Tripodal Organic Cages with Unconventional CH•••O Interactions for Perchlorate Remediation in Water

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ABSTRACT: Perchlorate anions used in industry are harmful pollutants in groundwater. Therefore, selectively binding perchlorate provides solutions for environmental remediation. Here, we synthesized a series of tripodal organic cages with highly pre-organized C_{sp3}–H bonds that exhibit selectively binding to perchlorate in organic solvents and water. These cages demonstrated binding affinities to perchlorate of $10^{5\text{-}6}$ M^{-1} at room temperature, along with high selectivity over competing anions such as iodide and nitrate. Through single crystal structure analysis and density functional theory calculations, we identified unconventional C_{sp3}–H•••O interactions as the primary driving force for perchlorate binding. Additionally, we successfully incorporated this cage into a 3D-printable polymer network, showcasing its efficacy in removing perchlorate from water.

Perchlorates (ClO_4^-) are widely used in rocket propellants, explosives, oxidizing agents, and other industrial purposes.[1,2] These highly soluble but toxic compounds enter the water systems and the food chain, posing threats to human health and environmental safety.[3] Current methods for removing perchlorate, such as anion exchange,[4] lack sufficient selectivity in separating it from competing anions.[5] Therefore, there is a need to develop perchlorate-specific binding receptors with good affinity and selectivity in water.[6] These receptors, when integrated into polymer networks,[7-9] will facilitate the selective removal of perchlorate.

Early designs of receptors utilize NH or OH hydrogen bonding for ClO_4^- binding in organic solvents.[10] However, when applied to aqueous environments, these designs suffered from drastically reduced affinity and selectivity due to water's competition for hydrogen bonding sites.[11,12] Recent advancements have explored non-classical C_{sp2}–H[13,14] and C_{sp3}–H[15] hydrogen bonding motifs and halogen bonding moieties[16] for anion binding in water.[17,18] Some high affinitive anion binding was achieved through pre-organized hydrogen bonding arrays and hydrophobic effect.[19-22] Examples include a high-affinity chloride-binding cage reported by Flood *et al.* with polarized C_{sp2}–H donors,[23] and a water-soluble bambus[6]uril reported by Sindelar *et al.* that displays a strong affinity for ClO_4^- through serendipitously discovered C_{sp3}–H bonding interactions.[24,25] These discoveries inspired us to intentionally bring C_{sp3}–H bonds to design anion-binding receptors.

Herein, we designed rigid tripodal cages featuring piperazine-based pillars with highly pre-organized C_{sp3}–H bonds, which selectively bind ClO_4^- anion in organic solvent and water (Figure 1). X-ray diffraction and binding studies of the inclusion complexes provided an unambiguous understanding of the unconventional C_{sp3}–H•••O interactions. Furthermore, the cage was utilized as a 3D-printing material to create hydrogels capable of removing ClO_4^- anions from water.

Tripodal cage **C1** was synthesized in four steps (Scheme S1). First, **S1** was synthesized by reacting *Boc*-piperazine with benzenetricarbonyl-trichloride, followed by *Boc*-deprotection. The reaction of **S1** with cyanuric chloride yielded **S2**. Macrobicyclization of **S1** and **S2** under high dilution afforded **C1**. When dioxane was introduced as a co-solvent, **C1** was obtained in 55% yield without chromatography purifications. Substituting the remaining chloride in **C1** allows easy access to $\mathbf{C1}_{\text{allyl}}$, $\mathbf{C1}_{\textit{N-Boc}}$, $\mathbf{C1}_{\mathbf{NH3Cl}}$, and $\mathbf{C1}_{\mathbf{AM}}$ in good yields (Figure 1b).

$\mathbf{C1}_{\mathbf{allyl}}$ has good solubility in chlorinated solvents, 1,4-dioxane, and DMSO. Single crystals of $\mathbf{C1}_{\mathbf{allyl}}$ were obtained by diffusing hexane into a dioxane solution of $\mathbf{C1}_{\mathbf{allyl}}$. In the single-crystal X-ray diffraction (SCXRD) analysis, the top and bottom benzene moieties of $\mathbf{C1}_{\mathbf{allyl}}$ are 11.0 Å apart, and the piperazine moieties adopt chair conformations with equatorial C–H bonds oriented toward the center of the cavity (Figure 2a). $\mathbf{C1}_{\mathbf{allyl}}$ was filled by one dioxane with multiple C-H•••O interactions (Figure 2a), suggesting dioxane as a template for the macrobicyclization as confirmed earlier. ^{1}H NMR titration of dioxane to $\mathbf{C1}_{\mathbf{allyl}}$ in $CDCl_3$ at 298 K showed no noticeable binding, possibly due to $CDCl_3$ acting as a competing guest (Figure S36).

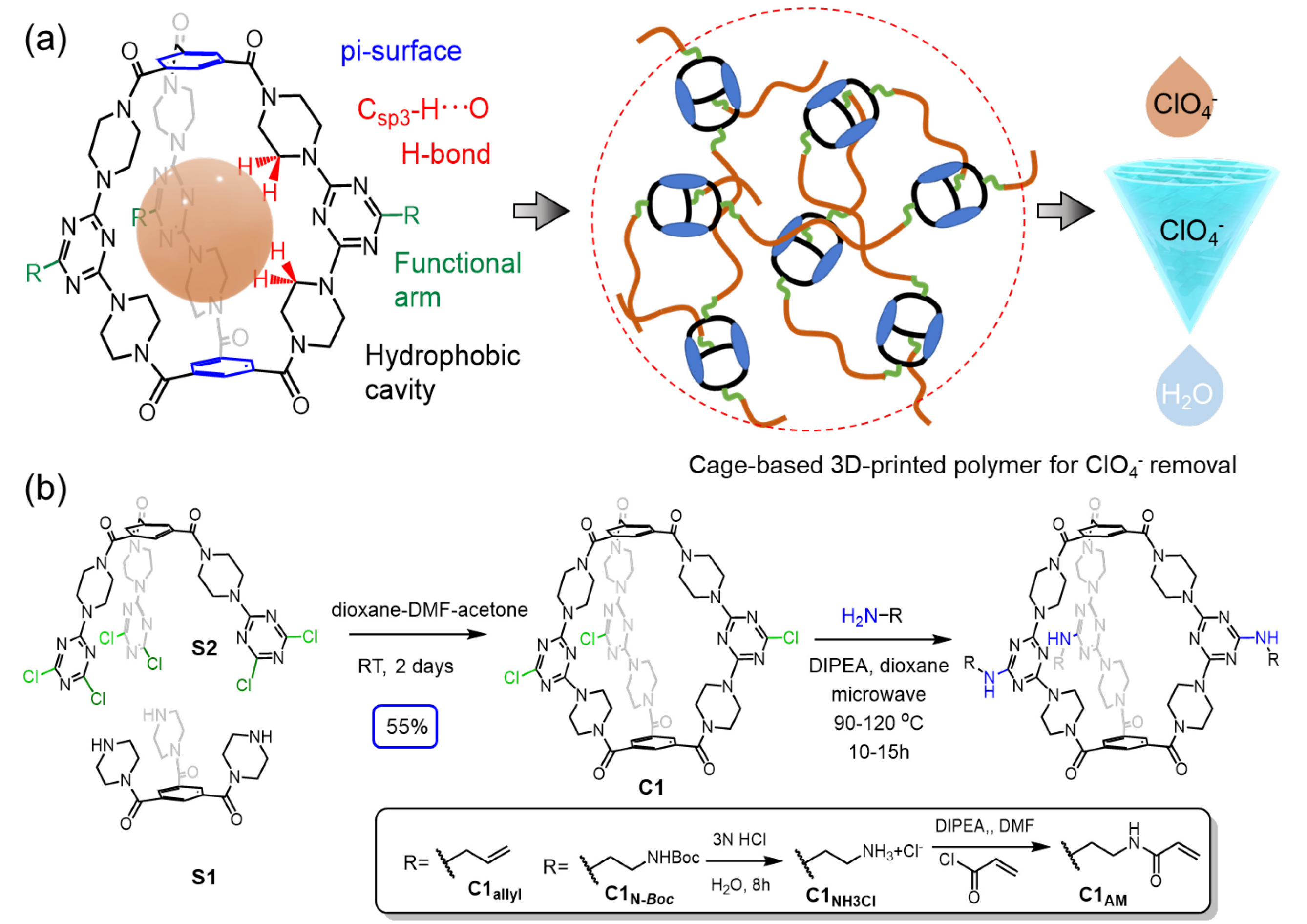

Figure 1. (a) Design of tripodal cages and their 3D-printed polymer networks for perchlorate recognition and remediation. (b) Synthesis of **C1**-based tripodal cages.

Unlike alkyl-piperazines,[26] the acyl-piperazine moieties of **C1**$_{\mathbf{allyl}}$ exhibit limited rotational freedom in solution, evident in the ^{1}H NMR spectra in $CDCl_3$ and DMSO-d_6 (Figure 2b). Four sets of non-equivalent protons connected to C_b, C_c, C_d, and C_e were assigned through 2D NMR experiments (Figures S10-S12, S16-S19). This phenomenon is similar to acyl-piperazine derivatives,[27] in which the chair flipping remained, but the C–N bond rotation is limited due to the enol-iminium resonance structure. The crystal structure of **C1**$_{\mathbf{allyl}}$ confirms the partial double bond nature of the O=C–N bonds with short C–N bond lengths (1.34–1.36 Å) and longer C=O bond lengths (1.22–1.24 Å, Figure S84). The *anti*-H_b and *anti*-H_c to the carbonyl oxygen atom point toward the cavity, providing a highly pre-organized binding site.

When **C1**$_{\mathbf{allyl}}$ was mixed with 10 equivalents of tetrabutylammonium (TBA) salts in $CDCl_3$, notable shifts were observed for the aromatic proton H_a and piperazine protons $H_{b/c/d/e}$ in the ^{1}H NMR spectra (Figure S37), indicating fast associations at the NMR time scale. In the ^{1}H NMR titration of **C1**$_{\mathbf{allyl}}$ and $TBAClO_4$ in $CDCl_3$, the H_a and H_b protons shifted upfield while H_c protons shifted downfield significantly (Figure 3a). The binding affinities between **C1**$_{\mathbf{allyl}}$ and these anions were fitted using a 1:1 binding model as K_a: $Cl^- < Br^- < NO_3^- < I^- < BF_4^- < PF_6^- < ClO_4^-$ (Table 1), which align with the Hofmeister series.[21,22] The binding affinity between **C1**$_{\mathbf{allyl}}$ and ClO_4^- reached 7.5×10^5 M^{-1}. Notably, the ClO_4^-/I^- selectivity of **C1**$_{\mathbf{allyl}}$ is calculated as 300, much larger than bambus[6]uril (~ 1), even though it has a lower affinity.[28] In comparison, an analogous open-formed **T1** (Scheme S5) showed no appreciable binding towards anions (Figure S69), highlighting the benefit of the pre-organized cavity.

Increasing the solvent polarity to DMSO-d_6 decreased the binding affinities towards all anions. In DMSO-d_6, **C1**$_{\mathbf{allyl}}$ showed binding affinities for I^- and ClO_4^- as 25 and 75 M^{-1}, respectively (Table 1). When 10% D_2O was added to DMSO-d_6, the binding affinities increased to 33 and 171 M^{-1}, respectively, with an improved ClO_4^-/I^- selectivity. These results suggest that the hydrophobic effect effectively promotes anion binding. The high affinitive anion binding in $CDCl_3$ and low affinitive binding in DMSO-d_6 resemble the behavior of many hydrogen-bond-based receptors.[29,30] Given that the solvophobic effect of DMSO is not the primary factor, we speculate that the anion•**C1**$_{\mathbf{allyl}}$ interaction may contain unconventional hydrogen bonding interactions.

To verify this, $TBAClO_4$•**C1**$_{\mathbf{allyl}}$ crystals were obtained for SCXRD analysis. In the solid state, one ClO_4^- anion was included in the cavity of **C1**$_{\mathbf{allyl}}$, and another ClO_4^- anion bound to the cage's aperture (Figures 3b, S88-S91).

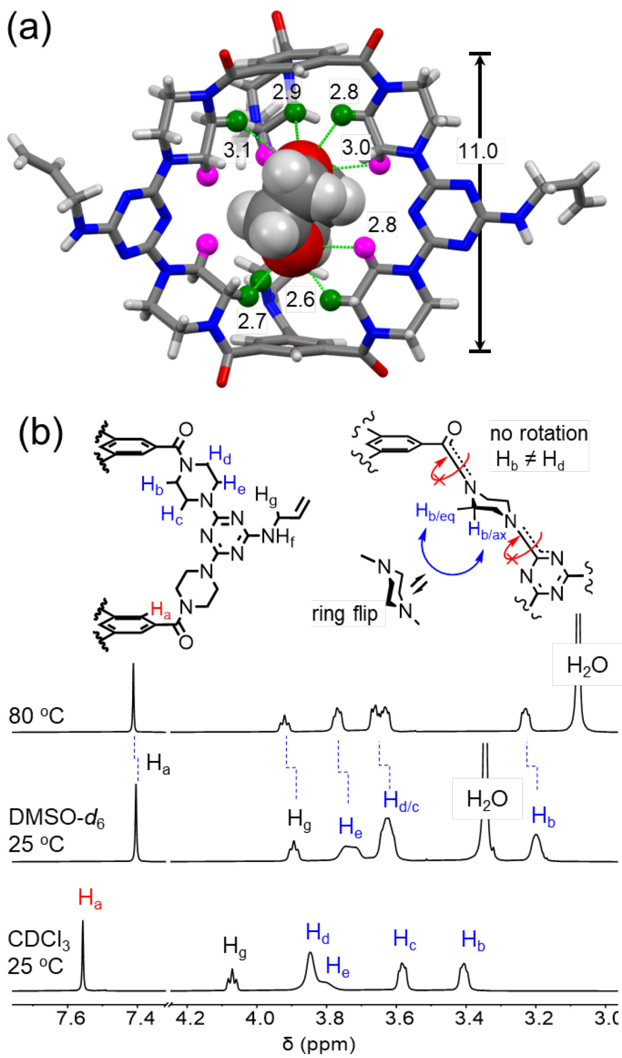

Figure 2. (a) X-ray structure of **C1$_{allyl}$** with a 1,4-dioxane. Equatorial C_{sp3}–H protons were highlighted in green and purple colors. The distances of the C_{sp3}–H•••O contacts are in Å. (b) ^{1}H NMR spectra of **C1$_{allyl}$** in different solvents and temperatures.

The included ClO_4^- anion fits within the cavity with multiple short C–H•••O distances ranging from 2.5 to 3.1 Å. The ClO_4^-•**C1$_{allyl}$** complex was simulated using density functional theory (DFT) with B3LYP-D3/6-31G** and subjected to an energy decomposition analysis.[31] The total bonding energy in vacuo (E_{int} = **–**229. 5 kJ/mol) between **C1$_{allyl}$** and ClO_4^- comprises various components, which allow for differentiation between attractive donor-acceptor (E_{orb} = –97.1 kJ/mol), electrostatic (E_{estat} = –166. 9 kJ/mol), dispersion (E_{disp} = –89.7 kJ/mol), and repulsive interactions (E_{Pauli} = +124.5 kJ/mol). Notably, E_{orb} is significant and consists of many small interactions between the lone pair of oxygens and piperazine's C–H σ* orbitals (Figure 3c). This analysis suggests that there are multivalent weak hydrogen bonds in the complex, which are stabilized further through dispersion and electrostatic attractions. Although each C_{sp3}–H•••O hydrogen bonding is weak, the multivalency and cooperativity in this highly pre-organized cage enabled good affinitive binding of ClO_4^-.

The hydrophobic binding site[32] and the multivalent C_{sp3}–H•••O interactions indicate that the binding for ClO_4^- could be further enhanced in water. Therefore, we synthesized a water-soluble **C1$_{NH3Cl}$** (Figure 1b) and investigated its binding with different anions using isothermal titration calorimetry (ITC, Figure 3d and Table 1). At 25 ºC, **C1$_{NH3Cl}$** demonstrated a good affinity for ClO_4^- of 2.5 × 10^5 M^{-1} and a high ClO_4^-/I^- selectivity of 14 in water, while the binding with SO_4^{2-} is very weak (< 5M^{-1}, Figure S68). Although the ion-ion interactions between the cationic ethylammonium arms and ClO_4^- may contribute to the overall binding, we conducted ITC experiments with 0.5 and 1 M NaCl to shield these Coulombic interactions,[21, 22] despite increasing the solvent's dielectric constant and introducing a competing Cl^- anion. Remarkably, **C1$_{NH3Cl}$** remained good affinitive binding for ClO_4^- in these highly concentrated NaCl solutions with K_a of 1.4–1.8 × 10^4 M^{-1} (Table 1). Notably, the enthalpy contribution remains significant to the overall binding, providing additional evidence for the nature of C_{sp3}–H•••O interactions as weak hydrogen bonds.

Table 1. Binding affinity (K_a) and thermodynamic parameters (ΔH, TΔS, and ΔG) of **C1$_{allyl}$** and **C1$_{NH3Cl}$** with anions (298 K).

	C1$_{allyl}$		**C1$_{NH3Cl}$**			
anion	CDCl$_3$*	DMSO-d_6* [10% D$_2$O]	H$_2$O			
	K_a (M^{-1})	K_a (M^{-1})	$K_a^{\#}$ (M^{-1})	ΔH (kJ/mol)	TΔS (kJ/mol)	ΔG (kJ/mol)
F^-	32 ± 1	< 5	< 5	n.d.	n.d.	n.d.
Cl^-	9 ± 2	< 5	51 ± 0.9	–27.2 ± 0.3	17.3 ± 1.0	–9.9 ± 0.1
Br^-	26 ± 2	< 5	308 ± 45	–17.1 ± 2.1	–2.8 ± 2.1	–14.3 ± 0.1
I^-	(2.4 ± 0.1) × 10^3	25 ±3 [*33 ± 2*]	(1.8 ± 0.4) × 10^4	–30.5 ± 2.0	–6.3 ± 1.4	–24.3 ± 0.6
NO_3^-	(1.0 ± 0.2) × 10^3	< 5	731 ± 46	–16.0 ± 0.3	0.4 ± 0.3	–16.4 ± 0.1
BF_4^-	(4.5 ± 0.9) × 10^4	18 ± 1	(6.6 ± 0.3) × 10^4	-35.8 ± 1.5	–8.5 ± 1.0	-27.4 ± 0.5
PF_6^-	(1.4 ± 0.1) × 10^5	66 ±1	(7.9 ± 0.8) × 10^5	-44.9 ± 2.4	-11.3 ± 1.6	-33.7 ± 1.2
ClO_4^-	(7.5 ± 0.2) × 10^5	75 ± 3 [*171 ± 4*]	(2.5 ± 0.1) × 10^5	–42.3 ± 0.3	–11.0 ± 0.2	–31.3 ± 0.4
in 1 mM Na$_2$SO$_4$ solution			(2.4 ± 0.1) × 10^5	–36.0 ± 0.3	–5.5 ± 0.2	–30.5 ± 0.3
in 0.5 M			(1.8 ± 0.1) × 10^4	–16.2 ± 0.1	8.0 ± 0.1	–24.2 ± 0.1
and 1 M NaCl solutions			(1.4 ± 0.2) × 10^4	–14.8 ± 0.9	8.7 ± 1.3	–23.5 ± 0.4

*TBA salts used for ^{1}H NMR titrations, $^\#$NaCl/Br/NO$_3$/BF$_4$, KI/ClO$_4$/PF$_6$ used for ITC. n.d. for not determined.

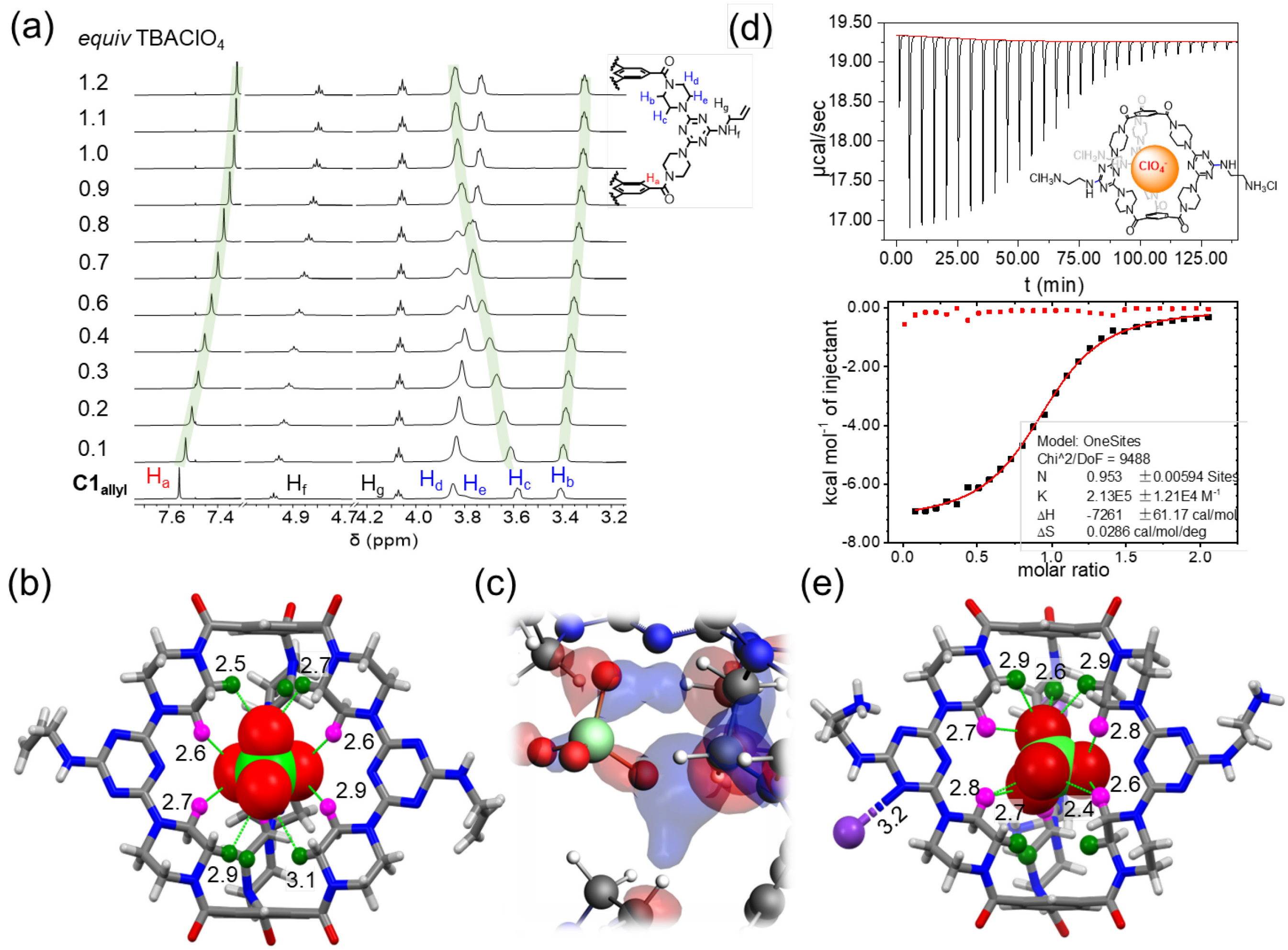

Figure 3. (a) ^{1}H NMR titration of $\mathbf{C1_{allyl}}$ (1 mM) with the addition of $TBAClO_4$ in $CDCl_3$ at 298 K. (b) Single-crystal structure of $TBAClO_4$•$\mathbf{C1_{allyl}}$ and the highlighted C_{sp3}–H•••O contacts in Å. (c) A snapshot of the interactions between lone pairs of oxygens and σ* orbitals of C–H bonds provided by DFT calculation. (d) The ITC experiment of adding $KClO_4$ to an aqueous solution of $\mathbf{C1_{NH3Cl}}$ (0.1 mM). The data were fitted to a 1:1 binding model. (e) Single-crystal structure of $KClO_4$•$\mathbf{C1_{NH3Cl}}$ and the highlighted C_{sp3}–H•••O contacts in Å.

Furthermore, the single crystal structure of $KClO_4$•$\mathbf{C1_{NH3Cl}}$ showed a similar conformation to the $TBAClO_4$•$\mathbf{C1_{allyl}}$ complex (Figure S94-S95), with short C-H•••O distances ranging from 2.4 to 2.9 Å (Figure 3e), compared to the combined van der Waals' radii of 2.72 Å (H + O).[33] The ethylammoniums of $\mathbf{C1_{NH3Cl}}$ are not flexible enough to fold backward for intramolecular ion-ion interactions, confirming that ion-ion interactions are not the key driving force for the complexation.

We incorporated **C1** as an active perchlorate removal moiety into a polymer network to investigate its suitability for ClO_4^- remediation in water. A $\mathbf{C1_{AM}}$ crosslinker was synthesized from $\mathbf{C1_{NH3Cl}}$ for the copolymerization with *N,N*-dimethylacrylamide (DMA, 100 equiv., Figure 4a). In the presence of 2,2-dimethoxy-2-phenylacetophenone (DMPA) and a 3D-printing template Pluronic F127, a hydrogel with good shear-thinning and self-healing properties (Figure S107) was formed via our hierarchical co-assembly direct-ink-writing method.[34, 35] This hydrogel was 3D-printed into a cone shape paired with a glass funnel to set up a purification stand. After 3D-printing, it was photo-polymerized to form a crosslinked 3DP-$\mathbf{C1_{AM}}$-net (Figure 4b).

When 3DP-$\mathbf{C1_{AM}}$-net was immersed in an aqueous solution of $KClO_4$ (0.125 mM, 17.3 ppm),[36] the conductance of the solution rapidly decreased over time (Figure 4c). After 2h, the residual ClO_4^- concentration reached 0.025 mM and after 20 h, it decreased to 0.017 mM. In comparison, a control **AM**-net synthesized using pentaerythritol triacrylate and DMA (Scheme S7) showed negligible ClO_4^- removal capability. We assessed the reusability of the 3DP-$\mathbf{C1_{AM}}$-net by subjecting it to five cycles of ClO_4^- removal and regeneration (Figure 4d, S116). The 3DP-$\mathbf{C1_{AM}}$-net hydrogel showed only a marginal decrease in performance, indicating its robustness for ClO_4^- remediation.

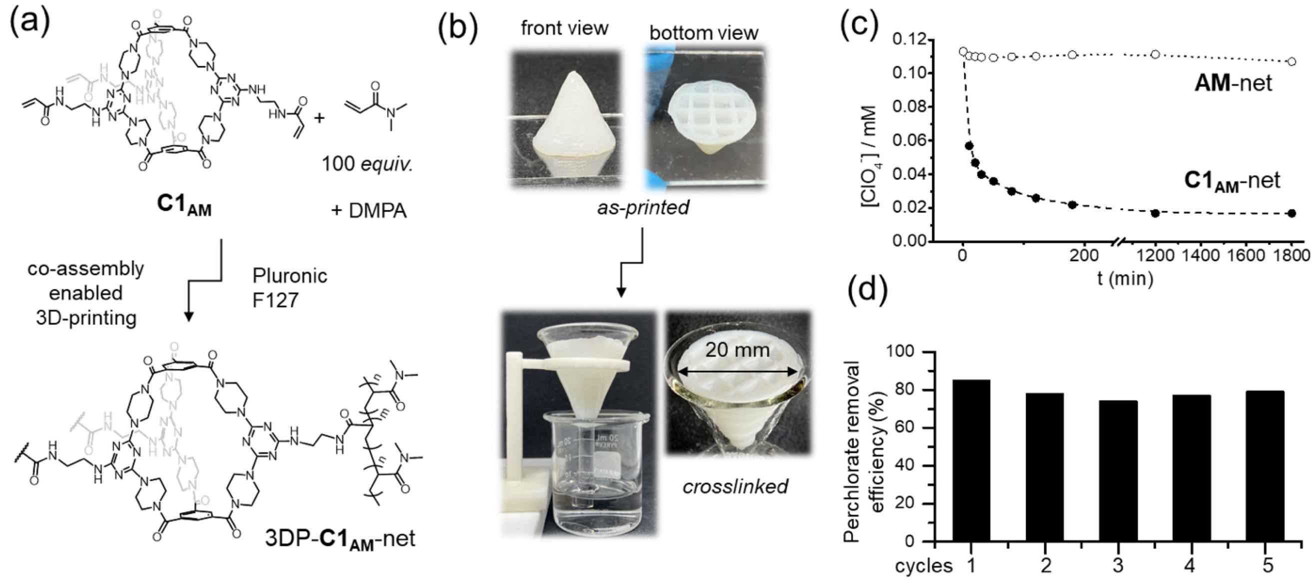

Figure 4. (a) Synthesis of crosslinked 3D-printed 3DP-**C1$_{AM}$**-net using **C1$_{AM}$**. (b) 3D-printed cone-shaped funnels before (top) and after crosslinking (bottom, with its perchlorate removal setup) using an F127 hydrogel (40 w/v%) with **C1$_{AM}$** (20 mM), DMA (1.8 M), and DMPA (78 mM). (c) Time-dependent conductance of $KClO_4$ solution (0.125 mM) in the presence of crosslinked **C1$_{AM}$**-net and **AM**-net. (d) Reusability of the crosslinked **C1$_{AM}$**-net for ClO_4^- removal.

In summary, our investigation of rigid tripodal cages featuring piperazine pillars leads to the understanding of unconventional C_{sp3}–H•••O hydrogen bonding interactions with perchlorate. X-ray diffraction analysis confirmed the short contacts between the C_{sp3}–H bonds and ClO_4^-. Titration studies provided quantitative analysis of the binding affinities and thermodynamic parameters of the complexes. DFT calculations reveal the C_{sp3}–H•••O interaction originates from the interaction between the lone pairs of oxygen atoms and the piperazine C–H σ* orbitals. These cages exhibited good affinity and selectivity for perchlorate in organic solvents and water. We also demonstrated their application as a 3D printing material, creating a hydrogel capable of efficiently and repeatedly removing ClO_4^- anions from water, presenting a promising pathway for incorporating molecular designs into useful polymer networks for clean water.

ASSOCIATED CONTENT

Supporting Information.
Synthesis and characterization of the compounds, NMR and ITC titration experiments, X-ray crystallographic analyses, DFT calculations, rheological data, 3D printing of polymers and ClO_4^- removal details are available free of charge (PDF).

Accession Codes
CCDC 2244494, 2244495, 2247551, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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