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Carbohydrate Recognition through H-Bonding and CH−π Interactions by Porphyrin-Based Receptors

Jung-Deog Lee, Yeon-Hwan Kim, and Jong-In Hong*

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, Korea

jihong@snu.ac.kr

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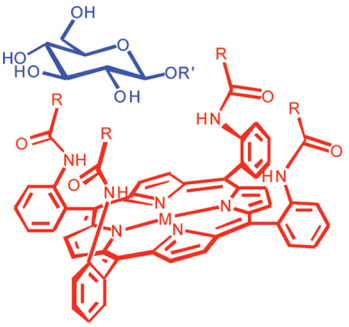

R = $NHCH_2C_6H_5$ (**1a**, **1b**)
NHC_6H_5 (**1c**, **1d**)
$NHC_6H_4COOCH_3$ (**1e**, **1f**)
$OCH_2C_6H_5$ (**1g**)
$CH_2CH_2C_6H_5$ (**1h**)
M = H_2 (**1a**, **1c**, **1e**)
Zn (**1b**, **1d**, **1f**, **1g**, **1h**)
R' = $(CH_2)_7CH_3$

Porphyrin-based synthetic receptors containing urea, carbamate, or amide groups were designed and synthesized for carbohydrate recognition. The receptors have equatorially and convergently directed hydrogen-bonding sites into which the urea, carbamate, or amide groups were introduced above the porphyrin plane. The receptors exhibited remarkable affinities to pyranoside/furanoside derivatives in organic media, demonstrating not only the importance of multiple hydrogen-bonding interactions but also CH−π interactions in carbohydrate recognition. Among the three hydrogen-bonding groups, urea NHs were used as the strongest H-bonding donors for sugar hydroxyl oxygens, and the porphyrin plane was used for mimicking CH−π interactions with sugar CHs, which are found in sugar-binding proteins. The binding interactions between the artificial receptors and carbohydrates were elucidated by various spectroscopic analyses such as UV−vis titration, ^{1}H NMR titration, CD measurement, and computer-assisted modeling.

Introduction

Carbohydrate recognition by artificial receptors has been a challenging subject for synthetic chemists in the field of supramolecular chemistry.[1] This is partly due to the various cellular recognition processes of oligosaccharides on cell surfaces[2] and partly due to the 3D complexity that is present even in monosaccharide structures.[3] From the X-ray crystallographic structures of sugar−protein complexes, it has been found that the multiple hydrogen bonds in the hydrophobic pocket of a protein play an important role in protein−carbohydrate interactions.[4] Numerous attempts have been made to develop artificial carbohydrate receptors.[5,6] However, most effective receptors working in aqueous media still depend on the formation of a boronic acid ester between the boronic acid of the receptors and the diol of the carbohydrates.[5b,e,f,p,q,s,t] On the other hand, a few outstanding studies have been reported on carbohydrate recognition through hydrogen-bonding interaction.[5c,h,n,u,w,6b,6j,6n] However, these studies have shown a fairly reduced recognition ability in an aqueous solution because carbohydrates are hydrophilic and highly solvated in water.[5g,j,k,n,u,v] Therefore,

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an effective method for mimicking the carbohydrate recognition in nature is still needed to develop artificial carbohydrate receptors.

Recently, we reported the synthesis of aspartate urea-appended porphyrins that displayed the highest current levels of binding for octyl pyranosides in chloroform.[7] In addition, Bonar-Law and co-workers found that analogous urea-appended porphyrins exhibited excellent affinity for various carbohydrates.[8] In the present study, we have conducted systematic studies to develop a method that can be used to control the binding affinities by varying the functional groups on the periphery of the porphyrin and elucidated the binding modes using various spectroscopic techniques and computer-assisted modeling. In this paper, we describe the syntheses and binding properties of porphyrin-based receptors **1a**−**h** with regard to monosaccharides and the binding modes between the selected receptors and monosaccharides.

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Results and Discussion

Design and Synthesis of Porphyrin-Based Receptors. As envisioned from the X-ray structures of sugar−protein complexes, an effective approach to carbohydrate recognition is to surround the polar hydroxyl groups of carbohydrates with complementary hydrogen-bonding groups and introduce aromatic surfaces into the receptor against carbohydrate CH moieties. This can be effectively realized in porphyrin-based carbohydrate receptors with a preorganized complementary and convergent arrangement of hydrogen-bond donor and acceptor functionalities in the αααα-positions of the porphyrin, along with a rigid platform (porphyrin skeleton) providing aromatic surfaces for CH−π interaction. Eight porphyrin-based receptors were prepared for carbohydrate recognition, as illustrated in Chart 1. In a series of urea-appended porphyrins, benzyl groups were introduced in **1a** and **1b**, phenyl groups in **1c** and **1d**, and methyl benzoate groups in **1e** and **1f**. By varying the attached groups in this way, we could investigate how the binding properties of porphyrins were affected by the attached groups. Carbamate-appended porphyrin **1g** and amide-appended porphyrin **1h** were also prepared to compare the hydrogen-bonding ability of a urea group with that of carbamate and amide groups toward carbohydrates.

The receptors were synthesized from *meso*-αααα-tetrakis-(*o*-aminophenyl)porphyrin, which was prepared by Collman's method,[9a] followed by Lindsey's atropisomerization method.[9b] Urea-appended porphyrins were synthesized from the reaction between *meso*-αααα-tetrakis(*o*-aminophenyl)porphyrin and appropriate isocyanates that were commercially available or generated in situ.[10] Commercially available carbobenzoxy chloride and phenylpropionyl chloride were utilized for the preparation of **1g** and **1h**, respectively. Zinc porphyrins were prepared in quantitative yields from free-base porphyrins and $Zn(OAc)_2$ in a mixture of chloroform and methanol. All of the compounds were characterized by ^{1}H NMR, ^{13}C NMR, high-resolution mass spectrometry, and elemental analysis.

Binding Affinities of the Receptors for Carbohydrates. UV−vis absorption experiments in chloroform showed that the Soret band of the receptors underwent a slight shift or was changed in intensity as the carbohydrates were bound in the inner space of the receptors. Without adding a large excess of carbohydrate, clear isosbestic points were observed, which indicates the existence of two states through the formation of a 1:1 complex. This was also confirmed by a Job's plot in the ^{1}H NMR experiments. The apparent association constants for the formation of the complexes of receptors (**1a**−**h**) and various carbohydrates (**2**−**6**) were estimated by fitting the curve of the absorbance at λ_{max} as a function of the change in carbohydrate concentration to a 1:1 binding isotherm (Table 1).

As shown in Table 1, the receptors showed high affinities for carbohydrates, and a general trend was seen in their affinities for guests in the order **4** ≈ **2** > **3** > **5** > **6**. Uridine and thymidine derivatives **5** and **6** having a ribose unit

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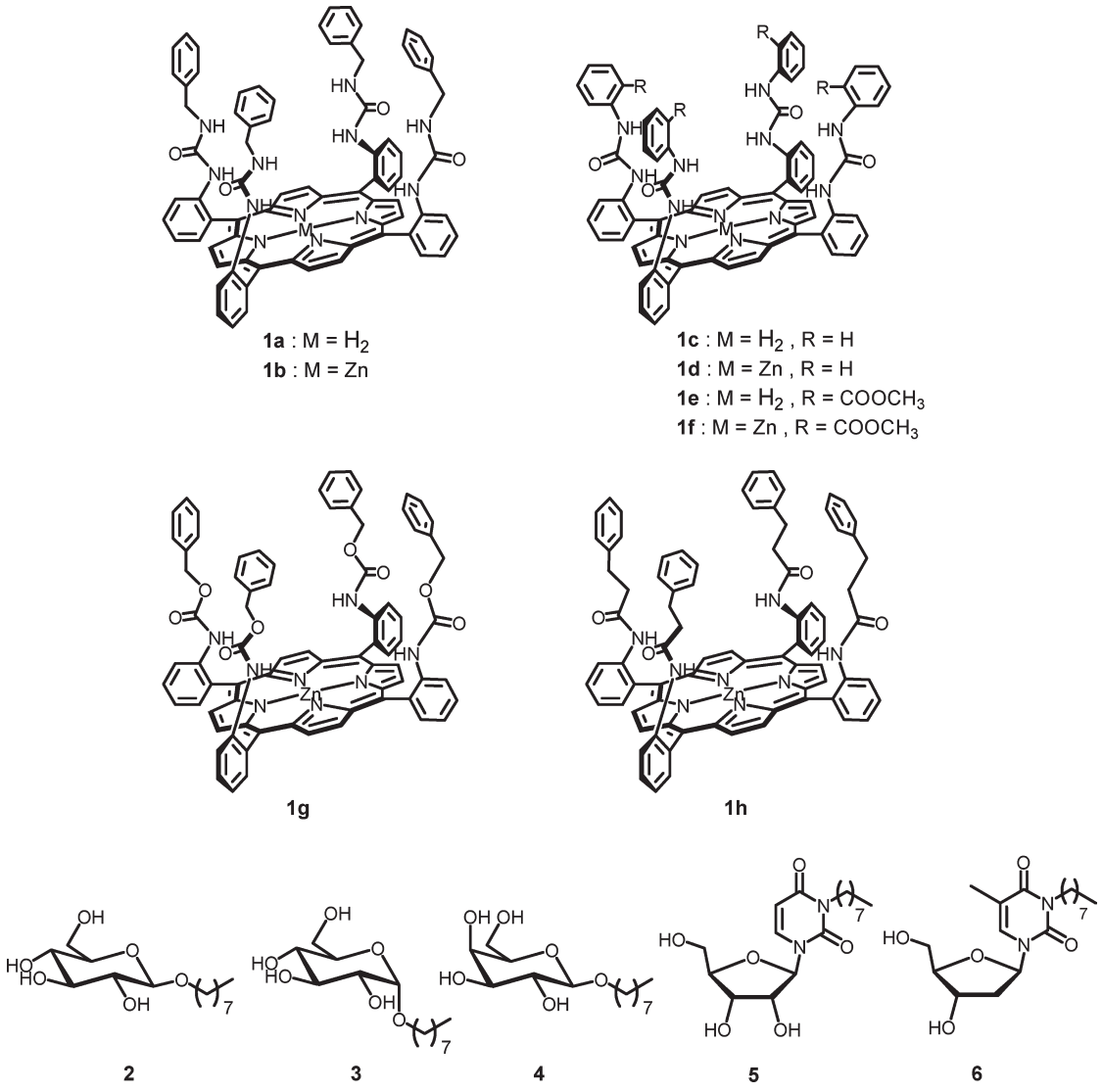
(10) Compounds **1c** and **1d** were previously synthesized and used as anion receptors by Burns' group: Jagessar, R. C.; Shang, M.; Scheidt, W. R.; Burns, D. H. *J. Am. Chem. Soc.* **1998**, *120*, 11684–11692. **1c**: HRMS calcd for $C_{72}H_{55}N_{12}O_4$ *m*/*z* 1151.4469, found 1151.4447. **1d**: HRMS calcd for $C_{72}H_{52}N_{12}O_4Zn$ *m*/*z* 1212.3526, found 1212.3536.

CHART 1



showed less affinity than the 6-membered carbohydrates possessing four hydroxyl groups. As expected, the inner space of the receptors had appropriately arranged hydrogen-bonding sites, which were able to recognize the hydroxyl groups of the carbohydrates through complementary interaction. A comparison of the free base porphyrins (**1c** and **1e**) with the corresponding zinc porphyrins (**1d** and **1f**) indicated that metal insertion played an ambiguous role in the binding of guests. This was presumably because two factors compete with each other in the binding of guests. The first is the fact that zinc porphyrins show the favorable effect of Lewis acid−Lewis base interaction (Zn···O coordination). The other is the fact that metal insertion caused less conformational freedom in the binding site and had more difficulty in adjusting to different guest structures, which resulted in decreased or similar affinities for guests in comparison with metal free receptors. Although several zinc porphyrins were reported to have better binding affinities,[11c] urea-appended porphyrins did not show significant improvements in their binding properties.[7,8] The binding affinities of **1b**, **1d**, and **1f** toward various carbohydrates were found to decrease in the order **1b** > **1d** > **1f**. Therefore, a possible explanation is that steric hindrance in the binding of guests increased in the order **1b** < **1d** < **1f** because of the different functional groups attached at the urea and prohibited guest sugars from properly interacting with H-bonding groups within the binding cavity, although the *o*-carbomethoxy group of **1f** would have provided more H-bonding sites. As for **1f**, the ester groups were considered to have formed either intermolecular hydrogen bonds with the hydroxyl groups of the guest or intramolecular hydrogen bonds with the NH of urea, competing with the intermolecular hydrogen-bonding interaction between the urea and guest. A systematic binding study with various receptors revealed that the ester group did not have a favorable effect on the hydrogen bonding with guests. The same trend was observed when compared with **1c** and **1e**. We were also able to investigate the hydrogen-bonding ability of urea, carbamate, and amide toward monosaccharides. Comparing **1b**, **1g**, and **1h**, it can be clearly seen that urea was the most effective functional group forming hydrogen bonds with guests, and more insight about the binding was obtained from the molecular modeling (vide infra).

TABLE 1. Binding Constants (K_a, M^{-1}) and Free Energy Changes (ΔG^o, kcal·mol^{-1}) from UV−vis Titrations of 1a−h with *n*-Octyl Pyranosides/Furanosides (2−6) in $CHCl_3$ at 298 K[a]

	2		3		4		5		6	
	K_a	$-\Delta G^o$	K_a	$-\Delta G^o$	K_a	$-\Delta G^o$	K_a	$-\Delta G^o$	K_a	$-\Delta G^o$
1a	ND[b]		ND[b]		ND[b]		ND[b]		ND[b]	
1b	$5.7(\pm0.68^c)\times10^5$	7.8	$4.8(\pm0.29)\times10^4$	6.4	$6.8(\pm0.48)\times10^5$	8.0	$2.5(\pm0.45)\times10^4$	6.0	$3.2(\pm0.22)\times10^3$	4.8
1c	$9.7(\pm2.0)\times10^4$	6.8	$3.1(\pm0.49)\times10^4$	6.1	$2.2(\pm0.25)\times10^5$	7.3	$2.7(\pm0.20)\times10^4$	6.0	$3.5(\pm0.33)\times10^3$	4.8
1d	$1.7(\pm0.16)\times10^4$	5.8	$6.9(\pm1.2)\times10^3$	5.2	$3.8(\pm0.37)\times10^4$	6.2	$1.0(\pm0.046)\times10^3$	4.1	$1.2(\pm0.21)\times10^3$	4.2
1e	$3.2(\pm0.16)\times10^3$	4.8	$8.9(\pm1.6)\times10^2$	4.0	$1.2(\pm0.19)\times10^3$	4.2	$9.8(\pm1.9)\times10^2$	4.1	$2.2(\pm0.28)\times10^2$	3.2
1f	$4.4(\pm0.43)\times10^3$	5.0	$2.0(\pm0.14)\times10^3$	4.5	$3.2(\pm0.38)\times10^3$	4.8	ND[b]		$7.1(\pm0.58)\times10$	2.5
1g	$6.2(\pm0.52)\times10^2$	3.8	$4.7(\pm0.32)\times10^2$	3.6	$1.2(\pm0.042)\times10^3$	4.2	$3.9(\pm0.16)\times10^2$	3.5	$5.8(\pm0.68)\times10$	2.4
1h	$3.8(\pm0.46)\times10^2$	3.5	$1.9(\pm0.19)\times10^2$	3.1	$1.3(\pm0.015)\times10^3$	4.2	$8.4(\pm0.30)\times10$	2.6	$4.9(\pm0.20)\times10$	2.3

[a]Experimental conditions: [**1b**] = 2.4 μM for all guests, [guest] = 0.00037−0.029 mM for **2**, 0.0068−0.38 mM for **3**, 0.00046−0.052 mM for **4**, 0.011−0.2 mM for **5**, and 0.12−2.9 mM for **6**; [**1c**] = 2.1 μM for **2**, **3**, and **6**, 2.0 μM for **4** and **5**, [guest] = 0.0003−0.078 mM for **2**, 0.0013−0.33 mM for **3**, 0.00073−0.19 mM for **4**, 0.0034−0.87 mM for **5**, and 0.005−1.3 mM for **6**; [**1d**] = 1.7 μM for all guests, [guest] = 0.00077−0.2 mM for **2**, 0.0065−1.7 mM for **3**, 0.0018−0.46 mM for **4**, 0.031−8.0 mM for **5**, and 0.24−6.2 mM for **6**; [**1e**] = 2.0 μM for all guests, [guest] = 0.019−4.9 mM for **2**, 0.03−7.8 mM for **3**, 0.024−6.1 mM for **4**, 0.017−4.3 mM for **5**, and 0.038−9.8 mM for **6**; [**1f**] = 1.75 μM for **2** and **4**, 1.74 μM for **3**, 1.76 μM for **6**, [guest] = 0.019−4.8 mM for **2**, 0.014−3.6 mM for **3**, 0.019−4.9 mM for **4**, and 0.060−15 mM for **6**; [**1g**] = 1.9 μM for **2** and **4**, 2.0 μM for **3**, **5**, and **6**, [guest] = 0.32−5.9 mM for **2**, 1.0−17 mM for **3**, 0.066−6.1 mM for **4**, 0.65−11 mM for **5**, and 0.94−17 mM for **6**; [**1h**] = 2.1 μM for **2**, **3**, and **4**, 2.0 μM for **5** and **6**, [guest] = 0.29−12 mM for **2**, 1.1−19 mM for **3**, 0.21−9.1 mM for **4**, 0.88−16 mM for **5**, and 1.4−25 mM for **6**. Each host concentration was determined from the standard curve using the Beer−Lambert law. [b]ND = not determined due to little change of the absorbance. [c]Standard deviations in K_a.

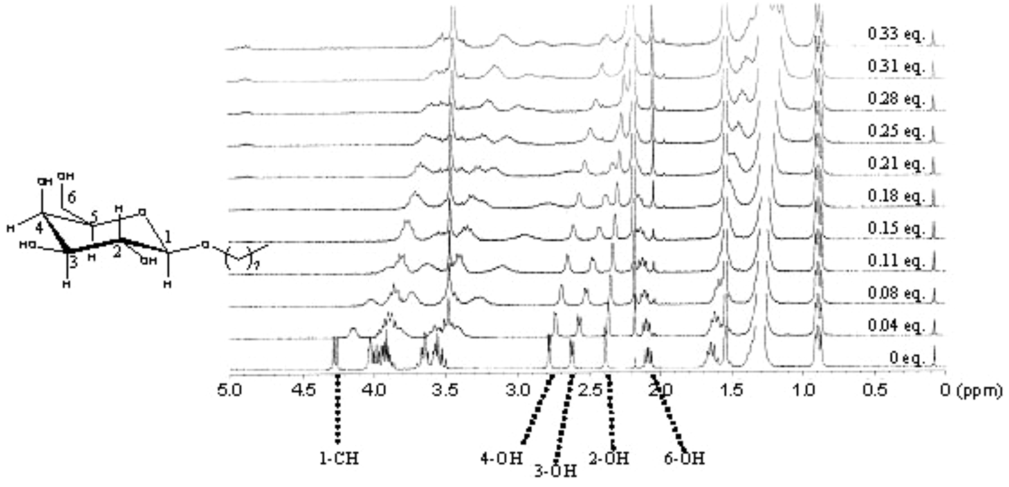


FIGURE 1. ^{1}H NMR spectra of a $CDCl_3$ solution of *n*-octyl β-D-galactopyranoside (**4**) in the presence of **1e** (0.04 equiv to 0.33 equiv from bottom to top) in $CDCl_3$ at 298 K.

^{1}H NMR Study of Binding and Computer-Assisted Conformational Searches. In order to elucidate the intermolecular binding mode, we performed ^{1}H NMR titrations of the receptors with various guests in $CDCl_3$. As the equivalent of carbohydrate increased, the chemical shift of the urea NHs moved toward the downfield region (see Figure S1 (Supporting Information) for the ^{1}H NMR titration of **1f** with **2** in $CDCl_3$ and the ^{1}H NMR titration of **1a** with **3** in $CDCl_3$). This implies that the urea NH protons of the receptors participate in hydrogen bonding with the hydroxyl oxygens of carbohydrates.

To investigate the binding mode in more detail, the complexation-induced shifts (CIS) of the guests were estimated by the inverse ^{1}H NMR titrations of various guests with receptors **1e** and **1f** in $CDCl_3$ (Figure 1 and Table 2). The CIS values increased linearly as the fraction of the carbohydrate bound by the receptor was increased, and the values determined by extrapolation to 100% complexation are listed in Table 2. CIS values are known to provide valuable information on the binding mode.[11] Two opposing anisotropic effects should be taken into account to interpret the CIS values for various carbohydrates upon complexation with the receptors: upfield shifts due to the ring current of the porphyrin when carbohydrate protons are located above the center of the porphyrin plane and potential downfield shifts of the OH protons if they participate in hydrogen bonds with urea groups. Table 2 indicates that the resonance of the 1-H proton of the guest underwent the largest upfield shift for all of the carbohydrates, which is ascribed only to the effect of the ring current. Therefore, the 1-H proton is expected to exist above the porphyrin plane. On the other hand, most of the OH protons were shifted only slightly upfield, perhaps because the hydrogen bonding compensated for the ring current effect. However, the 6-OH proton experienced a downfield shift upon the addition of **1e**, which indicates that the hydroxyl proton should be involved in hydrogen-bonding interaction with **1e**. Further, the CH protons in the ring of **4** also moved upfield, indicating that **4** is positioned

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TABLE 2. ^{1}H NMR Complexation-Induced Shifts (CIS, Δδ/ppm) of Guests upon the Addition of 1e and 1f in $CDCl_3$ at 298 K[a]

	Δδ$_{sat}$ (Δδ$_{max\ obs}$) by **1e**/**1f**				
	2	**3**	**4**	**5**	**6**
1-H	−3.4 (−0.68)/ −0.98 (−0.45)	−2.9 (−0.84)/ −1.2 (−0.27)	−3.6 (−0.38)/−1.8 (−0.41)	−2.9 (−0.93)/UP	−3.0 (−0.68)/ −2.7 (−0.60)
2-OH	ND[b]/ND	−0.43 (−0.13)/ +0.69 (+0.16)	−0.51 (−0.16)/−0.70 (−0.15)	−1.4 (−0.29)/UP	
3-OH	−2.2 (−0.34)/ND	−1.8 (−0.53)/ −1.4 (−0.43)	−1.4 (−0.29)/−3.1 (−0.59)	−1.9 (−0.61)/−1.3 (−0.40)	−0.68 (−0.16)/DN
4-OH	−2.5 (−0.39)/ND	+0.016 (+0.0086)/ −1.3 (−0.28)	−1.2 (−0.39)/−1.6 (−0.56)		
5-OH				+0.12 (+0.037)/+0.17 (+0.056)	DN/0
6-OH	ND/+0.27 (+0.13)	−1.4 (−0.32)/UP[c]	+0.33 (+0.061)/DN[c]		

[a] Δδ$_{sat}$ was obtained by extrapolating to 100% complexation from the CIS values at 0−30% complexation (Δδ$_{max\ obs}$). Signal assignments were made on the basis of the ^{1}H−^{1}H COSY experiments and reference. [b] ND = not determined due to the broadening or overlap of peaks. [c] UP = upfield shift, DN = downfield shift, CIS values could not be calculated because of the broadening or overlap of peaks, but the tendency of the shift could be estimated.

above the porphyrin plane of **1e**. This was supported by the molecular modeling study (see Figure 2). When **4** was bound by **1e**/**1f**, the patterns of the CIS values were similar to **2**, except that the CIS value of axial 4-OH was less than that of equatorial 3-OH. These results suggest that **2** and **4** have similar binding modes, but the axial 4-OH of **4** is expected to be farther from the porphyrin plane than the equatorial 4-OH of **2**. In the case of **3**, a different trend was seen, i.e., the 4-OH for **1e** and 2-OH for **1f** were shifted downfield, while 6-OH was shifted upfield in a manner opposite to **2** and **4**. Clearly, the α-anomer **3** is likely to have a different binding mode from **2** and **4**. In addition, the CIS values suggest that the carbohydrate portion of **5** and **6**, rather than the base portion, is located near and above the porphyrin plane, hydrogen bonded with urea NHs.

The calculated structures[13] revealed the multiple hydrogen bonds between the hydroxyl groups of the carbohydrate and the urea NH or ester C=O of the receptor (Figure 2). When **2** was bound by **1e**, the OH groups of **2** were near the center of the porphyrin plane, forming hydrogen bonds with the urea NH and/or ester C=O of **1e** (Figure 2). As mentioned previously, the 6-OH resonance of **2** was shifted downfield as bound by **1f** (Table 2), presumably because the 6-OH was hydrogen bonded to the ester C=O of **1f** at a distance from the porphyrin plane, which was revealed by the molecular modeling study. The carbohydrate is located above the porphyrin plane in the inner space of the receptor, which is almost in accordance with the CIS values obtained from the inverse ^{1}H NMR titration experiments. From the binding model and the unusual chemical shift (about 10 ppm) of one of the two urea NHs in the complexes in $CDCl_3$, it is likely that the ester C=O of **1e**/**1f**, which was introduced as a hydrogen-bonding acceptor to the ortho position of the urea NH, preferred an intramolecular hydrogen bond with the urea NH to an intermolecular hydrogen bond with the hydroxyl groups of the carbohydrate. This preference reduced the ability of the hydrogen bond donor of the urea NH. In Table 1, **1e** and **1f** show weaker affinities to various carbohydrates than **1c** and **1d** without the ester group. This

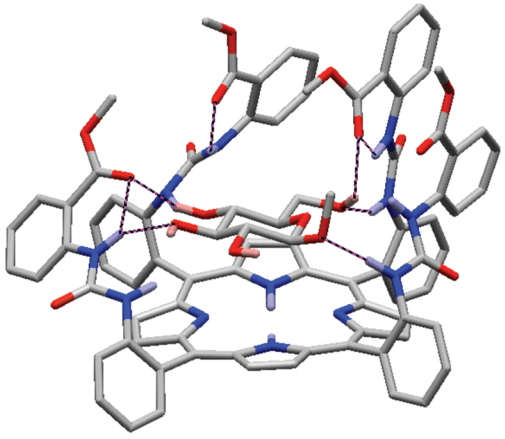

FIGURE 2. Baseline conformation resulting from a 1000-step Monte Carlo molecular mechanics study of **1e** plus **2** modeled as the analogous methyl β-D-glucoside. The five intermolecular and three intramolecular hydrogen bonds are shown as broken lines.

suggests that the number of hydrogen-bonding groups does not always determine the strength of the binding affinity. Instead, the proper orientation of the hydrogen-bonding groups of the host would be more desirable for strong binding to the guest.

We also performed computer-assisted conformational searches to investigate how urea groups make up the effective binding sites for carbohydrates on the porphyrin plane. Three porphyrins were chosen for the systematic study: **1a** and the free base porphyrins of **1g** and **1h**.[12] As shown in Figure S4 (Supporting Information), the calculated structures reveal the multiple hydrogen bonds between the hydroxyl groups of the carbohydrate and functional groups of the receptors.[13] The urea-appended porphyrin binds a carbohydrate with eight intermolecular hydrogen bonds, six of which are contributed by three bifurcated hydrogen bonds (Figure S4-aSupporting Information). On the other hand, the complex between the carbamate-appended porphyrin and carbohydrate could be potentially stabilized by five intermolecular hydrogen bonds, and NH···OH and OH···OCONH were shown as possible binding interactions (Figure S4-b, Supporting Information). Finally, only three hydrogen bonds were shown in the complex between the amide-appended porphyrin and carbohydrate (Figure S4-c, Supporting Information). From the calculated structures, it could be

(12) Although zinc porphyrins were used for UV−vis titration, free base porphyrins were selected for this study because a general optimized force field for Zn(II) does not exist.

(13) Conformational searches were performed with MacroModel 7.0, Amber* force field in chloroform solvent, Monte Carlo conformational searches, 1000 steps: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

inferred that the urea-appended porphyrin is able to form the most stabilized structure with the highest number of hydrogen bonds contributed by bifurcated hydrogen bonding. In addition, this study is considered to indirectly support the result from UV−vis titration that **1b** is much superior to **1g** and **1h** for carbohydrate recognition.

Induced Circular Dichroism (ICD) Study of Binding. The binding event was also confirmed by circular dichroism (CD). When excess *n*-octyl β-D-galactoside (**4**) was added to the CD silent receptor **1f**, the complex showed distinct biphasic CD in the Soret band with a positive Cotton effect at a short wavelength and negative Cotton effect at a long wavelength (Figure 3).

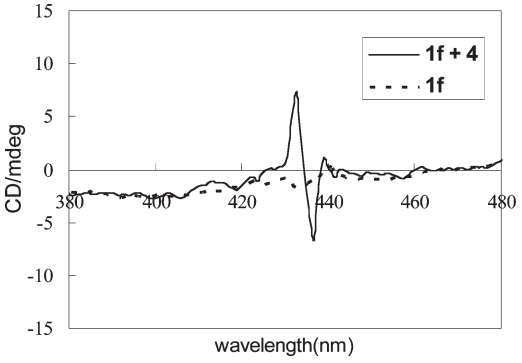

FIGURE 3. Circular dichroism induced in receptor **1f** by *n*-octyl β-D-galactoside (**4**) in $CHCl_3$ at 288 K: [**1f**] = 5.0×10^{-6} M and [**4**] = 1.0×10^{-3} M.

This result indicates that the relative orientations of the C−O and O−H moieties of the carbohydrate guest, which are located near the porphyrin plane, induced distinct CD spectra, as similar results were reported by Shinkai and co-workers and Mizutani et al., respectively.[7,11]

Carbohydrate Recognition in More Polar Solvent. Keeping in mind that **1b** was the strongest binder among the receptors from UV−vis titration, we performed ^{1}H NMR titration with **1a** and **1b** in a polar solvent system. The addition of *n*-octyl β-D-glucoside (**2**) to **1a** in $CDCl_3/CD_3OD$ (v/v, 10:1) showed distinct shifts of the other signals of **1a** despite the disappearance of the urea NHs (Figure 4). The ^{1}H NMR spectrum of **1a** was independent of the concentration within the range in which titration was conducted. The association constants could be calculated by 1:1 nonlinear least-squares curve fitting, and the apparent binding constants of **1a** and **1b** for *n*-octyl β-D-glucoside (**2**) were 950 and 470 M^{-1}, respectively. This implies that the interaction between the pyranoside and the receptors still remained effective in the presence of competing methanol, although the binding affinity decreased by a significant amount. The binding constants for the other guests are reported in Table 3. The selectivity trend (**2** > **4** > **3**) was the same as previously reported for urea-appended receptors, but the affinity increased 3-fold and furanosides **5** and **6** were also bound.

Conclusion

Porphyrin-based receptors containing urea, carbamate, or amide groups exhibited effective recognition behavior for

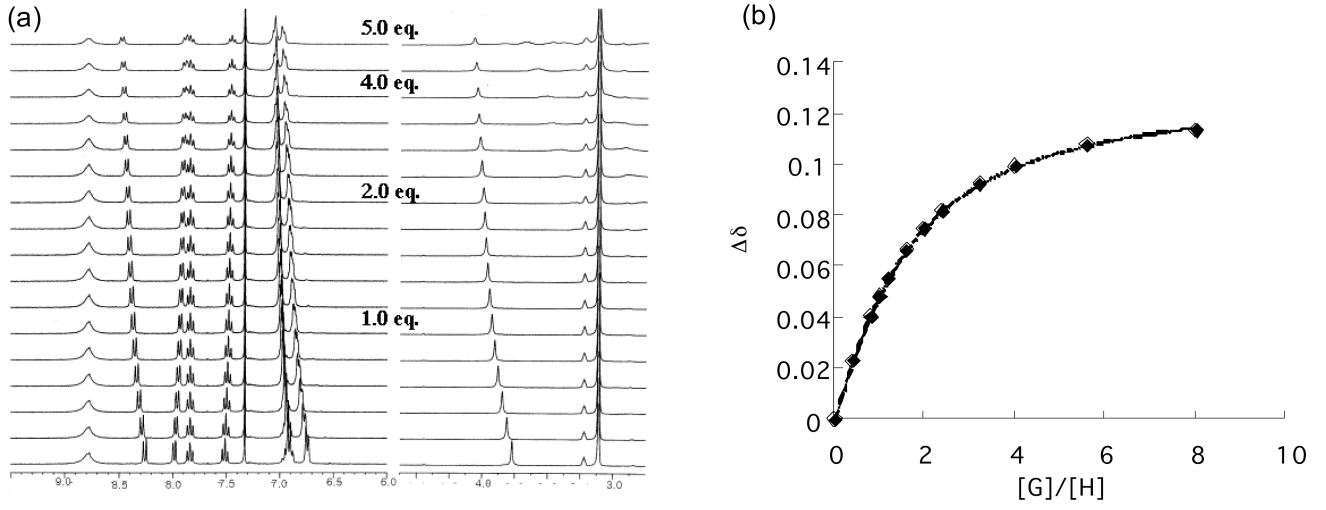

FIGURE 4. Titration of receptor **1a** (1.3 mM) with *n*-octyl β-D-glucoside (**2**). (a) ^{1}H NMR spectra ($CDCl_3/CD_3OD$ (v/v, 10:1), 298 K) of receptor **1a** after addition of 0.00−3.95 equiv (from bottom to top) of **2**. (b) ^{1}H NMR titration curve from the change in the chemical shift of benzyl CH_2.

TABLE 3. Binding Constants (K_a, M^{-1}) and Free Energy Change (ΔG^o, kcal/mol) from ^{1}H NMR Titrations of 1a and 1b with Octyl Pyranosides and Furanosides 2−6 in $CD_3OD/CDCl_3$ (1/10) at 298 K[a]

	2		3		4		5		6	
	K_a	$-\Delta G^o$	K_a	$-\Delta G^o$	K_a	$-\Delta G^o$	K_a	$-\Delta G^o$	K_a	$-\Delta G^o$
1a	950(11[b])	4.06	330(11)	3.43	510(5)	3.69	77(2)	2.57	68(4)	2.50
1b	470(7)	3.64	150(2)	2.97	250(4)	3.27	51(4)	2.33	34(5)	2.09

[a][**1a**] or [**1b**] is in the range 2.0−1.3 mM for titration with octyl pyranosides and furanosides. The ^{1}H NMR spectra of **1a** and **1b** were independent of the concentrations within this range. Guest concentrations: 0.4−16 mM for **2**, 0.8−20 mM for **3** and **4**, 1.2−18 mM for **5**, and 1.6−16 mM for **6**. [b]Standard deviations.

monosaccharides through multiple hydrogen bonds and CH−π interactions, and generally, the binding affinities of these receptors toward monosaccharides decreased in the following sequence: *n*-octyl β-D-galactoside (**4**) > *n*-octyl β-D-glucoside (**2**) > *n*-octyl α-D-glucoside (**3**) > *n*-octyluridine (**5**) > *n*-octyldeoxythymidine (**6**). UV−vis titration of receptors **1b**, **1g**, and **1h** demonstrated that urea was an excellent functional group to construct an efficient binding site for carbohydrates. In addition, receptors **1a** and **1b** interacted with *n*-octyl β-D-glucoside (**2**) in hydroxylic organic media, $CDCl_3/CD_3OD$ (v/v, 10:1). An effective approach to carbohydrate recognition is not only to surround the polar hydroxyl groups of the carbohydrates with complementary hydrogen-bonding groups of receptors but also to introduce aromatic surfaces into the receptor against carbohydrate CH moieties. This study showed that urea NHs can be used as strong H-bonding donors for sugar hydroxyl oxygens and that the porphyrin plane can be used for mimicking the CH−π interactions with sugar CHs, which are found in sugar-binding proteins. In addition, the four flexible phenyl groups of **1a** and **1b** could freely wrap the carbohydrate guest and, therefore, allowed for hydrophobic interaction with carbohydrate CHs, especially in hydroxylic cosolvents. We believe that this design principle can be applied to the development of artificial receptors for natural carbohydrates in water.

Experimental Section

UV−vis Titrations. Binding constants were determined through UV−vis titrations. Chloroform was used immediately after deacidification. No atropisomerization was observed in the solid state and during UV−vis titration. The prepared receptor solution was used as a solvent in the preparation of a 1−20 mM stock solution of various carbohydrates. Therefore, in spite of the volume change due to successive addition of the guest stock solution, the concentration of the receptor was maintained constant throughout the duration of UV−vis titration. The details concerning the determination procedure of the binding constant are as follows. The above-mentioned stock solution of various carbohydrates was successively added to the host solution in a 1-cm quartz UV−vis cell. The changes in absorbance in the Soret band at λ_{max} were monitored for different concentrations of carbohydrate. Assuming a 1:1 complexation, the binding constants were evaluated by least-squares parameter estimation. The calculated curves were well fitted to absorbance changes.

^{1}H NMR Titrations. $CDCl_3$ was completely deacidified by keeping it in anhydrous potassium carbonate for 1 day. Titration of 0.5 mL of a known concentration of $CDCl_3/CD_3OD$ (10:1, v/v) solution of the receptor (**1a** and **1b**) in an NMR tube by stepwise addition of an appropriate volume of carbohydrate solution was followed by ^{1}H NMR measurements; the spectrum was recorded after each addition. The chemical shifts of protons were monitored. The complex-induced chemical shifts were plotted against the molar percentage of added carbohydrate to obtain titration curves. If the calculated curve assuming 1:1 complexation was fitted to the experimental titration curve, the binding constants could be evaluated by least-squares parameter estimation. In reverse ^{1}H NMR titration (Figure 1 and Table 2), the signals of carbohydrate protons (2 mM solution) were monitored through stepwise addition of an appropriate volume of the receptor (**1e** and **1f**) to $CDCl_3$.

Compound 1a. To α,α,α,α-5,10,15,20-tetrakis(2-aminophenyl)-21*H*,23*H*-porphine (67 mg, 0.1 mmol) dissolved in 30 mL of distilled dichloromethane was slowly added benzyl isocyanate (250 μL, 2 mmol). After the reaction mixture was stirred at room temperature overnight under N_2, the solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel eluting with CH_2Cl_2/methanol = 20:1 (R_f = 0.35) and CH_2Cl_2/methanol = 40:1 to yield **1a** (97 mg, 80% yield): UV−vis ($CHCl_3$) λ_{max} (log ε) 423 (5.37), 517 (4.14), 553 (3.75), 591 nm (3.72); ^{1}H NMR (300 MHz, DMSO-d_6) δ −2.67 (s, 2H), 3.87 (d, J = 5.4 Hz, 8H), 6.34 (t, J = 5.3 Hz, 4H), 6.86 (m, 8H), 7.02 (m, 12H), 7.23 (s, 4H), 7.35 (t, 4H), 7.67 (d, J = 7.5 Hz, 4H), 7.76 (t, 4H), 8.46 (d, J = 8.5 Hz, 4H), 8.76 (s, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.3, 115.9, 122.4, 123.0, 127.1, 127.2, 128.4, 130.1, 132.4, 135.3, 138.8, 139.6, 155.5; HRMS calcd for $C_{76}H_{63}N_{12}O_4$ m/z 1207.5095, found 1207.5092. Anal. Calcd for $C_{76}H_{62}N_{12}O_4$: C, 75.59; H, 5.18; N, 13.93. Found: C, 75.50; H, 5.31; N, 13.91.

Compound 1b. To a solution of free-base porphyrin **1a** in $CHCl_3$ was added a solution of zinc acetate dihydrate dissolved in methanol. The resulting solution was stirred under N_2 for 24 h. Water was added, and the mixture was stirred for 30 min. The organic layer was separated, dried over Na_2SO_4, concentrated, and purified by flash chromatography (CH_2Cl_2/methanol = 40:1) to give rise to **1b** (quantitative yield): UV−vis ($CHCl_3$) λ_{max} (log ε) 428 (5.41), 553.5 (4.19); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (d, J = 5.5 Hz, 8H), 6.15 (t, J = 5.5 Hz, 4H,), 6.76 (s, 4H), 6.79 (m, 8H), 6.97 (m, 12H), 7.39 (t, J = 7.5 Hz, 4H), 7.76 (t, J = 8.2 Hz, 4H), 7.82 (dd, J = 7.5, 1.0 Hz, 4H), 8.44 (d, J = 8.2 Hz, 4H), 8.74 (s, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.4, 115.5, 120.8, 120.9, 126.4, 126.7, 127.8, 128.6, 131.6, 131.8, 135.1, 139.4, 139.4, 149.6, 154.9; HRMS calcd for $C_{76}H_{61}N_{12}O_4Zn$ m/z 1269.4230, found 1269.4248. Anal. Calcd for $C_{80}H_{60}N_{12}O_{12}Zn \cdot 2H_2O$: C, 64.85; H, 4.36; N, 11.35. Found: C, 64.62; H, 4.28; N, 11.50.

Compound 1e. Phosgene in toluene (20% solution, > 10 equiv, ~5 mL) was added to 10 mL of a dry tetrahydrofuran solution of 2-aminobenzoic acid methyl ester (150 mg, 1 mmol) and triethylamine (2 mL) under N_2. The mixture was stirred for 1 h at room temperature and then was brought to dryness on a rotary evaporator. The resulting solid was dissolved in 10 mL of dry dichloromethane. The reaction mixture was treated with α,α,α,α-5,10,15,20-tetrakis(2-aminophenyl)-21*H*,23*H*-porphine (67 mg, 0.1 mmol) in 10 mL of dry tetrahydrofuran. After being stirred at room temperature for 24 h, the reaction mixture was washed with 1 N HCl, 5% aq $NaHCO_3$, and then brine. The extracted organic phase was dried over Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography on silica gel, eluting with CH_2Cl_2/methanol = 20:1 (R_f = 0.4) and CH_2Cl_2/methanol = 40:1 to furnish **1e** (55 mg, 40% yield): UV−vis ($CHCl_3$) λ_{max} (log ε) 423 (5.53), 517 (4.33), 550.5 (3.87), 590 nm (3.78); ^{1}H NMR (300 MHz, $CDCl_3$) δ −2.53 (s, 2H), 2.86 (s, 12H), 6.40 (t, J = 7.8 Hz, 4H), 6.43 (s, 4H), 6.89 (t, J = 7.7 Hz, 4H), 7.16 (d, J = 7.8 Hz, 4H), 7.47 (t, J = 7.2 Hz, 4H), 7.66 (d, J = 8.6 Hz, 4H), 7.75 (t, J = 7.2 Hz, 4H), 7.99 (d, J = 7.2 Hz, 4H), 8.16 (d, J = 8.1 Hz, 4H), 8.82 (s, 8H), 9.22 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.4, 114.4, 115.5, 119.7, 120.8, 122.6, 122.9, 129.8, 130.1, 131.4, 132.5, 133.6, 135.0, 138.8, 141.3, 152.5, 167.7; HRMS calcd for $C_{80}H_{63}N_{12}O_{12}$ m/z 1383.4688, found 1383.4690. Anal. Calcd for $C_{80}H_{62}N_{12}O_{12}$: C, 69.44; H, 4.52; N, 12.15. Found: C, 69.31; H, 4.57; N, 12.18.

Compound 1f. 1f was obtained quantitatively from **1e** through the same procedure used for the preparation of **1b**: UV−vis ($CHCl_3$) λ_{max} (log ε) 428 (5.68), 557 (4.38), 595 nm (3.71); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 12H), 6.26 (s, 4H), 6.60 (t, J = 7.6 Hz, 4H), 7.09 (t, J = 7.4 Hz, 4H), 7.32 (d, J = 7.4 Hz, 4H), 7.58 (t, J = 7.2 Hz, 4H), 7.73 (d, J = 8.5 Hz, 4H), 7.83 (t, J = 7.6 Hz, 4H), 8.19 (d, J = 6.6 Hz, 4H), 8.26 (d, J = 8.1 Hz, 4H), 8.81 (s, 8H), 9.46 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 114.0, 115.2, 119.3, 120.9, 122.1, 123.2, 129.5, 130.2, 131.8, 133.9, 134.2, 134.6, 139.0, 141.5, 150.2, 152.7, 168.3; HRMS calcd for $C_{80}H_{60}N_{12}O_{12}Zn$ m/z 1444.3745, found 1444.3765.

Anal. Calcd for $C_{80}H_{60}N_{12}O_{12}Zn \cdot 2H_2O$: C, 64.85; H, 4.36; N, 11.35. Found: C, 64.62; H, 4.28; N, 11.50.

Compound 1g. Carbobenzoxy chloride (30−35% in toluene, 2 mL) and 2,6-lutidine (1 mL) were added to a tetrahydrofuran solution of α,α,α,α-5,10,15,20-tetrakis(2-aminophenyl)-21*H*,23*H*-porphine (67 mg, 0.1 mmol). The mixture was stirred at room temperature for 2 h, and then 5 mL of 0.5 N aqueous NaOH solution was added. After 10 min, the reaction mixture was brought to dryness on a rotary evaporator. The resulting mixture was dissolved in $CHCl_3$ and then washed with water. After the organic phase was dried under reduced vacuum, the crude product was dissolved in 15 mL of chloroform, followed by the addition of a solution of zinc acetate dihydrate dissolved in methanol. The resulting solution was stirred under nitrogen for 24 h. Water was added to the reaction mixture, the mixture was stirred for 30 min, and an organic layer was separated. The organic layer was dried over Na_2SO_4, evaporated, and purified by flash chromatography (hexane/ethyl acetate = 200:1) to yield **1g** (95 mg, 75% overall): UV−vis ($CHCl_3$) λ_{max} (log ε) 420 (5.70), 546 nm (4.36); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (s, 8H), 6.35 (s, 4H), 6.80 (m, 8H), 7.00 (m, 12H), 7.46 (t, J = 7.4 Hz, 4H), 7.84 (t, J = 8.0 Hz, 4H), 7.93 (d, J = 6.9 Hz, 4H), 8.48 (d, J = 6.9 Hz, 4H), 8.84 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.6, 115.3, 119.5, 122.2, 127.5, 127.7, 127.9, 128.1, 129.7, 132.4, 134.8, 135.7, 138.3, 150.5, 153.2; HRMS calcd for $C_{76}H_{56}N_8O_8Zn$ m/z 1272.3513, found 1272.3508. Anal. Calcd for $C_{76}H_{56}N_8O_8Zn \cdot H_2O$: C, 70.61; H, 4.52; N, 8.67. Found: C, 70.29; H, 4.39; N, 8.58.

Compound 1h. 3-Phenylpropionyl chloride (2 mL) and 2, 6-lutidine (1 mL) were added to a tetrahydrofuran solution of α,α,α,α-5,10,15,20-tetrakis(2-aminophenyl)-21*H*,23*H*-porphine (67 mg, 0.1 mmol). The mixture was stirred for 2 h at room temperature and then brought to dryness on a rotary evaporator. The resulting mixture was dissolved in $CHCl_3$ and then washed with water. After the organic phase was dried under reduced vacuum, the crude product was dissolved in 15 mL of chloroform, followed by the addition of a solution of zinc acetate dihydrate dissolved in methanol. The resulting solution was stirred under nitrogen for 24 h. Ethylenediamine (5 mL) was added to the solution to deactivate the remaining acid chloride, and then the solution was stirred for 30 min. Water was added to the reaction mixture, which was then stirred for 30 min and an organic layer was separated. The organic layer was dried over Na_2SO_4, evaporated, and purified by flash chromatography (CH_2Cl_2/methanol = 100:1) to yield **1h** (81 mg, 64% overall): UV−vis ($CHCl_3$) λ_{max} (log ε) 421 (5.68), 547 nm (4.36); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51 (br, 8H), 2.19 (br, 8H), 6.53 (m, 8H), 6.80 (m, 12H), 7.55 (t, J = 7.3 Hz, 4H), 7.81 (t, J = 7.7 Hz, 4H), 7.93 (d, J = 7.3 Hz, 4H), 8.17 (s, 4H), 8.24 (d, J = 7.2 Hz, 4H), 8.66 (s, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.4, 36.9, 115.9, 123.6, 124.0, 126.0, 128.1, 128.3, 129.1, 131.9, 135.3, 136.1, 138.5, 140.8, 149.9, 170.6; HRMS calcd for $C_{80}H_{64}N_8O_4Zn$ m/z 1264.4342, found 1264.4366. Anal. Calcd for $C_{80}H_{64}N_8O_4Zn \cdot H_2O$: C, 74.79; H, 5.18; N, 8.72. Found: C, 74.52; H, 5.10; N, 8.37.

Spectroscopic Measurements. The CD scanning conditions were as follows: scanning rate = 100 nm per min, bandwidth = 0.5 nm, response time = 2 s, accumulations = one1 time.

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Supporting Information Available: Job's plot, selected ^{1}H NMR titration spectra, UV−vis titration curves, and ^{1}H NMR spectra of **1a** in $CDCl_3/CD_3OD$ (v/v, 10:1) upon dilution. This material is available free of charge via the Internet at http://pubs.acs.org.