Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 10253–10260

Hydrogen bonding-mediated self-assembly of rigid and planar metallocyclophanes and their recognition for mono- and disaccharides

Ying-Qi Chen,[a,*] Xiao-Zhong Wang,[a] Xue-Bin Shao,[b] Jun-Li Hou,[b] Xin-Zhi Chen,[a] Xi-Kui Jiang[b] and Zhan-Ting Li[b,*]

[a]*Institute of Pharmaceutical Engineering, College of Materials Science and Chemical Engineering, Yuquan Campus, Zhejiang University, Hangzhou, Zhejiang 310027, China*

[b]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

Received 1 July 2004; revised 25 August 2004; accepted 27 August 2004

Abstract—A hydrogen bonding approach has been developed to facilitate the self-assembly of a new series of rigid and planar metallocyclophanes. Two new anthranilamide derivatives **1** and **2**, which are incorporated with two acetylene units, respectively, have been synthesized and characterized. X-ray analysis (for **1**), 1D and 2D ^{1}H NMR and IR experiments reveal that, due to the formation of intramolecular three-centered hydrogen bonding, both compounds adopt rigid and planar conformations with the two acetylene units located at the same side of the anthranilamide skeleton. Two new metallocyclophanes **17** and **18** have been constructed in moderate yields from the reaction of **1** and **2** with *trans*-$Pt(PEt_3)_2Cl_2$, respectively, in dichloromethane in the presence of diethylamine and cupric chloride. Fluorescent and ^{1}H NMR investigations reveal that both **17** and **18** can efficiently complex mono- and disaccharide derivatives in chloroform, with a binding selectivity for disaccharides, which is driven by intermolecular hydrogen bonding.

1. Introduction

In the past decade, the development of supramolecular macrocyclic architectures has received intensive interest.[1] Among various non-covalent forces, the coordination bonding motif between transition metal ions and organic ligands has proven itself to be a highly useful tool for their preparation.[2] In order to overcome the entropic disadvantage and to achieve high assembling efficiency, rigid aromatic ligands are usually used. Over years a large number of metallosupramolecular assemblies have been constructed from covalently bonded aromatic ligands. Nevertheless, functional metallocyclophanes are still relatively rare despite their perceived advantages over the constituent building blocks.[3]

Following the increasing applications of hydrogen bonding for controlling the folding and unfolding conformations of unnatural organic molecules,[4,5] we had recently initiated a project to develop new hydrogen bonding-mediated building blocks for constructing novel generation of functional supramolecular architectures. Previously, we have reported the self-assembly of a new class of oligoanthranilamides whose straight, rigid, and planar conformations could be stabilized by intramolecular three-centered hydrogen bonding.[6] In this paper, we report that similar approach has been successfully utilized to control the rigid conformation of acetylene precursors for the generation of a new series of rigid and planar metallocyclophanes. We also report the binding behavior of the new metallocyclophanes towards mono- and disaccharides in chloroform.

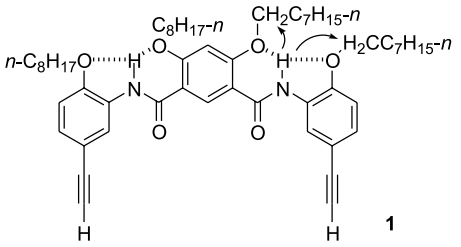
2. Results and discussion

A number of metallocyclophanes have been constructed from linear bisphenylacetylene ligands and coordinatively unsaturated metal complexes.[7] Previously, Hamilton and Gong have revealed that intramolecular three-centered hydrogen bonding can induce 1,3-substituted anthranilamide derivatives to adopt folding, rigid and planar conformation.[8] Recently, we have also reported that similar hydrogen bonding approach could be used to induce 1,4-substituted anthranilamides to generate unfolding, rigid and

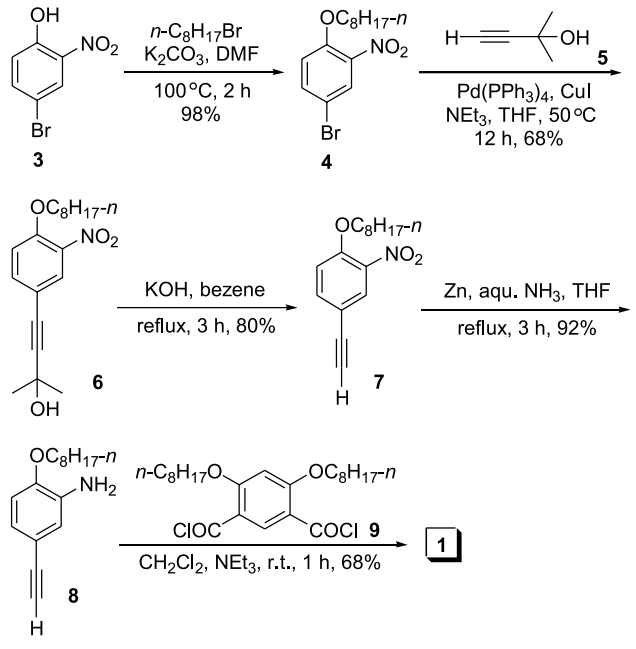
Keywords: Hydrogen bonding; Self-assembly; Metallocyclophane; Molecular recognition; Saccharide.
* Corresponding authors. Tel.: +86 571 87952693 (Y.-Q.C.); tel.: +86 21 64163300; fax: +86 21 64166128 (Z.T.L.);
e-mail addresses: yqchen@zju.edu.cn; ztli@mail.sioc.ac.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.099

straight conformations.[6] To explore the possibility of the intramolecular three-centered hydrogen bonding to control the rigidity and directionality of new bisphenylacetylene ligands for self-assembly of new kinds of metallocyclophanes, compounds **1** and **2** were designed and synthesized. The two acetylene units of both compounds were expected to be parallel to each other at the same side due to the formation of intramolecular hydrogen bonding. Such an arrangement should remarkably facilitate the formation of corresponding metallocyclophanes.

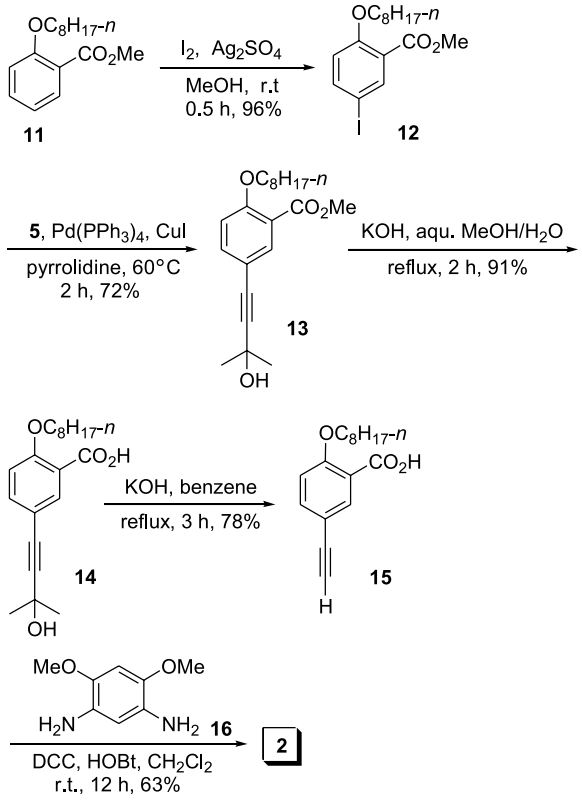


The synthetic route of compound **1** is shown in Scheme 1. In brief, compound **3** was first octylated in hot DMF in the presence of potassium carbonate to give bromide **4** in 98% yield. The latter was then coupled with compound **5** in THF with Pd(0) as catalyst to produce compound **6** in 68% yield. Hydrolysis of **6** with potassium hydroxide in refluxing benzene afforded acetylene **7** in 80% yield, which was then selectively reduced to amine **8** in 92% yield by zinc in water and THF solution of ammonia. Treatment of **8** with diacyl chloride **9** in dichloromethane with triethylamine as a base produced compound **1** in 68% yield.



Scheme 1.

For the preparation of compound **2** (Scheme 2), ester **12** was first produced in 96% yield from the reaction of **11** and iodine in the presence of silver sulfate in methanol. The coupling reaction of **12** with **5**, catalyzed by Pd(0), in hot pyrrolidine produced **13** in 72% yield. Compound **13** was then treated with potassium hydroxide in hot aqueous THF to give **14** in 91% yield. The latter was treated with potassium hydroxide again in hot benzene to afford **15** in 78% yield. Compound **15** was then coupled with diamine **16** in the presence of DCC and HOBt in dichloromethane to afford **2** in 63% yield.



Scheme 2.

Compounds **1** and **2** have been identified by ^{1}H NMR and MALDI-TOF mass spectroscopy, and microanalysis. ^{1}H NMR spectrum in chloroform-*d* revealed typical three-centered hydrogen bonding for both compounds (NH: 9.90 and 9.99 ppm, respectively). ^{1}H NMR experiments in chloroform-*d* revealed very small concentration dependence (<0.01 ppm) within the range of 20–0.3 mM and low temperature dependence ($<4.0\times10^{-3}$ ppm/K within the region of 10–55 °C) for the NH and aromatic proton signals of both compounds.[8] These observations are well consistent with the results observed in structurally similar rigid and straight oligoanthranilamides.[6] The observations also exclude any important intermolecular aggregation for both compounds. 2D-NOESY ^{1}H NMR studies in chloroform-*d* (10 mM) also revealed moderate strength of NOE connections between the NH and the neighboring OCH_3 and OCH_2

signals (see the structures). In addition, all the NH stretching frequencies (ν) of their IR spectra, measured in chloroform (4 mM) and with the KBr disk method, are $<3310\ cm^{-1}$ and independent of concentration changes.[9] All the results support that intramolecular three-centered hydrogen bonding is formed, which induces the rigid and planar conformation as shown in the text.

Single crystals of compound **2** were obtained by slow evaporation of its dichloromethane and methanol solution at room temperature. The X-ray structure of the compound is provided in Figure 1. It can be found that the compound adopts a nearly perfect planar conformation. The two acetylene units are nearly parallel, located at the same side due to the existence of two three-centered hydrogen bonding, which is well consistent with the above spectral observations.

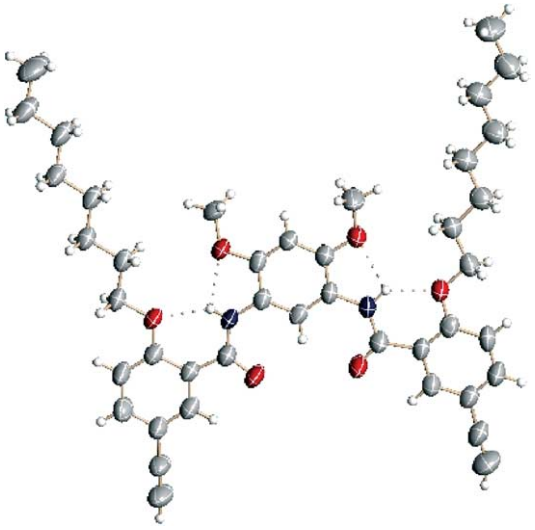
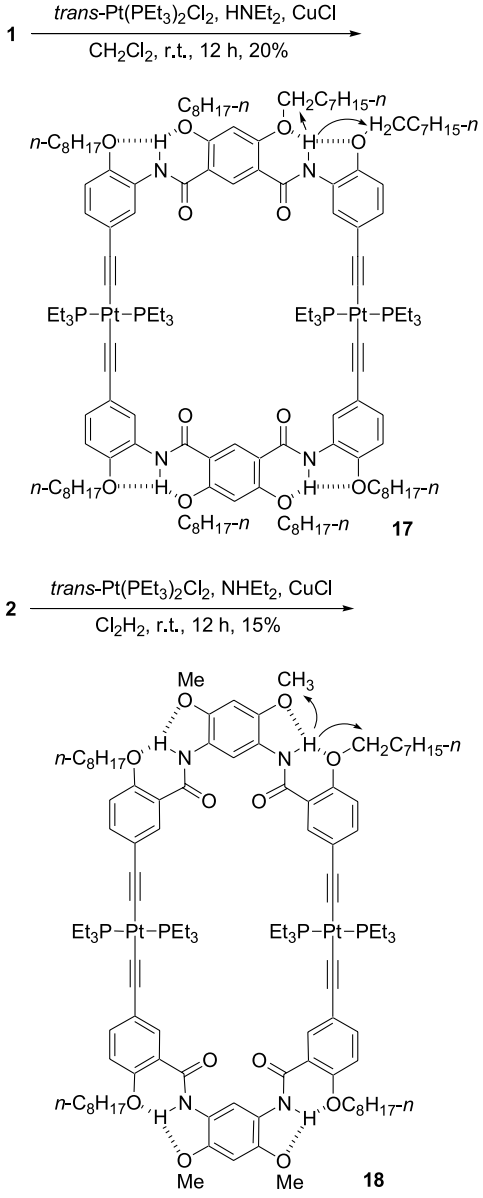


Figure 1. The crystal structure of compound **2**, revealing two typical three-centered NH–O hydrogen bonds and a rigid and planar conformation.

Treatment of compounds **1** and **2** with *trans*-$Pt(PEt_3)_2Cl_2$ in dichloromethane in the presence of diethylamine and cupric chloride produced metallocyclophanes **17** and **18** in 20 and 15% yields, respectively (Scheme 3).[7] Both **17** and **18** are soluble in common organic solvents such as chloroform and dichloromethane.

Compounds **17** and **18** were identified by ^1H and ^{13}C NMR and MALDI-TOF mass spectroscopy, and microanalysis. ^1H NMR spectrum of **17** and **18** in chloroform-*d* showed the signal of NH in the downfield area (9.80 and 9.97 ppm, respectively), indicating the existence of three-centered hydrogen bonding in the new metallocyclophanes. 2D-NOESY ^1H NMR experiments revealed NOEs between the NH and the neighboring OCH_3 and OCH_2 signals, as shown in Scheme 3. The IR spectrum obtained in chloroform showed the NH stretching frequency at 3330 and 3325 cm^{-1}, respectively, which are typically those of amides involved in intramolecular hydrogen bonding.[9] All these results indicate that the metallocyclophanes also possess rigid and planar conformation due to the formation of intramolecular three-centered hydrogen bonding. The maximum absorbance wavelength of **17** (267 nm) and **18**



Scheme 3.

(259 nm), obtained in chloroform, is significantly increased, compared to that of their constituents **1** (258 nm) and **2** (248 nm), respectively.

Molecular modeling revealed that both **17** and **18** possess a rigid cavity with all the C=O oxygen located to the center of the cavity. The distances between the two Pt atoms are about 12.3 and 10.6 Å in **17** and **18**, respectively, whereas the distances between the two oxygen atoms of one side are about 12.9 and 13.8 Å, respectively. Such an arrangement of all the carbonyl groups with the oxygen atoms pointing to the inner of the cavity is very favorable for binding multi-hydroxyl molecules. The binding behaviors of metallocyclophanes **17** and **18** towards mono- and disaccharide derivatives **19–25** were then investigated in chloroform.[10] The long aliphatic chains were introduced into the saccharides to provide solubility in less polar solvents like chloroform. Compounds **19–23** and **25** were prepared according to reported methods, while the synthetic route

α–D-Ribose (**19**) α–D-Glucose (**20**)

α-D-Galactose (**21**) β-D-Galactose (**22**)

α-D-Mannose (**23**) α–Lactose (**24**)

β-Maltose (**25**)

26 + n-$C_{12}H_{25}NH_2$ **27**

CH_3OH, reflux, 12 h, 53%

28

$C_{11}H_{23}COOCOMe$, NEt_3, THF, DMF, 12 h, r.t., 67% → **24**

Scheme 4.

for compound **24** is provided in Scheme 4. Initially, we had tried to prepare the *n*-dodecyl derivative of lactose similar to other saccharides, which was found to be insoluble in chloroform.

Adding **19**–**25** to the solution of **17** or **18** in chloroform led to important increase of the fluorescent emission of both compounds. The hydroxyl signals of the saccharides in ^{1}H NMR spectrum in chloroform-*d* also moved downfield remarkably upon addition of **17** or **18**. These observations indicate that the metallocyclophanes are able to complex the saccharides in chloroform. Job' plots for the mixture solution of **17** with **21** in chloroform-*d* revealed largest downfield shifting for the CH_2OH signal in the ^{1}H NMR spectrum when the ratio of **17** and **21** is 1:1,[11] which supported a 1:1 binding stoichiometry between the metallocyclophane and the saccharide. Similar 1:1 stoichiometry was also observed with the fluorescent method for the system of **17** and **24**. Quantitative binding studies were then preformed with both the fluorescent and ^{1}H NMR titration methods,[12] and the corresponding association constants K_{assoc} were derived by fitting the data to a 1:1 binding mode, which are listed in Table 1. As an example, the plot of the emission intensity of **17** vs [**25**] in chloroform is provided in Figure 2.

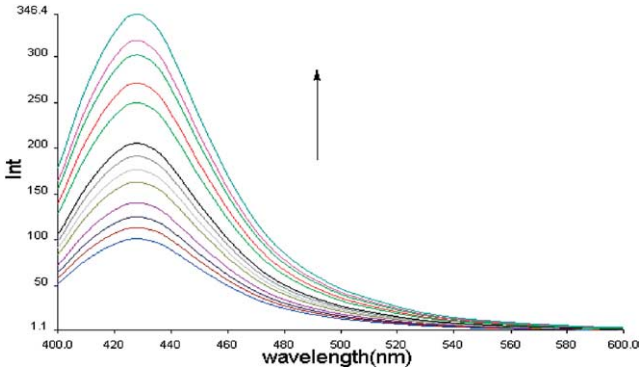


Figure 2. Fluorescent spectra of metallocyclophane **17** (5.5×10^{-5} M, excitation wavelength = 375 nm) in chloroform at 23 °C, increased gradually with the addition of disaccharide **25** (from 0 to 1.2×10^{-3} M).

It can be found that both **17** and **18** exhibit greater binding ability for disaccharides than for monosaccharides. This selectivity might suggest that, in addition to the expected binding between the C=O and OH groups, the OH groups of the longer disaccharides can also bind the ether oxygen or amide nitrogen of **17** and **18**. Table 1 also shows that, for all the saccharide guests, **17** displays greater binding ability than **18**, which may be ascribed to its larger cavity and consequently a reduced hindrance of the PEt_3 units. Since the binding between the metallocyclophanes and the saccharides are a dynamic process, we are not able to establish the exact binding pattern of the complexes at the present stage, but the 1:1 binding mode seems to indicate that the binding takes place in the cavity of the metallocyclophanes. The binding ability of **1** and **2** towards **19** was also investigated in chloroform-*d* with the ^{1}H NMR titration method, which gave a K_{assoc} value of 58 and 32 M^{-1} for complexes **1**·**19** and **2**·**19**, respectively.

Table 1. Association constants K_{assoc} (M^{-1}) of complex between **17** and **18** and mono- and disaccharide derivatives **19**–**25** in chloroform at 23 °C[a]

	17	**18**		**17**	**18**
19	1.4×10^3	7.4×10^2	**22**	3.0×10^3	9.4×10^2
20	5.6×10^3	2.1×10^3	**23**	6.4×10^3	2.9×10^3
20[b]	5.4×10^3	2.4×10^3	**24**	2.5×10^4	9.4×10^3
21	3.4×10^3	1.1×10^3	**25**	4.3×10^4	7.8×10^3

[a] With error of less than 20%.
[b] Determined by the ^{1}H NMR titration method.

3. Conclusion

In summary, we have demonstrated that intramolecular hydrogen bonding can be utilized to rigidify the conformation of bisphenylacetylene building blocks and consequently facilitate the self-assembly of a new series of rigid and planar metallocyclophanes. The hydrogen bonded metallocyclophanes represent a new series of synthetic receptors for saccharide derivatives albeit in the less polar chloroform. In principle, the spatial separation of the two acetylene units in the assembled building blocks can be increased conveniently by introducing longer oligo-anthranilamide linkers, which would lead to the formation of new metallocyclophanes with extended cavity size. Moreover, replacing the acetylene units with other functional groups such as pyridyl units would also provide new opportunity to construct other kinds of metallocyclophanes. Investigations along these lines are being performed in our laboratory.

4. Experimental

4.1. General methods

The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC Analytical Center. Unless otherwise indicated, all commercially available materials were used as received. All solvents were dried before use following standard procedures. All reactions were carried out under an atmosphere of nitrogen. Silica gel (1–4 μ) was used for column chromatography. Compounds **19**,[13] **20**,[14] **21**,[15] **22**,[16] **23**,[17] **25**[18] were prepared according to reported methods.

4.1.1. 4-Bromo-2-nitro-phenol (3). A suspension of 4-bromophenol (6.92 g, 40.0 mmol), oxone (24.4 g, 40.0 mmol), wet silica gel (0.40 g) and sodium nitrile (2.76 g, 40.0 mmol) in dichloromethane (120 mL) was stirred at room temperature for 2 h. The solid was filtered and the filtrate was washed with water (30 mL×3), brine (30 mL), dried over sodium sulfate, and evaporated in vacuo. The resulting residue was recrystallized from ethanol to afford compound **3** as a yellow sheet crystal (7.60 g, 88%). Mp 88–89 °C (87 °C, lit.[19]). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.07–7.10 (d, J=6.5 Hz, 1H), 7.67 (d, d, J_1=6.5 Hz, J_2=2.2 Hz, 1H), 8.25 (d, J=2.2 Hz, 1H), 10.5 (s, 1H). MS (EI): *m*/*z* 219 $[M]^+$.

4.1.2. 4-Bromo-2-nitro-1-*n*-octyloxy-benzene (4). A mixture of compound **2** (5.00 g, 25.0 mmol), 1-bromooctane (6.00 g, 30.0 mmol) and potassium carbonate (4.00 g, 30.0 mmol) in DMF (80 mL) was stirred at 100 °C for 2 h, and then poured into water (250 mL). The mixture was extracted with ethyl acetate (75 mL×3) and the combined organic phase was washed with water (100 mL), brine (100 mL), and dried over sodium sulfate. After the solvent was removed under reduced pressure, the resulting crude product was purified with column chromatography (petroleum ether/AcOEt 8:1) to give compound **4** as a yellow oil (7.57 g, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85–0.90 (m, 3H), 1.27–1.48 (m, 10H), 1.79–1.84 (m, 2H), 4.06 (t, J=6.2 Hz, 2H), 6.96 (d, J=6.6 Hz, 1H), 7.59 (d, d, J_1=6.6 Hz, J_2=2.2 Hz, 1H), 7.93 (d, J=2.2 Hz, 1H). MS (EI): *m*/*z* 329 $[M]^+$. Anal. Calcd for $C_{14}H_{20}BrNO_3$: C, 50.92; H, 6.10. Found: C, 51.14; H, 6.22.

4.1.3. 2-Methyl-4-(3-nitro-4-octyloxy-phenyl)-but-3-yn-2-ol (6). To a solution of compounds **4** (2.10 g, 6.30 mmol) and **5** (0.87 g, 10.0 mmol) in THF (30 mL) was added $[Pd(PPh_3)_4]$ (0.24 g, 0.30 mmol, 5%), CuI (60.0 mg, 0.30 mmol) and triethylamine (2.0 mL). The reaction mixture was stirred at 50 °C for 12 h and then poured into concentrated in vacuo. The resulting residue was triturated with ethyl acetate (150 mL) and the organic phase was washed with water (50 mL), brine (50 mL), dried over sodium sulfate. After removal of the solvent under reduced pressure, the resulting brown oil was subjected to flash chromatography (CH_2Cl_2/petroleum ether 1:2) to give compound **6** (1.43 g, 68%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz):δ 0.86–0.90 (m, 3H), 1.27–1.50 (m, 10H), 1.61 (s, 6H), 1.80–1.85 (m, 2H), 4.09 (t, J=6.5 Hz, 2H), 6.99 (d, J=6.6 Hz, 1H), 7.53 (d, d, J_1=6.5 Hz, J_2=2.2 Hz, 1H), 7.87 (d, J=2.2 Hz, 1H). MS (EI): *m*/*z* 333 $[M]^+$. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.12; H, 8.04; N, 4.05.

4.1.4. 4-Ethynyl-2-nitro-1-octyloxy-benzene (7). A suspension of compound **6** (1.20 g, 3.60 mmol) and potassium hydroxide (0.28 g, 5.00 mmol) in benzene (60 mL) was refluxed for 3 h and then concentrated in vacuo. The resulting residue was triturated with dichloromethane (60 mL) and the organic phase was washed with dilute hydrochloric acid (1 N, 20 mL), water (20 mL), brine (20 mL), and dried over sodium sulfate. After removal of the solvent in vacuo, the crude product was purified with column chromatography (CH_2Cl_2/petroleum ether 1:3) to afford compound **7** as a yellow solid (0.81 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86–0.90 (m, 3H), 1.25–1.49 (m, 10H), 1.78–1.88 (m, 2H), 3.07 (s, 1H), 4.10 (t, J=6.5 Hz, 2H), 7.00 (d, J=6.6 Hz, 1H), 7.59–7.62 (d, d, J_1=6.6 Hz, J_2=2.2 Hz, 1H), 7.94 (d, J=2.2 Hz, 1H). MS (EI): *m*/*z* 275 $[M]^+$. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.02; H, 7.81; N, 4.97.

4.1.5. 5-Ethynyl-2-octyloxy-phenylamine (8). To a solution of compound **7** (0.70 g, 2.50 mmol) in THF (20 mL) was added zinc powder (0.65 g, 10.0 mmol) and concentrated ammonia solution (30 mL). The mixture was stirred under reflux 3 h. After the solid was filtered, the filtrate was concentrated in vacuo and the resulting residue triturated with dichloromethane (150 mL). The organic phase was washed with aqueous sodium carbonate (0.5 N, 50 mL), water (50 mL), brine (50 mL), and dried over sodium sulfate. The solvent was then distilled under reduced pressure, the crude product was subjected to flash chromatography (CH_2Cl_2/petroleum ether 1:2.5) to give compound **8** (5.62 g, 92%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87–0.91 (m, 3H), 1.26–1.48 (m, 10H), 1.76–1.85 (m, 2H), 2.94 (s, 1H), 3.81 (br, 2H), 3.98 (t, J=6.4 Hz, 2H), 6.68 (d, J=6.6 Hz, 1H), 6.85 (d, d, J_1=6.6 Hz, J_2=2.2 Hz, 1H), 6.89 (d, J=2.2 Hz, 1H). MS (EI):

m/z 245 $[M]^+$. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.22; H, 9.43; N, 5.69.

4.1.6. *N,N′*-bis-(5-Ethynyl-2-octyloxy-phenyl)-4,6-bis-octyloxy-isophthalamide (1). Compound **9** was prepared from the reaction of oxalyl chloride and the corresponding diacid[20] in the presence of catalytic amount of DMF. After the volatile materials were removed under reduced pressure, the resulting oily compound **9** was used for the next step with further purification. To a solution of compound **9** (0.30 g, 0.29 mmol) in dichloromethane (30 mL) was added a solution of compound **8** (0.15 g, 0.61 mmol) and triethylamine (0.5 mL). After stirring at room temperature for 0.1 h, the mixture was washed with water, brine, dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting brown oil was subjected to flash chromatography (CH_2Cl_2/EtOAc 100:1) to give **1** (0.18 g, 68%) as a light green solid. Mp 201 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.88 (m, 12H), 1.25–1.43 (m, 40H), 1.77–1.82 (m, 4H), 1.89–1.94 (m, 4H), 2.98 (s, 2H), 4.04 (t, J=6.6 Hz, 4H), 4.22 (t, J=6.5 Hz, 4H), 6.49 (s,1H), 6.78 (d, J=6.5 Hz, 2H), 7.17 (d, d, J_1=6.5 Hz, J_2=2.2 Hz, 2H), 8.80 (d, J=2.2 Hz, 2H), 9.07 (s, 1H), 9.80 (s, 2H). IR: ν 3315, 3224, 2955, 2925, 2854, 2103, 1664, 1580, 1537, 1423, 1232, 1021, 799, 676 cm^{-1}. MS (MALDI-TOF): *m/z* 877 $[M]^+$. Anal. Calcd for $C_{56}H_{80}N_2O_6$: C, 76.67; H, 9.19; N, 3.19. Found: C, 76.35; H, 8.98; N, 3.42.

4.1.7. 5-Iodo-2-octyloxy-benzoic acid methyl ester (12). A mixture of compound **11**[20a] (14.0 g, 53.0 mmol), iodine (14.0 g, 55.0 mmol) and silver sulfate (17.0 g, 55.0 mmol) in methanol (200 mL) was stirred at room temperature for 0.5 h and then concentrated in vacuo. The resulting residue was triturated with ethyl acetate (300 mL). The organic phase was washed with water (120 mL×2), brine (120 mL), and dried over sodium sulfate. After the solvent was distilled under reduced pressure, the resulting residue was subjected to flash chromatography (dichloromethane) to give compound **12** (19.9 g, 96%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85–0.90 (m, 3H), 1.25–1.48 (m, 10H), 1.76–1.83 (m, 2H), 3.87 (s, 3H), 3.98 (t, J=6.4 Hz, 2H), 6.72 (d, J=6.6 Hz, 1H), 7.68 (d, d, J_1=6.6 Hz, J_2=2.2 Hz, 1H), 8.04 (d, J=2.2 Hz, 1H). MS (EI): *m/z* 390 $[M]^+$. Anal. Calcd for $C_{16}H_{23}IO_3$: C, 49.24; H, 5.94. Found: C, 49.11; H, 6.21.

4.1.8. 5-(3-Hydroxy-3-methyl-but-1-ynyl)-2-octyloxy-benzoic acid methyl ester (13). A suspension of compounds **12** (4.00 g, 10.3 mmol), **5** (1.30 g, 15.0 mmol), $Pd(PPh_3)_4$ (0.38 g, 0.50 mmol, 5%), and CuI (0.10 g, 0.50 mmol) in pyrrolidine (30 mL) was stirred at 60 °C for 2 h and then concentrated under reduced pressure. The resulting residue was triturated with ethyl acetate (150 mL) and the organic phase was washed with dilute hydrochloric acid (1 N, 50 mL), water (50 mL), brine (50 mL), and dried over sodium sulfate. After the solvent was distilled under reduced pressure, the resulting crude product was subjected to flash chromatography (CH_2Cl_2) to give compound **13** (2.58 g, 72%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86–0.90 (m, 3H), 1.28–1.50 (m, 10H), 1.60 (s, 6H), 1.77–1.84 (m, 2H), 3.87 (s, 3H), 4.02 (t, J=6.6 Hz, 2H), 6.88 (d, J=6.5 Hz, 1H), 7.47 (d, d, J_1=6.5 Hz, J_2=2.2 Hz, 1H), 7.85 (d, J=2.2 Hz, 1H). MS (EI): *m/z* 346 $[M]^+$. Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.67; H, 8.88.

4.1.9. 5-(3-Hydroxy-3-methyl-but-1-ynyl)-2-octyloxy-benzoic acid (14). Compound **13** (2.00 g, 5.80 mmol) and potassium hydroxide (0.56 g, 10.0 mmol) were added to a mixture of methanol (50 mL) and water (20 mL). The mixture was stirred under reflux for 2 h and concentrated to about 20 mL. The solution was neutralized with dilute hydrochloric acid (2 N) and then extracted with dichloromethane (30 mL×2). The combined organic phase was washed with water (20 mL×3), brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting brown residue was subjected to flash chromatography (CH_2Cl_2/EtOAc 10:1) to give intermediate **14** (1.75 g, 91%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85–0.90 (m, 3H), 1.25–1.49 (m, 10H), 1.60 (s, 6H), 1.88–1.93 (m, 2H), 4.22–4.26 (t, J=6.6 Hz, 2H), 6.96 (d, J=6.4 Hz, 1H), 7.56 (d, d, J_1=6.4 Hz, J_2=2.3 Hz, 1H), 8.22 (d, J=2.3 Hz, 1H). MS (EI): *m/z* 332 $[M]^+$. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.27; H, 8.64.

4.1.10. 5-Ethynyl-2-octyloxy-benzoic acid (15). To a solution of acid **13** in benzene (80 mL) was added potassium hydroxide (0.56 g, 10.0 mmol). The mixture was refluxed for 3 h. After normal workup, the crude product was chromatographed (CH_2Cl_2) to afford compound **15** as a pale yellow solid (1.50 g, 78%). Mp 63–64 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86–0.90 (m, 3H), 1.25–1.48 (m, 10H), 1.89–1.94 (m, 2H), 3.06 (s, 1H), 4.26 (t, J=6.5 Hz, 2H), 6.99 (d, J=6.6 Hz, 1H), 7.64 (d, d, J_1=6.5 Hz, J_2=2.2 Hz, 1H), 8.32 (d, J=2.2 Hz, 1H), 10.84 (br, 1H). MS (EI): *m/z* 274 $[M]^+$. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.30; H, 8.17.

4.1.11. *N,N′*-bis-(5-Ethynyl-2-octyloxy-benzoyl)-4,6-bis-methoxy-1,3-phenylenediamine (2). A solution of compounds **15** (0.14 g, 0.50 mmol) and **16**[21] (42.0 mg, 0.25 mmol), in dichloromethane (20 mL) was stirred in ice bath for 30 min. A solution of HOBt (90.0 mg, 0.58 mmol) and DCC (0.12 g, 0.58 mmol) in dichloromethane (10 mL) was added. Stirring was continued for another 12 h and the solid was filtered. The filtrate was evaporated in vacuo and the resulting residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc 10:1) to give compound **2** as a yellow solid (0.11 g, 63%). Mp 197 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.88 (m, 6H), 1.25–1.51 (m, 20H), 1.92–2.01 (m, 4H), 3.01 (s, 2H), 3.90 (s, 6H), 4.18 (t, J=6.6 Hz, 4H), 6.54 (s, 1H), 6.93 (d, J=6.5 Hz, 2H), 7.54 (d, d, J_1=6.5 Hz, J_2=2.2 Hz, 2H), 8.50 (d, J=2.2 Hz, 2H), 9.53 (s, 1H), 9.97 (s, 2H). IR: ν 3351, 3298, 3251, 2106, 1662, 1542, 1470, 1421, 1249, 1201, 1027, 810, 684 cm^{-1}. MS (MALDI-TOF): *m/z* 680 $[M]^+$, 703 $[M+Na]^+$, 719 $[M+K]^+$. Anal. Calcd for $C_{42}H_{52}N_2O_6$: C, 74.08; H, 7.70; N, 4.11. Found: C, 74.05; H, 7.73; N. 3.82.

4.1.12. Metallocyclophane 17. To a solution of compounds **1** (0.10 g, 0.11 mmol) and *trans*-$PtCl_2(PEt_3)_2$ (60.0 mg, 0.11 mmol) in dichloromethane (100 mL) was added diethylamine (0.5 mL) and cupric chloride (5 mg) with stirring. The mixture was stirred at room temperature for 12 h and washed with dilute hydrochloric acid (1 N, 20 mL),

water (20 mL×3), brine (30 mL), and dried over sodium sulfate. The solvent was removed in vacuo and the resulting residue purified by column chromatography (CH_2Cl_2/MeOH 200:1) to afford compound **17** as a light yellow solid (58 mg, 20%). Mp 253 °C (decomp.). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.88 (m, 24H), 1.19–1.44 (m, 116H), 1.77–1.82 (m, 8H), 1.93–1.98 (m, 8H), 2.22–2.29 (m, 24H), 4.05 (t, J=6.5 Hz, 8H), 4.26 (t, J=6.6 Hz, 8H), 6.53 (s, 2H), 6.72 (d, J=6.5 Hz, 4H), 6.95 (d, d, J_1=6.5 Hz, J_2=2.2 Hz, 4H), 8.78 (d, J=2.2 Hz, 4H), 9.27 (s, 2H), 9.90 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 8.1, 8.5, 14.2, 16.3, 16.5, 16.7, 22.6, 22.7, 22.71, 25.9, 25.9, 28.9, 29.3, 29.3, 29.4, 29.4, 29.5, 29.8, 31.8, 31.8, 31.9, 68.9, 70.0, 111.0, 116.7, 128.7, 145.5, 159.6, 162.0. IR: ν 3358, 2958, 2928, 2855, 2101, 1666, 1577, 1531, 1481, 1230, 1035, 766, 670 cm^{-1}. MS (MALDI-TOF): m/z 2613 $[M+H]^+$. Anal. Calcd for $C_{136}H_{216}N_4O_{12}P_4Pt_2$: C, 62.46; H, 8.37; N, 2.14. Found: C, 62.72; H, 8.53; N, 2.05.

4.1.13. Metallocyclophane 18. A suspension of compounds **2** (0.10 g, 0.16 mmol), *trans*-$PtCl_2(Et_3P)_2$ (83.0 mg, 0.16 mmol), cupric acid (5.0 mg), and diethylamine (0.5 mL) in dichloromethane (150 mL) was stirred at room temperature for 12 h. After workup as described **17**, the resulting crude product was purified by column chromatography (CH_2Cl_2/MeOH 40:1) to afford **18** as a light yellow solid (52 mg, 15%). Mp 250 °C (decomp.). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.88 (m, 12H), 1.21–1.50 (m, 80H), 1.95–2.00 (m, 8H), 2.20–2.28 (m, 24H), 3.90 (s,12H), 4.14 (t, J=6.6 Hz, 8H), 6.54 (s, 2H), 6.82 (d, J=6.3 Hz, 4H), 7.29 (d, d, J_1=6.3 Hz, J_2=2.2 Hz, 4H), 8.38 (d, J=2.2 Hz, 4H), 9.99 (s, 2H), 10.15 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 9.7, 15.4, 17.5, 17.7, 18.0, 24.0, 27.2, 30.5, 30.6, 30.7, 33.1, 56.9, 70.8, 96.2, 101.5, 113.2, 122.8, 123.4, 135.6, 137.5, 146.1, 155.7, 163.7. IR: ν 3353, 2960, 2929, 2855, 2101, 1666, 1542, 1469, 1421, 1201, 1036, 768, 733 cm^{-1}. MS (MALDI-TOF): m/z 2242 $[M+K]^+$. Anal. Calcd for $C_{108}H_{160}N_4O_{12}P_4Pt_2$: C, 58.42; H, 7.26; N, 2.52. Found: C, 58.76; H, 6.90; N, 2.14.

4.1.14. Compound 28. The method by Stadler et al. was used to prepare this compound.[22] A mixture of lactose **26** (1.70 g, 5.00 mmol) and lauryl amine **27** (1.00 g, 5.50 mmol) in methanol (10 mL) was stirred at 65 °C overnight and then concentrated under reduced pressure. The resulting residue was subject to column chromatography (CH_2Cl_2/MeOH 2:1) to afford compound **28** as a pale yellow solid (1.35 g, 53%). ^{1}H NMR (CD_3OD, 300 MHz): δ 0.88–0.93 (m, 3H), 1.29–1.37 (m, 18H), 1.509–1.52 (m, 2H), 2.58–2.67 (m, 1H), 2.84–2.91 (m, 1H), 3.10–3.16 (t, J=4.6 Hz, 1H), 3.30–3.31 (m, 2H), 3.33–3.37 (m, 1H), 3.49–3.60 (m, 4H), 3.70–3.87 (m, 5H), 4.34–4.37 (d, J=5.0 Hz, 1H). MS (ESI): m/z 510 $[M+H]^+$. $C_{24}H_{47}NO_{10}$: C, 56.56; H, 9.30; N, 2.75. Found: C, 55.67; H, 9.43; N, 2.62.

4.1.15. Compound 24. To a stirred solution of lauric acid (0.60 g, 3.00 mmol) and methyl chloroformate (0.33 g, 3.00 mmol) in THF (8 mL) was added triethylamine (0.42 mL, 3.00 mmol) dropwise at 0 °C. The mixture was stirred for another 1 h at room temperature and filtered rapidly. The filtrate was then added to a solution of **28** (1.52 g, 3.00 mmol) in DMF. After stirring for another 12 h, the solvent was removed under reduced pressure. The resulting residue was triturated with chloroform (100 mL) and the organic phase was washed with water (20 mL×3), brine (20 mL) and dried over magnesium sulfate. Upon removal of the solvent with a rotavapor, the resulting crude product was purified by column chromatography (CH_2Cl_2/MeOH 8:1) to give **24** as a white solid (0.14 g, 67%). Mp 134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88–0.92 (m, 6H), 1.29–1.37 (m, 34H), 1.59–1.63 (m, 4H), 2.45–2.48 (t, J=5.3 Hz, 2H), 3.29–3.31 (m, 4H), 3.47–3.60 (m, 8H), 3.71–3.87 (m, 6H), 4.36–4.385 (d, J=5.7 Hz, 1H). MS (ESI): m/z 692 $[M+H]^+$. Anal. Calcd for $C_{36}H_{69}NO_{11}\cdot H_2O$: C, 60.90; H, 10.08; N, 1.97. Found: C, 60.72; H, 10.02; N. 1.87.

4.1.16. Crystal data for compound 1. $C_{43}H_{54}N_2O_6C_{l2}$, M=765.78, triclinic, space group P-1, a=11.415(4) Å, b=12.505(4) Å, c=15.308(5) Å, α=94.678(7), β=99.096(7), γ=103.542(6), U=2081.7(12) Å^3, Z=2, calcd density=1.222 Mg/m^3, absorption coefficient=0.204 mm^{-1}, 12,824 reflections collected (unique 9300), R_{int}=0.1294, crystal size: 0.488×0.350×0.148 mm.

4.1.17. Binding studies. For the fluorescent titration experiments, 2.5 mL of the mixture solution with the fixed concentration of **17** or **18** and the changing concentration of saccharide guests was placed in a cuvette and the fluorescent spectra (usually 15–20 spectra) were sequentially recorded at 23 °C. The values of the emission strength at fixed wavelengths were used. Origin 6.0 software was used to fit the data to a 1:1 binding isotherm: $\Delta I=(\Delta I_{max}/[H])\times\{0.5[G]+0.5([H]+K_d)-0.5[[G]^2+(2[S](K_d-[H])+(K_d+[H])^2)^{1/2}]\}$, where $[H]$ is the concentration of metallocyclophane, $[G]$ is the concentration of saccharide, and $K_d=(K_{assoc})^{-1}$. Association constants reported are the average values of two experiments. The ^{1}H NMR titration followed the same principle.

Acknowledgements

We thank the Ministry of Science and Technology (No. G2000078101), the National Natural Science Foundation, and the State Laboratory of Bioorganic and Natural Products Chemistry of China for support of this work.

References and notes

1. (a) Dietrich, B.; Viout, P.; Lehn, J. M. Macrocyclic Chemistry: Aspects of Organic and Inorganic Supra Molecular Chemistry; VCH: Weinheim, 1993; p 384. (b) Parker, D., Ed.; Oxford University Press: Oxford, 1996; p 252.
2. Blanco, M.-J.; Jimynez, M. C.; Chambron, J.-C.; Heitz, V.; Linke, M.; Sauvage, J.-P. *Chem. Soc. Rev.* **1999**, *28*, 293–306. (b) Baxter, P. N. W.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J.* **1999**, *5*, 102–112. (c) Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005–2062. (d) Sanders, J. K. M. *Pure Appl. Chem.* **2000**, *72*, 2265–2274. (e) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, 509–518. (f) Seidel, S. R.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972–983.

(g) Baldini, L.; Hunter, C. A. *Adv. Inorg. Chem.* **2002**, *53*, 213–243. (h) Schalley, C. A.; Lützen, A.; Albrecht, M. *Chem. Eur. J.* **2004**, *10*, 1072–1080.

3. Dinolfo, P. H.; Hupp, J. T. *Chem. Mater.* **2001**, *13*, 3113–3125. (b) Merlau, M. L.; del Pilar, M. M.; Nguyen, S. T.; Hupp, J. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4239–4242. (c) Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Sakamoto, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **2001**, *123*, 10454–10459. (d) Yoshizawa, M.; Takeyama, Y.; Kusukawa, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1347–1349. (e) Lee, S. J.; Hu, A.; Lin, W. *J. Am. Chem. Soc.* **2002**, *124*, 12948–12949. (f) Gianneschi, N. C.; Bertin, P. A.; Nguyen, S. T.; Mirkin, C. A.; Zakharov, L. N.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 10508–10509.
4. Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015–2022. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180. (c) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714–723. (d) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4012. (e) Sanford, A. R.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649–1659.
5. Delnoye, D. A. P.; Sijbesma, R. P.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, *118*, 8717–8718.
6. Wu, Z.-Q.; Jiang, X.-K.; Zhu, S.-Z.; Li, Z.-T. *Org. Lett.* **2004**, *6*, 229–232.
7. Whiteford, J. A.; Lu, C. V.; Stang, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 2524–2533. (b) Lee, S. J.; Hu, A.; Lin, W. *J. Am. Chem. Soc.* **2002**, *124*, 12948–12949. (c) Jiang, H.; Hu, A.; Lin, W. *Chem. Commun.* **2003**, 96–97. (d) Jiang, H.; Lin, W. *Org. Lett.* **2004**, *6*, 861–865.
8. Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587–10593. (b) Parra, R. D.; Zeng, H.; Zhu, J.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem. Eur. J.* **2001**, *7*, 4352–4357.
9. Legon, A. C. *Chem. Soc. Rev.* **1990**, *19*, 197–238.
10. Wallimann, P.; Marti, T.; Fürer, A.; Diederich, F. *Chem. Rev.* **1997**, *97*, 1567–1608. (b) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2978–2996. (c) James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159–200. (d) Striegler, S. *Curr. Org. Chem.* **2003**, *7*, 81–102.
11. Job, P. *Ann. Chim. Ser. 10* **1928**, *9*, 113–134.
12. Conners, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley: New York, 1987.
13. Pathak, A. K.; Pathak, V.; Maddry, J. A.; Suling, W. J.; Gurcha, S. S.; Besra, G. S.; Reynolds, R. C. *Bioorg. Med. Chem.* **2001**, *9*, 3145–3151.
14. de Goede, A. T. J. W.; Benckhuijsen, W.; van Rantwijk, F.; Maat, L.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 567–576.
15. Konstantinovic, S.; Imitrijevic, B.; Adulovic, V.; Indian *J. Chem. Sect. B* **2002**, *41*, 598–604.
16. Droz, A. S.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 2243–2289.
17. Kikuchi, Y.; Toi, H.; Aoyama, Y. *Bull. Chem. Soc. Jpn* **1993**, *66*, 1856–1862.
18. Turnbull, W. B.; Bruce, W.; Harrison, J. A.; Kartha, K. P. R.; Schenkman, S.; Field, R. A. *Tetrahedron* **2002**, *58*, 3207–3216.
19. Zolfigol, M. A.; Ghaemi, E.; Madrakian, E. *Synlett* **2003**, 191–194.
20. Zeng, H.; Miller, R. S.; Flowers, R. A.; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 2635–2644. (b) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15129–15142.
21. Corbett, J. F. *J. Chem. Soc., Perkin Trans. 2* **1972**, 999–1005.
22. Lockhoff, O.; Stadler, P. *Carbohydr. Res.* **1998**, *314*, 13–19.