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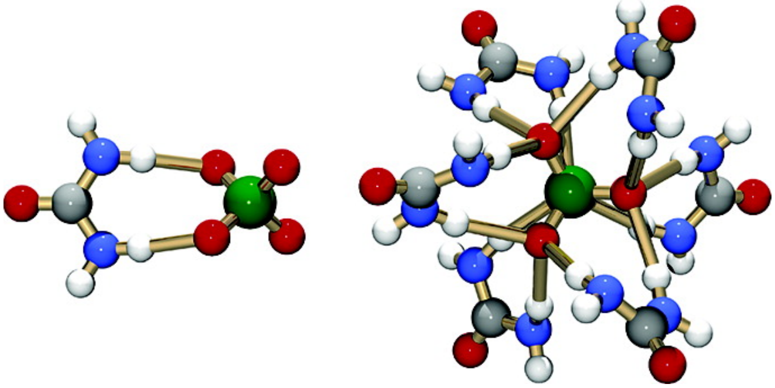

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Structural Design Criteria for Anion Hosts: Strategies for Achieving Anion Shape Recognition through the Complementary Placement of Urea Donor Groups

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Abstract: The arrangement of urea ligands about different shaped anions has been evaluated with electronic structure calculations. Geometries and binding energies are reported for urea complexes with Cl^-, NO_3^-, and ClO_4^-. The results yield new insight into the nature of urea−anion interactions and provide structural criteria for the deliberate design of anion selective receptors containing two or more urea donor groups.

Introduction

Anion complexation by synthetic host molecules is an important theme in supramolecular chemistry.[1] One of the key challenges is the design of hosts that recognize specific anions, overcoming the normal bias selectivity that exists in pure solution or in ion partitioning where bias is dictated by solvation effects dependent upon anion properties, such as basicity[2] and charge density.[3] Normal bias selectivity is almost always observed when anions are partitioned from an aqueous to an organic phase.[3] In these cases, the extent of partitioning is inversely related to the hydration free energy of the anion. For example, in the absence of recognition, the following selectivity would be observed for transfer of the anion from aqueous to organic phase: $ClO_4^- > NO_3^- > Cl^-$.

It should be possible to build hosts with shaped cavities that have been designed to complement specific anion geometries, thereby attenuating, perturbing, or even overturning normal bias selectivity.[4,5] One successful approach for preparing anion hosts has been to add hydrogen bond donor groups to an organic scaffold to yield receptors that interact with anions through hydrogen bonding.[1] Building recognition into such hosts requires an understanding of the geometric requirements for complementary hydrogen bonding. Our research interests lie in attaining this understanding and applying it to the computer-aided-design of host architectures with the use of molecule-building software, such as HostDesigner[6] and CAVEAT.[7] Criteria for structure-based design are derived from electronic structure calculations and, when available, crystal structure data. In prior studies, we developed structural design criteria for arranging simple monoprotic donor groups, such as methanol and *N*-methylacetamide, about different shaped anions.[8] In the current study, we turn our attention to a diprotic donor group, urea.

Urea is an attractive building block for anion receptors because it contributes two relatively strong hydrogen bonding sites.[9] The two N−H groups can bind with a single acceptor atom to yield a six-membered chelate ring or with two adjacent oxygen atoms in an oxyanion to yield an eight-membered chelate ring. A variety of urea-based hosts have been synthesized. Examples of acyclic tweezer,[5,10] tripodal,[11] and tetrapodal[12] architectures are shown in Figure 1. All of these structures have been shown to form complexes with anions.

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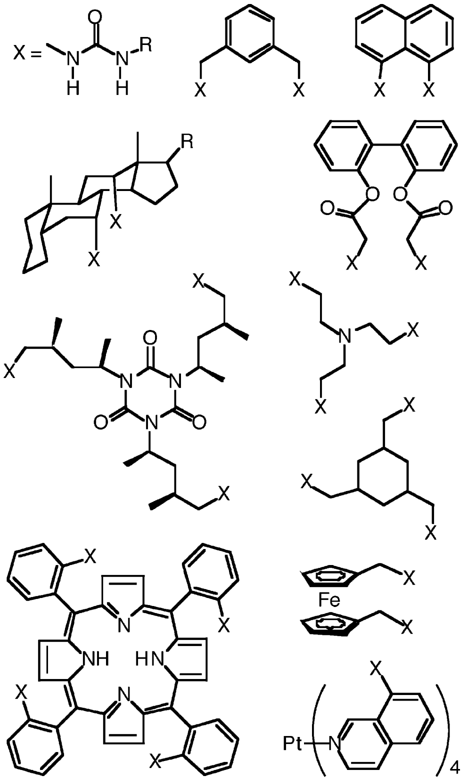

Figure 1. Examples of urea-based anion receptors.

It is difficult to judge the degree to which known urea-based host architectures actually organize the hydrogen bonding sites for anion complexation. Control experiments to compare the reactivity of a multi-urea host to that of single urea analogues are often missing. Because binding constant data are limited to small sets of anions under diverse solvent conditions, it is impossible to compare directly the effectiveness of different architectures toward a specific anion. There is scant structural data available for urea-based hosts or their anion complexes, and postulated anion binding mode(s) in solution are rarely confirmed by crystal structures. Even where structural data are available, it is not possible to assess the degree of binding site organization without first understanding what constitutes a complementary arrangement of binding sites within the host.

When two or more urea moieties are attached to an organic scaffold, their relative positions are, to a large extent, constrained in space. Steric recognition of a targeted anion will be achieved only when the urea groups are constrained such that they have a strong interaction with the targeted anion and weakened interactions with competing anions. Hosts that have been so constructed should exhibit an increased binding enthalpy for the targeted anion compared to that of the competing anions. The degree to which normal bias selectivity is perturbed by a host will depend on the magnitude of this enthalpy increase. Thermodynamic selectivity for the targeted anion will be attained only when the enthalpic advantage is large enough to overcome the energetic terms that give rise to normal bias selectivity, in other words, the enthalpic and entropic contributions from solvent restructuring during the complexation process.[13]

The possibility of introducing a sterically based recognition for an anion of particular shape relies upon the hypothesis that complementary positioning of the binding sites differs with different anion shape. To explore the validity of this hypothesis, we undertook a detailed study of the structural and energetic aspects of hydrogen bonding interactions between urea and three monoanions of different shapes: Cl^-, NO_3^-, and ClO_4^-. The results establish both the differences and the similarities in the optimal urea placement about spherical, trigonal planar, and tetrahedral anions, and suggest instances where host architecture might be exploited to achieve recognition on the basis of anion shape.

Methods

Electronic structure calculations were carried out using the NWChem program.[14] Geometries for **1**−**39** were optimized using density functional theory (DFT)[15] with the hybrid B3LYP functional[16,17] and a polarized double-ζ basis set (DZVP2).[18] No charge fitting was used. Frequency calculations were performed at this level of theory to determine which structures corresponded to minima on the potential energy surface. Due to an abundance of very low frequencies in many of these systems, standard optimization criteria often resulted in spurious negative frequencies. Therefore, all DFT computations were done with an extra-fine grid and by calculating all coulomb integrals above 10^{-14}, tight SCF convergence criteria (a maximum 10^{-8} au energy step, 10^{-7} density gradient, and 10^{-5} step size), and tight geometry optimization cutoffs.

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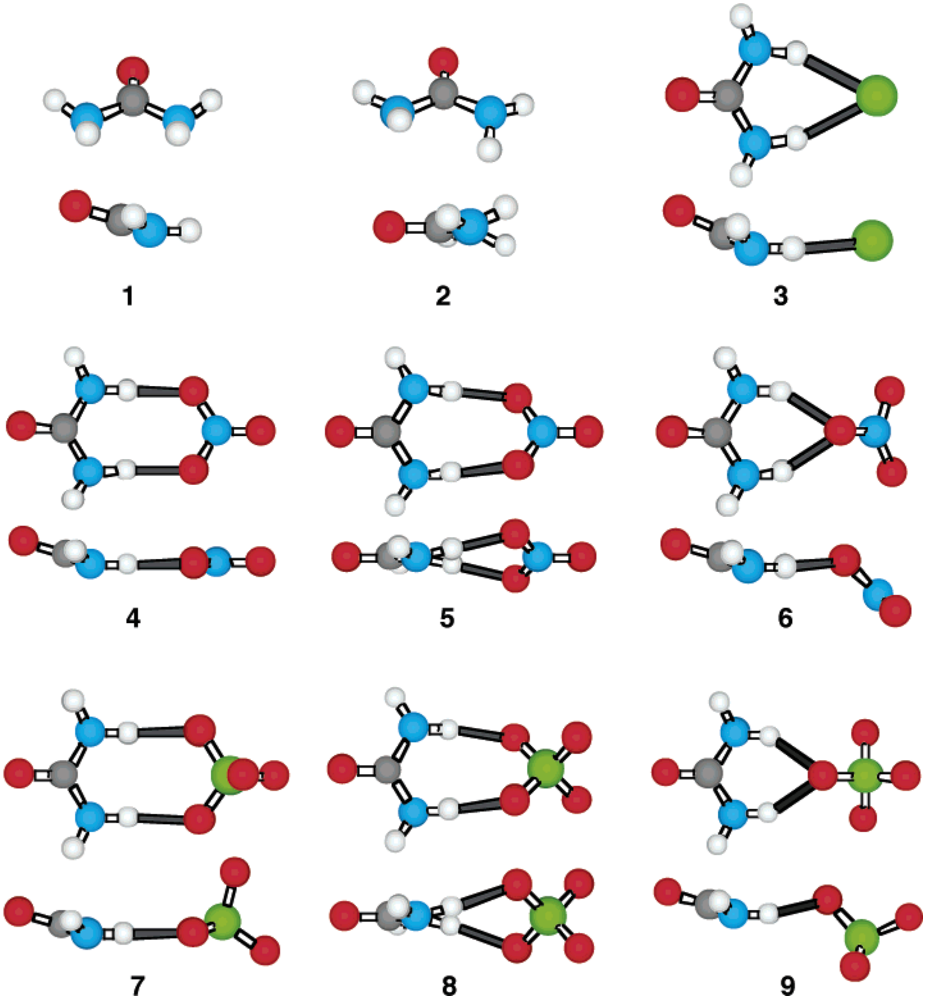

Figure 2. Top and side views of MP2/TZ optimized geometries for urea, **1** and **2**, and its 1:1 complexes with Cl^- (**3**), NO_3^- (**4**−**6**), and ClO_4^- (**7**−**9**).

To validate the performance of the DFT method, further calculations on urea, anions, and 1:1 urea:anion complexes, **1**−**9**, were performed using second-order Møller−Plesset theory (MP2).[19] Starting from their known minima on the DFT surface, the geometries were optimized at the MP2 level using first the augmented correlation consistent double-ζ basis set (aug-cc-pVDZ), followed by the larger triple-ζ basis set (aug-cc-pVTZ).[20] Frequency calculations were performed at the MP2/aug-cc-pVDZ level of theory to verify that the structures were minima on the potential energy surface.

Potential energy surfaces for geometric distortions of the 1:1 urea:anion complexes were obtained from single points on the MP2/aug-cc-pVDZ surface with geometries similar to their respective minimum, but distorted from that shape along a coordinate as described in the text.

Results and Discussion

1:1 Urea:Anion Complexes. Three levels of theory were used to study urea and 1:1 urea:anion complexes. Prior calculations on monoprotic hydrogen bond complexes with oxyanions establish that the highest level of theory used in this study, MP2/aug-cc-pVTZ (MP2/TZ), yields geometries that are consistent with experimental data and binding energies that are close to those obtained at the MP2 complete basis set limit.[8c] A lower level of theory, MP2/aug-cc-pVDZ (MP2/DZ), was used to perform optimizations and frequency calculations prior to the final optimization at MP2/TZ. Finally, calculations at the B3LYP/DZVP2 (DFT) level of theory were performed in order to benchmark this computationally more efficient method for use in the study of higher order complexes.

MP2/TZ geometries for urea, **1** and **2**, and 1:1 urea:anion complexes with Cl^-, NO_3^-, and ClO_4^-, **3**−**9**, are shown in Figure 2, and selected geometric parameters at the DFT and MP2/TZ levels are presented in Table 1. Examination of Table 1 establishes that the DFT method yields geometries that are in acceptable agreement with those obtained with MP2/TZ. The main difference in hydrogen bond geometric parameters is that MP2/TZ yields H···A distances that are on average 0.03 Å shorter than those obtained with DFT.

Energetic data for **1**−**9** at the DFT, MP2/ DZ, and MP2/TZ levels are presented in Table 2. Comparison of the DFT values with those obtained at MP2/TZ reveals the DFT method overestimates the binding energy for Cl^-, by 0.63 kcal/mol, and underestimates the binding energies for NO_3^- and ClO_4^-, by 1.35 and 2.24 kcal/mol, respectively, on average. We note, however, that for all species, the relative stability order at MP2/TZ is reproduced by DFT, and with one exception, **9**, relative energies are reproduced within a few tenths of a kcal/mol.

The two nitrogen atoms in urea are pyramidal in the computed geometries giving rise to two stable conformers for the free ligand. In the C_s symmetric syn conformer, **1**, the nitrogen atoms

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Table 1. Geometric Parameters for Urea, **1** and **2**, and 1:1 Urea:Anion Complexes, **3**−**9**, at Different Levels of Theory[a]

structure	theory	N–C–N	C–N–H	H··· H	H–N···N–H	H···A	N–H···A	H···O–X	H···O–X–O[b]
1, urea *syn*	MP2/TZ	114.6	120.0	2.308	0.0				
	DFT	115.0	120.0	2.345	0.0				
2, urea *anti*	MP2/TZ	113.6	117.2	2.405	52.5				
	DFT	114.0	117.0	2.455	55.2				
3, Cl^- *syn*	MP2/TZ	112.4	113.0	2.078	0.0	2.251	158.2		
	DFT	113.7	115.5	2.143	0.0	2.288	156.8		
4, NO_3^- *syn*	MP2/TZ	113.9	118.9	2.226	0.0	1.866	177.9	121.2	0.8
	DFT	114.3	118.7	2.260	0.0	1.892	177.7	121.0	1.0
5, NO_3^- *anti*	MP2/TZ	113.7	119.3	2.226	24.3	1.863	177.5	117.7	14.6
	DFT	114.3	119.8	2.265	21.8	1.889	177.8	119.2	11.4
6, NO_3^- *syn*	MP2/TZ	113.6	117.6	2.165	0.0	1.920	148.9	121.9	
	DFT	114.2	116.9	2.198	0.0	1.933	148.2	133.3	
7, ClO_4^- *syn*	MP2/TZ	114.4	119.7	2.268	0.0	1.938	177.2	121.6	24.0
	DFT	114.8	119.4	2.305	0.0	1.998	176.4	123.5	9.0
8, ClO_4^- *anti*	MP2/TZ	114.0	119.3	2.281	29.0	1.939	173.9	116.3	20.3
	DFT	114.8	120.3	2.320	25.5	1.998	178.5	121.4	13.2
9, ClO_4^- *syn*	MP2/TZ	113.8	117.9	2.190	0.0	2.044	147.8	113.9	
	DFT	114.3	117.5	2.224	0.0	2.053	148.0	127.8	

[a] DFT = B3LYP/DZVP2, MP2/TZ = MP2/aug-cc-pVTZ. Distances are given in angstroms. Angles are given in degrees. [b] Dihedral angle within eight-membered chelate rings.

Table 2. Energies for Urea, **1** and **2**, and 1:1 Urea:Anion Complexes, **3**−**9**, at Different Levels of Theory[a]

structure	sym	ΔE_{elec} DFT	ΔE_{elec} MP2/DZ	ΔE_{elec} MP2/TZ	rel *E* DFT	rel *E* MP2/DZ	rel *E* MP2/TZ
1, urea *syn*	C_s				1.02	1.06	0.94
2, urea *anti*	C_2				0.00	0.00	0.00
3, Cl^- *syn*	C_s	−28.90	−27.31	−28.27	0.00	0.00	0.00
4, NO_3^- *syn*	C_s	−25.87	−26.92	−26.72	0.00	0.00	0.00
5, NO_3^- *anti*	C_2	−25.50	−26.86	−26.66	0.38	0.06	0.06
6, NO_3^- *syn*	C_s	−22.84	−24.04	−23.86	3.04	2.88	2.86
7, ClO_4^- *syn*	C_s	−19.18	−21.90	−21.63	0.00	0.00	0.00
8, ClO_4^- *anti*	C_2	−18.87	−21.85	−21.63	0.30	0.05	0.00
9, ClO_4^- *syn*	C_s	−17.69	−20.27	−19.19	1.49	1.63	2.44

[a] DFT = B3LYP/DZVP2, MP2/DZ = MP2/aug-cc-pVDZ, MP2/TZ = MP2/aug-cc-pVTZ. Energies are given in kcal mol^{-1}. The electronic binding energy, ΔE_{elec}, is the energy difference *E*(complex) − *E*(anion) − *E*(**2**).

are pyramidalized in the same direction. In the C_2 symmetric anti conformer, **2**, the nitrogen atoms are pyramidalized in opposite directions. Consistent with prior theoretical studies of urea,[21] we find that when urea is in the uncomplexed state, **2** is approximately 1 kcal/mol more stable than **1**.

Optimal hydrogen bonding interactions between a urea donor and an anion receptor require linear N−H···A bonds.[22] This requirement is not achieved by either of the two urea conformers when binding with a single acceptor atom to form a six-membered chelate ring. As illustrated in Figure 3, placing a single acceptor atom 2.0 Å from both hydrogen atoms would yield nonlinear N−H···A angles of 145° for **1** and 128° for **2**. These hypothetical geometries suggest that the syn form, **1**, should provide a more stable hydrogen bonding arrangement than that in the anti form, **2**.

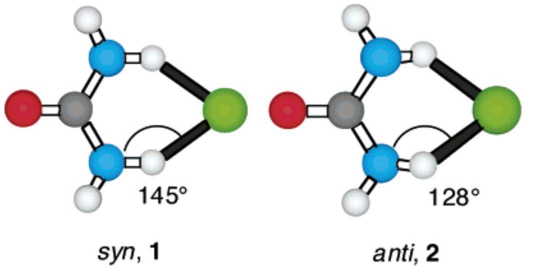

Figure 3. Geometries obtained by placing a Cl^- anion on the C_2 symmetry axis of **1** and **2** at a distance of 2.0 Å from each N−H donor group.

This observation is confirmed by geometry optimizations. The *syn*-urea conformation yields a stable geometry for a 1:1 complex between urea and Cl^-, **3**. Starting the calculation from a complex containing the *anti*-urea conformation leads to a transition state that is 1.07 kcal/mol higher in energy at the DFT level of theory. Comparison of the structure of free *syn*-urea, **1**, with that in the Cl^- complex, **3**, reveals that anion complexation causes distortions to the urea geometry. These distortions, which involve decreases in both C−N−C and C−N−H angles that significantly decrease the H···H distance, act to give more linear hydrogen bonds. As a result, the N−H···Cl angles increase from a hypothetical 145° (Figure 3) to 158° (Table 1).

An alternate mode of hydrogen bonding is possible with oxyanions, such as NO_3^- and ClO_4^-. Each N−H donor group can bind to a different oxygen atom in the anion, yielding an eight-membered chelate ring. As illustrated in Figure 4, placing oxygen atoms 2.0 Å from each N−H group in **1** and **2** such that the N−H···O angles are linear reveals that the syn form would give linear N−H···O angles at an O···O distance of 2.27 Å and the anti form would give linear N−H···A angles at an O···O distance of 3.37 Å. The O···O distances are 2.20 Å in NO_3^- and 2.46 Å in ClO_4^-, suggesting that it is the syn conformer that provides the most complementary geometry with respect to N−H···O angles.

There is another structural aspect that must be considered in the analysis of hydrogen bond geometries with oxyanions. In addition to linear N−H···O angles, directionality at the oxygen atom acceptors defines an optimal position for the placement of hydrogen atoms with respect to the anion in terms of an X−O···H angle and an O−X−O···H dihedral angle.[8] As illustrated in Figure 4, placing hydrogen atoms 2.0 Å from each oxygen atom in the optimal orientations, 115° N−O···H angle and 0° O−N−O···H dihedral for NO_3^-, 122° Cl−O···H angle

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(21) Dixon, D. A.; Matsuzawa, N. *J. Phys. Chem.* **1994**, *98*, 3967−3977. (b) Godfrey, P. D.; Brown, R. D.; Hunter, A. N. *J. Mol. Struct.* **1997**, *413*, 405−414. (c) Masunov, A.; Dannenberg, J. J. *J. Phys. Chem. A* **1999**, *103*, 178−184. (d) Dobrowolski, J. Cz.; Kolos, R.; Sadlej, J.; Mazurek, A. P. *Vib. Spectrosc.* **2002**, *29*, 261−282. (e) Lecomte, F.; Lucas, B.; Gregoire, G.; Schermann, J. P.; Desfrancois, C. *Phys. Chem. Chem. Phys.* **2003**, *5*, 3120−3125. (f) Bharatam, P. V.; Moudgil, R.; Kaur, D. *J. Phys. Chem. A* **2003**, *107*, 1627−1634.

(22) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Truhlar, D. G., Ed.; Oxford University Press: Oxford, 1997.

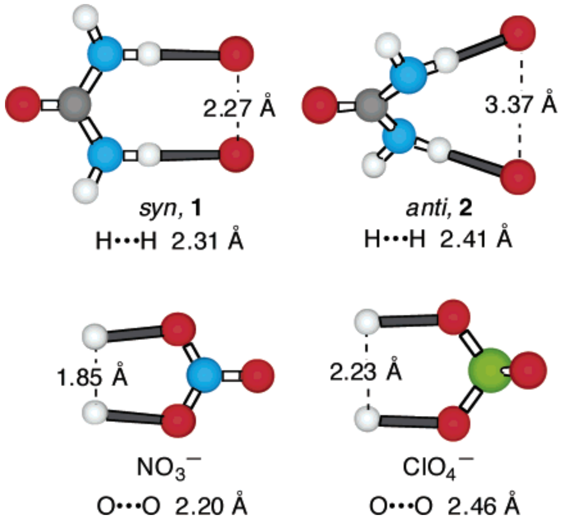

Figure 4. Complementary placement of two oxygen acceptor atoms for **1** and **2** (top) and the complementary placement[8] of two hydrogen donor atoms on adjacent oxygen atoms in NO$_3^-$ and ClO$_4^-$ anions (bottom).

and 0° O−Cl−O···H dihedral for ClO$_4^-$, yields an H···H distance of 1.85 Å for NO$_3^-$ and 2.23 Å for ClO$_4^-$. The H···H distances are 2.31 Å in *syn*-urea, **1**, and 2.41 Å in *anti*-urea, **2**, providing further evidence that the syn form is more complementary for binding oxyanions than the anti form.

The foregoing analysis is fully consistent with results obtained from geometry optimizations. Both NO$_3^-$ and ClO$_4^-$ form eight-membered chelate rings with *syn*- and *anti*-urea that are minima on the DFT and MP2 potential surfaces. At the MP2/TZ level, the global minimum syn forms, **4** and **7**, are very close in energy to that in the anti forms, **5** and **8**. Geometric data in Table 1 reveal that this energetic equivalence arises because the more stable anti conformer, **2**, is destabilized by structural distortions on anion complexation more so than the syn conformer, **1**. The anti form is significantly flattened, as illustrated by the dihedral angle H−N···N−H, which goes from 52.5° in **1** to 24.3° in **5** and 29.0° in **8**. In both syn and anti complexes, the N−C−N and C−N−H angles are decreased, leading to shorter H···H distances. However, the change in H···H distance in the anti conformer, 0.18 Å for NO$_3^-$ and 0.12 Å for ClO$_4^-$, is larger than the change in the syn conformer, 0.05 Å for NO$_3^-$ and 0.04 Å for ClO$_4^-$.

Attempts to locate minima for single oxygen binding modes with the oxyanions, analogous to that observed with the Cl$^-$ complex, **3**, were unsuccessful. Structures **6** and **9** were obtained only after enforcing C_s symmetry during the optimization. Each structure exhibited multiple negative frequencies at the MP2/DZ level. On removing the symmetry constraints, **6** reverted to **4** and **9** reverted to **7**. Energetic data in Table 2 reveal that forcing urea to bind to a single oxygen atom yields complexes that are >10% less stable than those involving hydrogen bonds to two oxygen atoms.

The preceding analysis demonstrates that significant distortions in urea structure occur upon binding anions. These distortions are rationalized by the strengthened interactions that occur with linear hydrogen bonds and, in the case of the oxyanions, optimal X−O···H angles and O−X−O···H dihedral angles. The distortions induce strain within the urea ligand. This induced strain, calculated as the difference in energy between the bound form of the ligand and the binding conformation of the ligand, provides an energetic measurement of how well a given host configuration complements a guest.[23] At the DFT level of theory, anion binding to the syn conformer induces strain of 1.50 kcal/mol with Cl$^-$, **3**, 0.81 kcal/mol with NO$_3^-$, **4**, and 0.35 kcal/mol with ClO$_4^-$, **7**. These values decrease as the extent of structural distortion decreases (see Table 1) and indicate that *syn*-urea is structurally most complementary for the ClO$_4^-$ anion. Anion binding to the anti conformer induces strain of 1.74 kcal/mol with NO$_3^-$, **5**, and 1.10 kcal/mol with ClO$_4^-$, **8**. For a given anion, the amount of strain in the anti form is larger than that in the syn form, reflecting the greater extent of structural reorganization that occurs on binding the less complementary anti conformer.

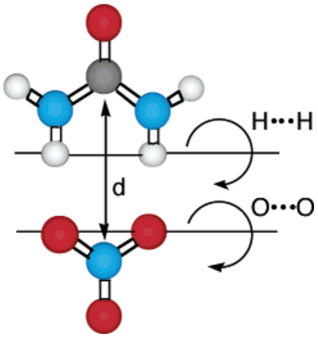

Figure 5. Geometric distortions used to derive the potential energy surfaces shown in Figure 6.

The electronic binding energies, ΔE_{elec}, given in Table 2 reveal that the hydrogen bonding interactions between urea and monoanions are significant. The relative bond strengths range from −28.3 kcal/mol for Cl$^-$, **3**, −26.7 kcal/mol for NO$_3^-$, **5**, to −21.6 kcal/mol for ClO$_4^-$, **7**. Dividing by two yields individual hydrogen bond strengths of −14 to −10 kcal/mol, which fall in the range of other moderate hydrogen bonds that are mainly electrostatic in nature.[22] The bond strengths decrease in the same order as the heats of hydration −87.7 kcal/mol for Cl$^-$, −74.6 kcal/mol for NO$_3^-$, and −58.8 kcal/mol for ClO$_4^-$, reflecting the degree of charge delocalization in the anions.[13]

To evaluate the sensitivity of ΔE_{elec} to changes in structure, potential energy surfaces were generated for several geometric distortions in **3**, **4**, **5**, **7**, and **8** at the MP2/DZ level of theory. These include variation of the H···A distance, variation in N−H···O angle by rotation about the H···H axis, and, for the oxyanions, variation in O−X−O···H dihedral angle by rotation about the O···O axis, as shown in Figure 5. The resulting potential energy surfaces (Figure 6) are remarkably similar for all structures examined. Variations of ±0.2 Å in H···A distance and ±15° rotation about the H···H axis destabilize the complexes by approximately 1 kcal/mol. In oxyanions, the potential energy surface for rotation about the O···O axis is very flat, indicating a weak O−X−O···H preference over the range of values that were examined. These results are consistent with potential energy surfaces reported for similar geometric distortions in oxyanion complexes with monoprotic donor groups.[8]

2:1 Urea:Anion Complexes. With the insights gained from the examination of 1:1 complexes, an exhaustive analysis was performed to locate all stable geometries for 2:1 urea:anion complexes containing six-membered chelate rings formed by

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(23) Hay, B. P.; Zhang, D.; Rustad, J. R. *Inorg. Chem.* **1996**, *35*, 2650−2658.

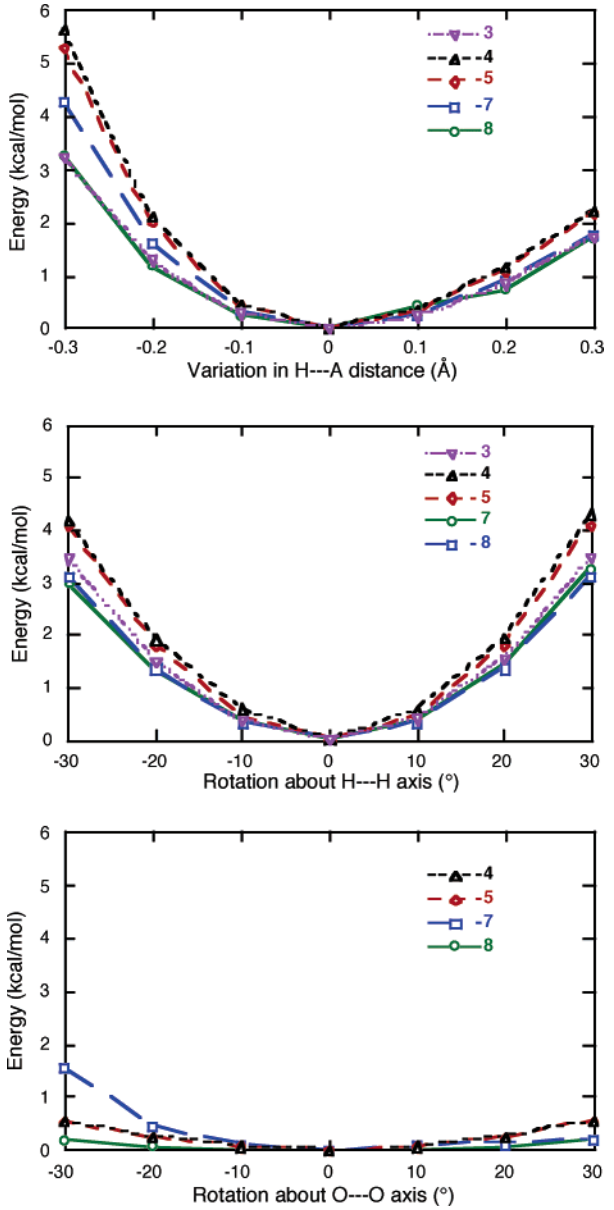

Figure 6. MP2/DZ potential energy surfaces for geometric distortions of **3**, **4**, **5**, **7**, and **8**.

syn-urea and Cl^- or eight-membered chelate rings formed by *syn*- and *anti*-urea and an oxyanion. At the DFT level of theory, this analysis yielded a single minimum for Cl^-, six minima for NO_3^-, and 14 minima for ClO_4^-. Hydrogen bond distances, electronic binding energies, and relative stabilities for these structures are summarized in Table 3. The global minimum geometry for each 2:1 complex is shown in Figure 7 (Cartesian coordinates for all 2:1 urea:anion structures are available as Supporting Information).

There is one minimum energy geometry for placing two urea molecules about the spherical Cl^- ion, **10**. In this C_2 symmetric structure, inverting either one or both of the *syn*-urea ligands leads to an energetically degenerate form.

In contrast to Cl^-, the oxyanions exhibit multiple stable conformations. This situation arises because both syn and anti forms are present, and for any pair of these two forms, there is more than one way to orient them with respect to one another. In addition, with the ClO_4^- anion, the urea ligands can occupy either adjacent edges or opposite edges of the tetrahedron. A procedure for naming the different configurations was developed. First, the oxyanion is oriented with respect to the Cartesian coordinate system (see Figure 8). The trigonal planar NO_3^- anion is placed in the *xy*-plane with the C_3 axis aligned with the *z*-axis. The tetrahedral ClO_4^- anion is oriented with one face in the *xy*-plane and the perpendicular C_3 axis aligned with the *z*-axis. The tetrahedral face placed in the *xy*-plane contains both occupied edges when the urea ligands chelate adjacent edges, *adj*, or one occupied edge when the urea ligands chelate opposite, *opp*, edges.

The ligand conformation and orientation relative to this coordinate system are indicated by use of the labels as defined in Figure 8. When an occupied edge is in the *xy*-plane, a *syn*-urea is designated as s^+ when the oxygen atom is in the $+z$ direction with respect to the plane defined by the O−X−O edge and s^- when the oxygen atom is in the $-z$ direction. When an occupied edge is not in the *xy*-plane, as occurs when opposite edges are occupied in ClO_4^-, the *syn*-urea orientation is assigned by viewing the tetrahedron from the $+z$ direction. The s^+ label indicates the carbonyl group is to the right of the O−Cl−O plane (clockwise), and the s^- label indicates the carbonyl group is to the left of the O−Cl−O plane (counterclockwise). The *anti*-urea orientation is designated as a^+ when it is rotated clockwise with respect to the occupied edge or a^- when it is rotated counterclockwise with respect to the occupied edge.

In the 2:1 urea:NO_3^- complexes, the two urea ligands bind to adjacent edges of the triangle defined by the oxygen atoms. With four possible urea orientations on one pair of edge positions, there are a total of 16 possible configurations. Some of these configurations are structurally equivalent because of symmetry, while others are isoenergetic enantiomers. The six energetically unique configurations, **11**−**16**, are listed in Table 3. All six forms are similar in energy, differing by less than 0.7 kcal/mol. Consistent with the behavior of the 1:1 complexes, at this level of theory, the syn,syn forms are more stable than the syn,anti forms, which are more stable than the anti,anti forms. These stability differences would be expected to be diminished at higher levels of theory. The most stable orientation, **11**, occurs when the urea ligands are in the s^+s^- orientation.

Two urea ligands bind to either adjacent or opposite edges of the tetrahedral anion in the 2:1 urea:ClO_4^- complexes. With four possible urea orientations on two pairs of edge positions, there are a total of 32 possible configurations. The 14 energetically unique configurations, **17**−**30**, are listed in Table 3. As with that of NO_3^-, these configurations are similar in energy, spanning a range of only 0.71 kcal/mol. Again, at the DFT level of theory, the syn,syn forms are more stable than the syn,anti forms, which are more stable than the anti,anti forms. Unexpectedly, comparison of structures in which urea conformation is constant reveals that the position of the chelates on the tetrahedral edges has very little impact on stability. Placements on opposite edges, where each oxygen atom in the anion has a single hydrogen bond, are isoenergetic with placements on adjacent edges, where one oxygen atom is shared between two urea ligands. For example, the *opp* s^+s^+ configuration, **17**, is within 0.02 kcal/mol of both the *adj* s^+s^- configuration, **18**, and the *adj* s^-s^- configuration, **19**. Similar behavior is observed

Table 3. Geometric and Energetic Data (DFT) for 2:1 Urea:Anion Complexes **10**−**30**[a]

structure	sym	degenerate orientations	H···A	cavity radius	ΔE_{elec}	rel *E*
10, Cl^- (s^+s^+)	C_2	s^+s^-, s^-s^+, s^-s^-	2.363	2.363	−50.08	0.00
11, NO_3^- (s^+s^-)	C_2	s^-s^+	1.966	2.840	−45.66	0.00
12, NO_3^- (s^+s^+)	C_s	s^-s^-	1.966	2.843	−45.59	0.07
13, NO_3^- (s^+a^-)	C_1	s^-a^+, a^+s^+, a^-s^-	1.965	2.826	−45.36	0.30
14, NO_3^- (s^+a^+)	C_1	s^-a^-, a^+s^-, a^-s^+	1.965	2.830	−45.30	0.36
15, NO_3^- (a^+a^+)	C_2	a^-a^-	1.963	2.811	−45.07	0.59
16, NO_3^- (a^+a^-)	C_s	a^-a^+	1.964	2.819	−44.99	0.67
17, ClO_4^- (*opp* s^+s^+)	C_2	s^+s^-, s^-s^+, s^-s^-	2.051	3.114	−34.78	0.00
18, ClO_4^- (*adj* s^+s^-)	C_1	s^-s^+	2.049	3.118	−34.78	0.00
19, ClO_4^- (*adj* s^-s^-)	C_s	none	2.049	3.118	−34.76	0.02
20, ClO_4^- (*adj* s^+s^+)	C_s	none	2.051	3.144	−34.59	0.19
21, ClO_4^- (*opp* s^+a^+)	C_1	s^+a^-, s^-a^+, s^-a^-, a^+s^+, a^+s^-, a^-s^+, a^-s^-	2.051	3.128	−34.56	0.22
22, ClO_4^- (*adj* s^-a^-)	C_1	a^+s^-	2.048	3.107	−34.56	0.23
23, ClO_4^- (*adj* s^+a^-)	C_1	a^+s^+	2.048	3.106	−34.55	0.24
24, ClO_4^- (*adj* s^-a^+)	C_1	a^-s^-	2.052	3.100	−34.54	0.24
25, ClO_4^- (*adj* s^+a^+)	C_1	a^-s^+	2.052	3.105	−34.37	0.41
26, ClO_4^- (*opp* a^+a^-)	S_4	a^-a^+	2.051	3.111	−34.35	0.43
27, ClO_4^- (*opp* a^+a^+)	D_2	a^-a^-	2.051	3.114	−34.34	0.45
28, ClO_4^- (*adj* a^+a^-)	C_s	none	2.046	3.098	−34.33	0.45
29, ClO_4^- (*adj* a^+a^+)	C_1	a^-a^-	2.051	3.088	−34.31	0.47
30, ClO_4^- (*adj* a^-a^+)	C_s	none	2.054	3.089	−34.07	0.71

[a] DFT = B3LYP/DZVP2. Energies are given in kcal mol^{-1}. Distances are given in angstroms. Cavity radius is the average distance from the N−H hydrogen atoms to the center of the anion. The electronic binding energy, ΔE_{elec}, is the energy difference *E*(complex) − *E*(anion) − 2 × *E*(**2**).

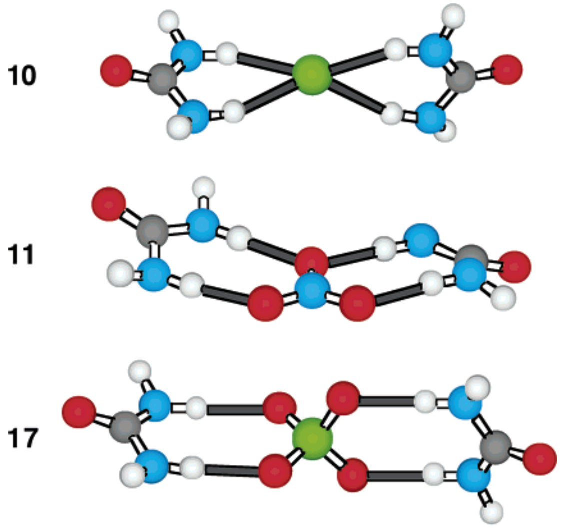

Figure 7. B3LYP optimized geometries for the lowest energy structures of 2:1 urea:anion complexes with Cl^- (**10**), NO_3^- (**11**), and ClO_4^- (**17**).

on comparison of syn,anti configuration **21** with **22**−**24**, and anti,anti configurations **26** or **27** with **28** and **29**.

Positioning Three or More Urea Groups about the Anion. The evaluation of the 2:1 urea:anion complexes revealed the general positioning of the urea groups about these anions was limited to one arrangement for Cl^-, one arrangement for NO_3^- (adjacent edges), and two arrangements for ClO_4^- (adjacent versus opposite edges). Although various combinations of syn and anti forms led to many local minima, the influence of chelate ring conformation on binding energy was established to be relatively small. Therefore, an exhaustive search for all stable conformers for 3:1 and higher urea:anion complexes was not undertaken. Instead, complexes of three *syn*-urea groups with each anion were optimized (DFT) to yield representative examples of one minimum for Cl^-, one minimum for NO_3^-, and three minima for ClO_4^-. Similarly, complexes of four *syn*-urea groups with Cl^- and ClO_4^- were optimized to yield one representative minimum for each anion. Attempts to locate minima for complexes containing five or more urea groups failed. Hydrogen bond distances, cavity radii, and electronic binding energies for these structures are summarized in Table 4. Representative structures containing three or more urea groups are presented in Figures 9 and 10.

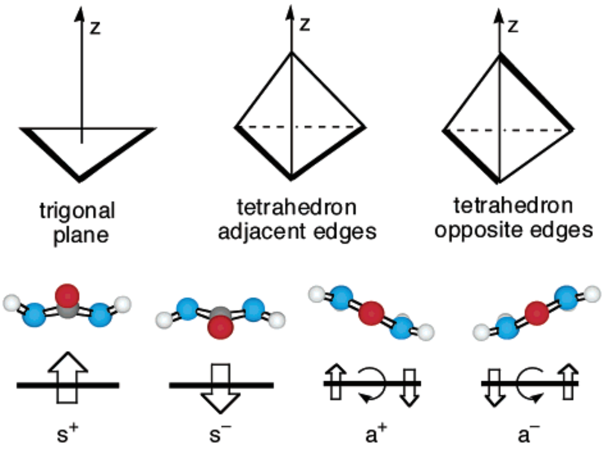

Figure 8. Nomenclature scheme for 2:1 urea:oxyanion conformations.

A C_3 symmetric structure was obtained when three ureas were placed on the Cl^- anion, **31**. In this structure, the urea groups are arranged in a trigonal array about the anion. The urea ligands are twisted so that hydrogen atoms are positioned to form a pseudo-octahedral coordination sphere about the anion in a fashion analogous to the geometries observed for trischelate metal complexes.[24] Placing four urea groups on the Cl^- anion yields a C_1 symmetric minimum in which the urea groups are arranged in an approximate tetrahedral array about the anion, **36**. The results reveal that when urea groups are placed about the spherical Cl^- anion, they adopt arrangements that lead to the greatest separation from one another: linear for two ureas, trigonal for three ureas, or tetrahedral for four ureas.

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[24] Kepert, D. L. *Prog. Inorg. Chem.* **1977**, *23*, 1−65.

Table 4. Cavity Size and Binding Energy (DFT) as a Function of the Number of Urea Ligands, *n*[a]

No.	[anion(urea)$_n$]	sym	H···A	cavity radius	ΔE_{elec}	$\Delta E_{\text{elec}}/n$
3	$[\text{Cl(urea)}]^-$	C_s	2.295	2.295	−28.90	−28.90
10	$[\text{Cl(urea)}_2]^-$	C_2	2.363	2.363	−50.08	−25.04
31	$[\text{Cl(urea)}_3]^-$	C_3	2.439	2.439	−65.89	−21.96
36	$[\text{Cl(urea)}_4]^-$	C_1	2.509	2.509	−77.29	−19.32
4	$[\text{NO}_3\text{(urea)}]^-$	C_s	1.892	2.778	−25.87	−25.87
11	$[\text{NO}_3\text{(urea)}_2]^-$	C_2	1.966	2.840	−45.59	−22.80
32	$[\text{NO}_3\text{(urea)}_3]^-$	C_3	2.026	2.895	−61.05	−20.35
7	$[\text{ClO}_4\text{(urea)}]^-$	C_s	1.998	3.106	−19.18	−19.18
17	$[\text{ClO}_4\text{(urea)}_2]^-$	C_2	2.051	3.143	−34.78	−17.39
33	$[\text{ClO}_4\text{(urea)}_3]^-$	C_3	2.094	3.133	−47.55	−15.85
34	$[\text{ClO}_4\text{(urea)}_3]^-$	C_1	2.100	3.154	−47.13	−15.71
35	$[\text{ClO}_4\text{(urea)}_3]^-$	C_3	2.103	3.172	−46.89	−15.63
37	$[\text{ClO}_4\text{(urea)}_4]^-$	S_4	2.150	3.197	−56.82	−14.20
38	$[\text{ClO}_4\text{(urea)}_6]^-$	T	2.239	3.140	−73.58	−12.26
39	$[\text{SO}_4\text{(urea)}_6]^{2-}$	T	1.982	2.995	−195.44	−32.57

[a] DFT = B3LYP/DZVP2. Energies are given in kcal mol^{-1}. Distances are given in angstroms. Cavity radius is the average distance from the hydrogen donor atoms to the center of the anion. The electronic binding energy, ΔE_{elec}, is the energy difference $E(\text{complex}) - E(\text{anion}) - n \times E(\mathbf{2})$.

Given the constraint that each urea must chelate an edge of an oxyanion, the placement of three ureas about NO_3^- leads to a trigonal arrangement of the ligands. Unlike the spherical Cl^- anion, the strongest bonding interaction is achieved when the urea groups are oriented so that hydrogen donor atoms lie within the plane of the anion. With four possible conformations for each urea, there are a total of 64 possible conformations for this complex. One of these structures is illustrated by **32**.

There are three ways to distribute three urea groups on the edges of the tetrahedral ClO_4^- anion. As with NO_3^-, there are a total of 64 possible conformations for each arrangement, but only one example for each arrangement was calculated. The first arrangement, illustrated by **33**, is obtained when each urea is positioned on the edge of the same triangular face. The second arrangement, illustrated by **34**, is obtained by placing two urea groups on opposite edges and the third on an edge that connects the other two. The third arrangement, illustrated by **35**, is obtained when the urea groups occupy the three edges emanating from one oxygen atom. Consistent with the results on 2:1 urea:anion complexes, these three forms are relatively close in energy, differing by $\leq$0.7 kcal/mol. A representative 4:1 complex was obtained by adding a fourth urea to **34**, yielding **37**.

With six edges, a tetrahedral anion could accommodate up to six urea ligands. However, attempts to locate a stable 6:1 complex for ClO_4^- failed. One possible configuration, **38**, obtained by imposing T symmetry during the optimization, was not a minimum (two negative frequencies). A hypothesis that this structure could be stabilized by increasing the anion charge density was confirmed by further calculations. Optimization after replacing the monoanion ClO_4^- with the dianion SO_4^{2-} anion yields a 6:1 complex, **39**, with a configuration analogous to that of **38**, that is, a minimum on the B3LYP potential surface (no negative frequencies).

Examination of the data in Table 4 reveals expected trends in both binding energy and geometry as the number of urea ligands, n, is increased. The average binding energy, $\Delta E_{\text{elec}}/n$, decreases as the coordination number increases. The H···A distances increase as the coordination number increases. When the latter data is plotted, linear dependencies of H···A distance with n were observed for all cases: $\text{H}\cdots\text{Cl} = 2.215 + 0.0739 \times n$, $r = 0.9998$; $\text{H}\cdots\text{O-NO}_2 = 1.824 + 0.0680 \times n$, $r = 0.9994$; $\text{H}\cdots\text{O-ClO}_3 = 1.954 + 0.0479 \times n$, $r = 0.9994$. The H···A distances obtained at higher values of n are in good agreement with H···A ranges that have been observed in crystal structures.[8c,25]

Design Strategies for Shape Recognition. The structures of urea:anion complexes **10**−**39** define stable configurations for placing two or more urea groups about spherical, trigonal planar, and tetrahedral anions. Observed differences in these configurations provide a basis for designing urea-based host structures with steric recognition for a specific anion shape. Such hosts would be constructed by covalently attaching two or more urea groups together to yield acyclic, tripodal, tetrapodal, or macrocyclic architectures. In the ideal case, the scaffolding used to connect the urea groups would yield a rigid preorganized structure, in other words, a structure that exists in one anion binding conformation with urea groups that are tightly constrained in space to complement the target anion. Although it may not be possible to achieve this degree of conformational constraint, achieving steric recognition requires that the host is able to adopt at least one conformation in which the binding sites have a strong interaction with the target anion and, at the same time, is unable to adopt any conformations that provide a strong interaction with competing anions.

Hosts that are constructed by combining two or more urea groups will have four or more N−H groups that define a binding cavity. Regardless of whether the cavity is a shallow cleft, as with acyclic tweezers, or a spherical structure, as with an encapsulating cage, it is possible to define a cavity radius when the hydrogen donor atoms lie approximately on the surface of a sphere. This criterion is met in structures **10**−**39**, where the cavity radius is taken as the mean distance from the hydrogen donor atoms to the center of the anion. In all cases, the urea groups must be oriented such that both N−H groups are pointing into the cavity. The optimal cavity radius depends on the anion and, to a lesser extent, on the number of urea groups bound to the anion (see Table 4).

At higher coordination numbers, the Cl^- complexes exhibit a significantly smaller cavity radius, 2.45 ± 0.05 Å, than cavity radii observed for either NO_3^-, 2.85 ± 0.05 Å, or ClO_4^-, 3.15 ± 0.05 Å. Thus, one way to achieve steric recognition is by adjusting the size of the cavity to match the size of the anion. Size-match recognition has been observed in the complexation of halides by macrobicyclic[26] and macrotricyclic amines.[27] In

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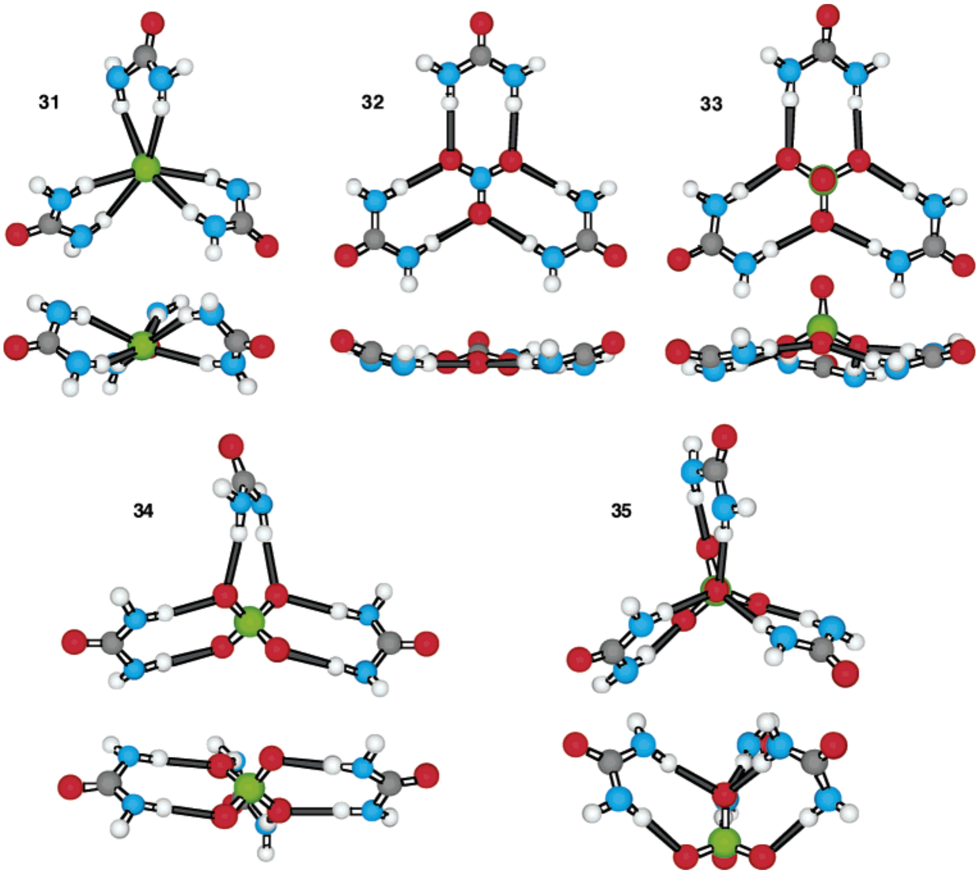

Figure 9. Top and side views of B3LYP optimized geometries for representative examples of 3:1 urea:anion complexes with Cl^- (**31**), NO_3^- (**32**), and ClO_4^- (**33**−**35**).

these examples, the rationalization for the recognition is the same as that given for alkali cation recognition by cryptands.[28] Large ions cannot enter small cavities without large strain penalties. Although small ions can enter large cavities, they cannot simultaneously contact all the binding sites.

Although size-match recognition is expected be most pronounced in architectures with well-defined cavities, it is still possible for size effects to occur in the clefts formed by rigid acyclic hosts. The potential surfaces for H···A bond stretching in 1:1 urea:anion complexes (Figure 6) indicate that distortions of more than 0.2 Å lead to weakening of the interaction by more than 1 kcal/mol. Thus, rigid cleft with a cavity radius appropriate for Cl^- should exert a significant steric penalty against NO_3^- and an even stronger steric penalty against ClO_4^-. Support for this hypothesis is provided by a recent report by Davis et al. in which a higher than expected affinity for Cl^- by a highly preorganized bis-urea cleft was rationalized by a complementary cavity radius of 2.5 Å.[5]

Hydrogen bond directionality at the acceptor atoms in oxyanions provides a further structural difference that might be exploited to achieve steric recognition with urea-based receptors. The calculations reveal that while urea groups pack around the spherical Cl^- ion in such a way as to minimize interligand repulsion, achieving optimal hydrogen bonding interaction with oxyanions requires placing the urea groups such that the hydrogen donor atoms are along the edge of the polyhedron defined by the oxygen atoms.

Optimal hydrogen bonding with the trigonal planar NO_3^- anion requires that all hydrogen donor atoms lie in the plane of the anion.[8] With a bis-urea host, the two urea groups must occupy two adjacent edges. With a tris-urea host, all three edges are occupied, giving rise to the trigonal planar array of urea groups exemplified by **32**. This arrangement of donor groups could be achieved with a 3-fold symmetric macrocyclic architecture. Although such structures have not been prepared with urea binding sites, analogous tris-guanidinium[29] and tris-thiourea[30] macrocyclic architectures have been studied, with one of the latter structures yielding among the highest NO_3^- association constants obtained for neutral hosts in DMSO.

Comparison of 2:1 urea:anion structures shows that when binding to adjacent edges in either NO_3^- or ClO_4^-, the orientations of two urea groups are similar. Similarly, when three urea groups are placed on one face of the ClO_4^- tetrahedron, as in **33**, the resulting urea placement is very similar to that observed for NO_3^-, **32** (see Figure 9). Thus, urea arrangements that complement NO_3^- will also complement the edges on the face of a tetrahedral anion. Achieving an optimal orientation for a trigonal planar anion may provide a host with a strong affinity for NO_3^-, but it does not represent a sufficient criterion for achieving significant steric penalty against tetrahedral oxyanions. One strategy for achieving this recognition would be to sterically hinder the top and bottom of a trigonal tris-urea cavity such that a three-dimensional tetrahedron could not enter.

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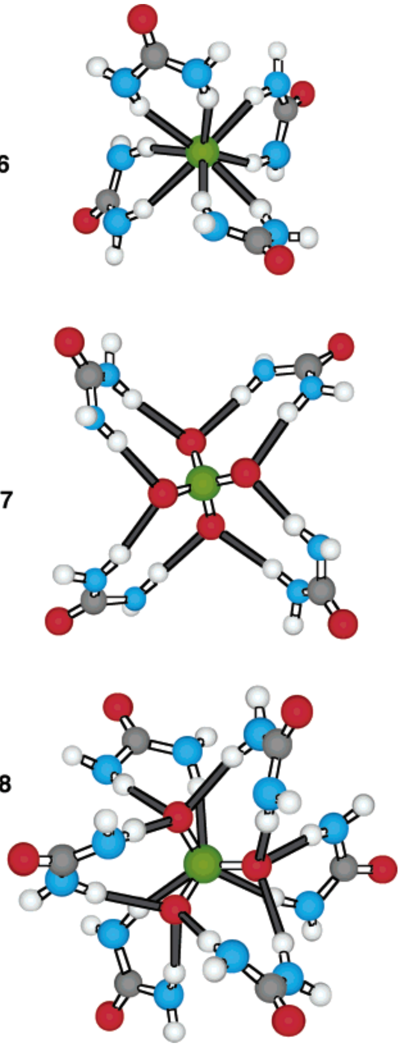

36

37

38

Figure 10. B3LYP optimized geometries for representative examples of 4:1 urea:anion complexes with Cl^- (**36**) and ClO_4^- (**37**), and a 6:1 urea:anion geometry for ClO_4^- (**38**).

Some precedent for this approach is provided by a bicyclic cyclophane bearing amide donor groups.[31] Although this host fails to offer the preferred planar array of hydrogen bond donors, it presents a flattened cavity that allows the entry of NO_3^-, but precludes the entry of nonplanar oxyanions, such as $H_2PO_4^-$ and HSO_4^-.

The foregoing analysis suggests that it would be difficult to achieve steric recognition for trigonal planar over tetrahedral oxyanions when the sole criterion is the spatial orientation of the urea groups. The reverse, however, is not true. There are ways to distribute urea groups on the edges of a tetrahedral anion that do not complement a trigonal planar anion. This can be achieved with two urea groups by positioning them to bind opposing edges of a tetrahedral anion to give a perpendicular orientation of the pairs of hydrogen donor atoms, such as in **17**. With three urea groups, there are two arrangements that complement ClO_4^-, **34** and **35**, but provide a steric penalty against NO_3^-.

The first arrangement, **34**, could be achieved with an acyclic architecture. To our knowledge, there are currently no examples of any linear acyclic tris-urea hosts. The second arrangement, **35**, exhibits C_3 symmetry that could be achieved with a tripodal architecture. There are several examples of anion complexation by tris-urea tripod hosts,[11] and there is evidence that one of the known architectures exhibits a steric recognition for the tetrahedral SO_4^{2-} anion.[11c] Whether this recognition results from hydrogen bonding interactions similar to those in **35** remains to be confirmed.

Finally, given that the coordination number varies with the anion size and shape, the degree of saturation of the anion represents another recognition criterion. Accordingly, it may be possible to obtain an added degree of selectivity by varying the number of urea binding sites in the host. The Cl^- ion can bind four urea ligands; NO_3^- can bind three urea ligands, and although ClO_4^- may not have sufficient charge density, a tetrahedral oxyanion like SO_4^{2-} can bind up to six urea ligands. If assemblies are formed between two bis-urea hosts and one anion, both spherical and tetrahedral anions could achieve an optimal interaction with all hydrogen bonding sites in each host, but trigonal planar anions could not. Such assemblies could give rise to the arrangements illustrated by **36** and **37**. An assembly of three bis-urea hosts with one tetrahedral anion could give rise to **38**. With tris-urea hosts, there is only one arrangement in which a combination of two identical hosts with one anion would yield a complex that utilized all 12 hydrogen-bonding sites. The arrangement in **38** could be formed in an assembly of two acyclic tris-urea hosts organized with the arrangement shown by **34**. It is not possible to form **38** with either alternate tris-urea arrangement, **33** or **35**.

In summary, the foregoing discussion has shown how variation of the cavity size, the spatial arrangement of the urea groups, and the number of urea groups can be manipulated to attain host architectures with enhanced binding and, in some cases, with a steric recognition for anions of specific shape. On the basis of this information, the search for scaffolds that provide the desired geometric properties is currently underway in our laboratories. The results of these studies will be reported in due course.

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Supporting Information Available: Cartesian coordinates and absolute energies for optimized structures **1**−**9** at the B3LYP/DZVP2, MP2/aug-cc-pVDZ, and MP2/aug-cc-pVTZ levels of theory, and optimized structures **10**−**39** at the B3LYP/DZVP2 level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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