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Macrocyclic Tetraimines: Synthesis and Reversible Uptake of Diethyl Phthalate by a Porous Macrocycle

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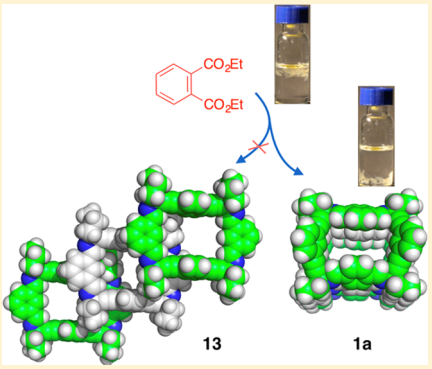
Supporting Information

ABSTRACT: The imine bond has attracted much attention for the synthesis of macrocycles used to construct porous materials. In the present article, we report on the synthesis of two series of isomeric macrocyclic tetraimines based on bis-alkynylbenzene diamines. Under heterogeneous solid−liquid conditions the condensation of the diamines with isophthalaldehyde or terephthaldehyde afforded mainly the corresponding [2 + 2] adducts. Among the eight macrocycles studied, only the macrocycle **1** has a porous structure. The article describes not only the synthesis of these macrocycles but also the encountered difficulties during their preparation. Finally, we expand the use of **1a** as a porous solid support by studying its reversible and preferential liquid−solid adsorption properties for diethyl phthalate in front of other commercial phthalates.



INTRODUCTION

Designed materials featuring permanent porosity have interest owing to their potential for applications in industrial chemistry, material science, and sustainable energy.[1] Among them, the large family of porous organic materials is of increasing importance. This group of materials comprises several categories including metal−organic frameworks (MOFs),[2] covalent organic frameworks (COFs)[3] and porous organic polymers (POPs).[4] All the above materials give infinitely extended tridimensional structures containing voids or channels used for adsorption-based applications.

A less known subset of organic nanoporous materials are porous organic materials (POMs). POMs are crystalline or amorphous materials based on discrete molecules held together by weak intermolecular forces.[5] They differ from MOFs, COFs, and POPs because the molecular-scale porosity of the solid does not derive from infinitely extended one-, two- or three-dimensional structures. In general, POMs are synthesized following two main approaches. One is based on the use of molecular units unable to pack efficiently in the solid state, leading to molecular solids with voids suitable for gas sorption (extrinsic porous materials).[6] The other is based on the solid-state self-assembly of constitutive molecular units featuring permanent inner cavities forming well-ordered pores (intrinsic porous materials). Examples of solid materials having both extrinsic and intrinsic pores are also known.[7] In cases where POMs are prepared by a solvent-based synthesis, the emergence of nanoporosity requires the removal of the solvent molecules included in the pores of the solid material. The solvent evacuation is critical to the success of the synthetic method since the resulting apohost is prone to collapse forming a denser and less porous crystal lattice.[8]

In general, POMs are implied in situations where molecules in the gas state diffuse trough the solid. However, the adsorption of molecules in the liquid state at ambient temperature is becoming increasingly relevant. For example, recently, Davis et al. described a set of extrinsic POMs based on steroidal ureas that adsorb a variety of aromatic guest molecules in the liquid state.[9] Another interesting example of selective liquid adsorption by POMs was reported by Shimizu and co-workers.[10] The authors demonstrated that intrinsic POMs based on bis-urea macrocycles showed a preferential adsorption of a variety of liquid polar guests. To preserve porosity, these materials took advantage of the establishment C═O···HN hydrogen bonding interactions between urea groups located in adjacent macrocyclic units.

Imine-based molecular structures are common in the synthesis of POM materials. The reversible nature of the covalent imine bond allows the correction of covalent connection mistakes during the synthesis, therefore providing the prevalent formation of the thermodynamically more stable structures in solution.[11] In this vein, Cooper, Mastalerz and co-workers demonstrated the use of the imine functionality for the

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construction of POM materials.[12] Also, Zhang and co-workers used imine metathesis to synthesize shape-persistent imine macrocycles.[13] Within the realm of imine-based POMs, recently we reported the macrocyclic tetraimine **1**, affording unprecedented POMs. The solid-state self-assembly of **1** generated a porous material **1a** grounded on the "Gulliver Principle", that is, the stabilization of one-dimensional pore channels originated by multiple and weak CH dispersive interactions acting synergically (Figure 1).[14]

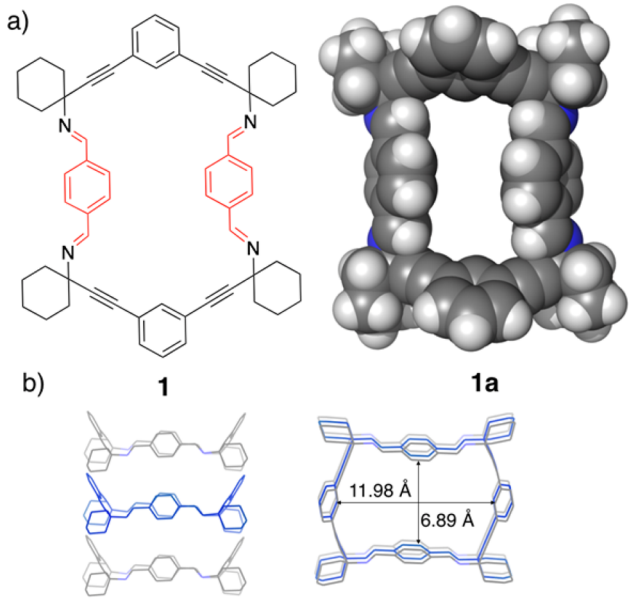


Figure 1. (a) Line drawing structure (left) and space-filling X-ray structures of **1a**. (b) Side and top views of the spatial arrangement of three consecutive macrocyclic units of **1** as observed in the packing of POM **1a** (CCDC 1012398).

We demonstrated the use of POM **1a** as solid support enabling the X-ray structure determination of included liquid guests. This strategy is reminiscent to the crystalline sponge method of Fujita.[15]

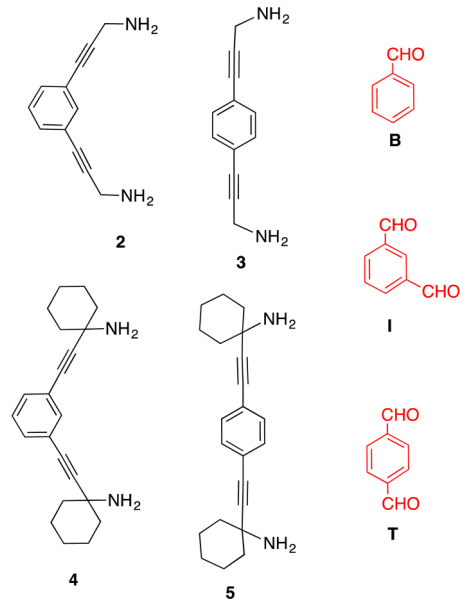
Our search for new macrocyclic units akin to **1** led us to consider the synthesis of other isomeric macrocyclic tetraimines featuring rectangle-shaped cavities with molecular dimensions close to 12 × 8 Å (Figure 1b). We hypothesized that the solid-state self-assembly of macrocycles featuring structures and functionalities closely related to **1** should provide POMs mainly based on intra- and interdispersive interactions.[16]

Herein, we report our findings on the macrocyclization reaction between four 1,3- and 1,4-phenylene bis-propargylic diamine monomers **2**–**5** and either, terephthalaldehyde (**T**) or isophthalaldehyde (**I**) (Chart 1). The condensation reaction of diamines **2**–**5** with terephthalaldehyde or isophthalaldehyde could, in principle, provide eight [2 + 2] macrocycles. We have studied the outcome of the eight possible combinations. However, despite all the condensations were viable only the macrocyclic tetraimine **1** exhibits a porous structure in the solid state, **1a**. To further demonstrate the use of **1a** as porous support, we investigated the selective liquid–solid uptake of diethyl phthalate over other phthalates.

RESULTS AND DISCUSSION

The eight macrocycles considered were attainable through [2 + 2] cyclocondensations of the semirigid 1,3- and 1,4-phenylene

Chart 1



bis-propargylic diamines **2** to **5** with terephthalaldehyde or isophthalaldehyde. We expected that the 1,1-cyclohexane substituents present in diamines **4** and **5** would improve the solubility of the resulting macrocycles in less polar solvents, and at the same time, they would promote the establishment of multiple dispersive contacts among adjacent macrocycles in the solid state. The diamines **2** to **5** were prepared by Sonogashira cross-coupling of 1,3- or 1,4-diiodo benzene with propargyl amines under "on water" conditions as previously reported by us.[17]

First, to evaluate the imine formation, we reacted benzaldehyde (B) with diamines **4** and **5** in separated reaction flasks. These reactions proceeded uneventfully and afforded the bis-imines **6** and **7** in 61 and 72% yields, respectively (Scheme 1).

Compounds **6** and **7** exhibited unique and sharp ^{1}H NMR signals that were indicative of their existence as a single stereoisomer in solution. Remarkably, the diagnostic imine protons of **6** and **7** appear at 8.84 and 8.86 ppm, respectively. These values are ca. 0.5 ppm deshielded compared to standard aromatic imines (see, Figure 3, for comparison), indicating the strong influence of the triple bond magnetic anisotropy and orientation. Single crystals of the bis-imine **7** were grown in chloroform and analyzed by X-ray diffraction. The X-ray structure of **7** is dictated by Y-shaped and parallel-displaced aromatic interactions[18] and confirmed the anti configuration of the imine bonds (Supporting Information).

To minimize undesired polymerization side reactions, the condensations leading to **1** and the macrocycles **8**–**14** were performed on relatively diluted EtOAc solutions ($<10^{-2}$ M) containing equimolar amounts of the corresponding diamines and dialdehydes at room temperature.[19] In all cases, upon standing for evolution, we observed the formation of a precipitate after a period ranging from one to 8 weeks since the start of the reaction.

The analysis of the solids isolated by filtration revealed the existence of marked differences among them. Thus, the reactions putatively leading to tetraimines **9** and **11** (Chart 2) afforded amorphous solids that were insoluble in common organic solvents. On the other hand, macrocycles **8** and **10**

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Scheme 1. Synthesis of the Bis-imines 6 and 7

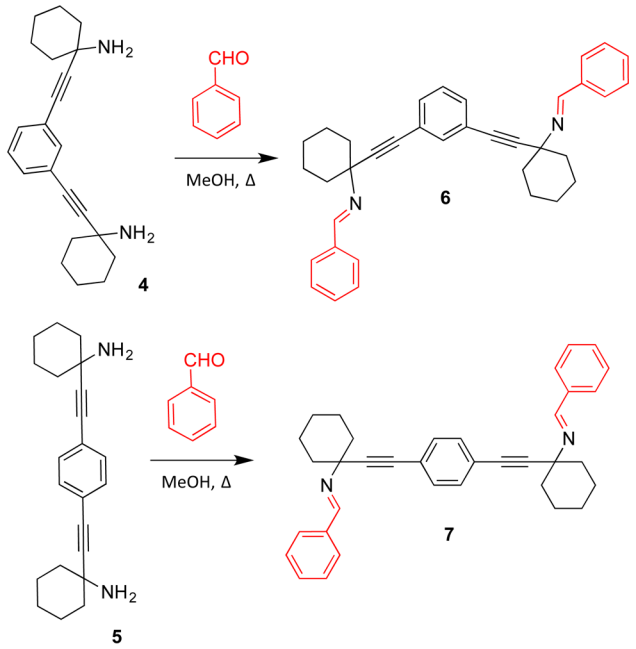
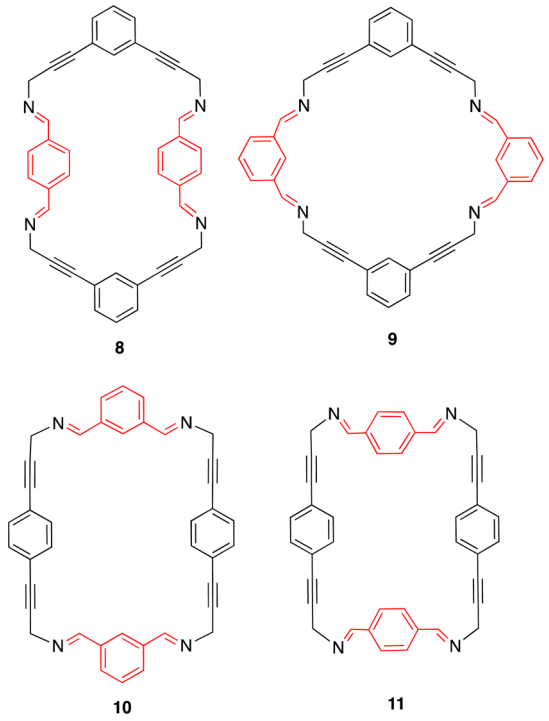


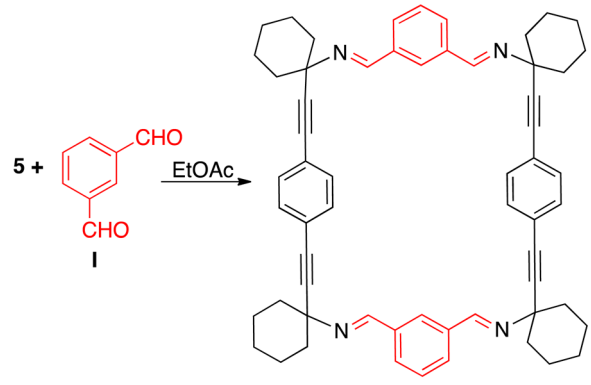
Chart 2



were isolated in 15 and 22% nonoptimized yields, respectively, as the exclusive components of the precipitate. The ^{1}H NMR spectra of **8** and **10** showed sharp signals for the imine protons at 8.69 and 8.75 ppm, respectively. In addition, we observed intense peaks at m/z 565.23 in the mass spectra of the solids that were assigned to the isomeric molecular ions $[M + H]^+$ of **8** and **10**, respectively. We crystallized macrocycle **10** by slow evaporation of a chloroform solution, but the resulting cotton-like crystals were unsuitable for X-ray analysis. Preliminary sorption experiments performed on macrocycles **8**–**11** using nitromethane as guest were unsuccesful. Thus, owing to the lack of sorption capabilities and the low solubility in nonpolar solvents exhibited by macrocycles **8**–**11**, we focused on the synthesis, characterization and study of the cyclohexane-substituted counterparts.

The macrocyclic tetraimines **1** and **12**–**14** bear 1,1-cyclohexane substituents at the four sp^3 hybridized carbon atoms (Scheme 2). Single crystals of **1** (monoclinic, $C2/c$) as

Scheme 2. Synthesis of the Cyclohexane Substituted Tetraimines



4 + T ⟶ 1
4 + I ⟶ 12
5 + I ⟶ 13
5 + T ⟶ 14

EtOAc solvate, were obtained from a first crop of 15% yield as already reported.[14] Remarkably, after the initial solid was removed by filtration, the mother liquor was kept at room temperature for several days affording additional crops of **EtOAc@1** crystals. A total yield of 55% was reached summing up the crystals grown in four consecutive crystallizations. This result suggests that, under heterogeneous reaction conditions, the equilibrium providing the tetraimine is shifted toward the product formation by precipitation of **EtOAc@1** solvate, which is insoluble in the reaction medium. In general, the reaction yields for the synthesis of the macrocycles remained low to moderate in solvents of different polarity. For example, the yield of **1** isolated as an amorphous solid at room temperature was 16% in MeCN, 35% in MeCN/TFA(cat.), <5% in dichloromethane, and 10% in refluxing MeOH. After removal under a vacuum (4×10^{-2} mmHg, 12 h), of the EtOAc trapped in the **EtOAc@1** solid, the resulting empty material **1a** retained a porous structure. The latter material had a relatively low packing index of 54.39% compared to 72.15% calculated for the parent EtOAc solvate.

Following an identical procedure, we were able to obtain single crystals suitable for X-ray analysis for macrocycle **13** in 25% yield. Unfortunately, the precipitation-driven strategy was not effective for the isolation in pure and crystalline form of the macrocycles **12** and **14**. The crude reaction precipitates obtained in the synthesis of the isomeric macrocycles **12** and **14** were amorphous solids isolated in 16 and 21% yields, respectively. The ESI-MS analysis of the respective solid materials revealed the presence of the target [2 + 2] macrocycles (>70%). In both cases, we observed an intense ion peak at m/z 838.48 that was assigned to the molecular peak $[M + H]^+$ together with minor but significant ion peaks at

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855.5, 971.5, and 1157.7 m/z ratios, that were assigned to the 2 + 2, 2 + 3, and 3 + 2 linear oligomers, respectively. The ^{1}H NMR spectra of the solids dissolved in $CDCl_3$ also supported the presence of the macrocyclic component as the major species. All our attempts to purify the macrocyclic tetraimines **12** and **14** by column chromatography or by recrystallization in different solvent mixtures were unsuccessful.

Compounds **1** and **13** are constitutional (structural) isomers with similar geometric size and shape however their packing in the solid state is markedly different. Whereas **1** is obtained as an ethyl acetate solvate **EtOAc@1**, in identical experimental conditions **13** precipitated in a denser form that shows resemblance with **1b** (triclinic, $P1$) the nonporous form of polymorph **1** (Figure 2).

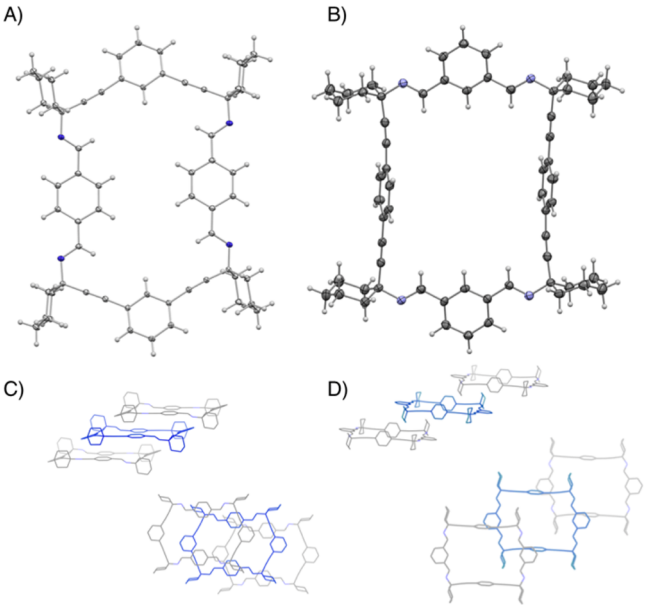

Figure 2. ORTEP representation (50% probability displacement ellipsoids) of the X-ray crystal structures of (A) **1b**, and (B) **13**. Hydrogen atoms are drawn as fixed-size spheres of 0.15 Å radius. (C) and (D) Side and top views of the spatial arrangement of three consecutive macrocyclic units in the crystal packing of **1b** and **13**, respectively.

Having four aliphatic centers in their structures, macrocycles **1** and **13** are indeed nonplanar. In principle, they can exist in solution as different conformers. In the solid state, we have identified so far two forms for **1**, namely **1a** and the denser and nonporous counterpart **1b**. The macrocycle **1** adopts slightly different conformations in the solid state of the two forms. The polymorph **1b** is obtained by heating crystals of **1a** at around 170 °C.[14] Remarkably, in this work we have promoted the same irreversible homotropic transition by just soaking crystals of **EtOAc@1** in MeOH for 48 h at room temperature.

In close analogy to **1b**, the X-ray structure of **13** (monoclinic, $P2_1/c$) revealed a flattened chairlike conformation for the macrocycle governed by aromatic stacking interactions in the solid. In the crystal lattice, each *p*-phenylene ring of **13** is involved simultaneously in two aromatic interactions, one stacked offset (R_{cen} = 3.644 Å) and the other perpendicular T-shaped ($R_{cen\text{-}H}$ = 2.693 Å). There are also several H(arom.)···H(alif.) dispersive contacts arising from the cyclohexyl residues at distances in the range 2.4−3.0 Å, well within the standard values for attractive dihydrogen contacts for alkanes.[16a] In the solid state, two pendant cyclohexane residues belonging to adjacent macrocyclic units are located up and down with respect to the aromatic cavity and block the formation of pore channels. In short, the key difference of form **1b** or **13** compared to form **1a** is that the macrocyclic tetraimines instead of forming centered columnar assemblies, they are placed into offset columnar arrangements (Figure 2C−D).[20]

The solid materials **1a**, **1b**, and **13** are sparingly soluble in $CDCl_3$ and totally insoluble in polar solvents such as MeOH-d_4 or DMSO-d_6. Even achieving solutions of these solids in concentrations suitable for NMR studies is challenging. To dissolve crystalline samples of **1a**, **1b** and **13** in $CDCl_3$ required long times and the help of vigorous shaking, high temperature, and/or sonication. Under these premises, the ^{1}H NMR spectra in $CDCl_3$ solutions of both, **1a** and **1b** recorded at room temperature displayed narrow well-resolved signals that were completely superimposable. This result indicated that the dissolution process promoted the conversion of macrocycle **1** into a single conformer or to a mixture of conformers that interconverted rapidly on the NMR time scale. Given that **1b** is the thermodynamic form of **1**, we propose that the energetically more favorable conformation of **1** in solution must be similar to the one adopted in form **1b**.

To support the hypothesis of the presence of a preferred or exclusive stereoisomer in solution, we performed the condensation reaction affording **1** in refluxing MeOH. In this solvent, the templating effect of the EtOAc disappears, and the condensation reaction of macrocycle formation is much faster. After 6 h at reflux, the resulting solid product was collected by filtration and analyzed by NMR (^{1}H and ^{13}C, ^{1}H−^{1}H COSY, ROESY, HSQC). The spectroscopic analyses revealed the presence of two sets of separate proton signals that were not involved in chemical exchange on the ROESY time scale. We assigned these two sets of proton signals to two different macrocyclic conformers of the teraimine, **1** and **1′** produced under these conditions. By integration of selected signals, we assigned a ratio of 60/40 of the two conformers. We also observed additional proton signals in the proton spectrum that corresponded to minor amounts of open and linear oligomers. The ESI-HRMS analysis of the mixture of cyclic conformers **1** + **1′**, showed an intense peak at m/z 837.4891 in complete agreement with the formula $C_{60}H_{61}N_4$ that we assigned to $[M + H]^+$, the molecular ion for the macrocyclic tetraimine **1** (Supporting Information). Taken together, these results indicated that under the harsh reaction conditions of refluxing MeOH two diastereomeric conformers were formed and that they were involved in a slow interconversion process on the chemical shifts and ROESY time scales. Unfortunately, all our attempts to isolate the minor stereoisomer **1′**, through fractional recrystallization or column chromatography (Al_2O_3; $CHCl_3$), were unsuccessful and resulted in the isolation of mixtures containing both stereoisomers probably due to partial interconversion.

In order to evaluate the thermodynamic preference of the two conformers, we heated a $CDCl_3$ solution of the mixture of **1** and **1′** at 45 °C. We used ^{1}H NMR spectroscopy to monitor the changes of the mixture with time. We observed a gradual depletion of the proton NMR signals assigned to the less abundant conformer **1′** and the concomitant increase of the proton signals assigned to **1** (Supporting Information). At this point, owing to the dynamic nature of the imine bonds, we cannot rule out the possibility of interconversion between **1′** and **1** through a ring-opening-ring-closing reaction mechanism

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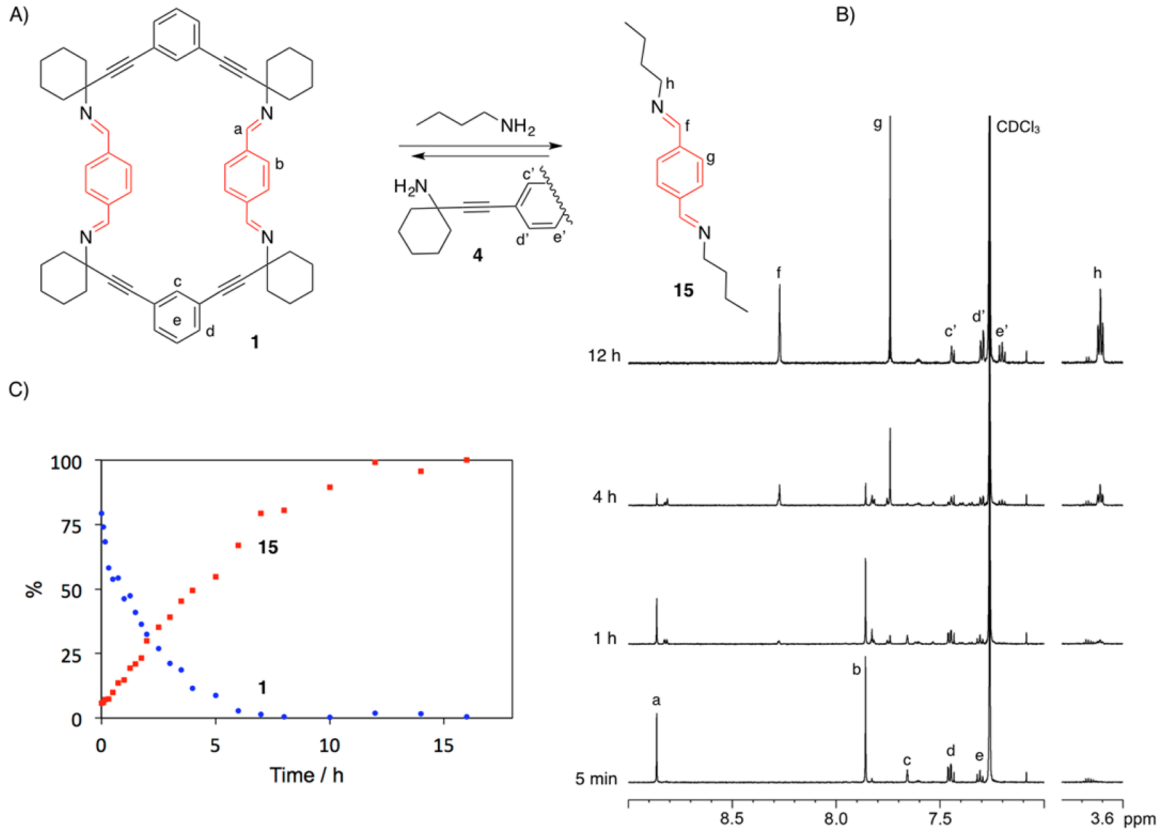

Figure 3. (A) Transimination reaction of macrocycle **1** with *n*-$BuNH_2$ in $CDCl_3$ at 25 °C. (B) Representative sections of the ^1H NMR (600 MHz) spectra registered at time intervals. The letters indicate NMR assignation. (C) Graphical representation showing the evolution of the imine-exchange with time.

or by imine metathesis. It is known that imine metathesis is catalyzed by small amounts of primary amines.[21] In fact, the addition of an excess of *n*-butylamine to a solution of the macrocyclic tetraimine **1** in $CDCl_3$ at room temperature produced the complete transimination of **1** into the bis-imine **15** (Figure 3).

In summary, the solid **1a** derived from the macrocycle **1** is the only porous material suitable for sorption experiments. Among the potential guests for liquid−solid sorption experiments, phthalates are interesting due to environmental and health issues.[22] In this work, we used different phthalates to investigate the geometric boundaries of **1a**. The sorption experiments were carried out by moving several prismatic crystals of both, the solvate **EtOAc@1** or the apohost **1a** into a test vial containing the phthalate under test. The lower density of the **EtOAc@1** crystals (1.089 g/mL) compared to diethyl phthalate (EtPh) (1.12 mg/L), allowed us to visually monitor the progress of the guest exchange (Figure 4A). Soon after being in contact with EtPh the crystals of **EtOAc@11** started to sink into the EtPh liquid.

The solid-state structure of **EtPh@1** was solved by single-crystal X-ray diffraction (Supporting Information). The analysis of the X-ray data showed that the EtPh molecules are in disordered positions within the channels of **1**, thus indicating the weak interaction existing between the walls of the porous material and the included guest. In fact, the uptake of the guest molecule could be reversed by just moving the **EtPh@1** or the **EtOAc@1** crystals into a vial containing fresh ethyl acetate or diethyl phthalate, respectively. After several EtOAc-EtPh exchanging cycles, we did not observe any morphological

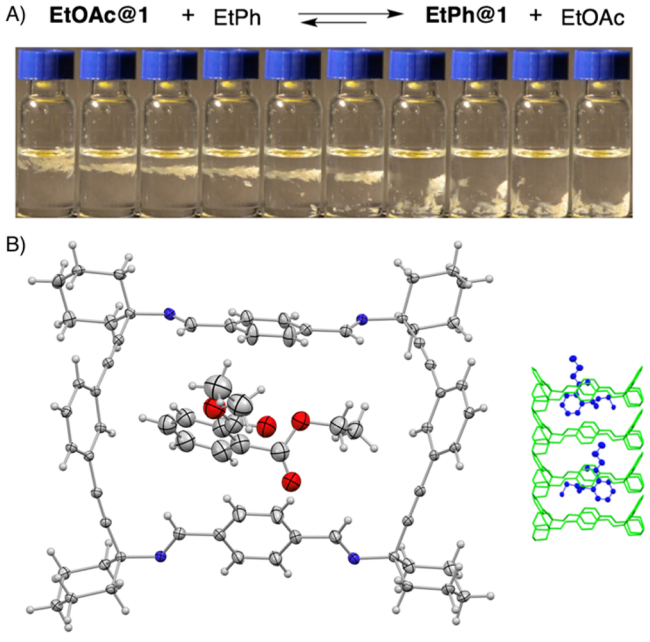

Figure 4. (A) Sequential images showing the progress of the diethyl phthalate uptake by **EtOAc@1** crystals. The images were taken every 5 min (t_{tot} = 50 min). (B) ORTEP representation (50% probability displacement ellipsoids) of the X-ray crystal structures of **EtPh@1** crystals. The disorder affecting the EtPh molecule was removed for clarity. The inset shows the relative orientation of two molecules of EtPh inside the channel.

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alteration of the crystal structure of **EtOAc@1**. However, if the crystals **EtPh@1** were immersed in MeOH instead of EtOAc, the exchange process became irreversible due to the irreversible transformation of **1a** into the nonporous polymorph **1b**. The irreversible release of EtPh by MeOH was monitored by ^{1}H NMR spectroscopy showing that desorption was complete after 12 h. Similar results were obtained using the apohost **1a** instead of the solvate **EtOAc@1**. In this case, the adsorption process of EtPh on **1a** was slow, and a steady rise of the amount of included EtPh guest on **1a** was observed until saturation took place after 48 h. It has to be noted that the adsorption rate on **1a** is much faster with other small molecules. For instance, adsorption of nitromethane (55.3 Å^3) on **1a** was complete in 5 min. In this case, the adsorption of nitromethane was evidenced by the massive air bubbles displacement from the solid **1a** (Supporting Information). The crystallographic stoichiometry 1:2 for **EtPh@1** was also confirmed by a weight loss of 12,9% in the thermogravimetric analysis of **EtPh@1** and by integration of the proton spectrum registered on a dissolved sample of **EtPh@1** (Supporting Information). The maximum available void volume per macrocycle is 274 Å^3 and the molecular volume calculated for EtPh is 232 Å^3 thus, taking into account the 1,2 stoichiometry of **EtPh@1**, (232 Å^3/2 × 274 Å^3) gives a packing coefficient close to 0.42. This value is smaller than the 55% rule of Mecozzi and Rebek for the optimal filling of capsules.[23] The molecular volumes of other common phthalates, namely dibutyl phthalate (BuPh, 305 Å^3), butyl benzyl phthalate (BnPh, 363 Å^3), and 2-diethylhexyl phthalate (OcPh, 451 Å^3) are higher than that of EtPh, and their packing coefficients are 0.55, 0.66, and 0.82, respectively. Hence, a preferential adsorption of EtPh over the other bulkier phthalates is expected. Pair-wise competitive sorption experiments were performed with crystals of **EtOAc@1** and 1:1 molar ratio liquid mixtures of pairs of phthalates. After 48 h of evolution at room temperature, the ^{1}H NMR analysis recorded on the dissolved samples showed the selective adsorption of EtPh over BuPh and BnPh in a 3:1 and 5:1 ratio, respectively. On the other hand, the absorption of OcPh was never detected. The size and volume of OcPh are larger than the geometrical limits imposed by the porous **EtOAc@1** material. All together, the sorption experiments serve to highlight the existence of a direct relationship between the volumes of the included guests and the sorption capabilities of the porous solids **EtOAc@1** and **1a**.

CONCLUSIONS

The condensation of 1,3- and 1,4-phenylene bis-propargylic diamines with terephthalaldehyde or isophthalaldehyde resulted in the formation of tetraimine macrocycles. The condensations were reversible but in all cases the products arising from a [2 + 2] cyclocondensation were predominant. In EtOAc as the solvent, the yields were low to moderate, but they provided the macrocycles as solid products readily isolable by filtration or decantation. However, several issues emerged. First, the unsubstituted macrocycles were very insoluble in all common organic solvents precluding any further study on them. This issue was solved synthesizing their cyclohexane-substituted equivalents. These macrocycles, featuring four 1,1-cyclohexane residues, were slightly soluble in chloroform, but they proved insoluble in EtOAc, MeOH, MeCN and DMSO. The lack of solubility cannot be considered disadvantageous since the macrocycles are intended for constructing porous organic molecular solids (POMs). The second, and more important issue is that only one member of this series of isomeric macrocycles showed porosity.

In this article, the synthesis of the porous macrocycle **1** has been modified to shorten the precipitation of the key EtOAc solvate **EtOAc@1**. Furthermore, we demonstrated for the first time the use of **1** both, as the EtOAc solvate or the apohost **1a**, for the preferential liquid−solid adsorption of diethyl phthalate over other commercial phthalates. Thus, expanding the use of a POM material based on the macrocycle **1** toward the reversible adsorption of sizable molecules in the liquid state at room temperature.

EXPERIMENTAL SECTION

All reagents were reagent grade and were used as purchased. ^{1}H, ^{13}C and 2D NMR spectra (at 300 and 600 MHz) and ^{13}C (at 75 and 150 MHz) spectra were recorded on 300 and 600 MHz spectrometers in $CDCl_3$ solutions at room temperature. The residual proton signal was used as reference. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Peaks assignments were aided by ^{1}H−^{1}H COSY, HMQC and HMBC experiments. Mass spectra were registered on Orbitrap mass spectrometer equipped with an electrospray module.

General Procedure for the Synthesis of the Bis-imines. The bis-propargyl diamine (0.21 g, 0.65 mmol) was dissolved in MeOH (20 mL) together with benzaldehyde (139 μL, 1.36 mmol). The resulting solution was refluxed for 8 h. The precipitation of a solid occurred after cooling to room temperature. The product was filtered, washed with MeOH and dried under a vacuum.

1,3-Dialkynylbenzene bis-imine 6. White solid, 0.2 g, 61% yield. mp = 121−124 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.84 (s, 2H), 7.82 (m, 4H), 7.64 (s, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.42 (m, 6H), 7.33 (t, J = 7.95 Hz, 1H), 1.87 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 158.2, 136.7, 134.8, 131.5, 130.6, 128.6, 128.5, 123.7, 92.0, 88.7, 63.6, 39.9, 25.5, 23.2; ESI-HRMS(+) m/z (%): calc. $C_{36}H_{37}N_2$ 497.2957; exp. 497.2949 $[M + H]^+$. Anal. Calcd for $C_{36}H_{36}N_2 \cdot 1/2H_2O$: C, 85.5; H, 7.38; N, 5.54. Found: C, 85.16; H, 7.34; N, 5.55.

1,4-Dialkynylbenzene bis-imine 7. Yellow solid, 0.25 g, 72% yield. mp = 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.86 (s, 2H), 7.84 (m, 4H), 7.50 (s, 4H), 7.45 (t, J = 3 Hz, 6H), 1.87 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 158.2, 136.7, 131.7, 130.7, 128.7, 128.5, 123.1, 93.1, 89.2, 63.7, 39.9, 25.6, 23.3; ESI-HRMS(+) m/z (%): calc. $C_{36}H_{36}NaN_2$ 519.2776; exp. 519.2770 $[M + Na]^+$. Anal. Calcd for $C_{36}H_{36}N_2$: C, 87.05; H, 7.31; N, 5.64. Found: C, 86.74; H, 7.30; N, 5.65.

Improved Synthesis of the Macrocyclic Tetraimine 1 (EtOAc@1). Terephthalaldehyde, (0.15 g, 0.468 mmol) and 1,1′-(1,3-phenylenebis(ethyne-2,1-diyl))bis(cyclohexan-1-amine) (0.063 g, 0.468 mmol), were dissolved in MeOH (55 mL). The resulting solution was refluxed for 5 h. After this period, the crude was evaporated under reduced pressure. The isolated solid was then suspended in EtOAc, and filtered. The solution was covered with parafilm and, after 5 days, 38 mg of the crystalline porous material was isolated (yield 10%). The remaining solution was covered again obtaining additional crops of the crystalline product as the EtOAc solvate (final practical yield ∼40−50%). This procedure is more convenient than the original one[14] as it reduces to a half the time spent on crystallization.

General Procedure for the Synthesis of the Isomeric Macrocyclic Tetraimines. A typical procedure was as follows: a solution of the propargyl diamine (400 mg, 1.248 mmol) and the dialdehyde (169 mg, 1.248 mmol) in EtOAc (120 mL) was placed in a 250 mL Erlenmeyer flask. The flask was covered with parafilm and let aside at room temperature for evolution. After a variable period ranging from several days to 8 weeks, the precipitated products were isolated by simple decantation of the solution. The solid whether amorphous or crystalline was washed with fresh EtOAc and dried.

Macrocyclic Tetraimine 8. White amorphous solid, (0.18g, 15%). mp >250 °C (dec.). ^{1}H NMR (600 MHz, $CDCl_3$, ppm), δ: 8.69 (s, 4H), 7.88 (s, 8H), 7.71 (s, 2H), 7.40 (t, J = 6.9 Hz, 6H), 4.77 (s, 8H);

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ESI-HRMS(+) m/z (%): calc. $C_{40}H_{29}N_4$ 565.2392; exp. 565.2379 $[M + H]^+$. The ^{13}C NMR spectrum could not be registered due to the low solubility of this compound.

Macrocyclic Tetraimine 10. White amorphous solid (0.28 g, 22%). mp >250 °C (dec.). ^1H NMR (600 MHz, $CDCl_3$, ppm), δ: 8.75 (s, 4H), 8.01 (d, J = 7.8 Hz, 4H), 7.97 (s, 2H), 7.51 (t, J = 7.2 Hz, 2H), 7.47 (s, 8 H), 4.81 (s, 8H); ^{13}C NMR (150.9 MHz, $CDCl_3$, ppm) δ 161.3, 136.6, 132.0, 131.3, 129.3, 129.2, 123.1, 87.9, 86.0, 47.7; ESI-HRMS(+) m/z (%): calc. $C_{40}H_{29}N_4$ 565.2392; exp. 565.2373 $[M + H]^+$; Anal. Calcd for $C_{40}H_{28}N_4$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.80; H, 4.99; N, 9.95.

Macrocyclic Tetraimine 12. White amorphous solid, (0.16g, 16%). mp >250 °C (dec.). ^1H NMR (600 MHz, $CDCl_3$, ppm), δ (ppm): 8.87 (s, 4H), 8.19 (s, 2H), 7.86 (s, J = 7.8 Hz, 4H), 7.63 (s, 2H), 7.45 (d, J = 7.5 Hz, 4H), 7.32 (t, J = 4.8 Hz, 4H), 1.80 (m, 40H); ESI-HRMS(+) m/z (%): calc. $C_{60}H_{61}N_4$ 837.4891; exp. 837.4891 $[M + H]^+$. The ^{13}C NMR spectrum could not be registered due to the low solubility of this compound.

Macrocyclic Tetraimine 13. Yellow crystals, (0.25g, 25%). mp >250 °C (dec.). ^1H NMR (600 MHz, $CDCl_3$, ppm), δ: 8.85 (s, 4H), 8.19 (d, J = 7.2 Hz, 4H), 7.62 (s, 2H), 7.48 (s, 10H), 1.81 (m, 40H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 157.3, 136.9, 133.1, 131.8, 129.3, 128.2, 123.1, 92.53, 89.5, 63.9, 39.9, 29.8, 25.5, 23.2; ESI-HRMS(+) m/z (%): calc. $C_{60}H_{60}N_4$ 837.4896; exp. 837.4905 $[M + H]^+$. Anal. Calcd for $C_{60}H_{60}N_4 \cdot H_2O$: C, 84.27; H, 7.31; N, 6.55. Found: C, 84.32; H, 7.29; N, 6.56.

Macrocyclic Tetraimine 14. White amorphous solid, (0.22 g, 21%). mp >250 °C (dec.). ^1H NMR (600 MHz, $CDCl_3$, ppm), δ: 8.84 (s, 4H), 7.85 (s, 8H), 7.47 (s, 8H), 1.83 (m, 40H); ESI-HRMS(+) m/z (%): calc. $C_{60}H_{61}N_4$ 837.4896; exp. 837.4885 $[M + H]^+$. The ^{13}C NMR could not be registered due to the low solubility of this compound.

Preparation of the Bis-imine 15.[24] Terephthalaldehyde (0.2 g, 1.461 mmol) and butan-1-amine (0.289 mL, 2.95 mmol) were dissolved in toluene (10 mL) and allowed to stir at room temperature for 2 h. The resulting solution was then concentrated under reduced pressure to afford 0.32 g of product as a yellow oil (320 mg, 89%). ^1H NMR (300 MHz, $CDCl_3$, ppm), δ: 8.28 (s, 2H), 7.75 (s, 4H), 3.62 (t, J = 7 Hz, 4H), 1.69 (q, J = 7 Hz, 4H), 1.39 (m, J = 7.5 Hz, 4H), 0.95 (t, J = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 159.8, 137.6, 129.5, 128.0, 127.7, 61.1, 32.5, 20.0, 13.4; Maldi-TOF m/z (%): calc. $C_{16}H_{25}N_2$ 245.201; exp. 245.208 $[M + H]^+$.

Liquid–Solid Sorption Experiments. A few single crystals of either, **1a** or **EtOAc@1** were soaked into the neat liquid guest (0.2–0.3 mL) to be included in the channels of the solid. After 48 h, the solution was removed, and the crystals rapidly washed with EtOAc (2 × 0.2 mL) and MeOH (2 × 0.2 mL) and dried under a vacuum for 5 min.

X-ray Crystal Structure Analysis. Single crystal X-ray diffraction data were collected at 100 K on a Bruker-Nonius FR591 Mo Kα rotating anode single crystal diffractometer equipped with an Apex II CCD area detector and Montel mirrors and an Oxford Cryostream Plus 700 Series. For the data collection the software *Apex2 V2010.7–0* (Bruker AXS 2010) was used. Crystal data for **7** (CCDC no. 1469775): $C_{36}H_{36}N_2$, M = 496.67, monoclinic, a = 9.710(10) Å, b = 5.980(4) Å, c = 24.309(15) Å, α = 90°, β = 92.459(16)°, γ = 90°, V = 1410.3(19) Å^3, T = 100(2) K, space group $P2(1)/c$, Z = 2, 7581 reflections measured, 2792 independent reflections (R_{int} = 0.1508). The final R_1 values were 0.0840 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1940 ($I > 2\sigma(I)$). The goodness of fit on F^2 was 0.849. Crystal data for **EtPh@1** (CCDC no. 1012390): $C_{66}H_{67}N_4O_2$, M = 948.24, monoclinic, a = 34.890(3) Å, b = 5.8074(4) Å, c = 28.103(2) Å, α = 90.00°, β = 98.310(2)°, γ = 90.00°, V = 5634.4(7) Å^3, T = 100(2) K, space group $C2/c$, Z = 4, 24070 reflections measured, 24070 independent reflections (R_{int} = 0.0000). The final R_1 values were 0.0717 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.2167 ($I > 2\sigma(I)$). The goodness of fit on F^2 was 1.034. Crystal data for **13** (CCDC no. 1469781): $C_{60}H_{60}N_4$, M = 837.12, monoclinic, a = 10.9226(8) Å, b = 10.4233(9) Å, c = 20.7193(17) Å, α = 90.00°, β = 97.876(3)°, γ = 90.00°, V = 2336.6(3) Å^3, T = 100(2) K, space group $P2(1)/c$, Z = 2, 3982 reflections measured, 3982 independent reflections (R_{int} = 0.0000). The final R_1 values were 0.0674 ($I > 2\sigma(I)$). The goodness of fit on F^2 was 1.052.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00768.

^1H, ^{13}C NMR and 2D spectra of the new compounds, and additional experimental details. (PDF)

Crystal structure for **7**, **13** and **EtPh@1**. (ZIP)

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Notes

The authors declare no competing financial interest.

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