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Polar Organic Cages for Efficient Azeotropic Mixtures Separation

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Dihydroxy-based polar organic cages (DIHO-cage) are reported to selectively separate toluene with 99.5% purity from an equimolar toluene/pyridine mixture resulting in subsequent superior purification of pyridine. The efficient separation and purification, enhanced by strong and multiple host/guest C–H···O interactions between the cage and toluene, showcases DIHO-cages as a suitable candidate for remarkable separation of such azeotropes at industrial scale.

One of the representative polar organic solvents that have been identified as "preferred" or "usable" industrial solvents is pyridine.[1] Pyridine with the boiling point of 115.3 °C is an important catalyst and solvent that is widely used in agrochemical, pharmaceutical and petrochemical industries.[1] Most importantly, the demand for pyridine globally is mostly driven by increased pharmaceutical use and as a denaturant in antifreeze mixtures.[2] On the other hand, toluene is heavily used to manufacture pesticides, coatings, synthetic resins, explosives, polyesters and benzoic acid.[1] Both toluene and pyridine are important industrial chemicals but pyridine often forms a minimum-boiling binary azeotrope with toluene (boiling point 110.0 °C; pyridine/toluene 23:77, molar basis) during production making separation of toluene and pyridine a difficult task, therefore, their purification has remained a great challenge.[3,4] Although, several methods have been used to separate and purify azeotropic mixtures, including azeotropic distillation,[5] pressure-swing distillation,[6,7] and extractive distillation,[8] among other techniques with great success but these methods have always been bedevilled with high operating costs, high energy consumption and some technical complexities.[9] So, the need for better and cost effective methods is urgent and necessary. Some new separation strategies that have emerged recently involve the use of the differences in the noncovalent interactions that exist between guests and the crystalline nonporous adsorptive materials.[10-17] Presently, few examples of these crystalline nonporous adsorptive materials are reportedly used for separation of minimum-boiling binary azeotrope mixtures involving polar compounds such as pyridine.[3b,18-20] The report by Chi and coworkers involves the use of a new cavity-extended version of calix[4]pyrrole (C4P) that forms nonporous adaptive crystals for the effective separation of polar compounds from the azeotrope mixtures of pyridine/toluene and 1,4-dioxane/water.[18] In another study by Huang and coworkers, nonporous adaptive crystals of cucurbit[6]uril (Q[6]) could separate pyridine from the mixture of toluene/pyridine with 100 % purity due to the formation of host/guest complex.[19] Also, Isaacs and coworkers reported the separation of pyridine from azeotrope mixtures of toluene, benzene and pyridine with more than 99.9 % purity even in a system with low pyridine content using double-cavity Nor-Seco-cucurbit[10]uril (ns-Q[10]).[20a] Most recently, Li and coworkers reported the use of macrocycle cocrystals for efficient removal of pyridine from equal molar toluene/pyridine mixture with 99.2%.purity.[20b] Common with all these examples is the fact that the separation occurs using the intrinsic cavity[18-20a] of specific dimension as revealed by the crystal structures of their respective macrocycles and could only capture the smaller size pyridine.

As part of the ongoing work in our group on the quest for organic cages for excellent separation performances/applications, we have deliberately prepared and utilized a polar **DIHO-cage** endowed with some hydrogen bond donor hydroxyl (-OH) groups and the possibility of forming extrinsic pores in their crystal packing that can accommodate any of these mixtures for efficient separation when compared to macrocycles with fixed/pre-sized cavity. We have also recently established that pre-sized or fixed cavity dimension is not a prerequisite for excellent separation most especially when larger guest molecules are involved.[21] Herein, we utilized polar organic **DIHO-cage** as adsorptive materials to separate the equimolar mixture of toluene/pyridine. Surprisingly, **DIHO-cage**

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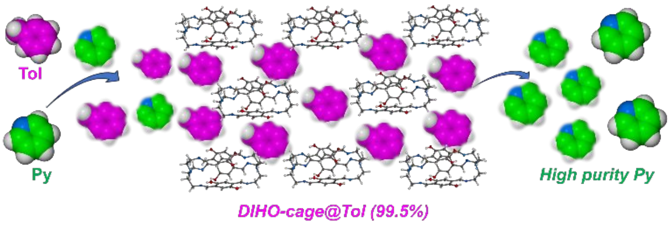
can capture and separate **Tol** from **Tol/Py** equimolar mixture with 99.5 % purity unlike most of the reported cases where pyridine is captured[18-20] instead of toluene (**Scheme 1**). To the best of our knowledge this is the first example of using a polar organic cage for efficient selective separation of **Tol** and subsequent purification of the polar compound **Py** in **Tol/Py** binary mixture.



Scheme1: Schematic representation of **DIHO-cage** as an adsorptive material for separation of toluene and pyridine equimolar mixture.

DIHO-cage was synthesized through a simple, cost effective and one-step condensation reaction of 1,5-dihydoxyterephtahaldehyde with flexible tris(2-aminoethyl) amine (TREN) in acetonitrile with good 70 % yield (**Scheme S1**).[22] Proton, ^{13}C NMR and mass spectra confirmed the successful synthesis of **DIHO-cage** (**Figures S1 and S2**). We have chosen **DIHO-cage** as our adsorbent as earlier mentioned because of its polar nature that would not only promote host/guest hydrogen bonding but also boost crystallinity.[23] Two different suitable single crystals **DIHO-cage@DCM** and **DIHO-cage@CHCl$_3$** were obtained when **DIHO-cage** was crystallized separately by diffusing acetonitrile into its DCM and Chloroform solutions respectively (**Figure S3 and Table S1**). **DIHO-cage@DCM** crystallizes in monoclinic system with $P2_1/c$ space group and **DIHO-cage@CHCl$_3$** crystallizes in monoclinic system with *C2/c* space group. The crystal structures of **DIHO-cage** with DCM and chloroform reveal that **DIHO-cage** has high propensity to form complex with most organic solvents utilizing the extrinsic pores in the crystal packing of the cage like some other reported (2+3) organic cages (**Figure S1**).[22,24-27] In fact in case of **DIHO-cage@DCM** there are two molecules of DCM guest molecules with one molecule of the cage in the asymmetric unit while the crystal structure of **DIHO-cage@CHCl$_3$** has one molecule of the cage with one molecule of chloroform in the asymmetric unit (**Figure S3**).

Thermogravimetric analysis (TGA) of the assynthesized **DIHO-cage** shows no appreciable weight loss below 300 °C indicating that it has no solvent left after the synthesis. Although there is no residual solvent left in the assynthesized cage, but we decided to activate at 40 °C for 2 h to ensure it remains empty before use for all the subsequent experiments (**Figure S4**). Powder X-ray diffraction (PXRD) confirmed the bulk purity of the as-synthesized **DIHO-cage**. The PXRD pattern of the activated **DIHO-cage** confirms that its crystallinity is retained after desolvation (**Figure S5**). The Brunauer–Emmett–Teller (BET) surface area of the activated **DIHO-cage** was determined to be 14 $m^2 g^{-1}$ by N_2 gas sorption isotherm at 77 K indicating that **DIHO-cage** is non-porous (**Figure S6**). The adsorption efficiency of the activated **DIHO-cage** in the presence of pyridine and toluene mixture was then tested through solid–vapour adsorption experiments. Notably, PXRD and ^1H-NMR results for single component and 1:1 (v/v) binary mixture experiments revealed that **DIHO-cage** may be selective toward toluene over pyridine (**Figure 1 and Figure S7**).

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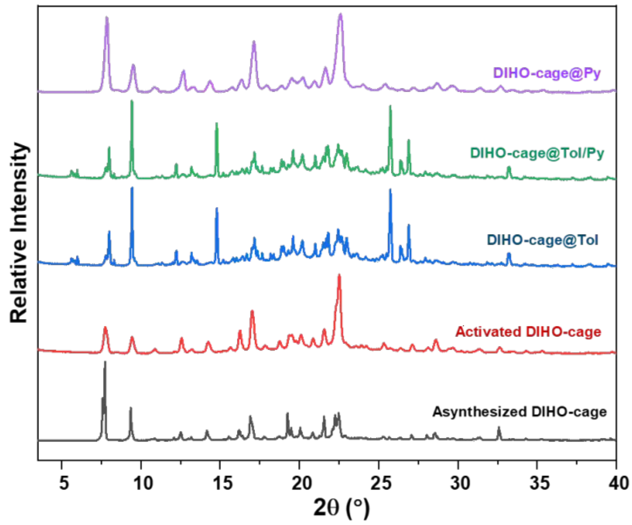

Figure 1: PXRD patterns showing the adsorption of **Tol** and **Py** by the **DIHO-cage** after 24 h exposure.

The adsorption performance of **DIHO-cage** was further investigated using different ratios of **Tol/Py** binary mixture (1:3 and 3:1 (v/v)) to replicate the ideal industrial situation to further understand the influence of these ratios on the **DIHO-cage** performance. The ^1H-NMR and gas chromatographic results of **DIHO-cage** after adsorption of different ratios of toluene and pyridine confirmed a selective adsorption of toluene over pyridine with relatively high purity of 97.4% and 99.9% for 1:3 and 3:1 (v/v) Tol/Py mixtures respectively after one adsorption process (**Figures S8 and S9**). To investigate the dynamics of the adsorption process, we carried out time-dependent solid-vapour sorption experiments. It took **DIHO-cage** about 10 h to accommodate *ca* 1.0 mole of **Tol** on average per cage with the adsorption capacity of 134.9 mg/g (**Figure S10**). To better understand the mechanism of the selective adsorption of **Tol** over **Py**, first, single crystals of **DIHO-cage@Tol** were grown by vapour diffusion of MeCN into toluene/DCM solution of **DIHO-cage** at room temperature (**Table S1**). Single crystals of **DIHO-cage@Py** were also obtained using the same approach with **Py**. In the crystal structure of **DIHO-cage@Tol**, the ratio of the **DIHO-cage** to **Tol** is 1:1 (**Figure S11**).

From the crystal structure, the **Tol** guest molecules were situated in the extrinsic cavity generated by the crystal packing as expected (**Figure 2 and Figure S12**). As exhibited in the crystal packing of **DIHO-cage@Tol**, **Tol** molecules are situated between the two layers and form a continuous channel when viewed along *b*-axis (**Figure S12**). There exist multiple C–H···O host/guest intermolecular interactions. The C–H···O interactions (3.434 Å, 3.497 Å and 3.756 Å) occur between some protons on the **Tol** and the oxygen atom of the -OH group on the cage molecule (**Figure 3, Figure S13 and Table S2**). The crystal packing also shows some other noncovalent

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intermolecular interactions (e. g. C–H···π = 3.703 Å, etc.) between some protons of the cage and the centroid of the aromatic ring of **Tol** guest (**Figure 3**).

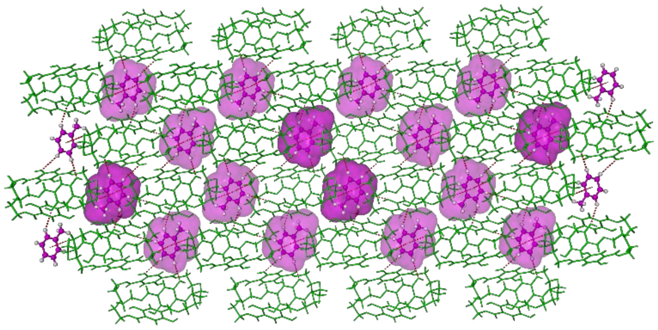

Figure 2: Perspective view showing **Tol** guest molecules (pink) in the crystal packing of **DIHO-cage@Tol**.

Also available are some host/host intermolecular interactions between two neighbouring cages (**Figure S14 and Table S3**). Unlike **DIHO-cage@Tol**, no **Py** guest molecule is found in the crystal structure of **DIHO-cage@Py**. The ability of **DIHO-cage** to form complex with only **Tol** suggests its bias to favour the uptake of **Tol** from **Tol/Py** mixture.

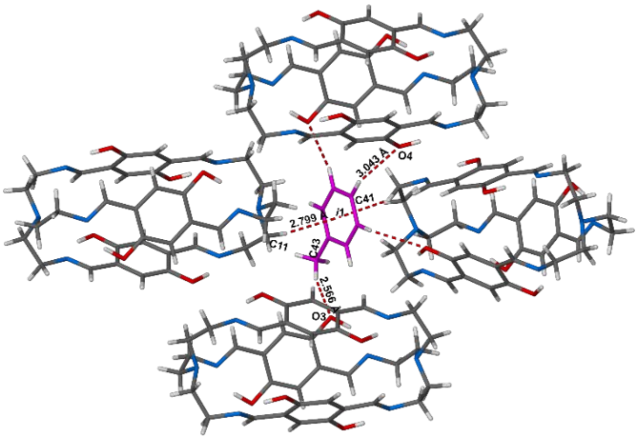

Figure 3: Crystal packing showing different host-guest intermolecular interactions in **DIHO-cage@Tol**.

Furthermore, from all the crystal structures available there are very strong O–H···N intramolecular hydrogen bonding interactions within the cage (**Figure S15**). These strong intramolecular interactions, apart from preventing the aromatic groups from rotating, appear therefore to also outcompete any possibly formed intermolecular interactions rendering the hydrogen atom on the -OH groups unavailable as H-bond donor for host-guest hydrogen bonding intermolecular interactions and this could apparently be the reason why **Py** (H-bond acceptor) is not captured by the **DIHO-cage**.[28] Having established the ability of **Tol** guest molecule to interact with the **DIHO-cage**, it is important to mention that the size and/or shape of **Tol** could have also contributed to this selective uptake. Since **DIHO-cage** uses its extrinsic cavity for the uptake, it simply implies that there is no limitation in the cavity size or dimension, therefore allows for the most favorable orientations with the larger **Tol** guest molecule and not the smaller size **Py** to form stable host-guest intermolecular interactions.[21,29]

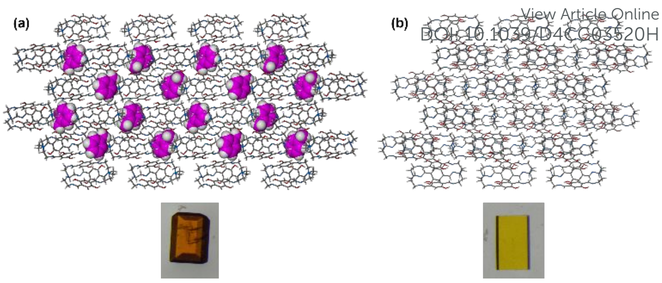

Figure 4: Crystal packing and images of **(a) DIHO-cage@Tol** and **(b)** empty **DIHO-cage@Py** showing the vapochromic behaviour of **DIHO-cage**.

To further show the selectivity of the **DIHO-cage** for **Tol**, we grew single crystal in 1:1 (v/v) mixture of toluene and pyridine. The orange single crystal obtained was analyzed using SCXRD and crystallizes in the same space group as when the crystal was obtained directly from toluene alone. This result confirms that **DIHO-cage** can selectively capture **Tol** in the mixture of **Tol/Py** and this can also be visualized in the different colours of the crystals with/without **Tol** (**Figure 4, Figures S16-S18 and Table S1**). We then confirm that the guest free **DIHO-cage** can be regenerated from **DIHO-cage@Tol** simply by washing with hexane and allow it to dry at very reduced temperature of 45 °C under vacuum. This approach ensures the robustness of the **DIHO-cage** to withstand several adsorption-desorption processes/cycles without dropping in its performance is retained (**Figures S19 and 20**).

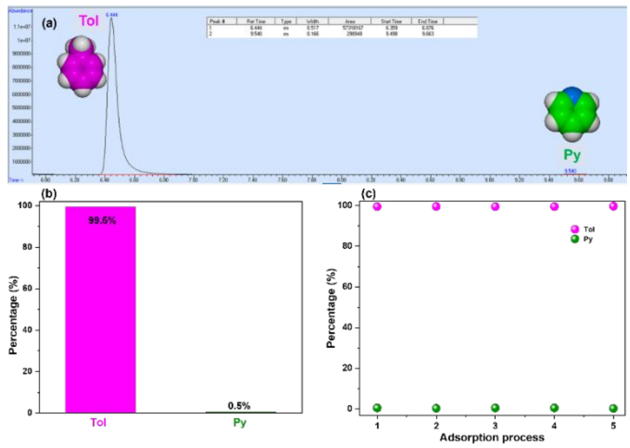

Figure 5: (a) Relative amount of **Tol** and **Py** adsorbed by activated DIHO-cage **(b)** Percentages of **Tol** and **Py** adsorbed by activated DIHO-cage as determined by GC-MS **(c)** relative uptake of **Tol** and **Py** after 5 adsorption processes/cycles.

To further establish and corroborate the fact that the **DIHO-cage** has affinity for **Tol**, gas chromatography (GC) analysis was carried out, the results confirmed the adsorption and selectivity of **Tol** over **Py** by **DIHO-cage** with 99.5 % purity (**Figure 5a&b**) in one adsorption process. The high percentage purity of the **Tol** captured persists at 99.5 % after five adsorption processes and this simultaneously improves the percentage purity of the **Py** left behind to *ca.* 100 % (**Figure 5c and Figure S21**). This observation further confirms that high purity **Py** could also be achieved.

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In summary, we have successfully demonstrated that a polar crystalline organic cage **(DIHO-cage)** can selectively adsorb only toluene in 1:1, 1:3 and 3:1 (v/v) binary mixtures of **Tol/Py**. In this work, the **DIHO-cage** shows double advantages of efficient **Tol** uptake (99.5%) and subsequent superior purification of pyridine after few adsorption processes. Although the **DIHO-cage** is fortified with hydrogen donor hydroxyl group (-OH) but could only act as a hydrogen bond acceptor forming host-guest complex with toluene (H-bond donor) instead of pyridine (H-bond acceptor) via numerous host/guest C–H···O and C–H···π intermolecular interactions as revealed by their crystal structures. This interesting phenomenon bestows **DIHO-cage** with the power to capture only toluene unlike some recently reported adsorptive materials for Tol/Py azeotrope mixture. This selective uptake and subsequent purification are accompanied with a color change enabling the direct visualization of the entire adsorption of **Tol** by **DIHO-cage**. We believe that this result would serve as an excellent precedent for more remarkable separations of other azeotrope mixtures using organic cages.

All authors have given approval to the final version of the manuscript.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI† with the crystallographic data for all the structures deposited at the CCDC and can be obtained from https://www.ccdc.cam.ac.uk/structures.

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Data availability

The data supporting this article have been included as part of the ESI† with the crystallographic data for all the structures deposited at the CCDC and can be obtained from https://www.ccdc.cam.ac.uk/structures.