

# Making molecular nanotubes by cross-linking stackable rings

Discrete chiral nanotubes have been synthesized with high efficiency by connecting rim-desymmetrized macrocycles through dynamic covalent linkages. These 2-nm long and 4.7-Å wide helical covalent organic pillars, resolved by chromatography and characterized by X-ray crystallography, show strong binding affinities for linear guest molecules with complementary lengths and electronic densities.

## This is a summary of:

Tian, Y. et al. Synthesis of covalent organic pillars as molecular nanotubes with precise length, diameter and chirality. *Nat. Synth.* <https://doi.org/10.1038/s44160-022-00235-w> (2023).

## Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Published online: 13 February 2023

## The problem

Nanotubes are attractive architectural motifs with potential applications in molecular recognition, separation, catalysis and cross-membrane transportation, as well as in the fabrication of nanoelectromechanical devices. Nonetheless, their nanotechnological applications are often hindered by their lack of well-defined structures. The bottom-up construction of atomically precise nanotubes is the key to unlocking their interior confined spaces. However, although stacking ring-shaped building blocks in a controlled manner through rational design and synthesis represents a straightforward approach to producing hollow tubes, the execution of such a strategy on the molecular level remains challenging. Indeed, not only must the individual macrocyclic components first be produced with appropriate shape, symmetry and chemical composition, but these nanorings have to then be accurately stitched together with stable linkages and in high efficiency. Furthermore, the full characterization of the structure and the associated properties of molecular nanotubes can be non-trivial.

## The solution

Inspired by the synthesis of covalent organic frameworks<sup>1</sup>, in which organic building blocks with judiciously selected geometries are connected by dynamic covalent chemical bonds, we envisioned that single molecular nanotubes could be made by stacking pillararene-based ring components<sup>2</sup> through reversible imine condensation reactions<sup>3</sup>. Pillararenes, consisting of aromatic units linked by methylene groups at the para positions, possess the ideal polygonal hollow prism shape for constructing double open-ended tubes; nonetheless, their two identical rims decorated with alkoxy groups are not suitable for constructing discrete assemblies. To create a stackable ring component, we first desymmetrized the pillar[5]arene scaffold, and subsequently added aldehyde handles exclusively on one rim. The resulting penta-aldehyde tiara[5]arene<sup>4</sup>, **p-formyl-T[5]**, was then reacted with *p*-phenylenediamine linkers through a [2 + 5] imine condensation reaction, affording the desired single molecular nanotubes, namely covalent organic pillars **COP-1** (Fig. 1).

By virtue of the covalent pre-organization of the ring-shaped precursor and the dynamic nature of the imine

linkages, the synthesis towards **COP-1** is highly efficient. In addition, the inherently chiral macrocyclic component shows narcissistic self-sorting during the condensation reaction, leading to the formation of a pair of helical **COP-1** nanotubes that can be resolved by employing a high-performance liquid chromatography system equipped with a chiral stationary phase. Most importantly, the decision to not include a long alkyl solubilizing group in our molecular design enabled the crystallization, and therefore unambiguous structural elucidation, of **COP-1**. X-ray crystallographic analysis showed that the twisted nanotubular structure of **COP-1** has a length of 2 nm and a diameter of 4.7 Å, while the one-dimensional interior channel has a void space of approximately 440 Å<sup>3</sup>.

## Future directions

The construction of **COP-1** opens a new avenue for the design and synthesis of deep-cavity synthetic hosts<sup>5</sup>. In addition to showing highly specific binding towards  $\alpha,\omega$ -disubstituted *n*-alkyl guests with both electron-withdrawing terminal groups and chain lengths above a critical value, the structurally precise **COP-1** nanotube grants easy access to the X-ray solid-state structures of their inclusion complexes. In a length-mismatched host–guest system, we observed that the alkyl thread inside the **COP-1** nanotube adopts an energetically unfavourable distorted gauche shape, which is reminiscent of the conformational changes often observed during the binding of flexible ligands by biological receptors.

Further studies on the confined space of **COP-1** will provide insight into the host–guest interactions within artificial molecular containers. So far, it is not clear if the helical channel of **COP-1** can distinguish enantiomeric guests with high selectivity. Moreover, synthetic efforts towards water-soluble analogues of **COP-1** will undoubtedly expand the scope of artificial biomimetic receptors.

Our work on covalent organic pillars presents a blueprint for constructing a broad range of nanotubular architectures, or even carbon nanotubes, with defined dimensions. Such advances will require further work on producing assorted rim-differentiated nanorings or nanobelts, as well as the development of synthetic methodologies to form highly reversible carbon–carbon bonds, potentially through metathesis.

**Andrew C.-H. Sue**

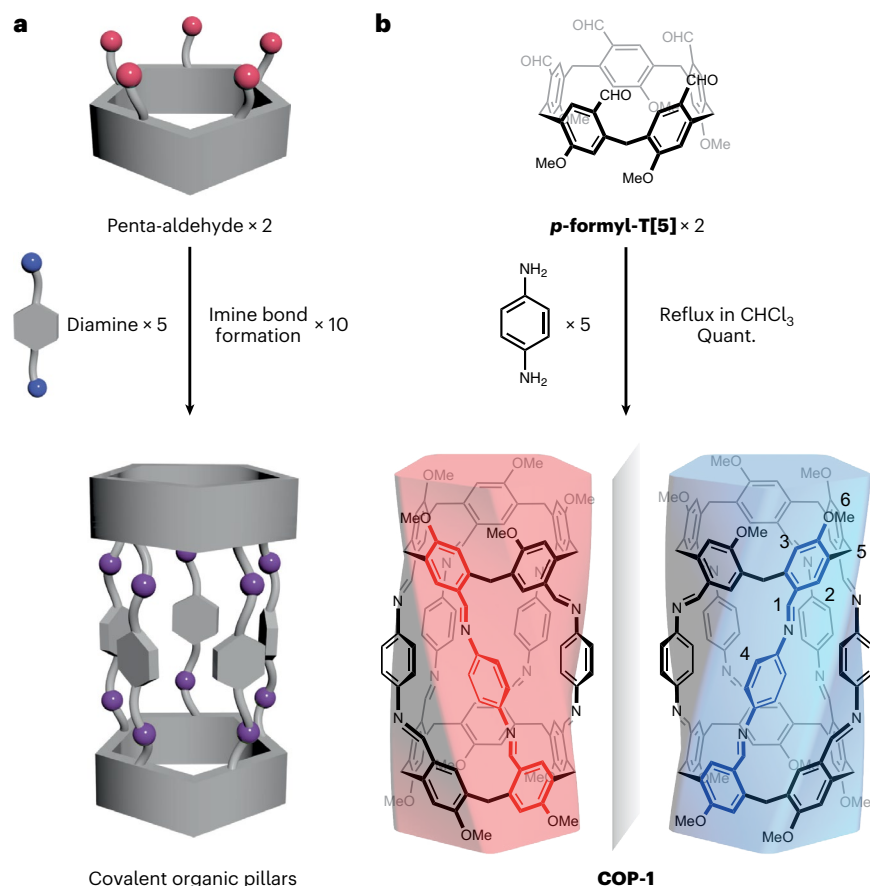
Xiamen University, Xiamen, China.

## EXPERT OPINION

“As well as the aesthetic appeal of the covalent organic pillar, the structure represents a potentially easily accessible complement to deep cavitands, which have

previously been the compounds of choice to encapsulate (disubstituted) alkanes.” **Max von Delius, Ulm University, Ulm, Germany.**

## FIGURE



**Fig. 1** | Design and synthesis of covalent organic pillars. **a**, Molecular design of our covalent organic pillars (COPs). **b**, Synthetic scheme for the formation of COP-1, involving the [2 + 5] imine condensation of *p*-formyl-T[5] macrocycles and *p*-phenylenediamine linkers. The reaction affords a pair of enantiomeric COP-1 nanotubes that can be later resolved by high-performance liquid chromatography. Quant., quantitative yield. © 2023, Tian, Y. et al. [CCBY 4.0](#)

## BEHIND THE PAPER

Overall, it has been a long and bumpy ride to get this research project to where it is today. After three years working on the synthesis of rim-desymmetrized macrocycles, we finally obtained our envisaged stackable rings by 2020. We subsequently set out to make the nanotube, but progress was severely impeded by the outbreak of COVID-19 and the many laboratory lockdowns throughout

the pandemic. Fortunately, two talented MSc students, Yaru Tian and Yunlong Guo, managed to get the project to the finish line with the assistance of the rest of the team. One eureka moment during the process was seeing the long-anticipated COP-1 nanotube crystal structure popping up on the monitor in the X-ray laboratory. **A.C.-H.S.**

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## FROM THE EDITOR

“This synthesis of these covalent organic pillars stood out because of the possibility of designing and making organic structures with cavities that can be used for catalysis or molecular recognition. The cavities have space to engulf long linear guest molecules and voids of around 440 Å<sup>3</sup>.” **Alison Stoddart, Chief Editor, Nature Synthesis.**