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Structural scaffold of 18-crown-6 tetracarboxylic acid for optical resolution of chiral amino acid: X-ray crystal analyses and energy calculations of complexes of D- and L-isomers of tyrosine, isoleucine, methionine and phenylglycine†

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To clarify the structural scaffold of (+)-18-crown-6 tetracarboxylic acid ((+)-18C6H$_4$) for the optical resolution of a chiral amino acid, the crystal structures of its equimolar complexes with L- and D-isomers of tyrosine (Tyr), isoleucine (Ile), methionine (Met) and phenylglycine (PheG) were analysed by X-ray diffraction methods. (+)-18C6H$_4$ took very similar conformations for all complexes. Although the chemical structure of (+)-18C6H$_4$ is *C*2-symmetric, it took a similar asymmetric ring conformation of radius *ca.* 6.0 Å. In all complexes, the amino group of chiral amino acids was located near the center of the ring and formed three hydrogen bonds and five electrostatic interactions with eight oxygen atoms of the ether ring and carboxyl groups. Also, the Cα atom of chiral amino acids participated in Cα–H $\cdots$ O interaction with the oxygen atom of (+)-18C6H$_4$. In contrast, the carboxyl group of chiral amino acids did not directly interact with (+)-18C6H$_4$. These results indicate that the structural scaffold of (+)-18C6H$_4$ for the optical resolution of chiral amino acids is mainly based on the mode of interaction of (+)-18C6H$_4$ with the amino and Cα–H groups of chiral amino acids. The differences in interaction pattern and binding energy between the L- and D-isomers of each amino acid are discussed in relation to the chiral recognition of (+)-18C6H$_4$.

Introduction

Crown ether, first introduced by Pedersen in 1967,[1] is a synthetic macrocyclic poly(ether) that can form a selective complex with a suitable cation. Generally, the optically active crown ether derivative has been used for the optical synthesis, resolution and analysis of chiral amino compounds. 18-Crown-6 tetracarboxylic acid (18C6H$_4$) is used as a chiral selector for primary amines in capillary electrophoresis (CE),[2] high-performance liquid chromatography (HPLC)[3] or gas chromatography.[4] This chiral separation could be due to the characteristic binding mode between a chiral amine and 18C6H$_4$.[2]

Several studies have been reported on the interaction between 18C6H$_4$ and amino compounds, ethylene diammonium,[5] *R*-(+)-1-(1-naphthyl) ethylamine[6] L- and D-phenylglycines and their methylester derivatives.[7] However, there are no systematic investigations on the structural scaffold of 18C6H$_4$ for the discrimination between D- and L-amino acids. Therefore, we analyzed the crystal structures of (+)-18C6H$_4$ complexes with L-Tyr (**L1**), D-Tyr (**D1**), L-Ile (**L2**), D-Ile (**D2**), L-Met (**L3**), L-Met (**D3**), L-phenylglycine (PheG, **L4**), and D-PheG (**D4**) by X-ray diffraction methods. Also, the heat of formation and total energy for each of these complexes was calculated by the molecular orbital PM3 method. Herein, we report the structural and interaction features of the complexes and discuss the structural scaffold of (+)-18C6H$_4$ for the chiral recognition of enantiomeric amino acids. The atomic numbering used for Tyr, Ile, Met, PheG and (+)-18C6H$_4$ in this work is given in Fig. 1.

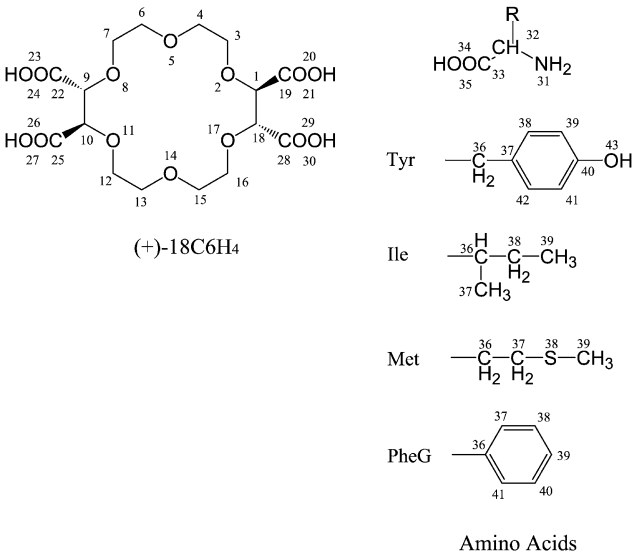

Fig. 1 Chemical structures and atomic numbering used for (+)-18C6H$_4$, Tyr, Ile, Met, and PheG.

Results and discussion

Chiral separation of enantiomeric amino acids by HPLC

It has already been reported[8] that a column chemically immobilized with (+)-18C6H$_4$ shows good chiral recognition for basic or nonpolar DL-amino acids. Thus, the optical resolution of each of the enantiomers Tyr, Ile, Met and PheG was examined, and their chromatographic results are given in Table 1. The effectiveness

† Electronic supplementary information (ESI) available: torsion angles of crown ether rings and dihydrate crystals of (+)-18C6H$_4$; selected torsion angles of amino acids; possible hydrogen bonds and short N–O contacts between amino acids and (+)-18C6H$_4$; hydrogen bonds and selected short contacts among neighboring molecules; details of crystal data, intensity collection, and structure refinement; enantiomer separation profile of DL-Tyr; stereoscopic superimposition of complexes **L1**–**L4** and **D1**–**D4**. See http://www.rsc.org/suppdata/ob/b4/b409482d/

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Table 1 Enantiomer separation of amino acid on CPS-18C6I by HPLC

	Tyr	Ile	Met	PheG
k_1[a]	0.93	0.43	0.95	1.28
k_2[b]	1.89	0.62	1.73	3.42
α[c]	2.03	1.45	1.82	2.68
R[d]	1.93	0.77	1.71	2.76

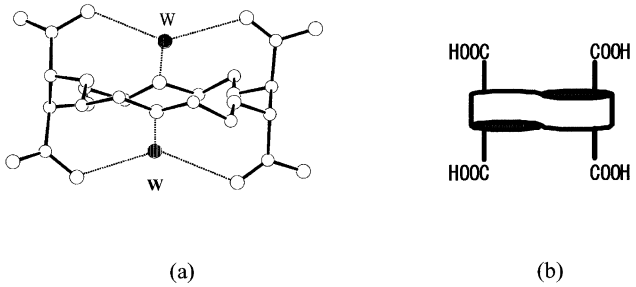
Mobile phase: 1 mM perchloric acid, column temperature: 0 °C.
[a] Capacity factor for the first eluted enantiomer. [b] Capacity factor for the second eluted enantiomer. [c] Separation factor. [d] Resolution factor.

of (+)-18C6H$_4$ as a chiral selector for enantiomer separation is clear, and could be interpreted as a positive correlation of the electrostatic and hydrophobic interactions between the host and guest molecules: these interactions are possible between the basic amino group of the amino acid and the oxygen atoms of the crown ether and carboxyl groups of (+)-18C6H$_4$ and between the side chain of the amino acid and the hydrocarbon chain of (+)-18C6H$_4$. Concerning the elution order of DL-isomers, L-amino acids are commonly eluted prior to D-amino acids. This indicates that D-amino acids form more stable interactions with (+)-18C6H$_4$ than L-amino acids.

X-ray analysis

The crystal and structural features clarified by X-ray analyses are as follows: All crystals consist of a 1 : 1 complex of (+)-18C6H$_4$ and an amino acid. **D4** crystals contain two crystallographically independent complexes per asymmetric unit, whereas the other crystals consist of one complex. All the crystals, except **D1**, include one to six independent water molecules, whereas **D1** crystals include one perchloric ion per asymmetric unit. The C39 atoms of L- and D-Ile in **L2** and **D2** complexes were disordered in two positions with occupancies of 3/5 and 2/5, respectively. Also, the C13 atom of (+)-18C6H$_4$ of **L1** was disordered in two positions with occupancies of 3/5 and 2/5.

Molecular conformation of (+)-18C6H$_4$. As a standard conformation of (+)-18C6H$_4$, it would be reasonable to consider the *C*2-symmetric structure. However, there is no report on the *C*2-symmetric conformation of (+)-18C6H$_4$, which indicates that the *C*2-symmetric conformation is not necessarily favorable for the 18-membered crown ether ring structure. The most symmetric structure has been observed in the crystals of (+)-18C6H$_4$ dihydrate (Fig. 2)[9] and ethylenediamine complexes,[5] and its conformation could be characterized as a planar crown ether ring with the axial orientation of four carboxyl groups perpendicular to the ring. On the other hand, the present X-ray analyses clarified that the conformation of (+)-18C6H$_4$ is not as rigid as expected and changes depending on external effects such as an interaction with a guest molecule. To clarify the



(a) (b)

Fig. 2 Planar conformation (a) and schematic model (b) of (+)-18C6H$_4$. The figure was based on the dihydrate crystal. The molecule is depicted with the ball and stick model. The shaded circles marked W represent water molecules. Dotted lines represent hydrogen bonds.

conformational variation of (+)-18C6H$_4$ in the complexes, the torsion angles around the crown ether ring are grouped into three types in Table 2, where the torsion angles of the dihydrate crystal[9] are also given for comparison. In the complexes, the crown ether ring of (+)-18C6H$_4$ takes an asymmetrical convex structure. It is clear from the comparison with the dihydrate crystal that this conformational change from the planar form is mainly due to the difference among the ϕ_4, ϕ_5 and ϕ_9 torsion angles. The convex conformations could be classified into three types (conformer I, II and III) according to the different orientations around the C10–O11–C12–C13–O14–C15–C16–O17 bond sequence, as shown in Fig. 3. The conformational feature of (+)-18C6H$_4$ could be described as follows: the ϕ_{10}, ϕ_{11} and ϕ_{13} torsion angles differ depending on the interaction with an enantiomeric amino acid, whereas the rest are all kept in the same region. This implies that (+)-18C6H$_4$ can overcome any conformational constraint imposed on the ring conformation by complex formation by changing these three torsion angles. In conclusion, (+)-18C6H$_4$ forms a convex bend conformation by changing its ϕ_4, ϕ_5 and ϕ_7 torsion angles to accept a guest molecule, and overcomes the conformational constraints imposed on its ring structure by changing its ϕ_{10}, ϕ_{11} and ϕ_{13} torsion angles.

Characteristically, the carboxyl group IV (see Fig. 4a) is in an anionic form, whereas the other three groups are all in the neutral state in all complexes, except for **D1**. This electronic feature could be due to the hydrogen-bonding ability of the carboxyl group IV being different from those of the remaining groups. The **D1** is exceptional because of the interaction of carboxyl group IV with perchloric acid, and its four carboxyl groups I–IV being all in the neutral form. The carboxyl groups I and IV are nearly perpendicular to the plane formed by six O atoms of the crown ether ring, while groups II and III lie almost horizontal to the ring. By the complex formation of (+)-18C6H$_4$ with the amino acid, the carboxyl groups I and III found on the convex ring side are far away from each other, leading to the easy acceptance of a guest molecule. This open form of the ring structure is stabilized

Table 2 Selected torsion angles characterizing four different conformations of crown ether rings of (+)-18C6H$_4$.[a] Because of *C*2-symmetrical chemical structure of (+)-18C6H$_4$ and the planar molecular conformation of crown ether ring moiety, the respective torsion angles of conformer 1 are related with those of conformer 2 by the relations of $\phi_1 \leftrightarrow \phi_{10}$, $\phi_2 \leftrightarrow \phi_{11}$, $\phi_3 \leftrightarrow \phi_{12}$, $\phi_4 \leftrightarrow \phi_{15}$, $\phi_5 \leftrightarrow \phi_{14}$, $\phi_6 \leftrightarrow \phi_{13}$, $\phi_7 \leftrightarrow \phi_{16}$, $\phi_8 \leftrightarrow \phi_{17}$, and $\phi_9 \leftrightarrow \phi_{18}$, respectively.

Convex conformation (**L1**–**D4**)	
Conformer I (**D1**, **D2**, **L3**, **L4**, **D4 Mol. A**)	ϕ_{10}: 158–169°, ϕ_{11}: −50–(−66)°, ϕ_{12}: −162–(−174)°, ϕ_{13}: 158–174°, ϕ_{14}: 58–66°, ϕ_{15}: 169–177°
Conformer II (**L2**, **D3**, **D4 Mol. B**)	ϕ_{10}: 121–133°, ϕ_{11}: 43–55°, ϕ_{12}: 174–179°, ϕ_{13}: 83–99°, ϕ_{14}: 55–58°, ϕ_{15}: 161–165°
Conformer III (**L1**)	ϕ_{10}: 162/105°, ϕ_{11}: −56/51°, ϕ_{12}: −94/−162°, ϕ_{13}: −160/165°, ϕ_{14}: −42°, ϕ_{15}: −159°
Torsion angles commonly observed in all complexes	ϕ_1: 171–182°, ϕ_2: 66–72 °, ϕ_3: −172–(−179)°, ϕ_4: 78–87°, ϕ_5: 62–69°, ϕ_6: −161–(−170)°, ϕ_7: −152–(−165)°, ϕ_8: −60–(−72)°, ϕ_9: −122–(−146)°, ϕ_{16}: −153–(−169)°, ϕ_{17}: −58–(−65)°, ϕ_{18}: −158–(−169)°
Planar conformer (dihydrate crystal)	
Conformer 1[a]	ϕ_1: 166°, ϕ_2: 66°, ϕ_3: −179°, ϕ_4: 177°, ϕ_5: −60°, ϕ_6: −163°, ϕ_7; −112°, ϕ_8: −55°, ϕ_9: −96°, ϕ_{10}: −165°, ϕ_{11}: −64°, ϕ_{12}: 176°, ϕ_{13}: 175°, ϕ_{14}: 61°, ϕ_{15}: 175°, ϕ_{16}: −172°, ϕ_{17}: −60°, ϕ_{18}: 175°
Conformer 2	ϕ_1: −165°, ϕ_2: −64°, ϕ_3: 176°, ϕ_4: 175°, ϕ_5: 61°, ϕ_6: 175°, ϕ_7; −172°, ϕ_8: −60°, ϕ_9: 175°, ϕ_{10}: 166°, ϕ_{11}: 66°, ϕ_{12}: − 179°, ϕ_{13}: 177°, ϕ_{14}: −60°, ϕ_{15}: −163°, ϕ_{16}: −112°, ϕ_{17}: −55°, ϕ_{18}: −96°

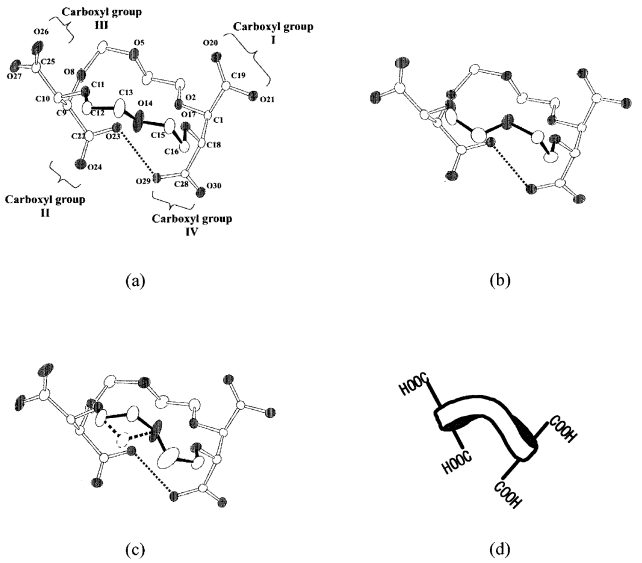


Fig. 3 Three different conformers (a), (b) and (c) of (+)-18C6H$_4$ and a schematic model showing the overall distorted conformation (d). Conformer I (a): **D1**, **D2**, **L3**, **L4** and **D4**; Conformer II (b): **L2**, **D3** and **D4**; Conformer III (c): **L1**. Two conformers are possible for the conformation of **L1** (c) because of the disordered position of the C13 atom. The dotted lines represent intramolecular hydrogen bond between the carboxyl groups II and IV.

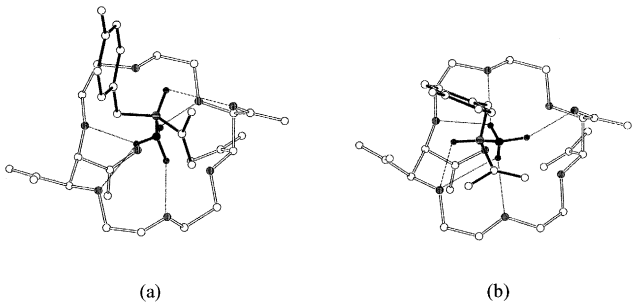


Fig. 4 Views of interactions of L-Tyr (a) and D-Tyr (b) (filled bonds) with (+)-18C6H$_4$ (open bonds) in complexes **L1** and **D1**. Dotted lines represent the N–H $\cdots$ O and Cα–H $\cdots$ O interactions.

by an O–H $\cdots$ O intramolecular hydrogen bond between the carboxyl groups II and IV, formed by the approach of both groups located on the concave side of the ring: O23 $\cdots$ O29 = 2.56–2.65 Å, H $\cdots$ O29 = 1.59–1.83 Å and ∠O23–H $\cdots$ O29 = 153.7–172.1°.

Amino acids. To estimate the extent at which the molecular conformation of an enantiomeric amino acid is affected by (+)-18C6H$_4$, the molecular structures and conformations of D- and L-isomers were compared. No notable differences were observed concerning the electronic and covalent structures; their bond lengths and angles show normal values in all complexes, as compared with their respective free forms or HCl salts.[10] The respective amino acids took the zwitterionic form, where α-amino and α-carboxyl groups are protonated and deprotonated, respectively (N31–C32 = 1.47–1.50 Å and C33–O34/C33–O35 = 1.18–1.23/1.28–1.32 Å); the phenol OH groups of L- and D-Tyr were also deprotonated. Concerning the molecular conformation, however, a slight energetic disadvantage could be observed between D- and L-isomers, although their respective torsion angles were all within the energetically allowable region. The (ψ, χ^1) torsion angle set prefers (±20°, −60/180/60°) for Tyr and Phe, (−15/−45°, 60/180/−60°) for Ile, and (±20°, 180/−60/60°) for Met.[11] The L-amino acids are closer to the standard combination than the D-isomers, indicating that the influence of complex formation on the conformational state of L-amino acids is not as significant as that on the conformational state of D-amino acids.

Interaction of enantiomeric amino acid with (+)-18C6H$_4$

Concerning the binding pattern of these amino acids with respect to (+)-18C6H$_4$, no notable difference was observed between L- and D- isomers in all complexes, despite the different side chains of the amino acids. Similarly, concerning the interaction mode between the amino acids and (+)-18C6H$_4$, many common interactions are formed between L- and D-amino acids. The interaction mode between (+)-18C6H$_4$ and L- and D-Tyr in **L1** and **D1** is shown in Fig. 4. The commonly observed features of the interaction are as follows: the amino group of the amino acids is located near the center of the crown ether ring of radius *ca.* 6.0 Å and forms N–H $\cdots$ O hydrogen bonds and/or N $\cdots$ O electrostatic short contacts with the eight oxygen atoms of the crown ether ring and the carboxyl group of (+)-18C6H$_4$. Although the carboxyl group of the amino acids did not participate in the direct interaction with (+)-18C6H$_4$, the Cα–H $\cdots$ O interaction is commonly formed between the amino acids and the carboxyl oxygen of (+)-18C6H$_4$, thus stabilizing the complex formed (Table 3). In these common interaction modes, however, some characteristic differences could be observed between the complexes of the D- and L-amino acids (see Fig. 4). In the L-amino acid, the amino group forms three hydrogen bonds with O2, O8, and O14 atoms of the crown ring, whereas O5, O14 and O20 atoms participate in the hydrogen bonds in the D-amino acid. Concerning the Cα-H $\cdots$ O interaction, the L-amino acid interacts with the O20 of carboxyl group I, while the O11 of the crown ether ring participates in the D-amino acid.

The crystal structures of respective complexes were stabilized by the hydrogen bonds and short contacts formed between the neighboring molecules and *via* water molecules or perchlorate ions. Examples of **L3** and **D3** are shown in Fig. 5. Although molecular packing patterns and the interactions among neighboring molecules are different in the respective complexes, the carboxyl group of the amino acids did not participate directly in the hydrogen bonds with the partner's (+)-18C6H$_4$, but with neighboring (+)-18C6H$_4$ and/or water molecules. Thus, this may simply suggest that the direct chiral recognition of 18C6H$_4$ for enantiomeric amino acids is mainly possible by the N–H $\cdots$ O and Cα–H $\cdots$ O interactions formed in the amino acid–(+)-18C6H$_4$ pair, although an involvement of the carbonyl O of the guest molecule has also been suggested in the solution state.[7]

Possible optical separation mechanism of 18C6H$_4$ for enantiomeric amino acids

The optical separation of various chiral amino acids by 18C6H$_4$ in CE and HPLC was achieved through the difference between

Table 3 Possible Cα $\cdots$ O interactions/Å

								D4	
	L1	D1	L2	D2	L3	D3	L4	Mol.A	Mol.B
C $\cdots$ O	2.990(7)	3.100(5)	3.097(6)	3.016(6)	3.18(1)	3.193(6)	3.107(5)	3.377(5)	3.001(5)
C–H $\cdots$ O	2.67	2.90	2.85	2.57	2.68	2.42	2.41	2.56	2.19
∠C–H $\cdots$ O	100	92	96	109	114	138	130	144	142

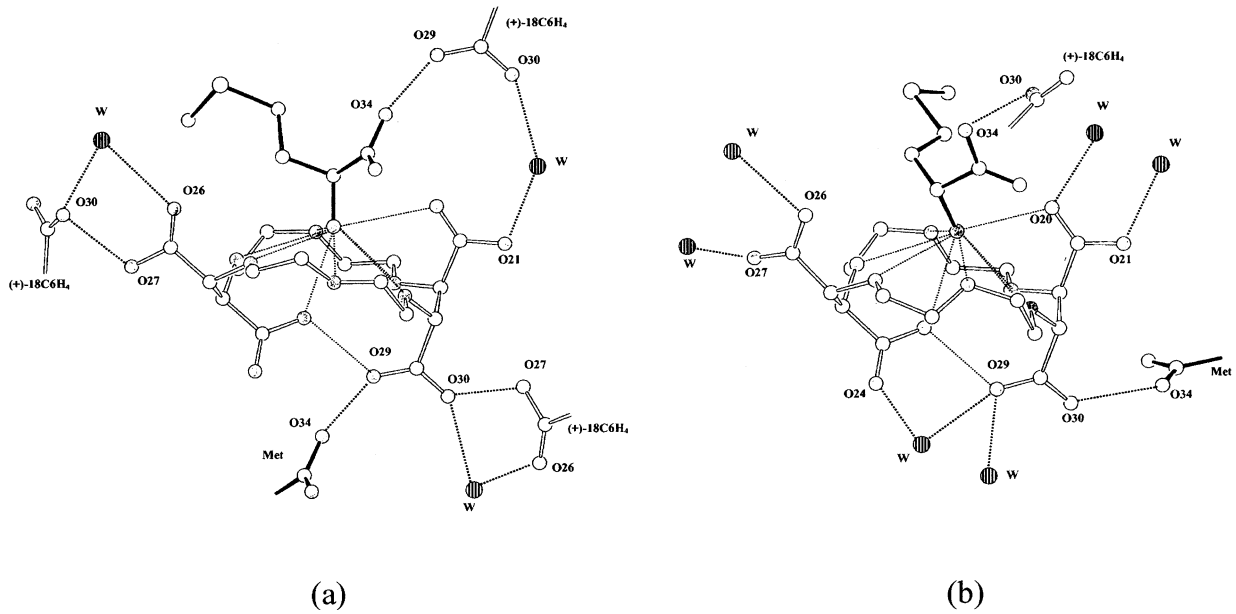


Fig. 5 Hydrogen bonds and short contacts of Ile–(+)-18C6H$_4$ pair with its neighboring molecules in complexes **L3** (a) and **D3** (b). Hydrogen bonds and short contacts are indicated by dotted lines.

the binding constants for their complex formations. Crystal structure analyses showed that the molecular conformation of (+)-18C6H$_4$ is significantly distorted from its *C*2-symmetric chemical structure by the complex formation with a chiral amino acid, and this characteristic deformation participates in the optical separation that mainly originates from the different intermolecular interaction patterns of (+)-18C6H$_4$ with the amino and Cα–H groups of chiral amino acids. A possible model of the optical separation mechanism of enantiomeric amino acid by (+)-18C6H$_4$ is proposed in Fig. 6.

To accept an enantiomeric amino acid, (+)-18C6H$_4$ takes a convex conformation similar to that shown in Fig. 4d by changing ϕ_4, ϕ_5 and ϕ_9 torsion angles, in which the crown ether ring forms a bowl-like shape having two hollows (one big and one small) on the rim. On the other hand, the amino and carboxyl groups of L- and D-amino acids are commonly located at the center and on the big-hollow side of the bowl, respectively, and the side chain of the D-amino acid and the H-atom-linked Cα atom of the L-amino acid are consequently located on the small-hollow side of the bowl. Either amino acid is primarily locked at the center of the crown ether ring of (+)-18C6H$_4$ *via* tight N–H $\cdots$ O hydrogen bonds and N $\cdots$ O short contacts. Then, the Cα–H $\cdots$ O interaction is formed between either amino acid and (+)-18C6H$_4$. In this case, the Cα–H bond of the D-amino acid is perpendicularly located on the bowl-shaped plane of (+)-18C6H$_4$, as compared with the Cα–N bond of the L-amino acid located at an acute angle towards the plane. This could provide a situation in which the acceptor O atom of (+)-18C6H$_4$ becomes located at a preferable position for the Cα–H $\cdots$ O interaction with the D-isomer rather than with the L-isomer, as is obvious from the Cα–H $\cdots$ O parameters (Table 3).

To confirm this hypothesis, the heat of formation and total energy for each complex were calculated by the PM3 method and are given in Tables 4 and 5. In all complexes, the results suggest the structural stability of the complex with the D-isomer as compared with the L-isomer. Concerning the heat of formation, the energy difference between **D4** and **L4** (**D4**–**L4** in Table 5) was much larger than those of the others, and this could be due to the existence of two complexes per asymmetric unit in the **D4** crystal; the stable interaction of PheG with (+)-18C6H$_4$ could be more easily formed in **D4** than in **L4**, because the complex formation in the **L4** crystal (one complex per asymmetric unit) is severely constrained by the crystallographic symmetric requirement. On the other hand, the total energy showed a large difference between **L1** and **D1**, which could primarily be due to the effect of perchloric acid included in **D1** and the difference between the charge states of the carboxyl group IV in **D1** (anionic) and **L1** (neutral). Thus, except for the **L1**—**D1** pair, the negative heat of formation difference and total energy difference for the **D**- and **L**-complexes are in agreement with the order of separation factor for the optical separation of enantiomeric amino acid by HPLC analysis: PheG > Met > Ile (see Table 1).

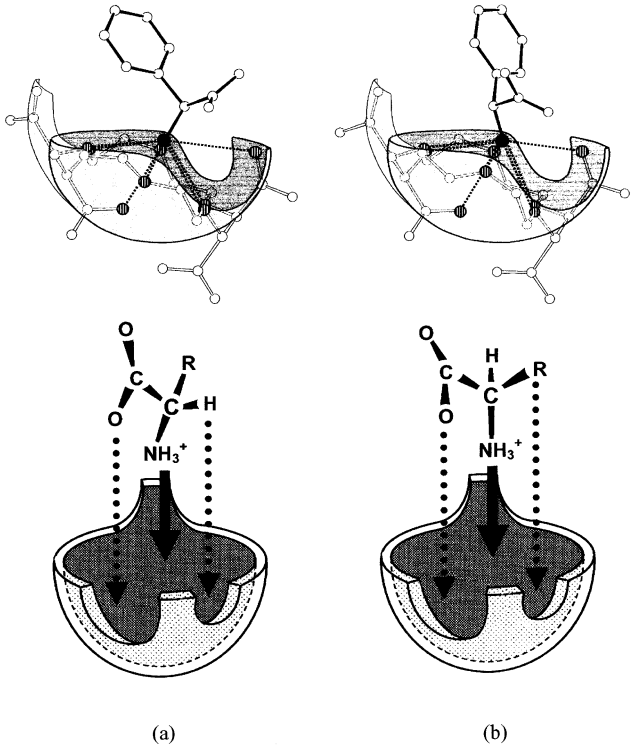


Fig. 6 Possible interaction model of (+)-18C6H$_4$ for (a) L- and (b) D-amino acids. The conformation of (+)-18C6H$_4$ is depicted with a bowl-like shape with two hollows (one big and one small) on the rim. The interaction of L- and D-PheGs (Mol-A) depicted by the ball-and-stick model is shown on the upper side. A general interaction mode of chiral amino acid with (+)-18C6H$_4$ is shown on the lower side, where the orientation of the (+)-18C6H$_4$ molecule is rotated clockwise by 90° from that on the upper side.

Table 4 The formation energy and the total energy of the complexes

	L1	D1	L2	D2	L3	D3	L4	D4 Mol. A	D4 Mol. B
Heat of formation/kcal mol^{-1}	−543.47	−588.15	−585.29	−500.80	−546.46	−588.83	−592.02	−556.15	−551.48
Total energy/E_h	−8651.45	−8036.21	−8073.11	−8208.37	−8666.91	−8036.24	−8073.40	−8210.77	−8210.57

Table 5 The differences of the formation energy and the total energy between the complexes of L- and D-enantiomers

	Ile	Met	PheG Mol. A	PheG Mol. B
Heat of formation/kcal mol^{-1}	−0.66	−6.73	−55.35	−50.68
Total energy/E_h	−0.03	−0.29	−2.40	−2.20

In conclusion, the interaction of enantiomeric amino acids with the convex conformation of 18C6H$_4$ is primarily performed through multiple N–H···O hydrogen bonds, and the Cα–H···O interaction plays an important role in the optical recognition of these amino acids, in which the asymmetric two hollows of bowl-shaped (+)-18C6H$_4$ provide the structural scaffold for optical separation.

Experimental

HPLC analysis

The experiments were performed on a Shimadzu LC-10 system with a Shimadzu Chromatopac C-R7A plus data processor. The separation column used is a chiral stationary-phase (CSP-18C6I) column (2.0 mm id, 45 cm length) of chemically immobilized (+)-18C6H$_4$ on 3-aminopropylsilanized silica gel manufactured by Machida *et al*.[8] An aqueous solution containing 1 mM perchloric acid was used as the mobile phase. Chromatographic runs were performed at a constant flow rate of 0.2 mL min^{-1} and a constant temperature of 0 °C. One microliter of a 0.3% solution of Tyr, Ile, Met or PheG racemate in 0.5 M L^{-1} hydrochloric acid was injected and the eluted solution was detected at 200 nm (for Ile and Met) or 254 nm (for Tyr and PheG).

X-ray crystal analysis‡

Complex crystals were prepared from 0.1 mol L^{-1} perchloric acid containing equimolar amounts of (+)-18C6H$_4$ and D- or L-Tyr, Ile, Met or PheG by slow evaporation at 293 K. The obtained crystals were colorless prisms or plates. X-ray data were collected with a Rigaku AFC-5R diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.5418 Å) at 253 K for the complexes **L1**, **D1**, **L4**, **D4** or at 293 K for the other complexes. Details of cell parameter determination and reflectional intensity data collection are available as an electronic supplementary material.† Intensity data within $5 \leq 2\theta \leq 130°$ were measured by employing an ω–2θ scan mode. Three standard reflections monitored every 150 or 300 reflections showed no significant time dependence (< ±5%).

Each crystal structure was determined by the direct method with the SHELXS-97 program.[12] The positional parameters of non-H atoms were refined by full-matrix least-squares method with anisotropic temperature parameters using the SHELXL-97 program.[13] The atomic scattering factors and terms of anomalous dispersion corrections were taken from *International Tables for X-Ray Crystallography*.[14] In the solution of **L1**, **L2** and **D2**, the problem of disorder was encountered. The progress of Fourier refinement revealed the disordered two positions for the C13 atom of (+)-18C6H$_4$ in **L1** and for the C39 atoms of L- and D-Ile in **L2** and **D2**; the final occupancies were 3/5 and 2/5 for C13 (**L1**) and 3/5 and 2/5 for C39 atoms (**L2** and **D2**) respectively, as a result of the refinement. The positions of the H-atoms of amino and carboxyl groups were determined from a difference Fourier map, while those of other H-atoms were calculated on the basis of their stereochemical requirements. They were treated as riding with fixed isotropic displacement parameters ($U_{iso} = 1.2U_{eq}$ for the associated C or N atoms, or $U_{iso} = 1.5U_{eq}$ for methyl C or O atoms) and were not included as variables for the refinements. The H-atoms of water molecules and of the disordered carbon atoms were not included in the refinements. The function of $\Sigma w(Fo^2 - Fc^2)^2$ was minimized using the weighting scheme of $w = 1/[\sigma^2(F^{o2}) + (0.1000P)^2]$, where $P = (F^{o2} + 2F^{c2})/3$. In the final stage of the refinement, none of the positional parameters of non-H atoms shifted more than one-third from their estimated standard deviations. The final R value (no. of reflections with $I > 2\sigma(I)$) was 0.070 (2647) for **L1**, 0.064 (1800) for **D1**, 0.061 (2716) for **L2**, 0.069 (2655) for **D2**, 0.059 (2629) for **L3**, 0.063 (2690) for **D3**, 0.046 (2632) for **L4**, and 0.045 (4617) for **D4**, respectively.

Molecular orbital calculations

The molecular volume, heat of formation and total energy for each complex were calculated by the molecular orbital PM3 method[15] with the MOPAC system.[16] The atomic coordinates from the present X-ray results were used for the calculations, in which all solvent molecules were not included in the calculations. The energy values used for the comparison were obtained by the single point calculation of respective complexes and the stability of electronic energy of each complex was used as a check for convergence in the iteration calculations.

‡ CCDC reference numbers 242874–242881. See http://www.rsc.org/suppdata/ob/b4/b409482d/ for crystallographic data in .cif or other electronic format.

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