

“Smart” molecules “trained” to know how to assemble circularly

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A system with more disorders is in a higher “entropy” state and more stable. Naturally, things spontaneously move from low entropy to high entropy state. Down to the molecular level, molecules in a chaotic state whereby they can move freely in their own will tend to be “happier” and energetically more stable. To force these “happy” molecules to be more organized in a low entropy state, a lot of energy is required to ease the frustrations from the molecules. Even more difficult is to inter-connect the chaotic molecules in a head-to-tail fashion to form a well-organized macrocycle.

A distinctive buy-in benefit of having an organized macrocyclic backbone is commonly referred to as “macrocyclic effect” whereby a dramatically enhanced recognition of other “guest” molecules by these macrocyclic “host” molecules can be achieved with respect to the acyclic hosts toward the same “guest” molecules. Creative utilization of this macrocyclic effect has led to many useful applications in such as catalysis, sensor development, novel separation technology and even new pharmaceuticals.

Traditionally, to arrive at this magic “macrocyclic effect”, molecules called macrocyclic repeating units are covalently connected to each other in a sequential manner by many steps of organic reactions after a lengthy separation process and purification over an extended period of time to first form a linear precursor molecule, which further undergoes the last step of an intramolecular head-to-tail cyclization to produce a macrocyclic product. The whole process occurs in a way akin to a typical industrialized assembly line. However, differing from the highly efficient assembly line nowadays, the head-to-tail macrocyclization at the molecular level is entropically highly disfavored. This largely accounts for the low yield production of the desired macrocycles along with an observation of many unwanted products, including linear/cyclic intermediates of various lengths, a reason why such a cyclization reaction has to be carried out under conditions of high dilution.¹

To diminish this entropic penalty, various strategies have been developed.¹ The most noteworthy ones include conformation-directed and hydrogen bonding-assisted macrocyclizations. For the former, a curved backbone is designed into macrocyclic repeating units. The more units incorporated, the more curved the resulting molecular backbone until it reaches a point where the two terminal reactive sites are placed within reacting distances, leading to an efficient macrocyclization reaction that prevents the chain from overgrowth. For the latter, non-covalent hydrogen bonds formed between electron rich atoms (e.g. oxygen) and electron deficient atoms (e.g hydrogen) are utilized to lock the resulting molecular backbones into a crescent shape. This conformational “locking” by hydrogen bonds can dramatically improve the macrocyclization efficiency as demonstrated by Gong.^{3j} The hitherto reported examples on both categories and others are still very limited, and critical challenges remain in the efficient construction of macrocycles with precise control over the ring sizes and variable functionalizations around the periphery of the macrocycle.

In our effort to at least partly alleviate the above challenges and after extensive research, recently we successfully discovered phosphoryl trichloride, POCl₃, as a powerful macrocyclization reagent for selectively promoting one-pot

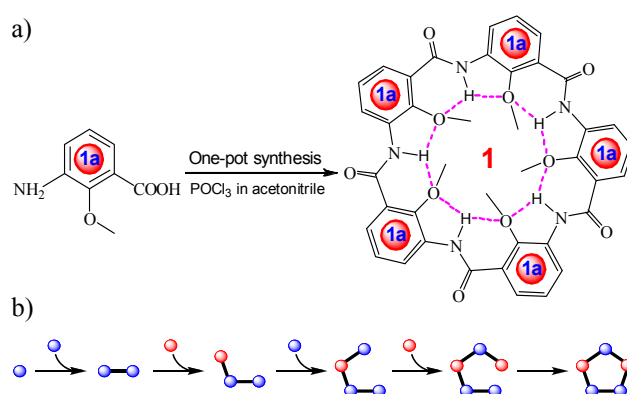


Figure 1. a) Under suitable conditions, five molecules of monomer **1a** can assemble circularly into one molecule of pentamer **1** via the intramolecular hydrogen bonds (dotted purple lines) among oxygen and hydrogen atoms. b) A chain-growth mechanism underlying the one-pot formation of five-residue macrocycles in a).

synthesis of aromatic pentamer **1** from its monomeric units **1a** (Figure 1a).^{3a} That is to say, five molecules of **1a** can be simultaneously assembled in a circular fashion via forceful intramolecular hydrogen-bonds (Figure 1a) to form a giant macrocyclic molecule of **1** in just one reactor within a few hours and with a very good conversion yield of 44%. This greener one-pot protocol compares very favorably with the fact that the same molecule was previously made by us after more than 15 steps in about 2-5% yields after months’ effort.^{4a} Even more interestingly, our continued exploration reveals further that POCl₃ also selectively produces hybrid five-residue macrocycles comprised of building blocks that differ from **1a** by their exterior side chains.^{3b} The formation of these variable hybrid pentamers is a direct demonstration of a chain-growth mechanism and variable functionalization around the pentameric periphery (Figure 1b). To the best of our knowledge, we are not aware of any other macrocyclic systems that allow specific hybrid macrocycles containing variable repeating units to be prepared via one-pot comacrocyclization as the major product that is determined predominantly by a chain-growth mechanism rather than more or less by a statistical distribution pattern. Suitable modifications of these pentagon-shaped molecules around their modifiable interior and exterior may promise some good applications in chemistry, materials sciences and biology.⁴

References

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