# That's No Moon, it's a Molecular Capsule

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Molecules are small - even those of a non-scientific background appreciate this fact. Chemists have a precise view of the molecular scale; the smallest molecules are of the order of an Ångström in size (0.1 nm), whereas the largest discrete synthetic structures are rarely larger than a couple of nanometres. The word discrete here is crucial, as there are numerous particulate materials, including metal nanoparticles, metal organic frameworks and polymers, whose constituent units can range in size from tens to hundreds of nanometres. However, in the realm of materials chemistry, particles are polydisperse, with any particular batch containing particles of many sizes. In order to build large structures with absolute monodispersity, a carefully controlled bottom-up approach is required. Molecular self-assembly provides such an approach.

Taking advantage of the well-defined coordination geometries of transition metal ions and with the careful synthesis of organic ligands to coordinate to these metals, it is possible to pre-program smaller components to come together into more complex architectures with complete control. This technique has seen extensive use in recent years to construct a plethora of molecular capsules, most of these based on Platonic solids such as the tetrahedron and cube, where the metal ions occupy the vertices and the organic ligands the edges. The guest binding properties of these capsules have seen them employed in a host of applications, from catalysis to sensing. However, they are still limited to little more than a nanometre or two in diameter. Larger capsules require larger pieces and apart from

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the obvious drawback of more laborious ligand synthesis, the greater flexibility of longer ligands can reduce the preference for assembly into a single structural type.

In recent years the Fujita group has been in the vanguard of the campaign to synthesise large well-defined capsules. Rather than focus on simple tetrahedra and cubes, they have targeted structures incorporating much larger numbers of building blocks that do not define symmetry axes directly. This approach allows access to greater sizes whilst allowing the individual pieces to remain small. Their efforts must be described as a *tour de force* in self-assembly, which has seen them construct progressively larger $M_6L_{12}$ octahedra, Suzuki et al., 2009[1] $M_{12}L_{24}$ cuboctahedra, Tominaga et al., 2004[2] and $M_{24}L_{48}$ rhombicuboctahedra. Sun et al., 2010[3] These polyhedra all contain a $Pd^{2+}$ ion at each vertex and a bent organic ligand along each edge. Their ligands incorporate a pyridine nitrogen at each end to coordinate to the metal and are carefully tailored to favour a particular structural type. The ligands that self-assemble into each of these capsules are shown in **Figure 1**, along with spheres scaled to illustrate the relative sizes of the capsules and onto which the polyhedral structure has been projected to show how the symmetry of these capsules more closely approaches that of a sphere as they increase in size and nuclearity.
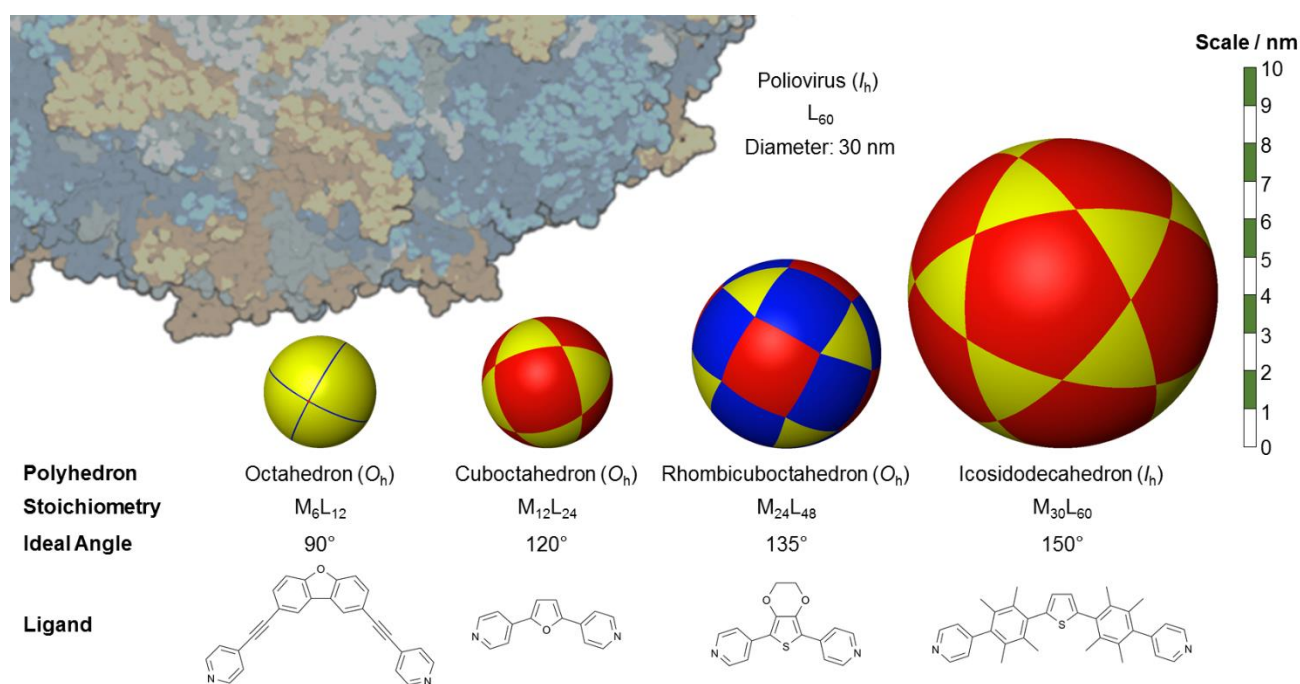


| Polyhedron | Octahedron ($O_h$) | Cuboctahedron ($O_h$) | Rhombicuboctahedron ($O_h$) | Icosidodecahedron ($I_h$) |
|---|---|---|---|---|
| Stoichiometry | $M_6L_{12}$ | $M_{12}L_{24}$ | $M_{24}L_{48}$ | $M_{30}L_{60}$ |
| Ideal Angle | 90° | 120° | 135° | 150° |
| Ligand | | | | |

**Figure 1:** *A size comparison of Fujita's $M_6L_{12}$ octahedral, $M_{12}L_{24}$ cuboctahedral, $M_{24}L_{48}$ rhombicuboctahedral and $M_{30}L_{60}$ icosidodecahedral capsules with Nature's poliovirus.*

The earlier structures reported by the Fujita group are dwarfed in size by the subject of their most recent study, an $M_{30}L_{60}$ icosidodecahedron, which is reported in their latest publication in *Chem*. Fujita et al., 2016[4] This structure is a far more challenging target than the previous three. In addition to the increased entropic penalty incurred when assembling capsules of ever greater nuclearity, this capsule represents the first in the series with overall icosahedral ($I_h$) rather than octahedral ($O_h$) point group symmetry. The angles around the vertex in a true icosidodecahedron are 108° and 60°, a considerable departure from the ideal 90° of square planar $Pd^{2+}$. The key breakthrough was the introduction of tetramethylphenylene spacer units between the terminal pyridine moieties and the central thiophene unit (which enables the requisite bend angles). This spacer unit engenders sufficient flexibility (described as a 'slight sag' in the ligand) to allow the angles between ligands around the $Pd^{2+}$ to approach 90° whilst still maintaining a ligand bend angle close to the ideal 150°. Remarkably, this additional flexibility did not lead to the formation of lower nuclearity assemblies, as is common with flexible ligands. The effect of the tetramethylphenylene spacer must thus be more nuanced than just allowing a sag in the ligand; it will affect factors such as the dihedral angles between adjacent rings, and the amplification of subtle differences such as these can have significant ramifications in the structures of large assemblies.

The capsule has been well characterised by MS, $^1$H and $^1$H DOSY NMR analyses, even though employing these techniques is challenging on an object of this size. The *pièce de résistance* of characterisation is clearly their single-crystal X-ray structure, however. Obtaining data on this enormous structure with such a large void volume is truly remarkable, and their special operational procedures, such as the refrigerated handling of samples and the collection of data at room

temperature, are key points of note. Growing single crystals of sufficient quality for X-ray analysis has been many chemists' bane. The authors' comment that this structure was only obtained after years of perseverance should be a source of inspiration to all in the field: hard work pays off.

Turning attention to potential applications of this structure, the interior volume of 157,000 $\text{Å}^3$ provides opportunities for encapsulation of larger guests than has previously been possible and the authors comment that this is sufficiently large to encapsulate proteins. The realisation of protein encapsulation nonetheless represents a still-significant challenge and a worthy goal.

Self-assembly is the key construction technique for making the higher order structures of life, with virus capsids and the iron storage protein capsule ferritin providing examples of how hierarchical complexity may be generated within living systems. Synthetic chemists still have a long way to go to compete with Nature's benchmark in this field. The poliovirus, part of which is pictured in **Figure 1**, is viewed as one of the simplest significant viruses. It contains 60 protein subunits, organised into 12 pentamers that self-assemble to form the 30 nm diameter icosahedral procapsid of the virus. Hogle et al., 1985[5] When placed alongside these largest spherical synthetic capsules to date, it still towers over them. The Fujita group's efforts are clearly making rapid progress, with this latest 8.2 nm-diameter capsule representing an important milestone on the road to accessing self-assembled structures of the same size and complexity as their natural counterparts. Achieving the synthesis of such large, closed capsules represents one of the salient challenges for this discipline over the next quarter century.

It is truly an exciting time for the field of supramolecular cages and capsules, with new structures and functions just beyond the horizon. Perhaps even higher order polyhedra can be assembled, and there may yet be more exotic, non-polyhedral structures that can be accessed by this synthetic methodology. It is now clear that discrete, well-defined molecular objects can be prepared on a length scale of 10 nm, extending the previous state-of-the-art by an order of magnitude. Just as the

crew of the *Millennium Falcon* initially couldn't believe that the large spherical object in the distance could have been assembled by man and that it had to be a moon, Lucas, 1977[6] we must readjust our preconceptions of what is possible in the world of molecular self-assembly. The possibilities out there are endless, but if size is what you are after, then clearly these are the capsules you're looking for.

**Author Contributions**

B.S.P. wrote the original draft and review and editing was done by both authors.

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