Crystal Structure of (*R*)-3-Phenoxy-2-propanol-1-benzylammonium (*R*)-2-Phenoxypropionate

Tetsuro WATADANI,* Yukio TAKAHASHI,* and Isao FUJII**†

*Daito Chemical Co., Ltd, 2700 Suga, Hiratsuka, Kanagawa 254-0022, Japan

**Department of Biological Science and Technology, Tokai University, 317 Nishino, Numazu, Shizuoka 410-0321, Japan

The crystal structure of (*R*)-3-phenoxy-2-propanol-1-benzylammonium (*R*)-2-phenoxypropionate [(*R*)-BAPP·(*R*)-PPA] has been determined. In the crystal packing, the hydrophobic and hydrophilic layers are separated along the *b*-axis. The amphipathic-protonated BAPP molecule with two phenyl rings bridges two neighboring-hydrophobic layers. The N1–O4 chain of BAPP and the carboxy group of PPA are strongly recognized by each other, and they make the 9-membered ring connected by intermolecular-hydrogen bonds.

(Received October 26, 2004; Accepted January 18, 2005; Published on web March 22, 2005)

Production of optically active compounds has a great importance in the pharmaceutical industry. One of such optical active compounds, 1-benzylamino-3-phenoxy-2-propanol (BAPP), has been known to be a good chiral resolution agent of organic acids, such as tartaric acid and malic acid.^{1,2} In this paper, we focus on the molecular-recognition mechanism of the title compound, (I), shown in Fig. 1.

(*R*)-BAPP and racemic 2-phenoxypropionic acid (PPA)^{3,4} in a molar ratio of 1:2 were dissolved in hot 2-propanol. The solution was slowly cooled at room temperature, and some fine rod-shaped colorless-crystals were obtained after a few days in a vial. (*S*)-PPA 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 using the program SAPI91,⁵ and refined by full-matrix least-squares. The absolute configuration was not determined, but was chosen to correspond to that of (*R*)-BAPP. Non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms were located in a difference-Fourier map, and were refined isotropically but 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.⁶

An ORTEP-3⁷ drawing 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 shows the molecular recognition between (*R*)-BAPP and (*R*)-PPA. The (*R*)-BAPP molecule displays the extended-protonated shape with the long *trans*-connection of the C13–C20 chain except for the (–*ac*) N1–C10 bond, the rotation of which is considered to be restricted by hydrogen bonds. The (*R*)-PPA molecule except for deprotonation has an almost identical structure with the extended-ethoxy group against the phenyl ring, as we already reported.

In the crystal packing, the hydrophobic and hydrophilic layers are separated along the *b*-axis. The amphipathic BAPP molecule with two phenyl rings at a distance bridges two neighboring-hydrophobic layers. Since the N1–C10–C11–O4 and O3–C7–O2 moieties are strongly recognized by each other, they make the 9-membered ring connected by the intermolecular-hydrogen bonds [N1–H...O2 = 2.701(3) Å, ∠N1–H...O2 = 173(2)° and O4–H...O3 = 2.776(2) Å, ∠O4–H...O3 = 179(3)°]. The former bond and the bifurcated bond

Fig. 1 Chemical structure of (I) with the ring labeling system.

Fig. 2 ORTEP-3 drawing representing heavy atoms as 50% probability ellipsoids and H atoms as circles of arbitrary size. The dashed lines show intermolecular-hydrogen bonds.

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

Table 1 Crystal and experimental data

Formula: $C_9H_9O_3 \cdot C_{16}H_{20}NO_2^+$
Formula weight = 423.49
Crystal system: orthorhombic
Space group: $P2_12_12_1$ $Z = 4$
$a = 16.257(2)\text{\AA}$
$b = 22.313(2)\text{\AA}$
$c = 6.4439(5)\text{\AA}$
$V = 2337.5(4)\text{\AA}^3$
$D_x = 1.203\text{ g/cm}^3$
No. of reflections used = 2762
$2\theta_{\max} = 149.8^\circ$ with $Cu K\alpha$
$R = 0.043$
$(\Delta/\sigma)_{\max} = 0.0007$
$(\Delta\rho)_{\max} = 0.20\text{ e}\text{\AA}^{-3}$
$(\Delta\rho)_{\min} = -0.22\text{ e}\text{\AA}^{-3}$
Measurement: Enraf-Nonius CAD4-Turbo
Program system: Rigaku teXsan
Structure determination: direct method (SAPI91)
Refinement: full-matrix least-squares

Table 2 Atomic coordinates and equivalent isotropic thermal parameters (B_{eq})

Atom	x	y	z	B_{eq}
O(1)	-0.1107(1)	0.5606(1)	0.5460(3)	4.60(5)
O(2)	-0.0789(1)	0.5112(1)	0.0382(3)	3.95(4)
O(3)	-0.0148(1)	0.47839(9)	0.3232(3)	4.03(4)
O(4)	0.1297(1)	0.4767(1)	0.0938(3)	4.62(5)
O(5)	0.2114(1)	0.5916(1)	0.0762(4)	5.56(6)
N(1)	0.0140(1)	0.4595(1)	-0.2597(4)	3.14(4)
C(1)	-0.0575(2)	0.6074(1)	0.5283(5)	4.10(7)
C(2)	-0.0348(3)	0.6350(2)	0.3437(5)	5.66(9)
C(3)	0.0226(3)	0.6812(2)	0.3492(7)	6.9(1)
C(4)	0.0572(3)	0.6996(2)	0.5335(8)	7.0(1)
C(5)	0.0335(3)	0.6721(2)	0.7146(7)	6.5(1)
C(6)	-0.0234(2)	0.6271(2)	0.7137(5)	5.33(9)
C(7)	-0.0714(2)	0.5060(1)	0.2303(4)	3.23(5)
C(8)	-0.1404(2)	0.5335(1)	0.3596(4)	3.81(6)
C(9)	-0.2009(2)	0.4856(2)	0.4258(5)	5.18(8)
C(10)	0.0955(2)	0.4903(1)	-0.2684(5)	3.55(6)
C(11)	0.1191(2)	0.5198(1)	-0.0648(4)	3.52(6)
C(12)	0.1976(2)	0.5547(1)	-0.0995(5)	4.36(7)
C(13)	0.2665(2)	0.6374(1)	0.0563(6)	4.67(7)
C(14)	0.3150(2)	0.6469(1)	-0.1159(6)	5.10(8)
C(15)	0.3687(2)	0.6953(2)	-0.1192(7)	6.2(1)
C(16)	0.3750(3)	0.7330(2)	0.045(1)	7.3(1)
C(17)	0.3276(3)	0.7231(2)	0.2173(9)	7.0(1)
C(18)	0.2724(2)	0.6756(2)	0.2243(7)	5.97(9)
C(19)	0.0174(2)	0.3946(1)	-0.2098(5)	4.39(7)
C(20)	-0.0664(2)	0.3671(1)	-0.2132(6)	4.18(7)
C(21)	-0.1174(2)	0.3698(1)	-0.0413(6)	5.21(8)
C(22)	-0.1958(3)	0.3460(2)	-0.0501(9)	7.1(1)
C(23)	-0.2228(2)	0.3187(2)	-0.221(1)	7.9(1)
C(24)	-0.1735(3)	0.3144(2)	-0.3924(9)	7.7(1)
C(25)	-0.0946(2)	0.3390(2)	-0.3894(7)	5.66(9)

$$B_{eq} = (4/3)\sum_i \sum_j B_{ij}(\mathbf{a}_i \cdot \mathbf{a}_j).$$

Table 3 Selected bond lengths ($\text{\AA}$), bond angles ($^\circ$) and torsion angles ($^\circ$)

Bond lengths	($\text{\AA}$)	Bond lengths	($\text{\AA}$)
O(1)—C(1)	1.361(4)	O(5)—C(12)	1.418(4)
O(1)—C(8)	1.429(3)	O(5)—C(13)	1.365(4)
O(2)—C(7)	1.249(3)	N(1)—C(10)	1.494(3)
O(3)—C(7)	1.259(3)	N(1)—C(19)	1.483(4)
O(4)—C(11)	1.413(3)	C(10)—C(11)	1.517(4)
Bond angles	($^\circ$)	Bond angles	($^\circ$)
C(1)—O(1)—C(8)	118.0(2)	N(1)—C(10)—C(11)	113.1(2)
C(12)—O(5)—C(13)	117.6(3)	O(4)—C(11)—C(10)	111.2(2)
C(10)—N(1)—C(19)	115.1(2)	O(4)—C(11)—C(12)	110.7(2)
O(2)—C(7)—O(3)	126.0(3)	C(10)—C(11)—C(12)	108.0(2)
Torsion angles	($^\circ$)	Torsion angles	($^\circ$)
O(4)—C(11)—C(10)—N(1)	64.2(3)	C(1)—O(1)—C(8)—C(9)	-177.1(2)
O(5)—C(12)—C(11)—C(10)	168.7(2)	C(10)—N(1)—C(19)—C(20)	-177.6(3)
N(1)—C(10)—C(11)—C(12)	-174.1(2)	C(11)—C(10)—N(1)—C(19)	-94.1(3)
C(1)—O(1)—C(8)—C(7)	62.1(3)	C(11)—C(12)—O(5)—C(13)	-163.9(2)

[N1-H...O3 ($x, y, z-1$) = 2.776(2) $\text{\AA}$, $\angle$ N1-H...O3 ($x, y, z-1$) = 179(3) $^\circ$] make unidimensional-hydrogen bonding-networks along the c -axis. The herringbone-stacking mode also stabilizes the supramolecular structure of (I) in the hydrophobic layers. The dihedral angles and the distances between three short-contacted phenyl rings are as follows: C/A[$-x, y-1/2, 1/2-z$] = 69.4(3) $^\circ$, Cg(C)...Cg(A) = 4.979(2) $\text{\AA}$; B/C[$-x, y+1/2, -1/2-z$] = 83.3(3) $^\circ$, Cg(B)...Cg(C) = 5.010(2) $\text{\AA}$; A/B[$x-1/2, 3/2-y, 1-z$] = 79.4(3) $^\circ$, Cg(A)...Cg(B) = 5.349(3) $\text{\AA}$; where Cg is the center of gravity of the phenyl ring.

References

1. G. Hasegawa, T. Watadani, and N. Fon, Japan Patent, **1996**, 045689.
2. G. Hasegawa, T. Watadani, and N. Fon, Japan Patent, **1996**, 339876.
3. Y. Takahashi and I. Fujii, *Anal. Sci.*, **2004**, 20, x77.
4. T. Watadani, Y. Takahashi, and I. Fujii, *Anal. Sci.*, **2004**, 20, x141.
5. SAPI91, H.-F. Fan, **1991**, Rigaku Corporation, Tokyo, Japan.
6. teXsan, "Single Crystal Structure Analysis Software, Version 1.6", **1993**, Molecular Structure Corporation, Texas, U.S.A.
7. ORTEP-3, L. J. Farrugia, *J. Appl. Cryst.*, **1997**, 30, 565.