J Incl Phenom Macrocycl Chem (2008) 62:193–196
DOI 10.1007/s10847-008-9438-0

Thoughts about an article of Yamato *and coll.*

Jacques Vicens

Received: 10 March 2008 / Accepted: 10 March 2008 / Published online: 1 April 2008

Abstract This highlight makes comments on recent article of Yamato *and coll.* as molecular machines.

Keywords Supramolecular chemistry · Molecular machines · From complex to complexity

> It is enough to create new names, estimations and probabilities in order to create in the long run 'things'
>
> Nietzche, F.: The Gay Science

> The designer and the inventor, who bring elements together in new combinations, are each able to assemble and manipulate in their minds devices that as yet do not exist.
>
> Ferguson, E. S.: Science **197**, 827 (1977)

> What is complexity? Even among scientists there is some disagreement as to the necessary and sufficient conditions for a system to be deemed "complex." By "complex" scientists do not mean "complicated" or "perplexing." Generally, complex systems include large numbers of components interacting in nonlinear ways, and often leading to surprisingly self-organized behaviour. In common language one is reminded of the saying that "the whole is greater than the sum of its parts." For many, complexity is something available in varying quantities. For some, a measure of complexity is the effort needed to describe a system's "effective regularities."
>
> Galanter, P., Levy, E.: Complexity/Art and complex sytems. Gallery guide of an Exhibition Samuel Dorsky Museum of Art September 14–November 24 (2002).

With an intuition that arises from handling molecular objects as a child is playing [1] with construction games (Meccano chemistry [2], Lego chemistry [3], Tinkertoy chemistry [4] etc.) chemists have recognized that forces, motions, signals or mechanical stimuli can indeed be transferred either within molecules or from one molecule to another in a manner that depends on the structure of the atomic assembly. In recent years, the adaptation of molecular objects to efficiently convert chemical energy into mechanical energy inspired many researchers in the field of supramolecular chemistry and nanotechnology. Molecular machines such as switches, devices, sensors and logic gates were synthesized which required chemical, electrical, or light energy to function. An impressive review on this topic has been recently published by Kay et al. with more than 1,000 references [5]. The integration of molecular machines into nano-engineered structures opens up the fascinating possibility of manipulating nano-sized materials at the molecular level [6].

In 2000, we published a review article entitled '*Molecular Machines*' describing only molecular-sized systems (either molecular or supramolecular) exhibiting mechanical properties interpretable in terms of classical mechanics [7]. Such systems are formed by the assembly of molecular segments via covalent linkages. They are designed to transmit or modify the application of power forces, eventually inducing motions within the system itself in a predetermined fashion. In contrast to the properties of molecular devices that result

J. Vicens (✉)
Université de Strasbourg, ECPM-CNRS-IPHC, Strasbourg
67087, France
e-mail: vicens@chimie.u-strasbg.fr

from a stimulation by an external energy source, the mechanical properties of these complex systems originate from the transmission of forces through their geometrical and rigid architectures. Some of these specific features were related to the *Theory of molecular machines* proposed by Schneider [8]. As proposed in our review, the molecular machines based on classical mechanics being currently developed provide a *mechanical alphabet* which could be used by chemists to associate individual molecular machines into new molecular devices. And, the end of our article, to illustrate our ideas, we made a comparison with the use of a mechanical alphabet taken from the work of Leonardo da Vinci. In 1493, Leonardo sketched a series of plates of weapons, loads, flying machines, geometry, and *machinery* known as the 'Tratado de Estetica y Mechanica en Italiano' as part of the *Codex of Madrid*. From his *mechanical* sketches, he drew a machine made of 13 like cogs in order to maintain a constant ratio of ten to one in each of them, seemingly with no use. In fact, he was designing the precursor of a so-called *device for calculation*, without knowing it.' [7].

A recent example of a transmission of forces through molecular association is given by Yamato *and coll.* [9]. Thiacalix[4]arenes **1** and **2** (see Scheme 1) were prepared by usual procedures in the 1,3-alternate conformation. **1** supports two distal 2-methyl pyridyl on one side of the macrocycle and two distal carboxylic functions on the other side. Similarly, **2** bears two distal 4-methyl pyridyl on one side and two ethyl ester functions on the other. The particular structure arrangement of these functional groups enables the formation of heterodimer **3** through hydrogen bonds involving the nitrogen atoms of the 4-methyl pyridines and the hydrogen atoms of the carboxylic acids. Evidence for the formation of **3** was provided by ^{1}H NMR and IR spectroscopy in $CDCl_3$. An association constant $K_{\mathrm{ass}} = 389 \pm 9\ \mathrm{M}^{-1}$ was calculated. In addition to the self-assembly study, the authors investigated titration experiments of **1**–**3** with $AgSO_3CF_3$ by ^{1}H NMR in the same solvent. They showed that addition of 1 equiv of $AgSO_3CF_3$ to a solution of **3** results in its disassembly into **1** and **2**. The disassembly was attributed to structural changes in response to the binding event of **1** to an Ag^+ ion (K_{ass} of $1{\bullet}Ag^+ = 1.28 \times 10^4\ \mathrm{M}^{-1}$). It was demonstrated that the Ag^+ ion is complexed by the nitrogen atoms of the 2-methyl pyridyl moieties and the phenolic oxygens.

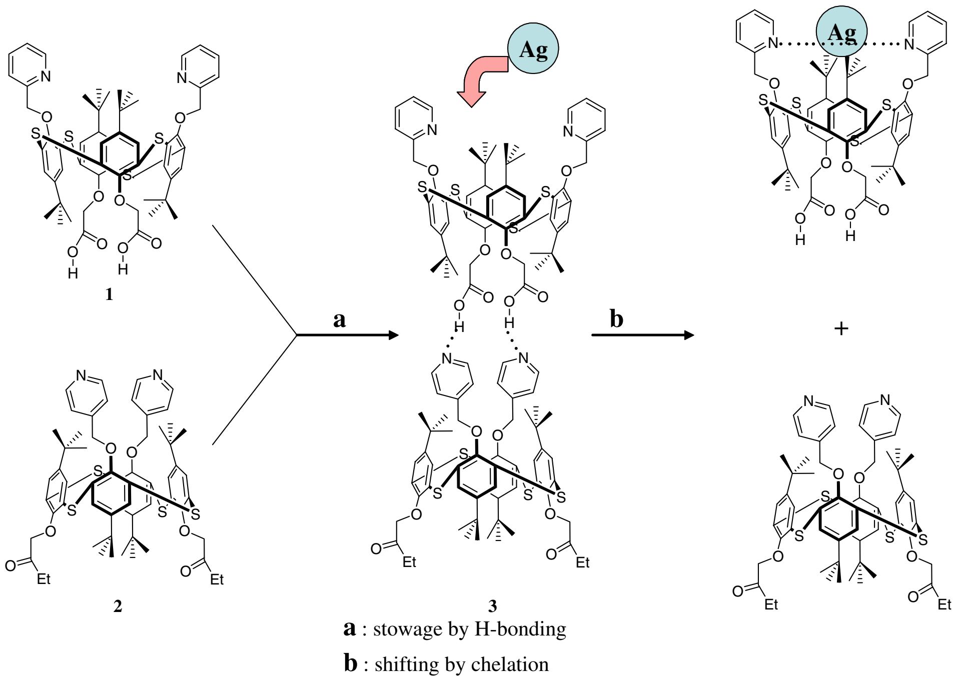
Here, we propose that the molecular system presented in the article by Yamato *and coll.* is a 'double' *mechanical molecular machine*. The binding forces induced by the chelation of the Ag^+ ion by the pyridines propagate through the 1,3-alternate conformation of **1** (acting as a level) to the opposite end of the thiacalix[4]arene where they alter its geometry and disrupt the hydrogen bonds formed with the second, more rigid, thiacalix[4]arene **2**. In short, this molecular system involves two entities made of covalent bonds (the constructed thiacalixes) that react in two different manners to two distinct informations (the intermolecular interactions). First, the entities are held together by intermolecular interactions (hydrogen bonds). Second, they are indirectly separated by a chelation (metal to nitrogen). Building such a complex system that reacts as expected represents a significant achievement. This device follows the concept of emergence recently developed in chemistry or more general systems. The concept of emergence sustains that 'the whole is bigger than the sum of its parts' [10]. The example of Yamato *and coll.* is more than two calixarenes and two kinds of molecular interactions. It represents a molecular system belonging to new systems of increasing complexity.

The conversion of complex systems into complexity [11], systems chemistry i.e., the study of complex mixtures of interacting synthetic molecules [12], complexity in chemistry [13] are in vogue. Not only the example of Yamato *and coll.* [9] is belonging to chemistry but it adds value by being a complex system. It is probably one example of the emergent properties that are now flourishing in many articles dealing with complexity in chemistry which are due to the investigations of intermolecular interactions by supramolecular chemists [14]. These chemical reports of complex systems directed by intermolecular interactions [14] exemplify the progressive ways in which supramolecular chemists, and maybe scientists in general, are now approaching these new challenges.

While physicists view atoms as a system of particles and theoreticians view molecules as a system of atoms and redistribution of electrons, organic synthetic chemists are more interested in finding suitable means to transform an arrangement of atoms into another. Each system has its own way of research with different words, techniques, objects and ideas digging a gap between each discipline. A new gap appears with supramolecular chemistry. A supermolecule or a molecular assembly is a system of interacting molecules and is studied by supramolecular (roughly by the bottom up approach) and nanomolecular (roughly by the top down approach) chemists. In this case, chemists are searching for ways to associate molecules into complex systems by learning about intermolecular interactions and geometrical parameters according to lock-and-key [15] and induced fit [16] principles.

The molecular system of Yamato *and coll.* [9] is termed 'a complex system' but is simple because it is well defined and it has been created by a bottom up approach. All the working elements and properties are known. The emergent complexity in chemistry is at a higher level, may be with this new gap, and because it is formed by complex systems

Scheme 1 Assembly of **1** and **2** and disassembly of **3**



working with many simple rules with large diversities but leading to complex behaviours.

Not too surprisingly, the creation of complex systems is a synthetic challenge for any chemist. In tackling such challenges, scientists develop a new vocabulary to express the novel underlying concepts, as well as new imageries (ensemble of images) to represent these complex systems (molecular concepts). In return, this imagery—the word 'imagination' has the same root—becomes a crucial driving force for the advancement of the field. Images and visual aspects of molecules and their complex systems are becoming readable signs and means of further construction [17]. This is well exemplified by the continuous development of mechanical molecular machines from the first molecular turnstiles of Bedard and Moore [18], to the recent nanovehicles [19]. According to Schummer [20], 'the production of molecular machines was inspired by an aesthetic phenomenon of 'gestalt switch', by certain images that referred to both molecules and ordinary objects, and thus symbolically bridged the two worlds. This opened up a new way of perceiving and drawing molecular images and new approaches to chemical synthesis. More generally, aesthetic phenomena can play an important role in directing scientific research and aesthetic theories can help understand such dynamics, such that they need to be considered in philosophy of science.' In this sense, the complex system of Yamato *and coll.* is a model of such a bridging between real-size life objects and molecular objects in chemistry. In his paper on supramolecular chemistry, complexes and complexity in chemistry, Gale [15] ends by this sentence: 'There can be no doubt that more esoteric complexes, with uses that can only now be dreamt of in the pages of science fiction novels, will emerge in coming years'. When looking at the mechanism of disassembly of **3** into **1** and **2** one can imagine heterodimer **3** as two spatial shuttles (**1** and **2**) stowed one to the other until the signal (silver complexation) of shifting is given.

Image 1 Stowage of Apollo and Soyouz modules (Image: NASA/JSC) [21]

References

1. Laszlo, P.: Playing with molecular models. HYLE Int. J. Philos. Chem. **6**, 85–97 (2000)
2. Cantrill, S.J., Pease, A.R., Stoddart, J.F.: A molecular meccano kit. J. Chem. Soc. Dalton Trans. 3715–3734 (2000)
3. Mathias, J.P., Stoddart, J.F.: Constructing a molecular LEGO set. Chem. Soc. Rev. **21**, 215–225 (1992)
4. Michl, J., Magnera, T.F.: Two-dimensional supramolecular chemistry with molecular Tinkertoys. PNAS **99**, 4788–4792 (2002)
5. Kay, E.R., Leigh, D.A., Zerbetto, F.: Synthetic molecular motors and mechanical machines. Angew. Chem. Int. Ed. **46**, 72–191 (2007)
6. For books and special issues on molecular machines cf.: (a) Balzani, V., Credi, A., Serena, S., Venturi, M.: Artificial nanomachines based on interlocked molecular species: recent advances. Chem. Soc. Rev. **35**, 1135–1149 (2006); (b) Balzani, V., Credi, A., Venturi, M.: Processing energy and signals by molecular and supramolecular systems. J. Incl. Phenom. Macrocyclic Chem. **60**, 173–185 (2008); (c) Balzani, V., Credi, A., Venturi, M.: in Molecular Devices and Machines—a Journey into the Nano World. Wiley-VCH, Weinheim (2003); (d) Balzani, V., Credi, A., Raymo, F.M., Stoddart, J.F.: Artificial molecular machines. Angew. Chem. Int. Ed. **39**, 3348–3391 (2000); (e) Acc. Chem Res. special issue on Molecular Machines on Molecular Machines **34**(issue 6) (2001); (f) Struct.Bond. special issue on Molecular Machines on Molecular Machines and Motors **99**, (2001); Top. Curr. Chem. special volume on Molecular Machines **262**, (2005)
7. Asfari, Z., Vicens, J.: Molecular machines. J. Incl. Phenom. Macrocyclic Chem. **36**, 103–118 (2000)
8. (a) Schneider, T.D.: Theory of molecular machines. I. Channel capacity of molecular machines. J. Theor. Biol. **148**, 83–123 (1991); (b) Schneider, T.D.: Theory of molecular machines. II. Enregy dissipation of molecular machines. J. Theor. Biol. **148**, 125–137 (1991)
9. Pére-Zcasas, C., Rahman, S., Begum, N., Xi, Z., Yamato, T.: Allosteric bindings of thiacalix[4]arene-based receptors with 1,3-alternate conformation having two different side arms. J. Incl. Phenom. Macrocycl. Chem. **60**, 173–185 (2008)
10. see for example: (a) Corning, P.A.: The re-emergence of “emergence”: a venerable concept in search of a theory. Complexity **7**, 18–30 (2002); (b) Cuff, J.M.: C. S. Peirce, G. W. F. Hegel, and Stuart Kauffman’s complexity theory: a response. Zygon, **42**(1), 249–254 (2007)
11. Gale, P.A.: Supramolecular chemistry: from complexes to complexity. Phil. Trans. R. Soc. Lond. **A358**, 431–453 (2000)
12. Ludlow, R. F., Otto, S.: Systems chemistry. Chem. Soc. Rev. **37**, 101–108 (2008)
13. Lehn, J.-M.: Supramolecular chemistry: from molecular information towards complex matter. Rep. Prog. Phys. **67**, 249–265 (2004)
14. Desiraju, G.R.: Crystal engineering: a holistic view. Angew. Chem. Int. Ed. **46**, 8342–8356 (2007)
15. Behr, J.P.: The Lock and Key principle. Wiley, (1994)
16. Koshland, D.E.: The key-lock and induced fit theory. Angew. Chem. Int. Ed. Engl. **33**, 2375–2378 (1995)
17. Hampe, M.: Visual essences, readable signs, means of construction: on the relevance of images in science. Angew. Chem. Int. Ed. **45**, 1028–1031 (2006)
18. Bedard, T.C., Moore, J.S.: Design and synthesis of molecular turnstiles. J. Am. Chem. Soc. **117**, 10662–10671 (1995)
19. Shirai, Y., Morin, J.-F., Sasaki, T., Guerrero, J.M., Tour, J.M.: Recent progress on nanovehicles. Chem. Soc. Rev. **35**, 1043–1055 (2006)
20. Schummer, J.: Gestalt switch in molecular image perception: the aesthetic origin of molecular nanotechnology in supramolecular chemistry. Found. Chem. **8**, 53–72 (2006)
21. www.space.gc.ca/.../publications/mondiale.asp