Programmable Atom Equivalents

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Nucleic Acid-Modified Nanostructures as Programmable Atom Equivalents: Forging a New "Table of Elements"**

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Introduction

The establishment of the Periodic Table of the Elements almost 150 years ago was the first step towards transforming how scientists organized and understood the elemental building blocks of matter. Before its introduction, elements were viewed as separate and independent entities, each with their own unique set of properties. By arranging elements based upon their characteristics, the Periodic Table enabled scientists to understand their behavior as members of collective sets. Their properties could be discussed in the context of logical trends, and these trends could be used to predict the properties of as-of-yet undiscovered elements and yet-to-be synthesized molecules, bulk materials, and extended lattice structures. Indeed, for decades the Periodic Table has served as a guide for the synthesis of new structures and given us a framework to understand important scientific advances.

Today, the field of nanoscience and nanotechnology offers scientists new ways to think about materials synthesis. Nanoscience is an interdisciplinary field focused on the synthesis, manipulation, characterization, and application of structures with at least one dimension on the 1 to 100 nm length scale. In this size regime, materials possess properties that are significantly different than their macroscopic analogues, and these properties are highly dependent on the nanostructure's composition, size, shape, and local environment.[1–7] In 2000, with the introduction of the National Nanotechnology Initiative (NNI),[8] nanoscience research and development were prioritized in the United States, and since then US scientists and other researchers around the globe have devised myriad methodologies to generate nanoparticles of many compositions (e.g., metallic,[3,9] semiconducting,[10–12] insulating,[13] carbon-based,[14] polymeric[15–17]) in high yield in the solid, solution, and gas phases, as well as on surfaces. Several methods also have been introduced to tune the size and shape of nanoparticles with nanometer precision,[18–22] and to couple materials of different compositions together to create hybrid structures (e.g., alloys,[23] core–shell structures[24,25]). These new nanoparticles have a variety of interesting chemical and physical properties, which have been applied in a range of fields from catalysis[26,27] to biomedicine[28–30] to energy.[31] This explosion in research aimed at discovering, understanding, and refining nanoparticle syntheses to realize highly sophisticated nanoscale architectures can be likened to the early rush in chemistry to discover new elements.

A key area of nanotechnology research deals with the assembly of these building blocks into more complex structures,[18,32–41] just as the discovery of different elements led to the synthesis of many new materials. Although analogues consisting of small clusters of nanoparticles have also been developed, we will focus herein primarily on extended networks.[18,42–46] In many cases, these assemblies have been shown to exhibit novel and extremely useful emergent properties[18,26,40,41] that are a direct result of the arrangement of the individual nanostructures within the assembly. As a result of these promising but nascent discoveries with nanoparticle-based constructs, there has been intense interest in devising strategies that can be used to organize nanoparticles of all types into well-defined hierarchical arrays, in which the spacing and symmetry between the particles are precisely controlled. Indeed, one of the main challenges currently facing nanoscience researchers is the

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development of a methodology whereby nanoparticles can be thought of as "atom equivalents", in which bonding interactions between particles are just as well understood and characterized as those between atoms in molecules and solid-state lattices. The development of such a methodology would open the door to more rigorous explanation and understanding of the emergent properties of assemblies based upon these atom-equivalent structures.

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Matthew N. O'Brien received a B.S. in chemistry and history with a certificate in African Studies (University of Wisconsin at Madison; 2011) with university, college, and departmental honors. While at UW-Madison, he studied the synthesis of lead chalcogenide structures by chemical vapor deposition under the supervision of Prof. Song Jin. He is currently a graduate student in Prof. Chad A. Mirkin's group at Northwestern University. His research interests include the synthesis and assembly of nanomaterials and understanding the emergent properties that arise from ordered nanoparticle systems.

Sarah Hurst Petrosko graduated from the University of Florida in 2002 with B.S. degrees in Chemistry and Physics and from Northwestern University in 2009 with a Ph.D. in Chemistry (under the guidance of Prof. Chad A. Mirkin). She was awarded a Director's Postdoctoral Fellowship from Argonne National Laboratory and worked with Dr. Tijana Rajh for two years at the Center for Nanoscale Materials before taking a position as a Research Assistant Professor at Northwestern University. She is interested in investigating the structure and properties of novel nano-bio conjugate structures and using them to solve problems in biology, chemistry, and materials synthesis.

Chad A. Mirkin holds a B.S. degree from Dickinson College and a Ph.D. degree from Penn State(working with Gregory Geoffroy). He was an NSF Postdoc at MIT (in the lab of Mark Wrighton) prior to becoming a Professor at Northwestern in 1991. He has authored over 520 manuscripts and is an inventor on over 900 patent applications worldwide (233 issued). He has received over 80 national and international awards and is the founder of four companies. His current research interests include nanomedicine, materials assembly, lithography, nanoparticle synthesis, and supramolecular chemistry.

It is important to note that we use the term "atom equivalent" when referring to the use of nanoparticles as building blocks, rather than the often used term "artificial atom", which has different meanings across scientific disciplines. Historically, "artificial atom" has referred to a metal or semiconductor nanoparticle whose electrons are confined into discrete states by its physical size or an applied electric field, thereby mimicking the quantized energy states of electrons found in atoms.[47–49] Coupling between the discrete electronic states of "artificial atoms" leads to the formation of extended states, as with atoms, which are described as "artificial bonds". However, while this analogy provides significant insight into the electronic properties of discrete nanoparticles and their assemblies, it fails in the context of forming materials, as nanoparticles alone do not inherently have the necessary components to create physical bonds between themselves in a controllable manner.

In 1996, we introduced the concept of a nucleic acid-nanoparticle conjugate that could be used as a "programmable atom equivalent" (PAE) to build higher ordered materials through deliberately designed hybridization events.[32] Initial research focused both on developing these constructs and understanding their fundamental behavior,[33–36] as well as applications in small molecule and biomolecule sensing and diagnostics.[50–56] More recently, they have also proven useful in the context of therapeutics and intracellular diagnostics.[57–59]

Since the initial development of the nucleic acid-nanoparticle conjugate, we and other research groups have made significant synthetic advances that have allowed us to create nanoparticle superlattices of multiple distinct crystalline symmetries with sub-nanometer control over their lattice parameters.[60–63] We have even developed a set of design rules[37] analogous to Pauling's Rules for ionic solids[64] that can be used as a guide for the rational construction of functional nanoparticle-based materials with specific structures (Table 1). Unlike atoms, however, which have a fixed set of properties and bonding possibilities dictated by their inherent electronic structure, the properties and bonding behaviors of PAEs can be tuned by manipulating their structure over a wide range of possibilities. These design possibilities allow for the development of nanoparticle-based materials that have exotic and versatile structures, properties, and functions.

Although structures built via DNA origami[65–68] are sometimes compared to the PAE superlattices that will be discussed herein (both utilize DNA base-pairing to build nanostructured materials), these two fields are actually quite distinct. DNA origami is defined as "*the process in which … DNA molecules are folded into arbitrary nanostructures*";[69] the DNA in these structures is both the assembly agent and the functional material being assembled. In the PAE lattices discussed herein, the DNA acts only as a synthetically programmable "glue", used to dictate how nanoparticles are

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Table 1: The design rules for PAE assembly.

Rule 1:	*PAEs will arrange themselves in a lattice that maximizes the number of DNA duplex bonds formed.*
Rule 2:	*PAEs of equal hydrodynamic radii will form an FCC lattice when using self-complementary DNA sequences, and BCC or CsCl lattices when using two PAEs with complementary DNA sequences.*
Rule 3:	*The overall hydrodynamic radius of a PAE, rather than the sizes of its individual NP or oligonucleotide components, dictates its assembly and packing behavior.*
Rule 4:	*In a binary system based upon complementary PAEs, favored products will tend to have equivalent numbers of each complementary DNA sequence, evenly spaced throughout a unit cell.*
Rule 5:	*Two systems with the same size ratio and DNA linker ratio exhibit the same thermodynamic product.*
Rule 6:	*PAEs can be functionalized with more than one oligonucleotide bonding element, providing access to crystal structures not possible with single element PAEs.*
Rule 7:	*The crystal symmetry of a lattice is dictated by the position of the inorganic cores; a PAE with no inorganic core can be used to "delete" a particle at a specified position within a unit cell.*
Rule 8:	*PAEs based upon anisotropic particles with flat faces can be used to realize valency and will assemble into a lattice that maximizes the amount of parallel, face-to-face interactions between particles.*

positioned next to one another, and is not typically used outside of its regular linear duplex form. The final nanoparticle superlattice therefore is defined not by the positions or arrangement of DNA strands, but rather by the positions of the inorganic cores. DNA origami is more like line-drawing, where the DNA outlines the edges (or in some cases the faces) of the object being constructed. Therefore, although significant advances have been made in the field of DNA origami, this Essay will not further discuss this area of research.

To more rationally think about our rapidly growing knowledge of nanoparticle superlattice design and synthesis, we often liken the nanoparticle-based PAEs to elements that fill the Periodic Table. However, PAEs are defined according to their nanoscale architectural features (e.g., composition, size, shape, and surface functionality; Figure 1) as opposed to their electronic properties. Although the Periodic Table of the Elements is marked by incremental, stepwise changes in atomic properties, the table of PAEs is marked by a continuum of structures along multiple axes. Using this table as a guide, we discuss the design considerations associated with using nucleic acids to assemble PAEs into superlattices. Further, we compare these materials with their atomic analogues, as many aspects of the nanoparticle-based system parallel the atomic system and offer a new way of looking at fundamental concepts in chemistry (such as bonding, valency, lattice packing, phase, and even impurities and doping). Our specific purpose herein is not to recreate the Periodic Table and replace its constituent parts with nanoparticles, but rather to use the analogy to help understand the similarities and differences between synthesizing extended matter with atomic and nanoparticle-based building blocks, respectively. The Periodic Table is a man-made arrangement designed to aid in understanding the behavior of naturally occurring structures that have inherent and unchangeable properties. In contrast, organizing nanoparticle-based PAEs according to structural feature enables one to realize both the continuum of nanostructures that can be created, as well as the necessity of developing a means to rationally assemble these structures in a predictable manner. Like its atomic analogue, the table of PAEs presents a map of current knowledge, but also highlights the necessity for continued discovery of new PAEs, and the continued development of means to control their

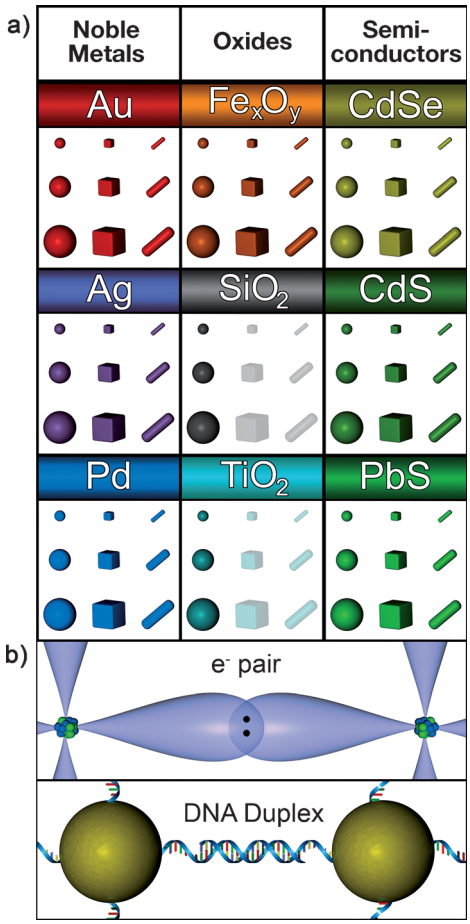

Figure 1. a) The table of "programmable atom equivalents" arranges nucleic acid–nanoparticle conjugates across multiple dimensions: composition, shape, and size. In reality, this table extends nearly infinitely in the size dimension within the nanoscale regime, and for many material compositions, further into the shape dimension. Not all particles in this nanoscale 'periodic table' have been experimentally realized, and some (semi-transparent images in the table) represent potential building blocks that may be discovered in future synthetic efforts. This table merely presents a representative concept to demonstrate that the table of PAEs has an inherently larger number of variables than the corresponding Periodic Table of the elements, rather than imply that there is a specific relationship between different blocks in the table. Thus, it is best used as an empirical guide to aid in materials development, rather than an inherent representation of the intrinsic properties and characteristics of these materials. b) The core composition and manner of bonding are compared between atoms and PAEs. Note that the comparison being drawn is only in the structural sense—DNA strands are the "glue" holding the nanoparticles in place and are not expected to directly mimic all of the inherent properties of electrons (such as band structure or orbital shape). In this sense, bonds between spherical PAEs could be considered more analogous to metallic-type bonds, while more covalent-like interactions can be observed by imparting anisotropy to nanoparticle interactions.

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behavior and explore the chemical and physical properties of these structures and their assemblies.

Discussion

A variety of different ligands have been utilized to control interactions between nanoparticles.[38,39,42,70–73] In 1996, we proposed that DNA is the ideal ligand to direct nanoparticle bonding in a manner analogous to atomic bonding.[32] This is because the length, strength, and character of nucleic acid bonds between particles can be systematically varied by changing the length, nucleobase sequence, or number of DNA strands conjugated to a nanoparticle. Furthermore, DNA is a ligand that exists on the same nanometer length scale as the nanoparticle building blocks. However, unlike the atomic system, where the electronic properties of a given atom are immutable, the nucleic acid bonds linking nanoparticles to one another can be changed, independent of the properties of the nanoparticle core. Therefore, while a given atom cannot be assembled into any desired structure with a given coordination number and lattice parameter, any nanoparticle core that can be functionalized with nucleic acids can be assembled into a wide range of structures using the universal bonding capabilities of nucleic acids. The analogy we draw between bonds based upon atomic interactions and ones formed by DNA-based PAEs extends only to structural considerations. Phenomena that emerge from orbital overlap behavior, such as the formation of valence and conduction bands are not directly represented in our analogy (although orbital directionality can be loosely mimicked in the context of nucleic acid modified non-spherical particles, as discussed later).

The first type of nucleic acid functionalized nanostructure that was developed by our group utilized a spherical gold nanoparticle core as a scaffold for the covalent attachment of single-stranded oligonucleotides in a densely functionalized and highly oriented manner. We described this PAE as a spherical nucleic acid (SNA)–nanoparticle conjugate because of the novel arrangement and dense packing of nucleic acids enabled by the shape of the nanoparticle core.[32,74] To date, nucleic acid-based PAEs have been developed using nanoparticles of different sizes (2–250 nm in diameter)[75] and compositions (e.g., silver,[76] Fe_2O_3,[77] silica,[78,79] CdSe[80]) for a variety of different classes of nucleic acids (e.g., ssDNA,[57] dsDNA,[32,50,58] RNA,[81,82] LNA[83]). Hollow, core-free versions of PAEs also have been developed by crosslinking the nucleic acids at the surface of the nanoparticle and subsequently dissolving the inorganic core.[84,85] Other three-dimensional arrangements of nucleic acids have been created by employing different-shaped nanoparticle cores as scaffolds (e.g., triangular prisms, rods, octahedra, rhombic dodecahedra).[86] In addition to being novel building block materials for the construction of lattices, these hybrid structures exhibit interesting properties that are a synergistic combination of those of the core and shell. For example, the nanoparticle core can impart upon the conjugate structure unique plasmon-based optical phenomena[4,34,87] or novel catalytic properties.[84] In addition, the tight packing and orientation of strands within the oligonucleotide shell leads to many interesting cooperative binding properties, and even leads to new properties that are not observed with free, linear DNA strands.[74,88–91]

Initial assemblies made from SNA–gold nanoparticle PAEs were synthesized by combining sets of complementary conjugates in solution below the melting temperature of the nucleic acid duplexes.[32,50] In these systems, particle arrangements and bonding patterns were not well defined, but this early work introduced the concept of building programmable matter from nucleic acid–nanoparticle conjugates and held promise for generating the desired atomic lattice analogues. Indeed, subsequent steps were taken in 2004 to demonstrate that annealing the conjugates allowed one to generate systems that exhibited short-range order, and also allowed for control over the distances between particles.[92]

In 2008, the first crystalline superlattices were generated using DNA as a programmable linker by our group and independently by the Gang group.[60,61,93] A key development in our strategy that enabled the formation of crystalline lattices of nanoparticles was to utilize only "weak" DNA interactions between particles.[60] Unlike the previous systems in which tracts of complementary bases between 10 and 30 bases long were used to effect assembly, short "sticky ends" containing as few as four complementary bases were employed. These weak interactions enable the reorganization of the PAEs within a lattice even after they have bonded to one another, such that any DNA bonds that trap particles in thermodynamically unfavorable states are easily broken to allow for particle reorganization.[62,94,95] By hypothesizing that the most stable lattice will always be the one that maximizes the number of DNA bonds formed, we have developed a set of design rules that can be used to precisely position a variety of nanoparticle types into multiple distinct crystalline lattices with sub-nanometer precision, including structures that have no mineral equivalent, with tunable control over lattice parameters (Table 1).[37,96]

These design rules are analogous to Pauling's Rules for ionic solids,[64] but in many respects more powerful, because they provide both greater predictive power and enhanced programmability. While Pauling's Rules present a masterful understanding of the complexity of atomic arrangements, these rules are merely guidelines, and the structure of many atomic systems cannot be perfectly predicted by these rules. The lack of control over factors such as ionic radius or electronegativity makes true predictability in assembled atomic lattices challenging, and the programmability of these lattices impossible. In other words, once a set of atomic or molecular building blocks is chosen, the resulting set of lattices that can be constructed is also predetermined. By using nucleic acid functionalized nanostructures however, one can recreate the diversity observed in atomic lattices, but also surpass the limitations in programmability and predictability inherent in atomic systems. Therefore, these PAEs can be used as a guide for the rational construction of functional nanoparticle-based materials for plasmonic, photonic, and catalytic applications.[18,26,31]

The first in this set of rules, from which the rest of the rules are derived, is: PAEs will arrange themselves in a lattice that

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maximizes the number of DNA duplex bonds formed. Because it is the DNA strands that are stabilizing the lattice, the more DNA bonds formed between particles, the more stable the lattice will be. Thus, the thermodynamic product will always maximize the number of DNA connections being formed, and the set of rules we present herein makes the synthesis of a stable crystal structure a simple matter of determining which DNA strands must be used to place a nanoparticle-based PAE at a desired lattice position.

The second of the design rules states: PAEs of equal hydrodynamic radii will form an FCC lattice when using self-complementary DNA sequences, and BCC or CsCl lattices when using two PAEs with complementary DNA sequences.[37] When the DNA "sticky ends" presented on the nanoparticle surface are self-complementary, every particle in solution can bind to all other nanoparticles in solution. In these systems, the number of DNA connections within the lattice is therefore maximized when each particle's total number of nearest neighbors is maximized. Thus, a face-centered cubic (FCC) lattice (the densest packing of spheres of a single size) is predicted to be most favorable, and this is the type of structure observed for this system (Figure 2). However, in a binary system, where two different sets of PAEs present, "sticky ends" that are complementary to each other and particles in solution that can only bind to their complement, the number of DNA connections is maximized when the particles are in a body-centered cubic (BCC) arrangement (Figure 2). While each individual nanoparticle in a BCC system does not have as many nearest neighbors as in an FCC lattice, it does have the maximum number of complementary nearest neighbors to which it can "bond." Importantly, this rule holds for nanoparticles of a large size range (5–80 nm) and for DNA lengths of up to 100 nm.[62,96] Further, the rise per base pair value (the additional distance between nanoparticles gained by making the linking DNA strands one nucleobase longer) was found to be approximately 0.26 nm for all combinations of nanoparticle size and DNA length.[62,96,97] This indicates that by using DNA to link nanoparticles together, sub-nm level precision in interparticle distances (i.e., "bond lengths"), can be attained, simply by synthesizing a DNA strand of a specified number of nucleobases.

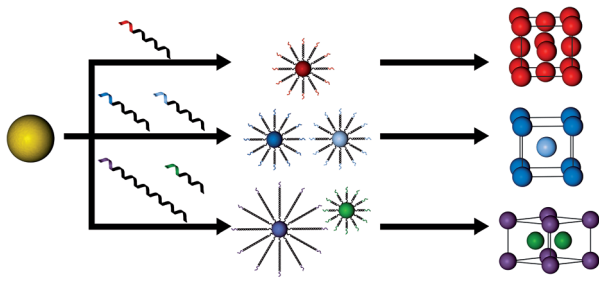

Figure 2. Different crystal structures can be constructed from nanoparticle building blocks of the same size and composition by changing the nature of the nucleic acid bonds (e.g. nucleobase sequence, length). Top: a single, self-complementary nucleic acid sequence enables all PAEs to bond to one another. This situation results in a crystal structure that maximizes the total number of nearest neighbors for each particle within a lattice: face-centered cubic (FCC). Middle: the terminus on the nucleic acid bonds has been changed from a single self-complementary sequence to two different, non-self-complementary sequences. Each sequence can bind to the other, but not to itself, which results in a body-centered cubic crystal structure (BCC). Bottom: nanoparticle size is kept constant, but two different DNA lengths are used. This results in nanoparticles with different hydrodynamic radii, and makes an AlB_2-type lattice most favorable.

In addition to altering superlattice symmetry by controlling the number, length, and nature of the self- or non-self-complementary sticky ends on the particle surface, the programmability of the DNA can also be used to control the strength of an individual DNA "bond", allowing kinetic products to be accessed. Therefore, a corollary to this second rule is: for two lattices of similar stability, kinetic products can be produced by slowing the rate at which individual DNA linkers de- and subsequently re-hybridize.[37] For example, each particle in a hexagonal close-packed (HCP) lattice has the same number of nearest neighbors as a particle in an FCC lattice. HCP lattices are only observed as kinetic products, owing to a slight favorability in the energetics of FCC lattices, as has been predicted by theory.[98] However, HCP lattices that are observed as kinetic products can be stabilized by slowing the rate of reorganization within a lattice (i.e., slowing the rate at which DNA bonds are formed and/or broken during the crystallization process). This promotes the growth of HCP seeds (present at early stages of crystal growth) over their reorganization to the more favored FCC lattice. Importantly, the ability to stabilize these structures by controlling the crystal formation rate highlights the exquisite level of control possible in these systems as a result of the programmable nature of the DNA interactions.

Because the DNA sticky ends that link nanoparticles together are found at the periphery of the hydrodynamic radius of a nucleic acid functionalized nanostructure, the third rule is: The overall hydrodynamic radius of a PAE, rather than the sizes of its individual NP or oligonucleotide components, dictates its assembly and packing behavior.[37] In other words, two PAEs behave equivalently, so long as they have the same overall hydrodynamic radius, even if they have different DNA lengths or inorganic nanoparticle core sizes. This rule was demonstrated by synthesizing binary CsCl-type lattices (which exhibit the same connectivity as the BCC lattices generated using Rule 2, see Table 1), in which each of the two nanoparticle types has the same overall hydrodynamic radius, but different inorganic core sizes. This rule provides an interesting comparison to the first of Pauling's Rules for atoms, which states that interatomic distances are also dictated by the sum of the radii of the atomic building blocks. However, because the PAE system allows us to independently control the nanoparticle radii and DNA lengths, we can control the lattice parameters of a crystal separately from the sizes of the nanoparticles used.

The fourth and fifth rules in DNA-programmed nanoparticle assembly are: in a binary system based upon complementary PAEs, favored products will tend to have equivalent numbers of each complementary DNA sequence, evenly spaced throughout a unit cell, and two systems with the same size ratio and DNA linker ratio exhibit the same thermodynamic product.[37] These rules truly highlight the

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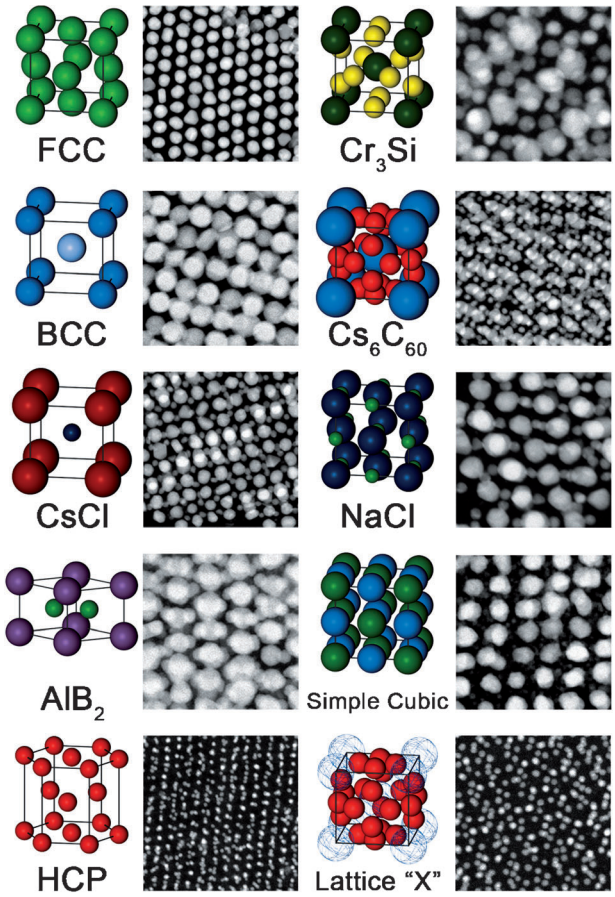

Figure 3. By varying the length and sequence of the nucleic acid "bonds", as well as the size and number of nanoparticle cores, a variety of crystal structures are accessible. Only a small number of those that have been made are shown, each with their corresponding TEM image. Over 100 different crystal structures, spanning 17 different crystal symmetries, have been made.

simplicity of the DNA programmed assembly process as compared to the complex nature of atomic assembly, as they enable the formation of a large number of crystal symmetries in a predictable manner (Figure 3). In all cases, the most stable lattice is the one that maximizes the number of DNA connections formed. This means that determining which crystal structure is most stable for a given set of parameters is a simple means of counting the number of DNA strands present in a unit cell of a given crystal symmetry, and determining which of these DNA strands are able to physically contact one another to form a DNA duplex. The hydrodynamic size ratio is therefore important because it determines both the distances between particles and how many nearest neighbors each particle can have. The DNA linker ratio (defined as the number ratio of DNA strands on the two particle types) dictates the relative amount of each type of DNA strand that is present in a given lattice unit cell. The general trends therefore are that: particles in the most stable arrangement are positioned such that the majority of the DNA strands can bind to DNA strands on adjacent particles, and the nanoparticle stoichiometry in the lattice is such that the overall number of each DNA type in a unit cell is nearly equal. This draws an interesting parallel to Pauling's second rule, which dictates that opposite charges in an ionic lattice must be balanced; the most stable PAE lattices typically balance the number of complementary DNA linker types within a unit cell.

In comparison to the complexity of atomic interactions, these two rules provide a very simple means of understanding the stability of a given crystal symmetry as a function of the nanoparticle size and DNA linker ratios. They also allow us to create a phase diagram that enables the synthesis of lattices whose symmetry and lattice parameters can be determined prior to synthesis.[37,95] In fact, to date, we have synthesized well over 100 unique lattices; the phase diagram and rules we have developed correctly predict the crystal structure obtained for over 95% of the crystals formed.

The sixth rule is: PAEs can be functionalized with more than one oligonucleotide bonding element, providing access to crystal structures not possible with single element PAEs.[37] In the ionic lattices examined in Pauling's Rules, each ion is attracted to ions of opposite charge and repelled by ions of the same charge, and there are only two fundamental types of building blocks: cations and anions. However, nanoparticles can be functionalized with many different DNA sequences, where interactions between particles occur when their respective DNA sequences are complementary. This effect allows the complexity of these lattices to be increased by adding multiple types of DNA linkers to a given nanoparticle. For example, a bi-functionalized nanoparticle can be synthesized that expresses both self-complementary and non-self-complementary sticky ends. On their own, the self-complementary sticky ends would favor the formation of an FCC lattice (as per the second design rule); the non-self-complementary sticky ends would favor the formation of a binary lattice when an appropriately functionalized second particle type is added. Together, however, the most stable crystal structure would allow for both of these types of interactions to be present. This principle was demonstrated in the synthesis of NaCl-type lattices: the self-complementary sticky ends on a bi-functionalized particle allow it to form an FCC lattice, while additional, non-self-complementary sticky ends also allow it to bind to a second particle type. When the hydrodynamic radii of the two particle types are appropriate, this secondary binding interaction allows the second particle type to fill the octahedral holes within the FCC lattice of the first particle type as that lattice forms; the end result is a NaCl arrangement of particles (Figure 3).

Another fundamental concept in chemistry and materials science that can be translated to PAE-based lattices is that of vacancies. In atomic lattices, vacancies represent point defects in crystalline lattices. In lattices of PAEs, the placement of vacancies within a unit cell can be precisely controlled using hollow, core-free nucleic acid functionalized structures, which exhibit the same binding and assembly behavior as the original gold nanoparticle conjugates.[85,99] We refer to this strategy as "design by deletion," which leads to the seventh design rule: The crystal symmetry of a lattice is dictated by the position of the inorganic cores; a PAE with no inorganic core can be used to "delete" a particle at a specified position within a unit cell. In any of the lattices discussed that contain

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more than one type of PAE, any set can be replaced with three-dimensional spacers that are composed solely of DNA attached to an organic shell that contains no inorganic core, and are therefore silent from the perspective of X-ray scattering and electron microscopy (EM) analyses. In this way, new types of lattices with structures never before seen in nature have been readily synthesized (e.g., "Lattice X", Figure 3). Unlike atomic vacancies, which are positioned randomly throughout a crystal, the "vacancies" introduced by using these core-free PAEs are placed at specified positions in every unit cell within a lattice and can therefore be used to control the overall symmetry of the lattice of inorganic nanoparticle core positions. However, because these "hollow" PAEs are indistinguishable from the PAEs with inorganic cores in terms of how they assemble, one can envision doping in a specified amount of the core-free NPs to introduce vacancies at random positions within a superlattice.

In the synthesis and assembly of PAEs described thus far, spherical nanoparticle cores were utilized to template an isotropic arrangement and spherical orientation of nucleic acid "bonds." Such an architecture is amenable to changes in the number, strength, and specificity of the DNA bonds, but ultimately confined to isotropic interactions. Directional bonding interactions, achieved via anisotropic surface functionalization of both isotropic and anisotropic particles (e.g., Janus particles,[100] asymmetric or face-selective functionalization,[45,46,101–104] patchy particles[105]) or anisotropic nanoparticle scaffolds[86,106] extend the range of possible binding motifs and thus crystalline geometries achievable. The use of anisotropic functionalizion of particles relies upon spatial localization of certain molecules capable of forming bonds with incoming species. The use of anisotropic nanoparticle scaffolds, more relevant to this discussion, utilizes the shape of the nanoparticle scaffold as a template to control the orientation of the resulting DNA bonds, similar to a covalent bond. Thus, PAEs formed from anisotropic building blocks—nanoparticles with at least one unique dimension (e.g., triangular prisms,[107–111] rods,[112–114] rhombic dodecahedra,[115,116] concave cubes,[117] octahedra[118,119])—provide synthetic control over another design dimension and allow novel superlattice structures to be accessed that cannot be realized with spherical particles (Figure 4).

Atoms rely on valency—the oriented overlap of atomic orbitals—to control molecular and crystallographic shape and symmetry. Among the tenets of valency is the relationship between electron density and bond strength: the greater the amount of shared electron density between two atoms, the stronger the bond. If this concept is extended to PAEs with anisotropic nanoparticle cores, one would expect particle orientations that align the largest faces of the particles in a parallel placement to be favored, as this would result in a greater number of DNA connections and create stronger bonds between particles. For example, two-dimensional triangular prism structures will form stronger "bonds" with their large triangular faces aligned parallel to one another, as compared to orientations that align their (relatively smaller) rectangular sides (Figure 4). This effect results in triangular prisms assembled into 1D lamellar stacks. This relationship has been further demonstrated with octahedra, rod, and

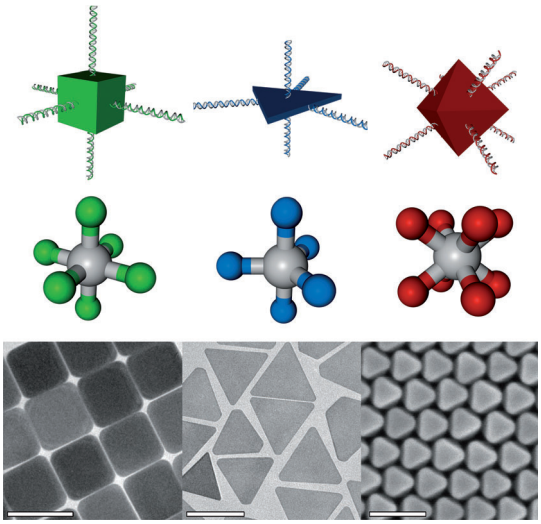

Figure 4. The distinct crystallographic facets of anisotropic nanoparticles enable directional hybridization (covalent-like) interactions between nanoparticles. Six-sided cubes, five-sided triangular prisms, and eight-sided octahedra are shown with DNA strands that demonstrate the directional bonding interactions for each particle shape. Note, however, that in this assembly strategy, each surface is densely functionalized with oligonucleotides. Below each nanoparticle is the corresponding ball-and-stick model of its bonding pattern and an electron microscopy image of synthesized particles. Scale bars in electron microscopy images are 100 nm.

rhombic dodecahedra nanoparticle templates, where each structure assembles along the crystal facet that forms the greatest number of nucleic acid bonds.[86] The eighth design rule is therefore: PAEs based upon anisotropic particles with flat faces can be used to realize valency and will assemble into a lattice that maximizes the amount of parallel, face-to-face interactions between particles. These assemblies are also accessible by alternative bonding methods, such as with the pH-mediated association of carboxylic acid-terminated ligands attached to gold triangular prisms, demonstrating that anisotropic nanoparticle assembly is ligand general, where the ultimate structure is heavily influenced by the shape of the nanoparticle.[120]

Alignment of DNA bonds along the lengths of flat crystal facets also negates the radius of curvature effects associated with spherical particles, which enables greater overlap of DNA bonds and results in stronger connections between particles.[120–122] In fact, thermodynamic and kinetic enhancement of the bonding (hybridization) events between functionalized anisotropic nanoparticles leads to binding constants (analogous to bond strengths) several orders of magnitude higher than their spherical counterparts. For example, the directionality imparted by the large, flat triangular faces of triangular prisms results in a sizeable increase in nanoparticle binding constant over spheres ($5.3 \times 10^{17}\,\text{M}^{-1}$ vs. $1.5 \times 10^{11}\,\text{M}^{-1}$; over six orders of magnitude).[120]

Differences in the binding constants of PAEs of different shapes and/or sizes enable the separation of nanoparticle mixtures in a manner similar to the separation of elemental or molecular impurities. For example, molecular impurities are

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often isolated from organic syntheses by crystallization, a technique in which a desired product is isolated from a mixture by the thermodynamic favorability of creating an ordered crystal consisting of only a single substance. When nanoparticles of disparate shape are functionalized with DNA, differences in binding constants (and therefore melting temperatures) can be used to separate them in an analogous manner. For example, for a solution of DNA-functionalized triangular prisms and spheres held between the melting temperatures of aggregates of the two shapes, the prisms are selectively associated with one another and precipitated out of solution, while the spheres remain free in solution, disassociated from one another. The precipitated phase (containing prisms) can then be easily separated from the solution phase (containing spheres) to obtain a pure solution of the desired product.[123] This concept of purification by crystallization has also been demonstrated with spherical nanoparticles of different sizes (where larger particles precipitate at higher temperatures because of the larger number of DNA connections that can be formed between particles with greater surface area),[124,125] but with less-pronounced separation, owing to the lack of directional bonding interactions.

Outlook

Despite the rapid progress in the area of nucleic acid functionalized nanoparticle assembly, especially since 2008, several challenges remain as the focus of ongoing efforts. A primary challenge is to expand the nanoscale table of PAEs, filling in the empty spots with additional PAEs of varying size, shape, and composition. Much like the early versions of the Periodic Table, one can project the existence of many different nanoparticles that cannot yet be synthesized, but whose properties can be predicted based upon theoretical calculations and general trends established for existing nanoparticles.[1,4] Certain existing building blocks also cannot currently be utilized because they only exist in impure mixtures containing multiple nanoparticle types (much like elements that were initially unknown as isolated species).[87,126,127] Therefore, in order to expand the table of PAEs, one must first develop methods to synthesize a wider range of nanostructures in a controlled and predictable fashion, where the factors that influence size and shape are well understood. Furthermore, purification techniques (such as the one described above) must also be explored to separate desired products from undesirable ones. Together, the development of these methodologies should allow for the synthesis of new nanoparticle building blocks with highly tunable structural characteristics and physical properties.

An additional challenge beyond simply synthesizing the nanoparticle building blocks is to functionalize them with nucleic acids without altering their structure or desired physical properties. However, other nanoparticle shapes, compositions, and sizes are not necessarily as amenable to surface modification with a high density of nucleic acids as the spherical gold nanoparticle systems that employ robust thiol gold chemistry.[77–80,86,128] Two potential approaches are: 1) to develop appropriate nucleic acid linking chemistries for each particle type or 2) to devise a general methodology for the surface modification of any nanoparticle core. Toward this end, methods have been developed in which particles have been coated in a shell of another material, such as silica,[78,79] polymer,[18] or metal,[25,129] such that DNA can be attached to this layer using a more well-established methodology. However, at the present time, no truly universal strategy exists.

Another challenge focuses on increasing the stability of the nanoparticle superlattice structures after they have been synthesized. Since such lattices are held together by DNA bonding interactions, they are only stable in aqueous saline solutions at temperatures below the melting temperature of the DNA duplex linkages. To be useful in a wide range of applications, methods must be found to increase their stability toward changes in temperature, pH value, and solvent, and the presence of denaturing molecules or harsh environmental factors (such as the X-ray beams currently used to analyze the superlattices). We have recently made steps in this direction by developing a method that can be used to encase the nanoparticle lattices in porous silica.[130] Small-angle X-ray scattering (SAXS) and electron microscopy data confirm that the encapsulated lattices maintain their original symmetry and lattice parameters when dispersed in organic solvents (e.g., ethanol, acetone), at elevated temperatures above the melting temperature of the DNA duplex linkages, and in air and vacuum with no solvent present. Further, the encapsulated lattices were shown to be relatively unaffected by the X-ray beams utilized for structural characterization. These data indicate that the nanoparticles have been locked in place by the silica network, which is chemically and physically more robust than the DNA duplexes. Ongoing work in this area involves understanding the full extent of stability conferred and examining the collective plasmonic, catalytic, and magnetic behaviors of the encased structures and comparing them to the unencapsulated structures where possible. Although this strategy represents a step in the right direction, other strategies may still be needed depending on the intended use of the lattices.

It would also be beneficial to either transfer superlattice materials from the solution phase to surfaces, or to grow the superlattices directly at a specific surface location. Ideally, a method to control layer-by-layer deposition of PAEs in a manner analogous to atomic layer deposition needs to be developed, such that each layer could be uniquely tailored.[131–133] This would both allow for integration of these materials into prototype devices, where chemical and physical properties can be measured, and allow for greater control of superlattice size.

One can also envision that it would also be advantageous to design and synthesize dynamic nanoparticle structures in which the lattice parameters or the crystal symmetry of a given nanoparticle superlattice can be varied at will, effectively turning these static lattices into "smart" functional structures. Steps in this direction have already been made utilizing the temperature or ionic strength of the solution to vary the lattice parameter of these crystals, albeit over a limited range.[62,134] It is also possible to imagine using DNA hairpins to bring about such structural changes in

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a reversible manner, as initial work by Gang and co-workers suggests this is a viable strategy.[135]

Finally, now that substantial progress has been made towards reliably synthesizing nanoparticle superlattices, more research effort must be put into developing new ways to analyze and ultimately utilize their properties (e.g., optical, plasmonic, magnetic, catalytic). It has long been known that individual nanoparticles possess a wide variety of tunable phenomena that are significantly affected by the local environment and position of nearby nanoscale objects.[3,4,18,26,32,40,41] The DNA-based assembly strategy discussed herein allows such parameters to be tailored (these parameters include interparticle distance, number of nearest neighbors, number of unique nanoparticle types) and thus dictate the resulting physical and chemical characteristics. Recent developments in understanding how to individually control this parameter space coupled with the silica embedding methodology that makes the superlattices stable to a wider range of environmental conditions (including those necessary to perform certain types of characterization) allow us to begin to explore this area. Once desirable properties are elucidated and potential functions are defined, research will likely shift toward applications for these novel structures in many areas of chemistry, materials science, physics, and biology.

Ultimately, determination of the chemical and physical properties of these crystal structures will involve both experimental measurements as well as theoretical calculations. Theory has been used in this system as a guide for determining the relative stability of different lattice structures and for explaining their behavior.[4,36,37,95,136] It will also be helpful for determining which structures should be targeted for a given purpose and how the assembly process can be expanded to create additional crystal symmetries and lattices with larger (or smaller) lattice parameters than those currently accessible. Fundamental investigations of the kinetics of crystallization, probed by both experiment and theory, may also allow the size and morphology of the crystal domains to be controlled and the role of defects—such as grain boundaries, vacancies, and interstitial sites—to be understood. Each of these factors can be used in atomic systems to control materials properties, and we expect similar effects to be seen with the nanoparticle superlattice systems.

While the goals outlined in this Essay are most certainly ambitious, they are well worth the efforts it would take to achieve them. The potential benefit to understanding scientific phenomena at the nanoscale, developing novel materials by design, and predictably creating and controlling the physical and chemical characteristics of nanoparticle-based structures holds promise to usher in a new era of materials science. Despite the magnitude of this scientific challenge, the progress both our group and others have made in recent years in synthesizing nanoparticle building blocks and developing a means to assemble them in a programmable manner indicates that these goals are achievable with the appropriate level of effort and innovation. The coming years undoubtedly hold promise for discoveries that fill out the table of PAEs, allow for new lattices to be realized, and demonstrate uses for the novel plasmonic, photonic, magnetic, and catalytic properties of these structures. We therefore invite the scientific community to adopt the concept of the nucleic acid–nanoparticle conjugate as a "programmable atom equivalent" and to use the table and design rules presented herein as a guiding principle in materials development. Approaching the field of nanoscience and technology with the same level of scientific rigor and intensity as chemists approached elemental discovery and usage in the previous two centuries will enable this burgeoning field to take on an important and highly influential role in the development of the chemistry, materials science, physics, biology, and engineering communities.

Since the document's initial submission, additional work not covered in this manuscript has been done in this field to further the concept of PAEs as nanoscale building blocks that warrants mention here.[137,138]

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