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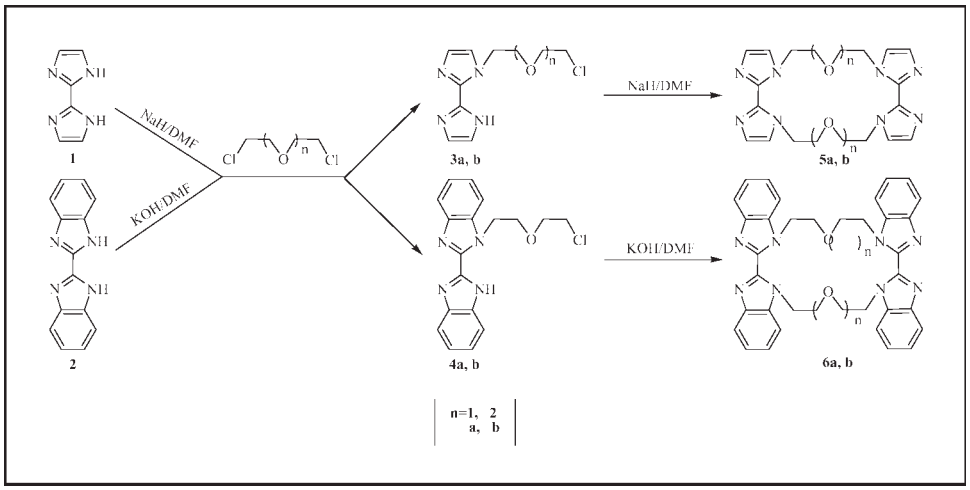

Cyclophanes based on 2,2′-biimidazole and 2,2′-bibenzimidazole were synthesized as receptors. UV spectroscopic titration in chloroform at 25°C showed 1:1 complexes between the cyclophanes and the guests, and the binding constants (K) and Gibbs free energy changes ($-\Delta G_0$) were calculated according to the modified Benesi-Hildebrand equation.

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INTRODUCTION

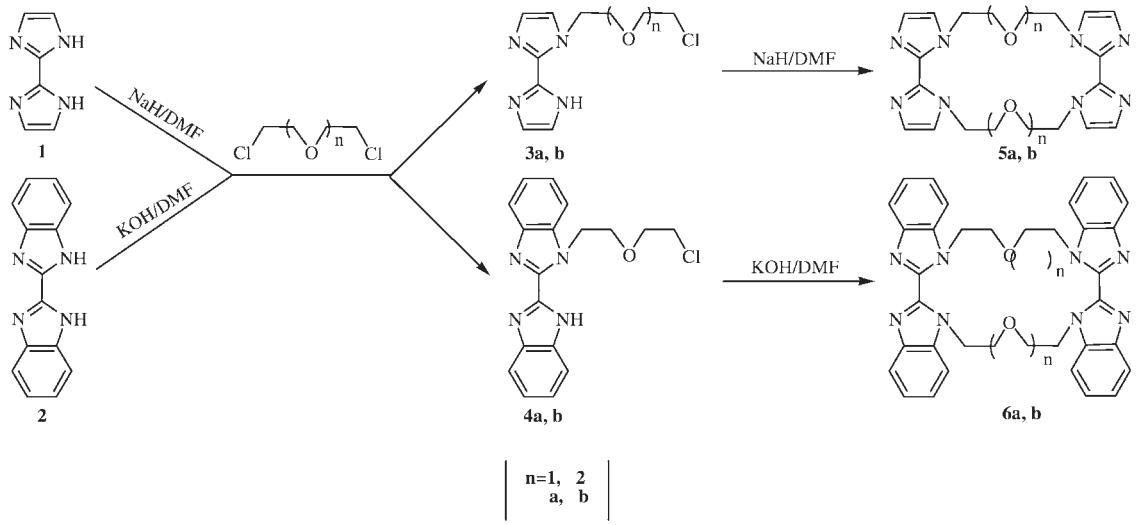
It is known that molecular recognition is a fundamental characteristic of biochemical system. The design and synthesis of receptors is of prime importance in supramolecular chemistry, due to its biological, medical, and environmental relevances [1,2]. During the last two decades, considerable attention have been addressed to develop systems capable of recognizing, self-assembling, catalyzing, and sensing, but the design of effective hosts for guests are still particularly challenging because of the characteristics of guests [3].

In biochemical host-guest processes, noncovalent interactions, such as, hydrogen bonding and coordination bonding play a central role in the creation of a variety of molecular architectures for molecular recognition, molecular self-assembly, and supramolecular catalysis. Imidazole can serve as proton donor-acceptor, general acid-base, nucleophile, and selective binding group [4]. Compounds with imidazole ring systems have many pharmaceutical activities and play important roles in biochemical processes [5]. Imidazole-based cyclophanes have received increasing attention in host-guest chemistry and biomimetic chemistry. Pioneering work has been carried out by Shi and Thummel [6]. Although much progress has been achieved [7], the construction of cyclophanes are of only one or two imidazole rings and has not yet overtaken the natural high efficiency and selectivity. We recently synthesized novel multiimidazole cyclophanes linked by alkyl groups [8]. However, these receptors only show poor recognition ability for amino acid esters. Noncovalent interactions, especially, hydrogen bonding and π-π stacking interaction may contribute to the attractive forces between hosts and guests. Because of the greater chemical stability and bidentate chelating sites [9], 2,2′-biimidazole (**Biim**) and 2,2′-bibenzimidazole (**BiBim**) are chosen as the component. We report, herein, the facile synthesis and characterization of novel multiimidazole cyclophanes which are comprised of four imidazole rings linked by ether chains (Scheme 1), and found that these artificial receptors exhibit excellent recognition ability toward amino acid esters.

RESULTS AND DISCUSSION

Design and synthesis of cyclophanes 5a,b and 6a,b. Cyclophanes **5a,b** and **6a,b** with different cavity and structure were designed and synthesized.

Scheme 1



Cyclophane **5a** contains four imidazole rings that could function as binding sites and two oxygen atoms on the macrocyclic skeleton that might serve as two hydrogen bonding recognition sites. Cyclophane **5b** also has four imidazole rings but with bigger cavity. For comparison, cyclophanes **6a**,**b** with more aromatic **BiBim** subunits linked to polyether dichlorides were also synthesized.

The multiimidazole compounds are generally considered to be difficult to prepare because of low solubility and several reactive sites. The reaction conditions have a significant influence on the selectivity. The *N*-alkylation of **Biim** and **BiBim** may have many possible substitutions at different sites, such as, quaternization or *N*,*N*′-bridged cyclization, 1,1′-disubstitution. By optimizing conditions, these competitive reactions can be minimized. Temperature and basicity are important in obtaining products. The temperature of the reaction affects on the yields of [1 + 1] and [2 + 2] cyclization. Excessive heating may lead [1 + 1] condensation. If excessive base are used, the mixture of quaternization, *N*,*N*′-bridged cyclization and 1,1′-disubstitution are formed. Under equivalent basicity to **Biim** and **BiBim**, 1-substitution of **Biim** and **BiBim** are produced. The bridged **Biim** and **BiBim** intermediates were synthesized by the *N*-alkylation of **Biim** and **BiBim**, respectively, with the corresponding polyether dichlorides in the presence of a slight excess of NaH or KOH in dry DMF at 70°C. The cyclization reactions of the bridged

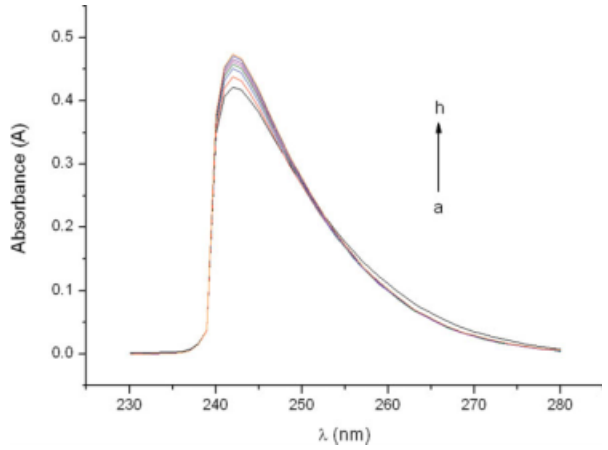


Figure 1. Spectrum of **5a** with varying Val-OMe concentration at 25°C ± 0.1°C. The concentration of **5a** is 6.8×10^{-5} mol dm^{-3}. The concentration of Val-OMe (mol dm^{-3}) are 0, 10×10^{-5}, 20×10^{-5}, 30×10^{-5}, 40×10^{-5}, 50×10^{-5}, 60×10^{-5}, and 70×10^{-5} reading from a to h. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

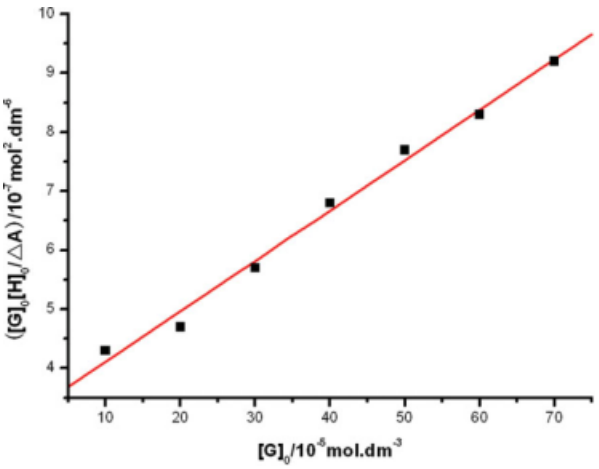


Figure 2. Typical plots of $[G]_0[H]_0/\Delta A$ versus $[G]_0$ for the host-guest complexation of Val-OMe and **5a** at 25°C ± 0.1°C. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 1

Binding constants (K) and Gibbs free energy of complexation ($-\Delta G_0$) for the 1:1 complexes between cylcophanes and guests in $CHCl_3$ at 25°C.

Entry	Host	Guest[a]	K (dm^3 mol^{-1})	$-\Delta G_0$ (kJ mol^{-1})
1	**5a**	Ala-OMe	377	14.71
2	**5a**	Val-OMe	2656	19.55
3	**5a**	Leu-OMe	707	16.27
4	**5a**	Pro-OMe	1330	17.83
5	**5a**	Gly-OMe	160	12.58
6	**5b**	Ala-OMe	429	15.03
7	**5b**	Val-OMe	960	17.02
8	**5b**	Leu-OMe	480	15.31
9	**5b**	Pro-OMe	2750	19.64
10	**5b**	Gly-OMe	687	16.20
11	**6a**	Ala-OMe	913	16.90
12	**6a**	Val-OMe	3295	20.08
13	**6a**	Leu-OMe	1502	18.13
14	**6a**	Pro-OMe	544	15.61
15	**6a**	Gly-OMe	734	16.36
16	**6b**	Ala-OMe	980	17.08
17	**6b**	Val-OMe	960	17.02
18	**6b**	Leu-OMe	725	16.33
19	**6b**	Pro-OMe	723	16.32
20	**6b**	Gly-OMe	1358	17.89

[a] Ala-OMe, alanine methyl ester; Leu-OMe, leucine methyl ester; Pro-OMe, proline methyl ester; Val-OMe, valine methyl ester; Gly-OMe, glycine methyl ester.

intermediates were carried out in DMF at 95°C. The slow addition of the intermediates made the cyclization facile and efficient. The structures proposed for these novel multiimidazole cyclophanes were confirmed by elemental analysis, MS, and ^{1}H NMR.

Molecular recognition of hosts in UV spectroscopic titration. Among the various methods to characterize host-guest interactions, the UV-vis titration method is widely used for its high sensitivity to host-guest binding [1,10]. In this article, the binding constants (K) of inclusion complexes of aforementioned receptors with amino acid esters were determined on the basis of the differential UV spectrometry in chloroform. In UV spectroscopic titration experiments, addition of varying concentration of amino acid derivatives resulted in a gradual increase of the characteristic absorptions of the host molecules. Typical UV spectral changes upon the addition of valine methyl ester (**Val-OMe**) to host **5a** are shown in Figure 1.

With the assumption of a 1:1 stoichiometry, the complexation of amino acid derivatives (G) with cyclophane (H) is expressed by eq. (1):

$$H + G \rightleftharpoons GH \tag{1}$$

Under the conditions used, the concentration of the receptors (6.8×10^{-5} mol dm^{-3}) is much lower than that of amino acid derivatives, that is, $[H]_0 << [G]_0$. Therefore, the stability constant of supramolecular system formed can be calculated according to the modified Hildebrand-Benesi equation [11], eq. (2).

$$[G]_0[H]_0/\Delta A = 1/K\Delta\varepsilon + [G]_0/\Delta\varepsilon \tag{2}$$

where $[H]_0$ represents the total concentration of host, $[G]_0$ denotes the total concentration of guest amino acid derivatives, $\Delta\varepsilon$ is the difference between the molar extinction coefficient for the free and complexing cyclophane, ΔA denotes the changes in the absorption of the host on adding amino acid derivatives. For all guest molecules examined, plots of calculated $[G]_0[H]_0/\Delta A$ values as a function of porting the 1:1 complex formation. Typical plots are shown for the complexation of compound **5a** with Val-OMe in Figure 2.

The association constants (K) and the free-energy change ($-\Delta G_0$) calculated from the slope and the intercept are shown in Table 1. Inspection of Table 1 shows that these receptors can recognize the differences between the cyclophane size and shape of amino acid derivatives. Our study clearly demonstrates that the different cavity size strongly influences the recognition ability of the cyclophane receptor. The multiimidazole cyclophane **5a** shows selective binding to amino acid derivatives in chloroform. For example, the association constants (K) of **5a** and **5b** for Val-OMe are 2656 and 960, respectively. The similar structure of **5a** and **6a** gives us the similar association constants (K) for Val-OMe, which are 2656 and 3295, respectively. Thus, the

cavity size, steric effects, and structural rigidity of the receptors may play an important role in the selective recognition.

Figure 3 and Table 1 show the selective recognition ability of the receptor **6a** with α-animo acid esters, affording the K of 544–3295 and the ΔG_0 of 15.61–20.08 KJ mol^{-1}. The selectivity is highly sensitive to the chain length and shape of the substituted group in amino acids. Indeed, the receptor **6a** exhibits stronger binding for amino acid esters containing an acyclic group, inferring the hydrogen bonding interaction between the receptor and the amino acid is the principal attractive interaction involved. The acyclic Val-OMe is included most effectively by **6a**, giving the highest and the strongest binding. According to CPK model, when Val-OMe is embedded into the cavity, the supramolecular complex should be formed (Fig. 4). It has been proposed that the dimension of the cavity of cyclophane **6a** is more suitable for Val-OMe than other amino acid esters.

Different structure strongly influences the recognition ability of the receptor for amino acid esters. The similar structures **5b** and **6b** give us the association constants (K) for Gly-OMe, which are 687 and 1358, respectively. From this result, we think that the π-π stacking interaction between the receptor and the aromatic side chain of amino acid play an important role in recognition. Because **5b** and **6b** have bigger cavity, they cannot be propitious to the formation of stable supramolecular system. They give us low selective ability.

CONCLUSION

In conclusion, a facile synthesis led to cyclophanes based on biimidazole and bibenzimidazole units as molecular recognition motifs for amino acid esters. These receptors exhibit excellent recognition ability toward amino acid derivatives. The cavity size, steric effects, and structural rigidity, hydrogen bond, and π-π stacking interaction between the aromatic groups may be responsible for the recognition of amino acid derivatives.

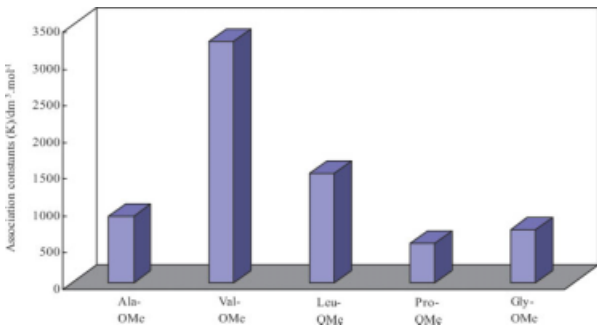


Figure 3. Recognition ability of the cyclophane **6a** for α-animo acid esters. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

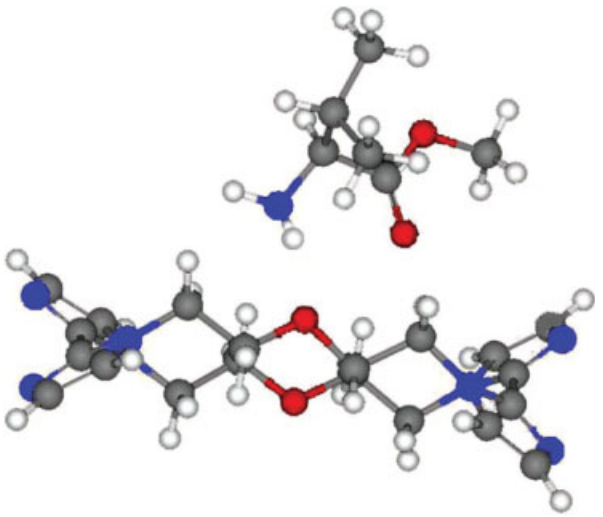


Figure 4. Proposed recognition mechanism of Val-OMe by host **5a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

EXPERIMENTAL

Physical measurements. Melting points were taken on a X-6 micro-melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE/400 MHz instrument, and chemical shifts in ppm were reported with TMS as the internal standard. Mass spectra (ms) were measured on a VG Autospec 3000 mass spectrometer. Elemental analyses were performed on a Carlo Erba 1106 instrument. UV-vis spectra were obtained with TU-1810 spectrophotometer.

Reagents and general techniques. Anhydrous DMF was purified according to the standard method. **Biim** [12], **BiBim** [13], and polyether dichlorides [14] were prepared according to literature procedure. Amino acid methyl ester hydrochloride used was prepared by adding dropwise $SOCl_2$ into a suspension of the free amino acid in absolute methanol at 0°C. Free amino acid esters were obtained by neutralization with $NH_3{\cdot}nH_2O$ before use. All other chemicals and reagents were obtained commercially and used without further purification.

General procedure for preparation of 3a, b and 4a, b. In a 25-mL flask, **Biim** or **BiBim** (5 mmol), DMF (10 mL) and NaH or KOH (6 mmol) were stirred at room temperature. Polyether dichlorides (5 mmol) was added quickly. The mixture was stirred for 12 h at 70°C. The solid was filtered and washed with a less absolute ethanol. The combined solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (dichloromethane/ethanol 19:1 or petroleum ether/ethyl acetate 4:1) to give the pure products **3a,b** and **4a,b**.

1-(5-Chloro-3-oxa-pentyl)-2,2′-biimidazole, 3a. Red viscous liquid, yield 63.1% ^{1}H NMR ($CDCl_3$) δ: 3.539–3.564 (t, 2H, CH_2Cl), 3.681–3.709 (t, 2H, $ClCH_2$—CH_2O), 3.912–3.937 (t, 2H, NCH_2—CH_2O), 4.875–4.900 (t, 2H, NCH_2), 7.114 (d, 2H, BiIm 5,5′-H), 7.144 (d, 2H, BiIm 4,4′-H) ppm; ms (m/z): 241.08 ($M+H^+$). Anal. Calcd for $C_{10}H_{13}ClN_4O$: C 49.90, H 5.44, N 23.28, Cl 14.73; found: C 50.08, H 5.47, N 23.48, Cl 14.85.

1-(8-Chloro-3,6-dioxa-octyl)-2,2′-biimidazole, 3b. Red viscous liquid, yield 42.1% ^{1}H NMR ($CDCl_3$) δ: 3.575–3.590 (t, 2H, CH_2Cl), 3.598–3.612 (t, 2H, $ClCH_2$—CH_2O), 3.678–3.850 (m, 4H, OCH_2—CH_2O), 3.869–3.914 (t, 2H, NCH_2—CH_2O), 4.876–4.900 (t, 2H, NCH_2), 7.114 (d, 2H, BiIm 5,5′-H), 7.154 (d, 2H, BiIm 4,4′-H) ppm; ms (*m/z*): 285.10 ($M+H^+$). Anal. Calcd for $C_{12}H_{17}ClN_4O_2$: C 50.62, H 6.02, N 19.68, Cl 12.45; found: C 50.83, H 6.15, N 19.80, Cl 12.54.

1-(5-Chloro-3-oxa-pentyl)-2,2′-bibenzimidazole, 4a. Pale yellow solid, yield 61.6% ^{1}H NMR ($CDCl_3$) δ: 3.498–3.508 (t, 2H, CH_2Cl), 3.724–3.733 (t, 2H, $ClCH_2$—CH_2O), 4.149–4.158 (t, 2H, NCH_2—CH_2O), 5.294–5.302 (t, 2H, NCH_2), 7.261–7.850 (m,8H, Ar—H) ppm; ms (*m/z*): 343.12 ($M+H^+$). Anal. Calcd for $C_{18}H_{19}ClN_4O$: C 63.06, H 5.59, N 16.34, Cl 10.34; found: C 63.16, H 5.61, N 16.56, Cl 10.50.

1-(8-Chloro-3,6-dioxa-octyl)-2,2′-bibenzimidazole, 4b. Pale yellow solid, yield 40.9% ^{1}H NMR ($CDCl_3$) δ: 3.534–3.586 (t, 2H, CH_2Cl), 3.641–3.669 (t, 2H, $ClCH_2$—CH_2O), 3.925–3.950 (m, 4H, OCH_2—CH_2O),4.116–4.125 (t, 2H, NCH_2—CH_2O), 5.186–5.194 (t, 2H, NCH_2), 7.186–7.781 (m,8H, Ar—H) ppm; ms (*m/z*): 285.10 ($M+H^+$). Anal. Calcd for $C_{12}H_{17}ClN_4O_2$: C 50.62, H 6.02, N 19.68, Cl 12.45; found: C 50.83, H 6.15, N 19.80, Cl 12.54.

General procedure for the synthesis of cyclophanes 5a, b and 6a, b. To a stirred and warmed (95°C) solution of NaH or KOH (2.5 mmol) and DMF (5 mL), compounds **3a, b** and **4a, b** (2.1 mmol) in DMF was added dropwise over 5 h. The mixture was stirred at this temperature for 20 h. The solid was filtered and washed with a less absolute ethanol. The combined solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (dichloromethane/ethanol 14:1 or petroleum ether/ethyl acetate 1:1) to give the pure products **5a, b** and **6a, b**.

Cyclophane 5a. Off-white solid, yield 45.6%, mp 186–188°C. ^{1}H NMR ($CDCl_3$) δ: 3.770–3.794 (t, 8H, OCH_2), 3.950–3.971 (t, 8H, NCH_2), 7.192 (s, 4H, BiIm 5,5′-H), 7.323 (s, 4H, BiIm 4,4′-H) ppm; ms (*m/z*): 409.5 ($M+H^+$). Anal. Calcd for $C_{20}H_{24}N_8O_2$: C 58.81, H 5.92, N 27.43; found: C 58.63, H 5.95, N 27.23.

Cyclophane 5b. Off-white solid, yield 24.1%, mp 172–174°C. ^{1}H NMR ($CDCl_3$) δ 3.610–3.632 (t, 8H, OCH_2—CH_2O), 3.683 (s, 8H, NCH_2—CH_2O), 3.735–3.757 (t, 8H, NCH_2), 7.030 (s, 4H, BiIm 5,5′-H), 7.149 (s, 4H, BiIm 4,4′-H) ppm; ms (*m/z*): 497.2 ($M+H^+$). Anal. Calcd for $C_{24}H_{32}N_8O_4$: C 58.05, H 6.50, N 22.57; found: C 57.87, 6.46, 22.28.

Cyclophane 6a. Off-white solid, yield 42.3%, mp 161–163°C. ^{1}H NMR ($CDCl_3$) δ: 3.797–3.821 (t, 8H, OCH_2), 4.189–4.212 (t, 8H, NCH_2), 7.405–7.948 (m, 16H, Ar—H) ppm; ms (*m/z*): 609.1 ($M+H^+$). Anal. Calcd for $C_{36}H_{32}N_8O_2$: C 71.04, H 5.30, N 18.41; found: C 70.87, H 5.28, N 18.23.

Cyclophane 6b. Off-white solid, yield 22.3%, mp 124–126°C. ^{1}H NMR ($CDCl_3$) δ: 3.424–3.474 (m, 8H, OCH_2—CH_2O), 3.559–3.644 (m, 8H, NCH_2—CH_2O), 4.053–4.080 (t, 8H, NCH_2), 7.259–7.717 (m, 16H, Ar—H) ppm; ms (*m/z*): 697.0 ($M+H^+$). Anal. Calcd for $C_{40}H_{40}N_8O_2$: C 68.95, H 5.79, N 16.08; found: C 70.13, H 5.77, N 15.96.

UV titration. UV spectra were recorded on a TU-1810 UV-vis spectrophotometer at 25°C ± 0.1°C with a 1-cm quartz cell. A 3.0 mL of chloroform solution of host was put into the cell. After the cell temperature had become constant at 25°C with a thermostatic cell compartment, the solution of amino acid esters in chloroform was added in portions via microsyringe to the cell. The concentration of guest increased along with each addition, as far as the concentration of guest reached about 15-fold of the concentration of host. Different absorption spectra were obtained directly using the instrument according to its normal procedure. The absorption of the guest was cancelled by using the guest solutions of $[G]_0$ concentration for each titration as the reference solution. The whole volume of guest solution added to the cell did not exceed 100 μL to dispel the effect of volume change. For example, when the concentration of host **5a** was 6.8×10^{-5} mol dm^{-3}, its maximum absorption wavelength was at 242 nm, and the absorbance A_0 was 0.422. When the guest Val-OMe was portion-wise added to the cell to make its concentration of 10×10^{-5}, 20×10^{-5}, 30×10^{-5}, 40×10^{-5}, 50×10^{-5}, 60×10^{-5}, 70×10^{-5} mol dm^{-3}, respectively, the maximal absorption increased orderly and gave the corresponding ΔA ($A-A_0$) values 0.016, 0.029, 0.036, 0.040, 0.044, 0.049, 0.052. According to eq. (2), plots of calculated $[G]_0[H]_0/\Delta A$ values as a function of $[G]_0$ values gave an excellent linear relationship (Fig. 2). From Figure 2, we can obtain the association constant $K = 2655$ dm^3 mol^{-1}.

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