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Acyclic cucurbituril as sequestrant for acetaminophen

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Acyclic CB[*n*]-type host H4 functions as a solid state sequestrant for pharmaceutical micropollutants (PMs) from water, reaching up to 99.8% removal efficiency for acetaminophen within 5 minutes. A head-to-head study shows H4 performs at least as well as activated charcoal (DARCO®) at sequestering acetaminophen from simulated gastric fluid.

The field of chemistry greatly impacted both the quality of human life and life expectancy throughout the 20th century by the development of a wide range of pharmaceuticals including antibiotics, oral contraceptives, antidepressants (*e.g.* citalopram), cardiovascular medicines (*e.g.* propranolol), opioid analgesics, and non-steroidal anti-inflammatory drugs (*e.g.* ibuprofen and acetaminophen).[1] The over-reliance of modern society on over-the-counter and prescription medications along with issues of non-compliance, improper disposal, and abuse has led to numerous societal problems including antibiotic resistance, pollution of water bodies by PMs, and high levels of drug overdose deaths.[2,3] In this context, acetaminophen – which is the first-line analgesic in pain treatment and one of the most widely consumed over-the-counter and prescription pharmaceuticals – is of particular importance.[4,5] This widespread use makes acetaminophen and its metabolites key contaminants in water bodies causing direct oxidative stress and neurotoxicity to aquatic organisms.[1,2,6,7] In the United States, acetaminophen overdoses account for nearly 56 000 emergency room visits, 2600 hospitalizations, and 500 deaths a year.[8] Additionally, acetaminophen is metabolized by hepatic cytochrome P450's into *N*-acetyl-*p*-benzoquinoneimine (NAPQI) which depletes hepatic glutathione and increases NAPQI-protein adducts leading to significant hepatic injury.[8] Acetaminophen toxicity accounts for 50% of acute liver failure and 20% of liver transplants in the United States.[8] Activated charcoal is currently used as the primary adsorbent in emergency overdose treatment and waste water treatment plants.[9–11] *N*-Acetyl cysteine – which increases glutathione synthesis – is FDA approved as a specific antidote for acetaminophen toxicity.

Over the years, a variety of methods to remove micropollutants from water have been reported including flocculation, coagulation, filtration, reverse osmosis, photodegradation, chemical oxidation, and adsorption.[12] The pioneering work of Dichtel on the use of β-cyclodextrin (CD) derived polymers[13,14] for the removal of micropollutants from water stimulated supramolecular chemists to explore the use of other classes of macrocycles including calixarenes, calix[4]pyrroles, pillararenes, cavitands, and naphthotubes in this application.[15–21] In this context, macrocyclic cucurbit[*n*]urils (CB[*n*]) are particularly attractive due to their high affinity binding, very low aqueous solubility (CB[6]: 6.5 μM, CB[8]: 10 μM), high biocompatibility, and accessibility from inexpensive starting materials.[22–29] Over the past 15 years, the Isaacs group has synthesized a variety of water soluble acyclic CB[*n*]-type hosts, studied their molecular recognition properties, and explored their application as *in vivo* sequestrants for neuromuscular blockers, anesthetics, and drugs of abuse.[30–33] Along the way, we synthesized numerous water insoluble variants including the catechol walled glycoluril tetramer derived host **H4** (water solubility: 3.4 μM, Fig. 1a) which acts as a solid state sequestrant for endocrine disrupters (bisphenol A, bisphenol S), dyes (methyl violet), perfluoroalkyl substances, and iodine.[25,34] A limitation of **H4** in these applications is that a large molar excess is required to achieve >90% removal efficiencies (RE). In this work, we present the use of **H4** as a solid state sequestrant for pharmaceutical micropollutants from water at both low (250 μM) and high PM concentration (≤90 mM) to simulate water body contamination and overdose scenarios.

Initially, we investigated the solid state sequestration efficiency of **H4** toward phenol and the panel of PMs (Fig. 1b) which are prevalent in water bodies.[6,11] Experimentally, we incubated a fixed amount of **H4** (2.0 mg) for 2 hours at 25 °C using a ThermoMixer™ with different volumes of each PM

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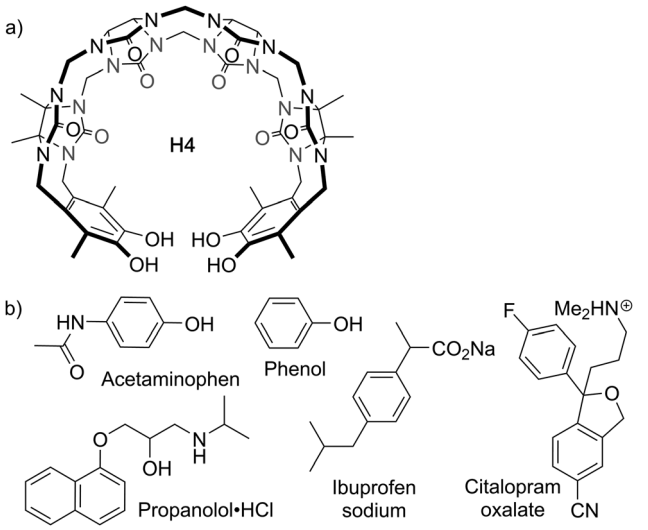

Fig. 1 Chemical structure of: (a) acyclic CB[*n*]-type receptor **H4** and (b) five compounds (PMs and phenol) used in this study.

(0.25 μM) to create different **H4**:PM molar ratios. Following centrifugation, the concentration of each PM in the supernatant was determined by UV/vis spectroscopy and the removal efficiency (RE) values were calculated as described previously (SI, eqn (S1)).[25] Fig. 2a shows the UV/vis spectra collected for acetaminophen (250 μM) alone and after sequestration with solid **H4** (0.5, 1, 2, 4, 8 equivalents). Fig. 2b shows that **H4** functioned as a solid-state sequestrant for all five compounds with RE values ranging from 35% (ibuprofen) to 99.8% (acetaminophen) at an 8 : 1 **H4** : PM molar ratio. Significantly, **H4** functioned as a very effective solid state sequestrant for acetaminophen (RE: 95%) even at a 2 : 1 **H4** : acetaminophen molar ratio. Conversely, **H4** functioned poorly for ibuprofen sodium (RE = 35% at 8 : 1 molar ratio); this is likely due to unfavorable electrostatic interactions between its anionic carboxylate and the electrostatically negative C═O portals of **H4**.[35] **H4** also functioned poorly for citalopram with 39% RE, presumably due to its steric bulk. Conversely, **H4** functioned moderately well as a sequestrant for propranolol (RE: 78%) and phenol (RE: 82%) at an 8 : 1 **H4** : PM molar ratio. Interestingly, the RE for propranolol is lower than would be expected based on its structure due to the fact that propranolol increases the solubility of **H4** by forming the **H4**·propranolol complex which can be detected by ^{1}H NMR spectroscopy of the supernatant (SI, Fig. S14). In addition to achieving a high RE value, it is important that a solid sequestrant is recyclable and exhibit rapid adsorption. Previously, we showed that **H4** could be recycled and reused for the sequestration of organic micropollutants over five cycles.[25] As part of this study, we confirmed that **H4** can be recycled by washing with methanol and water and maintains its high RE values for acetaminophen removal over three cycles (SI, Fig. S34). We also performed kinetic studies varying the incubation time of acetaminophen (250 μM) with **H4** at an 4 : 1 **H4** : acetaminophen molar ratio (SI, Fig. S10). Under these conditions, **H4** achieved a RE value of 93% after only 60 seconds showcasing **H4** as a fast acting and effective

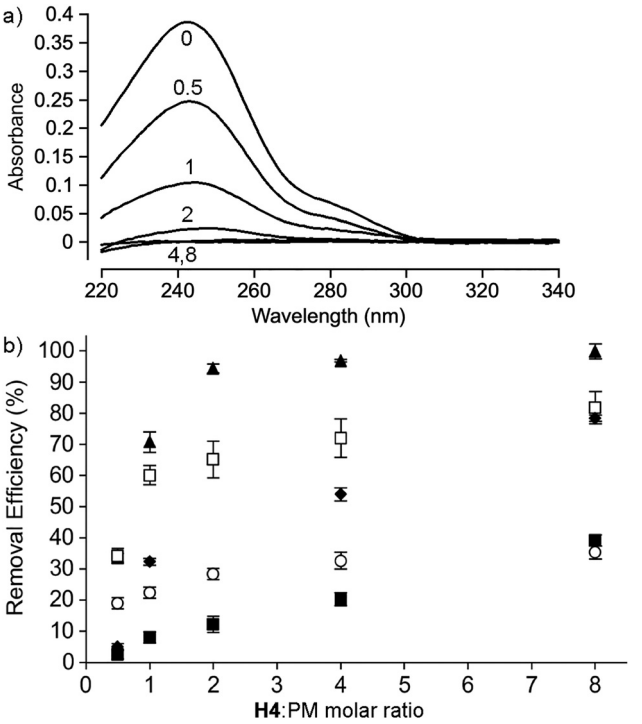

Fig. 2 (a) Representative UV/vis spectra recorded for acetaminophen (250 μM) alone and after incubation with solid **H4** (0.5, 1, 2, 4, 8 equivalents) for 2 hours. (b) Plot of removal efficiency of PMs (250 μM) from water determined by UV/vis measurements of the supernatant after incubation with **H4** for 2 hours at RT as a function of **H4**:PM molar ratio. Key: Acetaminophen (▲), phenol (□), propranolol (♦), ibuprofen (○), citalopram (■). Experiments were performed in triplicate. Error bars were determined by propagation of uncertainty.

adsorbent for acetaminophen. For comparison, Dichtel's porous CD polymer exhibits rapid uptake of a variety of micropollutants (seconds to minutes) whereas Sessler's porous calix[4]pyrrole polymer requires 10 minutes to reach 90% RE for methylene blue.[13,15] We previously measured the BET surface area of **H4** as 25 $m^2\ g^{-1}$ which is substantially lower than Dichtel's CD polymer (263 $m^2\ g^{-1}$).[25] The excellent removal efficiency of **H4** for acetaminophen despite its low BET surface area strongly suggests that acetaminophen is included in the cavity of solid **H4**.

Next, we performed additional experiments to uncover some of the reasons behind the outstanding removal efficiency of **H4** toward acetaminophen. First, we used ^{1}H NMR spectroscopy to confirm the high removal efficiency determined by UV/vis spectroscopy. Experimentally, we performed the solid-state sequestration of acetaminophen (0.25 mM or 90 mM) in D_2O using 2 equivalents of **H4**. ^{1}H NMR spectra recorded for the supernatants (SI, Fig. S12 and S13) did not show any resonances for acetaminophen confirming the high RE values determined by UV/vis spectroscopy. Next, high resolution mass spectrometry of the supernatant (SI, Fig. S17) was performed, which revealed the presence of ions corresponding to [**H4**·acetaminophen + H]$^+$ at *m*/*z* 1172.46584, [**H4** + Na]$^+$ at *m*/*z* 1043.38498, [**H4**·acetaminophen + 2Na]$^{2+}$ and [**H4** + 2Na]$^{2+}$ at *m*/*z* 533.18716 with ≤ 6 ppm accuracy which confirms the affinity of **H4** for acetaminophen in water.

Given the water insolubility of **H4** and the **H4**·acetaminophen complex, we attempted to perform a ^{1}H NMR titration in CF_3CO_2H (TFA) which is one of the only solvents capable of dissolving **H4**. Unfortunately, we observed the formation of a new AA'BB' pattern in the aromatic region of the ^{1}H NMR spectrum; GC-MS established that acetaminophen undergoes trifluoroacetylation under these conditions (SI, Fig. S15).[36] We also performed solid state magic angle spinning ^{13}C NMR spectroscopy of the solid obtained upon sequestration of acetaminophen from water using **H4** (SI, Fig. S16). The spectra clearly demonstrate the presence of both **H4** and acetaminophen in the solid and display small changes in chemical shift relative to uncomplexed acetaminophen. However, we could not use this data to elucidate the geometry of interaction between **H4** and acetaminophen in the solid.

Attempts to grow crystals of **H4**·acetaminophen from TFA by slow evaporation and vapor diffusion methods (antisolvents: MeOH, EtOH, *i*-PrOH and acetone) were not successful. Therefore, a different crystallization protocol was employed (Fig. 3a). First, **H4** was crystalized from TFA by vapor diffusion of *i*-PrOH. Then, TFA was removed and the crystals were washed with EtOH. Next, the crystals were soaked in a solution of acetaminophen (550 mM) in EtOH which provided crystals suitable for single crystal X-ray diffraction. Unfortunately, the disorder within the cavity of the **H4** was too high for accurate structural elucidation of the complex. Therefore, the crystals were crushed and soaked in an ethanolic solution of acetaminophen (550 mM). The structure of the microcrystalline **H4**·acetaminophen complex was solved by electron diffraction (Fig. 3b).[37–39] Acetaminophen is held inside the cavity of **H4** by a combination of three H-bonds (*a*, *b*, *c*) and π–π interactions. The three H-bonds possess the following H···O distances (*a*: 2.03, *b*: 2.01, *c*: 1.76 Å), O···O(N) distances (*a*: 2.98, *b*: 3.02, *c*: 2.71 Å), and (N)O–H···O angles (*a*: 158.95, *b*: 163.16, *c*: 156.95°). A fourth H-bond (*d*) is formed between the tips of the aromatic sidewalls (H···O: 1.97 Å, O···O: 2.76 Å, O–H···O angle: 134.00°). The acetaminophen guest also engages in π−π interactions with one of the aromatic sidewalls. The distance of the phenylene C-atoms of acetaminophen from the mean plane of the C-atoms of the aromatic sidewall average 3.461 Å which is in agreement with the accepted π−π stacking distance of 3.4 Å.[40] Fig. 3c shows the packing of four equivalents of the **H4**·acetaminophen complex roughly along the *y*-axis in the solid. The convex face of one equivalent of **H4**·acetaminophen engages in head-to-tail type offset π−π interactions with the adjacent equivalent of **H4**·acetaminophen. The CH_2-bridges of the *o*-xylylene sidewalls of one molecule of **H4** are located above the opposing aromatic sidewall of the adjacent **H4**. The distance of the C-atoms of one aromatic sidewall to the mean plane of the opposing sidewall averages 3.388 Å.

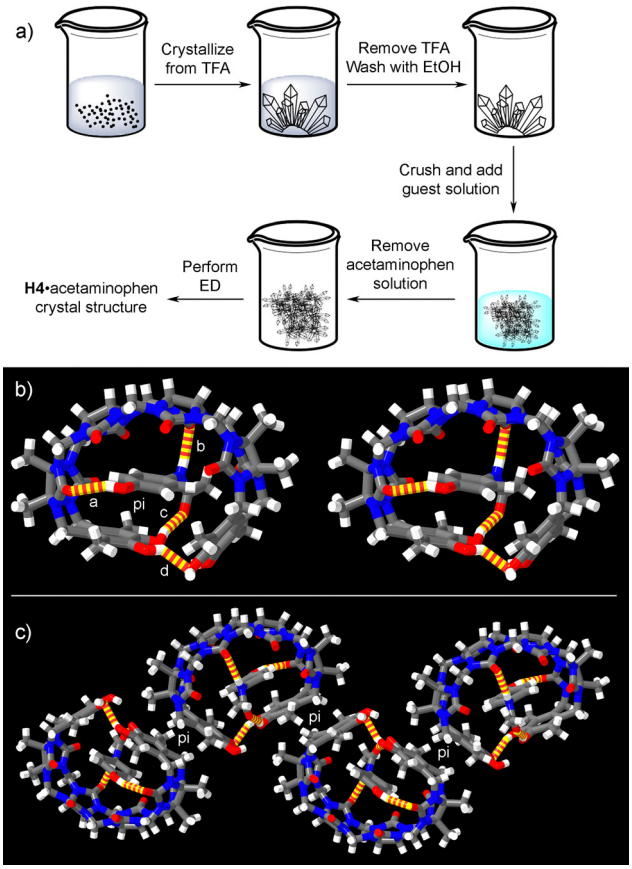

Fig. 3 (a) Illustration of the crystallization process for **H4**·acetaminophen complex. 3D-ED structure of **H4**·acetaminophen: (b) cross-eyed stereo-view of a single complex (**H4**·acetaminophen) in the crystal. (c) Representation of the tape-like packing of the **H4**·acetaminophen complex in the crystal. Color code: C, grey; H, white; N, blue; O, red; H-bonds red-yellow striped.

Given the excellent RE values achieved by **H4** toward low [acetaminophen] (250 μM) relevant for environmental pollution of water bodies, we wondered whether **H4** would perform as well at high [acetaminophen] (≤90 mM) more relevant in an overdose situation. Fig. 4a and b show the RE values achieved for a series of different acetaminophen concentrations (10, 30, 50, 70, 90 mM) at 1 : 2 and 2 : 1 **H4** : acetaminophen molar ratios upon incubation at 37 °C for 5 minutes in H_2O. At a 2 : 1 **H4** : acetaminophen ratio, the RE values are very high whereas at a 1 : 2 ratio roughly half the acetaminophen is removed which provides additional support for our conclusion that acetaminophen is captured inside the cavity of **H4**. As a comparator, we selected DARCO® activated charcoal (mesh size 12–20) and used equal masses relative to **H4** to sequester acetaminophen under identical conditions (37 °C, H_2O, 5 min) and the results are reported in Fig. 4a and b. These results show that **H4** performs as well as activated charcoal which is used clinically as an antidote for acetaminophen poisoning. To more fully mimic an oral acetaminophen overdose situation, we performed related sequestration experiments at 37 °C using simulated gastric fluid (SGF, Biochemazone BZ175) as the medium. SGF contains NaCl (200 mM) and pepsin (3.2 g L^{-1}) and has pH 1.5 which we thought might interfere with the sequestrant abilities of **H4** but not activated charcoal. Fig. 4c and d shows the RE values determined during the sequestration of acetaminophen (10, 30, 50, 70, 81 mM) from SGF at 37 °C by **H4** or an equal mass of DARCO® activated charcoal.

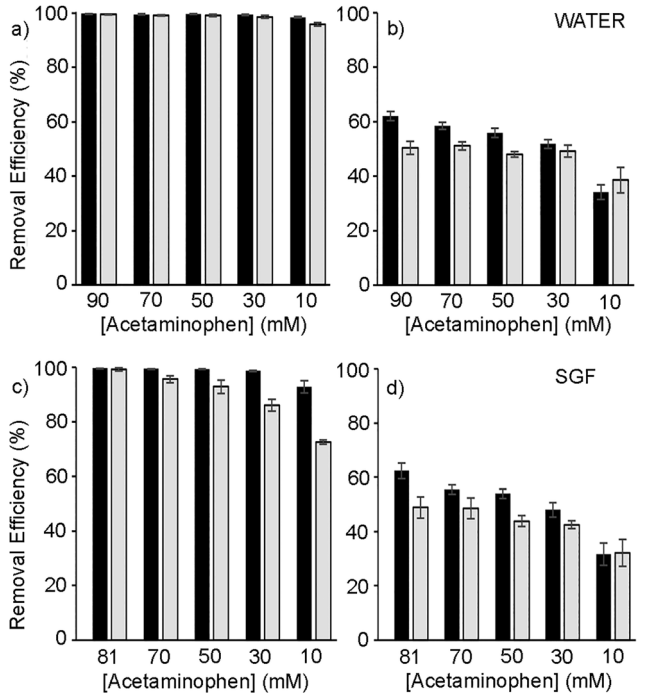

Fig. 4 Plots of removal efficiency *versus* [acetaminophen] (mM) at 37 °C using **H4** or an equal mass of DARCO® activated charcoal. Sequestered from deionized water using: (a) a 2 : 1 sequestrant : acetaminophen molar ratio, (b) a 1 : 2 sequestrant : acetaminophen molar ratio. Sequestered from SGF using: (c) a 2 : 1 sequestrant : acetaminophen molar ratio, (d) a 1 : 2 sequestrant : acetaminophen molar ratio. **H4** (■) and DARCO (□).

We were delighted to find **H4** performs slightly better than DARCO® activated charcoal under identical conditions. A control experiment performed using SGF lacking pepsin showed slightly higher RE values for both **H4** and DARCO® which indicates that pepsin inhibits removal of acetaminophen. In addition, we monitored the removal efficiency of acetaminophen from SGF using **H4** and DARCO® activated charcoal as a function of time (SI, Fig. S35 and S36) and find they both exhibit rapid uptake within 60 seconds. As another control experiment, we tested the ability of CB[6] and CB[8] as sequestrants for acetaminophen from SGF at 37 °C at 1 : 2 and 2 : 1 CB[*n*] : acetaminophen molar ratio (SI, Fig. S27–S32). We observed that CB[6] is a very poor sequestrant for acetaminophen whereas CB[8] performs well (RE = 84% at 2 : 1 molar ratio) but is less efficient than **H4**.

We have shown that **H4** is an effective solid state sequestrant for a panel of PMs at environmentally relevant levels (250 μM). The uptake of acetaminophen by **H4** is especially impressive reaching a RE of 93% at a 4 : 1 molar ratio after 60 seconds and 99.8% after 2 h. At high acetaminophen concentrations (≤90 mM) relevant in overdose cases, **H4** performs as well as activated charcoal and outperformed macrocyclic CB[6] and CB[8]. In conclusion, the work suggests that water insoluble hosts (*e.g.* **H4** and its analogues) hold great promise as solid state sequestrants for detoxification and clean-up of water bodies.

Conceptualization: S. P. and L. I.; funding acquisition, project administration, and supervision: L. I., M. P.; investigation: J. S. M., T. M. H., S. P., Y. L.; writing – original draft: J. S. M. and T. M. H.; writing – review and editing: all authors.

Conflicts of interest

L. I. is co-founder and holds equity in Reversal Therapeutics (College Park, Maryland) and holds equity in Clear Scientific (Cambridge, Massachusetts). The other authors have no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). The electronic data that support this publication can be freely downloaded from the Digital Repository at the University of Maryland (https://drum.lib.umd.edu/home) using the following DOI: https://doi.org/10.13016/yuud-ag8i. Supplementary information is available. See DOI: https://doi.org/10.1039/d6cc01879c.

CCDC 2539579 contains the supplementary crystallographic data for this paper.[41]

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