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PII: S0032-3861(17)30880-7

DOI: 10.1016/j.polymer.2017.09.018

Reference: JPOL 19987

To appear in: *Polymer*

Received Date: 19 July 2017

Revised Date: 8 September 2017

Accepted Date: 9 September 2017

Please cite this article as: Carmo dos Santos NA, Lorandi F, Badetti E, Wurst K, Isse AA, Gennaro A, Licini G, Zonta C, Tuning the reactivity and efficiency of copper catalysts for atom transfer radical polymerization by synthetic modification of tris(2-methylpyridyl)amine, *Polymer* (2017), doi: 10.1016/ j.polymer.2017.09.018.

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Tuning the reactivity and efficiency of copper catalysts for atom transfer radical polymerization by synthetic modification of tris(2-methylpyridyl)amine

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Keywords: Tris(2-methylpyridyl)amine ligand, Atom Transfer Radical Polymerization, catalyst activity tuning, electrochemically mediated polymerization, controlled aqueous polymerizations

Abstract

Copper complexes bearing ligands based on tris(2-methylpyridyl)amine (TPMA) are leading catalysts in atom transfer radical polymerization (ATRP). In recent years, the TPMA structure has been finely modified to enhance the catalytic activity of the corresponding Cu complex. In this study, we report the synthesis of eight novel copper TMPA complexes, and the evaluation of the catalytic activity for electrochemically mediated ATRP in both organic and aqueous media. The TPMA skeleton was modified by inserting differently *m*-functionalised phenyl substituents. Complete characterizations and electrochemical investigations were performed to define the structural and redox properties of the new complexes and compare them to the archetype

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Cu/TPMA. Well-controlled polymerizations of some hydrophobic, hydrophilic and acidic monomers are presented, with conversions > 80%, low dispersity and predetermined molecular weights, thus confirming that these compounds are suitable ATRP catalysts for different systems.

1. Introduction

Over the past years, atom transfer radical polymerization (ATRP) strongly impacted the world of polymer sciences thanks to its capability to generate macromolecules with predictable architectures, functionalities and compositions [1-3]. This versatile process was successfully applied to a large variety of monomers [4], showing great flexibility towards solvents, functional groups and potential impurities. ATRP is a controlled radical polymerization technique catalysed by transition metal complexes, mainly copper with polyamine ligands. The process is initiated by the transfer of a halogen atom from an alkyl halide initiator (R-X) to the active form of the catalyst, $[Cu^{I}L]^{+}$. This generates a free radical and the metal complex at a higher oxidation state, $[XCu^{II}L]^+$ (Scheme 1) [5,6]. The radical propagates for a short period, adding only to few monomer units, before it is converted back to a dormant state (P_n-X) by a deactivation reaction with $[XCu^{II}L]^+$. ATRP equilibrium is strongly shifted towards the dormant species [7], so that the concentration of propagating radicals is very low and radical-radical termination events are predominantly suppressed. Therefore, the key-feature of the process is the continuous activation-(propagation)/fast deactivation cycle, which enables concurrent growth of all chains and hence very low molecular weight dispersity ($M_w/M_n < 1.5$).

$$R-X + [CuIL]+ \xrightarrow{k_a} R^{+} + [X-CuIIL]^{+}$$

Scheme 1. General ATRP mechanism.

The catalyst plays a fundamental role, regulating the equilibrium between dormant and active species along the whole process. A considerable disadvantage of ATRP, as it was originally conceived, was the large amount of copper catalyst needed. Recently, several methods using low-ppm levels of copper catalysts have been developed. These include activators re-generated by electron transfer (ARGET) ATRP [8,9], initiators for continuous activator regeneration (ICAR) ATRP [9,10], supplemental activator and reducing agent (SARA) ATRP [11] also known as SET-LRP [12], photochemically mediated ATRP [13,14] and electrochemically mediated ATRP (*e*ATRP) [15-18].

Besides these advanced techniques, the quest to decrease the catalyst loading led to the synthesis of novel ligands for the preparation of more active copper catalysts. Copper complexes with ligands based on tris(2-methylpyridyl)amine (TPMA) are among the most active catalysts in ATRP [19-21]. In particular, Cu/TPMA is the best performing catalyst in aqueous media [17]; it is also a fundamental catalyst in dispersed media combined with anionic surfactants [22]. The reactivity of ATRP catalysts can be directly related to the standard reduction potential (E°) of the Cu(II)/Cu(I) couple. Both the activation rate constant and the equilibrium constant of ATRP increase by enhancing the reducing power of the catalyst, *i.e.* decreasing E° [21,23]. In this context, the ligand plays a fundamental role in regulating the catalyst activity; it can modify the charge density on the metallic centre, influencing the relative stability of Cu(II) and Cu(I). Therefore, the ligand structure can be modified in order to tune the electronic properties of the metallic

centre. Copper complexes with TPMA bearing methyl and methoxy groups on one or more pyridine rings have been recently prepared to enhance catalyst activity in ATRP [19,20]. However, catalysts with extremely high activity are not necessarily required and can be even detrimental in particular environments, like in the presence of water, which dramatically increases the activity of traditional Cu complexes [15,24]. In fact, one of the major drawbacks to controlling aqueous ATRP has been identified as high $K_{\text{ATRP}} = k_{\text{act}}/k_{\text{deact}}$, resulting from the extremely fast activation, combined with low stability of [XCu^{II}L]⁺ deactivators [16,17,25]. More important in aqueous media is the stability of the catalyst over a broad range of pH, a requirement that is not fulfilled by many aliphatic ligands, thus TPMA and its analogues are generally used [15,22,26,27].

In this study, we report eight novel TPMA copper complexes in which the skeleton has been modified by adding functionalised phenyl substituents. The redox properties of these complexes, in the absence and presence of halide ions, were analysed by cyclic voltammetry and compared with the unmodified TPMA system, henceforth referred to as **TPMA**, in order to predict their reactivity in *e*ATRP systems. Among the advanced ATRP techniques that use low-ppm levels of catalyst, *e*ATRP is receiving a growing interest, mainly because it allows to gain a deep understanding of the process besides introducing additional tools for control [28]. Herein, we used *e*ATRP on various monomers with [Cu^{II}L]²⁺ as catalyst, where L is **TPMA** or one of our modified ligands. By comparing redox and catalytic features, it was possible to identify systems in which phenyl-substitution can be successful and even beneficial.

2. Materials and Methods

2.1. Chemicals

Acetonitrile (VWR) was distilled over CaH₂ and stored under N₂. Milli-Q ultrapure water was used to prepare aqueous solutions. Methyl methacrylate (MMA, Sigma-Aldrich, 99%), oligo(ethylene glycol) methyl ether methacrylate (OEOMA, Sigma-Aldrich, M_n = 500) were purified by passing through a column filled with active basic aluminium oxide (Al₂O₃, VWR chemicals) to remove polymerization inhibitors. Methacrylic acid (MAA, Sigma-Aldrich, 99%) was distilled through a 10 cm Vigreux column to remove polymerization inhibitors. Tetraethylammonium tetrafluoroborate ((C₂H₅)₄NBF₄, Alfa Aesar, 99%), used as supporting electrolyte, was recrystallized from ethanol and dried in a vacuum oven at 70 °C for 48 h. Tetraethylammonium bromide ((C₂H₅)₄NBr, Sigma-Aldrich, 99%) and tetraethylammonium chloride ((C₂H₅)₄NCl, Sigma-Aldrich, \geq 98%), used as source of halide ions, were recrystallized from ethanol and ethanol/acetone (2/1 v/v), respectively, and dried at 70 °C under vacuum for 48 h. All other commercial products were used without further purification.

2.2. Experimental techniques

¹H and ¹³C{¹H} NMR spectra were recorded at 301 K on a Bruker AC-400, AC-300, and AC-200 MHz instruments. The ¹H NMR spectra were referenced to the solvent residual peak of MeOD-d₄ (3.31 ppm) or CD₃CN-d₃ (1.94 ppm); the ¹³C NMR spectra (50 MHz) were referenced to MeOD (49.00 \pm 0.02 ppm) or CD₃CN peaks (1.32 \pm 0.02 and 118.26 \pm 0.02 ppm). Monomer conversion was determined by ¹H NMR at room temperature. Spectra of samples collected in organic solvents were recorded in CDCl₃, whereas D₂O was used for water-soluble monomers. Cyclic Voltammetry (CV) and polymerization experiments were carried out in a three-electrode cell by means of an Autolab PGSTAT 30 potentiostat/galvanostat (EcoChemie, The Netherlands) run by a PC with Autolab GPES 4.9 software. In CV experiments, a Pt ring was used as counter electrode, whereas the working electrode was a glassy carbon (GC) disk, fabricated from a 3 mm diameter GC rod (Tokai GC-20). Before each experiment, the GC surface was cleaned by polishing with a 0.25-µm diamond paste, followed by ultrasonic rinsing in ethanol for 5 min. In eATRP experiments, a Pt mesh and a Pt foil were used as working and counter electrodes, respectively. The working electrode was electrochemically activated by cycling the potential between -0.7 and 1 V vs. Hg/Hg₂SO₄ in 0.5 M H₂SO₄, for 30 min at a scan rate of 0.05 V/s. The counter electrode was separated from the cathodic compartment through a glass frit and a methylcellulose gel saturated with (C₂H₅)₄NBF₄. In aqueous media, the reference electrode was a saturated calomel electrode (SCE), whereas Ag|AgI|0.1 M n-Bu₄NI in DMF was used as a reference electrode in organic solvents. In the latter case, the reference electrode was calibrated versus the ferrocenium/ferrocene couple (Fc⁺/Fc) after each experiment and potentials were converted to the SCE scale by using the known values of $E^{\circ}(Fc^+/Fc)$ vs. SCE: -0.390 in CH₃CN and 0.476 V in DMF [29]. During electrolysis, the cathodic compartment was maintained under vigorous magnetic stirring and Ar atmosphere. The cell had a double wall jacket through which water was circulated from a thermostated bath (Thermo Scientific, HAAKE SC100), to keep the temperature constant at 25 °C. Activation rate constants were measured by means of a Rotating Disk Electrode, following a procedure previously reported in full details [5,6]. During polymerizations, samples were withdrawn periodically and analysed by GPC to determine number average molecular weight (M_n) and dispersity (M_w/M_n) . The GPC instrument (Agilent 1260 Infinity) was equipped with

PLGel Columns and a refractive index detector. The mobile phase was either THF (PMMA analysis) or DMF containing 1% v/v triethylamine and 1% v/v glacial acetic acid for the analysis of POEOMA. The flow rate was 1 mL/min, and the columns and detector were thermostated at 70 °C and 50 °C, respectively for POEOMA, and at 35 °C for PMMA. The column system was calibrated with 12 linear PMMA ($M_n = 634-1944000$). GPC analysis of polymethacrylic acid was carried out on PL aquagel-OH columns at 30 °C; the mobile phase was aqueous 0.1 M Na₂HPO₄ at a flow rate of 1 mL/min.

Ligands structures were characterized by ESI-MS experiments, carried out in positive mode with an Agilent Technologies LC/MSD Trap SL AGILENT instrument. The mobile phase was either methanol or acetonitrile. MS peaks are reported as monoisotopic mass. Microanalyses were performed with a Flash 2000 Thermo Scientific Analyser.

X-ray analysis of each structure was performed, and supplementary crystallographic data were deposited as CCDC-1542046-49 (**2a** 1542046, **2d** 1542047, **3a** 1542048 and **3c** 1542049). Copies of the data can be obtained, free of charge, at the Cambridge Crystallographic Data Centre.

2.3. General procedure of eATRP

All electrodes, electrolyte, solvent and reagents, except the initiator RX, were introduced into the cell, and thermostated at 25 °C. After degassing with Ar for 20 min, cyclic voltammetry of $[XCu^{II}L]^+$ was recorded to measure the standard reduction potential of the catalyst and to select the suitable E_{app} value. The initiator was then added and the cell was carefully degassed for 20 min. Last, the selected potential was applied, under continuous vigorous magnetic stirring. Samples were withdrawn periodically to determine polymer molecular weight and conversion.

2.4. General synthetic procedures of copper complexes

0.25 mmol of ligand **1a-d** were dissolved in anhydrous acetonitrile (15 mL) and 43 mg (0.25 mmol) of the desired copper salt ($Cu(ClO_4)_2 \bullet 6H_2O$ or $CuCl_2 \bullet 2H_2O$) were added. The solution was left at room temperature for 15 min, then diethyl ether was added to give a precipitate that was filtered off. The residual solvent was then removed under reduced pressure to give the desired copper complex. **Caution!** Perchlorate salts of metal complexes with organic ligands are potentially explosive. They should be handled in small quantity and with caution.

2*a* Dark blue crystal (85%). IR (KBr, cm⁻¹): 3057, 2333, 1605, 1449, 1074, 769, 619. ESI+ MS (m/z) Calc. $C_{24}H_{22}N_4CuClO_4$ 528.1, Found 528.0 (M⁺). Elemental analysis Calc. $C_{24}H_{22}N_4Cu$. 2 ClO₄. CH₃CN: C= 46.61 %, H = 3.76 %, N = 10.45 %, Found: C =46.25 %, H = 3.93 %, N = 10.45 %.

2b Dark green solid (97%). IR (KBr, cm⁻¹): 3482, 2353, 1693, 1606, 1448, 1172, 776, 622. ESI+ MS (m/z) Calc. C₂₅H₂₂N₄CuClO₅ 556.1, Found 556.1 (M⁺). Elemental analysis Calc. C₂₅H₂₂N₄Cu. 2 ClO₄. 6 H₂O: C= 45.7 %, H = 3.38 %, N = 8.53 %, Found: C = 45.26 %, H = 3.66 %, N = 8.79 %.

2c Blue solid (95%). IR (KBr, cm⁻¹): 3357, 2354, 1660, 1610, 1572, 1442, 1082, 764, 620. ESI+ MS (m/z) Calc. $C_{25}H_{23}N_5CuClO_5$ 571.1, Found 571.0 (M⁺). Elemental analysis Calc. $C_{25}H_{23}N_5OCu$. 2 ClO₄. 3H₂O: C= 41.36 %, H = 4.03 %, N = 9.65 %, Found: C = 41.71 %, H = 3.60 %, N = 9.98 %.

2*d* Dark blue solid (80%). IR (KBr, cm⁻¹): 3467, 3086, 1601, 1449, 1094, 786, 619. ESI+ MS (m/z) Calc. C₂₅H₂₄N₄CuClO₅ 558.1, Found 558.0 (M⁺). Elemental analysis Calc.

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C₂₅H₂₄N₄OCu. 2 ClO₄. CH₃CN: C= 46.33 %, H = 3.89 %, N = 10.01 %, Found: C = 46.07 %, H = 4.07 %, N = 10.27 %.

3a Green crystals (87%). IR (KBr, cm⁻¹): 1583, 1445, 765, 692. ESI+ MS (m/z) Calc. C₂₄H₂₂N₄CuCl 464.1, Found 464.1 (M+). Elemental analysis Calc. C₂₄H₂₂N₄CuCl₂: C= 57.55 %, H = 4.43 %, N = 11.19 %, Found: C = 57.82 %, H = 4.59 %, N = 11.42 %.

3b Green solid (89%). IR (KBr, cm⁻¹): 3401, 3065, 1662, 1573, 1448, 801, 771. MS (m/z) ESI+ MS (m/z) Calc. C₂₅H₂₂N₄OCuCl 492.1, Found 492.1 (M⁺). Elemental analysis Calc. C₂₅H₂₂N₄OCuCl₂. CH₃CN: C= 56.77 %, H = 4.19 %, N = 10.59 %, Found: C =55.97 %, H = 4.27 %, N = 10.57 %.

3c Light green needle shape crystal (93%). IR (KBr, cm⁻¹): 3404, 3064, 2353, 1601, 1439, 1382, 763. ESI+ MS (m/z) Calc. $C_{25}H_{23}N_5OCuCl$ 507.1, Found 507.0 (M⁺). Elemental analysis Calc. $C_{25}H_{23}N_5OCuCl_2$. CH₃CN: C= 55.44 %, H = 4.48 %, N = 14.37 %, Found: C = 55.54 %, H = 4.52 %, N = 14.57 %.

3d Dark green crystal (85%). IR (KBr, cm⁻¹): 3382, 3020, 2915, 1589, 1439, 1288, 1186, 1005, 799. ESI+ MS (m/z) Calc. $C_{25}H_{24}N_4OCuCl$ 494.1, Found 494.0(M⁺). Elemental analysis Calc. $C_{25}H_{24}N_4OCuCl_2$: C= 56.56 %, H = 4.56 %, N = 10.55 %, Found: C = 56.33 %, H = 4.78 %, N = 10.72 %.

3. Results and discussion

Tris(2-methylpyridyl)amine complexes are widely used in catalysis and molecular recognition. This is due to their polydentate nature, which allows the formation of stable metal complexes also under turnover conditions. In the recent years, we have been interested in the study of the catalytic and molecular recognition properties of this class of

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complexes [30-33]. In particular, Co(II) complexes in which the ligand bears different functional groups have been synthesized and studied as hydrogen evolving catalysts, in light-assisted conditions [34].



Scheme 2. General synthetic procedures for compounds 2a-d and 3a-d.

The initial findings on the catalytic properties of these newly developed systems have driven our interest to study eATRP activity of a series of Cu(II) complexes. Our investigation was directed to evaluate if the phenyl substitution and/or the presence of extra functionalities in the ligand backbone were affecting the catalytic properties of the complexes. This goal has been achieved by i) synthetizing and studying the Cu(II) coordination chemistry of a series of ligands having different functionalities, ii) studying their electrochemistry in solution and iii) performing eATRP in organic and aqueous solvents.

3.1. Coordination Chemistry

Ligands **1a-d**, as well as the corresponding copper complexes **2a-d** and **3a-d** (Scheme 2), have been prepared according to a recently reported methodology [34]. The method consists in the synthesis of a bromo derivative *via* reductive amination of commercially available 6-bromo-2-pyridinecarboxaldehyde and di(2-picolyl)amine, followed by a Suzuki coupling with appropriate boronic acid. The general procedure for the synthesis of

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Cu(II) complexes requires the mixing of an equimolar amount of copper salt with the corresponding ligand **1a-d** in acetonitrile. The solution is stirred at room temperature for 10 min and the desired compounds are obtained as crystalline powders or by recrystallization with diethyl ether.



= Cl

Fig. 1. X-ray crystal structures of complexes 2a,d and 3a,c.

Table 1

Thermodynamic data for Cu(II) and Cu(I) complexes in $CH_3CN + 0.1 \text{ M} (C_2H_5)_4 \text{NBF}_4$ at 25 °C.

			[Cu ^{II} L]	2+ a	[ClC	u ^{II} L] ^{+ b}	[BrCu ^{II} L] ^{+ c}			
Entry	L	R	E° (V vs. SCE)	$\beta^{II} \beta^{Id}$	E^{\bullet} (V vs. SCE) $K^{\rm II}_{\rm Cl}/K^{\rm I}_{\rm Cl}^{\rm e}$	E° (V vs. SCE)	$K^{II}_{Br}/K^{I}_{Br}^{e}$		
1	_f	-	1.056				X			
2	TPMA	-	-0.019	1.49×10 ¹⁸	-0.363	6.53×10 ⁵	-0.282	2.79×10 ⁴		
3	1a	Н	0.043	1.33×10 ¹⁷	-0.197	1.14×10 ⁴	-0.130	8.40×10 ²		
4	1b	СНО	0.071	4.48×10 ¹⁶	-0.203	4.28×10 ⁴	-0.157	7.15×10 ³		
5	1c	CONH ₂	0.039	1.56×10 ¹⁷	-0.218	2.21×10^{4}	-0.136	9.08×10 ²		
6	1d	CH ₂ OH	0.045	1.23×10 ¹⁷	-0.200	1.39×10^{4}	-0.131	9.44×10^{2}		

^a Obtained by dissolving crystalline complexes in acetonitrile. ^b Obtained by dissolving crystalline complexes **2a-d** in acetonitrile, followed by the addition of 2 equivalents of $(C_2H_5)_4NCl$. ^c Obtained by dissolving crystalline complexes **2a-d** in acetonitrile, followed by the addition of 2 equivalents of $(C_2H_5)_4NBr$. ^d β^{II} and β^{I} are the stability constants of $[Cu^{II}L]^{2+}$ and $[Cu^{I}L]^{+}$, respectively. ^e K^{II}_X and K^{I}_X are the association constants of X^- with $[Cu^{II}L]^{2+}$ and $[Cu^{I}L]^{+}$, respectively. ^fNo added ligand, E^{\bullet} of $Cu^{II}(OTf)_2$ taken from ref. 36.

The obtained complexes have been characterized by ESI-MS, FT-IR spectroscopy and/or elemental analysis, confirming the purity of the desired compounds (see supporting information). Among the different structures, it was possible to obtain crystals suitable for X-ray diffraction of complexes **2a,d** and **3a,c**. All the monocationic structures (Fig. 1) show a distinctive Jahn-Teller effect with a strong distorted octahedral coordination for the Cu(II) centre. The four short bonds of **2a,d** and **3a,c**, arranged in a square planar manner, come from the amino group N(1) in the range between 203 and 206 pm, the two unsubstituted pyridine moieties N(3), N(4) with bond lengths between 197 and 202 pm and finally from acetonitrile N(5) at **2a,d** with equal distances of 198 pm and Cl anions at

3a,c around 225 pm, respectively. The elongated bonds at complexes **2a** and **2d** (N(2): 234, O(1): 281 and N(2): 249, O(2): 254 pm) are comparable to well described Cu(II) complexes of pentadentate bispidine ligands with two amino groups and three pyridine moieties, and a coordinated acetonitrile [35]. The molecules of **3a,c** form a dimer, whereas the chloride anions generate additional elongated bonds to the other Cu(II) centre with lengths of 295 at **3c** and 328 pm at **3a**. The distances of the nitrogen atoms are elongated to 245 and 250 pm (N(2) and N(7)) at **3c** and 252 pm at N(2) of **3a**. The dimerization could be favoured by additive π - π interactions between the pyridine rings with carbon-carbon distances of 342 (**3c**) and 354 pm at (**3a**).

It should be noted that while the reported complexes display octahedral geometries in the solid state, and in two cases are dinuclear, previous solution studies of related complexes suggest a monomeric character and C_3 trigonal-bypiramidal symmetry [20].

3.2. Cyclic voltammetry of copper complexes

The redox properties of the overall complexes were investigated in acetonitrile by cyclic voltammetry. Examples of typical voltammetric pattern for binary [Cu^{II}L]²⁺ and ternary [XCu^{II}L]⁺ complexes are reported in Fig. 2. A reversible peak couple, corresponding to one electron transfer was observed for each complex.

$$[Cu^{II}L]^{2+} + e^{-} \rightleftharpoons [Cu^{I}L]^{+}$$
(1)

$$[XCu^{II}L]^{+} + e^{-} \Longrightarrow [XCu^{I}L]$$
(2)

The peak-to-peak separation, ΔE_p , was greater than the typical value for a fast or Nernstian electron transfer ($\Delta E_p = 60 \text{ mV}$) and increased with the scan rate. These results agree with previous reports on the electrochemical behaviour of copper-amine complexes employed as catalysts for ATRP, confirming that electron transfer is accompanied by significant reorganizations [23]. The standard potential (E^{Θ}) of the Cu(II)/Cu(I) couple was determined as $E^{\Theta} \approx E_{1/2} = (E_{pc} + E_{pa})/2$, where E_{pc} and E_{pa} are the cathodic and anodic peak potentials, respectively. The average of $E_{1/2}$ values measured with scan rates ranging from 0.02 V/s to 0.2 V/s is reported in **Table 1** as an estimate of E^{Θ} for each complex.

As reported in Fig. 2a and **Table 1**, small differences on E° values were observed within the class of compounds formed by Cu(II) and ligands **1a-d**. E° is weakly affected by the substituent on the phenyl ring, probably because of the large distance separating it from the metallic centre. Crystal structures (Fig. 1) support this statement, evidencing that the biarylic system can rotate, increasing the distance between the substituent and the metal.

Although the substituent effect is small, E° of these compounds is 58-90 mV more positive than the redox potential of $[Cu^{II}TPMA]^{2+}$. It appears that the presence of the phenyl ring significantly decreases the charge density on the metal centre, making it more easily reducible. The reactivity of Cu(I) complexes with these ligands is also expected to be smaller in comparison to $[Cu^{I}TPMA]^{+}$.



Fig. 2. Cyclic voltammetry of 1 mM Cu(II) complexes in $CH_3CN + 0.1$ M (C_2H_5)₄NBF₄, recorded on a GC electrode at a scan rate of 100 mV s⁻¹.

The relative stability of Cu(II) and Cu(I) can be calculated from the standard potentials of $[Cu^{II}L]^{2+}/[Cu^{I}L]^{+}$ and solvated Cu^{2+}/Cu^{+} [36]:

$$\ln \frac{\beta^{\rm II}}{\beta^{\rm I}} = \frac{F}{RT} \left(E^{\Theta}_{\rm Cu^{2+}/\rm Cu^{+}} - E^{\Theta}_{\rm [Cu^{\rm II}\rm L]^{2+}/\rm [Cu^{\rm I}\rm L]^{+}} \right)$$
(3)

where β^{I} and β^{II} are the stability constants of $[Cu^{I}L]^{+}$ and $[Cu^{II}L]^{2+}$. Calculated β^{II}/β^{I} values are reported in **Table 1**. As previously found for similar copper-amine complexes [36], $[Cu^{II}L]^{2+}$ is much more stable than $[Cu^{I}L]^{+}$. It is however important to stress that β^{II}/β^{I} decreased by about one order of magnitude when ligands **1a-d** replaced **TPMA**. As

a consequence of enhanced Cu(I) stabilization, a reduced reactivity of $[Cu^{I}L]^{+}$ (L = 1a-d) towards RX activation is anticipated, compared to $[Cu^{I}TPMA]^{+}$.

When halide ions were added to a solution of $[Cu^{II}L]^{2+}$, ternary complexes $[XCu^{II}L]^+$ were readily formed. Cyclic voltammetry of these compounds (Fig. 2b) showed a negative shift of the Cu(II)/Cu(I) peak couple (Eq. 2). E° values calculated from the peak potentials as previously described are reported in **Table 1**. The trend of E° values is quite similar to that observed for the binary complexes: all $[ClCu^{II}L]^+$ complexes have similar E° values that are 145-163 mV more positive than E° of $[ClCu^{II}TPMA]^+$. Analogously, E° values of $[BrCu^{II}L]^+$ are 125-152 mV more positive than E° of $[BrCu^{II}TPMA]^+$. Nonetheless, the standard potentials of $[XCu^{II}L]^+$ are more negative (by 0.18-0.34 V) than those of the corresponding binary complexes $[Cu^{II}L]^{2+}$. This negative shift of E° can be used to determine the relative affinity of $[Cu^{II}L]^{2+}$ and $[Cu^{IL}]^+$ for halide ions:

$$\ln \frac{K_{\rm X}^{\rm II}}{K_{\rm X}^{\rm I}} = \frac{F}{RT} \left(E_{\rm [Cu^{\rm II}L]^{2+}/[Cu^{\rm I}L]^{+}} - E_{\rm [XCu^{\rm II}L]^{+}/[XCu^{\rm I}L]}^{\rm e} \right)$$
(4)

where K_X^{I} and K_X^{II} are the equilibrium constants of X⁻ binding to $[Cu^IL]^+$ and $[Cu^{II}L]^{2+}$, respectively. The calculated values of K_X^{II}/K_X^{II} are in the range from 10³ to 4×10⁴ (**Table 1**). With all ligands **1a-d**, Cu(II) shows much better affinity than Cu(I) for halide ions. This is a fundamental prerequisite for a good ATRP catalyst: Cu(II) must be predominantly present in the deactivator form, $[XCu^{II}L]^+$, whereas Cu(I) is desired to give a less stable $[XCu^IL]$ complex that readily dissociates to regenerate the activator $[Cu^IL]^+$ [5, 37].

3.3. General considerations on copper-catalysed electrochemically mediated ATRP

As shown in **Table 1** the new complexes have similar E^{Θ} values that are all more positive than E° of the corresponding **TPMA**-based complexes. Of particular relevance to ATRP are the redox properties of the ternary complexes [ClCu^{II}L]⁺ and [BrCu^{II}L]⁺, since usually they are the predominant species present in solution under typical ATRP conditions [36]. E° of these complexes is only slightly affected by the substituent on the phenyl ring with overall variations of 21 mV for chlorides and 27 mV for bromides. On the other hand, it has recently been shown that the catalyst activity increases with decreasing standard reduction potential of $[XCu^{II}L]^+$ [21, 37]. It is therefore reasonable to assume that the new complexes have comparable reactivity and are less active than the copper complex with unmodified **TPMA**. For this reason, all polymerizations were performed with L = 1a, chosen as a model catalyst for the new series of copper complexes. Electrochemically mediated atom transfer radical polymerization (eATRP) of different monomers was tested in both organic solvents and water. The experimental conditions and the measured E° values of the catalyst in different solvent/monomer mixtures are reported in Table 2. All eATRP experiments were performed under potentiostatic control, setting E_{app} to tune the reactivity of the catalyst according to the particular system.

Table 2

Entry	Solvent	Monomer ^b	L	X	E^{\bullet}	RX	E_{app}	t	Conv.	Q	$k_{ m p}^{ m app}$	M _n	$M_{\rm n,th}$	$M_{\rm w}/M_{\rm n}$
					$(V)^{c}$		$(V)^{c}$	(h)	(%)	(C)	$(h^{-1})^d$	10-3	10-3	
1	CH ₃ CN ^e	MA (50%)	1a	Br⁻	-0.030	MBiB	-0.09	6	0	-	-	-	-	-
2	DMF ^e	MA (50%)	1a	Br⁻	-0.091	MBiB	-0.15	6	0	-		-	-	-
3	DMF ^e	MA (50%)	TPMA	Br⁻	-0.196	MBiB	-0.26	6	92	4.43	0.40	51.7	43.8	1.07
4	DMF ^e	MMA (50%)	1a	Br⁻	-0.134	EBPA	-0.19	14	83	8.71	0.12	44.6	38.7	1.21
5	DMF ^e	MMA (50%)	TPMA	Br⁻	-0.214	EBPA	-0.15	12	77	8.93	0.11	45.9	36.0	1.12
6	H_2O	OEOMA (20%)	1a	Br⁻	-0.133	HEBiB	-0.07	3	88	0.77	0.84	90.9	96.6	1.16
$7^{\rm f}$	H_2O	OEOMA (10%)	TPMA	Br⁻	-0.260	HEBiB	-0.20	4	95	3.10		63.0	51.0	1.17
8	H_2O	MAA $(10\%)^{g}$	1a	Cl	-0.120 ^h	BiBA	-0.18	5	81	3.56	0.35	21.4	13.9	1.49
9 ⁱ	H_2O	MAA $(10\%)^{g}$	TPMA	Cl	-0.120 ^h	BiBA	-0.18	4	96	3.20	0.84	18.0	16.8	1.42

Potentiostatic *e*ATRP of different monomers catalysed by $[XCu^{II}L]^+(L = 1a \text{ or TPMA}).^a$

^a General conditions: $C_{Cu^{2+}} = 10^{-3}$ M, T = 25 °C, $V_{tot} = 15$ mL, $C_M/C_{RX}/C_{Cu^{2+}}/C_L/C_X$ -: 555/1/0.1/0.1/0.2 (entries 1-3); 467/1/0.1/0.1/0.2 (entries 4-5); 225/1/0.5/0.5/50 (entry 6); 200/1/0.1/0.4/50 (entry 8). ^bVol%. ^cvs. SCE. ^dSlope of the ln(C_M^0/C_M) vs. time plot. ^e0.1 M (C₂H₅)₄NBF₄ as supporting electrolyte. ^fTaken from ref. [17]. ^gpH = 0.9 by addition of HCl. ^hCathodic peak potential, $E_{p,c}$ (irreversible voltammetric response). ⁱTaken from ref. [40].

3.4. eATRP in organic solvents

Polymerization of methyl acrylate (MA) in CH₃CN was unsuccessful: no polymer formation was observed after 6 h, even by using $E_{app} = E^{\Theta} - 60$ mV to enhance the amount of the activator, Cu(I). Indeed, this E_{app} value should generate in solution a concentration of Cu(I) that is 10-times higher than $C_{Cu^{II}}$, as can be derived from Equation 5, thus maximizing the extent of the activation process.

$$E_{\rm app} = E_{1/2} + \frac{RT}{F} \ln \frac{[\rm XCu^{II}L]^+}{[\rm XCu^{I}L]}$$
(5)

A similar result was obtained also in DMF, which usually accelerates ATRP with respect to CH₃CN [38]. In contrast, when **TPMA** was used as ligand (**Table 2**, entry 3) very high conversion was achieved in 6 h; the polymerization was well-controlled with linear firstorder kinetics and very low dispersity (Fig. S2-S3). A possible explanation for the failure of polymerization with the catalytic system Cu/**1a**/Br⁻ is the inefficient activation of the secondary alkyl bromide dormant species (R'CH(Br)C(O)OCH₃) by the activator complex [Cu¹L]⁺ (L = **1a**). This hypothesis is corroborated by activation rate constants (k_{act}) measured for the initiator methyl 2-bromoisobutyrate (MBiB) by [Cu¹L]⁺ in CH₃CN/MA (50% v/v). The obtained values were k_{act} = 1.1×10³ mol⁻¹dm³s⁻¹ for L = **TPMA** and 1.3×10⁻² mol⁻¹dm³s⁻¹ for L = **1a** (Fig. S1). It is noted that k_{act} depends on the structure of RX, increasing in the order primary < secondary alkyl halide of the same type of MBiB, therefore its activation rate constant is expected to be at least one order of magnitude lower than k_{act} of MBiB [21].

When $[Cu^{II}(1a)]^{2+}$ is used as catalyst, its reactivity toward the initiator is already low and it becomes even lower when propagating chains are converted to dormant species, P_n-X. The polymerization rate of ATRP, R_p , depends on several factors (Eq. 6) among which an important role is played by the ratio between the activation and deactivation rate constants, k_{act}/k_{deact} , that is K_{ATRP} :

$$R_{\rm p} = k_{\rm p}[M][P^{\bullet}] = k_{\rm p}[M]K_{\rm ATRP} \frac{[PX][Cu^{\rm I}L]^{+}}{[X - Cu^{\rm II}L]^{+}}$$
(6)

Both K_{ATRP} and k_{act} are generally at least one order of magnitude higher for methacrylates than for acrylates, mainly because of the higher stability of tertiary radicals arising from methacrylates than secondary radicals from acrylates. Therefore, a fourth eATRP experiment was run in DMF using methyl methacrylate (MMA) in place of MA and ethyl 1-phenyl-1-bromoacetate (EBPA) as initiator. Note that homopolymerization of MMA by *e*ATRP catalysed by Cu complexes has never been reported. So far, only the Fe(II)/Fe(III) redox couple was used as catalyst [39]. EBPA was selected as initiator because of its extremely high reactivity and proved suitability for methacrylate polymerizations [8]. This reaction yielded good results (Fig. 3 and Table 2, entry 4): linear kinetic plot and low dispersity indicated a well-controlled process, reaching 83% conversion in 14 h. Cu/TPMA also performed quite well for eATRP of MMA but the huge activity of [Cu^I**TPMA**]⁺ required a careful tuning of the applied potential to achieve a controlled polymerization under analogous conditions (supporting information). When E° - 60 mV was used, dispersity grew with time, reaching $M_w/M_n > 2$ after only 40% conversion. Poor control was still observed with $E_{app} = E^{\circ}$, which implies $C_{Cu^{I}} \approx C_{Cu^{II}}$, while $M_w/M_n = 1.12$ and linear first-order kinetics were obtained when the Cu^{II} to Cu^{II} ratio was reduced to ca. 0.1 by applying $E_{app} = E^{\circ} + 60$ mV (**Table 2**, Entry 5). In fact, molecular weights distribution depends on the amount of Cu^{II} deactivator, among several parameters, according to Equation 7 (where p is the conversion and $DP = C_{Monomer}^0 / C_{RX}^0$). Relatively high $C_{Cu^{II}}$ can help improve control over molecular weight distribution (*i.e.* lower $M_{\rm w}/M_{\rm n}$), particularly in the case of fast propagation (high $k_{\rm p}$) or slow deactivation (low k_{deact}). k_p of MMA at ambient temperature is quite low (*ca.* 300 M⁻¹ s⁻¹), however, $[Cu^{I}TPMA]^{+}$ is much more active than $[Cu^{I}1a]^{+}$, thus more radicals are generated and the

instantaneous amount of dormant chains, $C_{[P_nX]}$, is lower. Therefore, when L = 1a was used, it was not necessary to raise $C_{Cu^{II}}$, in contrast to the experiment with **TPMA**, whereby enhanced $C_{Cu^{II}}$ was needed to deactivate radicals and control the process.

$$\frac{M_{\rm w}}{M_{\rm n}} = 1 + \frac{1}{\rm DP} + \left(\frac{k_{\rm p} C_{\rm [P_{\rm n} X]}}{k_{\rm deact} C_{\rm [XCu^{\rm II}L]^+}}\right) \left(\frac{2}{p} - 1\right)$$
(7)

When Cu/**TPMA** was used, low dispersity was achieved at the expense of the polymerization rate, which decreased by increasing $C_{Cu^{II}}$ (Eq. 6), and the process was slightly slower than with L = **1a**. Moreover, measured MWs exceeded the theoretical values at high conversions, probably because of termination via radical coupling, as proved by a small shoulder at high MWs in the GPC traces (Fig. S6). A better accordance between experimental and theoretical MWs was observed with L = **1a**, despite the slightly higher dispersity, $M_w/M_n = 1.2$ (Fig. 3).



Fig. 3. *e*ATRP of MMA 50% v/v in DMF + 0.1 M (C_2H_5)₄NBF₄. [MMA]:[EBPA]:[Cu^{II}]:[Br⁻] = 467:1:0.1:0.2, L = **1a**, $E_{app} = E_{1/2} - 0.060$ V, $C_{Cu^{2+}} = 10^{-3}$ M, T = 25 °C, $V_{tot} = 15$ mL. a) First-order kinetic plot and b) molecular weights and dispersity evolution as function of conversion.

3.5. eATRP in aqueous media

Challenging features of ATRP in aqueous media include: *i*) very high activation rate leading to high concentration of radicals, *ii*) poor deactivation efficiency due to the facile dissociation of $[X-Cu^{II}L]^+$, *iii*) high tendency of Cu(I) species towards disproportionation, (iv) instability of the amine ligands in acidic media.

Recently, these problems have been overcome by using **TPMA** as ligand, in combination with the advantages of eATRP [17].

*e*ATRP of oligo(ethylene glycol) methyl ether methacrylate (OEOMA) was performed with $[Cu^{II}1a]^{2+}$ according to the guidelines defined for aqueous *e*ATRP: large X⁻ excess, low monomer percentage, and $E_{app} > E^{\Theta}$ [17]. The results are reported in Table 2, entry 6, and Fig. 4. Polymerization of OEOMA was well-controlled showing linear first-order kinetics and good agreement between experimental and theoretical molecular weights. The reaction reached 88% conversion in 3 h with very low dispersity ($M_w/M_n < 1.2$). The result well matches with that obtained using [Cu^{II}**TPMA**]²⁺ as catalyst (**Table 2**, entry 7): 95% conversion in 4 h with $M_w/M_n = 1.17$ [17]. Also notice that the amount of monomer used herein is twice as that of the previously reported electrosynthesis with [Cu^{II}**TPMA**]²⁺.

Very recently, aqueous *e*ATRP was successfully applied to methacrylic acid [40]. The harmful reaction preventing ATRP of this acidic monomer was identified as an intramolecular cyclization process, leading to the formation of a lactone, with the loss of chain-end functionalities. Low pH, excess of Cl⁻ instead of Br⁻, and $E_{app} < E^{\Theta}$ allowed to control the polymerization of MAA using **TPMA** as ligand. 96% conversion in 4 h and $M_w/M_n = 1.49$ were reported at pH = 0.9, [NaCl] = 0.3 M and $E_{app} = E^{\Theta} - 120$ mV (**Table 2**, entry 9). By replacing **TPMA** with **1a**, a comparable result was obtained with 83% conversion in 5 h and $M_w/M_n = 1.49$ (**Table 2**, entry 8 and Fig. 4).

Overall, the copper complex with 1a is a suitable catalyst for aqueous *e*ATRP, even in acidic conditions, providing a catalytic efficiency comparable to the one observed with copper/**TPMA** in identical conditions.





Fig. 4. *e*ATRP of OEOMA 20% v/v in $H_2O + 0.1$ M (C_2H_5)₄NBr (circles) and MAA 10% v/v in $H_2O + 0.1$ M NaCl (+HCl, pH = 0.9) (squares). a) Conversion and first-order kinetic plots and b) molecular weights and dispersity evolution with conversion. Polymerization conditions: **Table 1**, entries 6 and 8.

4. Conclusions

In summary, eight novel copper complexes with modified **TPMA** ligands were synthesized and fully characterized. Electrochemical studies have shown a small influence of the substituents in the phenyl ring on the redox properties of the catalyst and hence on its reactivity, the dominant effect being the electron-withdrawing nature of the phenyl substituent itself. The small influence of the substituents can be explained considering that the possible rotation of the biarylic system moves the substituents away from the metal centre.

Surprisingly, the presence of one phenyl ring on the TPMA backbone reduced significantly the activity of $[Cu^{I}L]^{+}$, while substituents on that ring had virtually no effect on catalyst activity. Nevertheless, the novel copper complexes are robust and suitable catalysts for *e*ATRP in organic solvents with reactive monomers such as methyl

methacrylate or in aqueous media. Indeed, PMMA with $M_n = 44600$ and $M_w/M_n = 1.21$ was obtained in DMF, while low dispersity POEOMA and poly(methacrylic acid) were produced in water reaching high conversions in less than 5 h. Although the new catalyts are less reactive than the parent TPMA complex, their lower catalytic activity may be exploited to gain easy control of extremely reactive systems, where the activation rate is not an issue.

Acknowledgements

Financial support from the University of Padova (PRAT CPDA150001 and CPDA153122, Progetto Attrezzature Scientifiche finalizzate alla Ricerca 2014) is gratefully acknowledged.

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Tuning the reactivity and efficiency of copper catalysts for atom transfer radical polymerization by synthetic modification of tris(2-methylpyridyl)amine

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Highlights

- TPMA modified with functionalized phenyl groups as ligand for Cu-mediated *e*ATRP.
- Crystallographic and electrochemical characterization of 8 new Cu complexes.
- Tuning the control over *e*ATRP of MMA with different ligands.
- Good performances of a new Cu catalyst in *e*ATRP of hydrophilic and acid monomers.