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# Hyperbranched polyethylenimine-supported copper(II) ions as a macroliganted homogenous catalyst for strict click reactions of azides and alkynes in water

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# Abstract

Loading hyperbranched polyethylenimine (PEI) with copper(II) ions leads to the formation of a new water-soluble metallodendritic polymer Cu(II)-PEI that has been found to effectively catalyze the clickable azide-alkyne [3+2] cycloaddition reactions in water under ambient conditions, in the lack of any external reducing agent. A positive dendritic effect on the catalyst activity was observed in the click of 1,2,3-triazole by lowering the reduction potential of copper(II) into the *in-situ* generation of the catalytically active species copper(I). The reaction proceeds straightforwardly to afford the corresponding 1,4-disubstituted-1,2,3-triazole derivatives in a regioselective manner. The precatalystCu(II)-PEI has been easily recovered and reused for up to tensequential applications with a decrease in its catalytic activity.

**Keywords:** Hyperbranched polyethylenimine; CuAAC; homogenous catalysis; copper(I)-acetylide; 1,2,3-triazoles; DFT

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# 1. Introduction

Alternative reaction media and procedures that use the immobilization of homogenous catalysts to facilitate the catalysts separation play very important roles in green chemistry by offering synthetic strategies with a low environmental cost. Indeed, efforts are being made to apply environmentally benign solvents such as water, fluorinated, ionic liquids and supercritical fluids as reaction media instead of toxic and/or hazardous organic solvents together with inexpensive reagents and reusable catalytic systems under very mild conditions, to set-up efficient greener synthesis of organic compounds[1].

The Huisgen azide-alkyne cycloaddition reaction catalyzed by copper(I) (CuAAC) is a relatively well-established strategy within the context of "click chemistry" which is used for the formation of 1,4-disubstituted-1,2,3-triazoles and that has found broad applicability in chemistry and biology. The 1,2,3-triazole unit, other than finding a large use in molecular and polymer functionalization, has been applied to robust, chemically orthogonal ligations for the study of complex biological systems[2-5]. The use of copper(I) as a catalyst in CuAAC reactions, either as copper(I) or copper(II) salts generated in situ by the reduction of Cu(II) with sodium ascorbate, is at the root of its immense success as a fast kinetically and regioselective clickable process. However, the direct employment of copper(I) presents many problems under aerobic conditions due to its thermodynamic instability because of its oxidation into copper(II)[6]. In addition, the copper ions are toxic and hazardous to the environment and human health[7,8], in particular,copper(I) that passes through the biological membrane of living organisms, being favored by the coordination environment of most of the biological cells[9, 10].

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Consequently, special attention has recently been paid to metal-free strategies for the click reaction of azides and alkynes [11, 12] by using stretched cycloalkynes [13] or by adding electron-withdrawing substituents at the  $\alpha$  position of the triple bond. Another approach makes use of the substituted dibenzocyclooctyne[14]. However, these strategies are limited up to now to certain applications and these reactions are not expected to replace CuAAC on a large scale, at least in the near future. In order to overcome the presence of copper ions in both the final products as well as in the reaction media, stable solid supports for copper catalysts, including copper(I/II)immobilized on silica[15], carbon[16,17], zeolite[18], alumina[19], biopolymers such asCellulose[20], Chitosan[21], Alginate[22], and the chelation of copper to dimethylaminomethyl-grafted cross-linked polystyrene (Amberlyst A-21 resin)[23-25] have been developed as recoverable and reusable heterogeneous catalytic systems, with improved catalytic activity in the lack of any external reducing agent. Other easy-torecover and to-reuse copper(I)-metallodendrimers have been scarcely explored as polymeric catalysts in CuAAC under homogenous and heterogeneous fashions (see Scheme 1), including the homogenous water-soluble copper-loaded poly(amidoamine) (PAMAM) dendrimers, which proved to efficient in a model CuAAC reaction between azido propanol and propargyl alcohol in water, as well as the heterogeneous copperstabilized cross-linked branched polyethylenimine employed for the click of polymeric compounds[26].



Scheme 1.CuAAC using dendritic polymers as supports for the copper ion catalyst.

In most of the CuAAC reactions, a mixture of water and water-miscible organic solvents has been used as solvent system. Water is the ideal solvent for greener chemical organic processes because it is eco-friendly, non-toxic, cheap and abundant. From this point of view, the performance of CuAAC reactions in water using a water-soluble copper-loaded polymer without any organic solvent and reducing agent are meaningful and valuable. We herein report on the employment of polyethylenimine (PEI), a well-known biocompatible hyperbranched polyamine with high affinity and selectivity for copper ions, to stabilize copper(II) sulfate and on the subsequent use of the copper(II)-polyethylenimine complex [Cu(II)-PEI] under homogenous fashion in clicking a series of azide and alkynes in water as reaction medium at room temperature in absence of any external reducing agent. 1,4-Disubstituted-1,2,3-triazoles were obtained regioselectively in excellent yields by simple precipitation in water. The Cu(II)-PEI complex was reused for up to ten cycles without any loss of its activity and selectivity.

# 2. Results and discussion

The Cu(II)-PEI macroligated complex was prepared by a simple complexation reaction at room temperature of hyperbranchedpolyethylenimine (PEI10K;  $M_n = 1 \times 10^4$  g mol<sup>-1</sup>,  $M_w/M_n = 2.5$ , NH<sub>2</sub>:NH:N = 33:40:27) and copper(II) sulfatepentahydrate in DMF as solvent (Fig. 1). The complex was purified by dialysis against methanol to remove any excess of CuSO<sub>4</sub>·5H<sub>2</sub>O affording a waxy-blue solid (see Scheme 2). The UV-visible absorption spectra of the CuSO<sub>4</sub>·5H<sub>2</sub>O salt and the Cu(II)-PEI complex dissolved in water were recorded in the wavelength range 200-800 nm. PEI is a hyperbranched organic polymer that has no absorption over this range (Fig. 1a) whereas the CuSO<sub>4</sub>·5H<sub>2</sub>O salt displays a typical absorption peak at 800 nm corresponding to d-d transitions. Upon the coordination of the copper(II) ions to the colorless hyperbranched PEI in solution, the mixture rapidly becomes deep blue, and the absorption spectrum exhibits two absorption peaks at 275 and 610 nm (Fig. 1a).



Scheme 2. Preparative route for the metallodendritic polymer Cu(II)-PEI.

The hydrophilic and biocompatible PEI serves as a chelating polyamine for the copper(II) ions. The occurrence of these absorption bands is due to the formation of the Cu(II)-PEI complex (possibility 1-3, scheme 2). Both  $CuSO_4 \cdot 5H_2O$  and Cu(II)-PEI display two absorption bands in the region 200-800 nm. In the UV region, the absorption bands below 280 nm are attributed to intra-ligand transitions while in the

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visible region, the absorption band at 610 nm for Cu(II)-PEI and that at 800 nm for CuSO<sub>4</sub>· 5H<sub>2</sub>O are due to d-d transitions. In the spectrum of the Cu(II)-PEI complex (Fig. 1a), the absorption band at 800 nm found for CuSO<sub>4</sub>· 5H<sub>2</sub>O undergoes a hypsochromic shift to smaller wavelengths by 190 nm, this shift clearly indicating the complexation of copper(II) to the PEI backbone. In order to quantify the amount of copper(II) ions coordinated to the PEI backbone, we carried out a UV-visible spectroscopic study of the absorption of the Cu(II) ions before and after complexation with PEI ( $\lambda$ max = 610 nm), by varying the amount of copper (Fig. 1b and Fig. S1 in Supplemental Data). Increasing amounts of CuSO<sub>4</sub>· 5H<sub>2</sub>O were added to an aqueous solution containing a fixed amount of PEI, and the absorption monitoring of this band shows that the loaded copper(II) ions per PEI is about 2.62 mmol (0.65 g).

Aiming at understanding the interactions between the copper(II) and PEI, FT-IR spectra of PEI and Cu(II)-PEI were recorded. The spectrum of PEI reveals the typical frequencies of polyamines, such as the features at 3362 cm<sup>-1</sup> [stretching vibration v(N-H)], 2948 and 2841 cm<sup>-1</sup> [stretching vibrations v(CH<sub>2</sub>) and v(C-H)], 1569.7 [deformation vibration v(N-H)], and 1473.5 cm<sup>-1</sup> [deformation vibration v(CH<sub>2</sub>)] and finally the peaks at 1303 and 1472 cm<sup>-1</sup> corresponding to the stretching vibration v(C-N)[27]. The FT-IR spectrum of Cu(II)-PEI shows a new absorption peak around 619 cm<sup>-1</sup> which corresponds to the Cu-N bond. In addition, a shift of the v(N-H) signals to 3447 cm<sup>-1</sup>, v(NH<sub>2</sub>) (deformation vibration) to 1735 cm<sup>-1</sup>, v(CH<sub>2</sub>) (deformation vibration vibration) to 1637 cm<sup>-1</sup> and v(C-N) (stretching vibration) to 1398 cm<sup>-1</sup> also occur. These shifts support the coordination of the copper(II) ions to the PEI backbone[28], confirming the formation of the Cu(II)-PEI species (Fig. S2 in Supplemental Data).



**Fig. 1.** a) UV-Visible spectra of the  $CuSO_4 \cdot 5H_2O$  salt and the Cu(II)-PEI complex in water. b) Evolution of the absorbance at 610 nm as a function of the amount of copper(II) loaded by PEI.

The coordination mode of copper(II) to the nitrogen-containing polyethylenimine backbone has been addressed by Electronic Paramagnetic Resonance (EPR). Variabletemperature Q-band EPR study shows a quasi-isotropic signal with a line width of 22 G at ca. 1.15 T (g = 2.120) in the temperature range 300-10 K. Below 10 K, the EPR signal shows a slight broadening due to the increase of the anisotropy of the signal (Fig. 2). This EPR feature resembles those observed in other copper(II)-amine complexes with a small anisotropy of the g factor. The lack of the expected hyperfine coupling in these complexes is attributed to the slight anisotropy of the g factor and to the presence of Cu(II)-Cu(II) interactions in the solid state[29]. This EPR signal confirms that the copper(II) ions are bound to the amine groups of the hyperbranched PEI in a regular coordination environment, adopting the surrounding indicated by the possibility 3 in Scheme 1.



Fig. 2. Normalized Q-band EPR spectra of the Cu(II)-PEI complex at different temperatures.

The redox properties of copper(II) ions coordinated to the hyperbranched polymer PEI backbone were studied by cyclic voltammetry in order to evaluate its potential reduction and then tendency to form the catalytic active copper(I) species. Cyclic voltammograms of CuSO<sub>4</sub>·5H<sub>2</sub>O and Cu(II)-PEI are shown in Fig. 3. The cathodic ( $E_{pc}$ ) and anodic ( $E_{pa}$ ) peak potentials of copper(II) sulfate are -405 mV and 276 mV respectively, with a large peak-to-peak separation ( $\Delta E_p$ ) of 705 mV. The ratio of cathodic to anodic peak current ( $i_{pc}/i_{pa}$ ) is 1, indicating a quasi-reversible redox process [30]. The formal potential ( $E_{1/2}$ ) which is taken as the average value of  $E_{pc}$  and  $E_{pa}$  is -0.052 V. For the Cu(II)-PEI complex, a positive cathodic shift to  $E_{pc} = 122$  mV is clearly observed with a better reversible redox ( $E_{1/2} = 0.077V$ ) together with a decrease in  $\Delta E_p$  of 530 mV with respect to the parent copper(II) sulfate, which indicates that a charge transfer from the nitrogen-containing polymer to the copper(II) ions is easier in the Cu-PEI complex than in the precursor salt (*vide infra*), facilitating its reduction to copper(I) ions. These results are in good agreement with those previouslyreported results, where the Cu(II)/Cu(I) redox process was observed for copper(II) complexes containing polydentate nitrogen ligands[31].



Fig. 3.Voltammograms of the  $CuSO_4 \cdot 5H_2O$  salt and the Cu(II)-PEI complex.

# Catalytic activity and reusability of Cu(II)-PEI in CuAAC

Optimization of the catalyst loading and reaction conditions for the [3+2] cycloaddition process using phenylacetylene (**1a**) and benzyl azide (**2a**) were performed in water as a benign reaction solvent. The results were very encouraging because the reaction was completed after 24 hours at room temperature by simple precipitation of the desired 1,2,3-triazole product (**3a**), which was obtained in a quantitative yield. The progress of the reaction can be followed visually because of the cycloadduct precipitates during the reaction in the aqueous medium (Fig. 4).



**Fig. 4.** Pictures of the resulting products before and after completion of the reaction by using the Cu(II)-PEI complex.

**Table 1.** Catalyst loading and conditions screening for the click reaction of phenylacetylene and benzyl azide.<sup>a</sup>



<sup>a</sup>Reaction conditions: azide (0.751 mmol), alkyne derivative (0.622 mmol), Cu(II)-PEI and 5 mL of water.<sup>b</sup>Isolated yield.

It deserves to be noted that no external reducing agent was needed to perform the copper(I)-catalyzed cycloaddition reaction between azides and alkynes, most likely because the catalytically active copper(I) species was generated *in situ* by the reduction of copper(II) into copper(I) by the terminal alkyne under the known Glaser reaction;[32]a process which is facilitated by the presence of amine groups that lead to a lowering of the redox potential of copper(II) ions. [33]No difference in the yield and reaction times were observed when the amount of the catalyst was reduced from 10 to

5mol %. However, the reaction time was prolonged (48 h) when 1mol % of the catalyst was used (Table 1).

The scope of Cu(II)-PEI in [3+2] cycloaddition reactions in water was explored, once the optimal reaction conditions for the cycloaddition of benzyl azide and phenylacetylene were established. Several [3+2] cycloaddition reactions of parasubstituted benzyl azide and phenyl azide derivatives by withdrawing/releasing groups with different terminal phenylalkynes were carried out. The electron withdrawing/releasing substituent groups do not have any particular effect, as most of the reactions were completed within 24 h. A new triazole library has been created (Table 2) and in all the cases, excellent yields of one regioisomer, namely 1,4disubstituted-1,2,3-triazole type, were obtained in good turnover numbers ranging from 16 and 19. All the synthesized triazole derivatives have been characterized by NMR spectroscopy and HRMS analysis (see Supplemental Data).

On the basis of our best knowledge of previous reports[34-41], a stepwise mechanism of cycloaddition is outlined in Fig. 5. The electron density of the alkyne in the proposed mechanism is reduced by the copper(I) ion forming the dinuclear copper-acetylide B, enabling an easy nucleophilic attack by the organoazide, resulting in the corresponding complex C. The next step is a nucleophilic attack at N3 of the organoazide by the acetylide carbon C4 forming the first covalent C–N bond and then producing the intermediate D. The ring contraction of D leads to the formation of the triazolyl-copper (E). The last step corresponds to a fast protonation of the copper triazolide, releasing the final 1,2,3-triazole product as 1,4-regioisomer.

**Table 2.** Synthesis of the 1,2,3-triazoles (3a-3v) by clicking azides with alkynes in the presence of the Cu(II)-PEI precatalyst.<sup>a,b,c</sup>



<sup>a</sup>Reaction conditions: Azide (0.751 mmol), alkyne derivative (0.622 mmol) and 5 mol% of the Cu(II)-PEI complex were placed in a reaction tube and 5 mL of water was added. <sup>b</sup>Isolated yield. <sup>c</sup>TON = Turnover number catalyst moles of substrate/moles of catalyst.



**Fig. 5.** The proposed mechanism for the formation of 1,4-disubstituted-1,2,3-triazoles catalyzed by Cu(II)-PEI.

The reusability of the catalyst is an important point when thinking of its practical application. In order to address this issue, the reaction for the synthesis of the product (3a) was chosen as a model reaction to explore the reusability of the catalytic water-soluble system Cu(II)-PEI. After completion of the cycloaddition reaction in water at room temperature, the organic precipitate was recovered by simple filtration and then, additional phenylacetylene and benzyl azide were added to the remaining water containing Cu(II)-PEI for a further run. This process of filtration-refilling with organic reactants was performed until six times without any significant loss of efficiency and selectivity of the Cu(II)-PEI and it undergoes a gradual decrease from the sixth recycling as shown in the catalytic histogram of Fig. 6.



Fig. 6. Influence of the recycling on the efficiency of the Cu(II)-PEI species.

# **3.** Conclusions

In summary, the preparation, characterization and applicability of the copper(II)loaded hyperbranchedpolyethylenimine Cu(II)-PEI as a new efficient and selective water-soluble homogeneous catalyst in the CuAAC are reported. By using water as a benign solvent medium, 1,4-disubstituted-1,2,3-triazoles were obtained as waterinsoluble white precipitates in excellent yields and in a regioselective manner at room temperature in absence of any reducing agent or specific separation method. The recovery/reusability of the catalyst was performed until ten catalytic cycleswitha decrease in itscatalytic activity. These features make this protocol a reliable alternative for the green synthesis of 1,2,3-triazole-1,4-disubstituted compounds.

# 4. Experimental procedure

### 4.1. Materials and methods

Hyperbranchedpolyethylenimine (PEI10K;  $M_n = 1 \times 104 \text{ g mol}$ ,  $M_w/M_n = 2.5$ ,  $NH_2:NH:N = 33:40:27$ ) and copper(II) sulfate pentahydrate were purchased from Sigma-Aldrich. All other reagents were purchased from Sigma-Aldrich and Across and they were used as received without further purification. Anhydrous MgSO<sub>4</sub> was used for drying organic extracts and all volatiles were removed under reduced pressure. Benzoylated cellulose tubings (MWCO 1000) for dialysis were purchased from Sigma. The reactions were performed in the open air. All reaction mixtures were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F254). The plates were observed under UV-light at 254 nm. NMR analyses were carried out on a Brucker AC-400 MHz spectrometer (400 MHz for proton, 100 MHz for carbon) by using deuterated chloroform as solvent. The chemical shifts ( $\delta$ ) are expressed in ppm. The high-resolution mass spectra (HRMS) were recorded in the EI (70 eV) or FAB mode at the mass spectrometry service of the University of Valencia. FT-IR spectra (400-4000 cm<sup>-1</sup> range) were recorded on with a Nicolet 5700 FT-IR spectrometer. Melting points were determined using a Stuart melting point apparatus SMP3, employing the capillary tubes. EPR measurements were performed with a Qband (34 GHz) Bruker E-580 ELEXSYS spectrometer on a powder sample in the 4-300 K temperature range.

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# 4.2. Procedure for synthesis of the benzyl azide derivatives

A given benzyl bromide derivative (5.85 mmol) and  $NaN_3$  (17.5 mmol) were dissolved in 20 mL of DMF. The reaction mixture was stirred and protected from light for 20 hours at room temperature. After filtration, water was added to the filtrate and the product was extracted with dichloromethane three times. The organic phases were combined and dried over anhydrous MgSO<sub>4</sub> then filtered and solvents were evaporated under vacuum, affording a liquid product.

*Caution*! Azide salts are potentially explosive and should be handled with care and in small quantities.

# 4.3. Procedure for synthesis of the aryl azide derivative

The aniline derivative (13 mmol) was suspended in 80 mL hydrochloric acid (17 %) at room temperature and then ethanol was added until a clear solution was obtained. The solution was cooled to 0 °C and NaNO<sub>2</sub> (19.5 mmol) was added in small amounts. After stirring at 0 °C for 15-30 min. NaN<sub>3</sub> (19.5 mmol) was slowly added and the mixture was stirred for additional 2 h at room temperature. The reaction mixture was extracted with diethyl ether (3 x 80 mL) and the combined organic fractions were washed with a saturated NaHCO<sub>3</sub> solution (3 x 50 mL) and with brine (50 mL). After drying over MgSO<sub>4</sub>, the ether was removed under reduced pressure and the wanted azides were obtained without further purification.

# 4.4. General procedure for the synthesis of Cu(II)-PEI complex

The polyethylenimine PEI (1 g, 0.02 mol of amine groups) was dissolved in 30 mL of DMF and  $CuSO_4$ · 5H<sub>2</sub>O (0.005 mol, 1.2 g) was added and stirred for 30 min at room temperature, after evaporation of the solvent under vacuum, the complex was washed with hexane and diethyl ether and purified by dialysis (dialysis tubing,

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benzoylatedcellulose MWCO 1000) in MeOH over two days to afford Cu(II)-PEI as a waxy blue solid that was dried and then characterized by FT-IR on a NaCl film, UV-Visible spectroscopy, electronic paramagnetic resonance (EPR) and cyclic voltammetry.

4.5. General procedure for Cu(II)-PEI–catalyzed [3+2] cycloaddition reaction of azidealkyne derivatives

Azide (0.751 mmol), alkyne derivative (0.622 mmol) and 5 mol% of the Cu(II)-PEI complex were placed in a reaction tube and 5 mL of water was added. The reaction tube was placed on a magnetic stirrer and the reaction mixture was stirred for 24 h at room temperature. After completion of the reaction that can be visually monitored, due to the precipitation of the triazolic product, the mixture was filtered off and the white solid was dried. The recovered Cu(II)-PEI in the aqueous phase was reused at least ten times by adding the starting azide and alkyne reagents.

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# HIGHLIGHTS

- Copper-catalyzed azide-alkyne [3+2] cycloadditon reactions were efficiently achieved by using hyperbranched polyethylenimine loaded by a copper(II) precursor.

- The click of 1,2,3-triazoles was performed in a regioselective manner under ambient conditions in water in absence of any external reducing agent.

- The dendritic catalyst was recovered and reused with a decrease in its catalytic activity, evidencing its sustainable nature.

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