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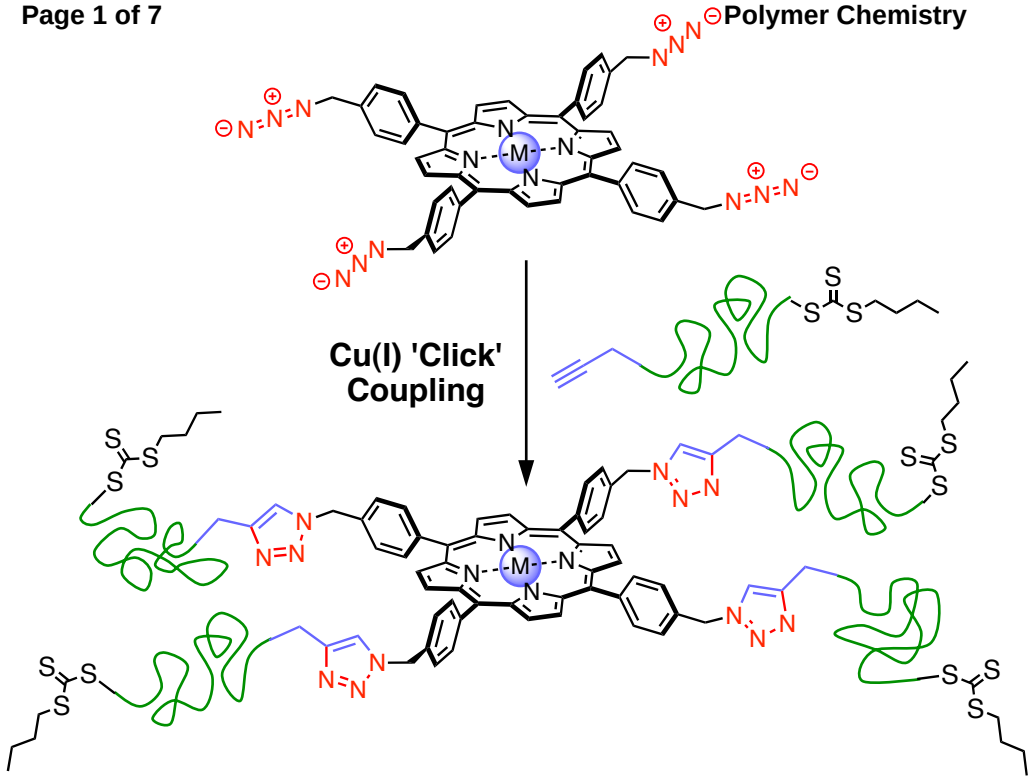

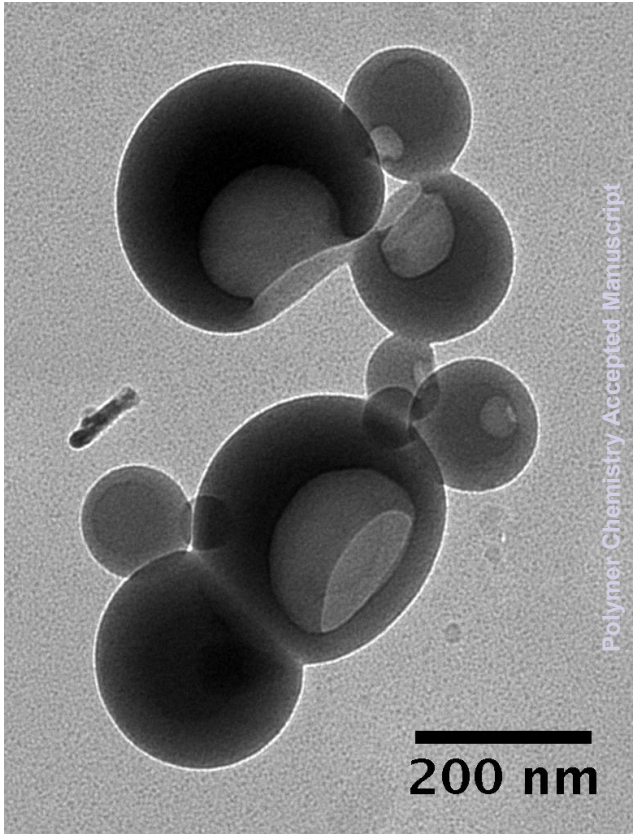

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ARTICLE

Fluorescent Bowl-shaped Nanoparticles from 'Clicked' Porphyrin-Polymer Conjugates

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We report the synthesis and post-synthetic modification of a library of hydrophilic and hydrophobic 'clicked' triazole-linked porphyrin-polymer conjugates (PPCs). A detailed study of the reaction conditions was undertaken, revealing a competition between copper(I)-catalysed and thermal Huisgen azide-alkyne cycloaddition pathways. Remarkably, porphyrin-polystyrene conjugates assembled into fluorescent bowl-shaped nanoparticles whose morphology depended on the porphyrin/polystyrene ratio of constituent PPC. Nanoparticles prepared from freebase PPCs exhibited colorimetric aqueous pH sensing, indicating that the PPC nanoparticles may be a useful platform for chemical sensing applications.

Introduction

The biological ubiquity of porphyrins and related macrocycles has inspired much research into their technological applications, from artificial photosynthesis and photodynamic medicine to catalysis and supramolecular chemistry.[1] In recent years there has been growing interest in covalently attaching synthetic polymers to porphyrin derivatives as a means of expanding their physicochemical properties, modifying their solubility and driving their self-assembly into nanostructured soft materials. Depending on the nature of the attached polymer chain, porphyrin–polymer conjugates (PPCs) can display a wide range of properties not typically associated with porphyrin derivatives, such as water solubility,[2] amphiphilicity,[3] thermoresponsivity,[4] and gelation.[5] Furthermore, embedding a porphyrin within a well-defined polymer microenvironment can greatly reduce aggregation and excited-state quenching, which are deleterious to many photophysical processes.[6] Consequently, there is broad interest in simple, modular and efficient methods for preparing PPC libraries from easily synthesised precursors.

Porphyrin-cored PPCs can be prepared either by coupling end-functionalised polymers to a central porphyrin core (arm-first strategy), or by growing polymer chains from a central porphyrin macroinitiator or chain transfer agent (core-first strategy). Early work on PPCs focused on arm-first methods using the Williamson ether synthesis to prepare porphyrin-cored architectures.[7] This approach, however, suffered from poor yields due to the substantial steric bulk and low chain-end reactivity of even relatively short polymers. Consequently, the core-first approach has been favoured in the subsequent literature.[8] The drawback of the core-first approach, however, is that the polymer arms must be cleaved from the porphyrin core in order to measure their molecular weight and dispersity. The development of highly efficient coupling reactions, e.g., 'click' chemistry,[9] has caused a recent resurgence in the popularity of arm-first strategies, especially since these methods enable facile control over the polymer arm morphology and size distribution prior to grafting.[10]

Recently we reported the synthesis and coordination-driven self-assembly of hydrophobic PPCs using the microwave-assisted copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction.[11] Herein, we investigate expanding the scope of this methodology to include hydrophilic and thermoresponsive PPCs with different metalloporphyrin cores, and explore the limitations of this reaction and side reactions that accompany successful porphyrin–polymer coupling. We also examine the physical properties of both hydrophilic and hydrophobic PPCs, documenting the good solubility in both organic and aqueous solvents, and improved processability of the PPCs using methods not typically applicable to porphyrin derivatives. For instance, we discovered that bowl-shaped fluorescent nanoparticles could be prepared from polystyrene-PPCs using a co-solvent precipitation method, which would typically result in aggregation and uncontrolled precipitation of symmetric non-polymer appended porphyrins.

Results and Discussion

Synthesis of PPC Library

PPCs were prepared from the corresponding di- and tetraazidoporphyrins, which were themselves synthesised in four steps from 4-(bromomethyl)benzonitrile in 7% and 32% overall yield, respectively. The azidoporphyrins were highly

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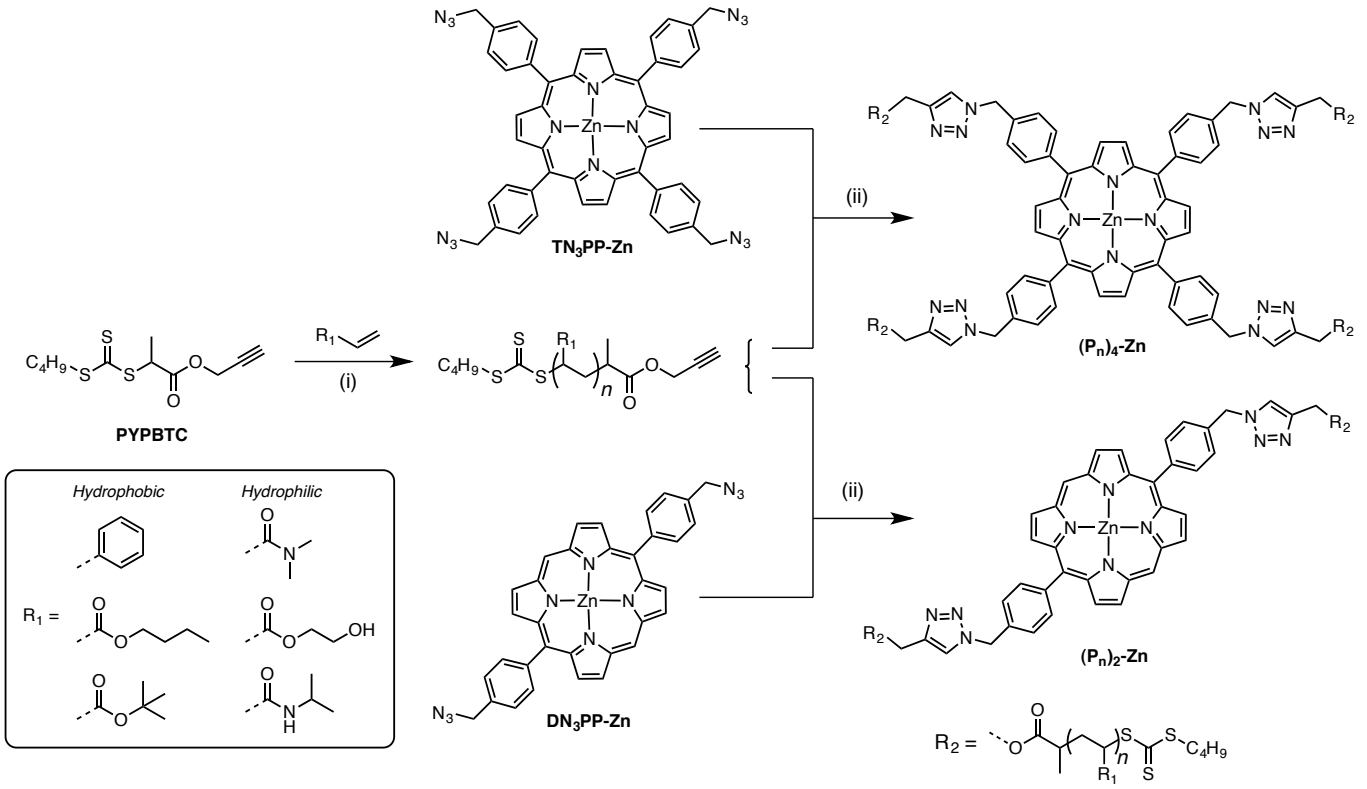

Scheme 1. Synthesis of triazole-linked porphyrin-polymer conjugates by microwave-assisted CuAAC coupling. Reaction conditions: (i) AIBN, 70-90 °C, 1-4 h; (ii) $CuSO_4 \cdot 4H_2O$, sodium ascorbate, DMF, MW irradiation (100 W, 100 °C), 25 min.

soluble in coordinating organic solvents (DMF and THF in particular), and stable at room temperature for more than a year without any degradation. Since freebase porphyrins are known to interfere with copper-catalysed reactions due to adventitious Cu(I)/Cu(II) coordination,[12] the freebase azidoporphyrins were converted to their Zn(II) chelates for CuAAC coupling. Alkyne-functionalised polystyrene (PS), poly(butyl acrylate) (PBA), poly(*tert*-butyl acrylate) (P*t*BA), poly(*N*,*N*-dimethyl acrylamide) (PDMA), poly(hydroxyethyl acrylate) (PHEA) and poly(*N*-isopropyl acrylamide) (PNIPAM) were prepared by RAFT polymerisation using alkyne-functionalised chain-transfer agent PYPBTC.[13] The alkyne-polymer precursors had average degrees of polymerisation (DP) of 15–42 repeat units, were of low dispersity ($1.17 < Đ < 1.30$) and showed good end-group retention after polymerisation (see ESI†, Section S1.4).

The reaction between **TN_3PP-Zn** and alkyne-PS_{30} was used to optimise the porphyrin–polymer coupling methodology (see ESI†, Section S1.5). Initial attempts to perform the reaction in mixtures of THF, water and pyridine led to poor conversion and non-uniform product mixtures due to phase separation of the hydrophobic polymers and azidoporphyrins from the aqueous solvent component.

The reaction performed best in DMF due to its excellent solvating power for both organic compounds and inorganic salts, and its efficient response to microwave dielectric heating (Scheme 1).[14] CuAAC coupling gave most consistent results when using a 5–10 mol% excess of alkyne polymer. This requirement most likely arises from the dispersity in molecular weight of the alkyne polymers and the presence of initiator-derived chains, which places uncertainty on the correct polymer stoichiometry for the reaction. Fortunately, excess free polymer was easily removed using preparative size-exclusion chromatography (SEC, Biobeads SX-1).

As reported previously,[11] CuAAC coupling of hydrophobic polymer substrates was highly efficient (89–98% NMR conversion with respect to porphyrin), affording the target number of polymer arms per porphyrin core (Table 1). Efficient consumption of the azidoporphyrin starting materials, as determined by ^{1}H NMR analysis, corroborates the low-to-moderate dispersities of the conjugates by GPC. Conversion was independent of the polymer arm length, which is a testament to the efficiency of the CuAAC reaction despite low diffusivity and poor end-group availability associated with macromolecular coupling.

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Table 1. Molecular weight and conjugation efficiency data for hydrophobic and hydrophilic PPCs. Average molar masses (g mol^{-1}) and dispersity values were determined by GPC under differential refractive index (DRI) detection and calibrated against linear polystyrene narrow standards. Conjugates marked with an asterisk are reported in ref. **11**, and are included here for convenient comparison.

	Polymer Precursor			Porphyrin–polymer Conjugate			
Conjugate	$M_{n,NMR}$[a]	$M_{n,GPC}$	$Đ$	$M_{n,NMR}$[a]	$M_{n,GPC}$	$Đ$	Conversion[d] (%)
$(PS_{20})_2$-Zn[b,*]	2350	2050	1.17	5350	5170	1.18	92 ± 6
$(PS_{30})_2$-Zn[b,*]	3400	2900	1.13	7450	7150	1.19	93 ± 6
$(PS_{40})_2$-Zn[b,*]	4450	5150	1.19	9500	10200	1.25	87 ± 11
$(PS_{20})_4$-Zn[b,*]	2350	2050	1.17	10340	9400	1.30	94 ± 6
$(PS_{20})_4$-Pd[b]	2350	2050	1.17	10380	7800	1.70	97 ± 2
$(PS_{30})_4$-Zn[b,*]	3400	2900	1.13	14500	10800	1.26	89 ± 9
$(PS_{40})_4$-Zn[b,*]	4450	5150	1.19	18700	15250	1.25	92 ± 5
$(PBA_{15})_4$-Zn[b,*]	2200	2350	1.15	9700	9200	1.24	91 ± 4
$(PtBA_{19})_4$-Zn[b,*]	2700	2800	1.24	11750	11800	1.20	98 ± 3
$(PDMA_{15})_4$-Zn[c]	1750	1125	1.30	7950	4200	1.59	97 ± 4
$(PNIPAM_{33})_4$-Zn[c]	4000	5900	1.13	16950	14550	1.23	60 ± 8
$(PHEA_{42})_4$-Zn[c]	5150	4300	1.24	11300	18400	1.35	59 ± 1

[a] $M_{n,NMR}$ was calculated from the average degree of polymerisation of the grafted polymer chains (determined by ^{1}H NMR) and the molar masses of the porphyrin, CTA and repeat unit.
[b] GPC eluent: THF, flow rate 1 mL min^{-1}, 40 °C with toluene as flow rate marker.
[c] GPC eluent: DMF, flow rate 0.7 mL min^{-1}, 50 °C with water as flow rate marker.
[d] Conversion determined by ^{1}H NMR integration. See ESI†, Section S3 for details.

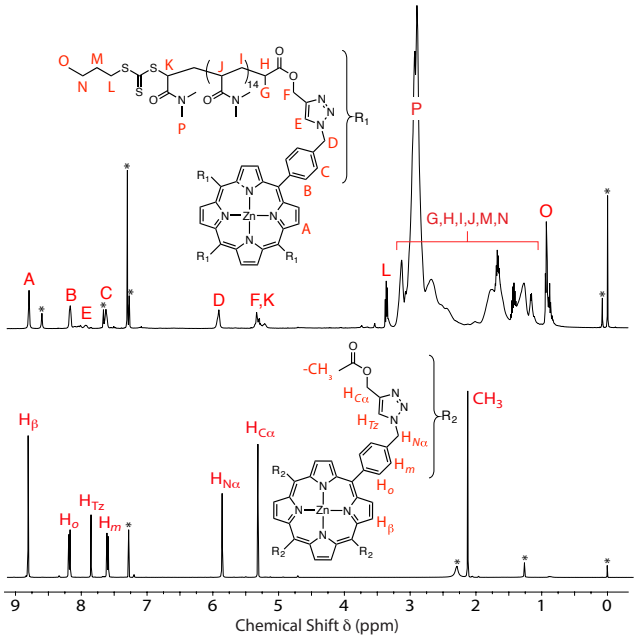

Figure 1. Assigned ^{1}H NMR spectra (500 MHz, 300 K, $CDCl_3/d_5$-pyridine = 98:2, *v*/*v*) of (*top*) **$(PDMA_{15})_4$-Zn** after SEC purification and (*bottom*) tetra(triazolyl acetate) porphyrin derivative[11] for comparison. Asterisks denote residual solvent peaks ($CHCl_3$, pyridine).

Coupling reactions using hydrophilic alkyne-polymers were, with the exception of PDMA (Figure 1), less efficient than their hydrophobic counterparts, proceeding to ~60% conversion for PHEA and PNIPAM conjugates (Table 1). We postulate that the reduced reaction efficiency arises due to unfavourable interactions between the polar polymer repeating units and the hydrophobic azidoporphyrins, which prevents the reactants from efficiently diffusing into close proximity. It is also possible that Cu(I)/(II) species are partially coordinated by the secondary amide and primary alcohol repeating units of PHEA and PNIPAM, thus reducing their availability for catalysis. Poon *et al.* avoid this complication by performing the CuAAC reaction with a large excess (~20 equiv.) of copper(II) sulfate.[15] Our attempts to perform CuAAC coupling with large excesses of copper(II), however, greatly complicated purification of the hydrophilic PPCs and caused incipient transmetallation of the porphyrinatozinc(II) core. Despite partial coupling, PHEA and PNIPAM-PPCs showed good solubility in water (20–30 mg mL^{-1}), forming viscous gels at higher concentrations. **$(PNIPAM_{33})_4$-Zn** also displayed thermoresponsive water solubility, with a lower critical solution temperature of 21 °C—approximately 10 °C lower than a linear PNIPAM of comparable length, presumably due to the greater entropic penalty of solvating the porphyrin core in water.[16]

Evidence of Thermal Huisgen Side Reaction

Complex splitting of the aromatic triazole and adjacent methylene resonances in the ^{1}H NMR spectra of the PPCs revealed an unexpected side reaction that occurs during porphyrin–polymer coupling. Previously we attributed this splitting to a combination of diastereotopic induction from a nearby stereocenter and partial formation of the 1,5-triazole isomer (≤ 20% by ^{1}H NMR) due to thermal Huisgen cycloaddition competing with the copper(I)-catalysed

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pathway.[11] We have obtained HSQC, HMBC and variable temperature NMR data that are consistent with this hypothesis (see ESI†, Section S5.1). To further confirm that the thermal cycloaddition pathway operates under the reaction conditions, we reacted **TN_3PP-Zn** and alkyne-PS at 100 °C without a copper catalyst and monitored PPC formation by GPC and ^{1}H NMR spectroscopy (see ESI†, Section S5). Partial coupling was apparent after 25 min, and integration showed approximately equal proportions of the 1,4- and 1,5-triazole isomers. This result establishes that the thermal cycloaddition reaction can occur under the conditions used to prepare the PPCs. We suggest that the random coil conformation of the alkyne-polymer partially shields the alkyne end-group functionality, hindering copper acetylide formation and thus slowing the copper(I)-catalysed pathway. This result is noteworthy for the polymer chemistry community, considering that the microwave-assisted CuAAC reaction at elevated temperature is often used for polymer coupling reactions.[15, 17]

Post-synthetic Modification of PPCs

PPCs with different metalloporphyrin cores were prepared either by metallation of the azidoporphyrin precursor or post-synthesis transmetallation of the PPC. The azidoporphyrins were compatible only with mild metallation reactions, e.g., $Pd(OAc)_2$ in $CHCl_3$/MeOH, which proceeded smoothly from **TN_3PP-H_2** (see ESI†, Section S1.3). The high efficiency of palladium insertion into **TN_3PP-H_2** directly contrasts the difficulties High *et al.* faced when attempting metallation of porphyrin-cored ATRP macroinitiators.[8d] **TN_3PP-Zn** was, however, unstable under more aggressive conditions, such as those use for tin(IV) metallation.[18] Alternatively, demetallating a zinc(II)-PPC under acidic conditions followed by remetallation with tin(IV) proceeded without any apparent degradation of the porphyrin core or polymer shell (see ESI†, Section S7). ^{1}H NMR and UV-Vis data did, however, reveal that the trithiocarbonate residue was cleaved during metallation, indicating that reinitiation of a subsequent polymer block is not possible after transmetallation. Aside from this limitation, it should be possible to prepare a wide range of transition metal-containing PPCs using either of these two methods.

Preparation and Characterisation of PPC Nanoparticles

Precipitating dilute THF solutions of polystyrene-PPCs (PS-PPCs) (0.01–0.1 wt%) into water afforded iridescent pink suspensions, which were left to stand overnight in a sealed vessel to allow any large aggregates to settle. The supernatant was removed to obtain stable suspensions of PPC nanoparticles, which were analysed by dynamic light scattering and transmission electron microscopy (TEM) (see ESI†, Section S7-S8). The suspensions contained polydisperse particles with diameters typically below 900 nm after settling. Interestingly, TEM revealed that the particles possessed an unanticipated bowl-shaped morphology, typified by a single dimple on the surface of the otherwise spherical particles (Figure 2). PS-PPCs were the only conjugates noted to form well-defined particles; for example, **$(PNIPAM_{33})_4$-Zn** and **$(PBA_{15})_4$-Zn** both precipitated as amorphous aggregates (see ESI†, Section S8).

Previously, de Loos *et al.* reported on the assembly of porphyrin-PS monoconjugates in aqueous solution.[19] Cu(II) and Mn(III) porphyrins conjugated to a ~10, 000 g mol^{-1} PS chain assembled into small spherical micellar aggregates, whereas an Mn(III)-porphyrin PS conjugate with a 1, 500 g mol^{-1} PS tail formed vesicular structures. In our work, TEM analysis of ultra-cryomicrotomed nanoparticle suspensions revealed that the particles are solid and do not have any internal morphology (see ESI†, Figure S19). Similar bowl-shaped particles have been observed in other reports that employ block copolymer amphiphiles, which are known to support nanoparticle shape transformations.[20] It is therefore remarkable that non-amphiphilic PS-PPCs can also give rise to bowl-shaped particles.

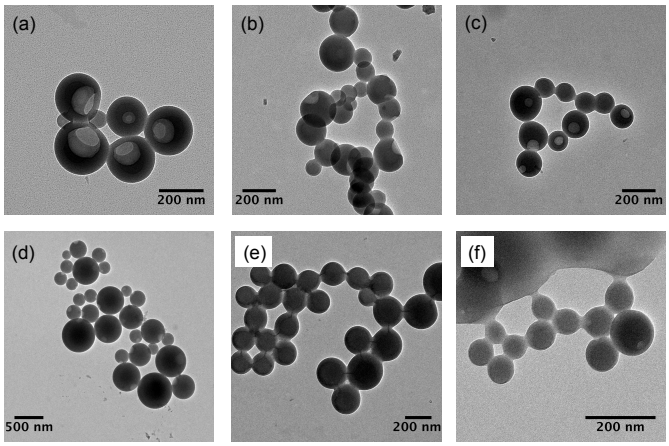

Figure 2. Representative TEM images of polystyrene-PPC nanoparticles: (a) **$(PS_{20})_2$-Zn**; (b) **$(PS_{20})_4$-Zn**; (c) **$(PS_{30})_2$-Zn**; (d) **$(PS_{30})_2$-H_2**; (e) **$(PS_{30})_4$-Zn**; (f) **$(PS_{30})_4$-H_2**. There is an apparent correlation between dimple diameter and the size of the polymer shell around the porphyrin core.

Eisenberg and co-workers have proposed a model describing how bowl-shaped nanoparticles form in aqueous mixtures of water-miscible organic solvents.[21] According to this model, adding water to a THF solution of a glassy polymer affords a suspension of solvent-rich polymer particles dispersed in an aqueous bulk phase. These nascent particles are initially permeable, allowing trapped THF and water to diffuse from the particle into the bulk solvent. When the THF content of the particle falls below a critical level, small water droplets are thought to form within the particle matrix. Depending on the fluidity of the particle matrix at this point, these water droplets can be trapped within the particle, completely liberated or become frozen at some point in between (i.e., a porous sphere). While the studies by Eisenberg and coworkers focused on block copolymers capable of forming large compound micelles, their explanation is intuitively consistent with dimple formation in PS-PPC nanoparticles. It is also interesting to note that our THF-into-water precipitation methodology, which is the reverse of Eisenberg's water-into-THF method, yields particles with similar size distributions and morphologies. This observation suggests that the path dependence for PPC nanoparticle

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formation is inverted compared to the block copolymer amphiphiles used in the studies of Eisenberg and co-workers.

We noted that the size of the dimple correlated approximately with the porphyrin/polymer ratio of the PPCs (Figure 2). According to the Eisenberg model, the internal viscosity of the nascent solvent-swollen nanoparticles most strongly influences the number and size of the dimples. It appears that the internal viscosity of the PPC particle decreases with decreasing porphyrin/polymer ratio, possibly due to reduced π-π and zinc-triazole interactions as larger polymer shells cause greater steric shielding of the PPC cores. Thus, water droplets trapped within the nascent nanoparticles are more rapidly expelled at smaller porphyrin/polymer ratios, resulting in shallower dimples.

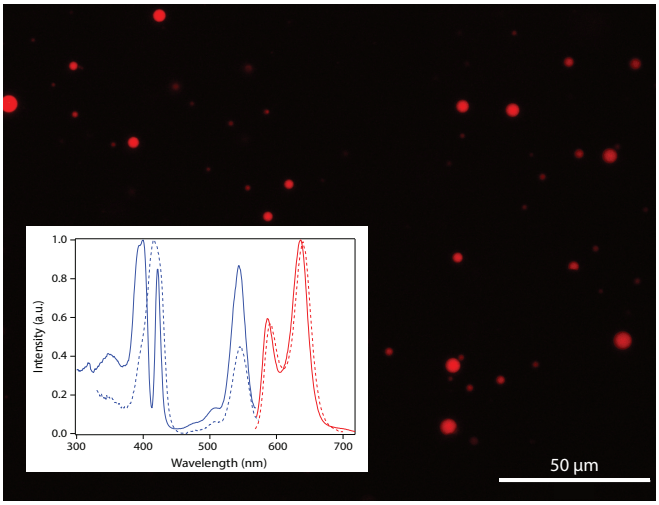

Figure 3. False-colour fluorescence micrograph of **$(PS_{30})_2$-Zn** in water prior to settling. A relatively small proportion of microparticles dominate these images due to their much greater fluorescence than smaller nanoparticles. Inset: Comparison of fluorescence spectra of **$(PS_{30})_2$-Zn** in THF (2 mM) (dashed lines) and a suspension of **$(PS_{30})_2$-Zn** (ca. 0.1 mg mL^{-1}) (solid lines). Details provided in ESI†, Section S10.

Fluorescence microscopy and conventional steady-state fluorescence measurements confirmed that the porphyrin fluorescence is localised to the particles, rather than the surrounding solution, and that the porphyrins do not form excitonically-coupled aggregates within the particles. These features afford highly fluorescent dimpled spheres with spectral profiles similar to the molecularly dissolved conjugates (see ESI†, Section S9). Sensing properties of the particles were demonstrated by adding HCl to an aqueous suspension of freebase PPC nanoparticles. A characteristic red-to-green colorimetric response was noted upon addition of HCl, suggesting that the nanoparticles are sufficiently permeable to allow colorimetric aqueous pH sensing (see ESI†, Section S10). Further investigation into the specific sensing of other chemical species is the focus of future work on this system.

Conclusions

In conclusion, the CuAAC reaction was used to prepare a library of hydrophobic and hydrophilic triazole-linked porphyrin-polymer conjugates. We have elucidated the reaction pathway of PPC formation and have explored the scope and limitations of expanding the methodology to include hydrophilic PPCs and other metalloporphyrin cores. Hydrophobic PS-PPCs were shown to form fluorescent bowl-shaped nanoparticles capable of colorimetric pH sensing. The modular nature of the CuAAC coupling methodology thus offers a convenient route to a wide range of porphyrin-containing particles with potential applications in chemical sensing.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, assigned 1D and 2D NMR spectra, molar mass and reaction efficiency calculations, raw GPC data and nanoparticle characterisation (DLS, TEM, fluorescence microscopy and fluorescence spectroscopy). See DOI: 10.1039/b000000x/

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