CRYOGELS AS NOVEL SOLID-SUPPORTED COPPER CATALYST SYSTEM FOR CLICK CHEMISTRY AND THEIR USE IN COLUMN REACTORS

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Introduction

In this research contribution, we have investigated macroporous gels as macromolecular carriers (ligands) for metal catalysts. Catalyst immobilization on solid supports represents a widely explored strategy in the chemical industry for efficient catalyst separation and re-use.[1]

However, solid-supported catalyst systems also show some disadvantages: mainly as a result of diffusion problems, a lower reactivity is often observed compared to the corresponding homogeneous systems. Thanks to the macroporosity of the network structures that we have applied in this work, diffusion problems could be circumvented. The macroporous structure also results in a lower back pressure compared to traditional solid supported systems, allowing continuous flow applications.

The macroporous structures that we are using as a solid support for the copper catalyst are produced by radical copolymerization of two monomers with a crosslinker in partially frozen media (see **Figure 1**).

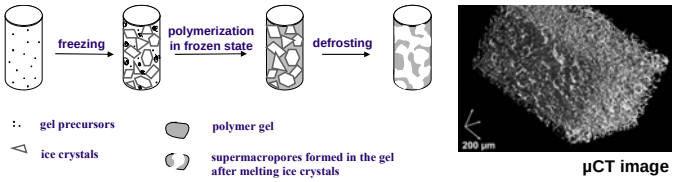

Figure 1: Schematic drawing of the synthesis of macroporous cryogels and 3D reconstruction of micro-CT images.[2,3]

The dissolved monomers and initiator are concentrated in small fractions of non-frozen liquid. In these non-frozen fractions the polymerization proceeds despite that the whole system looks like a frozen ice block. The ice crystals formed after partial freezing perform as porogen. The resulting so-called cryogels are elastic and have a unique structure of large interconnected pores with pore sizes from 10 up to 100 µm and a total porosity of 94-97%, as determined by micro-computed tomography (see **Figure 1**).[2]

In this work, macroporous hydrogels have been prepared by copolymerization of hydroxyethyl methacrylate (HEMA), a ligand-modified methacrylate and the cross-linker dimethylacrylamide (DMAA) in semi-frozen state.

These materials have been applied as solid-supported catalyst systems for copper-catalyzed 1,3 dipolar cycloaddition reactions ("click" chemistry) with small and macromolecular structures.

Experimental

Materials. 1-ethoxyethyl acrylate (EEA)[4] was synthesized as described before. Propargyl 2-bromopropionate was prepared by esterification of propargyl alcohol and 2-bromopropionic acid, adapting a literature procedure.[5] Isobornyl acrylate (iBA, Aldrich, tech.) was purified by vacuum distillation (121 °C/18 mmHg). Me6TREN was synthesized according to literature.[6] HEMA (97%, Aldrich), *n*-BuLi (1,6 M in hexane, Fluka), DMAA (99%, Aldrich), methylene-*bis*-acrylamide (MBAA, 97%, Aldrich), $CuBr_2$ (99%, Aldrich), benzylbromide (98%, Aldrich), NaN_3 (99.5%, Aldrich), phenylacetylene (98%, Aldrich), ethyl acetate were used as received. Cu(I)Br (98%, Aldrich) was purified by stirring with acetic acid, washed with methanol and ethanol, and finally dried under vacuum at 70°C.

Instrumentation. UV-Vis spectra were recorded on a Specord 200 (AnalytikJena) in quartz precision cells having a 10 mm light path at a wavelength of 732 nm. Details of all other instrumentation can be found elsewhere.[7]

Synthesis of benzyl azide. Benzyl bromide is dissolved in DMSO and stirred with a 3 fold excess of NaN_3 overnight. Water is added and the product is extracted with ether. The organic phase is evaporated and the product is dried under reduced pressure.

Synthesis of alkyn terminated poly(1-ethoxy ethylacrylate) (PEEA-≡). ATRP of EEA with propargyl 2-bromopropionate as initiator to yield alkyne-functionalized PEEA-≡ was performed with a Cu(I)Br/PMDETA catalyst system at 70 °C, with [EEA]/[In]/[Cu(I)Br]/[PMDETA] = 100/1/1/1, following a procedure described before.[4]

Synthesis of poly(isobornyl acrylate)-N_3 (PiBA-N_3). Poly(isobornyl acrylate) (PiBA) was prepared by ATRP as described elsewhere, followed by nucleophilic substitution of the bromide end group to an azide using azidotrimethylsilane and tetrabutylammoniumfluoride in a tetrahydrofuran solution.[7,8]

Synthesis of TMDETA. At -78°C, 11 mmol (1.6 M) *n*-BuLi was slowly added to a solution of 2.22 g (9.6 mmol) of Me_6TREN in 18 ml of hexane. When the addition was complete, the sample was stirred for 30 min at this temperature and another 90 min at 25 °C. The Li salt was filtered and dissolved in 200 ml aqueous 5 M NaOH. After extraction with $CHCl_3$ (3 x 100 ml) and drying ($MgSO_4$), evaporation of the solvent yielded a colourless liquid (83 %).

Synthesis of ligand monomer EMA-ligand. A mixture of 1.52 mmol (0.28 g) HEMA and 3.04 mmol (0.48 g) TMDETA were stirred overnight. The excess of TMDETA was removed by filtration over a column filled with neutral Al_2O_3.

Synthesis of ligand-containing cryogel. The macroporous cryogels were prepared in glass tubes. The total content of monomers (DMAA and EMA-ligand) and crosslinker MBAA was 6 w/v%, monomers/MBAA = 8/1. The amount of TEMED as wel as APS was 1.2 w/w% of the total weight of monomers and MBAA. The solution in the tubes was frozen at -12°C and kept at this temperature for 20h. After thawing and washing with water, the cryogels were dried at 50 °C and stored in dry state. The Cu-loading was measured as follows. A cryogel was washed with an excess of 0.2 M $CuBr_2$. Then the column was washed with distilled water after which elution with 0.1 M EDTA pH 7.2 was performed. The optical density at 732 nm was measured and the amount of Cu ions adsorbed per unit of dry weight of the cryogel (mmol/g) was calculated.

Column packing and Cu(I)-loading In a glass column, the ligand containing cryogel is reswollen in EtOAc after which it is flushed with a degassed DMF/EtOAc solution (50/50 v/v). The Cu(I)-catalyst is loaded by pumping a Cu(I)Br solution in DMF/EtOAc through the cryogel. Then, the excess of Cu(I) is removed by washing with DMF/EtOAc and finally the solvent is changed to EtOAc.

"Click" reaction using ligand-containing cryogel. A typical "click" reaction is as follows. A solution of 0,269 g (0.203 mmol) benzylazide and 0.245 g (0.223 mmol) phenylacetylene in 10 ml of EtOAc were circulated with a flow of 2 ml/min through 0,318 g of ligand containing cryogel loaded with Cu(I)Br (see **Figure 2**). The reaction is monitored via real-time ATR-FTIR and ^{1}H-NMR.

Results and Discussion

In this work, we report on a novel solid-supported copper catalyst system that can be applied for continuous synthesis applications. The solid supported catalyst system is packed in a column reactor, as can be seen in **Figure 2**. The advantage of packing the solid-supported catalyst is that after completion of the reaction, there is no need for separation of the solid support.

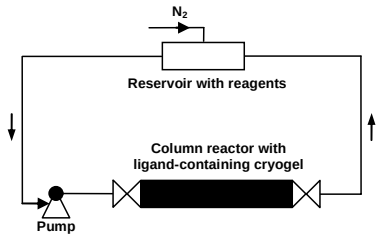

Figure 2: Schematic drawing of column reactor with circulation of reagents.

For the choice of the ligand that is chemically attached to our solid-supported sytem, tetramethyl diethylene triamine (TMDETA) was chosen as a model ligand because it is an analogue of pentamethyl diethylene triamine (PMDETA), a widely used ligand for homogeneous ATRP and "click" reactions. The synthesis of TMDETA starts from Me_6TREN.[6] TMDETA is then modified to introduce a methacrylate group. This was done by Michael addition onto an acrylate (EMA-acrylate) that was obtained by reaction of acryloyl chloride with hydroxyethyl methacrylate (HEMA), as shown in **Figure 3**.

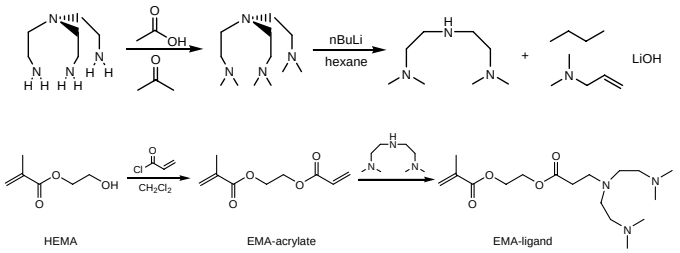

Figure 3: Synthesis of TMDETA and ligand-monomer (EMA-ligand).

In a next step, ligand-containing macroporous hydrogels were synthesized at subzero temperatures by the direct incorporation of the ligand-containing monomer (EMA-ligand) during the synthesis of the cryogel. The final cryogel was a sponge like hydrogel with a highly porous structure. After drying at 50°C, the polymer reswels within less than a minute when submerged into water.

The Cu(I)-loading capacity of the ligand containing cryogels was determined by the amount of $Cu(II)Br_2$ that can be ligated by the cryogels. It is expected that the ligand containing cryogels can bind the same amount of Cu(I)Br and $Cu(II)Br_2$ since they are coordinated by the same amount of TMDETA. A $Cu(II)Br_2$-loading of 0.121 mmol/g cryogel was determined by UV/Vis.

After packing a glass column with ligand containing cryogel and loading it with Cu(I)Br, these macroporous hydrogels could be used to mediate different types of copper-catalyzed 1,3 dipolar cycloaddition reaction ("click" chemistry).

A first example of the use of ligand containing cryogels as solid support for "click" chemistry was the cycloaddition of benzylazide and phenylacetylene. The results are summarized in **Table 1.** The kinetics of the "click" reaction were measured by ^{1}H-NMR analysis.

Table 1: Results of the "click" reaction of benzyl azide and phenylacetylene using ligand containing cryogel as support for CuBr ($V_{reagents}/V_{solvent}$ = 1:13; 0.067 eq. CuBr to azide).

Entry	Solvent	Time (hours)	Conv. (%)[a]	[Cu] ppm[b]
1[c]	EtOAc	16	< 1	-[d]
2	EtOAc	2.2	57	
3	EtOAc	13	96	
4	Acetone	4.5	95	

[a.] conversion determined by ^{1}H-NMR, [b] copper concentration in end product, [c] no Cu(I) loaded on cryogel, [d] not determined.

Precipitation of the triazole end product indicates that benzylazide is reacting with phenylacetylene. This is confirmed by the disappearance in ^{1}H-NMR of the benzylic proton signal of the azide (4.2 ppm) and the signal of the alkyne proton at 3 ppm. Moreover, a triazole signal is appearing around 8 ppm. High conversions (> 95%) were obtained within a reasonable time scale both in EtOAc and acetone. Nevertheless, a detailed kinetic analysis shows that the "click" reaction is faster in acetone than in EtOAc (64% versus 40% conversion after 1.5 h).

When no Cu(I)Br is loaded on the cryogel, almost no conversion is observed (**Table 1,** entry 1). This shows that the Cu(I)/TMDETA complex is essential to perform a "click" reaction.

To further demonstrate the applicability of the ligand containing cryogel as solid support for "click" reactions, amphiphilic block copolymers were synthesized based on poly(isobornyl acrylate) and poly(acrylic acid). These homopolymers were synthesized via ATRP. Since acrylic acid can not be polymerized by ATRP in a direct way, the 1-ethoxyethyl acrylate (EEA) precursor strategy was used.[4] Alkyne functionalities were introduced in PEEA via polymerization of EEA with an alkyne containing initiator propargyl 2-bromopropionate, while azide-containing PiBA polymers were obtained either *via* nucleophilic substitution of the bromide end group of hydrophobic (PiBA) into an azide. and "clicked" by means of the ligand-containing cryogel. After thermal deprotection of the PEEA-segment, the desired amphiphilic PiBA-*b*-PAA block copolymer was obtained.

Having demonstrated the applicability of these ligand-containing cryogels as a solid-supported copper catalyst system for "click" chemistry of some model reactions, the application field is currently broadened to other types of "click" chemistry.

Conclusion

In this work, a new type of solid-supported copper catalyst system based on macroporous hydrogels was developed for the use in column reactors. The copper ligand (TMDETA) was chemically incorporated in the cryogels. After successful synthesis, these ligand-containing cryogels were packed in a column and loaded with Cu(I)Br. Subsequently, the column reactors were used for the Cu(I) catalysis of several azide/alkyne "click" reactions. A first type of reaction was the cycloaddition of benzylazide and phenylacetylene. High conversions were obtained in different solvents. A detailed kinetic study was performed by means of ^{1}H-NMR analysis. Next, amphiphilic PAA-containing block copolymers were synthesized by combination of azide-containing PiBA and alkyne-containing PEEA.

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References

(1) Shen, Y. Q.; Tang, H. D.; Ding, S. J. *Progr. Polym. Sci.* **2004**, *29*, 1053.

(2) Savina, I. N.; Cnudde, V.; D'Hollander, S.; Van Hoorebeke, L.; Mattiasson, B.; Galaev, I. Y.; Du Prez, F. *Soft Matter* **2007**, *3*, 1176.

(3) Lozinsky, V. I.; Galaev, I. Y.; Plieva, F.; Savina, I. N.; Jungvid, H.; Mattiasson, B. *Trends in biotechnology* **2003**, *21*, 445.

(4) Van Camp, W.; Du Prez, F. E.; Bon, S. A. F. *Macromolecules* **2004**, *37*, 6673.

(5) Tsarevsky, N. V.; Sumerlin, B. S.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 3558.

(6) Xia, J. H.; Gaynor, S. G.; Matyjaszewski, K. *Macromolecules* **1998**, *31*, 5958.

(7) Van Camp, W.; Germonpre, V.; Mespouille, L.; Dubois, P.; Goethals, E. J.; Du Prez, F. E. *React. Func. Polym.* **2007**, *67*, 1168.

(8) Matyjaszewski, K.; Nakagawa, Y.; Gaynor, S. G. *Macromol. Rapid Commun.* **1997**, *18*, 1057.