Efficient optical resolution of secondary alkyl alcohols by chiral supramolecular hosts

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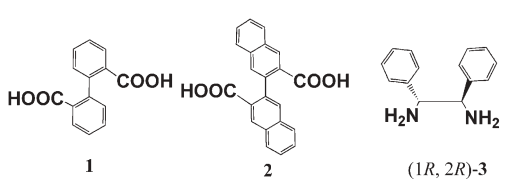
A novel tunable multi-chiral supramolecular host system was developed from non-chiral dicarboxylic acid and (1*R*, 2*R*)-diphenylethylenediamine *via* chirality transfer, which enabled highly efficient optical resolution of secondary alkyl alcohols by simple crystallization of host compounds from alcohol solution.

Recently, supramolecular compounds that include various guest molecules have been reported.[1] For example, crystal engineering of metal-organic polymers with functional building blocks produced structures with tunable properties.[2] Several unique hydrogen-bonded 3D structures consisting of two different molecules have also been reported.[3] By using these complexes, a guest molecule is selectively included and the guest molecule in the complex is stereoselectively reacted. However, for chiral guest molecules, chiral hosts used for recognition and enantioselective reactions have consisted of only one molecular species.[4] Thus, to change or improve guest-selectivity, cumbersome synthetic work is required to introduce a suitable substituent into the host compound.

In this paper, we report a simple chiral supramolecular host system composed of two different molecules, which is tunable and highly efficient for optical resolution of secondary alkyl alcohols. The novel feature of this work is to change guest-selectivity not by modifying the host compound but by changing the combination of its component molecules. Thus, it is possible to tailor the host system to a particular guest molecule. The supramolecular system is composed of a carboxylic acid and an amine derivative, the carboxylic acid being either biphenic acid (**1**) or 2,2′-binaphthyl-3,3′-dicarboxylic acid (**2**), and the amine being (1*R*, 2*R*)-diphenylethylenediamine ((1*R*, 2*R*)-**3**). These dicarboxylic acids are not chiral in solution due to rotation around the central carbon–carbon bonds, however, they can exhibit axial chirality when rotation is restricted.

The complexation behavior of host comprising **1** and (1*R*, 2*R*)-**3** was investigated. Crystallization of the two compounds from an EtOH (ethanol) solution produced inclusion crystal **I** with **1**:(1*R*, 2*R*)-**3**:EtOH = 1:1:2. Its crystal packing analysis revealed a characteristic hydrogen bonding pattern, *i.e.*, a columnar intermolecular hydrogen-bond network formed by the ammonium hydrogen of amine/H^+ and the carboxylate oxygen of a biphenic acid anion around the 2_1-axis (Fig. 1).



1 **2** (1*R*, 2*R*)-**3**

Scheme 1

The torsion angle of **1** is near perpendicular, *i.e.*, 88.2°, with the (a*R*)-conformation. One of the two included ethanol molecules (shown in purple in Fig. 1) is partially imbedded in the column linking the hydroxy group of **1** and the amine/H^+ of **3**, whereas the other ethanol (shown in red in Fig. 1) is trapped in a cavity formed between two columns by a hydrogen bond to the carboxylate oxygen. The distance between the biphenyl molecules along the 2_1-axis is 8.52 Å.

Optical resolution of secondary alkyl alcohols with OH group at the α-position, $RCH(CH_3)OH$, by the host structure was examined. Generally, it is difficult to carry out optical resolution of this type of secondary alkyl alcohols[5] due to the subtle structural difference between the enantiomers as the methyl group and hydrogen atom attached to the chiral carbon have to be discriminated. Five chiral secondary alkyl alcohols were studied. When a solution of **1** and (1*R*, 2*R*)-**3** in racemic alcohol was kept at room temperature for several days, an inclusion complex was obtained as colourless crystallines for 2-butanol, 2-pentanol and 2-hexanol. The optical purity of the guest alcohol was determined by GC analysis using a Chiral-DEX CB capillary column (Table 1). The reproducibility of ee (enantiomeric excess) was good. The enantioselectivity decreased as the size of the guest alcohol molecule increased, and ee as high as 91% was achieved for (*S*)-2-butanol (BuOH). This excellent high ee is in sharp contrast to those based on the standard method using tartaric acid derivatives, which are 0%, 0.2% and 0.05% ee for 2-butanol, 2-pentanol, and 2-hexanol, respectively. When only (1*R*, 2*R*)-**3** was used as a host compound, no inclusion crystals were produced for any of the three alcohols. Thus, formation of chiral supramolecular structure with two chiral centres is vital for the chiral discrimination of the alcohols. 2-Heptanol and 2-octanol did not produce inclusion crystals.

Crystals **II**, obtained from a racemic 2-butanol solution of **1** and (1*R*, 2*R*)-**3** were of good quality and hence were analyzed by X-ray diffractometry.† No good crystals were obtained for other alcohols. Crystals **II** included water which was present in the solvent and the stoichiometry was **1**: (1*R*, 2*R*)-**3**:H_2O:2-butanol = 1:1:1:1. Although the space group is different from that of **I**, **II** exhibits common structural features, *i.e.*, a columnar supramolecular hydrogen-bonded network around the 2_1-axis, which is formed using ammonium hydrogens and carboxylate oxygens (Fig. 2). In this case, the guest molecule is too large to be included within the hydrogen-bonded column structure, and hence

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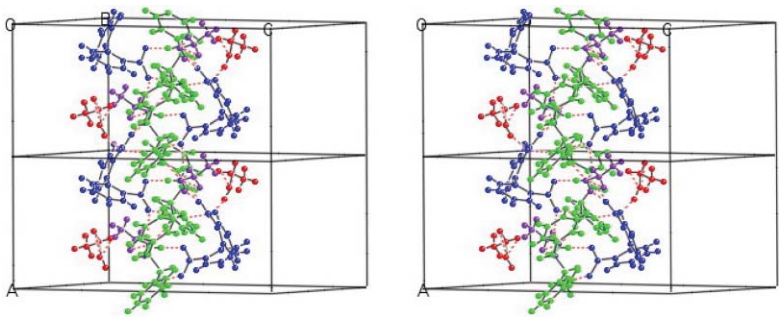

Fig. 1 A stereoview of the crystal structure of (**I**), showing a columnar hydrogen-bonded network parallel to the *a*-axis. EtOH molecules involved in the columnar hydrogen-bonded network represented in purple and those not involved in red.

Table 1 Resolution of alkyl alcohol by **1** and (1*R*, 2*R*)-**3**

Entry	Alcohol	ee[a]	Absolute configuration
1	2-Butanol	91% ee	(*S*)-2-Butanol
2	2-Pentanol	61% ee	(*S*)-2-Pentanol
3	2-Hexanol	22% ee	(*R*)-2-Hexanol
4	2-Heptanol	no inclusion crystals	
5	2-Octanol	no inclusion crystals	

[a] Determined by chiral GC analysis using a Chiral-DEX CB capillary column.

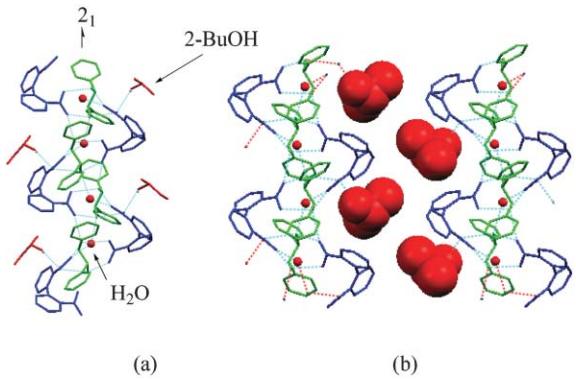

Fig. 2 Crystal structure of (**II**). (a) Columnar hydrogen-bonded network parallel to the *b*-axis. (b) View down the *c*-axis. (*S*)-2-BuOH is shown in the spacefill view.

cannot contribute to the maintenance of the column framework, unlike the EtOH molecule in **I**. Instead, a water molecule that was present in the 2-BuOH solvent takes this role in **II**. Under dry conditions using meticulously dried 2-BuOH, no inclusion complex was formed. In the cavity formed between columns, (*S*)-2-BuOH is trapped by a hydrogen bond between the hydroxyl group of (*S*)-2-BuOH and the carboxylate oxygen of a biphenic acid anion. An electron density corresponding to the small amount of (*R*)-2-BuOH is observed as disorder but no hydrogen bond was apparent between (*R*)-2-BuOH and the host. The minor disordered OH group was not refined.

The torsion angle of **1** is 78.2°, which is smaller than that of **I**, and the axial chirality was fixed to the (a*R*)-conformation by chirality transfer from the amine. Consequently, although only one chiral molecule (1*R*, 2*R*)-**3** is used, this supramolecular host has two kinds of chiral moieties in the crystal. The distance between the biphenyl molecules along the 2_1-axis is 9.44 Å, which is longer than that of **I**. Overall, the hydrogen-bond lengths in crystal **II** are slightly longer (by about 0.1 Å) than those in crystal **I**. Thus, it is clear that this supramolecular host is able to change its structure accommodating structural differences in guest molecules.

To achieve higher enantioselectivity for larger alcohols, binaphthyldicarboxylic acid **2**, instead of **1**, was employed to construct a supramolecular host. Similar to **1**, compound **2** can exhibit axial chirality when a rotation around the central carbon–carbon bonds is restricted, but it possesses a larger aromatic moiety than **1**. Enantioselectivity for inclusion of secondary alkyl alcohols in **2**·(1*R*, 2*R*)-**3** host was investigated. It increased as the size of the guest alcohol increased, a reversed trend that was observed in the case of **1**·(1*R*, 2*R*)-**3** host (Table 2). Highest ee was *ca*. 70% for (*S*)-2-hexanol and (*S*)-2-heptanol. 2-Octanol did not form inclusion crystals. Unfortunately, the inclusion complexes of **2** and (1*R*, 2*R*)-**3** did not produce good quality crystals suitable for X-ray structure determination under the various crystallization conditions attempted.

The combination of **1** and (1*R*, 2*R*)-**3** appears to be suitable for the resolution of small alcohols, whereas the combination of **2** and (1*R*, 2*R*)-**3** is better for larger alcohols. The difference in the guest selectivity depends on the presence of hydrogen bonding between the host and guest molecules, as well as the adaptability of guest molecules in the cavity. Hydrogen bonding is directional. In the case of the combination **1** and (1*R*, 2*R*)-**3** where the size of the cavity is small, a large guest molecule cannot be fixed to the host by a hydrogen bond but is simply included in the cavity. This may explain why the enantioselectivity decreases for larger guest molecules. In the case of 2-hexanol, even the preferred absolute configuration was reversed. The alcohol may be too large to be included in the cavity, and hence may form a different type of cavity exploiting the tunable nature of the supramolecular system. Further effort to obtain single crystals of **1** - (1*R*, 2*R*)-**3** - 2-hexanol is being made to understand the intriguing phenomenon.

Table 2 Resolution of alkyl alcohol by **2** and (1*R*, 2*R*)-**3**

Entry	Alcohol	ee[a]	Absolute configuration
1	2-Butanol	42% ee	(*S*)-2-Butanol
2	2-Pentanol	57% ee	(*S*)-2-Pentanol
3	2-Hexanol	71% ee	(*S*)-2-Hexanol
4	2-Heptanol	70% ee	(*S*)-2-Heptanol
5	2-Octanol	no inclusion crystals	

[a] Determined by chiral GC analysis using a Chiral-DEX CB capillary column.

In the case of the combination of **2** and (1*R*, 2*R*)-**3**, on the other hand, small guest molecules can be trapped in a cavity by a hydrogen bond, however, the large size cavity cannot recognize the stereochemistry of the guest molecule. Hence, the enantiomeric selectivity may decrease for the smaller guest molecules. Thus, enantioselectivity of the guest alcohol depends on the structure of the dicarboxylic acid. This means that we can design a host structure that is suitable for a guest molecule by changing the combination of its component molecules.

In conclusion, a two-component host system consisting of carboxylic acid and amine derivatives was successfully created with high enantioselectivity for secondary alkyl alcohols. Although only the amine molecule has chirality, the supramolecular host possesses two kinds of chirality by chirality transfer. The host system is versatile as the optical resolution of guest molecule can be tuned by the combination of the host component molecules. It is expected that this type of host system can be used for a variety of chiral recognition and asymmetric reactions.

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Notes and references

† Crystallographic data of **I:** $C_{14}H_{18}N_2{\cdot}C_{14}H_8O_4{\cdot}2(C_2H_5OH)$, M = 546.64, orthorhombic, space group $P2_12_12_1$, a = 9.7328(7), b = 13.7878(9), c = 22.0639(14) Å, U = 2960.8(3) Å^3, Z = 4, Dc = 1.2263(1) g cm^{-3}, μ(Mo Kα) = 0.085 mm^{-1}, 22219 reflections measured, 7357 unique (Rint = 0.0402), final$R(F^2)$ = 0.0464 using 4670 reflections with $I > 2.0\sigma(I)$, R(all data) = 0.0726, T = 293 K. CCDC 267537. Crystallographic data of **II:** $C_{14}H_{18}N_2{\cdot}C_{14}H_8O_4{\cdot}C_4H_{10}O{\cdot}H_2O$, M = 546.40, monoclinic, space group $P2_1$, a = 11.3720(8), b = 9.4378(7), c = 13.8177(10) Å, β = 97.694(2)°, U = 1469.66(18) Å^3, Z = 2, Dc = 1.2347(2) g cm^{-3}, μ(Mo Kα) = 0.085 mm^{-1}, 10974 reflections measured, 6872 unique (Rint = 0.0186), final$R(F^2)$ = 0.0430 using 5469 reflections with $I > 2.0\sigma(I)$, R(all data) = 0.0531, T = 293 K. CCDC 267538. As the crystals contain only non-heavy atoms, the Flack parameters for both absolute configurations were not refined. See http://www.rsc.org/suppdata/cc/b5/b504164c/ for crystallographic data in CIF or other electronic format.

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