Original citation:
Nikolaou, Vasiliki, Simula, Alexandre, Droesbeke, Martijn, Risangud, Nuttapol, Anastasaki, Athina, Kempe, Kristian, Wilson, Paul and Haddleton, David M.. (2016) Polymerisation of 2-acrylamido-2-methylpropane sulfonic acid sodium salt (NaAMPS) and acryloyl phosphatidylcholine (APC) via aqueous Cu(0)-mediated radical polymerisation. Polymer Chemistry.

Permanent WRAP url:
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Publisher statement:
First published by Royal Society of Chemistry 2016
http://dx.doi.org/10.1039/C5PY02016F

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Well-defined polyelectrolytes and polyzwitterions via aqueous Cu(0)-mediated living radical polymerisation

Vasiliki Nikolaou, Alexandre Simula, Martijn Droesbeke, Nuttapol Risangud, Athina Anastasaki, Kristian Kempe, Paul Wilson and David M. Haddleton

The scope of aqueous single electron transfer living radical polymerisation has been expanded for the preparation of a range of polyelectrolytes and polyzwitterions. Manipulation of the reaction conditions furnishes well-defined polymers, capable of undergoing chain extension and the synthesis of block copolymers at 0 °C.

Polyelectrolytes are key ingredients that have been employed as rheology modifiers, absorbents, coatings, hydrogel swelling agents, stabilisers and key components of biological devices and membranes. They are macromolecules that contain ionisable groups capable of undergoing dissociation in aqueous solution resulting in the accumulation of charge which occurs with concomitant release of counterions into solution. This build-up of charge engenders distinguishing surface and solution properties into polyelectrolytes which differentiates them from neutral polymers. At the simplest, non-quantitative level, accumulated charge results in intra chain repulsive interactions that impose a more extended and less coil-like conformation as compared to neutral polymers. The effect of repulsion can be dissipated by the addition of electrolyte solutes which can shield the prevailing polymer charge leading to adoption of a more common coiled conformation.

The opposite, or ‘anti-polyelectrolyte effect,’ is true for polyzwitterions, which incorporate monomers, such as sulfobetaine, carboxybetaine and phosphorylcholine, into the polymer. In aqueous solution opposing charges promote intra chain charge shielding leading to a coil-like conformation which can be swollen, and expanded, upon addition of electrolytes. Furthermore, betaine monomers give additional properties including variable wettability (super hydrophilicity), bio- and heamocompatibility and universal low-fouling potential.

Thus, the properties of polyelectrolytes and polyzwitterions in aqueous solution make them attractive targets for controlled radical polymerisation, however, they also make handling and characterising the monomers and ensuing polymers challenging. Nevertheless, a number of groups have been successful in the polymerisation of some common electolytic monomers. For example, 2-acrylamido-2-methylpropane sulfonic acid (AMPS) and its sodium salt (NaAMPS) have been employed in atom transfer radical polymerisation (ATRP) and reversible addition fragmentation chain transfer polymerisation (RAFT). Likewise, both ATRP and RAFT have been exploited for the controlled polymerisation of betaine monomers. The resulting polymers have found use in protein/peptide conjugation and surface modification technologies as well as in the fabrication of polymer nanoparticles decorated in, and possessing the desirable properties of polyzwitterionic constituents.

The solubility of electrolytes and zwitterions dictates that the polymerisation is limited to aqueous solution or binary mixtures with complimentary, highly polar organic solvents (e.g. MeOH). In 2013, an aqueous based variation of Cu-mediated living radical polymerisation (Cu(0)-mediated LRP) was introduced. Relying on the rapid disproportionation of Cu(0)Br/N-aliphatic ligand complexes in water, this technique facilitates the rapid polymerisation of (meth)acrylates and acrylamides at ambient temperature and below and is most commonly carried out at 0 °C so as to reduce any increase in reaction temperature from the reaction exotherm.

Since the introduction of aqueous Cu(0)-mediated LRP, a number of investigations have been carried out to ascertain the scope and limitations of this reaction. Primarily, the polymerisation has been shown to be tolerant of complex aqueous mixtures, whilst ongoing work includes investigations into monomer compatibility as well as the degree of functionality present in the initiating species.
To this end, functional initiators have been employed for the preparation of α-functional and α,ω-telechelic linear polymers capable of undergoing further chemistry at their chain termini, such as conjugation to peptides and the introduction of hydrophobic moieties. Furthermore, multifunctional initiating species, derived from proteins, have been prepared and aqueous Cu(0)-mediated LRP has been demonstrated in a ‘grafting-from’ process. Herein, we report, the use of aqueous Cu(0)-mediated LRP for the synthesis of polyacrylate and polyacrylamide polyelectrolytes, containing a neutralised sulfonic acid group, as well as acrylic phosphorylcholine derived polyzwitterions.

A caveat of the aqueous system which needs to be noted is the frequent requirement to adjust the polymerisations conditions, particularly the [I] : [CuBr] : [Me₆-Tren] = [20] : [1] : [0.4] : [4], depending on the targeted degree of polymerisation (DPₙ,th). In line with previous investigations, the initial polymerisation of NaAMPS (50 wt.% in H₂O) was carried out using [NaAMPS] : [I] : [CuBr] : [Me₆-Tren] = [20] : [1] : [0.4] : [4]; conditions which have proved to be almost universal for the polymerisation of a variety of acrylates and acrylamides.

### Table 1. Synthesis of PNaAMPS with various DP via aqueous Cu(0)-mediated LRP

<table>
<thead>
<tr>
<th>DP</th>
<th>[Cu]:[L]</th>
<th>Time (min)</th>
<th>Conv. (%)</th>
<th>Mₙ,th (g.mol⁻¹)</th>
<th>*Mₙ,SEC (g.mol⁻¹)</th>
<th>*Đ</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>[0.4]:[0.4]</td>
<td>30</td>
<td>100</td>
<td>4800</td>
<td>11500 (4600)</td>
<td>1.16</td>
</tr>
<tr>
<td>40</td>
<td>[0.4]:[0.4]</td>
<td>30</td>
<td>100</td>
<td>9400</td>
<td>23500 (10500)</td>
<td>1.20</td>
</tr>
<tr>
<td>80</td>
<td>[0.8]:[0.4]</td>
<td>30</td>
<td>100</td>
<td>18600</td>
<td>29700 (19700)</td>
<td>1.30</td>
</tr>
<tr>
<td>160</td>
<td>[1.6]:[1]</td>
<td>30</td>
<td>100</td>
<td>36900</td>
<td>36900</td>
<td>1.70</td>
</tr>
</tbody>
</table>

* Determined by aqueous SEC (see ESI for conditions). Number in parentheses are those obtained from ¹H NMR (not applicable for DP = 160).

The polymerisation was monitored by ¹H NMR which showed full monomer conversion within 30 min, according to disappearance of the vinyl signals between 5.5 and 6.5 ppm (Figure S1). The controlled nature of the polymerisation was demonstrated by aqueous SEC, which showed a symmetrical, mono-modal molecular weight distribution (Mₙ,SEC = 11500 g.mol⁻¹, Đ = 1.16) with kinetic analysis revealing a relatively linear increase of ln([M]₀/[M]ₜ) vs. time (Figure 1).

Under identical conditions, the full polymerisation of NaAMPS (DPₙ,th = 40) was also complete within 30 mins, with comparable control retained throughout the reaction (Mₙ,SEC = 23500 g.mol⁻¹, Đ = 1.20, Table 1, Figure S2). When targeting DPₙ,th ≥ 80, optimised conditions of [I] : [CuBr] : [Me₆-Tren] = [1] : [0.8] : [0.4] have been established. Under these conditions the amount of deactivating species [Cu(Me₆-Tren)Br₂] formed during the disproportionation step is maximised which enhances the control over the polymerisation without compromising the rate of reaction. Thus, the polymerisation of NaAMPS was realised using [NaAMPS] : [I] : [CuBr] : [Me₆-Tren] = [80] : [1] : [0.8] : [0.4] (Mₙ,SEC = 29700 g.mol⁻¹, Đ = 1.30, Table 1, Figure S3). Attempts to prepare higher molecular weight PNaAMPS (DPₙ,th = 160) were unsuccessful (Table 1, Figure S4-S5).

A similar trend was observed with sulfopropyl acrylate potassium salt (KSPA) monomer. Short chain PKSPA (DPₙ,th ≤ 40) was synthesised using [I] : [CuBr] : [Me₆-Tren] = [1] : [0.4] : [0.4] (Đ = 1.20), whereas longer chain PKSPA (DPₙ,th = 80) again required an increased amount of deactivating species to be formed in the disproportionation step. In this case [I] : [CuBr] : [Me₆-Tren] = [1] : [0.6] : [0.4] was sufficient to regain control over the polymerisation (Đ = 1.31, Table S1, Figure S6). Under the same conditions the dispersity was found to increase when with a target DPₙ,th = 20. The polymerisation was monitored by ¹H NMR which showed full monomer conversion within 30 min, according to disappearance of the vinyl signals between 5.5 and 6.5 ppm (Figure S1). The controlled nature of the polymerisation was demonstrated by aqueous SEC, which showed a symmetrical, mono-modal molecular weight distribution (Mₙ,SEC = 11500 g.mol⁻¹, Đ = 1.16) with kinetic analysis revealing a relatively linear increase of ln([M]₀/[M]ₜ) vs. time (Figure 1).

A similar trend was observed with sulfopropyl acrylate potassium salt (KSPA) monomer. Short chain PKSPA (DPₙ,th ≤ 40) was synthesised using [I] : [CuBr] : [Me₆-Tren] = [1] : [0.4] : [0.4] (Đ = 1.20), whereas longer chain PKSPA (DPₙ,th = 80) again required an increased amount of deactivating species to be formed in the disproportionation step. In this case [I] : [CuBr] : [Me₆-Tren] = [1] : [0.6] : [0.4] was sufficient to regain control over the polymerisation (Đ = 1.31, Table S1, Figure S6). Under the same conditions the dispersity was found to increase when

Fig. 1 Kinetic data for the polymerisation of AMPS (top) and the aqueous SEC of PNaAMPS using [NaAMPS] : [I] : [CuBr] : [Me₆-Tren] = [20] : [1] : [0.4] : [4], Mₙ = 11500 g.mol⁻¹ Đ = 1.16.

higher molecular weight polymers were targeted (DP\(_{n,th}\) = 160, 320, \(D \approx 1.47-1.84\)).

The polymerisation of the zwitterionic biocompatible monomer 2-methacryloyloxyethyl phosphorylcholine (MPC) has been studied and the ensuing properties of the polymers in solution and on surfaces have been characterised.\(^{19,20,38}\) However,

\begin{table}[h]
\centering
\caption{Synthesis of PAPC via aqueous Cu(0)-mediated LRP}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{DP} & \textbf{[Cu]:[L]} & \textbf{Time (min)} & \textbf{Conv. (\%)} & \textbf{\(M_{n,th}\) (g.mol\(^{-1}\))} & \textbf{\(M_{n,SEC}\) (g.mol\(^{-1}\))} \textbf{*D} \\
\hline
10 & [0.4]:[0.4] & 30 & 100 & 3100 & 2800 (3100) & 1.16 \\
20 & [0.6]:[0.8] & 30 & 100 & 5900 & 4300 (5600) & 1.20 \\
50 & [0.8]:[1.0] & 120 & 93 & 14300 & 6900 (14900) & 1.30 \\
100 & [1.0]:[1.2] & 1140 & 45 & 28400 & 7100 (34200) & 2.00 \\
\hline
\end{tabular}
\end{table}

\(* \text{Determined by aqueous Cu(0) for conditions.}
\] Number in parentheses are those obtained from \(^1\)H NMR.

the controlled polymerisation of the acrylate analogue, 2-acryloyloxyethyl phosphorylcholine (APC) has not yet been reported. Using aqueous Cu(0)-mediated LRP, low molecular weight (DP\(_{n,th}\) = 10) PAPC was synthesised using \([\text{CuBr}]:[\text{Me}_2\text{Tren}] = [10]:[50]:[25]:[1]:[0.8]:[0.4]\). Well controlled block copolymers were obtained when targeting low molecular weights (DP\(_n\) = 25/50) with good agreement \(M_{n,th}\) and \(M_{n,SEC}\) and low dispersions according to previous literature\(^{43}\) and employed for the polymerisation of NaAMPS using \([\text{NaAMPS}]:[\text{CuBr}]:[\text{Me}_2\text{Tren}] = [100]:[50]:[25]:[1]:[0.8]:[0.4]\). \(M_{n,th}\) was maintained throughout the polymerisation and each subsequent chain extension, exemplified by good agreement between \(M_{n,th}\) and \(M_{n,SEC}\) and the low dispersity of the final P(\([\text{APC}]_n\) \(-b\)-\([\text{APC}]_n\)) polymer (\(D = 1.23\), Figure S9).

Double hydrophilic block copolymers containing NaAMPS were prepared from linear a poly(ethylene glycol) (PEG) and P(2-hydroxyethyl acrylamide) (PHEAm) macroinitiator synthesised \textit{in situ} using the aqueous conditions (Table S2). The linear PEG initiator was prepared according to previous literature\(^{42}\) and employed for the polymerisation of NaAMPS using \([\text{PEG}]:[\text{CuBr}]:[\text{HEAm}]:[\text{CuBr}]:[\text{Me}_2\text{Tren}] = [10]:[20]:[1]:[0.4]:[0.4]\) was complete within 30 mins at which point an aliquot of NaAMPS (50 wt%, \(N_2\) purged, DP\(_{n,th}\) = 20) was added to each reaction. Co-polymerisation was complete within 30 min in both reactions (Figure S11-S12) and SEC analysis revealed shifts to higher molecular weight and low dispersity values for the P(\([\text{PEG}]_n\) \(-b\)-\([\text{NaAMPS}]_n\)) \(D = 1.30\) and P(\([\text{HEAm}]_n\) \(-b\)-\([\text{NaAMPS}]_n\)) \(D = 1.15\) respectively (Figure 2 b,c). Block copolymerisation was also attempted from a PNaAMPS macroinitiator (Figure S13-S14) using \(N\)-isopropylacrylamide (NIPAm) as the comonomer. Co-polymerisation was complete within 30 min of the addition of an aliquot of NIPAm (50 wt%, \(N_2\) purged, DP\(_n\) = 20) to the PNaAMPS macroinitiator. Unfortunately, SEC analysis of the targeted P(\([\text{NaAMPS}]_n\) \(-b\)-\([\text{NIPAm}]_n\)) polymer was not possible due to the insolubility to the copolymer in DMF and \(H_2\text{O}\) under the operating conditions of the SEC.

PAPC decorated polymer nanoparticles with high biocompatibility and low fouling potential were prepared from a P(\([\text{APC}]_n\) \(-b\)-\([\text{NIPAm}]_n\)) block copolymer (Table S5). The PAPC macrolonomer was synthesised (Table 2).
References