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Synthesis and Binding Properties of Hybrid Cyclophane−Azamacrocyclic Receptors

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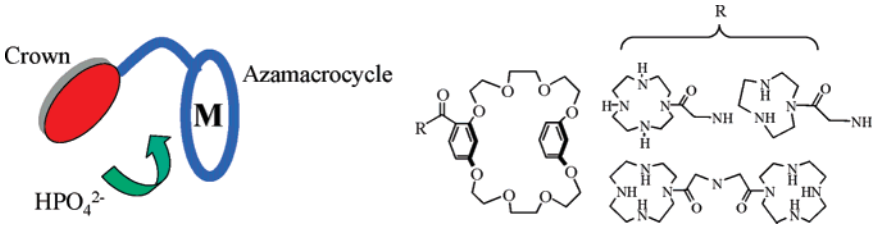

Three new azamacrocyclic-cyclophane hybrid receptors $\mathbf{L_1}$, $\mathbf{L_2}$, and $\mathbf{L_3}$ have been synthesized that incorporate either 1,4,7,10-tetraazacyclododecane (cyclen) or 1,4,7-triazacyclononane (tacn) unit(s) tethered via a short amidic spacer to an electron donor and a H-bonding crown ether polycycle. The crown ether is designed to act as a host toward biologically relevant guests, whereas the macrocycle can coordinate a zinc(II) or a copper(II) ion. The pK_a of this bound water in the zinc(II) complex of $\mathbf{L_1}$ and $\mathbf{L_2}$ is ~7.5. Isothermal calorimetry experiments carried out on $[Zn\mathbf{L_1}(OH_2)](CF_3SO_3)_2$ and $[Zn_2\mathbf{L_2}(OH_2)_2](CF_3SO_3)_4$ in buffered water (pH 7.4) at 25 °C show that the host strongly binds a series of phosphate derivatives. In comparison, the complex $[Cu\mathbf{L_3}(OH_2)_2](CF_3SO_3)_2$ is a poor receptor toward phosphate substrates.

Introduction

It has long since been recognized that Nature holds the upper hand in the biological catalysis arena, especially with metal-based enzymes that perform varied and critical organic transformations.[1] Bovine carboxypeptidase A, for example, is a natural enzyme that efficiently hydrolyzes C-terminal phenylalanine amino acids from peptide substrates.[2] Within the enzyme, the phenyl group resides in a hydrophobic pocket with amino acid residues Arg-145 and Tyr-248, providing secondary H-bonding sites. The active center is a zinc(II) ion containing a bound hydroxyl ion that acts as a nucleophilic center in the hydrolysis of the amide bond.[3] Mimicking this enzyme using artificial systems has been the impetus for many research groups[4−15] over the past 20 years or so. Kimura and co-workers[16] have shown that zinc(II) complexes of the azamacrocycles 1,5,9-triazacyclodecane and 1,4,7,10-

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tetrazacyclododecane (cyclen) bind a water molecule with a pK_a value that is dramatically reduced when compared to that of the bulk water molecule. Owing to the generation of the nucleophilic center, these complexes catalytically hydrolyze ester groups of simple substrates.[17] The next stage of development of artificial enzymes has witnessed the inclusion of secondary structures such as cyclodextrins,[18] calixarenes,[19] dendrimers,[20] cavitands,[21] and polymer supports.[22] These groups tend to mimic the second-coordination sphere and beyond and serve to protect reactants, bind substrates, and promote reactions. However, these secondary host sites generally do not possess multiple specific groups capable of promoting simultaneous H-bonding, $\pi-\pi$-stacking, and dipole−dipole interactions that are found in the protein structure of enzymes. This task requires the design of more multifunctional second-coordination sphere assemblies. For some time, it has been recognized that specific crown ether polycycles such as **DBC8**[23] have the ability to play host to molecules using multiple noncovalent interactions, including $\pi-\pi$ stacking of electron-deficient aromatics[24] and H-bonding via the oxygen atoms.[25] Thus, we rationalized that grafting a crown cyclophane to a macrocycle core would mimic the binding and active site of enzymes. Our initial synthetic efforts toward this goal are described in this paper along with binding of the receptors in HEPES-buffered water (pH 7.4).

Results and Discussion

Synthetic Procedures. A common theme of artificial enzyme mimics is that they generally require the use of macrocyclic metal complexes that contain a single metal ion or use compartmentalized ligands that bind two or more metal centers (see later). Our program of work has focused on cyclic polyethers as the host site since the ring size is readily controlled by synthetic means and thus are easily functionalized with other groups. We also considered that many systems have been developed for anion recognition and the design features of our own system are comparable to previously reported examples.[26] The synthetic protocols used in the preparation of the hybrid model enzyme receptor $\mathbf{L_1}$ are illustrated in Scheme 1. One of our initial design themes was to prepare a crown polycycle containing an aldehyde functional group and use reductive amination to graft the azamacrocycle directly onto the superstructure. This method, however, was abandoned because of very poor yields, but the aldehyde group was left in place since it is readily converted to other functional groups. To prepare the crown polycycle, it was decided to construct it in a stepwise manner and use well-established synthetic procedures.[27] Compound **1** was thus prepared from the commercial material 2,4-dihdroxybenzaldeyde with good yield (∼80%) using a previously reported method.[28] The terminal alcohol group of **1** was converted to a leaving group via two standard steps to afford diiodide derivative **2** in an overall 40% yield. Cyclization of **2** with 1,3-dihydroxybenzene using mildly basic conditions (K_2CO_3) afforded the aldehyde-functionalized crown **3** in 25% yield. Our first effort at this stage of the procedure was to convert the aldehyde to a leaving group and directly attach the macrocycle. Although **3** could be easily reduced to the benzyl alcohol, all attempts in our hands to convert the alcohol into either bromide, OTs, OMs, or OTf groups failed to afford pure materials. We therefore

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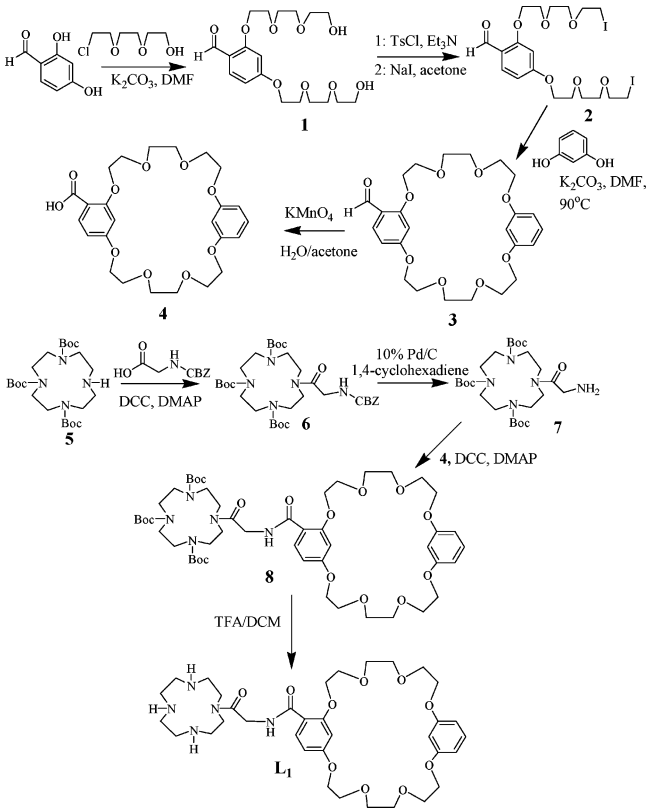
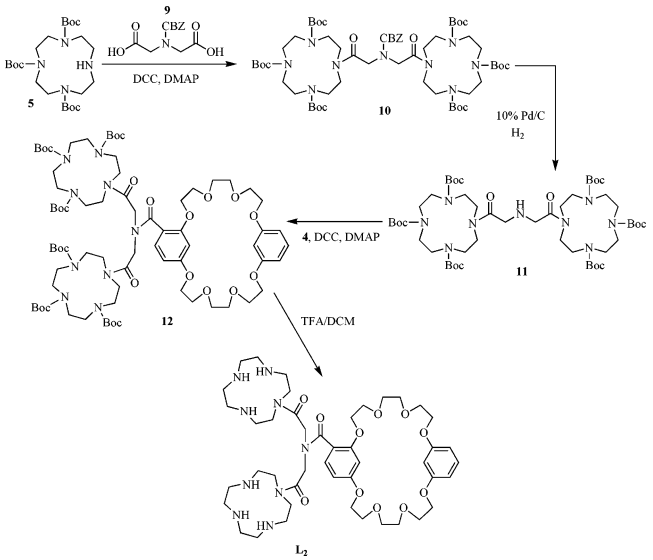
SCHEME 1. Synthetic Procedures Used in the Preparation of the Hybrid Ligand L_1



SCHEME 2. Synthetic Procedures Used in the Preparation of the Multitopic Ligand L_2



decided to oxidize the aldehyde to a carboxylate and attach the macrocycle to the crown superstructure using standard peptide-coupling methods.[29] Oxidation of **3** was carried out using $KMnO_4$ in water/acetone to afford **4** in 63% yield. The reaction of **4** with **5** using coupling agents (e.g., DCC) gave materials that were problematic due to their instability and was thus abandoned. Instead, the alternative strategy of attaching a short spacer to the azamacrocycle and coupling this to the crown polycycle was attempted. Hence, reaction of **5** with the CBZ-protected aminoacetic acid gave **6** in 95% yield. Removal of the CBZ group and coupling of the amino group with **4** gave the derivative **8** in 79% yield. Final BOC deprotection of **8** using acid conditions gave the desired hybrid ligand $\mathbf{L_1}$. The zinc(II) complex was prepared by reacting $\mathbf{L_1}$ with $Zn(CF_3SO_3)_2$ in methanol. The complex $[Zn\mathbf{L_1}(OH_2)](CF_3SO_3)_2$ was readily soluble in water as well as protic solvents.

Many enzyme systems such as superoxide dismutase, ribonucleotide reductase, and alcohol dehydrogenase contain bimetallic reactive sites for the activation and reaction of substrates.[30] Since functionalization of **5** is readily carried out, we envisaged that a receptor could be produced containing two azamacrocycle sites for the synthesis of a bimetallic enzyme mimic. Thus, shown in Scheme 2 is the procedure used in preparation of the tritopic ligand $\mathbf{L_2}$. Coupling of **5** to the protected (carboxymethylamino)acetic acid **9** produced compound **10** in 82% yield. Deprotection of **10** was first undertaken using 1,4-cyclohexadiene with Pd/C in ethanol, but this failed to give the desired product. However, H_2 gas using Pd/C catalyst in methanol removed the CBZ protecting group to afford **11** in 79% yield. Once again simple coupling of **11** with **4** afforded the Boc-protected derivative **12** in a 45% yield. Deprotection of **12** under acidic conditions yielded the functionalized ligand $\mathbf{L_2}$ in an unoptimized 75% yield. Reaction of $\mathbf{L_2}$ with $Zn(CF_3SO_3)_2$ in methanol gave the corresponding bimetallic complex $Zn_2\mathbf{L_2}(OH_2)_2(CF_3SO_3)_4$.

In addition to working with zinc-based systems, we were also interested in seeing if the outlined methodology in Scheme 1 could be used to attach a triazamacrocycle for complexation with biologically relevant copper(II).[31] The monofunctionalization of 1,4,7-triazacyclononane (tacn) is well documented and can follow a number of approaches.[32] Illustrated in Scheme 3 is the procedure to create a hybrid tacn−cyclophane starting from the Boc-protected derivative **13**. Conversion of **13** to the CBZ-protected aminoacetic acid **14** worked in 78% yield. Deprotection of **14** again worked best under reductive conditions to afford **15** as a colorless oil in 73% yield. Using standard peptide coupling conditions, **15** was coupled to **4** to give **16** in 61% yield. Final removal of the Boc groups under standard conditions produced the ligand $\mathbf{L_3}$, which was complexed with copper(II) to give a dark-blue solid.

Binding of Metals toward L_1−L_3. The transition metal ion Zn^{2+} has a high affinity for donors such a nitrogen and sulfur, and less affinity for the hard oxygen donor.[33] Even so, the hybrid ligand $\mathbf{L_1}$ has potentially two binding sites for a metal ion, namely, the azamacrocycle and the crown polycycle. A ^1H NMR titration experiment was carried out to ascertain the site of binding of the Zn^{2+}

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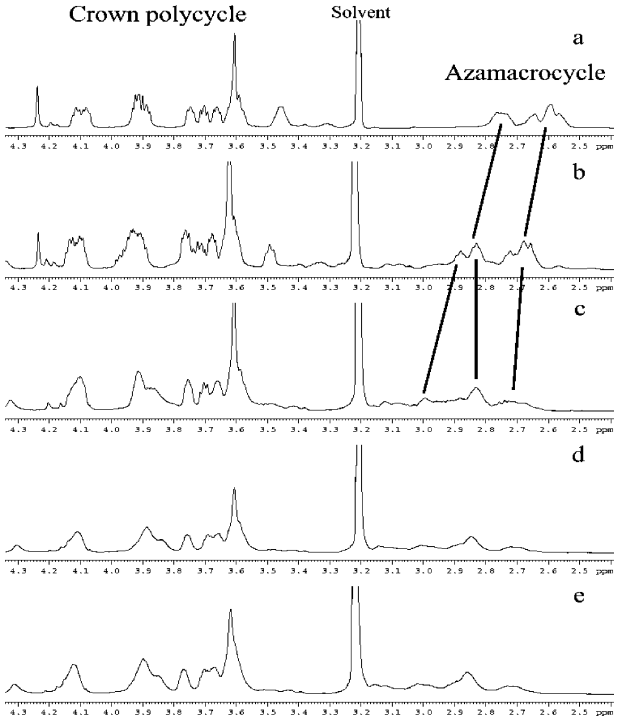
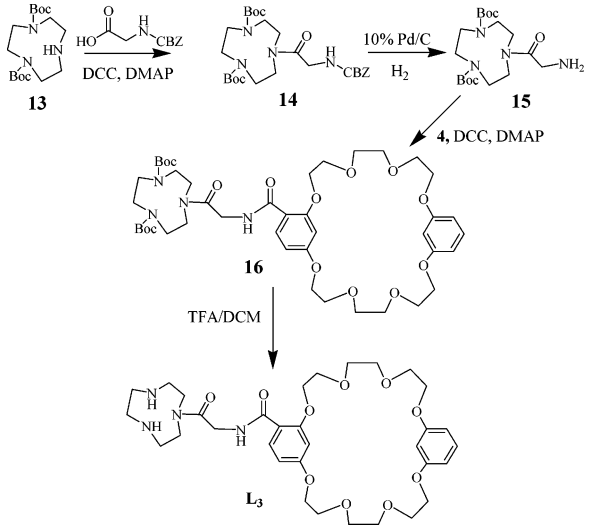


FIGURE 1. Partial 400 MHz ^{1}H NMR spectrum of $\mathbf{L_1}$ in d_4-methanol in the absence (a) and presence of 0.25 equiv of Zn^{2+} (b), 0.5 equiv of Zn^{2+} (c), 0.75 equiv of Zn^{2+} (d) and 1 equiv of Zn^{2+}.

SCHEME 3. Synthetic Procedures Used in the Preparation of Derivative $\mathbf{L_3}$



ion in the hybrid ligand $\mathbf{L_1}$. Figure 1 shows the partial ^{1}H NMR of $\mathbf{L_1}$ upon the addition of aliquots of Zn-$(CF_3SO_3)_2$ in d_4-methanol. The region 3.4−4.2 ppm is characteristic of methylene signals associated with the crown polycycle, whereas the region 2.5−3.0 ppm is assigned to methylene signals of the azamacrocycle. Upon addition of 0.25 equiv of Zn^{2+} ions, there is a clear shift in the signals associated with the azamacrocycle and only minor changes to the signals associated with the crown ether. Upon addition of successive portions of Zn^{2+} ions to a solution of the ligand, there is a considerable broadening of the azamacrocycle methylene signals and, to a lesser extent, the resonances associated with the crown ether. A control ^{1}H NMR titration experiment using the BOC-protected derivative **8** did not show any significant chemical shift alterations for the crown polycycle methylene signals. In view of these findings, it is clear that the Zn^{2+} ion is coordinated preferentially to the azamacrocycle.

A similar titration of Zn^{2+} into $\mathbf{L_2}$ as outlined above gave similar results, but because of the presence of two azamacrocycle sites, a bimetallic complex was formed. The binding of copper(II) toward $\mathbf{L_3}$ was confirmed by titration experiments and monitoring the absorbance change with added copper(II). A plot of absorbance change versus molar ratio of copper (II) leveled off at ∼1, indicating formation of a 1:1 complex. The strong blue color of the complex associated with the d−d transition is very much in line with copper(II) bound to the nitrogen donor groups rather than the oxygen atoms of the crown polycycle.[34]

Properties of ligands $\mathbf{L_1}$, $\mathbf{L_2}$, and $\mathbf{L_3}$. Natural enzymes contain within short distances domains that are hydrophilic and hydrophobic in nature. This unique blend of functionality for binding and reactivity is what makes enzymes such powerful catalysts. Artificial systems to work at the same level need somehow to mimic this diversity in physicochemical properties. The partition coefficient of $\mathbf{L_1}$, $\mathbf{L_2}$, and $\mathbf{L_3}$ were calculated to ascertain the lipophilic/hydrophobic nature of the ligands. The logP values for $\mathbf{L_1}$, $\mathbf{L_2}$, and $\mathbf{L_3}$ are 0.23, −1.16, and 0.97, respectively.[35] This indicates that $\mathbf{L_1}$ and $\mathbf{L_3}$ are amphiphilic, whereas $\mathbf{L_2}$ is slightly more hydrophilic due to the increased number of amines.

Binding of Complexes toward Phosphate Substrates. Clearly, natural enzymes work in an aqueous environment, and so one important criterion for an artificial system is to work under similar conditions. Thus, the binding behavior of $[Zn\mathbf{L_1}(OH_2)](CF_3SO_3)_2$, $[Zn_2\mathbf{L_2}(OH_2)_2](CF_3SO_3)_2$, and $[Cu\mathbf{L_3}(OH_2)_2](CF_3SO_3)_2$ toward various phosphate substrates was measured in buffered H_2O at 25 °C using isothermal calorimetry.[36] In a previous communication, we described the binding behavior of $[Zn\mathbf{L_1}(OH_2)](CF_3SO_3)_2$ toward phosphate and concluded that it behaves as an ion-pair binder using both the crown polycycle and zinc(II)-hydroxyl sites.[37] It is believed that the zinc(II) center binds the phosphate anion with crown polycycle, acting cooperatively to bind

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(35) We are confident that the calculated values of log P are reliable since the measured value for $\mathbf{L_1}$ (0.18) is in very good agreement.

(36) Attempts to confirm binding of phosphate derivatives by potentiometric titrations using the ligands alone were inconclusive because of solubility problems. It is noted that the presence of the crown ether in the hybrid ligands is essential for binding, as determined by simple control experiments (see ref 37).

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TABLE 1. Binding Constants and Thermodynamic Parameters Obtained by Isothermal Calorimetry for $[ZnL_1(H_2O)]^{2+}$, $[Zn_2L_2(OH_2)_2]^{2+}$, and $[CuL_3(OH_2)_2]^{2+}$ at 25 °C in the Presence of Various Substrates

ligand	ligand: substrate[a]	substrate	K/10[4b]	$\Delta G°$/kcal mol^{-1}	$\Delta H°$/kcal mol^{-1}	$-T\Delta S°$/kcal mol^{-1}
$[ZnL_1(H_2O)]^{2+}$	2:1	$Na[H_2PO_4]$	4.93 ± 0.69[c]	-6.39 ± 0.90	3.47 ± 0.16	9.86[f]
$[ZnL_1(H_2O)]^{2+}$	2:1	$K[H_2PO_4]$	9.32 ± 1.60[c]	-6.78 ± 0.17	2.44 ± 0.09	9.22[f]
$[ZnL_1(H_2O)]^{2+}$	1:1	sodium glycerophosphate	0.48 ± 0.06	-5.02 ± 0.63	0.48 ± 0.02	5.50[f]
$[ZnL_1(H_2O)]^{2+}$	1:1	disodium 4-nitrophenyl phosphate	0.39 ± 0.04	-4.90 ± 0.50	0.58 ± 0.04	5.48[f]
$[Zn_2L_2(H_2O)_2]^{4+}$	1:2[d]	$Na[H_2PO_4]$	*e*	na	na	na
$[Zn_2L_2(H_2O)_2]^{4+}$	1:2[d]	$K[H_2PO_4]$	*e*	na	na	na
$[Zn_2L_2(H_2O)_2]^{4+}$	1:1	sodium glycerophosphate	1.78 ± 0.21	-5.79 ± 0.68	3.89 ± 0.38	9.68[g]
$[Zn_2L_2(H_2O)_2]^{4+}$	1:1	disodium 4-nitrophenyl phosphate	1.23 ± 0.34	-5.57 ± 1.54	0.63 ± 0.11	6.21[g]
$[ZnL_3(H_2O)]^{2+}$	1:1	$Na[H_2PO_4]$	<0.05[h]			
$[ZnL_3(H_2O)]^{2+}$	1:1	$K[H_2PO_4]$	<0.05[h]			

[a] Ratio obtained from least-squares fit to isothermal calorimetry data. [b] mol^{-1} dm^3. [c] mol^{-2} dm^6. [d] Binding stoichiometry obtained from Job plot from UV−vis spectroscopy data and confirmed by ES-MS. [e] Unable to calculate from isothermal calorimetry data (see text), na, not available. [f] Data taken from ref 37. [g] This work. [h] Confirmed by UV−vis titrations. Note: Reported errors are from the least-squares ITC fitted data and are as reported from the output file (see Supporting Information).

the cation (i.e., Na^+, K^+). Thermodynamic data also reveal a large entropic driving force for complexation that is assigned to water expulsion from the crown ether. Collected in Table 1 is a summary of these data along with that for the other two complexes. A noticeable result is the lack of any tangible substrate binding by the copper complex of ligand **L**$_3$. It is well-known that copper(II) forms distorted five-coordinate complexes with triazamacrocyclic ligands similar to **L**$_3$.[38] The lack of strong phosphate binding could be due to a geometry mismatch of phosphate interaction at the copper.

The design of the bimetallic system $[Zn_2\mathbf{L_2}(OH_2)_2](CF_3SO_3)_2$ was specific to promote phosphate binding between the two zinc(II) centers and use the crown polycycle to shield the bound substrate. A molar ratio plot obtained by a UV−vis titration confirmed a 1:2 ($[Zn_2\mathbf{L_2}(OH_2)_2]^{4+}$/$HPO_4^{2-}$) binding stoichiometry. The ITC binding isotherm (Figure 2), however, reveals a more complicated process in fact takes place. The first segment of the ITC trace reveals an exothermic process takes place that is followed by an endothermic reaction. It should be noted that the binding of $[Zn_2\mathbf{L_2}(OH_2)_2]^{4+}$ toward sodium glycerophosphate and disodium 4-nitrophenyl phosphate is endothermic and does not follow this behavior. One possible argument to account for the data is that, at high ligand/substrate ratios (i.e., beginning of the titration), the phosphate anion acts as a template for cluster formation of two $[Zn_2\mathbf{L_2}(OH_2)_2]^{4+}$ moieties. Indeed, there is literature precedent for the templating action of anions, especially in helicate formation around a spherical chloride ion.[39] As the ligand:substrate ratio increases, the cluster is broken up, leading to 1:2 complex formation. Unfortunately, electrospray mass (ES-MS) spectrometry experiments carried out on solutions of varying $[Zn_2\mathbf{L_2}(OH_2)_2]^{4+}$/$HPO_4^{2-}$ ratios all displayed similar features. All ES-MS results revealed an intense cluster of peaks centered at $m/z = 701$, corresponding to $[Zn_2\mathbf{L_2}(HPO_4)_2Na_2]^{2+}$. This ratio of zinc complex to phosphate is in agreement with the UV/vis titration results (i.e., 1:2 (ligand/substrate) complexation).

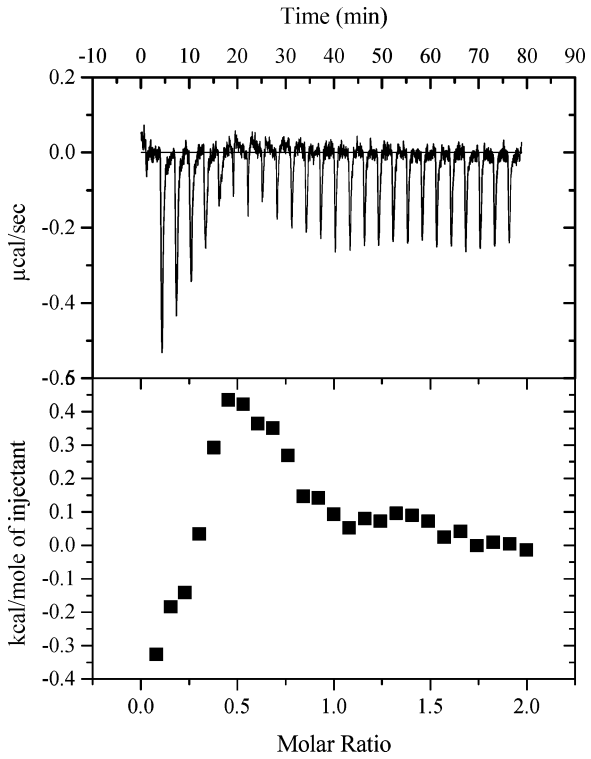

FIGURE 2. Isothermal calorimetry graphs showing the binding of $[Zn_2L_2(OH_2)_4]^{4+}$ toward NaH_2PO_4 in buffered water (pH = 7.4) at 25 °C.

Conclusions

We have shown that hybrid azamacrocycle−crown ether receptors can be readily produced using well-established synthetic procedures. The methodology used is modular since all three parts can be readily changed, and thus gives the opportunity for future systems of designer engineering each segment for a particular function. Our initial efforts at binding phosphate at physiological pH using the hybrid derivatives have been successful, and binding constants are comparable with those for previously reported supramolecular receptors.[8] Experiments are currently underway to see if hydrolysis of the P−O bond can be carried out, and these results will be reported at a later date.

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Experimental Section

Preparation of 2,4-Bis{2-[2-(2-hydroxyethoxy)ethoxy]-ethoxy}benzaldehyde (1). Solid 2,4-dihydroxybenzaldehyde (10.00 g, 72 mmol) was added to a stirred mixture of K_2CO_3 (29.85 g, 216 mmol) in dry DMF (60 mL) at 90 °C under N_2. The mixture was stirred at this temperature for 1 h before addition of 2-[2-(2-chloroethoxy)ethoxy]ethanol (24.28 g, 144 mmol) and KI (22.63 g, 158 mmol). The reaction mixture was refluxed for 48 h and cooled to room temperature. The DMF was removed by azeotropic distillation with toluene (3 × 250 mL) to leave a red oil, which was dissolved in CH_2Cl_2 (200 mL) and filtered to remove potassium salts. The organics were dried over $MgSO_4$ and concentrated under reduced pressure to yield a viscous red oil (23.14 g, 79.9%): ^{1}H NMR ($CDCl_3$) δ 2.56 (1H, t, J = 6 Hz, OH), 2.68 (1H, t, J = 6 Hz, OH), 3.60−3.63 (4H, m, CH_2), 3.68−3.75 (12H, m, CH_2), 3.86−3.92 (4H, m, CH_2), 4.21 (2H, t, J = 5 Hz, CH_2), 4.24 (2H, t, J = 5 Hz, CH_2), 6.53−6.58 (2H, m, Ar−H), 7.80 (1H, d, J = 8 Hz, Ar−H), 10.35 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ 68.2 (CH_2), 68.8 (CH_2), 69.75 (CH_2), 69.78 (CH_2), 70.1 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 71.0 (CH_2), 71.1 (CH_2), 72.5 (CH_2), 72.7 (CH_2), 72.8 (CH_2), 100.3 (CH), 107.4 (CH), 119.6 (C), 131.5 (CH), 163.1 (C), 165.5 (C), 189.1 (CHO). Note: the crude compound was carried through to the next stage as a result of purification difficulties.

Preparation of 2,4-Bis{2-[2-(2-iodoethoxy)ethoxy]-ethoxy}benzaldehyde (2). To a stirred solution of **1** (22.0 g, 54 mmol) and Et_3N (17.3 mL, 162 mmol) in dry CH_2Cl_2 (50 mL) cooled to 0 °C under an Ar atmosphere were slowly added portions of *p*-toluenesulfonyl chloride (27.31 g, 162 mmol). The mixture was allowed to warm to room temperature and the reaction monitored by TLC (silica gel, 5:1 ethyl acetate/petrol). After disappearance of the starting material, water (150 mL) was added to the reaction mixture. The product was extracted with CH_2Cl_2 (200 mL) and washed with brine (3 × 100 mL). The separated organic layer was dried over $MgSO_4$ and the solvent removed to afford a viscous brown oil, which was purified using flash chromatography (silica gel 5:1 ethyl acetate/petrol) to yield a yellow oil (20.06 g, 28.2 mmol, 52.3%). Elemental analysis calcd for $C_{33}H_{42}O_{13}S_2$: C, 55.76; H, 5.95; found C, 55.75; H, 5.81. ν_{max} (neat)/cm^{-1} 2861, 1731 (C=O), 1671, 1596, 1575, 1500 (Ar), 993, 933, 873, 815; ^{1}H NMR ($CDCl_3$) δ 2.36 (6H, s, CH_3), 3.51−3.56 (4H, m, CH_2), 3.58−3.63 (8H, m, CH_2), 3.77 (2H, t, J = 5 Hz, CH_2), 3.80 (2H, t, J = 5 Hz, CH_2), 4.10 (8H, m, CH_2), 6.42 (1H, d, J = 2 Hz, Ar−H), 6.47 (1H, dd, J = 8, and 1.4 Hz, Ar−H), 7.25 (4H, d, J = 8 Hz, Ar−H), 7.71 (5H, d, J = 8 Hz, Ar−H), 10.27 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ 22.0 (2xCH_3), 68.1 (CH_2), 68.6 (CH_2), 69.1 (CH_2), 69.6(CH_2), 69.8 (CH_2), 70.6 (CH_2), 71.1 (CH_2), 71.17 (CH_2), 71.2 (CH_2), 72.3 (CH_2), 99.9 (CH), 107.1 (CH), 119.6 (C), 128.3 (CH), 130.2 (CH), 130.6 (CH), 133.3 (C), 145.23 (C), 145.26 (C), 163.3 (C), 165.6 (C), 188.6 (CHO).

To a solution of the above compound 4-bis [2-{2-(2-tosyloxyethoxy)ethoxy}ethoxy] benzaldehyde (20.06 g, 28 mmol) in dry acetone (350 mL), at reflux, was added NaI (16.93 g, 113 mmol) over a 30 min period. The mixture was further refluxed for 14 h under an N_2 atmosphere. The solution was cooled to room temperature and the solvent removed under reduced pressure. To the mixture was added CH_2Cl_2 (150 mL) and the resultant solid residue filtered. Removal of the solvent afforded a yellow oil, which was further purified by silica gel column chromatography (5:1 ethyl acetate/petrol) to give pure product as a colorless oil **3** (13.77 g, 22 mmol, 77.7%). Elemental analysis calcd for $C_{19}H_{28}O_7I_2$: C, 36.65; H, 4.50; I, 40.84; found C, 36.65; H, 4.61; I, 40.89; HRMS (EI$^+$) calcd for $C_{19}H_{28}O_7I_2$ [M$^+$] m/z = 621.9925, found 621.9926; ^{1}H NMR ($CDCl_3$) δ 3.19 (4H, dt, J = 7 and 2 Hz, CH_2), 3.60−3.72 (12H, m, CH_2), 3.82 (2H, t, J = 5 Hz, CH_2), 3.86 (2H, t, J = 5 Hz, CH_2), 4.11−4.16 (4H, m, CH_2), 6.43 (1H, d, J = 2 Hz, Ar−H), 6.50 (1H, dd, J = 8 and 2 Hz, Ar−H), 7.73 (1H, d, J = 8 Hz, Ar−H), 10.28, (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ 68.1 (2 × CH_2), 68.6 (2 × CH_2), 69.9 (2 × CH_2), 70.6 (2 × CH_2), 71.2 (CH_2), 71.3 (CH_2), 72.3 (2 × CH_2), 100.0 (CH), 107.0 (CH), 119.7 (C), 130.7 (CH), 163.2 (C), 165.6 (C), 188.6 (CHO).

Preparation of 2,5,8,11,17,20,23,26-Octaoxatricyclo-[25.3.1.1^{12,16}]dotriaconta-1(30),12(32), 13,15,27(31),28-hexaene-13-carbaldehyde (3). To a stirred suspension of K_2CO_3 (10.71 g, 77 mmol) in dry DMF (30 mL) under N_2 were added simultaneously over a 28 h period separate solutions of 2,4-bis [2-{2-(2-iodo-oxyethoxy)ethoxy}ethoxy]benzaldehyde **2** (6.08 g, 9.7 mmol) in dry DMF (40 mL) and 1,3-dihydroxybenzene (1.07 g, 9.7 mmol) in dry DMF (40 mL). The mixture was heated at 90 °C for 5 days before being cooled to room temperature. The residue was dissolved in distilled water (100 mL) and the solution extracted with CH_2Cl_2 (3 × 50 mL). The organic washings were combined and washed with 2 M HCl (100 mL) and distilled water (2 L). Sodium chloride was added to break up the emulsion that formed during the partitioning process. The organic phase was isolated, dried over $MgSO_4$, and concentrated under reduced pressure to yield a crude product, which was chromatographed on silica gel (5:1 ethyl acetate/petrol) to give the target compound as a pale-yellow viscous oil (1.03 g, 22.5%). Elemental analysis calcd for $C_{25}H_{32}O_9$: C, 63.01; H, 6.76; found C, 62.60; H, 6.78; HRMS (EI$^+$) calcd for $C_{25}H_{32}O_9$ [M$^+$], m/z = 476.2046, found 476.2046; ν_{max} (neat)/cm^{-1} 2867, 1671 (C=O), 1594 and 1490, (Ar), 840, 815 (meta-disubstituted Ar); ^{1}H NMR ($CDCl_3$) δ 3.61−3.67 (8H, m, CH_2), 3.72−3.83 (8H, m, CH_2), 3.99 (2H, t, J = 5 Hz, CH_2), 3.99 (2H, t, J = 5 Hz, CH_2), 4.06−4.10 (4H, m, CH_2), 6.38−6.47 (5H, m, Ar−H), 7.05 (1H, t, J = 8 Hz, Ar−H), 7.68 (1H, d, J = 8 Hz, Ar−H), 10.34 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ 67.6 (CH_2), 67.8 (CH_2), 68.0 (CH_2), 68.5 (CH_2), 69.7 (CH_2), 69.8 (CH_2), 70.0 (CH_2), 70.1 (CH_2), 71.0 (CH_2), 71.2 (CH_2), 71.4 (CH_2), 71.6 (CH_2), 100.0 (CH), 102.4 (CH), 106.9 (CH), 107.0 (CH), 107.7 (CH), 119.6 (C), 130.1 (CH), 130.5 (CH), 160.3 (C), 160.36 (C), 163.4 (C), 165.7 (C), 188.7 (CHO).

Preparation of 2,5,8,11,17,20,23,26-Octaoxatricyclo [25.3.1.1^{12,16}]dotriaconta-1(30),12(32), 13,15,27(31),28-hexaene-13-carboxylic Acid (4). The macrocyclic aldehyde **3** (0.050 g, 1.0 mmol) was dissolved in acetone (2 mL) and treated with a solution of $KMnO_4$ (0.033 g, 2.1 mmol) in acetone/H_2O (1:1) (2 mL). The solution was stirred at room temperature for 6 h. The insoluble inorganic salts were removed by filtration through a short silica plug (10 g) and elution with ethyl acetate (100 mL). The filtrate was concentrated, redissolved in CH_2Cl_2 (20 mL) that was washed with brine (2 × 30 mL), separated, and dried over $MgSO_4$. Removal of the CH_2Cl_2 afforded a crude product, which was purified by silica gel chromatography using ethyl acetate/petrol (5:1) as eluent to yield the pure product as a colorless oil (0.032 g, 62%): HRMS (EI$^+$) calcd for $C_{25}H_{32}O_{10}$ [M$^+$], m/z = 492.1995, found 492.1997; ν_{max}(neat)/cm^{-1} 3272, 2869, 2360, 1720 (C=O), 1604, 1490, 1438, 1361, 1284, 1255, 1182, 1120, 1056, 987, 943, 836, 763, 682, 634; ^{1}H NMR ($CDCl_3$) δ 3.62−3.66 (8H, m, CH_2), 3.67−3.71 (2H, m, CH_2), 3.72 (2H, t, J = 4 Hz, CH_2), 3.77 (2H, t, J = 4 Hz, CH_2), 3.83 (2H, t, J = 4 Hz, CH_2), 3.88 (2H, t, J = 4 Hz, CH_2), 4.08 (2H, t, J = 4 Hz, CH_2), 4.12 (2H, t, J = 4 Hz, CH_2), 4.27 (2H, t, J = 4 Hz, CH_2), 6.29 (1H, t, J = 2 Hz, Ar−H), 6.36 (1H, t, J = 2 Hz, Ar−H), 6.38 (1H, t, J = 2 Hz), 6.45 (1H, d, J = 2 Hz, Ar−H), 6.55 (1H, dd, J = 10 and 2 Hz, Ar−H), 6.99 (1H, t, J = 8 Hz, Ar−H), 7.92 (1H, d, J = 8 Hz, Ar−H); ^{13}C NMR ($CDCl_3$) δ 67.3 (CH_2), 67.7 (CH_2), 68.2 (CH_2), 69.1 (CH_2), 69.6 (CH_2), 69.8 (CH_2), 70.0 (CH_2), 70.1 (CH_2), 70.7 (CH_2), 71.2 (CH_2), 71.4 (CH_2), 71.8 (CH_2), 101.0 (CH), 102.3 (CH), 106.4 (CH), 107.6 (CH), 108.0 (CH), 111.5 (C), 130.2 (CH), 135.5 (CH), 159.1 (C), 160.2 (C), 160.3 (C), 164.5 (C), 165.8 (C).

Preparation of 1,4,7,10-Tetraazacyclododecane-1,4,7-tricarboxylic Acid Tri-*tert*-butyl Ester (5). Under an N_2 atmosphere at room temperature, a solution of di-*tert*-butyl dicarbonate (3.42 g, 15.6 mmol) in $CHCl_3$ (10 mL) was added slowly over 3 h to a solution of cyclen (1 g, 6 mmol) and Et_3N (1.76 g, 16.1 mmol) in $CHCl_3$. The reaction mixture was stirred for a further 24 h, and the solvent was removed under vacuum

to give crude product, which was purified by column chromatography on silica gel (5:1 ethyl acetate/petrol) to afford the pure product as a white solid (2.25 g, 82%): mp 54−55 °C; HRMS (EI$^+$) calcd for $C_{23}H_{45}N_4O_6$ [MH$^+$] *m/z* = 473.3339, found 473.3338; ν_{max}(neat)/cm^{-1} 3313, 2975, 2802, 1666 (C=O), 1463, 1413, 1386, 1363, 1319, 1288, 1247, 1149, 1116, 1087, 1058, 983, 943, 892, 858, 821, 773; ^{1}H NMR ($CDCl_3$) δ 1.37 (18H, s, CH_3), 1.39 (9H, s, CH_3), 2.77 (4H, s (broad), CH_2), 3.21−3.31 (8H, m, CH_2), 3.54 (4H, s (broad), CH_2); ^{13}C NMR ($CDCl_3$) δ 27.5 (9 × CH_3), 43.9 (CH_2), 44.9 (CH_2), 47.8 (CH_2), 48.4 (2 × CH_2), 48.8 (CH_2), 49.9 (2 × CH_2), 78.1 (2 × C), 78.4 (C), 154.4 (C=O), 154.6 (2 × C=O).

Preparation of 10-(2-Phenoxycarbonylaminoacetyl)-1,4,7,10-tetraazacyclododecane-1,4,7-*tert*-butylcarbamate (6). To a stirred solution of CBZ-Gly (0.27 g, 1.3 mmol) in CH_2Cl_2 (2 mL) under an N_2 atmosphere was added dropwise neat DCC (0.26 g, 1.3 mmol), followed by slow addition of 1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylic acid tri-*tert*-butyl ester (0.61 g, 1.3 mmol) and DMAP (0.16 g, 1.3 mmol). The solution was left to stir overnight at room temperature and then filtered to remove the urea side product. The solvent was removed under reduced pressure to give a crude material, which was purified by silica gel column chromatography (5:1 ethyl acetate/petrol) to yield the pure product as a white solid (0.64 g, 75%): mp 66−67 °C; ν_{max} (neat)/cm^{-1} 2973, 1685 (amide), 1465, 1409, 1363, 1245, 1157, 1106, 1043, 971, 856, 775. Elemental analysis calcd for $C_{33}H_{53}N_5O_9$: C, 59.71; H, 8.05; N, 10.55; found C, 59.80; H, 8.24; N, 10.49; HRMS (EI$^+$) calcd for $C_{33}H_{53}N_5O_9$ [M$^+$] *m/z* = 663.3843, found 663.3841; ^{1}H NMR ($CDCl_3$) δ 1.31−1.45 (27H, m, CH_3), 3.10−3.60 (16H, m, CH_2), 3.95 (2H, d, *J* = 4 Hz, CH_2), 5.05 (2H, s, CH_2), 5.65 (1H, s (broad), NH), 7.20−7.30 (5H, m, Ar−H).

Preparation of 10-(2-Aminoacetyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylic Acid Tri-*tert*-butyl Ester (7). To a stirred solution of **6** (0.34 g, 51 mmol) in absolute EtOH (5 mL) at room temperature, was slowly added 10% Pd/C (0.34 g, 1 equiv), followed by 1,4-cyclohexadiene (0.41 g, 5.1 mmol). The solution was stirred for 2 h and filtered through a Celite pad, and the solvents were removed under reduced pressure to yield pure product as a white solid that required no further purification (0.25 g, 91%): mp 96−97 °C; HRMS (EI$^+$) calcd for $C_{25}H_{47}N_5O_7$ [M$^+$] *m/z* = 529.3475, found 529.3473; ν_{max} (neat)/cm^{-1} 2975, 1683 (C=O), 1467, 1409, 1363, 1247, 1159, 1106, 970, 856, 777; ^{1}H NMR ($CDCl_3$) δ 1.39−1.41 (27H, m, CH_3), 3.20−3.65 (18H, m, CH_2).

Preparation of 10-{2-[(2,5,8,11,18,21,24,27-Octaoxatricyclo[26.3.1.0^{12,17}]dotriaconta-1(31),12(17),13,15,28(32),-29-hexaene-29-carbonyl)-amino]-acetyl}-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylic Acid Tri-*tert*-butyl Ester (8). To a stirred solution of **4** (60 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) under N_2 atmosphere was added dropwise DCC (0.25 g, 0.13 mmol), followed by the addition of 10-(2-aminoacetyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylic acid tri-*tert*-butyl ester **7** (0.064 g, 0.13 mmol) and DMAP (0.014 g, 0.13 mmol). The solution was left to stir overnight at room temperature and filtered to remove the urea side product. The solvent was removed under reduced pressure to give a crude material, which was purified by silica gel column chromatography (5:1 ethyl acetetate/petrol) to yield pure product as a white solid (0.74 g, 61%): HRMS (EI$^+$) calcd for $C_{50}H_{78}N_5O_{16}$ [MH]$^+$ *m/z* = 1004.5444, found 1004.5446; ν_{max} (neat)/cm^{-1} 2931, 1685, 1641, 1604, 1465, 1409, 1365, 1249, 1159, 1106, 973, 848, 775; ^{1}H NMR ($CDCl_3$) δ 1.40−1.60 (27H, m, CH_3), 3.40−3.65 (16H, m, CH_2), 3.70−3.75 (8H, m, CH_2), 3.81 (2H, t, *J* = 2 Hz, CH_2), 3.87 (4H, t, *J* = 4 Hz, CH_2), 4.03 (2H, t, *J* = 5 Hz, CH_2), 4.07 (2H, t, *J* = 5 Hz, CH_2), 4.10 (2H, t, *J* = 4 Hz, CH_2), 4.16 (2H, t, *J* = 4 Hz, CH_2), 4.21 (2H, t, *J* = 4 Hz, CH_2), 4.28 (2H, d, *J* = 4 Hz, CH_2), 6.47−6.58 (5H, m, Ar−H), 7.12 (1H, t, *J* = 8 Hz, Ar−H), 8.12 (1H, d, *J* = 8 Hz, Ar−H), 8.80 (1H, s (broad), NH); ^{13}C NMR ($CDCl_3$) δ 28.8 (9 × CH_3), 49.9−51.5 (m, 8 × CH_2), 67.5 (CH_2), 67.8 (CH_2), 67.9 (CH_2), 68.8 (CH_2), 69.4 (CH_2), 69.8 (CH_2), 69.9 (CH_2), 70.1 (CH_2), 70.9 (CH_2), 71.2 (CH_2), 71.3 (CH_2), 71.4 (CH_2), 80.7 (C), 80.8 (C), 80.9 (C), 100.7 (CH), 102.4 (CH), 106.4 (CH), 107.1 (CH), 107.6 (CH), 114.8 (C), 130.1 (CH), 133.8 (CH), 156.0 (C), 157.1 (C), 158.9 (C), 160.3 (C), 162.9 (C), 165.2 (C).

Preparation of 2,5,8,11,18,21,24,27-Octaoxatricyclo-[26.3.1.0^{12,17}]dotriaconta-1(31),12(17),13,15,28(32),29-hexaene-29-carboxylic Acid [2-Oxo-2-(1,4,7,10-tetraazacyclododec-1-yl)-ethyl]-amide (L_1). To a stirred solution of **8** (0.26 g, 0.25 mmol) in CH_2Cl_2 (3 mL) at room temperature under an N_2 atmosphere was added dropwise TFA (1 mL). The solution was stirred for 3 h then quenched by addition of 3 M NaOH (10 mL). The organic layer was washed with brine (3 × 20 mL), separated, and dried over Na_2SO_4. Removal of the solvent afforded the pure product as a colorless oil (0.13 g, 72%): HRMS (FAB$^+$) calcd for $C_{35}H_{54}N_5O_{10}$ [MH$^+$] *m/z* = 704.3871, found 704.3866; ν_{max}(neat)/cm^{-1} 3361, 2867, 1631 (C=O tertiary amide), 1600 (C=O) secondary amide), 1521, 1452, 1353, 1257, 1184, 1106, 1056, 941, 800, 767; ^{1}H NMR ($CDCl_3$) δ 2.55−2.90 (12H, m, CH_2), 3.45−3.48 (2H, m, CH_2), 3.52−3.55 (2H, m, CH_2), 3.61−3.69 (8H, m, CH_2), 3.72 (2H, t, *J* = 5 Hz, CH_2), 3.78 (4H, t, *J* = 5 Hz, CH_2), 3.95 (2H, t, *J* = 5 Hz, CH_2), 3.99−4.03 (4H, m, CH_2), 4.07 (2H, t, *J* = 5 Hz, CH_2), 4.13 (2H, t, *J* = 5 Hz, CH_2), 4.30 (2H, d, *J* = 4.0 Hz, CH_2), 6.39 (5H, m, Ar−H), 7.05 (1H, t, *J* = 8 Hz, Ar−H), 8.02 (1H, d, *J* = 8 Hz, Ar−H), 8.78 (1H, s, NH); ^{13}C NMR ($CDCl_3$) δ 43.1 (CH_2), 45.3 (CH_2), 46.8 (CH_2), 47.8 (CH_2), 48.5 (CH_2), 48.6 (CH_2), 49.0 (CH_2), 49.8 (CH_2), 67.5 (CH_2), 67.8 (CH_2), 67.87 (CH_2), 68.9 (CH_2), 69.4 (CH_2), 69.8 (CH_2), 69.9 (CH_2), 70.1 (CH_2), 70.9 (CH_2), 71.1 (CH_2), 71.3(CH_2), 71.4 (CH_2), 100.6 (CH), 102.3 (CH), 106.3 (CH), 107.0 (CH), 107.7 (CH), 114.8 (C), 130.1 (CH), 133.9 (CH), 158.9 (C), 160.3 (2 × C), 162.9 (C), 165.2 (C), 170.6 (C).

Preparation of [ZnL_1(OH$_2$)](CF$_3$SO$_3$)$_2$. To a stirred solution of L_1 (0.06 g, 0.08 mmol) in MeOH (1 mL) at room temperature under an N_2 atmosphere was added zinc(II) triflate (0.034 g, 0.080 mmol). The mixture was stirred for 2 h and filtered through glass fiber paper. The solution was concentrated under reduced pressure to yield the product as a white solid (0.062 g, 78%): mp 76−77 °C; HRMS (FAB) calcd for [Zn**L**(CF_3SO_3)]$^+$ *m/z* = 916.2557, found 916.2492; ν_{max} (neat)/cm^{-1} 3397, 2009, 1957, 1598 (C=O amide), 1452, 1222, 1166, 1025, 831, 761; ^{1}H NMR (MeOD) δ 2.76−3.28 (16H, m, CH_2), 3.68−3.84 (12H, m, CH_2), 3.90 (4H, t, *J* = 4 Hz, CH_2), 3.93 (t, 2H, *J* = 4 Hz, CH_2), 4.13 (2H, t, *J* = 4 Hz,CH_2), 4.19 (2H, t, *J* = 4 Hz, CH_2), 4.25 (2H, t, *J* = 4 Hz, CH_2), 4.32 (2H, s, CH_2(Gly)), 6.31−6.41 (1H, d, *J* = 11 Hz, Ar−H), 6.44 (2H, t, *J* = 5 Hz, Ar−H), 6.56 (1H, t, *J* = 8 Hz, Ar−H), 7.86 (1H, dd, *J* = 16 and 8 Hz, Ar−H); ^{13}C NMR (MeOH-d_4) δ 45.1 (CH_2), 45.3 (CH_2), 45.5 (CH_2), 46.8 (2 × CH_2), 47.8 (3 × CH_2), 68.8 (CH_2), 69.0 (CH_2), 69.4 (CH_2), 70.4(CH_2), 70.6 (CH_2), 70.9 (CH_2), 71.2 (CH_2), 71.8 (CH_2), 72.1 (CH_2), 72.2 (2xCH_2), 72.3(CH_2), 102.1 (CH), 103.6 (CH), 108.0 (CH), 108.4 (CH), 108.5 (CH), 117.5 (C), 120.5 (C), 123.7 (C), 127.1 (C), 131.3 (CH), 134.7 (CH), 161.0 (C), 161.83 (C), 161.85 (C).

Preparation of [(2-Hydroxy-acetyl)phenoxycarbonylamino]acetic Acid (9). To a solution of aminodiacetic acid (0.30 g, 2.2 mmol) in 2 M NaOH (10 mL) was added dropwise benzyl chloroformate (0.35 mL, 2.4 mmol) and a further 2 M NaOH (5 mL) at 5 °C. The mixture was stirred at room temperature for 2 h, washed with diethyl ether (2 × 10 mL), acidified to pH 2 with 1 M HCl, and extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield pure product as a colorless oil (0.42 g, 70%). Elemental analysis calcd for $C_{12}H_{13}N_5O_6$: C, 53.93; H, 4.87; N, 5.24, found C, 53.78; H, 4.90; N, 5.27; HRMS (CI$^+$) calcd for $C_{12}H_{14}N_3O_6$ [MH$^+$] *m/z* = 268.0821, found 268.0820; ν_{max} (neat)/cm^{-1} 3570, 2565, 1708, 1687, 1474, 1406, 1303, 1194 1081; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 2H, CH_2), 4.10 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 7.18−7.32 (m, 5H, Ar−H); ^{13}C NMR ($CDCl_3$) δ 50.2 (CH_2), 50.4 (CH_2), 69.0 (CH_2), 128.3 (2 × CH), 128.8 (CH), 129.0 (2 × CH), 135.9 (C), 156.5 (C), 174.1 (C), 174.8 (C).

Preparation of 10. To a solution of **9** (0.20 g, 0.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise DCC (0.32 g, 1.5 mmol), followed by **5** (0.92 g, 1.9 mmol) in CH_2Cl_2 (10 mL) and DMAP (0.19 g, 1.5 mmol) at room temperature under an N_2 atmosphere. The reaction solution was stirred for 24 h before being filtered through glass fiber paper under suction to remove the urea side product. The solvent was removed under reduced pressure and purified by silica gel column chromatography (5:1, ethyl acetate/petrol) to yield pure product as a white solid (1.85 g, 82%): mp 97−98 °C. Elemental analysis calcd for $C_{58}H_{97}N_9O_{16}$: C, 59.21; H, 8.31; N, 10.72, found C, 59.27; H, 8.41; N, 10.60; HRMS (FAB$^+$) calcd for $C_{58}H_{98}N_9O_{16}$ [MH]$^+$ *m/z* =1175.7053, found 1175.7050; ν_{max} (neat)/cm^{-1} 3054, 2986, 2305, 1686, 1421, 1265, 1160, 896, 746, 705, 585, 429; ^{1}H NMR ($CDCl_3$) δ 1.30−1.50 (m, 54H, CH_3), 3.10−3.60 (m, 32H, CH_2), 4.31 (s, 4H, CH_2), 5.07 (s, 2H, CH_2), 7.20−7.30 (m, 5H, Ar−H).

Preparation of 11. To solution of **10** (0.34 g, 0.28 mmol) in MeOH (4 mL) was added slowly Pd/C 10% (0.34 g) under an N_2 atmosphere at room temperature. The vessel was evacuated, filled with H_2, and left to stir overnight. After this period, the H_2 was expelled, the solution filtered through a Celite pad, and the solvent removed under reduced pressure to yield pure product as a colorless oil (0.24 g, 79%): mp 92−93 °C. Elemental analysis calcd for $C_{50}H_{91}N_9O_{14}\cdot 0.5H_2O$: C, 57.12; H, 8.82; N, 11.99, found C, 57.15; H, 8.75; N, 11.84; ν_{max} (neat)/cm^{-1} 3054, 2985, 1690, 1466, 1420, 1367, 1265, 1162, 896, 748, 705, 584, 435; ^{1}H NMR ($CDCl_3$) δ 1.41 (54H, s, CH_3), 3.10−4.00 (37H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 28.45 (6 × CH_3), 28.48 (6 × CH_3), 28.6 (6 × CH_3), 49.4−52.0 (broad multiplet, 34 × CH_2), 80.1 (2 × C), 80.2 (2 × C), 80.3 (2 × C), 155−158 (8 × C).

Preparation of 12. To a solution of **4** (0.060 g, 0.13 mmol) in CH_2Cl_2 (2 mL) was added dropwise DCC (0.30 g, 1.3 mmol), followed by the addition of **11** (0.14 g, 0.13 mmol) in CH_2Cl_2 (3 mL) and DMAP (0.16 g, 0.13 mmol) at room temperature under an N_2 atmosphere. The reaction solution was stirred for 24 h before being filtered through glass fiber paper under suction to remove the urea side product. The reaction solution was then washed with 1 M NaOH (20 mL) and brine (50 mL) before the solvent was removed under reduced pressure and purified by silica gel column chromatography (10:1, ethyl acetate/methanol) to yield pure product as a white solid (0.090 g, 45%): mp 72−73 °C; HRMS (FAB) calcd for $C_{75}H_{122}N_9O_{23}$ [MH$^+$] *m/z* =1516.8643, found 1516.8654; ν_{max} (neat)/cm^{-1} 2984, 1751, 1465, 1447, 1374, 1240, 1097, 1047, 938, 847, 634, 608, 443, 434, 410, 405; ^{1}H NMR ($CDCl_3$) δ 1.35−1.50 (54H, m, CH_2), 2.95−3.55 (32H, m, CH_2), 3.58−3.65 (8H, m, CH_2), 3.71−3.81 (8H, m, CH_2), 3.98−4.07 (8H, m, CH_2), 4.19 (2H, s, CH_2), 4.51 (2H, s, CH_2), 6.39−6.44 (3H, m, Ar−H), 6.45 (1H, d, J = 2 Hz, Ar−H), 6.48 (1H, t, J = 2 Hz, Ar−H), 7.04 (1H, t, J = 8 Hz, Ar−H), 7.11 (1H, d, J = 8 Hz, Ar−H); ^{13}C NMR ($CDCl_3$) δ 28.3 (6 × CH_3), 28.4 (6 × CH_3), 28.5 (6 × CH_3), 48.5−50.11 (16 × CH_2), 51.2 (CH_2), 53.4 (CH_2), 60.3 (CH_2), 67.3 (CH_2), 67.5 (CH_2), 67. 6 (CH_2), 68.8 (CH_2), 69.2 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 69.7 (CH_2), 70.73 (CH_2), 70.76 (CH_2), 70.9 (CH_2), 80.2 (2 × C), 80.3 (2 × C), 80.4 (2 × C), 101.6 (CH), 102.1 (2 × CH), 107.0 (CH), 107.2 (2 × CH), 118.47 (C), 129.7 (CH), 155.4 (C), 155.7 (C), 156.3 (2 × C), 156.7 (C), 157.1 (C), 159.9 (2 × C), 160.0 (2 × C), 161.0 (2 × C), 169.7 (C).

Preparation of 2,5,8,11,17,20,23,26-Octaoxatricyclo-[25.3.1.1^{12,16}]dotriaconta-1(30),12,14,16(32),27(31),28-hexaene-13-carboxylic Acid ({Bis-[2-oxo-2-(1,4,7,10-tetraazacyclododec-1-yl)-ethyl]carbamoyl}methyl)amide (L_2). To a stirred solution of **12** (0.059 g, 0.038 mmol) in CH_2Cl_2 (2 mL) under N_2 at room temperature was slowly added TFA (1 mL), and the solution stirred for 4 h. The reaction was quenched with 3 M NaOH (10 mL), and the organics were extracted with CH_2Cl_2 (3 × 10 mL) and further washed with brine (30 mL) before being dried over Na_2SO_4. The solvent was removed under reduced pressure to yield pure product as white solid (0.025 g, 70%): mp 83−84 °C. Elemental analysis calcd for $C_{45}H_{73}N_9O_{11}$: C, 59.00; H, 8.03; N, 13.76, found C, 58.79; H, 8.25; N, 13.67; HRMS (FAB$^+$), calcd for $C_{45}H_{74}N_9O_{11}$ [MH$^+$] *m/z* =916.5463, found 916.5457; ν_{max} (neat)/cm^{-1} 3741, 2927, 1974, 1646, 1542, 1461, 1361, 114, 817; ^{1}H NMR ($CDCl_3$) δ 2.40−3.54 (38H, m, NHs and CH_2), 3.58 (4H, s, CH_2), 3.62 (4H, s, CH_2), 3.71 (4H, t, J = 5 Hz, CH_2), 3.74 (4H, t, J = 5 Hz, CH_2), 3.99 (4H, t, J = 5 Hz, CH_2), 4.02 (4H, t, J = 5 Hz, CH_2), 4.22 (2H, d, J = 14 Hz, CH_2), 4.40 (1H, s (broad), CH_2), 4.46 (1H, s (broad), CH_2), 6.35−6.50 (5H, m, Ar−H), 7.04 (1H, t, J = 8 Hz, Ar−H), 7.12 (1H, d, J = 8 Hz, Ar−H); ^{13}C NMR ($CDCl_3$) δ 45.2 (CH_2), 45.4 (CH_2), 45.8 (CH_2), 46.4 (CH_2), 47.1 (CH_2), 47.2 (CH_2), 47.5 (CH_2), 47.7 (CH_2), 48.1 (2 × CH_2), 48.2 (CH_2), 48.3 (CH_2), 48.7 (CH_2), 48.7 (CH_2), 49.0 (CH_2), 49.4 (CH_2), 49.8 (CH_2), 51.4 (2 × CH_2), 67.3 (CH_2), 67.5 (CH_2), 67.59 (CH_2), 68.7 (CH_2), 69.3 (CH_2), 69.5 (CH_2), 69.7 (CH_2), 70.5 (CH_2), 70.8 (CH_2), 70.91 (CH_2), 70.92 (CH_2), 101.2 (CH), 102.3 (CH), 106.6 (CH), 106.9 (CH), 107.21 (CH), 118.4 (C), 129.8 (CH), 129.88 (CH), 155.9 (C), 160.01 (C), 160.02 (C), 160.9 (C), 169.9 (C), 170.2 (C), 170.25 (C).

Preparation of $[Zn_2L_2(OH_2)_2](CF_3SO_3)_4$. To a stirred solution of L_2 (0.012 g, 0.011 mmol) in anhydrous MeOH (0.5 mL) under an Ar atmosphere was added zinc triflate (0.010 g, 0.024 mmol). The reaction was stirred for 4 h at room temperature before the excess zinc triflate was filtered off through glass fiber paper and the solvent removed to yield pure product as a white solid (0.020 g, 91% yield): mp 82−83 °C. Elemental analysis calcd for $C_{49}H_{73}F_{12}N_9O_{23}S_4Zn_2$: C, 35.82; H, 4.48; N, 7.67, found C, 36.01; H, 4.59; N, 7.90; HRMS (FAB$^+$) calcd for $C_{49}H_{74}N_9O_{11}Zn_2$ [M$^+$] *m/z* = 1045.3981, found 1045.3976; ν_{max} (neat)/cm^{-1} 3752, 3397, 2927, 1977, 1716, 1691, 1658, 1495, 1365, 121, 830, 764.

Preparation of [1,4,7]Triazecane-1,7-dicarboxylic Acid Di-*tert*-butyl Ester (13). To a solution of tacn (0.16 g, 1.3 mmol) and TEA (0.23 mL, 1.8 mmol) in $CHCl_3$ (10 mL) was added $(Boc)_2$ (0.50 g, 2.3 mmol) in $CHCl_3$ (5 mL) via a syringe pump over a 4 h period and left to stir overnight at room temperature under an N_2 atmosphere. The solvent was removed under reduced pressure to yield a white solid, which was purified by silica gel chromatography (10:1, ethyl acetate/methanol) to give pure product as a colorless oil (0.27 g, 62%): HRMS (FAB$^+$) calcd for $C_{16}H_{31}N_3O_4$ [M$^+$] *m/z* = 329.2315, found 329.2315; ^{1}H NMR ($CDCl_3$) δ 1.41 (18H, s, CH_3), 2.85−2.87 (4H, m, CH_2), 3.15−3.22 (4H, m, CH_2) 3.35−3.42 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$) (rotamers) δ 28.9 (6 × CH_3), 47.7 (CH_2), 48.1 (CH_2), 48.5 (CH_2), 48.6 (CH_2), 49.9 (CH_2), 50.2 (CH_2), 50.8 (2 × CH_2), 52.0 (CH_2), 52.7 (CH_2), 52.8 (CH_2), 53.4 (CH_2), 80.0 (C), 80.1 (C), 156.1 (C), 156.4 (C).

Preparation of 4-(2-Benzyloxycarbonylaminoacetyl)-[1,4,7]triazecane-1,7-dicarboxylic Acid Di-*tert*-butyl Ester (14). To a solution of CBZ-GLY (0.13 g, 0.63 mmol) in CH_2Cl_2 (3 mL) were added sequentially DCC (0.14 g, 0.69 mmol), **13** (0.21 g, 0.63 mmol) in CH_2Cl_2 (3 mL), and DMAP (0.076 g, 0.63 mmol) under an N_2 atmosphere at room temperature and stirred overnight. The reaction solution was filtered to remove excess urea and solvent removed under reduced pressure before purification by silica gel chromatography (5:1, ethyl acetate/petrol) to give pure product as a white solid (0.26 g, 78%): mp 85−87 °C; HRMS (EI$^+$) calcd for $C_{26}H_{40}N_4O_7$ [M$^+$] *m/z* = 520.2896, found 520.2897; ν_{max} (neat)/cm^{-1} 3050, 2360, 2341, 1739, 1364, 1265, 1156, 1109, 901, 759; ^{1}H NMR ($CDCl_3$) δ 1.30−1.50 (18H, m, CH_3), 3.10−3.60 (12H, m, CH_2), 3.95 (2H, s, CH_2), 5.04 (2H, s, CH_2), 5.57−5.73 (1H, m, NH), 7.25 (5H, m, Ar−H); ^{13}C NMR ($CDCl_3$) (rotamers) δ 28.8 (6 × CH_3), 43.1 (CH_2), 43.3 (CH_2), 47.3 (CH_2), 47.6 (CH_2), 48.7 (CH_2), 49.0 (CH_2), 49.4 (CH_2), 49.8 (CH_2), 50.1 (CH_2), 50.4 (CH_2), 50.7 (CH_2), 52.2 (CH_2), 52.9(CH_2), 67.1 (CH_2), 80.5 (C), 80.7 (C), 80.8 (C), 128.3 (2 × CH), 128.4 (2 × CH), 128.8 (CH), 155.7 (C), 156.1 (C), 156.4 (2 × C).

Preparation of 4-(2-Amino-acetyl)-[1,4,7]triazecane-1,7-dicarboxylic Acid Di-*tert*-butyl Ester (15). To solution of **14** (0.25 g, 0.49 mmol) in MeOH (3 mL) was added slowly Pd/C 10% (0.20 g) under an N_2 atmosphere. The vessel was

then evacuated and filled with H_2 and left to stir overnight. After this period, the H_2 was expelled, the solution filtered through a Celite pad, and the solvent removed under reduced pressure to yield pure product as a colorless oil (0.14 g, 73%): mp 93−94 °C; HRMS (FAB$^+$) calcd for $C_{18}H_{34}N_4O_5$ [M$^+$] m/z = 386.2529, found 386.2534; ν_{max} (neat)/cm^{-1} 3366, 2924, 2855, 2363, 2340, 1693, 1515, 1461, 1409, 1364, 1320, 1246, 1032, 987, 821; ^{1}H NMR ($CDCl_3$) δ 1.30−1.50 (18H, m, CH_3), 1.59 (2H, s, NH_2), 3.10−3.60 (14H, m, CH_2); ^{13}C NMR, because of different rotamers, it was not possible to interpret the spectrum.

Preparation of 4-{2-[(2,5,8,11,17,20,23,26-Octaoxatricyclo-[25.3.1.1^{12,16}]dotriaconta-1(30),12,14,16(32),27(31),28-hexaene-13-carbonyl)amino]acetyl}-[1,4,7]triazecane-1,7-dicarboxylic Acid Di-*tert*-butyl Ester (16). To a solution of **4** (0.070 g, 0.15 mmol) in CH_2Cl_2 (2 mL) was added dropwise DCC (0.030 g, 0.15 mmol), followed by the addition of **15** (0.060 g, 0.15 mmol) in CH_2Cl_2 (2 mL) and DMAP (0.02 g, 0.3 mmol) at room temperature under an N_2 atmosphere. The reaction solution was stirred for 24 h before being filtered through glass fiber paper under suction to remove the urea side product. The reaction solution was then washed with 1 M NaOH (20 mL) and brine (50 mL) before the solvent was removed under reduced pressure and purified by silica gel column chromatography (10:1 ethyl acetate/methanol) to yield pure product **16** as a colorless oil (0.080 g, 61%): HRMS (FAB$^+$) calcd for $C_{43}H_{64}N_4O_{14}Na$ [M + Na] m/z =883.4333, found 883.4317; ν_{max} (neat)/cm^{-1} 3753, 2935, 1711, 1651, 1535, 1461, 1365, 1226, 1087, 821, 653, 543; ^{1}H NMR ($CDCl_3$) δ 1.30−1.50 (18H, m, CH_3), 3.10−3.57 (12H, m, CH_2), 3.61 (2H, d, J = 6 Hz, CH_2), 3.66 (6H, s (broad), CH_2), 3.72 (2H, t, J = 4 Hz, CH_2), 3.77 (4H, dd, J = 4 and 2 Hz, CH_2), 3.96−4.04 (6H, m, CH_2), 4.07 (2H, t, J = 5 Hz, CH_2), 4.13 (2H, t, J = 5 Hz, CH_2), 4.19 (2H, s (broad), CH_2), 6.39−6.50 (5H, m, Ar−H), 7.04 (1H,t, J = 8 Hz, Ar−H), 8.02 (1H, t, J = 8 Hz, Ar−H), 8.68−8.82 (1H, m, NH); ^{13}C NMR ($CDCl_3$) δ 28.4 (6 × CH_3), 42.4−51.1 (12 × CH_2 isomers of tacn), 67.2 (CH_2), 67.5 (CH_2), 68.5 (CH_2), 68.6 (CH_2), 69.1 (CH_2), 69.52 (CH_2), 69.58 (CH_2), 69.6 (CH_2), 69.7 (CH_2), 70.4 (CH_2), 70.6 (CH_2), 70.8 (CH_2), 71.0 (CH_2), 80.0 (C), 80.3 (C), 100.3 (CH), 102.0 (CH), 106.0 (CH), 106.8 (CH), 107.3 (CH), 129.7 (2 × CH), 133.5 (CH), 155.5 (C), 155.7 (C), 158.5 (C), 160.0 (2 × C), 162.5 (C), 164.8 (C), 169.4 (C).

Preparation of 2,5,8,11,17,20,23,26-Octaoxatricyclo-[25.3.1.1^{12,16}]dotriaconta-1(30),12,14,16(32),27(31),28-hexaene-13-carboxylic Acid (2-Oxo-2-[1,4,7]triazecan-4-yl-ethyl)amide (L_3). To a solution of **16** (0.059 g, 0.066 mmol) in CH_2Cl_2 (2 mL) under N_2 at room temperature was slowly added TFA (1 mL) and the solution stirred for 4 h. The reaction was quenched with 3 M NaOH (10 mL), and the organics were extracted with CH_2Cl_2 (3 × 10 mL) and further washed with brine (30 mL) before being dried over $NaSO_4$. The solvent was removed under reduced pressure to yield pure product as white solid (0.033 g, 75%): mp 76−77 °C; HRMS (FAB) calcd for $C_{33}H_{49}N_4O_{10}$ [MH$^+$] m/z = 661.3449, found 661.3455; ν_{max} (neat)/cm^{-1} 3741, 2927, 1708, 1646, 1538, 1457, 1365, 1226, 1087, 821; ^{1}H NMR ($CDCl_3$) δ 2.10 (2H, s, NH), 2.65 (4H, m, CH_2), 3.01 (4H, m, CH_2), 3.36 (2H, t, J = 5 Hz, CH_2), 3.46 (2H, t, J = 5 Hz, CH_2), 3.62−3.69 (8H, m, CH_2), 3.72 (2H, t, J = 5 Hz, CH_2), 3.78 (4H, t, J = 5 Hz, CH_2), 3.96−4.06 (6H, m, CH_2), 4.07 (2H, dd, J = 8 and 4 Hz, CH_2), 4.14 (2H, t, J = 4 Hz, CH_2), 4.22 (2H, d, J = 4 Hz, CH_2) 6.39−6.50 (5H, m, Ar−H), 7.04 (1H, t, J = 8 Hz, Ar−H), 8.05 (1H, d, J = 8 Hz, Ar−H), 8.84 (1H, s (broad), NH); ^{13}C NMR ($CDCl_3$) δ 42.7 (CH_2), 47.1 (CH_2), 48.0 (CH_2), 49.6 (CH_2), 49.7 (CH_2), 53.0 (CH_2), 53.6 (CH_2), 67.2 (CH_2), 67.5 (CH_2), 67.57 (CH_2), 68.6 (CH_2), 69.1 (CH_2), 69.54 (CH_2), 69.59 (CH_2), 69.7 (CH_2), 70.6 (CH_2),70.8 (CH_2), 71.0 (CH_2), 71.1 (CH_2), 100.3 (CH), 102.0 (CH), 106.0 (CH), 106.7 (CH), 107.3 (CH), 114.5 (C), 129.7 (CH), 133.5 (CH), 158.7 (C), 160.0 (2xC), 162.6 (C), 164.9 (C), 169.2 (C).

Preparation of [Cu(L_3)(OH_2)$_2$](CF_3SO_3)$_2$. To a solution of Cu(CF_3SO_3)$_2$ (0.03 g, 0.8 mmol) in MeOH (1.0 mL) was added L_3 (0.05 g, 0.8 mmol) in MeOH (0.5 mL) at room temperature under an N_2 atmosphere. The reaction solution was stirred for 1 h before an insoluble blue solid precipitated out of solution. The solid was filtered off and washed with MeOH before being slowly recrystallized from nitromethane over 24 h to form pure product as a blue solid (0.061 g, 92%): mp 110−111 °C. Elemental analysis calcd for $C_{35}H_{48}N_4O_{16}F_6S_2Cu$: C, 41.11; H, 4.73 N, 5.48, found C, 40.95; H, 4.81; N, 5.41; ν_{max} (neat)/cm^{-1} 3569 (OH stretch), 3476 (N−H stretch), 2927, 1654, 1604, 1492, 1458, 1260, 1162, 1124, 1031, 639, 575; HRMS (FAB$^+$) calcd for $C_{33}H_{48}N_4O_{10}Cu$ [M$^+$] m/z = 723.2666, found 723.2621.

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Supporting Information Available: General experimental methods, ^{1}H NMR and ^{13}C NMR spectra of all new compounds, as well as isothermal calorimetry traces, UV−vis titrations, and ES-MS results. This material is available free of charge via the Internet at http://pubs.acs.org.

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