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De Novo Structure-Based Design of Bis-amidoxime Uranophiles

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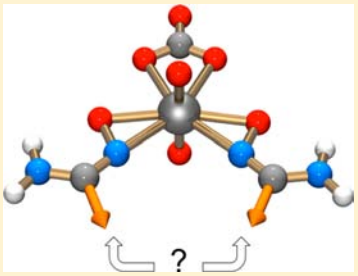
Supporting Information

ABSTRACT: This paper presents a computational approach to the deliberate design of host architectures that recognize and bind specific guests. De novo molecule building software, HostDesigner, is interfaced with molecular mechanics software, PCModel, providing a tool for generating and screening millions of potential structures. The efficacy of this computer-aided design methodology is illustrated with a search for bis-amidoxime chelates that are structurally organized for complexation with the uranyl cation.



INTRODUCTION

Supramolecular chemistry focuses on host−guest complexes that are held together in unique structural relationships by forces other than full covalent bonds, such as hydrogen bonding, ion pairing, ion−dipole interactions, and van der Waals forces.[1] This paper addresses a central and recurrent objective facing researchers in this field: the design of host structures that recognize and bind specific guests. It is generally agreed that chemical recognition can be achieved when three criteria are met. First, the host contains two or more binding sites that each exhibit an intrinsic affinity to interact favorably with the guest. Second, the host is able to adopt a conformation in which all binding sites are structurally positioned to simultaneously engage in favorable interactions with the guest; in other words, the host provides a complementary array of binding sites.[2] Third, the host should exhibit a limited number of stable conformations, and the binding conformation should be low in energy relative to other possible forms.[3] In the ideal case, the host would be preorganized such that the binding conformation is the most stable form.

Design begins with the selection of a set of binding sites that are appropriate in type and number for interaction with the guest. Once this set of binding sites is selected, the design process becomes the identification of host architectures that provide a complementary and preorganized arrangement of the binding sites. This process is not trivial, and a general approach toward achieving the desired result is needed. One approach is to use computer-aided molecular design methods to generate host molecules and evaluate host−guest interactions. With few exceptions, CAVEAT[4] and ConCept,[5] de novo design software that can be applied to a wide range of supramolecular systems is lacking. To address this issue, we created de novo structure-based design software, HostDesigner.[6a] Although originally developed for application to metal ion hosts,[6] this software has been adapted to handle a wider range of host−guest interactions and has been used successfully in the design of anion hosts[7] and components that direct the formation of high-symmetry molecular polyhedra.[8]

This paper further demonstrates the utility of the computer-aided design approach by describing how it was used to identify chelate architectures for bis-amidoximes that are structurally organized for binding the uranyl cation. The amidoxime functional group is unique because polymeric adsorbents that contain this group have been shown to be one of the few materials that are able to concentrate uranium from seawater.[9] The impetus for the current research is to enhance the performance of such adsorbents by incorporating modified chelation sites with improved uranium binding affinity and selectivity. Recent elucidation of how single amidoximate anions interact with the uranyl cation[10] provides a basis for chelate design, in other words, the definition of a complementary geometry when two of these groups coordinate to uranium. Herein, we report how de novo structure-based design and subsequent scoring methods were able to locate candidates with desirable properties that include (a) complementary placement of the binding sites, (b) low conformational reorganization energy, and (c) a minimal number of restricted bond rotations on guest complexation.

METHODOLOGY

Electronic Structure Calculations. Following prior calculations on uranyl amidoximate complexes,[10] electronic structure calculations were used to optimize geometries for uranyl complexes containing amidoximate and carbonate ligands. These calculations were performed with the Gaussian 09 A2 package[11] using density functional theory (DFT) at the B3LYP level of theory.[12] The Stuttgart RSC 1997 effective core potential (ECP) was used for uranium, replacing 60 core electrons to account for scalar relativistic effects.[13] The valence electrons in this basis set are represented by a contracted [8s/7p/6d/4f] basis; 6-31+G(d,p) basis sets were used for carbon, nitrogen, oxygen, and hydrogen atoms. This level of theory is known to yield accurate geometries and energetics for actinyl complexes.[14] Frequency calculations were performed to verify that geometries were minima. Solvation free energies have been calculated with the IEFPCM

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method.[15] The entire calculation method is labeled and referred to as B3LYP/6-31+G(d) SSD sc60 ECP IEFPCM. Data for reported structures (optimized atomic coordinates and absolute energies) are provided as Supporting Information.

Molecular Mechanics Calculations. Molecular mechanics calculations were performed with the MM3 force field[16] as implemented in PCModel,[17] a program that is capable of performing both geometry optimizations and conformational analyses. Geometries and potential energy surfaces from electronic structure calculations were used to extend the default MM3 parameter set to handle amidoximes and uranyl complexes. A list of added parameters is provided as Supporting Information. Conformational searching was accomplished using Monte Carlo random sampling and stochastic simulation strategy with default settings.[17] During the searches, trial structures were generated by alternating between the "bonds method" and the "Cartesian method". In the bonds method, trial structures are generated by randomly rotating a subset of bonds. In the Cartesian method, trial structures are generated by removing hydrogen atoms, randomly moving the remaining atoms, and replacing the hydrogen atoms. A search was terminated when one of the stopping criteria was met, either exceeding a limit of 100,000 trials or after 50 consecutive trials in which no new conformation was located within 3.5 kcal mol^{-1} of the global minimum.

Structure Generation. Bis-amidoxime molecules were constructed using the de novo structure-based design software, HostDesigner (HD).[6] This software assembles structures by combining user-defined input fragments with hydrocarbon fragments taken from the HD database. As will be described in Results and Discussion, information needed to create the input fragment was obtained from MM3 optimized geometries and potential energy surfaces. The HD input file is provided as Supporting Information.

Scoring Methods. HD outputs a series of host structures presented in order of decreasing complementarity for the guest. The initial evaluation of complementarity is based on geometric factors.[6a] Although approximate in nature, the geometry-based scoring method used by HD provides a rapid means for selecting the best candidates from a large group of potential structures.

Subsequent molecular mechanics analyses were applied to provide a more accurate prioritization of the top candidates. It is convenient to partition the complexation event into a two-step process (Figure 1). In the first step, the host goes from the free form, defined as the lowest-energy conformation of the host, to the binding form.[18] The difference in free energy between these two forms, ΔG_1, provides a measure of the degree of preorganization in the host. In the second step, the host and guest form the complex. The free energy change for this step, ΔG_2, is a measure of the degree of complementarity offered by the binding conformation.

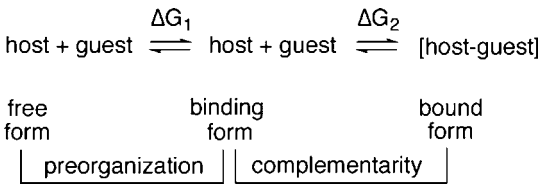

Figure 1. Irrespective of the actual complexation mechanism, it is convenient to partition the reaction into two steps defining three distinct structural states for the host: bound form, binding form, and free form.[16] The bound form is the structure of the host when complexed with the guest. The binding form is the host conformation obtained after removing the guest and optimizing the host. The free form is the global minimum conformation of the host.

The molecular mechanics evaluations occur in two steps. In the first step, ligand strain energies, ΔU_2 = U(bound form) − U(binding form), are calculated. The ΔU_2 values can be related to the free energy change ΔG_2 (see Figure 1) if it is assumed that (a) the interaction energy associated with forming two amidoxime−uranyl bonds is constant and (b) entropic contributions are constant except for restricted bond rotation associated with the formation of the host−guest complex.[19] The magnitude of the latter term is given by the empirical relationship $0.31N_{rot}$ kcal/mol, where N_{rot} is the number of freely rotating bonds restricted on complexation.[19] Thus, ΔG_2 values in kilocalories per mole are provided by eq 1, consisting of an enthalpic component, ΔU_2, an entropic component, $0.31N_{rot}$, and some constant contribution c_1.

$$\Delta G_2 = \Delta U_2 + T\Delta S_2 = \Delta U_2 + 0.31N_{rot} + c_1 \quad (1)$$

In the second step, conformational analyses are performed to obtain values for ΔU_1, taken as U(binding form) − U(global minimum). The ΔU_1 values yield an estimate for ΔG_1 if it is assumed that (a) in the absence of the guest, the majority of the host is in the global minimum conformer and (b) entropic contributions are constant. Thus, ΔG_1 values are provided by eq 2, consisting of an enthalpic component, ΔU_1, and some constant contribution c_2.

$$\Delta G_1 = \Delta U_1 + T\Delta S_1 = \Delta U_1 + c_2 \quad (2)$$

Combining ΔG_1 and ΔG_2 provides an estimate for the overall free energy change upon going from the free host to the bound host. With the assumption that the terms c_1 and c_2 are constant for a series of host molecules that contain the same set of binding sites, it is possible to arrive at eq 3, which gives the relative free energy change for host−guest complexation, ΔG_{rel}. This value can be used to rank a series of constant-donor candidates, with the top candidate having the lowest value of ΔG_{rel}. The lowest possible ΔG_{rel} value is 0, which would occur when the host is preorganized ($\Delta U_1 = 0$), the host is complementary ($\Delta U_2 = 0$), and there are no frozen bond rotations ($N_{rot} = 0$).

$$\Delta G_{rel} = \Delta U_1 + \Delta U_2 + 0.31N_{rot} \quad (3)$$

Candidate chelate structures presented in this report are labeled with ΔG_{rel}, and their Cartesian coordinates are given in the Supporting Information.

RESULTS AND DISCUSSION

Design Basis and Input Fragment. The initial step in the design of a host molecule is to select the number and type of binding sites that will interact with the guest. In the current study, the guest is a uranyl ion in seawater. Because the uranyl ion exists as a stable tris-carbonate species, $[UO_2(CO_3)_3]^{4-}$, under seawater conditions,[9a] the goal was to identify a simple chelate containing two binding sites that is capable of displacing two carbonate ligands on the uranyl ion. Prior studies indicate that the amidoxime functional group represents one of the few binding sites able to do this at the pH 8.3 of seawater.[9,10] This behavior can be attributed to both electronic and steric factors. Electronically amidoximate is a stronger Lewis base, pK_a > 11.5,[20] than carbonate, pK_a = 10.3.[21] With respect to steric effects, amidoximate binds uranyl ion in an η^2 motif[10] with an N−O distance of only 1.39 Å, occupying less space than the 2.17 Å O···O distance of carbonate.

The next step in the design process is to determine geometries that represent the complementary arrangement of these binding sites on the guest. Geometries of uranyl complexes containing two amidoxime groups and one carbonate were investigated by quantum mechanics. As shown in Figure 2, this complex exists in three possible configurations. Thermodynamically the most stable complex is when the C−H groups are facing carbonate. The other two orientations are slightly higher in energy (0.50 and 1.56 kcal/mol). Because a chelate will be formed by attaching a connecting fragment from HD's library from one amidoxime carbon to the other (orange arrows), the only viable configuration occurs when the two C−H groups are facing each other (Figure 2, bottom).

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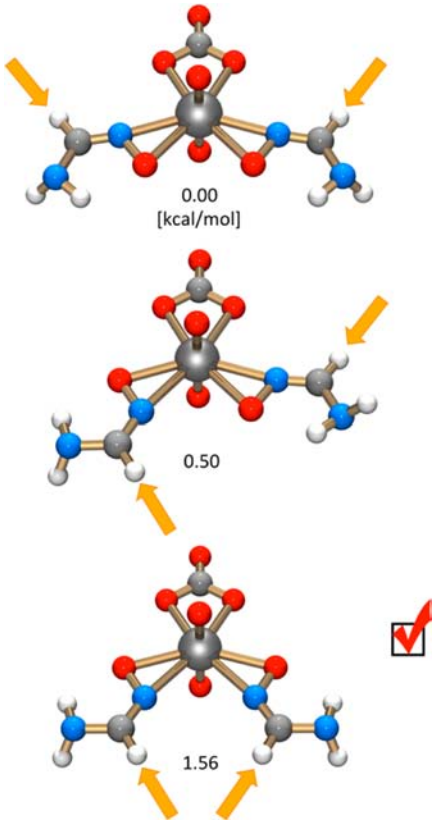

Figure 2. Relative free energies in water of optimized geometries for uranyl complexes containing two amidoximates and one carbonate (computed by B3LYP/6-31+G(d) SSD sc60 ECP IEFPCM). Orange arrows point at hydrogen atoms that will be replaced by insertion of a connecting fragment.

The input file for a host–guest fragment may also contain a specification of structural degrees of freedom (i.e., distances, angles, and dihedral angles) that can be varied during the building process. This feature takes into account known flexibility within the structure and allows HD to sample a larger extent of structure space, leading to more hits. The degrees of freedom specified for two amidoxime fragments are depicted in Figure 3. The extent of flexibility within the complexes was based on the displacements of the geometrical parameters from their equilibrium values that would result in an approximately 1 kcal/mol decrease in binding energy. MM3 potential energy surfaces for selected structural distortions, shown in Figure 3, yield the following ranges of values assigned to each degree of freedom applied: ±20° for in-plane angle variation of two amidoxime groups, ±20° for twist of amidoxime group around the bisector of the N–O bond, and ±15° for rotation about the N–O bond.

Structure Generation and Evaluation. An HD run was performed to sample all possible vector poses of the host–guest fragment based on its flexibility as shown in Figure 3. HD constructed and scored 180 million geometries within 20 min—a rate of 9 million geometries per minute per CPU! The initial scoring performed by HD ranks the host candidates with respect to their complementarity for the guest based on geometric parameters. As described in Scoring Methods, subsequent molecular mechanics analyses were then applied in two steps to achieve a more accurate ranking. In the first step, ligand strain associated with metal ion complexation, ΔU_2, was calculated for the top 1000 candidates. After these candidates had been reordered by ΔU_2, conformational searches were performed on the top 200 candidates to allow a final ranking by ΔG_{rel} values. This process identified a total of 87 candidates with $\Delta G_{rel} \leq 10$ kcal/mol.

The top 10 candidates from this run are presented in Figure 4. These structures all exhibit ΔG_{rel} values less than 5 kcal/mol, with the *cis*-bicyclo[4.4.0]decane connecting fragment exhibiting the top score of 2.70 kcal/mol. On visual inspection of the most highly ranked candidates, one can gain insight about the optimal number length of the carbon linkage needed to obtain a complementary arrangement of the two amidoximate binding sites. Four atoms are observed when there are only sp^3 carbons in the linkage. Either four or five atoms are observed when the linkage contains one or more sp^2 carbons.

Although the top candidates are well-organized for uranyl complexation, inspection of Figure 4 reveals an inherent problem with the de novo approach to molecule construction. When structures are indiscriminately assembled from molecular fragments, the process will produce numerous candidates that

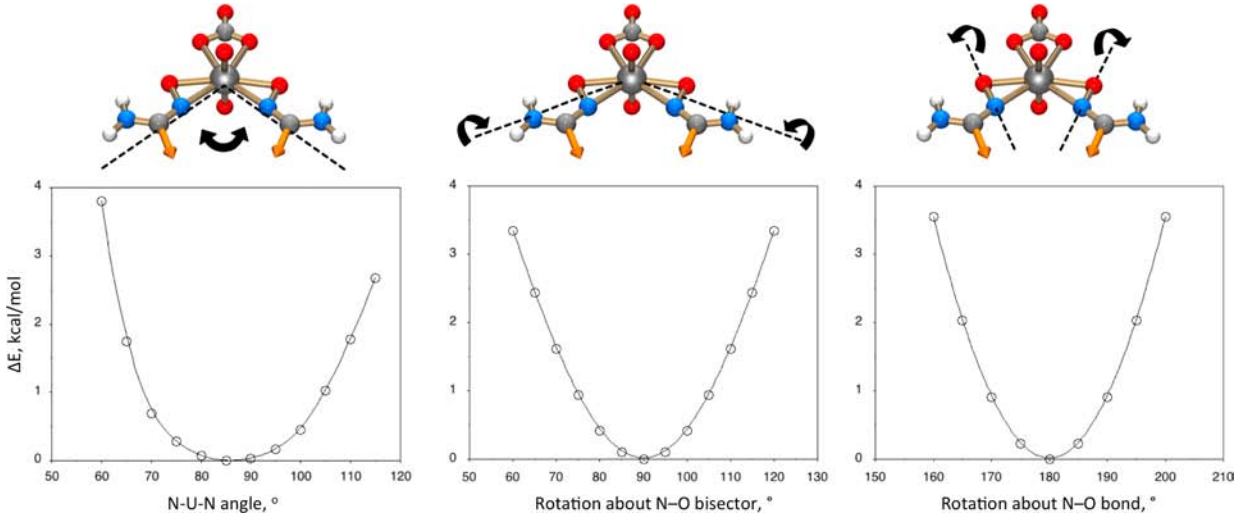

Figure 3. MM3 potential energy surfaces for variation in N–U–N angle (left), rotation about a vector bisecting the N–O bond (middle), and rotation about the N–O bond (right) were used as a basis for assigning the extent of flexibility in the host–guest input fragments.

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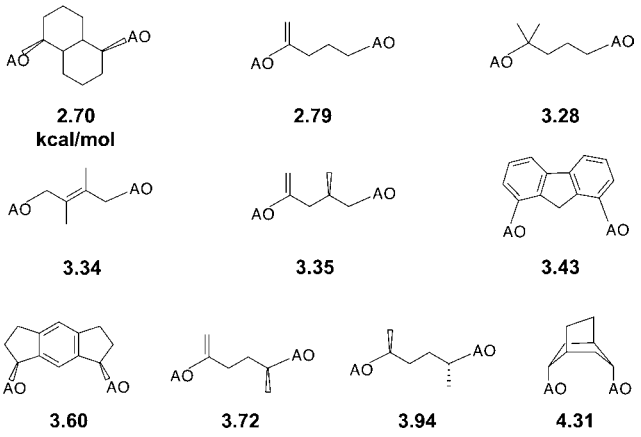

Figure 4. Top hits identified by HD and ranked by ΔG_{rel} energy (AO = amidoxime).

range from difficult to impossible to synthesize. Linkages that contain chiral centers are problematic because the preparation of enantiomerically pure precursors is expensive and subsequent synthesis often results in low synthetic yields and difficulties in isolating the desired product. In addition, linkages containing alkene or diene functionality are chemically reactive and not likely to survive synthetic conditions. Thus, to focus attention on those candidates deemed most synthetically accessible, we removed all structures containing prochiral and chiral linkages as well as those containing alkenes. With these restrictions, only two linkages remain from the top 10, 1,1-dimethylbutane and fluorene.

One synthetically accessible series of linkages is the linear alkane chains presented in Figure 5. Consistent with the previous observation about the number of carbons in the link, ΔG_{rel} revealed that butane is the optimal connecting fragment (ranked as number 17 in the output). The butane fragment exhibits the same backbone conformation as that observed for other four-carbon linkages shown in Figure 4. The reason that the other linkages score better can be traced to a lowering of the relative energy of the binding conformation either through cancellation of *gauche* interactions via the addition of methyl substituents, as in 1,1-dimethylbutane or 1,4-dimethylbutane, or through constraint of rotatable bonds, as in *cis*-bicyclo[4.4.0]-decane. However, given its ease of synthesis, the higher ΔG_{rel} of butane (4.35 kcal/mol) is acceptable because of difficulties associated with synthesis of 1,1-dimethylbutane (3.28 kcal/mol, entails functionalization of a tertiary carbon center), 1,4-dimethylbutane (3.94 kcal/mol, involves two chiral centers), and *cis*-bicyclo[4.4.0]decane (2.70 kcal/mol, involves four chiral centers).

Another series of linkages that are readily synthesized are derivatives of benzene, toluene, and xylene. However, only members of the xylene derivatives, Figure 6, are able to achieve a complementary arrangement of amidoxime groups. Again consistent with the number of carbon atoms for the best possible linkage, *meta*-xylene with five carbon atoms within the connecting backbone between two amidoxime groups is the optimal choice among the three possible xylene derivatives (ranked as number 40 in the output list).

SUMMARY

This paper has presented a strategy for the computer-aided molecular design of bis-amidoxime architectures that are structurally organized to complex the uranyl cation. The optimized geometry for the $[UO_2(AO)_2CO_3)]^{2-}$ species and potential energy surfaces for selected structural distortions provided the basis for the design strategy. The HD program was used to rapidly search a large area of structural space and produce a list of top candidates, using geometry to rank them with respect to how well they complement the guest. When interfaced with the PCModel program, subsequent evaluation of these candidates using force field-based scoring methods identified structures with desirable properties that include (a) complementary placement of binding sites, (b) low conformational reorganization energy, and (c) a minimal number of restricted bond rotations on guest complexation. This scoring approach identifies architectures that provide an optimal interaction between each binding site and the guest with a minimum of host reorganization, a structural characteristic required to maximize the binding interaction. Further filtering of the results based on synthetic considerations allowed the selection of candidates for subsequent preparation and testing summarized in Figure 7. Although the success of the current design effort remains to be experimentally validated, we note that the design approach applied herein has proven to be efficacious with other host–guest systems[6−8] and provides a rational alternative to serendipitous discovery through repeated cycles of trial-and-error research.

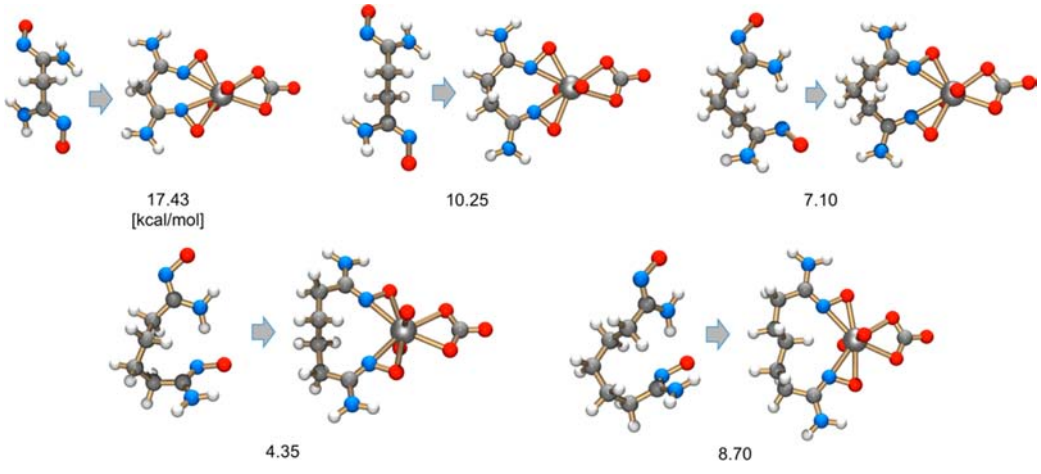

Figure 5. MM3 optimized geometries and ΔG_{rel} values for a series of linear alkane linkages.

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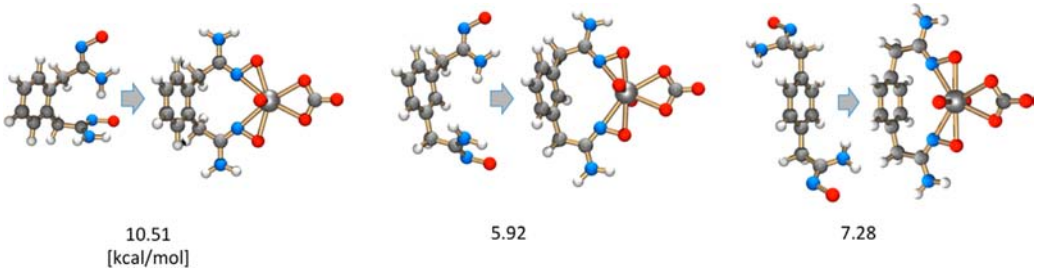

Figure 6. MM3 optimized geometries and ΔG_{rel} values for a series of xylyl linkages.

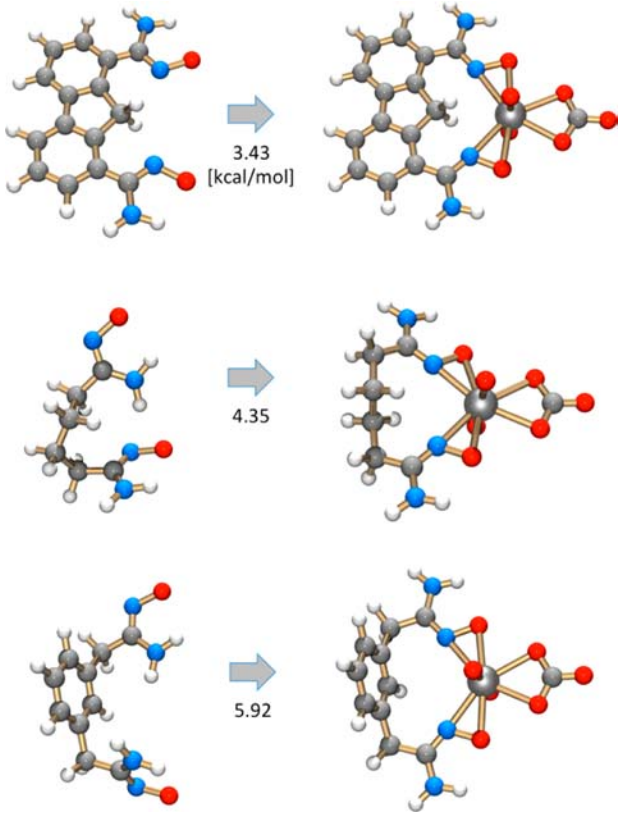

Figure 7. Viable candidates for synthesis and testing.

■ ASSOCIATED CONTENT

Supporting Information

Basis set, B3LYP optimized Cartesian coordinates, and absolute energies for the structures in Figure 2, additional MM3 parameters, HostDesigner input file, table of candidates with ΔG_{rel} values of ≤10 kcal/mol, and MM3 optimized Cartesian coordinates for all structures shown in Figures 4−7. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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