Self-assembling DNA-caged particles: Nanoblocks for hierarchical self-assembly

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DNA is an ideal candidate to organize matter on the nanoscale, primarily due to the specificity and complexity of DNA based interactions. Recent advances in this direction include the self-assembly of colloidal crystals using DNA grafted particles. In this paper we theoretically study the self-assembly of DNA-caged particles. These nanoblocks combine DNA grafted particles with more complicated purely DNA based constructs. Geometrically the nanoblock is a sphere (DNA grafted particle) inscribed inside a polyhedron (DNA cage). The faces of the DNA cage are open, and the edges are made from double stranded DNA. The cage vertices are modified DNA junctions. We calculate the equilibrium yield of self-assembled, tetrahedrally caged particles, and discuss their stability with respect to alternative structures. The experimental feasability of the method is discussed. To conclude we indicate the usefulness of DNA-caged particles as nanoblocks in a hierarchical self-assembly strategy.

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I. INTRODUCTION

DNA is one of the most celebrated tools in the nanoscience toolbox. This approach was pioneered in the laboratory of N. Seeman, where some of the first schemes for building nanostructures from specially engineered oligonucleotide sequences were proposed. A number of objects have been successfully constructed, including DNA cubes, multiple armed DNA junctions, DNA crystals, and DNA knots [1-4]. There have been several recent experimental advances in this direction [5,6], including the encapsulation of a single molecule inside a DNA tetrahedron [7]. There has also been a surge of interest in utilizing the specific interactions of complementary single-stranded DNA (ssDNA) to organize particles on the nanoscale. One recent advance in this direction is the self-assembly of three dimensional body centered cubic crystals from DNA grafted nanoparticles [8,9]. Up until this point, most of the studies reported the formation of small clusters or random aggregation of particles, as opposed to the self-assembly of ordered structures [10–12].

The potential complexity of DNA based interactions provides a means to design significantly more complicated nanoblocks. In this paper we propose a method to selfassemble DNA-caged particles (see Fig. 1). These nanoblocks are composite materials which are constructed by combining DNA grafted nanoparticles with specially designed DNA sequences. Geometrically the nanoblock is a sphere (DNA grafted nanoparticle) inscribed inside of a polyhedron (DNA cage). The polyhedron faces are open, and the cage edges are made of double-stranded DNA (dsDNA). The cage vertices are modified DNA junctions [13,14]. Each vertex of the cage carries a unique ssDNA sequence available for hybridization. This vertex "coloring" makes these nanoblocks ideal candidates as building blocks for hierarchical selfassembly strategies.

The plan for the paper is the following. We first introduce of our self-assembly proposal. Details of the proposal are discussed for a particular implementation in which the DNA cage is a regular tetrahedron. We theoretically calculate the melting profile for the DNA cage self-assembled around the DNA grafted particle. We demonstrate an equilibrium regime in which the DNA-caged particle is the dominant structure in solution, and discuss its stability with respect to alternative structures. We conclude by discussing how DNA-caged particles could be used as the building blocks in a hierarchical self-assembly strategy.

II. SELF-ASSEMBLY PROPOSAL

In this section we discuss the details of our self-assembly proposal. The proposal is to self-assemble DNA-caged particles by combining DNA grafted nanoparticles with rodlike DNA linkers. There is only one type of particle, i.e., all of the ssDNA grafted onto the nanoparticle surface have the same nucleotide sequence. The rodlike DNA linkers are ds-DNA, but each end of the rod terminates in a ssDNA sequence. The dsDNA rods can bend significantly when their length L is comporable to the persistence length $l_p \approx 50$ nm



FIG. 1. (Color online) Graphical depiction of the scheme for self-assembling DNA-caged particles. The cage edges are constructed from dsDNA rods with terminal ssDNA sequences on either end.



FIG. 2. (Color online) The vertex architecture is a modified four arm DNA junction. The arrowheads label the 3' end of the ssDNA arms. Note that the portion of arm 1 which is normally complementary to arm 4 is missing. Hence the 3' end of arm 4 provides the vertex with a unique "color," i.e., a ssDNA sequence available for hybridization.

for dsDNA [15]. In what follows we consider the case $L \ll l_p$ and treat the dsDNA as rigid rods. There are *n* types of rodlike DNA linkers, since the terminal ssDNA sequences on each linker are unique. The particle and linkers are all of the components necessary for the self-assembly proposal. The number of types of linkers is determined by the cage architecture, in general there will be one type for each edge of the cage. We now turn to discuss how the cage can be assembled from the DNA linkers.

For the sake of concreteness we will consider a particular implementation of this idea in which the DNA cage is a regular tetrahedron. In this case there are n=6 types of DNA rods, one for each edge of the tetrahedron.

These rods can be joined to assemble the cage in the following manner. To construct each vertex of the tetrahedron, four ssDNA sequences must be joined. Three of these ssDNA sequences are the terminal ssDNA sequences of the rodlike DNA linkers. The fourth ssDNA sequence comes from the ssDNA grafted onto the particle surface, which binds the particle to the cage. The DNA architecture that accomplishes this task is known as a four arm DNA junction (see Fig. 2). These junctions have been studied extensively, and the sequences can be designed so that the vertex is stable [13,14,16].

The problem is now to assign particular sequences to the terminal ssDNA sequences of the DNA rods which result in the desired tetrahedral cage, taking into account the proposed vertex architecture. One such assignment is proposed below in Fig. 3. We now provide an explanation of how Figs. 2 and 3 can be read together to understand the cage construction.

Examine vertex A in Fig. 3. We can see that rods R_1 , R_4 , and R_6 are joined together at this vertex. Let A_n denote the nucleotide sequence which plays the role of arm n (see Fig. 2) in vertex A, where $n \in \{1, 2, 3, 4\}$. The sequence assignments in the caption of Fig. 3 tell which rod provides each arm of the DNA junction. For example, $R_1=A_2-S-B_2$ means that rod R_1 provides arm 2 of vertex A and arm 2 of vertex B. For vertex A, rod R_1 provides arm 2, R_4 provides arm 4, and R_6 provides arm 3. Only arm 1 remains, which is provided by the ssDNA grafted onto the particle. In addition, since all of the ssDNA grafted onto the particle have the same sequence, by performing this enumeration procedure for each vertex we can see that the following four sequences are identical: $A_1=B_1=C_1=D_3$.



FIG. 3. (Color online) The proposed sequence assignment to the ssDNA ends of the DNA rods which self-assembles into the tetrahedral cage. If *S* denotes a dsDNA spacer, the sequence assignments for the six rods are $R_1=A_2-S-B_2$, $R_2=B_4-S-C_4$, $R_3=C_2-S-D_2$, $R_4=A_4-S-D_4$, $R_5=B_3-S-D_1$, $R_6=A_3-S-C_3$. The detailed structure of the vertex architecture (the circles in this diagram) is presented in Fig. 2.

Since it may be difficult (e.g., for steric reasons) to introduce the particle into the fully assembled cage, we would like for the particle to assist in the cage building process. This has been explicitly taken into account in the sequence designation process. Note that rod R_4 cannot bind at vertex Din the absence of the particle, since it hybridizes to arm 3 of the vertex (which comes from the particle).

With the basic framework in hand, the next task is to determine the relative abundance of the various structures that form in a solution of DNA linkers and DNA-grafted nanoparticles. A similar type of analysis has been performed in our related work on DNA-grafted nanoparticles [17,18]. In the next section we calculate the equilibrium yield for a variety of these structures. If the self-assembly process is experimentally feasible we should be able to demonstrate a regime in which our nanoblock, a single particle surrounded by a fully assembled DNA cage, is the dominant structure in solution.

III. DNA CAGE MELTING

We first determine the melting profile for DNA cages in the absence of the nanoparticle. By taking the proposed vertex numbering scheme (see Fig. 3) into account, we can enumerate all of the possible DNA structures which can form in solution (see Fig. 4).

Let c_i denote the concentration of linker R_i . In what follows $c_o = 1M$ is the standard reference concentration. In addition, we use natural units where the Boltzmann constant $k_B = 1$. In equilibrium the chemical potential of the various phases will be the same. The chemical potential has a contribution from the entropy of dilution, and the effective hybridization free energy for creating the the DNA connections at the vertex. For example, consider the reaction in which DNA linker rods R_1 and R_6 hybridize to form a dimer. Equilibriating the chemical potentials yields the following equation:



FIG. 4. (Color online) The subsets of the DNA cage (tetrahedron) which can be formed in the absence of the particle. For each topologically distinct diagram only one variety is shown.

$$T\ln\left(\frac{c_1}{c_o}\right) + T\ln\left(\frac{c_6}{c_o}\right) = T\ln\left(\frac{c_{16}}{c_o}\right) + \varepsilon_{16}.$$
 (1)

Here ε_{16} is the free energy for the formation of the dimer pair from the two monomers. In this case ε_{16} is simply the hybridization free energy associated with joining rods R_1 and R_6 together at vertex A. The resulting concentration of the dimer c_{16} is then

$$c_{16} = \frac{c_1 c_6}{c_o} \exp\left(\frac{-\varepsilon_{16}}{T}\right).$$
(2)

The total concentration of dimers \overline{C}_2 is determined by considering all of the possible dimer varieties,

$$\bar{C}_2 = c_{16} + c_{46} + c_{15} + c_{25} + c_{26} + c_{36} + c_{35}.$$
 (3)

The dimers can be considered freely jointed rigid rods, owing to the flexibility of the DNA junctions which constitute the vertex.

In general the free energy ε_{ij} is equal to the hybridization free energy $\Delta G_{ij} = \Delta H_{ij} - T \ln(\Delta S_{ij})$ for joining rods R_i and R_j . These free energies will depend on the particular choice of the DNA nucleotide sequences $\{A_i, B_j, C_k, D_l\}$. In what follows ε denotes the average hybridization free energy $\langle \varepsilon_{ij} \rangle$.

The reasoning for the trimer structures is largely the same. To write the hybridization free energies for the *n*-mers compactly, we label them by the indices for the rods which constitute the structure. For example, for the trimer composed of rods R_1 , R_2 , and R_5 the effective free energy is written ε_{125} . Looking at Fig. 3, ε_{125} can be decomposed into a sum of hybridization free energies for joining two arms at a vertex, i.e., $\varepsilon_{125} = \varepsilon_{15} + \varepsilon_{25}$. The same decomposition can be done for all of the *n*-mers. We adopt the same notation for the concentration of the structures. The concentration of the trimer c_{125} formed by the reaction $R_1 + R_2 + R_5$ is

$$c_{125} = \frac{c_1 c_2 c_5}{c_o^2} \exp\left(\frac{-\varepsilon_{125}}{T}\right).$$
 (4)

For some of the DNA structures there is one additional complication. For any diagram which contains a closed loop, we must calculate the change in configurational entropy associated with making the connection which closes the loop. In these cases we calculate the overlap density c_{eff} which relates the effective hybridization free energy $\tilde{\varepsilon}$ to the bare hybridization free energy ε [18,19],

$$\exp\left(\frac{-\tilde{\varepsilon}}{T}\right) = \frac{c_{eff}}{c_o} \exp\left(\frac{-\varepsilon}{T}\right),\tag{5}$$

$$c_{eff} = \frac{\int P(\mathbf{r}_1, \mathbf{r}) P(\mathbf{r}_2, \mathbf{r}) d^3 \mathbf{r}}{\left[\int P(\mathbf{r}, \mathbf{r}') d^3 \mathbf{r}\right]^2}.$$
 (6)

Here $P(\mathbf{r}, \mathbf{r}')$ is the probability distribution for the chain of DNA linkers which starts at \mathbf{r}' and ends at \mathbf{r} . The canonical example is the conversion of a trimer which is a chain of three freely jointed links into a closed triangle. For rigid DNA linkers each of length *L* the result is quite simple,

$$c_{eff} = \frac{1}{8\pi L^3}.\tag{7}$$

Details for the calculation are provided in the Appendix.

Continuing the enumeration procedure for the tetramers, 5-mers, and 6-mer, we can write down expressions for the concentration of all the DNA structures which can form in the absence of the particle. Writing down the equations for conservation of DNA linkers results in a system of six coupled polynomial equations of order 6 in the concentrations of monomers c_j . Here c_j^{tot} is the total initial concentration of linkers of type j,

$$c_{1}^{tot} = c_{1} + c_{15} + c_{16} + c_{125} + c_{146} + c_{126} + c_{135} + c_{136} + c_{156} + c_{1235} + c_{1236} + c_{1246} + c_{1346} + c_{1256} + c_{1356} + c_{1456} + c_{12346} + c_{12356} + c_{12456} + c_{13456} + c_{123456},$$
(8)

$$c_{2}^{tot} = c_{2} + c_{25} + c_{26} + c_{125} + c_{236} + c_{126} + c_{235} + c_{246} + c_{256} + c_{1235} + c_{1236} + c_{1246} + c_{2346} + c_{1256} + c_{2356} + c_{2456} + c_{12346} + c_{12356} + c_{12456} + c_{23456} + c_{123456},$$
(9)

$$c_{3}^{tot} = c_{3} + c_{35} + c_{36} + c_{236} + c_{135} + c_{136} + c_{235} + c_{346} + c_{356} + c_{1235} + c_{1236} + c_{1346} + c_{2346} + c_{2356} + c_{1356} + c_{3456} + c_{12346} + c_{12356} + c_{13456} + c_{23456} + c_{123456},$$
(10)

 $\begin{aligned} c_4^{tot} &= c_4 + c_{46} + c_{146} + c_{246} + c_{346} + c_{1246} + c_{1346} + c_{2346} + c_{1456} \\ &+ c_{2456} + c_{3456} + c_{12346} + c_{12456} + c_{13456} + c_{23456} + c_{123456}, \end{aligned} \tag{11}$

$$c_{5}^{tot} = c_{5} + c_{15} + c_{25} + c_{35} + c_{125} + c_{135} + c_{156} + c_{235} + c_{256} + c_{356} + c_{1235} + c_{1256} + c_{2356} + c_{1356} + c_{1456} + c_{2456} + c_{3456} + c_{12356} + c_{12456} + c_{13456} + c_{23456} + c_{123456},$$
(12)



FIG. 5. (Color online) The mass fraction for the partially assembled cages which can form in the absence of the nanoparticle. M_1, M_2, M_3, M_4, M_5 , and M_6 are the mass fractions for the monomers, dimers, trimers, tetramers, 5-mers, and 6-mer, respectively. In the plot $c_i^{tot}=1$ nM.

$$c_{6}^{tot} = c_{6} + c_{16} + c_{26} + c_{36} + c_{46} + c_{146} + c_{236} + c_{126} + c_{136} + c_{156} + c_{246} + c_{256} + c_{346} + c_{356} + c_{1236} + c_{1246} + c_{1346} + c_{2346} + c_{1256} + c_{2356} + c_{1356} + c_{1456} + c_{2456} + c_{3456} + c_{12346} + c_{12356} + c_{12456} + c_{13456} + c_{23456} + c_{123456}.$$
 (13)

By solving these equations for the monomer concentrations we can plot the melting profile (see Fig. 5). The plot is for the symmetrical case $\varepsilon_{16} = \varepsilon_{46} = \varepsilon_{15} = \varepsilon_{25} = \varepsilon_{26} = \varepsilon_{36} = \varepsilon_{35} \equiv \varepsilon$. The results are plotted in terms of the dimensionless variable $(T_m - T) / \delta T$ defined as

$$\frac{(T_m - T)}{\delta T} = \frac{\varepsilon}{T} - \ln\left(\frac{\sum_i c_i^{tot}}{4c_o}\right). \tag{14}$$

Here δT is the width of the melting transition,

$$\delta T = \frac{T}{\Delta S + \ln(\Sigma_i c_i^{tot}/4c_o)}.$$
 (15)

 T_m is the melting temperature (neglecting the trimers and higher order structures) for which the fraction of rods in the dimer phase $F = (2\bar{C}_2)/(\bar{C}_1 + 2\bar{C}_2) = 1/2$.

$$T_m = \frac{\Delta H}{\Delta S + \ln(\Sigma_i c_i^{tot}/4c_o)}.$$
 (16)

The concentrations for of all the *n*-mers \overline{C}_n are

$$\bar{C}_1 = \sum_i c_i,\tag{17}$$

$$\bar{C}_2 = \sum_{j>i} c_{ij},\tag{18}$$

$$\bar{C}_3 = \sum_{k>j>i} c_{ijk},\tag{19}$$

$$\bar{C}_4 = \sum_{l>k>j>i} c_{ijkl},\tag{20}$$

$$\bar{C}_5 = \sum_{m > l > k > j > i} c_{ijklm},\tag{21}$$

$$\bar{C}_6 = \sum_{n > m > l > k > j > i} c_{ijklmn}, \qquad (22)$$

where each index runs over the set {1, 2, 3, 4, 5, 6}. For the summations it is understood that the set of indices must form a connected diagram. For example, the term c_{1234} does not appear in the sum for \overline{C}_4 since the vertex architecture (see Fig. 3) stipulates that this diagram represents two disconnected dimers, c_{12} and c_{34} . The mass fraction of the *n*-mers M_n is then defined as

$$M_n = \frac{nC_n}{\sum_{k=1}^6 k\bar{C}_k}.$$
(23)

At low temperatures the dominant structure is the 6-mer, which is the fully assembled cage except for the binding of rod R_4 at vertex D of the cage. With this information at hand, we are now in a position to determine the melting profile for the full system, DNA linkers together with the DNA grafted nanoparticles.

IV. DNA-CAGED PARTICLES

In this section we determine the concentration of nanoparticles decorated with DNA structures. We can determine the concentration of particles decorated with DNA structures by applying the same rules for the chemical potential as before. For example, consider decorating a free particle with concentration c_p with the monomer c_1 . We have

$$T\ln\left(\frac{c_p}{c_o}\right) + T\ln\left(\frac{c_1}{c_o}\right) = T\ln\left(\frac{c_{p1}}{c_o}\right) + \tilde{g}_1$$
(24)

The effective binding energy \tilde{g}_1 has two contributions. The first comes from the hybridization free energy g_1 of the DNA arms on the particle hybridizing with the ssDNA ends of rod R_1 . As before these hybridization free energies can be decomposed as a sum of contributions from joining two arms at a vertex. Analogous to the definition of ε , we let g denote the average hybridization free energy for joining two rods at the vertex, one of which came from the DNA grafted on the nanoparticle surface.

The second contribution is an entropic contribution associated with localizing the DNA structure on the surface of the particle. Since there are N_{arms} DNA strands grafted onto the particle surface, there is a combinatorial factor associated with the number of ways to make the first connection between the particle and the DNA structure. Let $\sigma = N_{arms}/(4\pi r^2)$ be the average areal grafting density of DNA on the nanoparticle surface for a particle of radius r, and $h \approx 1$ nm a localization length. The entropic contribution can be estimated in terms of the concentration $\psi = \sigma/h$ which relates \tilde{g} to g in the following manner: SELF-ASSEMBLING DNA-CAGED PARTICLES:...

$$\widetilde{g} = (2\delta_{R_1} + 2\delta_{R_3} + \delta_{R_4})g - T\ln\left[N_{arms}\left(\frac{\psi}{c_o}\right)^{N-1}\right].$$
 (25)

The factor $\delta_{R_j} = 1$ if rod R_j is present in the structure, and $\delta_{R_j} = 0$ otherwise. Here *N* is the number of vertices of the cage to which the nanoparticle is bound. In our example case we have N=2. Putting everything together we have

$$c_{p1} = \frac{c_p c_1}{c_o} \exp\left(\frac{-\tilde{g}_1}{T}\right),\tag{26}$$

$$\widetilde{g}_1 = 2g - T \ln \left(N_{arms} \frac{\psi}{c_o} \right).$$
(27)

The same general procedure can be applied to decorating the particles with all of the DNA structures considered in the previous section, making sure to take into account the vertex architecture. For example, we cannot decorate a particle with the dimer c_{25} since at each of the vertices the DNA arms which come from the particle cannot directly hybridize to the arms which come from the dimer. The concentration of particles decorated with *n*-mers is $c_p^{(n)}$,

$$c_p^{(0)} \equiv c_p, \tag{28}$$

$$c_p^{(1)} = c_p \sum_i \frac{c_i}{c_o} \exp\left(\frac{-\tilde{g}_i}{T}\right),\tag{29}$$

$$c_p^{(2)} = c_p \sum_{j>i} \frac{c_{ij}}{c_o} \exp\left(\frac{-\tilde{g}_{ij}}{T}\right),\tag{30}$$

$$c_p^{(3)} = c_p \sum_{k>j>i} \frac{c_{ijk}}{c_o} \exp\left(\frac{-\tilde{g}_{ijk}}{T}\right), \tag{31}$$

$$c_p^{(4)} = c_p \sum_{l>k>j>i} \frac{c_{ijkl}}{c_o} \exp\left(\frac{-\tilde{g}_{ijkl}}{T}\right), \tag{32}$$

$$c_p^{(5)} = c_p \sum_{m > l > k > j > i} \frac{c_{ijklm}}{c_o} \exp\left(\frac{-\tilde{g}_{ijklm}}{T}\right), \tag{33}$$

$$c_p^{(6)} = c_p \sum_{n > m > l > k > j > i} \frac{c_{ijklmn}}{c_o} \exp\left(\frac{-\tilde{g}_{ijklmn}}{T}\right).$$
(34)

If c_p^{tot} is the total initial particle concentration, we can write the equation for particle conservation in the following form:

$$c_p^{tot} = \sum_{n=0}^{6} c_p^{(n)} + O(c_p^2).$$
(35)

This equation is then solved to determine the concentration of free particles c_p and hence the concentration for particles decorated with DNA structures. The mass fraction m_n for particles decorated with *n*-mers is



FIG. 6. (Color online) The mass fraction m_n for nanoparticles decorated with *n*-mers. Note that the fully assembled tetrahedral cage surrounding the particle, m_6 , is the dominant equilibrium structure for low temperatures. For comparison the mass fraction of the cage in the absence of the particles M_6 is also plotted. In the plot $g = \varepsilon$.

$$m_n = \frac{c_p^{(n)}}{\sum_{k=0}^{6} c_p^{(k)}}.$$
(36)

The results for the mass fraction are plotted (see Fig. 6) for the case $g = \varepsilon$. For low temperatures the dominant structure in solution is our desired nanoblock, a DNA-caged particle.

It is of crucial interest for the experimental feasibility of the proposal that the tetrahedrally caged particle is the dominant structure close to room temperature. We can see from Fig. 6 that the caged particle is the dominant equilibrium structure for $(T_m - T) / \delta T \leq -5$. This in turn determines the standard enthalpy ΔH and the standard entropy ΔS for the hybridization between two DNA arms at the vertex. We find that $\Delta H \simeq -100$ kcal/mol and $\Delta S \simeq -270$ cal K⁻¹ mol⁻¹. For DNA rods with concentration $c_i^{tot} = 1$ nM in a 0.2 M NaCl solution this gives $T_m \simeq 35$ °C and $T \simeq 25$ °C. This information can be used to determine the number of DNA bases in each arm of Fig. 2 (i.e., the length of the ssDNA ends on the rods). Using the average nearest neighbor parameters of [20], the DNA arms should be 28 base pairs long. Hence each of the dsDNA arms of the four arm DNA junction is 14 base pairs long.

The essential result is that there is an experimentally accessible regime for which the dominant equilibrium structure is the DNA-caged particle. In this regime, $(T_m - T)/\delta T \le -5$, we do not expect the assembly of the DNA-caged particle to be kinetically limited. The reason is that in this regime, even in the absence of the particle the dominant structure is the 6-mer, which is then trivially converted into the DNA-caged particle.

V. DNA-PARTICLE PARASITES

In this section we pause to discuss some other DNAparticle structures (parasites) which could potentially de-



FIG. 7. (Color online) Some of the undesired structures which can form. (A) One particle attached to the outside of a cage. (B) Two particles attached to the same cage. (C) One particle surrounded by two cages.

crease the overall yield of our nanoblock (see Fig. 7). One competing structure is the particle attached to the outside of a DNA cage. In this case the particle can bind to at most three of the tetrahedron vertices. As a result, the equilibrium yield of this structure will be proportional to the yield of the DNA-caged particle, but suppressed by a factor of the Bolt-zmann weight for the missing connection $\exp(\frac{-g}{T})$, and thus negligible for low temperature.

We should also consider the stability of our nanoblock with respect to two particle structures, i.e., including terms of order c_p^2 in Eq. (35). For example one can consider a particle pair attached to the same DNA cage. Building such a structure does not necessarily cost binding energy with respect to the DNA-caged particle. However, there is still a cost is associated with the loss in translational entropy of the free particle $T \ln(\frac{c_p}{c_o})$. As a result these particle pairs will be relatively rare and should not decrease the overall yield of the DNA-caged particle.

In principle, a particle may have several DNA cages assembled around it. As it turns out, these are the most problematic of the competing structures. If we denote the concentration of the cage $c_{123456} \equiv c_{cage}$ and the free energy for the particle binding to the cage $\tilde{g}_{123456} = \tilde{g}_{cage}$ then concentration of particles with *m* cages $C_p^{(m)}$ is

$$C_p^{(m)} = c_p \left(\frac{c_{cage}}{c_o}\right)^m \exp\left(\frac{-m[\tilde{g}_{cage} + (m-1)\alpha]}{T}\right).$$
 (37)

Here α is an energetic parameter which characterizes the interaction between two cages attached to the same particle. Since the dsDNA rods (the cage edges) are charged, this interaction is presumably dominated by the electrostatic repulsion of the rods. Within the Debye-Huckel approximation this problem has been treated [21–23]. The electrostatic energy $E(R, \theta)$ of two rods separated by a minimum center to center distance *R* which make an angle θ when viewed along *R* is

$$\frac{E(R,\theta)}{T} = \left(\frac{2\pi\lambda_B}{\kappa l^2}\right) \frac{\exp(-\kappa R)}{\sin\theta}.$$
 (38)

Here the rods have the same effective linear charge density $\nu = \frac{e}{l}$, $\lambda_B = \frac{e^2}{\epsilon_T}$ is the Bjerrum length, and $\kappa^{-1} = 1/\sqrt{4\pi\lambda_B n}$ is

the Debye screening length for monovalent counterions of concentration n. Assuming that the electrostatic energy for the cage-cage interactions can be expressed in terms of a pairwise sum of contributions from rod-rod interactions we have

$$\alpha \simeq \frac{N_c}{2} \langle E(R,\theta) \rangle. \tag{39}$$

Here the angular brackets denote the average, and N_c is the number of rod-rod contacts between two cages. An energetically favorable orientation of the cages has N_c =6. To suppress the formation of particles with two cages, we require the following ratio to be small:

$$\frac{C_p^{(2)}}{C_p^{(1)}} = \frac{c_{cage}}{c_o} \exp\left(\frac{-\left[\tilde{g}_{cage} + \alpha\right]}{T}\right) \ll 1.$$
(40)

The electrostatic energy can be quite significant. For perpendicular orientations of the dsDNA rods Ref. [22] reports a contact potential $E(d, \frac{\pi}{2}) \approx 50$ T (here $d \approx 2.4$ nm is the ds-DNA diameter) in n = 0.005 M NaCl. At fixed temperature and salt concentration, Eq. (40) imposes a condition on the DNA linker concentration which must be met in order to suppress the assembly of more than one cage around the particle. If the DNA linker concentration is not too high, and the salt concentration fairly low, the assembly of more than one cage around the particle can be prevented.

VI. HIERARCHICAL SELF-ASSEMBLY

The DNA-caged nanoparticles in this paper are interesting nanoblocks in a hierarchical self-assembly scheme. Part of their usefulness stems from the fact that interactions between nanoblocks are highly anisotropic. Recall that at each vertex of the DNA cage there is a unique ssDNA sequence available for hybridization. As a result two nanoblocks can be made to interact in a very specific manner by introducing another set of vertex-vertex DNA linkers. Moreover, the number of these vertices is explicitly determined by the cage architecture, which translates into a well defined "valence" for the interactions between nanoblocks.

Here we discuss a particular hierarchical self-assembly proposal where DNA-caged particles are the natural building blocks. The basic proposal of the Voronoi scheme (see Fig. 8) is the following. Any target structure not necessarily crystalline can be represented as a discrete set of points, i.e., the location of particles in the structure. With this set, one performs the Voronoi decomposition [24]. The Voronoi cells for the structure can be used to design the cages surrounding the particles in the following manner. For any given particle, place a vertex at the midpoint between that particle and each of its Voronoi neighbors. In this way we map the target structure onto the set of caged particles, with certain pairs of vertices to be connected. These vertices can be connected by introducing a set of DNA linkers which perform the vertexvertex binding. By construction the target structure must be the ground state of the system. What remains to be seen is whether or not the target structure is favored kinetically. A task for future research is a detailed consideration of this question using Monte Carlo simulations.



FIG. 8. (Color online) A simple example of the Voronoi scheme in two dimensions.

VII. CONCLUSIONS

In this paper we discussed a proposal to self-assemble DNA-caged particles. The basic components are several types of rodlike dsDNA linkers with ssDNA ends, and nanoparticles grafted with ssDNA. By designing the ssDNA sequences appropriately, the dsDNA rods self-assemble into a cage surrounding the particle. The edges of the cage are ds-DNA, and the vertices are multiarm DNA junctions. A particular implementation of this idea was discussed for the selfassembly of tetrahedrally caged particles. We calculated the equilibrium yield of the DNA-caged particles and discussed their stability with respect to alternative structures. At low temperature, the nanoparticle surrounded by one cage is the dominant equilibrium structure. Although the calculations were performed for a tetrahedral cage geometry, the ideas are generally applicable to many types of polyhedral cages. Each vertex of the cage with degree V can be constructed from a V+1 arm DNA branched junction. Such junctions have been constructed with up to 12 arms, which leads open the possibility of much more complicated cages [25,26]. A natural next step would be to consider a particle inside a DNA cube, since the same vertex architecture proposed in this paper would apply.

We concluded by discussing the usefulness of DNA-caged particles in a hierarchical self-assembly proposal. The Voronoi scheme maps the problem of self-assembling a particular target structure onto a set of caged particles for which the target structure is the ground state. The experimental realization of self-assembled DNA-caged particles would represent an important step towards realizing the technological potential of DNA.

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APPENDIX: OVERLAP DENSITY ceff

In this appendix we calculate the overlap density c_{eff} used to determine the effective hybridization free energy for the DNA structures in Fig. 4. It is helpful to consider the associated problem of determining the probability distribution for the end vector of a freely jointed chain made up of N linkers, each of length L. The probability distribution for the chain composed of one linker is simply.

$$\rho_1(\mathbf{R}) = \frac{\delta(R-L)}{4\pi L^2}.$$
 (A1)

Therefore for a chain composed of N such linkers we have

$$\rho_N(\mathbf{R}) = \prod_{j=1}^N \int d^3 \mathbf{r}_j \rho_1(\mathbf{r}_j) \,\delta^3 \left(\sum_{i=1}^N \mathbf{r}_i - \mathbf{R} \right). \tag{A2}$$

The inverse Fourier transform of the probability distribution has a particularly simple form [27],

$$\tilde{\rho}_N(\mathbf{k}) = \int d^3 \mathbf{R} \exp(i\mathbf{k} \cdot \mathbf{R}) \rho_N(\mathbf{R}) = \left(\frac{\sin(kL)}{kL}\right)^N, \quad (A3)$$

$$\rho_N(\mathbf{R}) = (2\pi)^{-3} \int d^3 \mathbf{k} \exp(-i\mathbf{k} \cdot \mathbf{R}) \widetilde{\rho}_N(\mathbf{k}).$$
(A4)

Working in spherical coordinates, performing the angular integration yields

$$\rho_N(\mathbf{R}) = (2\pi)^{-3} \int_0^\infty k^2 \left(\frac{\sin(kL)}{kL}\right)^N dk \int d\Omega \exp(-ikR\cos\theta)$$
$$= (2\pi)^{-2} \frac{2}{R} \int_0^\infty k \sin(kR) \left(\frac{\sin(kL)}{kL}\right)^N dk$$
$$= \frac{1}{2\pi^2 L^3} \int_0^\infty u^2 j_0 \left(\frac{Ru}{L}\right) [j_0(u)]^N du.$$
(A5)

Here $j_0(z) = \frac{\sin z}{z}$ is the spherical Bessel function [28] of order 0.

We are now in a position to determine the overlap density c_{eff} for the triangle structure. Of particular interest for this calculation is [29,30]

$$\rho_2(\mathbf{R}) = \frac{\theta(2L-R)}{8\pi L^2 R}.$$
 (A6)

Here $\theta(x)$ is the Heaviside step function. The overlap density for the triangle is then calculated as

$$c_{eff} = \int d^{3}\mathbf{R} \int d^{3}\mathbf{r} \rho_{2}(\mathbf{R})\rho_{1}(\mathbf{r})\delta^{3}(\mathbf{R}-\mathbf{r})$$

$$= \frac{1}{8\pi L^{2}} \frac{1}{4\pi L^{2}} \int d^{3}\mathbf{R} \int d^{3}\mathbf{r} \frac{\theta(2L-R)}{R} \delta(r-L)\delta^{3}(\mathbf{R}-\mathbf{r})$$

$$= \frac{1}{32\pi^{2}L^{4}} \int d^{3}\mathbf{r} \frac{\theta(2L-r)}{r} \delta(r-L) = \frac{1}{8\pi L^{3}}.$$
(A7)

There are two remaining overlap densities which need to be calculated. One of them is for forming an equilateral parallelogram, i.e., a diamond. In Fig. 4 this structure is the third structure in the tetramer row. Forming this structure can be viewed as joining the ends of two chains, each of which is composed of two links,

$$c_{eff} = \int d^{3}\mathbf{R} \int d^{3}\mathbf{r} \rho_{2}(\mathbf{R})\rho_{2}(\mathbf{r})\delta^{3}(\mathbf{R}-\mathbf{r})$$
$$= \left(\frac{1}{8\pi L^{2}}\right)^{2} \int d^{3}\mathbf{R} \int d^{3}\mathbf{r} \frac{\theta(2L-R)}{R} \frac{\theta(2L-r)}{r}\delta^{3}(\mathbf{R}-\mathbf{r})$$
$$= \frac{1}{64\pi^{2}L^{4}} \int d^{3}\mathbf{r} \frac{\theta(2L-r)}{r^{2}} = \frac{1}{8\pi L^{3}}.$$
(A8)

Alternatively, one can calculate the overlap density for the diamond structure as

$$c_{eff} = \int d^3 \mathbf{R} \int d^3 \mathbf{r} \rho_3(\mathbf{R}) \rho_1(\mathbf{r}) \,\delta^3(\mathbf{R} - \mathbf{r}) = \frac{1}{8 \,\pi L^3}.$$
(A9)

This is simply viewing the diamond as joining a chain of three links with a chain of one link. The results are the same, as they must be.

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The remaining overlap density to be calculated is associated with making the last connection in the tetrahedron. Assume that all the connections have been made, except for the connection between rod R_4 and vertex A. Taking vertex D as the origin, the position of vertex A is the end vector of a two segment chain, with each segment having length $l=\frac{L\sqrt{3}}{2}$. With one end of rod R_4 fixed at vertex D, the other end must connect to vertex A,

$$c_{eff} = \int d^{3}\mathbf{R} \int d^{3}\mathbf{r} \rho_{2}(\mathbf{R})\rho_{1}(\mathbf{r}) \delta^{3}(\mathbf{R} - \mathbf{r})$$

$$= \frac{1}{8\pi l^{2}} \frac{1}{4\pi L^{2}} \int d^{3}\mathbf{R} \int d^{3}\mathbf{r} \frac{\theta(2l-R)}{R} \delta(r-L) \delta^{3}(\mathbf{R} - \mathbf{r})$$

$$= \frac{1}{32\pi^{2} l^{2} L^{2}} \int d^{3}\mathbf{r} \frac{\theta(2l-r)}{r} \delta(r-L) = \frac{1}{8\pi l^{2} L} = \frac{1}{6\pi L^{3}}.$$

(A10)

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