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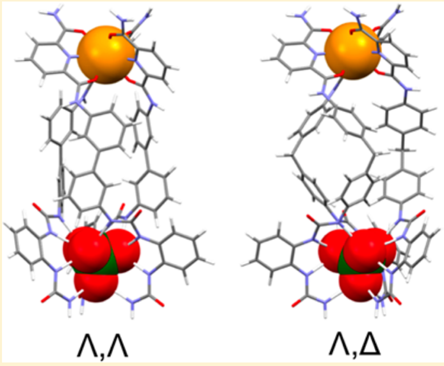
De Novo Structure-Based Design of Ion-Pair Triple-Stranded Helicates

Chuandong Jia, Benjamin P. Hay,* and Radu Custelcean*

Chemical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831-6119, United States

Supporting Information

ABSTRACT: We present a generalized approach toward the design of ion-pair ML_3A helicates assembled by coordination of metal cations (M) and anions (A) by ditopic chelating ligands (L). This computational approach, based on de novo structure-based design principles implemented in the HostDesigner software, led to identification of synthetically accessible ditopic ligands that are structurally encoded to form charge-neutral ion-pair helicates with $FeSO_4$ or $LnPO_4$.



INTRODUCTION

Triple-stranded M_2L_3 helicates constructed from bis-chelating ligands (L) and metal cations (M) represent one of the most recognizable classes of coordination architectures.[1] The helicity of these structures is determined by the twist in the ligands as they wrap around the metal centers and link the two ensuing C_3-symmetrical chelates. The relative stereochemistry of the two metal centers (Δ or Λ) determines whether the resulting structure is a helicate (ΔΔ or ΛΛ) or a mesocate (ΔΛ).[2]

Drawing analogies to metal-based M_2L_3 helicates, and employing principles of anion coordination chemistry,[3] Wu et al. demonstrated the assembly of the first anion-based A_2L_3 helicate from phosphate anions (A) and ligands functionalized with *o*-phenylene-bis(urea) (pbu) anion-chelating groups.[4] In this approach, three pbu groups coordinatively saturate the phosphate anion[5] by providing 12 hydrogen bonds from six urea groups arranged pseudooctahedrally around the tetrahedral oxoanion.[6]

By combining C_3-symmetrical metal and anion chelates in the same structure, one can build a triple-stranded ion-pair ML_3A helicate (Figure 1). This approach requires heteroditopic ligands containing cation and anion chelators connected by appropriate linkers. We recently put this concept into practice and reported the first examples of ion-pair helicates self-assembled from $NiSO_4$ or $FeSO_4$ and ditopic ligands functionalized with 2,2′-bipyridine (bpy) and pbu as metal and anion chelators, respectively (Figure 2).[7] Like the M_2L_3 or A_2L_3 analogs, the ML_3A ion-pair helicates can in principle adopt homochiral (ΔΔ or ΛΛ) or heterochiral (ΔΛ or ΛΔ) stereochemistry, depending on the relative twist of the metal and anion chelates.[8]

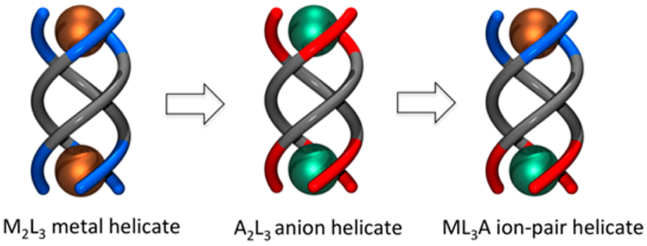


Figure 1. Conceptual evolution of triple-stranded helicates. (left) Traditional M_2L_3 helicate assembled from two metal cations and three bis-chelating ligands. (center) Anion-based A_2L_3 helicate assembled from two anions and three bis-chelating ligands. (right) Ion-pair ML_3A helicate assembled from a metal cation, an anion, and three ditopic chelating ligands.

In our continuing efforts to develop charge-neutral ML_3A ion-pair helicates as a common class of supramolecular structures, we seek a more generalized approach toward their design. As with other types of coordination architectures, one of the main challenges is to identify appropriate linkers between the binding sites so that the resulting ligands are predisposed to form the targeted structures upon ion coordination. To address this challenge, we have developed a de novo structure-based approach toward ligand design, implemented in the HostDesigner software.[9] Originally created for the development of metal ion hosts, HostDesigner has been adapted to handle a wider variety of host–guest interactions, as recently demonstrated by the successful design of anion hosts[10] or ligand components for high-symmetry coordination polyhedra.[11]

In this Paper we demonstrate the utility and generality of the computer-aided design approach toward identifying appropriate

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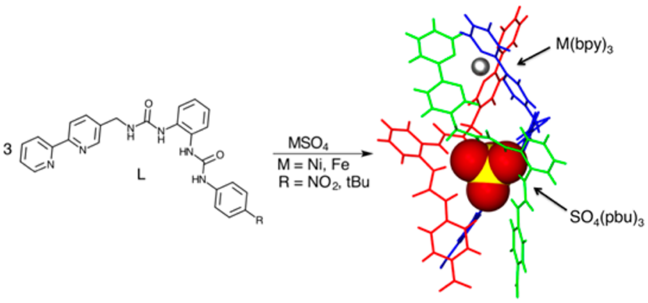

Figure 2. Prototypical ion-pair ML_3A helicate self-assembled from MSO_4 salts (M = Ni, Fe) and ditopic ligands (L) functionalized with bpy and pbu cation- and anion-chelating groups, respectively.[7] The crystal structure of the helicate formed by one of the two L ligands (R = NO_2) is shown on the right.

ditopic ligands that are structurally encoded to form triple-stranded ML_3A ion-pair helicates. In the first part of the Paper we describe how the de novo structure-based approach can be applied to the design of ditopic ligands predisposed to form ion-pair helicates with $FeSO_4$. In the second part we show how the same approach can be employed in the design of a new class of ion-pair helicates from lanthanide phosphates.

■ METHODS SECTION

Molecular Mechanics Calculations. Molecular mechanics calculations were performed with the MM3 force field[12] as implemented in PCModel.[13] Conformational searching was accomplished using Monte Carlo random sampling and stochastic simulation strategy with default settings.[13] A search was terminated when one of the stopping criteria was met, either exceeding a limit of 1,000 trials or after 50 consecutive trials in which no new conformation is located within 3.5 kcal mol^{-1} of the global minimum. The default MM3 parameter set was extended to treat urea−sulfate and metal−ligand interactions (see Supporting Information).

Structure Generation. Candidate ligands were constructed using the de novo structure-based design software HostDesigner.[9] This software quickly assembles structures by combining user-defined input fragments with hydrocarbon fragments taken from the HostDesigner linking fragment library (Figure 3). Each linking fragment in the library is a three-dimensional molecular structure with two specified binding vectors. The HostDesigner algorithm considers every pair of hydrogen atoms on the hydrocarbon scaffold as the two vectors. For example, in an ethyl linker, the two vectors could be in the 1,1 or 1,2 positions, and in each case all conformations within 3 kcal/mol above the global minimum are tested. The information needed to create the input fragments was obtained from MM3 optimized geometries. A representative HostDesigner input file is provided in the Supporting Information.

Scoring Methods and Structure Selection. Each HostDesigner run yielded a series of output structures presented in order of decreasing geometrical complementarity to the bound ion pair. In the first round of scoring, the top 500 candidate structures of each run were retained for further evaluation. These candidates were first assessed for their synthetic accessibility, and linkages containing chiral centers, spiranes, saturated polycycles, or reactive alkene functionalities were removed. Structures containing more than four rotatable bonds were also removed, as such highly flexible ligands were considered unlikely to form the targeted helicates due to unfavorable entropic contributions. Remaining candidate ligands were further analyzed by building the corresponding helicate assemblies and optimizing their geometries by molecular mechanics. Structures assuming ideal C_3 symmetry were retained and then subjected to repeated molecular dynamics (MD) simulation runs followed by geometry optimization. Structures that returned to the original C_3-symmetric geometry after optimization were retained.

Subsequent molecular mechanics calculations were performed to provide a final prioritization of the top candidates. The scoring was based on an estimate of the reorganization free energy of a single ligand (ΔG_{reorg}) on going from the bound form in the assembly to the global minimum. The reorganization energy of the single ligand is the energy difference from the free form (E_{free}, energy of a single ligand in the global minimum determined by conformational analysis) to the bound form (E_{bound}, single point energy of a single ligand in the bound

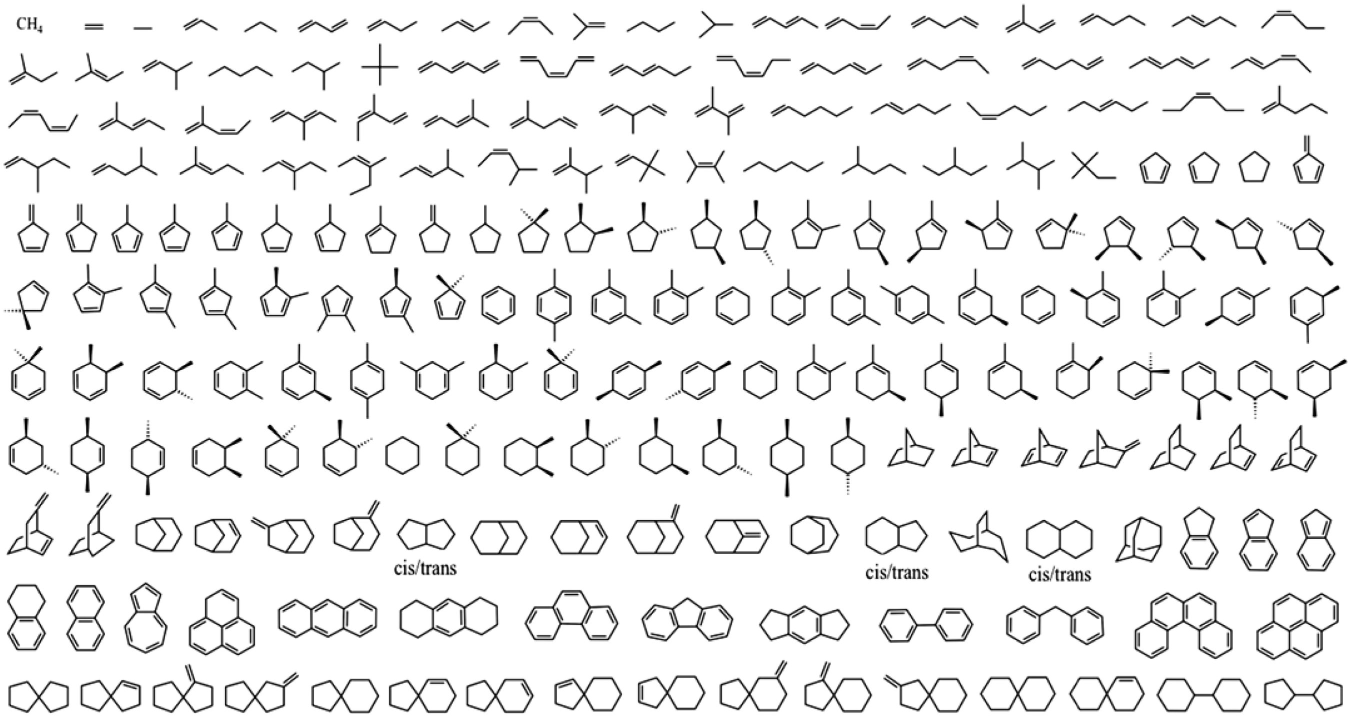

Figure 3. Hydrocarbons used to generate the HostDesigner linking fragment library.

geometry). The reorganization free energy, ΔG_{reorg}, is estimated from these energies after an empirical entropy correction for restricted bond rotation is applied, $0.31 \times N_{\text{rot}}$ kcal/mol, where N_{rot} is the number of freely rotating bonds restricted on complexation:[14]

$$\Delta G_{\text{reorg}} = (E_{\text{bound}} - E_{\text{free}}) + 0.31 \times N_{\text{rot}}$$

■ RESULTS AND DISCUSSION

Design of $FeSO_4$ Helicates. The first step in the de novo design of an ion-pair triple-stranded helicate is to choose the C_3-symmetric metal and anion chelates serving as helicate vertices. On the basis of the prototype $FeSO_4$ helicate,[7] we selected $[Fe(bpy)_3]^{2+}$ and $[SO_4(pbu)_3]^{2-}$ as metal- and anion-coordination vertices that would lead to a charge-neutral helicate structure. The two vertices were built in PCModel using coordinates from known crystal structures,[4,7] and their geometries were optimized using molecular mechanics with a modified MM3 force field. The next step was to define the linking positions for the two vertices (Figure 4). For this purpose, the H atoms in the fourth position of the bpy and the urea H atom *syn* to the C═O group were selected to be replaced upon connecting to the HostDesigner linker fragments. Because of its D_3 symmetry, only one type of connection vector is available from the metal-centered $[Fe(bpy)_3]^{2+}$ vertex. On the other hand, the symmetry of the anion-centered $[SO_4(pbu)_3]^{2-}$ vertex is reduced to C_3, so two types of vectors are available from the two terminals of the vertex, resulting in two different input structures (Figure 4, I vs II and III vs IV). Finally, the two vertices may have the same chirality, that is, Λ for both $[Fe(bpy)_3]^{2+}$ and $[SO_4(pbu)_3]^{2-}$ (Figure 4, I and II), or opposite chirality, that is, Λ for $[Fe(bpy)_3]^{2+}$ and Δ for $[SO_4(pbu)_3]^{2-}$ (Figure 4, III and IV).

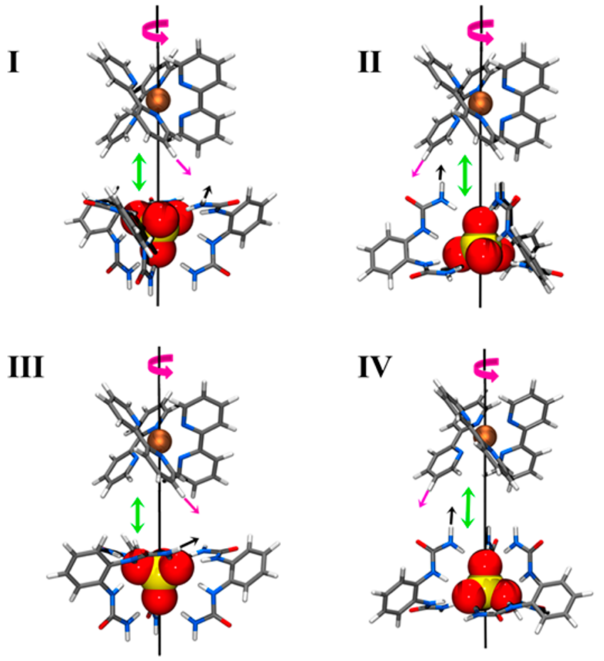

Figure 4. Input structures for Λ,Λ (I and II) and Λ,Δ (III and IV) $FeSO_4$ helicates. The vectors from $[Fe(bpy)_3]^{2+}$ and $[SO_4(pbu)_3]^{2-}$ are shown as purple and black arrows, respectively (only one of the three symmetry equivalent pairs is shown). The vector from $[Fe(bpy)_3]^{2+}$ is paired with the two types of vectors from $[SO_4(pbu)_3]^{2-}$. The structural freedoms of the vertex components are shown as purple curved arrows and green up−down arrows, corresponding to rotation about and movement along the C_3 axes, respectively.

To build the input files, the vertices were aligned along the C_3 axis, with a starting pose that had the metal and anion centers overlapped. The metal vertex was then allowed to translate along the C_3 axis in 0.1 Å increments to a maximum distance between the metal and anion centers of 10 Å and was allowed to rotate ±120° about the C_3 axis in 1° increments.

Using the four input structures shown in Figure 4, HostDesigner runs were performed in which all possible vector poses of the two vertices were sampled and connected by the hydrocarbon linkages in the fragment library (Figure 3). In a typical run, HostDesigner constructed and scored 6 million geometries within 40 min. The top 500 hits in each run were retained for further evaluation. After removing the structures deemed synthetically inaccessible (e.g., linkers containing chiral centers, spiranes, saturated polycycles, or reactive alkene functionalities) or too flexible (more than four rotatable bonds), the remaining ligand candidates were further evaluated by MM3 molecular mechanics calculations for their abilities to form stable C_3-symmetrical helicates. This resulted in 27 ligands (see Supporting Information, S3) that formed helicates with optimal C_3 symmetry after repeated MD simulation runs followed by geometry optimizations. These ligands were subjected to the final analysis to evaluate their reorganization free energy (ΔG_{reorg}) on going from the bound form in the helicate to the global minimum in the free form (see Methods Section). The top eight candidate structures with $\Delta G_{\text{reorg}} < 5$ kcal/mol are shown in Figure 5, and the corresponding energies are listed in Table 1. Regarding the stereochemistry of these structures, there are six Λ,Λ and two Λ,Δ helicates, originating from input structures I and III, respectively (Table 1).

Notably, the top candidate structure identified in this study, based on the methylene linker, coincides with our previously published $FeSO_4$ helicate assembly. Figure 6 depicts an overlay of the optimized structure of **1** and one of the available $FeSO_4$ helicate crystal structures. Despite some differences in the relative orientation of the ligands or the position of the sulfate anion, which could be attributed to steric effects arising from the terminal phenyl substituents on the urea groups and crystal packing forces in the experimental structure, there is a fairly good match between the linker geometries in the two structures. Like the experimental structure, the calculated helicate **1** prefers a Λ,Λ stereochemistry. The corresponding Λ,Δ stereoisomer of **1** was also identified when structure III was used as an input, but it was found to be 10 kcal/mol higher in energy than the Λ,Λ stereoisomer.

Design of $LnPO_4$ Helicates. Having validated our design approach to ion-pair helicates, we next targeted a completely new type of structure within this class of coordination assemblies, based on 3+/3− charge-balanced ion pairs, specifically lanthanide phosphates. For the purpose of this design, we selected Gd^{3+} as a representative lanthanide cation. As with the previous case, forming a helicate requires that each ion be chelated to form a C_3-symmetric vertex. This could be achieved using the same pbu ligand to chelate the PO_4^{3-} anion, while using 2,6-pyridine-dicarboxamide or dipicolinamide (dpa) to chelate the Ln^{3+} metal cations.[15] Geometries for $[Gd(dpa)_3]^{3+}$ and $[PO_4(pbu)_3]^{3+}$ were obtained from published crystal structures[4,15] and then optimized using an extended MM3 parameter set with the PCModel software. Figure 7 shows the four input files for HostDesigner, corresponding to

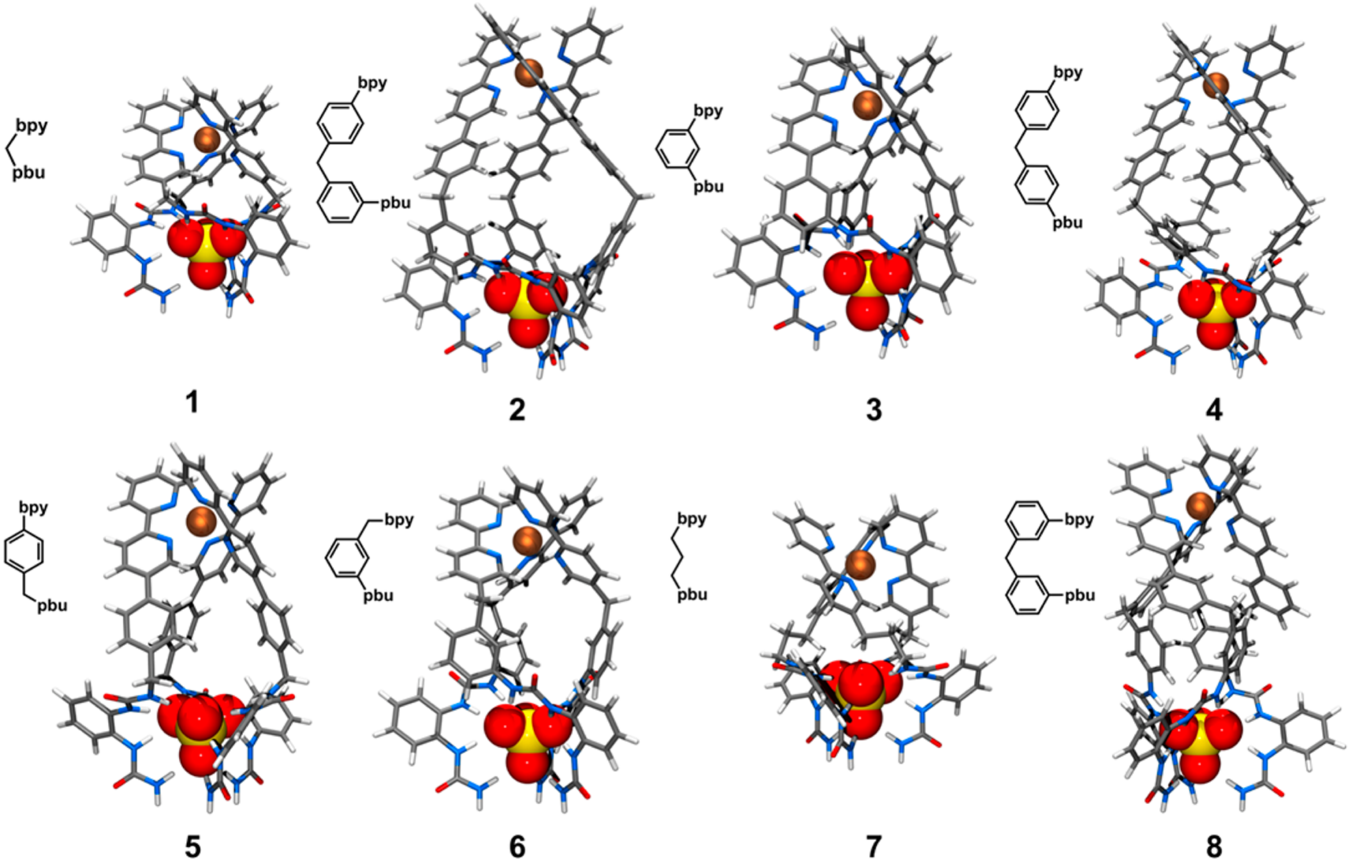

Figure 5. MM3 optimized structures of the top eight $FeSO_4$ helicate candidates with the corresponding linkers shown beside.

Table 1. Scoring Results for the $FeSO_4$ Helicates in Order of Increasing ΔG_{reorg}

hit[a]	input[b]	ΔE_{reorg}	$0.31 \times N_{rot}$	ΔG_{reorg}[c]
1	I	1.28	0.62	1.90
2	I	1.00	1.24	2.24
3	I	1.94	0.62	2.56
4	I	1.39	1.24	2.63
5	III	1.78	0.93	2.71
6	I	2.56	0.93	3.49
7	I	2.36	1.24	3.60
8	III	2.91	0.93	3.84

[a] See Figure 5. [b] See Figure 4. [c] Energies reported in kcal/mol.

Λ,Λ (I and II) and Λ,Δ (III and IV) helicates, and the two possible orientations of the $[PO_4(pbu)_3]^{3+}$ vertex.

All four input fragments were set with a start pose that bonding vectors between one of the dpa and pbu chelating groups were oriented toward one another. A series of vector poses were generated for each input structure by rotation of the $[Gd(dpa)_3]^{3+}$ vertex about the C_3 axis ±120° in 1° increments and translation along the C_3 axis from 0 to 10 Å in 0.1 Å increments. The top 500 candidate linkages identified by each run of HostDesigner were visually inspected for synthetic accessibility. Those deemed synthetically viable were then subjected to geometry optimization and checked for C_3 symmetry. On the basis of these screening tests, 48 C_3-symmetric structures were selected and subjected to repeated MD simulation runs followed by geometry optimization. This resulted in 11 structures that returned to the original C_3-symmetric geometry after optimization (see Supporting Information, S4). Finally, four structures were found to have $\Delta G_{reorg} < 5$ kcal/mol (Table 2) and are shown in Figure 8.

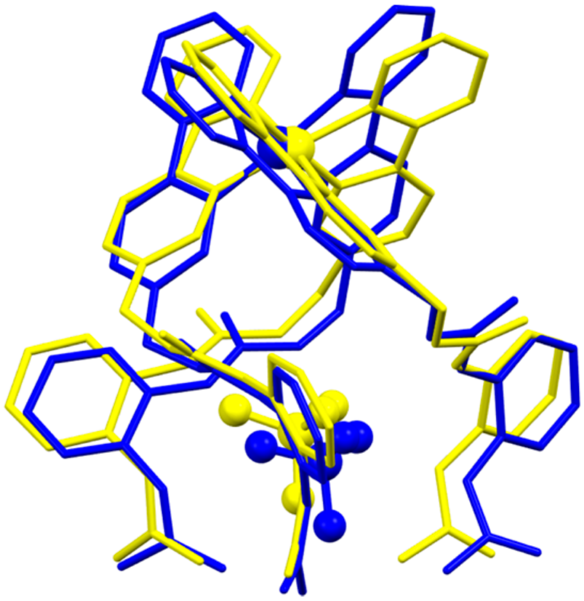

Figure 6. Overlay of the calculated (yellow) and experimental crystal structure (blue) of $FeSO_4$ helicate **1**.

■ SUMMARY

We presented here a generalized strategy for computer-aided design of triple-stranded ion-pair helicates. Our approach consists of first defining the C_3-symmetrical metal and anion

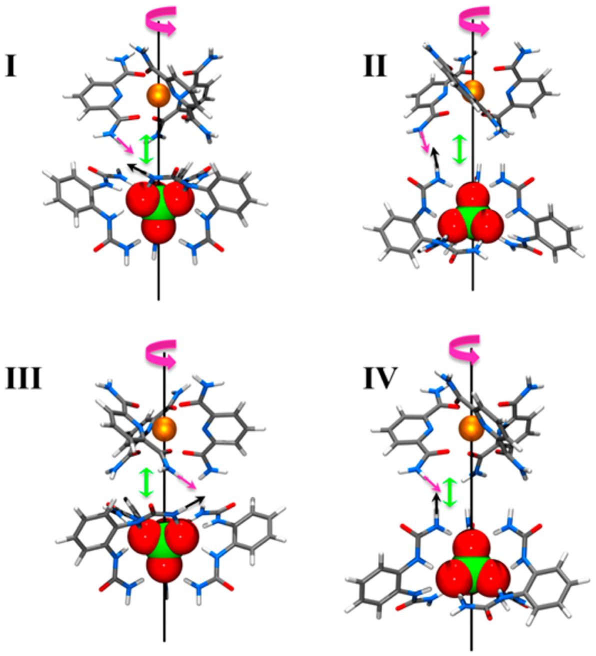

Figure 7. Input structures for Λ,Λ (I and II) and Λ,Δ (III and IV) $GdPO_4$ helicates. The vectors from $[Gd(dpa)_3]^{3+}$ and $[PO_4(pbu)_3]^{3-}$ are shown as purple and black arrows, respectively (only one of the three symmetry equivalent pairs is shown). The vector from $[Gd(dpa)_3]^{3+}$ is paired with the two types of vectors from $[PO_4(pbu)_3]^{3-}$. The structural freedoms of the vertex components are shown as purple curved arrows and green up−down arrows, corresponding to rotation about and movement along the C_3 axes, respectively.

Table 2. Scoring Results for the $GdPO_4$ Helicates in Order of Increasing ΔG_{reorg}

hit[a]	input[b]	ΔE_{reorg}	$0.31 \times N_{\text{rot}}$	ΔG_{reorg}[c]
1	III	1.94	0.62	2.56
2	I	3.09	0.93	4.02
3	III	2.85	1.24	4.09
4	I	3.69	0.62	4.31

[a] See Figure 8. [b] See Figure 7. [c] Energies reported in kcal/mol.

chelates based on existing structural data and then identifying appropriate linkers to connect the two vertices. The latter step was effectively done with the help of HostDesigner, a computer program that can rapidly explore a large area of structural space, generate a list of top candidate structures from an extensive linking fragment library, and rank them according to their geometrical complementarity. This structure-based approach led to identification of eight synthetically feasible ditopic ligands that are geometrically predisposed to form ion-pair helicates with $FeSO_4$. The top candidate structure, comprising the methylene linker, coincides with the previously published $FeSO_4$ helicate assembly, thereby validating our computational approach. This method was subsequently applied to the design of a new class of ion-pair helicates from $LnPO_4$ and ditopic ligands functionalized with dipicolinamide and *o*-phenylenebis(urea) chelating groups. Four synthetically accessible ligands were thus identified, and experimental efforts toward their synthesis are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional MM3 parameters, representative HostDesigner input file, lists of the top candidate ligands, and MM3 optimized Cartesian coordinates for top helicate structures in Figures 5 and 8. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: custelceanr@ornl.gov. (R.C.)
*E-mail: haybp@ornl.gov. (B.P.H.)

Notes

The authors declare no competing financial interest.

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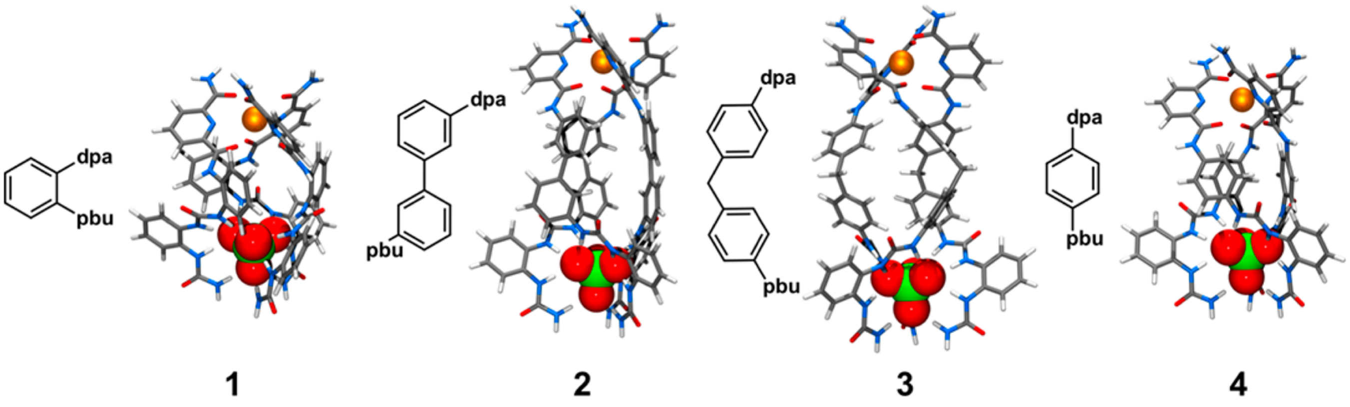

Figure 8. MM3 optimized structures of the top four $GdPO_4$ helicate candidates with the corresponding linkers shown beside.

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