CHEMISTRY

Harmony of the Self-Assembled Spheres

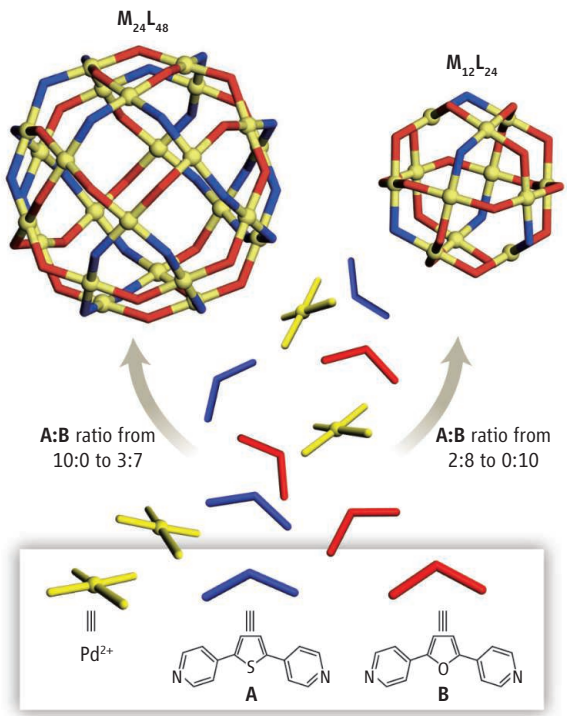
Slight changes in the shape of organic molecules can dramatically alter the size of hollow spheres that form spontaneously upon addition of palladium ions.

Artur R. Stefankiewicz and Jeremy K. M. Sanders

Chemists conventionally assemble molecules stepwise in the laboratory, but nature often relies on self-assembly, especially when it comes to combining smaller subunits into amazingly complex architectures on the nanoscale. Tobacco mosaic virus is an inspiring example of self-assembly: 2130 identical protein subunits self-organize around a single strand of RNA to form the final helical structure of the virus (*1*). Weak but numerous noncovalent interactions direct assembly between individual subunits. These processes can be dynamic; in such cases, assembly is accompanied by disassembly and occurs at or near equilibrium. In general, these processes are not only rapid but are intrinsically self-correcting (*2*). On page 1144 of this issue, Sun *et al*. (*3*) report a step forward toward synthetic analogs of large-scale self-assembly in which metal ions and organic ligands self-assemble into giant coordination spheres with intriguing thermodynamic behavior and astonishing precision.

The structural complexity characteristic of biology has until recently been considered irrelevant in coordination chemistry, in which metal centers form bonds to both organic and inorganic ligands, or even to other metals. In most coordination compounds, only a few metal centers might be joined by bridging organic ligands. However, Lehn and Stoddart separately suggested more than a decade ago that coordination bonds, which can also assemble reversibly, could be viewed in the same light as the weak inter- or intramolecular interactions formed during biological self-assembly (*4*, *5*).

Metal-assisted self-assembly has recently given access to a wide range of supramolecular entities of truly impressive architectural complexity (*6*). The final shape of the self-assembled entity is defined not only through the metal coordination geometry, but also through the size and shape of the ligand, which can determine the orientation of its interaction sites with the metal ions. Because the generation of well-defined metallosupramolecular architecture generally proceeds under thermodynamic equilibrium, it allows the desired product to be obtained with an accuracy similar to that achieved in conventional stepwise molecular synthesis. The dynamic nature of the assembly process also allows modification through the exchange of components added into solution at a later point (*7*).



Spheres are subtly influenced. Sun *et al*. have shown that slight changes in ligand shape (molecules **A** and **B** differ in bend angle) change the outcome of self-assembly with Pd ions dramatically. Only one type of sphere forms even when a mixture of ligands is used, and the size of sphere formed exhibits a threshold at a particular ratio of ligand concentrations. Such crossover behavior is an example of self-organized criticality.

This principle has been realized by recently developed syntheses beyond assembly around a few metal centers (*8*, *9*). In particular, coordination chemistry has been successfully used to construct such discrete structures as helices, grids, cages, and spheres, the last being particularly interesting because of their potential application as synthetic receptors and nanoreactors. Fujita and co-workers had already shown that simple banana-shaped organic molecules and palladium(II) ions self-organize into finite, spherical coordination networks with diameters of up to 5 nm (*10*). These impressive superstructures consist of 36 components (12 equivalent metal centers and 24 equivalent ligands) that self-organize into a well-defined object of cuboctahedral symmetry (ligand **B** in the figure, leading to $M_{12}L_{24}$).

It is synthetically easy to introduce a variety of new substituents and form multifunctional nanoscale architectures with specific physicochemical properties. Porphyrins and C_{60} have been attached to the outside of the spheres to generate a highly decorated surface. Alternatively, perfluoroalkyl groups were attached and a spherical complex formed with an interior filled with 24 perfluoroalkyl chains. The interior of the sphere can be regarded as a fluorous phase (one that can selectively dissolve fluorocarbons) while the surrounding solution cannot. Even more remarkably, photoisomerization of a chromophore functionality attached to the internal site of the ligand components gives access to a variety of photoresponsive "molecular nanoparticles" whose interior environments can be dramatically changed by light (*11*).

Sun *et al*. now describe an elegant and synthetically simple strategy for creating a massive spherical framework of 72 components that spontaneously self-assemble in solution. Building on their earlier experience, they obtained this new molecule by opening up the bend angle from 127° to 149° between the two metal-binding sites of the ligand to give **A**. Separately, these ligands, when combined with palladium ions, form spheres consisting of 72 and 36 components for **A** and **B**, respectively (see the figure). The authors then mixed the two ligands **A** and **B** in different ratios. At every ligand ratio from 9:1 to 1:9, there was no indication of forming a mix of different compounds. Only pure complexes of either $M_{12}L_{24}$ or $M_{24}L_{48}$ were

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observed. $M_{24}L_{48}$ was exclusively assembled until the ratio of **A**:**B** was 2:8, whereupon the outcome was $M_{12}L_{24}$.

This result is surprising. Even if the sphere constructed from **A** is enthalpically favored in $M_{24}L_{48}$ (that is, it has lower internal energy than structures made from **B**), the entropic cost of creating such a large ordered object might be expected to be prohibitive. Perhaps the stability of the bigger nanosphere results from its relatively huge internal volume. The solvent and counterions might be less ordered and more liquid-like than in the smaller sphere, thus shifting the equilibrium toward the bigger structure.

Whatever the explanation at the molecular or thermodynamic level, we are observing emergent behavior in this chemical system, in which small differences in geometry are effectively amplified into the production of the preferred sphere. The work of Sun *et al*. is an impressive demonstration of artificial multicomponent self-assembly similar to that observed in the assembly of biological structures. The success of this approach suggests that supramolecular nanoreactors with high stability could be made through relatively simple synthetic routes.

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IMMUNOLOGY

The Origin of T_H2 Responses

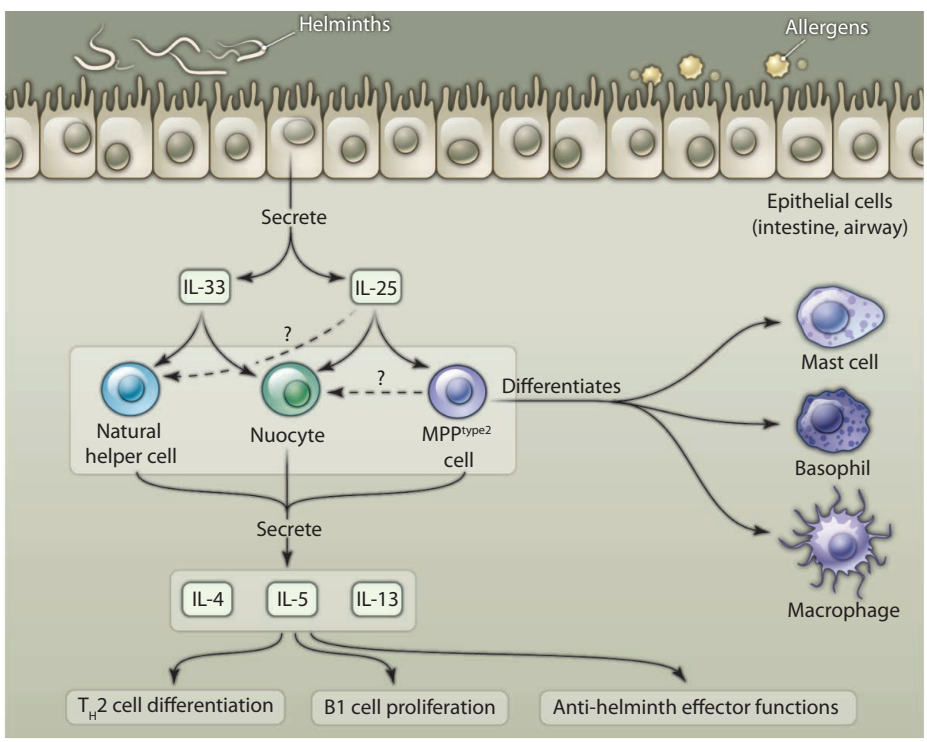
The adaptive immune response to helminth infection and allergens is stimulated by cytokines secreted by innate immune cells.

Robert L. Coffman

Helper T lymphocytes (T_H cells) have multiple functions during human immune responses, including stimulating B cells, the "help" needed to spur antibody production. Naïve T_H precursor cells give rise to four functionally distinct subsets that can be further divided into subtypes or regulated states. Once the first two T_H subsets were recognized—T_H1 and T_H2 cells (*1*)—the obvious question became: How does the immune system decide which response to make? Recent reports present an important advance in understanding the origins of T_H2 responses and mechanisms of immune recognition of two medically important classes of antigens: helminth parasites and allergens.

T_H1 cells produce proinflammatory cytokines, such as interferon-γ (IFN-γ), that trigger responses against intracellular pathogens. By contrast, T_H2 cells make cytokines such as interleukin (IL)–4, IL-5, and IL-13, which activate responses to allergens and parasitic helminths, such as increased eosinophil and mast cell production and immunoglobulin E (IgE) antibody responses (*2*). The essential features of T_H1 cell induction—including the key roles of IFN-γ, IFN-α, and IL-12—have long been understood (*3*). However, our understanding of T_H2 cell origins has been elusive. IL-4 itself turns out to be a key factor for the development of IL-4–producing T_H2 cells. Candidate sources of this initial IL-4 have been identified, but their link to recognition of allergens or helminths by the innate immune system (the less specific and more immediate arm of defense against infection) has been difficult to establish. Furthermore, it was gradually realized that T_H2 cell responses to some helminths did not require IL-4. Three cytokines—IL-25, IL-33, and thymic stromal lymphopoietin—have emerged as candidates for the link between the innate immune system's recognition of the pathogen and T_H2 cell action, the ultimate, adaptive immune system response (*4*).

IL-25 was identified a decade ago as the "odd" member of the IL-17 cytokine family. Although it stimulates many of the hallmark



Path to T_H2 responses. Parasitic helminths or allergens induce epithelial cells to produce cytokines that stimulate three populations of cells to produce other cytokines. This cytokine combination promotes differentiation of T_H2 and B1 cells and stimulates effector functions, leading to parasite expulsion. MPP^{type2} cells can give rise to multiple cell types, including basophils, which can bias toward T_H2 differentiation. It is not clear whether natural helper, nuocyte, and MPP^{type2} cells are different, or the same cell type viewed differently.

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