction in an organic medium (DMF or THF) allows functionalization of a wider range of more sensitive aliphatic polyesters without degradation.[15,16] At the time being, no example of the CuAAC reaction is reported in $scCO_2$, at least to the best of our knowledge. Nevertheless, due to its low cost, non toxicity and inertia towards reactive species (except anions), the use of supercritical carbon dioxide as a green reaction medium is a valuable alternative to the use of potentially toxic organic solvents. Moreover, the final material is directly collected as a dry product free of catalyst and residual reactant, if any, thanks to supercritical fluid extraction. In this paper, the modification of aliphatic polyesters by the CuAAC reaction in $scCO_2$ is first investigated. Due to the low critical parameters of CO_2, *i.e.* T_c = 31.2 °C and P_c = 73.8 bar, the CuAAC reaction was performed under mild conditions limiting any degradation risks. In a second step, polymer purification by supercritical fluid extraction of the copper catalyst is also discussed, leading to the preparation of functional polyesters with low catalytic residues.

Experimental

Materials

Prop-2-yn-1-ol (Aldrich), *N,N*-dimethylprop-2-yn-1-amine (Aldrich), *N*'-[2-(diethylamino)ethyl]-*N,N*-diethylethane-1,2-diamine (TEDETA, Aldrich), 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl prop-2-enoate (FDA, Aldrich) copper(I) iodide (Aldrich) and CO_2 (N48, Air Liquide) were used as received. The poly($\alpha N_3\varepsilon$CL-*co*-εCL) copolymers were prepared as previously reported.[16]

Synthesis of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl-3-(bis(2(diethylamino)ethyl)amino)-propanoate

FDA (2 ml, 6.2 10^{-3} mol) was introduced in a glass tube in the presence of 1 eq. of TEDETA (1.34 g, 6.2 10^{-3}

mol) and 5 ml of methanol. The mixture was then heated at 50 °C for 24 h. After reaction, methanol was removed from the reaction medium and the final product was collected as a pure orange oil (quantitative yield) that was analyzed by ^{1}H NMR without any additional purification step.

^{1}H NMR ($CDCl_3$): δ = 0.99 ppm (triplet, 12H); 2.1 ppm < δ < 2.5 ppm (multiplet, 20H); δ = 2.8 ppm (triplet, 2H); δ = 3.92 ppm (triplet, 2H).

IR (NaCl): 1743 cm^{-1} (C=O).

Solubility of the catalyst

The solubility of the catalyst was visually observed with the help of a 60 ml high pressure cell equipped with sapphire windows and a magnetic stirrer. In practice, 0.0842 g of CuI and 0.3329 g of 3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl-3-(bis(2(diethylamino)ethyl)amino)propanoate were introduced into the cell. The high pressure cell was equilibrated at 80 bar at room temperature. In these conditions, the CO_2 liquid phase rapidly becomes pale green attesting to the solubility of the catalyst in scCO_2.

Typical CuAAC reaction

Poly($\alpha N_3\varepsilon$CL-*co*-εCL) (1 eq. of azide, Mn = 10 000 g mol^{-1}, 30 mol% of $\alpha N_3\varepsilon$CL) was introduced into a 35 ml high pressure cell in the presence of 1.2 eq of alkyne, 0.1 eq of CuI and 0.1 eq of the perfluorinated ligand. The vessel was then equilibrated at 40 °C for 3 h at 300 bar. After the reaction, a sample was picked out from the reaction medium for SEC characterization and the final product was dissolved in THF before precipitation in heptane and drying under vacuum at room temperature overnight.

Cycloaddition of prop-2-yn-1-ol

^{1}H NMR ($CDCl_3$): 7.68 ppm (1H, s, C*H*=C triazole), 5.3 ppm (1H, s, triazole-C*H*-C(O)), 4.8 ppm (2H, s, CH_2-OH), 4.2 to 4 ppm (4H, 2 m, 2 CH_2-O-C(O)), 2.3 ppm (2H, t, CH_2-C(O)) and 2 to 1 ppm (12 H, m, 6 CH_2).

Cycloaddition of N,N-dimethylprop-2-yn-1-amine

^{1}H NMR ($CDCl_3$): 7.7 ppm (1H, s, C*H*=C triazole), 5.26 ppm (1H, s, triazole-C*H*-C(O)), 4.2 to 4 ppm (4H, 2 m, 2 CH_2-O-C(O)), 3.6 ppm (2H, s, CH_2-N(Me)$_2$, 2.3 ppm (2H, t, CH_2-C(O)) and 2 to 1 ppm (12 H, m, 6 CH_2), 1.31 ppm (6H, s, N(CH_3)$_2$).

Synthesis of alkyne-terminated PDMS

In a typical experiment, ω-hydroxyl-terminated PDMS (5 g, M_n = 5000 g mol^{-1}, 5 × 10^{-4} mol) was dried by 3 azeotropic distillations with toluene before being dissolved in dry CH_2Cl_2 (50 ml). The PDMS was then reacted for 36 h at room temperature with pentynoic acid (0.1 g, 10^{-3} mol) in the presence of dicyclohexylcarbodiimide (0.2 g, 10^{-3} mol) and dimethy-laminopyridine (3.2 mg, 10^{-4} mol). After reaction, the precipitate was removed by filtration and the solution was washed with a saturated solution of $NaHCO_3$. After drying of the organic phase under $MgSO_4$, PDMS was precipitated in methanol and dried under vacuum. Quantitative grafting of pentynoic acid was confirmed by ^{1}H NMR spectroscopy ($CDCl_3$) by the complete disappearance of the peak corresponding to the methylene protons of ω-hydroxyl terminated PDMS (δ = 3.75 ppm, CH_2-OH*)* and the apparition in the NMR spectrum of a peak characteristic of the methylene protons bearing an ester group (δ = 4.25 ppm, CH_2-OC(O)).

Characterization techniques

Size exclusion chromatography (SEC) was carried out in THF at 45 °C at a flow rate of 1 mL min^{-1} with a SFD S5200 autosampler liquid chromatograph equipped with a SFD refractometer index detector 2000 using PL gel 5 µm (10^5 Å, 10^4 Å, 10^3 Å and 100 Å) columns or in DMF at 40 °C at a flow rate 1 mL min^{-1}, using a Water 600 autosampler liquid chromatograph equipped with a differential refractometer index detector. Waters gel 5 µm (10^5 Å, 10^4 Å, 500 Å and 100 Å) columns were calibrated with polystyrene standards. ^{1}HNMR spectra were recorded in $CDCl_3$ at 400 MHz in the FT mode with a Brucker AN 400 apparatus at 25 °C. Infrared spectra were recorded with a Perkin-Elmer FT-IR 1720X. The IR samples were prepared by slow evaporation of a copolymer solution, in THF, onto NaCl crystals.

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Safety note

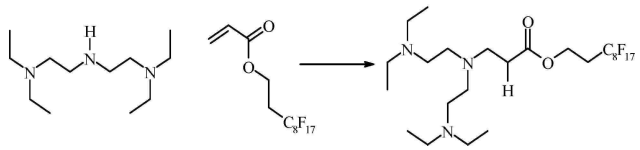
All the experiments were performed in a high pressure cell equipped with a burst disc and specially designed to resist pressure of 550 bars. After reaction, the pressure was slowly released in a fume hood in order to avoid the vaporization of the potentially toxic residual alkynes or catalyst in the air.

Results

In our group, the strategy recently developed for poly-lactone functionalization is based on the coupling of aliphatic polyesters bearing azido-pendant groups with various substituted alkynes.[15,16] Toward this end, poly(εCL-*co*-αN_3εCL) (αN_3εCL stands for α-azido-ε-caprolactone or 3-azidooxepan-2-one) was synthesized by the ring-opening copolymerization of αClεCL (αClεCL stands for α-chloro-ε-caprolactone or 3-chlorooxepan-2-one) and εCL,[19] followed by the quantitative conversion of pendant chlorines into azides by reaction with NaN_3 according to a previously reported procedure.[15,16]

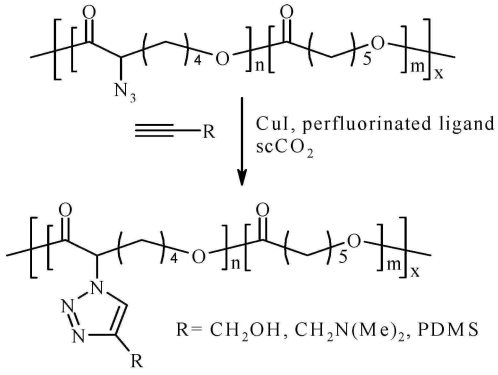
It is well-known that organometallic species often exhibit limited solubility or even insolubility in $scCO_2$[20-29] and copper salts usually used for the CuAAC reaction are accordingly poorly soluble in $scCO_2$. Before considering the functionalization of poly(εCL-*co*-αN_3εCL) by the CuAAC reaction in $scCO_2$, it turned out to be necessary to synthesize a perfluorinated aminoligand able to complex and to solubilize the copper catalyst in $scCO_2$. For this reason, a perfluorinated amino-ligand, *i.e.* 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl-3-(bis(2 (diethylamino)ethyl)amino)propanoate was prepared by the Michael addition of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl prop-2-enoate (FDA) with *N'*-[2-(diethyl-amino)ethyl]-*N*,*N*-diethylethane-1,2-diamine (Scheme 1). The reaction was performed in methanol at 50 °C during 24 h using an equimolar ratio of TEDETA and FDA. After removal of methanol under vacuum, the final product was collected as an orange oil and the completeness of the reaction was confirmed by ^{1}H NMR spectroscopy.

Scheme 1: *Synthesis of a perfluorinated amino-ligand.*



The heterogeneous CuAAC reaction between the CO_2-phobic (poly(εCL-*co*-αN_3CL) and prop-2-yn-1-ol, *N*,*N*-dimethylprop-2-yn-1-amine or alkyne end-functionalized PDMS was investigated in $scCO_2$ (Scheme 2) using copper iodide as a catalyst complexed by the perfluorinated ligand whose synthesis is shown in Scheme 1.

Scheme 2: *Modification of poly(εCL-co-αN_3εCL) random copoly-esters with different alkynes by the CuAAC reaction in $scCO_2$.*



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The grafting of prop-2-yn-1-ol onto poly(αN$_3$εCL-*co*-εCL) (30 mol% of αN$_3$εCL) was first tested (Table 1, entry 1) by introducing 1 g of poly(εCL-*co*-αN$_3$εCL) (M_n =10000 g mol^{-1}, 30 mol% of αN$_3$CL) in a 35 ml high pressure cell in the presence of prop-2-yn-1-ol (1.2 eq compared to αN$_3$εCL), CuI ([Cu]/[alkyne] = 0.1) and the perfluorinated aminoligand ([Cu]/[ligand] = 1) that is already soluble at room temperature in liquid CO_2 (80 bars). After 3 h at 40 °C and 300 bar, the high pressure cell was cooled, the pressure was released and the collected product was analyzed by IR and ^{1}H NMR spectroscopy. The IR spectrum showed the complete disappearance of the typical absorption of the azide group of the poly(αN$_3$εCL-*co*-εCL) random copolymer. The ^{1}H NMR spectrum confirmed this result by the complete disappearance of the peak corresponding to the methylene proton bearing the azide group (δ = 3.85 ppm, CH_2N_3) and the appearance of the peak characteristic of the CH group of the triazole unit (δ = 7.68 ppm). These characterizations, compared with previously published data,[16] showed unambiguously that the CuAAC went to completion in $scCO_2$ even though the aliphatic polyester was not soluble and despite the high dilution of the medium. This remarkable result can be accounted for by the exceptional mass transport properties and the diffusivity of $scCO_2$ comparable to those of gases. Consequently, the diffusion of prop-2-yn-1-ol into the very well plasticized poly (αN$_3$εCL-*co*-εCL) matrix[29] was rapid and the CuAAC reaction was fast and quantitative whatever the location of the azides. Interestingly enough, the SEC trace, using THF as an eluent, showed a narrow and monomodal molecular weight distribution and thus, no degradation was detected. When the same reaction was carried out in an organic medium (THF) rather than in $scCO_2$ under comparable conditions, a slight degradation by transesterification reactions was observed as witnessed by a bimodal distribution[16] (Fig. 1, Table 1, entry 25). As a rule, the grafting of prop-2-yn-1-ol was fast as a result of the rapid diffusion of prop-2-yn-1-ol and the catalyst into the polymer matrix and proceeded without any degradation of the aliphatic polyester due to the mild reactions conditions.

In order to optimize the experimental conditions for CuAAC, the same experiments were repeated at 100 and 300 bars but for shorter reaction times, *i.e.* 2 h, 1 h and 30 minutes (Table 1, entries 4-9). Whatever the pressure, even after 30 minutes, in the presence of 10 mol% of CuI compared to the alkyne, the grafting of prop-2-yn-1-ol onto poly(αN$_3$εCL-*co*-εCL) by CuAAC was quantitative, as evidenced by ^{1}H NMR spectroscopy. The effect of the catalyst content on reaction kinetics was then studied. So, the same experiment was repeated with 5% or 3% of CuI (instead of 10 mol% compared to the alkyne) or without addition of copper iodide for 30 minutes and 1 h at 100 or 300 bars (Table 1, entries 10-21). After reaction, the conversion of prop-2-yn-1-ol into triazole was determined by ^{1}H NMR spectroscopy for each experiment. From these data, it can be concluded that a decrease of the catalyst content from 10 to 3 mol% does not affect the yield. It is worth noting that, as expected, no reaction was observed in the absence of CuI (Table 1, entry 12, 15, 18 and 21).

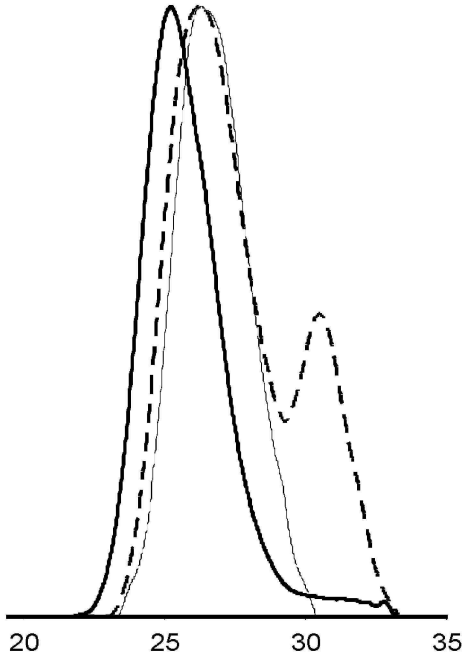
Table 1: *Grafting of propargyl alcohol, 3-dimethylamino-1-propyne or alkyne-terminated PDMS (M_n = 5000 g mol^{-1}) in $scCO_2$: T = 40 °C*

Entry	Alkyne derivative	Cu/ alkyne (%)	Alkyne/N_3	Time/h	P/bar	Yield (%)[a]
1	Alcohol	10	1.2	3	300	100
2	Alcohol	10	1.2	3	200	100
3	Alcohol	10	1.2	3	100	100
4	Alcohol	10	1.2	2	100	100
5	Alcohol	10	1.2	1	100	100
6	Alcohol	10	1.2	0.5	100	100
7	Alcohol	10	1.2	2	300	100
8	Alcohol	10	1.2	1	300	100
9	Alcohol	10	1.2	0.5	300	100
10	Alcohol	5	1.2	1	100	100
11	Alcohol	3	1.2	1	100	100
12	Alcohol	No Cu	1.2	1	100	—
13	Alcohol	5	1.2	0.5	100	100
14	Alcohol	3	1.2	0.5	100	100
15	Alcohol	No Cu	1.2	0.5	100	—
16	Alcohol	5	1.2	1	300	100
17	Alcohol	3	1.2	1	300	100
18	Alcohol	No Cu	1.2	1	300	—
19	Alcohol	5	1.2	0.5	300	100
20	Alcohol	3	1.2	0.5	300	100
21	Alcohol	No Cu	1.2	0.5	300	—

22	Amine	10	1.2	3	300	75
23	Amine	10	2	3	300	99
24	Alkyne-terminated PDMS[b]	10	1.0	24	300	5
25[b]	Alcohol	10	1.2	3	—	100

[a] estimated by ^{1}H NMR spectroscopy [b] carried out in THF

Fig. 1 *SEC characterization (in THF) of poly(εCL-co-αN$_3$CL) before (—) and after (· · ·) grafting of propargyl alcohol in scCO$_2$. Grafting of propargyl alcohol in THF (---).*



In the next step, the functionalization reaction was extended to the coupling of other substituted alkynes such as *N*,*N*-dimethylprop-2-yn-1-amine or alkyne-terminated PDMS. The grafting was attempted onto poly (αN$_3$εCL-co-εCL) (30 mol% of aN$_3$εCL) using the same conditions used for the grafting of prop-2-yn-1-ol (*cf* Table 1 entry 1). In the case of the grafting of the *N*,*N*-dimethylprop-2-yn-1-amine, when a [alkyne]/[N$_3$] molar ratio of 1.2 was used, the conversion was limited to only 75% (Table 1, entry 22). The origin of this slow kinetics could be accounted for by the competition between the perfluorinated ligand and the dimethylamino group for the complexation to the copper salt, which induces a decrease of the catalyst solubility in scCO$_2$ even though monodentate amines are known for being weaker ligands than tridentate aminoligands. Nevertheless, this problem could be overcome by increasing the alkyne content from 1.2 to 2 eq. compared to the azido groups, and the reaction went to completion (Table 1, entry 23). Besides, the grafting of a high molecular-weight CO$_2$-soluble macromolecule was also investigated. Alkyne-terminated PDMS (M_n = 5000 g mol^{-1}) was reacted with poly (εCL-*co*-αN$_3$CL) for 24 h in scCO$_2$ (Table 1, entry 24). Unfortunately, the conversion of the CuAAC reaction remained very low (5%). Although low molecular weight CO$_2$-soluble organic compounds can efficiently diffuse in the plasticized PCL, the diffusion of the high molecular weight PDMS is sterically hindered, which is detrimental to the success of the CuAAC reaction.

The use of copper catalysts that usually contaminate the "clicked" aliphatic polyesters is a severe limitation in view of future developments, particularly in the biomedical[30] or in the packaging field. Although some alternative strategies to get metal free products, such as heterogeneous catalysis[31-36] or metal-free Huisgen's cycloaddition,[37] have been reported in the literature, we evidenced that scCO$_2$ extraction is quite efficient to remove the copper catalyst from the functional aliphatic polyesters after reaction in this medium. Indeed, because aliphatic polyesters are insoluble in scCO$_2$ whereas the catalyst exhibits high solubility in this medium, purification of the polymer by supercritical fluid extraction (SFE) was investigated. In practice, grafting of prop-2-yn-1-ol onto poly (εCL-*co*-αN$_3$CL) was first performed before removal of the copper catalyst by supercritical

extraction at 300 bar and 40 °C with a CO_2 flow rate of 5 mL min^{-1}. After extraction with 200 mL of CO_2, the residual copper content was estimated by atomic absorption. In these conditions more than 96% of the catalyst was removed (residual copper content = 1853 ppm, $[Cu]_0$ = 50 000 ppm). SFE is a thus a very promising approach for purifying polymers and optimization of the extraction conditions is still under progress, for instance by addition of an excess of perfluorinated ligand, as well as experiments relying on the recycling of the catalyst.

Conclusion

In this short communication, we have reported the very first example of the CuAAC reaction in supercritical carbon dioxide.

The concept was tested for the modification of aliphatic polyesters that are insoluble in $scCO_2$ and sensitive to degradation. Even under heterogeneous and diluted conditions, the grafting of alcohol or amino groups onto the polyesters chains was quantitative as a result of the diffusion of the catalyst and the alkyne derivative into the polymer matrix. No degradation of the polymer chains was observed thanks to the mild reaction conditions.[16] In the case of grafting of prop-2-yn-1-ol onto poly (εCL-*co*-αN_3CL), it was demonstrated that the CuAAc was rapid with quantitative conversions after 30 minutes in the presence of 3 mol% of catalyst compared to the alkyne. Finally, removal of the copper catalyst was successfully realized by supercritical fluid extraction, leading to the formation of functional aliphatic polyester with more than 96% of the catalyst being extracted after short extraction time.

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