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Regular Article

Nanoparticles assemblies on demand: Controlled aggregation of Ag(0) mediated by modified peptoid sequences

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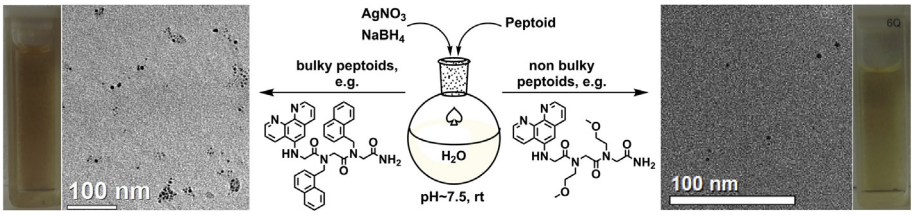
GRAPHICAL ABSTRACT

Assembly of Ag(0) NPs can be controlled by the reduction of Ag(I) salts in the presence of tunable biomimetic oligomers varied in their length and hydrophobic nature.



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ABSTRACT

Assemblies of metal nanoparticles (NPs) have been broadly used for the construction of materials with distinct spectroscopic properties towards sensing applications. On the other hand, well-dispersed NPs are exploit for applications in catalysis and medicine. Biopolymers or biomimetic oligomers can serve both as efficient stabilizers of NPs and as useful aggregation mediators that can lead to assemblies with unique properties. Controlling aggregation processes, however, is still challenging and often relies on trial and error rather than on defined thumb rules. Herein we develop specific guidelines for the controlled aggregation of Ag(0) NPs at room temperature in water near neutral pH and without any additives. We use short peptide mimics, N-substituted glycine oligomers called peptoids, as mediators, and investigate the influence of sequences variations on the NPs assembly. Spectroscopic and electron microscopy data reveal that both the length of the peptoids and their sequences have an effect on the NPs aggregation. Thus, we demonstrate that we can control both the degree of aggregation and the aggregates sizes by tuning these properties. Specifically we show that longer peptoid sequences as well as sequences consisting of aromatic side chains are required for the formation of uniform NPs assemblies in an average size of 70 nm, while a short hydrophilic sequence can stabilize well-dispersed Ag(0) NPs. Moreover, the catalytic activity of Ag(0) NPs towards the reduction of 4-nitrophenol to 4-aminophenol can be also controlled by varying the properties of the peptoid mediators.

1. Introduction

The organization of individual metal nanoparticles (NPs) into NP assemblies has gained significant attention in the last three decades due to the unique optical properties of these well-defined aggregates [1–3]. Assembly processes that exploit biopolymers or biomimetic oligomers as both capping agents of the metal NPs and mediators for the NPs aggregation are of special interest

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because the unique formed NPs and/or their aggregates can display properties of both components, leading to various applications in scientific disciplines ranging from biology to medicine to sensing [1]. Examples of such applications include probes for the separation and detection of DNAs, proteins and volatile organic compounds via interparticle amplification of optical and surface-enhanced Raman scattering (SERS) or fluorescence (SEF) signals [1,2]. This, as well as other sensing applications, require the use of Au(0), Cu(0) and Ag(0) NPs due to their ability to support a localized surface plasmon resonance (LSPR) at the visible region [1]. The LSPR absorbance corresponds to the gap width between the NPs such that assembly of NPs will result in a red shift from their original absorbance band, depending on the degree of aggregation and the final size of the aggregate. Therefore, UV–Vis spectroscopy is a useful tool for the characterization of NPs aggregation processes as it enables to differentiate between well-dispersed NPs and assembled NPs as well as between different sizes of NP assemblies. In this context we note that control over NPs assembly is essential for their utilization as sensors because the distance between the NPs must also be controlled. Thus, while an efficient SERS analysis requires dense assemblies with short distances between NPs [1], for SEF analysis, the distances should be larger (about 30 nm) to avoid any quenching of the signal [1,4–6]. Assembly of metal NPs can be mediated by biopolymers and their mimics [7] including DNA [8–12], peptides [13–18], peptide nucleic acids (PNA) [19,20], and peptoids [21,22]. The assembly process typically includes two steps, the first one being the synthesis of stable NPs and the second one is their aggregation. Stable NPs can be prepared by the indirect synthesis, in which the metal precursors are reduced by labile ligands, e.g. citrate [23] and ethylene glycol [24]. These ligands are further replaced by unique capping agents (e.g. biomimetic molecules), which are typically unstable under the initial reducing reaction conditions [7,8,21]. This method, however, cannot ensure full displacement, and thus could lead to heterogeneous mixture of capped NPs. A different approach is the direct synthesis, in which the unique capping agents can stabilize the NPs under varied reaction conditions [8,23]. NPs will start aggregate due to intermolecular attraction forces between the capping ligands including hydrophilic interactions and/or hydrophobic effects [17], hydrogen bonding [16,25], π-π stacking [25], DNA sticky ends [8,9], and more [14,17]. One approach for controlling NPs aggregation is by modifying the properties of the capping agent(s). When the capping ligand is a natural or a synthetic biopolymer, tuning its length and sequence may lead to NPs assemblies with desired size, morphology, etc. Nevertheless, a comprehensive study, which monitors the effect of systematic modifications at a specific biomimetic scaffold on its ability to control NPs aggregation and/or the properties of the final NP assemblies is yet to be accomplished.

Peptoids, N-substituted glycine oligomers, which have higher pH and temperature stabilities in comparison with other biological molecules (e.g. DNA, PNA or peptides) [26], can be efficiently generated from primary amines on solid support via the sub-monomer approach [27]. This synthetic protocol facilitates sequence modifications and should enable the creation of peptoid sets that contain oligomers varied in their (i) length, (ii) monomer properties such as hydrophobicity/hydrophilicity and bulkiness, and (iii) the type and location of the capping ligand(s). Investigating the ability of such peptoid sets to mediate the assembly of metal NPs should provide specific guidelines for controlling NPs aggregation. These could serve as a tool kit for the design of NPs assemblies with a desired size, shape and/or morphology. Herein we choose to study the assembly of Ag(0) NPs because their aggregation is more difficult to control in comparison to other NPs such as Au(0) [28]. In 2011, Maayan et al. reported on spherical assemblies of Ag(0) NPs prepared via the indirect synthesis with citrate ions as capping agents that were further replaced by 1,10-phenantroline (Phen) or a Phen-functionalized peptoid oligomer (Fig. 1A) [21]. The peptoid structure included one Phen ligand at the N-terminus, which functions as a linker to Ag(0) NPs, and six S-1-phenylethylamine (Nspe) side chains at the other positions (**PHP**, see Fig. 1). The formation of these spherical assemblies was obtained in a mixed water: acetonitrile solution only at pH = 3.5, which is the pKa of Phen. It was proposed that the aggregation process involves π-π stacking interactions between the peptoid chains, and hence the aromatic monomers play an important role in the ability of this peptoid to mediate Ag(0) NPs assembly. Herein, we investigate this assembly process and the factors that control it as well as the interaction between Ag(0) and other Phen-based peptoid sequences (where Phen is introduced at the N-terminus), and set up the rules for obtaining either well-dispersed Ag(0) NPs or Ag(0) NP assemblies (Scheme 1).

2. Results and discussion

Direct synthesis of Ag(0) NP aggregates mediated by PHP, and its role in the assembly process. In order to ensure that the direct approach is compatible with the formation of Phen-protected Ag(0) NPs at neutral pH, we exploit **PHP** as a mediator using the direct NPs synthesis and compared the resultant Ag(0) assemblies with the ones obtained when **PHP** was a mediator in the indirect synthesis of Ag(0) assemblies (Fig. 1). The direct synthesis proceeds by adding 1 equiv. of aqueous $NaBH_4$ solution (10 mM) to 2 ml aqueous solution mixture containing 1 equiv. of **PHP** (10 mM in acetonitrile) and 6.4 equiv. of aqueous $AgNO_3$ (10 mM). This reaction was followed by the appearance of an immediate yellow color indicating the formation of well dispersed Ag(0) NPs [1]. At this point, the measured pH was 7.2. This solution was kept unstirred for 24 h yielding a pink-orange color that showed a UV–Vis absorbance band at about 436 ± 2 nm (Fig. S38). As well-dispersed Ag(0) NPs exhibit an absorption band at about 400 nm [29], this red shift signifies their aggregation to NP assemblies. Transmission electron microscope (TEM) analysis of the **PHP** stabilized Ag(0) NPs indicated the formation of quasi-spherical assemblies (Fig. 1B) with average diameter of about 70 nm (Figs. 1D and S51), which contain about 10 NPs each with diameter range of 6–9 nm. These results are consistent with the spherical **PHP**-Ag(0) assemblies formed via the indirect approach having an average diameter of about 50 nm (Fig. 1A). These assemblies were stable for months. In order to eliminate the possibility that the NPs aggregation occurs as a result of fast solvent evaporation on the grid during sample preparation for TEM analysis, cryo TEM measurements were performed in a frozen reaction solution. The obtained micrographs showed NPs assemblies surrounded by a bright 'cloud' (Fig. S67). Electron energy loss spectroscopy (EELS) analysis acquired by High Resolution TEM measurements revealed the presence of nitrogen atoms within the 'cloud' area (Fig. S65), indicating that this 'cloud' is actually **PHP** molecules, which contain nitrogen atoms in their backbone and in the Phen side chain. These results support the notion that the NPs assemblies are mediated by **PHP**. Additionally, we performed a control experiment in which we used Phen as a capping ligand for Ag(0) NPs in the same concentrations and reaction conditions; this combination resulted in a color change accompanied by a broad absorbance band near 420 nm (Fig. S35) and the TEM image demonstrated that the aggregation was not uniform as both assemblies and single NPs were observed (Fig. 1C). Moreover, these NPs and assemblies were not stable as evident from the black precipitation obtained after only one week. These results suggest that the peptoid backbone has a significant role in mediating the aggregation of stable Ag(0) NP-assemblies via the direct synthesis approach.

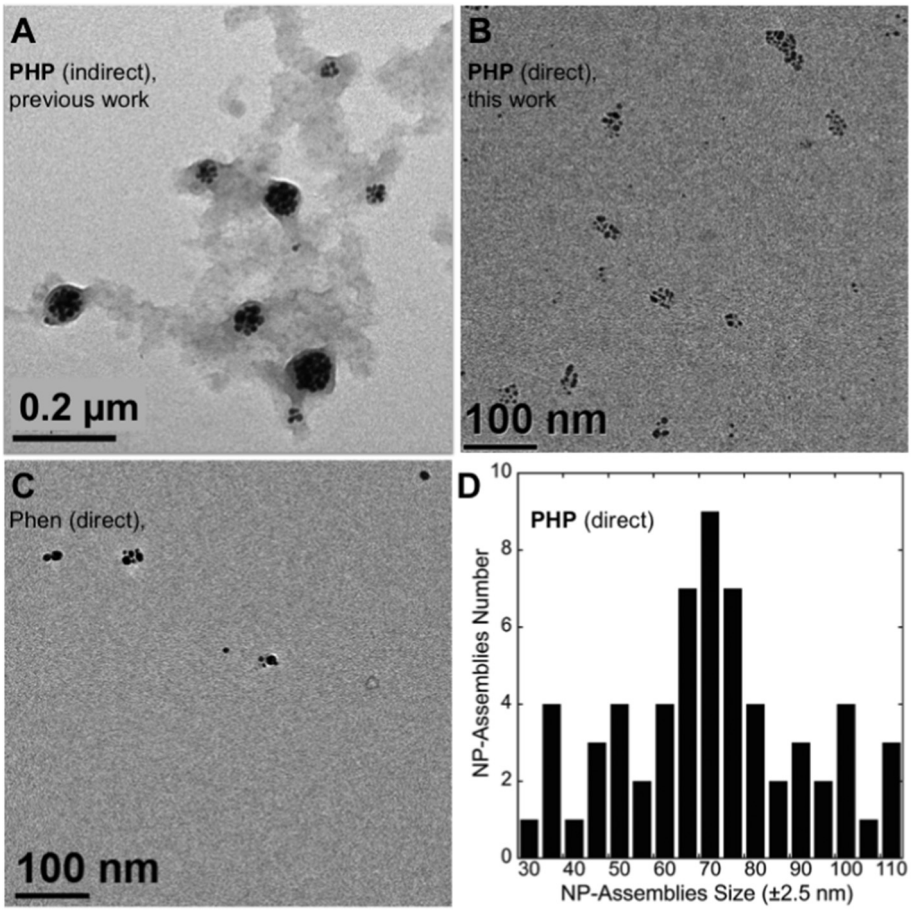
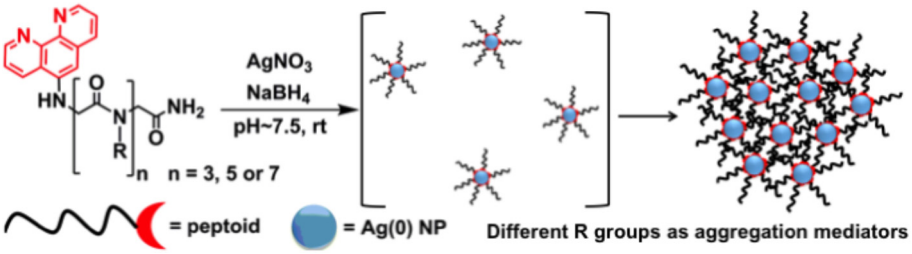


Fig. 1. TEM micrograph of Ag(0) NPs assemblies mediated by (A) PHP via the indirect approach, (B) PHP via the direct approach and (C) Phen via the direct approach. (D) Size distribution of Ag(0) NPs assemblies mediated by PHP via the direct approach.



Scheme 1. Rational design of Ag(0) NPs synthesis (via the direct approach) and aggregation using Phen-peptoids as both capping agents and mediators.

In order to better understand the role of **PHP** in the aggregation of Ag(0) NPs we decided to investigate (1) whether the assembly process results from intermolecular interactions between the peptoid oligomers in water and (2) how do these oligomers interact with the Ag(0) NPs. To answer the first question, 10 µL of **PHP** solution (10 mM in acetonitrile) were diluted in 2 mL of water, stirred vigorously for 10 min and stand undisturbed for 30 min. This sample was analyzed by TEM using negative staining showing spherical particles with an average diameter size of about 60 nm (see Fig. S68). The results indicate that **PHP** oligomers assemble spontaneously in water due to intermolecular interactions, which can either be related to π-π stacking between the aromatic rings of the Nspe side chains or simply be hydrophobic forces, leading to micelles.

To answer our second question and understand the interaction (s) between **PHP** and the Ag(0) NPs, we first synthesized a modified version of **PHP** – an Nspe homohexamer that does not contain Phen and apply it to the direct synthesis of Ag(0). This solution remained colorless and no evidence for the formation of NPs was obtained. This implies that the binding to Ag(0) is via the Phen side chain. The interaction between Phen and Ag(0) surface can be described either as an "edge on" or "flat" orientation (Fig. 2A). It was previously reported that Phen binds to the surface of Ag(0) in an "edge on" orientation based on Raman spectroscopy by comparing the relative values of specific absorbance bands [30]. We therefore analyzed a sample containing **PHP** mediated Ag(0) NPs assemblies and a fresh sample of Phen mediated Ag(0) NPs by Raman spectroscopy and compared between the two spectra. We found that the Raman spectra of **PHP**-Ag(0) is very similar to this of Phen-Ag(0) with major absorbance bands at 232, 1149, 1408 and 1600 cm^{-1} (Fig. 2B), indicating that **PHP** interacts with the surface of the Ag(0) NPs via the Phen side chain in an "edge on"

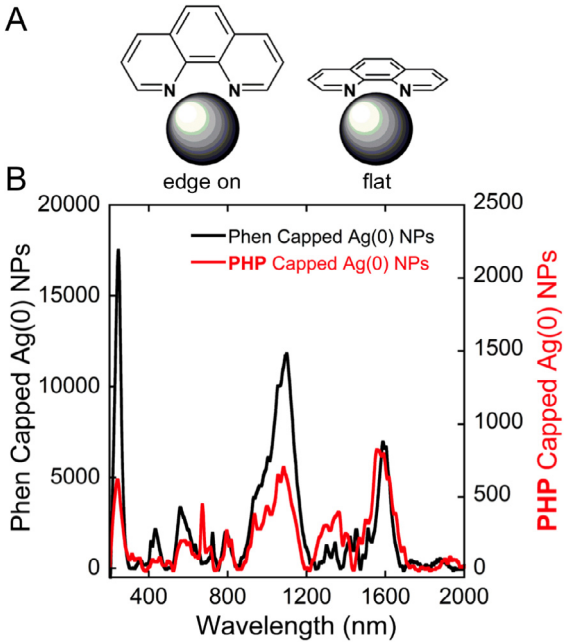


Fig. 2. (A) Schematic representation of the "edge on" and "flat" orientations describing the binding mode of Phen to Ag(0) surfaces. (B) Raman spectra of Ag(0) NPs assemblies mediated by Phen (black line) or PHP (red line), performed in water using the same solutions prepared for UV–Vis measurements. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

orientation. Overall we suggest that the Ag(0) bound **PHP** oligomers self assemble due to intermolecular interactions between the peptoids. This is also supported by the average size of the NPs assemblies (about 70 nm), which is in agreement with the average diameters of the **PHP** particles and the Ag(0) NPs (about 60 nm and 8 nm, respectively).

Direct synthesis of Ag(0) NP aggregates mediated by various peptoid trimers, and the role of the peptoid sequence in the assembly process. After demonstrating the ability to assemble Ag(0) NPs via the direct approach in water at neutral pH, we wished to gain some understanding about the factors that control the NPs assembly process. Thus, we decided to investigate both the influence of the peptoid length and the peptoid sequence, namely the type of pendent groups, on the aggregation products. To this aim, we generated a set of seven peptoid sequences different in their length and sequence, in addition to **PHP** (Fig. 3). Initially, the trimer **Tri1**, which contains two Nspe groups in addition to Phen, was synthesized in order to evaluate the minimal peptoid length required for mediating the aggregation of Ag(0) NPs. Likewise, the trimers **Tri2**-**Tri5**, which consist of monomers different than Nspe, were prepared in order to understand the sequence requirements for achieving uniform aggregation. All the peptoids were synthesized on solid support, analyzed by HPLC and MS and purified by HPLC (>95% purity). Applying the direct approach, at the same reaction conditions as with **PHP**, to the peptoid **Tri1** resulted in an immediate color change and after 24 h the final color of the solution was yellow-orange. UV–Vis measurements revealed an absorbance band at 435 nm indicating the presence of aggregates in the solution. TEM analysis suggested that only partial aggregation took place, as evident by the presence of well-dispersed NPs in the sample, and the formation of aggregates not uniform in their sizes (Fig. 4A). These include assemblies with an average aggregate diameter length of 53 ± 13 nm containing NPs with an average size of about 4.5 nm, as well as small assemblies containing only two or three NPs. Moreover, according to the TEM images, not all the NPs aggregated into assemblies uniform in their morphology (Fig. 4A).

These results indicate that the oligomer length indeed effects the aggregation process and that **Tri1** is too short to fully mediate Ag(0) NPs aggregation in water. The peptoid **Tri2** was designed in order to test whether a larger aromatic monomer (naphthyl rather than benzyl), which is anticipated to increase both the hydrophobicity of the peptoid trimer and its ability to form intermolecular π-π interactions, will enable to mediate uniform aggregation. **Tri3**, having non aromatic bulky hydrophobic cyclohexyl monomers, **Tri4**, with non bulky hydrophobic (pentyl) monomers and **Tri5** having hydrophilic (methoxyethyl) monomers, were designed as control peptoids aiming to further explore the significance of

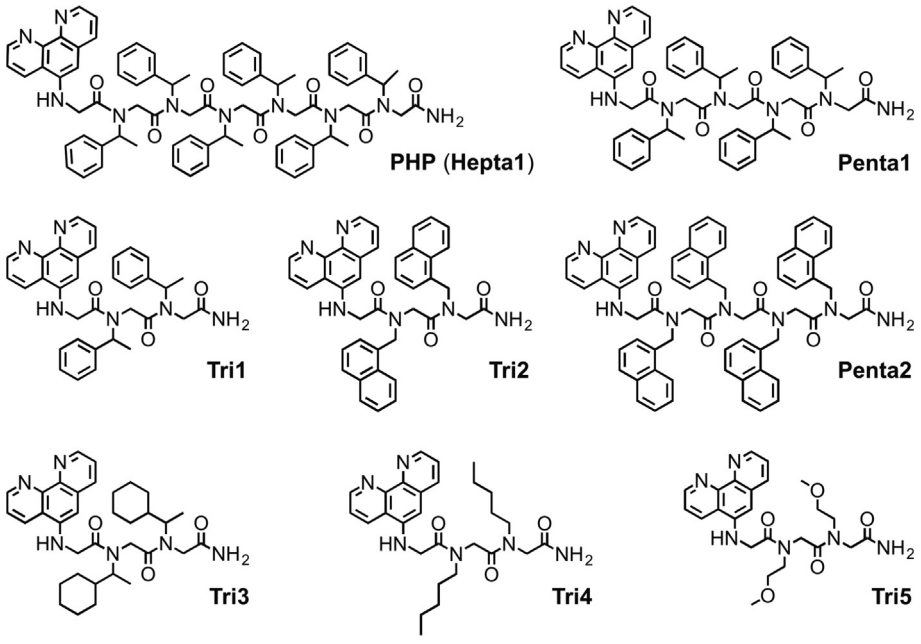


Fig. 3. Initial sequences of peptoid oligomers designed as mediators for Ag(0) NPs assembly.

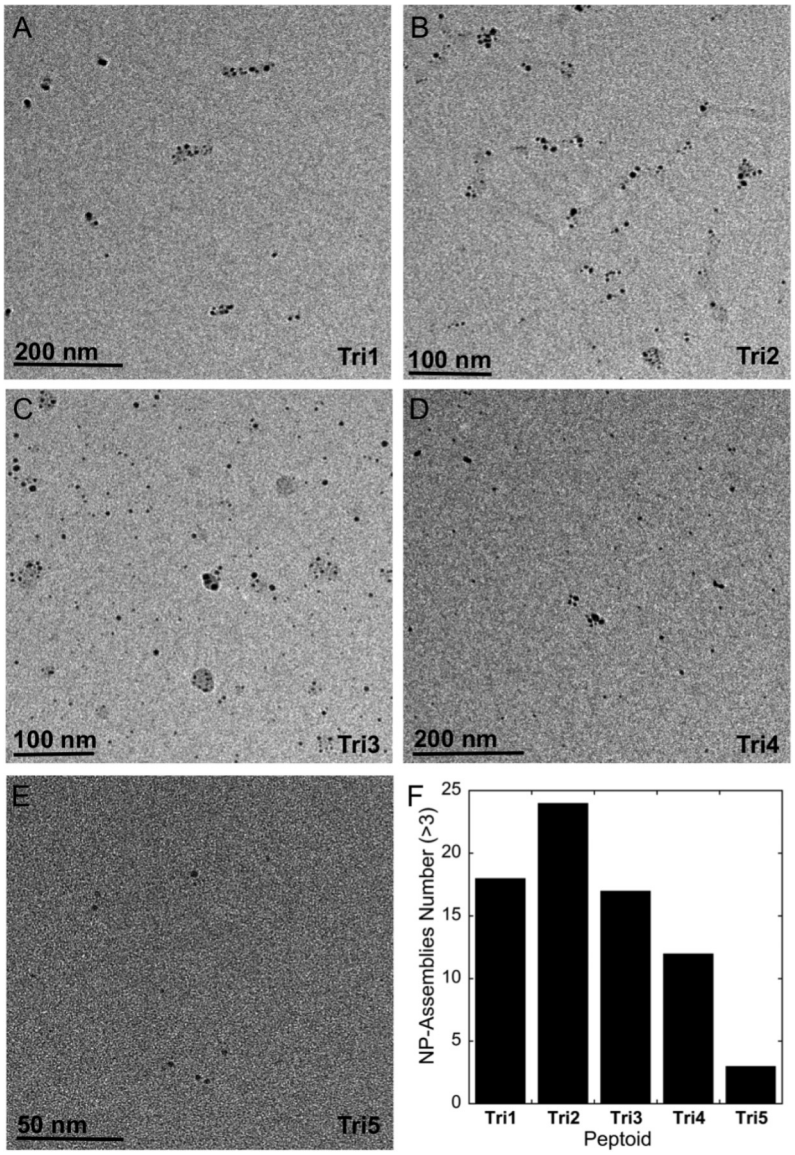


Fig. 4. (A-E) TEM micrographs for Ag(0) NPs assemblies mediated by peptoids Tri1–Tri5. (F) A graphical summary of the number of NPs assemblies containing more than 3 Ag (0) NPs.

aromatic monomers, bulky monomers and hydrophobicity in the aggregation process. Ag(0) NPs mediated by **Tri2** were obtained via the direct synthesis as described above followed by their aggregation in water, which resulted in an orange solution. UV–Vis measurements revealed an absorbance band at 432 ± 1 nm and TEM images showed Ag(0) NPs assemblies with an average size of 55 ± 12 nm containing NPs with an average size of about 7 nm, accompanied by some random NPs and smaller NPs aggregates (Fig. 4B). The total number of the random NPs was lower, while the number of NPs assemblies containing >3 NPs was higher than these numbers observed when **Tri1** was used as a mediator (see Fig. 4F). Using **Tri3** as a mediator for the aggregation of Ag(0) NPs was less efficient than using **Tri1** or **Tri2**; UV–Vis measurements revealed an absorbance band at 426 ± 3 nm and TEM images indicating only partial formation of NPs assemblies. These were also much smaller with a larger size distribution exhibiting an average size of 36 ± 15 nm, which contain NPs with an average diameter of about 6 nm (Fig. 4C).

The use of **Tri4** and **Tri5** as mediators led to only poor aggregation as reflected both by the UV absorbance bands and TEM images. When **Tri4** was used as a mediator, the assemblies absorbance band was located at 416 ± 3 nm and TEM analysis revealed that Ag(0) NPs with an average size of about 7 nm were obtained but their aggregation resulted in only a few small NPs assemblies, in the diameter of 22 ± 10 nm, accompanied by many random NPs, as shown in Fig. 4D. Finally, when **Tri5** was used as a mediator, the color of the solution remained yellow even after 24 h, and its UV–Vis spectra displayed an absorbance band at 403 ± 2 nm, which is comparable to this of the well dispersed Ag(0) NPs. TEM analysis revealed that only Ag(0) NPs with an average size of about 6 nm were obtained and that their aggregation was not efficient (Fig. 4E). Although none of the peptoid trimers exhibited homogeneous and complete aggregation pattern, our results suggest that the presence of aromatic and/or bulky pendant peptoid side chains is an important factor in the aggregation of Ag(0) NPs in water. Hence, despite of their short length, **Tri1** and **Tri2** could mediate the assembly of Ag(0) NPs, while **Tri5** completely prevented their aggregation. Interestingly, a TEM micrograph of the peptoid **Tri5** in water, using negative staining, did not show formation of spherical particles like in the case of **PHP** (and also in the case of **Tri1**,

see SI), indicating that in the absence of intermolecular interactions in water, there is no aggregation.

Catalytic activity of Ag(0) NPs and Ag(0) NP assemblies. These initial results demonstrate the ability to control the degree of Ag(0) NPs aggregation simply by changing the sequence of the peptoid mediator. Consequently, we were interested to explore whether it is also possible to change a specific activity of Ag(0) NPs as we alter the sequence of the peptoid mediator, and have decided to study the catalytic reduction of 4-nitrophenol to 4-aminophenol [31–35] by some of our Ag(0)-peptoid particles. We choose this reaction because 4-nitrophenol adsorbs on NPs surfaces [36], and the reaction rate can be controlled by diffusion and monitored by UV–Vis at 400 nm (the absorbance of 4-nitrophenol in alkaline conditions) and at short time intervals. As a result, we anticipated that well-dispersed NPs (these mediated by **Tri5**) would catalyze this reaction faster than the aggregated NPs (e.g. these mediated by **PHP**), due to a higher catalyst concentration, de facto, in solution. To test this assumption, aqueous solutions of Ag(0) NPs or NP-assemblies were added to solutions of 4-nitrophenol (1×10^{-4} M, 2 mL) and $NaBH_4$ (0.1 M, 0.32 mL) in a UV–Vis cuvette, and a UV–Vis spectrum was immediately measured in intervals of 6 s (for **Tri5**) or 1 min (for **PHP**). The solutions were not stirred during the measurements. The results of the reaction catalyzed by **PHP** and **Tri5** are described in Fig. 5 as the changes in the absorbance at 400 nm. As **PHP**-mediated Ag(0) NP assemblies require a relatively long induction period [37] of about 10 min before initiating catalytic activity, full conversion of 4-nitrophenol to 4-aminophenol was obtained after about 20 min (Fig. 5A). In the case of **Tri5**, upon addition of 4-nitrophenol to the NPs solution, we assume that a large amount of the 4-nitrophenol molecules are being adsorbed on the Ag(0) NPs due to the NPs large surface area and their high effective concentration in solution. When $NaBH_4$ is added, all the adsorbed 4-nitrophenol molecules immediately get reduced to 4-aminophenol, hence the sharp decrease in the absorbance band of 4-nitrophenol at the beginning of the catalytic reduction reaction (Fig. 5B). After all the initially adsorbed substrate molecules have been reduced, other substrate molecules start to adsorb on the NPs by diffusion but their amount at a given time is lower than the amount of the initially adsorbed molecules because this process is diffusion controlled. Thus, the reaction proceeds in a constant slower rate, represented by the milder slope of the graph (Fig. 5B). Full conversion was obtained in only 3 min. These results support our hypothesis and demonstrate the ability to control a specific catalytic activity by altering the sequence of the peptoid mediating Ag(0) NPs assembly.

The role of the peptoids length in the aggregation of Ag(0) NPs. In attempts to obtain a more homogeneous aggregation, we decided to prepare two more peptoids: **Penta1**, which its oligomer length lays between **Tri1** and **PHP** such that it might be long enough to mediate uniform Ag(0) aggregation, and still be shorter than **PHP**, and **Penta2**, as a comparison (see Fig. 3), and to examine their ability to mediate the assembly of Ag(0) NPs. The use of either **Penta1** or **Penta2** as mediators for Ag(0) NPs assembly resulted in nearly complete aggregation. UV–Vis absorbance bands of **Penta1** and **Penta2** are located about 434 ± 2 nm and 435 ± 3 nm respectively, and the final color of their solutions was pinkish-orange. TEM micrographs of **Penta1** and **Penta2** mediated Ag(0) NPs assembly displayed quasi-spherical aggregates in a similar average diameter of 62 ± 16 nm and 64 ± 19 nm respectively, that resembles the average diameter of the **PHP** mediated Ag(0) NPs assemblies (Fig. 6). Notably, only in the case of **Penta1** some random NPs are observed.

These results suggest that a pentamer length peptoid is enough for efficient aggregation given that it contains aromatic side chains. In order to determine the length limit when using peptoids incorporating non bulky and non aromatic side chains, we prepared and characterized the peptoids **Hepta4** and **Hepta5**, which contain pentyl or methoxyethyl side chains, respectively (Fig. 7), and compare their ability to mediate the aggregation of Ag(0) to the peptoids **Tri4** and **Tri5** that bear the same side chains.

The use of **Hepta4** and **Hepta5** as mediators for the aggregation of Ag(0) NPs resulted in yellowish-orange solution color, and the UV–Vis spectra exhibited absorbance bands at 431 ± 2 nm and 427 ± 4 nm respectively. TEM analysis revealed partial Ag(0) NPs aggregation in both cases (Fig. 8A and B). **Hepta4** mediated Ag(0) NPs assemblies were obtained in a quasi-spherical morphology with an average diameter of 34 ± 17 nm and an average diameter of single NP of about 7 nm (Fig. 8A). In comparison, **Hepta5** mediated Ag(0) NPs assemblies were obtained in a low amount with a non uniform morphology with an average diameter 24 ± 18 nm, and an average diameter of single NP of about 5 nm (Fig. 8B and D). These results demonstrate the contribution of the peptoid's length to NPs aggregation; the poor aggregation obtained by **Tri4** is highly increased by the use of **Hepta4** as a mediator and the inability of **Tri5** to mediate the assembly of Ag(0) NPs has changed with the increase in its length such that **Hepta5** could induce some aggregation resulting in a small number of NPs assemblies. Due to the fact that the peptoid become more hydrophobic when its length increases (the length of **Hepta4** and **Hepta5** is more then double the length of **Tri4** and **Tri5**), we attribute the ability of **Hepta4** and **Hepta5** to mediate NPs aggregation

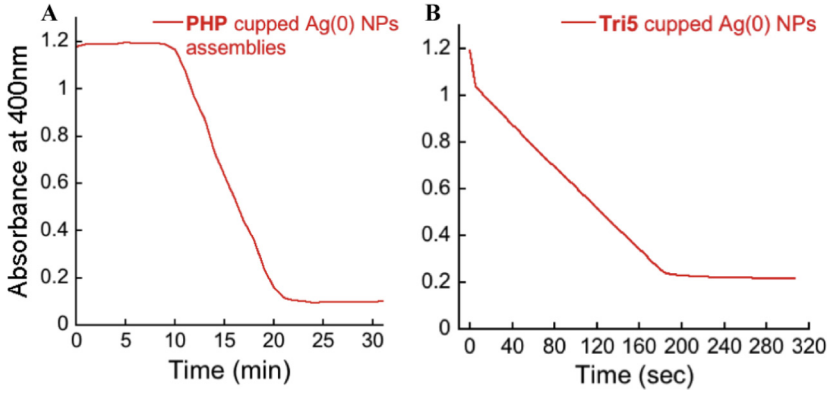


Fig. 5. Plot of the time dependent absorbance at 400 nm, during the catalytic reduction of 4-nitrophenol by PHP mediated Ag(0) NP assemblies (A), and Tri5 mediated Ag(0) NPs (B).

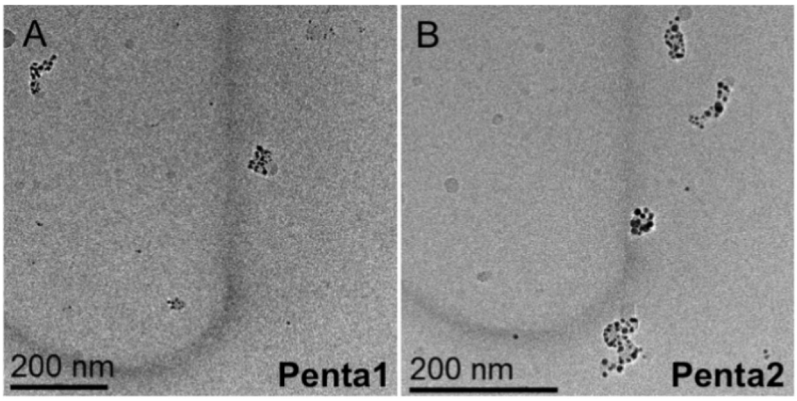


Fig. 6. TEM micrographs of Ag(0) NPs assemblies mediated by Penta1 (A) and Penta2 (B).

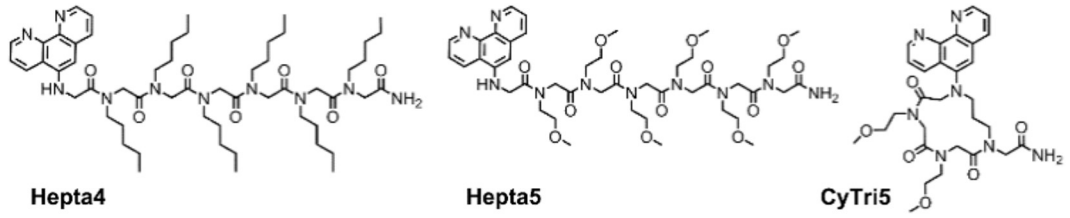


Fig. 7. Sequences of peptoid oligomers designed as mediators for testing the influence of length and hydrophobicity on Ag(0) NPs assembly.

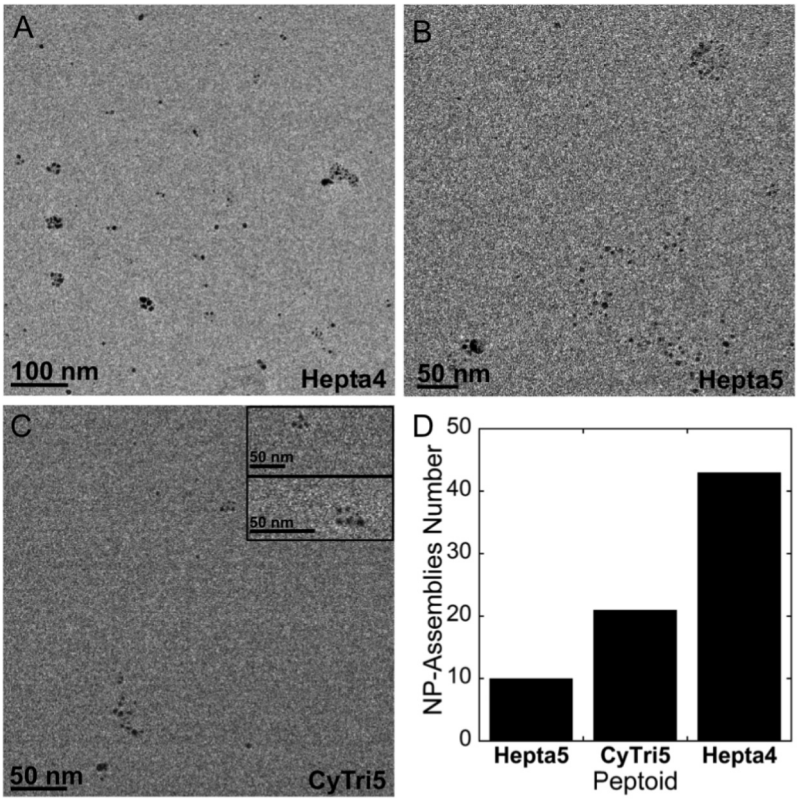


Fig. 8. TEM micrographs of Ag(0) NPs assemblies mediated by Hepta4 (A), Hepta5 (B) and CyTri5 (C). (D) A graphical summary of the number of NPs assemblies containing > 3 NPs.

to intermolecular hydrophobic effects, as was demonstrated with the aromatic peptoids. To further probe this point we decided to cyclize **Tri5** and test the ability of the cyclic peptoid **CyTri5** (Fig. 7) to mediate the assembly Ag(0) NPs.

It is known that cyclization of peptoids rigidify their structure and lead to increased hydrophobicity [38]. Moreover, we have recently published a facile strategy for peptoids cyclization via a simple substitution reaction, which takes place on-resin utilizing

Table 1
Summary of the data obtained regarding the assembly of Ag(0) NPs by various peptoids.

Entry	Sequence	λ_{max} (nm)	Aggregation	Average Ag(0) NPs assemblies diameter (nm)	Average Ag(0) NPs diameter (nm)
1	$(Nspe)_2Nphen$ (**Tri1**)	431 ± 2	Partial	53.12	4.50
2	$(Nnm)_2Nphen$ (**Tri2**)	432 ± 1	Partial	55.01	6.91
3	$(Nch)_2Nphen$ (**Tri3**)	426 ± 3	Partial	36.53	6.06
4	$(Naal)_2Nphen$ (**Tri4**)	416 ± 3	Poor	22.71	7.30
5	$(Nme)_2Nphen$ (**Tri5**)	403 ± 2	Non	–	6.23
6	$(Nspe)_4Nphen$ (**Penta 1**)	434 ± 2	Full	62.01	6.20
7	$(Nnml)_4Nphen$ (**Penta2**)	435 ± 3	Full	61.37	5.19
8	$(Naa)_6Nphen$ (**Hepta4**)	431 ± 2	Partial	34.68	7.02
9	$(Nme)_6Nphen$ (**Hepta5**)	427 ± 4	Partial	24.31	5.43
10	$(Nspe)_6Nphen$ (**PHP**)	436 ± 2	Full	70.14	6.5
11	$(Nspe)_2Nphen$ (**CyTri5**)	416 ± 2	Partial	28.06	6.91

a microwave irradiation for 30–40 min [39,40]. According to this procedure, we have synthesized the linear peptoid **Tri5** and cyclized it on resin using microwave irradiation (see SI for details). The use of **CyTri5** as a mediator for Ag(0) NPs assembly produced an yellowish-orange solution and the UV–Vis spectrum exhibited an absorbance band at 416 ± 2 nm. TEM analysis revealed the formation of NPs assemblies with an average diameter of 28 ± 18 nm, which contain Ag(0) NPs with an average diameter of about 7 nm (Fig. 8C). The NP-assemblies morphology is mixed, and includes quasi-spherical NPs assemblies (>15 aggregates, see Fig. 8D) as well as random shaped assemblies, both accompanied with well-dispersed NPs. Overall, the results obtained with **Hepta4**, **Hepta5** and **CyTri5** demonstrate the contribution of both the peptoid's length and hydrophobicity to the NPs assembly process. These results, as well as all the information obtained with peptoids **Tri1**-**Tri5**, **Penta1**-**Penta2**, **hepta4**-**Hepta5** and **PHP**, describing their behavior as mediators for the assembly of Ag(0) NPs is summarized in Table 1.

3. Conclusions

The use of natural and synthetic biomimetic polymers/oligomers as mediators for NP assembly, offers a major advantage over the use of small organic molecules or synthetic polymers mediators because their versatile sequences and structures can be precisely tuned towards better control over the size, shape and morphology, and consequently over the functionality, of the final aggregated products [8,18,25,41]. Nevertheless, long oligomer sequences as well as specific solvents, pH condition and/or additives are required for NPs assembly by these biopolymers/oligomers [8,9,14,16,17,25]. In this context, our work demonstrates that the stabilization of Ag(0) NPs and/or their aggregates can be achieved by relatively short peptoids of 3–7 monomers lengths and can occur in aqueous environment under nearly neutral conditions. We show that the aggregation can be controlled by changing the peptoid length and the type of side chains, being either aromatic, bulky, hydrophobic or hydrophilic. Our results indicate that partial aggregation can be already achieved by peptoids sequences as short as trimer oligomers, while nearly perfect quasi spherical NP assemblies can be generated by the addition of only two monomers to form pentamer peptoids. Importantly, our systematic study shows that a careful design of the peptoid mediator, which includes length, monomer type and structure (linear vs. cyclic) considerations, result in precise control over Ag(0) NPs aggregation. Thus, short hydrophilic peptoid sequences will result in well dispersed Ag(0) NPs, which are required for some specific applications [1] (e.g. catalysis [6] and antibacterial surfaces [42]), while longer and/or hydrophobic sequences will lead to uniform assemblies with small inter-particle gaps, which are often used for sensing applications. In addition to control over the degree of aggregation, we demonstrate that control over catalytic reduction of 4-nitrophenol to 4-aminophenol can be also achieved using Ag (0) NPs stabilized by different peptoid sequences. With that, we define a new tool kit for the design of NPs and NP-assemblies-based materials. The use of peptoids – that can be synthesized easily in a sequence specific manner and have side chain chemical diversity greater than these of peptides, as well as higher thermal and pH stabilities – for controlling NPs aggregation, hold great potential in the development of unique biomimetic NPs assemblies.

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Appendix A. Supplementary material

Synthesis, analytical data, characterization of products, TEM, HR-TEM and Cryo-TEM images. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcis.2017.08.039.

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