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Self-Assembled Cages

Computer-Aided Design of a Sulfate-Encapsulating Receptor**

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One of the most ambitious endeavors of chemists is to mimic protein receptors or enzymes in their abilities to effectively bind substrates, stabilize reactive intermediates or high-energy conformations, and catalyze chemical transformations.[1] Toward this end, self-assembled capsules and cages represent a very promising class of artificial host platforms.[2] These easily accessible nanocontainers have well-defined cavities with specific chemical environments, which can impart size and shape selectivity on guest inclusion, or unusual guest reactivity. Although some of the self-assembled cages reported to date have been rationally designed, their inclusion chemistry has generally not been predetermined. Instead, the usual approach is to first make the cage and then to find out what guests fit into it.[3] For instance, although a number of self-assembled anion-encapsulating cages have been reported,[4,5] their binding cavities were not deliberately designed for a particular anion guest. As most of these cages provide hydrophobic internal environments, they are mainly suitable for binding less hydrophilic anions, such as BF_4^-, PF_6^-, or ClO_4^-, typically from organic solvents. Efficient encapsulation of more hydrophilic guests from highly competitive solvents, such as water, requires not only internal functionalization of the cages with appropriate binding groups,[1c,d6,7] but also the very difficult task of precisely positioning these groups in space for optimal complementarity to the guest.

Our interest in synthetic anion receptors[8] has prompted us to seek new hosts that can effectively bind strongly hydrophilic anions from competitive aqueous environments.[9] We thus focused our recent efforts on sulfate,[10] an anion that is representative of a broad class of tetrahedral oxoanions.[8d] Sulfate has a particularly high free energy of hydration,[11] which makes the design of receptors that can effectively bind this anion in water extremely challenging.[8e] With an association constant of $8.3\times10^6\,mol^{-1}\,L$ for SO_4^{2-} binding in water,[12] the sulfate-binding protein remains the most effective receptor for this anion, far surpassing any synthetic receptor reported to date. Herein, we demonstrate for the first time a de novo computer-aided approach to self-assembled metal–organic cage hosts that were designed to optimally fit the sulfate guest by precise functionalization with urea hydrogen-bonding groups.[13,14] The molecular design was validated by synthesis and characterization of one such cage, which proved to be an exceptionally strong sulfate receptor in water.

The design of a capsule interior that is tailor-made for a specific guest ideally begins with a consideration of the optimal placement of donor sites within the cavity. These sites should be arranged to complement the guest. In the case of sulfate, theoretical calculations of water clusters indicated that this anion can accept up to 12 hydrogen bonds from water molecules in its first hydration shell.[15] Electronic structure calculations[16] and X-ray crystallography[17] confirmed that this coordination number is also achieved with six urea groups, each chelating an edge of the tetrahedral anion. The calculated $[SO_4(urea)_6]^{2-}$ complex exhibits T symmetry, with each S–O bond aligned to one of the four C_3 axes and each C=O bond aligned to one of the six C_2 axes (Figure 1a). In this case, the design target is to identify cage architectures with urea-lined cavities that achieve this geometry of the hexaurea complex, thereby providing a complementary host for sulfate. For a self-assembled cage, this task becomes one of identifying urea-containing molecular components that spontaneously assemble to form this arrangement of binding sites.

We opted for coordination-driven self-assembly[2d] as our approach to cage construction. This strategy has been successfully applied to assemble a variety of metal–organic polyhedra.[2–7] Among them, the M_4L_6 metal–organic tetrahedron is attractive because it has symmetry elements that are commensurate with the $[SO_4(urea)_6]^{2-}$ target.[2c] In the M_4L_6 cage, four metal ions serve as C_3-symmetric vertices and six C_2-symmetric ligands serve as edges of the tetrahedron. By appropriately functionalizing the edge molecules with urea moieties, the desired urea arrangement could be achieved through self-assembly. M_4L_6 cages typically contain tris-chelate metal complexes at the vertices because they possess the requisite C_3 symmetry axes.[2c] We chose Ni^{2+} as the metal center, and 2,2′-bipyridine (bpy) as the chelating ligand, based on the very high association constant ($\log K = 20.16$) for the formation of $[Ni(bpy)_3]^{2+}$ complex in water,[18] which we reasoned would confer high aqueous stability on the ensuing coordination cages. The geometry of the $[Ni(bpy)_3]^{2+}$ complex was taken as an average of the X-ray structures found in the

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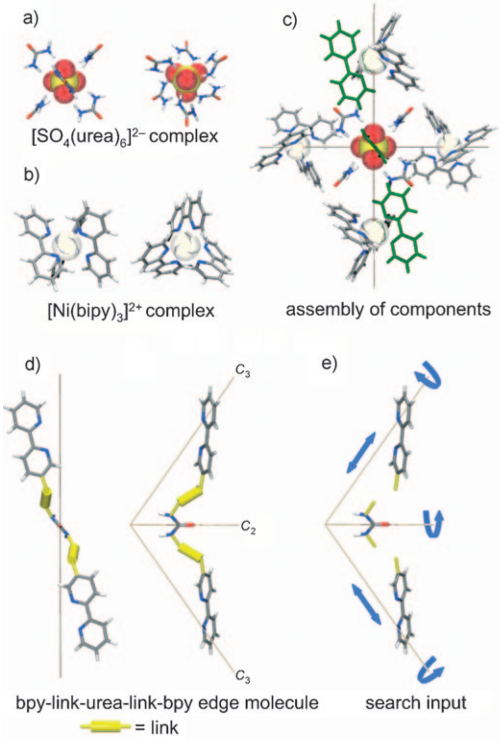

Figure 1. The design of the sulfate cage receptor. a) Structure of the tetrahedral $[SO_4(urea)_6]^{2-}$ complex obtained by electronic structure calculations,[16] viewed down the C_2 (left) and C_3 (right) axes (C gray, H white, N blue, O red, S yellow). b) Structure of the $[Ni(bpy)_3]^{2+}$ complex, obtained from the Cambridge Structural Database. c) Placement of the $[SO_4(urea)_6]^{2-}$ and $[Ni(bpy)_3]^{2+}$ components in a tetrahedral assembly. d) Rendering of a generic edge molecule showing its orientation relative to the symmetry axes, and the structural relationship between the bpy and urea groups. e) *HostDesigner* input, with the symmetry-constrained drivers depicted as blue arrows.

Cambridge Structural Database (CSD 5.29, November 2007; Figure 1b).

Using the $[SO_4(urea)_6]^{2-}$ complex to define the location of urea donor sites and $[Ni(bpy)_3]^{2+}$ complexes as the cage vertex components, it was possible to define the structural basis for the design of the urea-containing ligands. First, a vector was extended out from each S−O bond of the sulfate complex. Next, one $[Ni(bpy)_3]^{2+}$ complex was placed at each of these vectors, such that (a) the C_3 axis of the complex was aligned with the vector and (b) all Ni atoms were equidistant from the central S atom. Finally, the $[Ni(bpy)_3]^{2+}$ complexes were rotated about their C_3 axes such that the resulting assembly had *T* symmetry (Figure 1c). This assembly illustrated how each of the six urea-containing edge molecules would have the form bpy-link-urea-link-bpy, and defined a spatial relationship between the bpy and urea groups (Figure 1d). Thus, the design task became one of identifying linking fragments that could bridge the bpy and urea groups. This task was complicated by the fact that the placement of bpy and urea groups was not unique. For example, there is an infinite number of bpy positions achieved by translation of the $[Ni(bpy)_3]^{2+}$ complexes along their C_3 axes, provided that all Ni atoms remain equidistant from the center. At any given Ni–center distance, there is an infinite number of bpy positions achieved by synchronous rotation of the $[Ni(bpy)_3]^{2+}$ complexes about their C_3 axes to ensure that the *T* symmetry of the assembly is maintained. In addition to these variations in bpy placement, the urea groups could rotate about their C_2 axes to adopt several stable positions.[19]

The search for links that bridge between the central urea group and the two terminal bipyridine groups was conducted using de novo structure-based design methods, implemented in the *HostDesigner* software.[20,21] With this approach, over 8,000 hydrocarbon fragments taken from a database were assessed on their ability to bridge between bonding vectors on the pyridine C5 atom and the urea N atom. The method accounted for the variability in pyridine and urea positions by evaluating a large number of vector pairs generated by symmetry-constrained geometric drivers. As discussed above, three movements were allowed: translation of the $Ni(bpy)_3]^{2+}$ groups along the C_3 axes with Ni–center distances ranging from 7.5 to 17.5 Å in 0.1 Å increments, rotation of the $[Ni(bpy)_3]^{2+}$ groups around the C_3 axes from −90 to +90° in 2° increments, and rotation of the urea group about the C_2 axis from −45 to +45° in 3° increments, yielding a total of 270,000 vector poses (Figure 1e). By excluding chiral linkages and retaining only the most rigid linkages, visual inspection of the output resulted in a small number of viable candidates. To further evaluate these candidates, full cages were constructed and optimized with an extended MMFF94 force field model (see the Supporting Information). Cages that failed to retain *T* symmetry and those with severe steric congestion between adjacent edges were rejected. The remaining candidates (Figure 2) had relatively rigid conformations that were able to both span between the Ni vertices and achieve the targeted hexa-urea host cavity.

For the initial study, we selected the synthetically most accessible edge molecule containing the simple -CH_2- linkage (**L1**; Figure 3), which was expected to form the self-assembled cage **1** with the formula $[Ni_4(\mathbf{L1})_6(SO_4)]^{6+}$. **L1** was synthesized in five steps from commercially available precursors (see the Supporting Information). Crystallization of **L1** with $NiSO_4$ in H_2O/MeOH yielded the complex $[Ni_4(\mathbf{L1})_6(SO_4)](SO_4)_3$ ($\mathbf{1}(SO_4)_3$), as evidenced by single-crystal X-ray diffraction analysis.[22] As designed, a metal–organic tetrahedral cage encapsulating one sulfate anion was formed (Figure 3). All four $[Ni(bpy)_3]^{2+}$ vertices had the same chirality, which resulted in an overall homochiral cage, as noted in other M_4L_6 coordination tetrahedra.[2c,i,j,4,5d] The observed C_3 symmetry of the cage deviated slightly from the anticipated *T* symmetry, with two very similar Ni–Ni distances of 11.57 and 11.71 Å, and Ni-Ni-Ni angles of 60.00 and 59.61°. This small perturbation is apparently caused by the remaining three SO_4^{2-} anions sitting outside the cage and interacting with three of the four tetrahedral $[Ni(bpy)_3]^{2+}$ vertices through C−H⋯O hydrogen bonding, which results in a trigonal packing of the tetrahedra (Figure 3c). The C_3 symmetry of the cage thus propagates throughout the crystal, which adopts the chiral *R*3 space group. As expected, the targeted hexa-urea arrangement providing 12 hydrogen bonds to the encapsulated sulfate was achieved (Figure 3d). The detected NH⋯O hydrogen bond lengths and N−H⋯O angles ranging between 2.035 and 2.070 Å, and 168.8 and

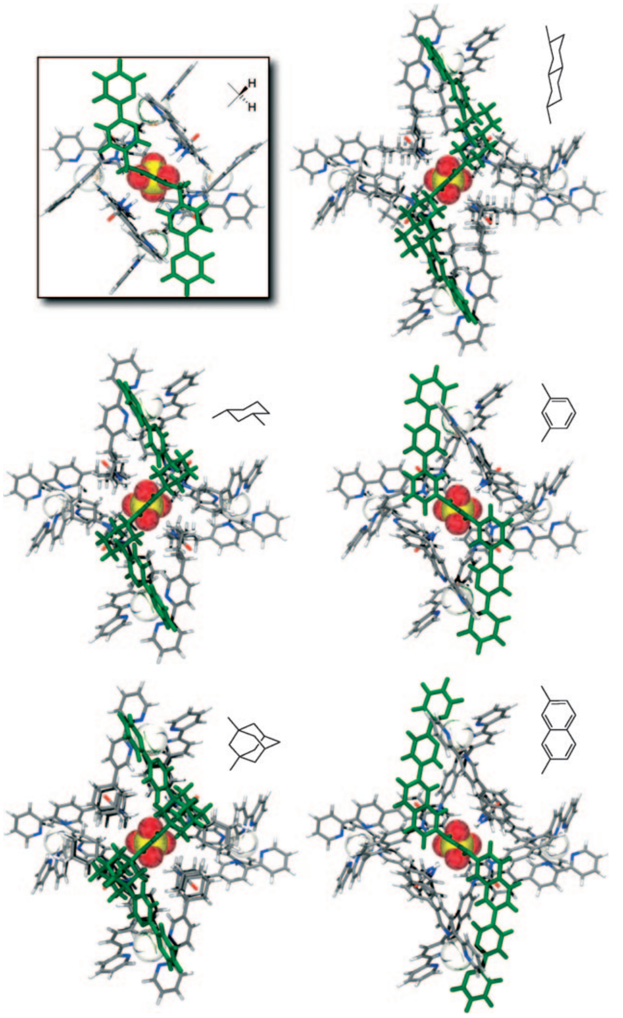

Figure 2. Top cage candidates obtained from molecular design, visualized along their C_2 axes (C gray, H white, N blue, O red, S yellow). One of the six edge molecules for each cage is highlighted in green. The corresponding linkers, identified by *HostDesigner*, are shown as ChemDraw diagrams. The cage selected for the initial experimental study is outlined in a box.

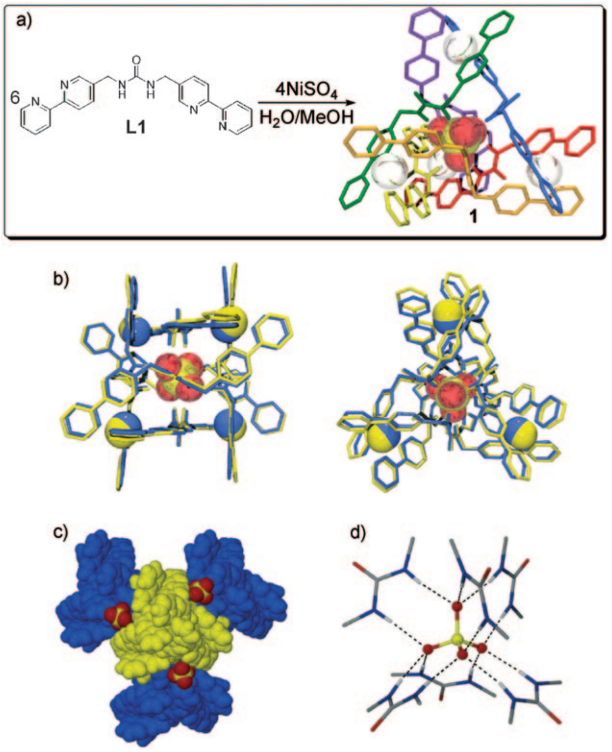

Figure 3. a) Self-assembly of the cage **1** from **L1** and $NiSO_4$. The structure of the resulting cage, as obtained by single-crystal X-ray diffraction, is shown on the right, with each of the 6 edges depicted in a different color (stick model), the 4 Ni^{2+} ions shown as silver balls, and the encapsulated sulfate as a space-filling model. The other three SO_4^{2-} anions, situated outside the cage, and the water and methanol molecules included in the crystal are omitted for clarity. b) Overlay of the predicted structure of cage **1** (yellow) and the experimental crystal structure (blue), shown along the C_2 (left) and C_3 (right) axes. c) Trigonal packing of the cages (yellow and blue) and the external SO_4^{2-} anions in the crystal. d) Detailed view of the sulfate-binding site (C gray, H white, N blue, O red, S yellow), with six urea groups (stick model) donating 12 hydrogen bonds (black dotted lines) to SO_4^{2-} (ball-and-stick model).

176.1°, respectively, are close to the calculated values in the $[SO_4(urea)_6]^{2-}$ complex (1.982 Å and 174.0°). It should be noted that, in agreement with the molecular design for this particular linkage, the sulfate orientation is inverted relative to the cage, with each S–O vector pointing to a face of the tetrahedron rather than to a vertex.[19]

Electrospray ionization mass spectrometry provided evidence that the self-assembled cage **1** persists in solution. A solution obtained by dissolving $\mathbf{1}(SO_4)_3$ in H_2O/MeOH (1:1 v/v) gave distinct peaks at $m/z = 451.2$ and 700.6, corresponding to $[Ni_4(\mathbf{L1})_6(SO_4)]^{6+}$ (expected $m/z = 451.3$) and $[Ni_4(\mathbf{L1})_6(SO_4)_2]^{4+}$ (expected 700.9), at concentrations as low as 1 μM. Unfortunately, NMR spectroscopy provided limited information regarding the structure and dynamics of the cage in solution, owing to the extensive broadening caused by the paramagnetic Ni^{2+} ions. We therefore opted for competition experiments with Sr^{2+} and Ba^{2+} as a means to quantitatively probe the formation of **1** in water and obtain preliminary estimates of the sulfate binding constant.

On the basis of the $[Ni_4(\mathbf{L1})_6(SO_4)](SO_4)_3$ formula derived from the X-ray structure, there are two distinct sulfate anions in $\mathbf{1}(SO_4)_3$: one SO_4^{2-} tightly encapsulated inside the cage and three SO_4^{2-} situated outside the cage. Addition of four equivalents of $Sr(NO_3)_2$ to a solution containing one equivalent of $\mathbf{1}(SO_4)_3$ in water resulted in precipitation of three equivalents of $SrSO_4$, which coincides with the number of SO_4^{2-} anions outside the cage. The fourth sulfate is thus unavailable for reaction with Sr^{2+}, which is consistent with quantitative formation of **1** and tight encapsulation of SO_4^{2-}.

To obtain a more quantitative estimate of the sulfate binding strength, we turned to the more competitive Ba^{2+}, whose less soluble sulfate salt has a solubility product K_{sp} three orders of magnitude smaller than the corresponding value for $SrSO_4$.[23] Two aliquots of 0.66 equivalents of $Ba(NO_3)_2$ were added sequentially to an aqueous solution of the $[Ni_4(\mathbf{L1})_6(SO_4)](NO_3)_6$ obtained from the previous experiment, resulting in the formation of 0.33 and 0.50 equivalents of $BaSO_4$, respectively, as determined gravimetrically. These results, in conjunction with the known K_{sp} of $BaSO_4$,[23] converge to an apparent sulfate binding constant K_{app} of $(6 \pm 1 \times 10^6)\ \mathrm{mol}^{-1}\,\mathrm{L}$ (see the Supporting Information). The association constant is denoted here as apparent, as the dynamics of the cage once sulfate is removed are unknown. Whereas the actual association constant, $K(\mathrm{SO_4}^{2-})$, for sulfate binding by the tetrahedral $[\mathrm{Ni_4}(\mathbf{L1})_6]^{8+}$ remains uncertain, the calculated K_{app} represents a lower limit estimate of $K(\mathrm{SO_4}^{2-})$.[24]

Finally, addition of a small amount of methanol to the final filtrate and subsequent slow evaporation yielded a crystalline solid. Single-crystal X-ray diffraction of the isolated crystals revealed the same $[\mathrm{Ni_4}(\mathbf{L1})_6(\mathrm{SO_4})]^{6+}$ cage as before, but with disordered nitrate anions replacing the sulfate anions outside the cage. Elemental analysis was consistent with the formula $[\mathrm{Ni_4}(\mathbf{L1})_6(\mathrm{SO_4})](\mathrm{NO_3})_6{\cdot}(\mathrm{H_2O})_{26}{\cdot}(\mathrm{MeOH})_3$ (see the Supporting Information), establishing the persistence of the self-assembled cage **1** under these competitive conditions.

The designed self-assembled cage reported herein is an exceptional sulfate host, surpassing any synthetic receptor known to date,[8d,9] and on a par with sulfate-binding protein.[12] While the high +8 charge of the cage undoubtedly enhances its anion affinity, it cannot fully account for the remarkable sulfate binding observed. This statement is supported by a recent example of an identically charged metal–organic receptor functionalized with noncomplementary hydrogen-bonding groups, which was found to bind $\mathrm{SO_4}^{2-}$ in water with an association constant two orders of magnitude smaller than the one reported here.[25] This reinforces the importance of precise placement of binding groups inside the host for optimal encapsulation of the guest. The approach illustrated here has implications extending beyond anion receptors; in principle it could be generally applied to the design of a wide variety of self-assembled molecular containers tailor-made for any designated guest.

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[1] a) M. Yoshizawa, M. Tamura, M. Fujita, *Science* **2006**, *312*, 251–254; b) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85–88; c) T. Iwasawa, R. J. Hooley, J. Rebek, Jr., *Science* **2007**, *317*, 493–496; d) Y. Ferrand, M. P. Crump, A. P. Davis, *Science* **2007**, *318*, 619–622; e) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2007**, *119*, 8741–8743; *Angew. Chem. Int. Ed.* **2007**, *46*, 8587–8589; f) M. D. Pluth, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2008**, *130*, 11423–11429.

[2] a) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1668; b) L. R. MacGillivray, J. L. Atwood, *Angew. Chem.* **1999**, *111*, 1080–1096; *Angew. Chem. Int. Ed.* **1999**, *38*, 1018–1033; c) D. L. Caulder, K. N. Raymond, *Acc. Chem. Res.* **1999**, *32*, 975–982; d) S. R. Seidel, P. J. Stang, *Acc. Chem. Res.* **2002**, *35*, 972–983; e) M. Fujita, M. Tominaga, A. Hori, B. Therrien, *Acc. Chem. Res.* **2005**, *38*, 369–378; f) M. Albrecht, R. Frohlich, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 797–808; g) S. J. Dalgarno, N. P. Power, J. L. Atwood, *Coord. Chem. Rev.* **2008**, *252*, 825; h) D. J. Tranchemontagne, Z. Ni, M. O'Keeffe, O. M. Yaghi, *Angew. Chem.* **2008**, *120*, 5214–5225; *Angew. Chem. Int. Ed.* **2008**, *47*, 5136–5147; i) R. W. Saalfrank, H. Maid, A. Scheurer, *Angew. Chem.* **2008**, *120*, 8924; *Angew. Chem. Int. Ed.* **2008**, *47*, 8794; j) P. Mal, D. Schultz, K. Beyeh, K. Rissanen, J. R. Nitschke, *Angew. Chem.* **2008**, *120*, 8421; *Angew. Chem. Int. Ed.* **2008**, *47*, 8297.

[3] C. Schmuck, *Angew. Chem.* **2007**, *119*, 5932–5935; *Angew. Chem. Int. Ed.* **2007**, *46*, 5830–5833.

[4] a) J. S. Fleming, K. L. V. Mann, C.-A. Carraz, E. Psillakis, J. C. Jeffery, J. A. McCleverty, M. D. Ward, *Angew. Chem.* **1998**, *110*, 1315–1318; *Angew. Chem. Int. Ed.* **1998**, *37*, 1279–1281; b) R. L. Paul, Z. R. Bell, J. C. Jeffery, J. A. McCleverty, M. D. Ward, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4883–4888; c) R. L. Paul, S. P. Argent, J. C. Jeffery, L. P. Harding, J. M. Lynam, M. D. Ward, *Dalton Trans.* **2004**, 3453–3458; d) I. S. Tidmarsh, T. B. Faust, H. Adams, L. P. Harding, L. Russo, W. Clegg, M. D. Ward, *J. Am. Chem. Soc.* **2008**, *130*, 15167–15175.

[5] a) R. D. Schnebeck, E. Freisinger, B. Lippert, *Angew. Chem.* **1999**, *111*, 235–238; *Angew. Chem. Int. Ed.* **1999**, *38*, 168–171; b) F. Fochi, P. Jacopozzi, E. Wegelius, K. Rissanen, P. Cozzini, E. Marastoni, E. Fisicaro, P. Manini, R. Fokkens, E. Dalcanale, *J. Am. Chem. Soc.* **2001**, *123*, 7539–7552; c) H. Amouri, C. Desmarets, A. Bettoschi, M. N. Rager, K. Boubekeur, P. Rabu, M. Drillon, *Chem. Eur. J.* **2007**, *13*, 5401–5407; d) C. R. K. Glasson, G. V. Meehan, J. K. Clegg, L. F. Lindoy, P. Turner, M. B. Duriska, R. Willis, *Chem. Commun.* **2008**, 1190–1192.

[6] M. Tominaga, K. Suzuki, T. Murase, M. Fujita, *J. Am. Chem. Soc.* **2005**, *127*, 11950–11951.

[7] C. Olivier, Z. Grote, E. Solari, R. Scopelliti, K. Severin, *Chem. Commun.* **2007**, 4000–4002.

[8] a) C. Caltagirone, P. A. Gale, *Chem. Soc. Rev.* **2009**, *38*, 520–563; b) P. A. Gale, *Chem. Commun.* **2008**, 4525–4540; c) O. A. Okunola, P. V. Santacroce, J. T. Davis, *Supramol. Chem.* **2008**, *20*, 169–190; d) E. A. Katayev, Y. A. Ustynyuk, J. L. Sessler, *Coord. Chem. Rev.* **2006**, *250*, 3004–3037; e) R. Custelcean, B. A. Moyer, *Eur. J. Inorg. Chem.* **2007**, 1321–1340; f) S. O. Kang, R. A. Begum, K. Bowman-James, *Angew. Chem.* **2006**, *118*, 8048–8061; *Angew. Chem. Int. Ed.* **2006**, *45*, 7882–7894; g) F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609–1646.

[9] S. Kubik, C. Reyheller, S. Stuwe, *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, *52*, 137–187.

[10] a) R. Custelcean, V. Sellin, *Chem. Commun.* **2007**, 1541–1543; b) R. Custelcean, P. Remy, P. V. Bonnesen, D.-e. Jiang, B. A. Moyer, *Angew. Chem.* **2008**, *120*, 1892–1896; *Angew. Chem. Int. Ed.* **2008**, *47*, 1866–1870; c) R. Custelcean, P. Remy, *Cryst. Growth Des.* **2009**, *9*, 1985–1989.

[11] Y. Marcus, *J. Chem. Soc. Faraday Trans.* **1991**, *87*, 2995–2999.

[12] B. L. Jacobson, F. A. Quiocho, *J. Mol. Biol.* **1988**, *204*, 783–787.

[13] Recent reviews on metal–organic anion hosts: a) J. Pérez, L. Riera, *Chem. Soc. Rev.* **2008**, *37*, 2658–2667; b) V. Amendola, L. Fabbrizzi, *Chem. Commun.* **2009**, 513–531; c) J. W. Steed, *Chem. Soc. Rev.* **2009**, *38*, 506–519.

[14] Recent examples of urea anion receptors: a) C. Caltagirone, J. R. Hiscock, M. B. Hursthouse, M. E. Light, P. A. Gale, *Chem. Eur. J.* **2008**, *14*, 10236–10243; b) D. Meshcheryakov, F. Arnaud-Neu, V. Bohmer, M. Bolte, J. Cavaleri, V. Hubscher-Bruder, I. Thondorf, S. Werner, *Org. Biomol. Chem.* **2008**, *6*, 3244–3255; c) M. Allevi, M. Bonizzoni, L. Fabbrizzi, *Chem. Eur. J.* **2007**, *13*, 3787–3795; d) D. R. Turner, M. J. Paterson, J. W. Steed, *J. Org. Chem.* **2006**, *71*, 1598–1608; e) A. L. Sisson, J. P. Clare, A. P. Davis, *Chem. Commun.* **2005**, 5263–5265.

[15] B. Gao, Z.-f. Liu, *J. Chem. Phys.* **2004**, *121*, 8299.

[16] B. P. Hay, T. K. Firman, B. A. Moyer, *J. Am. Chem. Soc.* **2005**, *127*, 1810–1819.

[17] R. Custelcean, B. A. Moyer, B. P. Hay, *Chem. Commun.* **2005**, 5971–5973.

[18] R. M. Smith, A. E. Martell, *Critical Stability Constants*, *Vol. 2*, Plenum, New York, **1975**.

[19] Figure 1c shows only one of four possible $[SO_4(urea)_6]^{2-}$ orientations within the cage. Since this complex is chiral, a second orientation is simply the mirror image of the first. The other two orientations, which direct the S–O vectors towards the cage faces rather than the cage vertices, are obtained by inversion of the first two orientations. In all cases, each C=O bond remains aligned to a C_2 axis and the effect on urea position is rotation about this axis.

[20] The *HostDesigner* code is available free of charge by request from B. P. Hay (haybp@ornl.gov).

[21] a) V. S. Bryantsev, B. P. Hay, *J. Am. Chem. Soc.* **2006**, *128*, 2035–2042; b) B. P. Hay, A. A. Oliferenko, J. Uddin, C. G. Zhang, T. K. Firman, *J. Am. Chem. Soc.* **2005**, *127*, 17043–17053.

[22] Crystal data for **1**$(SO_4)_3(MeOH)_4(H_2O)_{22}$: $C_{142}H_{120}N_{36}Ni_4O_{48}S_4$; $M = 3461.82$; orange prism; crystal size $0.19 \times 0.13 \times 0.06$ mm; trigonal; space group $R3$ (No. 146); $a = b = 20.094(2)$, $c = 38.045(4)$ Å; $V = 13303(2)$ Å^3; $Z = 3$; $\rho_{calcd} = 1.296\ g\,cm^{-3}$; $Mo_{K\alpha}$ radiation; $\lambda = 0.71073$ Å; $\mu = 0.550\ mm^{-1}$; $T = 173(2)$ K; $2\theta_{max} = 50.1°$; 34751 reflections collected, 10340 unique ($R_{int} = 0.0793$) $R_1 = 0.0850$; $wR_2 = 0.2122$; 6341 reflections with $I > 2\sigma(I)$. CCDC 711013 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] J. W. Davis, A. G. Collins, *Environ. Sci. Technol.* **1971**, *5*, 1039–1043.

[24] Measurements made at 25 °C, and at an estimated ionic strength of 0.03–0.04 M. For the general case in which the $[Ni_4(\mathbf{L1})_6]^{8+}$ tetrahedral host rearranges into other aggregates, $K_{app} = [[Ni_4(\mathbf{L1})_6(SO_4)]^{6+}]/[H_{aggr}][SO_4^{2-}]$, where $[H_{aggr}]$ is the total concentration of host species. As $[[Ni_4(\mathbf{L1})_6]^{8+}]$ is a fraction f of $[H_{aggr}]$, then $K_{app} = fK(SO_4^{2-})$. Since $f \leq 1$, it follows that $K(SO_4^{2-}) \geq K_{app}$. The apparent constant is thus a lower limit estimate of $K(SO_4^{2-})$. In the ideal case that the tetrahedral host remains intact, the measured apparent constant becomes the actual sulfate binding constant for the tetrahedral cage: $K_{app} = K(SO_4^{2-}) = [[Ni_4(\mathbf{L1})_6(SO_4)]^{6+}]/[Ni_4(\mathbf{L1})_6][SO_4^{2-}]$. For a similar analysis of the apparent association constant for guest binding by a self-assembled host, see: T. Martin, U. Obst, J. Rebek, Jr., *Science* **1998**, *281*, 1842.

[25] M. Roitzsch, B. Lippert, *Angew. Chem.* **2006**, *118*, 153–156; *Angew. Chem. Int. Ed.* **2006**, *45*, 147–150.