

# Access to Amide-Linked Organic Cages by in situ Trapping of Metastable Imine Assemblies: Solution Phase Bisamine Recognition

Keith G. Andrews<sup>\*,[a]</sup> and Kirsten E. Christensen<sup>[a]</sup>

**Abstract:** Molecular cages are sought after as receptors and catalysts. However, typical dynamic covalent chemistry approaches restrict the shape-persistence, solubility and stability of self-assembled organic cages. As a result, organic cages occupy a narrow chemical and functional space, and solution-phase applications and studies remain rare. We report an in situ trapping protocol, using Pinnick oxidation conditions, to convert *soluble* metastable imine assemblies to robust amide cages, and exemplify the method to access

previously inaccessible organic cages. The new cages are internally functionalised with two constrained and diametrically opposed carboxylic acid groups that can distinguish between functionalised piperazines in THF. We anticipate our approach will broaden access to robust, soluble, self-assembled organic cages of an unsymmetrical or semi-flexible nature, which in turn will drive advances in solution-phase applications of molecular cages.

## Introduction

Organic cages are covalent polycyclic scaffolds featuring a cavity in which guest binding or catalysis might occur.<sup>[1–4]</sup> Cages can be assembled in a traditional step-wise manner, or by dynamic covalent chemistry (DCvC) self-assembly<sup>[5]</sup> from appropriate starting fragments (Figure 1A). Step-wise synthesis can produce strained, soluble, functionalised and asymmetric structures for high impact solution-phase applications,<sup>[6–11]</sup> at the cost of more intense labour or statistical separations. In contrast, DCvC is advantageous for modular cage library generation in high yields, with lower dependence on bespoke templates or statistical separations. However, DCvC requires relatively rigid precursors,<sup>[12–16]</sup> directional bonding,<sup>[17]</sup> reversible bond formation<sup>[5]</sup> (commonly imine bonds<sup>[1]</sup>), and some kinetic or thermodynamic driving force<sup>[1,18]</sup> to aid isolation. Most organic cages are isolated by precipitation and applied in the solid state as adsorbents.<sup>[1,19–21]</sup> Precipitation may be a natural kinetic driving force (for cages with low-solubility),<sup>[22–26]</sup> or can be triggered by addition of an anti-solvent (for stable cages whose solubility comes from rotatable bonds<sup>[1,27,28]</sup>). Either way, self-assembled organic cages occupy a narrow chemical space (Figure 1A) which, along with the labile nature of imine bonds, restricts solution-phase application<sup>[29,30]</sup> and hinders post-func-

tionalisation. To address these limitations, the group of Mastalerz has an extensive and successful programme in the post-functionalisation of labile self-assembled imine cages to yield stable cages.<sup>[14,23,31–36]</sup> Many of these procedures maintain or improve the shape-persistence of imine cages, unlike reductive procedures (Figure 1Aii),<sup>[28,29,37–41]</sup> which introduce structural flexibility that can vitiate cavity properties.<sup>[39]</sup> To address the lability of imine bonds without introducing flexibility, adapted<sup>[42,43]</sup> Pinnick oxidation<sup>[44,45]</sup> conditions have been used by Yaghi<sup>[46]</sup> and Cui<sup>[47]</sup> to convert imine COFs to amide COFs, and applied to imine cages by Mastalerz.<sup>[33,35]</sup> In each of these examples, stable imines are first isolated by precipitation or crystallisation, and resubjected to oxidation (Figure 1B). The resulting cages are therefore still reliant on relatively low solubility and a stabilising driving force (e.g. phenolic hydrogen bonding) (Figure 1Ai). In one case, alkoxy chains were added to shape-persistent cages, which improved their solubility for solution phase study.<sup>[26]</sup> Nonetheless, the reactivity of phenol and imine groups hinders further chemistry and application.<sup>[36]</sup>

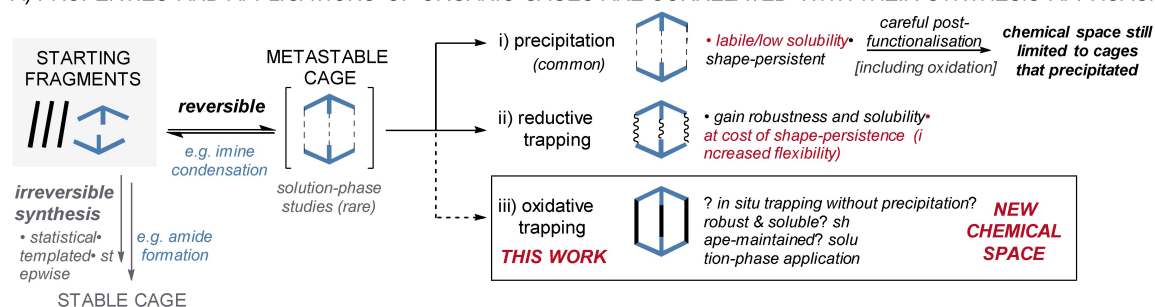
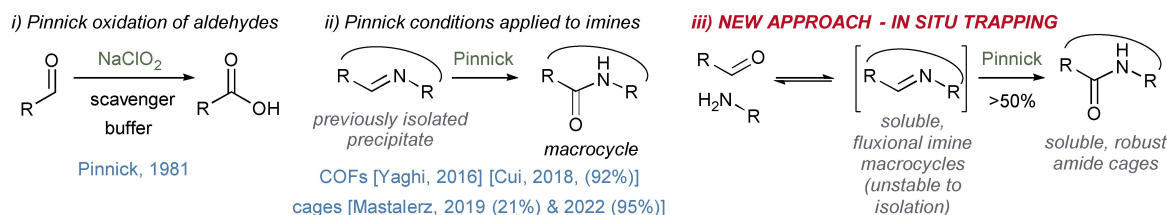
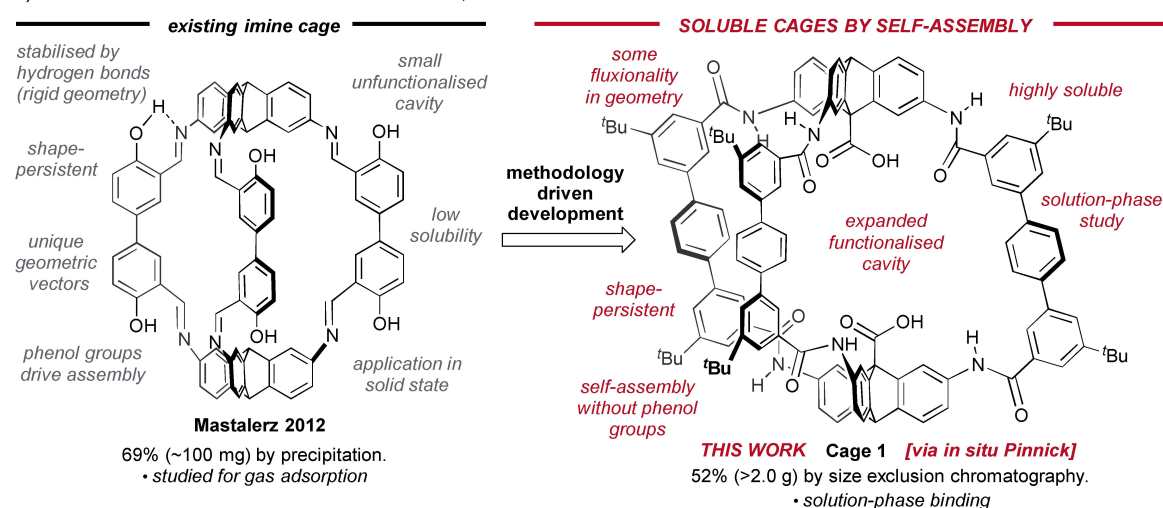
Our interest in the field of organic cages was inspired by the geometric potential of the [2+3] triptycene-based cages developed by Mastalerz and co-workers, which have applications as solid-state adsorbents (Figure 1C).<sup>[13]</sup> We were attracted by the unique directional vectors available to the triptycene units, hoping to develop them to solve challenges in solution-phase molecular recognition and catalysis. In our attempts to solubilise the cage, we found that it was no longer amenable to precipitation as the kinetic product - nor did our proposed cage emerge as the thermodynamic product. Herein, we report our solution to this fundamental restriction on soluble organic cage synthesis by self-assembly: the in situ trapping of transiently formed hexamine cages (Figure 1Aiii) using Pinnick oxidation conditions (Figure 1Biii).

[a] Dr. K. G. Andrews, Dr. K. E. Christensen  
Department of Chemistry  
University of Oxford  
12 Mansfield Rd, Oxford, OX1 3TA (UK)  
E-mail: keith.andrews@chem.ox.ac.uk

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## A) PROPERTIES AND APPLICATIONS OF ORGANIC CAGES ARE CORRELATED WITH THEIR SYNTHESIS APPROACH

B) METHODOLOGY DEVELOPMENT: *IN SITU* PINNICK REACTION TO TRAP UNSTABLE INTERMEDIATESC) EXAMPLE: DEVELOPMENT OF A SOLUBLE, FUNCTIONALISED ORGANIC CAGE REQUIRING *IN SITU* TRAPPING

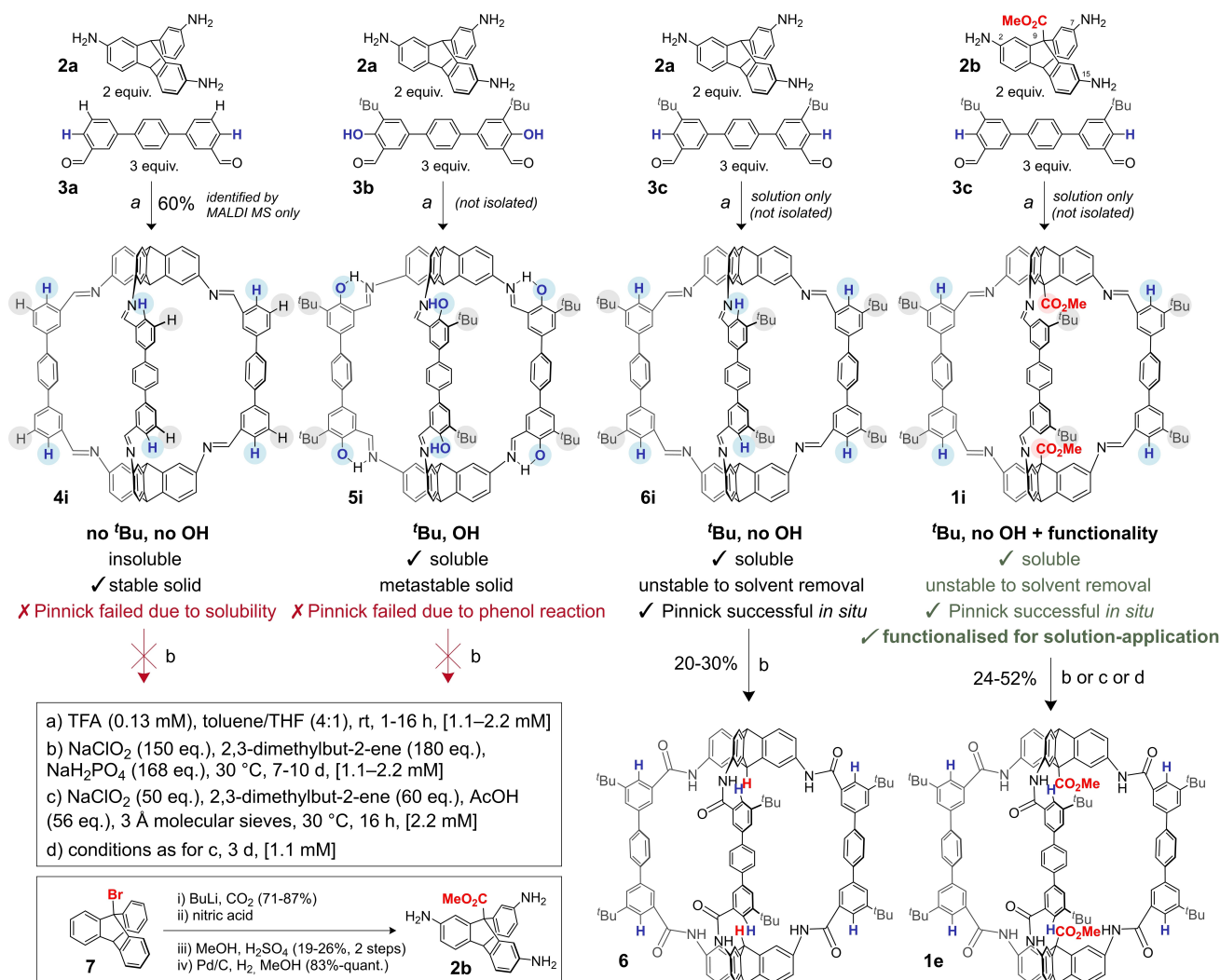
**Figure 1.** Development of an *in situ* trapping approach that allows insoluble or unstable imine cages to be converted into soluble, functional, robust amide cages for solution-phase application.

## Results and Discussion

## Cage synthesis is dictated by solubility &amp; stability

Initial experiments examined [2+3] imine cage formation by mixing triptycenes **2a–b** with bisaldehydes **3a–c** in a 2:3 ratio in the presence of a trifluoroacetic acid catalyst<sup>[23]</sup> (Scheme 1). Pursuit of undecorated cage **4i** yielded 60% mass recovery of a solid consistent by MALDI-ToF spectroscopy (Figure S2), but that was too insoluble to characterise by NMR spectroscopy,<sup>[21,48,49]</sup> and that failed to give the corresponding hexaamide cage using Pinnick oxidation conditions. Guided by the observations of Mastalerz and co-workers, we sought to use *ortho*-hydroxyl groups to enhance cage assembly<sup>[14]</sup> and *tert*-butyl groups to confer solubility (**5i**).<sup>[50,51]</sup> Although the *tert*-

butylated hydroxyl-containing hexamine cage **5i** is more soluble, only small amounts of solid could be accessed by precipitation, which showed moderate purity, even after GPC purification (some instability here). Transiently formed cage **6i**, meanwhile, proved unstable to solvent removal,<sup>[22,52]</sup> to filtration through potassium carbonate or magnesium sulfate, and to precipitation (e.g. with petrol, ether, etc). Although MALDI-ToF spectra indicated product formation, and analytical size-exclusion chromatography indicated dominant formation of a cage-sized material, only insoluble polymer could be isolated,<sup>[24]</sup> and we reached the conclusion that highly soluble and isolable imine cages of the type<sup>[53]</sup> pursued might be paradoxical.



Scheme 1. Access to soluble amide cages by imine self-assembly and in situ oxidative trapping by Pinnick oxidation.

### In situ Pinnick oxidation is required to access soluble, robust hexaamide cages

Instead of pursuing isolation of unstable imine cages, the crude solution containing non-phenolic *tert*-butyl cage **6i** and related oligomers was subjected directly to Pinnick oxidation conditions<sup>[43]</sup> by addition of oxidant (sodium chlorite), 2,3-dimethylbut-2-ene as a HOCl scavenger,<sup>[33]</sup> and acid (Scheme 1). (Hydroxyl-containing imine cage **5i** was not tolerant of Pinnick conditions, in agreement with other observations.<sup>[33]</sup>) To avoid competing imine hydrolysis (although see<sup>[53,54]</sup>), we initially trialled water-free oxidation conditions using NaH<sub>2</sub>PO<sub>4</sub> as the proton donor.<sup>[43]</sup> These reactions were slow and solvent sensitive (Table S1),<sup>[23,43]</sup> and the partially oxygenated intermediates were monitored by MALDI-ToF mass spectrometry over 7–10 days (Figure S3,S5). Pleasingly, hexaamide cage **6** could be isolated after GPC purification. Optimisation (Table S1) led us to acetic acid conditions<sup>[43]</sup> at higher dilution (1.1 mM) in the presence of molecular sieves, which lowered the reaction time to 16 h. Side-products include oxidised aldehyde monomers

(i.e. the corresponding dicarboxylic acid) and unidentified species slightly larger than the cage (determined by size-exclusion i.e. gel-permeation chromatography analysis, see for example Figure S4, S6–S16). In situ <sup>1</sup>H NMR monitoring of the imine cage formation step shows equilibrium within 2.5 h to a mixture with significant (~32%) aldehyde signals remaining (Figure S19). GPC analysis suggests these aldehydes signals are from unclosed oligomers of similar size to the cage. Longer reaction times or higher temperatures resulted in increased levels of the (larger) oligomers (Figure S8, S12). Thus, cage **1** is not the thermodynamically favoured product, and nor can it be kinetically trapped by precipitation,<sup>[18,23,25]</sup> due to its high solubility and the absence of stabilising phenolic hydrogen-bonds. Importantly, our conditions can operate at significantly reduced times and temperatures than those recently reported<sup>[35]</sup> by Mastalerz for previously precipitated material, vital for the oxidation of low-stability/kinetic assemblies. We therefore conclude that this in situ Pinnick oxidation strategy is a strong contender to allow meaningful access to cages existing on the cusp of stability in solution<sup>[53]</sup> – such an approach may be

particularly coveted for unsymmetric cages,<sup>[55–57]</sup> which precipitate with less reliability.

### Gram scale preparation of an internally functionalised cage

With a soluble cage synthesis approach in hand, efforts turned to accessing cages with internal functionalisation using carboxylic acid-functionalised triptycene **2b**. Such cages, we reasoned, might be active as molecular receptors or as catalysts.<sup>[58]</sup> A key factor in adapting the triptycene cages of Mastalerz was the excellent work in the development of 2,7,15-triamino-9-functionalised triptycenes reported by Chenoweth and co-workers.<sup>[59,60]</sup> We adapted this chemistry to convert triptycene **7** to **2b** (Scheme 1) finding it scalable, highly reproducible, and requiring of only one significant chromatography event (the separation of the nitration isomers). As originally noted,<sup>[60]</sup> the presence of a carboxylic acid at the 9-position directs nitration to the desired face, affording 19–26% yield after methylation (c.f. a statistical probability of 12.5%, lit. 30%<sup>[60]</sup>) (see Figure S1). Modified triptycene **2b** underwent the in situ Pinnick reaction (conditions d) to give >2.0 g dimethyl ester cage **1e** in 52% yield after purification by recycling GPC (12 bonds @ 95% efficiency per bond). The cage is very soluble in THF (>20 mg/mL) and DMSO, with moderate solubility in chloroform. We have yet to find crystallisation conditions to purify this cage directly from the reaction mixture.

### Crystal structure of **1e**

Single crystals of **1e** were grown by vapour diffusion of methanol into a solution of cage in THF (full refinement details are given in the Supporting Information (CIF)). Cage **1e** crystallised in the monoclinic space group  $P2_1/n$  with four molecules in the unit cell. In cage **1e**, four of the six amide carbonyl groups are pointing out of the cage, with the remaining two, at the top and bottom of two separate edges, pointing inwards (Figure 2). The cage maintains a shape-persistent cavity with the two carboxylic acid carbon atoms 8.8 Å apart ( $r_{cc}$ ) and wide windows (12.9 Å between the terphenyl axes).

### Hydrolysis of **1e** to give diacid cage

Imine cages are rarely stable to aqueous hydrolysis. In contrast, diester hexaamide cage **1e** is cleanly hydrolysed with aqueous sodium hydroxide in dioxane at 25 °C to provide the diacid cage **1**. We were able to synthesise this bench-stable, free-flowing solid cage **1** on a 2.0 gram scale (Scheme 2).

### <sup>1</sup>H NMR binding titrations of cage **1** with bisamine guests

Unlike imine cages, amide cages are expected to be stable in the presence of competitor amines. We therefore sought to probe if cage **1** might be a suitable receptor for piperazines.<sup>[61]</sup>

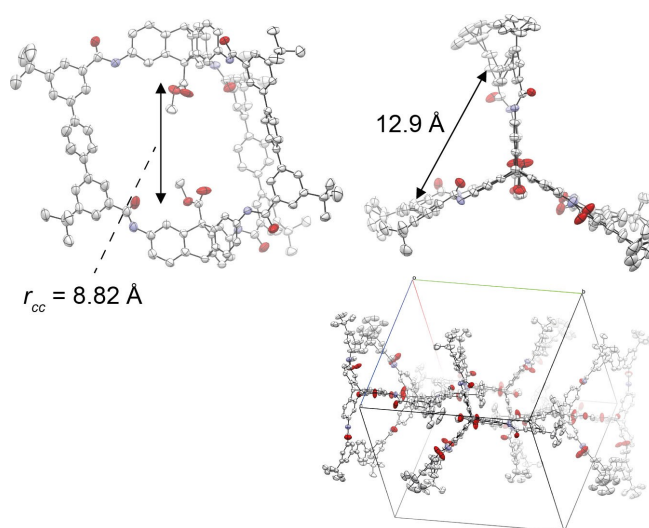
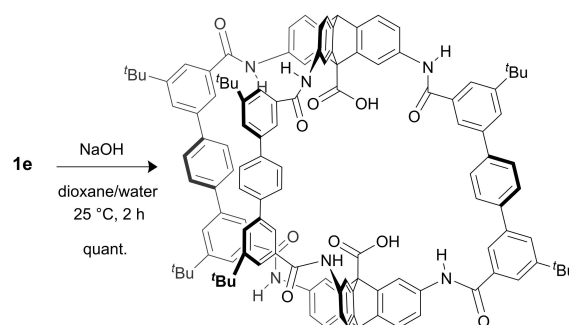


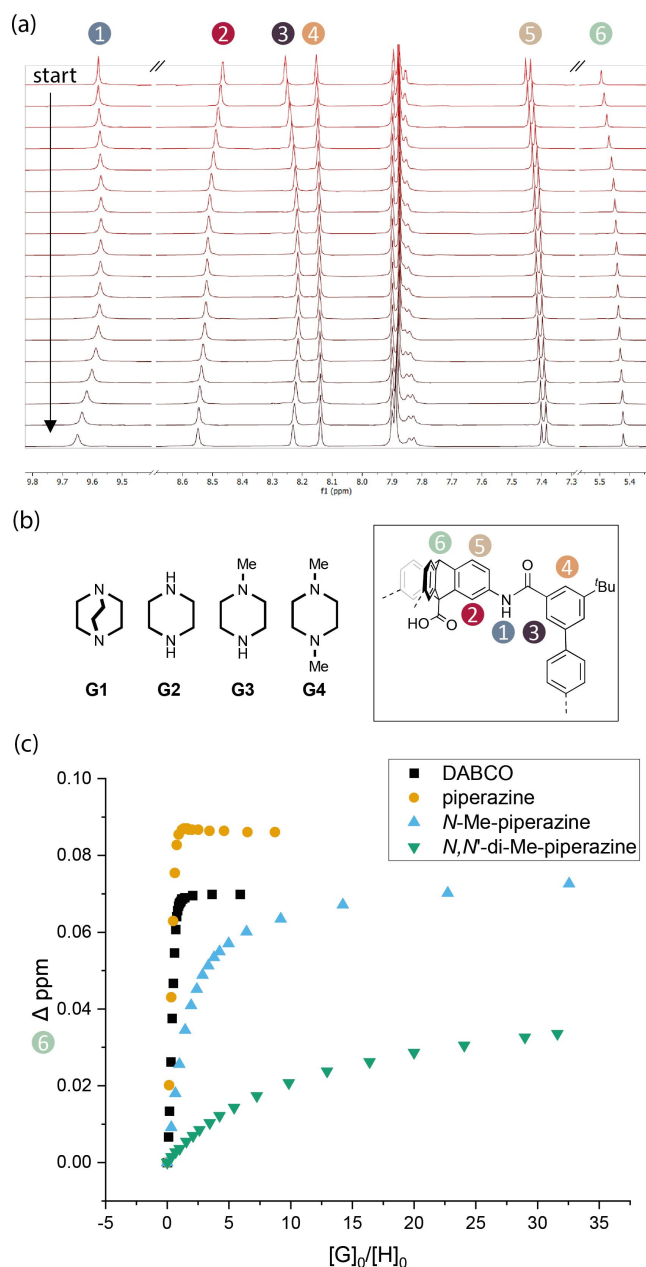
Figure 2. Crystal structure of cage **1e**.



Scheme 2. Amide cage **1e** undergoes hydrolysis to give biscarboxylic acid **1**. CORRECTION TO FIGURE 1: The bullet points for "labile/low solubility" have been corrected so there is a red bullet point for the red text, and a black bullet point for the black text. Also corrected for "at the cost of shape-persistence". In addition, a light blue box, which was present due to a copy paste error, has been deleted. It previously intersected the words "NEW CHEMICAL SPACE". These changes do not edit the size of the image.

<sup>1</sup>H NMR titration (298 K) in  $d_8$ -THF (Figure 3a, Figure S17) of guests **G1–4** (Figure 3b) at constant cage concentration (typically 0.2–0.6 mM) showed strong 1:1 binding (Figure 3c) for DABCO **G1** ( $K_a = 3.2 \times 10^5 \text{ M}^{-1}$ ), piperazine **G2** ( $K_a = 1.3 \times 10^5 \text{ M}^{-1}$ ), *N*-Me-piperazine **G3** ( $K_a = 1.6 \times 10^3 \text{ M}^{-1}$ ), and *N,N'*-dimethylpiperazine **G4** ( $K_a = 2.2 \times 10^2 \text{ M}^{-1}$ ), with a drop in affinity for each methyl group added. Fitting the data to a 1:2 model indicated a weak competitive binding of a second guest, with  $K_2 \sim 100$ -fold lower than  $K_1$  in all cases. <sup>1</sup>H NMR shows significant cage chemical shift changes on binding, but no new signals, indicating fast chemical exchange (Figure 3a, Table S6).<sup>[62]</sup> The triptycene bridgehead signal ( $H^6$ , Figure 3b) was relatively insensitive to the second binding event (Figure 3c, Figure S18). The bisacid binding motif of cage **1**, modelled after the lysozyme active site,<sup>[63]</sup> is reminiscent of the well-studied Rebek diacid clefts, which can engage bisamines in two-point binding<sup>[64]</sup> with  $K_a$  values typically between  $10^3$ – $10^5 \text{ M}^{-1}$  in a solvent uncompetitive for the acid groups ( $\text{CDCl}_3$ ).<sup>[65–69]</sup> Indeed,





**Figure 3.** (a) Example titration of hexaamide diacid cage **1** with **G3** in d<sub>8</sub>-THF; (b) Guests that bind in the diacid cavity of cage **1**; (c) Cage **1** distinguishes between differentially substituted piperazines in d<sub>8</sub>-THF solution.

the carboxylic acid C–C distances are very similar (cage **1**  $r_{CC}$  = 8.82 Å, cleft  $r_{CC}$  = 8.03 Å, crystal structures).<sup>[64]</sup> For the Rebek clefts, the primary literature<sup>[65]</sup> quotes DABCO as binding  $\sim 10^5$  M<sup>−1</sup>; *N,N'*-dimethylpiperazine is mentioned in passing as being “much less efficiently bound”<sup>[70]</sup> as the methyl groups cannot fit in the cleft. Unlike the U-shaped clefts, cage **1** has a well-defined cavity that can tolerate the extra space required for the methyl groups, and that could be elaborated for more specific recognition modes of larger substrates.

## Conclusion

We have reported the first approach to trap highly soluble and non-thermodynamic imine cages by in situ oxidation of meta-stable imine assemblies. The resulting amide cages are rare examples of self-assembled, shape-persistent, robust and soluble organic cages. Notably, we were able to access cages with expanded cavities and increased solubility by reducing the stability of the initially formed imine cages by removing the stabilising hydrogen bonds offered by phenol-groups. We demonstrated this new chemical space with three modes unexplored with imine cages: i) strong hydrolysis conditions to unmask carboxylic acid functional groups; ii) solution-phase binding studies in which we; iii) recognise bisamines that would pose an exchange threat for imine cages. Our protocol allowed gram-scale isolation of an internally functionalised cage with a pair of antipodally aligned carboxylic acids, which was a suitable receptor for piperazines ( $K_a = 10^{-2.5}$  M<sup>−1</sup>, d<sub>8</sub>-THF). We anticipate that this methodology will be applicable to other organic cage architectures that currently rely on kinetic precipitation, and that the ability to access more soluble, functionalised, and unsymmetric cages will result in a broadening of the applications available to self-assembled organic cages.

## Experimental Section

Full experiment details and procedures are available in the Supporting Information.

## Synthesis of cages **1 i** and **1**

**Imine cage 1 i:** In a 5 L flask containing 3 Å molecular sieves (15 g, vacuum dried), triptycene **2 b** (1.50 g, 4.20 mmol) was dissolved in THF (750 mL) and the solution diluted with toluene (1500 mL) containing trifluoroacetic acid (150 μL, 1.96 mmol). Separately, bisaldehyde **3 c** (2.51 g, 6.30 mmol) was dissolved in toluene (1500 mL) and the solution added to the main flask over 60 seconds. After stirring for 2 h at ambient temperature, analytical GPC and MALDI-ToF analysis indicated high conversion to the desired hexamine cage. Added was 2,3-dimethyl-2-butene (15.0 mL, 126 mmol, 60 eq), sodium chlorite (9.49 g, 105 mmol, 50 eq) and glacial acetic acid (6.73 mL, 118 mmol, 56 equiv.). The reaction was stirred vigorously in the dark for 3 d. The reaction was filtered to remove solids, quenched with aqueous sodium thiosulfate, and extracted three times with ethyl acetate. The organics were washed with aqueous sodium hydroxide (0.5 M) and brine, and the resulting organics purified in five batches by recycling gel-permeation chromatography (THF, 5 × 90 min cycles). The resulting tan solid was triturated with petrol/diethyl ether to remove impurities from the THF (gamma-butyrolactone, butylated-hydroxytoluene (BHT)) to give **1 e** as an off-white solid (2.09 g, 52% over two steps).

**Diacid cage 1:** Dimethyl ester cage **1 e** (2.09 g, 1.10 mmol) was dissolved in dioxane (120 mL) and added was an aqueous

sodium hydroxide solution (3.3 g, 41.3 mL, 2 M, 75 Eq, 82.6 mmol). The reaction was followed by TLC until complete (~1–2 h) and then cautiously quenched with dilute HCl until acidified. The mixture was extracted with ethyl acetate, and the organics washed with water and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting solid was triturated in pentane, and the desired cage **1** was collected by filtration and vacuum dried at 55 °C, 0.3 mbar (2.06 g, quant.).

Deposition Number(s) 2208379 (for **1e**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

## Additional reference annotations are available in the Supporting material.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are openly available in CCDC at <https://doi.org/10.5517/>, reference number 2208379.

**Keywords:** cage crystal structure • host–guest chemistry • molecular recognition • organic cages • Pinnick oxidation

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