Chiral recognition of amino acid esters by zinc porphyrin derivatives

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Three novel chiral zinc porphyrins (**4a**–**4c**) with protected chiral amino acid substituents as chiral sources were synthesized. Their chiral recognition of amino acid methyl esters was investigated using UV-vis spectrophotometric titration. Some enantioselectivities obtained are higher than that of the known system, and the highest achieved in our study is 21.54 using host **4a** with $PheOCH_3$ as guest. We also show that higher enantioselectivity can be obtained at lower temperature. Circular dichroism spectra of chiral porphyrin derivatives binding to enantiomers of guests show great shape and intensity differences. Molecular modeling was performed to understand chiral recognition on a molecular level, and the results are in good agreement with the experimental data.

Chiral recognition is an attractive subject in the area of host–guest chemistry, since it is a fundamental process for a range of chemical and biological phenomena.[1–3] Several types of host molecules for chiral recognition studies have been reported[4–10] because of their biological and chemical importance. Among them, porphyrins are relatively accessible molecules, and this can be seen in the zinc and aluminium porphyrin studies reported over the past 15 years.[11–16] Methyl esters of amino acids are usually employed as guest molecules in chiral recognition studies. Certain chiral porphyrin receptors exhibit an enantioselectivity for amino acid esters as high as 7.5, the highest value reported so far.[11]

In current studies, the focus on chiral recognition is to enhance the enantioselectivity. It has been proposed that the enantioselectivity of the host for amino acid esters could be effectively enhanced by constructing a specific chiral environment derived from protected amino acids on host molecules. Therefore a series of chiral porphyrin-amino acid derivatives have been prepared from 5α,10β,15α,20β-tetrakis(*o*-aminophenyl)porphyrin (α,β,α,β-TAPP) and protected amino acids for an amino acids enantioselectivity study. The compound α,β,α,β-TAPP[17] was selected because it is one of the most commonly used for biochemical models. Protected amino acids were chosen because they can be easily obtained and are available in abundance.[18] As anticipated, they proved to be effective hosts for chiral recognition and their zinc complexes achieved surprising enantioselectivities, as high as 21.54, the highest value to date that we know of. The causes of their high selectivities will be investigated in this paper.

Experimental

Materials and physical measurements

All reagents and solvents were of commercial reagent grade and were used without further purification. Dry dichloromethane was obtained by distilling over $CaCl_2$. Amino acid methyl esters were prepared according to the reported methods.[11] BocAla and BocPro, benzoyl-Gln[19] and α,β,α,β-TAPP[20] were all prepared following previously documented methods.

^1H NMR spectra were recorded on either a Varian INOVA 500Nb or Bruker AC-P 200 NMR spectrometer, tetramethylsilane (TMS) was used as internal reference for all spectra. UV-vis spectra were measured on a Beckman DU-8B spectrophotometer with a thermostatted cell compartment. Circular dichroism (CD) spectra were taken on a JASCO-715 spectropolarimeter with a thermostatted cell compartment. Infrared spectra (KBr disc) were recorded on a Bio-Rad FTS 135 FT-IR spectrometer. Carbon, hydrogen and nitrogen contents were determined with a Perkin–Elemer 240 elemental analyzer. Molecular modeling was carried out with the Sybyl 6.3 program (Tripos Inc. St. Louis, MO, 1998) using the Tripos force field on an SGI Indigo II workstation.

Syntheses

Synthesis of chiral porphyrins (3a–c). To a solution of 67.52 mg (0.1 mmol) of α,β,α,β-TAPP in 40 mL of dichloromethane was added 0.5 mmol of proctected amino acid. The reaction mixture was stirred at −10 °C for 10 min. After addition of 103 mg (0.5 mmol) of dicyclohexylcarbodiimide (DCC), the solution was stirred at 0 °C for 12 h. After filtration through a glass frit under vacuum, the solution was washed successively with 5% aqueous citric acid solution, water, 5% aqueous sodium carbonate solution, and water. The solution was dried and evaporated. The residue obtained was dissolved in 5 mL of dichloromethane and column chromatographed on silica gel (dichloromethane–ether 5 : 1).

3a. 108 mg (80% yield); ^1H NMR ($CDCl_3$): δ −2.60 (s, 2H, pyrrole-NH), 0.44 (d, 12H, CH_3), 0.73–2.05 [m, 36H, $(CH_3)_3$], 4.06 (m, 4H, CH), 4.30 (s, 4H, CONH), 7.11 (s, 4H, ArNH), 7.24–7.82 (m, 16H, ArH), 8.63–8.77 (m, 8H, β-pyrrole-H). Anal. calc. for $C_{76}H_{86}N_{12}O_{12}$: C, 67.14; H, 6.38; N, 12.36; found: C, 67.01; H, 6.03; N, 12.53%. UV-vis (CH_2Cl_2): λ_{max}/nm 419.6 (Soret), 514.6, 548.8, 590.4, 647.2; IR (KBr, cm^{-1}): 3380.93 (CON–H), 3323.03 (pyrrole N–H), 2931.04 (–CH_3), 2854.96 (–CH_2–), 1700.72 (C=O), 1522.28 (pyrrole).

3b. 112 mg (77% yield); ^{1}H NMR ($CDCl_3$): δ −2.64 (s, 2H, pyrrole-NH), 0.83–0.89 (m, 24H, CH_2), 1.15–1.41 (m, 36H, CH_3), 3.43–3.51 (m, 4H, CH), 5.27 (s, 4H, CONH), 7.10 (s, 4H, ArNH), 7.33–7.84 (m, 16H, ArH), 8.61–8.74 (m, 8H, β-pyrrole-H). Anal. calc. for $C_{84}H_{94}N_{12}O_{12}$: C, 68.93; H, 6.47; N, 11.48; found: C, 68.52; H, 6.21; N, 11.53%. UV-vis (CH_2Cl_2): λ_{max}/nm 419.8 (Soret), 514.2, 547.8, 590.8, 647.0; IR (KBr, cm^{-1}): 3380.18 (CON–H), 3328.43 (pyrrole N–H), 2931.43 (–CH_3), 2854.72 (–CH_2–), 1698.18 (C=O), 1528.97 (pyrrole).

3c. 132 mg (82% yield); ^{1}H NMR ($CDCl_3$): δ −2.66 (s, 2H), 0.89 (t, 4H), 1.21 (s, 8H), 1.51 (m, 20H), 3.44 (s, 4H), 6.81 (s, 4H), 7.05–8.76 (m, 36H), 8.79 (s, 8H). Anal. calc. for $C_{92}H_{82}N_{16}O_{12}$: C, 68.90; H, 5.15; N, 13.97; found: C, 68.88; H, 5.02; N, 13.71%. UV-vis (CH_2Cl_2): λ_{max}/nm 422.1 (Soret), 516.4, 550.4, 589.6, 546.6; IR (KBr, cm^{-1}): 3379.18 (CON–H), 3312.7 (pyrrole N–H), 1665.46 (C=O), 1525.7 (pyrrole).

Synthesis of zinc(II) porphyrins (4a–c). To a solution of 0.05 mmol of porphyrin (**3a**–**c**) in 50 mL of dichloromethane, was added l0 mL of a saturated solution of $Zn(OAc)_2$ in methanol. The reaction mixture was stirred at room temperature for 2 h, and the solvent evaporated. The solid obtained was dissolved in 50 mL of dichloromethane. The organic layer was washed twice with water, then dried over anhydrous Na_2SO_4 overnight and concentrated. The crude product was column chromatographed on silica gel (dichloromethane–ether 5 : 1).

4a. 64 mg (90% yield); ^{1}H NMR ($CDCl_3$): δ 0.84 (d, 12H, CH_3), 1.18–1.42 [m, 36H, $(CH_3)_3$], 3.40 (m, 4H, CH), 4.31 (s, 4H, CONH), 7.07 (s, 4H, ArNH), 7.30–7.98 (m, 16H, ArH), 8.71 (s, 8H, β-pyrrole-H). Anal. calc. for $C_{76}H_{84}N_{12}O_{12}Zn$: C, 64.15; H, 5.95; N, 11.81; found: C, 63.85; H, 5.71; N, 11.65%. UV-vis (CH_2Cl_2): λ_{max}/nm 426.3 (Soret), 557.0, 594.8; IR (KBr, cm^{-1}): 3398.62 (CON–H), 2932.44 (–CH_3), 1688.96 (C=O), 1522.78 (pyrrole).

4b. 66 mg (87% yield); ^{1}H NMR ($CDCl_3$): δ 0.82–0.90 (m, 24H, CH_2), 1.15–1.31 [m, 36H, $(CH_3)_3$], 3.44–3.47 (m, 4H, CH), 5.10 (m, 4H, CONH), 7.31 (m, 4H, ArNH), 7.44–7.80 (m, 16H, ArH), 8.67 (s, 8H, β-pyrrole-H). Anal. calc. for $C_{84}H_{92}N_{12}O_{12}Zn$: C, 66.07; H, 6.07; N, 11.01; found: C, 65.85; H, 5.82; N, 11.36%. UV-vis (CH_2Cl_2): λ_{max}/nm 405.7 (sh), 427.1 (Soret), 557.8, 595.5; IR (KBr, cm^{-1}): 3381.62 (CON–H), 2975.68, 2928.1 (–CH_3), 2854.46 (–CH_2–), 1699.97 (C=O), 1520.66 (pyrrole).

4c. 71 mg (85% yield); ^{1}H NMR ($CDC1_3$): δ 0.91 (t, 4H), 1.23 (s, 8H) 1.52 (m, 20H), 3.45 (s, 4H), 6.86 (s, 4H), 7.03–8.73 (m, 36H), 8.75 (s, 8H). Anal. calc. for $C_{92}H_{80}N_{16}O_{12}Zn$: C, 66.28; H, 4.84; N, 13.44; found: C, 66.12; H, 4.45; N, 13.19%. UV-vis (CH_2Cl_2): λ_{max}/nm 428.5 (Soret), 558.0, 595.8; IR (KBr, cm^{-1}): 3387.52 (CON–H), 929.37 (–CH_3), 2856.03 (–CH_2–), 1665.71 (C=O), 1523.63 (pyrrole).

UV-vis spectrophotometric titrations

To a solution of about 5.0×10^{-6} M of **4** in dichloromethane was added a solution of α-amino acid esters in dichloromethane at room temperature. Changes in the absorbance of the Soret band were monitored at ten different concentrations of the guest compounds in the range 10^{-3}–10^{-2} M.

Molecular modeling of the chiral recognition of $AlaOCH_3$ using 4a

Molecular modeling was performed with the Tripos force field as implemented in Sybyl 6.3 software (Tripos Inc.) on an SGI Indigo II workstation. The 3D structure of **4a** was constructed by using the SKETCH module. The macrocyclic ring of the porphyrin was constrained and energy minimization was carried out with a gradient of 0.05 kcal mol^{-1}. Taking the optimized geometry as the starting conformation, conformer searching of host **4a** involved random search and simulated annealing to ensure the last result is a minimum energy conformation at a high level. Consequently D,L-$AlaOCH_3$ were added on the porphyrin plane and systematic conformational searches were carried out. With the conformations of the **4a**·L-$AlaOCH_3$ and **4a**·D-$AlaOCH_3$ complexes obtained above energetic analyses were performed.

Results and discussion

The chiral framework of these porphyrin derivatives (**4a**–**c**) was constructed by condensing α,β,α,β-TAPP **1**[20] with protected amino acids **2** to give the chiral porphyrins **3a**–**c**. Their zinc complexes **4a**–**c** were prepared based on a previously reported method (Scheme 1).[21] Complexation experiments were performed in dichloromethane solution. Visible spectroscopy, circular dichroism spectra (CD), and molecular modeling were employed to study the enantioselectivity of L and D amino acid esters by chiral zinc porphyrins.

UV-vis spectrophotometric titration

Absorption spectra of zinc porphyrins binding with amino acid esters of varying concentrations show an isosbestic point in the Soret band, which indicates 1 : 1 complexation between the host and guest molecules. The absorption spectra of **4a** are shown in Fig. 1. The association constant K is given by eqn. (1):

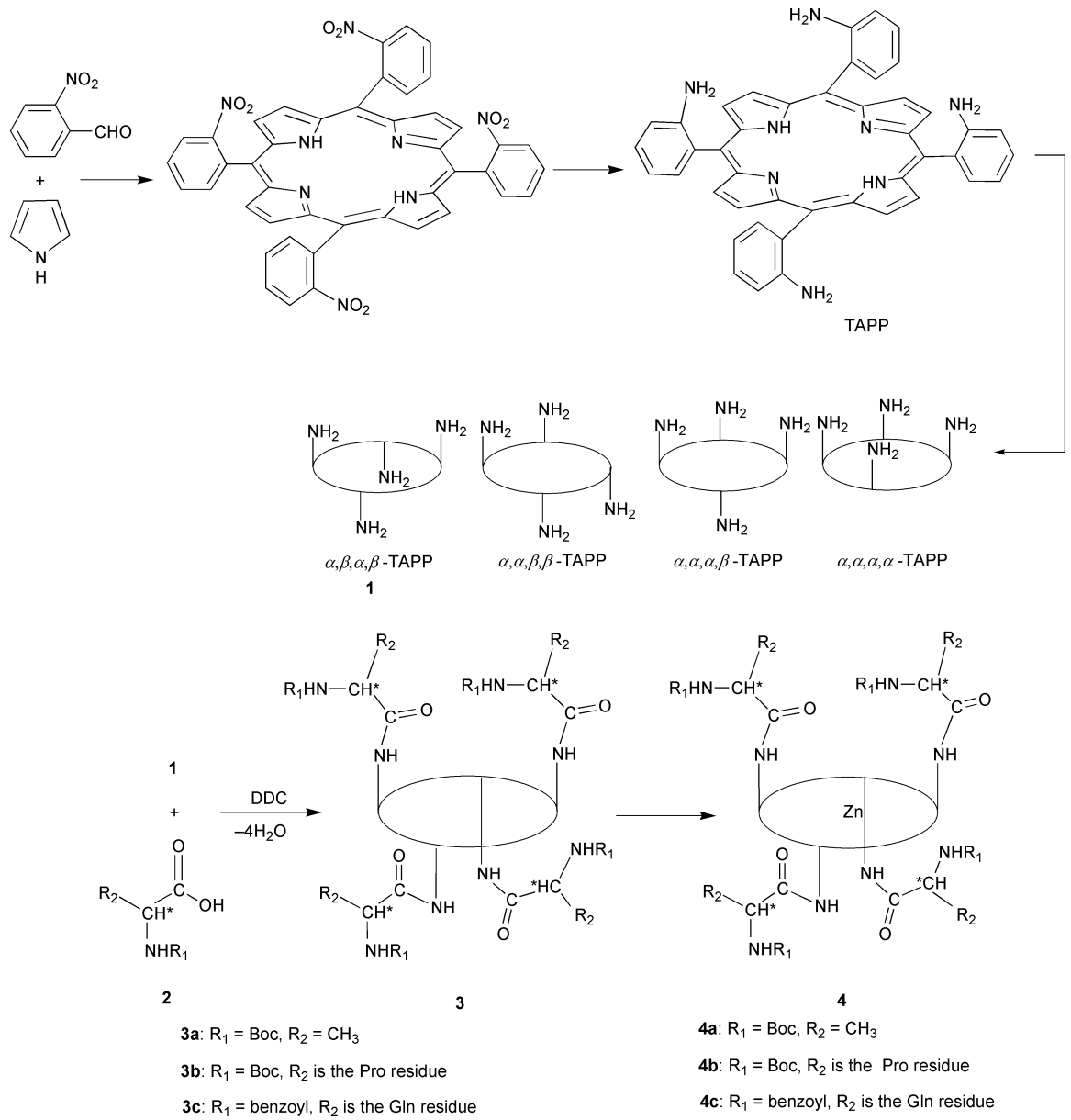
$$\frac{1}{A_0 - A} = \frac{1}{K\alpha} \cdot \frac{1}{c_L} + \frac{1}{\alpha} \quad (1)$$

where A_0 is the absorbance of zinc porphyrin solution, A is the absorbance in the presence of a guest at concentration c_L, and α is a constant. The quantity $1/(A_0 - A)$ has a linear relation to $1/c_L$; the association constant, K, can be obtained from the ratio of the intercept to the slope. The results are presented in Table 1. The binding between **4b** and amino acid esters was too weak to be accurately determined and therefore the results are not included.

Association constants between hosts and amino acid esters are in the range 10^2–10^4, which are much smaller than that of ZnTPP.[22,23] The relatively weak binding abilities are ascribed to the steric repulsion between the side chain of the amino acid esters and the branch group of the zinc porphyrins. For host **4a**, the association constants of D-amino acid esters are larger than that of their optical antipodes. It is worthy of note that the enantioselectivity for D,L-$PheOCH_3$ is very high at 21.54, which is the highest value that we are aware of. This is believed to arise from the bulkier aromatic group in $PheOCH_3$. The structure of the D-enantiomer of the guest molecules can be better aligned with the host **4a**, the simplified recognition process is shown in Scheme 2. The steric repulsion between the larger groups in **4a** and the L-enantiomer is unfavorable for "close binding" of the host and guest. Accordingly, the association of **4a** with the L-guest becomes weaker and the association constant smaller than with the D-guest.

Table 1 Enantioselectivity of **4a** and **4c** binding to amino acid esters in dichloromethane at 25 °C

Guest	K(**4a**)	K_D/K_L(**4a**)	K(**4c**)	K_L/K_D(**4c**)
L-$AlaOCH_3$	1967	4.18	464	1.38
D-$AlaOCH_3$	8230		336	
L-$LeuOCH_3$	195	12.06	876	1.11
D-$LeuOCH_3$	2351		786	
L-$PheOCH_3$	136	21.54	752	4.27
D-$PheOCH_3$	2930		176	
L-$IleOCH_3$	288	6.26	1025	1.14
D-$IleOCH_3$	1802		900	



Scheme 1

On the other hand, host **4c** prefers to bind with the L-enantiomer rather than the D. As a consequence, the ratio of K_D to K_L is less than 1; the values of K_L/K_D are presented in Table 1 to characterize the enantioselectivity. The selectivity of host **4c** for PheOCH$_3$ ($K_L/K_D = 4.27$) is also much higher than that for other amino acid esters. The data in Table 1 also

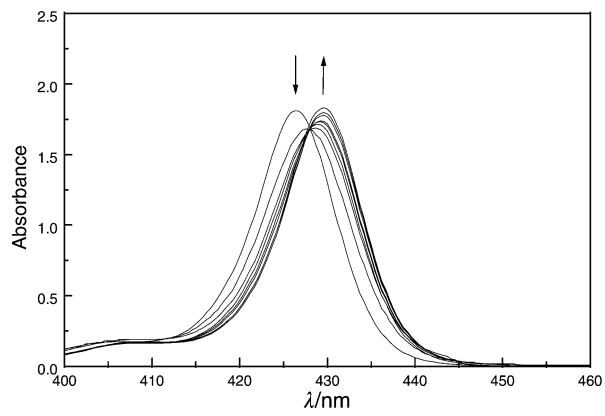
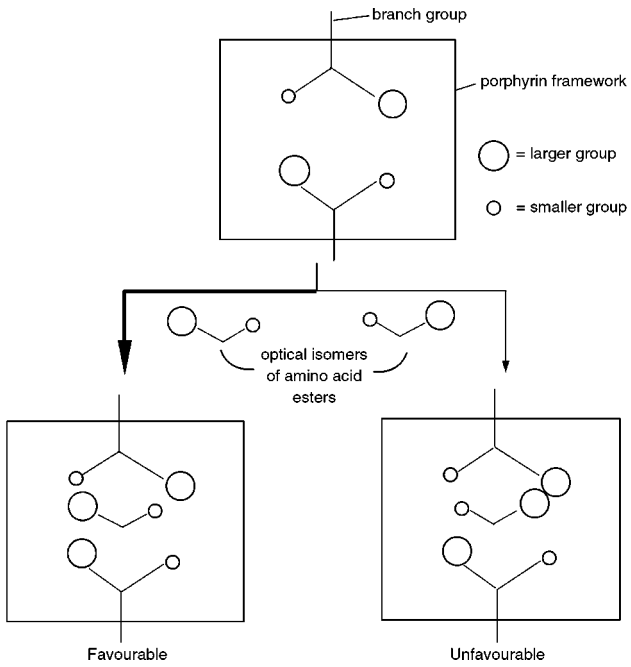


Fig. 1 UV-vis titration of **4a** with L-LeuOCH$_3$ in dichloromethane at 298 K: [**4a**] = 8.23 × 10^{-6} M; [L-LeuOCH$_3$] = 0, 0.8, 1.0, 1.2, 2.0, 4.0, 8.0 and 12.0 × 10^{-3} M.



Scheme 2

indicate that the chiral recognition ability of **4a** is much stronger than that of **4c**.

The enantioselectivity of hosts is temperature dependent; this can be see in the $LeuOCH_3$ binding study (Fig. 2). The enantioselectivity at 15 °C is nearly halved at 30 °C. This phenomenon can be explained by the van't Hoff equation:

$$\ln K_D = -\frac{\Delta H_D}{RT} + \frac{\Delta S_D}{R} \quad (2)$$

$$\ln K_L = -\frac{\Delta H_L}{RT} + \frac{\Delta S_L}{R} \quad (3)$$

By combining eqns. (2) and (3), one finds:

$$\ln \frac{K_D}{K_L} = -\frac{\Delta H_D - \Delta H_L}{RT} + \frac{\Delta S_D - \Delta S_L}{R}$$

$$= -\frac{\Delta\Delta H}{RT} + \frac{\Delta\Delta S}{R} \quad (4)$$

In Fig. 2, $\ln(K_D/K_L)$ shows a good linear relationship with $1/T$. From the slope, the value of $\Delta\Delta H$ is negative, therefore, the value of K_D/K_L will decrease exponentially as the temperature increases.

Enthalpy–entropy compensation relationship

Thermodynamic parameters are determined from the van't Hoff equation and an enthalpy–entropy compensation effect was found in our system. The relationship can be expressed as:[5]

$$T\Delta S = \alpha\Delta H + T\Delta S_0 \quad (5)$$

According to the classification of Rekarsky and Inoue[5] the slope α and intercept $T\Delta S_0$ provide good indexes as to conformational changes during complex formation and the extent of desolvation, respectively. A slope of $\alpha = 0.797$ and an intercept of 10.56 kJ mol^{-1} were obtained for **4a** [Fig. 3(a)] and a slope $\alpha = 0.828$ and intercept of 10.75 kJ mol^{-1} for **4c** [Fig. 3(b)]. The slopes are less than unity, which indicates that relatively small conformational changes may accompany the process complex formation in both cases. The slope using **4c** is smaller than with **4a**, indicating that the conformational change is comparatively easier. The intercepts of the two systems have almost the same value, which shows that the extent of desolvation is almost the same.

Circular dichroism studies

Fig. 4 shows the CD spectra of **4a** and **4a** with L-$AlaOCH_3$ or D-$AlaOCH_3$ in dichloromethane. In all complexes with

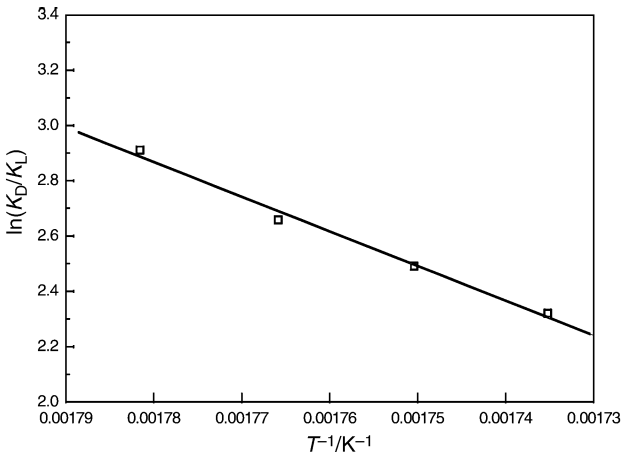


Fig. 2 The influence of temperature on the enantioselectivity of **4a** with $LeuOCH_3$ as guest.

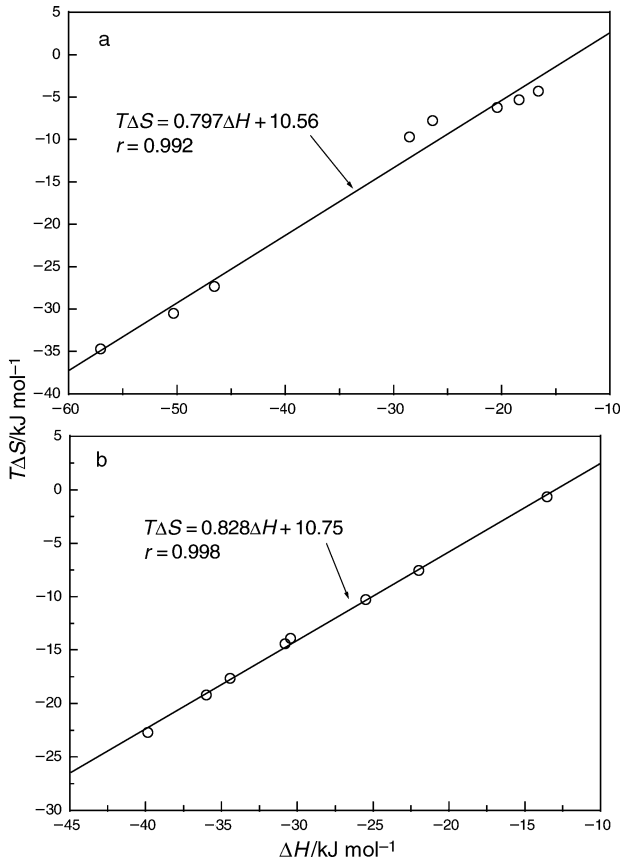


Fig. 3 Enthalpy–entropy compensation relationship of complexes of (a) **4a** and (b) **4c**.

L-amino acid esters, CD spectra exhibit a negative Cotton effect induced in the Soret band, which is very similar to that seen with **4a**. With D-amino acid esters, the spectra show positive Cotton effects. These results suggest that D-guest molecules are highly localized on hosts and bind more tightly than their optical antipodes.

The mechanism leading to the induced CD spectra of these systems is still ambiguous. The experimental results support the explanation given by Ogoshi and co-workers,[13,24] where the coupling between the electric and magnetic transition moments of the carbonyl group and the electric transition

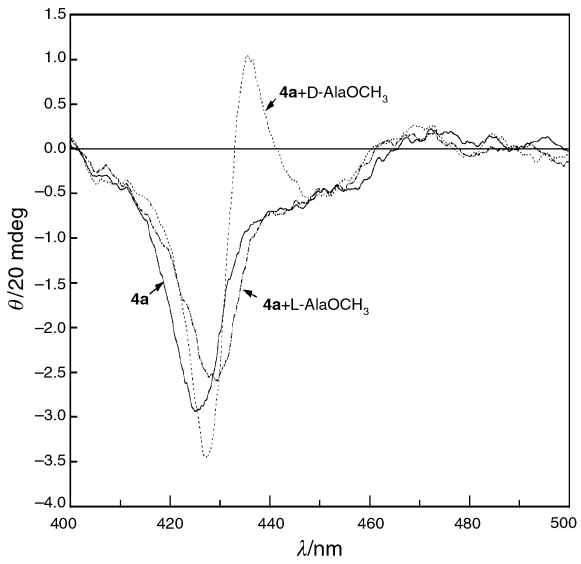


Fig. 4 Circular dichroism spectra of host **4a** (5×10^{-6} M) and its complexes with D,L-$AlaOCH_3$ (5×10^{-3} M) in dichloromethane at 298 K.

moments of porphyrin chromophores lead to the observed Cotton effects. This mechanism suggests that the D-enantiomer is more stable on the porphyrin **4a** plane. The orientations of the carbonyl groups of the two guest enantiomers are opposite but not symmetric.

Molecular modeling

The minimum energy conformation of **4a** [Fig. 5(a)] was obtained by the method of random search and simulated annealing. The conformation has C_2 symmetry. The branch groups of the host provide a chiral cavity for guest molecules. On the basis of this conformation, the minimum energy conformations of host **4a** binding with L- and D-AlaOCH$_3$ were obtained by rotating the Zn–N bond in 10° increments and then performing a geometry optimization. The resulting optimized geometries are shown in Fig. 5(b) and (c). The calculated energy of the L-AlaOCH$_3$ complex is 80.104 kcal mol^{-1} and that of D-AlaOCH$_3$ is 78.801 kcal mol^{-1}, indicating that the latter is more stable than the former. Consistent with this experiment, the D-enantiomer is more tightly bound to the host than its optical antipode and, as anticipated, the computed binding energies are overestimated because the effect of solvent is neglected.[25]

The energy components are included in Table 2. Energy in aggregates means total energy of the porphyrin ring (excluding substituents) defined as a plane, it includes total internal energy (bond stretching, angle bending, torsional, out-of-plane bending) and total external energy (1–4 van der Waals energy, van der Waals energy). The remaining terms are molecular energy components minus the energy of the porphyrin ring. The 1–4 van der Waals refers to interactions of non-neighbouring atoms, and van der Waals to the interactions of neighbouring ones. These energies depend on the potential functions and their associated parameters that make up the force field and, accordingly, are force field dependent. They have little physical significance. Nonetheless, we provide these energies to examine how the individual terms comprising particular force fields differ in D *vs.* L complexes. In Table 2 the largest difference in energy appears in the van der Waals energy. The D-enantiomer is thus more tightly bound in part because the system has less steric repulsion and the non-bonded interactions are more favorable.

These component energies are also partitioned into internal and external energies. The internal energy is simply the sum of the first four component energies, and external energy is the sum of the van der Waals and the 1–4 van der Waals contributions. Table 2 shows that the great differences between the two recognition processes originate from the external energy.

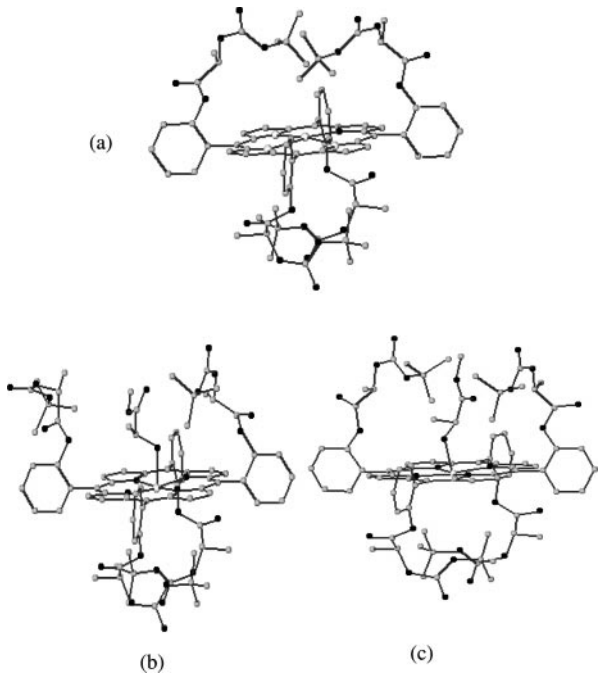


Fig. 5 The minimum energy conformations of **4a**: (a) alone, (b) complexed with L-AlaOMe, (c) complexed with D-AlaOMe.

Table 2 Average energies (kcal mol^{-1}) of L- and D-AlaOCH$_3$ with host molecule **4a**

Energy term	E_L	E_D	$E_L - E_D$
Energy in aggregates	61.05	61.05	0
Bond stretching	3.58	3.69	−0.11
Angle bending	22.23	22.90	−0.67
Torsional	44.92	44.90	0.02
Out-of-plane bending	0.57	1.08	−0.51
Total internal energy	71.30	72.57	−1.27
1–4 van der Waals	10.10	9.84	0.26
van der Waals	−62.35	−64.66	2.31
Total external energy	−52.25	−54.82	2.57
Total energy	80.10	78.80	1.30

Conclusion

This paper reports the enantioselective binding of D,L-amino acid esters to novel chiral porphyrins **4a**–**4c**. Experimental results reveal that the host **4a** prefers to bind with the D-enantiomers of guests, while **4c** prefers the optical antipodes, the L-enantiomers. The strongest enantioselective binding of D,L-amino acid esters is provided by **4a** with PheOCH$_3$ as guest, which is as high as 21.54 at 25 °C. The enantioselectivity K_D/K_L is temperature dependent. The induced CD spectra of the complexes verify the aforementioned results at a qualitative level. Molecular modeling has been performed to examine the enantioselectivity of host **4a**, which is found to arise mainly from the different steric repulsion with the two guest enantiomers.

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