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Deliberate Design of Ligand Architecture Yields Dramatic Enhancement of Metal Ion Affinity

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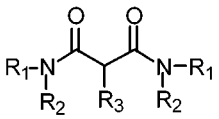
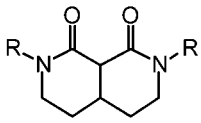
A successful design strategy for the development of effective metal ion receptors is to preorganize the host molecule to obtain a single conformation that is optimal for complexation, that is, with all binding sites positioned to structurally complement the metal ion.[1] Although this strategy is readily understood, its application is less straightforward, and examples of the deliberate design of highly efficient preorganized hosts remain limited.[2] Herein we provide an example of how these design concepts have been applied to a bidentate ligand to obtain a dramatic enhancement in metal ion binding affinity.

Alkylated malonamides, such as **1**−**5**, have been studied extensively for use as trivalent actinide and lanthanide extractants.[3] These ligands can chelate metal ions through coordination with two amide oxygen atoms. However, studies of malonamide conformation[4] and the geometries of coordinated amides[5] reveal that the malonamide backbone presents an architecture that is poorly organized for chelation.





1 $R_1 = R_2 = n$-Hx, $R_3 = H$
2 $R_1 = Me$, $R_2 = n$-Bu, $R_3 = n$-$C_{14}H_{29}$
3 $R_1 = Me$, $R_2 = n$-Bu, $R_3 = n$-$C_{18}H_{37}$
4 $R_1 = Me$, $R_2 = cy$-C_6H_{11}, $R_3 = n$-$C_{14}H_{29}$
5 $R_1 = Me$, $R_2 = Ph$, $R_3 = n$-$C_{14}H_{29}$
6 $R_1 = R_2 = Me$, $R_3 = H$

7 R = Me
8 R = *n*-Oct

First, the malonamide structure must adopt a higher-energy conformation to allow chelation. A thorough conformational analysis of a simple analogue, **6**, yielded only two stable structures (Figure 1, a and b).[4] In the low-energy form (a), the two carbonyl groups point in opposite directions such that it is not possible for the two oxygen atoms to simultaneously contact the same metal ion. Rotation about one of the two C−C bonds yields a second form (b), 3.0 kcal/mol higher in energy.

Second, rotation about the two C−C bonds in **6** is prohibited upon chelation with a metal ion. Analysis of the entropies of hydrocarbon cyclization and entropies of freezing for organic compounds suggest a mean typical interval of 0.8−1.2 kcal/mol for the $-T\Delta S$ contribution from the loss of each free rotation.[6] This gives an estimate of $-T\Delta S = 2.0$ kcal/mol for the entropically disfavored restricted rotation associated with the malonamide chelation.

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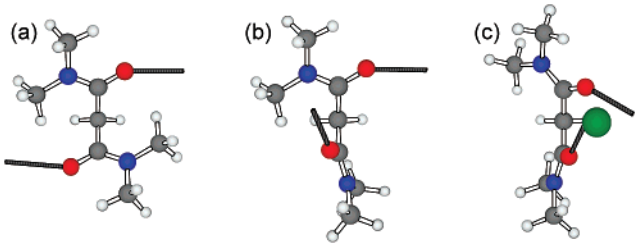

Figure 1. Structural reorganization of **6** during the chelation of a lanthanide metal ion. Structures of the low-energy form (a) and high-energy form (b) obtained from MP2/aug-cc-pVDZ optimizations.[4] Example of a bound form (c) observed in the $[Sm(\mathbf{6})_4]^{3+}\cdot 3PF_6^-$ crystal structure.[7] Vectors attached to each oxygen atom, which show the optimal direction of approach for lanthanide ions, fail to converge in (c).

Finally, the malonamide metal-binding conformer (Figure 1b) fails to provide a complementary array of binding sites. The geometries of simple amides coordinated with lanthanide metal ions show the presence of a distinct oxygen donor directionality in which the metal ion lies in the plane of the amide moiety with a C=O−M angle of 143 ± 1°.[5] This directionality is illustrated in Figure 1 by attaching a vector to each oxygen atom. In a complementary architecture, the two vectors would intersect at a point where the metal ion is located.[1d] In the binding conformer of **6** (Figure 1b), however, these vectors diverge, and metal ion chelation necessitates further structural change to the ligand that involves rotation about both C−C bonds. An example of this structural change, which can be observed in crystal structures of malonamide lanthanide complexes,[7] is shown in Figure 1c. Even after the structural changes induced by metal chelation, the vectors do not intersect at the metal ion. MM3 calculations[8] on a Eu^{3+}−**6** chelate ring show that this structural change results in an additional 2.5 kcal/mol increase in ligand strain, giving a total strain energy, ΔU_{reorg},[9] of 5.5 kcal/mol on going from the low-energy form to the bound form.

The foregoing analysis suggests that a considerable increase in binding affinity, on the order of 10^5 at 298 K, might result if the diamide could be conformationally constrained in a complementary architecture, thereby eliminating unfavorable enthalpic (5.5 kcal/mol) and entropic (2.0 kcal/mol) terms. After examination of a variety of possible bicyclic architectures, we discovered that the desired structural attributes are realized in **7**. An MM3 analysis of **7** and the Eu^{3+}−**7** chelate ring shows that both the *trans* and *cis* stereoisomers of **7** meet the desired criteria.[8] The *trans* isomer has a single stable conformer in which the vectors intersect at a point 2.27 Å from each oxygen atom (Figure 2b). The structure does not change on Eu^{3+} chelation and $\Delta U_{reorg} = 0.0$ kcal/mol. The *cis* isomer has four stable conformers with relative energies of 0.0,

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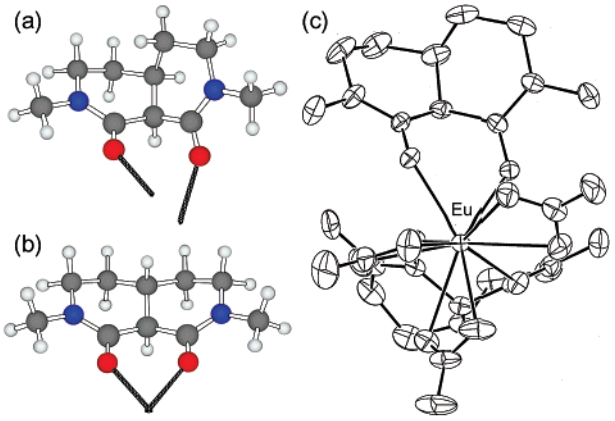

Figure 2. MM3 calculations of (a) the lowest-energy conformer of the *cis* form of **7** and (b) the only stable conformer of the *trans* form of **7** with oxygen vectors as described in Figure 1. The X-ray crystal structure of the Eu^{3+} complex of the *cis* form of **7** $[Eu(\mathbf{7})_2(NO_3)_3]$ is shown in (c).

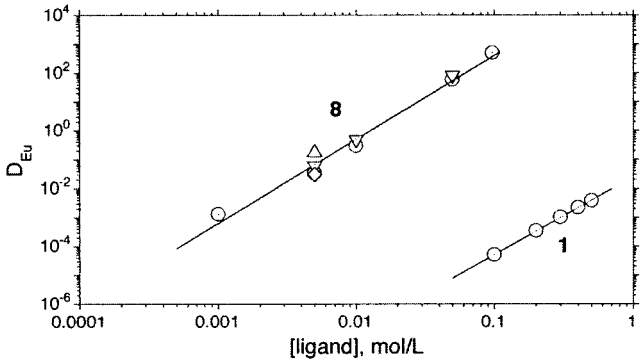

Figure 3. Plot of distribution coefficients for Eu^{3+}, D_{Eu}, versus ligand concentration for **1** and **8**. (○) 1.0 M $NaNO_3$, 0.0015 M HNO_3, (▽) 0.9 M $NaNO_3$, 0.1 M HNO_3, (△) 0.5 M $NaNO_3$, 0.5 M HNO_3, (◇) 1.0 M HNO_3.

2.7, 3.6, and 3.9 kcal/mol. The most stable *cis* conformer (Figure 2a) chelates Eu^{3+} with only minor structural reorganization and $\Delta U_{reorg} = 0.1$ kcal/mol.

Diamides **7** and **8** were each prepared in six steps from commercially available materials in overall yields of 45 and 41% respectively. Analytical and spectral data for **7** and **8** are provided in the Supporting Information. Comparison of the X-ray crystal structure of $[Eu(\mathbf{7})_2(NO_3)_3]$ (Figure 2c) shows that the ligand's structure is the same as that predicted for the *cis* ligand conformation (Figure 2a).

Solvent extraction distribution coefficients provide a convenient measurement of the relative metal ion binding affinity for series of ligands.[1a,10] Prior studies have shown that variation of alkyl substituents observed in **1**−**5** has very little effect on lanthanide(III) distribution coefficients at low-to-moderate acid concentrations.[3] For example, malonamides **1**−**5** give D_{Eu} values ranging from 10^{-4} to 10^{-5} when $Eu(NO_3)_3$ is extracted from aqueous solution containing 1 M nitrate into *tert*-butylbenzene solution containing 0.1 M ligand.[3b,d,f] To allow this measurement with the preorganized architecture of **7**, it was necessary to increase the hydrophobicity of the ligand. This was accomplished by preparing **8** that contains *n*-octyl instead of methyl substituents on the amide nitrogens. A plot of D_{Eu} versus ligand concentration for **1** and **8** (Figure 3) reveals the anticipated large enhancement in Eu^{3+} affinity (details of the extraction experiments are provided as Supporting Information). At 0.1 M ligand concentration, the poorly organized structure, **1**, gives a D_{Eu} of 5×10^{-5}, whereas the preorganized structure, **8**, gives a D_{Eu} of 500—*an increase of 7 orders of magnitude*. The ligand dependence is roughly 3:1 in both cases, suggesting that the organic phase complexes of **1** and **8** exhibit the same stoichiometry. To verify that the high extraction efficiency of **8** is not due to the presence of plausible acidic impurities, measurements were made from 1 M nitrate solutions containing increasing mole fractions of HNO_3. As shown in Figure 3, increasing the amount of acid present in the system had no significant impact on the D_{Eu} values.

In summary, a new ligand architecture has been designed and experimentally shown to exhibit a dramatic enhancement in Eu^{3+} affinity. Further investigations and elaboration of this ligand architecture are currently underway. The results, including details of the syntheses of **7** and **8**, will be published in a forthcoming report.

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Supporting Information Available: Details of the MM3 calculations, characterization data for **7** and **8**, solvent extraction procedures, and crystal structure data for the *cis*-$[Eu(\mathbf{7})_2(NO_3)_3]$ complex (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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