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Supramolecular Architecture Consisting of an Enantiopure Amine and an Achiral Carboxylic Acid: Application to the Enantioseparation of Racemic Alcohols

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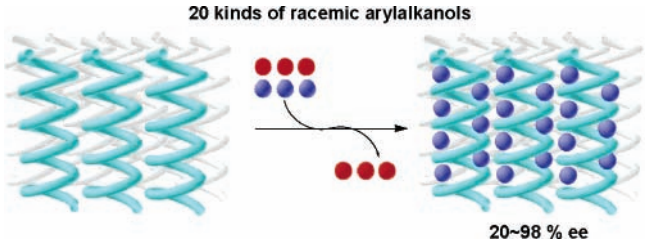
ABSTRACT



Three-dimensionally dissymmetric cavities are created from an enantiopure amine and an achiral carboxylic acid, which can incorporate the third components to realize the formation of closely packed crystals. The combination demonstrates enantioselective inclusion for 20 kinds of racemic alcohols. The inclusion phenomenon occurs not only during crystallization but also in the solid state.

Porous metallaorganic crystals have been attracting much attention as versatile materials for the construction of cavities and channels.[1] Controllability of pore and channel sizes by the appropriate selection of metal ions and organoligands make metallaorganic frameworks superior.[2] However, the resultant architectures are usually highly symmetrical as a result of the fixed direction of the coordination sites of the metal ions. On the other hand, porous organic crystals can offer more complex cavities to show a high molecular recognition ability for guests. Among them, enantiopure porous organic crystals have been applied for the enantioseparation of racemic guests.[3] However, the individual synthesis of a new component is inevitably required for tuning the cavities in such porous organic crystals for given racemic guests. In contrast, the cavities in multicomponent porous crystals are easily tunable for guests upon changing the components; multicomponent crystals are very fascinating candidates for enantioselective inclusion.

We have previously reported that in two-component crystals consisting of enantiopure primary amines and achiral carboxylic acids, the ammonium cations and carboxylate anions generally formed a hydrogen-bonding network with a 2-fold screw axis in the center (2_1-column), when the molecular lengths and/or shapes of the components were similar to each other.[4] As a result, the components were helically arranged around the 2_1-column by self-assembly to give a closely packed crystal, and there exists a vacant

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(2) (a) Harrison, R. G.; Fox, O. D.; Meng, M. O.; Dalley, N. K.; Barbour, L. J. *Inorg. Chem.* **2002**, *41*, 838−843. (b) Hagrman, P. J.; Hagrman, D.; Zubieta, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2638−2685. (c) Eddaoudi, M.; Moler, D. B.; Li, H.; Chen, B.; Reineke, T. M.; O'Keeffe, M.; Yaghi, O. M. *Acc. Chem. Res*, **2001**, *34*, 319−330.

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hydrogen-bonding site for each carboxylate anion, which can form another hydrogen bond. These characteristics of the salt crystals prompted us to consider an inverse idea; if we use an enantiopure amine and an achiral carboxylic acid with a different molecular length and/or shape, three-dimensionally dissymmetric cavities would be formed along a 2_1-column, which incorporate third components to realize close packing of a crystal, and the vacant sites of the carboxylate anions would be exposed to the outside of the 2_1-column to form hydrogen bonds with the third components (Figure 1).

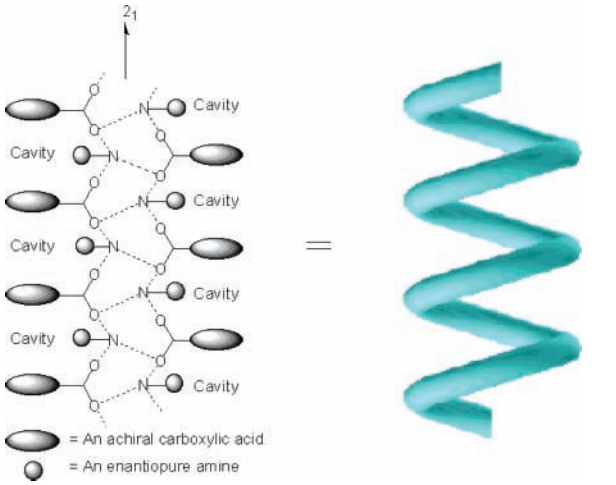


Figure 1. Schematic representation of a 2_1-column in which cavities and vacant hydrogen-bonding sites exist.

Subsequently, the enantioselective inclusion of the third components in the cavities thus formed would be achieved (see the Abstract graphic).

In the present study, we used the combination of (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**1**) and benzoic acid (**2**) (Figure 2) for the formation of a three-component supramolecular

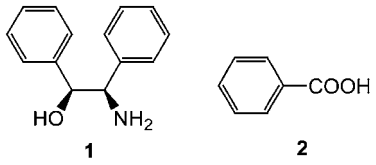


Figure 2.

self-assembly, since the molecular shapes of **1** and **2** are quite different from each other and the two phenyl groups in **1** favorably take a gauche conformation[5] to afford considerably large cavities.[6] As a guest, we selected 1-phenylethanol (**3a**) with the expectations that the hydroxy hydrogen of **3a** would form a hydrogen bond with the carboxylate oxygen of **2** and that the phenyl group of **3a** would afford some π/π and/or CH/π interaction with the phenyl groups in **1** and **2**. When the **1·2** combination was crystallized from water/acetonitrile in the presence of racemic **3a**, the corresponding three-component crystal (**1·2·3a**), in which **3a** was included in a ratio of 1:1:1, was obtained. The X-ray crystallographic analysis of **1·2·3a** revealed that the **1·2** combination formed a 2_1-column to afford suitable cavities for the third component 3a, as we expected.

This successful result prompted us to examine the generality of this inclusion phenomenon by the **1·2** combination; we tried the cocrystallization of the **1·2** combination with 19 kinds of chiral arylalkanols (**3b**−**t**) other than **3a** (the cocrystallization method). As shown in Table 1, all of **3b**−**t** were commonly included to give the corresponding three-component crystals **1·2·3** in a ratio of 1:1:1. Moreover, chiral recognition by the **1·2** combination was also commonly observed for all of the alcohols **3b**−**t** as well as **3a** by the formation of three-component crystals. Especially, very efficient chiral recognition was achieved in the cases of 1-(2,4-dimethylphenyl)ethanol (**3l**) (entry 12) and 2-methyl-1-phenylpropanol (**3o**) (entry 15); the selectivities were 98% and 92% ee, respectively. These results clearly show that the **1·2** combination has not only an inclusion ability but also a chiral recognition ability for a wide variety of guest alcohols.

We then carried out X-ray crystallographic analyses of the three-component crystals **1·2·3** in order to explain the chiral recognition ability of the **1·2** combination. 2_1-Columns were commonly constructed from **1** and **2** in all of the three-component crystals **1·2·3** we could examine, and the inclusion modes of **3** in the 2_1-columns were fundamentally similar to each other. Figures 3 and 4 show the crystal structure of **1·2·3b**[7] as a typical example of the crystal structures of **1·2·3**.[8] The top view of the 2_1-column indicates

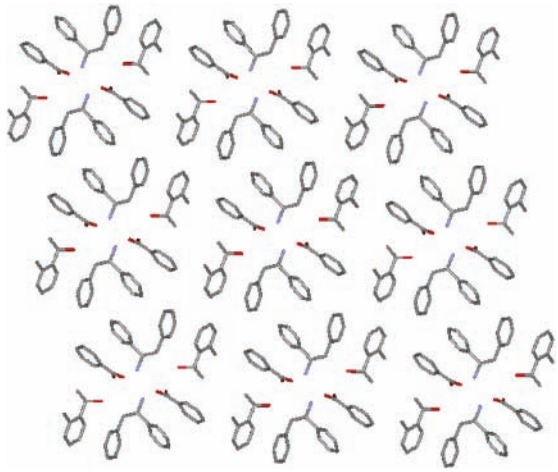
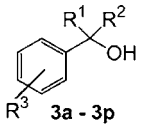


Figure 3. X-ray crystal structure of **1·2·3b** viewed down from the 2_1-column axis.

(4) (a) Kinbara, K.; Hashimoto, Y.; Sukegawa, M.; Nohira, H.; Saigo, K. *J. Am. Chem. Soc.* **1996**, *118*, 3441−3449. (b) Kinbara, K.; Sakai, K.; Hashimoto, Y.; Nohira, H.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2615−2622.

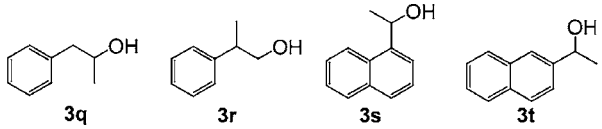
(5) Kinbara, K.; Kobayashi, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1767−1775.

Table 1. Inclusion and Chiral Recognition of Racemic Arylalkanols by the **1·2** Combination



3a - 3p

3a: R^1 = Me, R^2 = H, R^3 = H
3b: R^1 = Me, R^2 = H, R^3 = *o*-Me
3c: R^1 = Me, R^2 = H, R^3 = *m*-Me
3d: R^1 = Me, R^2 = H, R^3 = *p*-Me
3e: R^1 = Me, R^2 = H, R^3 = *p*-Et
3f: R^1 = Me, R^2 = H, R^3 = *p*-^{n}Pr
3g: R^1 = Me, R^2 = H, R^3 = *o*-OMe
3h: R^1 = Me, R^2 = H, R^3 = *m*-OMe
3i: R^1 = Me, R^2 = H, R^3 = *p*-OMe
3j: R^1 = Me, R^2 = H, R^3 = *p*-F
3k: R^1 = Me, R^2 = H, R^3 = *p*-Cl
3l: R^1 = Me, R^2 = H, R^3 = *2,4*-Me_2
3m: R^1 = Et, R^2 = H, R^3 = H
3n: R^1 = ^{n}Pr, R^2 = H, R^3 = H
3o: R^1 = ^{i}Pr, R^2 = H, R^3 = H
3p: R^1 = Me, R^2 = Et, R^3 = H



3q **3r** **3s** **3t**

entry	arylalkanols	yield (%)[a]	ee (%)[b]	abs config[c]
1	**3a**	91	87	*R*
2	**3b**	86	72	*R*
3	**3c**	91	80	*R*
4	**3d**	85	20	*R*
5	**3e**	85	80	*R*
6	**3f**	86	73	*R*
7	**3g**	85	82	*S*
8	**3h**	91	85	*R*
9	**3i**	97	67	*S*
10	**3j**	89	32	*S*
11	**3k**	95	70	*S*
12	**3l**	87	98	*S*
13	**3m**	89	46	*R*
14	**3n**	98	60	*R*
15	**3o**	70	92	*R*
16	**3p**	67	39	*S*
17	**3q**	89	24	*R*
18	**3r**	93	32	*R*
19	**3s**	75	64	*R*
20	**3t**	65	36	*R*

[a] Yield based on an amount of **1·2**. [b] ee determined by HPLC. [c] Absolute configuration of the major enantiomers determined by the comparison of the elution order in HPLC or the optical rotations with those reported in the literatures.

that cavities are formed upon partitioning the space in the 2_1-column by the aromatic rings of **1** and **2** molecules and that the molecules of the third component **3b** are aligned along the 2_1-columns. The molecule of **3b** is tightly fixed in the cavity by two hydrogen bonds between the hydroxy hydrogen of **3b** and the carboxylate oxygen of **2** and between the hydroxy oxygen of **3b** and the hydroxy hydrogen of **1**. In addition, CH/π interactions of **3b** with **1** and **2** highly contribute to the stabilization of the three-component crystal (the arrows in Figure 3).[9] As a result, the direct CH/π

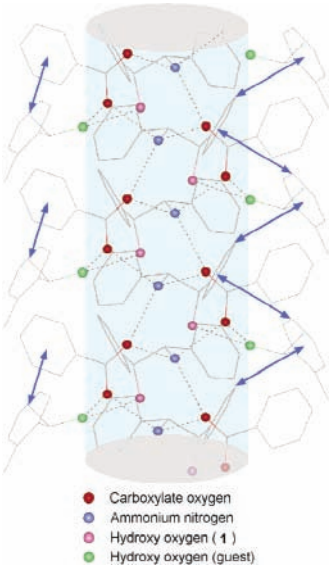


Figure 4. X-ray crystal structure of **1·2·3b**, side view.

interaction between the methyl group at the α-position of **3b** and the aromatic ring of **2** is realized, which plays a very significant role for the chiral recognition. In the other three-component crystals **1·2·3**, the shape of the cavities can change depending on the shape of the molecule of **3** by subtly sliding the hydrogen-bond motif of the 2_1-column and/or by slightly changing the conformation of the two phenyl groups of **1** to make CH/π interaction effective.

We next examined the chiral recognition ability of the salt **1·2**, prepared in advance, for **3a** (the suspension method). The apo-salt **1·2** was obtained as white powdery crystals upon crystallizing a mixture of **1** and **2** from MeOH, followed by the removal of MeOH included in the salt. When a suspension of the apo-salt **1·2** was stirred with racemic **3a** in hexane, the corresponding three-component crystal **1·2·3a** in a ratio of 1:1:1 was obtained with a high enantioselectivity of 83% ee, which is very close to the value

(6) Kinbara, K.; Kobayashi, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 111−119.

(7) Crystal data for **1·**(1*S*,2*R*)-**2·**(*R*)-**3b**: FW = 471.59, monoclinic, space group $P2_1$, a = 14.167(3), b = 6.0636(11), c = 15.534(3) Å, β = 101.632(8)°, V = 1306.9(5) Å^3, Z = 2, R = 0.0620, D_c = 1.20 Mg m^{-3}.

(8) Although the *R* values are still unsatisfactory due to the preliminary examinations, the data indicate the existence of a 2_1-column commonly in the crystals. Crystal data for **1·**(1*S*,2*R*)-**2·**(*R*)-**3a**: FW = 457.57, orthorhombic, space group $P2_12_12_1$, a = 5.919(6), b = 13.69(1), c = 30.16(3) Å, V = 2443.6(35) Å^3, Z = 4, R = 0.0510, D_c = 1.24 Mg m^{-3}. Data for **1·**(1*S*,2*R*)-**2·**(*R*)-**3f**: FW = 499.65, monoclinic, space group $P2_1$, a = 13.92(2), b = 5.883(7), c = 17.85(2) Å, β = 107.98(2)°, V = 1390.5(30) Å^3, Z = 2, R = 0.1260, D_c = 1.19 Mg m^{-3}. Data for **1·**(1*S*,2*R*)-**2·**(*S*)-**3g**: FW = 487.59, orthorhombic, space group $P2_12_12_1$, a = 5.758(7), b = 13.84(2), c = 31.95(4) Å, V = 2546.2(50) Å^3, Z = 4, R = 0.1460, D_c = 1.27 Mg m^{-3}. Data for **1·**(1*S*,2*R*)-**2·**(*R*)-**3j**: FW = 475.56, monoclinic, space group $P2_1$, a = 14.79(2), b = 5.936(6), c = 15.40(2) Å, β = 114.60(2)°, V = 1229.5(21) Å^3, Z = 2, R = 0.0990, D_c = 1.28 Mg m^{-3}. Data for **1·**(1*S*,2*R*)-**2·**(*S*)-**3l**: FW = 485.62, monoclinic, space group $P2_1$, a = 13.954(1), b = 6.3090(4), c = 15.864(2) Å, β = 104.469(4)°, V = 1352.3-(2) Å^3, Z = 2, R = 0.0510, D_c = 1.19 Mg m^{-3}. Data for **1·**(1*S*,2*R*)-**2·**(*S*)-**3p·**H_2O: FW = 503.64, monoclinic, space group $P2_1$, a = 15.251(2), b = 6.0530(5), c = 15.484(2) Å, β = 96.972(4)°, V = 1418.8(2) Å^3, Z = 2, R = 0.0540, D_c = 1.18 Mg m^{-3}.

(9) The distances between the CH and the π-plane: the CH (**3b**) and the π-plane (**2**) 2.86 Å, the CH (**1**) and the π-plane (**3b**) 2.77 Å, the CH (**3b**) and the π-plane (**1**) 2.98 Å.

(10) Sada, K.; Shiomi, N.; Miyata, M. *J. Am. Chem. Soc.* **1998**, *120*, 10543−10544.

achieved by the cocrystallization method (Table 1, entry 1). Thus, **3a** was included spontaneously and enantioselectively at room temperature from a hexane solution into the cavities created in the apo-salt **1·2**. The powder XRD patterns of **1·2·3a** crystals obtained by the cocrystallization method and by the suspension method were identical to each other (see Supporting Information). This fact implies that the porous organic crystal constructed by self-assembly of the enantiopure amine **1** and the achiral carboxylic acid **2** can offer three-dimensionally dissymmetric cavities suitable for the chiral guests **3**.

Removal of the third component **3** was very easy. For example, upon heating **1·2·3a** crystals at 80 °C under reduced pressure (0.3 mmHg) for 1 h, the molecules of the third component **3a** were completely removed from the crystals (by a ^{1}H NMR analysis). The XRD analysis of the resultant crystals revealed that the 2_1-column architecture has been partially deconstructed after heating. However, the resultant crystals again included the third component **3a** enantioselectively (84% ee) when the crystals were left in a hexane solution of **3a**; the 2_1-column architecture was reconstructed in the form of **1·2·3a**. Moreover, the powder XRD pattern of the included crystals was almost the same as that of the original three-component crystals (see Supporting Information). This means that the enantioselective inclusion of the third components **3** in the apo-salt **1·2** is reversible.

Although the inclusion of solvent molecules in amine/carboxylic acid salts has been reported so far,[10] the present study demonstrated that three-dimensionally dissymmetric cavities can be constructed in a supramolecular hydrogen-bonded 2_1-column architecture by the self-assembly of an enantiopure primary amine and an achiral carboxylic acid and that the cavities can reversibly include the third components (guests) and recognize their chirality. The results strongly suggest that the construction of supramolecular solid architectures for inclusion with a chiral recognition ability is possible by crystal engineering using combinations of enantiopure primary amines and achiral carboxylic acids, which are easily tunable for the third components since a great number of enantiopure amines and achiral carboxylic acids are available.

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Supporting Information Available: Experimental procedures, spectral characterization of **1·2·3a**−**t**, crystallographic data of **1·2·3b** in CIF format, and XRD chart of **1·2·3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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