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Solvent-Induced Chirality Switching in the Enantioseparation of Hydroxycarboxylic Acids with a Quaternary Stereogenic Center

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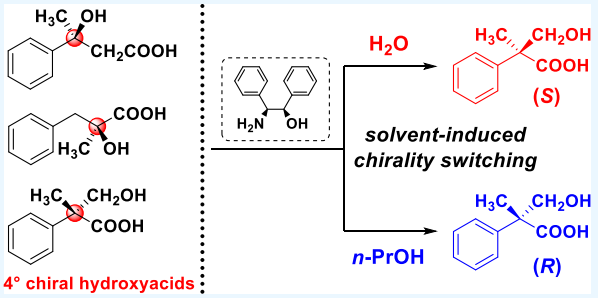
ABSTRACT: The enantiomer separation of three isomeric hydroxycarboxylic acids with a quaternary stereogenic center via diastereomeric salt formation with (1*R*,2*S*)-2-amino-1,2-diphenylethanol was demonstrated. Racemic acid **1**, with a quaternary chiral center at the *β*-position, was separated with nearly ideal efficiency. The stereochemistry of acids **2** and **3** incorporated in the less-soluble salts was reversed depending on the recrystallization solvents, and both enantiomers were accessible. The mechanism of this chirality switching was discussed based on the crystal structures of the less-soluble diastereomeric salts; the solvation of the salt with an alcohol molecule changed the hydrogen-bonding network and its stability.



INTRODUCTION

Chiral hydroxycarboxylic acids (HAs), which contain both hydroxy and carboxy groups, are useful synthetic intermediates for obtaining biologically active and pharmaceutical compounds. Asymmetric synthesis is an efficient method for obtaining HAs in their enantiomeric form.[1] However, the enantioselective construction of quaternary stereogenic centers in chiral HAs remains difficult, and multistep reactions are generally required.[2]

Enantiomer separation from racemates via diastereomeric salt formation is another useful method for obtaining pure enantiomers. Although this is a classical method, it has been widely applied not only to laboratory-scale production but also to industrial-scale production of enantiomers.[3] We have been studying the enantiomer separation of chiral HAs via diastereomeric salt formation using the resolving agent (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol (ADPE). We found that the stereochemistry of HA in the deposited salt changed depending on the recrystallization solvent despite, using a single resolving agent. For example, during the crystallization of the salt of racemic mandelic acid (MA) and (−)-ADPE, the (*R*)-MA·(−)-ADPE salt was deposited from the *n*-PrOH solution, while the (*S*)-MA·(−)-ADPE salt precipitated from the *i*-PrOH solution.[4] This chirality switching enables to obtain both enantiomers of MA from its racemate by changing only the recrystallization solvent.[5] Because the polarities of these solvents are similar, the key to solvent-induced chirality switching is the incorporation of the solvent into the crystal lattice of the diastereomeric salts to change their solubility. However, this method does not apply to all HAs examined thus far. For example, during the enantiomer separation of three isomeric HAs (**1H**−**3H**), all the HAs were efficiently separated; however, chirality switching was observed only for **2H** and **3H** (Scheme 1).[6,7] This indicates that the applicability of the chirality switching method depends on the subtle structural differences of HAs.[8,9]

To further extend the scope of this chirality switching method, three isomeric HAs (**1**−**3**) with a quaternary chiral center were selected as the target racemates in this study (Scheme 1). The hydrogen atom at the chiral center of **1H**-**3H** was replaced with a methyl group in HAs **1**−**3**, respectively. Studies regarding obtaining enantiomers of HAs **1**−**3** via asymmetric synthesis[10−13] or enzymatic kinetic resolution are limited.[14−16] Although the enantioseparation of HAs **1**−**3** via diastereomeric salt formation has been reported, it depends on highly toxic alkaloid-type resolving agents such as morphine, brucine, and quinine.[17−19] In this study, we report the solvent effect on the enantiomer separation of **1**−**3** via diastereomeric salt formation with (−)-ADPE and discuss the chirality switching phenomenon based on the crystal structures of the diastereomeric salts.

RESULTS AND DISCUSSION

Enantioseparation of 3-Hydroxy-3-phenylbutanoic Acid (1) and Crystallographic Analysis of Its Diastereomeric Salts. 3-Hydroxy-3-phenylbutanoic acid (**1**) has a quaternary stereogenic center at the *β*-position of the carboxy group, which generally complicates chiral recognition. Racemic

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Scheme 1. Structures of the Resolving Agent, (1*R*,2*S*)-ADPE, and Target Hydroxycarboxylic Acids with a Quaternary Chiral Center (1−3)

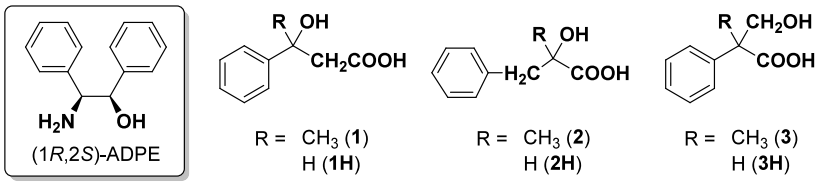

Table 1. Enantioseparation of Racemic 3-Hydroxy-3-phenylbutanoic Acid (1) with (1R,2S)-ADPE[a]

entry	solvent (L/mol)	solvent inclusion (%)[b]	yield (%)[c]	ee (%)[d]	efficiency[e]
1	H_2O (9)	100[f]	114	32 (*S*)	0.36
2	CH_3CN (10)	not included	77	77 (*S*)	0.59
3	THF (2)	not included	106	93 (*S*)	0.99
4	EtOAc (16)	not included	71	89 (*S*)	0.63

[a]*Rac*-**1** and (1*R*,2*S*)-ADPE (0.5 mmol) were used. [b]The solvent inclusion was determined by ^{1}H NMR analysis. [c]Yield of the precipitated salt is based on the half amount of the initial salt. [d]Ee was determined by HPLC analysis after derivatization of their methyl esters. Absolute configuration of the major enantiomer is shown in the parentheses. [e]Efficiency = yield (%) × ee (%)/10,000. [f]Determined by crystallographic analysis.

1 was prepared via the Reformatsky reaction, followed by hydrolysis of the ester under basic conditions (Scheme S1). Equimolar amounts of *rac*-**1** and (−)-ADPE were mixed to prepare a mixture of the two diastereomeric salts. After a preliminary investigation of its solubility in solvents with various polarities, the salt was recrystallized from the selected solvents. The deposited solid was weighed and analyzed using ^{1}H NMR spectroscopy. Part of the salt was decomposed, and the liberated **1** was derivatized to its methyl ester to determine its enantiopurity by HPLC analysis. The results are summarized in Table 1. The efficiency values, which were products of the yield and enantiomeric excess (ee) values, were calculated to evaluate whether the resolution was successful. Recrystallization of the diastereomeric salts from water resulted in a salt of (*S*)-**1** with moderate efficiency (Entry 1). Recrystallization from organic solvents also resulted in the (*S*)-**1** salt with a higher efficiency of up to 0.6 (Entries 2−4). Notably, the resolution efficiency was high when recrystallized from a tetrahydrofuran (THF) solution, and nearly an ideal enantiomer separation for obtaining (*S*)-**1** with high enantiopurity was achieved via single recrystallization (Entry 3). These organic solvents were not incorporated into the precipitated salt, and the salt of (*S*)-**1** was consistently deposited; solvent-induced chirality switching was not observed, similar to the enantioseparation of *rac*-**1H**.

To better understand this enantioselectivity for (*S*)-**1**, a crystallographic analysis of the less-soluble diastereomeric salts was performed. The crystal structure of the less-soluble (*S*)-**1**·(−)-ADPE salt obtained from CH_3CN solution is illustrated in Figure 1. The carboxylate group of (*S*)-**1** hydrogen bonds with the ammonium group of (−)-ADPE to form a salt. They construct a layerlike, zigzag two-dimensional (2D) hydrogen-bonding network along the *ac* plane. The hydroxy group of (−)-ADPE forms an additional hydrogen bond with the carboxylate group of (*S*)-**1**, reinforcing the hydrogen-bonding network. The hydroxy group of (*S*)-**1** at the β-position is fixed by a hydrogen bond with the ammonium group of (−)-ADPE, as well as an intramolecular hydrogen bond with its carboxyl group. There are two independent (*S*)-**1** molecules with the same conformation. The methyl and phenyl groups on their stereogenic center are fixed to one another with CH/π interactions (the distance between CH and π-plane is 2.91 Å),

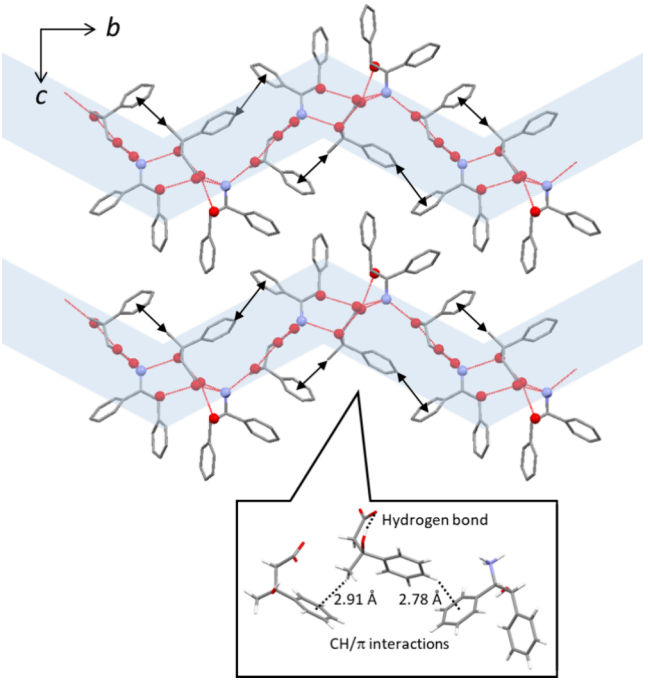

Figure 1. Crystal structure of (*S*)-**1**·(−)-**ADPE** salt viewed from the *a* axis. Oxygen and nitrogen atoms are represented with red and blue balls, respectively. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively.

which explains the high enantioselectivity for (*S*)-**1**. The neighboring layers are densely packed (the crystal density is 1.275 g cm^{-3}) to provide a stable crystal.

The structure of the same (*S*)-**1**·(−)-ADPE salt crystallized from water varied from the aforementioned structure, as shown in Figure 2. The water molecule is incorporated at a molar ratio of 1:1 to provide a hydrated (*S*)-**1**·(−)-ADPE·H_2O salt. The water molecules form hydrogen bonds with (*S*)-**1** and (−)-ADPE, and a 1D columnar hydrogen-bonding network is constructed along the *a* axis. This change in the network from 2D to 1D can be attributed to the increased volume of the hydrophilic part caused by the incorporation of water. This 1D columnar hydrogen-bonding network was also observed for the previously reported (*S*)-**1H**·ADPE salt (Figure S1).[7] A

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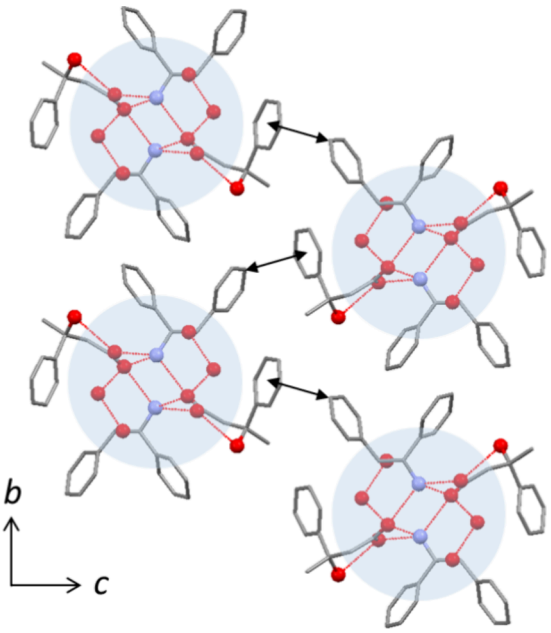

Figure 2. Crystal structure of (*S*)-**1**·(−)-**ADPE**·H_2O salt viewed from the *a* axis. Oxygen and nitrogen atoms are represented with red and blue balls, respectively. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively.

comparison of these two structures revealed that the positions of the oxygen atoms in the column were apparently similar; however, a water molecule replaced one of the carboxylate oxygen atoms of (*S*)-**1H**. In the (*S*)-**1**·(−)-ADPE crystal, the hydrophobic methyl group substituted on the stereogenic center is pushed out from the hydrophilic region, and the β-hydroxy group is simultaneously directed remotely from the inside of the columnar structure. The water molecule is embedded in this vacant site to maintain a columnar network. Only the phenyl group of (*S*)-**1** is fixed by a weak CH/π interaction (the distance between CH and π-plane was 2.76 Å). Although the crystal structure of the corresponding more-soluble (*R*)-**1**·(−)-ADPE salt is unknown, the decreased dimensionality of the hydrogen-bonding network of the less-soluble salts from 2D to 1D by incorporation of the water molecules probably resulted in a lower enantioselectivity for (*S*)-**1** when crystallized from water. Finally, chirality switching was not achieved during the enantiomer separation of *rac*-**1**.

Chirality Switching in the Enantioseparation of 2-Hydroxy-2-methyl-3-phenylpropanoic Acid (2). Racemic 2-hydroxy-2-methyl-3-phenylpropanoic acid (**2**) with a benzyl group on the quaternary chiral center is a type of α,α-disubstituted glycolic acid and was synthesized from methyl pyruvate via a Grignard reaction followed by the hydrolysis of the ester moiety under basic conditions (Scheme S2). The results of the enantiomer separation of *rac*-**2** with (−)-ADPE are summarized in Table 2. When the salt was crystallized from an aqueous ethanol solution, the (*R*)-**2** salt was preferentially obtained with low selectivity (Entry 1). Less polar solvents also afforded (*R*)-**2**·(−)-ADPE salts with higher efficiencies (entries 5 and 6). Conversely, recrystallization from alcohol solvents resulted in (*S*)-**2** salt with high efficiencies, up to 0.59 (Entries 2−4). The ^{1}H NMR analysis revealed that these alcohol solvents were included in the precipitated salts, which stabilized the (*S*)-**2**·(−)-ADPE salt and induced chirality switching. Such chirality switching was also observed during the separation of *rac*-**2H** from the (*R*)-isomer to the (*S*)-isomer by the incorporation of EtOH or *i*-PrOH.[7] Although the detailed mechanism of this chirality switching is unknown because a crystallographic analysis of the less-soluble salts was unsuccessful owing to the powdery nature of the salts, the remote phenyl group of **2** and **2H** from the hydrogen-bonding moieties may leave a cavity around the hydrophilic part and permit the incorporation of alcohol molecules to induce chirality switching.[20]

Chirality Switching in the Enantioseparation of 3-Hydroxy-2-methyl-2-phenylpropanoic Acid (3) and Crystallographic Analysis of the Diastereomeric Salts. 3-Hydroxy-2-methyl-2-phenylpropanoic acid (**3**) is a α-methylated derivative of tropic acid, which is an important intermediate of atropine (an anticholinergic drug).[21] However, the only reported enantioseparation of *rac*-**3** relies on the toxic quinine as a resolving agent.[19] *Rac*-**3** was synthesized by introducing a benzyloxymethyl group to racemic phenylpropionate, followed by deprotection via hydrogenolysis and hydrolysis (Scheme S3). The results of the enantioseparation of *rac*-**3** with (−)-ADPE are summarized in Table 3. Crystallization from water and aqueous ethanol resulted in the salt of (*S*)-**3** with a low selectivity (Entries 1 and 2). Less polar EtOAc and $CHCl_3$ also resulted in the salt of (*S*)-**3**, with a slightly higher efficiency of up to 0.19 (entries 5 and 6). Conversely, crystallization from the *n*-PrOH solution resulted in the salt of (*R*)-**3** with moderate efficiency, and the chirality switching method could be applied. An ^{1}H NMR analysis demonstrated that *n*-PrOH was present in the deposited salt (Entry 3). In contrast to *n*-PrOH, its isomer (*i*-PrOH) was not included in the deposited solid, and the salt of (*S*)-**3** was obtained (Entry 4). This indicates that not the polarity of the solvents but the inclusion of the *n*-PrOH molecule changed the stereochemistry of **3** in the precipitates.

The crystal structure of the less-soluble salt prepared from water is shown in Figure 3. The salts of **3** and (−)-ADPE

Table 2. Enantioseparation of Racemic 2-Hydroxy-2-methyl-3-phenylpropanoic Acid (2) with (1*R*,2*S*)-ADPE[a]

entry	solvent (L/mol)	solvent inclusion (%)[b]	yield (%)[c]	ee (%)[d]	efficiency[e]
1	50% EtOH (13.3)	not included	33	12 (*R*)	0.04
2	EtOH (2.5)	50	77	48 (*S*)	0.39
3	*n*-PrOH (6.7)	100	52	58 (*S*)	0.30
4	*i*-PrOH (16.7)	80	101	58 (*S*)	0.59
5	EtOAc (15)	not included	85	16 (*R*)	0.14
6	$CHCl_3$ (30)	not included	75	27 (*R*)	0.20

[a]*Rac*-**2** and (1*R*,2*S*)-ADPE (0.3 mmol) were used. [b]The solvent inclusion was determined by ^{1}H NMR analysis. [c]Yield of the precipitated salt is based on the half amount of the initial salt. [d]Ee was determined by HPLC analysis after derivatization of their methyl esters. Absolute configuration of the major enantiomer is shown in the parentheses. [e]Efficiency = yield (%) × ee (%)/10,000. [f]Determined by crystallographic analysis.

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Table 3. Enantioseparation of Racemic 3-Hydroxy-2-methyl-2-phenylpropanoic Acid (3) with (1*R*,2*S*)-ADPE[a]

entry	solvent (L/mol)	solvent inclusion (%)	yield (%)[b]	ee (%)[c]	efficiency[d]
1	H_2O (10)	50[e]	32	15 (*S*)	0.05
2	50% EtOH (10)	not included	50	25 (*S*)	0.12
3	*n*-PrOH (11.4)	60[f]	36	70 (*R*)	0.25
4	*i*-PrOH (11.4)	not included	32	29 (*S*)	0.09
5	EtOAc (30)	not included	111	17 (*S*)	0.19
6	$CHCl_3$ (23.3)	not included	34	16 (*S*)	0.05

[a]*Rac*-**3** and (1*R*,2*S*)-ADPE (0.30 or 0.35 mmol) were used. [b]Yield of the precipitated salt is based on the half amount of the initial salt. [c]Ee was determined by HPLC analysis after derivatization of their methyl esters. Absolute configuration of the major enantiomer is shown in the parentheses. [d]Efficiency = yield (%) × ee (%)/10,000. [e]The water inclusion was determined by TG analysis. [f]The solvent inclusion was determined by ^{1}H NMR analysis.

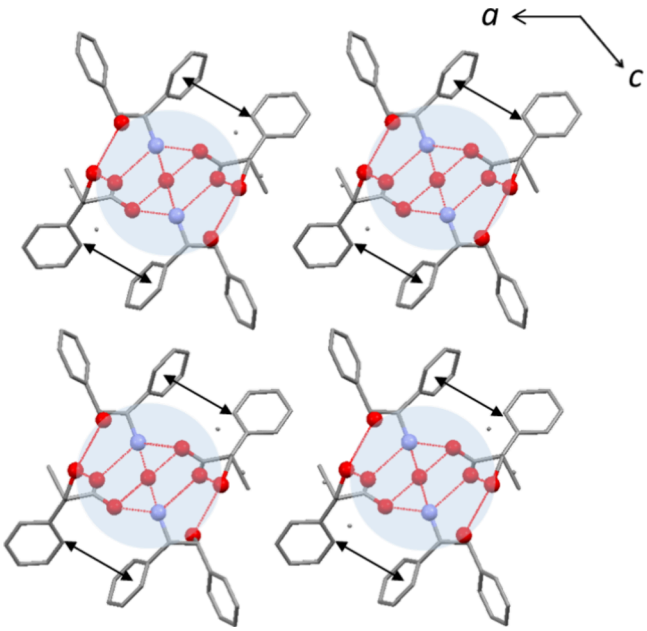

Figure 3. Crystal structure of **3**·(−)-**ADPE·0.5H$_2$O** salt viewed from the *b* axis. Oxygen and nitrogen atoms are represented with red and blue balls, respectively. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively.

forms a columnar structure, and water molecules are embedded in the center of the column. The salt-to-water molar ratio is 2:1 to give a hemihydrated salt. A TGA of the salt crystallized from water showed a decrease in weight at approximately 100 °C before melting, which indicated that water was included in this salt (Figure S2). The inclusion ratio was estimated to be 49%, which is consistent with the above result of the crystallographic analysis. The structure is disordered, and the two enantiomers of **3** coexist in the crystal to give a solid solution crystal. The (*S*)-**3**:(*R*)-**3** ratio is calculated to be 62:38, and a preference for (*S*)-**3** was observed, which was consistent with the enantiomer separation results (Table 3). Although the position of the hydroxy group of **3** is fixed via hydrogen bonds between the carboxylate group of **3** and the hydroxy group of (−)-ADPE, the flexible methylene moiety and lower recognition of the methyl group permit the disorder of both enantiomers (Figure S3).

Finally, the crystal structure of the salt prepared from the *n*-PrOH solution differed compared to the previous structures (Figure 4). (*R*)-**3** and (−)-ADPE form a salt; however, no

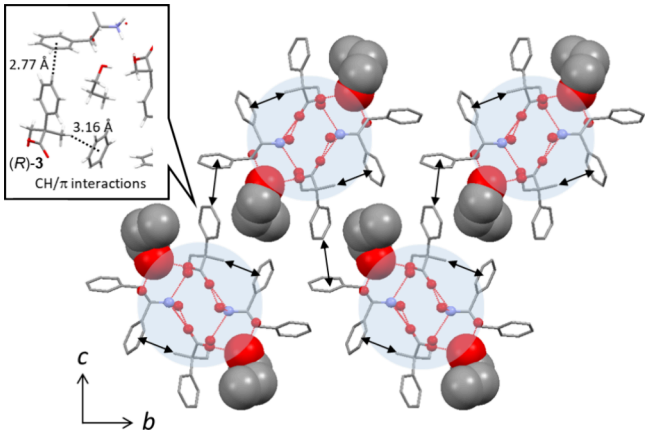

Figure 4. Crystal structures of (*R*)-**3**·(−)-**ADPE·***n*-**PrOH·H$_2$O** salt viewed from the *a* axis. Oxygen and nitrogen atoms are represented with red and blue balls, respectively. The dotted lines and arrows show hydrogen bonds and CH/π interactions, respectively.

disordered structure was observed; they construct a columnar hydrogen-bonding network, and both water and *n*-PrOH molecules are included in the salt at a ratio of 1:1:1 to give the four-component (*R*)-**3**·(−)-ADPE·*n*-PrOH·H_2O salt. Water molecules occupy the interior of the column to expand the volume of the hydrophilic part. There are *n*-PrOH molecules between the columns via the formation of hydrogen bonds with the carboxylate group of (*R*)-**3** and the hydroxy group of (−)-ADPE. The position of acid (*R*)-**3** is regulated by the presence of *n*-PrOH. The phenyl group of (*R*)-**3** is fixed by a CH/π interaction between its CH and the phenyl ring of (−)-ADPE (the distance between CH and π-plane was 2.77 Å). In addition, the methyl group at the stereogenic center of (*R*)-**3** is also recognized by a weak CH/π interaction with the phenyl ring of (−)-ADPE (the distance between CH and π-plane was 3.16 Å). This multipoint recognition of **3** resulted in a specific preference for the (*R*)-isomer during recrystallization from *n*-PrOH. This chirality switching induced by including alcohol was also observed during the separation of *rac*-**3H** with (−)-ADPE; however, the absolute configurations of the HAs were reversed. Namely, the (*R*)-**3H**·(−)-ADPE salt was obtained from water, and the (*S*)-**3H**·(−)-ADPE salt was obtained from the *i*-PrOH solution.[6] Based on a comparison of their solvated salt crystals (Figure S4), the structures of the (*S*)-**3H**·(−)-ADPE·*i*-PrOH and (*R*)-**3**·(−)-ADPE·*n*-PrOH·H_2O salts were apparently similar; however, the orientations of the HAs in these salts varied. Namely, the hydrophobic methyl group introduced at the stereogenic center of (*R*)-**3** was directed outside the columnar structure, resulting in a reversed stereoselectivity together with incorporation of water and *n*-PrOH. It appears the size and shape of the *n*-PrOH molecule are suitable for efficient molecular packing among the examined alcohols.

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CONCLUSIONS

In this study, the enantiomer separation of three HAs with a quaternary stereogenic center (**1**−**3**) was investigated via diastereomeric salt formation using (−)-ADPE. HA **1**, with a stereogenic center at the remote β-position, was separated with nearly ideal high efficiency. Although the salt crystallized upon the inclusion of water, chirality switching was not observed. Solvent-induced chirality switching was successfully applied to HAs **2** and **3** to obtain both enantiomers by using only a single chiral resolving agent. Crystallization from *n*-PrOH resulted in the (*R*)-**3** salt, whereas the (*S*)-**3** salt was obtained from other solvents. Based on the crystal structure of the less-soluble diastereomeric salts, the (*R*)-**3**·ADPE salt was stabilized by incorporating *n*-PrOH as well as water molecules. Although the methyl group introduced at the quaternary stereogenic center changed the crystal structure owing to its hydrophobicity, the applicability of the chirality switching for **1**−**3** was consistent with that of their parent HAs **1H**−**3H**. HAs **1**−**3** in their enantiomeric forms are useful as chiral synthetic intermediates. This is the first study regarding the chemical enantiomer separation of HAs **1**−**3** without the use of toxic chiral compounds. Further investigations of this chirality switching method for other HAs are currently underway.

EXPERIMENTAL SECTION

General Methods. All of the reagents and solvents were purchased and used as received. Racemic HAs (**1**−**3**) were synthesized according to previous literatures (Schemes S1−S3).[22−24] The ^{1}H NMR spectra of the salts were recorded by using 300- or 400-MHz NMR spectrometers. Thermogravimetric analysis (TGA) was performed at a heating rate of 10 °C·min^{-1}. The enantiomeric excess (ee) was determined by chiral HPLC analysis on a Daicel Chiralcel OD-3 or ChiralPak IA-3 column with detection at 254 nm.

Enantioseparation Procedure of Hydroxycarboxylic Acids (1−3) with (1*R*,2*S*)-(−)-ADPE. Equimolar amounts (0.3−0.5 mmol) of racemic hydroxycarboxylic acids and (1*R*,2*S*)-(−)-ADPE were dissolved in methanol. After the solution was concentrated, the resulting solid was dissolved in an appropriate solvent by heating and allowed to cool to ambient temperature to recrystallize the diastereomeric salt. The precipitated solids were filtered and dried under reduced pressure. The salt yield was calculated based on half the amount of the initial racemic acid, considering the molar amount of included solvent determined by ^{1}H NMR or TG data. A portion (20−30 mg) of the salt was decomposed upon addition of a 1 M aqueous hydrochloric acid solution, and the resulting aqueous solution was extracted with diethyl ether. After drying over anhydrous sodium sulfate, the organic layer was concentrated to obtain the acid as a white solid. The liberated acids (**1** and **3**) were derivatized to their methyl esters upon reaction with $TMSCHN_2$ in methanol to determine their enantiomeric excess (ee) via chiral HPLC, whereas the liberated acid **2** was directly analyzed via chiral HPLC. The absolute configurations of **1**−**3** were determined by comparing the elution order in the HPLC analysis with those in the literatures.[25−27]

Single Crystal X-ray Analysis of the Diastereomeric Salt Crystals. Single crystals suitable for X-ray diffraction analysis were prepared by slowly evaporating a saturated solution of the diastereomeric salt. X-ray crystallographic data were collected on a Bruker Smart APEX II diffractometer using graphite-monochromated Mo Kα radiation. The data were collected at 150 K. The structures were solved via a direct method (SIR 2014) and refined using the SHELXL-2018 program.[28] All crystallographic information was deposited in the Cambridge Structural Database.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c10205.

Experimental detail, synthetic schemes, crystal structures, TGA chart, summary of the crystallographic data, copies of ^{1}H NMR and IR spectra, and copies of HPLC charts (PDF)

(*S*)-**1**·(−)-ADPE (CIF)

(*S*)-**1**·(−)-ADPE·H_2O (CIF)

3·(−)-ADPE·0.5H_2O (CIF)

(*R*)-**3**·(−)-ADPE·*n*-PrOH·H_2O (CIF)

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Notes

The authors declare no competing financial interest.

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