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ORIGINAL ARTICLE

Synthesis of [2+2] Schiff base macrocycles by a solvent templating strategy and halogen bonding directed assembly

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Abstract

Schiff base imine condensations are a useful tool for macrocycle synthesis and applications within supramolecular chemistry. Here we address the mixtures of products that can arise from template free synthesis using dicarbonylheterocycles and diamines, and look to develop metal-free template methods for selective macrocycle formation. A range of alkyl α,ω-diamines were combined with phenanthroline and pyridine heterocyclic dicarbaldehydes under standard literature conditions. The reaction conditions were modified to demonstrate a relationship between choice of solvent and product equilibria. It was observed that benzene and toluene could shift a mixture of products and unreacted starting materials to form predominantly one imine product for a number of systems. Once the macrocyclic products had been characterized in selected solvents, iodinated halogen bonding guest molecules were added to direct macrocycle assemblies using non-covalent interactions. Studies to investigate host – guest suitability and halogen bond interactions were conducted, and it was found that tetraiodoethylene had an influence on the formation of a phenanthroline based macrocycle. Proof of concept experiments were performed to show the influence of the guest molecule, tetraiodoethylene, on the macrocyclic products formed under competitive dynamic combinatorial chemistry conditions.

Keywords Schiff base · Halogen bond · Host – guest · Solvent control · Templation

Introduction

Schiff base imine formation has been used for the preparation of macrocycles as a comparatively mild, facile, and simple procedure relative to other ring closing reactions, such as the Mukaiyama method [1], the Corey method [2], or Mitsunobu reactions [3]. The reversible imine bond has been further employed in the field of macrocyclic chemistry because it allows for investigation into templating, self-sorting, and dynamic covalent chemistry [4]. The majority of Schiff base macrocycle reactions use α,ω-diamines, with aliphatic linear diamines being particularly reactive towards imine formation because the amine groups can react separately. Despite being readily accessible, macrocycle synthesis is impeded by the formation of mixed products, oligomeric and polymeric products, or larger ring condensations (Fig. 1). Other studies have shown that although the [2+2] macrocycle is often the stated major product, [3 +3] and [4+4] condensation products are also common under template free synthesis conditions [5]. Without a template, the reactions typically produce oligomeric condensation products [6]. Often the [2+2] condensation product is the target molecule because of its symmetrical structure, size, and functionalisation. To afford this product, reaction conditions are modified by manipulating reactant concentrations, choice of solvents, and relative stoichiometric ratios to increase regioselectivity [7, 8]. The solvent must be polar enough to the dissolve the starting materials (which are typically more polar than the desired product), and for this reason, acetonitrile, methanol or ethanol are common choices [9]. The reaction is usually stirred for at least 12 h at room temperature until a precipitate is formed. Stoichiometric ratios and high dilutions ($\leq 10^{-3}$ M) are typically employed to reduce the intermolecular reactions that lead to oligomeric products [10–12]. The dynamic and reversible nature of the imine bond means that even if the precipitate is the desired [2+2] macrocycle product initially, it can readily change once redissolved [13]. The reaction is so robust that the combination of aldehyde and amine can be mechanically ground in solvent free conditions

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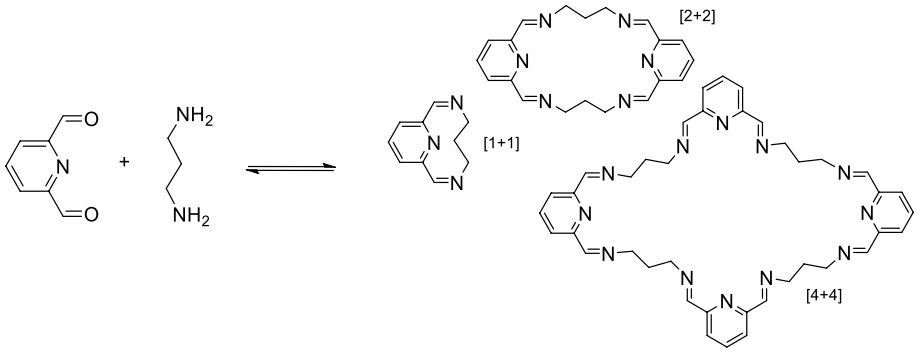


Fig. 1 Three examples of the many potential product outcomes for a Schiff base macrocycle reaction; pictured here are the [1+1], [2+2] and [4 + 4] macrocyclic products

and still produce an imine, yet the presence of additional water can quickly reverse the reaction [14].

Templation is a common technique used in macrocycle assembly. Typically, a metal cation is used to direct a particular size, arrangement, conformation, or geometry of the macrocycle [15–18]. The objective of the synthesis will determine if the template must be removed at a later stage. There has been interest in developing a metal-free template synthesis for Schiff base macrocycles. Although the literature methods suggest the formation of the [2+2] macrocycle is readily achievable, mixed and larger condensations are often reported, and additional purification can be difficult or time consuming [5, 19]. Other works have looked to overcome the need for cation templation, and instead used hydrogen bonding interactions to direct macrocycle assembly [20]. Non-covalent templation can be solely for the purpose of selective macrocycle assembly, but it also has direct applications within self-sorting and dynamic combinatorial libraries [7].

The manipulation and fine tuning of experimental conditions to control macrocyclic products has been explored in detail [21], and has provided insight into alternative methods for macrocycle templation. Prior studies have been able to demonstrate the impact of solvent selection on the size and conformations of Schiff base macrocycles [22, 23]. It has been shown that a co-solvent can control Schiff base macrocycles, converting a [2+2] macrocycle to [1+1] macrocycle when methanol is substituted with a mixed methanol – water solvent system [23].

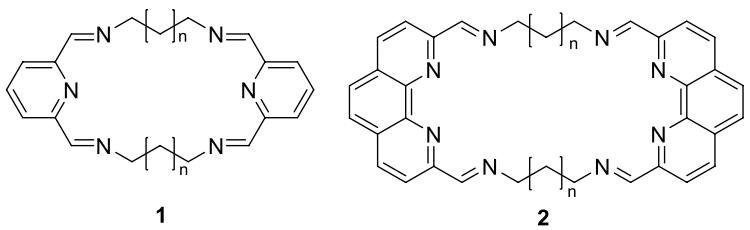
The addition of metal cations is often used to direct macrocycle formation, and it has been observed that the choice of metal and stoichiometry can be used to control macrocycle size [24]. A sandwich conformation of a previously flat octaaza Schiff base macrocycle was induced by forming the barium(II) complex [15]. In other studies, a covalent bonding template molecule has been shown to transform a mixture of imine products to a single macrocycle product [25].

The primary aim of our investigation was to control Schiff base macrocycle assembly using a halogen bond template molecule as an alternative to metal templation. During this investigation, it was observed that macrocycles could be selectively synthesized under two different methods of metal-free templation: the choice of solvent in which the dicarbaldehyde and diamine were combined; or through the addition of halogen bonding guest molecules that shifted macrocycle product distribution through non-covalent intermolecular interactions.

Results and discussion

Synthesis of Schiff base macrocycles

In this work we attempted to assemble a library of different sized macrocycles from 2,6-pyridinedicarboxaldehyde and 1,10-phenanthroline-2,9-dicarbaldehyde with different alkyl chain length α,ω-diamines (Fig. 2). The macrocycles **1c** and **2c** were initially synthesized according to the literature procedures for the condensation of 2,6-pyridinedicarbaldehyde or 1,10-phenanthroline-2,9-dicarbaldehyde and 1,4-diaminobutane [10, 26]. When analysed by ^{1}H NMR spectroscopy in deuterated chloroform ($CDCl_3$), mixtures of products were observed. The desired [2+2] macrocycle resonances were



1 **2**

1a, **2a** n = 0
1b, **2b** n = 1
1c, **2c** n = 2
1d, **2d** n = 3
1e, **2e** n = 4
1f, **2f** n = 5
1g, **2g** n = 6
1h, **2h** n = 10

Fig. 2 Structure and naming of target macrocycles

identified by comparison to those reported in the literature, but there was also a mixture of other macrocyclic products and starting materials present. Multiple synthesis attempts with modifications to concentrations, time and stoichiometry had no significant impact on the distribution of the observed products. Although this outcome differed to that reported in the literature synthesis, similar synthetic procedures when analysed by MALDI-TOF mass spectrometry have shown that many different sized macrocycles are present, ranging from [1 + 1] to [7 + 7] condensation products [22]. There are three types of diamines: aliphatic being the most flexible and nucleophilic; cycloaliphatic being nucleophilic but rigid; and aromatic, being rigid but less nucleophilic. The product outcome of Schiff base macrocycle formation can be unpredictable and is thought to be highly dependent on the nature of the diamine [22]. For example, the condensation of 2,6-diformylanisoles with *N*'-(2-aminoethyl)ethane-1,2-diamine was reported to give [2+2] Schiff-base macrocycles in 65–80% yield, [27] while diformyl derivatives combined with 1,4-di(amino methyl)benzene produced only 33% of the [2+2] Schiff-base macrocycle [28].

The azeotropic distillation of toluene

The condensation of an amine and an aldehyde produces an equivalent of water, and it is known that the presence of water can impact the equilibrium of the Schiff base reaction [29], and influence the product outcomes [23, 30]. The role of water in imine synthesis can vary greatly; in the aforementioned study [23], water was used as a co-solvent to manipulate macrocycle condensation, while other claims regarding imines formed in aqueous solution were later revealed to involve imine formation during isolation and analysis [13, 23].

Our reaction procedure was modified to use a Dean Stark apparatus with toluene as a solvent. The azeotropic distillation of toluene allowed for the removal of water as the imine formation progressed. The attempted **1c** macrocycle synthesis performed in the Dean Stark apparatus combined 2,6-pyridinedicarboxaldehyde and 1,4-diaminobutane in toluene, heating the mixture at reflux until the formation of water ceased. Later experiments showed higher yields of isolated macrocycles when the solution was stirred before heating, possibly due to the system reaching equilibrium prior to the removal of water [31]. The macrocycles of interest were partially soluble in toluene, and the solvent was removed using rotary evaporation to isolate the product as a yellow solid in 78% yield. The crude reaction product isolated from the Dean Stark apparatus was found to be a single macrocyclic product by ^{1}H NMR spectroscopy in $CDCl_3$, showing a characteristic singlet imine resonance at 8.39 ppm (N = C-H), a doublet at 7.96 ppm (ar) and a triplet at 7.75 ppm (ar), comparable to literature values [26], and residual toluene resonances from the reaction procedure (7.26–7.14, 2.32 ppm). The product was dried under vacuum and a second ^{1}H NMR spectrum was collected, indicating a mixture of products similar to those found for our synthesis attempted following the original literature method using methanol [10, 26]. The difference between the two samples was the presence of residual toluene. It was hypothesized that the presence of residual toluene may have influenced the product equilibrium. The templation effect of toluene has previously been shown to selectively assemble macrocycles as nanocages [32]. Whilst it was thought the toluene may be having a favourable impact on the product equilibrium, it was also considered that other conditions could be having an adverse effect on product equilibria. For example, the chloroform-*d* NMR solvent could be potentially impacting the observed product distribution [33, 34]. The literature has many examples of solvent impacting the outcome of macrocyclizations and imine formation [7, 35–37]. To probe this idea, small scale macrocycle syntheses of **1c** were performed in a range of deuterated solvents. Stoichiometric amounts of 2,6-pyridinedicarbaldehyde and 1,4-diaminobutane were combined in acetone-d_6, acetonitrile-d_3, methanol-d_4, pyridine-d_5, dimethyl sulfoxide-d_6, toluene-d_8, benzene-d_6 and chloroform-*d*. Comparison of the ^{1}H NMR spectra obtained showed a mixture of products or incomplete reaction mixtures observed in all solvents except benzene-d_6, which produced a majority product (Fig. 3—some solvents were not included due to precipitation). Notably, at these concentrations the macrocycle **1c** was only moderately soluble in toluene, which made benzene the preferable solvent choice for later experiments. Observationally, toluene is providing a similar influence as benzene, but the precipitation from solution may be amplifying the relative proportions of the starting material resonances relative to the imine product. This could make toluene a desirable solvent choice for synthetic methods where products are collected by precipitation.

Macrocycle equilibria under solvent control

The observed solvent influence was further tested by performing a ^{1}H NMR titration in which a solution of macrocycle **1c** in benzene-d_6 was monitored during the addition of aliquots of chloroform-*d*. Each ^{1}H NMR spectra collected showed the slowly increasing presence of chloroform-*d* had a minimal impact on macrocycle composition for the first 40 µL added. The final 60 µL additions showed a transition to more products, observable by the formation of multiple imine resonances.

To test the applicability of this solvent effect on other systems, reactions between 2,6-pyridinedicarbaldehyde and α,ω-diamines were conducted and analysed in chloroform-*d* and benzene-d_6. 2,6-Pyridinedicarbaldehyde (1 equivalent) was dissolved in hot methanol (0.40 mL/mol) and the

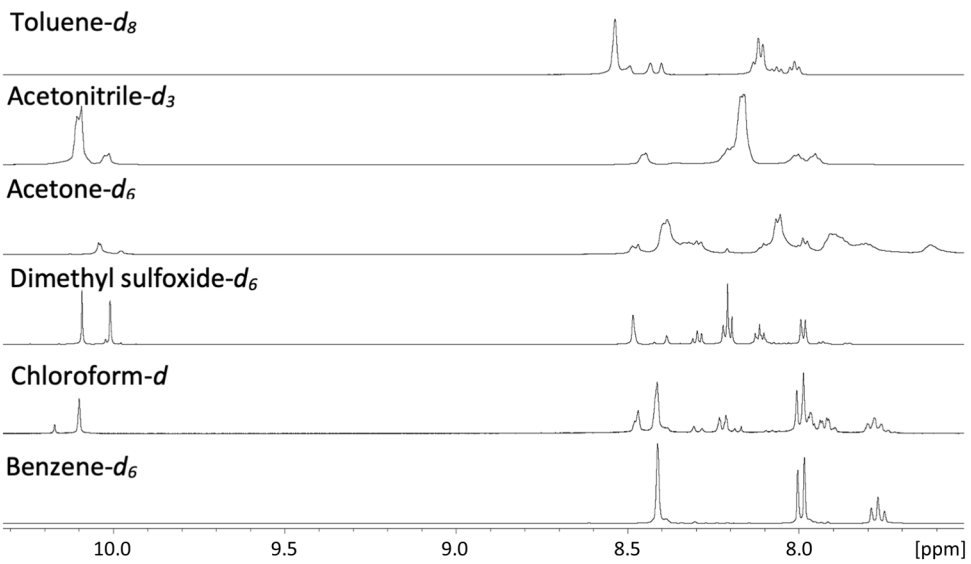


Fig. 3 ^{1}H NMR spectra showing the product outcomes of the attempted formation of macrocycle **1c** from stoichiometric amounts of 2,6-pyridinedicarbaldehyde and 1,4-diminobutane in different solvents (10.0 – 6.5 ppm). The carbaldehyde resonances are observed in the ~ 10 ppm region

solution was cooled to room temperature. This solution was added dropwise to a solution of diamine (1 equivalent) in methanol (1.5 mL/mol) at ~ 0.40 mL/minute. The reaction mixture was stirred overnight, and a precipitate formed. The precipitate was collected on a glass frit and was washed with additional cold methanol, and thoroughly dried before being dissolved in the deuterated solvents. The diamines chosen ranged in size from 1,3-diaminopropane to 1,12-diaminododecane (Fig. 2). Macrocycles **1b**, **1d**, **1e**, **1f** and **1g** behaved similarly; when analysed in chloroform-*d* they presented a mixture of macrocycle products and residual starting materials. The same macrocycles (**1b**, **1d**, **1e**, **1f**, **1g**) concurrently analysed using benzene-d_6 showed a majority of imine product (Fig. 4; macrocycle **1e,** spectra a and b). Notably, the largest macrocycle **1h**, showed a mixture of starting materials and multiple imine products when analysed in chloroform-*d*, but two distinct sets of imine resonances when analysed in benzene-d_6. Given the flexibility and potentially unfavourable kinetics of large condensation products for the 1,12-diamine, we postulate that these were the [1+1] and [2+2] macrocycles (Fig. 5). Molecules containing imines are highly responsive to reaction conditions, and in our hands, benzene was the most useful solvent for a dynamic sorting study. Toluene provided similar effects but had lower solubility limits for the larger macrocycles, making it less effective for the purpose of comparative experiments and NMR spectroscopic analysis.

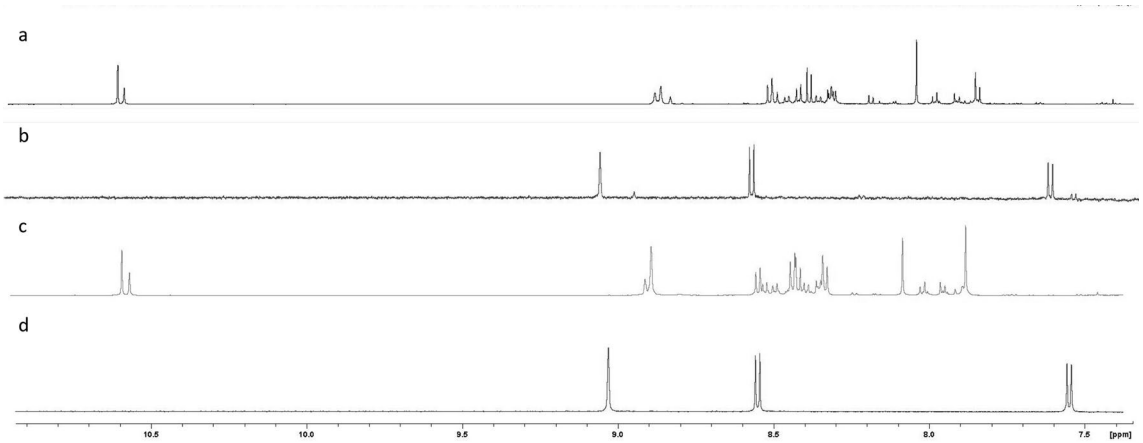


Fig. 4 ^{1}H NMR spectra comparing the product composition when 2,6-pyridinedicarbaldehyde was combined with 1,6-diaminohexane (**a** & **b**) and 1,7-diaminoheptane (**c** & **d**) in heated methanol and analysed in chloroform-*d* and benzene-d_6. **1e** in $CDCl_3$ = a, **1e** in C_6D_6 = b; **1f** in $CDCl_3$ = c, **1f** in C_6D_6 = d

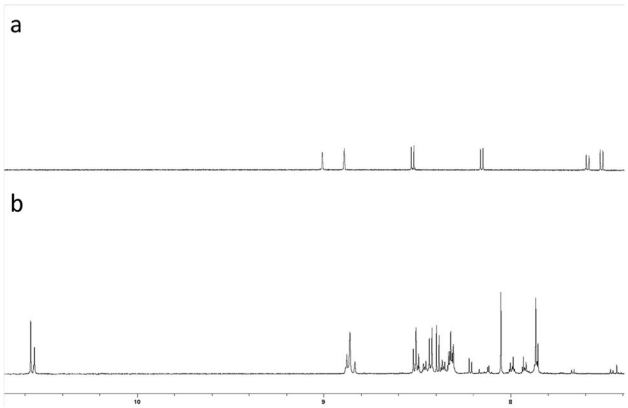


Fig. 5 ^{1}H NMR spectra of comparing the product composition when 2,6-pyridinedicarbaldehyde was combined with 1,12-diaminododecane analysed in benzene-d_6 = a, and chloroform-d = b

Halogen bond directed macrocycle formation

In addition to solvent control, intermolecular non-covalent interactions with guest molecules can also act to template target macrocycles. Directional non-covalent bonds are a valuable tool in supramolecular chemistry, with hydrogen bonding being commonly used. Halogen bonds are similar to hydrogen bonds, and although often not as strong, the hydrophobicity of the halogen bond can facilitate non-covalent interactions in polar or aqueous media [38–40]. A halogen bond occurs between a positively polarized halogen donor atom and an acceptor atom in a colinear fashion, and is characterized by an interaction length less than the sum of the van der Waals radii and at an angle approximating 180°. The *N*-heterocycles chosen for this work are strong halogen bond acceptors [41]. The guest molecule primarily used in this work was tetraiodoethylene, which was chosen for its rectangular size and multiple halogen bond donor sites. Other iodinated guest molecules were also considered, specifically 1,4-diiodotetrafluorobenzene and diiodoacetylene. Iodinated molecules were chosen because iodine typically forms the strongest halogen bonding interactions, and 1,4-diiodotetrafluorobenzene was specifically chosen because the electron withdrawal from fluorine can facilitate halogen bonding whilst also providing a secondary NMR spectroscopic handle [42, 43].

Diiodoacetylene is considered hazardous because it can explosively decompose. Due to the potential risks of experimenting with diiodoacetylene, tetraiodoethylene was used as a proxy [44]. We wanted to consider both the potential for halogen bonding to induce macrocycle assembly by templation, and for pre-organized macrocycles to bind guest molecules through halogen bonding.

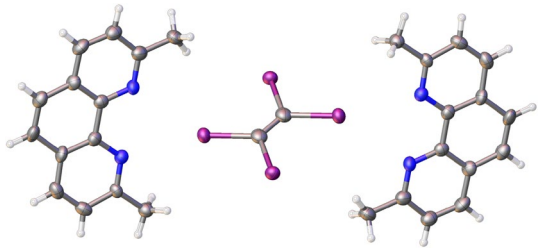


Fig. 6 Unit cell crystal structure of 2,9-dimethyl-1,10-phenanthroline cocrystallized with tetraiodoethylene

Host – guest complex formation can sometimes stabilize or prevent decomposition [45], giving rise to the suggestion that diiodoacetylene could be a stabilized as a guest with a suitable host.

Crystallographic implications for host – guest matching

Preliminary host – guest matching was probed by cocrystallizing tetraiodoethylene with 2,9-dimethyl-1,10-phenanthroline. The assembly crystallized in the triclinic space group *P*-1, with the asymmetric unit containing one 2,9-dimethyl-1,10-phenanthroline and half of the tetraiodoethylene molecule, related around the crystallographic inversion centre (Fig. 6). Halogen bonds are the primary intermolecular feature of the structure. One iodine of the tetraiodoethylene interacts with the phenanthroline nitrogen atoms through a bifurcated halogen bond at distances of 3.2147(2) and 3.2178(3) Å. The iodine atom is 2.9098(2) Å from a centroid between the two nitrogen atoms, with a C–I···N centroid angle of 166.006(2)°). The second iodine atom forms a halogen bond to one of the two nitrogen atoms of a symmetry related phenanthroline at a distance of 3.1855(2) Å (ca. 90% of the sum of the van der Waals radii) and with a C–I···N angle of 161.385(2)°. Figure 6 also illustrates the potential for a bis(1,10-pheanthroline) macrocycle to encapsulate a halogen bonding guest, if the methyl groups were tethered together through an appropriately sized linker. The Cambridge Crystallographic Database was examined to establish a range of relevant distances and angles suitable for macrocyclic host – tetraiodoethylene guest adduct formation [46]. The crystallographic database was used to identify bifurcated halogen bonds between phenanthroline and carbon-bound iodine. These interactions were examined from the centroid between the two nitrogen atoms and an iodine atom. These database results were used to calculate an average I – bifurcated N-centroid distance of 2.86 Å, and an average tetraiodoethylene C – I bond length of 2.12 Å.

Tetraiodoethylene has the potential to form four halogen bonding interactions through the four iodine atoms, which may suggest it could bind to a macrocyclic guest through

cis, *trans* or *gem* interactions. An interrogation of the Cambridge Crystallographic Database reveals that most crystal structures of tetraiodoethylene feature four halogen bonding interactions. Based on the determined bond parameters, the *cis*, *trans* and *gem* arrangements of iodine atoms would allow for a nitrogen centroid distance to nitrogen centroid distances of 6.82, 8.32 and 10.74 Å respectively (Fig. 7).

When the dataset is limited to interactions with two nitrogen halogen bond acceptors, the general trend is that the halogen bonds to nitrogen occur in a trans arrangement, with the remaining interactions to neighbouring iodides, and to arene π systems. The size of the macrocycle cavity can only be estimated due to potentially varied conformations of the alkyl chain diamines. To illustrate, the macrocycle **2c** was prepared and recrystallized from methanol. The crystal structure of **2c** reveals a partially folded, hyperbolic paraboloid-like conformation which suggests a N-centroid to N-centroid cavity length of ~ 6.94(2) Å (Fig. 8). The packing diagram for the crystal structure of **2c** shows a stack of saddle-like molecules along the b axis, reminiscent of the packing in a tube of Pringles®. Our attempts at cocrystallizing **2c** and tetraiodoethylene from a range of polar and non-polar solvents failed to give a cocrystal, prompting further solution phase experiments.

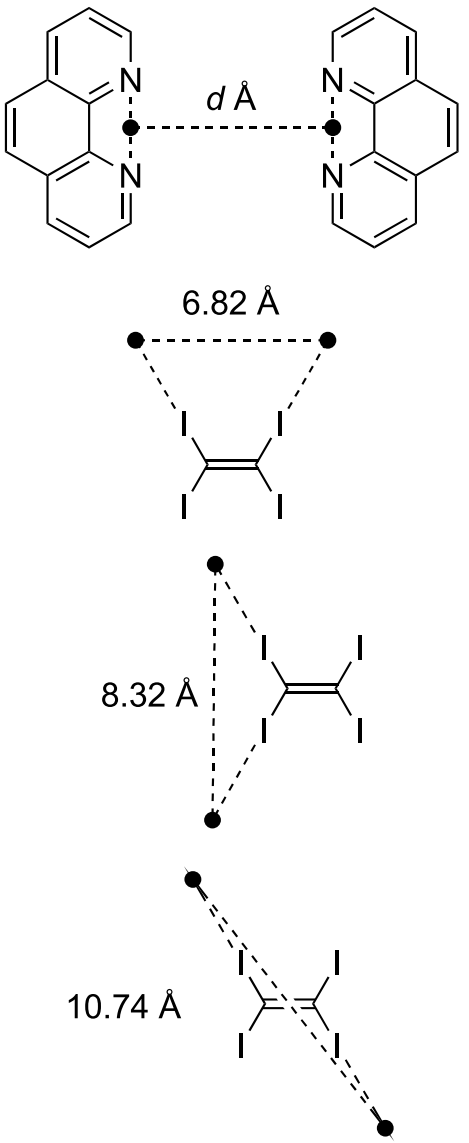


Fig. 7 The potential nitrogen-centroid spacing for halogen bonding to tetraiodoethylene was determined from crystal structures of halogen bonding phenanthroline cocrystals, and tetraiodoethylene cocrystals. Trigonometry was applied to the average bond lengths and angles to determine approximate nitrogen centroid—nitrogen centroid distances

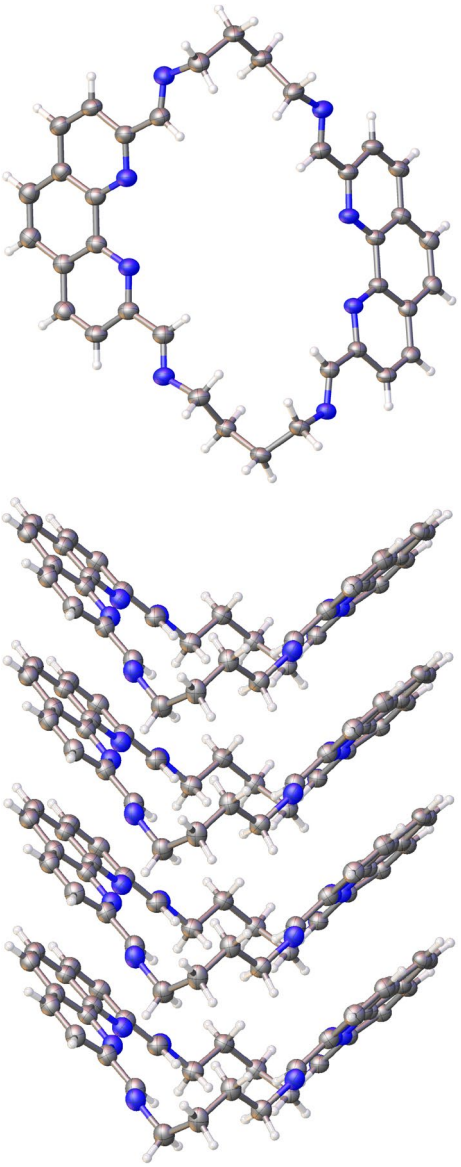


Fig. 8 Crystal structure and crystal packing for macrocycle **2c**. Cocrystallized solvent within the cavity was poorly defined, and was modelled using a solvent masking technique

Tetraiodoethylene guest and template effects in solution

To understand the interactions of tetraiodoethylene and macrocycle **2c** in solution, a ^{1}H NMR spectroscopy titration experiment was conducted, by monitoring the resonances of the preformed **2c** macrocycle (prepared and isolated from methanol) upon addition of aliquots of tetraiodoethylene. From a stock solution of macrocycle **2c** (9.1×10^{-4} M) in benzene-d_6, a 400 µL sample was prepared. As previously observed for macrocycle **2c** prepared in methanol, the initial ^{1}H NMR spectrum showed two sets of macrocycle resonances (Fig. 9a). To this sample, 0.5 molar equivalents of tetraiodoethylene were added in aliquots, and the mixture analysed by ^{1}H NMR spectroscopy.

The addition of tetraiodoethylene caused the relative proportions of the imine resonance at 8.98 ppm to decrease as the 9.02 ppm imine resonance increased, suggesting a shift in the product equilibrium (Fig. 9d). Another four equivalents of tetraiodoethylene were added, further changing the observed resonances. At these concentrations, no precipitation was observed. The sample was analysed 24 h later to check for changes to the product equilibrium, but there was no further change once the final addition of tetraiodoethylene had been made. Notably, the addition of tetraiodoethylene to macrocycle **2c** changes the physicochemical properties of the system. When tetraiodoethylene is combined with macrocycle **2c** in benzene at concentrations above approximately 10^{-3} M, a precipitate is formed. Characterisation of the precipitate by ^{1}H NMR spectroscopy showed a single set of resonances as expected for macrocycle **2c**. The presence of the guest in the solid sample was supported by ATR infrared spectroscopy ($\nu = 1495.85$ cm^{-1}, C = C). Prior to guest addition, macrocycle **2c** had been readily soluble in benzene. If these changes in physical properties are due to guest binding it was considered this concept could be used to encapsulate and stabilize volatile guest molecules [47]. For example, the previously mentioned diiodoacetylene is a volatile and toxic molecule despite being the most stable of the dihaloalkynes [48]. Diiodoacetylene has similar physical properties to tetraiodoethylene and is geometrically more accessible for binding, but was not tested due to the noted experimental risks [49, 50].

Photochemical stabilization

It was observed that iodinated guest molecules in solution tended to decompose when exposed to sunlight. Decomposition was indicated by the development of colour from elemental iodine in solution. The presence of iodine is known to promote the decomposition of imines [29, 51] When various macrocycle samples were combined with an iodinated guest molecule and exposed to light, the solution became orange or purple in colour (depending on the solvent and concentration of the iodinated guest molecule), and ^{1}H NMR spectroscopic analysis showed an absence of imine resonances. On occasion, it was noted that particular samples did not undergo visible decomposition despite containing an iodinated guest molecule and being exposed to sunlight. Experiments were conducted in which macrocycle **1c** and macrocycle **2c** were assembled in heated methanol prior to the addition of tetraiodoethylene. Both samples showed macrocyclic products and an absence of starting material immediately after analysis in benzene-d_6. These solutions were exposed to natural light over the course of one day. The volatile components were removed using rotary evaporation and the solid remaining was dissolved in benzene-d_6 for ^{1}H NMR spectroscopic analysis. Macrocycle **1c** and guest sample (8) underwent decomposition after extended exposure to natural light whilst macrocycle **2c** and guest sample (7) did not (Fig. 10 and Table 1). This may be due to the fluxionality, or the

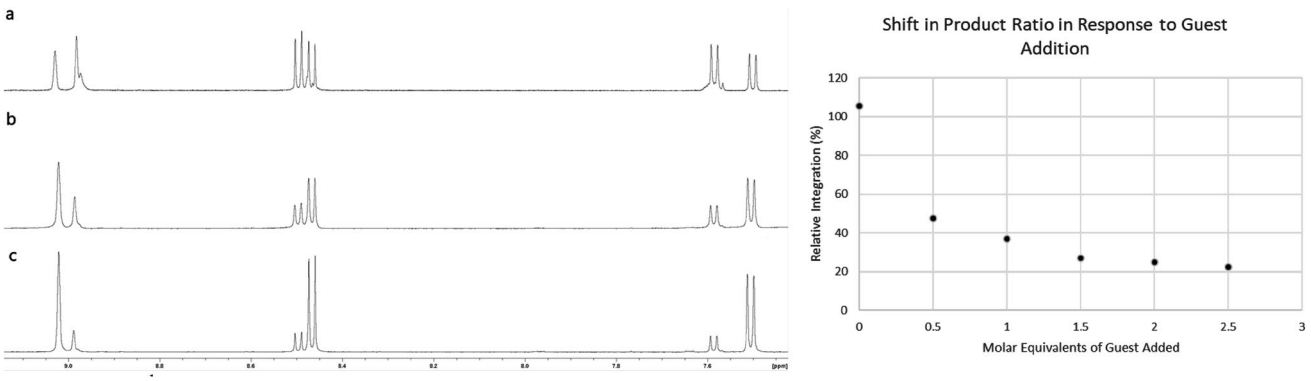


Fig. 9 The ^{1}H NMR spectra collected from a tetraiodoethylene titration in benzene-d_6. Spectrum **a** shows the composition of products prior to guest addition. Spectra **b** and **c** show the changes observed when a total of 0.5 and 2.5 equivalents of tetraiodoethylene have been added. The plot shows the change in the relative intensity of the second imine peak in response to guest addition

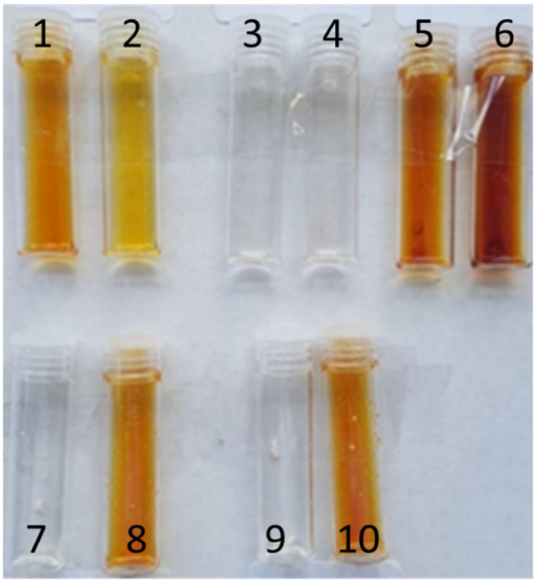


Fig. 10 Photodecomposition experiment results as described in Table 1; Solutions of macrocycles (0.001 M) that were prepared in heated methanol, were combined with tetraiodoethylene in a 1:1 molar ratio

lack of host – guest compatibility in macrocycle **1c**. The samples were left in natural light for multiple days, and the combined macrocycle **2c** and tetraiodoethylene sample did not undergo decomposition. This experiment suggested the combination of a macrocycle and guest molecule could result in a protective or stabilizing effect, but also demonstrated that the in-situ formation of a macrocycle in the presence of tetraiodoethylene had an influence on the phenanthroline-based system, but no discernible effect on the pyridine-based system. Comparison with a sample containing 1,10-phenanthroline-2,9-dicarbaldehyde (Sample 2) suggests that the effect is greater than the presence of a phenanthroline chromophore alone.

Competitive macrocycle formation in the presence of a halogen bonding guest

Tetraiodoethylene was considered a potential template molecule for the demonstration of self-sorting under dynamic combinatorial conditions. The ability of tetraiodoethylene to influence the product equilibrium of a reaction mixture was undertaken with a mixture containing two dicarbaldehydes and one diamine. The experiment was designed so the excess of dicarbaldehyde could be used as a ^{1}H NMR spectroscopic handle to observe changes in relative product composition. A solution of 1,10-phenanthroline-2,9-dicarbaldehyde (1 equivalent), 2,6-pyridinedicarboxaldehyde (1 equivalent), and 1,4-diaminobutane (1 equivalent) in methanol was stirred for 48 h. This formed a mixture of products, with the ^{1}H NMR spectrum showing at least 4 imine resonances and remaining free dicarbaldehyde resonances. An aliquot was removed and combined with one molar equivalent of tetraiodoethylene, and stirred for an additional hour. The range of mixed condensation products resulted in an overlapping of the resonances in the imine region, whilst the dicarbaldehyde resonances could be easily identified and integrated to monitor changes in their relative proportions.

The ^{1}H NMR spectrum of the solution without tetraiodoethylene showed 2,6-pyridinedicarboxaldehyde and 1,10-phenanthroline-2,9-dicarbaldehyde at a 1:1.9 ratio, indicating preferential formation of imines containing 2,6-pyridinedicarbaldehyde. The aliquot that was combined with tetraiodoethylene indicated a change in the relative integrations of dicarbaldehyde peaks. The integration showed that 2,6-pyridinedicarboxaldehyde and 1,10-phenanthroline-2,9-dicarbaldehyde were present in a 1:1.4 ratio, indicating that in the presence of tetraiodoethylene, there is less 1,10-phenanthroline-2,9-dicarbaldehyde remaining in solution. This suggests that 1,10-phenanthroline-2,9-dicarbaldehyde had been incorporated into imine products when tetraiodoethylene was present.

Table 1 Sample labelling and contents for light exposure experiment

Sample number	Content in methanol	Pre light exposure	Post light exposure
1	Tetraiodoethylene	Colourless	Orange
2	1,10-Phenanthroline-2,9-dicarbaldehyde and tetraiodoethylene	Colourless	Orange
3	**2c**	Colourless	Colourless
4	**1c**	Colourless	Colourless
5	**2c** and iodine	Orange	Orange
6	**1c** and iodine	Orange	Orange
7	**2c** and tetraiodoethylene	Colourless	Colourless
8	**1c** and tetraiodoethylene	Colourless	Orange
9	In-situ prepared **2c** and tetraiodoethylene	Colourless	Colourless
10	In-situ prepared **1c** and tetraiodoethylene	Colourless	Orange

Conclusions

The choice of solvent and the presence of a halogen bonding guest have been shown to influence the formation of Schiff base macrocycles. The aromatic solvents toluene and benzene were observed to give primarily [2+2] macrocycles with a range of alkyl α,ω-diamines, which were obtained as mixed products from other solvents. This solvent effect on macrocycle equilibrium highlights the importance of solvent choice when isolated Schiff base macrocycles are used in subsequent reactions, such as metal complexation. The halogen bonding guest tetraiodoethylene was observed to influence the product equilibria in the formation of Schiff base macrocycles from phenanthroline dicarbaldehydes with alkyl α,ω-diamines. The formation of a host–guest adduct was investigated, and a possible photoprotective effect of tetraiodoethylene was observed in the presence of phenanthroline macrocycles. Future work will look to incorporate the influence of macrocycle equilibrium with halogen bonding guests through dynamic combinatorial chemistry in the hope of forming macrocycles as selective halogen bonding hosts.

Experimental

All reagents were purchased from Sigma-Aldrich or Combi-Blocks and were used as received. Deuterated solvents were purchased from Novachem and used as received. 2,6-Pyridinedicarboxaldehyde and 1,10-phenanthroline-2,9-dicarbaldehyde were prepared by literature methods [52, 53]. ^{1}H NMR spectroscopy was performed using a 400 MHz Bruker Avance 3 HD Wide Bore Spectrometer (5 mm BBFO probe) at room temperature (293 K) in $CDCl_3$ and C_6D_6. ^{1}H NMR spectra were obtained at 399.58 MHz and referenced to residual ^{1}H solvent resonances. ^{1}H, ^{13}C and ^{19}F NMR spectroscopy was performed using a 600 MHz Bruker Avance 3 HD Narrow Bore Spectrometer (5 mm TCI tuneable probe) at room temperature (293 K) in $CDCl_3$ and C_6D_6. ^{1}H NMR spectra were obtained at 600.1 MHz and referenced to residual ^{1}H solvent resonances. ^{13}C NMR spectra were obtained at 150.9 MHz and referenced to ^{13}C solvent resonances. ^{19}F NMR spectra were obtained at 376.0 MHz. NMR spectra were processed using Bruker Topspin 3.5 software.

Structure determinations

X-ray crystallographic data for the structural data were collected using synchrotron radiation (λ = 0.7108 Å) on the MX1 Beamline of the Australian Synchrotron [54] or with copper radiation (λ = 1.54178 Å) on a Bruker D8 Quest. The structures were solved by intrinsic phasing methods with SHELXT[55] and refined with SHELXL[56] in OLEX2 [57].

Tetraiodoethylene. Bis(2,9-dimethyl-1,10-phenanthroline)

$C_{14}H_{12}N_2{\cdot}0.5(C_2I_4)$, $M = 474.07$, colourless block, $0.39 \times 0.27 \times 0.23$ mm^3, triclinic, $P1$, $a = 7.7984$ (7), $b = 4.6090$ (9), c = 26.274 (5) Å, $\alpha = 76.204$ (4) β = 78.624 (3), $\gamma = 67.520$ (4)°, $V = 741.54$ (12) Å^3, $Z = 2$, $2\theta_{max} = 64.19°$, $D_c = 2.123$ g cm^{-3}, $\mu = 33.2$ mm^{-1}. Bruker D8 Quest, λ = 1.54178 Å, 18,350 reflections collected, 2867 unique ($R_{int} = 0.062$). Final GooF = 1.07, $R_1 = 0.061$, $wR_2 = 0.177$, R indices based on 2527 reflections with $I > 2\sigma(I)$, $|\Delta\rho|_{max}$ 2.986 e Å^{-3}, 174 parameters, 0 restraints. CCDC number 2107298.

2c

$C_{36}H_{32}N_8$, $M = 576.69$, colourless plate, $0.20 \times 0.05 \times 0.05$ mm^3, monoclinic, $P2_1$ (No. 4), $a = 13.497$ (3), $b = 4.6090$ (9), c = 26.274 (5) Å, β = 90.51 (3)°, $V = 1634.4$ (6) Å^3, $Z = 2$, $2\theta_{max} = 64.19°$, $D_c = 1.172$ g cm^{-3}, $\mu = 0.07$ mm^{-1}. Synchrotron, λ = 0.7108 Å, 14,889 reflections collected, 8334 unique ($R_{int} = 0.046$). Final GooF = 1.12, $R_1 = 0.051$, $wR_2 = 0.151$, R indices based on 7421 reflections with $I > 2\sigma(I)$, $|\Delta\rho|_{max}$ 0.279 e Å^{-3}, 397 parameters, 1 restraint. CCDC number 2107297.

Variata

The crystal structure indicated a large void running through the centre of the stacked macrocycles. Attempts to model the visible Fourier peaks failed to give a satisfactory refinement, and a solvent mask was applied.

General procedure for synthesis of 2,6-pyridinedicarboxaldehyde and diamine macrocycles

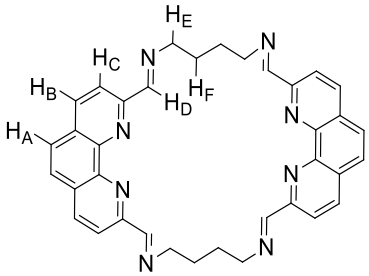
This procedure was performed using a modified literature method [26]. A solution of 2,6-pyridinedicarboxaldehyde (1 equivalent) in acetonitrile (1.5 mL/mol) was added dropwise to a solution of diamine (1 equivalent), in acetonitrile (4.0 mL/mol) at ~ 0.40 mL/minute. The reaction mixture was stirred overnight, and a precipitate is formed. The precipitate was collected on a glass frit and was washed with additional acetonitrile.

General procedure for synthesis of 1,10-phenanthroline-2,9-dicarbaldehyde and diamine macrocycles

This procedure was performed using a modified literature method [15]. A solution of 1,10-phenanthroline-2,9-dicarbaldehyde (1 equivalent) in methanol (1.5 mL/mol) was added dropwise to a solution of diamine (1 equivalent), in methanol (4.0 mL/mol) at ~ 0.40 mL/minute. The reaction mixture was stirred overnight, and a precipitate is formed. The precipitate was collected on a glass frit and was washed with additional cold methanol.

Synthesis of macrocycle from 2,6-pyridinedicarboxaldehyde and 1,4-diaminobutane, 1c

2,6-Pyridinedicarboxaldehyde (0.12 g, 8.8 mmol) in acetonitrile (25 mL). 1,4-Diaminobutane (0.08 g, 9.0 mmol) in acetonitrile (75 mL). The ^{1}H NMR spectroscopic data for the major product was consistent with literature values [58]. Yield: 0.09 g (27%). ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 2H), 7.96 (d, 2H, J = 7.74 Hz), 7.74 (t, 1H, J = 7.74 Hz), 3.71 (m, 4H), 1.80 (m, 4H) ppm ^{13}C NMR ($CDCl_3$) δ 161.7, 154.3, 137.1, 125.2, 122.2, 61.2, 28.5 ppm.



Synthesis of macrocycle from 1,10-phenanthroline-2,9-dicarbaldehyde and 1,4-diaminobutane, 2c

1,10-Phenanthroline-2,9-dicarbaldehyde (0.03 g, 0.13 mmol) in hot methanol (2.6 mL). 1,4-Diaminobutane (0.011 g, 0.13 mmol) in methanol (1.6 mL). Crystals for solid state X-ray diffractometric analysis were formed using hot recrystallisation from methanol. Yield: 0.03 g (40%). ^{1}H NMR (C_6D_6) δ 8.97 (H_D, s, 4H), 8.38 (H_B, d, 4H, J = 8.4 Hz), 7.51 (H_C, d, 4H, J = 8.8 Hz), 7.17 (H_A, m, 4H), 3.64 (H_E, m, 8H), 1.82 (H_F, m, 8H) ppm ^{13}C NMR ($CDCl_3$) δ 163.3, 154.7, 145.6, 136.6, 129.5, 127.2, 120.1, 60.4, 27.1 ppm. LR MS calculated for $C_{36}H_{33}N_8$ (M^+) 577.28, found 577.28.

Synthesis of templated macrocycle from 1,10-phenanthroline-2,9-dicarbaldehyde and 1,4-diaminobutane

1,10-Phenanthroline-2,9-dicarbaldehyde (0.04 g, 0.12 mmol) and tetraiodoethylene (0.05 g, 0.12 mmol) was dissolved in hot methanol (30 mL) and the solution was cooled to room temperature. This solution was added dropwise to a solution of 1,4-diaminobutane (0.10 g, 0.12 mmol) in methanol (20 mL) over 20 min. The reaction mixture was stirred overnight, and a precipitate was formed. The precipitate was collected on a glass frit and was washed with additional cold methanol. Yield: 0.04 g (69%). ^{1}H NMR (C_6D_6) δ 8.54 (m, 4H), 8.14 (m, 4H), 8.12 (m, 4H), 7.10 (m, 4H), 2.43 (m, 8H), 1.12 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 152.7, 145.9, 137.9, 131.6, 129.0, 120.5, 60.4, 28.63. V_{max}/cm^{-1} 3479 (br, C-H) 2899 (C-H), 1652 (s, C = N), 673 (s, C-I).

General procedure for crystallisation of macrocycles

A dried macrocycle sample was transferred to a glass vial. A minimal amount of solvent was added and stirring was used to assist dissolution. The sample was heated to encourage dissolution, and hot solvent was added until the solid was entirely dissolved. The solution was boiled until the solvent was reduced to a minimum volume without precipitation. The vial was removed from the heat and was left to cool slowly to room temperature. Methanol, propan-2-ol, benzene, toluene, dimethyl sulfoxide, carbon tetrachloride, cyclohexane and acetonitrile were used throughout.

General procedure for cocrystallisation

Dicarbonylheterocycle and guest molecule were combined in a 1:1 molar equivalent. A minimal amount of solvent was added, and the solution was heated until the solids are entirely dissolved. The solution was capped and allowed to cool to room temperature. The choice of solvent depends on the dicarbonylheterocycle and guest solubility. Dichloromethane, methanol, propan-2-ol, benzene and acetonitrile were used throughout.

General procedure for ^{1}H NMR titration analysis

A stock solution of macrocycle (0.001 M, 1000 µL) in deuterated solvent was prepared using a micro syringe. A stock solution of guest molecule (0.020 M, 1000 µL) was prepared in the same manner. A 400 µL sample of the macrocycle stock solution was transferred to an NMR tube using a volumetric syringe. The sample was then analysed using ^{1}H NMR spectroscopy. Aliquots of guest stock solution were added via a septum lid using a micro syringe and analysed sequentially [0.1, 1, 10 equivalents].

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Declarations

Conflict of interest All authors contributed to the study conception and design, material preparation, data collection and analysis. The first draft of the manuscript was written by Chloe M. Taylor and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. We declare no competing financial interests.

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