Self-assembly
**Characteristics**

<table>
<thead>
<tr>
<th><strong>building block</strong></th>
<th>atom</th>
<th>molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>target</strong></td>
<td>molecules</td>
<td>assemblies</td>
</tr>
<tr>
<td><strong>bond type</strong></td>
<td>covalent</td>
<td>ionic, hydrophobic, metal-coordination, H-bond</td>
</tr>
<tr>
<td><strong>bond energy</strong></td>
<td>35-135 kcal/mol</td>
<td>2 - 20 kcal/mol</td>
</tr>
<tr>
<td><strong>kinetic stability</strong></td>
<td>high</td>
<td>low (dynamic structures !!!)</td>
</tr>
</tbody>
</table>

Paddon-Row *et al.*  

Stang *et al.*  
*JACS* **1999**, *121*, 2741
Figure 3  Comparison of reversible and irreversible steps and their effects on the supramolecular assembly.
design principles

Figure 2  Schematic assembly of building blocks with various shapes to form discrete supramolecular structures.

information inserted in the building blocks
Supramolecular Coordination: Self-Assembly of Finite Two- and Three-Dimensional Ensembles

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2.1. Directional Bonding Approach

(coordination, H-bonds, dynamic covalent bonds)

Figure 1. Combination of various building units for accessing convex polygons and canonical polyhedra.

There are two basic structural requirements for the construction of supramolecular architectures by this approach. First, the complementary precursor units must be structurally rigid with predefined bite angles; and second, the appropriate stoichiometric ratio of the precursors must be used. The donor building blocks are generally organic ligands having two or more binding sites possessing angular orientations ranging from 0 to 180° (Figure 1).
<table>
<thead>
<tr>
<th>Tritopic Subunit</th>
<th>60°</th>
<th>90°</th>
<th>109°</th>
<th>120°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ditopic Subunit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80–90°</td>
<td>trigonal bipyramid</td>
<td>double square</td>
<td>truncated tetrahedron</td>
<td></td>
</tr>
<tr>
<td>109°</td>
<td>trigonal bipyramid</td>
<td>adamantanoid</td>
<td>cuboctahedron</td>
<td></td>
</tr>
<tr>
<td>180°</td>
<td>tetrahedron</td>
<td>cube</td>
<td>dodecahedron</td>
<td>trigonal prism</td>
</tr>
</tbody>
</table>

**Figure 2.** Three-dimensional architectures formed by the combination of ditopic and tritopic subunits by the directional bonding approach.
Preparation of a Macrocyclic Polynuclear Complex, [(en)Pd(4,4'-bpy)]₄(NO₃)$_₈$, Which Recognizes an Organic Molecule in Aqueous Media

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Received March 23, 1990

An ethanol (4 mL) solution of 4,4'-bpy (0.5 mmol) was added at room temperature to a methanol–water (1:1) solution (4 mL) of (en)Pd(NO₃)$_₂$ (2), prepared from (en)PdCl$_₂$ (0.5 mmol) and AgNO₃ (1.0 mmol), and the solution was stirred for 10 min at that temperature. Upon addition of ethanol (4 mL), a pale yellow powder immediately precipitated. The elemental analysis of the

The structure of this complex is estimated to be a macrocyclic tetramer 1 by the following facts: (i) all pyridine nuclei of the complex are completely equivalent in NMR spectrometry (vide ante); (ii) the empirical formula predicted by CHN analysis was reproduced even if the complex was prepared with excess 4,4'-bpy (2 equiv); (iii) right bond angles (N–Pd–N(cis) = 90°) rule out the formation of other cyclic oligomers which must have significant ring strain.
of bpy. Furthermore, the spectrum of Figure 1c (0.6 equiv of bpy) was completely identical with the spectrum obtained when pure 1 and 2 were mixed so that the ratio Pd:bpy became the same. These observations support rapid equilibrium which mainly lies on the stable cyclic tetramer 1 as shown in Scheme 1. It is noteworthy that the thermodynamic cyclization realized quantitative formation of 1 without employing any special conditions such as high dilution.

Figure 1. $^1$H NMR spectra (270 MHz, D$_2$O) obtained from mixtures of 2 and 4,4'-bpy: (a) 2:bpy = 1:0.2; (b) 2:bpy = 1:0.4; (c) 2:bpy = 1:0.6; (d) 2:bpy = 1:0.9.
Self-Assembled $M_{24}L_{48}$ Polyhedra and Their Sharp Structural Switch upon Subtle Ligand Variation

Qing-Fu Sun,¹ Junji Iwasa,¹ Daichi Ogawa,¹ Yoshitaka Ishido,¹ Sota Sato,¹ Tomoji Ozeki,² Yoshihisa Sei,³ Kentaro Yamaguchi,³ Makoto Fujita¹*

Self-assembly is a powerful technique for the bottom-up construction of discrete, well-defined nanoscale structures. Large multicomponent systems (with more than 50 components) offer mechanistic insights into biological assembly but present daunting synthetic challenges. Here we report the self-assembly of giant $M_{24}L_{48}$ coordination spheres from 24 palladium ions (M) and 48 curved bridging ligands (L). The structure of this multicomponent system is highly sensitive to the geometry of the bent ligands. Even a slight change in the ligand bend angle critically switches the final structure observed across the entire ensemble of building blocks between $M_{24}L_{48}$ and $M_{12}L_{24}$ coordination spheres. The amplification of this small initial difference into an incommensurable difference in the resultant structures is a key mark of emergent behavior.

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2.2. Symmetry Interaction Approach

clusters using metal—ligand bonds. It is based on the geometric relationship between the chelating ligands and the metals used. The strong binding affinity and coordination mode of chelating ligands, along with the inherent symmetry of the coordination sites available on the naked metal center, act as the driving force for the assembly process. In general, multibranched chelating ligands with rigid backbones are used in conjunction with transition metals or main group metals. The orientation of the multiple binding sites that are rigidly fixed is critical to the selectivity of a particular molecular geometry and helps to avoid the formation of oligomers and polymers. Similar to the directional bonding approach, it relies on the thermodynamic control and kinetic reversibility for error checking and self-correction.

Figure 3. Coordinate vector and chelate plane for the symmetry interaction method.
Figure 4. Design of a $D_3$-symmetrical triple helicate.

For example, to design a $M_2L_3$ triple helicate having an idealized $D_{3h}$ symmetry, it must be ensured that both the $C_2$ and $C_3$ axes are orthogonal and are preprogrammed into the chelating ligand and the metal center. Since the two pseudo-octahedral metal centers share the same $C_3$ axis, the two chelating planes must be parallel to achieve the triple helicate (Figure 4).
2.3. Paneling Approach

Figure 6. Representation for assembling a tetrahedron and an octahedron using triangular panels.

equilateral triangles, squares, and pentagons.\(^{10}\) Thus, 3D molecular architectures can, in principle, be designed by reducing these polyhedra to molecular components. For example, a tetrahedron can be designed by stitching together four triangular panels, while an octahedron can be prepared by bringing together eight such triangular panels (Figure 6). Similarly, the paneling of squares
Self-assembly of ten molecules into nanometre-sized organic host frameworks

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† Chemical Analysis Center, Chiba University, Yayoicho, Inageku,
Chiba 263, Japan

FIG. 1. a, The reaction scheme for the self-assembly of compound 3.
b, The crystal structure of the clathrate complex 3a···(4)₄ (a space-filling model presentation). A crystal with dimensions 0.42 × 0.40 × 0.34 mm

a. Ar = none; b. Ar = ; c. Ar =
The structure of 3a was confirmed by X-ray crystallographic analysis of its clathrate complex with four adamantyl carboxylate ions (4) (Fig. 1b). Crystals were grown by allowing an aqueous

\[ \text{COOH} \]

\[ \text{Chemical shift (p.p.m.)} \]

**FIG. 3** Monitoring of the titration of 3a with 4 by \(^1\)H NMR (400 MHz, D\(_2\)O, external TMS). The ratios 3a:4 are: a, 1:1; b, 1:2; c, 1:4; d, 1:8. Components (signals) are as follows: uncomplexed 3a (peaks A\(_1\) and A\(_2\)); complexed 3a (peaks B\(_1\) and B\(_2\)); uncomplexed 4 (peaks a\(_1\), a\(_2\), a\(_3\) and a\(_4\)); complexed 4 (peaks b\(_1\), b\(_2\), b\(_3\) and b\(_4\)).
2.4. Weak Link Approach

Scheme 1

In this design strategy, pioneered by Mirkin and co-workers, both 2D and 3D supramolecular assemblies are accessible using hemilabile ligands and transition metals.\(^\text{11}\) The hemilabile, flexible ligands coordinate in a bidentate chelating mode to the metal center such that one of the metal—ligand bonds is weaker than the other. The formation of the kinetically controlled product is driven by the chelating effect of the bidentate ligands and the \(\pi-\pi\) interaction between the two central bridging units (Scheme 1). The weak ligands of this condensed intermediate structure can be selectively displaced upon treatment with small molecules or ions that have stronger affinity for the metal center, thereby generating the thermodynamically controlled product.
What about hydrogen bonding?

G-quartet

trimesic acid

rosette
Isolation of the rosette motif

- peripheral crowding
Linear tapes are formed preferentially with melamines with small substituents $Y$, such as $F$, $Cl$, or $CH_3$. Increasing the size of substituent $Y$, for example, $C(=O)OCH_3$, promotes the selective formation of crinkled tapes, primarily as a result of the relief of unfavorable steric interactions between the $Y$ substituents on adjacent melamine units that are present in the corresponding linear tapes. A further increase in size, for example, when $Y$ is $C(CH_3)_3$, finally gives exclusively the rosette structure, in which all the repulsive steric interactions are minimized relative to those in the corresponding tape-like structures.
Isolation of the rosette motif

- covalent preorganization
Scheme 13. Self-assembly of $19 \cdot (CA)_3$ (a) and $20 \cdot 21$ (b).
Positive cooperativity is due to entropic and enthalpic contributions to binding.

Entropy: loss of motion of the molecule, including internal rotation and vibrations
(contribution already paid for in connecting together the recognition elements)

Enthalpy: secondary functional groups interactions, conformational changes, polarization of the interacting groups
Figure 3. Structures based on the CA·M lattice, arranged in approximate order of stability. These structures are also organized by the number of rosettes (designated mono-, bis-, and tris-) they incorporate. Only one conformational isomer of each aggregate is shown; the stable conformer is, in general, not known. "Particles" is the number (N) of separate molecules comprising the aggregates—the larger the value, the greater the unfavorable entropic cost of aggregation. HB is the number of hydrogen bonds in the aggregates—the larger the value, the greater the favorable enthalpic gain of aggregation. HB/(N - 1) is an empirical parameter incorporating these trends; it is discussed in more detail in the text. MW is molecular weight of the aggregate. Aggregates discussed in the text are identified by compound number, (Cmpd. Number).
What about 3D-hydrogen bonded structures?

Scheme 23. Four strategies for the noncovalent synthesis of molecular containers.
How reliable is the self-assembly process?

Self-Sorting: The Exception or the Rule?

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Abstract: In this paper, we pose the question of whether self-sorting in designed systems is exceptional behavior or whether it is likely to become a more general phenomenon governing molecular recognition and self-assembly. To address this question we prepared a mixture comprising two of Davis’ self-assembled ionophores, Rebek’s tennis ball and calixarene tetraurea capsule, Meijer’s ureidopyrimidinone, Reinholdt’s calixarene bis(rosette), and two molecular clips in CDCl₃ solution and observed the behavior of this ensemble by ¹H NMR. As hypothesized, high-fidelity self-sorting behavior was observed. The influence of several key variables—temperature, concentration, equilibrium constants, and the presence of competitors—on the fidelity of self-sorting is described. These results show that self-sorting is neither the exception nor the rule. They suggest, however, that the subset of known molecular aggregates that exceed the criteria required for thermodynamic self-sorting is larger than previously appreciated and potentially quite broad.
DNA Nanofabrication

Figure 1 DNA structure and examples of DNA assembly: (a) right-handed B- and A-forms and left-handed Z-form of DNA duplexes and (b) DNA tiles, assembled from (i) double crossover (DX), (ii) cross-motif (CM), (iii) 3-point star, (iv) T-junction, and (v) 5-point star into periodic 2D arrays. (c) DNA origami. (d) Geometrically well-defined ssDNA templates with organic vertices are used to organize gold nanoparticles and encoded to allow for write/erase experiments. (e) Hydroxypyridone insertions into DNA are used to selectively coordinate Cu(II) within the DNA duplex. (f) Two different ligands are site specifically incorporated to generate DNA-templated coordination environments selective for metals.
DNA Nanofabrication
Table 1  Reversible covalent reactions.

_C\equiv N_ exchange

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$R_1 \equiv N R_2 + R_3 \equiv N R_4$</th>
<th>$\xleftrightarrow{\text{Acid}}$</th>
<th>$R_1 \equiv N R_4 + R_3 \equiv N R_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transamination</td>
<td>$R_1 \equiv N R_2 + R_3 \equiv N R_4$</td>
<td>$\xleftrightarrow{\text{Acid}}$</td>
<td>$R_1 \equiv N R_4 + R_3 \equiv N R_2$</td>
</tr>
<tr>
<td>Hydrazone exchange</td>
<td>$R_1 \equiv N R_2 + R_3 \equiv N R_4$</td>
<td>$\xleftrightarrow{\text{Acid}}$</td>
<td>$R_1 \equiv N R_4 + R_3 \equiv N R_2$</td>
</tr>
<tr>
<td>Oxime exchange</td>
<td>$R_1 \equiv N O R_2 + R_3 \equiv N O R_4$</td>
<td>$\xleftrightarrow{\text{Acid}}$</td>
<td>$R_1 \equiv N O R_4 + R_3 \equiv N O R_2$</td>
</tr>
</tbody>
</table>

_Acyl exchange

<table>
<thead>
<tr>
<th>Reaction</th>
<th>$R_1 O R_2 + R_3 O R_4$</th>
<th>$\xleftrightarrow{\text{Base}}$</th>
<th>$R_1 O R_4 + R_3 O R_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transesterification</td>
<td>$R_1 O R_2 + R_3 O R_4$</td>
<td>$\xleftrightarrow{\text{Base}}$</td>
<td>$R_1 O R_4 + R_3 O R_2$</td>
</tr>
<tr>
<td>Transthoesterification</td>
<td>$R_1 S R_2 + R_3 S H$</td>
<td>$\xleftrightarrow{\text{Base}}$</td>
<td>$R_1 S R_3 + R_2 S H$</td>
</tr>
<tr>
<td>Transamidation</td>
<td>$R_1 N H R_2 + R_3 N H R_4$</td>
<td>$\xleftrightarrow{\text{Protease or metal}}$</td>
<td>$R_1 N H R_4 + R_3 N H R_2$</td>
</tr>
<tr>
<td>Michael-addition</td>
<td>$R_1 C O R_2 + R_3 S H$</td>
<td>$\xleftrightarrow{\text{Base}}$</td>
<td>$R_1 S O R_2 R_3$</td>
</tr>
</tbody>
</table>

Self-assembly beyond noncovalent interactions
Miscellaneous

Disulfide exchange

\[
R_1S\equiv S\equiv R_2 + R_3S\equiv S\equiv R_4 \rightleftharpoons R_1S\equiv S\equiv R_4 + R_3S\equiv S\equiv R_2
\]

Boronic ester exchange

\[
R_1\overset{\text{O}}{\overset{\text{B}}{\text{O}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}} + \overset{\text{HO}}{\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{HO}}{\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}} \rightleftharpoons \overset{\text{R}}{\overset{\text{B}}{\overset{\text{O}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}} + \overset{\text{HO}}{\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{HO}}{\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}}
\]

Olefin metathesis

\[
R_1\overset{\text{C}}{\overset{\text{C}}{\text{C}}}\overset{\text{C}}{\overset{\text{C}}{\text{C}}}R_2 + R_3\overset{\text{C}}{\overset{\text{C}}{\text{C}}}\overset{\text{C}}{\overset{\text{C}}{\text{C}}}R_4 \rightleftharpoons R_1\overset{\text{C}}{\overset{\text{C}}{\text{C}}}\overset{\text{C}}{\overset{\text{C}}{\text{C}}}R_4 + R_3\overset{\text{C}}{\overset{\text{C}}{\text{C}}}\overset{\text{C}}{\overset{\text{C}}{\text{C}}}R_2
\]

Acetal exchange

\[
\overset{\text{O}}{\overset{\text{O}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}} + \overset{\text{O}}{\overset{\text{O}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}'}\overset{\text{R}}{\overset{\text{R}}{\text{R}}'} \rightleftharpoons \overset{\text{O}}{\overset{\text{O}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}} + \overset{\text{O}}{\overset{\text{O}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}}\overset{\text{R}}{\overset{\text{R}}{\text{R}}'}\overset{\text{R}}{\overset{\text{R}}{\text{R}}'}
\]

Diels–Alder
Figure 2  Possible pathways for the formation of a dynamic covalent system based on disulfide bonds.
Figure 3  Possible pathways for the formation of a dynamic covalent system based on imine bonds.
Multicomponent Assembly of Boronic Acid Based Macrocycles and Cages**

Nicolas Christinat, Rosario Scopelliti, and Kay Severin*
\[
\begin{align*}
4 \text{ of 14} + 2 \text{ of 15} + 2 \text{ of 16} &\rightarrow -12 \text{ H}_2\text{O} \quad \Delta \quad \text{THF/Toluene} \\
&\rightarrow \text{17}
\end{align*}
\]