Supporting Information 1

What Molecular Assembly Can Learn from Catalysed Assembly in Living Organisms?

Zhi-Chao Lei,[a,b]‡ Xinchang Wang,[c]‡ Liulin Yang,*[a] Hang Qu,[a] Yibin Sun,[d] Yang Yang,[a] Wei Li,[b] Wen-Bin Zhang,[d] Xiao-Yu Cao,[a] Chunhai Fan,[e] Guohong Li,[b] Jiarui Wu,[f] Zhong-Qun Tian*[a]

a. State Key Laboratory of Physical Chemistry of Solid Surfaces, Collaborative Innovation Center of Chemistry for Energy Materials (iChEM), Innovation Laboratory for Sciences and Technologies of Energy Materials of Fujian Province (IKKEM), College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China. E-mail: zqtian@xmu.edu.cn, llyang@xmu.edu.cn
b. National Laboratory of Biomacromolecules, CAS Center for Excellence in Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, P. R. China; University of Chinese Academy of Sciences, Beijing 100049, P. R. China
c. School of Electronic Science and Engineering, State Key Laboratory of Physical Chemistry of Solid Surfaces, Xiamen University, Xiamen 361005, P. R. China
d. Beijing National Laboratory for Molecular Sciences, Key Laboratory of Polymer Chemistry & Physics of Ministry of Education, Center for Soft Matter Science and Engineering, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P. R. China
e. School of Chemistry and Chemical Engineering, Frontiers Science, Center for Transformative Molecules and National Center for Translational Medicine, Shanghai Jiao Tong University, Shanghai 200240, P. R. China
f. Key Laboratory of Systems Biology, Center for Excellence in Molecular Cell Science, Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, Shanghai, 200031, P. R. China. School of Life Science and Technology, ShanghaiTech University, Shanghai, 201210, P. R. China. Key Laboratory of Systems Health Science of Zhejiang Province, School of Life Science, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Hangzhou, 310024, P. R.China.

1 The terminology of "catassembly"

In 2014, learning from catalysis for chemical reactions, we coined the term of "catassembly" in molecular assembly.[1] Quoted from that review, "*we suggest "catassembly" as an abbreviation of catalysed-assembly, as it combines the words "catalysed" and "assembly", has a set of syllables that can be read easily, and identifiably retains the Greek root "cat-" of catalysis. In addition, the noun form is defined as: a catassembler is a substance (or a group of substances working synergistically) that increases the rate of an assembly process without modifying the overall standard Gibbs energy change; the process is called catassembly. The corresponding verb and adjective forms are catassemble and catassembled. This series of terms will completely avoid any confusion with supramolecular catalysts and noncovalent catalysts.*"

At that time, we didn't know that the Greek prefix "cata" carries meaning of "down", "against", and "back", which conflicts with the "assembly". Interestingly, same stories happened in the history of catalysis. The "catalysis item was first coined by Jöns Jakob Berzelius (1779-1848), comes from the Greek words "kata" meaning down and "lyein" meaning loosen.[2] Initially, the term "catalysis" was mainly associated with decomposition reactions, for example, the decomposition of starch to glucose. This historical association has led to the continued use of the term "catalysis", despite its broader application to various types of reactions, for example, polymerization. Therefore, we reasonably argued that in modern chemistry, when the word "cata" pops up, the concept is always related to "catalysis", "catalysed", "catalyst" and "catalytic". The "cata" in our concept is an abbreviation for "catalysed".

In our 2014 paper, we highlighted the ability of catassemblers to accelerate.[1] However, we gained deeper insight into the complexity of assembly pathways, realizing that selectivity is another important feature of catassembly. Therefore, in this review we define catassemblers as molecules that can accelerate and control molecular assembly and are not incorporated in the final product.

2 Can catassembly called "chaperoned assembly"?

The concept of chaperone is well-known in biology. One may wonder can the catassembly called chaperoned assembly. As discussed in part 4 of the main text, the disassembly and reassembly are quite important in biological assembly systems. For instance, the disassembly of nucleosome facilitates transcription, while the reassembly inhibits it. The catalysed assembly, disassembly and reassembly all share a common mechanism in which assisting agents facilitate the formation or disruption of noncovalent interactions. In these cases, the term "chaperoned" may not be entirely appropriate, as "chaperone" typically conveys positive functions.

Compared to chaperone, catalysis is more commonly recognized by chemists. Therefore, in the context of the assembly process, "catalysed assembly" is equal to "chaperoned assembly". Instead, for other processes, the term "catalysed disassembly", "catalysed reassembly" or "noncanonical catassembly" might offer a more accurate description.

3 Can the whole system with catassemblers involved be thought as self-assembly?

The most acceptable definition of self-assembly is given by Whitesides and his colleagues "*Here, we limit the term to processes that involve pre-existing components (separate or distinct parts of a disordered structure), are reversible, and can be controlled by proper design of the components. "Self-assembly" is thus not synonymous with"formation."*[3] Traditionally, the study of self-assembly focuses on the design of building blocks and assembling them into the final structures. Many

researchers in this field conventionally equate “components” with building blocks, often overlooking species that play other roles in the system.

As stated in the main text, living organisms could be viewed as “self-assembly” as a whole system. However, when we focus on the kinetic process of assembly and regulation strategies, the concept of catassembly becomes indispensable. The unbounded use of the concept of self-assembly has led to a kind of inertia thinking, that as long as the assembly building blocks are well designed, mixing them will give the desired assembled products. Unfortunately, due to the lack of precise regulation of the self-assembly process, the finally obtained assemblies are often not the expected products. Such an approach encounters greater challenges in multi-component assembly systems, people have to rely more on the self-sorting processes to obtain target products. In the *Chem. Soc. Rev.* paper published in 2014, we mentioned that the overreliance of “self” has limited the development of this field.[1] In 2019, a perspective from E.W. Bert Meijer’s group also echoed this.[4]

What’s more, although the catassembler and the subunits are in one system, the clear definition of catassembly and catassembler are still needed. The classification of catalyst and reactant in chemical reaction have greatly change the research of chemical reactions. Like that, making clear distinctions between assisting species and subunits will also help the development of molecular assembly. We believe that a new concept will help us exert more precise and efficient control over the assembly process, thereby constructing complex assembly systems with multi-component and hierarchical structures.

4 Can solvent be regarded as catassembler?

This review primarily focuses on catassembly in living organisms, which predominantly occurs in aqueous environments. Therefore, we have omitted a discussion on solvent effect in this review. However, in synthetic systems where various solvents are used, the question of whether a solvent can be regarded as a catassembler will rise.

Solvation effects can lower reaction barrier, change reaction pathways, accelerate reactions. Although these features are quite similar to catalysts, solvent is not usually called a catalyst in chemical reaction. The main reason is that solvation effects often lack selectivity, while specifically designed catalysts have definite active sites with substrates, generate intermediates with definite structures, and have high selectivity. In addition, the accelerating effect of solvents on reactions is usually far less than that of catalysts, and they exist more as the medium of the reaction, controlling the mass transfer and diffusion of each component. Of course, there are also studies that have clearly observed solvent molecules participating in forming the intermediate of the reaction, co-catalysing the reaction, in which case the solvent molecules can also be called catalysts.[5]

Unfortunately, the boundary between solvent effects and catassembly may be more blurred, because both solvent molecules and catassemblers regulate molecular assembly via non-covalent interactions. However, like catalysis, we also emphasize the selectivity of catassemblers. Higher binding constants are often a prerequisite for high selectivity, catassemblers should be designed to have relatively strong binding affinity with the substrate, or have definite active sites, forming intermediates with specific structures, and thereby regulating the assembly process. However, there are indeed transitional zones as well. When the binding between the catassembler and the substrate is weak, its role may be intermediate between a solvent and a catassembler. In the 2014 paper, we also introduced another category known as assisted-assembly.[1] Catassembly is a subset of assisted-assembly. Assembly processes that involve assisting species but without clear features of catassembly can be categorized into assisted-assembly.

5 Is dialysis-assisted assembly catassembly?

In biochemical experiments, denaturing chemicals such as guanidine hydrochloride and urea are often used to unfold proteins.[6] Removing these denaturing chemicals through dialysis can facilitate the refolding of proteins. Similarly, a large amount of formamide can inhibit the intrachain folding of DNA. Removing formamide by dialysis can induce the formation of DNA origami structures.[7] Since the denaturing chemicals added lack selectivity for DNA or protein, we tend to think this process is closer to an assisted assembly process by changing the assembly environment under external force.

6 The limitations of catassembly

Catassembly is a novel concept currently under exploration. It cannot be considered the "ultimate answer" to molecular assembly. Briefly, catassembly is not as straightforward as self-assembly and may cost additional energy. The introduction of catassemblers to the system increases the complexity of the system paradoxically. Catassembly systems usually involve the synergistic integration of multiple interactions across multiple sites. Subunits within catassembly are typically characterized by their ability to undergo inducible structural changes. The catassembly processes are often mediated by intricate and transient intermediates. These complexities pose great challenges in the study of catassembly. However, certain functional assemblies cannot be obtained without catassemblers under complex environment like cells. Catassemblers also enhance the ability to control the system by deciding when, where and how the assembly begins. For example, histone chaperones and remodelers determine the specific chromatin structure at a precise time and location, thereby regulating cell fate during differentiation. While there are currently only a few reports on artificial catassembly, living organisms possess abundant catassembly systems. Therefore, it is necessary to summarize and analyze biological catassemblies to understand their mechanisms and apply this knowledge to artificial catassembly. The study of catassembly presents significant challenges but also offers opportunities for the development of complex assembly systems. Additionally, the study of catassembly provides a possible bridge between the realms of chemistry and biology.

References

1 Y. Wang, H.-X. Lin, L. Chen, S.-Y. Ding, Z.-C. Lei, D.-Y. Liu, X.-Y. Cao, H.-J. Liang, Y.-B. Jiang and Z.-Q. Tian, *Chem. Soc. Rev.*, 2014, **43**, 399–411.

2 J. Wisniak, *Educ. Quím.*, 2010, **21**, 60–69.

3 G. M. Whitesides and B. Grzybowski, *Science*, 2002, **295**, 2418–2421.

4 G. Vantomme and E. W. Meijer, 2019, **363**, 1396–1397.

5 J. S. Adams, A. Chemburkar, P. Priyadarshini, T. Ricciardulli, Y. Lu, V. Maliekkal, A. Sampath, S. Winikoff, A. M. Karim, M. Neurock and D. W. Flaherty, *Science*, 2021, **371**, 626–632.

6 K. Luger, A. W. Mäder, R. K. Richmond, D. F. Sargent and T. J. Richmond, *Nature*, 1997, **389**, 251.

7 R. Jungmann, T. Liedl, T. L. Sobey, W. Shih and F. C. Simmel, *J. Am. Chem. Soc.*, 2008, **130**, 10062–10063.