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ARTICLE TYPE

Water Soluble Octa-Functionalized POSS: All Click Chemistry Synthesis and Efficient Host-Guest Encapsulation

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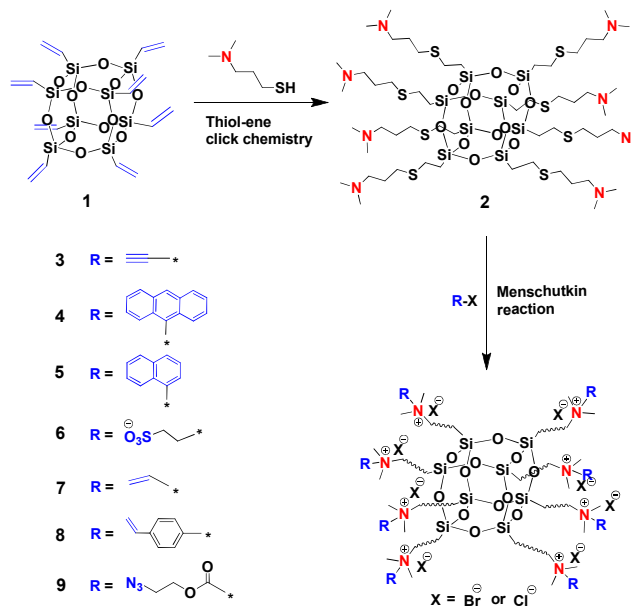
A series of water soluble octa-functionalized POSSs were facilely synthesized via thiol-ene and Menshutkin click chemistry. Among them, octa-alkynyl POSS further reacted with azide-terminal alkyl long chains offered well-defined, amphiphilic octopus-like POSS. For the first time, it was used for host-guest encapsulation and exhibited an ultrahigh loading capability.

Polyhedral oligomeric silsesquioxane (POSS) compounds possess uniform cubic structure, inherent nanoscale dimension (about 0.5 nm in diameter), and multi-functionality, enabling them excellent building blocks for organic-inorganic hybrid materials and nano composites.¹ Because of its highly hydrophobic Si-O-Si skeleton, POSS is oil-soluble but water-insoluble in nature, which limits its hydrophilic applications such as drug carrier and gene delivery. So far, only the octa-ammonium POSS and a PEO-containing POSS reported by Chujo and Frey *et al.*, respectively, were water soluble,² whereas both of them are hard to be further modified due to the unavailability of reactive sides.³ Therefore, to synthesize water soluble octa-functional POSS remains a big challenge yet. Here, we report a novel approach to synthesis of water soluble quaternary ammonium POSSs with desired octa-functional groups, such as, propargyl, azido, styrenyl, and allyl, by sequential chemistry of thiol-ene, Menshutkin and CuAAC click reactions⁴ in a fast, effective and reliable manner (Scheme 1). Originally, we discovered that the amphiphilic POSSs made by further functionalization of octa-clickable POSSs with hydrophobic chains could be used as host molecules to load guest molecules efficiently, opening the door to the host-guest supramolecular chemistry of POSS.

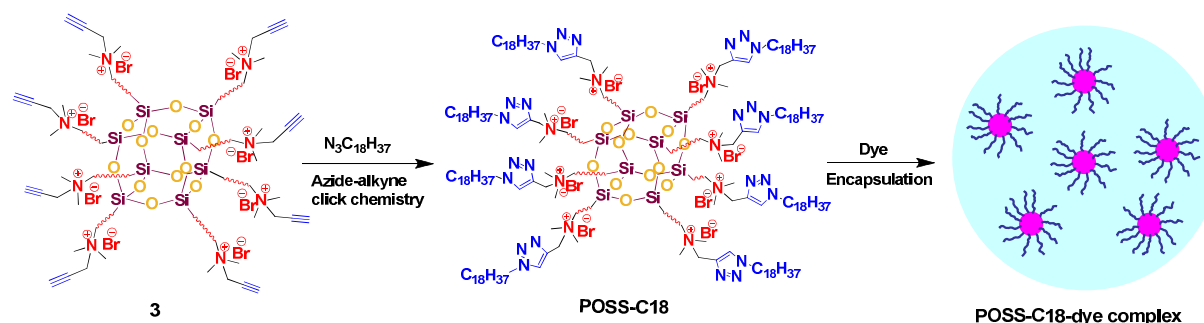
In the experiments, octa-ternary amino groups were firstly introduced to commercial octa-vinyl POSS, **1**, by thiol-ene click chemistry. Under UV-initiation, 3-(dimethylamino)-1-propanethiol (DPT) was reacted with **1** at room temperature for 1 h, affording octa-(N, N-dimethylamino propylthioethyl) POSS, **2**. Subsequently, **2** was quaternarized by propargyl bromide (or propargyl chloride) in DMF at 0 °C for 10 min, achieving water soluble octa-alkyne quaternary ammonium POSS, **3**. Such a Menshutkin click reaction is ultrafast and highly controllable in a polar aprotic solvent.⁵ By the combination of thiol-ene and Menshutkin click chemistries without any precious metals,^{6,7} the water soluble octa-clickable POSSs are readily and massively prepared in a fast way. Moreover, both coupling reactions performed in mild medium smoothly, avoiding destruction of POSS skeleton.⁸

The chemical structures of **2** and **3** were confirmed by ¹H, ¹³C and ²⁹Si NMR (Fig. S1, ESI†) and FTIR (Fig. S2, ESI†)

measurements. In the ¹H NMR spectrum of **2**, the disappearance of the vinyl protons at 5.87-6.16 ppm and the new characteristic 3-(dimethylamino)-1-propanethioether (DPTE) resonances at 1.64-2.70 ppm imply all the vinyl groups of **1** turned into ternary amine groups. Similar results from ¹³C NMR spectrum of **2** also confirm it. For instance, no vinyl carbon signals at 173.5 and 128.8 ppm as well as the new signals corresponding to carbons of DPTE are obviously visible. The shift of silicon signal transfers from -79.3 ppm to -69.55 ppm in the ²⁹Si NMR, due to the changing of vinyl group into carbon-carbon single bond. Meanwhile, since octa-silicon protons of cubic POSS molecule exist in the same chemical environment, it shows a narrow single peak. Besides, the molecular weight of **2** measured by matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectroscopy was 1587.4 g mol⁻¹, which was well coincide with its theoretical value (1586.9 g mol⁻¹, Fig. S3, ESI†). These characterizations demonstrated the intact skeleton of POSS during the chemical reactions and 100% conversion of octa-ternary amine groups.



Scheme 1. Various octa-functional quaternary ammonium POSSs (**3-9**) synthesized *via* sequential thiol-ene and Menshutkin click chemistries.



Scheme 2. Synthesis of amphiphilic POSS-C18 and its application for dye encapsulation. In the POSS-dye complex, the diameter of hydrophobic inorganic silica-like core of it is about 0.53 nm, the thicknesses of hydrophilic quaternary ammonium salt middle layer and of the hydrophobic alkane periphery are about 0.95 nm and 2.52 nm based on theoretical calculation, respectively.

To demonstrate the universality and versatility of our strategy, variously reactive functional groups including alkyne, azide, allyl, styrenyl and 1, 3-propane sultone were incorporated into **2** by facile and fast Menschukin click chemistry, giving various water soluble octa-functional POSSs (**3-9** as shown in Scheme 1). Their chemical structures were confirmed by ^1H , ^{13}C , and ^{29}Si NMR spectra (Fig. S1 and S4-S11, ESI †). The solubility of the synthesized products in different solutions was summarized in Table S1, also declaring the synthesis success of targeted molecules. Notably, fluorescent POSSs containing octa-anthracene (**4**) and octa-naphthalene (**5**) were readily synthesized by our sequential click chemistry methodology (Fig. S6 and S7, ESI †), which are highly attractive for the organic light emitting diode (OLED) and other optical applications due to their precise and monodisperse molecular structure (Fig. S12, ESI †). Octa-zwitterionic POSS, **6**, was synthesized for the first time, which is highly promising for antifouling and special surfactant applications. In addition, we primarily investigated the cell viability of **3** for its potential application as drug carrier. It was even more biocompatible than poly (amido amine) dendrimer (Fig. S13-S16, ESI †).⁹ Detailed studies will be reported later. These platforms of water soluble octa-functional POSSs are easy to be further functionalized by the convenient reactions such as, CuAAC click reaction, epoxidation, radical polymerization and esterification, etc.

For exploring the reactivity of quaternarized octa-functional POSSs, typically, **3** was employed to react with aliphatic azides of $\text{N}_3\text{-C}_{12}\text{H}_{25}$ and $\text{N}_3\text{-C}_{18}\text{H}_{37}$ using $\text{CuI}/\text{Et}_3\text{N}$ as catalyst, giving rise to amphiphilic POSS-C12 and POSS-C18, respectively (Scheme 2). Their chemical structures were also confirmed by ^1H , ^{13}C and ^{29}Si NMR spectra (Fig. S1, ESI †). As shown in ^{29}Si NMR spectra, at -79.3 or -69.1 ppm, all the silicon signals appeared as sharp single peaks implying their cubic structures were intact in the process of post-modifications. Therefore, our synthesis strategy by all click chemistry is highly reliable for fast and full functionalization of base-sensitive POSS molecules.

It is well known that amphiphilic dendritic or hyperbranched polymers with plenty of intramolecular cavities were the good hosts for encapsulation of guest small molecules.¹⁰ Inspired by this effect, we used the amphiphilic POSS-C12 and POSS-C18 as hosts to encapsulate guests of dyes (Scheme 2). Here, hydrophilic dyes including methyl orange (MO), methylene violet 3RAX (MV), rose bengal (RB), and eosin Y (EY) were selected as guests. The CHCl_3 solution of POSS-C12 or POSS-C18 was

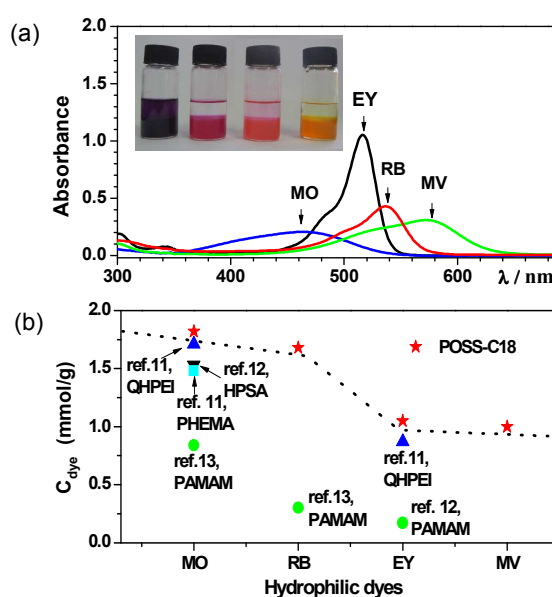


Fig. 1. Dye transfer effect of POSS-C18 to hydrophilic dyes (inserted picture) and UV-Vis spectra of the remained MO in aqueous solution after extraction by the chloroform solution of POSS-C18 (a); The highest C_{dye} values of typical hosts in previous reports and in this study (b). In the inset (Figure 2b), QHPEI, HPSA and PAMAM are the abbreviations of quaternized hyperbranched polyethyleneimine, hyperbranched poly(sulfonamide) and poly (amido amine), respectively.

vigorously mixed with an aqueous solution of dye, and the bottom organic phase was colorized due to the phase-transfer of dye from water to organic phase (Fig 1a). The loading capacities of dyes (C_{dye}) evaluated by UV-Vis spectrometer were listed in Table S2. The C_{dye} s of POSS-C18 are 1.82 to MO, 1.68 to RB, 1.05 to EY, and 1.0 mmol g^{-1} to MV. The C_{dye} s of POSS-C12 are also quite high, but slightly smaller than those of POSS-C18 mainly because of the lower polarity difference between core and shell. Correspondingly, the highest C_{dye} s for POSS-C18 and POSS-C12 reached up to 8.69 and 7.76 mol mol^{-1} (Table S2), respectively. This means that 1 molecule of POSS-C18 or POSS-C12 can load about 8 molecules of MO. Significantly, the C_{dye} s of POSS-C18 are generally higher than those of classic hosts of dendritic polymers (Fig. 1b). For instance, the C_{dye} (1.82 mmol g^{-1}

¹) of POSS-C18 to MO is the new record, which is higher than the ever highest C_{dye} (1.71 mmol g⁻¹) of dendritic polymers to MO by the contribution of quaternized hyperbranched polyethyleneimine (QHPEI).¹¹⁻¹³ In chloroform, both the amphiphilic POSS-C18 and the POSS-C18-dye complex exist in the form of micelles as evidenced by dynamic laser scattering (DLS) measurement. Notably, the hydrodynamic radii (R_h) of them are identical, indicating the dye molecules were embedded in the cavities of the complex (Fig. S19, ESI†).^{10, 14} Since octa-arms of POSS-C18 stretch outward, endowing the uniform micelles enough space for loading guest molecules. Therefore, the remarkable C_{dye} of amphiphilic POSS was mainly ascribed to its octopus-like architecture. The combination of precise structure and easy synthesis for our amphiphilic POSSs opens a new avenue to host-guest supramolecular chemistry.

Conclusions

In this work, we developed a general all-click chemistry methodology to readily synthesize water soluble octa-functional POSS by sequential use of thiol-ene, Menschutkin and CuAAC reactions. The synthesis process is fast, efficient, reliable, and controllable. Various desired functional groups such as azide, alkyne, styrenyl, allyl, hydroxyl, and carboxylic were introduced into octa-vertices of POSS fully. Versatile fluorescent and zwitterionic POSSs were also achieved facilely via our approach. The water soluble octa-functional POSSs promised potential application as drug carriers for their intrinsic low cytotoxicity, high cellular uptake ability, and precise structures. We designed and synthesized novel box-like molecules of amphiphilic POSSs. For the first time, we discovered their new property of host-guest encapsulation. Their unique octopus-like structure and relatively big cavities enable the amphiphilic POSSs load dyes in a very high efficiency. The POSS-dye complexes showed excellent coloring effect to plastics. Our results pave the way to water soluble multifunctional POSSs, and open the doors to host-guest supramolecular chemistry and bioapplications of POSSs.

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Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

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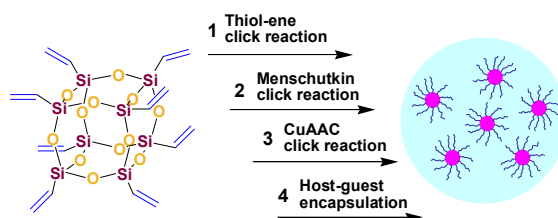
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- 3 Note: while ammonium groups changed into available amine ones in strong alkaline condition, the POSS skeleton would be destroyed since the Si-O-Si bond was quite base-sensitive.
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ARTICLE TYPE

Table of Contents artwork



⁵ Text:

Water soluble octa-functional POSSs were readily synthesized via all click chemistry, affording precise multifunctional platform for host-guest encapsulation and drug-delievery.