Crystal Structure of (R)-2-Phenoxypropionic acid-(S)-Valine

Isao Fujii,*† Tetsuro Watadani,** Shigeki Nunomura,** and Yukio Takahashi**

*Department of Biological Science and Technology, Tokai University, 317 Nishino, Numazu, Shizuoka 410-0321, Japan
**Daito Chemical Co., Ltd., 2700 Suga, Hiratsuka, Kanagawa 254-0022, Japan

The crystal structure of (R)-2-phenoxypropionic acid-(S)-valine has been determined. In the crystal packing, the hydrophobic and hydrophilic layers are well separated along the b-axis. The adjusted shallow pocket on the hydrophobic layers accommodates the bulky i-propyl group of (S)-valine. The amino and carboxy groups of (S)-valine are intermolecular hydrogen bonded to the carboxy groups of phenoxypropionic acid.

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Through diastereomer-salt formation, the separation of a racemic compound into its optically pure enantiomers is very commonly applied in industry. Optically active 2-phenoxypropionic acid (PPA)† has been known to be a useful chiral resolution agent of amines, such as 2-methylpiperazine.2 We clarified the optical difference of the molecular-recognition mechanism between the (R)-PPA and (S)-alanine ([S]-ALA) complex,3 and the (R)-PPA and (R)-pipelic acid ([R]-PIP) complex.4 The shallow pocket on the hydrophobic layers plays an important role for chiral separation. In this paper, we focus on the molecular-recognition mechanism of the title compound, (I), which consists of a bulky i-propyl group (Fig. 1).

(R)-PPA and racemic valine (VAL) in a molar ratio of 1:2 were dissolved in hot water. The solution was slowly cooled at room temperature, and some fine rod-shaped colorless-crystals were obtained after a few days in a vial. (R)-VAL was in solution and excluded from co-crystals. A size of 0.3 × 0.2 × 0.2 mm crystal was used in X-ray diffraction experiments. Crystal and experimental data are given in Table 1. The crystal structure of (I) was solved by direct methods, SIR88,5 expanded using DIRDIF94,6 and refined by full-matrix least-squares. The absolute configuration was not experimentally determined, but was chosen to correspond to that of (R)-PPA. Non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms were located in a difference-Fourier map, refined isotropically, and finally fixed. The atomic parameters for the non-hydrogen atoms are listed in Table 2. All calculations were carried out with the program package teXsan.7

An ORTEP-3 stereodrawing of (I) together with the atomic numbering is shown in Fig. 2. Selected bond lengths, bond angles and torsion angles are given in Table 3. The crystal structure demonstrates the molecular recognition between (R)-PPA and (S)-VAL, shown in Fig. 2. The (R)-PPA molecule has an almost identical structure, as we already reported. The (S)-VAL molecule also displays a similar inner-salt structure,8 but the i-propyl group is rotated around the C11-C12 bond.

In the crystal packing, the hydrophobic and hydrophilic layers are well separated along the b-axis. The phenyl rings are packed in a herringbone-stacking mode. The carboxy group of PPA projects into the hydrophilic layer. The clearances of the carboxy groups of PPA on a hydrophobic layer make hydrophobic pockets. The shallow pocket surrounded by the four carboxy-groups of PPA accommodates the bulky i-propyl group of (S)-VAL. The crystal packing form is essentially similar to those of (R)-PPA-(S)-ALA and (R)-PPA-(R)-PIP.

The projected size of the shallow pocket is roughly estimated from the rectangular area that is made from the four chiral C8 atoms: 41.36(3), 38.39(3) and 41.36(3)Å² in the (R)-PPA-(S)-VAL, (R)-PPA-(S)-ALA and (R)-PPA-(R)-PIP, respectively. The lengths of sides of the rectangles are 7.649(2) and 5.407(2), respectively.

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† To whom correspondence should be addressed.
E-mail: fujii@wing.ncc.u-tokai.ac.jp

Fig. 1 Chemical structure of (I).

Fig. 2 ORTEP-3 stereo-drawing representing heavy atoms as 50% probability ellipsoids and H atoms as circles of arbitrary size. Symmetry codes:
(i) x + 1/2, 1/2 − y, 2 − z, (ii) x − 1/2, 1/2 − y, 2 − z, (iii) x + 1/2, 1/2 − y, 1 − z, (iv) x − 1/2, 1/2 − y, 1 − z.
7.330(2) and 5.237(2), and 6.647(2) and 6.222(2) Å, respectively. It is considered that the phenyl groups, which are rearranged due to accommodation of the hydrophobic group of guest molecule, affect and restrict the shallow pocket form.

In the hydrophilic layer, the amino group is hydrogen-bonding to the carbonyl group of (R)-PPA on the same side of the hydrophobic layer [\(\text{N1} - \text{H} \cdot \cdot \cdot \text{O2}(x + 1/2, 1/2 - y, 2 - z) = 2.905(2)\) Å, \(\angle \text{N1} - \text{H} \cdot \cdot \cdot \text{O2} = 173(2)\)°]. The deprotonated carboxy group of (S)-VAL also undergoes hydrogen-bonding to the hydroxy group of (R)-PPA on the opposite side of the hydrophobic layer [\(\text{O3} - \text{H} \cdot \cdot \cdot \text{O5} = 2.559(2)\) Å, \(\angle \text{O3} - \text{H} \cdot \cdot \cdot \text{O5} = 168(2)\)°].

**References**