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Selective Anion Binding in Water with Use of a Zinc(II) Dipicolylamino Functionalized Diketopiperazine Scaffold

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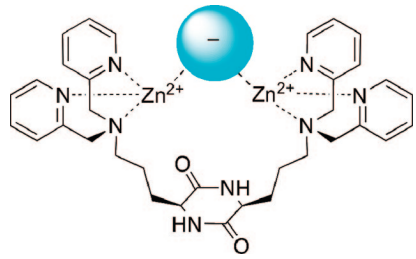

The design and synthesis of a diketopiperazine based anion receptor bearing two dipicolylamino arms complexed to zinc(II) ions is described. This receptor is readily prepared from the dipeptide precursor by a microwave-assisted intramolecular cyclization reaction. Upon addition of zinc(II), the receptor binds di- and triphosphate ions with high affinity and selectivity in aqueous solution, as determined by using a fluorescent indicator displacement assay.

Introduction

The selective recognition and sensing of anions is of significant interest. One of the reasons for this is that anions are ubiquitous in biological processes. Phosphate oxoanions such as pyrophosphate ($P_2O_7^{4-}$, PPi) and adenosine triphosphate (ATP) play important roles in metabolic and bioenergetic processes. Numerous enzymes catalyze hydrolysis of phosphate oxoanions and their derivatives, so sensors capable of discrimination between phosphate oxoanions have the potential for real time monitoring of such reactions.[1] However, selective sensing of phosphate oxoanions under physiological conditions remains a significant challenge. Recently a number of receptors capable of binding PPi in aqueous media have been reported, but strong selectivity for binding of PPi over similar anions such as ATP and ADP in water remains elusive.[2−4]

We recently described a molecular receptor with significant selectivity for PPi in aqueous solution, based on the bis[zinc(II)] complex of a large backbone modified cyclic peptide scaffold with pendant dipicolylamino (Dpa) arms (**1·Zn$_2$**, Figure 1).[4] We now report the synthesis and anion binding capabilities of a simplified version of this system in which the large cyclic peptide scaffold is replaced by a 2,5-diketopiperazine (DKP) ring (**2·Zn$_2$**). This second-generation receptor has the advantage that it can be prepared in a significantly reduced number of synthetic steps in comparison with **1·Zn$_2$** (6 vs. 15 steps from Boc-ornithine).

Results and Discussion

2,5-Diketopiperazine derivatives have been described as privileged structures for drug development.[5] This is in part due to their structural rigidity, a property that also makes them excellent scaffolds for supramolecular chemistry applications.[6]

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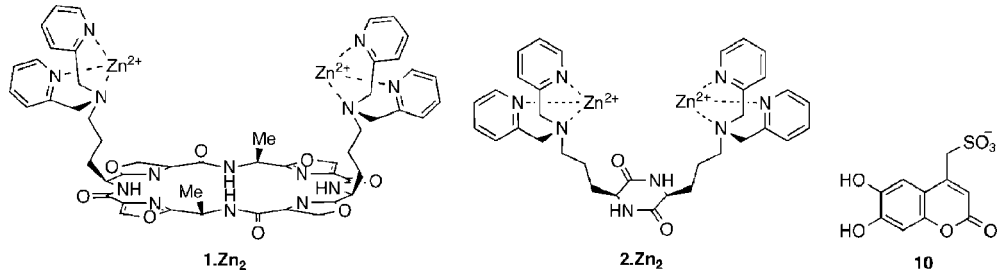
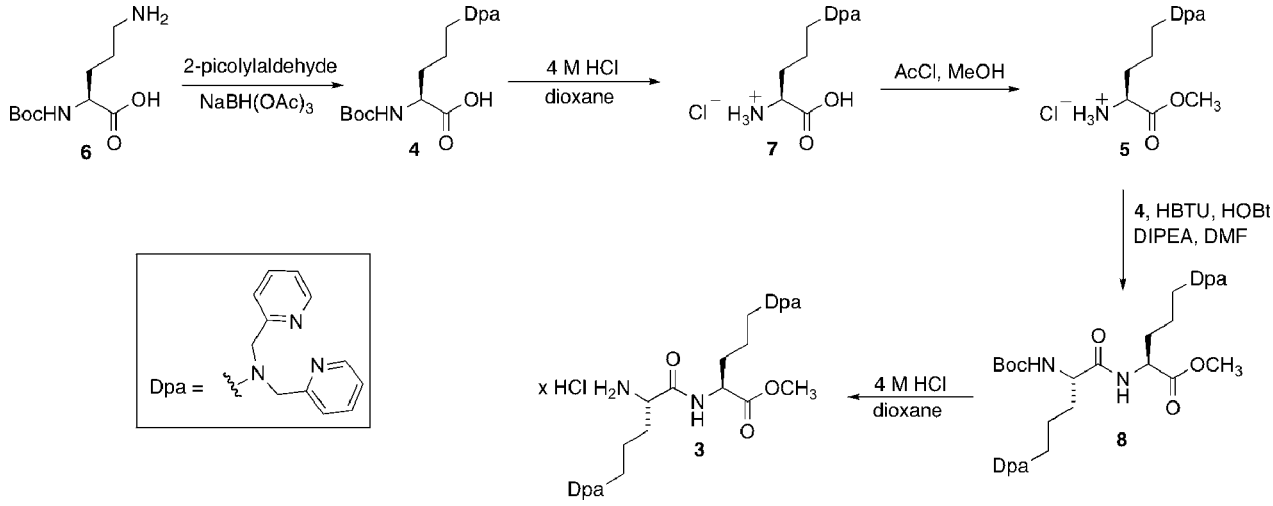


FIGURE 1. Structures of **1**·Zn_2, **2**·Zn_2, and **10**.

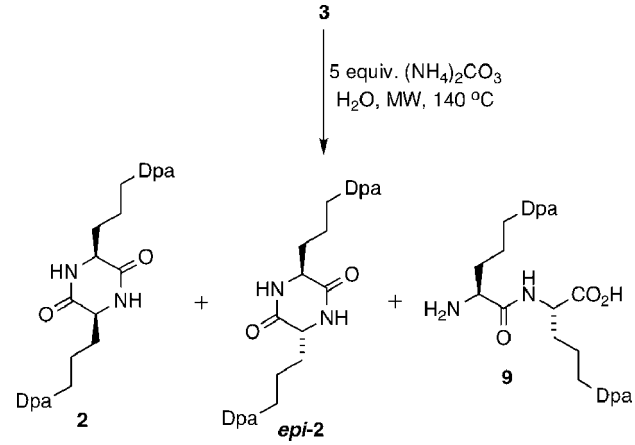
SCHEME 1. Synthesis of 3



A number of methods have been reported for the synthesis of DKPs including both intramolecular cyclization and multicomponent reactions.[7] We chose to prepare receptor **2** by cyclization of the dipeptide methyl ester **3**, which was in turn prepared from the appropriately functionalized amino acids **4** and **5** (Scheme 1). Boc-Orn(Dpa)-OH **4** was prepared by a reductive amination reaction between 2-picolylaldehyde and Boc-Orn-OH **6**.[8] This was followed by Boc-deprotection to give amine **7** as the hydrochloride salt. Amino acid **7** was then converted to the corresponding methyl ester **5** upon treatment with acetyl chloride and methanol.[9] Acid **4** and amine **5** were then coupled with HBTU in the presence of HOBt as the coupling agent to give dipeptide **8**, followed by removal of the Boc protecting group upon treatment with 4 M hydrochloric acid in dioxane to yield **3** as the hydrochloride salt.

Initial attempts to cyclize **3** by using acid or base catalysis and thermal heating were unsuccessful giving only low yields (<10%) of **2**. The use of microwave-assisted cyclization has recently been reported as an efficient method for DKP synthesis.[10] Therefore, **3** was treated with either acetic acid or ammonium carbonate in aqueous solution with microwave-assisted heating, resulting in the formation of **2** (Scheme 2). The optimum conditions (73% isolated yield of **2**) were found to be heating at 140 °C for 5 min in the presence of 5 equiv of ammonium carbonate. Longer reaction times or further equivalents of base resulted in the formation of significant amounts of the epimer *epi*-**2**, together with **2**, while use of acid to promote

SCHEME 2. Synthesis of 2



the cyclization resulted in the formation of significant amounts of dipeptide **9** in which the methyl ester has undergone hydrolysis (Table 1). The three products were readily separated by preparative reverse phase HPLC and the epimers distinguished by their optical rotation, since *epi*-**2** is a *meso*-compound. Addition of 2 equiv of $Zn(OAc)_2$ to **2** gave the bis[zinc(II)] complex **2**·Zn_2 for anion binding studies.[11]

The anion binding capabilities of **2**·Zn_2 were investigated by using an indicator displacement assay[12] with the fluorescent

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TABLE 1. Conditions for Cyclization of Dipeptide 3

reaction promoter	time (min)	conversion[a] 2	*epi*-2	9	3[b]
CH_3CO_2H (2.5 equiv)	10	17	4	18	61
CH_3CO_2H (2.5 equiv)	120	45	8	41	6
$(NH_4)_2CO_3$ (10 equiv)	10	68	26	6	0
$(NH_4)_2CO_3$ (10 equiv)	5	64	17	19	0
$(NH_4)_2CO_3$ (5 equiv)	5	75[c]	11[d]	14[e]	0
$(NH_4)_2CO_3$ (2 equiv)	5	18	1	1	80

[a] Ratios of products as determined by analytical HPLC. [b] Recovered starting material. [c] Isolated yield = 73%. [d] Isolated yield = 9%. [e] Isolated yield = 11%.

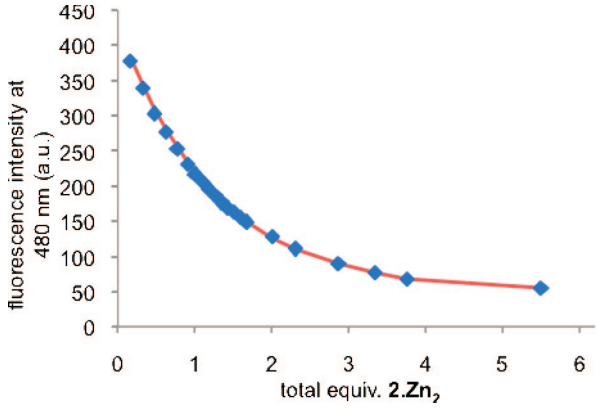

FIGURE 2. Fluorescence intensity of **10** at 480 nm in the presence of increasing amounts of **2·Zn₂**. The excitation wavelength was 347 nm.

coumarin derivative **10**. This indicator has recently been used in displacement assays to detect low concentrations of pyrophosphate under physiological conditions,[3] to detect phosphatidylserine in a bilayer membrane surface,[13] and was used in our original studies of the anion binding capabilities of **1·Zn₂**.[4] We found that **2·Zn₂** was capable of quenching the fluorescence emission of **10** (10 μM) in a concentration-dependent fashion at 37 °C in an aqueous solution (buffered at pH 7.4 with 5 mM HEPES and 145 mM NaCl to mimic physiological pH and ionic strength). An association constant log K_{in} = 5.3 ± 0.1 for binding of **10** to **2·Zn₂** was determined by fluorescence titration and subsequent nonlinear curve fitting to a standard 1:1 binding model (Figure 2).[14]

Indicator displacement assays were performed with a 1:1 receptor:indicator chemosensing ensemble by mixing equimolar amounts of **2·Zn₂** and **10** (10 μM each) in aqueous buffer solution. This solution was titrated with aliquots of the sodium salts of nitrate, sulfate, bromide, iodide, acetate, (+)-tartrate, citrate, hydrogenphosphate, PPi, phosphotyrosine, phosphothreonine, AMP, cAMP, ADP, ATP, and GTP. Fluorescence emission intensities (λ_{ex} = 347 nm, λ_{em} = 480 nm) from these titrations were analyzed by using a curve-fitting procedure based on the equilibria previously described for competition assays,[14] with our predetermined value for K_{in} to determine the binding constants (Table 2). Selectivity for di- and triphosphate derivatives (ADP, ATP, GTP, and PPi) over all other anions tested was observed, with citrate being the only nonphosphate derivative to show significant indicator displacement. Selectivity

TABLE 2. $K_{association}$ for 1·Zn₂ and 2·Zn₂ with Anionic Species

anion	log $K_{association}$ **1·Zn₂**[a]	**2·Zn₂**[b]
10	5.1(±0.1)	5.3(±0.1)
PPi	8.0(±0.1)[c]	6.0(±0.2)
ATP	5.9(±0.5)	5.3(±0.3)
GTP	nd[d]	5.3(±0.2)
ADP	5.6(±0.1)	4.9(±0.4)
citrate	5.0(±0.2)	4.8(±0.4)

[a] Values from ref 4 (pH 7.2). [b] Titrations were performed at 37 °C in aqueous solutions buffered at pH 7.4 with 5 mM HEPES in the presence of 145 mM NaCl. Each value represents the average of at least three separate experiments. [c] At pH 7.4 a value of log K = 7.9(±0.4) was obtained. [d] Not determined.

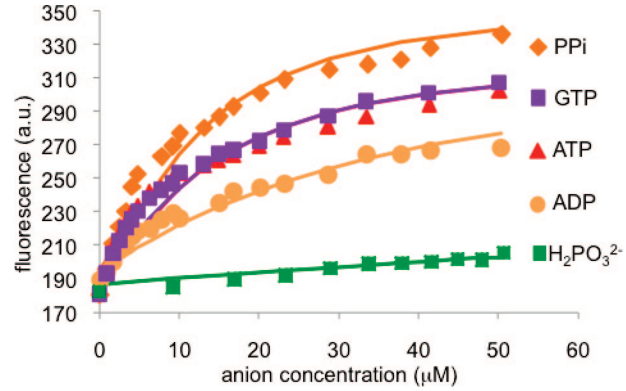

FIGURE 3. Fluorescence titration curves of **2·Zn₂**:**10** (1:1, 10 μM) with various anions at pH 7.4 (5 mM HEPES, 145 mM NaCl). Experimental points shown together with calculated curves of best fit (solid lines).

between polyphosphate derivatives is in the order PPi > ATP ≈ GTP > ADP (Figure 3). Significant selectivity for di- and triphosphate anions over monophosphate anions (hydrogenphosphate, AMP, cAMP, phosphotyrosine, and phosphothreonine) was observed. None of these monophosphate derivatives showed significant displacement of the indicator (<10% fluorescence recovery upon addition of 5 equiv of hydrogenphosphate or phosphotyrosine). Selectivity for di- and triphosphate derivatives can be attributed to the +4 charge of the receptor, together with the spatial positioning of the two binding sites.

Despite binding with similar affinity to indicator **10**, in comparison to the larger cyclic peptide derivative **1·Zn₂**,[4] **2·Zn₂** shows lower affinity for PPi (Table 2). Selectivity for PPi over ATP and ADP is also reduced for **2·Zn₂** in comparison to **1·Zn₂**. Given that these compounds differ only in the cyclic peptide scaffold, this indicates the importance of correct scaffold choice in the design of receptors for phosphate oxoanions and suggests that **1·Zn₂** is geometrically better matched to PPi than **2·Zn₂**. This is attributable to the larger distance between the two zinc(II) ions in **1·Zn₂**, which better matches the size of the pyrophosphate ion. Molecular modeling of the PPi complexes of **1·Zn₂** and **2·Zn₂** indicates that the larger cyclic peptide receptor shields PPi better from the external environment than **2·Zn₂** and this may contribute to the higher binding constant observed for **1·Zn₂** (Figure 4).

In summary, we have reported the design, synthesis, and anion binding capabilities of a diketopiperazine-based receptor **2·Zn₂**, bearing two zinc(II) dipicolylamino binding sites. Compound **2·Zn₂** shows significant selectivity for di- and triphosphate oxoanions in aqueous solution at pH 7.4. Studies directed toward

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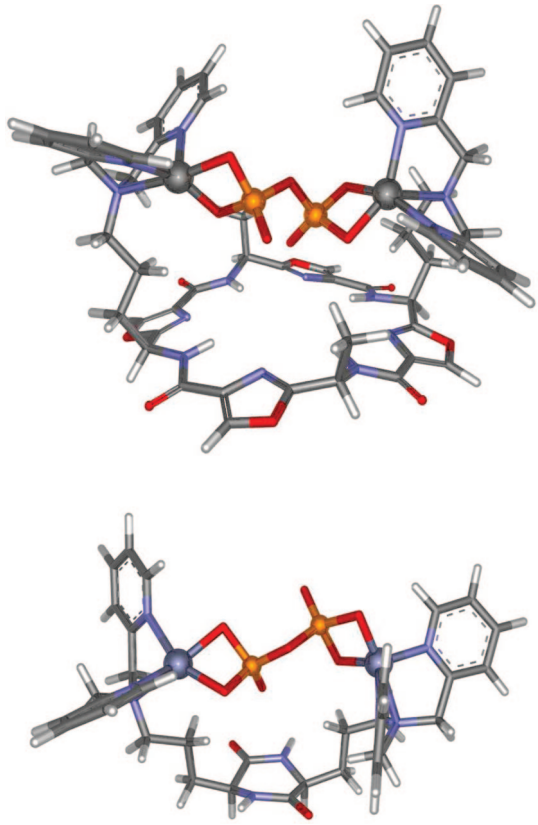

FIGURE 4. Molecular structures of the PPi complexes of **1·Zn$_2$** (top) and **2·Zn$_2$** (bottom) modeled with SPARTAN 04 (MMFF94).

understanding the differences in binding selectivity exhibited by **1·Zn$_2$** and **2·Zn$_2$** are currently in progress in our laboratories.

Experimental Section

***N*$^{\alpha}$-Boc- L-Orn-(DPA)-L-Orn(DPA)-OCH$_3$ (8).** Acid **4** (2.26 g, 5.47 mmol) was dissolved in DMF (25 mL) under an atmosphere of nitrogen. The resulting solution, HOBt·H$_2$O (1.11 g, 8.21 mmol), and HBTU (3.11 g, 8.21 mmol) were added to the amine **5** (2.58 g, 5.44 mmol) under nitrogen. DIPEA (8.53 mL, 48.96 mmol) was then added. The resulting mixture was stirred at rt under an atmosphere of nitrogen for 23 h. The solvent was removed under vacuum and the crude product dissolved in DCM (100 mL). This solution was washed with water (3 × 25 mL) and the combined water layers were back-extracted with DCM (2 × 25 mL). The organic layers were combined and washed with saturated NaHCO$_3$(aq), half-strength brine, and distilled water then dried (MgSO$_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel: 1:1 v/v CHCl$_3$/MeOH). Concentration of the appropriate fractions (R_f 0.64 on TLC using 90:9:1 v/v CHCl$_3$/MeOH/NH$_3$) afforded **8** (3.59 g, 91%) as a yellow oil: $[\alpha]_D$ −4.23 (*c* 1.0 in MeOH); IR ν_{max} (NaCl)/cm^{-1} 3267 (br, m), 1709 (s), 1435 (m), 1171 (m); ^{1}H NMR (200 MHz, MeOD) δ 8.45 (d, J = 4.3 Hz, 4H), 7.81 (m, 4H), 7.63 (m, 4H), 7.29 (m, 4H), 4.37 (m, 1H), 4.05 (m, 1H), 3.80 (s, 8H), 3.68 (s, 3H), 2.56 (t, J = 5.6 Hz, 4H), 1.94−1.58 (complex m, 8H), 1.41 (s, 9H), NH signals not observed; ^{13}C NMR (75 MHz, MeOD) δ 175.3 (C═O), 174.0 (C═O), 160.6 (C═O), 149.4 (C), 138.7 (CH), 125.0 (CH), 124.9 (CH), 123.8 (CH), 80.5 (C), 61.1 (CH$_2$), 60.9 (CH$_2$), 55.6 (CH), 55.1 (CH$_2$), 54.9 (CH$_2$), 53.5 (CH), 52.6 (CH$_3$), 31.3 (CH$_2$), 30.2 (CH$_2$), 28.7 (CH$_3$), 24.2 (CH$_2$), 5 signals obscured or overlapping; MS (ESI) *m*/*z* 725.4145 (C$_{40}$H$_{52}$N$_8$O$_5$ requires 725.4134) ([M + H]$^+$, 100%), 747 ([M + Na]$^+$, 54%); found C, 64.8; H, 7.4; N, 15.2 (C$_{40}$H$_{52}$N$_8$O$_5$·H$_2$O requires C, 64.7; H, 7.3; N, 15.1).

H$_2$N-L-Orn-(DPA)-L-Orn(DPA)-OCH$_3$ Hydrochloride (3). Dipeptide **8** (2.76 g, 3.80 mmol) was N^{α}-Boc deprotected according to the general method. Hydrochloride salt **3** was afforded in quantitative yield (3.71 g) as a cream solid: mp 93−98 °C dec; $[\alpha]_D$ +7.80 (*c* 1.0 in MeOH); ^{1}H NMR (200 MHz, MeOD) δ 8.93 (m, 4H), 8.66 (m, 4H), 8.25 (m, 4H), 8.09 (m, 4H), 4.42 (s, 8H), 4.32 (s, 1H), 4.13 (s, 1H), 3.64 (s, 3H), 2.75 (br s, 4H), 2.12−1.71 (complex m, 8H), NH$_2$ and NH signals not observed; ^{13}C NMR (75 MHz, MeOD) δ 175.5 (C═O), 173.6 (C═O), 154.5 (C), 148.44 (CH), 148.37 (CH), 142.9 (CH), 128.6 (CH), 128.5 (CH), 127.5 (CH), 57.0 (CH$_2$), 56.7 (CH$_2$), 55.5 (CH), 55.3 (CH), 53.9 (CH$_3$), 53.3 (CH$_2$), 53.0 (CH$_2$), 30.1 (CH$_2$), 29.7 (CH$_2$), 23.9 (CH$_2$), 22.3 (CH$_2$), 3 signals obscured or overlapping; MS (ESI) *m*/*z* 625.3583 (C$_{35}$H$_{44}$N$_8$O$_3$ requires 625.3609) ([M + H]$^+$, 100%), 647 ([M + Na]$^+$, 17%).

Cyclo[L-Orn(DPA)-L-Orn(DPA)] (2). Dipeptide **3** (0.135 g, 0.20 mmol) and (NH$_4$)$_2$CO$_3$ (0.098 g, 1.02 mmol) were dissolved in distilled water (11.0 mL). The resulting solution was MW heated at 140 °C for 5 min in a sealed vessel. Power was maintained below 500 W and pressure below 20 barr. After cooling, the solvent was removed on the freeze-dryer then the crude product was purified via RP-HPLC to give 3 fractions A, B, and C. Concentration of fraction A (t_R 32.50 min) afforded diketopiperazine **2** (0.093 g, 73%) as a pale yellow oil: $[\alpha]_D$ −6.63 (*c* 0.5 in MeOH); IR ν_{max} (NaCl)/cm^{-1} 3111 (br, w, NH), 1682 (s, C═O); ^{1}H NMR (300 MHz, MeOD) δ 8.75 (d, J = 5.0 Hz, 4H), 8.13 (dd, J = 7.8, 7.8 Hz, 4H), 7.72 (d, J = 7.8 Hz, 4H), 7.64 (m, 4H), 4.52 (s, 8H), 4.03 (s, 2H), 3.16 (t, J = 6.0 Hz, 4H), 1.88−1.76 (m, 8H), NH signals not observed; ^{13}C NMR (75 MHz, MeOD) δ 170.4 (C═O), 152.7 (C), 148.8 (CH), 141.4 (CH), 126.2 (CH), 125.9 (CH), 58.2 (CH$_2$), 55.6 (CH), 55.1 (CH$_2$), 31.5 (CH$_2$), 21.6 (CH$_2$); MS (ESI) *m*/*z* 593.3342 (C$_{34}$H$_{40}$N$_8$O$_2$ requires 593.3347) ([M + H]$^+$, 97%), 615 ([M + Na]$^+$, 18%), 297 ([M + 2H]$^{2+}$, 100%); found C, 42.95; H, 3.9; N, 8.7 (C$_{34}$H$_{40}$N$_8$O$_2$·5TFA·4H$_2$O requires C, 42.8; H, 4.3; N, 9.1).

Concentration of fraction B (t_R 28.65 min) afforded *epi*-**2** (0.012 g, 9%) as a pale yellow oil: $[\alpha]_D$ −0.20 (*c* 1.0 in MeOH); ^{1}H NMR (200 MHz, MeOD) δ 8.79 (d, J = 5.1 Hz, 4H), 8.26 (dd, J = 7.8, 7.8 Hz, 4H), 7.84−7.72 (m, 8H), 4.46 (s, 8H,), 4.00 (br s, 2H), 3.03 (m, 4H), 1.98−1.72 (m, 8H), NH signals not observed; ^{13}C NMR (75 MHz, MeOD) δ 170.2 (C═O), 152.9 (C), 148.3 (CH), 141.9 (CH), 126.3 (CH), 126.0 (CH), 58.2 (CH$_2$), 55.7 (CH), 55.2 (CH$_2$), 30.9 (CH$_2$), 21.1 (CH$_2$); MS (ESI) *m*/*z* 593.3343 (C$_{34}$H$_{40}$N$_8$O$_2$ requires 593.3347) ([M + H]$^+$, 97%), 615 ([M + Na]$^+$, 18%), 297 ([M + 2H]$^{2+}$, 100%).

Concentration of fraction C (t_R 26.93 min) afforded **9** (0.015 g, 11%) as a yellow oil: $[\alpha]_D$ +5.67 (*c* 0.8 in MeOH); ^{1}H NMR (200 MHz, MeOD) δ 8.75 (d, J = 5.0 Hz, 4H), 8.18 (m, 4H), 7.78−7.65 (m, 8H), 4.50 (s, 4H), 4.45 (s, 4), 4.25 (s, 1H), 3.97 (s, 1H), 3.10 (m, 4H), 1.97−1.75 (m, 8H,), NH$_2$, NH, and OH signals not observed; ^{13}C NMR (75 MHz, MeOD) δ 174.3 (C═O), 170.0 (C═O), 153.2 (C), 152.8 (C), 148.1 (CH), 148.2 (CH), 142.2 (CH), 142.4 (CH), 126.3 (CH), 126.1 (CH), 58.1 (CH$_2$), 57.7 (CH$_2$), 55.6 (CH), 55.1 (CH), 53.7 (CH$_2$), 53.2 (CH$_2$), 29.7 (CH$_2$), 29.5 (CH$_2$), 22.7 (CH$_2$), 21.0 (CH$_2$), 2 signals obscured or overlapping; MS (ESI) *m*/*z* 611.3407 (C$_{34}$H$_{42}$N$_8$O$_3$ requires 611.3453) ([M + H]$^+$, 100%), 306 ([M + 2H]$^{2+}$, 32%); found C, 48.5; H, 4.5; N, 11.0 (C$_{34}$H$_{42}$N$_8$O$_3$·3TFA·2H$_2$O requires C, 48.6; H, 5.0; N, 11.3).

Cyclo[L-Orn(DPA)-L-Orn(DPA)] Bis[zinc(II)] Complex (2·Zn$_2$). An aqueous solution of zinc acetate dihydrate (0.0128 M, 0.996 mL, 0.0127 mmol) was added to a solution of **2** (0.00377 g, 0.00636 mmol) in deuterium oxide (0.700 mL) and the mixture was stirred for 5 min. The solution was then dried under vacuum, affording the bis[zinc(II)] complex **2·Zn$_2$** as a dark yellow oil: ^{1}H NMR (300 MHz, D$_2$O) δ 8.65 (d, J = 5.1 Hz, 4H), 8.07 (m, 4H), 7.60 (m, 8H), 4.30 (d, J = 16.0 Hz, 4H), 4.12 (d, J = 16.0 Hz, 4H), 3.99 (br s, 2H), 2.72 (m, 4H), 2.07 (s, 12H,) 1.66−1.42 (m, 8H), NH signals not observed; MS (ESI) *m*/*z* 359 ([M − 2H]$^{2+}$, 83%), 359.5

(32), 360 (100), 360.5 (57), 361 (96), 361.5 (41), 362 (45), 362.5 (19), 363 (18), 363.5 (7).

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Supporting Information Available: General experimental procedures and experimental details for compounds **5** and **7** and ^{1}H and ^{13}C NMR spectra of compounds **5**, **8**, **3**, **2**, *epi*-**2**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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