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Homochiral molecular tweezers as hosts for the highly enantioselective recognition of amino acid derivatives

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Abstract—Novel homochiral molecular tweezers comprised of two chiral macrocyclic polyamine skeletons have been developed. These homochiral artificial receptors exhibit excellent chiral recognition ability toward the enantiomers of L- and D-amino acid derivatives (up to $K_L/K_D = 7.9$, $\Delta\Delta G_0 = -5.12$ kJ mol^{-1}) in $CHCl_3$ at 25.0°C.

Molecular recognition is a fundamental characteristic of biochemical systems. The study of synthetic model systems could contribute to the understanding of these processes and, at the same time, offer new perspectives for the development of pharmaceuticals, enantiomer-selective sensors, catalysts, selectors and other molecular devices.[1] One area that has proven especially challenging is the creation of enantioselective artificial receptors.[2] Since Cram et al. reported their pioneering research on the use of chiral macrocyclic ligands in enantiomer recognition,[3] a great number of chiral artificial receptors have been synthesized and studied. Among these, the chiral macrocyclic compounds involving cyclophanes,[4] crown ethers[5] and cyclodextrins[6] are the dominant structures.

Recently, considerable attention has been addressed to macrocyclic oxo-polyamines because their structures bear the dual features of oligopeptides and macrocyclic polyamines.[7] However, few examples have been reported dealing with the synthesis and chiral recognition studies of chiral macrocyclic oxo-polyamines. We recently synthesized novel chiral macrocyclic tetraoxo-polyamines containing a pyridine ring and two functional side arms that are oriented in an *anti* fashion.[8] However, these receptors only show poor enantioselective recognition ability for D- and L-amino acid esters. Starting from bridged histidine ester, a chiral imidazole cyclophane receptors had been synthesized, and they exhibit good chiral recognition toward the enantiomers of L- and D-amino acid derivatives (up to $K_D/K_L = 3.52$).[9] The general shape of naturally occuring receptors often features a molecular tweezer. The molecular tweezers are particularly effective in regard to complementarity in size, shape and functional groups in molecular recognition, and share the advantage of the microenvironments complementarity to asymmetric molecules.[10] Herein, we describe the development of novel chiral molecular tweezers, which are comprised of two chiral macrocyclic oxo-polyamine skeletons linked by rigid spacers like xylene or diacylpyridine unit (Scheme 1), and found that these chiral artificial receptors exhibit excellent chiral recognition ability toward amino acid derivatives. To our knowledge, this is the first example of a chiral bis-macrocyclic oxo-polyamine type molecular tweezer as an excellent chiral recognition host.

Recently we reported the synthesis of a series of new chiral macrocyclic tetraoxo-polyamines containing a pyridine ring and two functional side arms **1**.[8] Chiral molecular tweezers **2**–**4** were prepared by the condensation of the macrocyclic polyamine **1** and the corresponding 2,6-bis(chlorocarbonyl)pyridine, α,α′-dibromo-*m*-xylene, and α,α′-dibromo-*p*-xylene with the yields of 40.0, 72.1 and 71.2%, respectively. The structures proposed for these novel molecular tweezers are consistent with data obtained from elemental analysis, MS and ^{1}H NMR.

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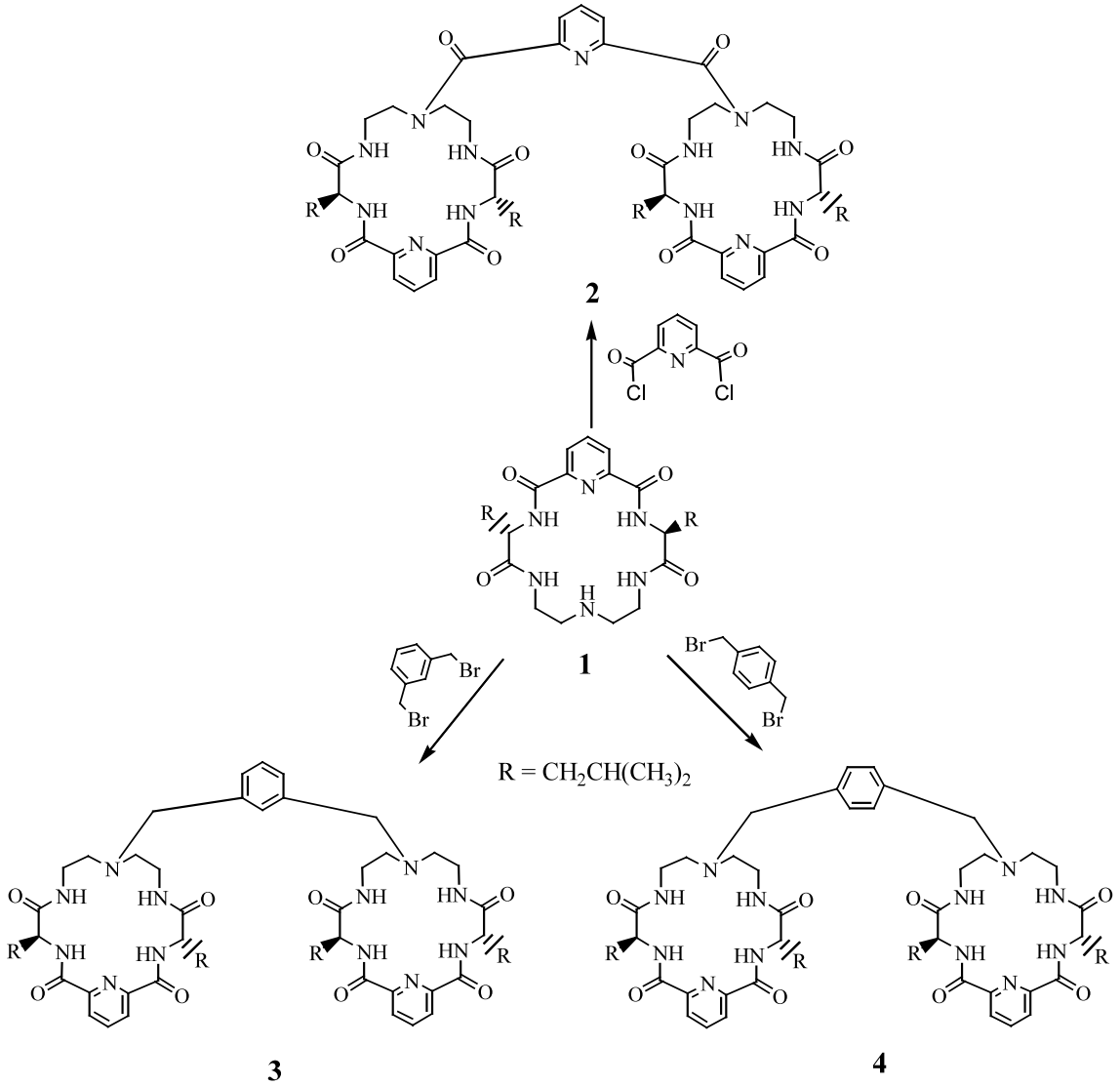

Scheme 1.

The binding constants (K) of inclusion complexes of above-mentioned tweezer-like receptors with amino acid esters were determined on the basis of the differential UV spectrometry in chloroform.[6b,11] Differential absorption spectra were obtained directly using the instrument according to its normal procedures. The quartz cells (1 cm) were kept at constant temperature (25±0.1°C) with a thermostated cell compartment.

In the titration experiments using UV spectrometry, as can be seen from Figure 1, the absorption maximum of all hosts gradually decreased with the addition of various concentrations of amino acid derivatives.

With the assumption of a 1:1 stoichiometry, the complexation of amino acid derivatives (G) with chiral bis-macrocyclic oxo polyamine type molecular tweezer (H) is expressed by Eq. (1):

$$H+G \overset{K}{\rightleftharpoons} G.H \quad (1)$$

Under the conditions employed, the concentration of the receptors (2.0×10^{-4} mol dm^{-3}) is much lower than that of amino acid derivatives, i.e. $[H]_0<<[G]_0$. Therefore, the stability constant of supramolecular system formed can be calculated according to the modified

$$[G]_0[H]_0/\Delta A = 1/K\Delta\varepsilon + [G]_0/\Delta\varepsilon \quad (2)$$

Hildebrand–Benesi equation,[12] Eq. (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 complexed chiral bis-macrocyclic oxo polyamine type molecular tweezer, 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 $[G]_0$ values give an excellent linear relationship, supporting the 1: 1 complex formation. Typical plots are shown for the complexation of compound **4** with L-Leu-OMe in Figure 2.

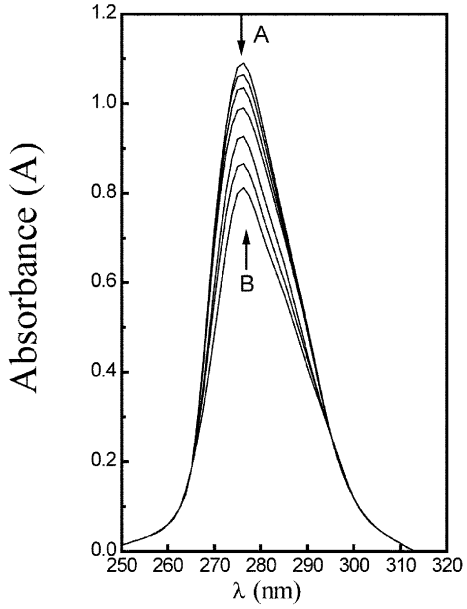

Figure 1. Spectrum of **4** with varying L-Leu-OMe concentration at 25±0.1°C. The concentration of the chiral tweezer **4** is 2.0×10^{-4} mol dm^{-3}. The concentrations of L-Leu-OMe (mol dm^{-3}) are 0, 5.0×10^{-4}, 10.0×10^{-4}, 25.0×10^{-4}, 50.0×10^{-4}, 75.0×10^{-4} and 100.0×10^{-4} reading from A to B.

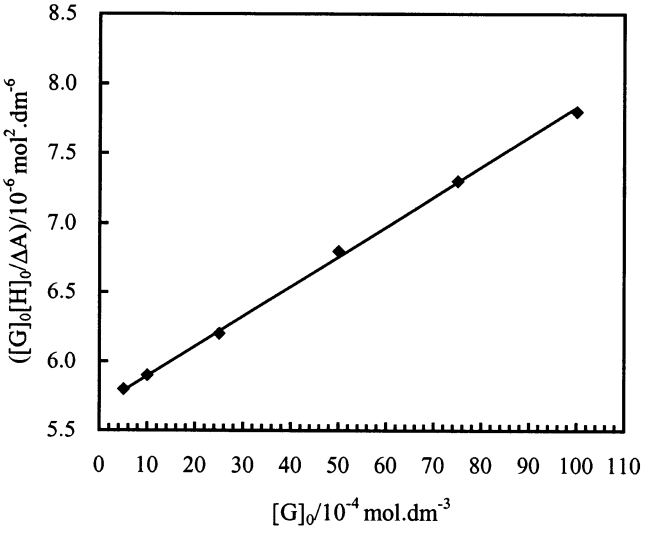

Figure 2. Typical plots of $[G]_0[H]_0/\Delta A$ versus $[G]_0$ for the host–guest complexation of L-Leu-OMe and **4** at 25±0.1°C.

The association constants (K) and the free-energy change ($-\Delta G_0$) calculated from the slope and the intercept are shown in Table 1, along with enantioselectivity K_L/K_D or $\Delta\Delta G_0$ calculated from $-\Delta G_0$ for the complexation of L/D-amino acid esters by these hosts. As shown in Table 1, chiral macrocyclic tetraoxo polyamine **1** only showed poor enantioselective recognition ability for D- and L-amino acid esters (entries 1–4). As expected, relative to the parent compound **1**, the chiral tweezers gave fairly good enantiomer recognition ability. More interestingly, these chiral clefts do show good recognition for the L-isomers of amino acid esters, while the parent receptor **1** prefers to the D-isomers. Inspection of Table 1 shows that these tweezer-like receptors can recognize not only differences between the molecular size and shape of amino acid derivatives, but also the chirality of the L- or D-isomer. The enhanced chiral recognition ability of these tweezer-like receptors has been suggested to arise from the cooperative binding of two chiral macrocyclic polyamines moieties.

Our study clearly demonstrates that the different spacer strongly influences the chiral recognition ability of the tweezer-like receptor. For example, the association constants (K) of **2** and **4** for L-Leu-OMe are 68.0 and 36.8, respectively, which correspond to L/D-selectivity (K_L/K_D) of 2.70 and 1.33 for leucine methyl ester. The similar structures of **2** and **3** give us the similar association constants (K) for L-Leu-OMe, which are 68.0 and 59.9, respectively. Thus, the cleft size, steric effects and structural rigidity of the tweezer-like receptor may play an important role in chiral recognition.

Figure 3 and Table 1 show the enantioselective recognition ability of the chiral tweezer **2** with α-amino acid esters, affording the K_L/K_D of 1.21–7.90 or the $\Delta\Delta G_0$ of −0.48 to −5.12 kJ mol^{-1}. The L/D-enantioselectivities is highly sensitive to the chain length and shape of the substituted group in amino acids. Indeed, the receptor **2** exhibits stronger binding and better enantioselectivity for amino acid esters containing an aromatic group than for those possessing an aliphatic group, inferring that the π–π stacking interaction between the receptor and the aromatic side chain of amino acid is the principal attractive interaction involved. The aromatic Trp-OMe is included most effectively by **2**, giving the highest L/D-selectivity ($K_L/K_D=7.9$, $\Delta\Delta G_0=-5.12$ kJ mol^{-1}) and the strongest binding ($K_L=1280$ dm^3 mol^{-1}, $K_D=162$ dm^3 mol^{-1}). According to CPK model, when L-Trp-OMe is embedded into the chiral cleft, the sandwich-like supramolecular complex should be formed (Fig. 4). It has been proposed that the strongest recognition ability of chiral tweezer **2** for L-Trp-OMe is due to the following interactions: the strong π–π stacking of indolyl unit with the pyridyl group of one macrocyclic tetraoxo polyamine moiety, and the felicitous binding of NH_2 group through hydrogen bonds with another macrocyclic tetraoxo polyamine unit.

Different linker strongly influences the chiral recognition ability of the tweezer-like receptor for amino acid esters. The similar structures of **2** and **3** give us the similar association constants (K) for L-Leu-OMe, which are 68.0 and 59.9, respectively. From this result, we think that the structure of tweezer-like receptor and the distance of two macrocyclic tetraoxo polyamine units maybe play an important role in chiral recognition. Because two macrocyclic tetraoxo polyamine units of host **4** are located at the 1-, 4-position of phenyl group, it cannot be propitious to the formation of supramolecular system. It gives us lower association constants and chiral recognition ability.

Table 1. Binding constants(K), the Gibbs free energy changes ($-\Delta G_0$), enantioselectivities K_L/K_D and $\Delta\Delta G_0$ calculated from $-\Delta G_0$ for the complexation of L/D-amino acid esters with the chiral receptors **1**–**4** in $CHCl_3$ at 25°C[a]

Enry	Host	Guest[b]	K (dm^3 mol^{-1})	K_L/K_D	$-\Delta G_0$ (kJ mol^{-1})	[c]$\Delta\Delta G_0$ (kJ mol^{-1})
1	**1**	L-Phe-OMe	46.3	0.75	9.50	0.73
2	**1**	D-Phe-OMe	62.0		10.23	
3	**1**	L-Trp-OMe	58.0	0.67	10.06	0.98
4	**1**	D-Trp-OMe	86.1		11.04	
5	**2**	L-Ala-OMe	74.1	1.21	10.67	−0.48
6	**2**	D-Ala-OMe	61.2		10.19	
7	**2**	L-Leu-OMe	68.0	2.70	10.45	−2.46
8	**2**	D-Leu-OMe	25.2		7.99	
9	**2**	L-Phe-OMe	213	3.92	13.28	−3.38
10	**2**	D-Phe-OMe	54.4		9.90	
11	**2**	L-Trp-OMe	1280	7.90	17.72	−5.12
12	**2**	D-Trp-OMe	162		12.60	
13	**3**	L-Leu-OMe	59.9	2.00	10.14	−1.71
14	**3**	D-Leu-OMe	30.0		8.43	
15	**4**	L-Leu-OMe	36.8	1.33	8.93	−0.72
16	**4**	D-Leu-OMe	27.7		8.23	

[a] The concentration of the receptors: 2.0×10^{-4} mol dm^{-3}.
[b] Ala-OMe: alanine methyl ester; Leu-OMe: leucine methyl ester; Phe-OMe: phenylalanine methyl ester; Trp-OMe: tryptophane methyl ester.
[c] $\Delta\Delta G_0 = \Delta G_{0(L)} - \Delta G_{0(D)}$.

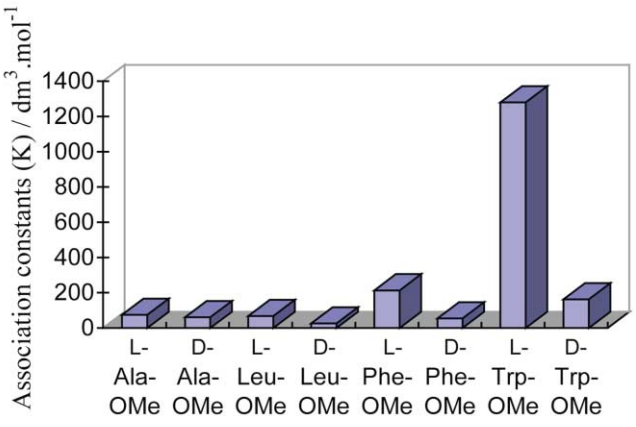

Figure 3. Recognition ability of the chiral tweezer **2** for α-amino acid esters.

In conclusion, these chiral molecular tweezers exhibit excellent chiral recognition ability toward the enantiomers of L- and D-amino acid derivatives. The tweezer shape, steric effects, structural rigidity, hydrogen bond and π–π stacking between the aromatic groups may be responsible for the enantiomeric recognition of amino acid derivatives.

1. Experimental

1.1. Physical measurements

Melting points were taken on a micro-melting apparatus and are uncorrected. ^1H NMR spectra were recorded at 400 MHz, and chemical shifts in ppm are reported relative to internal Me_4Si. Mass spectra data were recorded on a VG Autospec 3000 mass spectrometer. Elemental analyses were performed with a Carlo Erba 1106 instrument. Optical rotations were taken on a WZZ-1 polarimeter. UV spectra were measured on a Shimadzu UV-265FW spectrophotometer equipped with a thermostated cell compartment.

1.2. Reagents and general techniques

Anhydrous chloroform for UV measurements was prepared by washing with concentrated sulfuric acid and water to remove EtOH, drying with anhydrous magnesium sulfate, and distilling over phosphorus pentoxide. 2,6-Bis(chlorocarbonyl)pyridine,[13] α,α′-dibromo-*p*-xylene, α,α′-dibromo-*m*-xylene[14] and compound **1**[8] 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 $NH_3\cdot H_2O$ before use. All other chemicals and reagents were obtained commercially and used without further purification.

1.3. General procedures for the synthesis of chiral molecular tweezers

To a suspension of 0.22 mmol of compound **1** and 0.65 mmol of K_2CO_3 in 12 mL of $CHCl_3$, 0.108 mmol of 2,6-bis(chlorocarbonyl)pyridine, α,α′-dibromo-*p*-xylene or α,α′-dibromo-*m*-xylene in 20 mL of $CHCl_3$ was added dropwise at room temperature over 5 h. The mixture was stirred at this temperature for 20 hours, and 10 mL of water was then added. The organic layer was separated, and dried over anhydrous $MgSO_4$. The solvent was removed under vacuo to get a yellow solid. The resulting crude was purified by chromatography on silica gel using $CHCl_3/CH_3OH = 15{:}1$ as eluent to get a white solid.

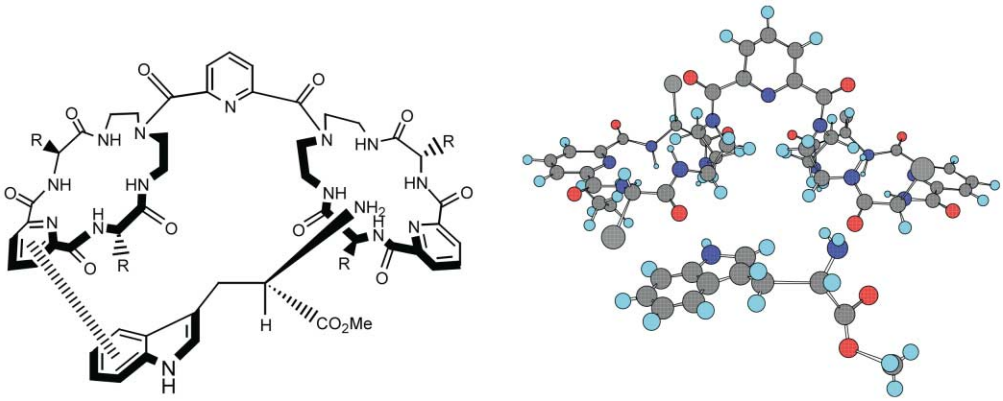

Figure 4. Proposed recognition mechanism of L-Trp-OMe by host **2**.

1.3.1. Bis{9-[(4*S*,14*S*)-4,14-diisobutyl-2,5,13,16-tetraoxo-3,6,9,12,15,21 - hexaazabicyclo[1.5.3.1]heneicosa - 1(21),17,19-triene]}-2′,6′-dicarbonylpyridine 2. Yield 40.0%; mp 209–210°C; $[\alpha]_D^{25}=-15.1$ (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 24H, $8CH_3$), 1.23 (m, 12H, $4CH_2CH(CH_3)_2$), 2.65 (m, 8H, $2CH_2NCH_2$), 3.72 (m, 8H, $4CONHCH_2$), 4.59 (m, 4H, $4CHCH_2$-$CH(CH_3)_2$), 7.20 (br, 4H, $4CH_2NHCO$), 8.01 (m, 9H, 3Py), 8.67 (br, 4H, 2PyCO*NH*) ppm. MS (m/z): 1053 (M^++1, 100). Anal. calcd for $C_{53}H_{73}O_{10}N_{13}$: C 60.49, H 6.99, N 17.31; found: C 60.11, H 6.98, N 17.00.

1.3.2. Bis{9-[(4*S*,14*S*)-4,14-diisobutyl-2,5,13,16-tetraoxo-3,6,9,12,15,21-hexaazabicyclo[1.5.3.1]heneicosa-1(21),17,19-triene]}-1′,3′-dimethylbenzene 3. Yield 72.1%; mp 182–184°C; $[\alpha]_D^{25}=+28.8$ (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 24H, $8CH_3$), 1.20 (m, 12H, $4CH_2CH(CH_3)_2$), 2.39 (m, 8H, $2CH_2NCH_2$), 3.77 (m, 8H, $4CONHCH_2$), 4.64 (m, 4H, $4CHCH_2CH(CH_3)_2$), 6.87 (m, 4H, Ph), 7.20 (br, 4H, $4CH_2NHCO$), 8.03 (br, 6H, 2Py), 8.84(br, 4H, 2PyCO*NH*) ppm. MS (m/z): 1024 (M^++1, 100). Anal. calcd for $C_{54}H_{78}O_8N_{12}$: C 63.38, H 7.68, N 16.43; found: C 62.91, H 7.39, N 16.18.

1.3.3. Bis{9-[(4*S*,14*S*)-4,14-diisobutyl-2,5,13,16-tetraoxo-3,6,9,12,15,21-hexaazabicyclo[1.5.3.1]heneicosa-1(21),17,19-triene]}-1′,4′-dimethylbenzene 4. Yield 71.2%; mp 180–181°C. $[\alpha]_D^{25}=+20.0$ (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 24H, $8CH_3$), 1.23 (m, 12H, $4CH_2CH(CH_3)_2$), 2.38 (m, 8H, $2CH_2NCH_2$), 3.78 (m, 8H, $4CONHCH_2$), 4.74 (m, 4H, $4CHCH_2CH(CH_3)_2$), 6.98 (m, 4H, Ph), 7.25 (br, 4H, $4CH_2NHCO$), 8.04 (br, 6H, 2Py), 9.01 (br, 4H, 4PyCO*NH*) ppm. MS (m/z): 1024 (M^++1, 100). Anal. calcd for $C_{54}H_{78}O_8N_{12}$: C 63.38, H 7.68, N 16.43; found: C 63.10, H 7.32, N 16.11.

1.4. UV titration

UV spectra were recorded on a JASCO U-530 UV/vis spectrophotometer at 25±0.1°C with a 1 cm quartz cell. A 3.0 mL of chloroform solution of host (concentration was 2.0×10^{-4} mol dm^{-3}) 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 (concentration was 5.0×10^{-1} mol dm^{-3}) in chloroform was added in portions via microsyringe to the cell. The concentration of guest increases along with each addition, as far as the concentration of guest reaches about 60-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. And 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 **4** was 2.0×10^{-4} mol dm^{-3}, its maximum absorption wavelength is at 276.4 nm, and the absorbance A_0 is 1.089. When the guest L-Leu-OMe was portion-wise added to the cell to make its concentration of 5.0×10^{-4}, 10.0×10^{-4}, 25.0×10^{-4}, 50.0×10^{-4}, 75.0×10^{-4}, 100.0×10^{-4} mol dm^{-3}, respectively, the maximal absorption decreases orderly and gives the corresponding ΔA (A_0-A) values 0.017, 0.034, 0.081, 0.147, 0.205, 0.256. According to Eq. (2), plots of calculated $[G]_0[H]_0/\Delta A$ values as a function of $[G]_0$ values give an excellent linear relationship (Fig. 2). From Figure 2, we can obtain the association constant $K_L=36.8$ dm^3 mol^{-1}.

Acknowledgements

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