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Excellent enantio-selective enclathration of (2*R*,3*S*)-3-methyl-2-pentanol in channel-like cavity of 3-epideoxycholic acid, interpreted by the four-location model for chiral recognition

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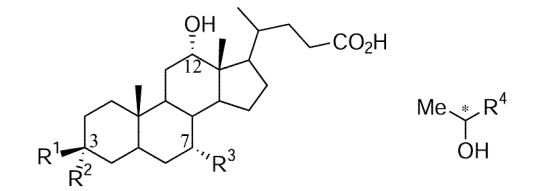
Pure (2*R*,3*S*)-3-methyl-2-pentanol is resolved from the racemates by a steroidal host; the interpretation of the recognition mechanism based on the crystal structure reveals that CH/O interaction between the host and guest plays a decisive role in enantio-selective enclathration of the small aliphatic secondary alcohol.

Enantioresolution of small aliphatic alcohols has been the subject of struggle for over a century.[1] There have been many attempts to find appropriate host compounds for enantio-selective enclathration of the alcohols in the crystalline state.[2] Tetraol host compounds exhibit a successful example of the acquisition of optically pure alcohol with a cyano group, but less than 70% ee purity of aliphatic secondary alcohols.[3] Here we describe the first example of excellent enantio-selective enclathration of the smallest aliphatic secondary alcohol with two chiral carbons, 3-methyl-2-pentanol (**4**), by using a steroidal host compound, 3-epideoxycholic acid (EDCA). And we propose a reasonable mechanism for such excellent chiral recognition on the basis of the four-location model proposed recently.[4] The important suggestion for crystal engineering is that epimerization of the host induces a fixation of the fourth location for the smallest hydrogen attached to chiral carbon through CH/O interaction.

EDCA and 3-epicholic acid (ECA) were synthesized from commercially available deoxycholic acid (DCA) and cholic acid (CA) by inversion of the hydroxyl groups at C3 *via* Mitsunobu condensation reaction, respectively.[5] Their inclusion compounds with four aliphatic secondary alcohols (**1–4**) were obtained by recrystallization from neat racemic alcohols or by suspension in *n*-hexane. The 1 : 1 stoichiometries of the hosts and guests were confirmed by thermal gravimetric analysis. The enclosed alcohols were recovered by micro-distillation. Enantiopurity of the alcohols was established by ^{13}C-NMR spectroscopy, using their camphorsulfonated derivatives.

Table 1 shows the resulting enantiomeric excess values and the predominant configurations. ECA prefers (*R*)-enantiomers of the alcohols regardless of the recrystallization or suspension method. The latter method yielded (*R*)-enantiomers of **3** and **4** with high enantio-selectivity. On the other hand, EDCA shows selective enclathration of **3** and **4** only by the former method. The most remarkable thing is that almost pure (2*R*,3*S*)-3-methyl-2-pentanol (**4**) was obtained by the first recrystallization from the racemates. To our knowledge, it is the first example of enantio-selective enclathration of the alcohol.



R^1	R^2	R^3	host	R^4	guest
OH	H	OH	; 3-epicholic acid (**ECA**)	Et	; **1**
OH	H	H	; 3-epideoxycholic acid (**EDCA**)	*i*Pr	; **2**
H	OH	OH	; cholic acid (**CA**)	*n*Pr	; **3**
H	OH	H	; deoxycholic acid (**DCA**)	*s*Bu	; **4**

The crystal structure of the inclusion compound of EDCA obtained by recrystallization from the racemic **4** was determined.‡ Figs. 1a and 1b illustrate the molecular packing diagram and the hydrogen-bonding network, respectively. Its host framework resembles that of CA rather than DCA due to the antiparallel molecular arrangement in their common bilayered structures.[6] Intermolecular hydrogen bonds form a cyclic network with the sequence OH(24b)···OH(3)···OH-(guest)···OH(12)···O(24a), where the hydrogen-bonding distances are 2.58, 2.76, 2.83 and 2.82 Å, respectively. The guest alcohols are enclosed within channel-like host cavities between the bilayers.

In order to focus on the environment around the guest alcohol, Figs. 2a and 2b depict sectional views of the cavity sliced by the planes formed by three atoms: (C25), (O), (C27) and (O), (H), (C27), respectively (see Fig. 2c with respect to these designations of the guest). Fig. 2a reveals locations of three substituents of the guest alcohol: hydroxyl group (O), *sec*-butyl group (C27), and methyl group (C25). First, the hydroxyl group (O) is fixed between two hydroxyl groups at O(3) and O(12) with OH/O hydrogen bonds. Secondly, the largest *sec*-butyl group (C27) is enclosed in the larger space. Thirdly, the

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Table 1 Enantioresolution of aliphatic secondary alcohols by ECA and EDCA

	ECA		EDCA		
Alcohols	Recrystallization[a]	Suspension[b]	Recrystallization	Suspension	Predominant configuration
1	31	25	GF[c]	GF	*R*
2	29	39	GF	GF	*R*
3	79	94	90	GF	*R*
4	67	> 99	> 99	GF	2*R*,3*S*

[a] Values of enantiomeric excess (ee%) by recrystallization method. [b] Values of enantiomeric excess (ee%) by suspension method. [c] Guest-free crystal.

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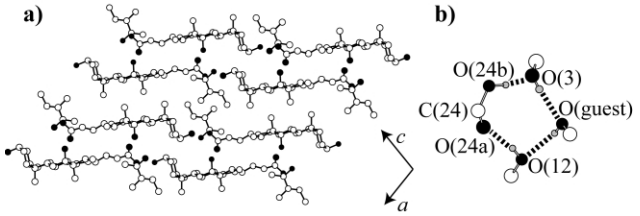

Fig. 1 a) Molecular packing diagram of inclusion crystal of EDCA with **4** and b) the corresponding hydrogen-bonding network. O(24a) and O(24b) represent the two oxygen atoms of carbonyl and hydroxyl group at C(24) of EDCA, respectively.

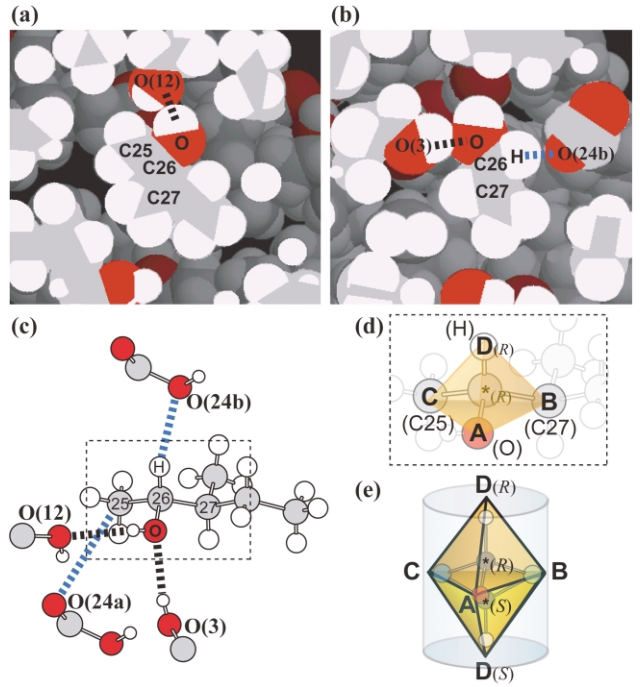

Fig. 2 Detailed profile of the environment around the guest alcohol (**4**) in the channel-like host cavity of EDCA. a) Sectional view of the cavity sliced by the plane formed by three atoms: (C25), (O) and (C27), and b) by three atoms: (O), (H) and (C27), respectively. The black and blue dashed lines represent OH/O and CH/O interactions, respectively. c) Summary of the OH/O and CH/O interactions among the hosts and the guest. d) Profile of four constituents around the chiral carbon of **4** in the host cavity. The chiral carbon is represented by *(*R*). The four locations: A, B, C and D, correspond to hydroxyl group (O), *sec*-butyl group (C27), methyl group (C25) and hydrogen atom (H), respectively. e) The state of coexistence of both enantiomers with the disordered asymmetric carbon; *(*R*) and *(*S*), in the condition that three sustituents around the chiral carbon (A, B and C) are designated.

methyl group (C25) is enclosed in the smaller space, which is not enough to enclose the *sec*-butyl group. It is impossible to replace the two positions of *sec*-butyl and methyl groups in the cavity. Besides, the methyl group (C25) has a CH/O interaction between the methyl carbon and O(24a) of the host with the distance of 3.55 Å. In this way, three locations around the chiral carbon of the guest alcohol are determined, as in the previous study of other steroidal hosts.[2c–e,7] Furthermore, as shown in Fig. 2b, the location of the hydrogen atom (H) is fixed by CH/O interaction between the chiral carbon (C26) and the carboxyl group (O(24b)). The distance between C26 and O(24b) is 3.54 Å and the hydrogen atom is located at a proper angle of 165.2° for C26–H–O(24b). A summary of the OH/O and CH/O interactions among the hosts and the guest is illustrated in Fig. 2c.

Mechanisms of chiral recognition between host and guest have been interpreted by various models.[7] In previous work, we reported that a four-location model[4] was suitable for interpreting the mechanism in channel-like host cavities.[8] In this case, four designated locations (A, B, C and D) are needed for enantio-selective enclathration. In the case of EDCA, the CH/O interaction mentioned above is decisive for determining the fourth location (D), which corresponds to the hydrogen atom. Actually, X-ray analysis shows the exact guest configurations (2*R*,3*S*) without disorder, meaning that other configurations are not involved as the status of coexistence of both enantiomer pyramids (Fig. 2e). Therefore, as shown in Fig. 2d, the CH/O interaction enables the selective enclathration of the (*R*)-enantiomer pyramid (A, B, C, and D(*R*)).

Although such CH/O interaction has not been found in other steroidal hosts, the epimerization of the α-hydroxyl group at C3 into the β-hydroxyl group induces the effective interaction for determining the fourth location. The two distinct directions of the hydroxyl groups result in the different hydrogen-bonding networks. For example, cholamide with an α-hydroxyl group at C3 captures the alcoholic guests with the hydrogen bonds branched from the cyclic network among the host molecules.[9] On the other hand, EDCA with the β-hydroxyl group at C3 captures the guest alcohol with the cyclic network among the hosts (Fig. 1b). Accordingly, the guest alcohol is lifted up to a closer position to the neighboring host molecule, as shown in Fig. 2b. As a result, the guest position is suitable for the CH/O interaction between the hydrogen atom and the carboxyl group (O(24b)).

In summary, we have demonstrated not only the first example of excellent enantio-selective enclathration of aliphatic secondary alcohols but also the detailed mechanism of enantioresolution based on the four-location model. This clear interpretation of the mechanism of enantio-selective enclathration will make a contribution to the clearer understanding of other systems.

Notes and references

‡ Crystal data for inclusion crystal of EDCA·**4** (1 : 1): $C_{24}H_{40}O_4{\cdot}C_6H_{14}O$, M = 494.75, monoclinic, a = 12.742(2), b = 8.054(3), c = 14.372(3) Å, β = 102.89(2)°, V = 1437.6(6) Å^3, T = 296 K, space group $P2_1$ (no. 4), Z = 2, μ(Cu-K$_\alpha$) = 0.075 mm^{-1}, D_c = 1.143 g cm^{-3}, 3707 reflections were unique, and 1724 observed reflections with $|F_o|^2 > 3\sigma|F_o|$ were used for further calculations after Lorenz and polarization corrections. The final R_1 and wR_2 were 0.060 and 0.056, respectively. The absolute configuration of the guest can be determined based on the known absolute configuration of EDCA. CCDC 212699. See http://www.rsc.org/suppdata/cc/b3/b309755b/ for crystallographic data in .cif or other electronic format.

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