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The Importance of the σ-hole in the Self-Assembly of Halogenated Polypeptoids

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Halogens are gaining increasing importance in designing functional polymeric materials. The most prominent feature of halogens is their high electronegativity, which facilitates the exploration of halogen-containing self-assembled structures. However, when halogens are involved in a covalent bond, the halogen atom tends to polarize and forms a region of positive electrostatic potential on its surface. This region of positive potential is referred to as a σ-hole [1]. The positive σ-hole then allows halogens to interact favorably with other electron-dense species and to form halogen bonds. To explore the effect of halogen bonding in polypeptoid crystals, a series of halogenated and non-halogenated polypeptoids were synthesized and the atomic-scale structure was determined using cryo-TEM.

The amphiphilic diblock copolypeptoids are comprised of a hydrophobic block of N-(2-phenylethyl)glycine (Npe) and hydrophilic block of poly(N-2-(2-(2-methoxyethoxy)ethoxy) ethylglycine) (Nte), as illustrated in Figure 1(A). In this study, the *para*-substituent (denoted by the *R* group) in Figure 1(A) is varied from a hydrogen, to a chlorine, and bromine atom. Figure 1(B) shows a 3-D atomic model of the nanosheets, where the hydrophobic block crystallizes to make up the core of the nanosheets and the hydrophilic block remains amorphous [2,3]. Figure 1(C) shows the projection through the *a*-*c* plane of the crystalline core of the nanosheets. Figure 1(D) is a representative TEM image of the dry Nte_4-Npe_6 (*para*-substituent = hydrogen) nanosheets from the direction of the *a*-*c* plane.
Low-dose cryo-TEM imaging was employed to minimize the radiation damage by the high energy electron beam on the nanosheets. The raw micrographs were first processed using an electron crystallography software to correct for distortions within the lattice [4]. Then, Relion was used to average tens of thousands of unit cells to produce the atomic-scale image shown in Figure 2(A) [5].
This image shows the projection through the *a*-*c* plane of the bromine-substituted nanosheets (the red *R* in Figure 1(A) is a bromine atom), where the brightest areas are the glycine backbone and the less bright V-shaped areas correspond to the phenyl side chains emanating from the backbones. The neighboring polypeptoids pack into an antiparallel V-shape formation when the *para*-substituent is a bromine, where the neighboring V-shaped formations point in opposite directions across columns, as seen in Figure 2(A). Conversely, when the *para*-substituent is a hydrogen atom, the neighboring polypeptoids pack into a parallel V-shape formation, meaning the V-shaped formations point in the same direction across columns.

In order to gain further insight into the effect of halogen substitution, molecular dynamics simulations were conducted. These simulations utilized a static, positive point charge to model the slight positive potential that occurs on the surface of a covalently-bonded halogen atom [6]. When the point charge is

included in the simulations of the halogen-containing peptoids, the parallel formation is destabilized and disassembles, while the antiparallel formation remains stable throughout the simulation. An analysis of the simulation results shows that bromine-substituted nanosheets in the antiparallel formation are stabilized by interconnected structures of neighboring halogen atoms and σ-holes on neighboring peptoid chains (see Figure 2(B)). The arrangement of chains in the parallel formation does not allow for as many interconnected structures, which leads to a less stable crystal structure.

The combination of atomic-scale imaging with molecular dynamics simulations has the potential to improve our understanding of factors that govern noncovalent interactions in synthetic materials. High resolution cryo-TEM allows us to directly image these radiation-sensitive materials in their preserved natural state while simulations provide insights into the intermolecular interactions. Developing a greater understanding of the relative importance of nonbonded intermolecular interactions can aid in designing molecules that yield a targeted crystal structure.

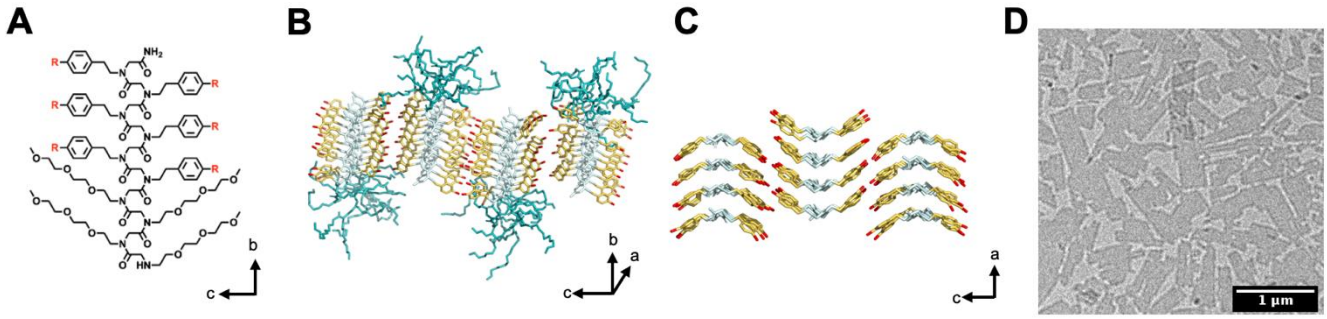

Figure 1. The chemical structure of the Nte_4-Npe_6 polypeptoids, with the variable R group in red (A). A 3-D atomic model of the Nte_4-$N4Brpe_6$ nanosheets in solution is shown in (B), where the amorphous, hydrophilic blocks are teal, the backbone of the aromatic blocks is white, the phenyl group on the aromatic block is yellow, and the bromine atom is red. The projection through the *a*-*c* plane of this atomic model is shown in (C). Panel (D) shows a representative image of the nanosheets formed by Nte_4-Npe_6 polypeptoids (R group = hydrogen).

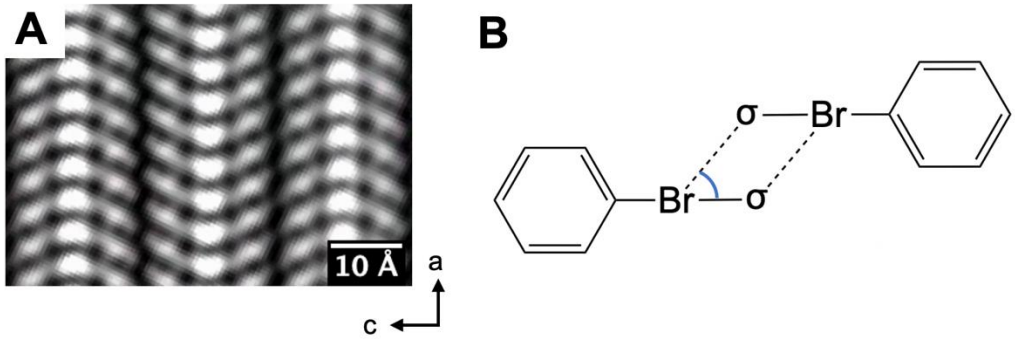

Figure 2. Averaged cryo-TEM image of the nanosheets formed by Nte_4-$N4Brpe_6$ polypeptoids (A). The light areas correspond to electron dense regions, where the brightest white spots are the glycine backbone and the phenyl groups form the V-shape structures to the sides. Panel (B) shows a diagram of an interconnected structure that occurs between halogen atoms and σ-holes on neighboring peptoids.

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