Chirality Switching in the Crystallization of 1-(4-Chlorophenyl) ethylamine with Binaphthoic Acid by Ketimine Formation

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Axially chiral binaphthoic acid (BNA) was studied as a resolving agent for a stereoselective crystallization of 1-(4-chlorophenyl)ethylamine (CPEA). The diastereomeric pair of (*R*)-BNA/(*S*)-CPEA crystallizes in methylene chloride, on the other hand, the pair of (*S*)-BNA/(*S*)-CPEA crystallizes in acetone. The switch of the solubility of the diastereomeric pair is due to the imine formation with acetone. The very low solubility of the BNA/imine pair appears to be responsible for the fast and complete imine formation. The crystal structure of the BNA part in both crystals of the diastereomers maintains a same feature. Asymmetric chiral channels and pockets composed by intermolecular packing of BNA molecules appear in the crystal structures, and the robustness of them seem to contribute to the recognition of the chirality of CPEA with high selectivity.

Keywords: Chirality switching, Ketimine, Stereoselective crystallization, Binaphthoic acid

Introduction

Optically pure chiral amines are important building blocks for the synthesis of pharmaceuticals, food ingredients, and drug intermediates.[1] The resolution of a racemate by a resolving agent using different solubilities of the diastereomeric salts is still a practical method[2] along with asymmetric synthesis using chemical and enzymatic catalysts.[3] Naphthylglycolic acid, hydrogen phthalate of isopropylidene glycerol, and phosphonothioic acid have been applied as resolving agents to resolve racemate of 1-arylalkylamines.[4–7] The solubility of a diastereomeric salt depends on the crystalline stability which is governed by composite inter- and intra-molecular interactions.[8] It is hardly predictable whether which resolving agent will give stereoselectively a insoluble diastereomeric salt. The choice of a resolving agent thus normally relies on just trials and errors. It is somewhat surprising that binaphthoic acid (BNA),[9] an axially chiral acid, was not studied as a resolving agent. In this study, BNA was applied as a resolving agent to obtain optically pure (*R*)-1-(4-chlorophenyl)ethylamine ((*R*)-CPEA), an important starting compound for the synthesis of a fungicide, capropamid (Chart 1).[10]

A solvent-induced chirality switching is frequently observed in the field of stereoselective crystallization.[11] Most of these are usually due to the alteration of noncovalent intermolecular interactions arisen by the crystalline solvent. In this study, we report an unusual chirality switching induced by covalent ketimine formation with acetone, which are apparently supported by the crystal structures of the diastereomeric salt pairs obtained in different solvents.

Experimental

General. Optically pure (*R*)-BNA and (*S*)-BNA were provided by Co. Aminologics (Gyunggi, Korea). The racemic compound of CPEA and solvents were purchased from Aldrich (Seoul, Korea) and used without further purification. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker AM 250 spectrometer in $CDCl_3$ and dimethylsulfoxide (DMSO-d_6) solutions containing tetramethylsilane as an internal standard. High Pressure Liquid Chromatography (HPLC) data were obtained with Agilient Technologies 1260 Infinity, equipped with chiral column chiralcell® OD-H.

Preparation of the Crystalline Pair, (*R*)-BNA/(*S*)-CPEA (1). (*R*)-BNA (1.0 g, 3.0 mmol) and racemic CPEA (0.93 g, 6.0 mmol) were dissolved together in CH_2Cl_2 (20 mL). The solution was clear in the beginning, and colorless crystals of block needle type were grown after 24 h. After 1 week, the crystals were collected (1.1 g). The crystal was slightly soluble in either CH_2Cl_2 or chloroform, but freely soluble in DMSO. Yield, 75% (based on the amount of the BNA used). ^{1}H NMR (DMSO-d_6, 250 MHz): δ

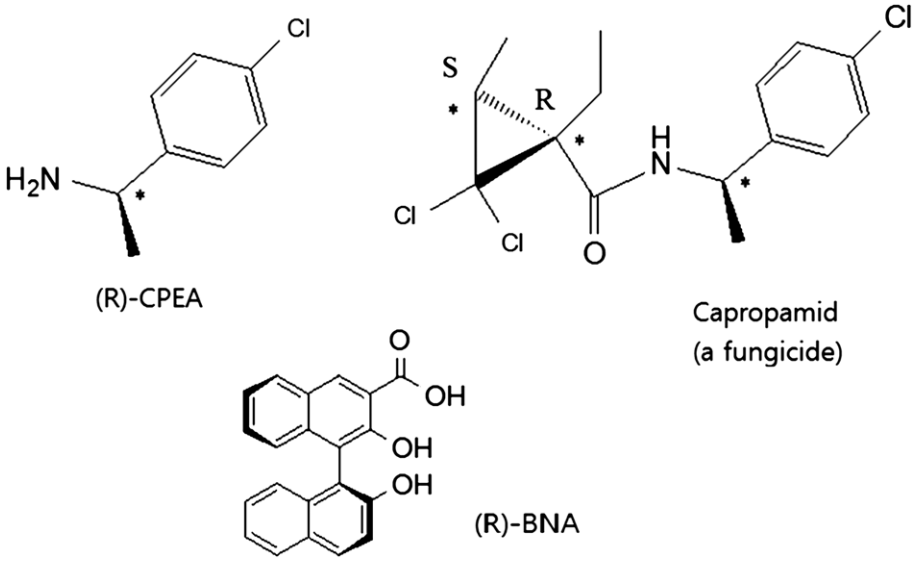
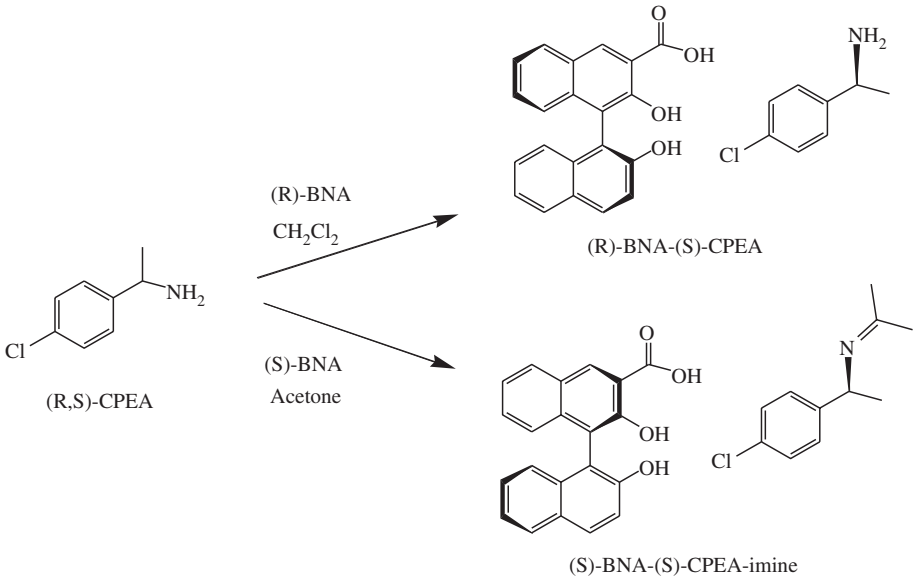


Chart 1. Chemical structure of (R)-CPEA, (R)-BNA and Capropamid.



Scheme 1. The stereoselective crystallization of CPEA with BNA in CH_2Cl_2 and acetone.

6.86–7.31 (7H, BNA-aromatic CHs), 7.81–8.42 (4H, BNA-aromatic CHs), 7.53 (s, 4H, CPEA-aromatic CHs), 4.47 (q, 1H, J = 6.6Hz, CPEA-asymmetric CH), 1.50 (d, 3H, J = 6.9Hz, CPEA-methyl).

Preparation of the Crystalline Pair, (*S*)-BNA/(*S*)-CPEA-Imine (2). (*S*)-BNA (1.0 g, 3.0 mmol) and racemic CPEA (0.93 g, 6.0 mmol) were dissolved together in CH_2Cl_2 (20 mL) containing acetone (1.0 mL). Yellowish crystals of block shape were grown after 24 h from the clear solution. After 1 week, the crystals were collected (1.2 g). The crystal was not soluble in CH_2Cl_2, chloroform, and acetone, but freely soluble in DMSO. Yield, 82% (based on the amount of the BNA used). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.87–7.33 (7H, BNA-aromatic CH), 7.83–9.04 (4H, BNA-aromatic CHs), 7.47 (br, 4H, CPEA-aromatic CHs), 5.10 (br, 1H, CPEA-asymmetric CH), 2.21(br, 3H, acetone-methyl), 2.29 (br, 3H, acetone-methyl), 1.48 (d, 3H, J = 6.9Hz, CPEA-methyl).

Measurements of Enantiomeric Excess for the Crystals. The crystals collected were extracted with CH_2Cl_2 and 1.0 N HCl water solution. The aqueous layer includes CPEA as HCl salt, which was analyzed by HPLC instrument, Agilient Technologies 1260 Infinity, equipped with chiral column chiralcell® OD-H under flow rate of 1 mL/min with an eluent of trimethylamine (0.1%), isopropanol (10%), and hexane (90%). The retention times of (*R*)- and (*S*)- form of CPEA were 21.5 and 26.4 min, respectively. The (*S*)-form in the crystals obtained from CH_2Cl_2 solution was 80.0% ee, and the (*S*)-form in the crystals obtained from acetone/CH_2Cl_2 was 87.4% ee.

X-Ray Crystallographic Data Collection and Refinement. Data were collected at ambient temperatures, on a CCD diffractometer with graphite monochromated Mo Kα radiation at Ewha Womans University. The structure was solved by direct methods[12] using the SHELX-2013 programs[13] and refined anisotropically by full matrix least squares on F^2 value for non-hydrogen atoms. The structure has been deposited with Cambridge Structural Database, CCDC 1421232 for crystal **1** and CCDC 1421233 for crystal **2**.

Results and Discussion

The addition of a solution of (*R*)-BNA (0.51 equiv) to a solution of racemic CPEA in CH_2Cl_2 gave crystalline solids of transparent colorless needle shapes. An integration of ^1H NMR spectrum for the bulk crystalline solids in $CDCl_3$ is coincident with the fact that they are in 1:1 pairing. The optical purity of the CPEA measured by HPLC for the crystalline solid was 80% ee. A single crystal, **1**, suitable for X-ray crystallographic study was obtained from the CH_2Cl_2 solution of (*R*)-BNA and (*S*)-CPEA.

On the other hand, the yellowish crystalline solids of block shapes were formed in a few hours when the acetone solutions of (*S*)-BNA and racemic CPEA are mixed together. The crystalline solids of same features could have also been obtained in the co-solvent of CH_2Cl_2 and acetone. The optical purity of the CPEA measured by HPLC for the crystalline solid was 87% ee. The optical sense of the CPEA in this crystalline solid, however, was opposite to the expected one based on the CH_2Cl_2 case, *i.e.*, it was (*S*)-form. The crystalline solids obtained in the presence of acetone were not soluble in CH_2Cl_2, which was strange enough. A single crystal, **2**, suitable for X-ray crystallographic study was obtained from the CH_2Cl_2 and acetone (5%) solution of (*S*)-BNA and (*S*)-CPEA.

The single crystals obtained from the CH_2Cl_2 only and from the mixed solvent of CH_2Cl_2 and acetone, respectively, were afforded to the study of X-ray crystallography. The amine in the crystal grown in the presence of acetone was in the form of imine, while the amine in the crystal grown in CH_2Cl_2 was in free form (Scheme 1). Table 1 lists crystallographic parameters for crystals of **1** and **2**. Both the crystals have similar unit cell systems.

The atomic structure and labeling scheme for crystal **1**, a diastereomeric salt of (*R*)-BNA/(*S*)-CPEA, are shown in Figure 1. The two naphthyl groups perpendicularly intercross each other. The torsion angle of C(1)-C(10)-C(11)-C(20) is 90.5(6)°. The amine was assumed to exist as a cationic form. The nitrogen keeps strong interactions with three molecules of BNA by direct hydrogen bond and with a water molecule. The participation of water molecule plays an important role in the formation of the stable compact structure of the diastereomeric pair. Short intermolecular distances such as N(1)—O(3) 2.7912(66), N(1)—O(1) 2.9313(62), N(1)—O(1W) 2.8453(76), O(1W)—O(2) 2.9457(68) Å demonstrate strong hydrogen bonds in the crystal.

Table 1. Crystallographic data for **1** and **2**.

Crystal	**1**	**2**
Empirical formula	$C_{21}H_{14}O_4{\cdot}C_8H_{10}NCl{\cdot}H_2O$	$C_{21}H_{14}O_4{\cdot}C_{11}H_{14}NCl$
Formula weight	503.97	525.17
Crystal system	Orthorhombic	Orthorhombic
Pace group	$P2_12_12_1$ (No. 19)	$P2_12_12_1$ (No. 19)
a (Å)	8.9513(7)	9.8663(1)
b (Å)	15.9304(13)	15.6864(2)
c (Å)	17.7919(15)	17.4463(2)
V (Å^3)	2537.1(4)	2700.11(5)
Z	4	4
d_{calcd} (g/cm^3)	1.314	1.294
μ (mm^{-1})	0.191	0.180
F(000)	754	1104
Crystal size (mm)	0.04 × 0.08 × 0.28	0.12 × 0.20 × 0.28
Crystal color	Transparent colorless	Yellow
θ range	1.72–28.29	1.75–28.44
Unique reflections (>2σ)	3084	3507
Restraints/ parameters	6/329	0/350
Good of Fitness on F^2	1.016	0.994
R1 (I>2sigma [I])	0.0681	0.0492
wR2	0.1451	0.1115
Largest diff. peak and hole (e/Å^3)	0.641 and −0.349	0.238 and −0.222
Flack parameter	0.03(7)	−0.05(4)

The atomic structure for diastereomeric salt **2**, (*S*)-BNA/(*S*)-CPEA-imine, obtained in the presence of acetone, undoubtedly reveals the imine form of the amine. The bond distance of N(1)—C(30) is 1.287(4) Å showing a double bond character and the distance of N(1)—C(28) is 1.494 (5) Å of regular single C—N bond. The crossing angle between two naphthyl planes is nearly perpendicular with the torsion angle of 89.5(4) for C(1)-C(10)-C(11)-C(20). The distance between N(1) and O(3) is 2.681(4) Å signifying strong interaction of hydrogen bond. The crystal, **2**, did not contain water molecules.

The interesting point is that the intermolecular arrays of BNA only in both crystals of **1** and **2** are almost not distinguishable from each other. The BNA molecules compose a polymeric semi-helical structure by hydrogen bond between carboxylate and 2′-hydroxy groups. Figure 2 compares the two structures, which are different only in their chiral senses. The polymeric semi-helical units assemble together

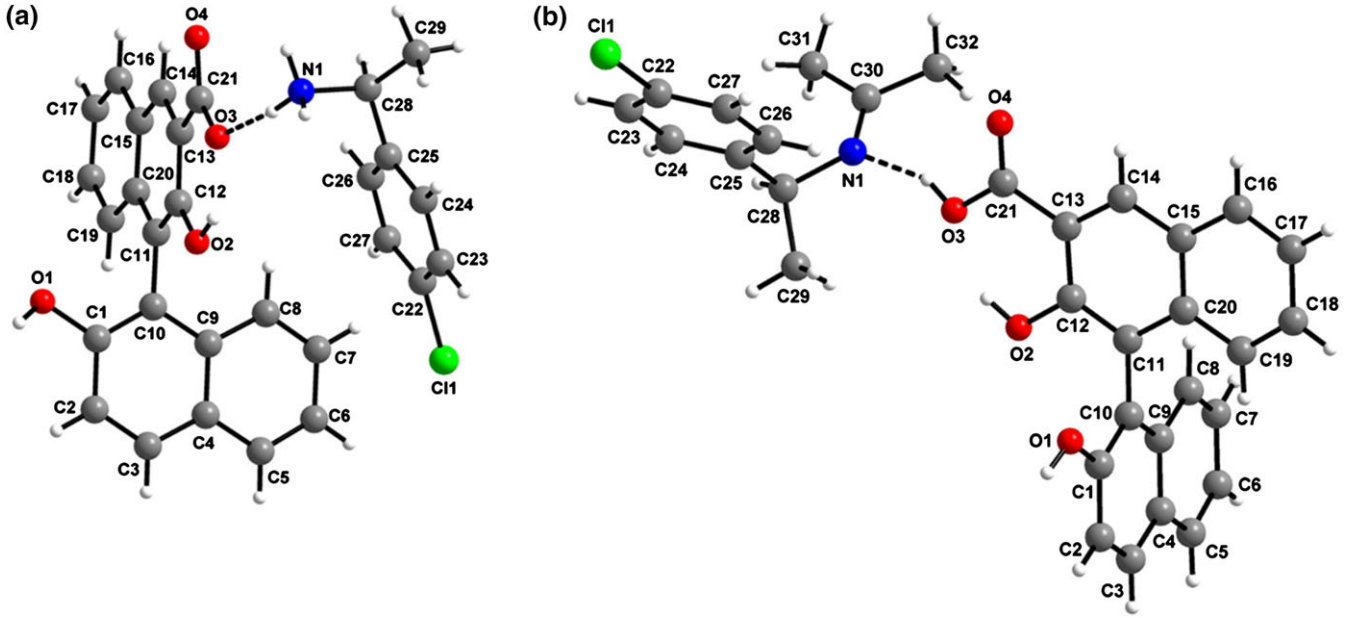


Figure 1 Atomic structures of the diastereomeric salts. (a) (*R*)-BNA/(*S*)-CPEA, **1** and (b) (*S*)-BNA/(*S*)-CPEA-imine, **2**.

by hydrophobic interactions between naphthyl rings to make chiral channels. Figure 3 shows the channel of crystal **1** whose shape is just same as that of crystal **2**. The same features of the chiral channels in both crystals reflect on the robustness of the channel and a high inclination of BNA toward the generation of them.

The robustness of the chiral channel is considered to be an important factor in the chiral recognition. The chirality of the substrate must fit to this robust channel, which would discriminate one enantiomer from the other one and thus increase the stereoselectivity of the crystal. The robustness of BNA pocket is probably originated in the axial chirality of the compound. The axial chirality governs simply the overall spatial dispositions, and thus limits the motional freedom of the molecule. The resolving agents so far reported were usually non-axially chiral compounds.[4–7] The axially chiral BNA molecule could have a potential as an efficient resolving agent.

In crystal **1**, the methyl group of CPEA is located in the hydrophobic pocket which is surrounded by naphthalene rings (Figure 4(a)). The space around the asymmetric hydrogen is narrower than that around the methyl group. On the other hand, in the crystal of **2**, the two methyl groups from acetone are placed in the hydrophobic pocket and the methyl group of CPEA positions at the center of the channel (Figure 4(b)).

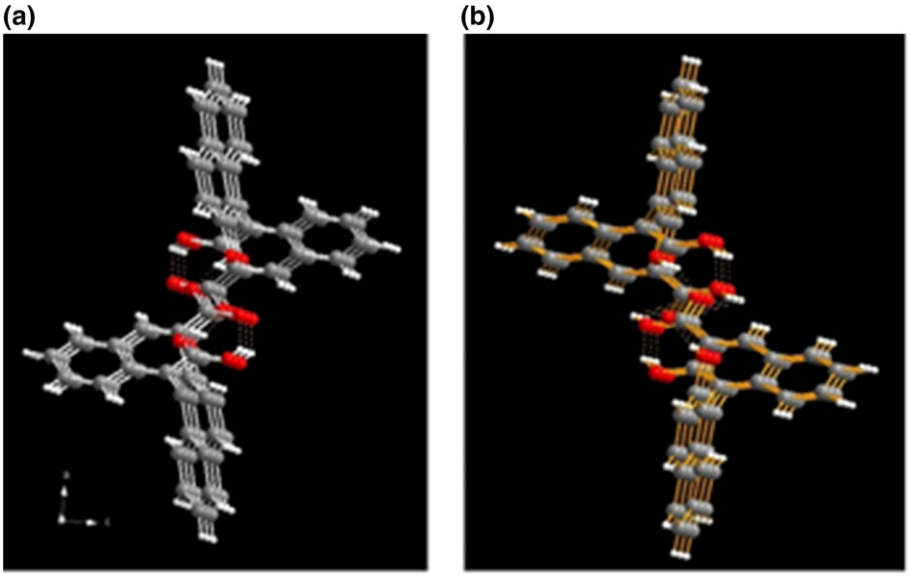


Figure 2 Comparison of semi-helical BNA polymeric chain in crystal **1** (a) and **2** (b). Both are different only in chiral senses.

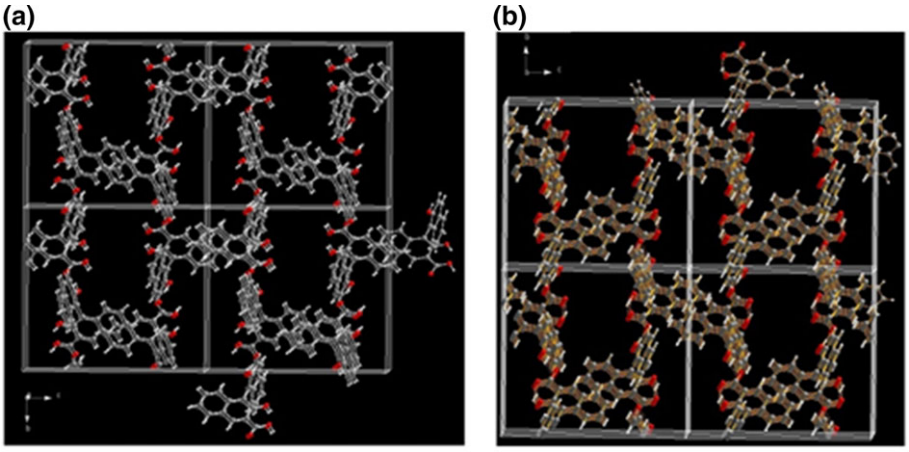


Figure 3 The chiral channels of **1** (a) and **2** (b). Both are different from each other only in chiral senses.

The positional arrangements of CPEA molecules in the channels of both crystals are quite different. Anyway, it is observed that the environment of the asymmetric hydrogen is apparently distinguished from the one of the methyl groups in both crystals of **1** and **2**. The imine nitrogen in crystal **2** keeps strong hydrogen bond with carboxylate oxygen. The amine nitrogen in crystal **1** maintains strong hydrogen bond with carboxylate group and also with ─OH group, which pull the nitrogen position toward slightly near to the hydrophobic pocket.

Crystal **2** is totally insoluble in solvents such as $CDCl_3$ and acetone, thus the ^{1}H NMR measurement for the crystal was only possible in a solvent such as DMSO-d_6. The ketimine was unstable in DMSO-d_6 and rapidly hydrolyzed to acetone and CPEA by the water content in the solvent. The half-life of the ketimine was within a few minute at room temperature in the NMR condition.

Equilibrium constant of ketimine formation between methylamine and acetone was known to be a poor value of 0.22/M.[14] The ketimine formation constant between pyridoxamine and 2-oxalopropionic acid was reported as 9.6 at pH 9.0.[15] Long reaction times and water removing conditions are generally required to obtain ketimine to overcome relatively small formation constants. The imine between (*S*)-1-phenylethylamine and acetone was obtained in hexane from refluxing for 2 days in the presence of catalytic amount of *p*-toluenesulfonic acid with $MgSO_4$ in 55% yield.[16] The fast and complete imine formation between acetone and CPEA observed in this work is a quite rare example. The very poor solubility of the imine captured in the polymeric channels of BNA probably drove the reaction to complete the imine formation.

Conclusions

In summary, we have shown that diastereomeric pair of (*R*)-BNA/(*S*)-CPEA crystallizes in CH_2Cl_2 and the (*S*)-BNA/(*S*)-CPEA pair crystallizes in the presence of acetone. The switch of the solubility of diastereomeric pairs was revealed to be due to the imine formation with acetone. The especially low solubility of the BNA–imine pair is responsible for the fast and complete imine formation. The structures of BNA part in the both crystals of **1** and **2** are in same features. The robustness of chiral channels and pockets composed by BNA might contribute to the recognition

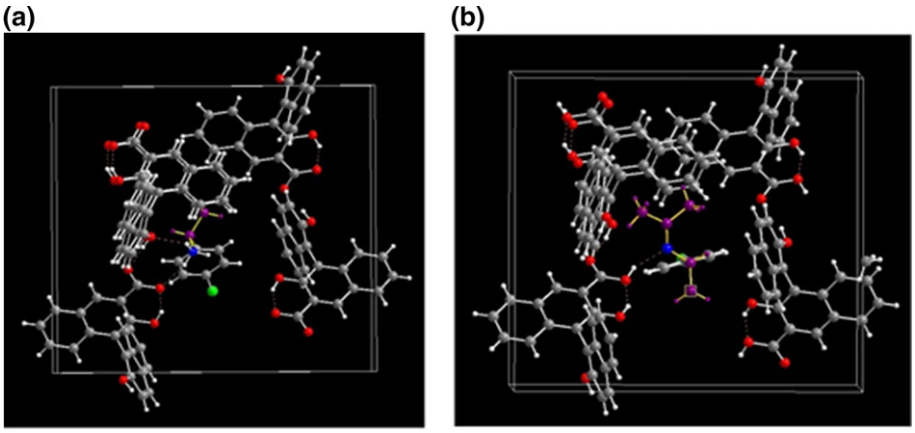


Figure 4 The arrangement of CPEA molecules inside the channels of **1** (a) and **2** (b).

of the chirality of CPEA with high selectivity. Even though the covalent influence of acetone in the resolution of *N*-formylphenylalanine with (*S*)-*N*-benzylaminobutanol has been assumed in the previous work,[17] the apparent covalent imine bond formation in the presence of acetone observed in this work is a rare example. Deliberate controls of the resolution processes would make BNA to be a practical agent to resolve optically pure CPEA of industrially important compound.

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References

1. a) T. C. Nugent Ed., *Chiral Amine Synthesis: Methods, Developments and applications*, Wiley-VCH, Weinheim, **2010**; b) V. Farina, J. T. Reeves, C. H. Senanayake, J. Song, *J. Chem. Rev.* **2006**, *106*, 2734; c) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Kessler, R. Stümer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788.
2. a) A. N. Collins, G. N. Sheldrake, J. Crosby, *Chirality in Industry*, Vol. 1, 1992, Vol. *2*, Wiley and Sons, Chichester, **1997**; b) J. W. Nieuwenhuijzen, R. F. P. Grimbergen, C. Koopman, R. M. Kellogg, T. R. Vries, K. Pouwer, E. van Echten, B. Kaptein, L. A. Hulshof, Q. B. Broxterman, *Angew. Chem. Int. Ed.* **2002**, *41*, 4281; c) F. Faigl, E. Fogassy, M. Nógrádi, E. Pálovics, J. Schindler, *Tetrahedron: Asymmetry* **2008**, *19*, 519; d) R. Siedlecka, *Tetrahedron* **2013**, *69*, 6331.
3. a) D. Mavrynsky, R. Leino, *J. Organomet. Chem.* **2014**, *760*, 161; b) E.-S. Park, M. S. Malik, J.-Y. Dong, J.-S. Shin, *ChemCatChem* **2013**, *5*, 1734.
4. K. Kinbara, Y. Harada, K. Saigo, *J. Chem. Soc. Perkin Trans.* **2000**, *2*, 1339.
5. K. Kodama, N. Hayashi, M. Fujita, T. Hirose, *RSC Adv.* **2014**, *4*, 25609.
6. Y. Kobayashi, J. Maeda, K. Saigo, *Tetrahedron: Asymmetry* **2006**, *17*, 1617.
7. a) H. B. Mereyala, S. R. Koduru, V. N. Cheemalapati, *Tetrahedron: Asymmetry* **2006**, *17*, 259; b) H. B. Mereyala, L. Fatima, P. Pola, *Tetrahedron: Asymmetry* **2004**, *15*, 585; c) H. B. Mereyala, P. Pola, *Tetrahedron: Asymmetry* **2003**, *14*, 2683.
8. a) P. G. Karamertzanis, S. L. Price, *J. Phys. Chem. B* **2005**, *109*, 17134; b) F. J. J. Leusen, *Cryst. Growth Des.* **2003**, *3*, 189.
9. H. Huang, Q. Chen, M. Choi, R. Nandhakumar, Z. Su, S. Ham, K. M. Kim, *Chem. Eur. J.* **2014**, *20*, 2895.
10. a) C. K. Y. Varma, P. Santhakumari, *Indian Phytopathol.* **2012**, *65*, 87; b) U. Kraatz, M. Littmann, *Pflanzenschutz-Nachr. Bayer (German Ed.)* **1998**, *51*, 203.
11. a) K. Kodama, N. Kurozumi, H. Shitara, T. Hirose, *Tetrahedron* **2014**, *70*, 7923; b) K. Kodama, H. Shitara, T. Hirose, *Cryst. Growth Des.* **2014**, *14*, 3549; c) H. Shitara, T. Shintani, K. Kodama, T. Hirose, *J. Org. Chem.* **2013**, *78*, 9309; d) K. Sakai, R. Sakurai, H. Nohira, *Top. Curr. Chem.* **2007**, *269*, 199.
12. A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435.
13. Bruker, *SHELXTL (ver. 6.10): Program for Solution and Refinement of Crystal Structures*, Bruker AXS Inc., Madison, WI, **2000**.
14. A. Williams, M. L. Bender, *J. Am. Chem. Soc.* **1966**, *88*, 2508.
15. a) R. M. Pollack, S. Ritterstein, *J. Am. Chem. Soc.* **1972**, *94*, 5064; b) G. Kubala, A. E. Martell, *J. Am. Chem. Soc.* **1983**, *105*, 449.
16. A. Bernardi, C. Gennari, J. M. Goodman, V. Leue, I. Paterson, *Tetrahedron* **1995**, *51*, 4853.
17. E. Pálovics, L. Bereczki, K. Marthi, G. Pokol, F. Faigl, E. Fogassy, *Tetrahedron: Asymmetry* **2007**, *18*, 2531.

