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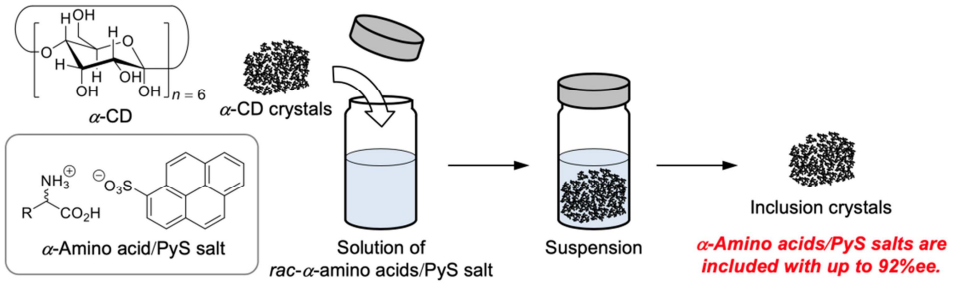
## Graphical Abstract



# Enantioselective inclusion of pyrene-1-sulfonate salts of $\alpha$-amino acids with crystals of $\alpha$-cyclodextrin

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**Abstract:**

Enantioselective inclusion of $\alpha$-amino acids with crystals of $\alpha$-cyclodextrin ($\alpha$-CD) has been achieved by converting the amino acids into sulfonate salts with pyrene-1-sulfonic acid (PyS). For example, crystals of $\alpha$-CD selectively include L-leucine/PyS (1:1) salt in a host/guest ratio of ~1 with 92%ee from a solution of the racemic salt in ethanol/*N*-methylformamide (91:9) at 40 °C. Under conditions optimized for individual amino acids, the PyS salts of valine, phenylalanine, and methionine are also included with good enantioselectivities (up to 86%ee). Mechanistic studies for the inclusion of leucine/PyS salt reveals that the enantioselectivity originates from the difference in stability between the inclusion complexes of D- and L-leucine/PyS salts with $\alpha$-CD in crystals.

**Keywords:**

Cyclodextrin, Nanoporous molecular crystal, Enantioselective inclusion, Amino acid

## 1. Introduction

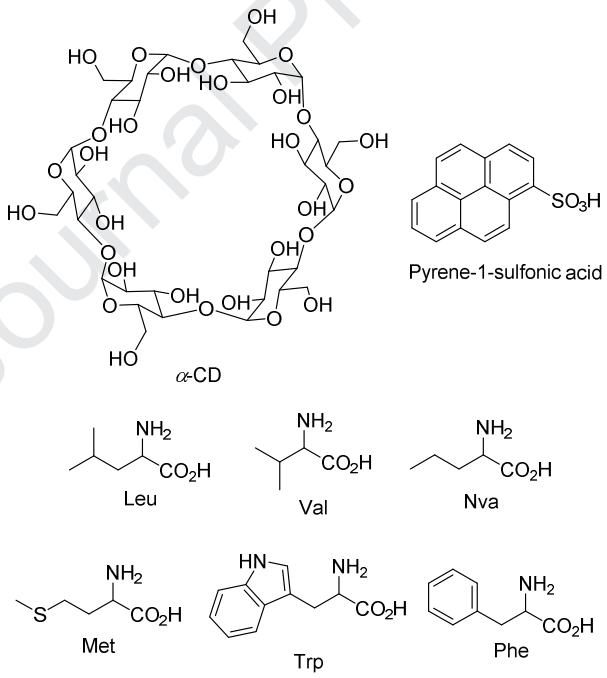
The development of solid materials that can capture particular inorganic gases and organic molecules by precisely recognizing their molecular structures is an important subject from the view point of reducing environmental load and energy costs through the simplification of separation and purification processes. Nanoporous materials, such as zeolite,[1] metal–organic frameworks (MOFs),[2] covalent organic network polymers (COFs),[3] and nanoporous molecular crystals (NMCs),[4] are widely investigated for the separation materials. Molecular crystals of calix[4]arenes are representative NMCs with "porosity without pores"[5] that include guest molecules into their disconnected spatial voids, accompanied by a structural change in the crystal packing.[6–10] We have been engaged in the development of this type of NMCs[11] and recently succeeded in the selective inclusion of various molecules, such as alcohols,[12a,b] amines,[12c] carboxylic acids,[12d] aromatic compounds,[12e] and alkanes,[12f] using crystals of *p-tert*-butylcalix[4]arene and its sulfur-bridged analogue. These studies substantiated that this type of NMCs have potential to precisely discriminate molecules not only by the difference in the stabilities of their inclusion crystals (thermodynamic factor) but also by the difference in the activation energies for the structural change of the crystal packing (kinetic factor).

The success in discriminating the achiral compounds with the calixarene crystals motivated us to extend this methodology to a chiral system. In relation to this, Toda et al. have reported a pioneering work of the enantioselective inclusion of chiral compounds with crystals of tartaric acid derivatives.[13] Crystals of acyclic hosts, such as amino acids, steroids, and carboxylate salts of chiral amines, have also been employed for the enantioselective inclusion of racemic alcohols and sulfoxides.[14] These are based on the formation of a clathrate-type inclusion crystal, in which guest molecules are disposed in the host lattice. On the other hand, to the best of our knowledge, there is no precedent of chiral recognition based on the formation of a complex-type inclusion crystal constructed by discrete host/guest complexes like the inclusion crystals of calix[4]arenes.[15]

Cyclodextrins (CDs) are representative chiral hosts widely used as chiral discriminators, such as those of chiral stationary phases for HPLC.[16,17] However, research on the optical resolution through the

formation of inclusion crystals with CDs is scarce in the literature.[18] In addition, there is no report on the inclusion of chiral compounds with CD crystals, despite the fact that the crystals have been used to include chlorinated aromatic compounds,[19] volatile organic compounds (e.g., aniline and toluene),[20] and other achiral compounds.[21] This is partly because inclusion crystals of CDs adopt a variety of packing structures;[16b,c,22] as a result, the uniformity of the packing structure, which is necessary to achieve high guest selectivity, cannot be secured. Yet another reason may be that it is difficult to fix the orientation of guest molecules in the large hydrophobic cavities of CDs with no coordinating groups. In this paper, we wish to report that crystals of $\alpha$-CD enantioselectively include amino acids by converting the amino acids into sulfonate salts with bulky pyrene-1-sulfonic acid (chart 1).

**Chart 1**

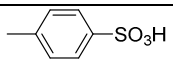
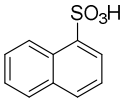
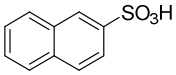
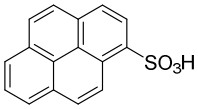


## 2. Results and Discussion

Enantioselective inclusion of arylsulfonate salts of $\alpha$-amino acids with crystals of $\alpha$-CD was carried out as follows. Powdery crystals of $\alpha$-CD were suspended in an ethanol solution of a racemic arylsulfonate salt, which was prepared in advance by the reaction of a DL-amino acid with a small excess of an arylsulfonic acid (1.05 molar equiv), and the suspension was stirred at a fixed temperature until inclusion reached equilibrium (24–48 h). The resulting crystals were collected by filtration and analyzed by $^1$H NMR spectroscopy to determine the inclusion ratio ($\bar{n}$), which is defined as the mean number of guest molecules included into the crystals per $\alpha$-CD molecule. The arylsulfonate salt was desorbed from the crystals by guest exchange with ethanol; $^1$H NMR analysis of the resulting crystals revealed that they contained no arylsulfonate salt of the amino acid, i.e., the guest exchange was quantitative. The enantiomeric excess (ee%) of the amino acid was determined by HPLC analysis on a chiral stationary phase, after conversion into the *N*-benzyloxycarbonyl (Cbz) derivative.

First, the inclusion of arylsulfonate salts of DL-leucine (Leu) was investigated, varying the sulfonic acid (Table 1). The *p*-toluenesulfonate salt of DL-Leu was included with $\bar{n}$ of ~1.0 from a 0.80 M solution of the racemic salt in ethanol (entry 1); an ethanol molecule was coinlcluded into the crystals. The $\bar{n}$ value indicates the formation of a 1:1 (host/guest) inclusion complex. The L-isomer was slightly enriched in the crystals (6%ee). The enantioselectivity was improved to 14%ee and 25%ee by changing the acid to 1- and 2-naphthalenesulfonic acid, respectively (entries 2 and 3). Further increase in the bulkiness of the sulfonic acid by replacing the aryl group with a 1-pyrenyl group afforded good enantioselectivity (79%ee) with almost quantitative inclusion ($\bar{n}$ = ~1.0) (entry 4). The bulky and rigid sulfonic acid seems to fix the orientation of the D- and L-Leu molecules in the cavity of $\alpha$-CD, which enables the precise discrimination of the two enantiomers, though the structures of the resulting diastereomeric inclusion complexes could not be determined in this study.

**Table 1.** Inclusion of arylsulfonate salts of DL-Leu with crystals of $\alpha$-CD[a]

| entry | sulfonic acid | $\bar{n}$ | | | ee% (L) |
|---|---|---|---|---|---|
| | | Leu | sulfonic acid | EtOH | |
| 1 |  | 0.92 | 0.93 | 1.01 | 6 |
| 2 |  | 1.06 | 1.04 | 1.86 | 14 |
| 3[b] |  | 0.44 | 0.44 | 0.95 | 25 |
| 4 |  | 1.03 | 1.05 | 2.40 | 79 |

[a] Conditions: powdery crystals of $\alpha$-CD (51.4 μmol), a sulfonate salt of DL-Leu (0.80 M), EtOH (1.1 mL), 30 °C, 24 h. [b] 0.34 M sulfonate salt was used because of its low solubility in EtOH.

The inclusion conditions were further investigated for the Leu salt of pyrene-1-sulfonic acid (PyS) (Table 2). We found that the concentration of the sulfonate salt in ethanol is a key parameter for the enantioselective inclusion. The inclusion from a low concentration solution (0.09 M) showed poor selectivity (27%ee) with a low $\bar{n}$ value (~0.15) (entry 1). The enantioselectivity and $\bar{n}$ value increased with increasing the concentration and reached to 79%ee and ~1.0, respectively, at the concentration of 0.80 M (entries 2–5). These results indicate that the concentration of the salt changes the partition ratios of the D- and L-enantiomers between the solid and liquid phase at different magnitudes, which causes a change in the enantioselectivity of Leu.

**Table 2.** Effect of salt concentration on the enantioselectivity for the inclusion of DL-Leu/PyS salt with crystals of $\alpha$-CD[a]

| entry | [DL-Leu/PyS salt] (M)[b] | $\bar{n}$ | | | ee% (L) |
|---|---|---|---|---|---|
| | | Leu | PyS | EtOH | |
| 1 | 0.09 | 0.15 | 0.16 | 1.01 | 27 |
| 2 | 0.23 | 0.32 | 0.33 | 1.12 | 58 |
| 3 | 0.42 | 0.63 | 0.63 | 1.90 | 69 |
| 4 | 0.61 | 0.77 | 0.76 | 2.34 | 71 |
| 5[c] | 0.80 | 1.03 | 1.05 | 2.40 | 79 |

[a] Conditions: powdery crystals of $\alpha$-CD (51.4 μmol), EtOH (1.1 mL), 30 °C, 24 h. [b] Initial concentration of DL-Leu/PyS salt. [c] Data from Table 1 (entry 4).

We envisaged that the enantioselectivity would be tuned by solvent because the partition ratios of the two enantiomers between the solid and liquid phase may be changed at different magnitudes also by solvent polarity. In relation to this, we recently succeeded in switching the guest selectivity in the competitive inclusion between dimethylamine and trimethylamine with crystals of *p-tert*-butylthiacalix[4]arene by changing solvent polarity.[12c] We then examined the effect of solvent polarity on the enantioselectvity in the inclusion of Leu/PyS salt, using ethanol/*N*-methylformamide (NMF) (Table 3). Solvent permittivity ($\varepsilon$) was used as a measure of solvent polarity, which was varied by changing the volumetric ratio of the two components.[23–25] The enantioselectivity in the inclusion of Leu/PyS salt increased with increasing the solvent permittivity and reached a plateau (89%ee) at $\varepsilon$ = 38.6 and then decreased with further increasing the solvent permittivity (entries 1–5). The use of methanol ($\varepsilon$ = 32.6), instead of ethanol/NMF (95:5) ($\varepsilon$ = 31.8), drastically decreased the enantiopurity with the coinclusion of methanol (entry 6 compared with entry 2). This indicates that the enantioselectivity is also affected by the molecular structure of the solvent coincluded in the $\alpha$-CD crystals; a similar observation has been made in a crystallization-based optical resolution of a

diastereomeric binaphthalene.[26] Increasing the temperature to 40 °C slightly improved the enantioselectivity (92%ee) in the ethanol/NMF with a volumetric ratio of 91:9 (entry 7).

**Table 3.** Dependence of the enantioselectivity on solvent permittivity ($\varepsilon$) for the inclusion of DL-Leu/PyS salt with crystals of $\alpha$-CD[a]

| entry | solvent | $\varepsilon$ | $\bar{n}$ | | | | ee% (L) |
|---|---|---|---|---|---|---|---|
| | | | Leu | PyS | alcohol | NMF | |
| 1[b] | EtOH | 24.3 | 1.03 | 1.05 | 2.40 | – | 79 |
| 2 | EtOH/NMF (95:5) | 31.8 | 1.03 | 1.07 | 2.49 | 0.91 | 84 |
| 3 | EtOH/NMF (91:9) | 38.6 | 1.01 | 1.00 | 1.18 | 1.43 | 89 |
| 4 | EtOH/NMF (88:12) | 42.4 | 1.04 | 1.05 | 2.00 | 1.57 | 83 |
| 5 | EtOH/NMF (80:20) | 55.8 | 1.01 | 1.04 | 1.10 | 1.82 | 69 |
| 6 | MeOH | 32.6 | 0.52 | 0.51 | 1.52 | – | 50 |
| 7[c] | EtOH/NMF (91:9) | 38.6 | 1.03 | 1.06 | 1.25 | 1.34 | 92 |

[a] Conditions: powdery crystals of $\alpha$-CD (51.4 μmol), DL-Leu/PyS salt (0.80 M), solvent (1.1 mL), 30 °C, 24–48 h. [b] Data from Table 1 (entry 4). [c] At 40 °C.

Enantioselective inclusion of PyS salts of various amino acids was investigated (Table 4); on the basis of the findings described above, experimental parameters, i.e., salt concentration, solvent and its polarity, and temperature, were optimized for each amino acid. Valine (Val) exhibited high enantioselectivity (82%ee) toward the L-isomer with $\bar{n}$ of ~1.0 (entry 1). Interestingly, the addition of an excess amount of PyS improves the enantioselectivities of some amino acids, giving inclusion crystals containing about two or four times excess of PyS over the amino acids. For example, phenylalanine (Phe) was not included as the PyS salt in $\alpha$-CD crystals but solely precipitated from a Phe/PyS (1:1) salt solution (0.41 M) in ethanol/DMF (10:1). However, the addition of PyS (3.5 molar equiv) suppressed the precipitation and afforded inclusion crystals with a molar ratio of 1.6 (PyS/Phe) with 86%ee (D) (entry 2). The enantioselectivity of methionine (Met) was improved from 40%ee to 86%ee by the addition of PyS (1.0

molar equiv) (entries 3 and 4). A similar observation was made for norvaline (Nva) and tryptophan (Trp) but the enantioselectivities after the addition of PyS were poor to moderate (entries 5–8).

**Table 4.** Enantioselective inclusion of PyS salts of various amino acids with crystals of $\alpha$-CD[a]

| entry | amino acid | [DL-amino acid/PyS salt] (M) | solvent | temp (°C) | $\bar{n}$ | | | | ee%[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | amino acid | PyS | EtOH | cosolvent | |
| 1 | Val | 0.80 | EtOH/ DMSO (10:2) | 30 | 1.12 | 1.13 | 3.15 | 3.75 | 82 (L) |
| 2[c] | Phe | 0.41 | EtOH/ DMF (10:1) | 70 | 0.57 | 0.91 | 0.61 | 1.10 | 86 (D) |
| 3 | Met | 0.59 | EtOH/ DMSO (10:5) | 30 | 0.91 | 0.92 | 2.61 | 4.90 | 40 (L) |
| 4[d] | Met | 0.65 | EtOH/ DMSO (10:5) | 50 | 0.31 | 1.25 | 0.92 | 4.26 | 86 (L) |
| 5 | Nva | 0.65 | EtOH/ DMSO (10:5) | 30 | 0.93 | 1.05 | 1.82 | 4.40 | 13 (L) |
| 6[d] | Nva | 0.40 | EtOH/ DMSO (10:5) | 30 | 0.51 | 1.10 | 0.97 | 4.02 | 44 (L) |
| 7 | Trp | 0.30 | EtOH/ NMF (10:32) | 50 | 0.72 | 0.42 | 0.80 | 4.02 | 0 |
| 8[d] | Trp | 0.80 | EtOH/ DMSO (10:5) | 50 | 0.78 | 1.40 | 1.24 | 3.48 | 12 (L) |

[a] Conditions: powdery crystals of $\alpha$-CD (51.4 μmol), DL-amino acid/PyS salt, solvent (1.1–1.3 mL), 24 h. [b] The major enantiomer is shown in parentheses. [c] PyS (3.5 molar equiv to DL-Phe/PyS salt) was added. [d] PyS (1.0 molar equiv to the DL-amino acid/PyS salt) was added.

We have found that the ee% values of the Leu, Val, and Met salts with PyS in $\alpha$-CD crystals increase with time during the inclusion under the optimized conditions (entry 3 in Table 3 for Leu, entries 1 and 4 in Table 4 for Val and Met, respectively). In the early stage of the inclusion of Leu/PyS salt, almost racemic Leu/PyS salt was included in the $\alpha$-CD crystals with an excess of PyS (entry 1 in Table 5). The D-amino acid salt was then gradually desorbed, whereas the L-counterpart was continuously absorbed, increasing the ee% value to reach 89% (entries 2–4); the molar ratio of PyS to Leu decreased to reach 1 with this change. In each case of Val/PyS and Met/PyS salts, the inclusion ratio of the L-amino acid salt was almost constant throughout the experiment, whereas that of the D-counterpart decreased with time, resulting in the selective inclusion of the L-amino acid salt (Tables S1 and S2); the molar ratio of PyS to the amino acid decreased to reach 1 for Val and increased to reach 4 for Met with this change. These changes in $\bar{n}$ and the PyS/amino acid ratio strongly suggest the inclusion approaching equilibrium. Therefore, we concluded that the enantioselectivities for these amino acids were controlled by thermodynamics.

**Table 5.** Time dependence of the inclusion ratios and enantioselectivity for the inclusion of Leu/PyS salt with crystals of $\alpha$-CD[a]

| entry | time (h) | $\bar{n}$ | | | | | ee% (L) |
|---|---|---|---|---|---|---|---|
| | | L-Leu | D-Leu | PyS | EtOH | NMF | |
| 1 | 0.5 | 0.34 | 0.28 | 0.83 | 0.55 | 1.13 | 10 |
| 2 | 6 | 0.44 | 0.20 | 0.69 | 1.15 | 0.91 | 38 |
| 3 | 12 | 0.51 | 0.19 | 0.74 | 1.60 | 1.07 | 45 |
| 4[b] | 24 | 0.95 | 0.05 | 1.00 | 1.18 | 1.43 | 89 |

[a] Conditions: powdery crystals of $\alpha$-CD (51.4 μmol), DL-Leu/PyS salt (0.80 M), EtOH/NMF (91:9) (1.3 mL), 30 °C. [b] Data from Table 3 (entry 3).

We next investigated the interaction between amino acid/PyS salts and $\alpha$-CD. Fig. 1 shows Job's plots for the complexation of D- and L-Leu/PyS salts with $\alpha$-CD in $D_2O$. They revealed that both the D- and L-salts form 1:1 inclusion complexes with $\alpha$-CD. The association constants ($K_a$) of the enantiomeric

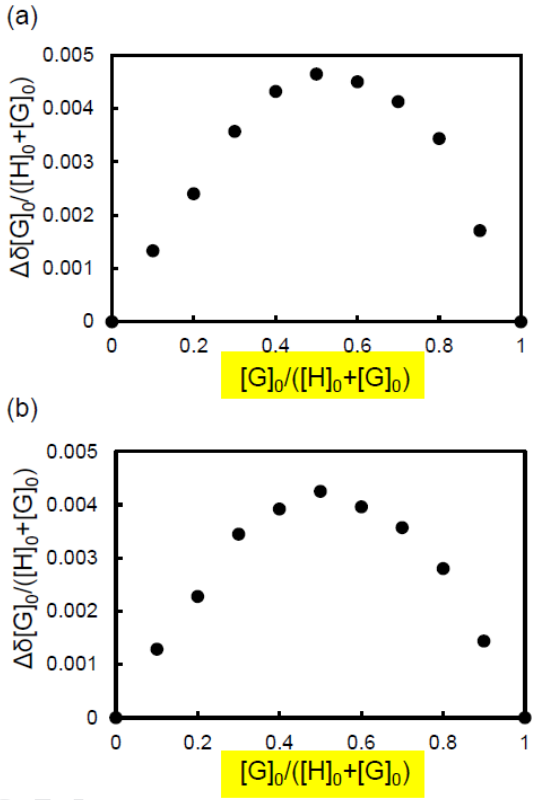



**Fig. 1.** Job's plots for the complexation of $\alpha$-CD with D-Leu/PyS (a) and L-Leu/PyS (b) in $D_2O$. The sum of the total concentrations of the host $[H]_0$ and guest $[G]_0$ was adjusted to 10 mM. $\Delta\delta$ denotes the difference in the chemical shift values of a Leu signal in the presence and absence of $\alpha$-CD.

Leu salts with $\alpha$-CD were then calculated, according to the Benesi-Hildebrand equation for 1:1 (host/guest) complexation (eq. 1).[27]

$$\frac{1}{\Delta\delta} = \frac{1}{\Delta_0\delta K_a[\mathrm{H}]_0} + \frac{1}{\Delta_0\delta} \qquad (1)$$

Where $[H]_0$ is the total concentration of $\alpha$-CD, and $\Delta\delta$ and $\Delta_0\delta$ are the difference in the chemical shift values of a Leu signal in the presence and absence of $\alpha$-CD and that between free and complexed states,

respectively; the methyl signal of Leu was used for the analysis. The $1/\Delta\delta$ against $1/[H]_0$ plots exhibited linear relationships (Fig. 2), from the slopes and *y*-intercepts of which $K_a$s were calculated to be $2.84 \times 10$ mol$^{-1}$ for L-Leu/PyS and $2.71 \times 10$ mol$^{-1}$ for D-Leu/PyS. The $^1$H NMR experiments were also carried out for Val. Job's plots exhibited the formation of 1:1 inclusion complexes for D- and L-Val/PyS salts with $\alpha$-CD in $D_2O$ (Fig. S1) but their association constants could not be determined because of very small peak shifts upon complexation. The small difference in $K_a$ between D- and L-Leu/PyS salts, combined with the fact that the inclusion selectivity exhibited a time-dependent change characteristic of an equilibrium system (vide supra), indicates that the enantioselective inclusion originates from the

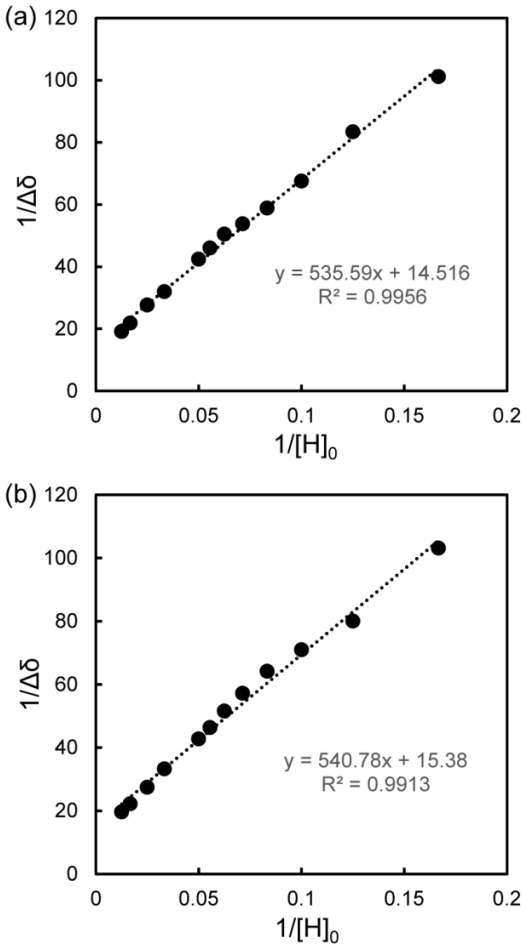



**Fig 2.** $1/\Delta\delta$ vs $1/[H]_0$ plots for D-Leu/PyS·salt (a) and L-Leu/PyS salt (b) in the complexation with $\alpha$-CD. Conditions: $[G]_0$ = 2 mM, $[H]_0$ = 6–80 mM, $D_2O$.

difference in stability between the inclusion complexes of D- and L-Leu/PyS salts with α-CD in crystal lattices, i.e., not discrete inclusion complexes, which confirms the validity of the present chiral discrimination method using a crystalline phase.

One may suspect that amino acids are not included in α-CD crystals as PyS salts. To investigate how amino acids are included in the crystals, FT-IR analysis was carried. Fig. 3 shows IR spectra measured by the KBr pellet method for α-CD, Leu, Leu/PyS salt, and inclusion crystals of Leu/PyS. In the IR spectrum of α-CD (Fig. 3a), a broad absorption is observed at 1643 $cm^{-1}$, which is assigned to the H–O–H bending vibration of $H_2O$ molecules included in the crystals.[28] Zwitterionic Leu shows a stretching vibration for the carboxylato group and bending vibration for the ammonio group at 1617 and 1589 $cm^{-1}$, respectively (Fig. 3b). In the spectrum of Leu/PyS salt (Fig. 3c), the C=O stretching vibration appears at a considerably higher wavenumber (1751 $cm^{-1}$) than that of Leu, indicating that the carboxyl group was liberated by the sulfonic acid with stronger acidity. This absorption somewhat shifted to a lower wavenumber side (1662 $cm^{-1}$) upon inclusion into α-CD (Fig. 3d). This is attributable to the association of the carboxy group with hydroxy group(s) of α-CD. Similar observations were made for Met (Fig. S2), except that the C=O stretching vibration of Met included in α-CD appeared at almost the same wavenumber as that of Met/PyS salt. These results clearly indicate that the amino acids are included in α-CD as PyS salts. However, the IR analysis did not uncover the role of PyS in excess of the amount used for the 1:1 salt formation with Met.

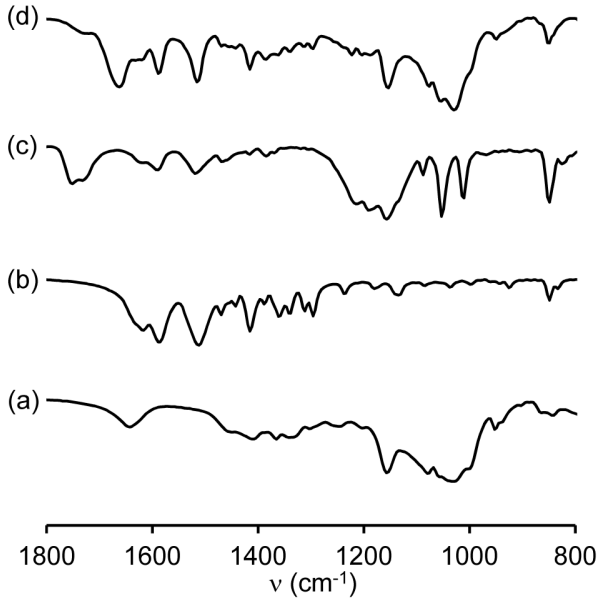



**Fig. 3.** FT-IR spectra of $\alpha$-CD (a), Leu (b), Leu/PyS (c), and inclusion crystals of Leu/PyS (d) measured by the KBr pellet method. The inclusion crystals were prepared under the optimized conditions (entry 7 in Table 3).

In CD chemistry, powder X-ray diffraction (PXRD) analysis is a useful technique to know the arrangement of CD molecules in crystals.[16b,c,29–32] Fig. 4 shows the PXRD patterns of the host crystal and inclusion crystals prepared under the conditions optimized for the individual salts in the competitive inclusion experiments. The PXRD patterns of the $\alpha$-CD crystal and the inclusion crystal of Leu/PyS salt have three peaks characteristic of a cage-type structure (Fig. 5a) at $2\theta$ = ~10, 14, and 22° (Fig. 4a,b);[30–32] the difference between the two PXRD patterns can be attributed to some change in the arrangement of the cage-type structure through the inclusion of Leu/PyS salt. On the other hand, the inclusion crystals of PyS salts of Val, Phe, and Met exhibit a strong diffraction at $2\theta$ = ~20° (Fig. 4c–e), which is characteristic of a channel-type structure (Fig. 5b).[29,31] Although the packing structures must have an intimate relation to the observed stereoselectivities, as well as the inclusion ratios of the amino acids and PyS, we could not investigate the relationship because the inclusion complexes did not give single crystals suitable for X-ray analysis.

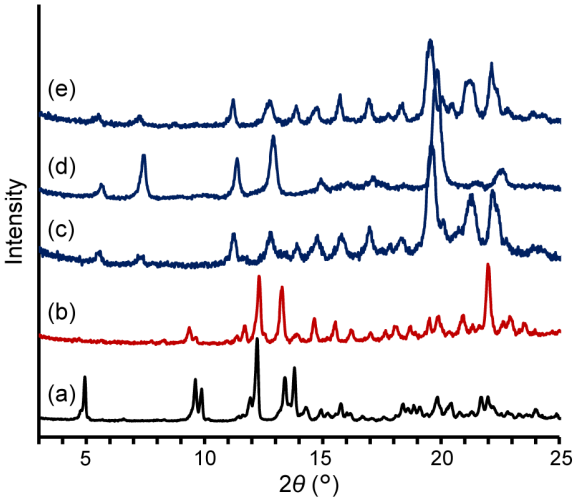



**Fig. 4.** PXRD patterns of $\alpha$-CD (a) and inclusion crystals of Leu/PyS (b), Val/PyS (c), Phe/PyS (d), and Met/PyS (e) prepared under the same conditions optimized for each salt (entry 7 in Table 3 for Leu/PyS, and entries 1, 2, and 4 in Table 4 for Val/PyS, Phe/PyS, and Met/PyS, respectively). Amino acids were used as a racemic modification.

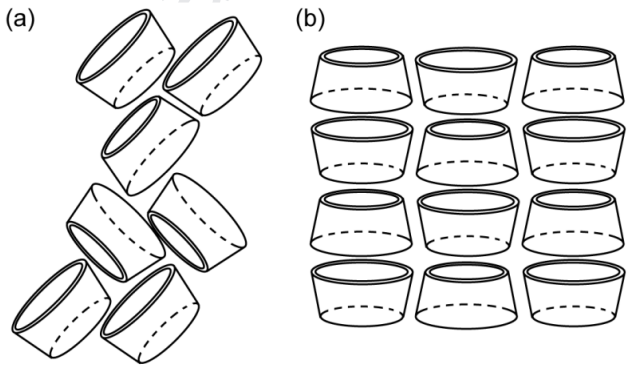



**Fig. 5.** Schematic representation for the crystal structures of $\alpha$-CD: (a) cage-type and (b) channel-type.

## 3. Conclusion

We have shown here that crystals of $\alpha$-CD include $\alpha$-amino acids with high enantioselectivity by converting the amino acids into sulfonate salts with bulky PyS. $^{1}$H NMR experiments and time course

analysis of the $\bar{n}$ and ee% values revealed that the selectivity is originated from the difference in stability between the resulting diastereomeric inclusion complexes of D- and L-amino acid/PyS salts with $\alpha$-CD in crystals. This study provides the first example of chiral recognition using an NMC with porosity without pores through a transition into complex-type inclusion crystals constructed by discrete host/guest complexes. Further studies on improving the crystallinity of the inclusion complexes by the chemical modification of $\alpha$-CD are in progress to clarify the host/guest interaction in crystals.

## 4. Experimental

### 4.1. General

$^1$H NMR spectra were recorded on a Bruker Avance-400 spectrometer using $D_2O$ as the solvent. PXRD data were collected on a Rigaku RINT-2200VHF powder X-ray diffractometer using Cu–K$\alpha$ radiation at increments of 0.02° and an exposure time of 1.2 s/step in an angular range ($2\theta$) of 3–30° at room temperature. $\alpha$-CD crystals were purchased from FUJIFILM Wako Chemicals. Pyrene-1-sulfonic acid was prepared by the reaction of pyrene with chlorosulfonic acid, according to the literature procedure.[33] Other materials were used as purchased. Sulfonate salts of amino acids were prepared as follows. A mixture of a DL-amino acid and arylsulfonic acid (1.05 molar equiv) was stirred in methanol/$H_2O$ (1:1) at 60 °C overnight to give a clear solution. After the solvent was evaporated, the resulting powder was dried in vacuo (0.5–1.0 kPa) at 70 °C for 2 h to give the sulfonate salt of the amino acid. The ee% values of amino acids were determined by HPLC analysis on a Daicel CHIRALCEL OD-H (250 mm × 4.6 mm i.d.), CHIRALPAK AD-H (250 mm × 4.6 mm i.d.), or CROWNPAK CR-I (+) (150 mm × 3.0 mm i.d.).

### 4.2. Typical procedure for the inclusion of a sulfonate salt of an amino acid with crystals of $\alpha$-CD

Powdery crystals of $\alpha$-CD (50.0 mg, 51.4 μmol) were placed in a screw cap vial equipped with a stir bar and suspended by the addition of a solution of DL-Leu/PyS salt (364 mg, 880 μmol) in ethanol (1.1

mL). The suspension was stirred at 30 °C for 24 h, and the resulting crystals were collected by filtration and dried in vacuo (0.5–1.0 kPa) at room temperature for 2 h. A portion of the crystals was dissolved in $D_2O$ and analyzed by $^1$H NMR spectroscopy, which determined the $\bar{n}$ value to be ~1.0 (entry 4 in Table 1). The enantiomeric excess (ee%) of the Leu included in the crystals was determined as follows. The residual inclusion crystals were suspended in ethanol/acetonitrile (1:10) at room temperature for 2 h and the crystals were collected by filtration. This manipulation was repeated four times to desorb the Leu/PyS salt from the crystals via guest exchange with ethanol. The resulting crystals were analyzed by $^1$H NMR spectroscopy, indicating that no Leu/PyS salt was left in the crystals. The combined filtrate was evaporated to leave a residue, which was treated with benzyl chloroformate according to the literature procedure[34] to give *N*-bezyloxycarbonylleucine (Cbz-Leu). The enantiopurity of the Cbz-Leu was determined to be 79%ee (entry 4 in Table 1) by HPLC analysis on a Daicel CHIRALCEL OD-H using 2-propanol/hexane/TFA (15:85:0.1) as the eluent: flow rate = 0.5 mL/min, 30 °C, $\lambda$ = 254 nm, *t* (Cbz-L-Leu) = 9.8 min, *t* (Cbz-D-Leu) = 14.3 min.

The ee% values of other amino acids were determined after conversion into their Cbz derivatives by HPLC. The analysis conditions are as follows. Val: CHIRALCEL OD-H, 2-propanol/hexane/TFA (10:90:0.1), flow rate = 0.5 mL/min, 30 °C, $\lambda$ = 254 nm, *t* (Cbz-L-Val) = 11.7 min, *t* (Cbz-D-Val) = 43.6 min. Phe: CHIRALPAK AD, 2-propanol/hexane/TFA (10:90:0.1), flow rate = 0.5 mL/min, 30 °C, $\lambda$ = 254 nm, *t* (Cbz-L-Phe) = 43.4 min, *t* (Cbz-D-Phe) = 52.1 min. Met: CHIRALCEL OD-H, 2-propanol/hexane/TFA (15:85:0.1), flow rate = 0.5 mL/min, 30 °C, $\lambda$ = 254 nm, *t* (Cbz-L-Met) = 13.8 min, *t* (Cbz-D-Met) = 19.5 min. Nva: CHIRALCEL OD-H, 2-propanol/hexane/TFA (15:85:0.1), flow rate = 0.5 mL/min, 30 °C, $\lambda$ = 254 nm, *t* (Cbz-L-Nva) = 12.9 min, *t* (Cbz-D-Nva) = 32.2 min. Trp: CROWNPAK CR-I(+), aq $HClO_4$ (pH 1.5)/acetonitrile (80:20), flow rate = 0.2 mL/min, 30 °C, $\lambda$ = 200 nm, *t* (L-Trp) = 9.1 min, *t* (D-Trp) = 16.6 min.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/xxxx.

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**Highlights:**

- Enantioselective inclusion of $\alpha$-amino acids with crystals of $\alpha$-cyclodextrin ($\alpha$-CD) has been achieved by converting the amino acids into sulfonate salts with pyrene-1-sulfonic acid (PyS).
- Under conditions optimized for individual amino acids, the PyS salts of leucine, valine, phenylalanine, and methionine are included with good enantioselectivities (up to 92%ee).
- The enantioselectivity originates from the difference in stability between the inclusion complexes of D- and L-leucine/PyS salts with $\alpha$-CD in crystals.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: