Highly Efficient Enantioresolution of 2,2-Dimethyl-3-hexanol with Cholamide Crystals on the Basis of Intercalation and Bilayer Inversion

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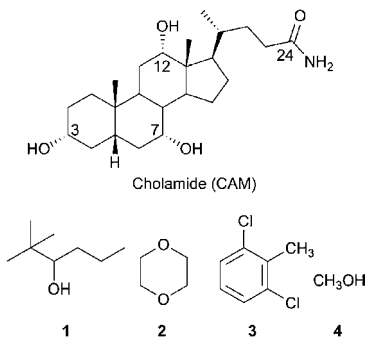
Enantioresolution of racemic 2,2-dimethyl-3-hexanol in solid state was achieved with four kinds of crystalline matrices of cholamide, yielding its S enantiomer in high purity and yields. This intercalation method accompanied bilayer inversion on their lipophilic sides.

Solid-state dynamic behavior has lately received much attention in the field of material science.[1–6] For example, coordination polymers with nanopores have been applied to gas sorption and storage materials.[7–9] Organic inclusion crystals are also attractive owing to their guest-responsive flexibility and diversity for the purpose of separation and recognition.[10]

We studied intercalation phenomena by using cholic acid, which is a classical host compound.[11] In addition, we have reported that cholamide (3α,7α,12α-trihydroxy-5β-cholamide, CAM, Scheme 1) functions as an excellent host for enantioresolution of 2,2-dimethyl-3-hexanol (**1**) among secondary aliphatic alcohols, and that such chirality recognition comes from a reversed bilayer on lipophilic sides.[12] This successful result prompted us to attempt an intercalation method rather than a recrystallization method, leading us to green chemistry.[13] Here we report highly efficient enantioresolution of **1** by the intercalation method by using different matrices which consist of CAM crystals with four types of host frameworks.

CAM was prepared via a conventional condensation reaction from commercially available cholic acid and ammonia by a mixed anhydride method at 243 K.[14] The inclusion compounds of CAM·**1**–**4** were obtained by recrystallization by previously reported methods.[12,15] Guest-free (GF) crystals were prepared by desorption of CAM·**2** inclusion crystals. The guest component was completely removed from the crystals upon heating at 150 °C under reduced pressure for 1 h, which was confirmed by thermal gravimetric analysis (TG). The entire inclusion ratios of the intercalated crystals were determined by TG (Figure S1) and gas chromatographic (GC) analyses.[16] Enantiopurity of **1** was established by chiral GC analyses (CP Chirasil DEX CB) (Figures S2–S6). The crystals before and after the intercalation were characterized by means of powder X-ray diffraction (PXRD) with a Rigaku RINT-2100 at room temperature (Figures S7 and S8).



Scheme 1.

Table 1. The intercalation of **1** into four types of crystalline matrices of CAM, which was evaluated by enantiomeric excess, absolute configuration, and inclusion ratio[a]

Compound	Framework	ee/%	Absolute configuration	Inclusion ratio/%[c]
CAM	GF	96	S	96
CAM·**2**	α-trans	95	S	86
CAM·**3**	DCA	97	S	77
CAM·**4**	Triangular[b]	96	S	$<$10

[a]Four equivalent amounts of racemic **1** to CAM crystals were used. [b]This crystalline matrix included water. [c]A 1:1 molar ratio of guest-to-host corresponds to a 100% inclusion ratio.

The intercalation of **1** was performed by using four kinds of crystalline matrices of CAM, as summarized in Table 1. First, we examined the intercalation with GF crystals. The crystals were suspended in a hexane solution containing four equivalent amounts of racemic **1** for 24 h.[17] The filtered crystals accommodated **1** in an inclusion ratio of 96% and in 96% enantiomeric excess (ee) with S absolute configuration. This ee value was close to the value (98% ee) by the recrystallization.[12] Next, we examined the intercalation by using three other inclusion crystals, CAM·**2**, CAM·**3**, and CAM·**4** with different host frameworks, α-trans, DCA, and triangular,[15b] respectively. Although the ee values were similar to each other, the inclusion ratios were different. The guest exchange moderately took place in the α-trans- and DCA-crystals, but slightly in the triangular-crystals. These results are considered to reflect a notable effect of the initial matrices in the guest exchange events.

We employed PXRD analyses to reveal changes of the crystal structures before and after the intercalation (Figures 1 and S7). Figure 1a shows the PXRD pattern of initial crystals of CAM·**2** before the guest exchange, while Figure 1b shows that of the intercalated crystals after the guest exchange. The latter pattern is very similar to that obtained by simulation from the X-ray crystal structure of a single crystal of CAM·**1** (Figure S8). The intercalated crystals of GF CAM and CAM·**3** have PXRD patterns which are similar to that of the intercalated CAM·**1** from the CAM·**2** (Figures S7a–S7d). In contrast, CAM·**4** exhibits a small change of the patterns (Figures S7e and S7f).

Figure 2 displays bilayer structures of CAM·**1** and CAM·**2**. It can be seen that bilayers of CAM·**1** are parallel arrangements while those of CAM·**2** are antiparallel ones, as shown by arrows. This result indicates that the guest exchange event accompanies

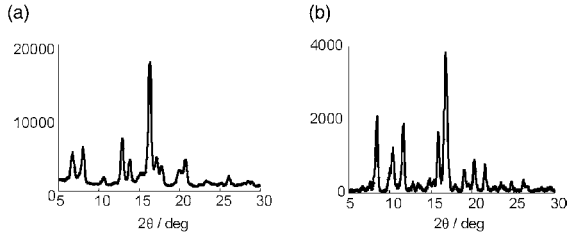


Figure 1. PXRD patterns of (a) initial CAM·**2** crystals obtained by recrystallization and (b) intercalated CAM·**1** crystals obtained by the guest exchange from the CAM·**2**.

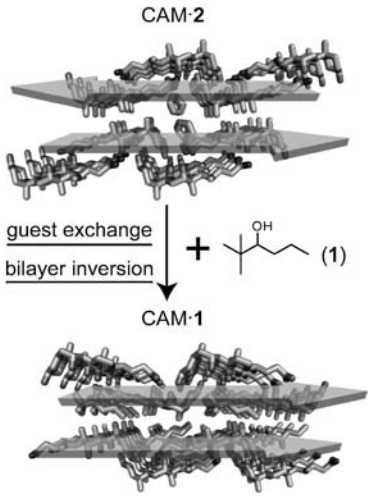


Figure 2. Schematic representation of crystal structures of CAM·**2** before guest exchange (upper) and CAM·**1** after the guest exchange (lower). The guest exchange accompanies bilayer inversion on their lipophilic sides.

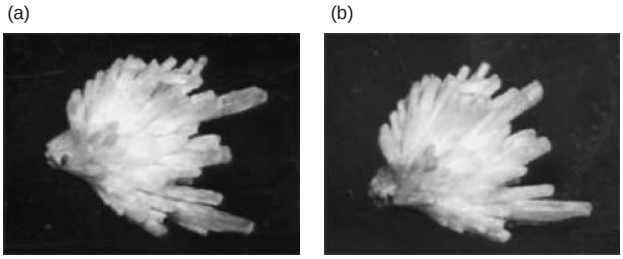


Figure 3. Optical micrographs of CAM crystals; (a) CAM·**2** crystals obtained by recrystallization of CAM from **2**, (b) CAM·**1** crystals after soaking the CAM·**2** crystals into a solution of **1** for 8 days.

a directional reversion of the bilayers on the lipophilic sides. Such a drastic structural change is very rare in solid states. Furthermore, the guest exchange event proceeded with slight deterioration of the crystals for eight days (Figure 3), suggesting that insertion of **1** may induce the bilayer inversion with efficient molecular movement. At this moment, inversion mechanism remains unrevealed. However, we assume that the inversion takes place via molecular rotation and slide at a microscopic part in the crystal followed by subsequent domino transformation.

In summary, we have demonstrated that the successful enantioresolution of racemic 2,2-dimethyl-3-hexanol was accomplished by intercalation. It is noteworthy that the guest exchange depended on the initial host matrices. We now extensively investigate dynamic chiral recognition of other steroidal inclusion compounds by the intercalation.

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16 Supporting Information is available electronically on CSJ-Journal web site, http://www.csj.jp/journals/chem-lett/index.html.
17 The crystals of **1** are insoluble in hexane.

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