



Cite this: *Soft Matter*, 2025, 21, 2654

The underappreciated role of nonspecific interactions in the crystallization of DNA-coated colloids†

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Over the last decade, the field of programmable self-assembly has seen an explosion in the diversity of crystal lattices that can be synthesized from DNA-coated colloidal nanometer- and micrometer-scale particles. The prevailing wisdom has been that a particular crystal structure can be targeted by designing the DNA-mediated interactions, to enforce binding between specific particle pairs, and the particle diameters, to control the packing of the various species. In this article, we show that other ubiquitous nonspecific interactions can play equally important roles in determining the relative stability of different crystal polymorphs and therefore what crystal structure is most likely to form in an experiment. For a binary mixture of same-sized DNA-coated colloidal micrometer-scale particles, we show how changing the magnitudes of nonspecific steric and van der Waals interactions gives rise to a family of binary body-centered tetragonal crystals, including both cesium–chloride and copper–gold crystals. Simulations using pair potentials that account for these interactions reproduce our experimental observations quantitatively, and a theoretical model reveals how a subtle balance between specific and nonspecific forces determines the equilibrium crystal structure. These results highlight the importance of accounting for nonspecific interactions in the crystal-engineering design process.

Received 1st January 2025,
Accepted 5th March 2025

DOI: 10.1039/d5sm00001g

rsc.li/soft-matter-journal

1 Introduction

Self-assembly is a powerful approach for making materials with complex microstructures, whereby individual components spontaneously organize due to interparticle interactions.¹ In recent years, DNA has emerged as a useful tool to design and control the interactions between colloidal particles owing to the sequence-specific nature of DNA base pairing.^{2–4} This approach has been used to assemble a rich diversity of crystal lattices from both DNA-coated nanoparticles^{5–8} and DNA-coated micrometer-scale particles.^{9–13} Across this wide spectrum of length scales and crystal structures, the conventional approach has focused on controlling the specific, DNA-mediated attractions,^{14,15} along with the particle diameters, in order to specify the formation of a given assembly or stabilize a particular crystal lattice.

Beyond the specific DNA-mediated attractions, however, other surface forces can in principle also play a crucial role in

dictating the outcome of colloidal crystallization. Prominent examples include screened-Coulomb repulsion between like-charged particles, steric repulsion between polymer-grafted particles (including DNA-coated particles), and van der Waals (vdW) attraction between particles dispersed in a solvent.^{16,17} Although these nonspecific interactions are often overlooked, they can play equally important roles in stabilizing a certain crystal polymorph, especially in cases where there are multiple competing crystal structures with similar free energies. Indeed, recent reports demonstrate how rationally controlling the steric repulsion between DNA-coated nanoparticles can lead to the formation of different crystals,¹⁸ including crystals that have been notoriously difficult to assemble, like those isostructural to sodium chloride (NaCl).^{7,10}

In this paper, we show how nonspecific interactions affect the assembly of micrometer-scale DNA-coated colloids. In particular, we show that the interplay between specific DNA-mediated attraction, nonspecific vdW attraction, and nonspecific steric repulsion favors the self-assembly of body-centered tetragonal (BCT) crystals, rather than crystals with cubic unit cells. We find that the BCT unit-cell dimensions depend sensitively on the relative magnitude and range of the nonspecific interactions, which we tune by varying the molecular weight of the polymer brush on the particle surface, the particle

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d5sm00001g>



diameter, and the mixing of complementary grafted DNA strands. Using simulations, we confirm that pair potentials that account for these design choices give rise to equilibrium BCT crystals in quantitative agreement with experiments. Then, to understand these observations, we develop a theory to predict the relative stability of different crystal lattices for particles with both specific and nonspecific attraction. Taken together, our results showcase how nonspecific interactions can play an important role in dictating the equilibrium crystal structures, as well as how they can be controlled by tuning various experimental parameters. Our results might also help to explain why seemingly similar experimental systems produce different crystal structures,^{10,12,13,19} and why some predicted structures have remained inaccessible.²⁰

2 Results and discussion

2.1 Characterizing the crystal structures for various polymer-brush lengths

We synthesize DNA-coated colloids with a range of polymer-brush molecular weights using a combination of physical grafting and click chemistry by following a modified version of ref. 21 (see ESI† for more details). Initially, we use polystyrene colloidal particles

with 600-nm diameters and four different polyethylene oxide (PEO) block molecular weights, $M_w = 6.5, 11, 34,$ and 67 kDa. We fluorescently dye the two particle species (referred to as A and B) different colors to distinguish their compositional order within the crystal phase. The ssDNA sequence is 65 bases long with a 7 base-long region at the end that is complementary between the two sequences. The net result is a binary suspension of same-sized particles coated with a dense brush of PEO polymers, which are end-grafted with single-stranded DNA (Fig. 1A).

We characterize the binary crystals that self-assemble by determining the two-dimensional radial distribution functions (RDFs) of their surface crystallographic planes. We first assemble crystals at a constant temperature just below their melting point (see ESI† for a detailed protocol). We then lower the sample to room temperature at a ramp rate of $0.05\text{ }^{\circ}\text{C}$ every two hours until most of the free monomers have been consumed by the growing crystals, so that we can transfer it to a confocal fluorescence microscope to image the crystal symmetry and composition. Next, we characterize the structures of roughly one hundred single crystals (Fig. 1B) by finding the particle centers using standard image-analysis routines²² and computing the two-dimensional RDFs. Two examples for crystals with the longest and shortest polymer lengths are shown in Fig. 1C.

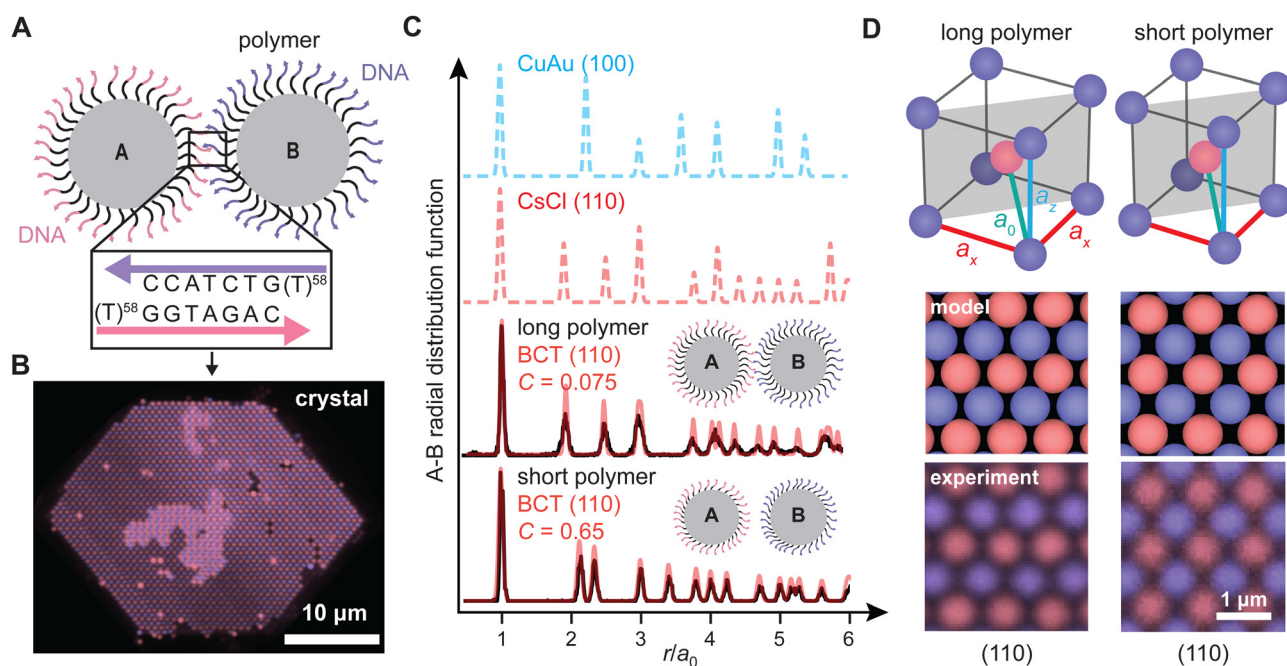


Fig. 1 Overview of the experimental system. (A) Our experimental system consists of 600-nm-diameter spherical colloidal particles that are coated with a brush of polyethylene oxide to which 65-nucleotide-long single-stranded DNA is attached (not to scale). The DNA terminates in a seven-base-long region designed to hybridize with its complement. Two species of particles (A) and (B) are defined by the sequences of DNA attached to their surfaces. (B) An equimolar mixture of A and B particles self-assembles to form binary crystals, which we characterize using confocal fluorescence microscopy. (C) The A–B radial distribution functions (RDF) of facets of single crystals assembled with a 6.5 kDa molecular weight (M_w) polymer brush and a 67 kDa M_w polymer brush are compared to the RDFs of the closest-matching planes of cesium–chloride (CsCl) and copper–gold (CuAu) crystals, indicated by their miller indices. The distance between particle centers is denoted by r , and a_0 is the distance between nearest-neighbor A–B particle pairs. Black curves show experimental data. The particles with shorter polymers assemble into a BCT structure in between CsCl and CuAu, whereas the particles with longer polymers assemble into a structure that closely resembles CsCl. Solid red curves show the RDFs for the closest matching BCT crystallographic planes (110), as well as the corresponding C values. (D) By analyzing the A–B radial distribution functions, we generate the unit cells of the lattice structures assembled in experiment. Images of the surfaces of the crystals with long and short polymers are compared to the best-fit model lattices determined from the RDFs. Both examples correspond to (110) planes of BCT.

Because the particles are neither index matched nor density matched to the solvent, we image the surface facet that is parallel to the coverslip–water interface.

We classify the structure of each crystal by examining the measured RDF for A–B particle pairs, $g_{AB}(r)$, which provides a unique fingerprint. Specifically, we compare the measured RDF to a look-up table of RDFs for low-index crystallographic planes of body-centered tetragonal crystals. The look-up table comprises a variety of binary body-centered tetragonal crystals with various aspect-ratio unit cells, which we characterize by a dimensionless parameter C that lies between 0 and 1. If $C = 0$, the crystal has a cubic unit cell that is isostructural to cesium chloride (CsCl); if $C = 1$, the crystal again has a cubic unit cell, but this time is isostructural to copper gold (CuAu). Intermediate values of C correspond to crystals with non-cubic unit cells that are characterized by a nearest-neighbor A–B separation distance a_0 and primitive vectors $a_x\hat{x}$, $a_y\hat{y}$, and $a_z\hat{z}$:

$$a_0^* = \frac{\sqrt{3}a_0}{\sqrt{3} + (2\sqrt{3} - 2 - \sqrt{2})(C^2 - C)} \quad (1a)$$

$$a_x = a_y = \frac{2}{\sqrt{3}}a_0^*(1 - C) + a_0^*C \quad (1b)$$

$$a_z = \frac{2}{\sqrt{3}}a_0^*(1 - C) + \sqrt{2}a_0^*C. \quad (1c)$$

Interestingly, the crystals that we assemble are neither a perfect match for CsCl nor CuAu. Moreover, their crystal structure depends on the polymer brush molecular weight M_w . For example, Fig. 1C shows the measured RDFs for binary crystals composed of 600-nm-diameter particles with $M_w = 6.5$ kDa and 67 kDa, as well as reference RDFs for the closest matching crystallographic planes of CsCl and CuAu. By visual inspection, we can clearly see that the two experimental RDFs are different from one another and from the reference RDFs. The differences between the experimentally determined structures are also evident in the crystal images shown in Fig. 1D. In this way, we find that all four crystals correspond to different BCT lattices with different unit-cell aspect ratios. For the particles with the shortest polymer brush, we also assemble and characterize the crystal structure for three salt concentrations ranging from roughly 50–500 mM NaCl, which has a minimal effect on the equilibrium C parameter value (see Fig. S1 and S2 in ESI†).

We hypothesize that the BCT crystal structures that we observe are stabilized by a combination of specific DNA-mediated attraction and nonspecific interactions. Prior theoretical and simulation studies using simple models of DNA-coated particles, which do not account for potential nonspecific interactions present in our experimental system, have predicted that CsCl is the thermodynamically stable crystal phase for same-sized particles with attractive interactions between A and B particles only.^{20,23} This prediction is due to the greater entropy of hard-sphere CsCl crystals, which have body-centered cubic (BCC) unit cells, relative to hard-sphere CuAu crystals, which have face-centered cubic (FCC) unit cells.²⁴ However, this predicted entropic difference between CsCl and CuAu structures is smaller than the thermal

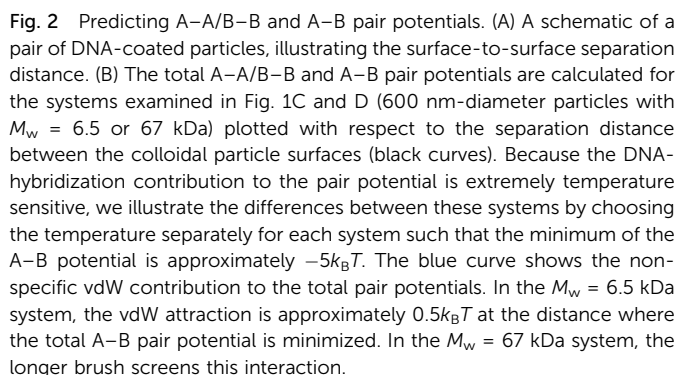
energy per particle. It is therefore plausible that other interactions with similar or greater magnitude can influence the thermodynamically stable crystal structure. For example, earlier experimental results showed that CuAu crystals can be stabilized relative to CsCl by introducing a small degree of DNA hybridization between particles of the same type,²³ which can only form contacts in the denser CuAu phase due to the narrow range of distances over which the DNA can hybridize. Our hypothesis follows similar reasoning, but differs in that the range of the various nonspecific interactions need not be the same as that of the specific DNA-mediated attractions. We propose that the sum total of these various surface forces, acting over a variety of different ranges, could plausibly stabilize non-cubic BCT crystal structures, which have different nearest-neighbor distances between A–A/B–B and A–B particle pairs.

2.2 Modeling microscopic interactions between DNA-coated colloids

To test this hypothesis, we first evaluate the pair-interaction free energies (referred to as ‘pair potentials’) in our experimental system using a recently developed microscopic model of the interactions between DNA-coated colloids.¹⁵ This microscopic model accounts for the free energy of DNA hybridization,²⁵ steric repulsion between polymer brushes, and vdW attraction between colloidal particles. Importantly, the model self-consistently accounts for the excluded-volume interactions between adjacent strands, which may or may not be hybridized, by minimizing the total free energy with respect to the fraction of hybridized strands. In this way, the total free energy of interaction can be computed as a function of the distance between the DNA-coated particles. For example, Fig. 2 shows predictions of the A–A/B–B and A–B pair potentials for the two systems investigated in Fig. 1C and D at temperatures near the melting points of the corresponding crystals. Notably, each A–B pair potential has a narrow attractive well when the particle surfaces are separated by a distance comparable to twice the equilibrium polymer brush height. By contrast, the contribution to the pair potentials due to vdW attraction acts over longer distances.

These predicted pair potentials suggest that our hypothesis is indeed plausible. First, we observe that the contribution to the pair potential from vdW attraction is predicted to be independent of M_w , as the vdW interaction is determined by the colloidal particle diameter and the Hamaker constant in ref. 15. Therefore, the vdW interaction is the same for both A–A/B–B and A–B particle interactions. By contrast, the steric contribution from the polymer brush and the grafted DNA molecules depends sensitively on the polymer M_w , whereby longer polymers shift the minimum of the pair potential to larger particle separations. These differences mean that the nonspecific vdW attraction is comparable to the thermal energy for both A–A/B–B and A–B particle pairs when the brushes come into contact in the short-polymer (6.5 kDa M_w) system, whereas the vdW attraction is negligible when the brushes come into contact in the long-polymer (67 kDa M_w) system. Indeed, this weak A–A/B–B attraction between DNA-coated colloids that depends on the polymer

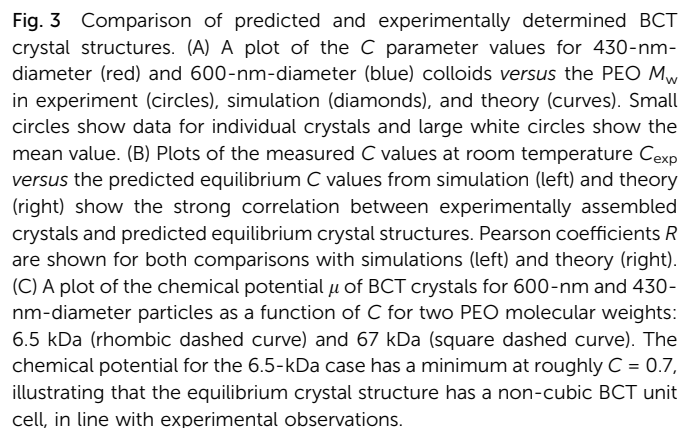




Second, we observe that the steric repulsion due to excluded volume interactions between the brushes occurs at different distances for the A-A/B-B and A-B particle pairs. This feature arises because the minimum-free-energy brush height in the microscopic model of ref. 15 depends on whether the grafted DNA is hybridized. Because the A-A/B-B particle pairs do not experience DNA-mediated attraction, the repulsion between their polymer brushes leads the pair potential to diverge at a greater separation between the particles. As we discuss below, this feature also has significant implications for the equilibrium binary crystal structure.

We next assess whether these pair potentials can explain the variations in the BCT structures that are observed in experiment. To this end, we use constant-pressure molecular dynamics simulations to predict the equilibrium crystal structure for each experimental system at room temperature, $T = 25^\circ\text{C}$ (see Appendix). For each polymer length, we prepare a 1024-particle binary crystal with initial BCT C parameters ranging from 0 to 1. We then set the applied pressure to be

Consistent with our experimental observations, these simulations predict that BCT crystals with C parameters between 0 and 1 are thermodynamically favored over both CsCl and CuAu. Moreover, the simulations predict equilibrium C parameters, computed *via* eqn (1), that depend on M_w and agree nearly quantitatively with the experimentally characterized crystals (Fig. 3A and B). Both simulations and experiments show that the C value decreases from roughly 0.6 (more CuAu-like) to 0.2 (more CsCl-like) as M_w increases from 6.5 to 67 kDa. We observe a relatively narrow distribution of C for each system,



crystal structure with a variable C parameter. To this end, we compute the free energies of these phases according to the thermodynamic perturbation theory and then equate their chemical potentials, μ , and pressures, P . At phase coexistence,

where η_{fluid} is the packing fraction of the fluid phase. For simplicity, we assume that the packing fraction of the crystal phase is uniquely determined by the BCT C parameter and is thus independent of the pressure. We solve eqn (2) as a function of the packing fraction for values of C in the range 0 to 1, and we predict the equilibrium crystal phase to be the one with the lowest coexistence chemical potential. Example plots of the coexistence chemical potential, μ_{coex} , as a function of C are shown in Fig. 3C for the two brush lengths and both particle types considered in Fig. 1C and D. In all cases, we find that μ_{coex} is a function of C with a single local minimum, which is consistent with the fact that systems initialized with various C values all converge to the same crystal structure in our simulations.

We validate the predictions of our theory by comparing both the crystal melting temperatures and the equilibrium C values at room temperature with experiments. First, we predict the melting temperature for each system theoretically by finding the temperature-dependent pair potentials at which the dilute-phase packing fraction, η_{fluid} , that is in coexistence with the equilibrium BCT crystal is equal to the overall colloidal volume fraction in our experiments, $\sim 0.5\%$. In this way, we find that the predicted and experimentally determined melting temperatures agree semi-quantitatively, with a Pearson correlation coefficient of $R = 0.98$ and absolute errors less than 2°C (see Fig. S3 in ESI[†]). The melting temperatures decrease monotonically with respect to increasing polymer M_w , resulting in a difference of approximately 10°C between $M_w = 6.5$ and 67 kDa.

Second, we predict the BCT C parameters at room temperature and find qualitative agreement with the experimentally determined values. Although these predictions are not as accurate as the simulation results that utilize the same pair potentials, most likely due to the approximations involved in the perturbation theory, we obtain a positive correlation of $R = 0.88$ with respect to the experimental values (Fig. 3B). We note that the discrepancy between the predictions and the experimental measurements for the 600-nm particles with a 34-kDa polymer brush is possibly due to the very flat free-energy landscape for this system (see Fig. S4 in ESI[†]), which makes the predicted C values highly sensitive to potential inaccuracies in the pair-potential model, the approximations used in the BCT crystal theory, or our assumption of a constant polymer density across all systems. Yet overall, our theory reproduces the observed trends with respect to the particle diameter and the polymer M_w . We can therefore examine the theory to understand the thermodynamic driving forces that select the equilibrium BCT crystal structures.

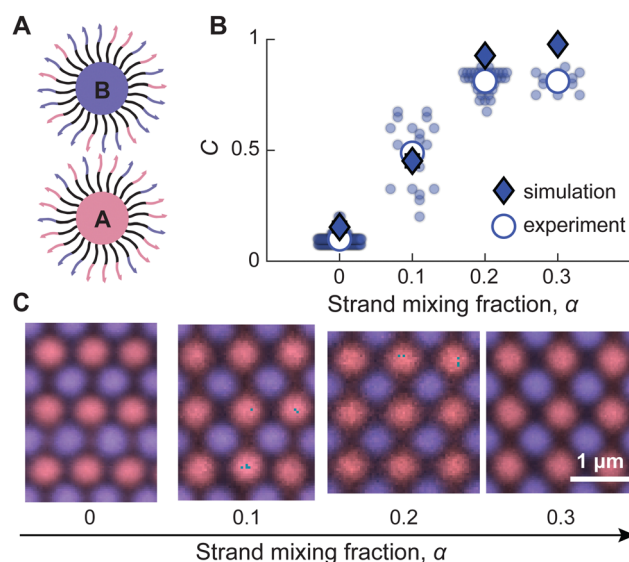
Specifically, our theory predicts that the coexistence chemical potential is affected by the harmonic and anharmonic contributions to the crystal entropy, as well as the vdW attraction. The harmonic contribution to the entropy, which arises

Given the predicted pair potentials, we seek the conditions for phase coexistence between a colloidal gas phase and a BCT

Overall, our theory predicts that the equilibrium BCT crystal structure is primarily determined by the balance between the anharmonic contribution to the crystal entropy and the vdW attraction. Both of these effects can be considered to be non-specific since neither is governed by DNA-mediated interactions. Taken together, these theoretical observations explain how subtle changes to the experimentally accessible system design parameters can simultaneously affect multiple weak driving forces and tune the equilibrium BCT crystal structure.

Based on our understanding of these thermodynamic driving forces, we hypothesize that alternative nonspecific attractive interactions could be used to systematically tune the BCT crystal structure. To test this idea, we devise an experiment in which the attraction between A-A/B-B particle pairs is due to DNA hybridization rather than vdW attraction. Specifically, we use a polymer brush with the largest PEO molecular weight (67 kDa) to screen the vdW attraction. We then coat the two

As anticipated, we find that increasing the strand mixing fraction α , and therefore the magnitude of the A-A/B-B attraction, induces a transition from CsCl-like to CuAu-like crystals (Fig. 4B). The experimentally observed C parameter value increases from approximately 0.1 to 0.8 upon increasing α from 0 to 0.3, and these observations are matched quantitatively by

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3 Conclusions

We highlight that a thorough examination of the determinants of a continuous transition from BCC to BCT to FCC *versus* a discontinuous transition directly from BCC to FCC could be an interesting question for future work. In particular, while it is tempting to draw direct comparisons between the phase behavior that we report and the myriad examples of DNA-mediated colloidal crystallization at the nanoscale and microscale,^{4,8} some of which report discontinuous transitions from BCC to FCC,^{27,28} making these connections is challenging owing to the wide diversity of length scales, particle shapes, conjugation strategies, and DNA motifs used across these many examples. As a result, it is difficult to conclude whether or not the resultant differences in the phase behavior are due to the fact that the vdW attraction is negligibly weak for nanometer-scale particles, that the entropic contributions to the crystal free

From a materials-design perspective, our results point to new possibilities in the programmable crystallization of DNA-coated particles. Whereas the vast majority of the crystal-engineering design rules have focused primarily on the specific DNA-mediated interactions,^{8,29} our work motivates the development of design approaches that include and utilize both specific and nonspecific interactions. Indeed, our experimental results show that including nonspecific attraction, even in simple binary mixtures of same-sized particles, can expand the diversity of crystals that can be self-assembled to include a family of crystal structures with non-cubic unit cells. This observation begs the question: What other crystal structures might be accessible to systems of DNA-coated colloidal particles if one can design both the specific, DNA-mediated attractions and the nonspecific attractions and repulsions?

Author contributions

H. S., S. C., W. M. J., and W. B. R. conceived the research. H. S. performed the experiments. H. S., T. E. V., and M. M. analyzed the data. S. C. and W. M. J. developed the theory and simulations. All authors contributed to writing the manuscript.

Data availability

Simulation, analysis, and theoretical modeling scripts are provided at <https://github.com/wmjac/dnacc-binary-crystal-pub>. Experimental data is available upon reasonable request.

Conflicts of interest

There are no conflicts to declare.

Appendices

Constant-pressure simulations

We perform molecular dynamics simulations using pair potentials computed from the microscopic model of DNA-coated colloidal particles¹⁵ at the experimental temperature $T = 25$ °C. For each system, we initialize binary crystals consisting of 1024 colloidal particles (512 particles of each type) in 11 different BCT crystal structures, $C \in [0, 0.1, \dots, 1]$. The initial lattice spacing is chosen such that the nearest-neighbor A-B particle pairs are separated by the distance at which the pair potential is minimized. We work in dimensionless units where the colloidal diameter is $d = 1$, the reduced simulation temperature is $k_B T = 1$, and the masses of the particles are set to $m = 1$, so that the time unit is $\tau = d\sqrt{m/k_B T}$. Because the potential well is extremely narrow, we choose a small timestep

equal to $\Delta t = 5 \times 10^{-5} \tau$. We then perform constant-pressure (NPT) simulations, allowing the orthorhombic simulation box dimensions to fluctuate independently, at a low pressure of $P = 10^{-4} k_B T/d^3$. We note that our results are quantitatively unchanged if the pressure is reduced to $P = 10^{-5} k_B T/d^3$. We run the simulation for 5×10^7 timesteps to ensure that equilibrium is reached. Since the simulation box dimensions are allowed to fluctuate independently, the BCT C parameter is determined directly from the box dimensions,

$$C = (a_{\max} - a_{\min}) / \left[(\sqrt{2} - 1) a_0^* \right], \quad (3)$$

where $a_{\min(\max)}$ is the minimum (maximum) unit cell dimension and a_0^* as defined in eqn (1) with a_0 calculated as the equilibrium distance between nearest-neighbor A-B particle pairs in simulations. Finally, we report the BCT C parameter for each system by averaging over the final 10^7 timesteps of the equilibrated simulation trajectories and over all 11 initial conditions, which we empirically find to all converge to the same equilibrium crystal structure. Error bars associated with the equilibrium C values, which are calculated as the standard error of the mean of the 11 initial conditions, are typically smaller than the symbol sizes in the figures.

Theoretical model of BCT crystal phase coexistence

Phase behavior of the reference system. We define a reference system based on the pair potential for A-B particle pairs in the absence of vdW interactions, u_{AB} . Under the conditions of interest, u_{AB} has a minimum at separation $r = \sigma$, where the free energy is $\varepsilon \equiv u_{AB}(\sigma)$. For small perturbations in the particle positions, u_{AB} can be approximated by a harmonic potential $u_{\text{ref}}(r) = \varepsilon + (k_{AB}/2)(r - \sigma)^2$, where k_{AB} is the second derivative of u_{AB} evaluated at $r = \sigma$.

In an ordered binary crystal phase, we assume that the average spacing between nearest-neighbor particle centers is exactly $r = \sigma$. The crystal-phase packing fraction is then

$$\eta_{\text{crystal}} = \left(\frac{\pi \sigma^3}{6} \right) \times \left(\frac{2}{a_x a_y a_z} \right), \quad (4)$$

where $v \equiv \pi \sigma^3/6$ is the volume associated with a particle and a_x , a_y , and a_z are the dimensions of the BCT unit cell, which contains two particles. Using the harmonic approximation u_{ref} , we can compute the free energy per particle in a crystal phase,³⁰

$$\beta f_{\text{crystal}}(C) = \frac{z_{AB} \beta \varepsilon}{2} - \frac{3}{2} \ln \frac{2\pi}{\beta \sigma^2 k_{AB}} + \frac{1}{2N} \sum_{\{\kappa\}_{N,C}} \log \kappa - k_B^{-1} \Delta S_{\text{symm}}, \quad (5)$$

where $z_{AB} = 8$ is the coordination number for A-B contacts and $\beta = 1$, since the pair potentials represent the potential of mean force and thus contain the actual temperature dependence of the system. The first term represents the free energy of the crystal in its equilibrium configuration, where all nearest-neighbor A-B particle pairs are spaced exactly $r = \sigma$ apart. The second term arises from the entropy change due to

confinement by a harmonic pair potential with spring constant k_{AB} . The third term accounts for the phonon modes of an N -particle lattice with BCT parameter C , where $\{\kappa\}_{N,C}$ is the set of nonzero eigenvalues of the Hessian matrix of the harmonic reference crystal with unit nearest-neighbor particle spacing and a unit spring constant. In practice, we numerically compute the Hessian of a lattice with $8 \times 8 \times 8$ unit cells and evaluate the eigenvalue spectrum. Finally, the fourth term, $k_B^{-1} \Delta S_{\text{symm}} = -\log(2)$, is a symmetry factor that accounts for the periodic translational order of particles in an ordered binary crystal. The chemical potential in a crystal phase is simply the Gibbs free energy per particle,

$$\beta \mu_{\text{crystal}}(P; C) = \beta f_{\text{crystal}}(C) + \frac{\beta P v}{\eta_{\text{crystal}}(C)}. \quad (6)$$

In the fluid phase, we use the Carnahan–Starling equation of state for a hard-sphere fluid with a mean-field correction for the short-range attractions between particles of different types,

$$\beta \mu_{\text{fluid}}(\eta) = \log \eta + \frac{8\eta - 9\eta^2 + 3\eta^3}{(1 - \eta)^3} + 2\Delta_\varepsilon \eta \quad (7)$$

$$\beta P_{\text{fluid}}(\eta) v = \frac{\eta + \eta^2 + \eta^3 - \eta^4}{(1 - \eta)^3} + \Delta_\varepsilon \eta^2, \quad (8)$$

where $\Delta_\varepsilon \equiv 4\beta\varepsilon[(1 + \delta/2\sigma)^3 - (1 - \delta/2\sigma)^3]$ and $\delta \equiv \sqrt{8/k_{AB}}$ is the approximate width of the harmonic well.

At phase coexistence, the chemical potentials and pressures of the fluid and a crystal phase are equal. Since we are assuming that the packing fraction of a given crystal phase is solely determined by the BCT parameter C , we only need to solve eqn (2) to find $\mu_{\text{coex}} = \mu_{\text{fluid}} = \mu_{\text{crystal}}$ as a function of η_{fluid} . The equilibrium crystal in coexistence with the fluid phase is the one with the lowest equilibrium chemical potential.

Accounting for A-A/B-B repulsion and vdW attraction. The chemical potential of a BCT crystal structure depends sensitively on both the repulsion between A-A/B-B particle pairs, which are not bonded and thus do not appear in the reference harmonic crystal, and additional nonspecific attractions among the particles. We first account for the pair potential between particles of the same type, $u_{AA} = u_{BB}$, which has a repulsive shoulder near $r \simeq \sigma$. We assume that this effect makes a negligible contribution in the fluid phase, since the Carnahan–Starling equation of state already accounts for hard-sphere repulsion among all the particles in the fluid. However, in a crystal phase, the shoulder reduces the accessible volume per particle due to repulsion between A-A/B-B particle pairs. The change in the entropy per particle is approximately

$$k_B^{-1} \Delta S_{AA} = \log \frac{V_{\text{acc},AA}}{V_{\text{acc},\text{ref}}} \approx \log \frac{\int_0^{d_{AA}} dx g_{AA,\text{ref}}(x) \exp[-\beta u_{AA}(x)]}{\int_0^{d_{AA}} dx g_{AA,\text{ref}}(x)}, \quad (9)$$

where $V_{\text{acc},\text{ref}}$ and $V_{\text{acc},AA}$ are the accessible volumes per particle under the reference and actual A-A/B-B potentials, respectively, and d_{AA} is the minimum distance between A-A/B-B particle



pairs in the crystal structure. In this approximation, the integrals describe the distance over which each particle can travel before being repelled by a particle of the same type within a lattice, assuming that all other particles are at their equilibrium positions. For simplicity, we approximate the radial distribution function for A-A/B-B particle pairs in the reference crystal as $g_{AA,ref}(x) \propto \exp[-(\alpha k_{AB}^2)(x - d_{AA}^2)^2]$, where the scaling factor α is chosen to be $\alpha \approx 1 \times 10^{-4}$ based on zero-pressure simulations of the reference crystal with $C = 0$. This choice accounts for the fact that the distance between nonbonded A-A/B-B particle pairs fluctuates to a much greater extent than the distance between bonded A-B particle pairs in the reference crystal. The entropy change given by eqn (9) modifies the chemical potential in the crystal phase, such that $\beta\Delta\mu_{crystal}^{AA} = -k_B^{-1}\Delta S_{AA}$. We emphasize that this anharmonic contribution to the crystal entropy is essential for stabilizing BCT crystals with low C values: in the absence of A-A/B-B repulsion, the C -dependent phonon contribution to eqn (5) actually favors crystal structures with high C values (see ESI†). Thus, the shoulder of the A-A/B-B pair potential plays an important role in determining the equilibrium crystal structure.

By contrast, nonspecific vdW interactions affect particles in both the fluid and crystal phases. We treat the pair potential u_{vdW} as a weak perturbation to the reference crystal structure using the λ -expansion.³¹ The corrections to the chemical potential and the pressure of the fluid phase are

$$\beta\Delta\mu_{fluid}^{vdW} = \frac{24\eta}{\sigma^3} \int_{\sigma}^{\infty} dr r^2 \beta u_{vdW}(r) \quad (10)$$

$$\beta\Delta P_{fluid}^{vdW} = \frac{12\eta}{\sigma^3} \int_{\sigma}^{\infty} dr r^2 \beta u_{vdW}(r). \quad (11)$$

For the crystal-phase calculation, we approximate the structure of the reference crystal by assuming that the particles are at their equilibrium positions in the binary lattice. The correction to the chemical potential of the crystal phase is thus

$$\beta\Delta\mu_{crystal}^{vdW} = \sum_i \beta u_{vdW}(r_i), \quad (12)$$

where the sum runs over all the particles in the lattice except a tagged particle at the origin, and r_i is the distance between the neighboring particle and the origin.

In practice, we incorporate these correction terms, eqn (9)–(12), and solve eqn (2) to compute μ_{coex} as a function of C , as shown in Fig. 3C. An extension of this theory to systems with specific A-A/B-B attraction, which follows a similar perturbative approach, is presented in the ESI.†

Acknowledgements

This work was supported by the National Science Foundation (DMR-2214590) as well as the Brandeis NSF MRSEC, Bioinspired Soft Materials (DMR-2011846).

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