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Copper(II) gluconate (a non-toxic food supplement/dietary aid) as a precursor catalyst for effective photo-induced living radical polymerisation of acrylates

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Copper gluconate, is employed as a precursor catalyst for the photo-induced living radical polymerisation of acrylates. Optimised reaction conditions for efficient ligand transfer leads to well-defined polymers within 2 h with near quantitative conversions (> 95%), low dispersities (*Đ* ~ 1.16) and high end-group fidelity, as demonstrated by MALDI-ToF-MS. Additionally, in the presence of ppm concentrations of NaBr, similar degree of control could also be attained by facilitating ligand exchange, furnishing narrow dispersed polymers *(Đ* < 1.12*)*.

Controlled living radical polymerisation (CRP) techniques, including atom transfer radical polymerisation (ATRP),[1, 2] single electron transfer living radical polymerisation (SET-LRP),[3, 4] reversible addition–fragmentation chain transfer polymerisation (RAFT)[5] and nitroxide mediated radical polymerisation (NMP)[6] have received widespread interest due to the ability to regulate molecular weight, molecular weight distributions, gain sequence/architecture control and high end-group fidelity. Conventional transition metal polymerisation techniques, in particular ATRP and SET-LRP, exploit the reversible catalytic activation of alkyl halides initiators by Cu(I)Br or Cu(0) (in the form of copper wire or powder) respectively to allow propagation while the deactivating $CuBr_2$ species shift the reaction equilibrium towards the dormant species gaining control over the propagating radical concentration and limiting the amount of termination events.

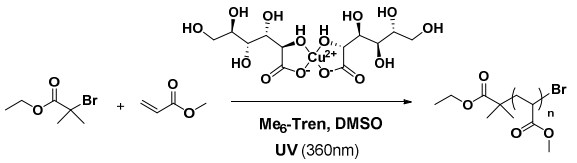
One of the main perceived drawbacks of the aforementioned techniques, is considered to be copper contamination of the products.[7] The presence of trace metal, is often heralded as a weakness, due to potential toxicity of "*heavy metals*", whilst we would argue organic ligands and residual monomers should be of more concern. It is noted that this concern is not restricted to polymerisation and the use of "*copper-free click*" reactions are also prevalent as a way of carrying out less toxic reactions.[8] A wide range of different protocols have been established with primary focus to minimize the catalyst loadings and to remove residual metals.[9-11] A diverse array of external stimuli,[12] including photochemical,[13-20] pressure[21] and electrochemical,[22] have been developed, with photochemical control exhibiting excellent results when combined with copper-mediated polymerisation.[23-31]

Although some heavy metals are indeed very toxic and poisonous, they are often essential for human life (*e.g.* Fe (haemoglobin), Co (vitamin B_{12}), Cu *etc.*).[32-35] Copper, is involved in various biological processes (hemoglobin formation, carbohydrate metabolism, the cross-linking of collagen, hair keratin, and the antioxidant defence mechanism *etc*.) while being incorporated into a number of metalloenzymes. Copper deficiency in humans, although relatively rare, is a known cause of hypochromic anaemia, leukopenia and various neurological manifestations.[36] Interestingly, the World Health Organization recommends a daily requirement of 0.6 mg per day with an estimated lethal dose in human adults of 10-20 g.[37, 38] Copper gluconate, the copper(II) salt of *D*-gluconic acid, is a widely used, commercially available dietary supplement, that can be exploited to metabolize copper and treat copper deficiency. Herein, we exploit this commercially available food supplement (Cu(II) gluconate) as a precursor catalyst for the photo-induced polymerisation of acrylates which is allowed to exchange with Me_6-Tren to form the active catalyst. This ligand was chosen as it has been shown to be very effective in this photo-mediated reaction. It is noted that depending on the application and levels of impurities it is often desirable to remove inorganic and organic impurities from products prior to use. In this polymerisation chemistry it is very often the monomer or the organic ligand that form the most toxic impurities in the products as opposed to the copper. In this work we seek to address this misconception about relative toxicity. We have recently demonstrated the use of a photo-process with copper(II) salts acting *via* a photoreduction and mechanistic details are given in our previous publications.[13, 31]

Initially, the solubility of copper gluconate in dimethyl sulfoxide (DMSO) was investigated. The commercially available tablet was ground into a fine powder and the reaction vessel was subsequently charged with methyl acrylate (MA), (DMSO), ethyl bromo isobutyrate (EBiB), 2% copper gluconate (approximately 200 mg tablet containing 1.1 mg copper(II)) and 12% Me_6-Tren.[13] A blurry solution immediately formed, suggesting that the copper gluconate and/or additives (stated bulking agents include calcium phosphate, cellulose and magnesium stearate) had limited solubility in this particular solvent. We are also keen to demonstrate polymerisation in the presence of multiple functional groups and thus the presence and effect of the formulating agents was of interest.[39] Despite these solubility issues, the polymerisation was allowed to proceed under UV irradiation (λ = 360 nm, Fig. S1, ESI) for 2 h yielding an uncontrolled polymer (96%, M_n = 5500 g mol^{-1}, $Đ$ = 2.30) (Table 1, entry 1, Fig. S2, ESI). To further investigate this result, commercial copper gluconate was employed, giving rise to an equally broad

dispersed polymer (98%, M_n = 5400 g mol^{-1}, $Đ$ = 1.80 after 2 h), while remaining partly insoluble (Table 1, entry 2, Fig. S3, ESI). There is a requirement for ligand exchange between the O-donor gluconate to *N*-donor ligands and a slow rate of the ligand exchange between the gluconate and Me_6-Tren could be responsible for the inefficient deactivation of the polymer chains. Upon stirring Me_6-Tren and copper gluconate for ~ 12 h, at ambient temperature, followed by the addition of both monomer and initiator and UV exposure for a further 2 h, 98% conversion was obtained with M_n = 5000 g mol^{-1} and an encouragingly slight reduction in the observed dispersity ($Đ$ = 1.50) (Table 1, entry 3, Fig. S4, ESI). Interestingly, when the pre-mixing took place for 2 weeks prior to polymerisation, a well-defined polymer (96%, M_n = 5500 g mol^{-1}, $Đ$ = 1.19, Fig. S5, ESI) was obtained (Table 1, entry 4), implying that when Me_6-Tren replaces the gluconate entirely, an efficient deactivation can be mediated. UV-Vis spectroscopy measurements were also performed. Upon addition of Me_6-Tren on the copper gluconate solution, an instantaneous change in UV was observed, resulting in identical absorbance characteristic peaks when compared with Me_6-Tren/$CuBr_2$ complex. No further change was monitored by UV within 2 weeks, despite the observed reduction in dispersity (Fig. S5c, ESI). Nevertheless, reduction in pre-mixing time scale to 1 week resulted in broad molecular weight distributions (97%, M_n = 5400 g mol^{-1}, $Đ$ = 1.38, Fig. S6, ESI) suggesting that the substitution needed significant time in order to reach the desired equilibrium.

Table 1: Photo-induced polymerisation of MA utilising copper gluconate as the catalyst precursor.



Entry	[M]:[I]:[Cu]:[L]	Time (h)	Conv[a]. (%)	$M_{n,th}$ (g mol^{-1})	$M_{n,sec}$[b] (g mol^{-1})	$Đ$
1	[50]:[1]:[0.02]:[0.12]	2	96	4300	5500	2.30
2[c]	[50]:[1]:[0.02]:[0.12]	2	98	4400	5400	1.80
3[d]	[50]:[1]:[0.02]:[0.12]	2	98	4400	5000	1.50
4[e]	[50]:[1]:[0.02]:[0.12]	2	96	4300	5500	1.19

[a] Measured by ^{1}H NMR; [b] $CHCl_3$ eluent, PMMA standards, [c] utilising pure copper gluconate, [d, e] premixing for 12 h and 2 weeks respectively, prior to polymerisation

In order to accelerate the ligand exchange rate, a solution of the pure gluconate (1 eq.) with Me_6-Tren (6 eq.) in DMSO was left under UV irradiation for ~ 2 h. Monomer and initiator were subsequently added in the polymerisation mixture yielding, within 2 h, a well-defined PMA (Table 2, 97%, M_n = 4900 g mol^{-1}, $Đ$ = 1.15, Fig. S7, ESI). Similar results were obtained when the food supplement was employed (98%, M_n = 5600 g mol^{-1}, $Đ$ = 1.16, Fig. S8, ESI), highlighting the potential of this protocol to operate in the presence of various chemical environments/impurities (Table 2). The high end group fidelity obtained during the polymerisation was confirmed by both ^{1}H NMR and MALDI-ToF unveiling a single mass distribution corresponding to bromo-terminated polymer chains (Fig. 1).

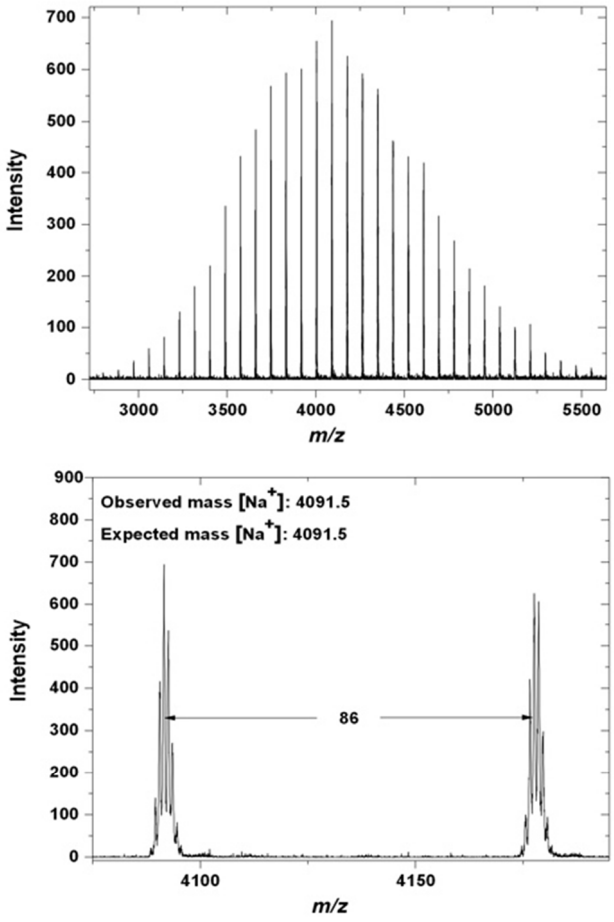


Fig. 1 MALDI-ToF-MS analysis of PMA obtained from the experiment [MA]:[EBiB]:[$Cu^{(II)}$]:[Me_6-Tren] = [50]:[1]:[0.02]:[0.12] in DMSO (50% *v/v*). The pre-mixed Cu/L solution was left under UV irradiation for 2 h prior to polymerisation.

In our previous work it has already been demonstrated that the temperature throughout the reaction fluctuates between 55 and 60 ^{o} C.[13] Consequently, we repeated polymerisations under UV irradiation utilising a cooling plate to maintain lower temperatures (~ 15 ^{o} C). After identical reaction times (2 h) 70% (M_n = 3900 g mol^{-1}, $Đ$ = 1.33, Fig. S9, ESI)) and 75% (M_n = 4200 g mol^{-1}, $Đ$ = 1.40, Fig. S10, ESI) conversions were obtained for pure gluconate and the food supplement respectively (Table 2), suggesting that light also mediates ligand exchange, however, not as effectively as when combined with heat. Conversely, under purely thermal conditions, (60^{o}C, no UV irradiation) well-defined polymers were attained in both cases (M_n = 4300 g mol^{-1}, $Đ$ = 1.18 for pure gluconate and M_n = 5200 g mol^{-1}, $Đ$ = 1.19 for the dietary supplement, Fig. S11-12, ESI) demonstrating that increased temperatures allows effective ligand exchange (Table 2).

Table 2: Optimised reaction conditions for the photo-induced polymerisation of methyl acrylate. Both formulated tablet and pure copper(II) gluconate used as a precursor to Me_6-Tren exchange.

	Conditions	Conv.[a] (%)	$M_{n,th}$ (g.mol^{-1})	$M_{n,SEC}$[b] (g.mol^{-1})	$Đ$
Tablet 	UV-Vis	98	4400	5600	1.16
	Cooling plate	75	3400	4200	1.40
	Heat 60 °C	97	4400	5200	1.19
	NaBr	99	4500	5400	1.15
Pure gluconate 	UV-Vis	97	4400	4900	1.15
	Cooling plate	70	3100	3900	1.33
	Heat 60 °C	95	4300	4300	1.18
	NaBr	98	4400	5100	1.12

For applications where elevated temperatures are undesirable, an alternative synthetic route was explored. The addition of ppm concentrations of NaBr in the reaction mixture,[40] gave rise to well-defined polymers without the need for elevated temperatures and /or pre-mixing protocols (Table 2). Near identical results were obtained for both the tablet (99%, M_n = 5400 g mol^{-1}, $Đ$ = 1.15, Fig. S13, ESI) and the pure copper gluconate (98%, M_n = 5100 g mol^{-1}, $Đ$ = 1.12, Fig. S14, ESI) with good correlation between the theoretical/experimental molecular weights and narrow molecular weight distributions. The excess bromide anion is able to promote ligand exchange presumably by coordinating to copper causing dissociation of a gluconate ligand.

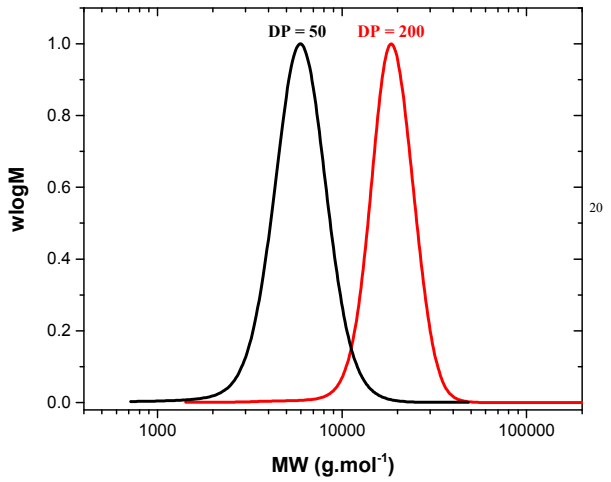


Fig. 2 SEC analysis of PMA with DP_n = 50, 200 prepared by photo-induced polymerisation utilising copper gluconate (supplement).

We were interested to assess whether the copper gluconate tablet could also support the synthesis of higher molecular weight polymers. In order to verify this, a higher degree of polymerisation (DP_n=200) was targeted. High conversions and narrow dispersity were attained within 2 h (95%, M_n = 20000 g mol^{-1}, $Đ$ = 1.09) (Fig. 2, Fig. S15, ESI). To further demonstrate the high end-group fidelity, *in situ* block copolymerisation of PMA (DP_n = 50, 96% in 2 h, M_n= 4400, $Đ$ = 1.13) with PEGA was attempted. Upon addition of a second aliquot of PEGA, a complete shift to higher molecular weight was evident by SEC, while the dispersity remained as narrow as 1.10 (DP_n = 15, 98% in 10 h, M_n= 11000) (Fig. 3, Fig. S16, ESI).

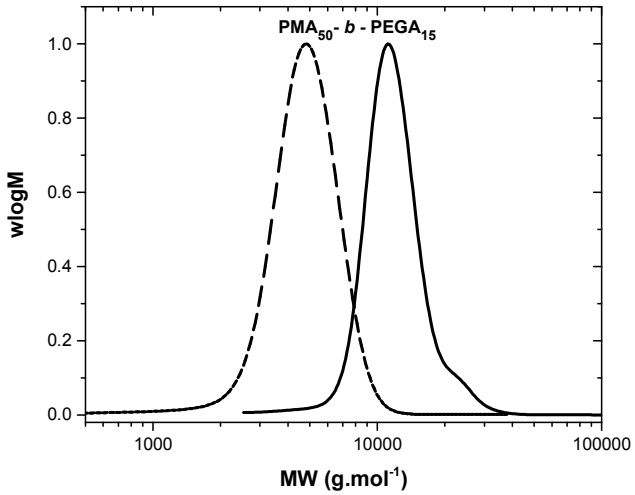


Fig. 3 *In situ* block copolymerisation from a PMA macroinitiator with PEGA. Initial conditions: [MA]:[EBiB]:[Cu^{II}(supplement)]:[Me_6-Tren]:[NaBr] = [50]:[1]:[0.02]:[0.12]:[0.04] in DMSO (50% *v/v*).

In summary, the photo-induced polymerisation of acrylates utilising copper(II) gluconate as a precursor catalyst has been investigated. Upon optimised conditions, narrow molecular weight distributions and near quantitative conversions were attained within 2 h, while the high-end group fidelity was exemplified by MALDI-ToF-MS and *in situ* block copolymerisation. The need for product purification and removal of inorganic and organic catalysts as well as residual monomer must be taken on a case by case basis. Although some applications may preclude the use of copper or other metallic catalysts these catalysts should not be ruled out in favour of non-metallic catalysts just on the basis of being "*metal-free*". .

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Notes and references

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†Electronic Supplementary Information (ESI) available. Synthesis details, NMR spectra, SEC chromatograms, MALDI spectra and crystallographic details. CCDC 1038878.

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