A class of organic cages featuring twin cavities

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A variety of organic cages with different geometries have been developed during the last decade, most of them exhibiting a single cavity. In contrast, the number of organic cages featuring a pair of cavities remains scarce. These structures may pave the way towards novel porous materials with emergent properties and functions. We herein report on rational design of a three-dimensional hexaformyl precursor 1, which exhibits two types of conformers, i.e. Conformer-1 and -2, with different cleft positions and sizes. Aided by molecular dynamics simulations, we select two triamino conformation capturers (denoted CC). Small-sized CC-1 selectively capture Conformer-1 by matching its cleft size, while the large-sized CC-2 is able to match and capture both conformers. This strategy allows the formation of three compounds with twin cavities, which we coin diphane. The self-assembly of diphane units results in superstructures with tunable proton conductivity, which reaches up to $1.37 \times 10^{-5}$ S cm$^{-1}$. 

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Conformational changes of small-molecule organic cages have been observed in the past few decades.

### Results

#### Design and characterization of the model compound

As briefly mentioned above, the region with the probability of containing formyl groups varies within the cleft of each conformer are determined by molecular dynamics simulations (see detailed MD simulation in Supplementary Fig. 10), which shows that molecule I exists in a single conformational form via all possible C–C single bond rotations. This conformation is stabilized by a hydrogen bond, and the latter has a higher rotational energy barrier (Supplementary Fig. 9). It, therefore, leads to the formation of two types of conformers, Conformer-1 and -2 (Figs. 1 and 2a). It reveals that Conformer-1 exhibits two clefts below and above the central arene, in each of which three formyl moieties are outward positioned (right, Fig. 2a). The energy difference of the two conformers is extremely low (ca. 0.1 kJ mol\(^{-1}\), Supplementary Table 1 and Supplementary Fig. 9), indicating their fast interconversion, which could have been otherwise challenging to be distinguished by conventional analytical tools such as variable-temperature NMR\(^{23,24}\) and time-resolved spectroscopies\(^{25,26}\).

Accordingly, molecule I is synthesized by Pd(PPh\(_3\))\(_4\) catalyzed Suzuki–Miyaura cross-coupling reaction using commercially available molecule (2-formyl phenyl)boronic acid as reactant (51% five-step overall yield, see Supplementary Fig. 1 for details). The rapid averaging of its possible conformers is confirmed by variable temperature \(^1\)H NMR spectroscopy in CDCl\(_3\), with symmetric splitting patterns of all protons even at 223 K (Fig. 2b).

Its single crystals suitable for X-ray crystallography are obtained by slow evaporation of solvent from its chloroform solution, and molecule I only exists the conformation corresponding to Conformer-1 in the crystal structure (Fig. 2c), which is common for the conformationally labile compounds that often crystallize into the most efficient molecular packing\(^{27}\).

#### Conformation capturing with diphane formation

As the framework of cages can experience complex motions in space—including continuous bending, twisting, stretching, and shrinking, they also provide an excellent platform for the study of molecular conformation and topology\(^{21}\). By taking advantage of the dynamic and reversible nature of DCC, and facilitated by DFT calculation (vide infra), we choose CC-1 and -2 with flexible amine-capped chains and different sizes to tentatively capture the above-mentioned conformations of molecule I by error-checking imine formation (Fig. 3).

We first use the small-size CC-1, i.e., tris(2-aminoethyl)amine, to react with molecule I in the presence of Sc(OTf)\(_3\), with a molar ratio of CC-1:Sc(OTf)\(_3\):I = 2:1:0.6 in chloroform, and the reaction mixture is then subjected to reduction with NaHB(OAc)\(_3\) (15 equiv.), yielding the amine-containing product for easy purification (64% two-step overall yield, see Supplementary Fig. 4 for details). The resulting product is examined by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), \(^1\)H and COSY NMR, and single-crystal X-ray diffraction (SC-XRD). MALDI-TOF MS shows a single ion peak at \(m/z\) 1384.7883, corresponding to the expected product with the formula \(C_{98}H_{95}N_8\) (M + H\(^+\)) \(_{calc}\) for 1384.7708.

The single crystals suitable for X-ray analysis are obtained by slow evaporation of endo-\([1,2,4]\)diphane solution in THF with additional trifluoroacetic acid (TFA) for better solubility. endo-\([1,2,4]\)Diphane crystallizes into triclinic space group \(P\) and unambiguously reveals only one isomer corresponding to Conformer-1 (Fig. 4a), in which the central arene is shared by two identical cavities. As this twin-cavity cage-like compound is composed of aromatic units and aliphatic chains, we, therefore, name it diphane. This molecule is given a systematic name endo-\([1,2,4]\)diphane, where “endo” indicates the central arene is embedded within the twin cavities, “1” refers to the number of central benzene rings, “2” denotes the number of aromatic units of every rigid arm, and “4” counts the backbone atoms forming each flexible chain. Due to the significant intramolecular strain, the aliphatic chains are twisted in an irregular fashion. The twisting of these three chains is highly uneven (Fig. 4b), in agreement with the complex yet distinct splitting of each proton in the \(^1\)H NMR spectrum (Fig. 4c). In addition, the X-ray structure of endo-\([1,2,4]\)diphane shows that the tertiary amines on the aliphatic chains are not protonated, even with the presence of TFA. This is presumably due to the steric hindrance of the irregularly stretched amine moiety caused by the rigid strain conformation, as well as the electrostatic repulsion of the
neighboring TFA molecules (Supplementary Fig. 12). These results, therefore, indicate that our tethering strategy with conformer capturers provides an efficient way to "visualize" the flexible conformers in solution, with an added bonus of discovering the 3D structures with appealing topology with tunable materials properties (vide infra).

On the other hand, we fail to capture Conformer-2 by the formation of hypothetical exo-[1,2,4]diphane (see above), where "exo" indicates the central arene located outside the two compositional cages. This result therefore confirms the efficacy of our size-matching strategy, which theoretically rules out the formation of exo-[1,2,4]diphane, as the maximally stretched amines of CC-1 still cannot reach the three formyl groups within each cleft of Conformer-2 (vide supra, Fig. 1 and Supplementary Fig. 10).

We then employ the large-sized conformational capturer CC-2, namely tris(3-aminopropyl)amine, with one more carbon unit on each chain as compared to CC-1. The stoichiometric imination between CC-2 and molecule 1 followed by subsequent reduction yields two isolated products with the same ion peak at m/z of 1468.8496, corresponding to the expected diphane isomers with the formula C104H107N8 ([M + H]⁺ calcd for 1468.8647). To our delight, these two products are identified as endo-[1,2,5]diphane (59% two-step overall yield) and exo-[1,2,5]diphane (16% two-step overall yield) by SC-XRD and NMR spectroscopy (Fig. 4d–f, g–i, respectively, see Supplementary Fig. 5 for details). endo-[1,2,5]Diphane adopts similar conformation with exo-[1,2,4] diphane (Fig. 4d–f). On the other hand, exo-[1,2,5]diphane exhibits a dumbbell-shaped structure13,14, with the middle arene
Fig. 2 Conformational interconversion of molecule 1 and its identification by NMR spectroscopy and SC-XRD. a Fast interconversion of Conformer-1 and -2 with extremely low isomerization barrier. Free energy of each isomer is determined by DFT calculation (B3LYP-D3 in PCM with chloroform as solvent). b Partial variable-temperature $^1$H NMR spectra (500 MHz) of molecule 1 in CDCl$_3$, showing rapid averaging of its possible conformers even at low temperature. The broadening of peaks of molecule 1 at low temperatures is due to its decreased solubility. c Molecular structure of molecule 1 revealed by SC-XRD, only able to identify Conformer-1 in solid-state. Solvent molecules and hydrogen atoms are omitted for clarity. Carbon atoms are labeled in gray, and oxygen in red. Dashed lines are used to facilitate the inspection of the orientation of formyl groups.

Mechanistic study of conformation capturing and diphane formation. In order to investigate the mechanism of exclusive capturing of Conformer-1 with small-sized CC-1 in solution, we designed the control experiments (Fig. 5). The triformal model compound 2 is the half truncated version of molecule 1, which eliminates the formation possibility related to the conformation of endo-[1,2,4]diphan or endo-[1,2,5]diphan. It, therefore, enables the direct inspection of the size effect of conformation capturers CC-1 and CC-2. When small-sized CC-1 is used, the formation of Cage-1 can only be detected by mass spectroscopy but not by NMR, which is presented here with its optimized structure by DFT calculation (Fig. 5); while Cage-2 is formed with large-sized CC-2 under the same reaction conditions (see Supplementary Fig. 3 for details). The single crystals of Cage-2 confirms its expected structure. The strain energies (SE) of both products are also examined, and it shows that Cage-1 exhibits a much higher stain as compared to Cage-2 (48.00 vs. 36.96 kJ mol$^{-1}$, Fig. 5). Besides, the rigid arm of the optimized Cage-1 is significantly bent with a torsion angle of $\tau_1 = 174.66^\circ$, while the arm of Cage-2 is much closer to the loose conformation with $\tau_1 = 176.57^\circ$. This high strain of Cage-1 presumably prevents its formation, which is also true as for exo-[1,2,4]diphan.

To gain further insight into the capturing process between Conformer-1 and -2 with the larger capturer CC-2, the kinetic experiment is carried out with $^1$H NMR at 298 K in CDCl$_3$ without reduction of the resulting imine bonds (Fig. 6a). Initially, all possible conformers of molecule 1 interconvert rapidly in solution, and the $^1$H NMR spectrum displays average splitting before the addition of CC-2 at 0 h. Upon addition of CC-2, the intensities of $H_A$ and $H_B$ of molecule 1 decrease steadily with time until their complete disappearance after four hours. Meanwhile, two groups of characteristic peaks, respectively, colored in light blue and red, emerge and gradually increase until the plateau at 4 h.

The peaks in light blue represent the formation of the imine form of endo-[1,2,5]diphan, denoted endo-[1,2,5]diphan', of which $H_C$ is the proton of shiff base and $H_D$ the aromatic proton adjacent to $H_C$. The peaks in light red are assigned to the imine form of exo-[1,2,5]diphan, namely exo-[1,2,5]diphan', of which $H_C'$ corresponds to the proton of shiff base and $H_D$ the aromatic proton in the immediate vicinity of $H_C'$. The evolution profile illustrates that the consumption of molecule 1 occurs simultaneously with the formation of two diphane isomers until the equilibrium, which has a product distribution of 75% endo- and 25% exo-[1,2,5]diphan', respectively. In addition, a parallel study shows that endo-[1,2,4]diphan' can be transformed to endo-[1,2,5]diphan' and exo-[1,2,5]diphan', when additional large-sized CC-2 is charged into the reaction mixture (Supplementary Fig. 8). It clearly indicates that endo- and exo-[1,2,5]diphan' are thermodynamically more stable than endo-[1,2,4]diphan'.

These results are in line with DFT calculations of SE and torsion angle of each amine form of diphane (Supplementary Fig. 11). The SE of exo-[1,2,4]diphan is the highest with 102.13 kJ mol$^{-1}$, larger than 96.38 kJ mol$^{-1}$ for endo-[1,2,4]diphan, and exo-[1,2,4]diphan is significantly bent with the smallest torsion angle of $\tau_1 = 174.12^\circ$, smaller than 175.04$^\circ$ for endo-[1,2,4]diphan. When using the large-sized CC-2, the SE values of the resulting diphanes are considerably lower, with
67.33 kJ mol$^{-1}$ for \textit{endo}-\{1,2,4\}diphane, and 77.00 kJ mol$^{-1}$ for \textit{exo}-\{1,2,5\}diphane, respectively, echoed with their corresponding torsion angles.

Proton conduction is an essential procedure in biology and proton-exchange membrane fuel cells\textsuperscript{27,28}. As our diphanes contain amine moieties, which can efficiently host protic acids and eventually crystallize into proton-conducting porous crystals. We, therefore, encapsulate TFAs into the crystalline superstructures of the three diphanes (denoted as diphanes–TFA) and evaluate their performances of proton conduction (Fig. 7). As determined by SC-XRD, \textit{endo}-\{1,2,4\}diphane and \textit{endo}-\{1,2,5\}diphane exhibit similar geometry, i.e. sandglass-shaped structure (Fig. 7a, c). However, their self-assembled superstructures are remarkably different. \textit{endo}-\{1,2,4\}Diphane molecules are closely packed, and it provides no clear transportation channels for protons hopping (Fig. 7b), where TFA molecules are trapped within the intrinsic and extrinsic cavities of the diphanes. In contrast, \textit{endo}-\{1,2,5\}diphane self-assemble into a crystalline phase with ordered channels (highlighted with red column) that allow the transportation of protons (Fig. 7d). \textit{exo}-\{1,2,5\}Diphane adopts a dumbbell-shaped geometry, and its corresponding superstructure also exhibits protons channels (Fig. 7f). Compared to the superstructure of \textit{endo}-\{1,2,5\}diphane–TFA with ordered channel ($d_1 = 6.7$ Å), the diphane molecules in \textit{exo}-\{1,2,5\}diphane–TFA are packed more tightly, and form zig-zag and narrower channels ($d_2 = 4.7$ Å), which might hinder the transportation of protons.

We subsequently measure the proton conductivity of these superstructures at 303 and 333 K, respectively, with a relative humidity (RH) of 48% (Table 1). Regardless of the geometry of diphanes, their proton conductivity increases smoothly with temperature (Supplementary Table 7), in line with the behaviors of previously reported porous materials\textsuperscript{29,30}. Although the exact location of water molecules within these superstructures is currently uncertain, their activation energies are lower than 0.4 eV, indicating the proton conduction was realized via the Grotthuss mechanism, where protons are hopping within the channels through interconnected hydrogen bonding\textsuperscript{30,31}. In addition, the dynamics of diphane–TFA are further investigated through various solid-state NMR (ssNMR) spectra\textsuperscript{32,33}. It is found from the comparison of the single-pulse $^1$H MAS and dipolar-based 1D $^1$H DQ/SQ NMR spectra (Supplementary Fig. 22), where the protonic peaks of diphanes–TFA are almost suppressed, while the rigid protons remained in 1D $^1$H DQ/SQ NMR spectra. These results clearly indicate that the –NH$_2^+$ related protons of diphanes–TFA are highly mobile, whose dipolar interactions are remarkably reduced by molecular motions. Furthermore, the conductivities of diphanes are significantly enhanced by doping with additional TFA (Supplementary Fig. 17), where the increased number of protons acting

![Fig. 3 Conformation capturing of molecule 1 leading to the formation of three diphanes with twin cavities. Schematic representation of conformation capturing of two conformers, i.e., Conformer-1 and -2 of model compound 1 among its infinite interconvertible conformers in solution, achieved by dynamic and reversible cycloimination and subsequent reduction. Small-sized conformer capturer CC-1 (presented in blue) exclusively captures Conformer-1, leading to the formation of \textit{endo}-\{1,2,4\}diphane. Large-sized CC-2 (showed in green) captures both Conformer-1 and -2, yielding \textit{endo}-\{1,2,5\}diphane and \textit{exo}-\{1,2,5\}diphane, respectively.](https://doi.org/10.1038/s41467-021-26397-3)
as charge carriers are essential to the formation of excess protons in the hydrogen bond network, facilitating the proton conduction\textsuperscript{34}. More importantly, the proton conductivity clearly depends on the packing of diphanes in their crystalline phases. The superstructure formed by endo-[1,2,4]diphanes–TFA without apparent channel exhibits the lowest proton conductivity at $2.44 \times 10^{-9}$ S cm$^{-1}$. This conductivity is significantly enhanced by the formation of proton channels, particularly for endo-[1,2,5] diphanes–TFA with the widest and most ordered channels, which reach up to $1.37 \times 10^{-3}$ S cm$^{-1}$, $\sim 1 \times 10^{3}$ times higher than bulk water\textsuperscript{29,35}.

**Discussion**

In the current study, we develop a size-matching strategy to identify and distinguish the interconverting conformational isomers that are otherwise difficult to be distinguished by conventional analytical tools. The proof-of-concept hexaformyl model compound 1 exhibits infinite conformers that fall into two types of conformers, namely Conformer-1 with a pair of upper and lower clefts and Conformer-2 with a pair of left and right clefts. As revealed by molecular dynamics simulations, the sizes of clefts are different for the two conformers. By making the most of the dynamic and reversible nature of cycloimination, we choose two triamino conformation capturers, i.e., CC-1 and -2 with different sizes to match and chemically tether the two conformers with different-sized clefts. It facilitates their retrospective differentiation by conventional NMR and X-ray analysis. This method allows us to discover three cage-like compounds with twin cavities, denoted diphanes. The sandglass-shaped endo-[1,2,4] diphanes and endo-[1,2,5] diphanes have two interconnected pockets by sharing a common aromatic vertex, while the dumbbell-like exo-[1,2,5] diphanes exhibit two individual apertures connected by a joint benzene ring. This method opens up avenues for the discovery of 3D molecules with exotic geometries and cavities. These molecules with unique shapes and configurations may be used as...

![Fig. 4 Molecular structures of three diphanes determined by SC-XRD and $^1$H NMR spectroscopy.](image)
**Fig. 5** Inspection of size effect of conformation capturers CC-1 and CC-2 with model compound 2. Small-sized CC-1 (blue) fails to form Cage-1, which is presented here with a geometry optimized structure (DFT, B3LYP-D3 in PCM with chloroform as solvent); While CC-2 (green) succeeds in yielding Cage-2, with its molecular structure determined by X-ray crystallography. Hydrogen atoms and solvent molecules are omitted for clarity. The insets show the enlarged rigid arm of the two cages, revealing their torsion angles and the corresponding strain energies, respectively.

**Fig. 6** $^1$H NMR study of the conformer capturing the progress of Conformer-1 and -2 with large-sized CC-2 as a function of time. a The $^1$H NMR spectra indicate that Conformer-1 and -2 are captured simultaneously with CC-2. b The evolution profile of molecule 1 in gray, endo-[1,2,5]diphane$'$ in blue and exo-[1,2,5]diphane$'$ in red, determined by the ratios of integral areas of the corresponding characteristic peaks with the internal reference peak of dioxane. $H_A$ represents the proton of aldehyde group of molecule 1, $H_B$ the nearest proton to $H_A$, $H_C$ the proton of Schiff base of endo-[1,2,5]diphane$'$, $H_D$ the nearest proton to $H_C$ on the rigid part of the molecule; $H_{C'}$ and $H_{D'}$ the corresponding protons of exo-[1,2,5]diphane$'$.
supramolecular synths for the construction of hierarchical superstructures\textsuperscript{36–38} with tunable properties. For example, here we show that self-assembly of diphanes results in superstructures with tunable proton conductivity. Structural differences on the diphane structure lead to different molecular packing and distinguished extrinsic channels of the corresponding superstructures. As a result of the structural changes, the conduction efficiency is enhanced up to 1000-fold. This structure–property correlation might provide a reasonable design principle for proton-conducting materials. Other potential applications of diphane-based materials related to ferroelectricity, selective separation and catalysis, are currently ongoing in our laboratories. Finally, the self-assembly approach reported herein is also suitable for preparing the cage-like compounds with two different pockets, denoted Janus diphanes, which we will report in due course.

Table 1 The proton conductivity ($\sigma$) of diphanes–TFA at 303 and 333 K, and their corresponding activation energy ($E_a$) at a relative humidity of 48%.

| Diphane–TFA | $\sigma$ (S cm$^{-1}$) | $E_a$ (eV) |
|-------------|---------------------|-------------|
| endo-[1,2,4]diphane–TFA | 1.50 × 10$^{-9}$ | 0.14 |
| endo-[1,2,5]diphane–TFA | 3.17 × 10$^{-6}$ | 0.39 |
| exo-[1,2,5]diphane–TFA | 1.00 × 10$^{-8}$ | 0.15 |

Methods

General information. Dimethyl terephthalate, tetakis(triphenylphosphine)palladium, phenyl lithium, Scandium(III) trifluoromethanesulfonate, tris(2-aminoethyl)amine, aniline are purchased from Beijing J&K Chemical Co. Ltd. 2-Formylbenzenephosphonic acid and tris(3-aminopropyl)amine are purchased from Beijing InnoChem Co. Ltd. All other reagents are bought from commercial sources and used without any purification unless stated. Tetrahydrofuran is dried over sodium/benzophenone under a nitrogen atmosphere before use.

Synthesis of model compounds. Model compounds 1 and 2 are synthesized by Pd(PPh$_3$)$_4$ catalyzed Suzuki–Miyaura cross-coupling reaction with commercially available molecule (2-formyl phenyl)boronic acid as a reactant, detailed procedures are shown in the Supplementary Information.

Fig. 7. The comparison of the molecular structure of three diphanes with the presence of TFA, their self-assembled superstructures with different proton-conducting channels. Molecular structures of a endo-[1,2,4]diphane, c endo-[1,2,5]diphane, and e exo-[1,2,5]diphane determined by SC-XRD, and their corresponding superstructures shown in b, d, and f. b Trifluoroacetic acid (TFA) molecules are trapped within the windows of endo-[1,2,4]diphane, whose superstructures exhibit no intermolecular channels. The intermolecular channels highlighted in red are present in the superstructures formed by d endo-[1,2,5]diphane and f exo-[1,2,5]diphane, respectively, providing the mobility of TFA molecules. TFA molecules are highlighted with bold stick model, with fluorine atoms labeled in green, oxygen in red, and carbon in gray.
endo- and exo-[1,2,5]diphane. Into a 100 mL flask is charged via www.ccdc.cam.ac.uk/data_request/cif. The data supporting the findings of this study are available within the article, its Supplementary Information, or from the corresponding authors upon reasonable request.

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**Author contributions**
Z.Y. and S.Z. conceived and designed this work. Z.Y., P.L., J.C., K.J.W. Q.-Y.Z. and X.L. performed the experiments. Z.Y. and S.Z. wrote the manuscript. C.Y. contributed to the theoretical calculations. J.D. and X.Z. contributed to the measurement of proton conductivity. H.L. and Y.Y. conducted the PXRD experiments. L.C., Y.-Q.Z. and S.Z. discussed the results and participated in the preparation of the paper.

**Competing interests**
The authors declare no competing interests.

**Additional information**

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