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Molecular-like selectivity emerges in nanocrystal chemistry

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FRONTIER

Molecular-like selectivity emerges in nanocrystal chemistry

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As a nanocrystal's structural characteristics relate strongly to its properties, designing increasingly precise syntheses is important for making nanocrystals that are most tailored for a particular application. Importing concepts traditionally associated with the chemistry of small molecules has historically expanded the array of tools available to exert fine control over a nanocrystal's shape and architecture, and consequently its function. Here, we focus on recent work on using concepts from molecular chemistry such as regioselectivity and chemoselectivity in seeded or template-engaged syntheses, and generally draw attention to the idea of having anisotropic, spatially controlled reactivity on a nanocrystal's surface by design.

Introduction

Nanomaterials with tailored structure-dependent properties have shown themselves to be highly promising in a wide array of applications, including catalysis, theranostics, and displays.[1-3] The need for precise spatial control over arrangements of atoms in inorganic nanomaterials is frequently exemplified by Moore's Law, which demands an exponential reduction in feature sizes over time. These feature sizes now stand at the nanoscale and are accessible using top-down or bottom-up approaches.[4] Bottom-up methods such as colloidal nanoparticle syntheses and protein engineering are promising routes to attaining extreme spatial control, for they use the same set of driving forces as are used in the reliable and inexpensive synthesis of intricate biological macromolecules. For example, heterostructure nanoparticles with unique and promising properties have been synthesized using these methods.[5-7] And in the extreme case of biochemical methods to engineer proteins with specific amino acid sequences,[8] bottom-up methods show that they can, in principle, replicate single-atom feature sizes. The specific methods involved in protein engineering do not, however, translate to typical nanocrystal syntheses, which therefore face the challenge of devising their own route from solution-phase experimental conditions toward atomic-scale control.

Recent years have seen nanoscale chemistry gain great mastery over the syntheses of colloidal nanocrystals with specific shapes and architectures.[5-7, 9-11] Notably, these advances have laid down guidelines for rationally designing future syntheses of nanocrystals with specific morphologies. These guidelines show increasing parallels with molecular chemistry. For example, kinetic control through manipulation of precursor reduction rates or the blocking of deposition sites on nanocrystals seeds have allowed for the reliable syntheses of concave nanocrystals, and those with anisotropic features, whereas thermodynamic control alone has accounted for surface expression in convex, relatively isotropic nanocrystals.[9-12] Whether isotropic or anisotropic nanocrystals are preferred depends on the desired property and intended application. Using synthetic levers derived from concepts used in molecular chemistry, we can reliably design syntheses of relatively isotropic products, usually with high symmetry; however, devising routes to highly anisotropic products remains a challenge. For colloidal nanocrystals, part of this challenge can be seen at the nanocrystal-solution interface. A growth solution is expected to be roughly the same in all directions surrounding a growing crystal, while the atoms in the nanocrystal itself, by virtue of the crystal's inherent translational symmetry, are expected to be symmetric to each other. How to rationally devise ways to increase anisotropy in an isotropic nanocrystal is, therefore, not obvious.

Ideally, synthetic methods for inorganic nanocrystals should possess a similar degree of control and predictability compared to their molecular-scale counterparts. In this Frontier article, we highlight recent work that shows progress in attaining such precise control, through the concepts of chemoselectivity and regioselectivity. Chemoselectivity can be defined as "*which* functional group will react," and regioselectivity as "*where* it will react."[13] Figure 1 illustrates how these definitions apply to molecules: the Markovnikov rule predicts regioselective hydrohalogenation of alkenes, with the halogen binding to the more substituted carbon in the alkene functional group, while the synthesis of paracetamol from 4-aminophenol has acetic anhydride react chemoselectively with the amine group over the hydroxyl group. A question then arises: for a nanocrystal, what is a functional group? One the one hand, nanocrystals composed of two different phases can be likened to molecules with two different functional groups, suggesting that a single phase may be compared to a single functional group. In this sense, a regioselective reaction would modify one part of the crystal phase over another, such as vertices over faces, while a chemoselective reaction would modify one crystal phase over another. This interpretation is illustrated in Figure 1 and will

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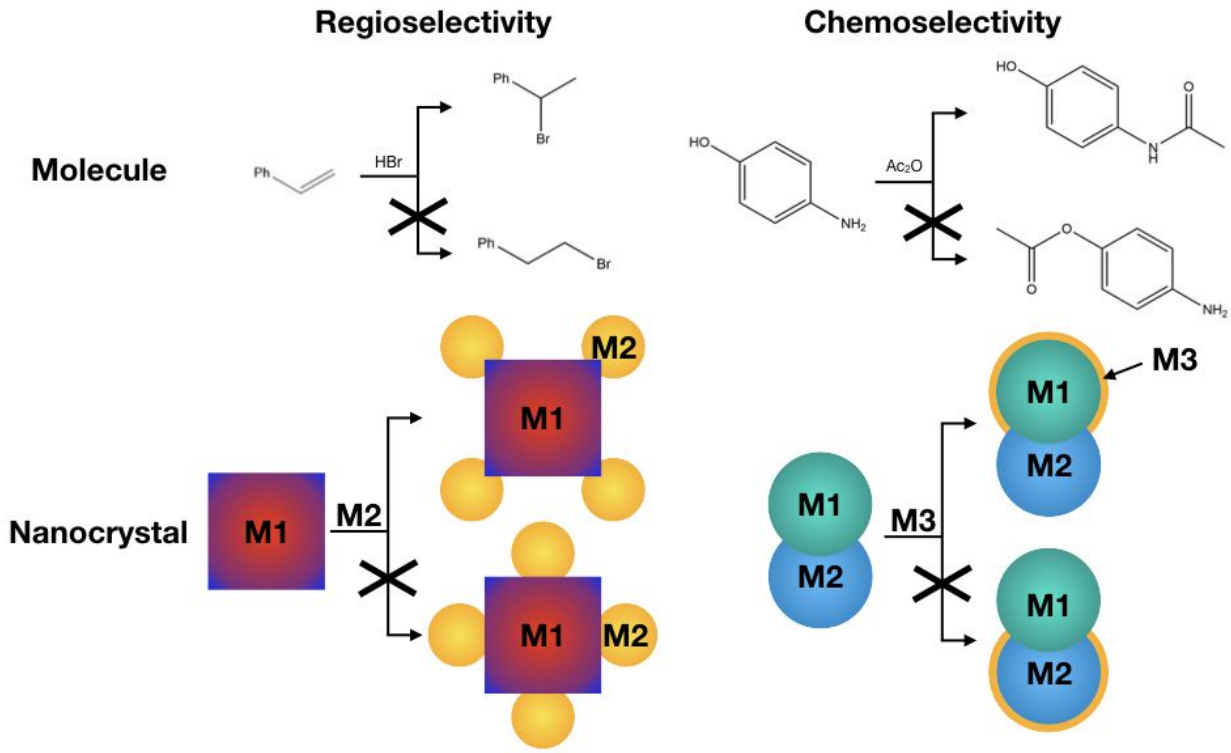

Figure 1. Scheme depicting examples of regioselectivity and chemoselectivity as the terms are used in molecular chemistry, and analogous examples applying the terms to nanocrystals.

largely be adopted here. On the other hand, crystal phases are larger than most molecules aside from polymers, and possess reactive sites that are so far from each other that it could be more appropriate to consider a nanocrystal as an inorganic polymer with many functional groups. In this sense, functional groups are complicated to define but could be as small as individual atoms, in which case the previous interpretation's regioselectivity would be folded into chemoselectivity. The examples highlighted in this Frontier article will shine light on both the value and limitations of applying the language of molecular chemistry to nanocrystal chemistry.

Discussion

We call reactions regioselective when a nanocrystal, considered as a single functional group, has only a select few of its many and similar reaction sites react. This form of regioselectivity lends itself to the rational design of syntheses of highly anisotropic nanostructures, as it directs us to look at subtle chemical differences between atoms of the same element that would cause one reactive site to be chosen over another. One such chemical difference is that between a nanocrystal's vertex and face sites, where face atoms are expected to have more bonds to neighboring atoms, and so are expected to be less reactive than vertex atoms. This difference has been exploited to preferentially deposit material on all vertices over all faces of nanocrystals, following the form of regioselectivity illustrated in Figure 1.[14-16] In a more extreme case, shown in Figure 2, regioselectivity manifests as nucleation and growth of Au-rich domains on some vertices of a Pd cube over all other vertices, edges, and faces. This outcome was achieved by slowing down the kinetics of a random nucleation event, trusting that the lower energy barrier for subsequent growth would discourage further nucleation events on any given seed. Specifically, when beginning with Pd cubes or octahedra as seeds, heterogeneous nucleation of Au-rich domains was made to occur at only a few out of many crystallographically equivalent vertices, thus breaking the original O_h symmetry of the seeds. Regioselectivity occurred between vertices and faces due to inherent differences in coordination. Regioselectivity occurred between different vertices by operating at very low supersaturation with a high concentration of capping agents; this condition severely

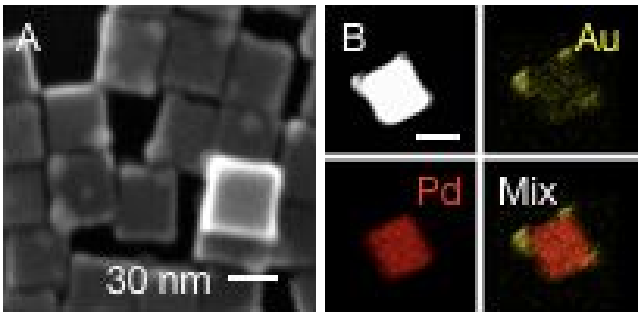

Figure 2. Regioselectivity in growth, where selectivity between different cube vertices is achieved. (A) Scanning electron micrograph and (B) scanning transmission electron micrograph (STEM) coupled with energy dispersive X-ray spectroscopy (EDS) elemental maps of product obtained from depositing Au-rich domains on Pd cubes at low supersaturation and in the presence of capping agents. Regioselectivity is evident as not all vertices have Au-rich domains. Adapted with permission from reference 17. Copyright (2017) American Chemical Society.

limits the number of stochastic nucleation events that could happen.[17]

Figure 3 shows another example of regioselectivity, but with a cation exchange reaction instead of depositing material onto a seed. Beginning with hexagonal $Cu_{1.81}S$ plates with D_{6h} symmetry, blocking the surface with an IrS_2 shell drastically slowed cation exchange kinetics. Such slowed kinetics should remind the reader of Figure 2, where nucleation was too slow to occur at all crystallographically equivalent vertices, pushing growth to occur at the few nuclei that did form. Similarly, formation of a single Au_2S or PdS phase at one point beneath the shell encouraged all further cation exchange to happen at one new Au_2S- or PdS-$Cu_{1.81}S$ interface, instead of at many exchange sites all over the plate. As a result, the D_{6h} symmetry of the original plates was broken, and hexagonal Janus particles formed.[18]

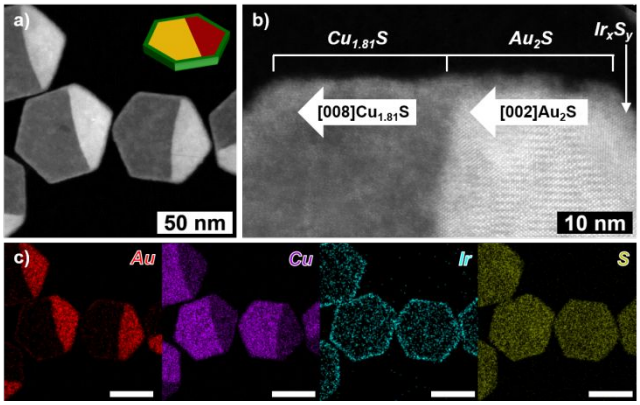

Figure 3. Regioselectivity in cation exchange on different sides of a plate. (a) STEM, (b) enlarged STEM and (c) STEM-EDS elemental maps of product obtained from cation exchange of $Cu_{1.81}S$@IrS_2 nanoplates with $HAuCl_4$. Adapted with permission from reference 18. Copyright (2018) American Chemical Society.

In Figures 2 and 3, by considering nucleation as a largely random event, and by ensuring that there were fewer nucleation events than there were nucleation sites, regioselectivity was imposed on systems with theoretically identical nucleation sites. We note, however, that while the many nucleation sites are crystallographically equivalent, stochastic variations at the seed surfaces likely exist (*e.g.,* slight variations in the curvature of vertices) and may contribute to the demonstration of regioselectivity, as we would expect of small chemical differences between parts of a functional group. Regardless, the symmetry and chemical isotropy of the original seeds are broken at this point, opening the way for further modifications.

Another form of regioselectivity takes advantage of crystallographically non-equivalent sites. Here, although the different reaction sites on the nanocrystal surface are of the same phase, differing atomic arrangements and surface energies produce reaction sites that are different enough to provoke selectivity. For example, cation exchange can occur selectively along certain crystallographic directions of metal chalcogenide nanocrystals.[19-21] As a result, crystallographic anisotropy allows apparent morphological isotropy to be broken, which in practice cleanly transforms outwardly

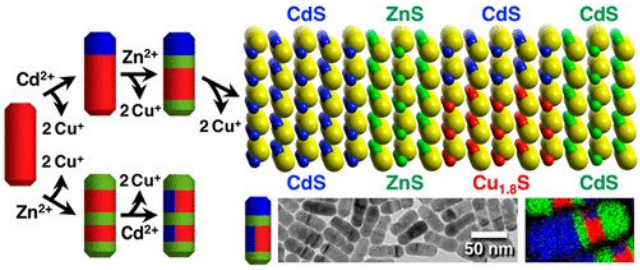

Figure 4. Regioselectivity in cation exchange of crystallographically non-equivalent sites. Scheme describing behavior of cation exchange of $Cu_{1.8}S$ nanorods with Zn^{2+} and Cd^{2+}. Reprinted with permission from reference 19. Copyright (2018) American Chemical Society.

isotropic templates into Janus dimers, or even higher-order structures such as nanocrystal trimers exhibiting clear spatial organization of multiple nanoscale phases.[19]

These concepts are exemplified in Figure 4. Here, $Cu_{1.8}S$ nanorods, whose pseudohexagonal unit cell possesses very different *a* and *c* lattice constants, and whose long axis corresponds to the *c*-axis, undergo partial cation exchange with Cd^{2+} and Zn^{2+} to form heterostructures. In this case, sites on the two axes can be compared to differently substituted sites on a functional group. The hexagonally close-packed unit cells of CdS and ZnS have lattice constants with minimal mismatch between $Cu_{1.8}S$ and CdS in the *c*-axis direction, and between $Cu_{1.8}S$ and ZnS in the *a*-axis direction. Manipulation of the order and extent of these exchange reactions proceeding in two different crystallographic directions can yield final nanorods with many different arrangements of $Cu_{1.8}S$, CdS and ZnS phases. For example, adding Zn^{2+} before Cd^{2+} can yield ZnS bars perpendicular to the length of the rod, maximizing ZnS interfaces with the *a*-axis of $Cu_{1.8}S$, and CdS bars parallel to the length of the rod, maximizing CdS interfaces with the *c*-axis of $Cu_{1.8}S$. However, as was noted in our first example of regioselectivity in nanocrystals, vertex sites tend to be more reactive than face sites, so adding Cd^{2+} first sees competition between regioselective exchange at the reactive nanorod tip to form a less stable interface, and regioselective exchange at the less reactive face to form a more stable interface. When adding Cd^{2+} before Zn^{2+}, this competition favors the formation of a CdS phase perpendicular to the length of the rod, as seen in Figure 4.[19] Similar selectivity was achieved with combinations involving Cd^{2+}, Zn^{2+}, In^{3+}, Ga^{3+} and Co^{2+}, for six phases total.[22] Cation exchange proved regioselective with regard to multiple Cu reaction sites, all on one crystalline $Cu_{1.8}S$ lattice, with relatively small differences in chemical state on different surfaces.[19, 22]

The degree of control demonstrated in the above examples shows that nanocrystals can grow or be transformed in a regioselective manner, where only some of the many similar reaction sites activate. At least with crystallographically non-equivalent sites, selectivity can be explained by differing lattice constants, or more generally, differences in coordination and thus chemical state of surface atoms. The strong selectivity seen in Figure 4 may even suggest that the different crystal planes should be considered as entirely different functional groups. Even with crystallographically equivalent sites, minor differences in vertex sharpness translate into potentially

significant differences in coordination. As an end result of such syntheses, we obtain heterostructures with separate, spatially controlled phases, of which each can be expected to show very different chemical reactivity.

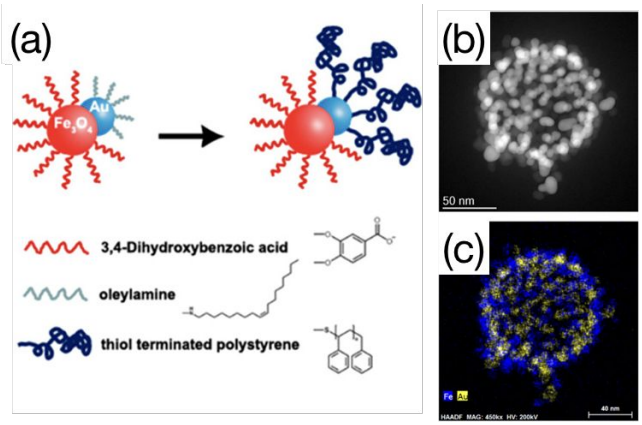

Figure 5. Chemoselectivity in ligand binding to select sides of a Janus particle. (a) Scheme of ligand exchange to coat the Au phase with polystyrene, (b) STEM and (c) STEM-EDS elemental map of assembly structures of Au-Fe_3O_4 Janus dumbbells, showing Fe in blue and Au in yellow. Reprinted with permission from reference 23. Copyright (2019) American Chemical Society.

When using heterostructures as templates for the synthesis of even more architecturally complex structures, we can expect chemically different phases to exhibit different behavior. Selectivity depending on large chemical differences, such as those between different functional groups, brings forward the concept of chemoselectivity, where a reaction proceeds with one functional group over another.[13] If the nanoparticle's two phases are compared to two functional groups, or to two differently functionalized blocks in a block copolymer, a chemoselective reaction would occur much more quickly at one of said phases. Figure 5 shows a method to anisotropically modify Au-Fe_3O_4 heterostructures; however, the work shown in Figure 5 does not require extraordinary conditions to do so, as it benefits from the greater selectivity offered by the existing highly anisotropic reactivity of a nanocrystal with separate Au and Fe_3O_4 phases, which can be compared to Au and Fe_3O_4 functional groups.

One logical next step to possessing such anisotropic reactivity is to functionalize the two sides of the nanocrystal with different, well-known ligands to induce predictable behavior. In the case of Figure 5a, the original oleylamine from synthesis of Au nanoparticles and 3,4-dihydroxybenzoic acid from addition of a Fe_3O_4 domain were replaced by mixing in solutions of another ligand. Thus, Au-Fe_3O_4 Janus dumbbells were functionalized with hydrophobic thiol-terminated polystyrene on the thiol-selective Au side, and with hydrophilic 3,4-dihydroxybenzoic acid via a similarly selective metallocyclic chelate on the Fe_3O_4 side, yielding plasmonic, magnetic, and amphiphilic products capable of self-assembling into vesicle-like structures.[23] Particle-ligand interactions have also been shown to be precise enough for direct metabolite detection in biological mixtures.[24] In a similar vein, one can move beyond selective ligand binding toward entire phases: chemoselective deposition of new phases has also been reported, for both the synthesis of nanocrystal heterotrimers from heterodimers and as a removable mask akin to a protecting group to prevent further reaction on one side of the heterodimer.[25]

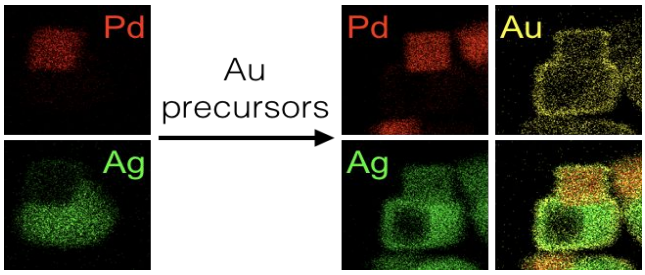

Figure 6. Chemoselectivity in galvanic replacement of a Janus particle. (left) STEM-EDS elemental maps of a Ag-Pd heterodimer (Ag and Pd signals of an individual particle shown separately in red and green) and (right) product obtained after being galvanically replaced by $HAuCl_4$, with the Pd (red), Au (yellow), and Ag (green) signals shown separately and also overlaid. Reprinted with permission from reference 27. Copyright (2019) American Chemical Society.

Or, like the exchange reactions mentioned above, a chemical transformation can be applied unequally across the particle. This was the case in Figure 6, when studying the galvanic replacement reaction of Ag-Pd heterodimers with Au salts. Chemoselectivity is shown here by the formation of a large void in the Ag domain and a AgAu alloyed shell around it, as is typical in the early stages of the galvanic replacement of Ag by Au,[26] while the Pd domain does not visibly change in terms of structure. Aside from the chemoselectivity seen in the galvanic replacement reaction, Ag also visibly diffused elsewhere in the particle, as seen when comparing the Ag signal in the original heterodimers to that in the product. Overall, Ag and Pd showed significantly different reactivity on multiple points during the galvanic replacement reaction.[27] These systems that possess phases that are different enough to be compared to different functional groups in chemoselective reactions can serve as ideal stepping stones toward products that require close spatial control over nanocrystal reactivity.

Conclusion

In summary, the recent years have seen the distance close between nanoscale and molecular-scale chemistry, as nanocrystal syntheses begin to use more concepts from molecular chemistry. Specifically, the concept of regioselectivity has explicitly been used in several works[17, 19-21] to point out that while surface atoms of a single-phase nanocrystal are chemically very similar, they have different reactivities that we may use to induce location-dependent reactions. This comparison may not be completely rigorous, for particles spanning tens of nanometers in length tend not to behave like a single functional group, in that modifications to a given site do not strongly impact the chemical states of distant sites. In this sense, the reactions that we have named regioselective due to their spatially selective mapping from template to product might also be named chemoselective, should we see the nanocrystal as a polymer with many distinct functional groups, of which only a few react. The blurred line between

regioselectivity and chemoselectivity may also be seen in the tendency to view flat surfaces as completely different reaction sites from defect-rich locations such as vertices. Heterostructures bring forward the concept of chemoselectivity most blatantly, where surface atoms are from entirely different elements or materials, and can therefore be used to bring a greater degree of spatial control to reactions at the nanoscale. Overall, the results surveyed here continue to close the gap of understanding between nanoscale and molecular systems. Ideally, continued progress in this direction would yield synthetic routes toward inorganic nanocrystals with precise spatial organization, tailorable in a manner similar to organic block copolymers.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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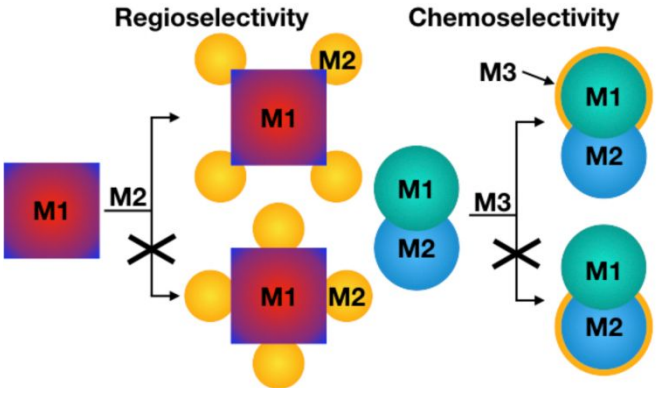

TOC Figure

TEXT: Applying the molecular concepts of regioselectivity and chemoselectivity to nanocrystal chemistry is giving access to complex nanostructures with spatial precision.