Chiral Discrimination of 1-Phenylethylamine by Diastereomeric Salt Formation with Bile Acids. Crystal Structures of Cholic Acid Salts with (*R*)- and (*S*)-1-Phenylethylamine

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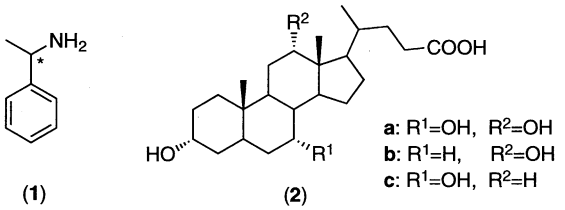
Chiral discrimination of 1-phenylethylamine (**1**) by diastereomeric salt formation with bile acids is described. X-ray crystallographic studies of the salts between cholic acid (**2a**) and (*R*)-, (*S*)-, and (*RS*)-**1** reveal that more densely packed (*S*)-**1**+**2a** salt crystallizes preferentially by treatment of **2a** from racemic **1**.

One of the most common methods to separate a racemic amine into its optically pure form is achieved by a diastereomeric salt formation with optically active acids.[1] When the difference in stability between diastereomeric salts as crystalline material is sufficiently large, the resolved amine is recovered from the crystallized salt by treatment with an alkaline. However, understanding of the selective crystallization of one of diastereomeric salts in connection to the crystal structures is limited due to lack of the systematic structural investigations of diastereomeric salts.[2]



(**1**) (**2**)

Steroidal bile acids (**2**) are known to form lattice inclusion compounds with various organic compounds. More recently, we showed optical resolution of some lactones by selective enclathration with cholic acid (**2a**).[3] However, there have been only a few reports on the utility as acid chiral resolving reagents for amines.[4] Moreover, structural investigations of the bile acids salts are focused on metal salts as models of bile acid micelles in aqueous solution or inclusion complexes.[5] Here, we wish to present chiral discrimination of 1-phenylethylamine (**1**) by the formation of diastereomeric salts with **2a** and crystal structures of both salts.

Mixing THF solution of bile acids (**2**) with racemic **1** at 1:2 molar ratios gave 1:1 salts in high yields. The resulting salts were treated with an alkaline solution followed by micro-distillation under reduced pressure to generate the partial resolved amine. Optical purity and predominant configuration of the recovered **1** was estimated by the polarimetry.[6] After one cycle recrystallization of the deposited salt of **1** with **2a**, (*S*) isomer was enriched, and its optical purity increased to about 50%. The results of resolution of **1** are summarized in Table 1. **2a** was a effective resolving agent for **1** by diastereomeric salt formation. However, **2b** and **2c** had no sufficient ability to chiral discrimination of **1**. This difference may result in absence of one hydroxy group on the steroidal skeleton. Single crystals of salts of **2a** with optically pure (*R*)-**1**, (*S*)-**1** and racemic **1** were prepared in a similar manner and subjected to crystal structural investigations. Figure 1 shows crystal structures of the salts.[7]

Table 1. Optical resolution of **1** by diastereomeric salt formation with **2**

Bile acid	Recover (%)[a]	O. P.(%)[b]	Configuration[b]
2a	85	45	(*S*)
2b	84	6	(*R*)
2c	83	3	(*R*)

[a] Based on recovered salts.
[b] O. P.: Optical purity determined by optical rotation.

Racemic **1** gave the same crystal structure as (*S*)-**1** (Figure 1a and 1b). The amine could be refined as (*S*)-isomer. It had no

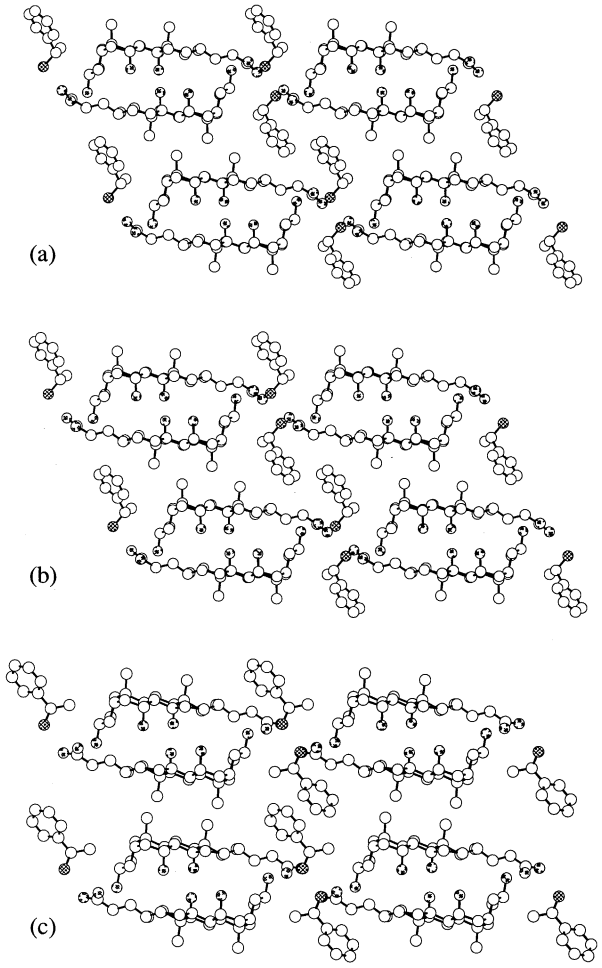


Figure 1. Crystal structures of (a) (*S*)-**1**+**2a**, (b) (*RS*)-**1**+**2a**, and (c) (*R*)-**1**+**2a**. Empty, shadowed and dotted circles represents carbon, nitrogen, and oxygen atoms, respectively.

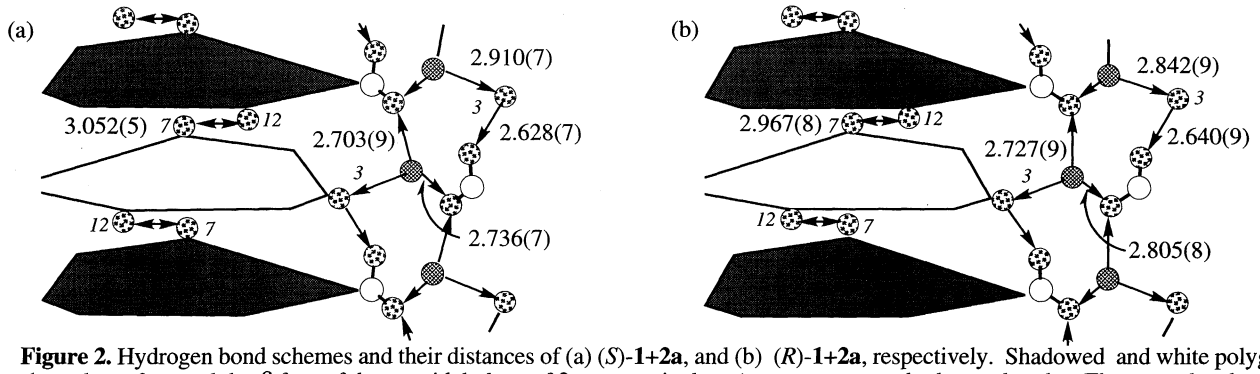


Figure 2. Hydrogen bond schemes and their distances of (a) (*S*)-**1**+**2a**, and (b) (*R*)-**1**+**2a**, respectively. Shadowed and white polygons show the α-face and the β-face of the steroidal plane of **2a**, respectively. Arrows represent hydrogen bonds. The arrow head means from a donor to an acceptor, and the arrow with both heads means a disordered hydrogen bond.

apparent disorder around the asymmetric carbon of **1**. This result is consistent to predominant (*S*)-configuration of the recovered amine by the large scale resolution experiment. Comparison of crystal structures of (S)-**1**+**2a** with (*R*)-**1**+**2a** reveals the correlation between the stability of the crystalline salts and preferential crystallization of (*S*)-**1** salt. Both have a multibilayered structure. Facial amphiphilic nature of **2a** yields such a bilayer structure through the association of lipophilic faces and the hydrogen bonds between hydrophilic faces. Bent molecular shape toward the hydrophilic face gives a corrugated sheet structure. This yields a one-dimensional lipophilic cavity in the lipophilic layers, which corresponds to a channel in the crystalline inclusion compounds of **2a** and **2b**. The lipophilic moieties of **1** is accommodated in the cavity.

In the hydrophilic layer, both salts have quite similar hydrogen bond networks. Hydrogen bond schemes are shown in Figure 2. The ammonium nitrogen acts as a three-hydrogen bond donor which links two carboxylate oxygen atoms and one hydroxy group of the three neighboring molecules of **2a**. Two other hydroxy groups at 7 and 12 position of host molecules are hydrogen-bonded to each other to hold the steroidal plain pararell to the hydrphilic layer.

The most striking difference of these two crystal structrues is the stacking manner of the sheet in the lipophilic layer. In the 1:1 complex of **2a** with (*S*)-**1**, the C19 methyl of the upper layer is located between the C18 and the C19 of the lower layers, whereas the C19 methyl group is eclipsed by the C18 methyl group of the lower layers in **2a** with (*R*)-**1**. This sliding in lipophilic layer increases the interlayer distances and deforms the cavities for **1**. Cross sectional view clearly illustrates that channel in the former is suitable for (*S*)-**1** and smaller than that in the latter.

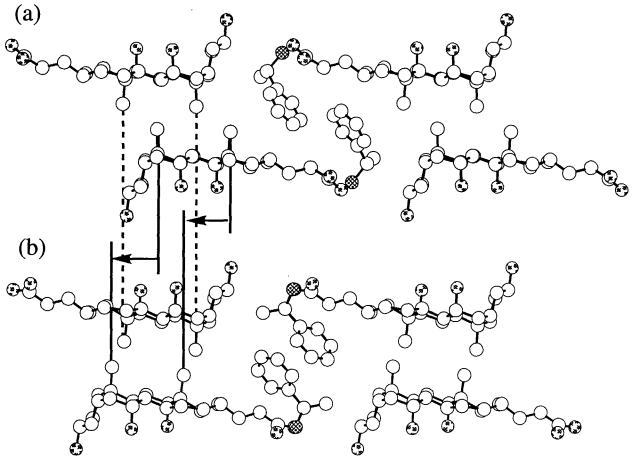


Figure 3. Lipophilic Layer of (a) (*S*)-**1**+**2a**, and (b) (*R*)-**1**+**2a**, respectively.

Structural investigation of both diastereomeric salts gives us an explanation for the selective crystallization. Similarity of hydrogen bond network in both crystals enables us to estimate the stability of crystals directly from packing efficiency. In the (*S*)-**1** salt, **2a** are arranged in the lipophilic layers more closely than in the (*R*)-**1** salt. Indeed, the unit volume of the (*S*)-**1** salt is much smaller than that of the (*R*)-**1** salt. This fact suggests that (*S*)-**1** salt might be more stable than (*R*)-**1** salt as crystalline state. This small difference of packing efficiency enables preferential crystallization of (*S*)-**1** salt from the racemate. Successive structural investigation of other bile acids salts are under investigation in order to explain their absence of chiral discrimination properties.

References and Notes

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7 X-ray crystal structure analyses a) (*S*)-**1**+**2a**, $C_{32}H_{51}NO_5$, M_r=529.76, monoclinic, $P2_1$, a=11.705(3), b=7.703(4), c=16.293(3) Å, β=103.55(2)°, V=1428.1(7) Å^3, Z=2, T=243 K, D_{calcd} =1.232 g cm^{-3}, R=0.050, 1735 unique reflections with $Fo>3\sigma(Fo)$. b) (*RS*)-**1**+**2a**, $C_{32}H_{51}NO_5$, M_r=529.76, monoclinic, $P2_1$, a=11.806(2), b=7.681(2), c=16.462(2) Å, β=104.08(1)°, V=1447.9(4) Å^3, Z=2, T=298 K, D_{calcd} =1.215 g cm^{-3}, R=0.053, 2292 unique reflections with $Fo>3\sigma(Fo)$. c) (*R*)-**1**+**2a**, $C_{32}H_{51}NO_5$, M_r=529.76, monoclinic, $P2_1$, a=10.990(5), b=7.662(4), c=17.999(3) Å, β=98.17(2)°, V=1500.3(8) Å^3, Z=2, T=243 K, D_{calcd} =1.173 g cm^{-3}, R=0.055, 1564 unique reflections with $Fo>3\sigma(Fo)$.