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A Hexapodal Capsule for the Recognition of Anions

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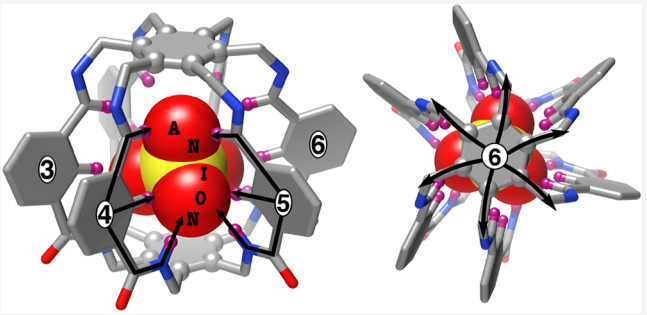
ABSTRACT: We herein describe the preparation, characterization, and recognition characteristics of novel hexapodal capsule **1** composed of two benzenes joined by six hydrogen bonding (HB) groups to encircle space. This barrel-shaped host was obtained by reversible imine condensation of hexakis-aldehyde **2** and hexakis-amine **3** in the presence of oxyanions or halides acting as templates. Fascinatingly, capsule **1** includes 18 HB donating (C_{sp2}−H and N−H) and 12 HB accepting groups (C═O and C═N) surrounding a binding pocket (78 Å^3). In this regard, the complexation of fluoride, chloride, carbonate, sulfate, and hydrogen phosphate was probed by NMR spectroscopy (DMSO) and X-ray diffraction analysis to disclose the adaptive nature of **1** undergoing an adjustment of its conformation to complement each anionic guest. Furthermore, the rate by which encapsulated chloride was substituted by sulfate or hydrogen phosphate was slow (>7 days) while the stability of $[SO_4⊂\mathbf{1}]^{2-}$ was greatest in the series with $K_a > 10^7$ M^{-1} in highly competitive DMSO. With facile access to **1**, the stage is set to probe this modular, polyvalent, and novel host to further improve the extraction of tetrahedral oxyanions from waste and the environment or control their chemistry in living systems.



INTRODUCTION

In the search for easily accessible and C_3 symmetric hosts capable of sensing, sequestering, or transporting important and biological molecules/ions,[2] hexasubstituted benzenes (Figure 1A) have, to date, played an important role.[3] At the fundamental level, the arms of hexa-substituted benzene rings tend to assume alternative ***ababab*** positions above (***a***) and below (***b***) the ring (Figure 1A).[4] The conformational bias (>3 kcal/mol),[5] arising from so-called steric gearing,[3] gives rise to a preorganized molecule possessing a functionalized cleft for hosting properly sized/shaped guests.[6] In addition, such preorganization has facilitated kinetic or thermodynamic macrocyclizations[7] for obtaining tripodal cages (Figure 1A).[2,37] With such concave molecules acting as effective and selective hosts of complementary guests/ions,[2,8] we wondered about developing a strategy for obtaining hexapodal capsules in which six, instead of three, functional groups converge above the benzene platform (Figure 1A).[9] Will a greater number of functional units within such capsules[10] (featuring amides, pyrroles, amines, ureas, pyridines etc.) permit an even more effective and selective binding of anions?[11] In line with the proposition, Mislow and co-workers found[4] that the ***aaaaaa*** conformer of hexasubstituted benzene is the least stable and more than 8 kcal/mol above the ***ababab*** form. To overcome the bias from steric gearing,[12] Allen and co-workers[13] employed six primary amides to form a seam of intramolecular N−H···O═C hydrogen bonds (HBs) around the benzene core for stabilizing its ***aaaaaa*** conformation.[14] Moreover, Ghosh and co-workers discovered[15] that the corresponding hexa-amide receptors would overcome the steric gearing by assuming conformations (***aaaaaa***, ***aaabbb***, etc.) complementary to a range of anionic guests in the solid state. It follows that by fastening six amides on one side of the benzene platform (Figure 1A) a binding pocket is created isolated from bulk solvent and rich in HB groups.[16] In particular, placing an anion within such pocket should be assisted by favorable entropic and enthalpic contributions[17] in which the release of solvent molecules and the formation of multiple hydrogen bonds ensue. From the results of computational studies (Figure 1B),[1] we anticipated that hexakis-aldehyde **2** and hexakis-amine **3** could give hexakis-imine **1** under thermodynamic control,[18] with or without a template[19] (Figure 1C).[20] Such a polyvalent capsule with six HB-donating amides and six HB-accepting imines, in addition to polarized C_{sp2}−H groups,[11] lining its inner space (78 Å^3)[21] might complement oxyanions[22] and/or halides.[2] We hereby delineate a method-

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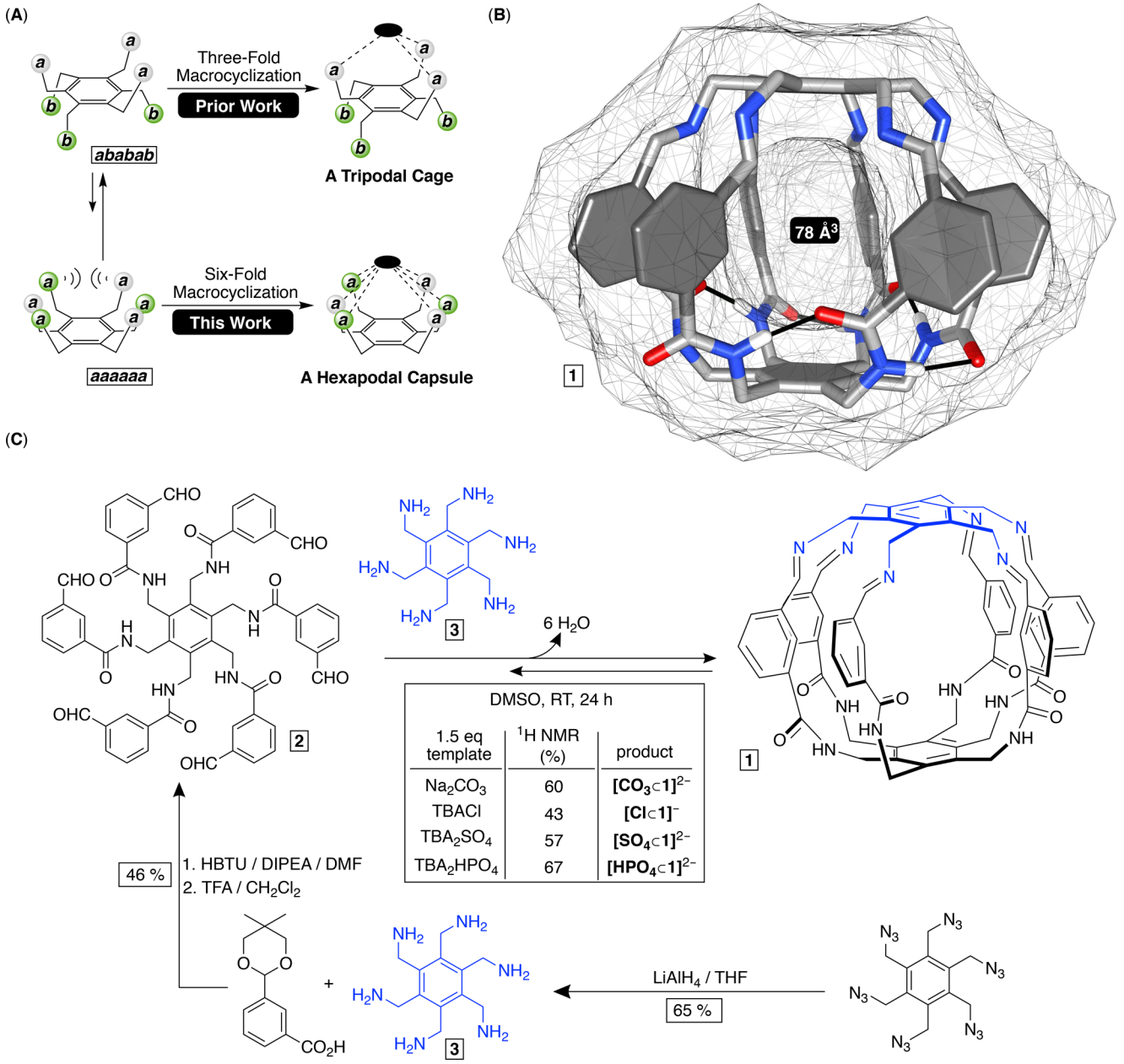

Figure 1. (A) Hexasubstituted benzenes assume eight conformations of which ***ababab*** and ***aaaaaa*** are the most and least stable. (B) A side view of the energy-minimized structure of **1** (Macrocycle Conformational Sampling; DFT/M06-2X:6-311++G**).[1] (C) (Top) A condensation of hexakis-aldehyde **2** and hexakis-amine **3** was anticipated, with or without a template, to give capsule **1**. (Bottom) The preparation of **2** and **3** from hexa(azidomethyl)benzene and ^{1}H NMR yields of templated-directed syntheses of $[\text{anion}\subset\mathbf{1}]^{n-}$ in DMSO (see Supporting Information (SI)).

ology for obtaining uniquely structured **1** and exemplify its capacity to recognize oxyanions and halides.

RESULTS AND DISCUSSION

First, we synthesized hexakis(aminomethyl)benzene **3**[14] and then converted it into hexakis-aldehyde **2** (Figure 1C and Scheme S1). After combining **2** and **3** in an equimolar ratio in DMSO, the appearance of ill-defined ^{1}H NMR signals followed, suggesting the emergence of oligomeric species (Figure S1). The result was hardly surprising, since **2** should, in DMSO, assume ***ababab*** form.[14] Considering the ability of anions to reorganize six amides around the benzene ring,[15] we decided to probe fluoride[23] as a template in directing the formation of **1**. Indeed, mixing equimolar **2** and **3** in DMSO with 4 equiv of TBAF (TBA = tetrabutylammonium) resulted in the formation of a single set of sharp ^{1}H NMR resonances in addition to broad signals corresponding to oligomeric species (Figure S1). However, adding 1 equiv of DBU as a base to the reaction mixture improved the templation by further minimizing oligomerizations (Figure S1). In this regard, a steady development of sharp ^{1}H NMR signals over 24 h, with the aldehyde singlet at 9.75 ppm disappearing and the imine singlet growing at δ = 8.20 ppm (Figure S2), reflected the reversible nature of imine condensations.[19a] After the product purification, its ^{1}H NMR spectrum (Figure 2A) suggested the formation of a C_6 symmetric molecule that we tentatively assigned to $[\text{anion}_x\subset\mathbf{1}]\text{TBA}_y$; the integration of ^{1}H NMR signals suggested that y = 2−3. In order to identify the anionic guest, we obtained the ^{19}F NMR spectrum of the product

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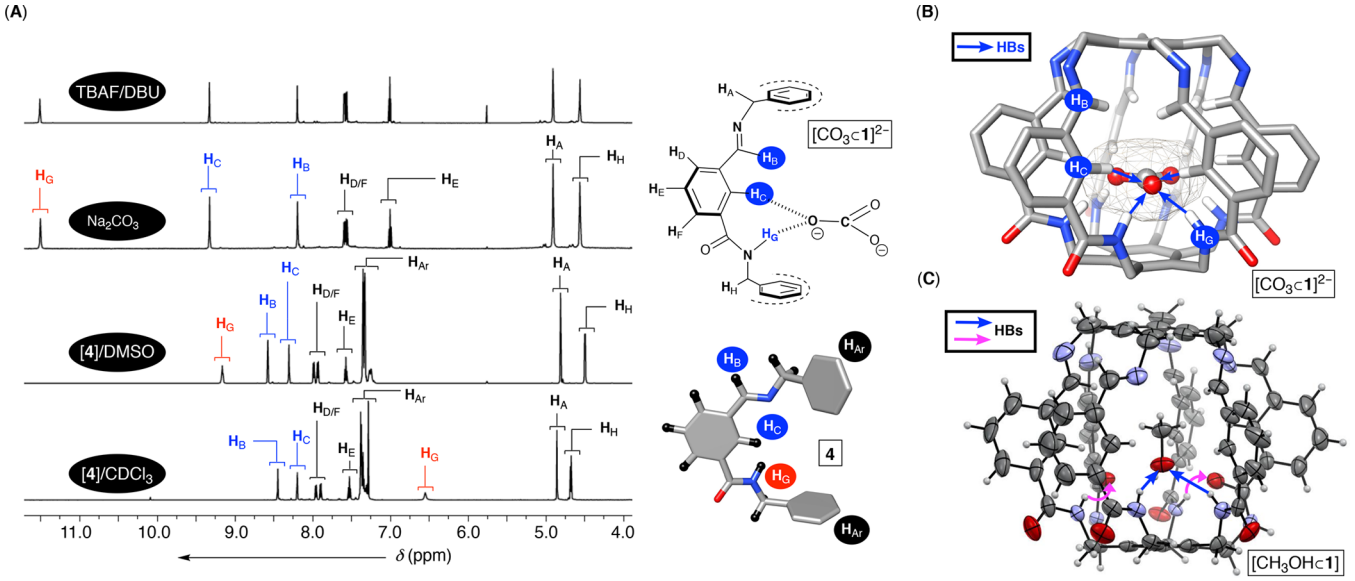

Figure 2. (A) ^{1}H NMR spectra (600 MHz, DMSO-d_6) of $[CO_3\subset\mathbf{1}]^{2-}$ obtained by the reaction of **2** (1.9 μmol) and **3** (1.9 μmol) in DMSO (500 μL) in the presence of (first spectrum) TBAF (7.6 μmol) and DBU (1.9 μmol) and (second spectrum) Na_2CO_3 (2.8 μmol). ^{1}H NMR spectra (600 MHz) of model **4** in DMSO-d_6 (third spectrum) $CDCl_3$ (fourth spectrum). (B) Energy-minimized structure (MCMM/OPLS3e and DFT/M06-2X:6-311++G**) of $[CO_3\subset\mathbf{1}]^{2-}$. (C) ORTEP diagram (50% probability) of the solid-state structure of $[CH_3OH\subset\mathbf{1}]$.

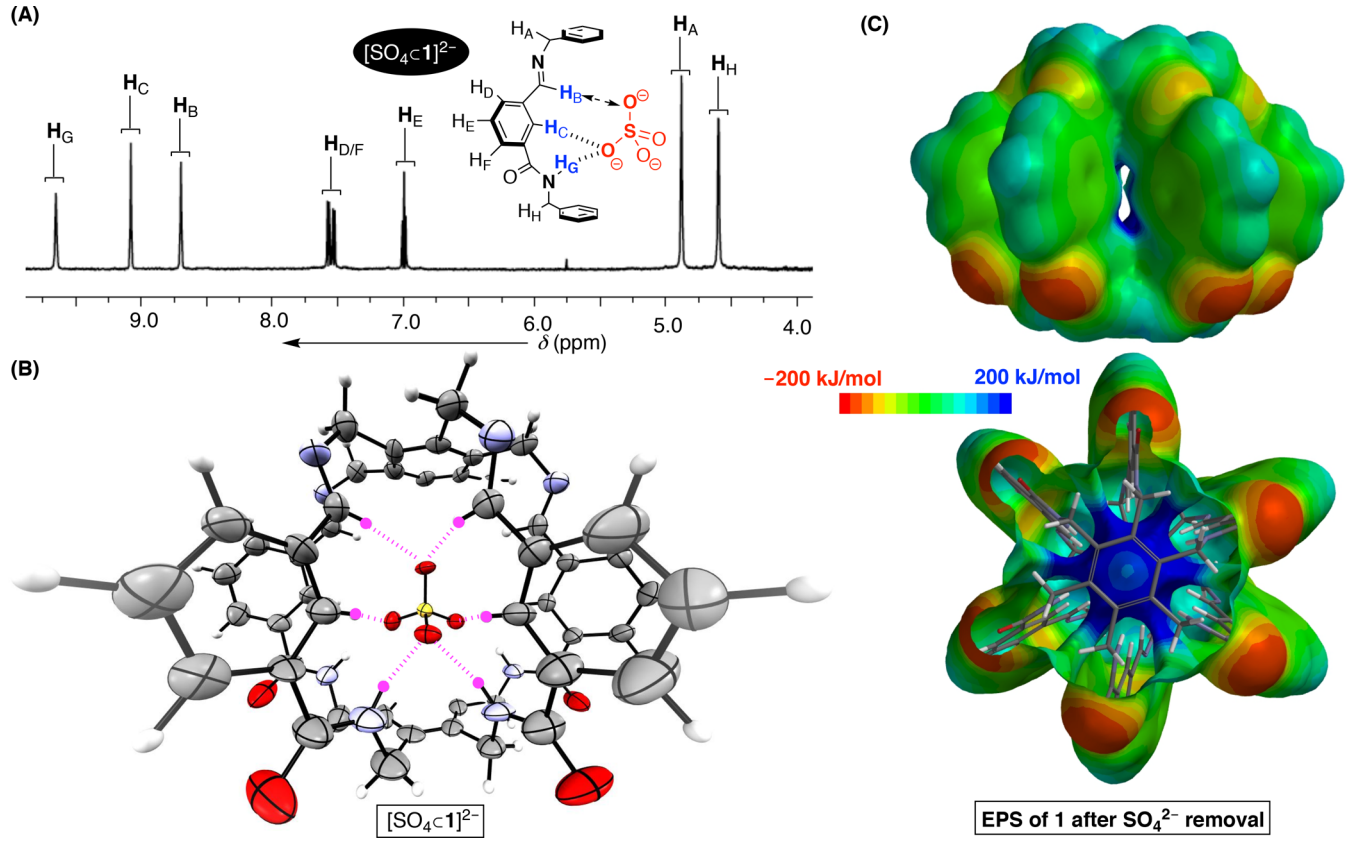

Figure 3. (A) ^{1}H NMR spectrum (600 MHz, 298 K) of $[SO_4\subset\mathbf{1}]TBA_2$ in DMSO-d_6. (B) ORTEP diagram (50% probability) of the solid-state structure of $[SO_4\subset\mathbf{1}]TBA_2$; the back side of the image is removed for clarity (see SI). (C) Top and side views of the electrostatic potential surface (DFT/B3LYP:6-31G*) of capsule $[SO_4\subset\mathbf{1}]^{2-}$, after the sulfate anion was removed.

(Figure S3) and found a negligible quantity of the fluoride. The results from ESI mass spectrometric measurements of $[anion_x\subset\mathbf{1}]TBA_y$ showed (Figure S4) a signal at 1189 au corresponding to $(\mathbf{1}+H)^+$ and another signal at 1249 a.u. having the isotopic pattern commensurate with the formation of $[HCO_3\subset\mathbf{1}]^-$. Since basic fluorides generate hydroxide in DMSO having adventitious water[24] and DBU assisted the "templation" (Figure 2A), we suspected that *in situ* formed carbonate/bicarbonate anions from hydroxide and dissolved carbon dioxide could be the true template. Accordingly, we

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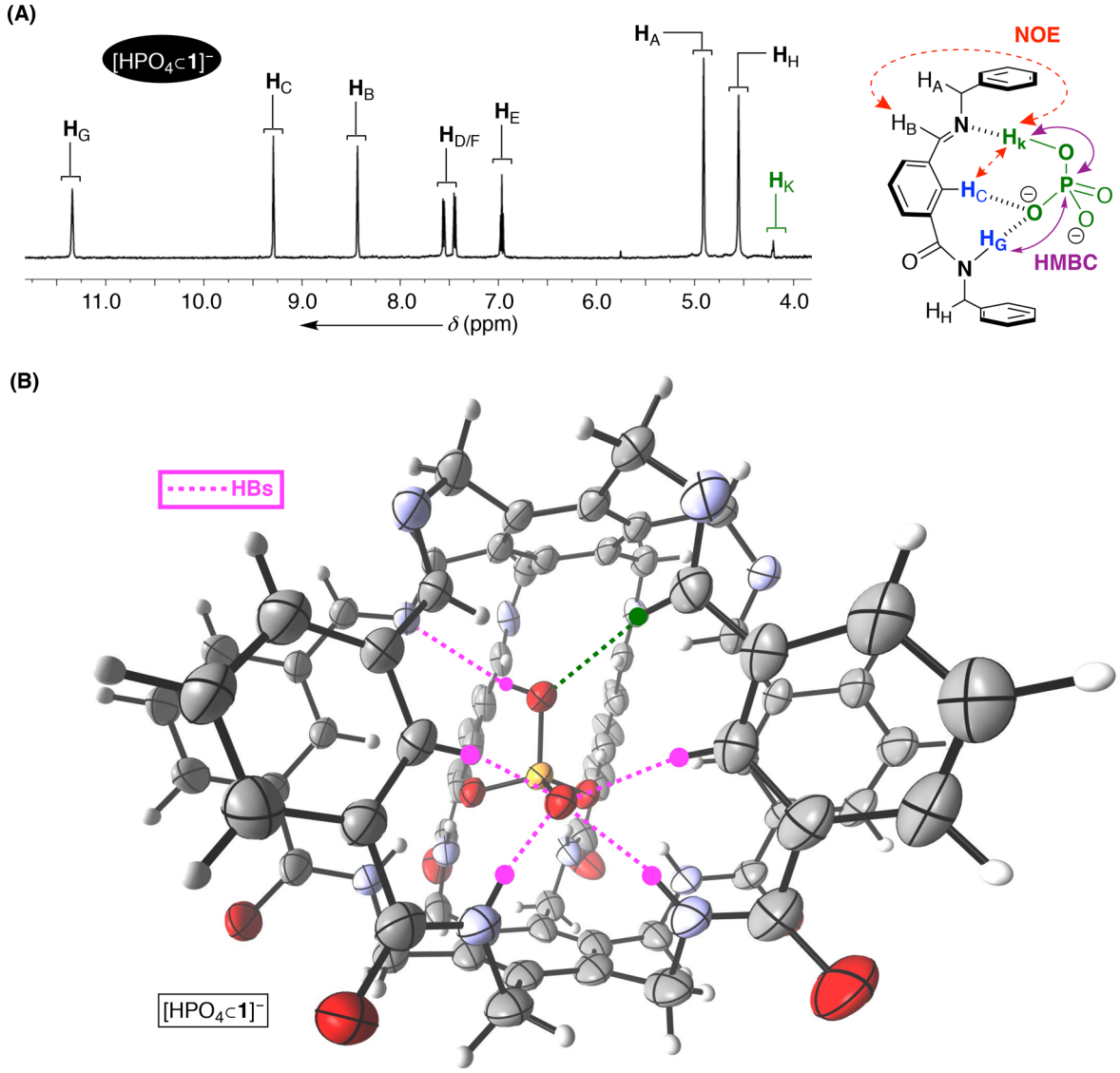

Figure 4. (A) ^{1}H NMR spectrum (600 MHz, 298 K) of $[HPO_4\subset\mathbf{1}]TBA_2$ in DMSO-d_6. (B) ORTEP diagram (50% probability) of the solid-state structure of $[HPO_4\subset\mathbf{1}]TMA_2$.

found that both Na_2CO_3 and $NaHCO_3$ could act as effective templates[25] (Figures S1 and S5) with ^{1}H NMR spectrum of $[CO_3\subset\mathbf{1}]^{2-}$ (Figure 2A) matching the spectrum of the product obtained in the studies with TBAF/DBU (Figure 2A). Moreover, a closer inspection of the ^{13}C NMR spectrum of $[CO_3\subset\mathbf{1}]^{2-}$ (from TBAF/DBU) and its comparison with that of $[^{13}CO_3\subset\mathbf{1}]^{2-}$ (from $Na_2{}^{13}CO_3$, Figure S6) further corroborated the formation of this binary complex; for the spectroscopic assignment of $[CO_3\subset\mathbf{1}]^{2-}$, see Figures S7−S9. Finally, the diffusion coefficient of $[CO_3\subset\mathbf{1}]^{2-}$ (DOSY NMR, Figure S10) corresponded to r_H = 8.1 Å, close to the computed value of **1** (7.5 Å, Figure 1B).

On the basis of computational study of $[CO_3\subset\mathbf{1}]^{2-}$ (Figure 2B),[1b] the carbonate occupies the southern part of the capsule by placing its three oxygens at the HB distance from N−$\mathbf{H}_G$ (D = 2.842−2.851 Å and Θ = 163.42°−164.84°)[26] and C_{sp2}−$\mathbf{H}_C$ (D = 3.048−3.321 Å and Θ = 159.99°−164.55°)[27] while six C_{sp2}−$\mathbf{H}_B$ protons cluster to populate the capsule's top; indeed, a small void at the top of carbonate, ∼30 Å^3, could in principle be populated with H_2O (19 Å^3). These results are in agreement with ^{1}H NMR observations in Figure 2A: large deshielding of amide $\mathbf{H}_G$ (δ = 11.5 ppm) and aromatic $\mathbf{H}_C$ (δ = 9.5 ppm) protons in $[CO_3\subset\mathbf{1}]^{2-}$ with respect to one-arm model compound **4** (δ = 9.1/6.5 and 8.2 ppm, respectively) evidenced their participation in host−guest HBs. When $[CO_3\subset\mathbf{1}]TBA_2$ was dissolved in methanol and the solution was subjected to vapor from diethyl ether, we obtained single crystals. X-ray diffraction analysis disclosed the formation of $[CH_3OH\subset\mathbf{1}]$ (Figure 2C) with two conformational stereoisomers of **1** (7:3 ratio) occupying the crystal lattice. In essence, the hexapodal capsule used two host−guest N−$\mathbf{H}_G$···O−CH_3 and two intramolecular N−$\mathbf{H}_G$···O═C (Figure 2B) HBs to stabilize the complex. At the northern side, three (1,3,5) imine C−$\mathbf{H}_B$ protons occupied the capsule's interior (akin to **1** in Figure 1B). By comparing structures of $[CO_3\subset\mathbf{1}]^{2-}$ and $[CH_3OH\subset\mathbf{1}]$, one can see the capsule assuming a conformation to complement different guests.

Importantly, the condensation of **2** and **3** in degassed DMSO-d_6 containing TBAF resulted in the formation of oligomers (Figure S1). We infer that fluoride was a poor guest of **1** and therefore ineffective in templating its formation. On the other hand, TBACl acted as an effective template giving

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[Cl⊂**1**]TBA in 43% yield (Figures S1 and S20−S23). By dissolving [Cl⊂**1**]TBA in CH_2Cl_2 and washing the solution with water, we obtained $\mathbf{1}_{apo}$ (apo = lacking an anionic guest, Figure S30); note that once exposed to water the hexaimino capsule was chemically stable although not soluble in it. Upon incremental addition of a standard solution of TBACl to $\mathbf{1}_{apo}$ (DMSO-d_6, Figure S30), a separate set of ^{1}H NMR resonances from $[Cl⊂\mathbf{1}]^-$ appeared allowing us to, via integration, determine a high association constant, $K_a = 2 \times 10^5$ M^{-1}, corresponding to its formation.[28] Indeed, the affinity of **1** toward anions is expected to drop in HB solvents (water, CH_3OH, etc.) and increase in nonpolar solvents (CH_2Cl_2, $CHCl_3$, etc.), albeit quantitative studies are still to be completed with either this imine based host or its more solvent compatible congeners.

To probe if tetrahedral oxyanions could template the formation of **1**, we ran condensations of **2** and **3** in the presence of TBA salts of $HPO_4^{2-}$and SO_4^{2-} (Figure S1). Since both templation processes were successful showing the formation of $[SO_4⊂\mathbf{1}]TBA_2$ (Figure 3A; Figures S10−S14) and $[HPO_4⊂\mathbf{1}]TBA_2$ (Figure 4A; Figures S10 and S15−S19), we decided to further examine the recognition of these two anions.

After addition of 1.5 mol equiv of Na_2SO_4 to 0.7 mM solution of [Cl⊂**1**]TBA in DMSO-d_6, a set of ^{1}H NMR signals corresponding to $[SO_4⊂\mathbf{1}]^{2-}$ grew over time (Figure S24). With the anion metathesis requiring about a week (Figures S24 and 25), the constrictive binding characterizing the entrapment of sulfate (55 Å^3) is rather large[29] with, supposedly, narrow apertures in $[SO_4⊂\mathbf{1}]^{2-}$ (Figure 3C) hindering the entrance of tetrahedral oxyanions; an addition of catalytic amounts of *p*-toluenesulfonic acid (Figures S24 and S25) expedited the anion metathesis by promoting the hydrolytic cleavage of imine linkages.[30] A more complete understanding of the exchange mechanism though would require additional computational and experimental studies. As in the case of the carbonate complex, magnetic deshielding of the amide N−$\mathbf{H}_G$ and aromatic C_{sp2}−$\mathbf{H}_C$ nuclei in **1** (Figure 3A) implied the formation of N−$\mathbf{H}_G$···O−S and C_{sp2}−$\mathbf{H}_C$···O−S hydrogen bonds. Moreover, the downfield shift of the imine C_{sp2}−$\mathbf{H}_B$ protons (Figure 3A) denoted attractive C_{sp2}−$\mathbf{H}_B$···O−S interactions as well. In this regard, single crystals of $[SO_4⊂\mathbf{1}]TBA_2$ were obtained by vapor diffusion of diethyl ether into its methanol solution. As expected, X-ray diffraction analysis showed one sulfate anion per hexapodal **1** (Figure 3B). Host−guest complexes $[SO_4⊂\mathbf{1}]^{2-}$ packed into columns along the crystallographic *a* axis so that benzene "tops and bottoms", from juxtaposed capsules, resided at the π−π stacking distance (3.6 Å). Furthermore, all six amides in **1** had their **N**−$\mathbf{H}_G$ groups pointing to the capsule's interior for participating in six N−$\mathbf{H}_G$···O−S hydrogen bonds (D = 2.77−2.91 Å and Θ = 157°−167°).[26] Fascinatingly, the cluster of amides resembles anion binding sites in proteins dubbed as nests.[31] Following, six aromatic C_{sp2}−$\mathbf{H}_C$ groups at the capsule's equator formed six C_{sp2}−$\mathbf{H}_C$···O−S hydrogen bonding contacts (D = 3.06−3.28 Å and Θ = 152°−171°).[27] And finally, six imine C_{sp2}−$\mathbf{H}_B$ protons grouped in the northern hemisphere to form a pocket composed of positively polarized hydrogens for holding the S−O$^-$ oxygen (D = 3.69−3.81 Å and Θ = 150°−168°, Figure 3B).[27] The solution and solid-state data suggest that the spherical pocket within $[SO_4⊂\mathbf{1}]^{2-}$ (Figure 3C) is lined with 18 positively polarized hydrogens contributing to a multitude of HBs for holding the sulfate anion.

To probe the encapsulation of HPO_4^{2-}, we added the standard solution of $HPO_4(TBA)_2$ to [Cl⊂**1**]TBA in DMSO and monitored the substitution by ^{1}H NMR spectroscopy (Figures S26 and 27). The displacement was slower than in the case of sulfate to suggest a somewhat different mechanism for the ingress/egress of similarly sized and shaped hydrogen phosphate (59 Å^3). The ^{1}H NMR spectrum of $[HPO_4⊂\mathbf{1}]^{2-}$ (Figure 4A) revealed downfield shifts of the capsule's amide N−$\mathbf{H}_G$ and aromatic C_{sp2}−$\mathbf{H}_C$ resonances. On the basis of 2D NOESY correlations (Figure 4A; Figure S19), the hydrogen phosphate placed its P−O$\mathbf{H}_K$ group in the northern hemisphere and the vicinity of $\mathbf{H}_B$ and $\mathbf{H}_C$. From ^{31}P−^{1}H HMBC measurement, the cross correlation between N−$\mathbf{H}_G$ and the phosphorus from the HPO_4^{2-} guest (Figure 4A, Figure S19) provided evidence for the amide $\mathbf{H}_G$ protons hydrogen bonding the anion's oxygens. Single crystals of $[HPO_4⊂\mathbf{1}]$-TMA_2 (TMA = tetramethylammonium) were obtained by vapor diffusion of tetrahydrofuran into its acetonitrile solution. The anion is docked in the cavity of **1** (Figure 4B) with its three negatively charged oxygens lodged in the amide nest thereby resulting in six N−$\mathbf{H}_G$···O−P hydrogen bonds (D = 2.76−2.83 Å and Θ = 165°−168°).[26] At the capsule's equator, there were six additional C_{sp2}−$\mathbf{H}_C$···O−P hydrogen bonds (D = 3.07−3.34 Å and Θ = 161°−168°).[27] And finally, five imines directed their C_{sp2}−$\mathbf{H}_B$ groups toward the $H_K\mathbf{O}$−PO_3^{2-} (D_{C-O} = 3.56−3.95 Å and Θ = 155°−167°),[27] while the same $\mathbf{H}_K$O−PO_3^{2-} formed a weak HB with one imine nitrogen (D = 3.27 Å and Θ = 163°).[26]

In summary, fluxional host **1** altered its conformation to complement different guests. Thus, when methanol occupied the interior of **1** (Figure 2B), the host placed three imine (C_{Sp2}−H) hydrogens inside and three outside while two amides held onto methanol via hydrogen bonding. With the sulfate (Figure 3B), the capsule assumed a conformation comprising a spherical nest (Figure 3C) with 18 positively polarized C_{sp2}−$H^{\delta+}$ and N−$H^{\delta+}$ groups facing the anion. And for hydrogen phosphate (Figure 4B), single imine nitrogen from **1** complemented the phosphate's hydroxyl while the remaining HB sites stayed in the host's interior.

CONCLUSION

In conclusion, barrel-shaped and easily accessible **1** (Figure 1C) encompasses 18 HB donating and 12 HB accepting groups surrounding its binding pocket (78 Å^3),[11] with stronger affinity toward anions (see below) than its acyclic analogues akin to **2**;[15] i.e., hexa-amide receptors do not complex chloride in DMSO.[15] While acting as a host, polyvalent **1** tunes its conformation to electronically and sterically complement the occupant's hydrogen bonding sites. The capsule accommodates tetrahedral oxyanions (i.e., hydrogen phosphate and sulfate) more effectively than chloride ($K_a = 2 \times 10^5$ M^{-1}), fluoride, or carbonate. The stability of $[SO_4⊂\mathbf{1}]^{2-}$ is $K_a > 10^7$ M^{-1} (Figure S30) while that of $[HPO_4⊂\mathbf{1}]^-$, on the basis of a competing templation experiment (Figure S28), is somewhat smaller. The high propensity of **1** for trapping sulfate in polar DMSO[32] makes it an excellent candidate for probing the selective extraction of tetrahedral oxyanions from waste or the environment.[33] In this regard, our work sets the stage for further broadening the scope and optimizing the characteristics of hexapodal **1** and its congeners as novel abiotic and multivalent anionic receptors with intriguing kinetic and thermodynamic characteristics.[34]

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12329.

Additional experimental and computational details (PDF)

Accession Codes

CCDC 2057358−2057360 contain 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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