

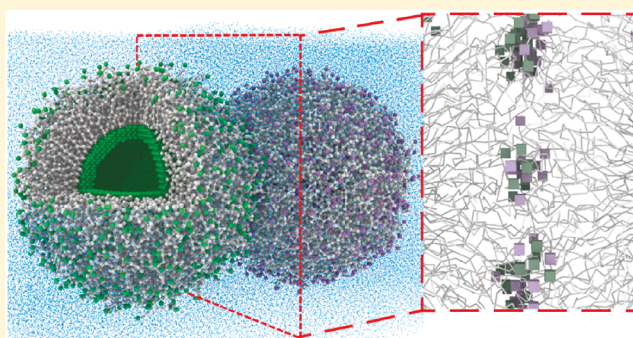
Dictating Nanoparticle Assembly via Systems-Level Control of Molecular Multivalency

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Supporting Information

ABSTRACT: Nanoparticle assembly can be controlled by multivalent binding interactions between surface ligands, indicating that more precise control over these interactions is important to design complex nanoscale architectures. It has been well-established in natural materials that the arrangement of different molecular species in three dimensions can affect the ability of individual supramolecular units to coordinate their binding, thereby regulating the strength and specificity of their collective molecular interactions. However, in artificial systems, limited examples exist that quantitatively demonstrate how changes in nanoscale geometry can be used to rationally modulate the thermodynamics of individual molecular binding interactions. As a result, the use of nanoscale design features to regulate molecular bonding remains an underutilized design handle to control nanomaterials synthesis. Here we demonstrate a polymer-coated nanoparticle material where supramolecular bonding and nanoscale structure are used in conjunction to dictate the thermodynamics of their multivalent interactions, resulting in emergent bundling of supramolecular binding groups that would not be expected on the basis of the molecular structures alone. Additionally, we show that these emergent phenomena can controllably alter the superlattice symmetry by using the mesoscale particle arrangement to alter the thermodynamics of the supramolecular bonding behavior. The ability to rationally program molecular multivalency via a systems-level approach therefore provides a major step forward in the assembly of complex artificial structures, with implications for future designs of both nanoparticle- and supramolecular-based materials.



INTRODUCTION

Nanoparticle assembly is commonly regulated by multivalent intermolecular binding events between surface ligands, where the collective interaction of multiple surface-bound molecules dictates the overall thermodynamics of interparticle bonding.¹ A significant amount of effort has therefore been put forth in examining how alterations of these molecular interactions affect nanoparticle behavior, and many strategies have been developed to control particle arrangements by fine-tuning the molecular structures that guide nanoparticle assembly.^{2–5} However, while the manipulation of molecular bonding has been shown to be a powerful means to control the thermodynamics of nanoscale assembly, it is also true that the nanoscale arrangement of these molecular binding groups can affect the overall strength of the bonds being formed.^{6–9} In other words, not only can changes to molecular geometry alter material ordering at larger length scales, but changes to these larger-scale structures can also cause alterations of the molecular behavior. Indeed, manipulating the relative positions of individual chemical moieties is a common design principle used in nature to control the strength and specificity of multivalent intermolecular interactions, including avidity in antibody–antigen binding,¹⁰ substrate selectivity at the active

site of catalytic enzymes,¹¹ and strong yet dynamic carbohydrate-regulated cell adhesion.¹² While synthetic materials typically try to generate hierarchical ordering from small length scales upward (e.g., changes to molecular motifs causing different nanoscale behaviors), these examples in nature demonstrate that structural hierarchy can also work in the opposite direction, where large-scale organization alters the behavior of individual building blocks (e.g., nanoscale organization affecting molecular multivalency). Methods to control hierarchical organization via interplay between structures both up and down multiple length scales simultaneously can be termed a “systems” approach to materials development.

In principle, it should be possible to develop a systems-level approach to nanoparticle assembly, where structural features at the length scales of individual molecular bonds, nanoscale particle geometry, and mesoscale arrangement of particles serve as integrated design handles to control the assembly process.^{13–15} For example, a systems-level approach to nanomaterials synthesis could use multivalent supramolecular

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bonding to dictate how nanoscale particles form into mesoscale lattices but also simultaneously use the nanoparticle coordination environment within those lattices to regulate the multivalency of molecular interactions and alter the strength of these bonds. The advantage of such a complex materials synthesis method would be the ability to more finely tune both particle assembly and supramolecular bonding by design features both above and below the length scales of the nanoparticle bonds themselves. In order to realize this goal, however, it is important first to understand how nanoscale structure affects the thermodynamics of these multivalent interactions in a rational manner. In this work, the hierarchical nature of a nanoparticle building block is used to methodically modify the degree to which supramolecular groups act collectively and therefore to control the overall interaction strength between nanoparticles.

This enables a systems-level approach to materials synthesis where the nanoscale geometry influences the molecular organization and those design parameters in conjunction control the mesoscale architecture, affording simultaneous control of material structure across multiple length scales in a programmable manner.

RESULTS AND DISCUSSION

We have recently demonstrated a new nanoparticle-based building block that is capable of directed assembly via complementary hydrogen-bonding motifs called the nanocomposite tecton (NCT).¹⁶ NCTs consist of rigid nanoparticle cores functionalized with deformable polymer chains in a dense brush architecture (Figures 1, S1–S5, and S8; the NCTs examined here consist of gold nanoparticles coated with polystyrene brushes and suspended in toluene). All of the polymer chains on the NCTs terminate in either a diaminopyridine (DAP) or thymine (Thy) group (Scheme S1); these groups constitute a complementary supramolecular pair.^{17,18} Complementary sets of NCTs can form many DAP–Thy complexes that behave as a collective nanoscale bond linking NCTs together into large superlattices. Indeed, with appropriate thermal annealing, NCTs can even form crystalline lattices with long-range ordering.

Each nanoscale NCT–NCT bond within these lattices is a multivalent structural feature, where the multivalency number (N) is the number of monovalent DAP–Thy complexes that act in a coordinated manner when two adjacent NCTs form an interparticle bond.^{19,20} As a result, the free energy driving NCT assembly can be regulated by modifying the NCT structure at either the molecular or nanometer length scale; the former controls the strength of each individual monovalent supramolecular complex, while the latter regulates how many supramolecular interactions constitute a multivalent NCT–NCT bond. These synthetically independent design handles in different size regimes make NCTs ideal for exploring how both nanoparticle assembly and the multivalency of individual NCT–NCT bonds are affected by changes in structure at both the chemical and nanometer length scales. The ability to rationally program multivalency as a function of nanoscale structural features is therefore the first step in understanding and using this systems-level approach to materials design.

Initial work has demonstrated that the collective binding enthalpy of an NCT–NCT bond is significantly greater than that of an individual DAP–Thy complex,¹⁶ a hallmark of a multivalent interaction. However, the calculated multivalency values for these NCT systems are surprisingly low. For

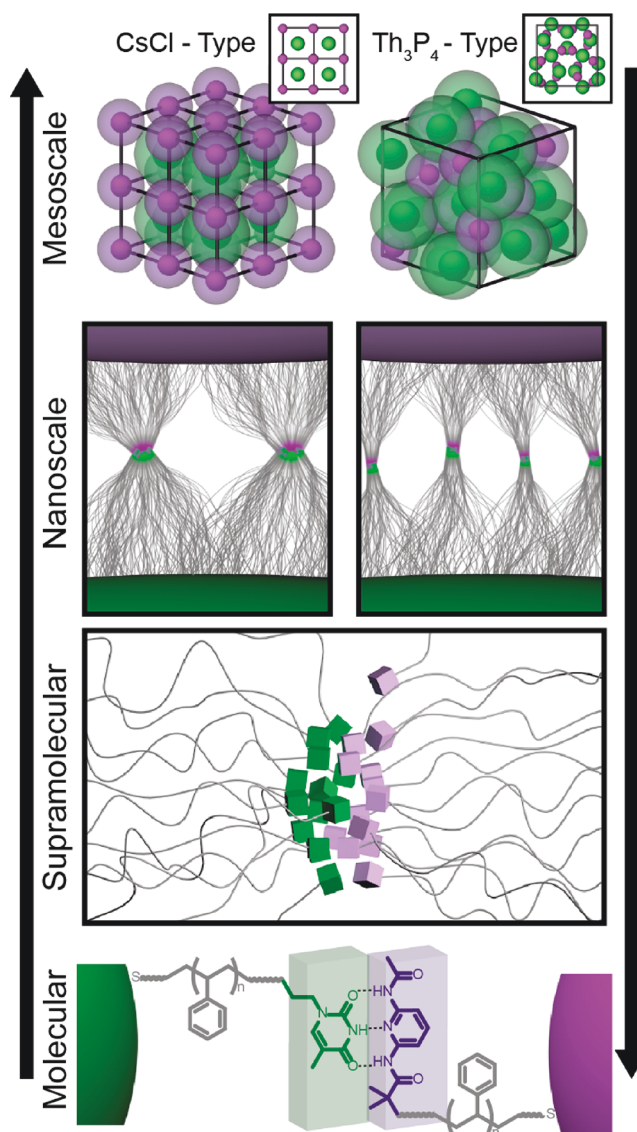


Figure 1. Typically, hierarchical structuring is understood as molecular structures causing the organization of larger-length-scale motifs, but these larger motifs can also influence how the smaller-length-scale components of a material behave. For example, NCTs functionalized with DAP- or Thy-terminated polymer chains engage in supramolecular bonding determined by the chemical identity of the ligands (molecular structures, bottom). The binding groups cluster into supramolecular bundles as a result of differences in intermolecular forces between the headgroups, polymer chains, and solvent molecules (supramolecular structures), and this bundling allows multiple molecular groups to act multivalently. Multiple bundles arranged around a nanoparticle surface (nanoscale structures) thereby drive the formation of ordered arrays of nanoparticles (mesoscale structure). However, the organization of particles within a mesoscale lattice can in turn affect the nanoscale arrangement of polymer chains surrounding each particle, and these alterations affect the polymer chain dynamics, thereby modulating the thermodynamics of the bundled molecular bonds. As a result, the structure of the entire system must be considered simultaneously to fully understand the different levels of hierarchical organization.

example, NCTs consisting of 26 nm particle cores functionalized with ~ 1000 polymer chains exhibit a multivalency value of only 10. While it is possible that each multivalent NCT–NCT bond consists of only 10 DAP–Thy complexes, the high

local concentration of hundreds of DAP and Thy groups between particles makes this explanation of a low multivalency number unlikely. An alternative reason for this low value of N could be that the total number of DAP–Thy complexes comprising each NCT–NCT bond is significantly greater than 10 but there exists a structural feature in between the nanoscale shape of the NCT and the individual molecular groups that regulates the number of complexes that can act in a coordinated, multivalent manner. More simply, each NCT–NCT bond consists of a large number of DAP–Thy complexes, but these complexes are arranged in tiny “bundles”, and only complexes within a single bundle could be considered to be multivalent (Figure 1, second row, right panel). Prior work has demonstrated that given an appropriate driving force, small-molecule ligands on the surface of nanoparticles will indeed bundle together.^{21,22} Similarly, polymer brushes on nanoparticles have also been shown to engage in bundling when exposed to a strong antisolvent.²³ On the basis of these prior observations, we hypothesize that the driving force behind bundling of supramolecular complexes here could be differences in the chemical potential between individual DAP and Thy groups and the surrounding solvent molecules. Nonpolar polymers modified with telechelic polar moieties are known to form reverse micelles in low-polarity solvents (Figure S11), which would be consistent with small clusters forming at the ends of the polymer brush.²⁴ If such bundling indeed dictates the multivalency in these NCT systems, the presence of these “bundle bonds” would represent a systems-level emergent phenomenon where the nanoscale sizes and shapes of the NCT could be used to regulate the thermodynamics of supramolecular complexation.

Since the positions of individual chain ends on an NCT cannot be readily measured because of their small size, their poor electron density contrast with the surrounding polymer and solvent, the presence of the significantly larger and more electron dense nanoparticle cores, and the transient nature of supramolecular complexes, the bundle bond hypothesis was first examined using molecular dynamics simulations to determine the most probable arrangement of individual DAP–Thy complexes within a multivalent NCT–NCT bond (Figure 2). A full atomistic description of NCTs would be computationally prohibitive, but a coarse-grained model with a consistent mapping of the geometry, volume fraction, and interaction parameters between experiments and simulations (see the Supporting Information for details and Figures S12 and S20) is sufficient to provide insight into the configuration of the multivalent NCT–NCT bond interface.^{21,22}

In a typical simulation where a pair of complementary NCTs is allowed to reach equilibrium, DAP and Thy groups that are not part of a supramolecular complex are randomly positioned at the periphery of the particles. However, DAP–Thy complexes that are part of a multivalent NCT–NCT bond do indeed coalesce into bundles that dynamically change shape throughout the simulation (Figures 2a and S13–S15). Thus, each multivalent NCT–NCT bond consists of multiple bundle bonds, where the degree of multivalency is determined by the number of DAP–Thy complexes that constitute a single bundle. Because the bundles are found only at the interface of NCTs connected via a multivalent NCT–NCT bond (Figure 2b), these data not only confirm the presence of the bundle bonds but also demonstrate that it is the act of forming a nanoscale NCT–NCT bond *itself* that drives supramolecular bundle formation. NCTs therefore present a previously

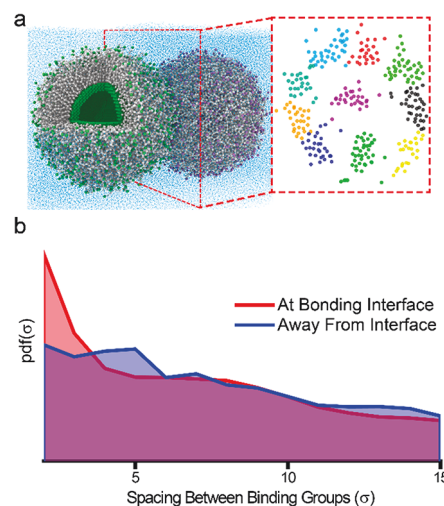


Figure 2. Molecular dynamics simulations of NCT assembly. (a) The equilibrium structure of the modeled NCTs shows the presence of bundles that emerge at the interface of two complementary NCTs. The dots in the inset denote positions of individual supramolecular groups at the NCT–NCT interface; the different colors denote algorithmically defined bundles that dictate the degree of multivalency (see the Supporting Information for clustering analysis). (b) Pair distribution function (PDF) analysis of the distance between supramolecular groups both at and away from the NCT–NCT interface. At the interface, the supramolecular binding groups associate into bundles, resulting in a distinct spike in the PDF that corresponds with the radius of the bundles. The absence of this peak away from the interface confirms that it is the act of forming the nanoscale NCT–NCT bond that drives the formation of this emergent structural feature.

unexplored opportunity to systematically study how nanoscale structure can be used to modulate molecular multivalency.

It is also important to note that this bundling behavior is distinct from previous examples of spontaneous symmetry breaking in the ligands of nanoparticles being assembled. These differences stem from the fact that the bundles of the supramolecular complexes observed here are significantly smaller than the cross section of the overall NCT–NCT bond, which means that any given NCT–NCT bond consists of multiple bundles. Moreover, the DAP–Thy connections are dynamic, and the exact sizes and shapes of the bundles are constantly changing. As a result, the bundling phenomenon is not entirely identical to the “patchiness” observed in other systems, such as those that are anisotropically functionalized^{23,25} or that form soft skyrmions via ligand rearrangement,²⁶ as the overall surface of the NCT would still be considered to be largely isotropic even with the bundling phenomena occurring (*vide infra*). This distinction means that NCTs affect material structuring at a level *in between* an individual molecular bond and an overall nanoparticle structure. The obvious question that therefore arises is whether design handles at both the molecular scale and the nanoscale can be used in conjunction to modulate the collective size and dynamic behavior of these bundle bonds.

In order to properly answer this question, it is important to understand how the thermodynamics of NCT assembly changes as a function of different nanoscale structural features. In a standard multivalent bond between NCTs, the strength of each supramolecular complex (each monovalent binding event) is described by the free energy equation:

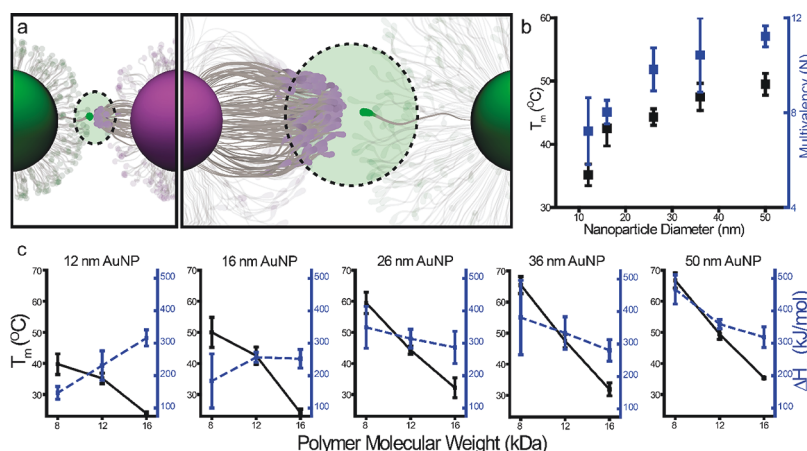


Figure 3. Thermodynamics of bundle bond formation is controlled via nanoscale design handles. (a) The thermodynamics of bundle bond formation is dictated by the number of supramolecular groups that can cluster together as well as the entropy penalty associated with confining polymer chain motion upon the formation of a supramolecular complex. In the case of a smaller particle with a short polymer, the number of supramolecular bonds is limited (left). When a longer polymer is used (right), the multivalency increases, but with an added entropic penalty. (b) Thermal melt analysis shows increases in ΔH_m and T_m with increasing nanoparticle diameter (decreased particle curvature). A decrease in NCT curvature results in a higher density of supramolecular binding groups, and therefore, a larger number of hydrogen bonds can bundle together. (c) NCT T_m decreases with increasing polymer length for all particle sizes examined (black traces), but the collective ΔH_m of the bonds either increases or decreases depending on the inorganic particle core diameter (blue traces).

$$\Delta G_s = \Delta H_s - T\Delta S_s \quad (1)$$

where ΔG_s , ΔH_s , and ΔS_s are the Gibbs free energy, enthalpy, and entropy associated with the formation of a single DAP–Thy complex. The strength of a multivalent “bundle bond” is therefore

$$\Delta G_m = \Delta H_m - T\Delta S_m \quad (2)$$

where ΔG_m , ΔH_m , and ΔS_m are the Gibbs free energy, enthalpy, and entropy of the collective bundle. By definition, the ratio of the enthalpy values of these reactions is the value of the multivalency (i.e., $N = \Delta H_m/\Delta H_s$). More simply, the multivalency number N is the average number of groups within a given bundle.

The most significant contribution to ΔH_m is expected to be the hydrogen bonds formed between DAP–Thy pairs, as these are by far the strongest types of interactions involved in the formation of a DAP–Thy complex. Additional enthalpic contributions such as dispersion forces or polymer mixing within the brush may also be possible, but these are expected to play a much smaller role in dictating the thermodynamics of NCT assembly because they are significantly weaker than the hydrogen-bonding interactions (additional discussion is provided in the [Supporting Information](#)). The most significant contribution to ΔS_m is expected to come from the reduction in polymer configurations upon formation of a DAP–Thy complex, which restricts the motion of the two adjoined polymer chains.

The value of ΔH_s for each DAP–Thy complex within a bundle bond can be assumed to be constant on the basis of prior evidence in simpler molecular systems.¹⁹ Thus, ΔH_m should be ΔH_s multiplied by the number of DAP–Thy complexes that constitute a bundle bond (i.e., $\Delta H_m = N\Delta H_s$). However, ΔS_s is not equivalent for all polymers within a bundle bond, as different polymers will have different amounts of conformational confinement upon the formation of a DAP–Thy complex, depending on where they are anchored on the surface of the nanoparticle core. As a result, ΔG_m can be expressed as a function of N , ΔH_s , and ΔS_s as follows:

$$\Delta G_m = N(\Delta H_s) - T\left(\sum_{i=1}^N \Delta S_i\right) \quad (3)$$

where the values of ΔS_i are the entropy changes associated with tethering the different polymer linkers via DAP–Thy complexes. As noted above, while there may be additional contributions to this simple approximation, such thermodynamic parameters are small enough that they do not significantly affect the conclusions drawn here, and these assumptions should hold for systems like the NCTs that possess long ligands and directional enthalpic interactions.^{27,28}

On the basis of these thermodynamic parameters, a bundle bond therefore represents a collection of DAP and Thy groups for which the entropy penalty for linking any given pair of polymer chains comprising that bundle is less than the strength of the DAP–Thy complex that is formed. In other words, if a polymer chain has to stretch so much to become a part of a bundle that $T\Delta S_i$ is greater than ΔH_s , that polymer will not be a part of that multivalent bundle.

This interplay between enthalpy and entropy explains why bundles of DAP and Thy groups emerge only within an NCT–NCT bond, as the enthalpy benefit of generating a supramolecular complex is necessary to offset the entropic penalty of restricting polymer motion; the reduced chemical potential of clustering the polar headgroups is not enough on its own to drive this behavior. Additionally, it indicates that changes in the NCT structure at the nanoscale should affect the multivalency by altering the extent to which polymer chain conformations are restricted upon formation of a bundle bond. Therefore, because the design of NCTs can be easily varied, a series of well-controlled experiments can provide further support for the bundle bond hypothesis and insights into the relationship between nanoscale structure and multivalency.

For example, changing the nanoscale shape of an NCT by modifying the particle core diameter is observed to increase the temperature at which NCT–NCT bonds break as well as the values of N and ΔH_m . The thermodynamics of NCTs was studied by monitoring the dissociation of particles with UV–

vis spectroscopy, and the resulting thermal transition was fit to the van't Hoff equation to extrapolate relevant thermodynamic values (see the [Supporting Information](#) and [Figures S6, S7, and S20](#) for further details).²⁹ The increase in T_m and ΔH_m with increasing nanoparticle core diameter can be explained as a function of changes in the particle nanoscale curvature. When two curved surfaces approach one another, different sets of points on the opposing surfaces are not necessarily equidistant. Additionally, the polymer chains extending perpendicularly from the curved surface are not all initially aligned in the same direction as the NCT–NCT bond ([Figure 3a](#), left). As a result, polymer chains further from the NCT–NCT bond axis need to stretch in order to form a DAP–Thy complex, while polymers directly at the center of the bond will likely compress in order to allow more polymer chain ends to reach one another and form supramolecular complexes ([Figure 3a](#), right). The more curved the particle surface, the greater the variation in compression and stretching as a function of where the polymers are grafted to the surface. The values of ΔS_i resulting from tethering polymer chains via a supramolecular complex would therefore be expected to vary more as a function of lateral distance between binders when the NCT particle cores have more curved surfaces. As a result, lowering particle curvature by increasing the particle diameter enables a larger number of polymer chains to bundle together and act multivalently. In other words, the value of N at which $T\sum_{i=1}^N \Delta S_i$ overcomes ΔH_m is higher for larger-diameter cores. This larger value of N correlates to larger bundle bonds and (on the basis of [eq 3](#)) explains the fact that the values of ΔH_m and T_m increase with particle core size, asymptotically approaching the limit corresponding to a flat surface ([Figure 3b](#)).

Increasing the height of the polymer brush can also use nanoscale geometric influence to modify NCT bonding thermodynamics but would be expected to have more complex effects on the multivalency and bundle bond formation. As the polymer length increases, the number of conformations (and thus the entropy) of each polymer chain should also increase. This means that tethering two longer polymer chains together should result in a larger entropy penalty, indicating that the value of N at which $T\sum_{i=1}^N \Delta S_i$ exceeds ΔH_m should decrease, resulting in lower T_m . Experiments demonstrate that T_m does indeed decrease with increasing polymer length for all systems studied ([Figure 3c](#)). However, while NCTs with larger particle diameters (26, 36, and 50 nm) also show a corresponding decrease in N , NCTs with smaller particle diameters (12 and 16 nm) exhibit values of N that instead *increase* with increasing polymer length.

These data indicate that the number of DAP–Thy complexes that constitute a bundle bond actually increases, which can be explained as a function of polymer packing density. Short polymers grafted onto particles form a dense, concentrated brush, but longer polymers extend further off of the particle surface into a semidilute brush regime.^{30,31} The transition from the concentrated to semidilute regimes is dependent on the degree of particle curvature, with larger spheres requiring longer polymer lengths to become semidilute. Polymer chain ends in this semidilute regime can occupy a greater number of conformations, which in turn allows a greater number of DAP groups to bind to complementary Thy groups on adjacent particles ([Figure 3a](#)). However, this would also mean that in a comparison of two NCT systems with the same bundle bond size, smaller

particle cores would require greater amounts of polymer chain confinement in order to form the bundles. These opposing thermodynamic effects explain the contrasting trends in ΔH_m as a function of polymer length on small and large nanoparticle cores. The greater surface curvature of the small cores inherently allows for more polymer flexibility and enables the formation of larger bundle bonds with increasing polymer length (increasing ΔH_m and N) but also requires greater polymer deformation to form these bundles (larger values of ΔS_i , which results in a decreased T_m despite the larger N).

In order to further show that the multivalent behavior observed in NCTs is an effect of nanostructure-induced bundle bonds and not just an increased local concentration of DAP and Thy groups at the particle surface, NCTs were coloaded with controlled ratios of “active” polymers terminating in a supramolecular binding group and “inert” polymers without any such functionality ([Figures S9 and S10](#)). In conventional model systems that explain multivalency solely on the basis of an increased local concentration of binding groups, reducing the number of active chains would be predicted to lower the degree of multivalency. However, in the NCT system, the values of N and ΔH_m did not exhibit any significant change as a function of density of DAP and Thy groups ([Figures 4a and S10](#)). These unexpected results imply that above a critical fraction of active polymer chains, the local bonding structure of an NCT–NCT connection must be constant, meaning that the size and shape of the bundle bonds do not change as a function of the number of “active” polymers within the range studied. The lower melting temperatures for the coloaded samples must therefore arise from a greater polymer entropy penalty for NCT bonding, as greater deformation would be required to maintain a constant multivalency. The importance of this finding is to reiterate the initial discovery that the act of forming a nanoscale bond results in an emergent structure (the bundle bond), where this new structural motif is the determining factor of the entire system's multivalency. The data and simulations presented above therefore indicate that the degree of multivalency in an NCT–NCT bond is indeed a complex interplay of building block structure across length scales and that nanoscale structure can be used to modulate bundle bond behavior.

Nevertheless, because each bundle bond still consists of multiple individual supramolecular complexes, it is also important to consider the effects of altering the molecular composition of the system. While this can be achieved via chemical alterations to the DAP or Thy complexes (as has been examined in previous molecular models³²), it is also possible to modify the overall structure and chemical behavior of an NCT via alterations of the solvent environment. Individual hydrogen-bonding interactions typically weaken in more polar solvents, which would be expected to reduce the value of ΔH_s .³³ However, the chemical potential between DAP and Thy groups and their local environment would also decrease with increasing solvent polarity, reducing the driving force for forming the bundles, which could lead to larger bundle bonds and greater multivalency.²⁴

Variable-temperature NMR experiments performed on small-molecule DAP and Thy analogues demonstrate that adding a more polar solvent (1,1,2,2-tetrachloroethane, TCE) does indeed decrease ΔH_s for individual DAP–Thy complexes. This enthalpy change reaches a minimum value at ~20% TCE as a result of preferential solvation^{34,35} of the moderately polar DAP–Thy complex ([Figures S18 and S19](#)). However,

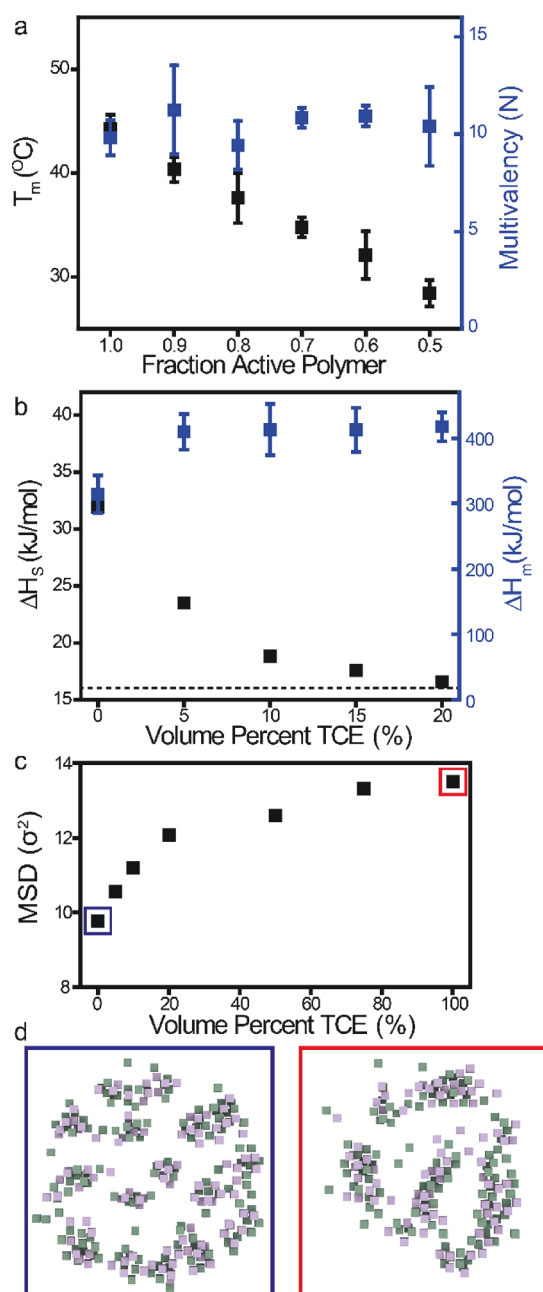


Figure 4. NCTs exhibit a maximum multivalency, implying saturated bonding behavior. (a) Decreasing the fraction of polymer chains that have a supramolecular binding group decreases the NCT T_m , but with no significant change in ΔH_m . (b) The bundling effect is hypothesized to originate from phase segregation of the polar supramolecular binding groups from the nonpolar toluene solvent. Introducing a polar solvent (1,1,2,2-tetrachloroethane, TCE) weakens individual supramolecular bonds (black data; the dotted line represents the DAP–Thy binding strength in 100% TCE), but surprisingly increases the binding enthalpy for the collective NCT–NCT interaction (blue data). (c) Molecular dynamics simulations show that increasing the solvent polarity decreases the restrictive effect on the supramolecular binding groups. This can be quantified by measuring the mean square displacement (MSD) of the binding groups, which is shown to increase with increasing TCE. (d) Positions of supramolecular groups at a modeled NCT–NCT interface show smaller, less multivalent bundles in a low-polarity solvent (blue), and larger, more diffuse bundles in a higher-polarity solvent (red).

although ΔH_s decreases with increasing solvent polarity, the collective ΔH_m of an NCT bond actually increases when TCE is added (Figure 4b). Because each individual hydrogen bond is weaker, the increase in ΔH_m indicates that N must dramatically increase in the more polar solvent: bundles in the more polar solvents exhibit multivalencies of up to $\sim 250\%$ of their value in pure toluene ($N = 10$ in toluene but 25 in 20% TCE for the system in Figure 4b). Simulations confirm that adding TCE increases both the average bundle bond size and the rate at which DAP–Thy complexes exchange between adjacent bundles (Figures S16 and S17). This enhanced mobility affords each supramolecular group a greater number of counterparts on a neighboring particle with which it can complex, enhancing the NCT multivalency (Figure 4c,d). Thus, although each individual hydrogen bond weakens with increased solvent polarity, the increased multivalency results in higher collective binding strength between NCTs. As a result, the hierarchical ordering of an NCT–NCT bond is dictated (and can be controlled) by a complex and integrated set of design variables across multiple size regimes. Alterations of the molecular composition of the solvent change the enthalpic driving force for bundle bond formation, while alterations of the NCT nanoscale structure alter its associated entropic penalty. NCTs therefore represent a multivalent supramolecular system that, just like natural systems, can be regulated and understood only by considering material structure at the molecular and nanoscale simultaneously.

Importantly, the fundamental understanding of NCT bond behavior from the above experiments potentially allows for the development of new design principles for systems-level control of assembly as a function of these integrated molecular and nanoscale handles. Prior work has shown that NCTs with symmetric particle sizes and polymer lengths form ordered, crystalline CsCl-type lattices upon thermal annealing.¹⁶ A crystalline lattice is hypothesized to be the thermodynamically favored state because it maximizes the number of NCT bonds that can form and minimizes the entropic penalty associated with polymer confinement upon binding. This implies that manipulating the overall morphology of the “bundled” bonds could allow new phases to be achieved, as these enthalpic and entropic factors that determine which crystal phase is thermodynamically preferred are inherently linked to the sizes and shapes of the bundles. As a result, alterations to nanoscale NCT architecture could be used to regulate both the thermodynamics of supramolecular complex formation and the mesoscale coordination environment of particles within a lattice.

For example, an asymmetric NCT system consisting of complementary large (20 nm diameter core and 12 kDa polymer) and small (12.5 nm core and 7 kDa polymer) NCTs was found to assemble into a lattice isostructural with Th_3P_4 after thermal annealing. The formation of this lattice symmetry is surprising, since it has a lower nanoparticle valency and thus fewer interparticle connections than CsCl-type lattices. It has been postulated in other nanoparticle assembly methods^{36,37} that the Th_3P_4 phase is favored over CsCl because it alleviates strain in linkers that are sterically limited in their mobility. This strain on the ligands induced by assembly also connects to the previously described bundling behavior, as increasing polymer strain correlates negatively with the amount of multivalency. In toluene, the strong driving force for segregation of the DAP and Thy groups drives the formation of small bundles ($N \approx 10$ as shown above), which restrict the motion of the supra-

molecular binding groups. Increasing the solvent polarity would be expected to increase the molecular bond mobility and soften the nanoscale polymer coronae, expanding the size of the supramolecular bundle bonds and increasing the multivalency of the NCT. In more polar solvents, the higher enthalpic driving force from the collective supramolecular interaction should be able to overcome the entropy penalty of straining the polymers and favor an alternate superlattice structure. To clarify, the collective supramolecular interaction of multiple molecular binding groups arranged around a nanoscale scaffold would result in a mesoscale superlattice architecture, but this mesoscale organization would also control the amount of nanoscale polymer reorganization needed to maintain the lattice, thereby affecting the supramolecular bundle sizes and thus collective molecular thermodynamics—a true “systems” approach to material design (Figure 1).

Adding TCE to NCT solutions during thermal annealing does indeed favor the formation of the 4% denser CsCl lattice (Figure 5), demonstrating that a single set of NCT building

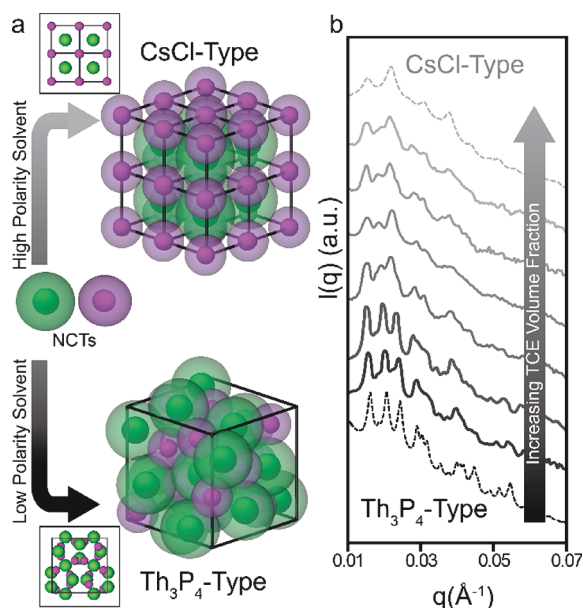


Figure 5. Solvent composition can be used to manipulate the NCT superlattice crystal structure. (a) Schematic diagram showing the unit cell of a Th_3P_4 -type NCT superlattice and eight unit cells of a CsCl-type lattice, which occupy a similar volume. (b) Small-angle X-ray scattering measurements on NCT superlattices in toluene with 0–10 vol % 1,1,2,2-tetrachloroethane (TCE) as a cosolvent. The top and bottom dashed patterns are simulated. Increasing the concentration of TCE modulates the bundle bond size, which then alters the resulting mesoscale structure of the NCTs.

blocks can be driven down two different assembly pathways using solely changes in solvent composition. The significance of this result is that the hierarchical ordering in this system cannot be predetermined by simply summing up the interactions of individual molecular binding groups or considering the larger lattices and NCT bonds to be just a consequence of the behavior of individual molecules. Rather, these structures are indeed an example of a systems-level design process, where the morphology at each length scale (molecular, nano, and meso) is both an effect and a cause of behavior at the others.

It is important to again note that this system-derived change in NCT coordination environment is different than prior particle assembly schemes that use “patchy” particles.^{23,25,38} Those methods typically control the particle coordination number by breaking the overall symmetry of the ligand shell around a particle. Here, the overall ligand shells surrounding the particles remain largely isotropic at the nanoscale, as each NCT–NCT bond consists of multiple emergent bundle bonds that are smaller than the length scale of the collective NCT–NCT interactions. Instead of altering the nanoscale symmetry of the particle building blocks, these bundles regulate the degree of multivalency to dictate the equilibrium lattice symmetry. The formation of these two unique superlattices and the ability to drive a single set of NCT building blocks to either crystallographic symmetry therefore demonstrate the potential for materials design using a combination of integrated handles across multiple size regimes.

CONCLUSION

In order to fully mimic the complexity of naturally occurring materials made via directed assembly, it is imperative to understand how the interactions between design features at multiple length scales dictate material structure. The systems-level design methodology presented here represents a unique platform for exploring the thermodynamics of multivalent behavior in a manner that is more similar to a natural system than a simple molecular model. While this work focuses on the first steps of controlling material structure and molecular assembly in a systems-level approach, the modularity of the NCT design potentially allows future exploration of different design handles (e.g., polymer compositions, supramolecular binding group structures, particle shapes) to further imitate and explore many different types of multivalent natural systems that use nanoscale structure to modulate their behavior and hierarchical ordering across multiple length scales. The understanding gained from the experiments performed here and these future investigations is critical for multiple fields where materials require sophisticated structures and interactions between features at the molecular, nano-, and macroscopic length scales, including catalysis, interface science, and biomimetics. Studying the interplay between molecular makeup and nanoscale spatial organization therefore presents a powerful opportunity for programming of hierarchical ordering and material behavior beyond the limitations of current reductionist design approaches.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b04999.

Materials and Methods, Schemed S1 and S2, Figures S1–S20, Tables S1–S8, and NMR spectra (PDF)

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Notes

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