Programmable two-dimensional nanocrystals assembled from POSS-containing peptoids as efficient artificial light-harvesting systems

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Inspired by the formation of hierarchically structured natural biominerals (e.g., bone and tooth), various sequence-defined polymers have been synthesized and exploited for design and synthesis of functional hybrid materials. Here, we synthesized a series of organic-inorganic hybrid peptoids by using polyhedral oligomeric silsesquioxane (POSS) nanoclusters as side chains at a variety of backbone locations. We further demonstrated the use of these hybrid peptoids as sequence-defined building blocks to assemble a new class of programmable two-dimensional (2D) nanocrystals. They are highly stable and exhibit an enhanced mechanical property and electron scattering due to the incorporated POSS nanoclusters. By varying peptoid side-chain chemistry, we further demonstrated the precise displacement of a large variety of function groups within these 2D nanocrystals and developed a highly efficient aqueous light-harvesting system for live cell imaging. Because these 2D nanocrystals are biocompatible and highly programmable, we expect that they offer unique opportunities for applications.

INTRODUCTION

In nature, biominerals, such as bones, teeth, and calcareous shells of marine organisms, are organic-inorganic hybrid materials with hierarchical structures and remarkable functions (e.g., high mechanical strength) as a result of the high information content of biomacromolecules and a precise control over the stereochemistry of inorganic (nano)crystals (1, 2). Inspired by nature, a variety of bioinspired “bottom-up” self-assembly approaches have been developed to design and synthesize hierarchically structured organic-inorganic hybrid materials due to their potential applications in photovoltaic and optoelectronic devices (3), catalysts (4), and sensors (5). Among various building blocks that have been used for this purpose, sequence-defined polymers and nanoclusters are both particularly interesting, because the former offers the potential of achieving high-level controls over the formation of hybrid materials as seen in the natural systems due to the embedded high information content (6–9), while the latter are promising as “artificial atoms” in the synthesis of hierarchically structured hybrid materials by incorporating their unique properties as a result of the strong quantum confinement effect (1, 10–17). While a combination of these two building blocks could generate a wide range of functional hybrid materials with unique properties (18–21), nanoclusters have been rarely used as side chains of sequence-defined polymers owing to the intrinsic difficulties in their synthesis (22, 23).

Inspired by the highly efficient light-harvesting systems in green plants and living organisms, in which well-positioned chromophores and protein complex formed an efficient Förster resonance energy transfer (FRET) system for converting light to chemical stored energy, many synthetic materials have been developed to mimic this natural light-harvesting process by achieving efficient energy transfer from donors to acceptors (24–26). However, despite great advances that have been made in this area, developing highly efficient light-harvesting systems in aqueous solution rather than in organic environments is still a challenging task (27–30). On the other hand, while two-dimensional (2D) nanomaterials assembled from sequence-defined molecules have recently received considerable interest because their embedded high information contents offer tremendous potentials in applications (7), organic-inorganic hybrid 2D nanomaterials assembled from these sequence-defined building blocks are extremely rare, and no studies have been reported to develop such hybrid materials as efficient artificial light-harvesting systems.

Here, we used polyhedral oligomeric silsesquioxane (POSS) nanoclusters as side chains to design and synthesize POSS-containing hybrid peptoids that self-assembled into a new class of membrane-mimetic 2D nanocrystals. Peptoids were chosen here as sequence-defined polymers for the precise placement of nanoclusters because they are highly stable protein mimetics and are biocompatible (31, 32). Moreover, their lack of backbone hydrogen bond donors simplifies tuning of interpeptoid interactions exclusively through side-chain chemistry (8, 27, 31, 33–44). We chose the POSS nanocluster for this work, because it is the smallest silica nanoparticle and adopts an atomically precise cage-like conformation. Furthermore, the high stability and strong hydrophobicity of POSS clusters make them attractive building blocks that can be covalently attached to self-assembling molecules to obtain composite materials with unique properties (e.g., enhanced thermal and mechanical properties) for a variety of applications (e.g., drug delivery and biological imaging) (11, 13–15, 45–48).

Homing POSS as the side chain of peptoids enabled the synthesis of sequence-defined 2D nanomaterials (7) with enhanced mechanical properties and high electron scattering for transmission electron microscopy (TEM) imaging. By taking advantage of the easy synthesis and high tunability of these hybrid peptoids, we synthesized a series of 2D nanocrystals with POSS located at various peptoid backbone locations using peptoids with a wide range of functional side-chain groups to achieve protein-like
side-chain complexity. Because of the high crystallinity of these POSS-containing 2D nanocrystals, we successfully built a highly efficient aqueous light-harvesting system with an energy transfer efficiency of 96.4%, by coassembly of dansyl (DNS: donor) and β-cyclodextrin (CD) containing hybrid peptoids to achieve the precisely controlled spatial distributions of donors and acceptors. We further demonstrated the use of this artificial light-harvesting system as a biocompatible probe for live cell imaging.

RESULTS AND DISCUSSION

Design of POSS-containing hybrid peptoids

These hybrid peptoids were synthesized by using aminopropyloctooctyl POSS dissolved in CH₂Cl₂ during the displacement step of the “submonomer” solid-phase synthesis method (see the Supplementary Materials) (37, 39, 49). This synthetic approach allowed us to easily and efficiently synthesize POSS-containing hybrid peptoids with a precise placement of POSS clusters at any designed backbone locations, generating self-assembling peptoids (Fig. 1) with programmable polar side chains. The successful synthesis of hybrid peptoids was confirmed by ultra-performance liquid chromatography (UPLC) coupled with mass spectroscopy (MS) (UPLC-MS) and nuclear magnetic resonance (NMR) spectroscopy (figs. S1 to S18).

To design hybrid peptoids that could form 2D nanocrystals, we first synthesized a lipid-like peptoid Pep-1 having N-(2-carboxyethyl) glycine (Nce) as the polar domain and POSS as the hydrophobic domain (Fig. 1 and Supplementary Materials). By doing so, we were motivated by our recent success in the development of membrane-mimetic crystalline 2D nanosheets from lipid-like peptoids (39, 43). Here, we hope to take advantage of the strong hydrophobic interactions among POSS groups (11, 13, 14, 45, 46) to drive the assembly of Pep-1 into a similar 2D nanocrystal by having Nce groups exposed outside and POSS groups packed inside.

Assembly of POSS-containing peptoids into membrane-mimetic 2D nanosheets

Pep-1 2D nanosheets were formed through a similar, evaporation-induced crystallization process (37, 39) from amorphous Pep-1 precursors in the presence of water (H₂O) and acetonitrile (CH₃CN) (fig. S19) (see Materials and Methods). Atomic force microscopy (AFM) studies showed that these hybrid peptoids formed uniform 2D nanosheets with straight edges, with a thickness of 4.4 ± 0.2 nm (Fig. 2A) and exhibiting a rhomboidal shape with an acute angle of nearly 80°. The formation of rhomboid-shaped 2D sheets was further confirmed by TEM (Fig. 2B) and scanning electron microscopy (SEM) results (fig. S20A). The energy-dispersive x-ray (EDX) result confirmed the presence of POSS within these 2D nanosheets (fig. S20B).

X-ray diffraction (XRD) data show that 2D nanosheets assembled from POSS-containing Pep-1 are highly crystalline (Fig. 2C). The first low q peak (d = 4.5 nm) corresponds to sheet thickness, consistent with the height obtained from AFM results. The d-spacing values (d = 10.7, 10, and 8.0 Å) are similar to those reported in

Fig. 1. Structures of peptoids Pep-1 to Pep-16 showing the POSS clusters at a variety of backbone locations.
other POSS-containing nanomaterials, indicating the typical POSS-POSS interaction that drives 2D nanocrystal formation (Fig. 2D) (14, 46, 47, 50). The peak at 4.5 Å shows the alignment of peptoid chains (Fig. 2D) (39, 44). The 3.6-Å spacing is the N···N distance along the backbone direction (Fig. 2D) (39, 44).

Time-dependent TEM and AFM results showed that peptides were packed anisotropically to form freestanding 2D nanocrystals. Pep-1 formed nanoribbons with a height of 4.2 ± 0.3 nm and nanosheets with rough edges before transforming into 2D nanocrystals (Fig. S21). These results indicate that POSS-POSS interactions along the backbone direction are stronger than those along the y direction, but interpeptoid interactions along both directions are strong enough to assemble peptoids forming a 2D nanostructure.

On the basis of these AFM, TEM, and XRD results, we proposed a molecular packing model of Pep-1 2D nanocrystals (Fig. 2D). The diagonal length of the POSS cluster is about 1.3 nm (46). The twisted Nce domain is about 1.6 nm based on the calculation of the N···N distance of 3.6 Å between Nce side-chain residues along the backbone direction (Fig. 2D) (39, 44). Therefore, the POSS groups are packed within Pep-1 sheet in an interdigitated pattern, similar to the packing of POSS clusters reported previously (46). Nce groups are distributed on sheet surfaces. The significant hydrophobic interactions between POSS groups and the diblock-like features of Pep-1 collectively contribute to a strong interpeptoid interaction, leading to the formation of freestanding 2D nanocrystals in solution.

To further confirm this model and demonstrate the significance of POSS-POSS interactions in 2D crystal formation, we modified the design of Pep-1 to form Pep-2 by moving the POSS location from the N to the C terminus, as well as Pep-3 by deleting the POSS group (Fig. 1). As expected, while Pep-2 formed a similar 2D nanocrystal (Fig. 3A), Pep-3 without POSS did not form any ordered structures (Fig. S3). To demonstrate that the ordering of hydrophobic POSS domains is critical for the formation of the 2D nanosheet structure, we synthesized Pep-4 to Pep-7 by changing the polar domain from Nce6 to (NaeNce)3 [Nae = N-(2-aminoethyl)glycine] (Pep-4), or to the noncarboxyl containing Nae6 (Pep-5), Nte6 [Nte = N-2-(2-methoxyethoxy)ethyl]glycine] (Pep-6), or Nte4 (Pep-7). As expected, all peptoids assembled into nanosheets (Fig. 3A and fig. S22A). XRD data showed that they are highly crystalline and exhibited typical POSS peaks and peptide packing peaks (Fig. 3B and fig. S23). To highlight the significance of POSS-POSS interactions in 2D structure formation, we synthesized peptoids Pep-8 to Pep-12 by either decreasing the number (n) of Nce groups from 6 (Pep-1) to 4 (Pep-8) or 5 (Pep-9), or increasing n to 8 (Pep-10), 10 (Pep-11), or 12 (Pep-12) (Fig. 1). As expected, all peptoids formed similar nanosheets (Fig. 3A and fig. S22A). While all peptoid assemblies exhibited a similar morphology (fig. S22), their sheet thickness increased from 3.5 to 5.6 nm when n increased from 4 to 12 (table S1). The presence of this richer variety of surface chemistries enabled POSS-containing nanosheets with various surface charges, as indicated by the zeta potential (fig. S22C).

The formation of 2D nanosheets was also observed for the self-assembly of Pep-4 in PBS buffer solution (fig. S24), although formation of sheets with straight edges typically required longer incubation times of ~72 hours. The importance of strong hydrophobic interactions among POSS groups that drive peptide assembly was also highlighted by the formation of 2D nanocrystals from Pep-13 with 16 Nce groups. As shown in fig. S25, large quantities of nanoribbons were observed before nanosheets appeared. XRD results show that nanocrystals assembled from Pep-13 exhibit a similar structure to those assembled from Pep-10, Pep-11, or Pep-12.

The formation of similar nanosheets from three-armed star-shaped peptoids (35) (Pep-14 with two POSS groups and Pep-15 with three POSS groups) (Fig. 1) further highlights the importance of POSS-POSS interactions in sheet formation (Fig. 3). XRD data show that nanosheets assembled from Pep-14 or Pep-15 are highly crystalline and have similar structures to those assembled from linear peptoids (Fig. 3B and fig. S26). These results suggest that POSS groups can be placed at a variety of backbone locations for the design of sheet-forming hybrid peptoids, significantly enriching the surface chemistry of POSS-containing 2D nanocrystals.

To further demonstrate that the enhanced hydrophobic interaction among POSS groups is the main driving force that leads to the formation of these POSS-containing 2D nanocrystals, and the self-assembly of these 2D nanosheets is robust to the addition of multiple functional groups, we designed and synthesized POSS-containing peptoid Pep-16 by changing the polar domain of Pep-1 from Nce6 to six different polar side chains (Figs. 1 and 3B), which include Nce, Nae, Noe [N-(2-hydroxyethyl)glycine, mimics serine], Nse [N-(2-thioethyethyl)glycine, mimics cysteine], Nhs [2-(4-imidazolyl)ethyl]amine)glycines, mimics histidine], and Ntrp [N-(2-(1H-indol-3-yl)ethyl)glycine, mimics tryptophan]. Pep-16 with six different polar side chains formed 2D nanocrystals structurally similar to Pep-1 nanocrystals (Fig. 3B), offering the potential of building crystalline 2D nanomaterials with highly programmable surface chemistries and protein-like high information content.
Stability and mechanical properties of POSS-peptoid–based 2D nanocrystals

To confirm that the incorporation of POSS into self-assembling peptoids results in 2D nanocrystals with high stability, we exposed Pep-1 nanocrystals to a range of solvents as well as high temperature. As shown in Fig. 4, Pep-1 nanocrystals were stable after being immersed in H₂O for almost 2 months (Fig. 4). The high stability of these Pep-1 nanocrystals was further evidenced as they survived after being incubated overnight in pure organic solvents, such as CH₃CN, methanol (MeOH), and ethanol, or after heating to 95°C in H₂O for 6 hours (Fig. 4 and fig. S27). Such high stability was also observed for 2D nanocrystals assembled from Pep-16 containing six different polar side chains (fig. S28).

One unique advantage of hybrid materials is that they often exhibit attractive mechanical properties. To determine whether incorporation of POSS nanoclusters could significantly enhance the mechanical property of assembled 2D nanocrystals, we evaluated the Young’s modulus of the POSS-peptoid–based 2D nanocrystals by using liquid-cell AFM with nanomechanics mode (51, 52). As shown in Fig. 4 (G and H), the effective Young’s modulus of POSS-containing 2D nanocrystals (assembled from Pep-1; 3.0 × 10⁸ Pa) increased almost five times compared to our previously reported non-POSS-containing 2D nanocrystals (39) (assembled from Pep-17; 6.4 × 10⁷ Pa). These results show that integration of POSS clusters into 2D nanosheets significantly increases the nanosheet mechanical properties.

Building a highly efficient FRET system using POSS-peptoid–based 2D nanocrystals

To demonstrate the potential application of this new class of programmable hybrid 2D nanosheets, we built a highly efficient aqueous light-harvesting system by incorporating donor/acceptor pairs as peptoid side chains with precisely controlled spatial distributions. The dansyl (DNS: donor)–modified hybrid peptoid Pep-DNS (fig. S29) and CD (β-cyclodextrin)–modified Pep-CD (fig. S30)
were synthesized and mixed with a molar ratio of 9:1 (Pep-DNS to Pep-CD) to assemble 2D nanosheets (Fig. 5 and fig. S31). The colloidal nanosheets suitable for cellular studies were obtained by sonication cutting (34, 37) (see the Supplementary Materials) and showed an average length of 34.97 ± 9.72 nm (revealed by dynamic light scattering data; fig. S31). Rhodamine B (RB) was used as the acceptor because it is a well-known guest molecule for CD (27), and its absorption band exhibits significant overlap with the fluorescence emission peak of DNS donor, thus fulfilling one of the requirements for high FRET efficiency. Because of strong binding between RB and CD cavity, RB can be easily loaded into the CD groups on sheet surfaces. As shown in Fig. 5, RB over a range of concentrations was added into the aqueous solution of colloidal nanosheets and the fluorescence emission spectra were used to evaluate the FRET process. The results show that upon the addition of RB, the emission of DNS at 515 nm gradually decreases, while the emission of RB at 584 nm gradually increases. The energy transfer efficiency estimated from the fluorescence quenching rate of the DNS in the nanosheets is as high as 96.4% (see the Supplementary Materials for details), which is significantly larger than our previously reported FRET-active hierarchical materials assembled from non–POSS-peptoid sequence (27). As far as we know, this is the most efficient aqueous light-harvesting system reported so far (27–30, 53), further highlighting the importance of the POSS cluster in the development of functional hybrid materials. In a negative control experiment, 2D nanocrystals without CD groups did not exhibit any FRET phenomena due to the absence of specific binding of RB to the 2D crystal surface (fig. S32). These results verified the FRET effect that happened on the nanocrystal surface. Time-resolved fluorescence measurements revealed a remarkable decrease in the donor fluorescence lifetime when increasing the acceptor molar ratio. The decay curve of DNS could be decreased from the exponential decay with a lifetime of τ = 14.2 ns to τ = 1.7 ns after gradually increasing the acceptor molar ratio (fig. S32B). Such an apparent shortening of the donor lifetime suggests the effective energy transfer from the donors to acceptors (54). We also noticed that the maximum energy transfer efficiency occurred when the molar ratio of donor/acceptor ([DNS]/[RB]) is about 25:1. This phenomenon is due to the high binding force between CD and RB acceptors within nanosheets, and the spacing between DNS and RB is optimal, thus resulting in a high FRET efficiency in the light-harvesting process. The strong intermolecular coupling in this light-harvesting system may result in the excitation energy being delocalized over more than one dye. During irradiation, the excitation energy rapidly migrated throughout the coupled surface dye until being received by the acceptor. The excitation migration rate constant was estimated to be 2.6 × 10^13 M^-1 s^-1, suggesting a fast energy migration rate (fig. S33) (30, 55–57). The RB emission by energy transfer from multiple DNS surpasses that by its own excitation owing to the antenna effect. We obtained the antenna effect as 5.9 at a doping concentration of 2.0 μM (fig. S34). It further demonstrated that these POSS-containing 2D nanocrystals functioned as excellent light-harvesting systems (28, 58).

To verify that these colloidal POSS-peptoid–based 2D nanocrystals are nontoxic for cellular studies, they were mixed with H1299 cells for cell viability tests. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay results showed that even when the 2D nanocrystal concentration is as high as 40 μM, more than 90% of the cells survived, showing that these POSS-containing nanosheets are highly biocompatible (fig. S31E). To further take advantage of such high biocompatibility and the highly efficient energy transfer of these hybrid nanosheets, they were incubated with H1299 live cells for FRET testing. This highly efficient FRET effect was further observed within these live cells for detecting RB model molecules. As a control, the live cells without RB molecules did not exhibit FRET (Fig. 5D). These results showed that hybrid 2D nanosheets exhibited a highly efficient energy transfer in aqueous solution and within live cells, which offer great potentials as biocompatible FRET–based sensors (53) for detecting biologically important biomarkers and for investigating the interactions of these hybrid nanosheets with biomolecular drugs (e.g., proteins and nucleic acids). By combining the highly efficient energy transfer, enhanced mechanical properties, high biocompatibility, and programmable compositions, these POSS-containing hybrid 2D nanosheets provide a new platform for the development of optoelectronic and theranostic materials.

In summary, by incorporating POSS clusters as peptoid side chains, we synthesized a series of POSS-containing sheet-forming
hybrid peptoids by having POSS at a variety of backbone locations. We demonstrated the self-assembly of these hybrid peptoids into a new class of sequence-defined 2D nanocrystals that have precise placement of POSS clusters. These nanocrystals are highly tunable and exhibit protein-like side-chain complexity by having six different polar side chains to construct surface chemistries. Because of the incorporated POSS clusters, these hybrid 2D nanosheets are highly stable and exhibit enhanced mechanical property and high TEM contrast, offering the opportunities of using liquid-cell TEM (59, 60) for investigating peptoid assembly pathways and dynamics. To demonstrate their potential applications, we programmed these sequence-defined 2D nanocrystals with precisely controlled locations and distances of donor and acceptor molecules and developed a highly efficient aqueous light-harvesting system with an energy transfer efficiency of 96.4%. These hybrid 2D nanosheets are highly biocompatible, and we further demonstrated their use as FRET-based probes within live cells. Because of the unique structural features and high energy transfer efficiency in aqueous systems, we expect these POSS-containing hybrid 2D nanosheets to offer tremendous opportunities for applications.

MATERIALS AND METHODS

Materials
Rink amide resin (0.7 to 0.9 mmol/g and 70 to 90 mesh), β-alanine tert-butyl ester hydrochloride, N,N′-diisopropylcarbodiimide, bromoacetic acid, and trifluoroacetic acid were purchased from Chem-Impex International Inc. (IL, USA). In addition, β-alanine tert-butyl ester hydrochloride was deprotected by the sodium hydroxide aqueous solution, then extracted with CH2Cl2, filtered, and rotary-evaporated for further reaction. Aminopropylsobutyl POSS (POSS-NH2) was purchased from Hybrid Plastics Inc. (MS, USA). Cysteamine hydrochloride, triphenylmethyl, RB, N,N-diisopropylethylamine, and trispropylsilane were purchased from Sigma-Aldrich (MA, USA) and used as received. Dansyl chloride was purchased from Acros Organics (part of Thermo Fisher Scientific Inc., CA, USA). Mono-6-amino-6-deoxy-cyclodextrin (CD-NH2) was synthesized according to the reported literature (39). All other amine submonomers and other reagents are obtained from commercial sources and used without further purification.

Solid-phase synthesis, purification, and characterization of peptoids
Generally, the peptoid sequences were synthesized and purified using modified solid-phase submonomer synthesis methods as described in the previously published work (37, 39). More details of synthesis methods are described in the Supplementary Materials. The purified peptoids were analyzed with UPLC (Waters, ACQUITY reverse-phase, the corresponding gradient at 0.4 ml/min over 7 min at 40°C with an ACQUITYBEH C18, 17 μm, and 2.1 mm × 50 mm column) that was connected with the MS system (Waters SQD2). Analysis v1.5 (Bruker, CA). The self-assembly pathways of Pep-1 were also captured by AFM in a time-dependent manner (2, 4, 9, and 16 hours). Because the sheet formation is too fast under 5.0 mM Pep-1, we used 0.5 mM peptoids to slow down the self-assembly process to capture the intermediates.

AFM studies
The self-assembled POSS-containing peptoids were characterized by ex situ AFM in air at room temperature using either tapping or peakforce Tapping mode in the nuclease-free environment using a Bruker MultiMode 8 instrument. AFM samples were prepared by diluting the self-assembled peptoids with Milli-Q water and using freshly cleaved mica as the substrate. The self-assembly pathways of Pep-1 were also captured by AFM in a time-dependent manner (2, 4, 9, and 16 hours) at 0.5 mM peptoid sample. The Young’s modulus of peptoid sheets was tested by in situ AFM. Peptoid sheet solutions were dropped onto freshly cleaved mica (Ted Pella, CA). After 5 min of incubation, the sample was gently rinsed by nuclease-free water (Ambion, Thermo Fisher Scientific). The AFM images and quantitative mechanical measurements were recorded with Peakforce Tapping mode in the nuclease-free water environment using a Bruker MultiMode 8 instrument. ScanAsyst-Fluid+ probes (Bruker, CA) with a standard spring constant of 0.7 N/m and a normal tip radius of 2 nm were used for imaging and mechanical measurement. The probes were calibrated before usage with the protocol in the user manual from Bruker. The raw data were further analyzed by offline software, Nanoscope Analysis v1.5 (Bruker, CA).

Zeta-potential measurement
Zeta-potential measurements of POSS-containing peptoid nanosheets were tested on SZ-100 brochure (HORIBA, Ltd., CA). Peptoid sheets were dispersed in H2O with a solution pH of 7.0 at a concentration of 1.5 mM.

Powder XRD experiments
Powder XRD data were collected at a multiple-wavelength anomalous diffraction and monochromatic macromolecular crystallography
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