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A New Hydrogen-Bonding Motif for Chiral Recognition in the Diastereomeric Salts of Racemic 1-Phenylethylamine Derivatives with Enantiopure *O*-Ethyl Phenylphosphonothioic Acid

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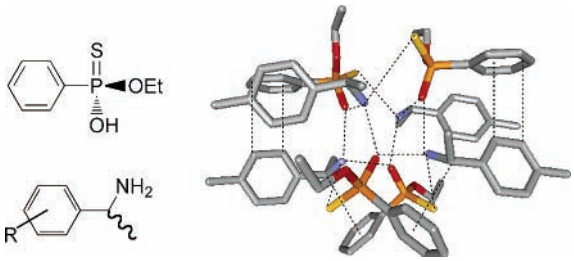
ABSTRACT



An enantiopure phosphonothioic acid showed a unique and superior chiral recognition ability, arising from its *P*-stereogenicity, for racemic 1-phenylethylamine derivatives through diastereomeric crystallization. Spherical molecular clusters, associated by hydrogen bonds and CH/π interactions, aggregated with high symmetry in the less-soluble diastereomeric salts.

Compounds containing chiral phosphorus atom(s) (*P*-chiral) have been attracting great interest in organic chemistry; enantiopure *P*-chiral phosphinothioic acids and phosphines are particularly known to be useful as solvating agents for the determination of enantiomeric excesses[1] and ligands for transition metal catalysts,[2] respectively. Moreover, in the field of biochemistry, the synthesis and application of enantiopure *P*-chiral nucleotide, DNA, and RNA analogues are hot topics.[3]

O-Substituted phosphonothioic acids, a series of *P*-chiral compounds, are stable Brønsted acids as carboxylic acids, sulfonic acids, and phosphonic acids. However, from the viewpoint of structural features, *O*-substituted phosphonothioic acids are quite different from the other organic Brønsted acids. The acidic functional group of *O*-substituted phosphonothioic acids is chiral, whereas those of the other organic Brønsted acids are achiral; the phosphorus atom in *O*-substituted phosphonothioic acids is not only an element of an acidic functional group but also a chiral center, as shown in Figure 1. This structural characteristic of *O*-substituted phosphonothioic acids suggests that enantiopure *O*-substituted phosphonothioic acids would be able to offer a rigorously controlled, three-dimensionally dissymmetric environment when the acidic functional group interacts with a substrate. Moreover, different from the acidic functional

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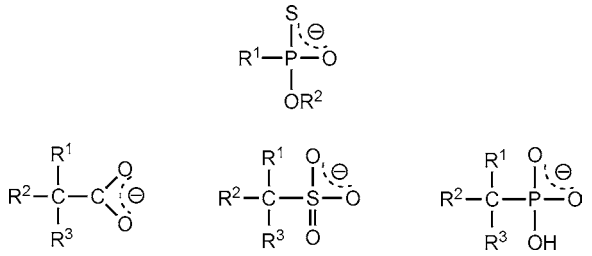


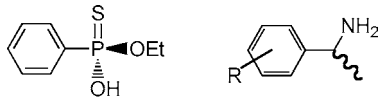
Figure 1.

groups of carboxylic acids, sulfonic acids, and phosphonic acids, the acidic functional group of *O*-substituted phosphonothioic acids can give two obviously different hydrogen-accepting sites, sulfur and oxygen atoms, upon transforming them into the corresponding anionic forms by interaction with a basic substrate. Although enantiopure *O*-substituted phosphonothioic acids have such distinct characteristics, only fragmented reports appear on their enantio-differenciating solvation ability[4] and biological activity.[5a] These facts prompted us to apply *O*-substituted phosphonothioic acids with unique stereogenicity to the enantioseparation of racemates as new resolving agents. We report here the chiral recognition ability of an enantiopure *O*-alkyl phosphonothioic acid in the enantioseparation of racemic 1-phenyletylamine derivatives by diastereomeric salt formation and a new hydrogen-bonding motif for the chiral recognition.

As an enantiopure *O*-substituted phosphonothioic acid, we chose *O*-ethyl phenylphosphonothioic acid (**1**) because the synthesis and enantioseparation of **1** have been reported.[5] Starting from commercially available phenylphosphonothioic dichloride, racemic *O*-ethyl phenylphosphonothioic acid was easily synthesized in 91% total yield via two steps, and enantiopure (*Sp*)-*O*-ethyl phenylphosphonothioic acid ((*Sp*)-**1**) was successfully obtained by the enantioseparation of the racemate with (*R*)-1-phenylethylamine.[6]

To clarify the chiral recognition ability of (*Sp*)-**1**, we at first carried out the enantioseparation of systematically selected 1-phenylethylamine derivatives by using (*Sp*)-**1** as a resolving agent.[7] As can be seen from Table 1, (*Sp*)-**1** showed a very unique chiral recognition ability with a series

Table 1. Enantioseparation of 1-Phenylethylamine Derivatives **2** with (*Sp*)-**1**



1 2

amine	R	yield (%)[a]	ee (%)[b]	efficiency[c]	abs config[d]
2a	H	78	98	0.76	*R*
2b	*o*-Me	not crystallized			
2c	*m*-Me	not crystallized			
2d	*p*-Me	52	>99	0.51	*R*
2e	*p*-OMe	45	>99	0.45	*S*
2f	*p*-F	84	96	0.81	*R*
2g	*p*-Cl	84	>99	0.83	*R*
2h	*p*-Br	83	95	0.79	*R*

[a] Yield of the crystallized diastereomeric salt based on a half amount of the racemic amine. [b] Enantiomeric excess (ee) of the liberated amine, which was determined by HPLC analysis. [c] Efficiency is the product of the yield and the ee. [d] Absolute configration of the major enantiomer, which was determined by a X-ray crystallographic analysis and/or deduced on the basis of the elution order in the HPLC analysis.

of 1-phenylethylamine derivatives **2**; once the salt crystals could deposit, (*Sp*)-**1** recognized the stereogenicity of **2** with excellent selectivity. Especially in the enantioseparations of **2d**, **2e**, and **2g**, the corresponding enantiopure amines were obtained by only single crystallization.

In the next stage, the X-ray crystallographic analyses of the less-soluble diastereomeric salts were carried out in order to extract the factors leading to such an excellent chiral recognition ability of (*Sp*)-**1**. Among six combinations of 1-phenylethylamine derivatives and (*Sp*)-**1** we succeeded in enantioseparating, the less-soluble diastereomeric salts of **2a**, **2d**, **2g**, and **2h** with (*Sp*)-**1** satisfactorily gave single crystals suitable for X-ray crystallographic analyses. All of the four less-soluble diastereomeric salt crystals have the same crystal system of tetragonal, and the space group is $P4_32_12$ with high symmetry, which is very rare for such organic salt crystals. Figures 2 and 3 show a typical example ((*Sp*)-**1**·(*R*)-**2d**) of the crystal structures of the less-soluble diastereomeric salts.[8] In the crystal, four molecules of (*Sp*)-**1** and four molecules of (*R*)-**2d** form a spherical cluster with a pseudo-two-fold axis, in which a hydrophilic core consisting of a hydrogen-bonding network is surrounded by the hydrophobic alkyl and aryl groups of (*Sp*)-**1** and (*R*)-**2d**. The hydrogen-bonding network is composed of hydrogen bonds not only between the nitrogen atom in (*R*)-**2d** and the oxygen atom in (*Sp*)-**1** but also between the nitrogen atom in (*R*)-**2d** and the sulfur atom in (*Sp*)-**1**. The characteristic spherical cluster makes the crystal highly symmetrical as tetragonal. The crystal of (*Sp*)-**1**·(*R*)-**2d** is consequently built up from the spherical clusters, which interact with each other by CH/π and van der Waals interactions along a two-fold screw axis.

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(6) For details of the synthesis and enantioseparation of racemic *O*-ethyl phenylphosphonothioic acid, see Supporting Information. In a similar manner, several kinds of enantiopure *O*-substituted phosphonothioic acids could be prepared. The application of the phosphonothioic acids as resolving agents is now in progress.

(7) The enantioseparations were carried out under almost the same conditions. The diastereomeric salt was crystallized from stirred ether/hexane at room temperature. The amount and ratio of the mixed solvent were adjusted to control the yield of the precipitated salt as close as possible within 50−80%.

(8) Crystal data for the less-soluble (*S*)-**1**·(*R*)-**2d**: FW = 337.42, tetragonal, space group $P4_32_12$, a = 13.6603(9), b = 13.6603(9), c = 40.7660(4) (Å), V = 7607.1(10) Å^3, Z = 16, R = 0.0660, Rw = 0.0710. For preliminary data for the other crystals, see Supporting Information.

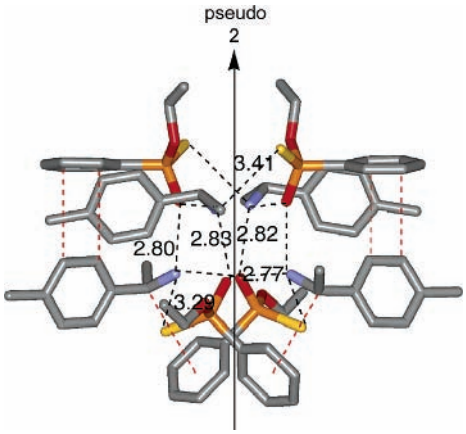

Figure 2. Hydrogen bonds and CH/π interactions in the spherical cluster of the less-soluble (*Sp*)-**1**·(*R*)-**2d**. The black and red dashed lines indicate hydrogen bonds and CH/π interactions, respectively. The values are the distances of the hydrogen bonds in angstroms. The pseudo-two-fold axis is not identical with the *c* axis.

The formation of a spherical cluster from four molecules of (*Sp*)-**1** and four molecules of an amine and the aggregation of the clusters by CH/π and van der Waals interactions were commonly observed in the crystals of the other less-soluble diastereomeric salts (*Sp*)-**1**·(*R*)-**2a**, (*Sp*)-**1**·(*R*)-**2g**, and (*Sp*)-**1**·(*R*)-**2h**. Such a closed hydrogen-bonding network is entirely unpredictable from the crystal structures of the less-soluble diastereomeric salts derived from conventional resolving agents; the less-soluble diastereomeric salt crystals commonly consist of an infinite columnar or sheetlike hydrogen-bonding network.[9] The formation of such a closed hydrogen-bonding motif in a chiral recognition phenomenon is the first example as far as we know.[10] The spherical cluster formation would arise from the structural characteristic of (*Sp*)-**1** that the phosphorus atom of the acidic functional group in (*Sp*)-**1** is chiral.

We could not determine the crystal structures of the corresponding more-soluble diastereomeric salts, because they were always oils even at low temperatures. However, the IR spectra in a region of 3100−2700 cm^{-1} assignable to the vibrations of the hydrogen bonds were similar to each other for the crystalline less-soluble salt and the oily more-soluble salt of **2d** with (*Sp*)-**1**. Although the similarity of the IR spectra is not direct evidence, it would suggest the formation of a similar spherical cluster in the more-soluble diastereomeric salt.

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(10) Very recently, the formation of a spherical cluster consisting of four carboxylic acid molecules and four amine molecules was reported. However, the carboxylic acid and amine are achiral; no chiral recognition phenomenon was observed. Sada, K.; Watanabe, T.; Miyamoto, J.; Fukuda, T.; Tohnami, N.; Miyata, M.; Kitayama, T.; Maehara, K.; Ute, K. *Chem. Lett*. **2004**, 160−161.

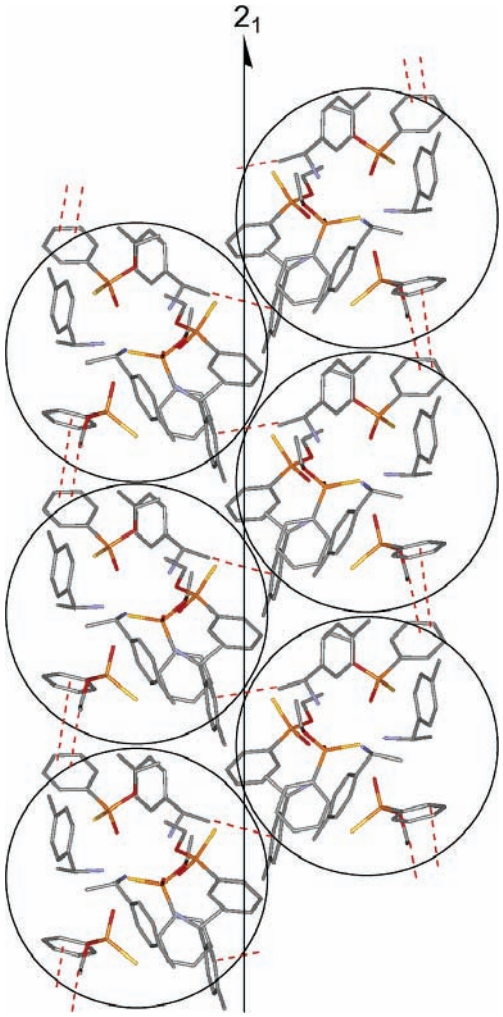

Figure 3. CH/π interactions to form a 2_1-column (side view) in the less-soluble (*Sp*)-**1**·(*R*)-**2d**. The red dashed lines indicate CH/π interactions.

On the basis of the consideration that quantitative information for the stability of the diastereomeric salts would be obtained owing to their definite hydrogen-bonding networks, we next carried out theoretical calculations for the less- and more-soluble salt clusters of **2d** with (*Sp*)-**1**. Geometries of the cluster units were optimized with B3LYP/3-21G*.[11] The optimized structures are shown in Figure 4. The hydrogen-bonding networks located at the centers of the spherical clusters are very similar to each other, and no significant difference in molecular repulsion can be observed between the optimized structures. However, the orientations of the molecules of **2d** to the molecule of (*Sp*)-**1** in the spherical clusters are remarkably different from each other. In the less-soluble salt cluster, the aromatic ring of (*R*)-**2d** locates closely and vertically to the aromatic ring of (*Sp*)-**1** so that three

(11) Geometry optimizations were performed with B3LYP/3-21G* using the Gaussian 98 package. Frisch, M. J. et al. *Gaussian 98*, Revision A.11; Gaussian, Inc.: Pittsburgh, PA, 1998 [Full reference is given in Supporting Information]. For the initial coordinates of the more-soluble salt, the enantiomeric molecules of the amine component in the less-soluble salt crystal were replaced by the antipodes.

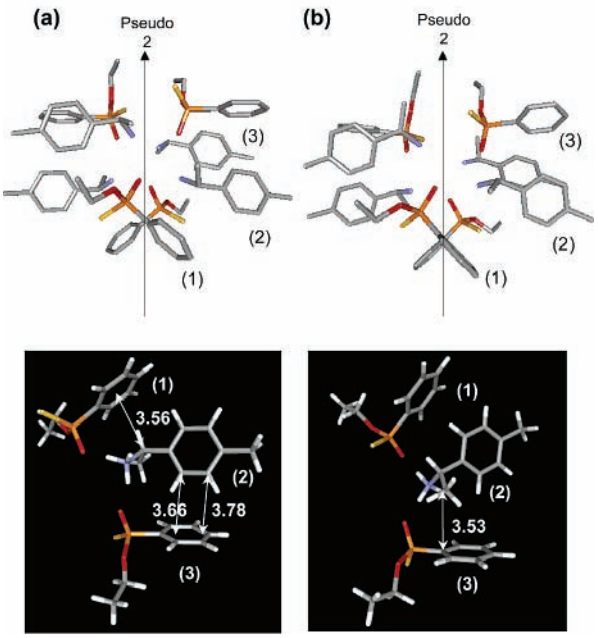

Figure 4. Molecular clusters of (a) (*Sp*)-**1**·(*R*)-**2d** and (b) (*Sp*)-**1**·(*S*)-**2d** optimized with B3LYP/3-21G*. The values are the distances between the C atom to the π-plane in angstroms.

kinds of CH/π interactions exist between the molecules of (*Sp*)-**1** and (*R*)-**2d** (Figure 4a), whereas there is only one CH/π interaction in the more-soluble salt cluster. The formation of the hydrophobic shell and the difference of the molecular orientation would arise from the chiral phosphorus atom in (*Sp*)-**1**; the *P*-chiral phosphonothioic acid would make its substituents more dendritic and give a more rigorously controlled chiral environment than conventional acidic resolving agents such as enantiopure carboxylic acids, sulfonic acids, and phosphoric acids. The energy difference between the two spherical clusters was estimated to be 16.2 kcal/mol. Although this energy difference seems to be considerably overestimated, the preferential stabilization of one of the two diastereomeric clusters, giving the less-soluble salt as crystals at room temperature and the more-soluble salt as oil even at low temperature, would be reasonably explained on the basis of the energy difference. The calculations also suggest that the chiral recognition would occur during the construction of the spherical clusters in a solution prior to crystallization.

In conclusion, we demonstrated an excellent chiral recognition ability of (*Sp*)-*O*-ethyl phenylphosphonothioic acid ((*Sp*)-**1**) for various racemic 1-phenylethylamine derivatives. The X-ray crystallographic analyses revealed that a very unique spherical cluster, in which there existed a definite hydrogen-bonding network, was formed to realize the excellent chiral recognition ability of (*Sp*)-**1**. Moreover, theoretical calculations suggested that the prediction of the chiral recognition ability of (*Sp*)-**1** for a given racemic amine would be possible, since the hydrogen-bonding network in the spherical cluster is definite.

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Supporting Information Available: Experimental procedure and characterization for (*Sp*)-**1**; general procedure for the enantioseparation by (*Sp*)-**1**; FT-IR spectra of the less-soluble salt (*Sp*)-**1**·(*R*)-**2d** and the more-soluble salt (*Sp*)-**1**·(*S*)-**2d**; preliminary crystal data for (*Sp*)-**1**·(*R*)-**2a**, (*Sp*)-**1**·(*R*)-**2g**, (*Sp*)-**1**·(*R*)-**2h**; and CIF data of (*Sp*)-**1**·(*R*)-**2d**, (*Sp*)-**1**·(*R*)-**2g**, and (*Sp*)-**1**·(*R*)-**2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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