Successive optical resolution of two compounds by one enantiopure compound

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By using (1R,2R)-1,2-diphenylethylenediamine as a single enantiopure compound, we achieved a novel successive optical resolution of more than one kind of racemic compound through supramolecular crystallization.

Recently, the creation of various functions by self-assembly has been actively investigated.[1] In chiral chemistry, optical resolution of a racemic compound is one of the most important functionalities, where generally one chiral compound acts on one kind of racemic compound.[2] Recently, we have reported a supramolecular host system consisting of an achiral carboxylic acid derivative and a chiral amine derivative. It turned out that the host system possesses two chiral molecules by chirality transfer from the amine to the achiral carboxylic acid, and resolved racemic alkyl alcohols with high enantiomeric efficiency.[3] Based on the high chiral recognition ability of the self-assembled supramolecular system, we have designed a system in which one chiral compound serves twice in successive optical resolutions.

(1R, 2R)-1   2   alkylalcohol
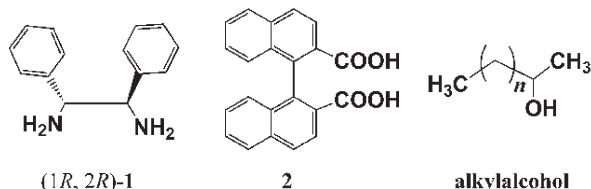
In this paper, we report the novel phenomenon of a successive optical resolution of two kinds of racemic compound in a batch of solution. The compounds employed are (1R,2R)-diphenyletylenediamine ((1R,2R)-1) as an enantiopure compound, and chiral 1,1′-binaphthyl-2,2′-dicarboxylic acid (2) and chiral alkyl alcohols as two kinds of racemic (rac) compounds.

In the case of 2-butanol, 5.0 mmol of (1R,2R)-1 and 5.0 mmol of rac-2 were dissolved in the racemic alcohol solution (60 ml) with heating and left to stand at room temperature. After a day, many colourless crystals (I) (1.21 g) were produced. These crystals were found to contain 1 and 2, and the chirality of 2 in the crystals was established by HPLC (Chiral OD-H (Daicel), hexane/EtOH/TFA = 90 : 10 : 0.1, 1.0 ml min^{-1}, 35 °C, 254 nm) as the (aS)-configuration with an ee as high as 98%. X-Ray crystal structure analysis of crystals I revealed they include water molecules with the stoichiometry (1R,2R)-1 : (aS)-2 : H$_2$O = 1 : 1 : 1 (Fig. 1).† The

space group is $P2_12_12_1$. As a characteristic of the structure, the crystal has a columnar supramolecular hydrogen-bonded network around the 2_1-axis. These networks are formed by the ammonium hydrogen of amine/H$^+$ and the carboxylate oxygen of a dicarboxylic acid anion. The included water molecule (Fig. 1, shown in red) links the carboxyl group and the amino group through hydrogen bonds and contributes to the maintenance of the column frame.

The 2-butanol solution was filtered to remove the crystals I and the resulting filtrate left to stand at room temperature. After two days, plenty of colourless crystals (II) (1.22 g) were formed again. Analysis showed that these crystals contain 1, 2 and 2-butanol. HPLC analysis has shown that the absolute configuration is the aR, opposite to that in crystal I, with an optical purity of 94% ee. This is slightly lower than in I as a very small amount of I crystals inevitably intermingled with the sample.

Only with (aR)-2, (1R,2R)-1 created a chiral cavity. The optical purity of 2-butanol included in the cavity of crystal II was studied by GC analysis using a Chiral-DEX CB capillary column. (S)-2-Butanol was selectively included in 21% ee. X-Ray crystal structure analysis was carried out to reveal the inclusion geometry and the mechanism for the enantioselectivity of the supramolecular cavity.† The stoichiometry of II is (1R,2R)-1 : (aR)-2 : H$_2$O : (S)-2-butanol = 1 : 1 : 1 : 1 (Fig. 2), with the space group of $P2_12_12_1$. It has a characteristic columnar hydrogen-bonded network around the 2_1-axis provided by the carboxyl and amino groups, as in crystal I. The water molecules (Fig. 2, molecules in red) link the carboxyl group and the amino group through hydrogen bonds and contribute to the maintenance of the column frame. Molecule 2, with the (aR) configuration, created a chiral cavity with (1R,2R)-1 in crystals II which is not present in crystals

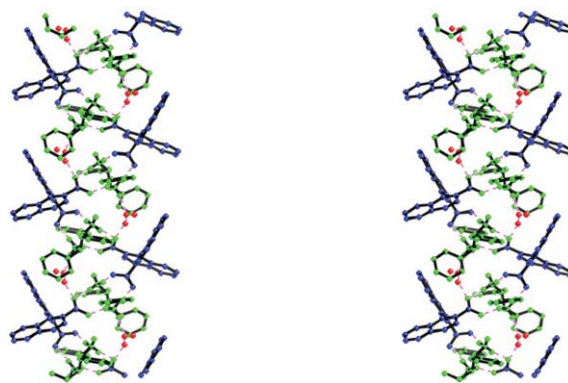[a]JST ERATO-SORST Kuroda Chiromorphology Team, 4-7-6 Komaba, Meguro-ku, Tokyo, 153-0041, Japan
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Fig. 1 Crystal structure of (1R,2R)-1·(aS)-2·H$_2$O (I). The columnar hydrogen-bonded network parallel to the a-axis is shown. The water molecule is displayed in red.
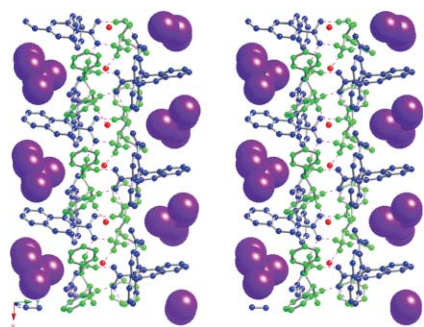
Fig. 2 Crystal structure of (1*R*,2*R*)-**1**·(a*R*)-**2**·H$_2$O·(*S*)-2-butanol (**II**). The columnar hydrogen-bonded network is parallel to the a-axis. The water molecule and 2-butanol molecule are represented in red and purple, respectively.

I, where **2** adopts the opposite (a*S*) configuration. (*S*)-2-Butanol molecules included in the cavity are shown in the space-filling model (Fig. 2, in purple). The bond between the guest and the host was not obvious. However, it is most likely that (*S*)-2-butanol molecules are hydrogen-bonded to the carboxyl group. Hydrogen bonds between the host and guests are in fact observed in other alkyl alcohol systems described below. An electron density corresponding to disordered (*R*)-2-butanol molecule was observed.

Thus, an interesting successive optical resolution system created by one chiral diamine compound is presented. Firstly, the chiral (1*R*,2*R*)-**1** molecule recognizes the chirality of **2** and forms the chiral supramolecular complex with (a*S*)-**2**. In the following step, after the removal of type **I** crystals, chiral (1*R*,2*R*)-**1** forms a chiral supramolecular host system with the remaining (a*R*)-**2** to create a chiral cavity, which then discriminates the chirality of *rac*-2-butanol molecules by a synergistic effect of (1*R*,2*R*)-**1** and selected (a*R*)-**2**.

Optical resolution of various *rac*-alkyl alcohols, *i.e.*, 2-methyl-3-butanol, 2-pentanol, 2-hexanol, 2-heptanol, and 2-octanol, by this system were investigated. In the same way as for 2-butanol, chiral (1*R*,2*R*)-**1** and *rac*-**2** were dissolved in *rac*-alkyl alcohols with heating, and the solutions kept standing at room temperature for

one day. Many colourless crystals were formed in all the five alcohol solutions, and each were proved to be of type **I**.
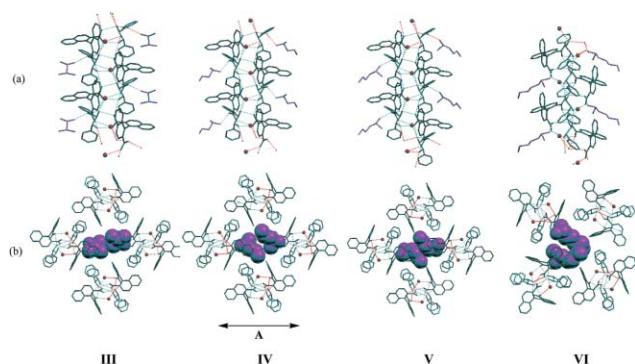
The enantiomeric purity of **2** in these crystals was determined by HPLC as before (Table 1). Only **2** of the (a*S*) configuration was involved with higher than 98% ee.

As before, the solutions were filtered to remove the crystals of type **I** and the filtrate left to stand at room temperature. In the cases of 2-methyl-3-butanol, 2-pentanol and 2-hexanol, the second batches of colourless crystals were obtained from the filtrates after about two days. When 2-heptanol and 2-octanol were used, the second batches of colourless crystals were obtained after about four days. The enantiomeric purities of **2** and alkyl alcohols in these crystals were determined by HPLC and GC analysis, respectively. In these crystals, (a*R*)-**2** molecules were involved with more than a 94% ee. The results are summarized in Table 2.

Good quality colourless crystals, **III**, **IV**, **V** and **VI**, were obtained from *rac*-2-methyl-3-butanol, 2-pentanol, 2-hexanol and 2-heptanol solutions, respectively, and their crystal structures analyzed (Fig. 3).† X-Ray analyses revealed the same stoichiometry for these inclusion crystals, *i.e.*, (1*R*,2*R*)-**1** : (a*R*)-**2** : H$_2$O : alkyl alcohol = 1 : 1 : 1 : 1, with the same $P2_12_12_1$ space group. These crystals share a common feature of a characteristic columnar hydrogen-bonded network around the 2$_1$-axis by the carboxyl and amino groups, as in crystals **II**. The included water molecules link the carboxyl group and the amino group through hydrogen bonds, and contribute to the maintenance of the columnar frame. Each alkyl alcohol (Fig. 3, indicated in purple) is maintained in the cavity by hydrogen bonding to the carboxyl group.

The optical purity of alkyl alcohols improves as the alkyl chain gets longer for the non-branched examples (*cf.* **II**, **IV** and **V**), probably due to it better fitting the size of the cavity. The optical purity of 2-pentanol is 41% ee. Although the ee for 2-hexanol in complex **V** is 62%, the preferred absolute configuration of the included alkyl alcohol changed to (*R*). From the X-ray analysis, it was found that steric repulsion between the alkyl chains in the cavity is larger for (*S*)-2-hexanol compared to that for (*R*)-2-hexanol (Fig. 4).

In complexes **II**–**V**, the packing style of the 2$_1$-columns, as well as each 2$_1$-column structure, is common. As the chain of the guest becomes longer from 2-butanol to 2-pentanol and 2-hexanol, the distance between the 2$_1$-columns (*A*, Fig. 3) and that between the (a*R*)-**2** molecules along a column increases (18.44, 18.63 and 18.75 Å, and 9.58, 9.58 and 9.67 Å, respectively, for **II**, **IV** and **V**). Thus, by slightly changing the packing of the 2$_1$-columns, it could accommodate these alkyl alcohols enantioselectively. When 2-heptanol was used, the enantioselectivity was poor (Table 1, entry 5). In fact, crystals **VI** had completely different cell parameters from those of crystals **II**–**V**. In complex **VI**,† though

Table 1 Optical purities of the first batches of colourless (a*S*-**2**) crystals in various alkyl alcohols

Entry	Alkyl alcohol	ee (%)^a
1	2-Butanol	98
2	2-Methyl-3-butanol	98
3	2-Pentanol	99
4	2-Hexanol	98
5	2-Heptanol	98
6	2-Octanol	99

^{a} Determined by chiral HPLC analysis.

Table 2 Optical purities of (a*R*-**2**) and various included alkyl alcohols in the second batches of colorless crystals

Entry	Complex	Alkyl alcohol	ee of (a*R*-**2**) (%)^a	ee of alcohol (%)^b	Absolute configuration
1	**II**	2-Butanol	94	21	(*S*)
2	**III**	2-Methyl-3-butanol	94	43	(*S*)
3	**IV**	2-Pentanol	95	41	(*S*)
4	**V**	2-Hexanol	98	62	(*R*)
5	**VI**	2-Heptanol	97	~0	—
6		2-Octanol	98	~0	—

^{a} Determined by chiral GC analysis. ^{b} Determined by chiral HPLC analysis.

Fig. 3 Crystal structures of **III**, **IV**, **V** and **VI**. The water molecule is shown in red and alkyl alcohol molecule in purple. (a) Columnar hydrogen-bonded network parallel to the a-axis. (b) View down the a-axis.
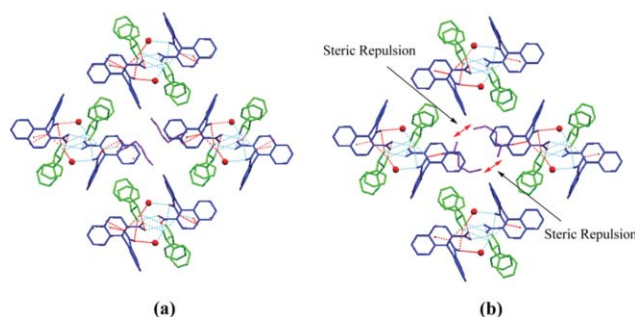
Fig. 4 Crystal structure of **V** viewed down the a-axis. Water and alkyl alcohol molecules are shown in red and purple, respectively. Inclusion of (a) (*R*)-2-hexanol and (b) (*S*)-2-hexanol.

each 2_1-column keeps the same structure, the packing of the 2_1-columns is different from that in crystals **II**–**V**, resulting in stronger interaction between guest molecules in the cavity and weaker interactions between the host and guest. This may explain the poor enantioselectivity for 2-heptanol. Thus, the supramolecular host system is versatile and accommodates many kinds of guest molecules by changing the packing mode of the 2_1-columns, although a particular packing mode is required for a high enantioselectivity for the guest molecule.

1,1′-Binaphthyl-2,2′-dicarboxylic acid (**2**) is one of the most important chiral sources for deriving various chiral organic compounds.[4] However, up to now, an effective optical resolving reagent for **2** had yet to be reported, except for caustic quinine and brucine, or toxic 1-cyclohexylamine.[5] Thus, our novel system provides a simple and excellent method for the optical resolution of this important compound.

Optical resolution of *rac*-alkyl alcohols is also known to be difficult compared with their aromatic counterparts.[6] In fact, Suda and co-workers reported chiral discrimination of *rac*-aromatic alcohols by using axially chiral **2**, but not of *rac*-alkyl alcohols.[7] Our simple two-step crystallization system provides an excellent method for the optical resolution of 2-alkyl alcohols as well.

In conclusion, successive optical resolution of *rac*-1,1′-binaphthyl-2,2′-dicarboxylic acid and alkyl alcohols was achieved in a single experiment by using one enantiopure compound, (1*R*,2*R*)-**1**. The first step provides a simple and excellent method for the optical resolution of *rac*-1,1′-binaphthyl-2,2′-dicarboxylic acid, for which a better method has yet to be

reported. In the second step, the effective optical resolution of *rac*-alkyl alcohols was achieved in the chiral cavity formed by (1*R*,2*R*)-**1** and (a*R*)-**2**. Although the ee is not very high, the optical resolution of secondary alkyl alcohols is generally not easy by other methods. A common 2_1-column structure was observed in all the crystals, but without strong interactions between them. Thus, a variety of guest molecules may be included by changing the packing of the 2_1-columns. The cavity houses more than one guest molecule and hence may be used as an asymmetric reaction site.

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